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2-Aryl-8-aza-3-deazaadenosine Analogues of 5'-*O*-[*N*-(Salicyl)sulfamoyl]adenosine: Nucleoside Antibiotics that Block Siderophore Biosynthesis in *Mycobacterium tuberculosis*

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ABSTRACT

A series of 5'-*O*-[*N*-(salicyl)sulfamoyl]-2-aryl-8-aza-3-deazaadenosines were designed to block mycobactin biosynthesis in *Mycobacterium tuberculosis* (*Mtb*) through inhibition of the essential adenylating enzyme MbtA. The synthesis of the 2-aryl-8-aza-3-deazaadenosine nucleosides featured sequential copper-free palladium-catalyzed Sonogashira coupling of a precursor 4-cyano-5-iodo-1,2,3-triazolonucleoside with terminal alkynes and Minakawa-Matsuda annulation reaction. These modified nucleosides were shown to inhibit MbtA with apparent K_i values ranging from 6.1 to 25 nM and to inhibit *Mtb* growth under iron-deficient conditions with minimum inhibitory concentrations ranging from 12.5 to >50 μM.

Keywords: 8-Aza-3-deazaadenosine; Modified Nucleoside; Tuberculosis; Siderophore Biosynthesis, Adenylation Inhibitor.

1. Introduction

Tuberculosis (TB) is an infectious disease primarily caused by the bacterium *Mycobacterium tuberculosis* (*Mtb*) that recently surpassed HIV as the leading cause of infectious disease mortality [1]. *Mtb* is easily spread from an actively infected individual by the aerosol route. Upon inhalation *Mtb* quickly replicates and becomes encased in granulomatous lesions in the lungs. A majority of healthy individuals infected with *Mtb* are asymptomatic and able to effectively contain, but not clear, the bacteria in these granulomas. Latently infected individuals provide a vast reservoir of the disease and include nearly one-third of the global population. However, individuals – who have an impaired immune system from aging, malnutrition, or co-infection with HIV – are much more likely to develop active TB or reactivate a latent infection. Active TB infections ensue when the granulomas rupture, releasing the bacteria into the sputum leading to the clinical manifestations of hemoptysis and cachexia. Treatment of simple drug-susceptible TB is very challenging, compared to most bacterial infections, requiring 6–9 months of a four-drug regimen comprised of isoniazid, rifampicin, ethambutol, and pyrazinamide [2]. The underlying cause of the persistence and drug tolerance of *Mtb in vivo* that necessitates this long treatment course is still not fully understood, but is likely multifactorial resulting from variability in the lesion environment and phenotype of individual bacteria [3, 4]. Considering the unique challenges posed by drug susceptible TB, the emergence and dissemination of multidrug resistance TB (MDR-TB) and extensively drug resistant TB (XDR-TB), which are minimally resistant to the two most effective antitubercular agents – isoniazid and rifampicin, is a global health crisis [5]. The European region alone accounts for more than a quarter of the global MDR-TB burden [6]. In order to bring TB back under control, a unified effort will be required to develop improved diagnostics, effective vaccines, and new anti-tubercular agents with novel modes of action.

Mtb requires iron, a trace micronutrient that is highly restricted in a mammalian host, to establish and maintain an infection. To circumvent the nutritional immunity imposed by the host, *Mtb* synthesizes and secretes a family of small-molecule iron chelators or siderophores known as the mycobactins that extract iron (Fe^{3+}) from host proteins [7]. The Fe^{3+}-mycobactin complex is then imported back into the bacterium through a specialized transport system and the iron is reductively released from the siderophore. The mycobactins share a common biosynthetic pathway for construction of the conserved peptidic core using a mixed non-ribosomal peptide synthetase–polyketide synthase (NRPS-PKS) assembly line of six proteins designated MbtA through MbtF [8]. The nucleoside derivative 5'-*O*-[*N*-

(salicyl)sulfamoyl]adenosine (Sal-AMS, **2**, Fig. 1) is a potent nanomolar inhibitor of MbtA, which catalyzes the first committed step in mycobactin synthesis, through the activation of salicylic acid to the mixed anhydride salicyl-AMP intermediate (**1**) and subsequent loading onto MbtB [9-11]. Sal-AMS blocks synthesis of the mycobactins and correspondingly inhibits growth of *Mtb* under iron-deficient conditions *in vitro* and *in vivo* [12]. Comprehensive SAR studies of **2** demonstrated the *N*-(salicyl)sulfamoyl moiety is essential for activity and only conservative substitutions to the salicyl ring were permitted [13]. By contrast, the nucleoside is substantially more tolerant to modification with addition of nonpolar aromatic substituents at C-2 exemplified by 2-phenyl-Sal-AMS (**3**) providing the most potent Sal-AMS derivatives [14]. These studies also showed the N-3 nitrogen atom of adenosine is dispensable for activity [14].

To extend the SAR investigation of base-modified Sal-AMS analogues we describe herein the synthesis and evaluation of a series of compounds bearing the isosteric 8-aza-3-deazaadenine nucleobase with various 2-aryl substituents (**6a**–**f**, Fig. 2) that uniquely capitalize on the existing SAR. The 8-aza-3-deazaadenine nucleosides have several useful attributes over adenosine and other modified purine nucleosides as elaborated below including stability to cyclonucleoside degradation, lack of intrinsic biological activity, and improved fluorescent properties. Purine nucleoside analogues containing an activated 5'-leaving groups like a sulfamate as found in Sal-AMS are prone to cyclonucleoside formation through attack of the N-3 purine atom onto the C-5' ribose to afford a 3,5'-cyclonucleoside [15]. This undesired degradation pathway is prevented in 8-aza-3-deazaadenines due to lack of a N-3 atom. As first reported by Franchetti, 8-aza-3-deazaadenosine is devoid of biological activity suggesting it binds poorly to ATP-utilizing proteins, a feature that we exploit to minimize potential off-target toxicity [16].

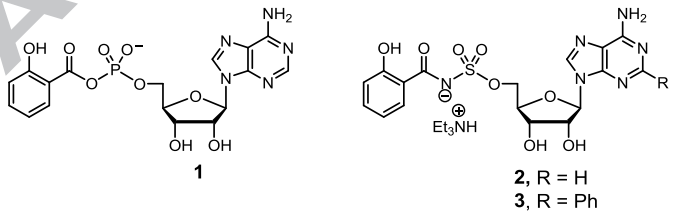


Figure 1. Structures of Sal-AMP (**1**), Sal-AMS (**2**) and 2-phenyl analog of Sal-AMS (**3**).

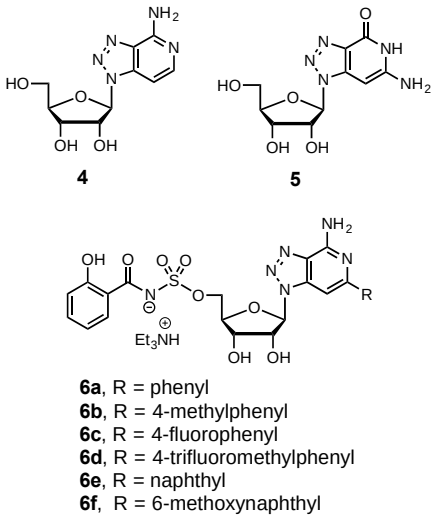


Figure 2. Structures of 8-aza-3-deazaadenosine (**4**), 8-aza-3-deazaguanosine (**5**), and 2-aryl-8-aza-3-deazaadenine analogs of Sal-AMS (**6a**–**f**).

