

Supplementary Materials

Virtual Screening and the In Vitro Assessment of the Antileishmanial Activity of Lignans

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Table S1. Lignans with good ADMET profiles.

Pharmacokinetics								
ID	GI ¹	BBB ²	P-gp ³	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
01	High	No	Yes	No	No	No	No	No
08	High	No	Yes	No	No	No	No	No
20	High	No	Yes	No	No	No	Yes	No
30	High	No	Yes	No	No	No	Yes	No
31	High	No	Yes	No	No	No	Yes	No
32	High	No	Yes	No	No	No	Yes	No
44	High	No	Yes	No	No	No	Yes	No
57	High	No	Yes	No	No	No	Yes	No
58	High	No	Yes	No	No	No	Yes	No
59	High	No	Yes	No	No	No	Yes	No
60	High	No	Yes	No	No	No	Yes	No
61	High	No	No	No	No	No	Yes	No
76	High	No	No	No	No	No	Yes	No
77	High	No	No	No	No	No	Yes	No
83	High	No	Yes	No	No	No	Yes	No
84	High	No	Yes	No	No	No	Yes	No
86	High	No	Yes	No	No	No	No	No
87	High	No	Yes	No	No	No	Yes	No
88	High	No	Yes	No	No	No	No	No
90	High	No	Yes	No	No	No	No	No
91	High	No	Yes	No	No	No	Yes	No
121	High	No	Yes	No	No	No	No	No
124	High	No	Yes	No	No	Yes	No	No
131	High	No	No	No	No	No	Yes	Yes
132	High	No	Yes	No	No	No	No	No
139	High	No	Yes	No	No	No	No	No
140	High	No	Yes	No	No	No	No	No
151	High	No	Yes	No	No	No	Yes	No
156	High	No	Yes	No	No	No	Yes	No
157	Low	No	Yes	No	No	No	No	No
158	Low	No	Yes	No	No	No	No	No
159	Low	No	Yes	No	No	No	No	No
160	Low	No	Yes	No	No	No	No	No

¹GI: Gastrointestinal absorption; ²BBB: Blood–brain barrier; ³P-gp: P-glycoprotein.

Table S2. Predictive assessment of lignan toxicity for the evaluated parameters.

ID	Mutagenic	Tumorigenic	Reproductive Effective	Irritant
1	No	No	No	No
8	No	No	No	No
20	No	No	No	No
30	No	No	No	No
31	No	No	No	No
32	No	No	No	No
44	No	Low	No	No
57	No	No	No	No
58	No	No	No	No
59	No	No	No	No

60	No	No	No	No
61	No	No	No	No
76	No	No	No	No
77	No	No	No	No
83	No	No	No	No
84	No	No	No	No
86	No	No	No	No
87	No	No	No	No
88	No	No	No	No
90	No	No	No	No
91	No	No	No	No
121	No	No	No	No
124	No	No	No	No
131	No	No	No	No
132	Low	Low	No	No
139	No	No	No	No
140	No	No	No	No
151	No	No	No	No
156	No	No	No	No
157	No	No	No	No
158	No	No	No	No
159	No	No	No	No
160	No	No	No	No

Table S3. Average of all energy values (EM) obtained from the five scoring functions, for each ligand, and the probability value of potential consensus docking activity (P_{DC}), for each studied enzyme in *L. major*. Absent values indicate the molecules that were eliminated during this evaluation.

ID	GPDH		DHODH		PTR1		TR		UGPase	
	EM	P _{DC}	EM	P _{DC}	EM	P _{DC}	EM	P _{DC}	EM	P _{DC}
44	58.90	0.82	43.43	0.69	68.81	0.83	63.96	0.91	63.96	0.91
60	63.50	0.89	46.47	0.67	67.38	0.82	62.45	0.89	62.45	0.89
83	63.94	0.90	59.44	0.67	73.90	0.89	64.63	0.92	64.63	0.92
86	63.53	0.89	60.87	0.72	72.16	0.87	63.19	0.90	63.19	0.90
87	63.39	0.89	58.81	0.70	-	-	63.95	0.91	63.95	0.91
124	57.36	0.64	68.34	0.67	75.47	0.91	69.58	1	69.58	1
132	64.43	0.90	49.07	0.66	-	-	62.21	0.89	62.21	0.89
157	67.91	0.95	41.51	0.81	72.03	0.87	-	-	50.43	0.72
158	66.48	0.93	54.86	0.75	77.00	0.93	-	-	49.97	0.71
159	63.43	0.89	53.39	0.87	83.63	1	53.32	0.76	65.55	0.94
160	71.03	1	-	0.81	82.16	0.98	53.58	0.77	53.58	0.77
PDB inhibitor	37.72	0.53	35.75	0.58	63.94	0.77	37.38	0.53	37.38	0.53

Table S4. Average of all energy values (EM) obtained from the five scoring functions, for each ligand, and the probability value of potential consensus docking activity (P_{DC}), for each studied enzyme in *L. braziliensis*. Absent values indicate the molecules that were eliminated during this evaluation.

