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Cyclin-dependent kinase 12 is a drug target for visceral leishmaniasis

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Strain	Country of origin	Year	Compound 7 EC ₅₀ (μM)	Miltefosine EC ₅₀ (μM)
<i>L. donovani</i> LV9	Ethiopia	1967	0.05, 0.09	0.36, 0.43
<i>L. donovani</i> SUKA 001	Sudan	2010	0.09	0.91
<i>L. donovani</i> BHU1 *	India	2002	0.11	0.50
<i>L. donovani</i> DD8	India	1980	0.13	0.51
<i>L. infantum</i> ITMAP263	Morocco	1967	0.50, 0.13	1.0, 0.79

* Antimony-resistant reference strain

Strains were tested as technical duplicates on a single (DD8, SUKA001, BHU1) or two (LV9, ITMAP263) occasions; the respective EC₅₀ values are shown for LV9 and ITMAP263.

Media	Final pH	Solubility [mg/mL]
SGF pH1.6	1.5	1.12
Fasted SIF pH6.5	6.5	0.017
Fed SIF pH6.5	6.5	0.025

SGF, simulated gastric fluid; SIF, simulated intestinal fluid.
Data were generated using crystalline polymorph form 1

Species	Concentration (μM)	Liver Microsomes Cli (mL/min/g tissue)	Hepatocytes Cli (mL/min/g tissue)
Mouse	0.5	0.52	0.84
Rat	0.5	<0.5	0.77
Dog	0.5	<0.4	0.31
Human	0.5	0.71	0.55

Cli, intrinsic clearance.

Intravenous	Mouse	Rat
	(male, CD1)	(male, SD)
	1 mg/kg	1 mg/kg
Cl (ml/min/kg)	169 ± 50	14 ± 9
V _{dss} (L/kg)	4.0 ± 0.5	0.4 ± 0.1
T _{1/2} (h)	0.3 ± 0.04	0.4 ± 0.2
AUC _(0-inf) (ng.h/mL)	104 ± 26	1514 ± 782
Oral	10 mg/kg	10 mg/kg
C _{max} (ng/mL)	561 ± 148	1043 ± 261
T _{max} (h)	2 ± 0.6	2 ± 0.0
AUC _(0-inf) (ng.h/mL)	1463 ± 362	6475 ± 2494
F% based on AUC _(0-inf)	>100	46 ± 18
Oral	100 mg/kg	100 mg/kg
C _{max} (ng/mL)	8813 ± 1966	8470 ± 3750
T _{max} (h)	3 ± 2.3	7.3 ± 1.2
AUC _(0-inf) (ng.h/mL)	39433 ± 23830	61202 ± 23591
F% based on AUC _(0-inf)	>100	40 ± 15
Oral	300 mg/kg	300 mg/kg
C _{max} (ng/mL)	11393 ± 4212	14833 ± 2676
T _{max} (h)	5 ± 1.2	7.3 ± 1.2
AUC _(0-inf) (ng.h/mL)	*66150 ± 636	136333 ± 24846
F% based on AUC _(0-inf)	>100	51 ± 22

* Back-extrapolated AUC greater than 20%

Cell line	Compound 4		Compound 5		Compound 7	
	pEC ₅₀ (SD)	Fold	pEC ₅₀ (SD)	Fold	pEC ₅₀ (SD)	Fold
Wild type (Start clone)	7 (0.1)	1	8.2 (0.4)	1	7.1 (0.3)	1
Wild type (Age-matched)	7.1 (0.2)	1	8.2 (0.1)	1	7.3 (0.2)	1
4-resistant clone 1	< 4.3	>500	7.2 (0.1)	11	5.8 (0.4)	20
4-resistant clone 2	< 4.3	>500	7.3 (0.1)	7	5.7 (0.2)	24
4-resistant clone 3	< 4.3	>500	7 (0.2)	17	5.4 (0.1)	48
5-resistant clone 1	< 4.3	>500	7.1 (0.2)	11	5.5 (0.2)	41
5-resistant clone 2	< 4.3	>500	7.1 (0.2)	14	5.5 (0.1)	35
5-resistant clone 3	< 4.3	>500	7.3 (0.1)	9	5.7 (0.1)	22

Values in parentheses denote standard deviation. n = 3

Compound	Cell line	pXC50	Host cell pXC₅₀	Fold difference
5	WT	7.5	<5.3	-
5	5 RES clone 1	6.6	<5.3	8.5
7	WT	5.9	<4.3	-
7	5 RES clone 1	5.2	<4.3	5.0