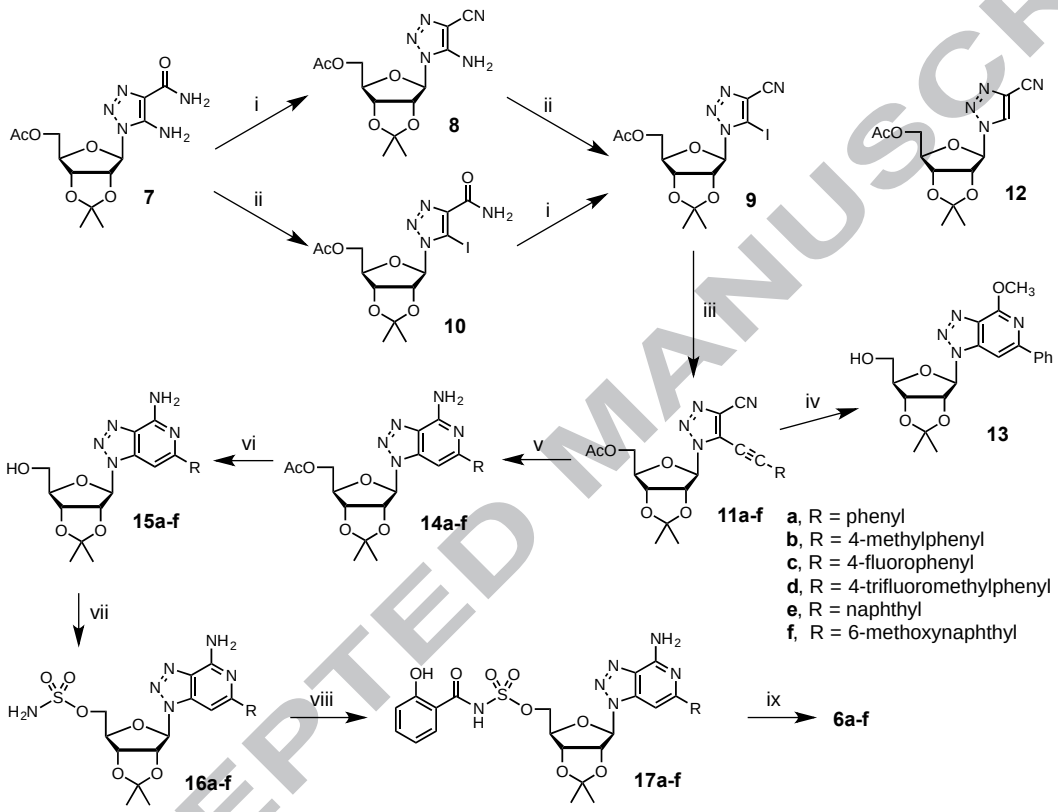
2. Results and discussion

2.1 Chemistry

There are two general synthetic approaches for the preparation of 8-aza-3-deazaadenosine (**4**) and the homologous guanosine derivative (**5**) that have been reported in the literature: (1) glycosylation of a protected sugar with a triazolo[4,5-*c*]pyridine heterocycle and (2) annulation onto a 1*H*-[1,2,3]triazole-1-β-D-ribofuranoside derivative generated from the glycosylation of the corresponding aglycone, or the 1,3-dipolar cycloaddition of a ribofuranosyl azide to an appropriate dipolarophile, or the Dimroth reaction. The glycosylation strategy suffers from poor selectivity resulting in a mixture of N(1), N(2) and N(3) regiosomeric products [16,17] while the latter procedure involving elaboration of a pre-formed triazole does not allow facile incorporation of C-6 aryl substituents [18-22]. We elected to adapt methodology first reported by Minakawa and Matsuda for the construction of 3-deazapurine nucleosides involving nucleophilic cyclization of 4-carbamoyl- or 4-cyano-substitued derivatives of 5-ethynyl-1-β-D-ribofuranosylimidazole [23,24]. We were inspired by the successful application of this method for the preparation of related carbocyclic 8-aza-3-deazainosine derivatives reported by Agrofoglio and co-workers [25]. Herein we present the synthesis of protected 5-alkynyl-1-β-D-ribofuranosyl-1*H*-[1,2,3]triazole-4-carbonitriles and their ring closure leading to the corresponding 2-aryl-8-aza-3-deazaadenosine analogues using a modified Minakawa-Matsuda annulation strategy.

Synthesis of the triazole nucleoside building block **9** was accomplished as shown in Scheme 1 starting from 5-amino-4-carboxamide-1,2,3-triazole nucleoside (**7**) prepared from

2,3-*O*-isopropylidene-β-D-ribofuranosyl azide as reported through Dimroth reaction with cyanoacetamide [26-28]. Dehydration of the amide in **7** to the respective nitrile **8** was accomplished by treatment with 4-toluenesulfonyl chloride [28]. Subsequent diazotization-iodination of **8** with diiodomethane and isoamyl nitrite afforded **9** in 75% over two steps, which was superior the inverse reaction sequence via **10** that provided a lower 41% overall yield.



Scheme 1. Synthesis of compounds **6a**–**f**. Reagents and conditions: (i) Pyr, TsCl, rt; (ii) CH_2I_2, isoamyl nitrite, 100 ºC; (iii) alkyne, K_2CO_3, $(PhCN)_2PdCl_2$, 1,4-dioxane, H_2O, 55–65 ºC; (iv) NH_3–MeOH, 80 ºC; (v) NH_3–DME, 85 ºC; (vi) MeONa–MeOH, 5 ºC, then Dowex 50WX8-100; (vii) NH_2SO_2Cl, MeCN, DMA, rt; (viii) salicylic acid, CDI, MeCN, 60 °C, then substrate, DBU, rt; (ix) 4:1 TFA–H_2O, 5 °C.

The Sonogashira coupling of **9** was first optimized with phenylacetylene. We explored a wide variety of conditions, catalysts, and additives (Supplementary data, Table S1) [29]. Optimal conditions were found using bis(benzonitrile)palladium(II) chloride as reported by Minakawa and co-workers [30], but employing K_2CO_3 as base in 1,4-dioxane with 10 equivalents of H_2O at 60 ºC to afford **11a** in 69% yield. These conditions minimized formation of homocoupled products (not shown) as well as hydrodehalogenated **12** and were used for the other terminal alkynes to afford products **11b**–**f** in 43–77% yield. The requisite

terminal alkynes, except phenylacetylene and 1-ethynyl-4-methylbenzene, were prepared by deprotection [31] of their trimethylsilyl precursors obtained using previously reported procedures [31,32] (Supplementary data).

We undertook the key Minakawa–Matsuda annulation of **11a** using MeOH saturated with NH_3, 80 °C [23,24]. However, we obtained the 4-methoxy-6-phenyl cyclized product **13** (68% yield) due to competitive reaction with methanol. Thus, we next examined non-nucleophilic solvents including 1,4-dioxane, THF, and 1,2-dimethoxyethane (DME). Using 1,4-dioxane saturated with NH_3, we obtained at 120 °C an encouraging 29% yield of the desired product **14a** along with 61% unreacted **11a**. The yield of **14a** was further improved to 58% (along with 32% recovered **11a**) employing THF saturated with NH_3. We attributed the improved yield to the greater solubility of ammonia in THF. Based on this hypothesis, we saturated DME with ammonia at -60 ºC then added **11a** and heated at 85°C to obtain **14a** in an impressive 95% yield. This optimized method was then successfully used for the synthesis of compounds **14b**–**f**.

Methanolysis of compounds **14a**–**f** afforded their corresponding 5'-deacetylated congeners **15a**–**f**, which were then converted to 5'-*O*-sulfamoyl derivatives **16a**–**f** by treatment with sulfamoyl chloride in MeCN–DMA [33]. These sulfamates **16a–f** were coupled to salicylic acid using CDI activation and DBU as a base in MeCN to provide **17a**–**f** [13]. Deprotection of the isopropylidene acetal was accomplished with 80% aqueous TFA and the final products **6a**–**f** were isolated as the triethylammonium salts following silica gel chromatography with 0.5% triethylamine as eluent, which were all greater than 99% pure as determined by HPLC.

We determined the fluorescence properties of compounds **6a**–**f** in MeOH and in aqueous solutions (Table 1). The emission maxima measured for all compounds in MeOH were in the range λ_{max} 409-420 nm (Stokes shifts 95.5-111.5 nm), and in H_2O in the range λ_{max} 420-442 nm (Stokes shifts 106.5-137.5 nm). These results are comparable with data given previously for 8-aza-3-deazaadenosine (**4**) in H_2O (λ_{max} 430 nm, Stokes shift 140 nm) [17]. Compounds **6a** and **6d**–**f** in MeOH exhibited relatively high values of fluorescence quantum yield (Φ_F = 0.32-0.5, compared with Φ_F = 1 assumed for 2-aminopurine), while compounds **6b** and **6c** were less fluorescent (Φ_F = 0.06 and 0.11). In contrast, the quantum yield values of **6a**–**f** in H_2O were decreased 30- to 250-fold.

Table 1. Fluorescence properties of compounds **6a–f**.

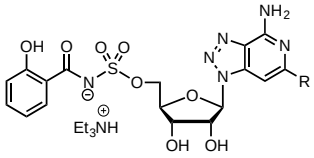
Compd	Fluorescence emission[a] (MeOH)		Fluorescence emission[a] (H_2O)	
	λ_{max} (nm)	Φ_F[b]	λ_{max} (nm)	Φ_F[b]
6a	419	0.37	433	0.0015
6b	412	0.06	433	0.0018
6c	420	0.11	442	0.002
6d	409	0.32	422	0.0019
6e	412	0.38	420	0.0025
6f	418	0.5	425	0.007

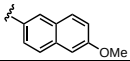
[a] Excitation at 305 nm. [b] Fluorescence quantum yields calculated relative to 2-aminopurine (Φ_F = 1).

2.2. Enzyme inhibition and antitubercular activity

Inhibitors **6a–f** were evaluated for enzyme inhibition against recombinant MbtA under initial velocity conditions as previously described (see Experimental Section) [34]. The apparent inhibition constants (appK_i) were determined by fitting the concentration–response plots to the Morrison equation (eq 1, see Experimental Section) since all compounds exhibited tight-binding behavior. The appK_i values ranged from 6.1 to 25 nM (Table 2). The first analogue in the series **6a** was 31-fold less potent than the isosteric analogue 2-phenyl-Sal-AMS (**3**) demonstrating simultaneous deletion of the N-3 atom and introduction of an N-8 atom in **6a** was not well tolerated. Nonetheless, **6a** is still an exceptionally potent compound and the appK_i vastly underestimates the true potency since the assay was performed using supersaturating concentrations of all substrates. Introduction of *p*-methyl, *p*-fluoro, and *p*-trifluoromethyl in **6b**, **6c**, and **6d**, respectively, had a relatively negligible impact on potency and these analogues were only 2–3 fold less potent than **6a**. Introduction of the 2-naphthyl substituent in **6e** provided the most potent 8-aza-3-deazaadenine analogue with an appK_i of 6.1 nM commensurate with **2** while further modification of the naphthyl moiety with a 6-methoxy substituent in **6f** was not beneficial leading to a 2-fold loss of potency relative to **6e**.

