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Synthesis and antiviral activity of 4,6-disubstituted pyrimido[4,5-*b*]indole ribonucleosides

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ABSTRACT

A series of new pyrimido[4,5-*b*]indole ribonucleosides bearing phenyl or hetaryl group at position 4 has been prepared by selective Pd-catalyzed cross-coupling reactions of the corresponding protected 4,6-dichloropyrimido[4,5-*b*]indole ribonucleoside with (het)arylboronic acids or stannanes followed by deprotection. Further cross-couplings under harsher conditions and employing X-Phos ligand proceeded at the position 6 leading to 4,6-disubstituted pyrimido[4,5-*b*]indole ribonucleosides. Some of these compounds displayed antiviral activity against Dengue virus.

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1. Introduction

Within the framework of our long-term programme on medicinal chemistry of base-modified nucleosides, we have recently discovered two novel classes of interesting biologically active 7-deazapurine ribonucleosides with broad spectrum of activities. 6-Hetaryl-7-deazapurine ribonucleosides **1** bearing either H or F at the position 7 and five-membered hetaryl groups (furyl, thienyl etc.) at the position 6 (Fig. 1) were found[1] to exert nanomolar in vitro cytostatic activities against a broad panel of cancer or leukemia cell lines. The second class, 7-hetaryl-7-deazaadenosines **2**, showed[2] similarly potent cytostatic effects. Both of them also possessed high but non-specific antiviral activities against HCV. Selected examples from each of these two classes of compounds now undergo in vivo testing as potential antitumor agents. On the other hand, sugar-modified derivatives[3] and phosphate prodrugs[4] derived from **1** were inactive or less active than the parent compounds. Encouraged by the fact that there is some space for substitution at the position 7, we have designed benzo-fused analogues of 7-deazapurines, that is pyrimido[4,5-*b*]indole ribonucleosides, as promising target for further investigation with the aim of complementing the SAR and possible modulating of selectivity of the cytostatic or antiviral activities (especially against RNA viruses).

Some pyrimido[4,5-*b*]indole heterocycles were reported as potent tyrosine kinase inhibitors, some of these compounds showed nanomolar activity.[5] These heterocycles can be prepared by Pd-catalyzed intramolecular arylation,[6] photolysis of tetrazoles[7] or, most frequently, by condensation of substituted 2-amino-indole-3-carboxylates with formamide or orthoformate.[8] Some pyrimido[4,5-*b*]indole nucleosides were also frequently utilized in nucleic acids chemistry. The corresponding 4-amino-6-methoxypyrimido[4,5-*b*]indole 2′-deoxyribonucleoside was reported[9] by Saito and used

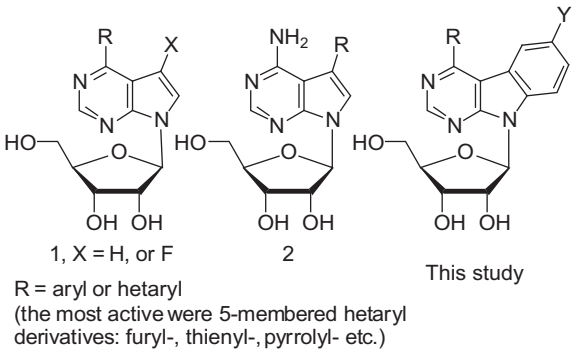

Figure 1. Structures of recently discovered 7-deazapurine ribonucleoside nanomolar cytostatics **1** and **2** and the target compounds for this study.

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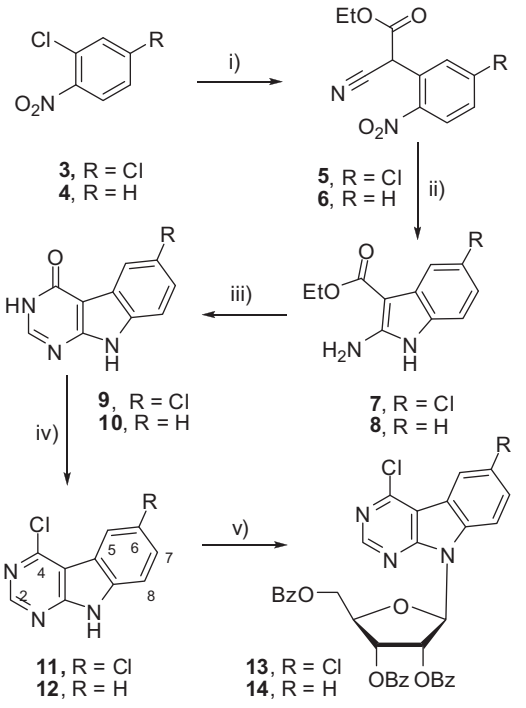
as fluorescent label for single-nucleotide polymorphism typing. This and other related derivatives were also used for the study of hole transport through DNA[10] and for the construction of DNA logic gates.[11] Apart from chemical synthesis of modified oligonucleotides containing the pyrimido[4,5-*b*]indole bases by phosphoramidite method, the corresponding 2′-deoxynucleoside triphosphate was successfully incorporated by DNA polymerase in PCR experiment[12] confirming the potential of these extended purine surrogates to be recognized as substrates by enzymes. However, to the best of our knowledge, neither synthesis nor biological activity of any pyrimido[4,5-*b*]indole ribonucleoside derivatives was reported.

2. Results and discussion

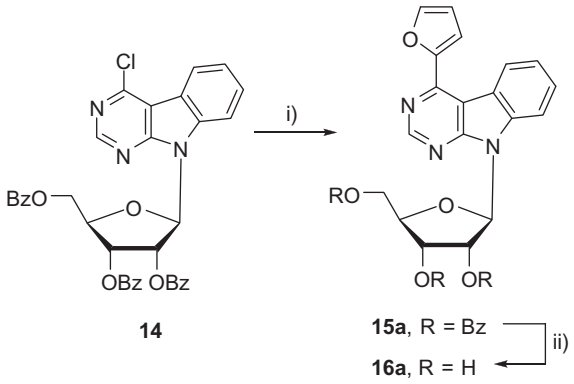
2.1. Chemistry

The proposed synthetic approach to our target 4-(het)aryl-substituted and 4,6-disubstituted pyrimidoindole nucleosides was based on palladium catalyzed cross-coupling reactions of suitably protected 4-chloro- and 4,6-dichloro-9*H*-pyrimido[4,5-*b*]indole ribonucleosides. In order to access these key intermediates, the synthesis of the corresponding pyrimido[4,5-*b*]indole heterocycles is needed followed by glycosylation.

The construction of the heterocyclic nucleobases (the same sequence was applied in parallel for 4-chloro- and 4,6-dichloro-9*H*-pyrimido[4,5-*b*]indole) started with the synthesis of ethyl-2-(2-nitrophenyl)cyanoacetates **5** and **6** from chloronitrobenzenes **3** and **4** and cyanoacetate according to literature procedure[13] (Scheme 1). In next step, indole derivatives **7** and **8** were prepared by reduction of **5** and **6** with zinc dust in acetic acid and followed by spontaneous cyclization. This reaction was exothermic and, even without external heating, the reaction temperature reached 55 °C. The subsequent cyclocondensation of **7** and **8** with formamide afforded 6-chloro-3*H*-pyrimido[4,5-*b*]indol-4(9*H*)-one (**9**) and



Scheme 1. Reagents and conditions: (i) $CNCH_2COOEt$, t-BuOK, THF, reflux, 48 h; (ii) Zn, AcOH, 55 °C, 150 min; (iii) formamide, 190 °C, 12 h; (iv) $POCl_3$, reflux, 4 h; (v) 1-*O*-acetyl-2,3,4-tri-*O*-benzoyl-β-D-ribofuranose, BSA, TMSOTf, 70 °C, 8 h.



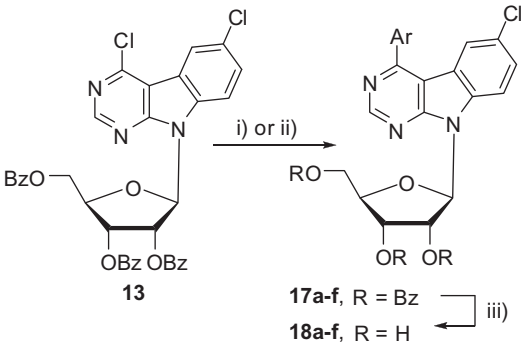
Scheme 2. Reagents and conditions: (i) (furan-2-yl)$SnBu_3$ (1.2 equiv): $PdCl_2(PPh_3)_2$ (0.05 equiv), DMF, 100 °C, 8 h; (ii) 1 M MeONa in MeOH (0.3 equiv), MeOH, rt., 24 h.

3*H*-pyrimido[4,5-*b*]indol-4(9*H*)-one (**10**). These fused pyrimidone derivatives were converted to chloropyrimidine derivatives **11** and **12** by treatment with $POCl_3$ under reflux. After one pot silylation by *N*-*O*-bis(trimethylsilyl)acetamide (BSA) and reaction with 1-*O*-acetyl-2,3,4-tri-*O*-benzoyl-β-D-ribofuranose in analogy to literature conditions published for glycosylation of deazapurines,[14] the desired protected nucleoside intermediates **13** and **14** were obtained in five steps in excellent overall yields of 28% and 30%, 'respectively' (Scheme 1).

The reactivity of the fused chloropyrimidine system towards Pd-catalyzed Stille cross-coupling reactions was first tested on the reaction of 4-chloro-9*H*-pyrimido[4,5-*b*]indole ribonucleoside **14** with 2-furyl(tributyl)stannane (Scheme 2). This reaction was performed under standard conditions[1] in presence of $PdCl_2(PPh_3)_2$ in DMF at 100 °C to give the desired 4-(2-furyl)pyrimido[4,5-*b*]indole ribonucleoside **15a** in excellent 82% yield. Its deprotection under the Zemplen conditions using NaOMe in methanol afforded the target free ribonucleoside **16a**.

As we were even more interested in derivatives bearing an additional substituent at the position 6, we have studied the regioselectivity of the Suzuki–Miyaura cross-coupling of the 4,6-dichloro nucleoside **13** with (hetero)aryl boronic acids and Stille cross-coupling reactions with heteroarylstannanes (Scheme 3). We assumed that the chlorine at position 4 should be much more reactive due to electron-poor nature of the pyrimidine part, whereas the chlorine at the electron-rich benzene portion (position 6) should be much less reactive. Both types of cross-coupling reactions were performed under standard conditions ($PdCl_2(PPh_3)_2$ in DMF for the Stille coupling and $Pd(PPh_3)_4$ and K_2CO_3 in toluene for the Suzuki coupling.[1] In all cases, the reactions proceeded smoothly and fully regioselectively to give 4-(het)aryl substituted 6-chloropyrimido[4,5-*b*]indole ribonucleosides **17a–f** in good yields (64–82%) (Table 1, Scheme 3). The follow up deprotection was again performed by treatment with sodium methoxide in methanol to give the series of target free nucleosides **18a–f** in good yields (78–93%) (Table 1).

In order to attach another substituent at the position 6, the second cross-coupling can be performed either on protected nucleosides **17** or unprotected nucleosides **18**. In recent years, a lot of successful Suzuki cross-couplings of unprotected nucleosides have been reported,[1,2,15] in particular in aqueous mixtures. Therefore, we first tested the Suzuki cross-coupling of 4-phenyl-6-chloro-substituted free nucleoside **18f** with phenylboronic acid (Scheme 4) in different solvents (DMF or aqueous mixtures) using different catalytic systems (including water-soluble ligands TPPTS and CataXCium F). The results summarized in Table 2 show that the use of aqueous solvent mixtures and TTPTS ligand gives no reaction while the use of CataXCium F resulted in ca. 60% conversion to a



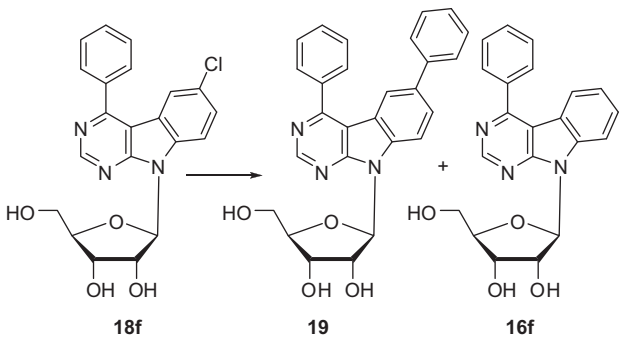
Scheme 3. Reagents and conditions: (i) ArM, M = $B(OH)_2$ (1.5 equiv): $Pd(PPh_3)_4$ (0.05 equiv), K_2CO_3 (2 equiv), toluene, 100 °C, 8 h; (ii) M = $SnBu_3$ (1.2 equiv): $PdCl_2(PPh_3)_2$ (0.05 equiv), DMF, 100 °C, 8 h; (iii) 1 M MeONa in MeOH (0.3 equiv), MeOH, rt., 24 h.

Table 1
Cross-coupling reactions of **13** followed by deprotection

Entry	Ar	–M	Coupling product	Yield (%)	Deprotectproduct	Yield (%)
1	2-Furyl	$SnBu_3$	**17a**	79	**18a**	86
2	3-furyl	$B(OH)_2$	**17b**	69	**18b**	91
3	2-thienyl	$SnBu_3$	**17c**	78	**18c**	93
4	3-thienyl	$B(OH)_2$	**17d**	70	**18d**	86
5	2-benzofuryl	$B(OH)_2$	**17e**	64	**18e**	78
6	phenyl	$B(OH)_2$	**17f**	72	**18f**	89

mixture of the desired cross-coupling product **19** with the product of dehalogenation **16f**. Somewhat better results were obtained using Buchwald ligands (S-Phos, Dave-Phos and X-Phos) in DMF where moderate-to-good conversions (20–60%) were achieved. However, due to moderate conversions and problematic separation of the product **19** from unreacted starting compound, this approach was not suitable for the synthesis of any larger series of 4,6-disubstituted derivatives.

Therefore, we further focused on the cross-coupling reactions of protected 6-chloro-derivatives of nucleoside **17a** under more classical conditions in organic solvents. Three Buchwald ligands were tested for cross-coupling reaction of **17a** with phenylboronic acid in DMF. While the conversions of the reactions using DavePhos or S-Phos ligands were still moderate (20–40%), nearly quantitative conversion was observed with X-Phos in 3 h. With these optimized conditions in hand, the synthesis of two examples of 4,6-disubstituted protected nucleosides **20b**,**f** was performed (Scheme 5). In both cases, the starting material disappeared within 3–4 h, but

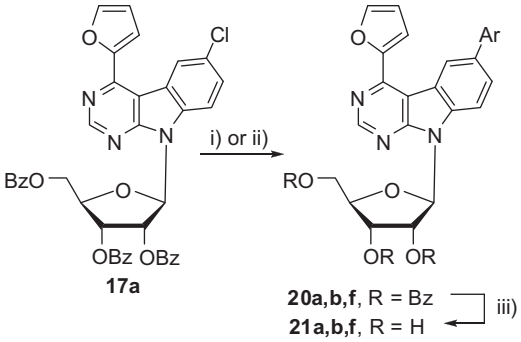


Scheme 4. Reagents and conditions: $Pd(OAc)_2$ (0.05 equiv) ligand (0.1 equiv), K_2CO_3 (3 equiv), $PhB(OH)_2$ (1.5 equiv), solvent, 95 °C, 12 h.

