Exploration of 6-Methyl-7-(Hetero)Aryl-7-Deazapurine Ribonucleosides as Antileishmanial Agents

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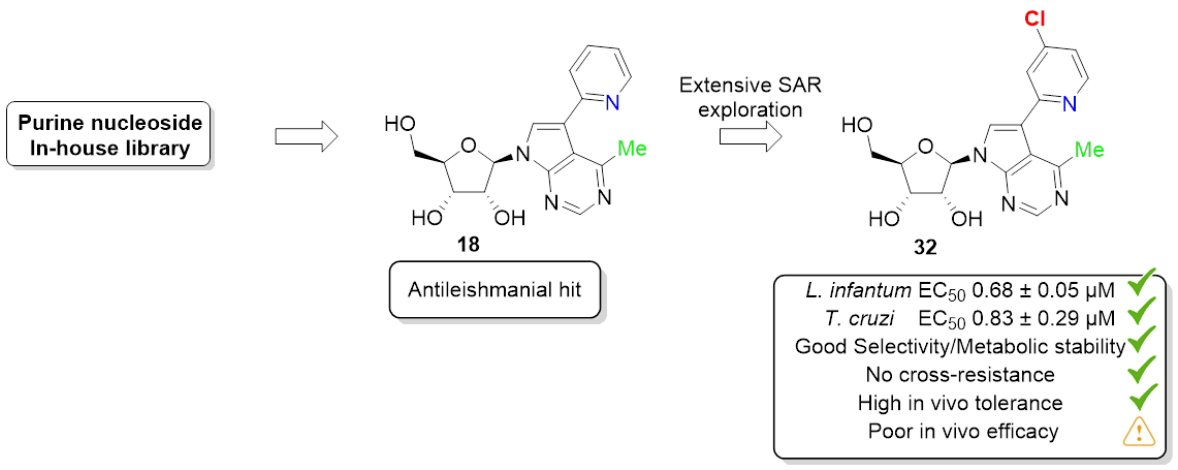
Graphic



Abstract

Leishmaniasis causes high mortality and morbidity in tropical and subtropical regions of Africa, Asia, the Americas and southern Europe, and is characterized by diverse clinical manifestations. As a neglected tropical disease, limited resources are allocated for antileishmanial drug discovery. The *Leishmania* parasite is deficient in *de novo* purine synthesis, and therefore acquires purines from the host and processes these using a purine salvage pathway. By making use of purine transport systems and interfering with this salvage pathway, purine (nucleoside) analogues might exert a selective detrimental impact on its growth and survival. *In vitro* screening of an in-house purine nucleoside library and analogue synthesis afforded the 6-methyl-7-(2-pyridyl)-7-deazapurine ribonucleoside analogue **18** as a promising hit. Optimization of the 7-substituent afforded **31** and **32** which displayed potent activity against wild-type and resistant *L. infantum*, intracellular amastigote and extracellular promastigote forms, and favorable selectivity versus primary mouse macrophages (Mϕ) and MRC-5 cells. Encouraged by the favorable *in vitro* metabolic stability of **32**, an *in vivo* study was performed using an early curative *L. infantum* hamster model. When orally administrated at 50 mg/kg once daily (s.i.d) for 10 days, **32** was devoid of side effects, however, it only poorly reduced amastigote burdens in the major target organs.

1. Introduction

Leishmaniasis is a poverty-related and neglected tropic disease (NTD) endemic in 98 countries in Asia, Africa, southern Europe, and South and Central America.[1] According to the World Health Organization, leishmaniasis is classified as a Category I (emerging or uncontrolled) disease responsible for 25,000 deaths and 700,000 to one million new cases each year.[2] *Leishmania* is an obligate intracellular protozoan of macrophages that is transmitted during a blood meal of infected female sand flies.[3, 4] The parasite has a complex life cycle, involving macrophage invasion as a promastigote and multiplication within host

phagolysosomes in an amastigote form. Intra-macrophage *Leishmania* may evade the host immune defenses by remodeling the phagosomal compartments and disturbing signaling pathways that generate lysosomal enzymes and toxic metabolites.[5]

Leishmaniasis has three main clinical manifestations: cutaneous (CL), mucocutaneous (MCL) and visceral (VL).[1] Unless treated, VL is fatal due to severe invasion of spleen, liver and bone marrow.[6] CL may potentially cause lifelong scarring. In the absence of vaccines for human leishmaniasis,[7] antileishmanial chemotherapy remains the sole front-line strategy to combat the disease. Several treatments are available such as the pentavalent antimonials, amphotericin B, miltefosine (MIL) and allopurinol (**Figure 1A**). MIL affects the parasite membrane composition through inhibition of phospholipid synthesis by blocking the transport of the choline precursor from the host, thereby impeding the synthesis of phosphatidylcholine and phosphatidylethanolamine.[8]Allopurinol is metabolized into aminopurinol riboside triphosphate followed by incorporation into RNA.[9] None of these drugs is ideal because of toxicity, cost, route of administration or drug resistance. Hence, there is an urgent and continuous need to identify new drugs.

Since *Leishmania* species (spp.) cannot synthesize purine rings *de novo*, they evolved an extensive set of transporters[10, 11] and salvage enzymes[12, 13] to scavenge external purines.[13] This salvage pathway enables *Leishmania* to dephosphorylate extracellular nucleotides into nucleosides via 3' and 5'-nucleotidases/nucleases[14] prior to uptake and intracellular conversion to the required nucleotides.[12, 15] This absolute reliance on scavenging host purine nucleobases or nucleosides renders *Leishmania* vulnerable to nucleoside analogues that interfere with active import processes or behave as subversive substrates as mentioned above for allopurinol.[13] Our steadily growing in-house synthesized library of nucleoside analogues earlier proved a valuable source of antitrypanosomal *in vitro* hits (**Figure 1B**). Notably, modifications of tubercidin on C7[16] (*e.g.* **1**), C-3'(*e.g.* **2**[17] and **3**[18]), C6 and C7 (*e.g.* **4**[19] and **5**[20]), as well as structurally related 1,7-dideazapurines (pyrrolo[2,3-*b*]pyridine)[21] (*e.g.* **6**), pyrazolopyrimidines[22] (*e.g.* **7**) and *C*-nucleosides[23] (*e.g.* **8**) displayed promising activity against different kinetoplastids. Also Michal Hocek's team has recently identified 6-alkoxy-7-methyltubercidin

derivatives (*e.g.* **9**, **Figure 1A**) with significant activity against *Trypanosoma brucei (T. b.) brucei* and *T. b. gambiense*.[24] Remarkably, the hit rate against *Leishmania* is comparatively low.

7-Deazapurine nucleoside analogues that do show *in vitro* antileishmanial activity include the 7-(3,4-dichlorophenyl) analogue **10**,[16] and the 6-methyl-7-3,6-(dihydro-2*H*-pyranyl) analogue **11** (**Figure 1C**).[26] The promising activity of **10** (7-aryl analogue) and **11** (6-Me analogue) led us to evaluate known[20] and new hybrid 6-methyl-7-aryl analogues against *L. infantum* in Mϕ.

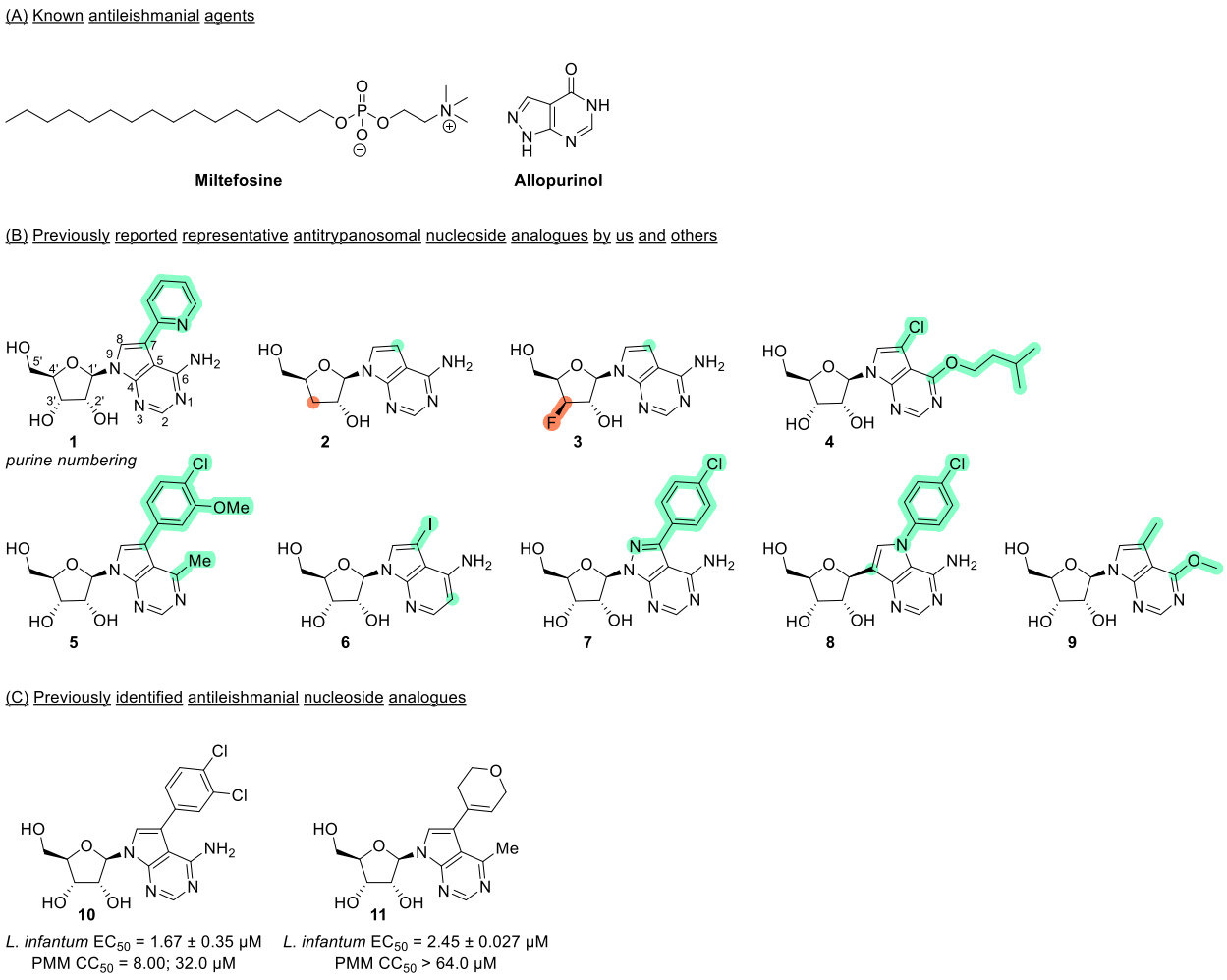
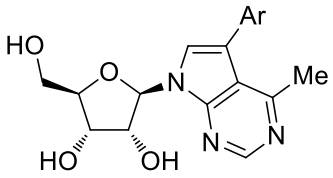
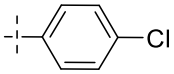
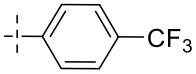
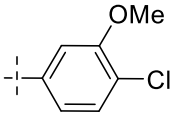
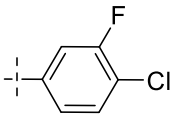
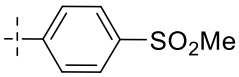
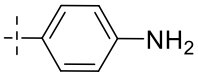
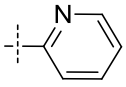
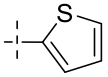


Figure 1. Known antileishmanial agents (A), representative examples of previously identified nucleoside analogues with antitrypanosomal activity (base and sugar modification highlighted in green and orange,

respectively) (B), and previously identified nucleoside antileishmanial nucleoside analogues (C). Throughout the text, purine numbering is used as depicted for compound **1**, while in the experimental section, systematic numbering is used.

Table 1. ***In vitro*** **activity of 6-methyl-7-aryl derivatives against** ***Leishmania*** **intracellular amastigotes**[a]



Cpd.[b]	Ar	*L. infantum* EC_{50} (μM)/5 days	Mϕ CC_{50} (μM))/5 days	SI
12		16.1 ± 5.4	> 64	> 3.5
13		11.3 ± 9.3	> 64	> 5.6
14		8.76 ± 0.76	> 64	> 7.3
15		7.9 ± 0.70	> 64	> 8.0
16		6.7 ± 3.9	> 64	> 9.5
17		6.7 ± 1.3	> 64	> 9.5
18		**2.3 ± 1.1**	**> 64**	**> 27**
19		*12.7*	*32*	*2.5*
MIL		8.3 ± 1.6		

[a]Evaluation of drug sensitivity against *L. infantum (*MHOM/MA (BE)/67*)* of known and new 6-methyl-7-aryl analogues (above and below dotted line respectively). Cytotoxicity was assayed on Mϕ. Values represent mean ± SEM, which originate from 2 to 3 independent experiments and are expressed in μM. SI, *in vitro* selectivity index is the ratio of the EC_{50} for the host cell (Mϕ) and the EC_{50} of the parasite. MIL was included as a reference (EC_{50} = 8.30 ± 1.64 μM). Values represent *in italics* indicate the data of a single experiment due to too low selectivity or activity. [b]Compounds **12**, **13**, **14** and **15** were reported in our previous study,[20] while **16**, **17**, **18** and **19** were synthesized for this study.

Compounds **12-15** showed reasonable *in vitro* activity and were devoid of cytotoxicity but failed to approximate **10** or **11** (**Table 1**). This led us to explore alternative aryl substituents and to introduce a heteroatom into the aromatic moiety. The 6-methyl-7-(2-pyridyl)-7-deazapurine nucleoside analogue **18** showed improved antileishmanial activity with a promising selectivity. To further expand the SAR different alternatives for the pyridin-2-yl ring were explored (**Figure 2**).

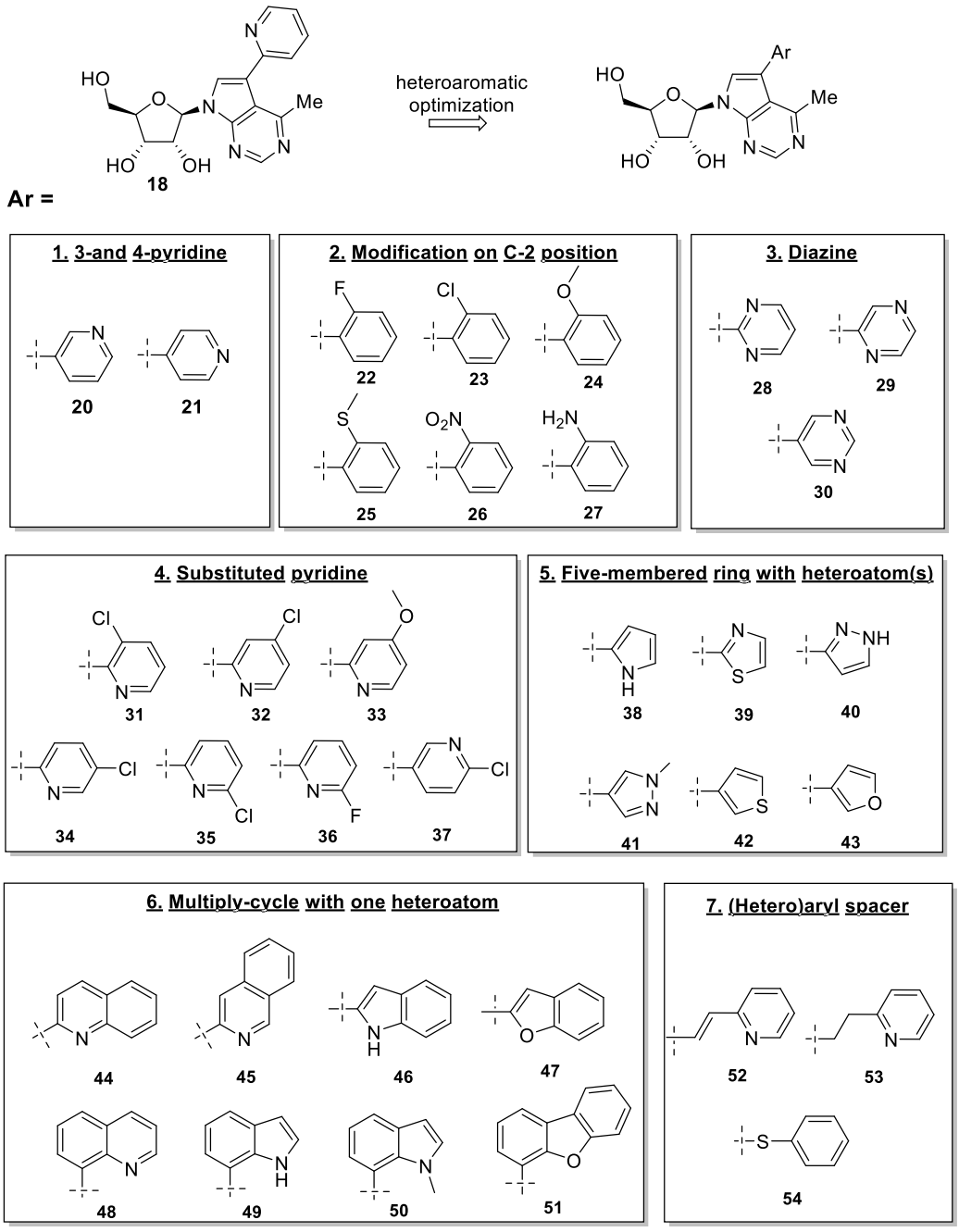


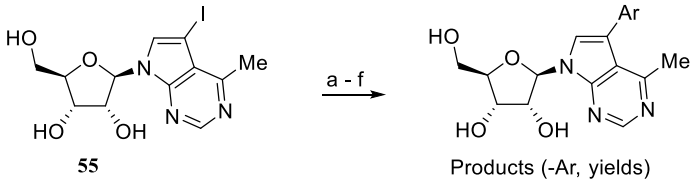
Figure 2. Overview of heteroaromatic optimization in seven devised structural modules