Table 2. Enzyme inhibition and antimycobacterial activity of **6a–f**.



Inhibitor	R	appK_i (nM)[a]	MIC (μM)[b]
2	na[c]	6.6 ± 1.5[d]	0.39[d]
3	na[c]	0.27 ± 0.07[d]	0.049[d]
6a		8.4 ± 1.0	25
6b		16.9 ± 1.9	25
6c		13.7 ± 2.3	19
6d		25.0 ± 1.9	>50
6e		6.1 ± 0.7	12.5
6f		10.5 ± 1.2	19

[a]Assay performed with 7 nM MbtA, 10 mM ATP, 250 μM salicylic acid, 1 mM PPi. [b]*M. tuberculosis* H37Rv grown in glycerol-alanine salts (GAS) medium without ferric ammonium citrate at pH 6.6. [c]not applicable. [d]reference 14.

Next, we evaluated these analogs against whole-cell *M. tuberculosis* H37Rv under iron-deficient and iron-replete conditions as previously described [11]. These antibacterial agents operate by a unique mechanism of action and target iron acquisition by inhibition of siderophore biosynthesis. Under iron-replete conditions, none of the compounds displayed any activity at the maximum concentration evaluated (50 μM) against whole-cell *M. tuberculosis* H37Rv consistent with their designed mechanism of action. Activity was revealed only under iron-deficient conditions. The minimum inhibitory concentrations (MIC) that resulted in complete inhibition of observable growth under iron-deficient conditions are shown in Table 1. The antitubercular activity of **6a–f** excluding **6d** ranged between 12.5 and 25 μM, consistent with their relatively flat biochemical SAR. Compared to the lead compound **2**, all of the compounds showed considerable loss in whole-cell activity despite displaying similar biochemical potency. These results suggest the nucleoside modification adversely impacted cellular accumulation.

3. Conclusion

The series of 2-aryl-8-aza-3-deazaadenine nucleobase analouges of 5'-*O*-[*N*-(salicyl)sulfamoyl]adenosine (**2**) were synthesized as siderophore inhibitors based on prior SAR studies and evaluated for biochemical activity against MbtA and whole-cell activity under iron-deficient conditions with *M. tuberculosis* H37Rv. We developed an optimized route to the 2-aryl-8-aza-3-deazaadenosine nucleosides using a modified Minakawa–Matsuda annulation strategy that was highly efficient and enabled facile introduction of C-2 aryl substituents. The SAR studies revealed concurrent introduction of an N-8 atom and deletion of the N-3 atom in the purine base was detrimental to biochemical potency and whole-cell activity. Despite these shortcomings, the compounds showed high chemical stability and promising fluorescent properties that could be useful to study mycobacterial accumulation and localization.

4. Experimental section

4.1. General chemistry methods

Melting points were determined on MEL-TEMP II capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 spectrometer operating at 400.1 MHz and 100.6 MHz, respectively, or on Unity 300 Varian spectrometer operating at 300 MHz and 75.4 MHz, respectively. ^{19}F NMR spectra were recorded on a Bruker 400 spectrometer at 376.4 MHz. The chemical shifts are reported in ppm (δ scale). Mass spectra were recorded using ESI-MS Thermo Q Exactive and Bruker micrOTOF-Q mass spectrometers. UV spectra were measured with Beckman Coulter DU 640 spectrophotometer. Fluorescence spectra were measured on a Shimadzu RF-5301 PC fluorescence spectrophotometer (excitation at 305 nm); quantum yields were calculated relative to 2-aminopurine (Φ_F = 1) Microwave heating was performed with Ertec-Poland MW reactor. Thin-layer chromatography (TLC) was carried out on Merck precoated 60 F_{254} silica gel plates, while column chromatography on Merck silica gel 60H (40-63 μm). Anhydrous 1,4-dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were prepared by stirring with iron(II) sulfate heptahydrate at room temperature, followed by drying with KOH, distillation with calcium hydride (CaH_2) and distillation with sodium/benzophenone. Other anhydrous solvents were prepared as follows: MeOH by treatment with magnesium turnings/iodine and distillation, MeCN and CH_2Cl_2 by distillation with P_2O_5, pyridine by drying with KOH and distillation with P_2O_5, dimethylformamide (DMF) by drying with CaH_2

and distillation, triethylamine by distillation with CaH_2. Anhydrous dimethylacetamide (DMA) was purchased from Acros. MeOH (Acros) and MeCN (J.T.Baker) used for UV and fluorescence spectra were of HPLC grade.

4.2. Chemical synthesis

*4.2.1. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-5-amino-1H-[1,2,3]triazole-4-carbonitrile (**8**)*

4-Toluenesulfonyl chloride (4.437 g, 22.81 mmol) was added to a solution of **7** [11] (3.975 g, 11.64 mmol) in dry pyridine (55 ml). After being stirred at room temperature for 24 h, the reaction mixture was treated with 5% aq $NaHCO_3$ (100 ml) at 0 ºC and with CH_2Cl_2 (400 ml). The organic layer was separated, while the aqueous one was extracted again with CH_2Cl_2 (300 ml). Combined organic layers were dried with $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc-hexane (1:2→2:1) as an eluent to afford solid **8** (3.398 g, 90% yield). UV (MeOH) λ_{max} = 247.5 nm (5900). ^{1}H NMR (DMSO-d_6) δ 7.42 (s, 2H, NH_2), 6.22 (d, $J_{1',2'}$=0.8 Hz, 1H, 1'-H), 5.46 (dd, $J_{2',1'}$=0.8 Hz, $J_{2',3'}$=5.8 Hz, 1H, 2'-H), 4.96 (dd, $J_{3',2'}$=5.8 Hz, $J_{3',4'}$=2.2 Hz, 1H, 3'-H), 4.37 (m, 1H, 4'-H), 4.02 (dd, $J_{5'a,5'b}$=11.6 Hz, $J_{5'a,4'}$=6.0 Hz, 1H, 5'a-H) 3.85 (dd, $J_{5'b,5'a}$=11.6 Hz, $J_{5'b,4'}$=7.2 Hz, 1H, 5'-H), 1.97 (s, 3H, OAc), 1.50 and 1.34 (2×s, 6H, 2×CH_3). ^{13}C NMR (DMSO-d_6) δ 169.90 (CO), 148.51 (C-5), 113.25 ((CH_3)$_2$*C*), 112.81 (CN), 101.19 (C-4), 88.46 (C-1'), 85.28 (C-4'), 83.33 (C-2'), 81.48 (C-3'), 63.41 (C-5'), 26.61 and 24.94 ((CH_3)$_2$C), 20.42 (CO-CH_3).

*4.2.2. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-5-iodo-1H-[1,2,3]triazole-4-carbonitrile (**9**)*

To a suspension of **8** (628 mg, 1.94 mmol) in diiodomethane (31.18 g, 116.4 mmol) isoamyl nitrite (797 mg, 6.8 mmol) was added. The resulting mixture was stirred at 100 ºC for 2.5 h, then it was applied onto a silica gel column. The column was eluted with CH_2Cl_2 (in order to collect diiodomethane) followed by CH_2Cl_2-MeOH (9:1). Isolated crude product was purified on a next silica gel column using EtOAc-hexane (1:2→2:1) to give **9** as a solid (704 mg, 83% yield). UV (MeOH) λ_{max} 239 nm (5400). ^{1}H NMR (DMSO-d_6) δ 6.22 (s, 1H, 1'-H), 5.67 (d, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.04 (dd, $J_{3',2'}$=5.8 Hz, $J_{3',4'}$=1.8 Hz, 1H, 3'-H), 4.49 (m, 1H, 4'-H), 3.92 (dd, $J_{5'a,5'b}$=12.0 Hz, $J_{5'a,4'}$=5.2 Hz, 1H, 5'-H), 3.82 (dd, $J_{5'b,5'a}$=11.8 Hz, $J_{5'b,4'}$=7.4 Hz, 1H, 5'-H), 1.91 (s, 3H, OAc), 1.53 and 1.36 (2×s, 6H, 2×CH_3). ^{13}C NMR (DMSO-d_6) δ 169.72 (CO), 128.46 (C-4), 112.93 ((CH_3)$_2$*C*), 112.04 (CN), 95.35 (C-5), 93.75 (C-1'), 86.23

(C-4'), 83.51 (C-2'), 81.16 (C-3'), 62.86 (C-5'), 26.58 and 24.88 ((*C*H_3)$_2$C), 20.36 (CO-*C*H_3). HRMS $[M+H]^+$ calcd for $C_{13}H_{16}IN_4O_5$: 435.0160; found: 435.0156.