Table 2
Optimization of cross-coupling reaction of free nucleoside **18f** with phenylboronic acid

Entry	Ligand	Solvent	Conversion[a]
1	CataXCium F	*n*-BuOH/H_2O, 2.5:1	60[b]
2	TPPTS	MeCN/H_2O, 2:1	0
3	S-Phos	DMF	30
4	DavePhos	DMF	20
5	X-Phos	MeCN/H_2O, 2:1	35
6	X-Phos	DMF	60

[a] Determined by NMR from crude reaction mixture.
[b] Reaction mixture contained a mixture of compounds **19** and **16f** in ratio 0.7:1.



Scheme 5. Reagents and conditions: i) RM, M = $B(OH)_2$ (1.5 equiv): $Pd(OAc)_2$ (0.05 equiv), X-Phos (0.1 equiv), K_2CO_3 (3 equiv), DMF, 95 °C 3 h;(ii) M = $SnBu_3$ (1.2 equiv): $Pd(OAc)_2$ (0.05 equiv), X-Phos (0.1 equiv), DMF, 95 °C, 3 h; (iii) 1 M MeONa in MeOH (0.3 equiv), MeOH, rt., 24 h.

Table 3
Synthesis of 4,6-disubstituted nucleosides

Entry	Ar	–M	Coupling product	Yield (%)	Deprotect product	Yield (%)
1	3-Furyl	$B(OH)_2$	**20b**	46	**21b**	90
2[a]	3-Furyl	$B(OH)_2$	**20b**	75		
3	Phenyl	$B(OH)_2$	**20f**	62	**21f**	81
4[a]	Phenyl	$B(OH)_2$	**20f**	64		
5	2-furyl	$SnBu_3$	**20a**	79	**21a**	89

[a] Boronic acid was added in three parts within 2 h.

the isolated yields were only moderate to good (46% and 62%, respectively). It is known, that furylboronic acid is rather unstable and its decomposition could cause the lower yield. Therefore, this reaction was repeated with addition of the furylboronic acids in three portions (at the beginning and after 1 and 2 h) to give the desired nucleoside **20b** in much better yield of 75% (Table 3, entry 2). On the other hand, the portions-wise addition of phenylboronic acid did not improve the yield significantly (Table 3, entries 3, 4). The same catalyst/ligand system was applied for the Stille cross-coupling of protected nucleoside **17a** with 2-furyl(tributyl)stannane to get the desired compound **21a** in good 79% yield (Table 3, entry 1). Final deprotection with sodium methoxide in methanol furnished free 4,6-disubstituted nucleosides **21a**,**b**,**f** in 81–90% yields (Table 3).

We have also attempted Pd-catalyzed Buchwald–Hartwig aminations at position 6 of nucleoside **17a**. Different sets of the conditions and catalytic systems were taken from relevant literature examples[16] of aminations of non-activated chloroarenes. $Pd_2(dba)_3$ and $Pd(OAc)_2$ were used in combination with Buchwald ligands (DavePhos, *t*-BuXPhos, BrettPhos, X-Phos, S-Phos, RuPhos) and different bases (K_3PO_4, Cs_2CO_3, LiHMDS, NaOt-Bu) in different solvents (THF, toluene, DME) using primary or secondary amines

Table 4
UV–vis and fluorescence spectral data

Compd	Absorption[a]				Emission[b]	
	λ_{max} (nm)	ε ($L \cdot mol^{-1}\ cm^{-1}$)	λ_{max} (nm)	ε ($L \cdot mol^{-1}\ cm^{-1}$)	λ_{max} (nm)	φ
18a	264	18,391	326	14,702	449	0.05
18b	264	20,110	303	11,090	427	0.03
18c	265	16,526	323	10,675	452	0.04
18d	257	15,295	303	7940	435	0.04
18e	272	19,799	342	22,087	467	0.08
18f	250	18,140	299	8751	442	0.05
16a	264	23,284	326	18,106	447	0.13
21a	250	29,235	326	25,098	435	0.02
21b	249	25,048	325	17,721	454	0.03
21f	254	39,270	286	24,148	485	0.08

[a] UV spectra were measured in methanol at 25 °C. All 5 × 10−5 μM solutions
[b] emission spectra were measured by excitation at 320 nm.

(Me_2NH, cyclohexylamine, piperidine). No reaction was observed in any case after 48 h of heating at 120 °C. This shows that the reactivity of the chlorine at the position 6 of pyrimido[4,5-*b*]indole is extremely low.

Inspired by the Saito's applications of the related nucleosides as fluorescent probes, we studied electronic spectra and photophysical properties of the title nucleosides (Table 4). All of them exerted fluorescence with emission maxima at 427–485 nm with moderate quantum yields (up to 0.13).

2.2. Biological activity profiling

All the title compounds **16**, **18** and **21** were tested for in vitro antiproliferative (human T-lymphoblastic leukemia line CCRF–CEM, promyelocyticleukemia HL-60 and cervical carcinoma HeLa S3) and antiviral activity (HCV and Dengue virus). None of them showed any significant cytostatic/cytotoxic effect or anti-HCV activity, except for compound **18a** which showed cytotoxicity in THP-1 and HepG2 cells with CC_{50} of 1.565 and 0.175 μM. However, three examples of 4-hetaryl-6-chloropyrimido[4,5-*b*]indole nucleosides **18a**, **18c** and **18e** (bearing 2-furyl, 2-thienyl or 2-benzofuryl groups at position 4) showed significant (submicromolar) effects against Dengue virus (Table 5). The level of activity is not sufficient for further development of these compounds as antivirals against Dengue, but this case clearly shows that further structural modifications of the parent 7-deazapurine moiety in the biologically active ribonucleosides can lead to more selective compounds with anti-RNA virus activities and decreased cytotoxicities.

2.3. Conclusions

In conclusion, we have developed the synthesis of 4-chloro- and 4,6-dichloro-9*H*-pyrimido[4,5-*b*]indole heterocycles and their ribosylation to protected nucleoside intermediates. The Suzuki or Stille couplings proceed with full regioselectivity at the position 4. Further arylation at position 6 is possible only under modified conditions using Buchwald ligands. Title 4-(het)aryl-6-chloropyrimido[4,5-*b*]indole ribonucleosides **18** and 4,6-disubstituted derivatives **21** were prepared and tested for biological activity. Three members of the series of compounds **18** showed interesting anti-dengue virus activities.

Table 5
Anti-dengue virus activities of title nucleosides

Comp.	Dengue replicon	Cytotoxicity	
	Huh7 IC_{50} (μM)	THP-1 IC_{50} (μM)	HepG-2 CC_{50} (μM)
18a	0.238 ± 0.066	1.565 ± 0.219	0.175 ± 0.021
18b	24.44 ± 17.9	>50	>50
18c	0.335 ± 0.12	45.89 ± 5.54	19.92 ± 0.26
18d	86.95 ± 12.03	>50	>50
18e	0.976 ± 0.166	>50	>50
18f	26.42 ± 3.05	>50	>50
16a	82.73 ± 2.44	>50	>50
21a	17.95 ± 1.11	>50	7.44 ± 4.35
21b	32.06 ± 1.58	44.95 ± 7.11	33.11 ± 1.18
21f	2.91 ± 0.52	41.32 ± 12.28	20.68 ± 0.28

3. Experimental part

NMR spectra were recorded using a 400 MHz (^1H at 400 MHz, ^{13}C at 100.6 MHz), 500 MHz (500 MHz for ^1H and 125.7 MHz for ^{13}C), or 600 MHz (600 MHz for ^1H and 151 MHz for ^{13}C) spectrometer. Melting points were determined using a Kofler block and are uncorrected. High resolution mass spectra were measured using electrospray ionization. Optical rotations were measured at 25 °C, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. UV–vis and fluorescence spectroscopy was measurements and quantum yields determinations were performed in the same way as in a previous paper.[17] The purity of final compounds (>95%) was confirmed by elemental analyses and clean NMR spectra.

3.1. Ethyl 2-(5-chloro-2-nitrophenyl)-2-cyanoacetate (5)

Compound **5** was prepared from 2,4-dichloronitrobenzene (**3**) (6 g, 31.3 mmol) and ethyl cyanoacetate (6.66 ml, 2 equiv, 62.6 mmol) according to literature conditions.[13] Compound **5** was obtained as a dark oil. The oil was purified by column chromatography (hexane/EtOAc 0–10% EtOAc). ^1H NMR is in agreement with literature.[18] The crude material was used directly for the next step.

3.2. Ethyl 2-(2-nitrophenyl)-2-cyanoacetate (6)

Compound **6** was prepared from 2-chloronitrobenzene (**4**) (20 g, 127 mmol) and ethyl cyanoacetate (27.1 ml, 2 equiv 254 mmol) according to literature conditions.[13] Compound **6** was obtained as dark oil. The oil was purified by column chromatography (hexane/EtOAc 0–10% EtOAc). ^1H NMR is in agreement with literature.[19] The crude material was used directly for the next step.

3.3. Ethyl 2-amino-5-chloro-1*H*-indole-3-carboxylate (7)

Compound **7** was prepared according to modified literature conditions.[13] Crude **5** (60 g, 221 mmol) was dissolved in glacial acetic acid (600 ml) and zinc dust (40 g) was added after parts during 45 min. The mixture was stirred for 2 h without external heating (reaction is exothermic, temperature in the flask reached 55 °C during reaction) and filtered through a pad of cellite. The pad was washed with acetic acid (400 ml) and solution was evaporated. The residue was then washed well with water and dried under reduced pressure. Compound **7** (46.1 g, 88%) was obtained as brown powder and further purified by column chromatography (hexane/chloroform, 0–60% chloroform); mp: 190–193 °C. ^1H NMR is in agreement with literature.[20] Crude material was used directly for the next step.

3.4. Ethyl 2-amino-1*H*-indole-3-carboxylate (8)

Compound **8** was prepared as described for **7** from crude **6** (44.2 g), product **8** (33.1 g, 86%) was obtained as brown powder. ^1H NMR is in agreement with literature.[20] Crude material was used directly for the next step.

3.5. 6-Chloro-3*H*-pyrimido[4,5-*b*]indol-4(9*H*)-one (9)

Indole derivative **7** (30 g, 126 mmol) was dissolved in formamide (100 ml, 2.5 mol) and after heating to 190 °C for 18 h reaction mixture was cooled down, filtered, washed well with water and dried under reduced pressure. Compound **9** (23.6 g, 85%) was obtained as dark powder. The crude compound was purified by column chromatography (chloroform/MeOH, 3% MeOH); mp: 188–193 °C. IR (ATR): ν = 2924, 1661, 1588, 1447, 1359, 1250, 794 cm^{-1}. ^1H NMR (600.1 MHz, DMSO-d_6): 7.34 (ddd, 1H, $J_{7,8}$ = 8.6, $J_{7,5}$ = 2.2, $J_{7,NH}$ = 0.4, H-7); 7.49 (ddd, 1H, $J_{8,7}$ = 8.6, $J_{8,5}$ = 0.6, $J_{8,NH}$ = 0.4, H-8); 7.91 (ddt, 1H, $J_{5,7}$ = 2.2, $J_{5,8}$ = 0.6, $J_{5,NH}$ = 0.4, H-5); 8.16 (bd, 1H, $J_{2,NH}$ = 3.5, H-2), 12.31 (br s, 1H, NH-3); 12.36 (br s, 1H, NH-9). ^{13}C NMR (150.9 MHz, DMSO-d_6): 99.9 (C-4a); 113.5 (CH-8); 119.7 (CH-5); 123.4 (C-4b); 124.2 (CH-7); 125.6 (C-6); 134.1 (C-8a); 148.4 (CH-2); 154.6 (C-9a); 158.3 (C-4). ESI MS *m*/*z* (rel.%): 242 (100) [M+Na], 244 (33) [M+2+Na]. HR MS (ESI) for $C_{10}H_6ClN_3ONa$ [M+Na]: calcd 242.00916; found 242.00915.

3.6. 3*H*-Pyrimido[4,5-*b*]indol-4(9*H*)-one (10)

Compound **10** was prepared as described for **9** from crude **8** (20.0 g, 108 mmol) to give 15.8 g, (87%) of **10** as dark powder. The crude compound was directly used in the next step. For analysis, the crude compound was further purified by column chromatography (chloroform/MeOH, 3% MeOH); mp: >300 °C. IR (ATR): ν = 3031, 2359, 2342, 1640, 1587, 1541, 1377, 1248, 750 cm^{-1}. ^1H NMR (500.0 MHz, DMSO-d_6): 7.23 (ddd, 1H, $J_{6,5}$ = 7.9, $J_{6,7}$ = 7.2, $J_{6,8}$ = 1.0, H-6); 7.32 (ddd, 1H, $J_{7,8}$ = 8.2, $J_{7,6}$ = 7.2, $J_{7,5}$ = 1.2, H-7); 7.48 (ddd, 1H, $J_{8,7}$ = 8.2, $J_{8,6}$ = 1.0, $J_{8,5}$ = 0.8, H-8); 7.99 (ddt, 1H, $J_{5,6}$ = 7.9, $J_{5,7}$ = 1.2, $J_{5,8}$ = $J_{5,NH}$ = 0.8, H-5); 8.12 (s, 1H, H-2), 12.17, 12.20 (2 × br s, 2 × 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 100.4 (C-4a); 111.9 (CH-8); 120.9 (CH-5); 121.4 (CH-6); 122.3 (C-4b); 124.4 (CH-7); 135.7 (C-8a); 147.7 (CH-2); 153.9 (C-9a); 158.6 (C-4). ESI MS *m*/*z* (rel.%): 186 (12) [M+H], 208 (100) [M+Na]. HR MS (ESI) for $C_{10}H_7N_3ONa$ [M+Na]: calcd 208.04813; found 208.04815.