ID	GPDH		DHODH		PTR1		TR		UGPase	
	EM	P _{DC}	EM	P _{DC}	EM	P _{DC}	EM	P _{DC}	EM	P _{DC}
8	59.21	0.86	43.99	0.58	72.53	0.80	-	-	-	-
20	58.17	0.85	50.00	0.66	74.64	0.83	56.19	0.76	-	-
31	60.39	0.88	48.93	0.65	78.41	0.87	57.66	0.78	62	0.77

32	59.15	0.86	48.32	0.64	78.54	0.87	55.41	0.75	63	0.78
44	45.54	0.66	48.07	0.64	82.79	0.92	55.57	0.75	64	0.80
57	55.88	0.81	47.32	0.63	80.91	0.90	54.14	0.73	64	0.80
58	50.37	0.73	46.09	0.61	68.36	0.76	53.10	0.72	64	0.80
59	49.23	0.72	44.79	0.59	70.40	0.78	-	-	64	0.80
60	56.97	0.83	46.11	0.61	77.81	0.86	54.06	0.73	66	0.83
61	56.56	0.82	52.94	0.70	-	-	55.24	0.75	-	-
76	-	-	44.90	0.59	-	-	-	-	-	-
83	59.50	0.87	54.88	0.73	77.25	0.86	64.98	0.80	61	0.77
87	60.87	0.89	49.12	0.65	71.98	0.80	59.44	0.80	62	0.78
91	61.54	0.90	48.37	0.64	78.16	0.87	57.35	0.77	61	0.77
121	61.30	0.89	47.32	0.63	76.26	0.85	-	-	-	-
124	56.49	0.82	51.88	0.69	81.29	0.90	65.78	0.89	-	-
156	53.24	0.78	51.39	0.68	74.87	0.83	54.11	0.73	66	0.83
157	58.25	0.85	63.68	0.84	89.59	1	60.59	0.82	66	0.83
158	68.18	1	55.11	0.73	77.40	0.86	62.11	0.84	68	0.85
159	68.07	0.99	55.19	0.73	82.16	0.91	73.53	1	79	1
160	57.54	0.84	74.97	1	79.52	0.88	-	-	76	0.95
PDB inhibitor	36.26	0.53	32.40	0.43	67.31	0.75	53.15	0.72	61	0.76

L. major MISTKRHINTNELLHLSKAVVFGSGAFGTALAMVLSKKCREVVCVWHIKEEEARLVNEKRE 60
L. braziliensis MLSANGKANANELLIYIKKAVVFGSGAFGTALATVLAKKCREVVCVWHIKEEEAQLVNRKRE 60

L. major NDLYLRGVQLASNIIFTSDDVEAYKGAELILFVPTQFLRQFFQKSGGNLIYAKARQVF 120
L. braziliensis NMMYIKGVKLASNITFTSNVEQAYKDAEIIILFVPTQFLRQFFQKSGGNLITYAKERKRVF 120

L. major VLVCTKGIERSTLKFPAQIVGEFFPSNLLSVLAGPSFAIEVATGVFTCVSVASADINVAR 180
L. braziliensis VLVCTKGIERSTLKFPAQIVGEFFADYPLSVLAGPSFAIEVAAGIFTCVGIASADINQAR 180

L. major RLQRIMTTGDRSFVCWATTDITVGCDEVASAVKNVLAIGSGVANGLGMLNARAALITRGLI 240
L. braziliensis RLQRIMTTGDRSFVCWATTDITIGFDEVASAVKNVLAIGSGVANGLGMLNARAALITRGLI 240

L. major EIRDLTAAALGGDGSATIFGLAGFGDLQLTCSSELSRNFTVGRKLGKELSLLEEIQRTSKAVA 300
L. braziliensis EIRDLTGALGGDGSAAVFLAGLGDQLTCSSELSRNFTVGRKLGKETSILEEIQRTSKAVA 300

L. major EGVATAEPLVRLAQQLKVTMPLCQQIYEVVYKKNPRAAIADLLSCGLQDEGLPPLFKKS 360
L. braziliensis EGVATAEPLMRLAQQLKVSMPCLKETIKIVYEKKNPRDAIADLLSCGLQDEGLPALFKKS 360

L. major AATPSKI 367
L. braziliensis SATLSKI 367

Figure S1. Alignment of the GPDH protein sequences. The gray regions show non-similar and non-identical amino acids. The red regions show identical amino acids. The yellow regions show similar amino acids. The black boxes indicate the active site.