*4.2.3. General procedure for the coupling of **9** with terminal alkynes*

A solution of **9** (dried *in vacuo* over P_2O_5 at 50 ºC) and bis(benzonitrile)palladium(II) chloride (0.1 equiv) in anhyd 1,4-dioxane (20 ml/mmol) was vigorously deoxygenated with argon for 15 min. To the solution was added K_2CO_3 (1.0-1.3 equiv), water (10 equiv) and alkyne (3 equiv). The reaction mixture was heated at 55-65 ºC overnight, then evaporated. The residue was chromatographed on silica gel column using toluene-EtOAc (98:2→95:5 or 95:5→9:1) to give a crude product. It was subsequently rechromatographed on next silica gel column using hexane-EtOAc (9:1 or 9:1→4:1) to isolate pure **11a**–**f**.

*4.2.4. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-5-phenylethynyl-1H-[1,2,3]triazole-4-carbonitrile (**11a**)*

Solid foam, 69% yield. UV (MeCN): λ_{max} 288.5 nm (14500), 306 nm (12600). ^{1}H NMR (DMSO-d_6) δ 7.74 (m, 2H, Ph), 7.62-7.52 (m, 3H, Ph), 6.48 (s, 1H, 1'-H), 5.64 (d, $J_{2',3'}$=5.8 Hz, 1H, 2'-H), 5.04 (dd, $J_{3',2'}$=5.8 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.56 (m, 1H, 4'-H), 4.00 (m, 2H, 5'-H), 1.90 (s, 3H, OAc), 1.54 and 1.37 (2×s, 6H, 2×CH_3). ^{13}C NMR (DMSO-d_6) δ 169.78 (CO), 132.12, 131.29 and 129.16 (Ph), 127.65 and 122.64 (C-4, C-5), 118.98 (Ph), 113.05 ((CH$_3$)$_2$*C*), 110.99 (CN), 105.54 (C≡*C*Ph), 93.01 (C-1'), 86.30 (C-4'), 83.80 (C-2'), 81.14 (C-3'), 70.40 (*C*≡CPh), 63.13 (C-5'), 26.57 and 24.87 ((*C*H$_3$)$_2$C), 20.29 (CO-*C*H$_3$). HRMS $[M+H]^+$ calcd for $C_{21}H_{21}N_4O_5$: 409.15120; found: 409.15039.

*4.2.5. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-5-(4-methylphenylethynyl)-1H-[1,2,3]triazole-4-carbonitrile (**11b**)*

Oily material, 77 % yield. UV (MeOH): λ_{max} 296 nm (18500), 312 nm (16100). ^{1}H NMR (DMSO-d_6) δ 7.62 (d, J=8.0 Hz, 2H, Ph), 7.36 (d, J=8.0 Hz, 2H, Ph), 6.45 (s, 1H, 1'-H), 5.63 (d, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.04 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.56 (m, 1H, 4'-H), 4.02 (dd, $J_{5'a,4'}$=5.0 Hz, $J_{5'a,5'b}$=11.8 Hz, 1H, 5'a-H), 3.96 (dd, $J_{5'b,4'}$=6.8 Hz, $J_{5'b,5'a}$=12.0 Hz, 1H, 5'b), 2.38 (s, 3H, Ph-CH_3), 1.90 (s, 3H, OAc), 1.53 and 1.37 (2×s, 6H, C(CH$_3$)$_2$). ^{13}C NMR (DMSO-d_6) δ 169.77 (CO), 141.62 (C-4$_{Ph}$), 132.06 (Ph) 129.76 (Ph), 127.81 and 122.45 (C-4, C-5), 115.95 (Ph), 113.04 ((CH$_3$)$_2$*C*), 111.03 (CN), 106.01 (C≡*C*Ph), 92.89 (C-1'), 86.28 (C-4'), 83.80 (C-2'), 81.14 (C-3'), 69.99 (*C*≡CPh), 63.12 (C-5'), 26.56 and 24.86

((CH_3)$_2$C), 21.22 (Ph-CH_3), 20.28 (CO-CH_3). HRMS $[M+H]^+$ calcd for $C_{22}H_{23}N_4O_5$: 423.16685; found: 423.16635.

*4.2.6. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-5-(4-fluorophenylethynyl)-1H-[1,2,3]triazole-4-carbonitrile (**11c**)*

Oily material, 43% yield. UV (MeOH): λ_{max} 290 nm (16900), 306.5 nm (14200). ^{1}H NMR (DMSO-d_6) δ 7.82 (m, 2H, Ph), 7.40 (m, 2H, Ph), 6.49 (s, 1H, 1'-H), 5.63 (d, $J_{2',3'}$=5.6 Hz, 1H, 2'-H), 5.04 (dd, $J_{3',2'}$=5.8 Hz, $J_{3',4'}$=2.2 Hz, 1H, 3'-H), 4.56 (m, 1H, 4'-H), 3.99 (m, 2H, 5'-H), 1.90 (s, 3H, OAc), 1.53 and 1.37 (2×s, 6H, C(CH_3)$_2$). ^{13}C NMR (DMSO-d_6) δ 169.79 (CO), 163.45 (d, $J_{C,F}$=251.84 Hz, C-4$_{Ph}$), 134.92 (d, $J_{C,F}$=8.83 Hz, C-2$_{Ph}$, C-6$_{Ph}$), 127.56 and 122.63 (C-4, C-5), 116.61 (d, $J_{C,F}$=22.74 Hz, C-3$_{Ph}$, C-5$_{Ph}$), 115.51 (C-1$_{Ph}$), 113.07 ((CH_3)$_2$*C*), 110.97 (CN), 104.57 (C≡*C*Ph), 92.99 (C-1'), 86.32 (C-4'), 83.83 (C-2'), 81.15 (C-3'), 70.26 (*C*≡CPh), 63.14 (C-5'), 26.57 and 24.88 ((CH_3)$_2$C), 20.29 (CO-CH_3). ^{19}F NMR (DMSO d_6) δ -30.69. HRMS $[M+H]^+$ calcd for $C_{21}H_{20}N_4O_5F$: 427.14177; found: 427.14114.

*4.2.7. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-5-(4-trifluoromethylphenylethynyl)-1H-[1,2,3]triazole-4-carbonitrile (**11d**)*

Oily material, 69 % yield. UV (MeOH): λ_{max} 287.5 nm (22600), 306 nm (17800). ^{1}H NMR (DMSO-d_6) δ 7.97 (d, J=8.4 Hz, 2H, Ph) ,7.90 (d, J=8.4 Hz, 2H, Ph), 6.54 (s, 1H, 1'-H), 5.65 (d, $J_{2',3'}$=5.8 Hz, 1H, 2'-H), 5.05 (dd, $J_{3',2'}$=5.6 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.57 (m, 1H, 4'-H), 4.00 (m, 2H, 5'-H), 1.89 (s, 3H, OAc), 1.54 and 1.37 (2×s, 6H, C(CH_3)$_2$). ^{13}C NMR (DMSO-d_6) δ 169.79 (CO), 133.02 (Ph), 130.73 (q, $J_{C,F}$=32.4 Hz, C-4$_{Ph}$), 127.09, 123.31 and 123.10 (C-4, C-5, Ph), 125.99 (q, $J_{C,F}$=3.7 Hz, C-3$_{Ph}$, C-5$_{Ph}$), 123.66 (q, $J_{C,F}$=272.8 Hz, CF_3), 113.06 ((CH_3)$_2$*C*), 110.85 (CN), 103.52 (C≡*C*Ph), 93.20 (C-1'), 86.39 (C-4'), 83.87 (C-2'), 81.15 (C-3'), 72.39 (*C*≡CPh), 63.15 (C-5'), 26.56 and 24.86 ((CH_3)$_2$C), 20.28 (CO-CH_3). ^{19}F NMR (DMSO d_6) δ 14.02. HRMS $[M+H]^+$ calcd for $C_{22}H_{20}N_4O_5F_3$: 477.13858; found: 477.13531.

*4.2.8. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-5-(naphth-2-ylethynyl)-1H-[1,2,3]triazole-4-carbonitrile (**11e**)*

From fractions containing homogenous **11e** white crystalline material was separated, while evaporation of the filtrate resulted in the oily residue (57% total yield). UV (MeCN): λ_{max} 266 nm (25900), 276.5 nm (35700), 312 nm (26700). ^{1}H NMR (DMSO-d_6) δ 8.44 (d, J=0.4Hz, 1H, naphthyl), 8.07 (m, 2H, naphthyl), 8.02 (m, 1H, naphthyl), 7.73 (dd, J=1.4 Hz,

J=8.6 Hz, 1H, naphthyl), 7.66 (m, 2H, naphthyl), 6.54 (s, 1H, 1'-H), 5.66 (d, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.06 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.58 (m, 1H, 4'-H), 4.01 (m, 2H, 5'-H), 1.90 (s, 3H, OAc), 1.56 and 1.38 (2×s, 6H, 2×CH_3). ^{13}C NMR (DMSO-d_6) δ 169.80 (CO), 133.46, 133.16, 132.28, 128.86, 128.40, 128.29, 127.88, 127.69, 127.47, 127.38, 122.66 and 116.23 (naphthyl, C-4, C-5), 113.06 ((CH_3)$_2$*C*), 111.05 (CN), 105.98 (C≡*C*-naphthyl), 92.99 (C-1'), 86.36 (C-4'), 83.86 (C-2'), 81.16 (C-3'), 70.65 (*C*≡C-naphthyl), 63.15 (C-5'), 26.58 and 24.87 ((CH_3)$_2$C), 20.30 (CO-*C*H_3). HRMS $[M+H]^+$ calcd for $C_{25}H_{23}N_4O_5$: 459.16685; found: 459.16596.