2. Results and discussion

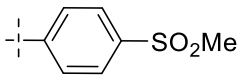
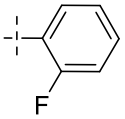
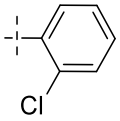
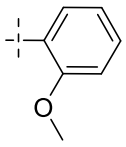
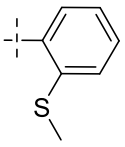
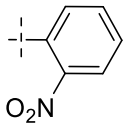
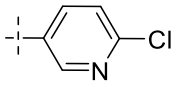
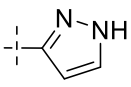
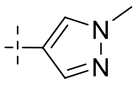
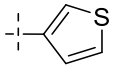
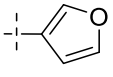
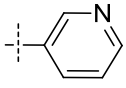
2.1. Chemistry

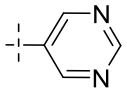
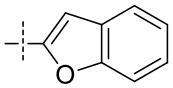
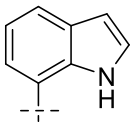
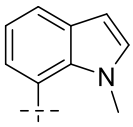
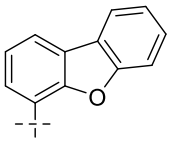
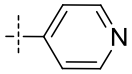
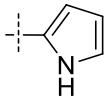
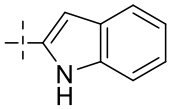
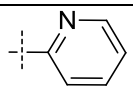
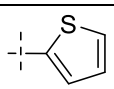
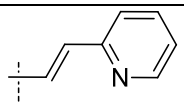
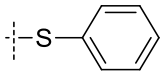
The target 6-methyl-7-(hetero)aryl nucleoside analogues were synthesized via transition-metal catalyzed coupling reactions from either benzoyl-protected or unprotected 6-methyl-7-deaza-7-iodopurine ribonucleoside precursors.[20, 27] Suzuki condition[28] employing $Pd(OAc)_2$ and TPPTS allowed to couple aryl boronic acids or their pinacol ester (**Scheme 1**). Alternative conditions were required to couple pyridin-4-ylboronic acid and $Pd_2(dba)_3$, $P(c\text{-}Hex)_3$ ligand and K_3PO_4 in a mixture of water/1,4-dioxane (1:2) at 100 °C gave satisfactory yields.[29] The 2-pyrrol-2-yl analogues **38** and **46** were obtained after removal of the Boc-protecting group under basic conditions. A Stille reaction proved favorable to produce the 2-pyridyl (**18**) and 2-thienyl (**19**) analogues, while the (*E*)-2-pyridin-2-ylethenyl group was introduced via a Heck reaction and a thiophenyl group under Ullmann conditions.[30, 31]

Scheme 1



a: arylboronic acid/arylboronic pinacol ester, $Pd(OAc)_2$, TPPTS, Na_2CO_3, MeCN / H_2O (1/2 ratio), 100 °C

16		50%	**22**		65%	**23**		31%
24		71%	**25**		78%	**26**		69%
37		26%	**40**		39%	**41**		71%
42		32%	**43**		53%	**20**		36%

29		54%	**46**		14%	**48**		64%
49		30%	**50**		8%			
b: pyridin-4-ylboronic acid, K_3PO_4, $Pd_2(dba)_3$, $P(c\text{-}Hex)_3$, H_2O/dioxane (1/2 ratio), 100 °C								
21		45%						
c: (i) arylboronic acid, $Pd(OAc)_2$, TPPTS, Na_2CO_3, MeCN / H_2O (1/2 ratio), 100 °C; (ii) 0.5 M NaOMe in MeOH								
38		28%	**46**		47%			
d: Ar-Sn(nBu)$_3$, $Pd(PPh_3)_4$, CuI, DMF, 100 °C								
18		79%	**19**		78%			
e: 2-vinylpyridine, $Pd(OAc)_2$, TPPTS, TEA, DMF, 100 °C								
52		39%						
f: thiophenol, CuI, K_2CO_3, ethyleneglyol, iPrOH, 130 °C								
54		92%						

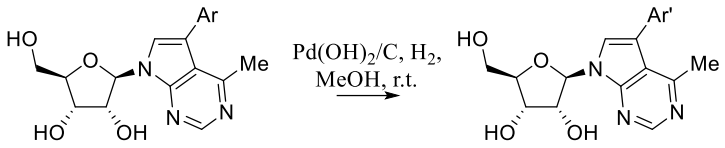
114

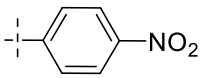
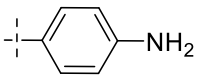
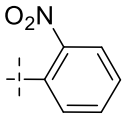
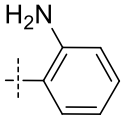
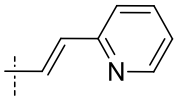
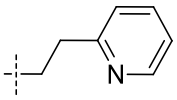
115 Next, the obtained nitro (**26** and **56**[20]) and (2-pyridyl)vinyl analogues (**52**) were further hydrogenated
116 into the corresponding amino (**17** and **27**) and (2-pyridyl)ethyl congeners (**53**) under $Pd(OH)_2$/C system
117 (**Scheme 2**), respectively.

118

119 **Scheme 2**

120



	Ar	yield	Ar'	
56		92%		**17**
26		69%		**27**
52		64%		**53**

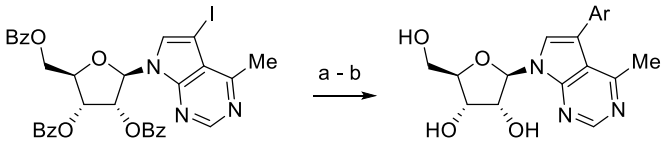
121

122

123 Substituted 2-pyridyl, diazinyl and quinolinyl analogues were prepared by Negishi coupling (**Scheme**
124 **3**).[16] Magnesium-iodine exchange with iPrMgCl·LiCl and subsequent transmetallation with $ZnCl_2$
125 solution of perbenzoylated 6-Me-7-iodopurine ribonucleoside **57**[28] afforded the zinc partner to couple
126 with heteroaromatic bromides. Due to the instability of 2-pyridyl organometallics,[32] the overall yields
127 were low to moderate. The 2-thiazolyl derivative was obtained via $Pd(PPh_3)_2Cl_2$-catalyzed Stille cross-
128 coupling followed by deprotection in 7 N NH_3/MeOH.

129

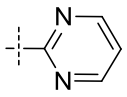
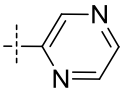
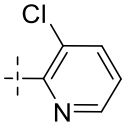
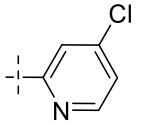
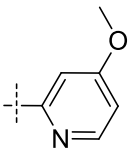
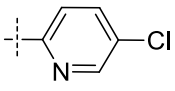
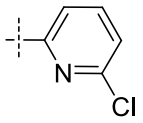
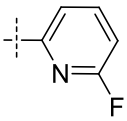
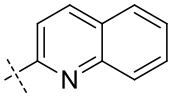
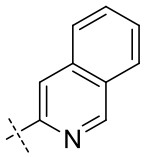
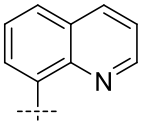
130 **Scheme 3**



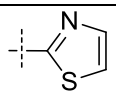
57 Products (-Ar, yields)

131

a: (i) iPrMgCl·LiCl, $ZnCl_2$, THF, -65 °C to r.t.; (ii) Ar-Br, $Pd_2(dba)_3$, RuPhos, THF, 60 °C, overnight; (iii) 7 N NH_3 in MeOH

28		63%	**29**		37%	**31**		33%
32		29%	**33**		23%	**34**		22%
35		18%	**36**		5%	**44**		30%
45		19%	**48**		46%			

b: (i) 2-(tripropylstannyl)thiazole, $Pd(PPh_3)_2Cl_2$, DMF, 100 °C; (ii) 7 N NH_3 in MeOH

39		56%						

132

133

134 **2.2. Biological evaluation**

135 **2.2.1. *In vitro* activity profile**

136 All prepared compounds were evaluated for *in vitro* activity against intracellular amastigotes of *L. infantum*
137 (MHOM/MA(BE)/67 strain), using MIL and allopurinol as the reference drug (**Table 2**). In parallel,
138 cytotoxicity was checked against the Mϕ and MRC-5 fibroblasts.

139 In contrast to the inactive phenyl analogue,[26] the pyridin-2-yl analogue showed relevant activity.
140 Shuffling of the nitrogen atom has a negative impact on the activity. *Ortho*-modification of the 7-phenyl
141 substituent with a fluoride (**22**) or chloride (**23**) or other hetero-containing substituents (**24**, **25**, **26** and **27**)
142 failed to improve the activity, underscoring the importance of the nitrogen atom in **18**. Introduction of an

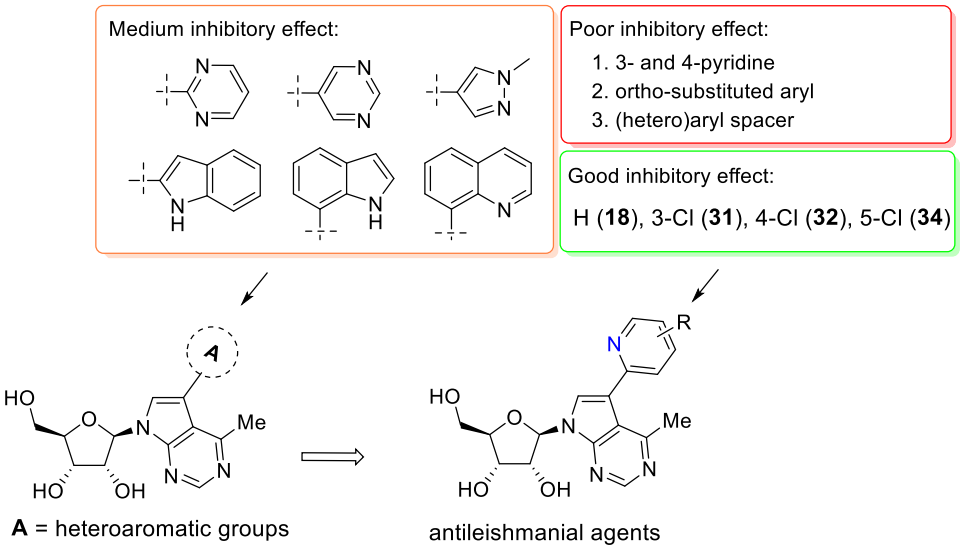
additional nitrogen atom in *ortho* or *para* position gave a 4- to 5-fold drop in activity (**28**, **29**). Interestingly, the 3,5-diazinyl derivative **30** (without *ortho* N atom) displayed similar micromolar activity as the above diazinyl analogues. Further derivatization focused on increasing the electron deficiency of the pyridine moiety. Incorporating a chloro in *ortho* position (**31**) slightly increased activity while remaining non-toxic for the host cells. Moving the chloro atom to the *meta* position afforded **32** with submicromolar activity and a favorable SI (> 94.1). Introduction of an electron-donating methoxy group in this position resulted in a complete loss of activity. Moving the chloro atom to the *para* position (**34**) further increased the activity and was 20-fold better than MIL. The compound with the highest antileishmanial *in vitro* activity (**34**) showed moderate cytotoxicity on MRC-5 cells while **31** and **32** were devoid of notable cytotoxicity. Further rotation of the chloro-atom (**35**) had a negative impact. Replacement in **35** of the chloro by a fluoro atom (**36**) and shifting the nitrogen of **34** to the *meta* position (**37**) proved detrimental for activity. Changing the pyridin-2-yl moiety for a 2-pyrrol-2-yl (**38**) boosted the activity (EC_{50} = 0.35 μM), however, at the expense of selectivity. Three azolo analogues (**39**, **40** and **41**) showed similar potency as the diazinyl analogues. Since the 2-thienyl **19** was only moderately active and the 2-furanyl derivative proved cytotoxic,[27] 3-thioenyl (**42**) and 3-furanyl (**43**) derivatives were investigated but failed to show activity. Fusion of the pyridine substituent with a phenyl to afford the 2- and 3-quinolinyl analogues **44** and **45** failed as well. Interestingly, the indolyl and benzofuran-2-yl analogues **46** and **47**, resulting from the fusion of a phenyl ring to the pyrrol-2-yl and furan-2-yl substituents, conferred lower cytotoxicity and the former showed low micromolar activity. Surprisingly, the 8-quinolinyl analogue **48** showed a similar potency as the 2-pyridyl analogue. The 7-indolyl analogue **49** was equipotent to **48**. The *N*-methyl-substituted analogue of **49** (**50**) was inactive. Analogues in which the heterocyclic moiety was attached to the purine via a short spacer (**52**, **53** and **54**) also proved inactive. The SAR trends of 7-heteroaryl modified 6-methyl nucleoside analogues are summarized in **Figure 3**.

167 **Table 2.** ***In vitro*** **activity of 7-heteroaromatic derivatives against** ***Leishmania*** **intracellular**
168 **amastigotes**[a]

Cpd.	*L. infantum* EC_{50} (μM)/5 days	Mϕ CC_{50} (μM))/5 days	MRC-5 CC_{50} (μM))/3 days	SI vs. Mϕ
18	2.3 ± 1.1	> 64	> 64	> 27
3- and 4-pyridine				
20	*22.6*	> 64	> 64	> 2.8
21	> 64	> 64	> 64	ND
Ortho-substituted phenyl				
22	> 64	> 64	> 64	ND
23	20.4 ± 9.0	> 64	> 64	> 3.1
24	*21.1*	> 64	> 64	> 3.0
25	> 64	> 64	> 64	ND
26	> 64	> 64	> 64	ND
27	> 64	> 64	> 64	ND
Diazine				
28	8.2 ± 3.1	> 64	> 64	> 7. 8
29	*10.1*	> 64	> 64	> 6.3
30	6.5 ± 0.5	> 64	> 64	> 9.9
Substituted pyridine				
31	1.2 ± 0.4	> 64	> 64	> 50
32	0.68 ± 0.05	> 64	> 64	> 94
33	> 64	> 64	> 64	ND
34	0.40 ± 0.05	> 64	26.3 ± 20.7	> 160
35	14.2 ± 7.0	> 64	> 64	> 4.51
36	> 64	> 64	> 64	ND
37	> 64	> 64	> 64	ND
Five-membered ring with heteroatom(s)				

38	*0.35*	*32*	*12.9*	*91.4*
39	*2.07*	*32*	*6.06*	*15.5*
40	*8.0*	> 64	27.9	> 8
41	8.0 ± 1.0	> 64	> 64	> 8
42	> 64	> 64	> 64; 22.6	ND
43	> 64	> 64	> 64	ND
Multiple-cycle with one heteroatom				
44	> 64	> 64	> 64	ND
45	> 64	> 64	> 64	ND
46	1.7 ± 0.0	> 64	23.6	> 36
47	*20.3*	*32*	*45.8*	*1.58*
48	3.7 ± 1.7	> 64	> 64	> 17
49	2.1 ± 0.3	> 64	> 64	> 30
50	> 64	> 64	> 64	ND
51	*50.8*	> 64	12.7	> 1.2
(Hetero)aryl spacer				
52	*19.0*	> 64	> 64	> 3.37
53	> 64	> 64	> 64	ND
54	> 64	> 64	> 64	ND
MIL	8.3 ± 1.6	ND	ND	ND
allopurinol*	3.5 ± 1.8	> 64	> 64	> 18

[a]Evaluation of drug sensitivity against *L. infantum* (MHOM/MA(BE)/67/ITMAP263). Cytotoxicity was assayed on Mϕ and MRC-5 fibroblasts. Values represent mean ± SEM which originate from 2 to 3 independent experiments and are expressed in μM. *In vitro* selectivity index (SI) is the ratio of the CC_{50} for the host cell (Mϕ) and the EC_{50} of the parasite. Values *in italics* indicate the data of a single experiment due to too low selectivity or activity. MIL and allopurinol were included as references. *The EC_{50} of allopurinol corresponds with that reported in our previous study.[22]



175

176 **Figure 3**. Summary of SAR trends for *L. infantum*

177 **2.2.2. *In vitro* profiling against drug-resistant strains**

178 The promising analogues **31** and **32** were evaluated against three *L. infantum* strains that are resistant to
179 potassium antimonyl [Sb(III)], sodium stibogluconate [Sb(V)], MIL and paromomycin (PMM) after 96 h
180 incubation (**Table 3**). **31** retained activity against all resistant strains. **32** retained activity against LEM3323-
181 Cl4 MIL5Cl3 and LEM3323-Cl4 PMM strains but exerted slightly lower activity against the parent Sb-
182 resistant LEM3323-Cl4 clinical isolate. It can be concluded that both compounds show no obvious cross-
183 resistance to the established drugs and retained potent activity against extracellular promastigotes.

184

185 **Table 3. *In vitro* evaluation of cross-persistence of selected nucleoside analogues[a]**

Cpd.	LEM3323-Cl4 EC_{50} (µM)	LEM3323-Cl4 MIL5Cl3 EC_{50} (µM)	LEM3323-Cl4 PMM EC_{50} (µM)	*L. infantum* EC_{50} (µM)	Mϕ CC_{50} (µM)
31	0.67	0.73	1.46	1.2 ± 0.4	> 64
32	2.21	0.73	0.79	0.68 ± 0.05	> 64

[a] Susceptibility of drug-resistant *L. infantum* promastigotes for analogues **31** and **32**. Strain MHOM/FR/96/LEM3323-Cl4 is resistant to sodium stibogluconate [Sb(V)] and potassium antimonyl tartrate [Sb(III)] ; LEM3323-Cl4 MIL5Cl3 strain is resistant to Sb(V), Sb(III) and MIL; LEM3323-Cl4 PMM is resistant to Sb(V), Sb(III) and PMM.[33]

2.2.3. *In vitro* evaluation against *Trypanosoma cruzi* (*T. cruzi)*

As some 6-methyl-7-aromatic-7-deazapurine nucleoside analogues possessed favorable activity against *T. cruzi*[20], *e.g.* **12**, analogues with the most promising *in vitro* activity against *Leishmania* were also evaluated for anti-*T. cruzi* activity (**Table 4**). The 2-pyridyl (**18**), 8-quinolinyl (**48**) and 7-indolyl analogue (**49**) displayed micromolar activity, while the chloropyridyl derivatives (**31** and **32**) exhibited submicromolar potency without apparent cytotoxicity on MRC-5 cells.

