Supporting Information

Species-selective pyrimidineamine inhibitors of *Trypanosoma brucei S*-adenosylmethionine decarboxylase.

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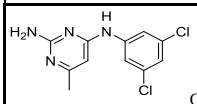
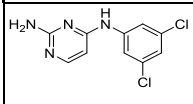
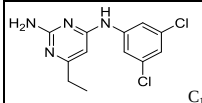
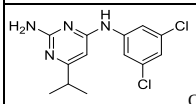
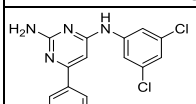
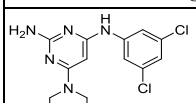
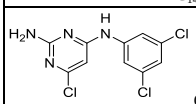
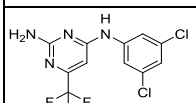
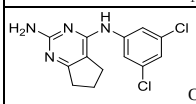
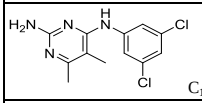
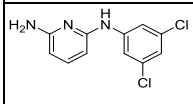
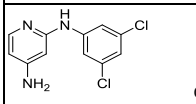
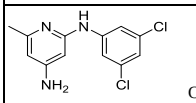
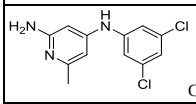
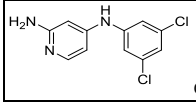
Table S1. Biological activity data for pyrimidineamine analogs

Chemical structure	Manuscript number	Code number	*Tb* IC_{50} pH 6.8, uM[b]	*Tb* IC_{50} pH 7.2, uM[c]	*Tb* IC_{50} pH 7.7, uM[d]	*Hs* IC_{50} pH 7.2, uM[e]	pK_a(N1)[f]	*Tb* 427 EC_{50}, uM[a]	EC_{50} Hill slope	Source
 $C_{11}H_{10}Cl_2N_4$	**7**	UTSAM30	0.5 (0.42–0.6)	3.7 (3.3–4.1)	36 (29–44)	27% at 180	7.3	5.6 (4.5–7.1)	-1.9	Maybridge
 $C_{10}H_8Cl_2N_4$	**8**	UTSAM473	nd	13 (11–15)	134 (96–188)	>180	6.6	9.9 (7.7–13)	-1.8	synthesized
 $C_{12}H_{12}Cl_2N_4$	**9**	UTSAM571	0.51 (0.46–0.56)	3 (2.7–3.3)	32 (29–36)	36% at 180	7.1	4.7 (4.1–5.4)	-2.9	synthesized
 $C_{13}H_{14}Cl_2N_4$	**10**	UTSAM574	1.9 (1.7–2.2)	12 (10–14)	187 (154–225)	>180	7.0	4.7 (3.9–5.8)	-1.6	synthesized
 $C_{16}H_{12}Cl_2N_4$	**11**	UTSAM569	4.6 (3.8–5.6)	24% at 21	>21	>21	6.1	7.2 (6.0–8.5)	-1.6	synthesized
 $C_{14}H_{15}Cl_2N_5O$	**12**	UTSAM580	31% at 180	>180	>180	>180	6.0	13 (10–17)	-4.5	synthesized
 $C_{10}H_7Cl_3N_4$	**13**	UTSAM533	nd	>180	>180	>180	–2.2	8.9 (7.3–11)	-2.4	synthesized
 $C_{11}H_7Cl_2F_3N_4$	**14**	UTSAM534	nd	>180	>180	>180	–3.3	10 (7.5–14)	-4.6	synthesized
 $C_{13}H_{12}Cl_2N_4$	**15**	UTSAM578	1.7 (1.5–2.0)	12 (11–14)	>21	>21	6.8	19 (15–24)	-0.96	synthesized
 $C_{12}H_{12}Cl_2N_4$	**16**	UTSAM576	0.88 (0.77–0.99)	4.8 (4.5–5.2)	39 (33–48)	25% at 180	7.0	17 (14–20)	-2.0	synthesized
 $C_{11}H_9Cl_2N_3$	**17**	UTSAM542	>180	>180	>180	>180	na	96 (66–140)	-1.2	synthesized
 $C_{11}H_9Cl_2N_3$	**18**	UTSAM556	34% at 180	>180	>180	>180	na	38 (31–47)	-4.7	synthesized
 $C_{12}H_{11}Cl_2N_3$	**19**	UTSAM558	186 (160–217)	24% at 180	>180	>180	na	13 (8.2–22)	-5.3	synthesized
 $C_{12}H_{11}Cl_2N_3$	**20**	UTSAM561	3.4 (3–3.9)	15 (13–18)	69 (55–87)	>180	9.6	2.2 (1.7–2.9)	-4.4	synthesized
 $C_{11}H_9Cl_2N_3$	**21**	UTSAM541	9.9 (8.9–11)	29 (27–31)	136 (115–161)	>180	9.4	11 (9.5–12)	-2.3	synthesized