*4.2.9. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-5-(6-methoxynaphth-2-ylethynyl)-1H-[1,2,3]triazole-4-carbonitrile (**11f**)*

For rechromatography CH_2Cl_2 was used to give **11f** as solid foam in 60% yield. UV (MeCN): λ_{max} 227 nm (21600), 281.5 nm (11800), 331.5 nm (11800). ^{1}H NMR (DMSO-d_6) δ 8.34 (d, J=0.8 Hz, 1H, naphthyl), 7.96 (m, 2H, naphthyl), 7.68 (dd, J=1.8 Hz, J=8.6 Hz, 1H, naphthyl), 7.43 (d, J=2.4 Hz, 1H, naphthyl), 7.28 (dd, J=2.6 Hz, J=9.0 Hz, 1H, naphthyl), 6.51 (s, 1H, 1'-H), 5.65 (d, $J_{2',3'}$=6.8 Hz, 1H, 2'-H), 5.06 (m, 1H, 3'-H), 4.57 (m, 1H, 4'-H), 4.00 (m, 2H, 5'-H), 3.92 (s, 3H, OCH_3), 1.90 (s, 3H, OAc), 1.55 and 1.38 (2×s, 6H, C(CH_3)$_2$). ^{13}C NMR (DMSO-d_6) δ 169.80 (CO), 159.12 (C-$6_{naphthyl}$), 135.27, 132.96, 129.96, 128.08, 127.88, 127.72, 127.64, 122.42 and 119.96 (naphthyl, C-4, C-5), 113.51 and 113.05 (naphthyl, (CH_3)$_2$*C*), 111.10 (CN), 106.58 and 106.27 (naphthyl, C≡*C*-naphthyl), 92.88 (C-1'), 86.32 (C-4'), 83.83 (C-2'), 81.16 (C-3'), 70.12 (*C*≡C-naphthyl), 63.15 (C-5'), 55.44 (OCH_3), 26.59 and 24.87 ((CH_3)$_2$C), 20.30 (CO-*C*H_3). HRMS $[M+H]^+$ calcd for $C_{26}H_{25}N_4O_6$: 489.17741; found: 489.17714.

4.2.10 General procedure for cyclization reactions

To a solution of 1-(5-*O*-acetyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-alkynyl-1*H*-[1,2,3]triazole-4-carbonitrile (**11a**–**f**; dried under vacuum at room temperature) in DME (10 ml/mmol) was added *ca* 10 M NH_3/DME (30 ml/mmol) and the resulting mixture was heated in a Parr reactor at 85 ºC for 40 h, then it was evaporated.

*4.2.11. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-4-amino-6-phenyl-1H-[1,2,3]triazole[4,5-c]pyridine (**14a**)*

Chromatography on silica gel column with hexane-EtOAc (2:1→1:1) resulted in **14a** as solid foam (95% yield). UV (MeOH): λ_{max} 249 nm (22900), 315 nm (9900). ^{1}H NMR

(DMSO-d_6) δ 8.10 (m, 2H, Ph), 7.63 (s, 1H, 7-H), 7.47 (m, 2H, Ph), 7.40 (m, 1H, Ph), 7.30 (s, 2H, NH_2), 6.70 (d, $J_{1',2'}$=1.6 Hz, 1H, 1'-H), 5.72 (dd, $J_{2',1'}$=1.6 Hz, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.10 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.4 Hz, 1H, 3'-H), 4.48 (m, 1H, 4'-H), 4.06 (dd, $J_{5'a,5'b}$=11.8 Hz, $J_{5'a,4'}$=5.4 Hz, 1H, 5'a-H), 3.87 (dd, $J_{5'b,5'a}$=11.8 Hz, $J_{5'b,4'}$=6.6 Hz, 1H, 5'b-H), 1.86 (s, 3H, OAc), 1.58 and 1.39 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 169.84 (CO), 152.65 and 151.41 (C-4, C-6), 139.49, 138.98, 130.71, 128.71, 128.39 and 126.87 (Ph, C-3a, C-7a), 113.05 ($(CH_3)_2C$), 90.85 and 90.48 (C-1', C-7), 84.90 (C-4'), 83.44 (C-2'), 81.51 (C-3'), 63.41 (C-5'), 26.69 and 25.01 ($(CH_3)_2C$), 20.31 (CO-CH_3). HRMS $[M+H]^+$ calcd for $C_{21}H_{24}N_5O_5$: 426.1772; found: 426.1787.

*4.2.12. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-4-amino-6-(4-methylphenyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**14b**)*

Solid (95% yield). UV (MeOH): λ_{max} 256.5 nm (31000), 316.5 nm (13500). ^{1}H NMR (DMSO-d_6) δ 8.01 (d, J=8.0 Hz, 2H, Ph), 7.60 (s, 1H, 7-H), 7.27 (m, 4H, Ph, NH_2), 6.69 (s, 1H, 1'-H), 5.72 (d, $J_{2',3'}$=5.6 Hz, 1H, 2'-H), 5.10 (dd, $J_{3',2'}$=5.8 Hz, $J_{3',4'}$=1.4 Hz, 1H, 3'-H), 4.48 (m, 1H, 4'-H), 4.06 (dd, $J_{5'a,5'b}$=11.8 Hz, $J_{5'a,4'}$=5.4 Hz, 1H, 5'a-H), 3.86 (dd, $J_{5'b,5'a}$=11.8 Hz, $J_{5'b,4'}$=6.6 Hz, 1H, 5'b-H), 2.35 (s, 3H, CH_3), 1.87 (s, 3H, OAc), 1.57 and 1.39 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 169.84 (CO), 152.64 and 151.34 (C-4, C-6), 139.55, 138.18, 136.19, 130.61, 129.00 and 126.77 (Ph, C-3a, C-7a), 113.04 ($(CH_3)_2C$), 90.80 (C-1'), 89.92 (C-7), 84.89 (C-4'), 83.42 (C-2'), 81.52 (C-3'), 63.41 (C-5'), 26.69 and 25.01 ($(CH_3)_2C$), 20.78 (Ph-CH_3), 20.31 (CO-CH_3). HRMS $[M+H]^+$ calcd for $C_{22}H_{26}N_5O_5$: 440.1934; found: 440.1925.

*4.2.13. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-4-amino-6-(4-fluorophenyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**14c**)*

Chromatography on silica gel column with hexane-EtOAc (2:1→1:2) resulted in **14c** as solid foam (80% yield). UV (MeOH): λ_{max} 248.5 nm (37000), 318 nm (15500). ^{1}H NMR (DMSO-d_6) δ 8.15 (m, 2H, Ph), 7.63 (s, 1H, 7-H), 7.30 (m, 4H, Ph, NH_2), 6.69 (d, $J_{1',2'}$=1.2 Hz, 1H, 1'-H), 5.72 (dd, $J_{2',1'}$=1.2 Hz, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.10 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.4 Hz, 1H, 3'-H), 4.48 (m, 1H, 4'-H), 4.07 (dd, $J_{5'a,5'b}$=11.6 Hz, $J_{5'a,4'}$=5.2 Hz, 1H, 5'a-H), 3.87 (dd, $J_{5'b,5'a}$=11.6 Hz, $J_{5'b,4'}$=6.8 Hz, 1H, 5'b-H), 1.87 (s, 3H, OAc), 1.57 and 1.39 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 169.84 (CO), 162.62 (d, $J_{C,F}$=245.88 Hz, C-4_{Ph}), 151.58 and 151.41 (C-4, C-6), 139.54, 135.44 and 130.63 (C-1_{Ph}, C-3a, C-7a), 128.93 (d, $J_{C,F}$=8.76 Hz, C-2_{Ph}, C-6_{Ph}), 115.22 (d, $J_{C,F}$=21.22 Hz, C-3_{Ph}, C-5_{Ph}), 113.05 ($(CH_3)_2C$), 90.83

(C-1'), 90.28 (C-7), 84.94 (C-4'), 83.45 (C-2'), 81.53 (C-3'), 63.41 (C-5'), 26.68 and 25.00 ((*C*H$_3$)$_2$C), 20.30 (CO-*C*H$_3$). ^{19}F NMR (DMSO d$_6$) δ -37.96. HRMS [M+H]$^+$ calcd for $C_{21}H_{23}N_5O_5F$: 444.16832; found: 444.16778.