L. major MGSSHHHHHSSGLVFASSHMASMTGGQMGREGMSLQVNLNNTFANPFMNAAGVMCTI 60
L. braziliensis MGSSHHHHHSSGLVFRSSHMASMTGGQMGREGMSLQVNLNNTFANPFMNAAGVMCS 60

L. major TEELVAMTESASGSLVSKSCTPALREGNFTFRYQALPLGSINSMLEPNKGFDFYLAYSAR 120
L. braziliensis EEEAAMTESASGSLITKXCTPALREGNFAFRYYTLPLGSINSMLEPNKGFDFYLAYSAR 120

L. major QADVGGKPLFLSMGLMRENVEKCKRLAAVATEKGVILELNLSCPNVPGRPQVAYDFDA 180
L. braziliensis HHDYSRKPLFISISGFIAEENAEKCKRLAPVAEEKGVILELNLSCPNVPGRPQVAYDFDA 180

L. major MRQCITAVSEVYPHSFGVKMPPYDFFAHFDAAAEILNEFPKVQFITCINSIGNGLVIDAH 240
L. braziliensis MRRYLAIISEAYPHEFGVKMPPYDFFAHFDAAAEILNEFPKVQFITCINSIGNGLVIDAH 240

L. major TESVVIKPRQGGFGLGGRYVLPALANINAFYRRCPPGKLIFGCGGVYTGEDAFHLVLAGA 300
L. braziliensis TESVVIKPRQGGFGLGGRYVLPALANVNAFYRRCPPGKLIFGCGGVYTGEDAFHLVLAGA 300

L. major SMVQVGTALQEEGPSIFERLISELLIGVMAKRRVQTLDEFRGKVRTLIGTAESTR 354
L. braziliensis SMVQVGTALHEEQAAIFERLVAELLDVMAKRGYKALDEFRGKVKAM 347

Figure 2. Alignment of the DHODH protein sequences. The gray regions show non-similar and non-identical amino acids. The red regions show identical amino acids. The yellow regions show similar amino acids. The black boxes indicate the active site.

L. major -MTAPVFPVALVTGAARKLRSLAEGLHAEGYAVCLHYHRSAAEANAALSATLNARRPNSA 59
L. braziliensis MTSVAVFPVALVTAARKRLCCGIAFI LHAQGYAVCLHYHRSAAEDANTL TATLNSRRPNSA 60

L. major ITVQADLSNVATAPVSGADGSAFVTFTRCAELVAACYTHWGRCDVLVNNAASFFYPTPLL 119
L. braziliensis IAVQADLSAVATASVSSAHDAAPISILVQRCAGLVDACYNHWGRCDVLVNNAASAYYPTPLL 120

L. major RNDEDGHEPCVGDREAMETA TADLFGSNIAI AHYFLIKAFARVAGTPAKHGNTNYSIINM 179
L. braziliensis NKVTEGHEFSMNEET-EAANAADLFGTNALAFFFLIKAFARQVADIPAEQSDNYSIVNI 179

L. major VDAMTNQELLCGYTIYTMARGALEGLTRSAALELAPLQIRVNGVGPGLSVLVDMPFAVWE 239
L. braziliensis IDAMTNQELLCGFTMYTMAKEALEGLTRSAALELAPLQVVRVNGVSPGLSIFPADMPSAVQA 239

L. major GHRSKVPLYQHDSSLAEVSDVMIIFLCSSKARYITGTXVKVDGGYSLTRA 288
L. braziliensis IYRSKVPLYQRESTEAEVAAAIFFLCSSAKYITGTCKVKVDGGYSLTRA 288

Figure 3. Alignment of the PTR1 protein sequences. The gray regions show non-similar and non-identical amino acids. The red regions show identical amino acids. The yellow regions show similar amino acids. The black boxes indicate the active site.

L. major MSRAYDLVVLGAGSGGLEAGWNAATYKKKVAVVDVQATHGPPFFAALGGTCVNVGCVPR 60
L. braziliensis MPRAYDLVVLGAGSGGLEAGWNAASINKKVAVVEAQLKEHGPECF AALGGTCVNVGCVPR 60

L. major KLMVTGAQYMDLIRESCGFGWEMNREILCPNWKTLIAAKNKVWNGINESYKSMFADTEGI 120
L. braziliensis KLMVTGAQYMDLIRESCGFGWEMDRDSIRS NWKKLTAKNKVVSIDNKS YTDMFENTTEGI 120

L. major SFHMFGALQDAHTVLVRKSEDPNSDVLETIDTEYILIATGSWPTRLGIPGDEF CITSNE 180
L. braziliensis SFHMFGALQDAHTVVVRKSEDESDVLETIEADYILIATGSWPTRLGIPGDEL CITSNE 180