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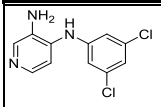
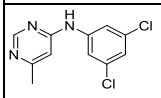
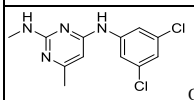
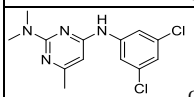
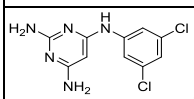
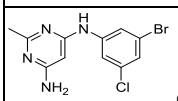
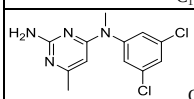
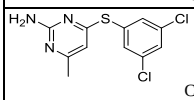
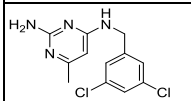
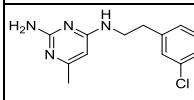
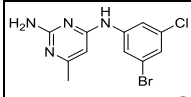
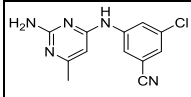
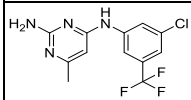
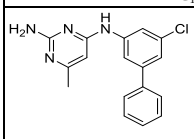
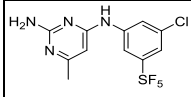
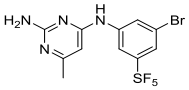
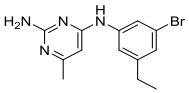
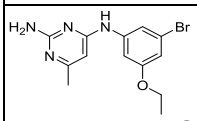
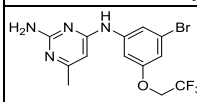
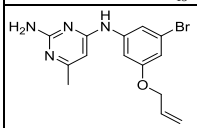
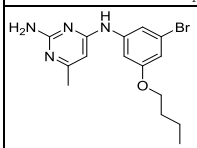
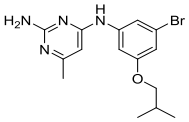
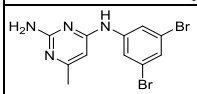
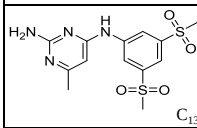
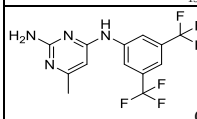
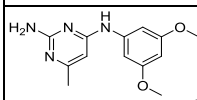
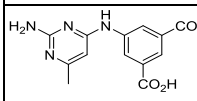
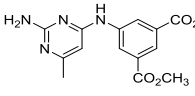
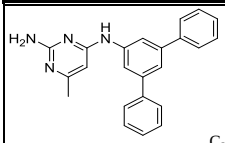
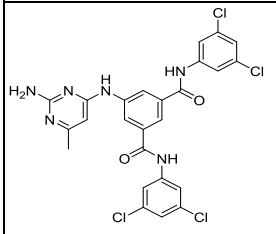
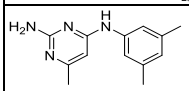
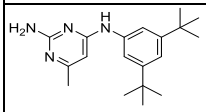
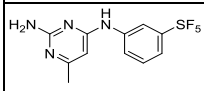
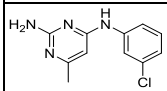
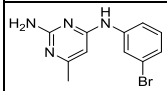
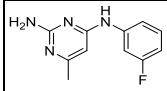
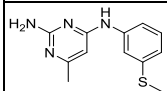
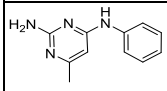
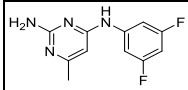
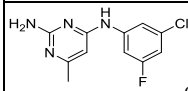
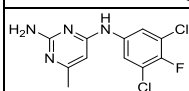
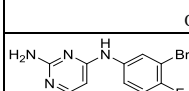
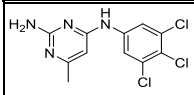
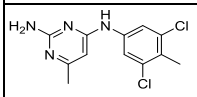
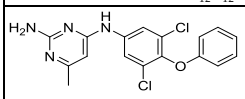
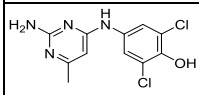
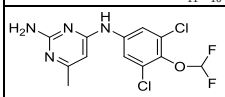
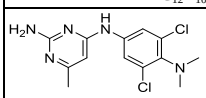
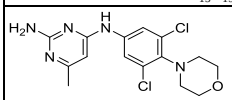
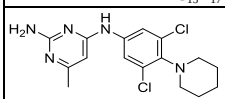
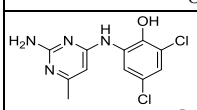
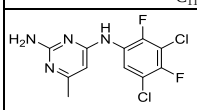
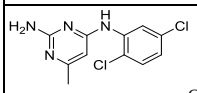
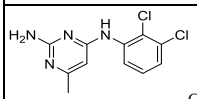
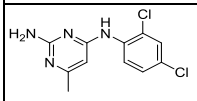
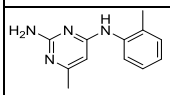
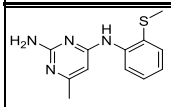
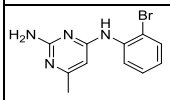
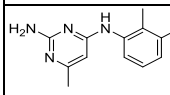
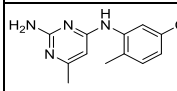
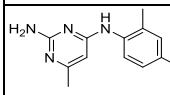
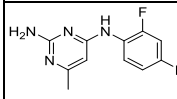
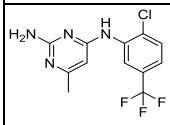
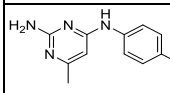
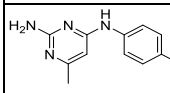
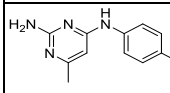
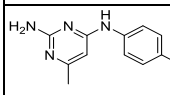
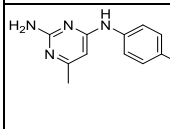
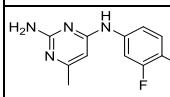
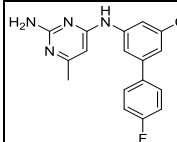
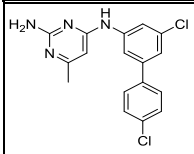
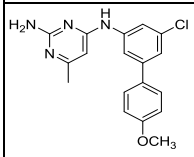
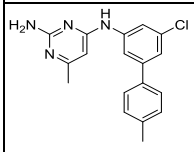
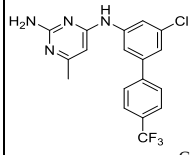
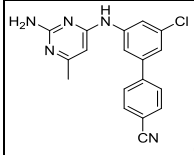
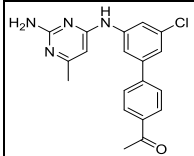
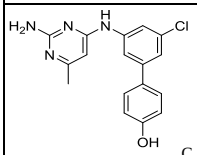
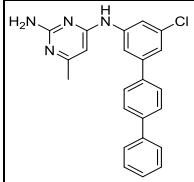
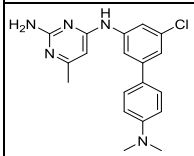
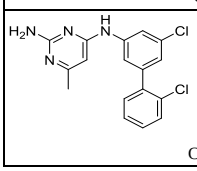
 $C_{11}H_9Cl_2N_3$	**22**	UTSAM562	135 (113–163)	21% at 180	>180	>180	8.4	18 (14–24)	-6.7	synthesized
 $C_{11}H_9Cl_2N_3$	**23**	UTSAM475	nd	>180	>180	>180	5.2	27 (22–33)	-1.9	synthesized
 $C_{12}H_{12}Cl_2N_4$	**24**	UTSAM539	16% at 63	>63	>63	>63	7.1	2.7 (2.4–3.1)	-3.5	synthesized
 $C_{13}H_{14}Cl_2N_4$	**25**	UTSAM540	>180	>180	>180	>180	7.0	14 (8.1–24)	-6.3	synthesized
 $C_{10}H_9Cl_2N_5$	**26**	UTSAM584	5.8 (4.9–6.8)	48 (43–54)	18% at 180	>180	6.4	14 (12–17)	-2.0	synthesized
 $C_{11}H_{10}BrClN_4$	**27**	UTSAM626	50 (34–72)	24% at 180	>180	>180	6.4	20 (17–24)	-2.7	synthesized
 $C_{12}H_{12}Cl_2N_4$	**28**	UTSAM544	21 (19–23)	81 (74–89)	23% at 180	>180	7.2	38 (34–43)	-4.0	synthesized
 $C_{11}H_9Cl_2N_3S$	**29**	UTSAM536	nd	>180	>180	>180	4.3	>25	na	synthesized
 $C_{12}H_{12}Cl_2N_4$	**30**	UTSAM579	31 (28–34)	139 (130–150)	17% at 180	>180	8.1	11 (9.9–13)	-2.6	synthesized
 $C_{13}H_{14}Cl_2N_4$	**31**	UTSAM575	6.6 (5.9–7.4)	28 (25–32)	45% at 180	29% at 180	8.2	5.7 (1.6–21)	-8.7	synthesized
 $C_{11}H_{10}BrClN_4$	**32**	UTSAM572	0.31 (0.28–0.35)	2.2 (2.0–2.4)	26 (23–30)	33% at 180	7.3	4.7 (3.9–5.8)	-4.2	synthesized
 $C_{12}H_{10}ClN_5$	**33**	UTSAM567	0.46 (0.41–0.52)	3.9 (3.2–4.83)	53 (45–63)	29% at 180	7.3	12 (10–14)	-1.9	synthesized
 $C_{12}H_{10}ClF_3N_4$	**34**	UTSAM564	0.71 (0.59–0.85)	3.9 (3.4–4.4)	42 (34–51)	39% at 180	7.3	13 (11–15)	-4.0	synthesized
 $C_{17}H_{15}ClN_4$	**35**	UTSAM573	0.52 (0.46–0.58)	3.3 (2.8–3.9)	40 (34–47)	30% at 63	7.3	4.5 (2.1–9.4)	-6.6	synthesized
 $C_{11}H_{10}ClF_5N_4S$	**36**	UTSAM606	1.9 (1.7–2.1)	16 (14–18)	38% at 180	>180	7.3	13 (11–15)	-4.5	synthesized