Table 4. *In vitro* activity of selected nucleoside analogues against *T. cruzi* intracellular amastigotes[a]

	T. cruzi	**MRC-5**	
Cpd.	**EC_{50} (µM)/7 days**	**CC_{50} (µM)/3 days**	**SI**
18	1.6 ± 0.6	> 64	> 39
28	5.9 ± 3.9	> 64	> 10
30	7.3 ± 1.5	> 64	> 8.8
31	0.70 ± 0.07	> 64	> 91
32	0.83 ± 0.29	> 64	> 77
34	0.49 ± 0.01	26.3 ± 20.7	53
38	*0.68*	*12.9*	*19*
39	*0.66*	*6.06*	*9.2*
46	0.62 ± 0.08	14.80 ± 8.77	24
48	9.6 ± 0.5	> 64	> 6.7

49	3.3 ± 0.4	> 64	> 19
Benznidazole	2.28 ± 0.05	ND	ND

[a]Evaluation of drug sensitivity against *T. cruzi* (Tulahuen strain expressing *β*-galactosidase). Cytotoxicity was assayed on MRC-5 fibroblasts. Values represent mean ± SEM which originate from 2 to 3 independent experiments and are expressed in μM. *In vitro* selectivity index (SI) is the ratio of the CC_{50} of MRC-5 and the EC_{50} of the parasite. Benznidazole was included as a reference (EC_{50} = 2.28 ± 0.05 μM). Values *in italics* indicate the data of a single experiment due to too low selectivity or activity.

2.2.4. *In vitro* metabolic stability

Compounds **31** and **32** were exposed to liver microsomal fractions originating from mouse, hamster and human to assess their metabolic stability (**Table 5**). The percentage of remaining parent compound was determined at three time points. Both were hardly metabolized under incubation with either NADPH fractions (Phase-I) or UGT fractions (Phase-II) regardless the originating species. The more potent **32** was selected for *in vivo* follow-up in the *L. infantum* hamster model.

Table 5. *In vitro* metabolic stability of selected nucleoside analogues in mouse, hamster and pooled human S9 microsomal fractions[a]

Microsomes	**Phase I / II**	**Time**	**Amount of compounds remaining (%)**			
			31		**32**	
			Mean	STDEV	Mean	STDEV
Mouse	**CYP – NADPH**	0	100	-	100	-
		15	98	5.7	109	9.2
		30	83	11.9	86	14.3
		60	74	16.8	94	5.9

	UGT	0	100	-	100	-
		15	92	0.6	103	2.2
		30	91	8.5	102	4.9
		60	98	3.7	100	8.9
Hamster	**CYP – NADPH**	0	100	-	100	-
		15	86	4.7	96	13.7
		30	98	1.6	95	16.4
		60	90	1.1	87	9.0
	UGT	0	100	-	100	-
		15	95	0.8	98	9.5
		30	96	5.2	92	7.2
		60	96	5.5	89	12.0
Human	**CYP – NADPH**	0	100	-	100	-
		15	107	4.0	92	3.6
		30	100	5.4	86	4.5
		60	99	7.4	75	0.8
	UGT	0	100	-	100	-
		15	93	7.5	93	4.4
		30	95	9.2	96	1.3
		60	101	11.7	98	5.3

[a]Values (mean and STDEV) represent the remaining percentage of parent compound after 0−15−30−60 min of incubation, based on two independent assays. CYP – NADPH refers to Phase-I metabolism, and UGT refers to Phase-II metabolism. Diclofenac, susceptible to Phase-I and Phase-II metabolism, was used as reference (*data not shown*). Mouse and hamster microsomal fractions were selected since these laboratory rodent species are respectively used for *T. cruzi* and *L. infantum* infection.

2.2.5. *In vivo* evaluation

2.2.5.1. Efficacy in the target organs liver, spleen, and bone-marrow in the early curative hamster model of *L. infantum*

Inspired by the encouraging *in vitro* activity against intracellular amastigotes, **32** was selected for *in vivo* evaluation in the early curative hamster model of *L. infantum*. Treatment was initiated at 21 days post-infection (dpi). **32** was orally administrated at 50 mg/kg s.i.d for 10 consecutive days and the efficacy was determined by the percentage reduction of amastigote burdens in the major target organs, namely liver, spleen and bone-marrow (**Table 6**). Percentage reduction compared to the burdens in the vehicle-treated infected control animals (VIC) was used as a measure for activity. MIL was included as reference (40 mg/kg, PO, s.i.d, 5 consecutive days). Unfortunately, **32** showed poor efficacy with organ burden reductions in liver, spleen and bone-marrow of 52.7%, -1.8% and 30.8%, respectively. (Supplementary figure in supporting information) A 'viable' residual burdens assay was performed for the individual organ samples using the promastigote back-transformation assay (**Table 7**). As could be expected, all samples turned positive, confirming that no sterile cure could be obtained.

Table 6. Percentage reduction in amastigote burdens in target organs with 32 in the early curative *L. infantum* infected hamster model[a]

Experimental Group	% reduction of amastigote burdens in target organs		
	Liver	**Spleen**	**Bone-marrow**
G1: VIC: 10% (v/v) PEG 400 and 1% Tween 80 (v/v) in water	-	-	-
G2: MIL 40 mg/kg PO SID for 5 days	94.0	99.2	93.1
G3: **32**: 50 mg/kg PO SID for 10 days	52.7	-1.8	30.8

[a]**G1**: Vehicle-treated control (VIC), **G2:** MIL-treated group, **G3**: **32**-treated group. Each experimental group was allocated randomly with five infected hamsters; Dosing started at 21 dpi; Amastigote burdens in the

different target organs (liver, spleen, bone-marrow) were determined 9 days after the last treatment (*i.e.* day 39 of the experiment).

Table 7. Promastigote back-transformation assay for the individual organ samples[a]

Experimental Group	n	Response of promastigotes in target organs		
		Liver	Spleen	Bone-marrow
G1: VIC: 10% (v/v) PEG 400 and 1%Tween 80 (v/v) in water	1	+++	+++	+++
	2	+++	+++	+++
	3	+++	++	+++
	4	+++	+++	+++
	5	+++	+++	++
G2: MIL 40 mg/kg PO SID for 5 days	1	++	+	++
	2	++	++	+
	3	++	++	++
	4	++	++	++
	5	+	+	+
G3: **32**: 50 mg/kg PO SID for 10 days	1	+++	+++	+++
	2	+++	++	+++
	3	+++	+++	++
	4	+++	+++	+++
	5	+++	+++	+++

[a]Incubation of small tissue samples in promastigote medium at room temperature with qualitative assessment of the presence of promastigotes after two weeks of incubation.

2.2.5.2. Pharmacokinetic (PK) profile

The absorption and elimination kinetics of **32** were studied by LC-MS/MS on dried blood spots (DBS) collected after the first dose on day 1 and after the morning dose of day 9. After dosing at 50 mg/kg, the maximum blood concentrations in infected hamsters were reached at 0.5 hours (T_{max}) with maximum blood levels (C_{max}) exceeding the *in vitro* IC_{50} value by about 4-fold, inferring that the concentration of **32** should in principle be sufficient to inhibit the growth of *L. infantum* (**Table 8**). With respect to elimination, Cl, AUC and $T_{1/2}$ indicated that **32** was not quickly cleared. Compared to single-dose treatment, the AUC after repeated-dose treatment increased, while the Cl decreased, indicating that a greater amount of **32** became systemically available. However, a decrease in volume of distribution (Vd) and $T_{1/2}$ suggests that the higher systemic exposure of **32** is unexpectedly accompanied by an inferior tissue distribution. The low Vd in particular in the Day 9 (Vd < 20 L/kg) indicates that **32** is predominately localized to plasma or extracellular fluid or is highly bound rather than extensively distributed throughout tissues, which probably accounts for the poor efficacy in the target organs. Besides, the nucleoside transporters in rodents are known to be unevenly distributed over different tissues,[34] which may explain the inconsistent reduction percentages in the different organs, despite the favorable *in vitro* activity and metabolic stability. A liposomal formulation[35] could be considered to improve the distribution and macrophage targeting of **32**.

Table 8. Non-compartmental pharmacokinetic parameters of 32 in blood after a single dose (Day 1: 50 mg/kg) and after repeated-dose administration (Day 9: 50 mg/kg s.i.d. for 10 days) in infected hamsters[a]

Experimental Group	T_{max} h	C_{max} ng/mL	C_{max} μM	$T_{1/2}$ h	$AUC_{0\rightarrow8}$ ng.h/mL	$AUC_{0\rightarrow24}$ ng.h/mL	Cl mL/min/kg	Vd L/kg
G4 Day 1-50 mg/kg	0.5	1096	2.9	2.7	1664	2080	56.6	13.0
G4 Day 9-50 mg/kg	0.5	1213	3.2	1.7	2844	3380	34.7	5.14

[a]Blood samples taken until 8 hours after morning dose on day 1. All samples were collected as DBS for analytical detection of parent compound. The calculated PK parameters are based upon the mean values

per time point using non-compartmental analysis. The areas under the curve ($AUC_{0\text{-}8h}$ and $AUC_{0\text{-}24h}$) were calculated using the linear trapezoidal rule. The standard PK parameters were determined using appropriate software (TopFit): C_{max}, T_{max}, AUC, Cl and Vd.

2.2.5.3. *In vivo* toxicity

After oral dosing of 50 mg/kg for 10 days, no clinical adverse effects, gross pathological changes nor severe weight losses (**Figure 4**) were noted in all **32**-treated hamsters.

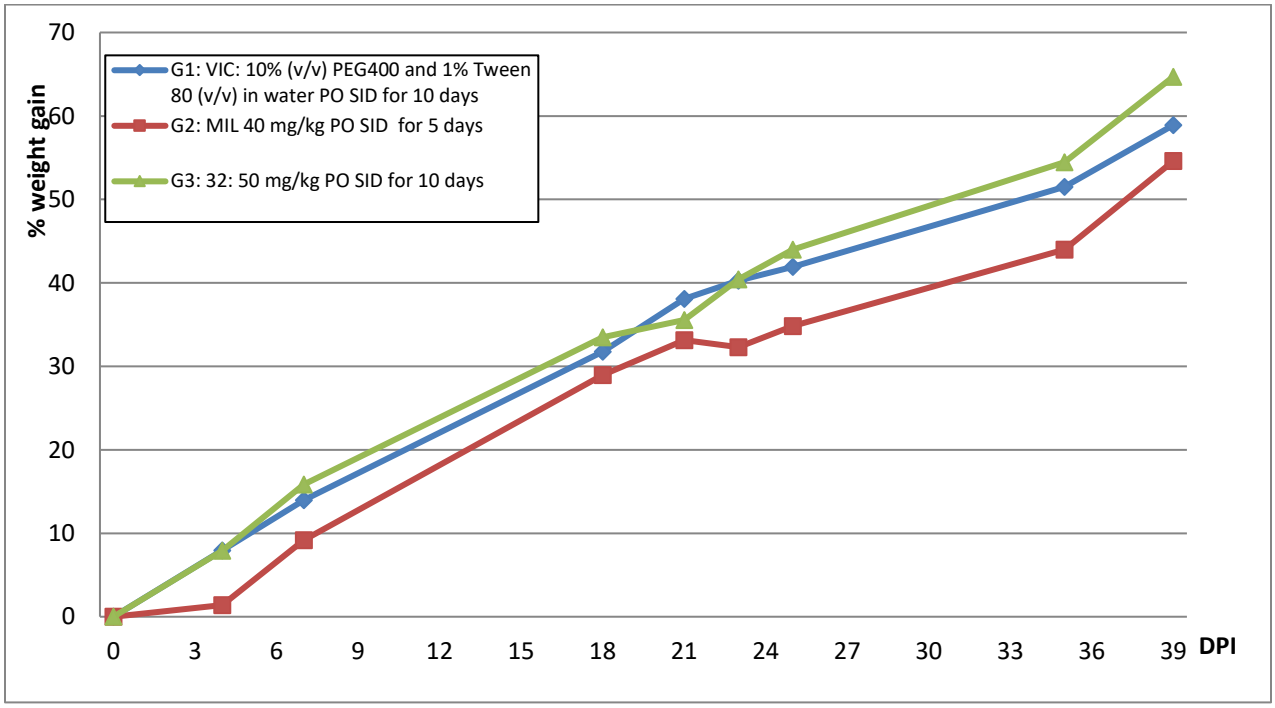


Figure 4. Evolution of body weight gain for 39 dpi. The percentage gain was compared to the start of the experiment, based on the mean from the five hamsters.

3. Conclusion

Phenotypic drug discovery is widely considered as an important strategy for the discovery of new agents for NTD.[36-38] In the present work, screening of a nucleoside library and further heteroaromaticity led to the identification of 6-methyl-7-(2-pyridyl)-7-deazapurine ribonucleoside as an antileishmanial hit. Heteroaromatic optimization afforded the 4-chloropyridyl analogue **32**, which combined submicromolar activity and high selectivity towards host cells. In view of its *in vitro* metabolic stability, **32** was evaluated in an early curative hamster model of *L. infantum*. Although **32** was well tolerated, it showed poor efficacy in eliminating the parasite from the target organs.

4. Materials and methods

4.1. General chemistry

All chemical reagents and solvents were supplied by standard commercial sources and had analytical grade. Compounds **12**, **13**, **14** and **15** were obtained from the previous stock.[20] Machery−Nagel precoated F254 aluminum plates were used for analytical thin-layer chromatography (TLC), which was visualized under UV light at 254 nm. Column chromatography was performed for the purification, using Machery-Nagel 60 M silica gel (40-63 μm) or on a Reveleris X2 (Grace) automated Flash unit. NMR spectra were recorded with a Bruker Avance Neo 400 MHz or a Varian Mercury 300 MHz spectrometer and referenced to the residual solvent peak signal. High-resolution mass spectrometry (HRMS) was performed with a Waters LCT Premier XE time-to-flight (TOF) mass spectrometer equipped with a standard electrospray ionization (ESI) and modular LockSpray interface. Purities of the final compounds were assessed via analytical LC-MS on a Waters AutoPurification system (equipped with ACQUITY QDa (mass; 100−1000 amu)) and 2998 Photodiode Array (220−400 nm) equipped with a Waters Cortecs C18 column (2.7 μm, 100 × 4.6 mm) and a gradient system of formic acid in H_2O (0.2% v/v)/MeCN at a flow rate of 1.44 mL/min and a gradient of 95:5 to 0:100 in 6.5 min. All the purities of final compounds for biological evaluation were > 95%. Purifications of final compounds using preparative High-performance liquid chromatography (HPLC) was

in the same system equipped with a Phenomenex Luna Omega Polar column (5 μm, 250 mm × 21 mm) with a gradient system of formic acid in H_2O (0.2% v/v)/MeCN at a flow rate of 20 mL/min.

4.2 The synthesis of target compounds

4.2.1. General procedure A of Suzuki coupling reaction (adapted from Ref.[27])

Iodo-nucleoside (1 eq.), boronic acid reagent (1.5 eq.), Na_2CO_3 (3 eq.), $Pd(OAc)_2$ (0.1 eq.) and TPPTS (0.2 eq.) were added to a 10 mL round-bottom flask, flushed with argon. Next, a mixed solution of MeCN/water (1/2 ratio, 6 mL/mmol SM) was added via syringe. The reaction mixture was stirred at ambient temperature for 5 min, and then stirred at 100 °C. When completion of the reaction was observed via LC-MS analysis (~0.5 to 3 h), the reaction mixture was cooled to room temperature, neutralized with 0.5 M aq. HCl, and evaporated. The residue was resuspended in MeOH and evaporated *in vacuo*, which was repeated three times. The residue was adsorbed by Celite® and washed through a short silica pad using 20% MeOH/DCM. The resulting solution was evaporated *in vacuo* and purified by column chromatography using MeOH/DCM gradient.

4.2.2. General procedure B of Negishi coupling reaction[16]

Iodo-nucleoside (1 eq.) was added in a 25 mL oven-dried round-bottom flask and co-evaporated three times with anhydrous toluene (10 mL). The resulting solid was dissolved in anhydrous THF (8.5 mL / mmol SM) under argon and cooled to -65 °C. iPrMgCl·LiCl solution (1.3 M in THF, 1.1 eq.) was added in one portion with a syringe. The reaction mixture was stirred at -65 °C for 30 min. Consumption of iodo-nucleoside was monitored via TLC analysis after quenching a small sample with sat. NH_4Cl solution. Then, $ZnCl_2$ solution (0.5 M in THF, 1.2 eq.) was added. The reaction mixture was stirred at -65 °C for 5 min and for 1 h at ambient temperature. $Pd_2(dba)_3$ (0.02 eq.), RuPhos (0.08 eq.) and the appropriate bromo-pyridine or bromo-quinoline (1.4 eq.) were added in a flame-dried Schlenk-tube (5 mL) purged with argon and dissolved in anhydrous THF (3 mL/mmol SM). The mixture was stirred for 5 min and then transferred via a syringe to the flask containing the nucleoside-zinc reagent. The mixture was stirred at 60 °C overnight,

cooled, quenched by adding water (~ 5 mL) and transferred to a separatory funnel. EA (10 mL) and aq. 1M EDTA (pH = 8) solution (5 mL) were added. The layers were separated and the water layer was extracted with EA two more times. The organic layers were combined, dried over Na_2SO_4, evaporated and purified by column chromatography unless indicated. The collected fractions were evaporated and the residue dissolved in 7 N methanolic NH_3 solution. The mixture was stirred at ambient temperature overnight after which it was evaporated until dryness and purified by column chromatography (0 → 10% MeOH/DCM).