*4.2.14. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-4-amino-6-(4-trifluoromethylphenyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**14d**)*

Chromatography on silica gel column with hexane-EtOAc (2:1) gave **14d** as crystalline material (80% yield), mp 154-157 °C. UV (MeOH): λ_{max} 248 nm (25600), 322.5 nm (10900). ^{1}H NMR (DMSO-d$_6$) δ 8.32 (d, J=8.0 Hz, 2H, Ph), 7.84 (d, J=8.4 Hz, 2H, Ph), 7.79 (s, 1H, 7-H), 7.42 (s, 2H, NH$_2$), 6.72 (d, $J_{1',2'}$=0.8 Hz, 1H, 1'-H), 5.73 (dd, $J_{2',1'}$=1.2 Hz, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.11 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.49 (m, 1H, 4'-H), 4.06 (dd, $J_{5'a,5'b}$=11.8 Hz, $J_{5'a,4'}$=5.4 Hz, 1H, 5'a-H), 3.87 (dd, $J_{5'b,5'a}$=11.6 Hz, $J_{5'b,4'}$=6.8 Hz, 1H, 5'b-H), 1.86 (s, 3H, OAc), 1.58 and 1.39 (2×s, 6H, C(CH$_3$)$_2$). ^{13}C NMR (DMSO-d$_6$) δ 169.83 (CO), 151.60 and 150.81 (C-4, C-6), 142.86 (Ph), 139.43 and 131.06 (C-3a, C-7a), 128.80 (q, $J_{C,F}$=31.70 Hz, C-4$_{Ph}$), 127.47 (Ph), 125.35 (q, $J_{C,F}$=3.51 Hz, C-3$_{Ph}$, C-5$_{Ph}$), 124.34 (q, $J_{C,F}$=272.20 Hz, CF$_3$), 113.04 ((CH$_3$)$_2$*C*), 91.69 (C-7), 90.92 (C-1'), 85.05 (C-4'), 83.48 (C-2'), 81.54 (C-3'), 63.39 (C-5'), 26.68 and 24.99 ((*C*H$_3$)$_2$C), 20.29 (CO-*C*H$_3$). ^{19}F NMR (DMSO-d$_6$) δ 14.75. HRMS [M+H]$^+$ calcd for $C_{22}H_{23}N_5O_5F_3$: 494.16513; found: 494.16504.

*4.2.15. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-4-amino-6-(naphth-2-yl)-1H-[1,2,3]triazole[4,5-c]pyridine (**14e**)*

Chromatography on silica gel column with hexane-EtOAc (2:1→1:1) afforded **14e** as solid (95% yield). UV (MeOH): λ_{max} 252.5 nm (59200), 325 nm (18100). ^{1}H NMR (DMSO-d$_6$) δ 8.67 (s, 1H, naphthyl), 8.27 (dd, J=1.6 Hz, J=8.8 Hz, 1H, naphthyl), 8.02-7.94 (m, 3H, naphthyl), 7.82 (s, 1H, 7-H), 7.55 (m, 2H, naphthyl), 7.38 (s, 2H, NH$_2$), 6.74 (s, 1H, 1'-H), 5.76 (d, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.12 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.50 (m, 1H, 4'-H), 4.08 (dd, $J_{5'a,5'b}$=11.6 Hz, $J_{5'a,4'}$=5.6 Hz, 1H, 5'a-H), 3.88 (dd, $J_{5'b,5'a}$=12.0 Hz, $J_{5'b,4'}$=6.8 Hz, 1H, 5'b-H), 1.87 (s, 3H, OAc), 1.59 and 1.40 (2×s, 6H, C(CH$_3$)$_2$). ^{13}C NMR (DMSO-d$_6$) δ 169.85 (CO), 152.41 and 151.50 (C-4, C-6), 139.60, 136.40, 133.10, 132.95, 130.82, 128.41, 127.83, 127.52, 126.50, 126.44, 125.99 and 124.82 (naphthyl, C-3a, C-7a), 113.04 ((CH$_3$)$_2$*C*), 90.95 and 90.88 (C-1', C-7), 84.97 (C-4'), 83.44 (C-2'), 81.55 (C-3'), 63.41 (C-5'), 26.71 and 25.03 ((*C*H$_3$)$_2$C), 20.32 (CO-*C*H$_3$). HRMS [M+H]$^+$ calcd for $C_{25}H_{26}N_5O_5$: 476.19340; found: 476.19348.

*4.2.16. 1-(5-O-Acetyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-4-amino-6-(6-methoxynaphth-2-yl)-1H-[1,2,3]triazole[4,5-c]pyridine (**14f**)*

Solid (88% yield). UV (MeOH): λ_{max} 260 nm (39600), 297 nm (15200), 327.5 (18600). ^{1}H NMR (DMSO-d_6) δ 8.59 (s, 1H, naphthyl), 8.22 (d, J=8.8 Hz, 1H, naphthyl), 7.90 (dd, J=3.4 Hz, J=8.6 Hz, 2H, naphthyl), 7.75 (s, 1H, 7-H), 7.34 (m, 3H, naphthyl, NH_2), 7.19 (m, 1H, naphthyl), 6.72 (s, 1H, 1'-H), 5.75 (d, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.11 (m, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=1.6 Hz., 1H, 3'-H), 4.50 (m, 1H, 4'-H), 4.07 (dd, $J_{5'a,5'b}$=11.8 Hz, $J_{5'a,4'}$=5.4 Hz, 1H, 5'a-H), 3.88 (m, 4H, 5'b-H, OCH_3), 1.87 (s, 3H, OAc), 1.59 and 1.40 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 169.86 (CO), 157.78 (C-$6_{naphthyl}$), 152.68 (C-6), 151.44 (C-4), 139.64, 134.51, 134.17, 130.70, 129.98, 128.34, 126.72, 125.90, 125.29 and 118.98 (naphthyl, C-3a, C-7a), 113.06 ($(CH_3)_2C$), 105.86 (naphthyl), 90.87 (C-1'), 90.36 (C-7), 84.94 (C-4'), 83.43 (C-2'), 81.56 (C-3'), 63.42 (C-5'), 55.23 (OCH_3), 26.72 and 25.03 ($(CH_3)_2C$), 20.32 (CO-CH_3). HRMS $[M+H]^+$ calcd for $C_{26}H_{28}N_5O_6$: 506.20396; found 506.20301.

4.2.17. General procedure for deacetylation reactions

To a cooled to 0 ºC solution of compound **14a**–**f** in anhyd 1,4-dioxane/MeOH (1:1; 20 ml/mmol) or in anhyd CH_2Cl_2/MeOH (1:1; 20 ml/mmol) was added 0.25 M MeONa in anhydrous MeOH (0.08 equiv). The mixture was allowed to react under argon at 5 ºC for 20 h. It was again cooled to 0 ºC and neutralized with Dowex 50WX8-100 ion exchange resin, which was then separated by filtration. The filtrate was evaporated and the residue was subjected to chromatography on silica gel column with CH_2Cl_2-MeOH (99:1→95:5) to afford purified product **15a**–**f** as solid or solid foam in 79-96% yield.

*4.2.18. 4-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-6-phenyl-1H-[1,2,3]triazole[4,5-c]pyridine (**15a**)*

Crude material after chromatography was crystallized from MeOH to give white crystals, mp 105 ºC. ^{1}H NMR (DMSO-d_6) δ 8.10 (m, 2H, Ph), 7.68 (s, 1H, 7-H), 7.46 (m, 2H, Ph), 7.40 (m, 1H, Ph), 7.34 (s, 2H, NH_2), 6.63 (d, $J_{1',2'}$=1.6 Hz, 1H, 1'-H), 5.65 (dd, $J_{2',1'}$=1.8 Hz, $J_{2',3'}$=6.2 Hz, 1H, 2'-H), 5.05 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 5.00 (t, $J_{5'OH,5'H}$=5.6 Hz, 1H, 5'-OH), 4.23 (m, 1H, 4'-H), 3.30 (m, 2H, 5'-H), 1.56 and 1.38 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 152.53 (C-6), 151.47 (C-4), 139.44, 139.05, 130.86, 128.77, 128.48 and 126.93 (Ph, C-3a, C-7a), 112.91 ($(CH_3)_2C$), 91.00 (C-1'), 90.73 (C-7), 87.86 (C-4'), 83.25 (C-2'), 81.72 (C-3'), 61.02 (C-5'), 26.80 and 25.05 ($(CH_3)_2C$). HRMS $[M+H]^+$ calcd for $C_{19}H_{22}N_5O_4$: 384.16718; found 384.16706.