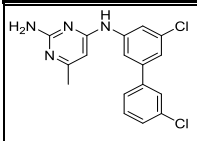
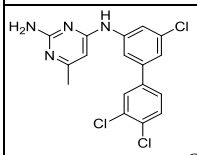
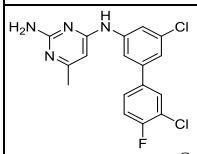
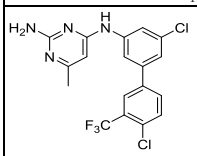
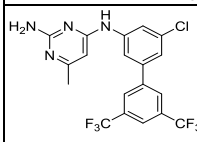
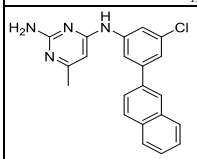
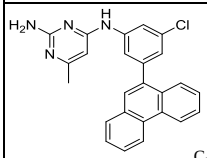
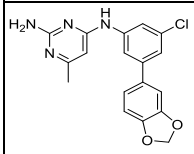
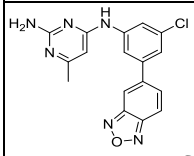
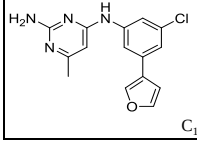
Chemical structure	Manuscript number	Code number	*Tb* IC_{50} pH 6.8, uM[b]	*Tb* IC_{50} pH 7.2, uM[c]	*Tb* IC_{50} pH 7.7, uM[d]	*Hs* IC_{50} pH 7.2, uM[e]	pK_a(N1)[f]	*Tb* 427 EC_{50}, uM[a]	EC_{50} Hill slope	Source
 $C_{11}H_{10}BrF_5N_4S$	**37**	UTSAM604	1.0 (0.93–1.1)	8.7 (7.4–10)	167 (110–253)	>180	7.3	0.45 (0.32–0.62)	-6.3	synthesized
 $C_{13}H_{15}BrN_4$	**38**	UTSAM628	1.2 (0.96–1.5)	7.6 (5.7–10)	80 (60–106)	>180	7.3	5.5 (4.6–6.6)	-3.8	synthesized
 $C_{13}H_{15}BrN_4O$	**39**	UTSAM633	1.0 (0.61–1.7)	6 (5.2–6.9)	57 (49–65)	36% at 180	7.3	4.4 (4.2–4.7)	=-8.0	synthesized
 $C_{13}H_{12}BrF_3N_4O$	**40**	UTSAM627	0.23 (0.17–0.32)	1.6 (1.1–2.4)	13 (8–23)	44 (33–58)	7.3	4.2 (3.6–4.8)	-3.8	synthesized
 $C_{14}H_{15}BrN_4O$	**41**	UTSAM634	0.64 (0.43–0.96)	4.5 (4.1–4.9)	52 (45–60)	28% at 180	7.3	4.4 (3.7–5.3)	-3.9	synthesized
 $C_{15}H_{19}BrN_4O$	**42**	UTSAM635	0.74 (0.56–0.98)	4.5 (4.0–5.1)	56 (45–70)	>180	7.3	1.9 (1.7–2.1)	-4.1	synthesized
 $C_{15}H_{19}BrN_4O$	**43**	UTSAM636	1.9 (1.2–2.8)	11 (9.5–12)	153 (124–187)	>180	7.3	4.4 (3.5–5.5)	-4.4	synthesized
 $C_{11}H_{10}Br_2N_4$	**44**	UTSAM568	0.21 (0.18–0.23)	1.9 (1.7–2.1)	20 (18–22)	31% at 180	7.3	4.8 (4.1–5.6)	-4.8	synthesized
 $C_{13}H_{16}N_4O_4S_2$	**45**	UTSAM602	0.20 (0.18–0.24)	1.5 (1.3–1.7)	15 (13–18)	39% at 180	7.3	>100	na	synthesized
 $C_{13}H_{10}F_6N_4$	**46**	UTSAM547	1.4 (1.1–1.6)	11 (9.8–12)	143 (116–176)	>180	7.3	14 (11–17)	-4.0	synthesized
 $C_{13}H_{16}N_4O_2$	**47**	UTSAM474	3.4 (2.7–4.2)	17 (14–20)	131 (110–56)	21% at 180	7.3	41 (33–51)	-1.7	synthesized
 $C_{13}H_{12}N_4O_4$	**48**	UTSAM565	>180	>180	>180	>180	7.3	>100	na	synthesized
 $C_{15}H_{16}N_4O_4$	**49**	UTSAM566	38 (32–44)	40% at 180	>180	>180	7.3	42 (22–78)	-5.7	synthesized