4.2.3. 4-Methyl-5-(4-(methylsulfonyl)phenyl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (16). **16** was prepared according to General procedure A. **55** (100 mg, 0.26 mmol) and (4-(methylsulfonyl)phenyl)boronic acid (62 mg, 0.31 mmol) gave rise to **16** (55 mg, 0.13 mmol) as a white solid in 50% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.65 (s, 3 H, CH_3), 3.28 (s, 3 H, CH_3), 3.50 - 3.60 (m, 1 H, H-5''), 3.60 - 3.73 (m, 1 H, H-5'), 3.94 (q, *J* = 3.7 Hz, 1 H, H-4'), 4.07 - 4.21 (m, 1 H, H-3'), 4.48 (t, *J* = 5.4 Hz, 1 H, H-2'), 5.05 (br. s., 1 H, OH-5'), 5.18 (br. s., 1 H, OH-3'), 5.40 (br. s., 1 H, OH-2'), 6.29 (d, *J* = 5.9 Hz, 1 H, H-1'), 7.80 (d, *J* = 8.5 Hz, 2 H, H-Ph), 7.93 - 8.09 (m, 3 H, H-Ph and H-6), 8.75 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.3 (CH_3), 43.6 (CH_3), 61.4 (C-5'), 70.5 (C-3'), 74.1 (C-2'), 85.3 (C-4'), 86.7 (C-1'), 115.5 (C-4a), 115.5 (C-5), 126.0 (C-6), 127.0 (2 C, C-Ph), 130.4 (2 C, C-Ph), 139.2 (C-Ph), 139.6 (C-Ph), 150.9 (C-2), 151.0 (C-7a), 159.3 (C-4). HRMS (ESI): calculated for $C_{19}H_{22}N_3O_6S$ ($[M+H]^+$): 420.1224, found: 420.1218.

4.2.4. 4-Methyl-5-(4-aminophenyl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (17). The p-nitrophenyl compound **56** (70 mg, 0.18 mmol) was dissolved in MeOH (5 mL) and H_2O (1 mL) and purged with N_2 atmosphere. A catalytic amount of $Pd(OH)_2$/C was added and the N_2 was exchanged with H_2 gas (balloon; bubbling). The reaction mixture was stirred at ambient temperature until LC-MS analysis showed full conversion of **56** (5 h). The reaction mixture was filtered over Celite® and rinsed with MeOH. The filtrate was evaporated and the residue was purified by column chromatography (5 → 20% MeOH/DCM) to give **17** (60 mg, 0.17 mmol) as a white solid in 92% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.45 (s, 3 H, CH_3), 3.51 - 3.56 (m, 1 H, H-5''), 3.60 - 3.65 (m, 1 H, H-5'), 3.91 (q, *J* = 3.6 Hz, 1 H, H-4'), 4.09 - 4.13

(m, 1 H, H-3'), 4.45 (q, *J* = 6.2 Hz, 1 H, H-2'), 5.04 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.14 (d, *J* = 4.5 Hz, 1 H, OH-3'), 5.17 (s, 2 H, NH_2), 5.33 (d, *J* = 6.1 Hz, 1 H, OH-2'), 6.24 (d, *J* = 6.3 Hz, 1 H, H-1'), 6.64 (d, *J* = 8.4 Hz, 2 H, H-Ph), 7.12 (d, *J* = 8.5 Hz, 2 H, H-Ph), 7.64 (s, 1 H, H-6), 8.63 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.6 (CH_3), 61.6 (C-5'), 70.6 (C-3'), 73.9 (C-2'), 85.1 (C-4'), 86.4 (C-1'), 113.6 (2 C-Ph), 116.2 (C-4a), 117.7 (C-5), 121.1 (C-Ph), 123.5 (C-6), 130.5 (2 C-Ph), 147.9 (C-Ph), 150.5 (C-7a), 150.5 (C-2), 159.2 (C-4). HRMS (ESI): calculated for $C_{18}H_{21}N_4O_4$ ($[M+H]^+$): 357.1557, found: 357.1553.

4.2.5. 4-Methyl-5-(pyridin-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (18). The iodo-precursor **55** (100 mg, 0.26 mmol) and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol, 0.1 eq.) were added to a 10 mL two-neck round-bottom flask purged with argon. Anhydrous DMF (2 mL) and 2-(tributylstannyl)pyridine (125 µl, 0.39 mmol, 1.5 eq.) were added with syringes. The mixture was heated to 100 °C. When full conversion of **55** was observed via LC-MS analysis (1 h), the reaction mixture was cooled and evaporated to dryness. The residue was purified by column chromatography (0 → 10% MeOH/DCM) to give **18** (70 mg, 0.20 mmol) as a white solid in 79% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.71 (s, 3 H, CH_3), 3.57 (ddd, *J* = 12.0, 5.8, 4.0 Hz, 1 H, H-5''), 3.66 (ddd, *J* = 12.0, 5.2, 3.9 Hz, 1 H, H-5'), 3.94 (q, *J* = 3.8 Hz, 1 H, H-4'), 4.15 (td, *J* = 4.8, 3.5 Hz, 1 H, H-3'), 4.48 (dd, *J* = 11.5, 6.2 Hz, 1 H, H-2'), 5.08 (t, *J* = 5.6 Hz, 1 H, OH-5'), 5.17 (d, *J* = 4.7 Hz, 1 H, OH-3'), 5.40 (d, *J* = 6.4 Hz, 1 H, OH-2'), 6.29 (d, *J* = 6.2 Hz, 1 H, H-1'), 7.35 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1 H, H-Pyr), 7.71 (dt, *J* = 7.9, 1.0 Hz, 1 H, H-Pyr), 7.88 (td, *J* = 7.7, 1.9 Hz, 1 H, H-Pyr), 8.14 (s, 1 H, H-6), 8.66 - 8.70 (m, 1 H, H-Pyr), 8.71 (s, 1 H, H-2). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 24.2 (CH_3), 61.4 (C-5'), 70.5 (C-3'), 74.0 (C-2'), 85.2 (C-4'), 86.6 (C-1'), 115.4 (C-4a), 117.2 (C-5), 121.7 (C-Pyr), 123.3 (C-Pyr), 126.7 (C-6), 136.7 (C-Pyr), 149.0 (C-Pyr), 150.9 (C-Pyr), 151.1 (C-7a), 153.2 (C-2), 160.3 (C-4). HRMS (ESI): calculated for $C_{17}H_{19}N_4O_4$ ($[M+H]^+$): 343.1401, found: 343.1405.

4.2.6. 4-Methyl-5-(thiophen-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (19[27]). 55 (100 mg, 0.26 mmol) and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol, 0.1 eq.) were added to a 10 mL two-neck round-bottom flask flushed with argon to which anhydrous DMF (2 mL) was added, followed by tributyl(thiophen-2-yl)stannane (124 µl, 0.39 mmol, 1.5 eq.). The mixture was heated at 100 °C. When full

conversion of **55** was observed via LC-MS analysis (1 h), the reaction mixture was cooled and evaporated to dryness. The residue was purified by column chromatography (0 → 10% MeOH/DCM) to give **19** (70 mg, 0.20 mmol) as a white solid in 78% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.54 (s, 3 H, CH_3), 3.56 (ddd, *J* = 11.8, 5.7, 4.0 Hz, 1 H, H-5''), 3.65 (ddd, *J* = 11.8, 5.2, 4.0 Hz, 1 H, H-5'), 3.94 (q, *J* = 3.8 Hz, 1 H, H-4'), 4.06 - 4.19 (m, 1 H, H-3'), 4.45 (dd, *J* = 11.4, 6.2 Hz, 1 H, H-2'), 5.08 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.17 (d, *J* = 4.7 Hz, 1 H, OH-3'), 5.39 (d, *J* = 6.4 Hz, 1 H, OH-2'), 6.26 (d, *J* = 6.4 Hz, 1 H, H-1'), 7.18 (dd, *J* = 5.3, 3.5 Hz, 1 H, H-Thio), 7.21 - 7.28 (m, 1 H, H-Thio), 7.61 (dd, *J* = 5.0, 1.2 Hz, 1 H, H-Thio), 7.95 (s, 1 H, H-6), 8.71 (s, 1 H, H-2). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 22.5 (CH_3), 61.4 (C-5'), 70.5 (C-3'), 74.1 (C-2'), 85.3 (C-4'), 86.5 (C-1'), 108.9 (C-5), 116.1 (C-4a), 126.0 (C-6), 126.2 (C-Thio), 127.6 (C-Thio), 128.1 (C-Thio), 134.7 (C-Thio), 150.5 (C-7a), 151.1 (C-2), 159.4 (C-4). HRMS (ESI): calculated for $C_{16}H_{18}N_3O_4S$ ($[M+H]^+$): 348.1013, found: 348.1010.

4.2.7. 4-Methyl-5-(pyridin-3-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (20). The title compound was prepared according to General procedure A. **55** (200 mg, 0.51 mmol) gave rise to **20** (63 mg, 0.18 mmol) as a white solid in 36% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.47 (s, 3 H, CH_3), 3.55 (dd, *J* = 11.4, 3.1 Hz, 1 H, H-5''), 3.65 (d, *J* = 11.9, 3.6 Hz, 1 H, H-5'), 3.94 (q, *J* = 3.7 Hz, 1 H, H-4'), 4.14 (br. s., 1 H, H-3'), 4.48 (br. s., 1 H, H-2'), 5.05 (br. s., 1 H, OH-5'), 5.18 (br. s., 1 H, OH-3'), 5.39 (d, *J* = 4.6 Hz, 1 H, OH-2'), 6.28 (d, *J* = 6.1 Hz, 1 H, H-1'), 7.51 (dd, *J* = 7.8, 4.8 Hz, 1 H, CH), 7.96 (t, *J* = 1.8 Hz, 1 H, H-Pyr), 7.98 (s, 1 H, H-6), 8.60 (dd, *J* = 4.8, 1.5 Hz, 1 H, H-Pyr), 8.73 (s, 1 H, CH, H-2), 8.74 (d, *J* = 2.1 Hz, 1 H, CH, H-Pyr). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.1 (CH_3), 61.7 (C-5'), 70.7 (C-3'), 74.2 (C-2'), 85.4 (C-4'), 86.8 (C-1'), 113.5 (C-5), 116.0 (C-4a), 123.5 (C-Pyr), 125.8 (C-6), 130.4 (C-Pyr), 137.4 (C-Pyr), 148.4 (C-Pyr), 150.0 (C-Pyr), 151.0 (C-7a), 151.1 (C-2), 159.4 (C-4). HRMS (ESI) calculated for $C_{17}H_{19}N_4O_4^+$ ($[M+H^+]$): 343.1401, found: 343.1407.

4.2.8. 4-Methyl-5-(pyridin-4-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (21). The iodo-precursor **55** (150 mg, 0.38 mmol), pyridin-4-ylboronic acid (71 mg, 0.58 mmol, 1.5 eq.), $Pd_2(dba)_3$ (17 mg, 0.019 mmol, 0.05 eq.), P(*c*-Hexyl)$_3$ (13 mg, 0.046 mmol, 0.12 eq.) and K_2PO_4 (1.27 M, 0.5 mL, 1.33

mL/mmol SM) were added to a 10 mL round-bottom flask purged with with argon. 1,4-Dioxane (1 mL, 2.67 mL/mmol SM) was added via syringe and the reaction mixture was stirred at ambient temperature for 5 min, and then stirred at 100 °C. Upon completion of the reaction as observed via LC-MS analysis, the reaction mixture was cooled to room temperature, neutralized with 0.5 M aq. HCl, and evaporated. The residue was resuspended in MeOH and then evaporated *in vacuo*, and this was repeated three times. The residue was adsorbed on Celite® and washed through a short silica pad using 20% MeOH/DCM. The resulting solution was evaporated *in vacuo* and purified by column chromatography (0 → 10% MeOH/DCM) to give **21** (59 mg, 0.17 mmol) as a white solid in 45% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.54 (s, 3 H, CH_3), 3.54 - 3.57 (m, 1 H, H-5''), 3.64 - 3.67 (m, 1 H, H-5'), 3.94 (q, *J* = 3.6 Hz, 1 H, H-4'), 4.14 (br. s., 1 H, H-3'), 4.47 (q, *J* = 5.4 Hz, 1 H, H-2'), 5.08 (br. s., 1 H, OH-5'), 5.20 (d, *J* = 3.4 Hz, 1 H, OH-3'), 5.41 (d, *J* = 5.9 Hz, 1 H, OH-2'), 6.28 (d, *J* = 6.0 Hz, 1 H, H-1'), 7.56 - 7.57 (m, 2 H, H-pyr), 8.06 (s, 1 H, H-6), 8.63 - 8.65 (m, 2 H, H-Pyr), 8.74 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.4 (CH_3), 61.5 (C-5'), 70.5 (C-3'), 74.1 (C-2'), 85.3 (C-4'), 86.7 (C-1'), 114.6 (C-5), 115.3 (C-4a), 124.5 (2 C, C-Pyr), 126.3 (C-6), 142.2 (C-Pyr), 149.4 (2 C, C-Pyr), 151.0 (C-7a), 151.1 (C-2), 159.4 (C-4). HRMS (ESI): calculated for $C_{17}H_{19}N_4O_4$ ($[M+H]^+$): 343.1401, found: 343.1402.

4.2.9. 4-Methyl-5-(2-fluorophenyl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (22). Compound **22** was prepared according to General procedure A. **55** (100 mg, 0.26 mmol) and (2-fluorophenyl)boronic acid (44 mg, 0.31 mmol) gave rise to **22** (60 mg, 0.17 mmol) as a white solid in 60% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.38 (s, 1 H, CH_3), 3.55 (ddd, *J* = 12.0, 5.6, 4.0 Hz, 1 H, H-5''), 3.64 (ddd, *J* = 12.0, 5.2, 4.0 Hz, 1 H, H-5'), 3.94 (q, *J* = 3.7 Hz, 1 H, H-4'), 4.08 - 4.19 (m, 1 H, H-3'), 4.48 (dd, *J* = 11.5, 6.4 Hz, 1 H, H-2'), 5.05 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.18 (d, *J* = 4.7 Hz, 1 H, OH-3'), 5.39 (d, *J* = 6.4 Hz, 1 H, OH-2'), 6.27 (d, *J* = 6.2 Hz, 1 H, H-1'), 7.24 - 7.42 (m, 2 H, H-Ph), 7.44 - 7.58 (m, 2 H, H-Ph), 7.91 (s, 1 H, H-6), 8.71 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.3 (CH_3), 61.5 (C-5'), 70.6 (C-3'), 74.0 (C-2'), 85.3 (C-4'), 86.7 (C-1'), 109.5 (C-5), 115.5 (d, *J* = 21.8 Hz, 1 C, C-Ph), 116.5 (C-4a), 122.0 (d, *J* = 16.0 Hz, 1 C, C-Ph), 124.6 (d, *J* = 2.9 Hz, 1 C, C-Ph), 125.8 (C-6), 130.0 (d, *J* = 8.0 Hz, 1 C, C-Ph), 132.6

(d, *J* = 2.9 Hz, 1 C, C-Ph), 150.5 (C-7a), 150.9 (C-2), 159.2 (C-4), 159.8 (d, *J* = 244.1 Hz, 1 C, C-Ph). ^{19}F NMR (376 MHz, DMSO-d_6) δ: −114.29. HRMS (ESI): calculated for $C_{18}H_{19}FN_3O_4$ ($[M+H]^+$): 360.1354, found: 360.1356.

4.2.10. 4-Methyl-5-(2-chlorophenyl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (23). Compound **23** was prepared according to General procedure A. **55** (100 mg, 0.26 mmol) and (2-chlorophenyl)boronic acid (61 mg, 0.39 mmol) gave rise to **23** (30 mg, 0.08 mmol) as a white solid in 31% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.28 (s, 3 H, CH_3), 3.55 (ddd, *J* = 11.8, 5.6, 4.2 Hz, 1 H, H-5''), 3.65 (ddd, *J* = 11.8, 5.3, 4.0 Hz, 1 H, H-5'), 3.94 (q, *J* = 3.8 Hz, 1 H, H-4'), 4.07 - 4.18 (m, 1 H, H-3'), 4.47 (dd, *J* = 11.5, 6.1 Hz, 1 H, H-2'), 5.04 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.18 (d, *J* = 5.0 Hz, 1 H, OH-3'), 5.38 (d, *J* = 6.4 Hz, 1 H, OH-2'), 6.26 (d, *J* = 6.2 Hz, 1 H, H-1'), 7.39 - 7.55 (m, 3 H, H-Ph), 7.56 - 7.70 (m, 1 H, H-Ph), 7.86 (s, 1 H, H-6), 8.70 (s, 1 H, H-2). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.1 (CH_3), 61.5 (C-5'), 70.5 (C-3'), 74.1 (C-2'), 85.2 (C-4'), 86.8 (C-1'), 113.4 (C-5), 116.7 (C-4a), 125.4 (C-6), 127.2 (C-Ph), 129.3 (2 C, C-Ph), 129.8 (C-Ph), 133.3 (C-Ph), 134.0 (C-Ph), 150.2 (C-7a), 150.9 (C-2), 159.0 (C-4). HRMS (ESI): calculated for $C_{18}H_{19}ClN_3O_4$ ($[M+H]^+$): 376.1059, found: 376.1066.