3.7. 4,6-Dichloro-9*H*-pyrimido[4,5-*b*]indole (11)

Compound **9** (24.0 g, 0.11 mol) was dissolved in $POCl_3$ (330 ml) and heated to 120 °C for 2 days. Solvent was evaporated under reduced pressure, residue was diluted with water and slowly neutralized with aqueous ammonia to pH 7. Crude product was filtered, washed well with cold water, then with hydrochloric acid and again with cold water. After drying under reduced pressure desired product **11** (21.5 g, 83%) was obtained as dark powder. The crude compound was purified by column chromatography (chloroform/MeOH, 3% MeOH), recrystallization (propan-2-ol) furnished **11** as white crystals; mp: 258 °C (sublimation). IR (ATR): ν = 2953, 2362, 2342, 1604, 1560, 1436, 1269, 1230, 1195 cm^{-1}. ^1H NMR (499.8 MHz, DMSO-d_6): 7.65 (d, 2H, $J_{7,5\&8,5}$ = 1.4, H-7,8); 8.21 (td, 1H, $J_{5,7}$ = $J_{5,8}$ = 1.4, $J_{5,NH}$ = 0.6, H-5); 8.81 (s, 1H, H-2), 12.94 (br s, 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 110.6 (C-4a); 114.2 (CH-8); 119.1 (C-4b); 121.7 (CH-5); 126.1 (C-6); 128.5 (CH-7); 137.2 (C-8a); 152.0 (C-4); 154.8 (CH-2); 156.5 (C-9a). ESI MS *m*/*z* (rel.%): 238 (100) [M+H], 240 (66) [M+2+H], 242 (16) [M+4+H]. HR MS (ESI) for $C_{10}H_5Cl_2N_3$ [M+H]: calcd 236.9861; found 236.9860.

3.8. 4-Chloro-9*H*-pyrimido[4,5-*b*]indole (12)

Compound **12** was prepared as described for **11** from crude **10** (10.0 g, 54.0 mmol) to give 9.9 g (90%) of brown crystals; mp 188–190 °C, IR (ATR): ν = 2361, 2340, 1719, 1558, 1265, 1225, 704 cm^{-1}. ^1H NMR (500.0 MHz, DMSO-d_6): 7.43 (ddd, 1H, $J_{6,5}$ = 8.0, $J_{6,7}$ = 6.0, $J_{6,8}$ = 2.2, H-6); 7.64 (m, 2H, H-7,8); 8.29 (bd, 1H, $J_{5,6}$ = 8.0, H-5); 8.78 (s, 1H, H-2), 12.79 (br s, 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 111.3 (C-4a); 112.5 (CH-8); 117.9 (C-4b); 121.9 (CH-6); 122.6 (CH-5); 128.6 (CH-7); 138.7 (C-8a); 151.4 (C-4); 154.1 (CH-2); 156.1 (C-9a). ESI MS *m*/*z* (rel.%): 204 (100) [M+H], 206 (33) [M+2+H]. HR MS (ESI) for $C_{10}H_6ClN_3$ [M+H]: calcd 204.03230; found 204.03229.

3.9. 4,6-Dichloro-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyrimido[4,5-*b*]indole (13)

Pyrimidoindole **11** (200 mg, 0.84 mmol) was suspended in acetonitrile (5 ml) and BSA (206 µl, 0.84 mmol) was added. Reaction mixture was stirred for 10 min at rt., TMSOTf (308 µl, 1.68 mmol) and protected ribofuranose (430 mg, 0.84 mmol) were added. Mixture was heated to 60 °C for 8 h. After cooling to rt, the mixture was extracted with EtOAc and water, organic layer was washed with $NaHCO_3$ and again with water, dried over $MgSO_4$ and evaporated under reduced pressure. Crude product was purified using column chromatography (hexane/EtOAc, 0–40% EtOAc). After crystallization from chloroform/methanol mixture, nucleoside **13** (572 mg, 54%) was observed as white crystals; mp: 164–165 °C. IR (ATR): ν = 1722, 1545, 1472, 1433, 1292, 1266, 1119, 1098, 714 cm^{-1}. ^1H NMR (600.1 MHz, DMSO-d_6):): 4.68 (dd, 1H, J_{gem} = 12.4, $J_{5'b,4'}$ = 4.3, H-5′b); 4.85 (dd, 1H, J_{gem} = 12.4, $J_{5'a,4'}$ = 3.2, H-5′a); 4.90 (ddd, 1H, $J_{4',3'}$ = 6.6, $J_{4',5'}$ = 4.3, 3.2, H-4′); 6.36 (t, 1H, $J_{3',2'}$ = $J_{3',4'}$ = 6.6, H-3′); 6.59 (dd, 1H, $J_{2',3'}$ = 6.6, $J_{2',1'}$ = 4.4, H-2′); 7.02 (d, 1H, $J_{1',2'}$ = 4.4, H-1′); 7.42 (m, 2H, H-*m*-Bz-2′); 7.49 (m, 4H, H-*m*-Bz-3′,5′); 7.60 (dd, 1H, $J_{7,8}$ = 9.1, $J_{7,5}$ = 2.2, H-7); 7.62 (m, 1H, H-*p*-Bz-2′); 7.68 (m, 2H, H-*p*-Bz-3′,5′); 7.84 (m, 2H, H-*O*-Bz-2′); 7.91 (m, 2H, H-*O*-Bz-5′); 7.99 (m, 2H, H-*o*-Bz-3′); 8.15 (dd, 1H, $J_{8,7}$ = 9.1, $J_{8,5}$ = 0.5, H-8); 8.28 (dd, 1H, $J_{5,7}$ = 2.2, $J_{5,8}$ = 0.5, H-5); 8.81 (s, 1H, H-2). ^{13}C NMR (150.9 MHz, DMSO-d_6): 63.1 (CH_2-5′); 70.3 (CH-3′); 72.5 (CH-2′); 78.9 (CH-4′); 86.4 (CH-1′); 111.7 (C-4a); 114.0 (CH-8); 119.4 (C-4b); 122.0 (CH-5); 128.6, 128.8 (C-*i*-Bz); 128.9 (CH-7); 128.9, 128.9, 129.0 (CH-*m*-Bz); 129.3 (CH-*o*-Bz-5′); 129.3 (C-*i*-Bz); 129.5 (CH-*O*-Bz-2′); 129.6 (CH-*O*-Bz-3′); 133.8, 134.1 (CH-*p*-Bz); 137.1 (C-8a); 152.7 (C-4); 154.6 (CH-2); 155.5 (C-9a); 164.8 (COPh-2′); 165.0 (COPh-3′); 165.5 (COPh-5′). ESI MS *m*/*z* (rel.%): 682 (100) [M+H], 684 (66) [M+2+H], 686 (26) [M+4+H]. HR MS (ESI) for $C_{36}H_{26}Cl_2N_3O_7$ [M+H]: calcd 682.11480; found 682.11423; for $C_{36}H_{25}Cl_2N_3O_7Na$ [M+Na]: Calcd 704.09660; found 704.09618.

3.10. 4-Chloro-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyrimido[4,5-*b*]indole (14)

Compound **14** was prepared as described for **13** from pyrimidoindole **12** (300 mg, 1.5 mmol) to give 440 mg (46%) of white crystals; mp 178–182 °C, IR (ATR): ν = 2360, 2336, 1718, 1546, 1442, 1261, 1090, 1068, 704 cm^{-1}.^1H NMR (600.1 MHz, DMSO-d_6): 4.69 (dd, 1H, J_{gem} = 12.4, $J_{5'b,4'}$ = 4.2, H-5′b); 4.85 (dd, 1H, J_{gem} = 12.4, $J_{5'a,4'}$ = 3.2, H-5′a); 4.91 (ddd, 1H, $J_{4',3'}$ = 6.6, $J_{4',5'}$ = 4.2, 3.2, H-4′); 6.36 (t, 1H, $J_{3',2'}$ = $J_{3',4'}$ = 6.6, H-3′); 6.61 (dd, 1H, $J_{2',3'}$ = 6.6, $J_{2',1'}$ = 4.6, H-2′); 7.03 (d, 1H, $J_{1',2'}$ = 4.6, H-1′); 7.41 (m, 2H, H-*m*-Bz-2′); 7.50 (m, 4H, H-*m*-Bz-3′,5′); 7.51 (ddd, 1H, $J_{6,5}$ = 7.8, $J_{6,7}$ = 7.3, $J_{6,8}$ = 1.0, H-6); 7.57 (ddd, 1H, $J_{7,8}$ = 8.4, $J_{7,6}$ = 7.3, $J_{7,5}$ = 1.3, H-7); 7.62 (m, 1H, H-*p*-Bz-2′); 7.68 (m, 2H, H-*p*-Bz-3′,5′); 7.84 (m, 2H, H-*o*-Bz-2′); 7.93 (m, 2H, H-*o*-Bz-5′); 7.99 (m, 2H, H-*o*-Bz-3′); 8.10 (ddd, 1H, $J_{8,7}$ = 8.4, $J_{8,6}$ = 1.0, $J_{8,5}$ = 0.7, H-8); 8.35 (ddd, 1H, $J_{5,6}$ = 7.8, $J_{5,7}$ = 1.3, $J_{5,8}$ = 0.7, H-5); 8.78 (s, 1H, H-2). ^{13}C NMR (150.9 MHz, DMSO-d_6): 63.1 (CH_2-5′); 70.3 (CH-3′); 72.2 (CH-2′); 78.8 (CH-4′); 86.2 (CH-1′); 112.1 (CH-8); 112.4 (C-4a); 118.0 (C-4b); 122.9 (CH-5); 123.3 (CH-6); 128.6, 128.8 (C-*i*-Bz); 128.9 (CH-*m*-Bz); 129.0 (CH-7); 129.3 (CH-*o*-Bz-5′); 129.4 (C-*i*-

Bz); 129.5 (CH-*o*-Bz-2′); 129.6 (CH-*o*-Bz-3′); 133.8, 134.1 (CH-*p*-Bz); 138.4 (C-8a); 152.1 (C-4); 154.0 (C-2-furyl); 154.0 (CH-2); 155.3 (C-9a); 164.8 (COPh-2′); 165.0 (COPh-3′); 165.5 (COPh-5′). ESI MS *m*/*z* (rel.%): 670 (100) [M+Na], 672 (33) [M+2+Na]. HR MS (ESI) for $C_{36}H_{27}ClN_3O_7$ [M+H]: calcd 648.15320; found 648.15318.

3.11. General procedure for the Suzuki coupling

Protected nucleoside **13** (0.5 mmol), boronic acid (1.5 equiv), K_2CO_3 (2 equiv) and $Pd(PPh_3)_4$ were dissolved in toluene and heated to 100 °C for 6 h. Then, the reaction mixture was diluted with water and extracted with chloroform. Organic layer was washed with saturated NH_4Cl, then with water and was dried over $MgSO_4$. After evaporation of solvent, the crude product was purified by column chromatography (hexane/EtOAc, 0–20% EtOAc). Products were obtained as white solid or crystals.

3.12. General procedure for the Stille coupling

Protected nucleoside **13** or **14** (0.5 mmol), tributylstannane (1.2 equiv) and $PdCl_2(PPh_3)_2$ were dissolved in anhydrous DMF and heated to 100 °C for 6–8 h. Then, solvent was evaporated under reduced pressure. Crude product was purified using column chromatography (hexane/EtOAc, 0-20% EtOAc). Products were obtained as white solid or crystals.

3.13. 6-Chloro-4-(furan-2-yl)-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (17a)

Protected nucleoside **13** (200 mg, 0.29 mmol) and 2-(tributylstannyl)furane (126 mg, 0.35 mmol) were used. Desired product **17a** (165 mg, 79%) was obtained as yellowish powder; mp: 92–93 °C. IR (ATR): ν = 2360, 2342, 1720, 1262, 1091, 1068, 706 cm^{-1}. ^1H NMR (500.0 MHz, DMSO-d_6): 4.69 (dd, 1H, J_{gem} = 12.4, $J_{5'b,4'}$ = 4.3, H-5′b); 4.85 (dd, 1H, J_{gem} = 12.4, $J_{5'a,4'}$ = 3.2, H-5′a); 4.90 (ddd, 1H, $J_{4',3'}$ = 6.6, $J_{4',5'}$ = 4.3, 3.2, H-4′); 6.39 (t, 1H, $J_{3',2'} = J_{3',4'}$ = 6.6, H-3′); 6.62 (dd, 1H, $J_{2',3'}$ = 6.6, $J_{2',1'}$ = 4.5, H-2′); 6.91 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 1.7, H-4-furyl); 7.04 (d, 1H, $J_{1',2'}$ = 4.5, H-1′); 7.41 (m, 2H, H-*m*-Bz-2'); 7.49 (m, 4H, H-*m*-Bz-3′,5′); 7.53 (dd, 1H, $J_{7,8}$ = 8.8, $J_{7,5}$ = 2.2, H-7); 7.62 (m, 1H, H-*p*-Bz-2′); 7.64 (dd, 1H, $J_{3,4}$ = 3.5, $J_{3,5}$ = 0.8, H-3-furyl); 7.66, 7.68 (2 × m, 2 × 1H, H-*p*-Bz-3′,5′); 7.84 (m, 2H, H-*o*-Bz-2′); 7.94 (m, 2H, H-*o*-Bz-5′); 7.99 (m, 2H, H-*o*-Bz-3′); 8.10 (dd, 1H, $J_{8,7}$ = 8.8, H-8); 8.38 (dd, 1H, $J_{5,4}$ = 1.7, $J_{5,3}$ = 0.8, H-5-furyl); 8.82 (d, 1H, $J_{5,7}$ = 2.2, H-5); 8.91 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 63.2 (CH_2-5′); 70.3 (CH-3′); 72.3 (CH-2′); 78.7 (CH-4′); 86.2 (CH-1′); 107.5 (C-4a); 113.2 (CH-8); 113.4 (CH-4-furyl); 115.8 (CH-3-furyl); 120.5 (C-4b); 124.1 (CH-5); 127.0 (C-6); 128.1 (CH-7); 128.7, 128.8 (C-*i*-Bz); 128.9, 128.9, 129.0 (CH-*m*-Bz); 129.4 (CH-*o*-Bz-5′); 129.4 (C-*i*-Bz); 129.5 (CH-*o*-Bz-2′); 129.6 (CH-*o*-Bz-3′); 133.7, 134.1 (CH-*p*-Bz); 137.2 (C-8a); 147.2 (CH-5-furyl); 148.3 (C-4); 152.2 (C-2-furyl); 154.4 (CH-2); 156.4 (C-9a); 164.8 (COPh-2′); 165.0 (COPh-3′); 165.6 (COPh-5′). ESI MS *m*/*z* (rel.%): 736 (100) [M+Na], 738 (42) [M+2+Na], 714 (50) [M+H]. HR MS (ESI) for $C_{40}H_{29}ClN_3O_8$ [M+H]: calcd 714.16382; found 714.16377.