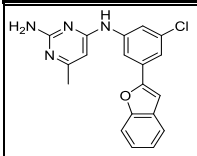
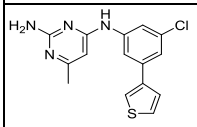
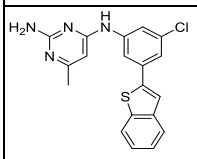
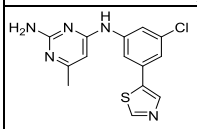
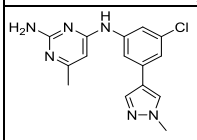
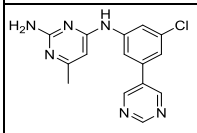
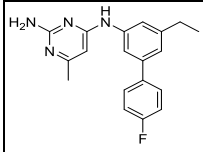
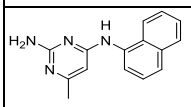
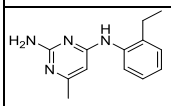
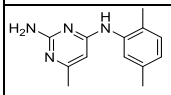
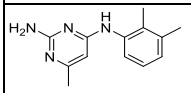
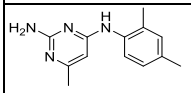
Chemical structure	Manuscript number	Code number	*Tb* IC_{50} pH 6.8, uM[b]	*Tb* IC_{50} pH 7.2, uM[c]	*Tb* IC_{50} pH 7.7, uM[d]	*Hs* IC_{50} pH 7.2, uM[e]	pK_a(N1)[f]	*Tb* 427 EC_{50}, uM[a]	EC_{50} Hill slope	Source
 $C_{23}H_{20}N_4$	**50**	UTSAM570	109 (90–132)	>180	>180	>180	7.3	1.5 (1.3–1.6)	=-8.0	synthesized
 $C_{25}H_{18}Cl_4N_6O_2$	**51**	UTSAM591	12% at 180	>180	>180	>180	7.3	2.0 (1.2–3.7)	=-8.0	synthesized
 $C_{13}H_{16}N_4$	**52**	UTSAM546	35 (32–38)	141 (119–167)	>180	>180	7.3	19 (17–22)	-1.8	synthesized
 $C_{19}H_{28}N_4$	**53**	UTSAM593	42 (36–49)	>63	>63	>63	7.3	4.1 (4.1–4.5)	=-8.0	synthesized
 $C_{11}H_{11}F_5N_4S$	**54**	UTSAM597	84 (72–99)	23% at 180	>180	>180	7.3	14 (11–17)	-4.1	synthesized
 $C_{11}H_{11}ClN_4$	**55**	UTSAM543	75 (69–83)	35% at 180	>180	>180	7.3	42 (34–52)	-1.7	synthesized
 $C_{11}H_{11}BrN_4$	**56**	UTSAM490	nd	41% at 180	>180	>180	7.3	22 (19–26)	-1.7	ChemBridge
 $C_{11}H_{11}FN_4$	**57**	UTSAM492	nd	>180	>180	>180	7.3	>25	na	ChemBridge
 $C_{12}H_{14}N_4S$	**58**	UTSAM488	nd	149 (122–181)	>180	23% at 180	7.3	>25	na	ChemBridge
 $C_{11}H_{12}N_4$	**59**	UTSAM477	nd	>180	>180	>180	7.3	>25	na	ChemBridge
 $C_{11}H_{10}F_2N_4$	**60**	UTSAM538	38 (35–41)	180 (160–201)	>180	>180	7.3	70 (61–80)	-1.6	synthesized
 $C_{11}H_{10}ClFN_4$	**61**	UTSAM560	3.3 (2.8–3.9)	32 (13–82)	41% at 180	>180	7.3	17 (15–20)	-2.4	synthesized
 $C_{11}H_9Cl_2FN_4$	**62**	UTSAM559	0.18 (0.15–0.23)	1.5 (1.4–1.8)	19 (16–22)	160 (135–191)	7.3	4.8 (3.3–7.0)	-5.9	synthesized
 $C_{11}H_9Br_2FN_4$	**63**	UTSAM589	0.21 (0.20–0.23)	1.6 (1.3–1.8)	16 (13–18)	43% at 180	7.3	4.6 (3.6–5.9)	-4.5	synthesized