4.2.11. 4-Methyl-5-(2-methoxyphenyl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (24). Compound **24** was prepared according to General procedure A. **55** (150 mg, 0.38 mmol) and (2-methoxyphenyl)boronic acid (87 mg, 0.58 mmol) gave rise to **24** (100 mg, 0.27 mmol) as a white solid in 71% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.28 (s, 3 H, CH_3), 3.50 - 3.57 (m, 1 H, H-5''), 3.58 - 3.67 (m, 1 H, H-5'), 3.72 (s, 3 H, OCH_3), 3.92 (q, *J* = 3.6 Hz, 1 H, H-4'), 4.10 – 4.13 (m, 1 H, H-3'), 4.48 (q, *J* = 6.3 Hz, 1 H, H-2'), 5.04 (t, *J* = 5.5 Hz, 1 H, OH-5'), 5.16 (d, *J* = 4.8 Hz, 1 H, OH-3'), 5.36 (d, *J* = 6.5 Hz, 1 H, OH-2'), 6.24 (d, *J* = 6.4 Hz, 1 H, H-1'), 7.03 (td, *J* = 7.4, 0.9 Hz, 1 H, H-Ph), 7.11 (d, *J* = 7.8 Hz, 1 H, H-Ph), 7.29 (dd, *J* = 7.4, 1.8 Hz, 1 H, H-Ph), 7.37 - 7.47 (m, 1 H, H-Ph), 7.70 (s, 1 H, H-6), 8.65 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.8 (CH_3), 55.0 (OCH_3), 61.6 (C-5'), 70.6 (C-3'), 73.8 (C-2'), 85.2 (C-4'), 86.5 (C-1'), 110.8 (C-Ph), 113.1 (C-5), 117.2 (C-4a), 120.3 (C-Ph), 123.1 (C-Ph), 124.7 (C-6),

129.4 (C-Ph), 131.6 (C-Ph), 150.4 (C-7a), 150.6 (C-2), 157.2 (C-Ph), 159.5 (C-4). HRMS (ESI): calculated for $C_{19}H_{22}N_3O_5$ ($[M+H]^+$): 372.1554, found: 372.1558.

4.2.12. 4-Methyl-5-(2-(methylthio)phenyl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (25). Compound **25** was prepared according to General procedure A. **55** (150 mg, 0.38 mmol) and (2-(methylthio)phenyl)boronic acid (97 mg, 0.58 mmol) gave rise to **25** (115 mg, 0.30 mmol) as a white solid in 78% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.23 (s, 3 H, CH_3), 2.37 (s, 3 H, SCH_3), 3.49 - 3.58 (m, 1 H, H-5''), 3.60 - 3.68 (m, 1 H, H-5'), 3.93 (q, *J* = 3.6 Hz, 1 H, H-4'), 4.09 - 4.14 (m, 1 H, H-3'), 4.44 (q, *J* = 6.0 Hz, 1 H, H-2'), 5.05 (t, *J* = 5.1 Hz, 1 H, OH-5'), 5.17 (d, *J* = 4.8 Hz, 1 H, OH-3'), 5.36 (d, *J* = 6.4 Hz, 1 H, OH-2'), 6.24 (d, *J* = 6.0 Hz, 1 H, H-1'), 7.20 - 7.25 (m, 1 H, H-Ph), 7.26 - 7.30 (m, 1 H, H-Ph), 7.34 (d, *J* = 7.5 Hz, 1 H, H-Ph), 7.41 - 7.48 (m, 1 H, H-Ph), 7.76 (s, 1 H, H-6), 8.67 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.2 (SCH_3), 21.0 (CH_3), 61.5 (C-5'), 70.5 (C-3'), 74.1 (C-2'), 85.1 (C-4'), 86.8 (C-1'), 114.0 (C-5), 116.7 (C-4a), 123.8 (C-Ph), 124.0 (C-Ph), 125.2 (C-6), 128.8 (C-Ph), 131.2 (C-Ph), 132.1 (C-Ph), 139.9 (C-Ph), 150.2 (C-7a), 150.8 (C-2), 159.2 (C-4). HRMS (ESI): calculated for $C_{19}H_{22}N_3O_4S$ ($[M+H]^+$): 388.1326, found: 388.1313.

4.2.13. 4-Methyl-5-(2-nitrophenyl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (26). Compound **26** was prepared according to General procedure A. **55** (200 mg, 0.51 mmol) and (2-nitrophenyl)boronic acid (129 mg, 0.77 mmol) gave rise to **26** (135 mg, 0.35 mmol) as a yellow solid in 69% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.22 (s, 3 H, CH_3), 3.51 - 3.56 (m, 1 H, H-5''), 3.61 - 3.66 (m, 1 H, H-5'), 3.93 (q, *J* = 3.6 Hz, 1 H, H-4'), 4.10 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.42 (q, *J* = 5.8 Hz, 1 H, H-2'), 5.03 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.18 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.39 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.23 (d, *J* = 6.0 Hz, 1 H, H-1'), 7.65 (d, *J* = 7.5 Hz, 1 H, H-Ph), 7.70 - 7.75 (m, 1 H, H-Ph), 7.80 - 7.83 (m, 1 H, H-Ph), 7.87 (s, 1 H, H-6), 8.12 (d, *J* = 7.9 Hz, 1 H, H-Ph), 8.71 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.3 (CH_3), 61.5 (C-5'), 70.5 (C-3'), 74.1 (C-2'), 85.2 (C-4'), 86.9 (C-1'), 111.1 (C-5), 116.9 (C-4a), 124.1 (C-Ph), 125.2 (C-6), 128.4 (C-Ph), 129.6 (C-Ph), 132.9 (C-Ph), 133.9 (C-Ph), 149.8 (C-Ph), 150.2 (C-7a), 151.1 (C-2), 158.9 (C-4). HRMS (ESI): calculated for $C_{18}H_{19}N_4O_6$ ($[M+H]^+$): 387.1299, found: 387.1310.

4.2.14. 4-Methyl-5-(2-aminophenyl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (27). Compound **26** (60 mg, 0.16 mmol) was dissolved in MeOH (2 mL). The flask was purged into a N_2 atmosphere. Next, a cat. amount of $Pd(OH)_2/C$ was added into the reaction solution. Then, the N_2 gas was exchanged with H_2 gas (balloon; bubbling). The reaction mixture was stirred at ambient temperature until LC-MS analysis showed full conversion of **26**. Then, the balloon was removed and the mixture was filtered over Celite® and rinsed by MeOH. The filtrate was evaporated until dryness. The residue was purified by column chromatography (5 → 20% MeOH/DCM) to give **27** (38 mg, 0.11 mmol) as a white solid in 69% yield.^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.35 (s, 3 H, CH_3), 3.52 - 3.58 (m, 1 H, H-5''), 3.62 - 3.67 (m, 1 H, H-5'), 3.93 (q, *J* = 3.5 Hz, 1 H, H-4'), 4.14 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.44 (q, *J* = 5.8 Hz, 1 H, H-2'), 4.71 (br. s., 2 H, NH_2), 5.05 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.14 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.33 (d, *J* = 5.9 Hz, 1 H, OH-2'), 6.26 (d, *J* = 5.8 Hz, 1 H, H-1'), 6.61 (td, *J* = 7.3, 0.9 Hz, 1 H, H-Ph), 6.76 (d, *J* = 7.5 Hz, 1 H, H-Ph), 7.02 (dd, *J* = 7.4, 1.4 Hz, 1 H, H-Ph), 7.08 - 7.12 (m, 1 H, H-Ph), 7.69 (s, 1 H, H-6), 8.65 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.8 (CH_3), 61.4 (C-5'), 70.5 (C-3'), 74.1 (C-2'), 85.0 (C-4'), 86.8 (C-1'), 113.3 (C-5), 114.2 (C-Ph), 115.8 (C-Ph), 117.0 (C-4a), 118.4 (C-Ph), 124.9 (C-6), 128.7 (C-Ph), 131.4 (C-Ph), 147.2 (C-Ph), 150.5 (C-7a), 150.7 (C-2), 159.4 (C-4). HRMS (ESI): calculated for $C_{18}H_{21}N_4O_4$ ($[M+H]^+$): 357.1557, found: 357.1546.

4.2.15. 4-Methyl-5-(pyrimidin-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (28). Compound **28** was prepared according to General procedure B. **57** (200 mg, 0.28 mmol) gave rise to **28** (55 mg, 0.16 mmol) as a white solid in 63% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.99 (s, 3 H, CH_3), 3.56 - 3.61 (m, 1 H, H-5''), 3.63 - 3.68 (m, 1 H, H-5'), 3.97 (q, *J* = 3.3 Hz, 1 H, H-4'), 4.14 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.48 (q, *J* = 6.0 Hz, 1 H, H-2'), 5.11 (t, *J* = 5.2 Hz, 1 H, OH-5'), 5.19 (d, *J* = 4.6 Hz, 1 H, OH-3'), 5.41 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.32 (d, *J* = 6.3 Hz, 1 H, H-1'), 7.38 (t, *J* = 4.8 Hz, 1 H, H-pyrimidine), 8.51 (s, 1 H, H-6), 8.73 (s, 1 H, H-2), 8.88 (d, *J* = 4.9 Hz, 2 H, H-pyrimidine). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 25.4 (CH_3), 61.4 (C-5'), 70.6 (C-3'), 74.3 (C-2'), 85.4 (C-4'), 86.6 (C-1'), 115.0 (C-4a), 116.2 (C-5), 118.7 (C-pyrimidine), 130.2 (C-6), 151.1 (C-2), 151.6 (C-7a), 157.3 (2 C, C-pyrimidine),

161.0 (C-4), 161.6 (C-pyrimidine). HRMS (ESI): calculated for $C_{16}H_{18}N_5O_4$ ($[M+H]^+$): 344.1353, found: 344.1359.

4.2.16. 4-Methyl-5-(pyrazin-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (29). Compound **29** was prepared according to General procedure B. **57** (200 mg, 0.28 mmol) gave rise to **29** (35 mg, 0.10 mmol) as a white solid in 37% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.73 (s, 3 H, CH_3), 3.55 - 3.60 (m, 1 H, H-5''), 3.65 - 3.71 (m, 1 H, H-5'), 3.95 (d, *J* = 3.4 Hz, 1 H, H-4'), 4.16 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.49 (q, *J* = 5.7 Hz, 1 H, H-2'), 5.09 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.20 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.43 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.30 (d, *J* = 5.9 Hz, 1 H, H-1'), 8.36 (s, 1 H, H-6), 8.59 (d, *J* = 2.1 Hz, 1 H, H-pyrazin), 8.74 - 8.75 (m, 2 H, H-pyrazin and H-2), 9.02 (s, 1 H, H-pyrazin). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.4 (CH_3), 61.4 (C-5'), 70.4 (C-3'), 74.1 (C-2'), 85.3 (C-4'), 86.8 (C-1'), 113.6 (C-4a), 115.3 (C-5), 127.8 (C-6), 142.2 (C-pyrazin), 143.7 (C-pyrazin), 144.1 (C-pyrazin), 149.2 (C-pyrazin), 151.3 (C-2), 151.3 (C-7a), 160.4 (C-4). HRMS (ESI): calculated for $C_{16}H_{18}N_5O_4$ ($[M+H]^+$): 344.1353, found: 344.1350.

4.2.17. 4-Methyl-5-(pyrimidin-5-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (30). Compound **30** was prepared according to General procedure A. **55** (150 mg, 0.38 mmol) gave rise to **30** (70 mg, 0.20 mmol) as a white solid in 54% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.54 - 3.58 (m, 1 H, H-5''), 3.63 - 3.68 (m, 1 H, H-5'), 3.94 (q, *J* = 3.8 Hz, 1 H, H-4'), 4.14 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.47 (q, *J* = 5.8 Hz, 1 H, H-2'), 5.04 (t, *J* = 5.5 Hz, 1 H, OH-5'), 5.20 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.41 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.29 (d, *J* = 6.0 Hz, 1 H, H-1'), 8.10 (s, 1 H, H-6), 8.75 (s, 1 H, H-2), 9.02 (s, 2 H, 2H-pyrimdine), 9.22 (s, 1 H, H-pyrimdine). (the peak of CH_3 is covered in the solvent peak). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.0 (CH_3), 61.5 (C-5'), 70.4 (C-3'), 74.1 (C-2'), 85.3 (C-4'), 86.7 (C-1'), 109.6 (C-5), 115.7 (C-4a), 126.4 (C-6), 128.6 (C-pyrimdine), 150.9 (C-7a), 151.2 (C-2), 156.8 (2 C, C-pyrimdine), 156.9 (C-pyrimdine), 159.3 (C-4). HRMS (ESI): calculated for $C_{16}H_{18}N_5O_4$ ($[M+H]^+$): 344.1353, found: 344.1359.

4.2.18. 4-Methyl-5-(3-chloropyridin-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (31). Compound **31** was prepared according to General procedure B. **57** (200 mg, 0.28 mmol) gave rise to **31** (54 mg, 0.14 mmol) as a white solid in 33% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.35 (s, 3 H, CH_3), 3.53 - 3.59 (m, 1 H, H-5''), 3.62 - 3.68 (m, 1 H, H-5'), 3.95 (q, *J* = 3.5 Hz, 1 H, H-4'), 4.13 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.46 (q, *J* = 6.0 Hz, 1 H, H-2'), 5.07 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.19 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.43 (d, *J* = 6.4 Hz, 1 H, OH-2'), 6.29 (d, *J* = 6.0 Hz, 1 H, H-1'), 7.49 (dd, *J* = 8.2, 4.7 Hz, 1 H, H-Pyr), 8.10 (dd, *J* = 8.1, 1.5 Hz, 1 H, H-Pyr), 8.12 (s, 1 H, H-6), 8.66 (dd, *J* = 4.6, 1.5 Hz, 1 H, H-Pyr), 8.73 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.2 (CH_3), 61.4 (C-5'), 70.5 (C-3'), 74.3 (C-2'), 85.3 (C-4'), 86.9 (C-1'), 113.1 (C-5), 116.3 (C-4a), 124.1 (C-Pyr), 127.1 (C-6), 131.2 (C-Pyr), 137.7 (C-Pyr), 147.7 (C-Pyr), 150.3 (C-7a), 150.9 (C-2), 151.1 (C-Pyr), 159.3 (C-4). HRMS (ESI): calculated for $C_{17}H_{18}ClN_4O_4$ ($[M+H]^+$): 377.1011, found: 377.1003.

4.2.19. 4-Methyl-5-(4-chloropyridin-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (32). Compound **32** was prepared according to General procedure B. **57** (2.00 g, 2.84 mmol) gave rise to a slightly impure **32** (500 mg, 1.32 mmol) as a white solid. **32** was purified by preparative RP-HPLC gradient: 0.2% formic acid in water:MeCN at a flow rate of 20 mL/min; The initial gradient composition (95% A/05% B) was held for 2.0 min, increased to 57% B in 10 min, then increased to 100% B in 1.5 min as a white solid (310 mg, 0.45 mmol) in 29% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.74 (s, 3 H, CH_3), 3.55 - 3.59 (m, 1 H, H-5''), 3.64 - 3.70 (m, 1 H, H-5'), 3.94 (q, *J* = 3.9 Hz, 1 H, H-4'), 4.15 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.48 (q, *J* = 6.1 Hz, 1 H, H-2'), 5.06 (t, *J* = 5.6 Hz, 1 H, OH-5'), 5.19 (d, *J* = 5.0 Hz, 1 H, OH-3'), 5.42 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.29 (d, *J* = 6.0 Hz, 1 H, H-1'), 7.49 (dd, *J* = 5.4, 2.0 Hz, 1 H, H-Pyr), 7.90 (d, *J* = 1.9 Hz, 1 H, H-Pyr), 8.27 (s, 1 H, H-6), 8.66 (d, *J* = 5.4 Hz, 1 H, H-Pyr), 8.73 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.5 (CH_3), 61.4 (C-5'), 70.4 (C-3'), 74.0 (C-2'), 85.2 (C-4'), 86.6 (C-1'), 115.2 (C-4a), 116.0 (C-5), 121.6 (C-Pyr), 122.7 (C-Pyr), 127.7 (C-6), 143.2 (C-Pyr), 150.4 (C-Pyr), 151.1 (C-2), 151.2 (C-7a), 154.9 (C-Pyr), 160.5 (C-4). HRMS (ESI): calculated for $C_{17}H_{18}ClN_4O_4$ ($[M+H]^+$): 377.1011, found: 377.1004.

4.2.20. 4-Methyl-5-(4-methoxypyridin-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (33). Compound **33** was prepared according to General procedure B. **57** (200 mg, 0.28 mmol) gave rise to **33** (28 mg, 0.075 mmol) as a white solid in 23% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.71 (s, 3 H, CH_3), 3.54 - 3.59 (m, 1 H, H-5''), 3.64 - 3.69 (m, 1 H, H-5'), 3.90 (s, 3 H, OCH_3), 3.94 (q, *J* = 3.8 Hz, 1 H, H-4'), 4.15 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.48 (q, *J* = 6.0 Hz, 1 H, H-2'), 5.09 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.18 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.41 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.28 (d, *J* = 6.0 Hz, 1 H, H-1'), 6.95 (dd, *J* = 5.8, 2.5 Hz, 1 H, H-Pyr), 7.25 (d, *J* = 2.4 Hz, 1 H, H-Pyr), 8.15 (s, 1 H, H-6), 8.49 (d, *J* = 5.8 Hz, 1 H, H-Pyr), 8.70 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.2 (CH_3), 55.4 (CH_3), 61.4 (C-5'), 70.4 (C-3'), 74.0 (C-2'), 85.1 (C-4'), 86.6 (C-1'), 108.2 (C-Pyr), 109.1 (C-Pyr), 115.5 (C-4a), 117.3 (C-5), 126.7 (C-6), 150.3 (C-Pyr), 150.9 (C-2), 151.0 (C-7a), 154.8 (C-Pyr), 160.3 (C-4), 165.6 (C-Pyr). HRMS (ESI): calculated for $C_{18}H_{21}N_4O_5$ ($[M+H]^+$): 373.1506, found: 373.1500.