3.14. 6-Chloro-4-(furan-3-yl)-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (17b)

Protected nucleoside **13** (500 mg, 0.73 mmol) and furane-3-boronic acid (125 mg, 1.1 mmol) were used. Desired product **17b** (360 mg, 69%) was obtained as white powder; mp: 120–124 °C. IR (ATR): ν = 2360, 2342, 1719, 1260, 1095, 1067, 705 cm^{-1}. ^1H NMR (500.0 MHz, DMSO-d_6): 4.70 (dd, 1H, J_{gem} = 12.4, $J_{5b,4'}$ = 4.3, H-5′b); 4.85 (dd, 1H, J_{gem} = 12.4, $J_{5'a,4'}$ = 3.2, H-5′a); 4.90 (ddd, 1H, $J_{4',3'}$ = 6.6, $J_{4',5'}$ = 4.3, 3.2, H-4′); 6.39 (t, 1H, $J_{3',2'} = J_{3',4'}$ = 6.6, H-3′); 6.65 (dd, 1H, $J_{2',3'}$ = 6.6, $J_{2',1'}$ = 4.6, H-2′); 7.03 (d, 1H, $J_{1',2'}$ = 4.6, H-1′); 7.12 (dd, 1H, $J_{4,5}$ = 1.8, $J_{4,2}$ = 0.8, H-4-furyl); 7.42 (m, 2H, H-*m*-Bz-2′); 7.50 (m, 5H, H-7, H-*m*-Bz-3′,5′); 7.62 (m, 1H, H-*p*-Bz-2′); 7.67, 7.68 (2 × m, 2 × 1H, H-*p*-Bz-3′,5′); 7.85 (m, 2H, H-*o*-Bz-2′); 7.94 (m, 2H, H-*o*-Bz-5′); 8.00 (m, 2H, H-*o*-Bz-3′); 8.02 (dd, 1H, $J_{5,4}$ = 1.8, $J_{5,2}$ = 1.5, H-5-furyl); 8.09 (d, 1H, $J_{5,7}$ = 2.0, H-5); 8.10 (dd, 1H, $J_{8,7}$ = 9.0, H-8); 8.56 (dd, 1H, $J_{2,5}$ = 1.5, $J_{2,4}$ = 0.8, H-2-furyl); 8.93 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 63.2 (CH_2-5′); 70.4 (CH-3′); 72.2 (CH-2′); 78.7 (CH-4′); 86.2 (CH-1′); 110.7 (C-4a); 110.7 (CH-4-furyl); 113.4 (CH-8); 120.5 (C-4b); 121.9 (CH-5); 124.2 (C-3-furyl); 126.7 (C-6); 128.0 (CH-7); 128.6, 128.8 (C-*i*-Bz); 128.9, 128.9, 129.0 (CH-*m*-Bz); 129.4 (CH-*o*-Bz-5′); 129.4 (C-*i*-Bz); 129.5 (CH-*o*-Bz-2′); 129.6 (CH-*o*-Bz-3′); 133.8, 134.1 (CH-*p*-Bz); 136.9 (C-8a); 144.7 (CH-2-furyl); 144.9 (CH-5-furyl); 153.5 (C-4); 154.6 (CH-2); 155.7 (C-9a); 164.8 (COPh-2′); 165.0 (COPh-3′); 165.6 (COPh-5′). ESI MS *m*/*z* (rel.%): 714 (100) [M+H], 716 (39) [M+2+H], 736 (10) [M+Na]. HR MS (ESI) for $C_{40}H_{29}ClN_3O_8$ [M+H]: calcd 714.16370; found 714.16377.

3.15. 6-Chloro-4-(thiophen-2-yl)-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (17c)

Protected nucleoside **13** (500 mg, 0.73 mmol) and 2-(tributylstannyl)thiophene (326 mg, 0.9 mmol) were used. Desired product **17c** (416 mg, 78%) was obtained as yellowish powder; mp: 148–155 °C; IR (ATR): ν = 2359, 2341, 1720, 1560, 1261, 1106, 1068, 1025, 704 cm^{-1}. ^1H NMR (600.1 MHz, DMSO-d_6): 4.69 (dd, 1H, J_{gem} = 12.3, $J_{5'b,4'}$ = 4.3, H-5′b); 4.85 (dd, 1H, J_{gem} = 12.3, $J_{5'a,4'}$ = 3.2, H-5′a); 4.90 (ddd, 1H, $J_{4',3'}$ = 6.6, $J_{4',5'}$ = 4.3, 3.2, H-4′); 6.39 (t, 1H, $J_{3',2'} = J_{3',4'}$ = 6.6, H-3′); 6.64 (dd, 1H, $J_{2',3'}$ = 6.6, $J_{2',1'}$ = 4.4, H-2′); 7.05 (d, 1H, $J_{1',2'}$ = 4.4, H-1′); 7.42 (dd, 1H, $J_{4,5}$ = 5.0, $J_{4,3}$ = 3.6, H-4-thienyl); 7.425 (m, 2H, H-*m*-Bz-2′); 7.50 (m, 4H, H-*m*-Bz-3′,5′); 7.53 (dd, 1H, $J_{7,8}$ = 8.9, $J_{7,5}$ = 2.2, H-7); 7.62 (m, 1H, H-*p*-Bz-2′); 7.66, 7.68 (2 × m, 2 × 1H, H-*p*-Bz-3′,5′); 7.85 (m, 2H, H-*o*-Bz-2′); 7.94 (m, 2H, H-*o*-Bz-5′); 8.00 (m, 2H, H-*o*-Bz-3′); 8.02 (dd, 1H, $J_{5,4}$ = 5.0, $J_{5,3}$ = 1.1, H-5-thienyl); 8.09 (dd, 1H, $J_{3,4}$ = 3.6, $J_{3,5}$ = 1.1, H-3-thienyl); 8.13 (d, 1H, $J_{8,7}$ = 8.9, H-8); 8.24 (d, 1H, $J_{5,7}$ = 2.2, H-5); 8.92 (s, 1H, H-2). ^{13}C NMR (150.9 MHz, DMSO-d_6): 63.2 (CH_2-5′); 70.3 (CH-3′); 72.3 (CH-2′); 78.7 (CH-4′); 86.3 (CH-1′); 109.4 (C-4a); 113.6 (CH-8); 120.4 (C-4b); 121.7 (CH-5); 126.7 (C-6); 128.2 (CH-7); 128.7 (C-*i*-Bz); 128.8 (CH-4-thienyl); 128.8 (C-*i*-Bz); 128.9, 129.0 (CH-*m*-Bz); 129.4 (CH-*o*-Bz-5′); 129.5 (CH-*o*-Bz-2′); 129.7 (CH-*o*-Bz-3′); 130.3 (CH-3-thienyl); 131.9 (CH-5-thienyl); 133.8, 134.1 (CH-*p*-Bz); 137.1 (C-8a); 140.8 (C-2-thienyl); 153.8 (C-4); 154.4 (CH-2); 156.1 (C-9a); 164.9 (COPh-2′); 165.1 (COPh-3′); 165.6 (COPh-5′). ESI MS *m*/*z* (rel.%): 752.3 (50) [M+Na], 730.3 (100) [M+H. HR MS (ESI) for $C_{40}H_{29}ClN_3O_7S$ [M+H]: calcd 730.14112; found 730.14093.

3.16. 6-Chloro-4-(thiophen-3-yl)-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (17d)

Protected nucleoside **13** (500 mg, 0.73 mmol) and thiophene-3-boronic acid (140 mg, 1.1 mmol) were used. Desired product **17d** (375 mg, 70%) was obtained as yellowish powder; mp: 171–184 °C; IR (ATR): ν = 2360, 2342, 1721, 1561, 1264, 1106, 1068, 705 cm^{-1}. ^1H NMR (500.0 MHz, DMSO-d_6): 4.70 (dd, 1H, J_{gem} = 12.4, $J_{5'b,4'}$ = 4.3, H-5′b); 4.85 (dd, 1H, J_{gem} = 12.4, $J_{5'a,4'}$ = 3.2, H-5′a); 4.90 (ddd, 1H, $J_{4',3'}$ = 6.6, $J_{4',5'}$ = 4.3, 3.2, H-4′); 6.40 (t, 1H, $J_{3',2'} = J_{3',4'}$ = 6.6, H-3′); 6.66 (dd, 1H, $J_{2',3'}$ = 6.6, $J_{2',1'}$ = 4.6, H-2′); 7.04 (d, 1H, $J_{1',2'}$ = 4.6, H-1′); 7.42 (m, 2H, H-*m*-Bz-2′); 7.50 (m, 5H, H-7, H-*m*-Bz-3′,5′); 7.62 (m, 1H, H-*p*-Bz-2′); 7.67 (m, 3H, H-4-thienyl, H-*p*-Bz-3′,5′); 7.85 (m, 2H, H-*o*-Bz-2′); 7.88 (dd, 1H, $J_{5,4}$ = 5.0, $J_{5,2}$ = 2.9, H-5-thienyl); 7.95 (d, 1H, $J_{5,7}$ = 2.0, H-5); 7.96 (m, 2H, H-*o*-Bz-5′); 8.00 (m, 2H, H-*o*-Bz-3′); 8.11 (dd, 1H, $J_{8,7}$ = 9.0, H-8); 8.34 (dd, 1H, $J_{2,5}$ = 2.9, $J_{2,4}$ = 1.3, H-2-thienyl); 8.96

(s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 63.2 (CH_2-5′); 70.4 (CH-3′); 72.3 (CH-2′); 78.7 (CH-4′); 86.2 (CH-1′); 110.6 (C-4a); 113.5 (CH-8); 120.6 (C-4b); 121.8 (CH-5); 126.6 (C-6); 127.6, 128.0, 128.2 (CH-7, CH-4,5-thienyl); 128.6, 128.8 (C-*i*-Bz); 128.9, 128.9, 129.0 (CH-2-thienyl, CH-*m*-Bz); 129.4 (CH-*o*-Bz-5′); 129.4 (C-*i*-Bz); 129.5 (CH-*o*-Bz-2′); 129.6 (CH-*o*-Bz-3′); 133.8, 134.1 (CH-*p*-Bz); 137.0 (C-8a); 139.0 (C-3-thienyl); 154.6 (CH-2); 155.8 (C-9a); 155.9 (C-4); 164.8 (COPh-2′); 165.0 (COPh-3′); 165.6 (COPh-5′). ESI MS *m*/*z* (rel.%): 752 (100) [M+Na], 754 (48) [M+2+H], 730 (13) [M+H]. HR MS (ESI) for $C_{40}H_{29}ClN_3O_7S$ [M+H]: calcd 730.14089; found 730.14093.

3.17. 4-(Benzofuran-2-yl)-6-chloro-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (17e)

Protected nucleoside **13** (500 mg, 0.73 mmol) and benzofurane-2-boronic acid (180 mg, 1.1 mmol) were used. Desired product **17e** (358 mg, 64%) was obtained as white powder; mp: 149–158 °C. IR (ATR): ν = 1716, 1582, 1559, 1446, 1280, 1125, 1065, 707 cm^{-1}. ^{1}H NMR (600.1 MHz, DMSO-d_6): 4.71 (dd, 1H, J_{gem} = 12.3, $J_{5'b,4'}$ = 4.3, H-5′b); 4.87 (dd, 1H, J_{gem} = 12.3, $J_{5'a,4'}$ = 3.2, H-5′a); 4.91 (ddd, 1H, $J_{4',3'}$ = 6.6, $J_{4',5'}$ = 4.3, 3.2, H-4′); 6.40 (t, 1H, $J_{3',2'}$ = $J_{3',4'}$ = 6.6, H-3′); 6.64 (dd, 1H, $J_{2',3'}$ = 6.6, $J_{2',1'}$ = 4.6, H-2′); 7.06 (d, 1H, $J_{1',2'}$ = 4.6, H-1′); 7.42 (m, 3H, H-*m*-Bz-2′, H-5-benzofuryl); 7.49 (m, 4H, H-*m*-Bz-3′,5′); 7.50 (dd, 1H, $J_{7,8}$ = 9.0, $J_{7,5}$ = 2.1, H-7); 7.55 (ddd, 1H, $J_{6,7}$ = 8.3, $J_{6,5}$ = 7.1, $J_{6,4}$ = 1.2, H-6-benzofuryl); 7.62 (m, 1H, H-*p*-Bz-2′); 7.65, 7.68 (2 × m, 2 × 1H, H-*p*-Bz-3′,5′); 7.78 (ddt, 1H, $J_{7,6}$ = 8.3, $J_{7,3}$ = 1.0, $J_{7,4}$ = $J_{7,5}$ = 0.8, H-7-benzofuryl); 7.85 (m, 2H, H-*o*-Bz-2′); 7.87 (ddd, 1H, $J_{4,5}$ = 7.8, $J_{4,6}$ = 1.2, $J_{4,7}$ = 0.8, H-4-benzofuryl); 7.95 (m, 2H, H-*o*-Bz-5′); 7.99 (d, 1H, $J_{3,7}$ = 1.0, H-3-benzofuryl); 8.00 (m, 2H, H-*o*-Bz-3′); 8.10 (dd, 1H, $J_{8,7}$ = 8.8, $J_{8,5}$ = 0.5, H-8); 8.92 (dd, 1H, $J_{5,7}$ = 2.2, $J_{5,8}$ = 0.5, H-5); 8.97 (s, 1H, H-2). ^{13}C NMR (150.9 MHz, DMSO-d_6): 63.2 (CH_2-5′); 70.3 (CH-3′); 72.3 (CH-2′); 78.7 (CH-4′); 86.2 (CH-1′); 108.9 (C-4a); 111.1 (CH-3-benzofuryl); 111.5 (CH-7-benzofuryl); 113.2 (CH-8); 120.2 (C-4b); 123.0 (CH-4-benzofuryl); 124.4 (CH-5-benzofuryl); 124.6 (CH-5); 127.1 (C-6); 127.4 (CH-6-benzofuryl); 127.6 (C-3-benzofuryl); 128.2 (CH-7); 128.7, 128.8 (C-*i*-Bz); 128.9, 128.9, 128.9 (CH-*m*-Bz); 129.4 (CH-*o*-Bz-5′); 129.4 (C-*i*-Bz); 129.5 (CH-*o*-Bz-2′); 129.6 (CH-*o*-Bz-3′); 133.7, 134.1 (CH-*p*-Bz); 137.4 (C-8a); 148.3 (C-4); 153.6 (C-2-benzofuryl); 154.3 (CH-2); 155.3 (C-7a-benzofuryl); 156.5 (C-9a) 164.8 (COPh-2′); 165.0 (COPh-3′); 165.6 (COPh-5′). ESI MS *m*/*z* (rel.%): 786 (100) [M+Na], 788 (45) [M+2+H], 764 (10) [M+H]. HR MS (ESI) for $C_{44}H_{30}ClN_3O_8Na$ [M+H]: calcd 786.16098; found 786.16136.