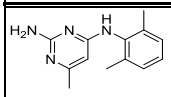
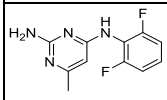
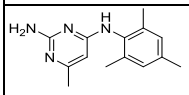
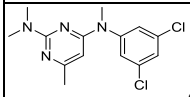
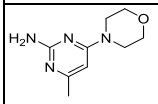
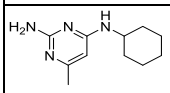
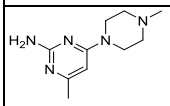
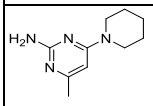
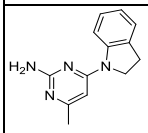
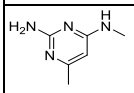
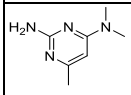
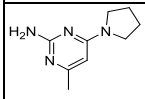
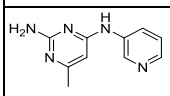
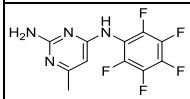
Chemical structure	Manuscript number	Code number	*Tb* IC_{50} pH 6.8, uM[b]	*Tb* IC_{50} pH 7.2, uM[c]	*Tb* IC_{50} pH 7.7, uM[d]	*Hs* IC_{50} pH 7.2, uM[e]	pK_a(N1)[f]	*Tb* 427 EC_{50}, uM[a]	EC_{50} Hill slope	Source
 $C_{11}H_9Cl_3N_4$	**64**	UTSAM563	1.1 (0.94–1.3)	11 (8.8–13)	31% at 63	>63	7.3	4.5 (3.4–5.9)	-5.2	synthesized
 $C_{12}H_{12}Cl_2N_4$	**65**	UTSAM590	3.4 (2.9–3.9)	20 (17–24)	14% at 63	>63	7.3	4.4 (4.2–4.8)	=-8.0	synthesized
 $C_{17}H_{14}Cl_2N_4O$	**66**	UTSAM603	25 (21–31)	38% at 180	>180	>180	7.3	1.1 (0.97–1.3)	-1.4	synthesized
 $C_{11}H_{10}Cl_2N_4O$	**67**	UTSAM586	35 (30–41)	33% at 180	>180	>180	7.0	13 (10–16)	-1.1	synthesized
 $C_{12}H_{10}Cl_2F_2N_4O$	**68**	UTSAM594	42% at 63	>63	>63	>63	7.3	4.5 (3.7–5.4)	-3.8	synthesized
 $C_{13}H_{15}Cl_2N_5$	**69**	UTSAM625	85 (71–104)	>180	>180	>180	7.3	5.8 (4.2–7.9)	=-8.0	synthesized
 $C_{15}H_{17}Cl_2N_5O$	**70**	UTSAM620	>180	>180	>180	>180	7.3	18 (14–24)	-7.4	synthesized
 $C_{16}H_{19}Cl_2N_5$	**71**	UTSAM623	226 (160–319)	>180	>180	>180	7.3	2.1 (1.3–3.2)	=-8.0	synthesized
 $C_{11}H_{10}Cl_2N_4O$	**72**	UTSAM577	4.2 (3.6–4.9)	37 (29–46)	23% at 180	>180	7.1	26% at 100	na	synthesized
 $C_{11}H_8Cl_2F_2N_4$	**73**	UTSAM617	0.33 (0.25–0.43)	2.2 (2.0–2.6)	21 (18–23)	>63	7.2	10 (8.5–12)	-2.3	synthesized
 $C_{11}H_{10}Cl_2N_4$	**74**	UTSAM501	nd	115 (89–150)	>180	>180	7.2	23% at 25	na	ChemBridge
 $C_{11}H_{10}Cl_2N_4$	**75**	UTSAM500	nd	137 (95–198)	>180	>180	7.3	27% at 25	na	ChemBridge
 $C_{11}H_{10}Cl_2N_4$	**76**	UTSAM502	nd	>180	>180	>180	7.3	28% at 25	na	ChemBridge
 $C_{12}H_{14}N_4$	**77**	UTSAM478	nd	>180	>180	>180	7.3	>25	na	ChemBridge

Chemical structure	Manuscript number	Code number	*Tb* IC_{50} pH 6.8, uM[b]	*Tb* IC_{50} pH 7.2, uM[c]	*Tb* IC_{50} pH 7.7, uM[d]	*Hs* IC_{50} pH 7.2, uM[e]	pK_a(N1)[f]	*Tb* 427 EC_{50}, uM[a]	EC_{50} Hill slope	Source
 $C_{12}H_{14}N_4S$	**78**	UTSAM487	nd	>180	>180	>180	7.3	>25	na	ChemBridge
 $C_{11}H_{11}BrN_4$	**79**	UTSAM491	nd	>180	>180	>180	7.3	>25	na	ChemBridge
 $C_{12}H_{13}ClN_4$	**80**	UTSAM496	nd	>180	>180	>180	7.3	29% at 25	na	ChemBridge
 $C_{12}H_{13}ClN_4$	**81**	UTSAM494	nd	>180	>180	>180	7.3	28% at 25	na	ChemBridge
 $C_{12}H_{13}ClN_4$	**82**	UTSAM495	nd	>180	>180	>180	7.3	>25	na	ChemBridge
 $C_{11}H_{10}BrFN_4$	**83**	UTSAM497	nd	>180	>180	>180	7.2	25% at 25	na	ChemBridge
 $C_{12}H_{10}ClF_3N_4$	**84**	UTSAM499	nd	199 (164–240)	>180	>180	7.3	28% at 25	na	ChemBridge
 $C_{11}H_{11}ClN_4$	**85**	UTSAM489	nd	>180	>180	>180	7.3	28% at 25	na	ChemBridge
 $C_{13}H_{16}N_4$	**86**	UTSAM480	nd	>180	>180	>180	7.3	19 (17–22)	-3.5	ChemBridge
 $C_{14}H_{18}N_4$	**87**	UTSAM481	nd	>180	>180	>180	7.3	11 (8.5–15)	-5.0	ChemBridge
 $C_{12}H_{11}F_3N_4$	**88**	UTSAM493	nd	>180	>180	>180	7.3	15 (13–17)	-3.1	ChemBridge
 $C_{17}H_{14}Cl_2N_4$	**89**	UTSAM592	42% at 180	>180	>180	>180	7.3	1.0 (0.88–1.2)	-2.9	synthesized
 $C_{11}H_{10}F_2N_4$	**90**	UTSAM498	nd	33% at 180	>180	>180	7.3	25% at 25	na	ChemBridge
 $C_{17}H_{14}ClFN_4$	**91**	UTSAM610	0.14 (0.12–0.15)	1.1 (0.95–1.2)	13 (7.5–21)	>21	7.3	1.6 (0.94–2.8)	-6.8	synthesized