4.2.21. 4-Methyl-5-(5-chloropyridin-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (34). Compound **34** was prepared according to General procedure B. **57** (2.00 g, 2.84 mmol) gave rise to **34** (430 mg, 1.14 mmol) as a white solid. **34** was purified by preparative RP-HPLC gradient: 0.2% formic acid in water:MeCN at a flow rate of 20 mL/min; The initial gradient composition (95% A/05% B) was held for 2.0 min, increased to 57% B in 10 min, then increased to 100% B in 1.5 min as a white solid (250 mg, 0.66 mmol) in 22% yield for two steps.^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.71 (s, 3 H, CH_3), 3.54 - 3.59 (m, 1 H, H-5''), 3.64 - 3.69 (m, 1 H, H-5'), 3.94 (q, *J* = 3.8 Hz, 1 H, H-4'), 4.15 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.48 (q, *J* = 5.8 Hz, 1 H, H-2'), 5.07 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.19 (d, *J* = 4.8 Hz, 1 H, OH-3'), 5.41 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.29 (d, *J* = 6.0 Hz, 1 H, H-1'), 7.77 (d, *J* = 8.5 Hz, 1 H, H-Pyr), 8.02 (dd, *J* = 8.4, 2.6 Hz, 1 H, H-Pyr), 8.20 (s, 1 H, H-6), 8.72 - 8.73 (m, 2 H, H-Pyr and H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.4 (CH_3), 61.4 (C-5'), 70.4 (C-3'), 74.0 (C-2'), 85.2 (C-4'), 86.6 (C-1'), 115.2 (C-4a), 116.0 (C-5), 124.4 (C-Pyr), 127.2 (C-6), 129.0 (C-Pyr), 136.6 (C-Pyr), 147.5 (C-Pyr), 151.1 (C-7a), 151.2 (C-2), 151.8 (C-Pyr), 160.3 (C-4). HRMS (ESI): calculated for $C_{17}H_{18}ClN_4O_4$ ($[M+H]^+$): 377.1011, found: 377.1019.

4.2.22. 4-Methyl-5-(6-chloropyridin-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (35). Compound **35** was prepared according to General procedure B. **57** (200 mg, 0.28 mmol) gave rise to **35** (25 mg, 0.066 mmol) as a white solid in 18% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.76 (s, 3 H, CH_3), 3.57 (ddd, *J* = 11.9, 5.7, 4.1 Hz, 1 H, H-5''), 3.65 - 3.69 (m, 1 H, H-5'), 3.95 (q, *J* = 3.8 Hz, 1 H, H-4'), 4.15 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.47 (q, *J* = 6.0 Hz, 1 H, H-2'), 5.08 (t, *J* = 5.5 Hz, 1 H, OH-5'), 5.19 (d, *J* = 5.0 Hz, 1 H, OH-3'), 5.42 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.29 (d, *J* = 6.0 Hz, 1 H, H-1'), 7.46 (dd, *J* = 7.9, 0.5 Hz, 1 H, H-Pyr), 7.76 (dd, *J* = 7.8, 0.5 Hz, 1 H, H-Pyr), 7.93 - 7.96 (m, 1 H, H-Pyr), 8.28 (s, 1 H, H-6), 8.73 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.6 (CH_3), 61.4 (C-5'), 70.4 (C-3'), 74.1 (C-2'), 85.2 (C-4'), 86.7 (C-1'), 115.1 (C-4a), 115.6 (C-5), 121.8 (C-Pyr), 127.6 (C-6), 140.3 (C-Pyr), 149.4 (C-Pyr), 151.2 (C-2), 151.2 (C-7a), 153.8 (C-Pyr), 160.4 (C-4). HRMS (ESI): calculated for $C_{17}H_{18}ClN_4O_4$ ($[M+H]^+$): 377.1011, found: 377.1019.

4.2.23. 4-Methyl-5-(6-fluoropyridin-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (36). Compound **36** was prepared according to General procedure B. **57** (200 mg, 0.28 mmol) gave rise to **36** (4 mg, 0.011 mmol) as a white solid in 5% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.76 (s, 3 H, CH_3), 3.54 - 3.60 (m, 1 H, H-5''), 3.64 - 3.70 (m, 1 H, H-5'), 3.95 (q, *J* = 3.7 Hz, 1 H, H-4'), 4.15 (q, *J* = 4.3 Hz, 1 H, H-3'), 4.47 (q, *J* = 5.8 Hz, 1 H, H-2'), 5.09 (t, *J* = 5.5 Hz, 1 H, OH-5'), 5.19 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.42 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.29 (d, *J* = 6.0 Hz, 1 H, H-1'), 7.13 (dd, *J* = 8.1, 2.6 Hz, 1 H, H-Pyr), 7.69 (dd, *J* = 7.4, 2.4 Hz, 1 H, H-Pyr), 8.07 (q, *J* = 8.3 Hz, 1 H, H-Pyr), 8.26 (s, 1 H, H-6), 8.73 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.5 (CH_3), 61.4 (C-5'), 70.4 (C-3'), 74.1 (C-2'), 85.3 (C-4'), 86.7 (C-1'), 106.9 (d, *J* = 37.8 Hz, 1 C, C-Pyr), 115.1 (C-4a), 115.5 (C-5), 120.7 (d, *J* = 3.6 Hz, 1 C, C-Pyr), 127.6 (C-6), 142.6 (d, *J* = 8.0 Hz, 1 C, C-Pyr), 151.1 (C-2), 151.2 (C-7a), 151.8(d, *J* = 14.5 Hz, 1 C, C-Pyr), 160.2 (C-4), 162.3 (d, *J* = 235.4 Hz, 1 C, C-Pyr). ^{19}F NMR (376 MHz, DMSO-d_6) δ: −68.00. HRMS (ESI): calculated for $C_{17}H_{18}FN_4O_4$ ($[M+H]^+$): 361.1307, found: 361.1319.

4.2.24. 4-Methyl-5-(6-chloropyridin-3-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (37). Compound **37** was prepared according to General procedure A. **55** (100 mg, 0.26 mmol) and (6-

chloropyridin-3-yl)boronic acid (49 mg, 0.31 mmol) gave rise to **37** (25 mg, 0.066 mmol) as a light grey solid in 26% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.48 (s, 3 H, CH_3), 3.50 - 3.60 (m, 1 H, H-5''), 3.60 - 3.71 (m, 1 H, H-5'), 3.94 (q, *J* = 3.8 Hz, 1 H, H-4'), 4.07 - 4.17 (m, 1 H, H-3'), 4.46 (t, *J* = 5.4 Hz, 1 H, H-2'), 5.05 (br. s., 1 H, OH-5'), 5.21 (br. s., 1 H, OH-3'), 5.42 (br. s., 1 H, OH-2'), 6.28 (d, *J* = 6.0 Hz, 1 H, H-1'), 7.63 (d, *J* = 8.3 Hz, 1 H, H-Pyr), 8.01 (s, 1 H, H-6), 8.05 (dd, *J* = 8.2, 2.6 Hz, 1 H, H-Pyr), 8.58 (d, *J* = 2.4 Hz, 1 H, H-Pyr), 8.73 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.0 (CH_3), 61.5 (C-5'), 70.4 (C-3'), 74.1 (C-2'), 85.2 (C-4'), 86.7 (C-1'), 111.9 (C-5), 115.7 (C-4a), 123.8 (C-Pyr), 125.9 (C-6), 129.7 (C-Pyr), 140.7 (C-Pyr), 149.0 (C-Pyr), 149.9 (C-Pyr), 150.8 (C-7a), 151.1 (C-2), 159.3 (C-4). HRMS (ESI): calculated for $C_{17}H_{18}ClN_4O_4$ ($[M+H]^+$): 377.1011, found: 377.1006.

4.2.25. 4-Methyl-5-(1*H*-pyrrol-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (38). The iodo-precursor **55** (150 mg, 0.38 mmol), (1-(tert-butoxycarbonyl)-1*H*-pyrrol-2-yl)boronic acid (122 mg, 0.57 mmol, 1.5 eq.), $Pd(OAc)_2$ (9 mg, 0.038 mmol, 0.1 eq.), TPPTS (43 mg, 0.076 mmol, 0.2 eq.) and Na_2CO_3 (121 mg, 1.14 mmol, 3 eq.) were added to a 10 mL round-bottom flask, purged with argon. Next, a MeCN/water (1/2 ratio, 6 mL/mmol SM) was added via syringe. The reaction mixture was stirred at ambient temperature for 5 min, and then at 100 °C. Upon completion of the reaction as monitored by LC-MS analysis, the reaction mixture was cooled to room temperature and evaporated *in vacuo*. The residue was treated with 0.5 M NaOMe in MeOH (5 mL) and stirred at ambient temperature for 1 h, after which it was neutralized with 0.5 M aq. HCl, and evaporated. The residue was purified by column chromatography (5 → 20% MeOH/DCM) to give **38** (35 mg, 0.11 mmol) as a yellow solid in 28% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.52 - 3.57 (m, 1 H, H-5''), 3.60 - 3.66 (m, 1 H, H-5'), 3.92 (q, *J* = 3.6 Hz, 1 H, H-4'), 4.10 - 4.13 (m, 1 H, H-3'), 4.43 (q, *J* = 6.2 Hz, 1 H, H-2'), 5.05 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.17 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.34 (d, *J* = 6.5 Hz, 1 H, OH-2'), 6.12 (q, *J* = 2.8 Hz, 1 H, H- pyrrole), 6.16 (br. s., 1 H, H-pyrrole), 6.25 (d, *J* = 6.1 Hz, 1 H, H-1'), 6.86 (br. s., 1 H, H-pyrrole), 7.76 (s, 1 H, H-6), 8.66 (s, 1 H, H-2), 11.04 (br. s., 1 H, NH). (the peak of CH_3 is covered in the solvent peak). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.1 (CH_3), 61.6 (C-5'), 70.6 (C-3'), 74.1 (C-2'), 85.2 (C-4'), 86.4 (C-1'), 108.1 (C-pyrrole), 108.6

(C-pyrrole), 109.3 (C-5), 116.3 (C-4a), 118.2 (C-pyrrole), 123.5 (C-6), 124.6 (C-pyrrole), 150.3 (C-7a), 150.8 (C-2), 159.5 (C-4). HRMS (ESI): calculated for $C_{16}H_{19}N_4O_4$ ([M+H]$^+$): 331.1401, found: 331.1414.

4.2.26. 4-Methyl-5-(thiazol-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (39). Compound **57** (200 mg, 0.28 mmol) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.011 mmol, 0.04 eq.) were added to a 10 mL two-neck round-bottom flask. The flask was charged with argon. Next, anhydrous DMF (2 mL) was added into the flask via syringe, followed by the addition of 2-tributylstannyltriazole (179 µl, 0.57 mmol, 2.0 eq.). The mixture was heated at 100 °C. When full conversion of **57** was observed via LC-MS analysis (2 days), the reaction mixture was cooled and evaporated until dryness. The residue was dissolved in 7 N NH_3 methanol solution. The mixture was stirred at ambient temperature overnight. Next, the reaction solution was evaporated until dryness and purified by column chromatography (0 → 10% MeOH/DCM) to give **39** (55 mg, 0.16 mmol) as a white solid in 56% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.86 (s, 3 H, CH_3), 3.56 - 3.62 (m, 1 H, H-5''), 3.69 (dt, *J* = 11.9, 4.5 Hz, 1 H, H-5'), 3.96 (q, *J* = 3.4 Hz, 1 H, H-4'), 4.16 (q, *J* = 4.4 Hz, 1 H, H-3'), 4.47 (q, *J* = 5.7 Hz, 1 H, H-2'), 5.15 (t, *J* = 5.3 Hz, 1 H, OH-5'), 5.19 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.45 (d, *J* = 6.1 Hz, 1 H, OH-2'), 6.28 (d, *J* = 5.9 Hz, 1 H, H-1'), 7.76 (d, *J* = 3.3 Hz, 1 H, H-thiazole), 7.96 (d, *J* = 3.3 Hz, 1 H, H-thiazole), 8.37 (s, 1 H, H-6), 8.75 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.8 (CH_3), 61.2 (C-5'), 70.3 (C-3'), 74.2 (C-2'), 85.3 (C-4'), 86.9 (C-1'), 110.3 (C-5), 114.6 (C-4a), 119.9 (C-thiazole), 128.0 (C-6), 143.3 (C-thiazole), 151.0 (C-7a), 151.5 (C-2), 160.6 (C-4), 160.8 (C-thiazole). HRMS (ESI): calculated for $C_{15}H_{17}N_4O_4S$ ([M+H]$^+$): 349.0965, found: 349.0960.

4.2.27. 4-Methyl-5-(1*H*-pyrazol-3-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (40). Compound **40** was prepared according to General procedure A. **55** (120 mg, 0.31 mmol) and (1*H*-pyrazol-3-yl)boronic acid (51 mg, 0.46 mmol) gave rise to **40** (40 mg, 0.12 mmol) as a white solid in 39% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.77 (s, 3 H, CH_3), 3.53 - 3.59 (m, 1 H, H-5''), 3.62 - 3.67 (m, 1 H, H-5'), 3.93 (d, *J* = 3.1 Hz, 1 H, H-4'), 4.13 (q, *J* = 4.3 Hz, 1 H, H-3'), 4.45 (q, *J* = 5.9 Hz, 1 H, H-2'), 5.08 (br. s., 1 H, OH-5'), 5.17 (br. s., 1 H, OH-3'), 5.38 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.26 (d, *J* = 6.3 Hz, 1 H, H-1'), 6.52 (br. s., 1 H, H-pyrazole), 7.82 (s, 1 H, H-pyrazole), 7.96 (s, 1 H, H-6), 8.67 (s, 1 H, H-2), 12.91 (br. s.,

1 H, NH).). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.4 (CH_3), 61.5 (C-5'), 70.6 (C-3'), 74.0 (C-2'), 85.2 (C-4'), 86.5 (C-1'), 104.8 (C-pyrazole), 110.3 (C-5), 115.8 (C-4a), 125.3 (C-6), 129.1 (C-pyrazole), 144.7 (C-pyrazole), 150.7 (C-2), 150.8 (C-7a), 160.1 (C-4). HRMS (ESI): calculated for $C_{15}H_{18}N_5O_4$ ($[M+H]^+$): 332.1353, found: 332.1334.

4.2.28. 4-Methyl-5-(1-methyl-1*H*-pyrazol-4-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (41). Compound **41** was prepared according to General procedure A. **55** (150 mg, 0.38 mmol) and (1-methyl-1*H*-pyrazol-4-yl)boronic acid (73 mg, 0.58 mmol) gave rise to **41** (14 mg, 0.041 mmol) as a white solid in 11% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.57 (s, 3 H, CH_3), 3.51 - 3.57 (m, 1 H, H-5''), 3.60 - 3.65 (m, 1 H, H-5'), 3.90 - 3.93 (m, 4 H, CH_3 and H-4'), 4.09 - 4.13 (m, 1 H, H-3'), 4.43 (q, *J* = 5.9 Hz, 1 H, H-2'), 5.04 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.15 (d, *J* = 4.8 Hz, 1 H, OH-3'), 5.35 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.23 (d, *J* = 6.3 Hz, 1 H, H-1'), 7.60 (s, 1 H, H-pyrazole), 7.73 (s, 1 H, H-6), 7.90 (s, 1 H, H-pyrazole), 8.65 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.5 (CH_3), 38.6 (CH_3), 61.5 (C-5'), 70.6 (C-3'), 74.0 (C-2'), 85.1 (C-4'), 86.4 (C-1'), 107.5 (C- pyrazole), 113.7 (C-5), 116.1 (C-4a), 124.3 (C-6), 130.2 (C-pyrazole), 139.0 (C-pyrazole), 150.5 (C-7a), 150.7 (C-2), 159.3 (C-4). HRMS (ESI): calculated for $C_{16}H_{20}N_5O_4$ ($[M+H]^+$): 346.1510, found: 346.1503.

4.2.29. 4-Methyl-5-(thiophen-3-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (42[27]). Compound **42** was prepared according to General procedure A. **55** (200 mg, 0.51 mmol) and thiophen-3-ylboronic acid (98 mg, 0.77 mmol) gave rise to **42** (56 mg, 0.16 mmol) as a white solid in 32% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.52 (s, 3 H, CH_3), 3.55 (d, *J* = 11.4 Hz, 1 H, H-5''), 3.60 - 3.68 (m, 1 H, H-5'), 3.89 - 3.98 (m, 1 H, H-4'), 4.12 (br. s., 1 H, H-3'), 4.45 (br. s., 1 H, H-2'), 5.06 (br. s., 1 H, OH-5'), 5.17 (br. s., 1 H, OH-3'), 5.36 (br. s., 1 H, OH-2'), 6.26 (d, *J* = 6.3 Hz,1 H, H-1'), 7.31 (dd, *J* = 4.9, 1.3 Hz, 1 H, H-Thio), 7.59 (dd, *J* = 2.9, 1.3 Hz, 1 H, H-Thio), 7.67 (dd, *J* = 4.9, 3 Hz, 1 H, H-Thio), 7.86 (s, 1 H, H-6), 8.69 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.6 (CH_3), 61.5 (C-5'), 70.5 (C-3'), 74.0 (C-2'), 85.2 (C-4'), 86.5 (C-1'), 111.7 (C-5), 116.0 (C-4a), 123.6 (C-Thio), 124.8 (C-6), 126.1 (C-Thio), 129.7

(C-Thio), 134.2 (C-Thio) 150.5 (C-7a), 150.7 (C-2), 159.3 (C-4). HRMS (ESI) calculated for $C_{16}H_{18}N_3O_4S^+$ ([M+H$^+$]): 348.1013, found: 348.1030.