3.18. 6-Chloro-4-phenyl-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (17f)

Protected nucleoside **13** (500 mg, 0.73 mmol) and phenyl boronic acid (134 mg, 1.1 mmol) were used. Desired product **17f** (382 mg, 72%) was obtained as white powder; mp: 175–180 °C; IR (ATR): ν = 2359, 2342, 1721, 1560, 1265, 1108, 701 cm^{-1}. ^{1}H NMR (600.1 MHz, DMSO-d_6): 4.70 (dd, 1H, J_{gem} = 12.4, $J_{5'b,4'}$ = 4.3, H-5′b); 4.85 (dd, 1H, J_{gem} = 12.4, $J_{5'a,4'}$ = 3.2, H-5′a); 4.91 (ddd, 1H, $J_{4',3'}$ = 6.6, $J_{4',5'}$ = 4.3, 3.2, H-4′); 6.41 (t, 1H, $J_{3',2'}$ = $J_{3',4'}$ = 6.6, H-3′); 6.68 (dd, 1H, $J_{2',3'}$ = 6.6, $J_{2',1'}$ = 4.5, H-2'); 7.06 (d, 1H, $J_{1',2'}$ = 4.5, H-1′); 7.42 (m, 2H, H-*m*-Bz-2′); 7.48–7.52 (m, 5H, H-*m*-Bz-3′,5′, H-7); 7.63 (m, 1H, H-*p*-Bz-2′); 7.66–7.70 (m, 6H, H-*p*-Bz-3′,5′, H-*m*,*p*-Ph, H-5); 7.86 (m, 2H, H-*o*-Bz-2′); 7.89 (m, 2H, H-*o*-Ph); 7.96 (m, 2H, H-*o*-Bz-5′); 8.00 (m, 2H, H-*o*-Bz-3′); 8.12 (d, 1H, $J_{8,7}$ = 8.9, H-8); 9.01 (s, 1H, H-2). ^{13}C NMR (150.9 MHz, DMSO-d_6): 63.2 (CH_2-5′); 70.4 (CH-3′); 72.4 (CH-2′); 78.7 (CH-4′); 86.3 (CH-1′); 110.9 (C-4a); 113.6 (CH-8); 120.5 (C-4b); 121.6 (CH-5); 126.6 (C-6); 128.2 (CH-7); 128.7, 128.8 (C-*i*-Bz); 129.0 (CH-*m*-Bz, CH-*o*-Ph); 129.1 (CH-*m*-Ph); 129.4 (CH-*o*-Bz-5′); 129.6 (CH-*o*-Bz-2′); 129.7 (CH-*o*-Bz-3′); 130.8 (CH-*p*-Ph); 133.8, 134.1, 134.2 (CH-*p*-Bz); 137.2 (C-8a); 137.5 (C-*i*-Ph); 154.8 (CH-2); 155.8 (C-9a); 160.7 (C-4); 164.9 (COPh-2′); 165.1 (COPh-3′); 165.6 (COPh-5′). ESI MS *m*/*z* (rel.%): 746.3 (100) [M+Na], 748.3 (35) [M+2+Na], 724.3 (33) [M+H]. HR MS (ESI) for $C_{42}H_{31}ClN_3O_7$ [M+H]: calcd 724.18463; found 724.18450.

3.19. 4-(Furan-2-yl)-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (15a)

Protected nucleoside **14** (450 mg, 0.69 mmol) and 2-(tributylstannyl)furane (296 mg, 0.83 mmol) were used. Desired product **15a** (390 mg, 82%) was obtained as yellowish powder; mp 89–91 °C;IR (ATR): ν = 2932, 2363, 2331, 1742, 1578, 1547, 1452, 1258, 804 cm^{-1}. ^{1}H NMR (600.1 MHz, DMSO-d_6): 4.71 (dd, 1H, J_{gem} = 12.4, $J_{5'b,4'}$ = 4.2, H-5′b); 4.85 (dd, 1H, J_{gem} = 12.4, $J_{5'a,4'}$ = 3.1, H-5′a); 4.91 (ddd, 1H, $J_{4',3'}$ = 6.7, $J_{4',5'}$ = 4.2, 3.1, H-4′); 6.39 (t, 1H, $J_{3',2'}$ = $J_{3',4'}$ = 6.7, H-3′); 6.64 (dd, 1H, $J_{2',3'}$ = 6.7, $J_{2',1'}$ = 4.7, H-2′); 6.89 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 1.7, H-4-furyl); 7.07 (d, 1H, $J_{1',2'}$ = 4.7, H-1′); 7.41 (m, 2H, H-*m*-Bz-2′); 7.45 (ddd, 1H, $J_{6,5}$ = 8.0, $J_{6,7}$ = 7.3, $J_{6,8}$ = 1.3, H-6); 7.48 (ddd, 1H, $J_{7,8}$ = 8.0, $J_{7,6}$ = 7.3, $J_{7,5}$ = 1.3, H-7); 7.50 (m, 4H, H-*m*-Bz-3′,5′); 7.60 (dd, 1H, $J_{3,4}$ = 3.5, $J_{3,5}$ = 0.8, H-3-furyl); 7.61 (m, 1H, H-*p*-Bz-2′); 7.66, 7.68 (2 × m, 2 × 1H, H-*p*-Bz-3′,5′); 7.84 (m, 2H, H-*o*-Bz-2′); 7.97 (m, 2H, H-*o*-Bz-5′); 7.99 (m, 2H, H-*o*-Bz-3′); 8.04 (ddd, 1H, $J_{8,7}$ = 8.0, $J_{8,6}$ = 1.3, $J_{8,5}$ = 0.6, H-8); 8.29 (dd, 1H, $J_{5,4}$ = 1.7, $J_{5,3}$ = 0.8, H-5-furyl); 8.892 (ddd, 1H, $J_{5,6}$ = 8.0, $J_{5,7}$ = 1.3, $J_{5,8}$ = 0.6, H-5); 8.893 (s, 1H, H-2). ^{13}C NMR (150.9 MHz, DMSO-d_6): 63.2 (CH_2-5′); 70.3 (CH-3′); 72.1 (CH-2′); 78.6 (CH-4′); 86.0 (CH-1′); 108.4 (C-4a); 111.4 (CH-8); 113.1 (CH-4-furyl); 115.2 (CH-3-furyl); 119.1 (C-4b); 122.7 (CH-5); 125.0 (CH-6); 128.2 (CH-7); 128.6, 128.8 (C-*i*-Bz); 128.9 (CH-*m*-Bz); 129.4 (CH-*o*-Bz-5′); 129.4 (C-*i*-Bz); 129.5 (CH-*o*-Bz-2′); 129.6 (CH-*o*-Bz-3′); 133.7, 134.1 (CH-*p*-Bz); 138.5 (C-8a); 146.8 (CH-5-furyl); 147.8 (C-4); 152.4 (C-2-furyl); 153.8 (CH-2); 156.2 (C-9a); 164.8 (COPh-2′); 165.0 (COPh-3′); 165.6 (COPh-5′). ESI MS *m*/*z* (rel.%): 702 (100) [M+Na], 704 (29) [M+2+Na], 680 (15) [M+H]. HR MS (ESI) for $C_{40}H_{30}N_3O_8$ [M+H]: calcd 680.20274; found 680.20275.

3.20. General procedure for deprotection of nucleosides

Protected nucleoside **15a**, **17a–f**, **20a**,**b**,**f** (0.2 mmol) was dissolved in methanol (10 ml) and 1 M solution of MeONa in MeOH (0.3 equiv) was added. Reaction mixture was stirred at rt. overnight. Solvent was evaporated under reduced pressure and crude products were purified using column chromatography (3% of MeOH in $CHCl_3$).

3.21. 6-Chloro-4-(furan-2-yl)-9-β-D-ribofuranosyl-9*H*-pyrimido[4,5-*b*]indole (18a)

Deprotection of **17a** (150 mg, 0.21 mmol) according to the general procedure afforded compound **18a** (72 mg, 86%) as white crystals: mp: 188-192 °C; $[\alpha]_D$ −33.1 (c 0.45, DMSO). IR (ATR): ν = 3320, 2922, 1592, 1565, 1538, 1460, 1435, 1398, 1308, 1291, 1221, 1130, 1075, 1037, 1012 cm^{-1}. ^{1}H NMR (600.1 MHz, DMSO-*d*6): 3.69 (ddd, 1H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.3, $J_{5'b,4'}$ = 3.9, H-5′b); 3.74 (ddd, 1H, J_{gem} = 12.0, $J_{5'a}$,OH = 5.3, $J_{5'a,4'}$ = 3.2, H-5′a); 4.00 (dt, 1H, $J_{4',5'}$ = 3.9, 3.2, $J_{4',3'}$ = 3.2, H-4'); 4.24 (ddd, 1H, $J_{3',2'}$ = 5.7, $J_{3',OH}$ = 4.7, $J_{3',4'}$ = 3.2, H-3'); 4.77 (ddd, 1H, $J_{2',1'}$ = 7.4, $J_{2',OH}$ = 6.4, $J_{2',3'}$ = 5.7, H-2′); 5.23 (d, 1H, $J_{OH,3'}$ = 4.7, OH-3′); 5.24 (t, 1H, $J_{OH,5'}$ = 5.3, OH-5'); 5.31 (d, 1H, $J_{OH,2'}$ = 6.4, OH-2'); 6.57 (d, $J_{1',2'}$ = 7.4, H-1′); 6.91 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 1.7, H-4-furyl); 7.62 (dd, 1H, $J_{3,4}$ = 3.5, $J_{3,5}$ = 0.9, H-3-furyl); 7.63 (dd, 1H, $J_{7,8}$ = 8.8, $J_{7,5}$ = 2.2, H-7); 8.17 (d, 1H, $J_{8,7}$ = 8.8, H-8); 8.38 (dd, 1H, $J_{5,4}$ = 1.7, $J_{5,3}$ = 0.9, H-5-furyl); 8.84 (d, 1H, $J_{5,7}$ = 2.2, H-5); 8.98 (s, 1H, H-2).

^{13}C NMR (150.9 MHz, DMSO-d_6): 61.7 (CH_2-5′); 70.2 (CH-3′); 70.6 (CH-2′); 85.8 (CH-4′); 87.0 (CH-1′); 107.1 (C-4a); 113.4 (CH-4-furyl); 114.8 (CH-8); 115.6 (CH-3-furyl); 120.7 (C-4b); 123.9 (CH-5); 126.6 (C-6); 127.9 (CH-7); 136.8 (C-8a); 147.0 (CH-5-furyl); 148.0 (C-4); 152.4 (C-2-furyl); 154.5 (CH-2); 157.1 (C-9a). ESI MS *m*/*z* (rel.%): 424 (100) [M+Na], 426 (34) [M+2+Na], 402 (26) [M+H] 404 (8) [M+2+H]. HR MS (ESI) for $C_{19}H_{17}ClN_3O_5$ [M+H]: calcd 402.08520; found 402.08512. Anal. Calcd for $C_{19}H_{16}ClN_3O_5$: C, 56.80; H, 4.01; Cl, 8.82; N, 10.46. Found C, 56.97; H, 4.02; N, 10.45.

3.22. 6-Chloro-4-(furan-3-yl)-9-β-D-ribofuranosyl-9*H*-pyrimido[4,5-*b*]indole (18b)

Deprotection of **17b** (400 mg, 0.56 mmol) according to the general procedure and crystallization ($CHCl_3$/MeOH) afforded compound **18b** (205 mg, 91%) as white crystals: mp: 238–242 °C; $[\alpha]_D$ −27.0 (*c* 0.28, DMSO). IR (ATR): ν = 3317, 3136, 2934, 1587, 1561, 1471, 1447, 1296, 1173, 1158, 1104, 1070 cm^{-1}. ^{1}H NMR (500.0 MHz, DMSO-*d*6): 3.69 (ddd, 1H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.3, $J_{5'b,4'}$ = 3.8, H-5'b); 3.74 (ddd, 1H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.3, $J_{5'a,4'}$ = 3.4, H-5′a); 4.01 (ddd, 1H, $J_{4',5'}$ = 3.8, 3.4, $J_{4',3'}$ = 3.0, H-4'); 4.24 (ddd, 1H, $J_{3',2'}$ = 5.8, $J_{3',OH}$ = 4.8, $J_{3',4'}$ = 3.0, H-3'); 4.78 (ddd, 1H, $J_{2',1'}$ = 7.4, $J_{2',OH}$ = 6.5, $J_{2',3'}$ = 5.8, H-2'); 5.21 (d, 1H, $J_{OH,3'}$ = 4.8, OH-3'); 5.21 (t, 1H, $J_{OH,5'}$ = 5.3, OH-5′); 5.28 (d, 1H, $J_{OH,2'}$ = 6.5, OH-2'); 6.54 (d, $J_{1',2'}$ = 7.4, H-1′); 7.13 (d, 1H, $J_{4,5}$ = 2.1, H-4-furyl); 7.59 (dd, 1H, $J_{7,8}$ = 8.9, $J_{7,5}$ = 2.2, H-7); 8.03 (dd, 1H, $J_{5,4}$ = 2.1, $J_{5,2}$ = 1.3, H-5-furyl); 8.11 (d, 1H, $J_{5,7}$ = 2.2, H-5); 8.16 (d, 1H, $J_{8,7}$ = 8.9, H-8); 8.55 (dd, 1H, $J_{2,5}$ = 1.3, $J_{2,4}$ = 0.8, H-2-furyl); 9.01 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 61.7 (CH_2-5′); 70.2 (CH-3′); 70.7 (CH-2′); 85.8 (CH-4′); 87.0 (CH-1′); 110.3 (C-4a); 110.7 (CH-4-furyl); 115.0 (CH-8); 120.7 (C-4b); 121.7 (CH-5); 124.3 (C-3-furyl); 126.3 (C-6); 127.8 (CH-7); 136.5 (C-8a); 144.5 (CH-2-furyl); 144.9 (CH-5-furyl); 153.2 (C-4); 154.7 (CH-2); 156.3 (C-9a). ESI MS m/z (rel.%): 402 (100) [M+H], 404 (35) [M+2+H]. HR MS (ESI) for $C_{19}H_{17}ClN_3O_5$ [M+H]: calcd 402.08520; found 402.08512. Anal. Calcd for $C_{19}H_{16}ClN_3O_5$: C, 56.80; H, 4.01; Cl, 8.82; N, 10.46. Found C, 56.74; H, 4.06; Cl, 8.81; N, 10.42.