Chemical structure	Manuscript number	Code number	*Tb* IC_{50} pH 6.8, uM[b]	*Tb* IC_{50} pH 7.2, uM[c]	*Tb* IC_{50} pH 7.7, uM[d]	*Hs* IC_{50} pH 7.2, uM[e]	pK_a(N1)[f]	*Tb* 427 EC_{50}, uM[a]	EC_{50} Hill slope	Source
 $C_{17}H_{14}Cl_2N_4$	**92**	UTSAM582	0.25 (0.22–0.28)	1.7 (1.6–2.0)	25 (20–30)	>63	7.3	2.2 (1.8–2.7)	-4.5	synthesized
 $C_{18}H_{17}ClN_4O$	**93**	UTSAM581	0.33 (0.29–0.37)	2.3 (2.1–2.6)	32 (26–40)	>180	7.3	4.5 (3.1–6.6)	-5.5	synthesized
 $C_{18}H_{17}ClN_4$	**94**	UTSAM583	0.58 (0.51–0.65)	4.6 (4.0–5.3)	66 (50–87)	>63	7.3	4.3 (3.3–5.7)	-5.1	synthesized
 $C_{18}H_{14}ClF_3N_4$	**95**	UTSAM585	0.72 (0.63–0.84)	4.7 (3.9–5.7)	28% at 21	>21	7.3	2.0 (1.4–3.0)	-6.3	synthesized
 $C_{18}H_{14}ClN_5$	**96**	UTSAM612	0.84 (0.67–1.1)	7.6 (3.2–18)	>6.8	>6.8	7.3	1.0 (0.96–1.1)	-3.7	synthesized
 $C_{19}H_{17}ClN_4O$	**97**	UTSAM608	5.7 (4.8–6.8)	28% at 21	>21	>21	7.3	6.7 (4.1–11)	=-8.0	synthesized
 $C_{17}H_{15}ClN_4O$	**98**	UTSAM588	20 (16–25)	143 (115–178)	>180	>180	7.3	9.7 (7.5–13)	-2.1	synthesized
 $C_{23}H_{19}ClN_4$	**99**	UTSAM609	14 (12–15)	167 (150–190)	>180	>180	7.3	0.91 (0.82–1.0)	-3.1	synthesized
 $C_{19}H_{20}ClN_5$	**100**	UTSAM614	26 (20–34)	34% at 180	>180	>180	7.3	5.0 (4.2–6.0)	-4.6	synthesized
 $C_{17}H_{14}Cl_2N_4$	**101**	UTSAM618	2.9 (2.0–4.1)	26 (22–33)	>180	>180	7.3	8.5 (7.6–9.5)	-2.3	synthesized

Chemical structure	Manuscript number	Code number	*Tb* IC_{50} pH 6.8, uM[b]	*Tb* IC_{50} pH 7.2, uM[c]	*Tb* IC_{50} pH 7.7, uM[d]	*Hs* IC_{50} pH 7.2, uM[e]	$pK_a(N1)$[f]	*Tb* 427 EC_{50}, uM[a]	EC_{50} Hill slope	Source
 $C_{17}H_{14}Cl_2N_4$	**102**	UTSAM616	9.2 (7.6–11)	81 (57–114)	>180	>180	7.3	1.9 (1.6–2.3)	-5.3	synthesized
 $C_{17}H_{13}Cl_3N_4$	**103**	UTSAM587	6.9 (6.1–8.0)	102 (82–125)	>180	>180	7.3	2.9 (1.3–3.6)	=-8.0	synthesized
 $C_{17}H_{13}Cl_2FN_4$	**104**	UTSAM615	14 (11–18)	157 (95–260)	>180	>180	7.3	3.2 (2.8–3.7)	-3.0	synthesized
 $C_{18}H_{13}Cl_2F_3N_4$	**105**	UTSAM607	6.6 (5.8–7.4)	53 (46–61)	16% at 180	>180	7.3	1.5 (1.0–2.2)	-5.8	synthesized
 $C_{19}H_{13}ClF_6N_4$	**106**	UTSAM611	2.7 (2.5–2.9)	28 (25–31)	13% at 180	>180	7.3	0.53 (0.47–0.59)	-4.6	synthesized
 $C_{21}H_{17}ClN_4$	**107**	UTSAM605	5.7 (5.1–6.3)	57 (51–64)	>180	>180	7.3	1.7 (1.4–2.0)	=-8.0	synthesized
 $C_{25}H_{19}ClN_4$	**108**	UTSAM613	198 (129–304)	>180	>180	>180	7.3	1.8 (1.5–2.1)	-5.1	synthesized
 $C_{18}H_{15}ClN_4O_2$	**109**	UTSAM624	0.86 (0.61–1.2)	6.2 (4.6–8.3)	19% at 21	>21	7.3	2.3 (1.6–3.2)	=-8.0	synthesized
 $C_{17}H_{13}ClN_6O$	**110**	UTSAM598	0.96 (0.66–1.4)	27 (21–35)	27% at 180	>180	7.3	0.57 (0.13–2.5)	-8.4	synthesized
 $C_{15}H_{13}ClN_4O$	**111**	UTSAM596	1.2 (1.0–1.4)	7.4 (6.2–8.7)	85 (72–100)	30% at 180	7.3	7.1 (5.7–8.8)	-5.1	synthesized