*4.2.19. 4-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-6-(4-methylphenyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**15b**)*

^{1}H NMR (DMSO-d_6) δ 8.00 (d, J=8.0 Hz, 2H, Ph), 7.63 (s, 1H, 7-H), 7.32 (s, 2H, NH_2), 7.27 (d, J=8.0 Hz, 2H, Ph), 6.61 (d, $J_{1',2'}$=1.6 Hz, 1H, 1'-H), 5.64 (dd, $J_{2',1'}$=1.2 Hz, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.05 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=1.6 Hz, 1H, 3'-H), 4.96 (brs, 1H, 5'-OH), 4.24 (m, 1H, 4'-H), 3.31 (m, 2H, 5'-H), 2.35 (s, 3H, CH_3), 1.57 and 1.38 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 152.22 (C-6), 151.25 (C-4), 139.43, 138.23, 135.98, 130.69, 129.01 and 126.79 (Ph, C-3a, C-7a), 112.86 ($(CH_3)_2C$), 90.99 (C-1'), 90.28 (C-7), 87.79 (C-4'), 83.17 (C-2'), 81.66 (C-3'), 60.98 (C-5'), 26.75 and 25.01 ($(CH_3)_2C$), 20.79 (Ph-CH_3). HRMS $[M+H]^+$ calcd for $C_{20}H_{24}N_5O_4$: 398.18283; found: 398.18213.

*4.2.20. 4-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-6-(4-fluorophenyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**15c**)*

^{1}H NMR (DMSO-d_6) δ 8.15 (dd, J=5.8 Hz, J=8.6 Hz, 2H, Ph), 7.66 (s, 1H, 7-H), 7.31-7.23 (m, 4H, Ph, NH_2), 6.60 (s, 1H, 1'-H), 5.63 (d, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.05 (dd, $J_{3',2'}$= 6.0 Hz, $J_{3',4'}$=1.6 Hz, 1H, 3'-H), 4.96 (t, $J_{5'OH,\ 5'H}$=5.4 Hz, 1H, 5'-OH), 4.24 (m, 1H, 4'-H), 3.31 (m, 2H, 5'-H), 1.57 i 1.38 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 162.58 (d, $J_{C,F}$=246.14 Hz, C-4_{Ph}), 151.38 (C-4, C-6), 139.37 (C-7a), 135.46 (d, $J_{C,F}$=2.97 Hz, C-1_{Ph}), 130.71 (C-3a), 128.90 (d, $J_{C,F}$=8.42 Hz, C-2_{Ph}, C-6_{Ph}), 115.18 (d, $J_{C,F}$=21.26 Hz, C-3_{Ph}, C-5_{Ph}), 112.87 ($(CH_3)_2C$), 91.03 (C-1'), 90.50 (C-7), 87.76 (C-4'), 83.17 (C-2'), 81.62 (C-3'), 60.97 (C-5'), 26.74 and 25.00 ($(CH_3)_2C$). ^{19}F NMR (DMSO d_6) δ -38.02. HRMS $[M+H]^+$ calcd for $C_{19}H_{21}N_5O_4F$: 402.15776; found: 402.15771.

*4.2.21. 4-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-6-(4-trifluoromethylphenyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**15d**)*

^{1}H NMR (DMSO-d_6) δ 8.32 (d, J=8.0 Hz, 2H, Ph), 7.83 (m, 3H, Ph, 7-H), 7.41 (s, 2H, NH_2), 6.64 (d, $J_{1',2'}$=1.6 Hz, 1H, 1'-H), 5.65 (dd, $J_{2',1'}$=1.6 Hz, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.06 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.97 (t, $J_{5'OH,5'H}$=5.4 Hz, 1H, 5'-OH), 4.25 (m, 1H, 4'-H), 3.31 (m, 2H, 5'-H), 1.57 and 1.38 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 151.59 and 150.66 (C-4, C-6), 142.90 (Ph), 139.27 (C-7a), 131.16 (C-3a), 128.76 (q, $J_{C,F}$=30.72 Hz, C-4_{Ph}), 127.47 (Ph), 125.34 (q, $J_{C,F}$=3.08 Hz, C-3_{Ph}, C-5_{Ph}), 124.35 (q, $J_{C,F}$=271.51 Hz, CF_3), 112.87 ($(CH_3)_2C$), 91.95 and 91.13 (C-1', C-7), 87.89 (C-4'), 83.24 (C-2'), 81.64 (C-3'),

60.97 (C-5'), 26.74 and 25.00 ((*C*H_3)$_2$C). ^{19}F NMR (DMSO-d_6): 14.79. HRMS $[M+H]^+$ calcd for $C_{20}H_{21}N_5O_4F_3$: 452.15456; found: 452.15393.

*4.2.22. 4-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-6-(naphth-2-yl)-1H-[1,2,3]triazole[4,5-c]pyridine (**15e**)*

Crystalline material, mp 167-170 ºC. ^{1}H NMR (DMSO-d_6) δ 8.68 (s, 1H, naphthyl), 8.28 (dd, J=1.8 Hz, J=8.6 Hz, 1H, naphthyl), 8.00 (d, J=8.8 Hz, 2H, naphthyl) ,7.95 (m, 1H, naphthyl), 7.85 (s, 1H, 7-H), 7.55 (m, 2H, naftyl-H), 7.36 (s, 2H, NH_2), 6.66 (d, $J_{1',2'}$=1.6 Hz, 1H, 1'-H), 5.68 (dd, $J_{2',1'}$=1.6 Hz, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.07 (dd, $J_{3',2'}$=6.4 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.99 (t, $J_{5'OH,5'H}$=5.4 Hz, 1H, 5'-OH), 4.26 (m, 1H, 4'-H), 3.33 (m, 2H, 5'-H), 1.58 and 1.39 (2×s, 6H, C(CH_3)$_2$). ^{13}C NMR (DMSO-d_6) δ 152.27 (C-6), 151.49 (C-4), 139.48 (C-7a), 136.43, 133.09 and 132.96 (naphthyl), 130.93 (C-3a), 128.43, 127.81, 127.51, 126.47, 126.41, 125.99 and 124.84 (naphthyl), 112.87 ((CH_3)$_2$*C*), 91.18 (C-7), 91.04 (C-1'), 87.87 (C-4'), 83.21 (C-2'), 81.68 (C-3'), 60.99 (C-5'), 26.77 and 25.02 ((*C*H_3)$_2$C). HRMS $[M+H]^+$ calcd for $C_{23}H_{24}N_5H_4$: 434.18283; found: 434.18195.

*4.2.23. 4-Amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)-6-(6-methoxynaphth-2-yl)-1H-[1,2,3]triazole[4,5-c]pyridine (**15f**)*

Crude material after chromatography was crystallized from hexane-EtOAc to give white crystals, mp 140 ºC. ^{1}H NMR (DMSO-d_6) δ 8.59 (s, 1H, naphthyl), 8.22 (dd, J=1.6 Hz, J=8.8 Hz, 1H, naphthyl), 7.89 (dd, J=5.6 Hz, J=8.8 Hz, 2H, naphthyl), 7.78 (s, 1H, 7-H), 7.36 (d, J=2.0 Hz, 1H, naphthyl), 7.30 (s, 2H, NH_2), 7.20 (dd, J=2.4 Hz, J=8.8 Hz, 1H, naphthyl), 6.64 (d, $J_{1',2'}$=1.6 Hz, 1H, 1'-H), 5.67 (dd, $J_{2',1'}$=1.4 Hz, $J_{2',3'}$=6.2 Hz, 1H, 2'-H), 5.07 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.98 (t, $J_{5'OH,5'H}$=5.4 Hz, 1H, 5'-OH), 4.26 (m, 1H, 4'-H), 3.90 (s, 3H, OCH_3), 3.32 (m, 2H, 5'-H), 1.58 and 1.39 (2×s, 6H, C(CH_3)$_2$). ^{13}C NMR (DMSO-d_6) δ 157.75 (C-$6_{naphthyl}$), 152.50 (C-6), 151,39 (C-4), 139.48 (C-7a), 130.78 (C-3a), 134.47, 134.18, 129.96, 128.33, 126.68, 125.85, 125.28 and 118.92 (naphthyl), 112.86 ((CH_3)$_2$*C*), 105.84 (naphthyl), 91.02 (C-1'), 90.56 (C-7), 87.79 (C-4'), 83.16 (C-2'), 81.65 (C-3'), 60.97 (C-5'), 55.21 (OCH_3), 26.75 and 25.01 ((*C*H_3)$_2$C). HRMS $[M+H]^+$ calcd for $C_{24}H_{26}N_5O_5$: 464.19340; found: 464.19342.

4.2.24. General procedure for sulfamoylation reactions

To a stirred solution of compound **15a**–**f** (dried *in vacuo* over P_2O_5 at room temperature) in MeCN (15 ml/mmol) containing DMA (50 equiv) was added 1.33 M sulfamoyl chloride

[35] in MeCN (2.5 equiv) at 0 ºC. The mixture was stirred on ice-cooling for 15 min, then at room temperature overnight. It was evaporated and the resulting residue was chromatographed on silica gel column with CH_2Cl_2-MeOH (98:2→95:5) to obtain product **16a**–**f** contaminated with DMA as solid foam (yields 51-71% calculated from ^{1}H NMR spectra).