3.23. 6-Chloro-4-(thiophen-2-yl)-9-β-D-ribofuranosyl-9*H*-pyrimido[4,5-*b*]indole (18c)

Deprotection of **17c** (340 mg, 0.47 mmol) according to the general procedure and lyophilization (*t*-BuOH) afforded compound **18c** (181 mg, 93%) as white lyophilisate: mp: 245–249 °C; $[\alpha]_D$ −16.7 (*c* 0.23, DMSO). IR (ATR): ν = 3327, 3307, 3289, 2928, 1561, 1461, 1439, 1396, 1288, 1119, 1077, 1044. ^{1}H NMR (500.0 MHz, DMSO-d_6): 3.70 (ddd, 1H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.3, $J_{5'b,4'}$ = 3.8, H-5′b); 3.74 (ddd, 1H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.3, $J_{5'a,4'}$ = 3.4, H-5′a); 4.02 (ddd, 1H, $J_{4',5'}$ = 3.8, 3.4, $J_{4',3'}$ = 3.1, H-4′); 4.25 (ddd, 1H, $J_{3',2'}$ = 5.8, $J_{3',OH}$ = 4.3, $J_{3',4'}$ = 3.1, H-3′); 4.78 (ddd, 1H, $J_{2',1'}$ = 7.4, $J_{2',OH}$ = 6.4, $J_{2',3'}$ = 5.8, H-2′); 5.22 (t, 1H, $J_{OH,5'}$ = 5.3, OH-5′); 5.23 (d, 1H, $J_{OH,3'}$ = 4.3, OH-3′); 5.30 (d, 1H, $J_{OH,2'}$ = 6.4, OH-2′); 6.56 (d, $J_{1',2'}$ = 7.4, H-1′); 7.43 (dd, 1H, $J_{4,5}$ = 5.1, $J_{4,3}$ = 3.7, H-4-thienyl); 7.61 (dd, 1H, $J_{7,8}$ = 8.9, $J_{7,5}$ = 2.2, H-7); 8.01 (dd, 1H, $J_{5,4}$ = 5.1, $J_{5,3}$ = 1.2, H-5-thienyl); 8.085 (dd, 1H, $J_{3,4}$ = 3.7, $J_{3,5}$ = 1.2, H-3-thienyl); 8.19 (d, 1H, $J_{8,7}$ = 8.9, H-8); 8.26 (d, 1H, $J_{5,7}$ = 2.2, H-5); 8.99 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 61.7 (CH_2-5′); 70.2 (CH-3′); 70.7 (CH-2′); 85.8 (CH-4′); 87.1 (CH-1′); 109.0 (C-4a); 115.1 (CH-8); 120.6 (C-4b); 121.4(CH-5); 126.3 (C-6); 128.0 (CH-7); 128.7 (CH-4-thienyl); 129.4 (CH-3-thienyl); 131.6 (CH-5-thienyl); 136.6 (C-8a); 141.0 (C-2-thienyl); 153.4 (C-4); 154.4 (CH-2); 156.7 (C-9a). ESI MS *m*/*z* (rel.%): 440 (33) [M+Na], 442 (12) [M+2+Na], 418 (100) [M+H], 420 (40) [M+2+H]. HR MS (ESI) for $C_{19}H_{17}ClN_3O_4S$[M+H]: calcd 418.06228; found 418.06228. Anal. Calcd for $C_{19}H_{16}ClN_3O_4S$: C, 54.61; H, 3.86; Cl, 8.48; N, 10.06. Found C, 54.51; H, 4.00; N, 9.95.

3.24. 6-Chloro-4-(thiophen-3-yl)-9-β-D-ribofuranosyl-9*H*-pyrimido[4,5-*b*]indole (18d)

Deprotection of **17d** (120 mg, 0.16 mmol) according to the general procedure and crystallization ($CHCl_3$/MeOH) afforded compound **18d** (59 mg, 86%) as white crystals: mp: 257–261 °C; $[\alpha]_D$ −29.2 (c 0.31, DMSO). IR (ATR): ν = 3356, 3272, 3107, 2920, 1566, 1468, 1442, 1289, 1129, 1078, 1037. ^{1}H NMR (600.1 MHz, DMSO-d_6): 3.69 (ddd, 1H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.3, $J_{5'b,4'}$ = 3.8, H-5′b); 3.74 (ddd, 1H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.3, $J_{5'a,4'}$ = 3.4, H-5′a); 4.01 (ddd, 1H, $J_{4',5'}$ = 3.8, 3.4, $J_{4',3'}$ = 2.9, H-4′); 4.24 (ddd, 1H, $J_{3',2'}$ = 5.8, $J_{3',OH}$ = 4.7, $J_{3',4'}$ = 2.9, H-3′); 4.78 (ddd, 1H, $J_{2',1'}$ = 7.4, $J_{2',OH}$ = 6.4, $J_{2',3'}$ = 5.8, H-2′); 5.24 (t, 1H, $J_{OH,5'}$ = 5.3, OH-5′); 5.25 (d, 1H, $J_{OH,3'}$ = 4.7, OH-3′); 5.32 (d, 1H, $J_{OH,2'}$ = 6.4, OH-2′); 6.55 (d, $J_{1',2'}$ = 7.4, H-1′); 7.59 (dd, 1H, $J_{7,8}$ = 8.8, $J_{7,5}$ = 2.1, H-7); 7.67 (dd, 1H, $J_{4,5}$ = 5.0, $J_{4,2}$ = 1.3, H-4-thienyl); 7.89 (dd, 1H, $J_{5,4}$ = 5.0, $J_{5,2}$ = 2.9, H-5-thienyl); 7.96 (dd, 1H, $J_{5,7}$ = 2.1, $J_{5,8}$ = 0.3, H-5); 8.17 (dd, 1H, $J_{8,7}$ = 8.8, $J_{8,5}$ = 0.3, H-8); 8.33 (dd, 1H, $J_{2,5}$ = 2.9, $J_{2,4}$ = 1.3, H-2-thienyl); 9.03 (s, 1H, H-2). ^{13}C NMR (150.9 MHz, DMSO-d_6): 61.8 (CH_2-5′); 70.3 (CH-3′); 70.7 (CH-2′); 85.8 (CH-4′); 87.0 (CH-1′); 110.2 (C-4a); 115.1 (CH-8); 120.8 (C-4b); 121.5 (CH-5); 126.2 (C-6); 127.8 (CH-7); 128.0 (CH-5-thienyl); 128.2 (CH-4-thienyl); 128.7 (CH-2-thienyl); 136.6 (C-8a); 139.2 (C-3-thienyl); 154.7 (CH-2); 155.7 (C-4); 156.4 (C-9a). ESI MS *m*/*z* (rel.%): 440 (100) [M+Na], 442 (33) [M+2+Na]. HR MS (ESI) for $C_{19}H_{17}ClN_3O_4S$[M+H]: calcd 418.06228; found 418.06227. Anal. Calcd for $C_{19}H_{16}ClN_3O_4S$: C, 54.61; H, 3.86; Cl, 8.48; N, 10.06. Found C, 54.51; H, 4.00; N, 9.95.

3.25. 4-(Benzofuran-2-yl)-6-chloro-9-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (18e)

Deprotection of **17e** (200 mg, 0.26 mmol) according to the general procedure afforded compound **18e** (92 mg, 78%) as yellow crystals: mp: 231–238 °C; $[\alpha]_D$ −32.2 (*c* 0.28, DMSO). IR (ATR): ν = 3294, 2922, 1585, 1564, 1532, 1467, 1437, 1289, 1102, 989 cm^{-1}. ^{1}H NMR (499.8 MHz, DMSO-d_6): 3.71, 3.75 (2 × m, 2 × 1H, H-5′); 4.02 (q, 1H, $J_{4',3'}$ = $J_{4',5'}$ = 3.4, H-4′); 4.25 (br m, 1H, H-3′); 4.78 (ddd, 1H, $J_{2',1'}$ = 7.4, $J_{2',OH}$ = 6.6, $J_{2',3'}$ = 5.6, H-2′); 5.24 (t, 1H, $J_{OH,5'}$ = 5.5, OH-5′); 5.25 (d, 1H, $J_{OH,3'}$ = 4.5, OH-3′); 5.33 (d, 1H, $J_{OH,2'}$ = 6.6, OH-2′); 6.60 (d, 1H, $J_{1',2'}$ = 7.4, H-1′); 7.44 (ddd, 1H, $J_{5,4}$ = 7.7, $J_{5,6}$ = 7.2, $J_{5,7}$ = 0.9, H-5-benzofuryl); 7.57 (ddd, 1H, $J_{6,7}$ = 8.4, $J_{6,5}$ = 7.2, $J_{6,4}$ = 1.2, H-6-benzofuryl); 7.66 (dd, 1H, $J_{7,8}$ = 8.7, $J_{7,5}$ = 2.1, H-7); 7.82 (dq, 1H, $J_{7,6}$ = 8.4, $J_{7,3}$ = $J_{7,4}$ = $J_{7,5}$ = 0.9, H-7-benzofuryl); 7.90 (ddd, 1H, $J_{4,5}$ = 7.7, $J_{4,6}$ = 1.2, $J_{4,7}$ = 0.9, H-4-benzofuryl); 8.03 (d, 1H, $J_{3,7}$ = 0.9, H-3-benzofuryl); 8.21 (d, 1H, $J_{8,7}$ = 8.7, H-8); 8.99 (d, 1H, $J_{5,7}$ = 2.1, H-5); 9.08 (s, 1H, H-2).^{13}C NMR (125.7 MHz, DMSO-d_6): 61.7 (CH_2-5′); 70.2 (CH-3′); 70.6 (CH-2′); 85.8 (CH-4′); 87.1 (CH-1′); 108.6 (C-4a); 111.0 (CH-3-benzofuryl); 111.6 (CH-7-benzofuryl); 114.9 (CH-8); 120.5 (C-4b); 123.0 (CH-4-benzofuryl); 124.4 (CH-5, CH-5-benzofuryl); 126.7 (C-6); 127.3 (CH-6-benzofuryl); 127.7 (C-3-benzofuryl); 128.1 (CH-7); 137.0 (C-8a); 148.1 (C-4); 153.8 (C-2-benzofuryl); 154.5 (CH-2); 155.3 (C-7a-benzofuryl); 157.2 (C-9a). ESI MS *m*/*z* (rel.%): 452 (100) [M+H], 454 (33) [M+2+H]. HR MS (ESI) for $C_{23}H_{19}ClN_3O_5$ [M+H]: Calcd 452.10075; found 452.10077.$C_{23}H_{19}ClN_3O_5$ (451.9): calc. C 61.14, H 4.02, Cl 7.85, N 9.30, O 17.70; found C 61.19, H 4.05, N 9.25.

3.26. 6-Chloro-4-phenyl-β-D-ribofuranosyl-9*H*-pyrimido[4,5-*b*]indole (18f)

Deprotection of **17f** (180 mg, 0.25 mmol) according to the general procedure and lyophilization (t-BuOH) afforded compound **18f**

(91 mg, 89%) as white lyophilisate: mp: 254–257 °C; $[\alpha]_D$ −24.5 (*c* 0.31). IR (ATR): ν = 3294, 3063, 2920, 1554, 1464, 1446, 1434, 1287, 1075, 1024 cm^{-1}. ^1H NMR (500.0 MHz, DMSO-d_6): 3.69 (ddd, 1H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.3, $J_{5'b,4'}$ = 3.8, H-5′b); 3.74 (ddd, 1H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.3, $J_{5'a,4'}$ = 3.4, H-5′a); 4.02 (ddd, 1H, $J_{4',5'}$ = 3.8, 3.4, $J_{4',3'}$ = 2.9, H-4′); 4.25 (ddd, 1H, $J_{3',2'}$ = 5.7, $J_{3',OH}$ = 4.8, $J_{3',4'}$ = 2.9, H-3′); 4.80 (ddd, 1H, $J_{2',1'}$ = 7.4, $J_{2',OH}$ = 6.4, $J_{2',3'}$ = 5.7, H-2′); 5.21 (t, 1H, $J_{OH,5'}$ = 5.3, OH-5′); 5.23 (d, 1H, $J_{OH,3'}$ = 4.8, OH-3′); 5.31 (d, 1H, $J_{OH,2'}$ = 6.4, OH-2′); 6.56 (d, $J_{1',2'}$ = 7.4, H-1′); 7.58 (dd, 1H, $J_{7,8}$ = 8.9, $J_{7,5}$ = 2.2, H-7); 7.66–7.72 (m, 4H, H-5, H-*m*,*p*-Ph); 7.90 (m, 2H, H-*o*-Ph); 8.165 (d, 1H, $J_{8,7}$ = 8.9, H-8); 9.09 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 61.8 (CH_2-5′); 70.2 (CH-3′); 70.7 (CH-2′); 85.8 (CH-4′); 87.1 (CH-1′); 110.4 (C-4a); 115.1 (CH-8); 120.7 (C-4b); 121.3 (CH-5); 126.1 (C-6); 127.8 (CH-7); 128.9 (CH-*o*-Ph); 129.1 (CH-*m*-Ph); 130.7 (CH-*p*-Ph); 136.6 (C-8a); 137.7 (C-*i*-Ph); 154.8 (CH-2); 156.3 (C-9a); 160.4 (C-4). ESI MS *m*/*z* (rel.%): 434 (25) [M+Na], 436 (6) [M+2+Na], 412 (100) [M+H], 414 (33) [M+2+H]. HR MS (ESI) for $C_{21}H_{19}ClN_3O_4$ [M+H]: calcd 412.10593; found 412.10586. Anal. Calcd for $C_{21}H_{19}ClN_3O_4$: C, 61.24; H, 4.41; Cl, 8.61; N, 10.20; O, 15.54. Found C, 61.14; H, 4.45; N, 10.20.

3.27. 4-(Furan-2-yl)-9-β-D-ribofuranosyl-9*H*-pyrimido[4,5-*b*]indole (16a)

Deprotection of **15a** (250 mg, 0.37 mmol) according to the general procedure afforded compound **16a** (108 mg, 80%) as white crystals: mp 106–110 °C,IR (ATR): ν = 3326, 1591, 1561, 1540, 1490, 1461, 1466, 1440, 1121, 1091, 1074, 741. ^1H NMR (500.0 MHz, DMSO-d_6): 3.69 (ddd, 1H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.6, $J_{5'b,4'}$ = 4.0, H-5′b); 3.75 (ddd, 1H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.1, $J_{5'a,4'}$ = 3.4, H-5′a); 4.00 (dt, 1H, $J_{4',5'}$ = 4.0, 3.4, $J_{4',3'}$ = 3.1, H-4′); 4.25 (ddd, 1H, $J_{3',2'}$ = 5.9, $J_{3',OH}$ = 4.9, $J_{3',4'}$ = 3.1, H-3′); 4.84 (ddd, 1H, $J_{2',1'}$ = 7.3, $J_{2',OH}$ = 6.4, $J_{2',3'}$ = 5.9, H-2′); 5.17 (d, 1H, $J_{OH,3'}$ = 4.9, OH-3′); 5.18 (dd, 1H, $J_{OH,5'}$ = 5.6, 5.1, OH-5′); 5.25 (d, 1H, $J_{OH,2'}$ = 6.4, OH-2′); 6.57 (d, $J_{1',2'}$ = 7.3, H-1′); 6.89 (dd, 1H, $J_{4,3}$ = 3.4, $J_{4,5}$ = 1.7, H-4-furyl); 7.44 (ddd, 1H, $J_{6,5}$ = 8.1, $J_{6,7}$ = = 7.2, $J_{6,8}$ = 1.0, H-6); 7.59 (dd, 1H, $J_{3,4}$ = 3.4, $J_{3,5}$ = 0.9, H-3-furyl); 7.60 (ddd, 1H, $J_{7,8}$ = 8.4, $J_{7,6}$ = 7.2, $J_{7,5}$ = 1.2, H-7); 8.08 (ddd, 1H, $J_{8,7}$ = 8.4, $J_{8,6}$ = 1.0, $J_{8,5}$ = 0.6, H-8); 8.29 (dd, 1H, $J_{5,4}$ = 1.7, $J_{5,3}$ = 0.9, H-5-furyl); 8.90 (ddd, 1H, $J_{5,6}$ = 8.1, $J_{5,7}$ = 1.2, $J_{5,8}$ = 0.6, H-5); 8.94 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 61.8 (CH_2-5′); 70.2 (CH-3′); 70.4 (CH-2′); 85.6 (CH-4′); 87.1 (CH-1′); 108.1 (C-4a); 112.9 (CH-8); 113.1 (CH-4-furyl); 114.9 (CH-3-furyl); 119.2 (C-4b); 122.2 (CH-6); 124.7 (CH-5); 128.1 (CH-7); 138.3 (C-8a); 146.6 (CH-5-furyl); 147.6 (C-4); 152.5 (C-2-furyl); 153.7 (CH-2); 156.7 (C-9a). ESI MS *m*/*z* (rel.%): 390 (100) [M+H]. HR MS (ESI) for $C_{19}H_{18}N_3O_5$ [M+H]: calcd 368.12410; found 368.12408. Anal. Calcd for $C_{19}H_{17}N_3O_5$: C, 62.12; H, 4.66; N, 11.44; O 21.78. Found C, 62.18; H, 4.69; N, 11.38.