Chemical structure	Manuscript number	Code number	*Tb* IC_{50} pH 6.8, uM[b]	*Tb* IC_{50} pH 7.2, uM[c]	*Tb* IC_{50} pH 7.7, uM[d]	*Hs* IC_{50} pH 7.2, uM[e]	pK_a(N1)[f]	*Tb* 427 EC_{50}, uM[a]	EC_{50} Hill slope	Source
 $C_{19}H_{15}ClN_4O$	**112**	UTSAM599	14 (11–18)	23% at 63	>63	>63	7.3	1.4 (1.4–1.5)	=-8.0	synthesized
 $C_{15}H_{13}ClN_4S$	**113**	UTSAM600	3.9 (3.2–4.8)	26 (22–32)	34% at 180	30% at 180	7.3	29 (23–35)	-4.5	synthesized
 $C_{19}H_{15}ClN_4S$	**114**	UTSAM601	4.9 (4.4–5.6)	41 (36–46)	14% at 180	>180	7.3	1.6 (1.5–1.8)	=-8.0	synthesized
 $C_{14}H_{12}ClN_5S$	**115**	UTSAM595	4.6 (3.8–5.6)	42% at 21	>21	>21	7.3	3.6 (3.1–4.1)	-3.2	synthesized
 $C_{15}H_{15}ClN_6$	**116**	UTSAM622	24 (18–34)	164 (132–203)	>180	>180	7.3	6.7 (4.7–9.6)	=-8.0	synthesized
 $C_{15}H_{13}ClN_6$	**117**	UTSAM621	36% at 180	>180	>180	>180	7.3	58 (33–100)	=-8.0	synthesized
 $C_{19}H_{19}FN_4$	**118**	UTSAM629	0.36 (0.26–0.49)	2.7 (2.2–3.4)	22 (18–27)	>180	7.3	1.3 (1.1–1.5)	-2.5	synthesized
 $C_{15}H_{14}N_4$	na	UTSAM476	nd	>180	>180	>180	7.3	27% at 25	na	ChemBridge
 $C_{13}H_{16}N_4$	na	UTSAM479	nd	>180	>180	>180	7.3	>25	na	ChemBridge
 $C_{13}H_{16}N_4$	na	UTSAM482	nd	>180	>180	>180	7.3	>25	na	ChemBridge
 $C_{13}H_{16}N_4$	na	UTSAM483	nd	>180	>180	>180	7.3	>25	na	ChemBridge
 $C_{13}H_{16}N_4$	na	UTSAM484	nd	>180	>180	>180	7.3	>25	na	ChemBridge

Chemical structure	Manuscript number	Code number	*Tb* IC_{50} pH 6.8, uM[b]	*Tb* IC_{50} pH 7.2, uM[c]	*Tb* IC_{50} pH 7.7, uM[d]	*Hs* IC_{50} pH 7.2, uM[e]	pK_a(N1)[f]	*Tb* 427 EC_{50}, uM[a]	EC_{50} Hill slope	Source
 $C_{13}H_{16}N_4$	na	UTSAM485	nd	>180	>180	>180	7.3	>25	na	ChemBridge
 $C_{11}H_{10}F_2N_4$	na	UTSAM503	nd	>180	>180	>180	7.1	>25	na	ChemBridge
 $C_{14}H_{18}N_4$	na	UTSAM504	nd	>180	>180	>180	7.3	>25	na	ChemBridge
 $C_{14}H_{16}Cl_2N_4$	na	UTSAM545	>180	>180	>180	>180	6.9	41 (33–50)	-4.4	synthesized
 $C_9H_{14}N_4O$	na	UTSAM548	28% at 180	>180	>180	>180	8.0	>100	na	synthesized
 $C_{11}H_{18}N_4$	na	UTSAM549	>180	>180	>180	>180	8.1	36% at 100	na	synthesized
 $C_{10}H_{17}N_5$	na	UTSAM550	>180	>180	>180	>180	8.1	>100	na	synthesized
 $C_{10}H_{16}N_4$	na	UTSAM551	28% at 180	>180	>180	>180	8.0	24% at 100	na	synthesized
 $C_{13}H_{14}N_4$	na	UTSAM552	142 (123–163)	>180	>180	>180	7.2	>100	na	synthesized
 $C_6H_{10}N_4$	na	UTSAM553	>180	>180	>180	>180	8.2	>100	na	synthesized
 $C_7H_{12}N_4$	na	UTSAM554	>180	>180	>180	>180	8.1	>100	na	synthesized
 $C_9H_{14}N_4$	na	UTSAM555	25% at 180	>180	>180	>180	8.0	>100	na	synthesized
 $C_{10}H_{11}N_5$	na	UTSAM557	54 (45–64)	35% at 180	>180	>180	7.3	>100	na	synthesized
 $C_{11}H_7F_5N_4$	na	UTSAM619	60 (46–80)	23% at 180	>180	>180	7.1	>100	na	synthesized

[a] Mean EC_{50} as measured in the ATP–bioluminescence *T. brucei* viability assay, in triplicate, with 95 % confidence interval (CI) shown in parentheses. [b,c,d] Mean IC_{50} for *T. brucei* AdoMetDC/prozyme at pH 6.8 ([b]), 7.2 ([c]), and 7.7 ([d]) determined using the RapidFire–MS-based enzyme activity assay, in triplicate, with 95 % CI shown in parentheses. [e] Mean IC_{50} for human AdoMetDC at pH 7.2 determined using the RapidFire–MS-based enzyme activity assay, in triplicate, with 95 % CI shown in parentheses. Percent inhibition at the maximal tested concentration (in µM) is shown when maximum mean inhibition was <50%. [f] The pKa value of the conjugated acid of the pyrimidine nitrogen N1 estimated using *MarvinSketch* . na, not applicable; nd, not determined.