4.2.30. 4-Methyl-5-(furan-3-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (43[27]). Compound **43** was prepared according to General procedure A. **55** (100 mg, 0.26 mmol) gave rise to **43** (46 mg, 0.14 mmol) as a white solid in 53% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.60 (s, 3 H, CH_3), 3.52 - 3.57 (m, 1 H, H-5''), 3.61 - 3.66 (m, 1 H, H-5'), 3.92 (q, *J* = 3.7 Hz, 1 H, H-4'), 4.12 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.43 (q, *J* = 6.1 Hz, 1 H, H-2'), 5.05 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.16 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.35 (d, *J* = 6.4 Hz, 1 H, OH-2'), 6.24 (d, *J* = 6.3 Hz, 1 H, H-1'), 6.77 (d, *J* = 1.0 Hz, 1 H, H-furan), 7.78 - 7.80 (m, 1 H, H-furan), 7.82 (s, 1 H, H-6), 7.87 (s, 1 H, H-furan), 8.67 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.6 (CH_3), 61.5 (C-5'), 70.5 (C-3'), 74.0 (C-2'), 85.2 (C-4'), 86.4 (C-1'), 107.1 (C- furan), 112.7 (C-5), 116.1 (C-4a), 118.2 (C-furan), 124.7 (C-6), 140.5 (C-furan), 143.4 (C- furan), 150.7 (C-7a), 150.8 (C-2), 159.3 (C-4). HRMS (ESI): calculated for $C_{16}H_{18}N_3O_5$ ([M+H]$^+$): 332.1241, found: 332.1246.

4.2.31. 4-Methyl-5-(quinolin-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (44). Compound **44** was prepared according to General procedure B. **57** (200 mg, 0.28 mmol) gave rise to a slight impure **44** (50 mg) as a white solid. **44** was purified by preparative RP-HPLC gradient: 0.2% formic acid in water:MeCN at a flow rate of 20 mL/min; The initial gradient composition (95% A/05% B) was held for 2.0 min, increased to 60% B in 13 min, then increased to 100% B in 1 min as a white solid (33 mg, 0.084 mmol) in 22% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.93 (s, 3 H, CH_3), 3.57 - 3.61 (m, 1 H, H-5''), 3.68 - 3.72 (m, 1 H, H-5'), 3.97 (q, *J* = 3.7 Hz, 1 H, H-4'), 4.18 (t, *J* = 4.2 Hz, 1 H, H-3'), 4.52 (t, *J* = 5.4 Hz, 1 H, H-2'), 5.13 (br. s., 1 H, OH-5'), 5.22 (br. s., 1 H, OH-3'), 5.46 (br. s., 1 H, OH-2'), 6.33 (d, *J* = 5.9 Hz, 1 H, H-1'), 7.58 - 7.62 (m, 1 H, H-quinoline), 7.76 - 7.80 (m, 1 H, H-quinoline), 7.95 (d, *J* = 8.5 Hz, 1 H, H-quinoline), 8.01 (d, *J* = 7.6 Hz, 1 H, H-quinoline), 8.06 (d, *J* = 8.4 Hz, 1 H, H-quinoline), 8.42 -8.44 (m, 2 H, H-quinoline and H-6), 8.75 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 25.2 (CH_3), 61.4 (C-5'), 70.4 (C-3'), 74.0 (C-2'), 85.2 (C-4'), 86.7 (C-1'), 115.5 (C-4a), 117.5 (C-5), 121.3 (C-quinoline), 126.2 (C-quinoline), 126.2 (C-quinoline), 127.9 (C-quinoline), 128.1 (C-6), 128.4 (C-quinoline),

129.9 (C-quinoline), 136.5 (C-quinoline), 147.2 (C-quinoline), 151.1 (C-2), 151.5 (C-7a), 153.1 (C-quinoline), 161.0 (C-4). HRMS (ESI): calculated for $C_{21}H_{21}N_4O_4$ ([M+H]$^+$): 393.1557, found: 393.1563.

4.2.32. 4-Methyl-5-(isoquinolin-3-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (45). Compound **45** was prepared according to General procedure B. **57** (200 mg, 0.28 mmol) gave rise to **45** (21 mg, 0.054 mmol) as a white solid in 19% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.68 (s, 3 H, CH_3), 3.56 - 3.60 (m, 1 H, H-5''), 3.64 - 3.70 (m, 1 H, H-5'), 3.96 (q, *J* = 3.8 Hz, 1 H, H-4'), 4.16 (q, *J* = 4.2 Hz, 1 H, H-3'), 4.51 (q, *J* = 6.1 Hz, 1 H, H-2'), 5.08 (t, *J* = 5.5 Hz, 1 H, OH-5'), 5.19 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.42 (d, *J* = 6.4 Hz, 1 H, OH-2'), 6.32 (d, *J* = 6.3 Hz, 1 H, H-1'), 7.67 - 7.71 (m, 1 H, H-quinoline), 7.82 (td, *J* = 7.5, 1.1 Hz, 1 H, H-quinoline), 8.02 (d, *J* = 8.1 Hz, 1 H, H-quinoline), 8.11 (s, 1 H, H-6), 8.16 - 8.18 (m, 2 H, 2 H-quinoline), 8.73 (s, 1 H, H-2), 9.44 (s, 1 H, H-quinoline). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.0 (CH_3), 61.5 (C-5'), 70.5 (C-3'), 74.1 (C-2'), 85.2 (C-4'), 86.5 (C-1'), 115.8 (C-4a), 117.4 (C-5), 119.1 (C-6), 126.3 (C-quinoline), 126.5 (C-quinoline), 126.8 (C-quinoline), 127.3 (C-quinoline), 127.6 (C-quinoline), 130.9 (C-quinoline), 135.8 (C-quinoline), 146.9 (C-quinoline), 150.9 (C-2), 151.1 (C-7a), 151.8 (C-quinoline), 161.0 (C-4). HRMS (ESI): calculated for $C_{21}H_{21}N_4O_4$ ([M+H]$^+$): 393.1557, found: 393.1549.

4.2.33. 4-Methyl-5-(1*H*-indol-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (46). The iodo-precursor **55** (150 mg, 0.38 mmol), (1-(tert-butoxycarbonyl)-1*H*-indol-2-yl)boronic acid (149 mg, 0.57 mmol, 1.5 eq.), $Pd(OAc)_2$ (9 mg, 0.038 mmol, 0.1 eq.), TPPTS (43 mg, 0.076 mmol, 0.2 eq.) and Na_2CO_3 (121 mg, 1.14 mmol, 3 eq.) were added to a 10 mL round-bottom flask purged with argon. MeCN/water (1/2 ratio, 3 mL, 6 mL/mmol SM) was added and the reaction mixture was stirred at ambient temperature for 5 min, and then at 100 °C. Upon complete conversion of the SM (LC-MS), the reaction mixture was cooled to room temperature and evaporated *in vacuo*. The residue was treated with 0.5 M NaOMe in MeOH (5 mL) at ambient temperature for 1 h. The mixture was neutralized with 0.5 M aq. HCl and evaporated. The residue was purified by column chromatography (5 → 20% MeOH/DCM) to give **46** (68 mg, 0.18 mmol) as a light yellow solid in 47% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.61 (s, 3 H,

724 CH_3), 3.55 - 3.60 (m, 1 H, H-5''), 3.63 - 3.68 (m, 1 H, H-5'), 3.96 (q, *J* = 3.6 Hz, 1 H, H-4'), 4.15 (q, *J* =
725 4.2 Hz, 1 H, H-3'), 4.47 (q, *J* = 6.0 Hz, 1 H, H-2'), 5.07 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.20 (d, *J* = 4.9 Hz, 1
726 H, OH-3'), 5.40 (d, *J* = 6.4 Hz, 1 H, OH-2'), 6.30 (d, *J* = 6.1 Hz, 1 H, H-1'), 6.58 (d, *J* = 1.3 Hz, 1 H, H-
727 indole), 7.00 - 7.04 (m, 1 H, H-indole), 7.09 - 7.13 (m, 1 H, H-indole), 7.40 (d, *J* = 7.8 Hz, 1 H, H-indole),
728 7.56 (d, *J* = 7.8 Hz, 1 H, H-indole), 8.01 (s, 1 H, H-6), 8.72 (s, 1 H, H-2), 11.37 (s, 1 H, NH). ^{13}C NMR
729 (100 MHz, DMSO-d_6) δ: 22.6 (CH_3), 61.5 (C-5'), 70.6 (C-3'), 74.2 (C-2'), 85.3 (C-4'), 86.6 (C-1'), 101.9
730 (C-indole), 108.7 (C-5), 111.0 (C-indole), 115.9 (C-4a), 119.1 (C-indole), 119.7 (C-indole), 121.1 (C-
731 indole), 125.8 (C-6), 128.3 (C-indole), 131.3 (C-indole), 136.5 (C-indole), 150.6 (C-7a), 151.0 (C-2), 159.7
732 (C-4). HRMS (ESI): calculated for $C_{20}H_{21}N_4O_4$ ($[M+H]^+$): 381.1557, found: 381.1577.

733 **4.2.34. 4-Methyl-5-(benzofuran-2-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (47).**
734 Compound **47** was prepared according to General procedure A. **55** (150 mg, 0.38 mmol) gave rise to **47** (20
735 mg, 0.052 mmol) as a white solid in 14% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.79 (s, 3 H, CH_3), 3.55
736 - 3.63 (m, 1 H, H-5'), 3.64-3.72 (m, 1 H, H-5''), 3.96 (d, *J* = 3.3 Hz, 1 H, H-4'), 4.16 (d, *J* = 3.5 Hz, 1 H,
737 H-3'), 4.49 (q, *J* = 5.8 Hz, 1 H, H-2'), 5.11 (t, *J* = 5.3 Hz, 1 H, OH-5'), 5.21 (d, *J* = 4.8 Hz, 1 H, OH-3'),
738 5.44 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.30 (d, *J* = 6 Hz, 1 H, H-1'), 7.16 (s, 1 H, H-benzofuran), 7.24 - 7.36 (m,
739 2 H, H-benzofuran), 7.66 (d, *J* = 18.7 Hz, 2 H, H-benzofuran), 8.32 (s, 1 H, H-6), 8.76 (s, 1 H, H-2). ^{13}C
740 NMR (100 MHz, DMSO-d_6) δ: 23.3 (CH_3), 61.4 (C-5'), 70.5 (C-3'), 74.2 (C-2'), 85.4 (C-4'), 86.7 (C-1'),
741 104.3 (C-benzofuran), 106.1 (C-5), 110.9 (C-benzofuran), 115.0 (C-4a), 120.9 (C-benzofuran), 123.1 (C-
742 benzofuran), 124.2 (C-benzofuran), 127.0 (C-6), 128.7 (C-benzofuran), 150.3 (C- benzofuran), 150.9 (C-
743 7a), 151.4 (C-2), 154.2 (C-benzofuran), 159.7 (C-4). HRMS (ESI) calculated for $C_{20}H_{20}N_3O_5^+$ ($[M+H^+]$):
744 382.1397, found: 382.1391.

745 **4.2.35. 4-Methyl-5-(quinolin-8-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (48).** Compound
746 **48** was prepared according to General procedure B. **57** (200 mg, 0.28 mmol) gave rise to **48** (37 mg, 0.094
747 mmol) as a white solid in 46% yield for two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.91 (s, 3 H, CH_3),
748 3.52 - 3.57 (m, 1 H, H-5''), 3.61 - 3.66 (m, 1 H, H-5'), 3.95 (d, *J* = 3.4 Hz, 1 H, H-4'), 4.13 (q, *J* = 4.2 Hz,

749 1 H, H-3'), 4.53 (q, *J* = 6.1 Hz, 1 H, H-2'), 5.03 (t, *J* = 5.3 Hz, 1 H, OH-5'), 5.18 (d, *J* = 4.8 Hz, 1 H, OH-
750 3'), 5.40 (d, *J* = 6.5 Hz, 1 H, OH-2'), 6.31 (d, *J* = 6.3 Hz, 1 H, H-1'), 7.57 (dd, *J* = 8.3, 4.1 Hz, 1 H, H-
751 quinoline), 7.70 (dd, *J* = 8.1, 7.1 Hz, 1 H, H-quinoline), 7.81 (dd, *J* = 7.0, 1.5 Hz, 1 H, H-quinoline), 7.85
752 (s, 1 H, H-6), 8.07 (dd, *J* = 8.3, 1.4 Hz, 1 H, H-quinoline), 8.46 (dd, *J* = 8.3, 1.7 Hz, 1 H, H-quinoline), 8.68
753 (s, 1 H, H-2), 8.82 (dd, *J* = 4.1, 1.8 Hz, 1 H, H-quinoline). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.4 (CH_3),
754 61.6 (C-5'), 70.6 (C-3'), 73.9 (C-2'), 85.2 (C-4'), 86.7 (C-1'), 114.6 (C-5), 118.4 (C-4a), 121.6 (C-
755 quinoline), 125.2 (C-6), 126.3 (C-quinoline), 128.1 (C-quinoline), 128.3 (C-quinoline), 131.4 (C-quinoline),
756 133.7 (C-quinoline), 136.4 (C-quinoline), 147.0 (C-quinoline), 150.3 (C-quinoline), 150.5 (C-7a), 150.6
757 (C-2), 159.4 (C-4). HRMS (ESI): calculated for $C_{21}H_{21}N_4O_4$ ($[M+H]^+$): 393.1557, found: 393.1568.

758 **4.2.36. 4-Methyl-5-(1*H*-indol-7-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (49).** Compound
759 **49** was prepared according to General procedure A. **55** (120 mg, 0.31 mmol) gave rise to 48 (75 mg, 0.20
760 mmol) as a white solid in 64% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.11 (s, 3 H, CH_3), 3.52 - 3.57 (m,
761 1 H, H-5''), 3.62 - 3.67 (m, 1 H, H-5'), 3.94 (q, *J* = 3.5 Hz, 1 H, H-4'), 4.16 (q, *J* = 4.8 Hz, 1 H, H-3'), 4.51
762 (q, *J* = 5.8 Hz, 1 H, H-2'), 5.02 (t, *J* = 5.4 Hz, 1 H, OH-5'), 5.18 (d, *J* = 5.0 Hz, 1 H, OH-3'), 5.35 (d, *J* =
763 6.3 Hz, 1 H, OH-2'), 6.32 (d, *J* = 5.8 Hz, 1 H, H-1'), 6.51 (dd, *J* = 2.9, 1.9 Hz, 1 H, H-indole), 7.06 - 7.11
764 (m, 2 H, 2 H-indole), 7.27 (t, *J* = 2.8 Hz, 1 H, H-indole), 7.60 (dd, *J* = 6.6, 2.3 Hz, 1 H, H-indole), 7.86 (s,
765 1 H), 8.70 (s, 1 H), 10.83 (br. s., 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.1 (CH_3), 61.4 (C-5'),
766 70.5 (C-3'), 74.1 (C-2'), 85.0 (C-4'), 86.9 (C-1'), 101.5 (C-indole), 113.0 (C-5), 117.2 (C-4a), 118.2 (C-
767 indole), 118.9 (C-indole), 119.7 (C-indole), 123.1 (C-indole), 125.1 (C-6), 125.7 (C-indole), 127.8 (C-
768 indole), 135.5 (C-indole), 150.5 (C-7a), 150.7 (C-2), 159.3 (C-4). HRMS (ESI): calculated for $C_{20}H_{21}N_4O_4$
769 ($[M+H]^+$): 381.1557, found: 381.1553.

770 **4.2.37. 4-Methyl-5-(1-methyl-1*H*-indol-7-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (50).**
771 Compound **50** was prepared according to General procedure A. **55** (150 mg, 0.38 mmol) gave rise to 49 (75
772 mg, 0.11 mmol) as a white solid in 30% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.07 (s, 3 H, CH_3), 3.22
773 (d, *J* = 14.3 Hz, 3 H, CH_3), 3.51 - 3.58 (m, 1 H, H-5''), 3.60 - 3.68 (m, 1 H, H-5'), 3.93 - 3.96 (m, 1 H, H-

4'), 4.11 - 4.16 (m, 1 H, H-3'), 4.47 (dq, *J* = 15.7, 5.8 Hz, 1 H, H-2'), 5.03 (dt, *J* = 9.0, 5.4 Hz, 1 H, OH-5'), 5.18 (d, *J* = 4.6 Hz, 1 H, OH-3'), 5.40 (dd, *J* = 6.2, 4.3 Hz, 1 H, OH-2'), 6.30 (t, *J* = 5.6 Hz, 1 H, H-1'), 6.51 (d, *J* = 3.1 Hz, 1 H, H-indole), 7.05 (dtd, *J* = 19.8, 7.3, 7.3, 1.8 Hz, 2 H, 2 H-indole), 7.27 (dd, *J* = 4.4, 3.2 Hz, 1 H, H-indole), 7.61 - 7.63 (m, 1 H, H-indole), 7.88 (d, *J* = 5.8 Hz, 1 H, H-6), 8.70 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.9 (CH_3), 35.3 (CH_3), 61.5 (C-5'), 70.5 (C-3'), 74.1 (C-2'), 85.1 (C-4'), 86.7 (C-1'), 100.6 (C-indole), 113.2 (C-5), 117.6 (C-indole), 118.4 (C-4a), 118.7 (C-indole), 120.5 (C-indole), 125.3 (C-indole), 125.6 (C-6), 129.1 (C-indole), 131.5 (C-indole), 134.8 (C-indole), 149.9 (C-7a), 151.0 (C-2), 159.3 (C-4). HRMS (ESI): calculated for $C_{21}H_{23}N_4O_4$ ($[M+H]^+$): 395.1714, found: 395.1738.