3.28. 4,6-Bis(furan-2-yl)-9-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (20a)

Protected nucleoside **17a** (500 mg, 0.7 mmol), 2-furyltributylstannane (300 mg, 0.84 mmol), $Pd(OAc)_2$ (7.9 mg, 0.035 mmol) and X-Phos (33.4 mg, 0.07 mmol) were dissolved in anhydrous DMF and heated to 95 °C for 3 h. Then, solvent was evaporated under reduced pressure. Crude product was purified using column chromatography (hexane/EtOAc, 10–20% EtOAc). Nucleoside **20a** (416 mg, 79%) was obtained as white crystals: mp 104–108 °C, IR (ATR): ν = 2360, 2349, 1724, 1560, 1533, 1468, 1449, 1266, 1094, 1027, 711 cm^{-1}. ^1H NMR (500.0 MHz, DMSO-d_6): 4.70 (dd, 1H, J_{gem} = 12.4, $J_{5'b,4'}$ = 4.1, H-5′b); 4.86 (dd, 1H, J_{gem} = 12.4, $J_{5'a,4'}$ = 2.9, H-5′a); 4.91 (ddd, 1H, $J_{4',3'}$ = 6.7, $J_{4',5'}$ = 4.1, 2.9, H-4′); 6.40 (t, 1H, $J_{3',2'}$ = $J_{3',4'}$ = 6.7, H-3′); 6.649 (dd, 1H, $J_{4,3}$ = 3.3, $J_{4,5}$ = 1.8, H-4-furyl-6); 6.652 (dd, $J_{2',3'}$ = 6.7, $J_{2',1'}$ = 4.5, H-2′); 6.94 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 1.7, H-4-furyl-4); 7.00 (dd, 1H, $J_{3,4}$ = 3.3, $J_{3,5}$ = 0.7, H-3-furyl-6); 7.06 (d, $J_{1',2'}$ = 4.5, H-1′); 7.42 (m, 2H, H-*m*-Bz-2′); 7.50 (m, 4H, H-*m*-Bz-3′,5′); 7.62 (m, 1H, H-*p*-Bz-2′); 7.63 (dd, 1H, $J_{3,4}$ = 3.5, $J_{3,5}$ = 0.9, H-3-furyl-4); 7.67, 7.68 (2 × m, 2 × 1H, H-*p*-Bz-3′,5′); 7.79 (dd, 1H, $J_{5,4}$ = 1.8, $J_{5,3}$ = 0.7, H-5-furyl-6); 7.81 (dd, 1H, $J_{7,8}$ = 8.7, $J_{7,5}$ = 1.7, H-7); 7.85 (m, 2H, H-*o*-Bz-2′); 7.96 (m, 2H, H-*o*-Bz-5′); 8.00 (m, 2H, H-*o*-Bz-3′); 8.09 (dd, 1H, $J_{8,7}$ = 8.7, $J_{8,5}$ = 0.3, H-8); 8.39 (dd, 1H, $J_{5,4}$ = 1.7, $J_{5,3}$ = 0.9, H-5-furyl-4); 8.90 (s, 1H, H-2); 9.14 (dd, 1H, $J_{5,7}$ = 1.7, $J_{5,8}$ = 0.3, H-5). ^{13}C NMR (125.7 MHz, DMSO-d_6): 63.2 (CH_2-5′); 70.3 (CH-3′); 72.2 (CH-2′); 78.6 (CH-4′); 86.1 (CH-1′); 105.3 (CH-3-furyl-6); 108.4 (C-4a); 112.0 (CH-8); 112.4 (CH-4-furyl-6); 113.3 (CH-4-furyl-4); 115.4 (CH-3-furyl-4); 119.5 (CH-5); 119.5 (C-4b); 124.1 (CH-7); 125.4 (C-6); 128.6, 128.8 (C-*i*-Bz); 128.9 (CH-*m*-Bz); 129.4 (CH-*o*-Bz-5′); 129.4 (C-*i*-Bz); 129.5 (CH-*o*-Bz-2′); 129.6 (CH-*o*-Bz-3′); 133.7, 134.1 (CH-*p*-Bz); 137.8 (C-8a); 143.0 (CH-5-furyl-6); 146.9 (CH-5-furyl-4); 148.1 (C-4); 152.3 (C-2-furyl-4); 153.3 (C-2-furyl-6); 154.1 (CH-2); 156.6 (C-9a); 164.8 (COPh-2′); 165.0 (COPh-3′); 165.6 (COPh-5′). MS ESI MS *m*/*z* (rel.%): 746 (100) [M+H], 768 (95) [M+Na]. HR MS (ESI) for $C_{44}H_{32}N_3O_9$ [M+H]: calcd 746.21331; found 746.21328.

3.29. 4-(Furan-2-yl)-6-(furan-3-yl)-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (20b)

Method A: Protected nucleoside **17a** (400 mg, 0.56 mmol), 3-furanboronic acid (94 mg, 0.84 mmol), K_2CO_3 (232 mg, 1.68 mmol), $Pd(OAc)_2$ (6.3 mg, 0.028 mmol) and X-Phos (26.7 mg, 0.056 mmol) were dissolved in anhydrous DMF and heated to 95 °C for 3 h. Solvent was evaporated under reduced pressure. Crude product was purified using column chromatography (hexane/EtOAc, 10–20% EtOAc). Nucleoside **20b** (192 mg, 46%) was obtained as white crystals: mp 87–91 °C, IR (ATR): ν = 2356, 2346, 1720, 1563, 1538, 1471, 1452, 1263, 1092, 1024, 706 cm^{-1}. ^1H NMR (500.0 MHz, DMSO-d_6): 4.71 (dd, 1H, J_{gem} = 12.3, $J_{5'b,4'}$ = 4.2, H-5′b); 4.87 (dd, 1H, J_{gem} = 12.3, $J_{5'a,4'}$ = 3.2, H-5′a); 4.91 (ddd, 1H, $J_{4',3'}$ = 6.6, $J_{4',5'}$ = 4.2, 3.2, H-4′); 6.39 (t, 1H, $J_{3',2'}$ = $J_{3',4'}$ = 6.6, H-3′); 6.64 (dd, 1H, $J_{2',3'}$ = 6.6, $J_{2',1'}$ = 4.6, H-2′); 6.92 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 1.7, H-4-furyl-4); 7.04 (dd, 1H, $J_{4,5}$ = 1.9, $J_{4,2}$ = 0.9, H-4-furyl-6); 7.06 (d, $J_{1',2'}$ = 4.6, H-1′); 7.41 (m, 2H, H-*m*-Bz-2′); 7.50 (m, 4H, H-*m*-Bz-3′,5′); 7.61 (m, 1H, H-*p*-Bz-2′); 7.62 (dd, 1H, $J_{3,4}$ = 3.5, $J_{3,5}$ = 0.9, H-3-furyl-4); 7.67, 7.68 (2 × m, 2 × 1H, H-*p*-Bz-3′,5′); 7.71 (dd, 1H, $J_{7,8}$ = 8.6, $J_{7,5}$ = 1.8, H-7); 7.82 (dd, 1H, $J_{5,4}$ = 1.9, $J_{5,2}$ = 1.6, H-5-furyl-6); 7.84 (m, 2H, H-*o*-Bz-2′); 7.97 (m, 2H, H-*o*-Bz-5′); 8.00 (m, 2H, H-*o*-Bz-3′); 8.06 (dd, 1H, $J_{8,7}$ = 8.6, $J_{8,5}$ = 0.5, H-8); 8.27 (dd, 1H, $J_{2,5}$ = 1.6, $J_{2,4}$ = 0.9, H-2-furyl-6); 8.48 (dd, 1H, $J_{5,4}$ = 1.7, $J_{5,3}$ = 0.9, H-5-furyl-4); 8.89 (s, 1H, H-2); 8.82 (dd, 1H, $J_{5,7}$ = 1.8, $J_{5,8}$ = 0.5, H-5). ^{13}C NMR (125.7 MHz, DMSO-d_6): 63.2 (CH_2-5′); 70.4 (CH-3′); 72.2 (CH-2′); 78.6 (CH-4′); 86.1 (CH-1′); 108.3 (C-4a); 109.1 (CH-4-furyl-6); 111.9 (CH-8); 113.2 (CH-4-furyl-4); 115.4 (CH-3-furyl-4); 119.6 (C-4b); 121.3 (CH-5); 126.1 (C-3-furyl-6); 126.2 (CH-7); 126.6 (C-6); 128.6, 128.8 (C-*i*-Bz); 128.9 (CH-*m*-Bz); 129.4 (CH-*o*-Bz-5′); 129.4 (C-*i*-Bz); 129.5 (CH-*o*-Bz-2′); 129.6 (CH-*o*-Bz-3′); 133.7, 134.1 (CH-*p*-Bz); 137.6 (C-8a); 139.1 (CH-2-furyl-6); 144.7 (CH-5-furyl-6); 147.2 (CH-5-furyl-4); 147.9 (C-4); 152.3 (C-2-furyl-4); 153.9 (CH-2); 156.5 (C-9a); 164.8 (COPh-2′); 165.0 (COPh-3′); 165.6 (COPh-5′). MS ESI MS *m*/*z* (rel.%): 746 (100) [M+H], 768 (95) [M+Na]. HR MS (ESI) for $C_{44}H_{32}N_3O_9$ [M+H]: calcd 746.21346; found 746.21331.

Method B: Protected nucleoside **17a** (400 mg, 0.56 mmol), K_2CO_3 (232 mg, 1.68 mmol), $Pd(OAc)_2$ (6.3 mg, 0.028 mmol), X-Phos (26.7 mg, 0.056 mmol) and one third of all amount of 3-furanboronic acid (94 mg, 0.84 mmol) were dissolved in anhydrous DMF (20 ml) and heated to 95 °C for 1 hour. Second third of boronic acid was added and reaction was stirred at 95 °C for one hour. Then, last

third of boronic acid was added and reaction was heated for another one hour at 95 °C. Solvent was evaporated under reduced pressure and crude product was purified by flash chromatography (hexane/EtOAc, 10–20% EtOAc). Nucleoside **20a** was obtained (88 mg, 75%) as white crystals.

3.30. 4-(Furan-2-yl)-6-phenyl-9-(2,3,5-tri-O/-benzoyl-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (20f)

Compound **20f** was prepared as described for **20a** from **17a** (Method A and Method B) (300 mg, 0.42 mmol). Nucleoside **20f** was obtained (196 mg, 62%, Method A), (202 mg, 64%, Method B) as white powder: mp 92–96 °C,IR (ATR): ν = 2359, 2342, 1723, 1470, 1264, 1093, 1069, 708 cm^{-1}.^{1}H NMR (500.0 MHz, DMSO-d_6): 4.72 (dd, 1H, J_{gem} = 12.3, $J_{5'b,4'}$ = 4.1, H-5′b); 4.88 (dd, 1H, J_{gem} = 12.3, $J_{5'a,4'}$ = 3.1, H-5′a); 4.93 (ddd, 1H, $J_{4',3'}$ = 6.6, $J_{4',5'}$ = 4.1, 3.1, H-4′); 6.39 (t, 1H, $J_{3',2'}$ = $J_{3',4'}$ = 6.6, H-3′); 6.65 (dd, 1H, $J_{2',3'}$ = 6.6, $J_{2',1'}$ = 4.7, H-2′); 6.91 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 1.7, H-4-furyl); 7.09 (d, $J_{1',2'}$ = 4.7, H-1′); 7.40 (m, 1H, H-*p*-Ph); 7.41 (m, 2H, H-*m*-Bz-2′); 7.51 (m, 4H, H-*m*-Bz-3′,5′); 7.54 (m, 2H, H-*m*-Ph); 7.62 (m, 1H, H-*p*-Bz-2′); 7.63 (dd, 1H, $J_{3,4}$ = 3.5, $J_{3,5}$ = 0.8, H-3-furyl); 7.67, 7.69 (2 × m, 2 × 1H, H-*p*-Bz-3′,5′); 7.73 (dd, 1H, $J_{7,8}$ = 8.6, $J_{7,5}$ = 1.9, H-7); 7.75 (m, 2H, H-*o*-Ph); 7.84 (m, 2H, H-*o*-Bz-2′); 7.99 (m, 2H, H-*o*-Bz-5′); 8.01 (m, 2H, H-*o*-Bz-3′); 8.12 (d, 1H, $J_{8,7}$ = 8.6, H-8); 8.34 (dd, 1H, $J_{5,4}$ = 1.7, $J_{5,3}$ = 0.8, H-5-furyl); 8.91 (s, 1H, H-2); 9.08 (dd, 1H, $J_{5,7}$ = 1.9, $J_{5,8}$ = 0.5, H-5). ^{13}C NMR (125.7 MHz, DMSO-d_6): 63.2 (CH_2-5′); 70.4 (CH-3′); 72.1 (CH-2′); 78.7 (CH-4′); 86.1 (CH-1′); 108.5 (C-4a); 112.0 (CH-8); 113.3 (CH-4-furyl); 115.3 (CH-3-furyl); 119.7 (C-4b); 122.7 (CH-5); 127.0 (CH-*o*-Ph); 127.2 (CH-7); 127.3 (CH-*p*-Ph); 128.6, 128.8 (C-*i*-Bz); 128.9 (CH-*m*-Bz); 129.4 (CH-*m*-Ph, CH-*o*-Bz-5'); 129.5 (C-*i*-Bz); 129.5 (CH-*o*-Bz-2'); 129.6 (CH-*o*-Bz-3′); 133.7, 134.1 (CH-*p*-Bz); 134.9 (C-6); 137.9 (C-8a); 140.6 (C-*i*-Ph); 146.8 (CH-5-furyl); 148.0 (C-4); 152.4 (C-2-furyl); 154.0 (CH-2); 156.6 (C-9a); 164.8 (COPh-2′); 165.0 (COPh-3′); 165.6 (COPh-5′). MS: ESI MS *m*/*z* (rel.%): 756 (62) [M+H], 778 (100) [M+Na]. HR MS (ESI) for $C_{46}H_{34}N_3O_8$ [M+H]: calcd 756.23404; found 756.23371.