Table S2. Crystallographic diffraction data and refinement statistics for the 44-bound *T. brucei* AdoMetDC/prozyme crystal structure

Data collection	
Symmetry	$P2_1$ (No. 4)
Unit cell dimensions (Å; °)	a=81.09, b=96.25, c=98.84; β=102.43
Wavelength (Å)	0.9191
Average mosaicity (°)	1.09
Resolution range (Å)	50–3.00 (3.05–3.00)[a]
Unique number of reflections before merging Friedel pairs	50,684
Unique number of reflections	30,294
Average redundancy	6.8 (6.3)
Completeness (%)	99.8 (99.1)
$R_{r.i.m.}$ (%)[b]	19.4
$R_{p.i.m.}$ (%)[c]	7.4 (38.2)
$\langle I \rangle / \langle \sigma_I \rangle$	10.0 (1.9)
$CC_{1/2}$ in the last resolution shell	0.71
CC* in the last resolution shell	0.91
Wilson *B*-factor (Å^2)[d]	49.2
Refinement	
Resolution range (Å)	45.8–2.98 (3.08–2.98)
Number of reflections R_{work}/R_{free}	29,991 / 1,499 (2,518 / 126)
Atoms (non-H protein/ligands/solvent)	10,183 / 127 / 7
Protein residues (resolved/sequence)	1,278 / 1,390[e,f]
R_{work} (%)	20.0 (27.5)
R_{free} (%)	25.3 (35.2)
RMSD bond length (Å)	0.003
RMSD bond angle (°)	0.56
Average B-factor (Å^2) (protein/ligands/solvent)	53.2 / 63.0 / 29.2
Ramachandran plot (%) (favored/allowed/disallowed)	97.5 / 2.5 / 0
Poor rotamers (%)	0.27
Clashscore	2.73

[a] Numbers in parentheses correspond to the last resolution shell.

[b] Redundancy-independent merging R factor, $R_{r.i.m.} = \sum_{hkl}\{N(hkl)/[N(hkl)-1]\}^{1/2} \times \sum_i \left| I_{i(hkl)} - \langle I(hkl) \rangle \right| / \sum_{hkl} \sum_i I_i$ (hkl)[1]

[c] Precision-indicating merging R factor, $R_{p.i.m.} = \sum_{hkl}\{1/[N(hkl)-1]\}^{1/2} \times \sum_i \left| I_{i(hkl)} - \langle I(hkl)\rangle \right| / \sum_{hkl}\sum_i I_i$ (hkl)[1]

[d] Maximum likelihood estimate of the overall *B*-value reported in *Phenix*.

[e] Residue count includes Pvl.

[f] Residue count excludes the first Ser after Ulp1 cleavage site.

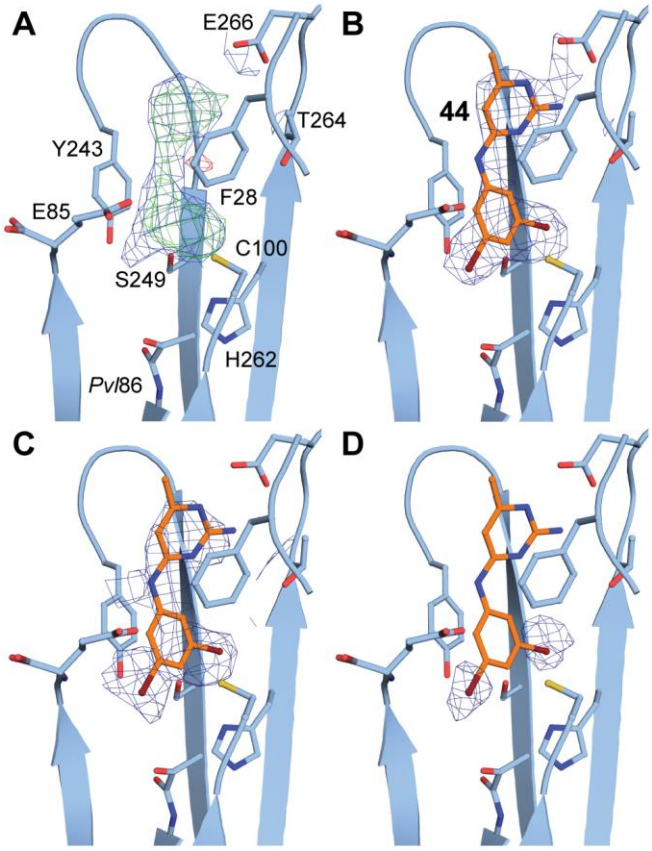


Figure S1. Placement of a ligand into the catalytic site of *Tb*AdoMetDC/prozyme co-crystallized with **44**. (**A**) Positive (green mesh) and negative (red mesh) mF_o-DF_c electron density countered at 3 and –3 σ, respectively, and $2mF_o-DF_c$ electron density (blue mesh) countered at 1 σ after the first round of positional refinement before ligand coordinates were included in the model. (**B**) $2mF_o-DF_c$ electron density (blue mesh) countered at 1 σ observed for the final refined model including the bound ligand. (**C**) Simulated annealing composite omit $2mF_o-DF_c$ electron density (blue mesh) countered at 1 σ based on the final refined model including the bound ligand. (**D**) Anomalous difference map (blue mesh) showing positions of bromines in bound ligand countered at 2 σ.

References

1. Weiss, M. S. (2001) Global indicators of X-ray data quality. *J Appl Crystallogr 34*, 130-135. DOI: 10.1107/S0021889800018227.