4.2.38. 4-Methyl-5-(dibenzo[*b,d*]furan-4-yl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (51). Compound **51** was prepared according to General procedure A. **55** (150 mg, 0.38 mmol) gave rise to **51** (13 mg, 0.030 mmol) as a white solid in 8% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.22 (s, 3 H, CH_3), 3.53 - 3.61 (m, 1 H, H-5'), 3.62 - 3.70 (m, 1 H, H-5''), 3.97 (d, *J* = 3.4 Hz, 1 H, H-4'), 4.15 (d, *J* = 3.9 Hz, 1 H, H-3'), 4.55 (q, *J* = 5.9 Hz, 1 H, H-2'), 5.05 (t, *J* = 5.3 Hz, 1 H, OH-5'), 5.20 (dd, *J* = 4.7, 2.1 Hz, 1 H, OH-3'), 5.44 (dd, *J* = 6.4, 2.0 Hz, 1 H, OH-2'), 6.33 (d, *J* = 6.1 Hz, 1 H, H-1'), 7.44 (t, *J* = 7.6 Hz, 1 H, H-dibenzofuran), 7.47 - 7.56 (m, 2 H, H-dibenzofuran), 7.59 (dd, *J* = 7.0, 0.8 Hz, 1 H, H-dibenzofuran), 7.67 (d, *J* = 2.8 Hz, 1 H, H-dibenzofuran), 8.05 (s, 1 H, H-6), 8.21- 8.23 (m, 2 H, H-dibenzofuran), 8.75 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.2 (CH_3), 61.5 (C-5'), 70.6 (C-3'), 74.0 (C-2'), 85.3 (C-4'), 86.8 (C-1'), 110.5 (C-5), 111.8 (C-dibenzofuran), 116.8 (C-4a), 119.0 (C-dibenzofuran), 120.6 (C-dibenzofuran), 121.4 (C-dibenzofuran), 123.3 (3 C, C-dibenzofuran), 123.7 (C-dibenzofuran), 125.9 (C-6), 127.8 (C-dibenzofuran), 129.2 (C-dibenzofuran), 150.6 (C-7a), 151.0 (C-2), 153.7 (C-dibenzofuran), 155.4 (C-dibenzofuran), 159.4 (C-4). HRMS (ESI) calculated for $C_{24}H_{22}N_3O_5^+$ ($[M+H^+]$): 432.1554, found: 432.1543.

4.2.39. 4-Methyl-5-((*E*)-2-(pyridin-2-yl)vinyl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (52). The iodo-precursor **55** (150 mg, 0.38 mmol), $Pd(OAc)_2$ (9 mg, 0.038 mmol, 0.1 eq.) and TPPTS (43 mg, 0.076 mmol, 0.2 eq.) were added to a 10 mL round-bottom flask, exchanged with a gas atmosphere with

argon. Next, TEA (106 μL, 0.76 mmol, 2 eq.) and DMF (2 mL, 5 mL/mmol SM) were added in the reaction mixture via syringes. The reaction mixture was stirred at ambient temperature for 5 min, and then stirred at 100 °C. When the completion of the reaction was observed via LC-MS analysis, the reaction was cooled to room temperature. The reaction mixture was evaporated *in vacuo* and purified by column chromatography (0 → 10% MeOH/DCM) to give **52** (55 mg, 0.15 mmol) as a pink solid in 39% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.87 (s, 3 H, CH_3), 3.53 - 3.63 (m, 1 H, H-5''), 3.64 - 3.78 (m, 1 H, H-5'), 3.94 (q, J = 3.8 Hz, 1 H, H-4'), 4.14 - 4.17 (m, 1 H, H-3'), 4.47 (q, J = 6.0 Hz, 1 H, H-2'), 5.11 (t, J = 5.6 Hz, 1 H, OH-5'), 5.19 (d, J = 5.0 Hz, 1 H, OH-3'), 5.41 (d, J = 6.3 Hz, 1 H, OH-2'), 6.24 (d, J = 6.1 Hz, 1 H, H-1'), 7.18 (d, J = 16.0 Hz, 1 H, HC═CH), 7.22 - 7.26 (m, 1 H, H-Pyr), 7.52 (d, J = 7.9 Hz, 1 H, H-Pyr), 7.78 (td, J = 7.7, 1.8 Hz, 1 H, H-Pyr), 7.98 (d, J = 16.0 Hz, 1 H, HC═CH), 8.31 (s, 1 H, H-6), 8.53 - 8.61 (m, 1 H, H-Pyr), 8.67 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.1 (CH_3), 61.5 (C-5'), 70.5 (C-3'), 74.0 (C-2'), 85.2 (C-4'), 86.5 (C-1'), 113.6 (C-5), 115.8 (C-4a), 121.8 (C-Pyr), 122.0 (C-Pyr), 123.5 (C═C), 123.7 (C-6), 127.6 (C═C), 136.8 (C-Pyr), 149.5 (C-Pyr), 150.8 (C-7a), 151.0 (C-2), 155.1 (C-Pyr), 159.4 (C-4). HRMS (ESI): calculated for $C_{19}H_{21}N_4O_4$ ($[M+H]^+$): 369.1557, found: 369.1571.

4.2.40. 4-Methyl-5-(2-(pyridin-2-yl)ethyl)-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (53). Compound **52** (50 mg, 0.14 mmol) was dissolved in MeOH (2 mL). The flask was purged into a N_2 atmosphere. Next, a cat. amount of $Pd(OH)_2$/C was added into the reaction solution. Then, the N_2 gas was exchanged with H_2 gas (balloon; bubbling). The reaction mixture was stirred at ambient temperature until LC-MS analysis showed full conversion of **52**. Then, the balloon was removed and the mixture was filtered over Celite and rinsed by MeOH. The filtrate was evaporated until dryness. The residue was purified by column chromatography (0 → 10% MeOH/DCM) to give **53** (32 mg, 0.086 mmol) as a white solid in 64% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.78 (s, 3 H, CH_3), 3.04 - 3.15 (m, 2 H, CH_2), 3.19 - 3.27 (m, 2 H, CH_2), 3.47 - 3.57 (m, 1 H, H-5''), 3.58 - 3.67 (m, 1 H, H-5'), 3.89 (q, J = 3.6 Hz, 1 H, H-4'), 4.08 (q, J = 4.5 Hz, 1 H, H-3'), 4.35 (q, J = 6.0 Hz, 1 H, H-2'), 5.05 (t, J = 5.4 Hz, 1 H, OH-5'), 5.14 (d, J = 4.9 Hz, 1 H, OH-3'), 5.29 (d, J = 6.4 Hz, 1 H, OH-2'), 6.16 (d, J = 6.1 Hz, 1 H, H-1'), 7.23 (ddd, J = 7.4, 4.9, 1.1 Hz,

1 H, H-Pyr), 7.33 (d, *J* = 7.8 Hz, 1 H, H-Pyr), 7.55 (s, 1 H, H-6), 7.71 (td, *J* = 7.6, 1.9 Hz, 1 H, H-Pyr), 8.48 - 8.55 (m, 1 H, H-Pyr), 8.59 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.3 (CH_3), 26.3 (CH_2), 38.5 (CH_2), 61.7 (C-5'), 70.6 (C-3'), 73.8 (C-2'), 84.9 (C-4'), 86.4 (C-1'), 114.9 (C-5), 116.8 (C-4a), 121.4 (C-Pyr), 122.9 (C-Pyr), 123.3 (C-6), 136.5 (C-Pyr), 149.1 (C-Pyr), 150.5 (C-2), 150.7 (C-7a), 158.9 (C-4), 160.7 (C-Pyr). HRMS (ESI): calculated for $C_{19}H_{23}N_4O_4$ ($[M+H]^+$): 371.1714, found: 371.1731.

4.2.41. 4-Methyl-5-phenylthio-N7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (54[39]). The iodo-precursor **55** (150 mg, 0.38 mmol), thiophenol (42 mg, 0.38 mmol, 1 eq.), CuI (4 mg, 0.019 mmol, 0.05 eq.) and K_2CO_3 (131 mg, 0.95 mmol, 2.5 eq.) were added to a 10 mL round-bottom flask purged with argon. Ethyleneglyol (106 μL, 1.90 mmol, 5 eq.) and iPrOH (2 mL, 5 mL/mmol SM) were added and the reaction mixture was stirred at ambient temperature for 5 min, and then at 130 °C. Upon reaction completion (LC-MS), the reaction mixture was cooled to room temperature and evaporated *in vacuo*. The residue was purified by column chromatography (0 → 10% MeOH/DCM) to give **54** (130 mg, 0.35 mmol) as a white solid in 92% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.61 (s, 3 H, CH_3), 3.55 - 3.60 (m, 1 H, H-5''), 3.65 - 3.703 (m, 1 H, H-5'), 3.96 (q, *J* = 3.4 Hz, 1 H, H-4'), 4.14 (q, *J* = 4.5 Hz, 1 H, H-3'), 4.46 (q, *J* = 5.7 Hz, 1 H, H-2'), 5.11 (t, *J* = 5.3 Hz, 1 H, OH-5'), 5.19 (d, *J* = 4.9 Hz, 1 H, OH-3'), 5.44 (d, *J* = 6.3 Hz, 1 H, OH-2'), 6.25 (d, *J* = 5.9 Hz, 1 H, H-1'), 7.05 - 7. 80 (m, 2 H, H-Ph), 7.13 - 7.17 (m, 1 H, H-Ph), 7.26 - 7.30 (m, 2 H, H-Ph), 8.27 (s, 1 H, H-6), 8.73 (s, 1 H, H-2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.6 (CH_3), 61.3 (C-5'), 70.4 (C-3'), 74.3 (C-2'), 85.3 (C-4'), 86.9 (C-1'), 100.4 (C-5), 117.6 (C-4a), 125.4 (2 C, C-Ph), 125.5 (C-Ph), 129.3 (2 C, C-Ph), 133.9 (C-6), 138.6 (C-Ph), 151.4 (C-7a), 151.6 (C-2), 159.7 (C-4). HRMS (ESI): calculated for $C_{18}H_{20}N_3O_4S$ ($[M+H]^+$): 374.1169, found: 374.1158.

4.3. *In vitro* evaluation

4.3.1. Test Substances and Formulations Test compounds were formulated in 100% dimethyl sulfoxide (DMSO) at 20 mM. The compounds were 4-fold serially diluted to obtain ten concentrations and an in-test concentration starting at 64 μM.

Intracellular amastigote assay of L. infantum (MHOM/MA(BE)/67/ITMAP263, WT strain): amastigotes (spleen-derived from an infected donor hamster) were maintained on primary peritoneal mouse macrophages (Mϕ, from Swiss mice) in RPMI-1640 medium, supplemented with 200 mM L-glutamine, 16.5 mM $NaHCO_3$ and 5% inactivated fetal calf serum. All cultures and assays were conducted at 37 °C and 5% CO_2 atmosphere. Assays were performed with 190 μL of Mϕ/parasite inoculum (3×10^4 cells + 4.5 $\times 10^5$ parasites/well). The Mϕ were infected for 48 h, and 10 μL of compound dilutions were added after 2 h of infection. Parasite growth was compared to untreated-infected controls (set as 100% growth) and uninfected controls (set as 0% growth). The incubation lasted for 5 days, and parasite burdens (mean number of amastigotes/Mϕ) were microscopically measured after staining with a 10% Giemsa solution. The results were given as percentage (%) reduction in growth compared to controls and was used to calculate the IC_{50} value. MIL was included as the positive drug control.

4.3.2 Cytotoxicity towards Mϕ was microscopically defined as the lowest concentration causing cell detachment, lysis and granulation. This was done by semi-quantitative scoring of at least 500 cells distributed over adjacent microscopic areas. The results were given as the percentage (%) reduction in cell viability compared to untreated controls. The percentage was used to calculate CC_{50} value.

4.3.3 Drug-resistant strains of *L. infantum* Compounds were assayed on promastigotes of *L. infantum* MHOM/FR/96/LEM3323-Cl4 (Sb-resistant) and derived isogenic strains with additional resistance against MIL (LEM3323-Cl4 MIL5Cl3) or PMM (LEM3323-Cl4 PMM). Promastigotes were cultured at room temperature in HOMEM promastigote medium (Gibco®, Life technologies) supplemented with 10% FCS. Mϕ were infected by metacyclic promastigotes at 2:1 multiplicity of infection (MOI). Infected Mϕ were incubated at 37 °C and 5% CO_2 atmosphere. After 24 h incubation, 10 μL of compound dilutions were added. After 96 h incubation, parasite burdens (mean number of amastigotes/Mϕ) were assessed

871 microscopically. The results were given as the percentage of reduction in parasite growth compared to
872 controls and used to calculate the EC_{50} values.

873 **4.3.4 Intracellular amastigote assay of *T. cruzi* (Tulahuen CL2 β-galactosidase reporter strain)**
874 Compounds were evaluated *in vitro* as described in previous report, as was the *in vitro* cytotoxicity assay
875 against MRC-5 fibroblasts.[40]

876 *In vitro microsomal stability assay*. Liver microsomes of mouse, hamster and human (pooled) were supplied
877 commercially from Corning® and stored at -80 °C. NADPH generating system solutions A and B, and
878 UGT reaction mix solutions A and B stored at -20 °C. Testing compounds and reference diclofenac were
879 formulated in 100% DMSO at 10 mM. The *in vitro* microsomal stability assays were performed exactly as
880 described previously.[40] The results were given as the percentage of remaining parent compound. The
881 percentages from two independent assays were used to calculate mean and STDEV.

882 **4.4. *In vivo* evaluation**

883 **4.4.1. Test substances and formulations 32** was formulated in 10% (v/v) PEG 400 and 1% Tween 80 (v/v)
884 in water at 25 mg/mL envisaging a dosing volume of 200 µL/100 g. The formulation at 25 mg/mL resulted
885 in a thick fine white suspension. MIL was formulated at 20 mg/mL in water.

886 **4.4.2. Efficacy in the early curative hamster model** Female golden hamsters (BW 75-85 g) were
887 purchased from Janvier-France and kept in quarantine for at least 5 days before starting the experiment.
888 Food for laboratory rodents and drinking water were available *ad libitum*. The animals were randomly
889 allocated to experimental units of 5 animals based on live body weight at the start of the experiment (Day
890 0 = day of infection). *L. infantum* (MHOM/MA(BE)/67) amastigotes were obtained from the spleens of
891 heavily infected donor hamsters were purified using two centrifugation steps and diluted to prepare an
892 infection inoculum containing 2×10^7 amastigotes/100 µL phosphate buffered saline (PBS). The infection

inoculum was administered intracardially (IC). Animals were treated orally s.i.d. for 10 days. Dosing started at 21 dpi.

- **G1**: Vehicle-treated infected control (VIC): 10% PEG 400 and 1% Tween 80 in water s.i.d. PO for 10 days (200 µL) [*n* = 5]
- **G2**: MIL: 40 mg/kg s.i.d. PO for 5 days (200 µL) [*n* = 5]
- **G3: 32**: 50 mg/kg s.i.d. PO for 10 days (200 µL/100g) [*n* = 5]

Amastigote burdens in the different target organs (liver, spleen, bone-marrow) were determined 9 days after the last treatment (*i.e.* day 39 of the experiment). The organs of individual animals were weighed (except bone-marrow); impression smears were stained with Giemsa for microscopic evaluation of the total amastigote burden (= mean number of amastigotes per cell × number of cells counted (minimum 500 nuclei). Percentage reduction compared to the burdens in the vehicle-treated infected control animals (VIC) is used as a measure for drug activity. Possible 'viable' residual burdens were assessed using the promastigote back-transformation assay (incubation of small pieces of tissue in promastigote medium at room temperature with qualitative assessment of the presence of promastigotes after 2 weeks of incubation).

4.4.3. *In vivo* toxicity The animals were observed daily for the occurrence of clinical or adverse effects. All animals were weighed twice weekly to monitor the general health status.

4.4.4. Pharmacokinetics For **G3** and **G4**, a series of blood samples were collected from the sublingual vein on the first and the last day of treatment. To reduce the number of samplings per individual animal and the associated the stress involved in the repeated blood sampling, subgroups of 3 and 2 animals were sampled on alternate time points. Samples were collected at 0.5, 1, 2, 4 and 8 h (before second dose) and at 24 h (before the morning dose of day 2 = 16 h post last treatment dose). On day 9, samples were taken pre-dose (0) and at 0.5, 1, 2, 4 and 8 h, and 24 h (16 h post last treatment dose). All samples were collected as DBS for analytical detection of parent compound using LC-MS/MS.

Bio-analysis used LC-MS/MS (UPLC) (Waters Aquity^{TM}) coupled with tandem quadrupole mass spectrometry (MS^2) (Waters Xevo^{TM}), equipped with an electrospray ionization (ESI) interface and

operated in multiple reaction monitoring (MRM) mode. The optimal MS parameters and control of the chromatographic separation conditions had been tuned before (**Table 1 in Supplementary material**). For calibration and validation, standard curves in blood were made and spotted onto DBS cards. The standard PK parameters were determined using appropriate software (TopFit): C_{max}, T_{max}, AUC_{0-24h}, Cl and Vd. The calculated parameters are based upon the mean values per time point using non-compartmental analysis. The areas under the curve (AUC_{0-8h} and AUC_{0-24h}) were calculated using the linear trapezoidal rule.

Ethics statement

The use of mice for the isolation of peritoneal macrophages and hamsters for splenic *Leishmania infantum* amastigotes was approved by the ethical committee of the University of Antwerp [UA-ECD 2019-10]. The use of laboratory rodents was carried out in strict accordance to all mandatory guidelines (EU directives, including the Revised Directive 2010/63/EU on the Protection of Animals used for Scientific Purposes that came into force on 01/01/2013, and the declaration of Helsinki in its latest version).

Supplementary material

Copies of ^{1}H and ^{13}C NMR spectra of synthesized compounds and UPLC-MS/MS conditions for the determination **32** and microphotographs of Giemsa-stained tissue imprints of various organs (liver, spleen and bone marrow) of vehicle-, MIL - and **32**-treated animals and mean concentration (ng/mL) of **32** in blood after a single dose (Day 1: 50 mg/kg) and after repeated-dose administration (Day 9: 50 mg/kg b.i.d. for 10 days) in infected hamsters.

Conflicts of interest

The authors declare no conflict of interest.

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