3.31. 4,6-Bis(furan-2-yl)-9-β-D-ribofuranosyl-9*H*-pyrimido[4,5-*b*]indole (21a)

Deprotection of **20a** (300 mg, 0.40 mmol) according to the general procedure afforded compound **21a** (72 mg, 86%) as white crystals: mp 92–95 °C, $[\alpha]_D$ −32.3 (c 0.29, DMSO). IR (ATR): ν = 3297, 2363, 2339, 1590, 1563, 1539, 1466, 1094, 1075, 1042, 743 cm^{-1}.^{1}H NMR (600.1 MHz, DMSO-d_6): 3.71, 3.76 (2 × bdt, 2 × H, J_{gem} = 11.7, $J_{5',4'}$ = $J_{5',OH}$ = 3.5, H-5′); 4.01 (q, 1H, $J_{4',3'}$ = $J_{4',5'}$ = 3.5, H-4'); 4.27 (br m, 1H, H-3'); 4.84 (bddd, 1H, $J_{2',1'}$ = 7.3, $J_{2',OH}$ = 6.1, $J_{2',3'}$ = 4.7, H-2′); 5.20 (br m, 2H, OH-3′,5′); 5.29 (d, 1H, $J_{OH,2'}$ = 6.1, OH-2'); 6.57 (d, $J_{1',2'}$ = 7.3, H-1′); 6.64 (dd, 1H, $J_{4,3}$ = 3.4, $J_{4,5}$ = 1.8, H-4-furyl-6); 6.93 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 1.7, H-4-furyl-4); 7.03 (dd, 1H, $J_{3,4}$ = 3.3, $J_{3,5}$ = 0.8, H-3-furyl-6); 7.62 (dd, 1H, $J_{3,4}$ = 3.5, $J_{3,5}$ = 0.8, H-3-furyl-4); 7.79 (dd, 1H, $J_{5,4}$ = 1.8, $J_{5,3}$ = 0.8, H-5-furyl-6); 7.95 (dd, 1H, $J_{7,8}$ = 8.6, $J_{7,5}$ = 1.8, H-7); 8.15 (dd, 1H, $J_{8,7}$ = 8.6, $J_{8,5}$ = 0.4, H-8); 8.38 (dd, 1H, $J_{5,4}$ = 1.7, $J_{5,3}$ = 0.8, H-5-furyl-4); 8.96 (s, 1H, H-2); 9.17 (dd, 1H, $J_{5,7}$ = 1.8, $J_{5,8}$ = 0.4, H-5). ^{13}C NMR (150.9 MHz, DMSO-d_6): 61.8 (CH_2-5′); 70.2 (CH-3′); 70.6 (CH-2′); 85.7 (CH-4′); 87.1 (CH-1′); 105.2 (CH-3-furyl-6); 108.1 (C-4a); 112.4 (CH-4-furyl-6); 113.3 (CH-4-furyl-4); 113.4 (CH-8); 115.2 (CH-3-furyl-4); 119.3 (CH-5); 119.6 (C-4b); 124.0 (CH-7); 124.9 (C-6); 137.6 (C-8a); 142.8 (CH-5-furyl-6); 146.7 (CH-5-furyl-4); 147.8 (C-4); 152.5 (C-2-furyl-4); 153.6 (C-2-furyl-6); 154.0 (CH-2); 157.1 (C-9a). ESI MS *m*/*z* (rel.%): 434 (100) [M+H]. HR MS (ESI) for $C_{23}H_{20}N_3O_6$ [M+H]: calcd 434.13466; found 434.13460. $C_{23}H_{19}N_3O_6$ (433.4): calcd C 63.74, H 4.42, N 9.70, O 22.15; found C, 63.68, H 4.38, N 9.75.

3.32. 4-(Furan-2-yl)-6-(furan-3-yl)-9-β-D-ribofuranosyl-9*H*-pyrimido[4,5-*b*]indole (21b)

Deprotection of **20b** (200 mg, 0.27 mmol) according to the general procedure afforded compound **21b** (68 mg, 90%) as white crystals: mp 110–115 °C, $[\alpha]_D$ −33.0 (*c* 0.25, DMSO). IR (ATR): ν = 3359, 2365, 2342, 1748, 1561, 1540, 1472, 1094, 1042, 748 cm^{-1}.^{1}H NMR (499.8 MHz, DMSO-d_6): 3.70 (ddd, 1H, J_{gem} = 11.9, $J_{5'b,OH}$ = 5.6, $J_{5'b,4'}$ = 4.0, H-5′b); 3.76 (ddd, 1H, J_{gem} = 11.9, $J_{5'a,OH}$ = 5.0, $J_{5'a,4'}$ = 3.3, H-5′a); 4.01 (ddd, 1H, $J_{4',5'}$ = 4.0, 3.3, $J_{4',3'}$ = 2.9, H-4′); 4.26 (ddd, 1H, $J_{3',2'}$ = 6.0, $J_{3',OH}$ = 4.8, $J_{3',4'}$ = 2.9, H-3′); 4.83 (ddd, 1H, $J_{2',1'}$ = 7.3, $J_{2',OH}$ = 6.4, $J_{2',3'}$ = 6.0, H-2′); 5.20 (d, 1H, $J_{OH,3'}$ = 4.8, OH-3′); 5.22 (d, 1H, $J_{OH,5'}$ = 5.6, 5.0, OH-5′); 5.29 (d, 1H, $J_{OH,2'}$ = 6.4, OH-2′); 6.57 (d, $J_{1',2'}$ = 7.3, H-1′); 6.92 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 1.7, H-4-furyl-4); 7.09 (dd, 1H, $J_{4,5}$ = 1.9, $J_{4,2}$ = 0.9, H-4-furyl-6); 7.61 (dd, 1H, $J_{3,4}$ = 3.5, $J_{3,5}$ = 0.9, H-3-furyl-4); 7.82 (dd, 1H, $J_{5,4}$ = 1.9, $J_{5,2}$ = 1.5, H-5-furyl-6); 7.87 (dd, 1H, $J_{7,8}$ = 8.5, $J_{7,5}$ = 1.7, H-7); 8.12 (d, 1H, $J_{8,7}$ = 8.5, H-8); 8.31 (dd, 1H, $J_{2,5}$ = 1.5, $J_{2,4}$ = 0.9, H-2-furyl-6); 8.48 (dd, 1H, $J_{5,4}$ = 1.7, $J_{5,3}$ = 0.9, H-5-furyl-4); 8.95 (s, 1H, H-2); 9.03 (d, 1H, $J_{5,7}$ = 1.7, H-5). ^{13}C NMR (125.7 MHz, DMSO-d_6): 61.8 (CH_2-5′); 70.2 (CH-3′); 70.6 (CH-2′); 85.6 (CH-4′); 87.1 (CH-1′); 108.0 (C-4a); 109.2 (CH-4-furyl-6); 113.2 (CH-4-furyl-4); 113.4 (CH-8); 115.1 (CH-3-furyl-4); 119.7 (C-4b); 121.1 (CH-5); 126.1 (CH-7); 126.1 (C-6); 126.3 (C-3-furyl-6); 137.3 (C-8a); 139.1 (CH-2-furyl-6); 144.7 (CH-5-furyl-6); 147.0 (CH-5-furyl-4); 147.7 (C-4); 152.5 (C-2-furyl-4); 153.9 (CH-2); 157.0 (C-9a). ESI MS *m*/*z* (rel.%): 434 (100) [M+H]. HR MS (ESI) for $C_{23}H_{20}N_3O_6$ [M+H]: calcd 434.13466; found 434.13452. Anal. Calcd for $C_{23}H_{20}N_3O_6$: C, 63.74; H, 4.42; N, 9.70; O 22.15. Found C, 63.62; H, 4.39; N, 9.63.

3.33. 4-(Furan-2-yl)-6-phenyl-9-β-D-ribofuranosyl)-9*H*-pyrimido[4,5-*b*]indole (21f)

Deprotection of **20f** (130 mg, 0.17 mmol) according to the general procedure afforded compound **21f** (62 mg, 81%) as white crystals: mp 174–177 °C, $[\alpha]_D$ −30.3 (c 0.26, DMSO). IR (ATR): ν = 3296, 2359, 2342, 1734, 1561, 1541, 1470, 1094, 1042, 758 cm^{-1}. ^{1}H NMR (500.0 MHz, DMSO-d_6): 3.72 (ddd, 1H, J_{gem} = 12.0, $J_{5'b,OH}$ = 5.6, $J_{5'b,4'}$ = 3.9, H-5′b); 3.77 (ddd, 1H, J_{gem} = 12.0, $J_{5'a,OH}$ = 5.2, $J_{5'a,4'}$ = 3.3, H-5′a); 4.02 (ddd, 1H, $J_{4',5'}$ = 3.9, 3.3, $J_{4',3'}$ = 3.0, H-4′); 4.27 (ddd, 1H, $J_{3',2'}$ = 5.9, $J_{3',OH}$ = 4.8, $J_{3',4'}$ = 3.0, H-3′); 4.85 (ddd, 1H, $J_{2',1'}$ = 7.3, $J_{2',OH}$ = 6.4, $J_{2',3'}$ = 5.9, H-2′); 5.19 (d, 1H, $J_{OH,3'}$ = 4.8, OH-3′); 5.22 (d, 1H, $J_{OH,5'}$ = 5.6, 5.2, OH-5′); 5.28 (d, 1H, $J_{OH,2'}$ = 6.4, OH-2′); 6.59 (d, $J_{1',2'}$ = 7.3, H-1′); 6.92 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 1.7, *H*-4-furyl); 7.40 (m, 1H, H-*p*-Ph); 7.54 (m, 2H, H-*m*-Ph); 7.62 (dd, 1H, $J_{3,4}$ = 3.5, $J_{3,5}$ = 0.9, *H*-3-furyl); 7.80 (m, 2H, H-*o*-Ph); 7.90 (dd, 1H, $J_{7,8}$ = 8.6, $J_{7,5}$ = 1.8, H-7); 8.18 (d, 1H, $J_{8,7}$ = 8.6, H-8); 8.34 (dd, 1H, $J_{5,4}$ = 1.7, $J_{5,3}$ = 0.9, *H*-5-furyl); 8.97 (s, 1H, H-2); 9.11 (d, 1H, $J_{5,7}$ = 1.8, H-5). ^{13}C NMR (125.7 MHz, DMSO-d_6): 61.8 (CH_2-5′); 70.2 (CH-3′); 70.5 (CH-2′); 85.6 (CH-4′); 87.1 (CH-1′); 108.2 (C-4a); 113.2 (CH-4-furyl); 113.4 (CH-8); 115.1 (CH-3-furyl); 119.9 (C-4b); 122.5 (CH-5); 127.0 (CH-*o*-Ph); 127.0 (CH-7); 127.2 (CH-*p*-Ph); 129.4 (CH-*m*-Ph); 134.4 (C-6); 137.7 (C-8a); 140.8 (C-*i*-Ph); 146.6 (CH-5-furyl); 147.8 (C-4); 152.5 (C-2-furyl); 153.9 (CH-2); 157.1 (C-9a). ESI MS *m*/*z* (rel.%): 444 (100) [M+H]. HR MS (ESI) for $C_{25}H_{21}N_3O_5$ [M+H]: calcd 444.15540; found 444.15513. Anal. Calcd for $C_{25}H_{21}N_3O_5$: C, 67.71; H, 4.77 N, 9.48; O 18.04. Found C, 67.93; H, 4.83; N, 9.39.

3.34. 4,6-Diphenyl-9-β-D-ribofuranosyl-9*H*-pyrimido[4,5-*b*]indole (19) and 4-phenyl-9-β-D-ribofuranosyl-9*H*-pyrimido[4,5-*b*]indole (16f)

Free nucleoside **18f** (50 mg, 0.12 mmol), phenylboronic acid (22 mg, 0.18 mmol), K_2CO_3 (33 mg, 0.24 mmol), $Pd(OAc)_2$ (1.3 mg,

7.5 μmol) and CataXCium F (8.3 mg, 15 μmol) were dissolved in mixture of n-butanol (2.5 ml) and water (1 ml) and heated to 95 °C for 12 h. Solvents were evaporated under reduced pressure and reaction mixture was separated by column chromatography (1–3% of MeOH in $CHCl_3$). Unseparable mixture of compounds **19** and **16f** (12 mg) was obtained as white powder. Products were identified and characterised by NMR and MS spectra. ESI MS *m*/*z* (rel.%): 378 (70) [**16f**+H]; 400 (100) [**16f**+Na]; 454 (25) [**19**+H]; 476 (32) [**19**+Na]. HR MS (ESI) for $C_{21}H_{19}N_3O_4$ [M+H]: calcd 377.1376; found 377.1375; for $C_{27}H_{23}N_3O_4$ [M+H]: calcd 453.16886; found 453.16890.

3.35. Dengue replicon and cell cytotoxicity assays

Dengue replicon assay[21] was used to test antiviral activity of compounds. Briefly, Capsid, prM and Envelope region of the Dengue 2 NGC was replaced by luciferase gene and a selectable marker, creating a subgenomic virus which can only propagate within the cells. The level of luciferase activity can be used as a surrogate readout to indicate viral replication. 5000 Huh-Ehr2 cells containing Dengue replicon was seeded overnight in DMEM media supplemented with 2% fetal calf serum in 384-well plates. After overnight incubation, serially diluted compounds were then added into each well and further incubated for 48 h. Luciferase activity was measured and EC_{50} calculated as previously described.[21] For the cytotoxicity assay, twenty five microliters of media containing either 400 HepG2 or 2000 THP-1 cells were dispensed into 384-well tissue culture plate per well. 125 nl of serial diluted compounds were added into the cells in each well and further incubated for another 96 h. Cell Counting Kit-8 (CCK-8, Dojindo) was then added into each wells and the cells were further incubated in 37 °C for another 3 h. The plate was then measured at 450 nm. CC_{50} readings were calculated based on the compound concentration which gave 50% of reduction in signal.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.08.021.

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