L. major AFYLEDAPKRMLCVGGGYIAVEFAGIFNGYKFERGYVDLCYRGDILLRGFTLEVRKSLIM 240
L. braziliensis AFYLDEAPKRALCVGGGYISVEFAGIFNAYKFPDQCVDLCYRGEVILLRGFTLEVRKSLIM 240

L. major QLEANGIRVRINLNFTKITKNE DGSNHVHNDGTEEDYDQVMLAIGRVPRSQTLQDKAG 300
L. braziliensis QLEANGIKIRTKVNESRITKNADGSKHVCFEDGTEADYDQVMLAVGRAPRSKALQDKAG 300

L. major VQTAKNGAVQVDAYSKTSVDNIYAIGDVTNIVMLIPVAINEGAAT AETVFGKPRATDHT 360
L. braziliensis VKMGKNGAVVVDAYSKTSVDNIYAIGDVTDLMLIPVAINEGSAFVETLFGCKPRATDHT 360

L. major KVACAVFSIPPICGCMTEEEAAKNHETVAVYESCF TPLMHNISGSKHETFMIRITTDQP 420
L. braziliensis KVACAVFSIPPICGCLTEEEAAKKYDVVAVYESSFTPLMHNISGSKHETFMIRIVTKKEK 420

L. major SGEVLGVHMLGDSAPEIIQSVGICMRMGAKISDFHSTIGVPEPSAPELLCSMRTPAYFYEN 480
L. braziliensis DGEVLGVHMLGDSAPEIIQSVGICMRMGAKISDFHSTIGVPEPSAPELLCSMRTPAYFYEN 480

L. major GKRVEKLSNL 491
L. braziliensis GKRVEKLSNLI 491

Figure S4. Alignment of the TR protein sequences. The gray regions show non-similar and non-identical amino acids. The red regions show identical amino acids. The yellow regions show similar amino acids. The black boxes indicate the active site.

L. major MENDMKSLSAAAQACVKKMRDAKVNEACIRTFIAQHVMVSKGETGSIIPDSAIMPVDSLDA 60
L. braziliensis MEIDMNAISAAAQACVKKMRDAKVNEACIRTFIAQHVMVSNGETGSIIPDSATRIE SLDE 60

L. major IDSLTI ECDNAVLQSTVVLKLNGLGTGMGLCDAKTLIE VKDGKTFLDFTALQVQYLRQH 120
L. braziliensis IEGLTI ECDNAVLQSTVVLKLNGLGTGMGLHDAKTLID VKDGKTFLDFTALQVQYLRQH 120

L. major CSEHLRFMLMDSFNSTASTKSFILKARYPWLYQVFDSEVELMQNQVPKILQDTLEFAAATA 180
L. braziliensis CSERLRFMLMNSFNSTASTRRFIEARYPWLYQVFDSEVELMQNQVPKILQDTLEPVTWPE 180

L. major NEAYEWAPPGHGDIYTALYGSGLQELVEQGYRYMFVSNNGDNLGATIDKRVLAYMEKEKI 240
L. braziliensis DFGCEWAPPGHGDIYTALYGSGLQELVNIQGYRYIFVSNNGDNLGATIDKRVLAYMEKEKI 240

L. major DFLMEVCRFTESDKKGGHRLARQTVYVHGKDGQPDAEK-RVLLLRRE SAQCPHADMESFQDI 299
L. braziliensis DFLMEVCRFTESDKKGGHRLARQVVCANSKGSQPDASTGGLLLLRRELAQCPHEDMNNFQDI 300

L. major NKYSFFNTNNLWIRLPVLLIETMQE HGGTLPLPVIRNEKTVDSSNSASPKVYQLETAMGAA 359
L. braziliensis NKHSFFNTNNLWIRLPALLIATMEKHGGTLPLPVIRNEKTVDPSNPASPKVYQLETAMGAA 360

L. major IAMFESASAIMVPPSRFAPVKTCADLLALRSDAYVVTDFRFLVDDRCHGHPVVDLNSA 419
L. braziliensis IAMFENASALMVPPSRFAPVKTCADLLALRSDAYVVTNDSRLVDDRCHGHPVVDLNSA 420

L. major HYKMMNGFEKLVQHGVPVSLVECKRVTVKGLVQFGAGNVLTGTVTIENTDSASAFVIPDGA 479
L. braziliensis HYKMMGGFEKLVQNGVPVSLVKCKRLIVKGLVQFGTDNVLTGTVKIENAHASASAFVTPDGA 480

L. major KLNDTTASPPQOSTNKMRPLEHHHHHH 505
L. braziliensis KLTDTTVSPP----- 490

Figure S5. Alignment of the UGPase protein sequences. The gray regions show non-similar and non-identical amino acids. The red regions show identical amino acids. The yellow regions show similar amino acids. The black boxes indicate the active site.