*4.2.25. 4-Amino-6-phenyl-1-(5-O-sulfamoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**16a**)*

^{1}H NMR (DMSO-d_6) δ 8.11 (m, 2H, Ph), 7.68 (s, 1H, 7-H), 7.55 (brs, 2H, SO_3NH_2), 7.43 (m, 3H, Ph), 7.31 (brs, 2H, NH_2), 6.77 (d, $J_{1',2'}$=1.2 Hz, 1H, 1'-H), 5.65 (dd, $J_{2',1'}$=1.2 Hz, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.13 (dd, 1H, $J_{3'2'}$=6.0 Hz, $J_{3',4'}$=2.4 Hz, 1H, 3'-H), 4.48 (dt, $J_{4',3'}$=2.3 Hz, $J_{4',5'}$= 6.5 Hz, 1H, 4'-H), 4.06 and 3.91 (2×dd, $J_{5',4'}$=6.6 Hz, $J_{5'a,5'b}$=10.6 Hz, 2H, 5'-H), 1.58 and 1.40 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 152.83 and 151.44 (C-4, C-6), 139.56 (C-7a), 138.94 (Ph), 130.66 (C-3a), 128.76, 128.41 and 126.91 (Ph), 113.29 ($(CH_3)_2C$), 90.38 and 90.31 (C-1', C-7), 84.80 (C-4'), 83.51 (C-2'), 81.50 (C-3'), 67.63 (C-5'), 26.68 and 25.00 ($(CH_3)_2C$). HRMS $[M+H]^+$ calcd for $C_{19}H_{23}N_6O_6S$: 463.1394; found: 463.1413.

*4.2.26. 4-Amino-6-(4-methylphenyl)-1-(5-O-sulfamoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**16b**)*

^{1}H NMR (DMSO-d_6) δ 8.02 (d, J=8.0 Hz, 2H, Ph), 7.65 (s, 1H, 7-H), 7.55 (s, 2H, SO_3NH_2), 7.27 (m, 4H, NH_2, Ph), 6.75 (d, $J_{1',2'}$=1.2 Hz, 1H, 1'-H), 5.65 (dd, $J_{2',1'}$=1.4 Hz, $J_{2',3'}$=6.2 Hz, 1H, 2'-H), 5.13 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.48 (dt, $J_{4',3'}$=2.1 Hz, $J_{4',5'}$=6.6 Hz, 1H, 4'-H), 4.06 and 3.91 (2×dd, $J_{5',4'}$=6.7 Hz, $J_{5'a,5'b}$=10.7 Hz, 2H, 5'-H), 2.35 (s, 3H, CH_3), 1.58 and 1.40 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 152.80 and 151.35 (C-4, C-6), 139.58 (C-7a), 138.21 and 136.13 (Ph), 130.53 (C-3a), 128.99 and 126.80 (Ph), 113.26 ($(CH_3)_2C$), 90.33 and 89.73 (C-1', C-7), 84.76 (C-4'), 83.48 (C-2'), 81.49 (C-3'), 67.61 (C-5'), 26.67 and 24.99 ($(CH_3)_2C$), 20.78 (CH_3). HRMS $[M+H]^+$ calcd for $C_{20}H_{25}N_6O_6S$: 477.1556; found: 477.1563.

*4.2.27. 4-Amino-6-(4-fluorophenyl)-1-(5-O-sulfamoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**16c**)*

^{1}H NMR (DMSO-d_6) δ 8.16 (m, 2H, Ph), 7.68 (s, 1H, 7-H), 7.56 (s, 2H, SO_3NH_2), 7.31 (m, 4H, NH_2, Ph), 6.75 (d, $J_{1',2'}$=1.2 Hz, 1H, 1'-H), 5.65 (dd, $J_{2',1'}$=1.2 Hz, $J_{2',3'}$=6.0 Hz, 1H,

2'-H), 5.13 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.4 Hz, 1H, 3'-H), 4.48 (dt, $J_{4',3'}$=2.1 Hz, $J_{4',5'}$=6.6 Hz, 1H, 4'-H), 4.07 and 3.92 (2×dd, $J_{5',4'}$=6.5 Hz, $J_{5'a,5'b}$=10.5 Hz, 2H, 5'-H), 1.58 and 1.40 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 162.66 (d, $J_{C,F}$=245.6 Hz, C-4_{Ph}), 151.73 and 151.44 (C-4, C-6), 139.58 (C-7a), 135.41 (Ph), 130.57 (C-3a), 128.97 (d, $J_{C,F}$=8.22 Hz, C-2_{Ph}, C-6_{Ph}), 115.24 (d, $J_{C,F}$=21.47 Hz, C-3_{Ph}, C-5_{Ph}), 113.30 ($(CH_3)_2C$), 90.40 and 90.12 (C-1', C-7), 84.81 (C-4'), 83.51 (C-2'), 81.48 (C-3'), 67.63 (C-5'), 26.67 and 24.99 ($(CH_3)_2C$). ^{19}F NMR (DMSO-d_6) δ: -37.94. HRMS $[M+H]^+$ calcd for $C_{19}H_{22}N_6O_6SF$: 481.1300; found: 481.1308.

*4.2.28. 4-Amino-1-(5-O-sulfamoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-6-(4-trifluoromethylphenyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**16d**)*

^{1}H NMR (DMSO-d_6) δ 8.32 (d, J=8.0 Hz, 2H, Ph), 7.84 (s and d, 3H, Ph, 7-H), 7.54 (brs, 2H, SO_3NH_2), 7.44 (s, 2H, NH_2), 6.78 (d, $J_{1',2'}$=1.2 Hz, 1H, 1'-H), 5.66 (dd, $J_{2',1'}$=1.1 Hz, $J_{2',3'}$=6.2 Hz, 1H, 2'-H), 5.14 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.4 Hz, 1H, 3'-H), 4.49 (dt, $J_{4',3'}$=2.0 Hz, $J_{4',5'}$=6.4 Hz, 1H, 4'-H), 4.07 and 3.92 (2×dd, $J_{5',4'}$=6.5 Hz, $J_{5'a,5'b}$=10.5 Hz, 2H, 5'-H), 1.58 and 1.40 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 151.61 and 150.94 (C-4, C-6), 142.80 (Ph), 139.42 (C-7a), 130.98 (C-3a), 128.80 (q, $J_{C,F}$=31.70 Hz, C-4_{Ph}), 127.49 (Ph), 125.34 (q, $J_{C,F}$=3.53 Hz, C-3_{Ph}, C-5_{Ph}), 124.34 (q, $J_{C,F}$=272.05, CF_3), 113.28 ($(CH_3)_2C$), 91.52 (C-7), 90.48 (C-1'), 84.85 (C-4'), 83.52 (C-2'), 81.43 (C-3'), 67.60 (C-5'), 26.67 and 24.99 ($(CH_3)_2C$). ^{19}F NMR (DMSO-d_6) δ14.78. HRMS $[M+H]^+$ calcd for $C_{20}H_{22}N_6O_6SF_3$: 531.1268; found: 531.1288.

*4.2.29. 4-Amino-6-(naphth-2-yl)-1-(5-O-sulfamoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**16e**)*

^{1}H NMR (DMSO-d_6) δ 8.68 (s, 1H, naphthyl), 8.28 (dd, J=1.6 Hz, J=8.8 Hz, 1H, naphthyl), 7.98 (m, 3H, naphthyl), 7.87 (s, 1H, 7-H), 7.55 (m, 4H, naphthyl, SO_3NH_2), 7.39 (s, 2H, NH_2), 6.80 (d, $J_{1',2'}$=1.2 Hz, 1H, 1'-H), 5.69 (dd, $J_{2',1'}$=1.2 Hz, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.15 (dd, $J_{3',2'}$=6.2 Hz, $J_{3',4'}$=2.2 Hz, 1H, 3'-H), 4.51 (dt, $J_{4',3'}$=2.3 Hz, $J_{4',5'}$=6.6 Hz, 1H, 4'-H), 4.08 and 3.93 (2×dd, $J_{5',4'}$=6.6 Hz, $J_{5'a,5'b}$=10.6 Hz, 2×1H, 5'-H), 1.60 and 1.41 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 152.58 and 151.51 (C-4, C-6), 139.63 (C-7a), 136.35, 133.12 and 132.95 (naphthyl), 130.75 (C-3a), 128.43, 127.83, 127.52, 126.52, 126.43, 126.04 and 124.85 (naphthyl), 113.28 ($(CH_3)_2C$), 90.78 and 90.43 (C-1', C-7), 84.84 (C-4'), 83.50 (C-2'), 81.51 (C-3'), 67.62 (C-5'), 26.69 and 25.00 ($(CH_3)_2C$). HRMS $[M+H]^+$ calcd for $C_{23}H_{25}N_6O_6S$: 513.1556; found: 513.1550.

*4.2.30. 4-Amino-6-(6-methoxynaphth-2-yl)-1-(5-O-sulfamoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**16f**)*

^{1}H NMR (DMSO-d_6) δ 8.60 (s, 1H, naphthyl), 8.23 (dd, J=1.8 Hz, J=8.6 Hz, 1H, naphthyl), 7.90 (m, 2H, naphthyl), 7.80 (s, 1H, 7-H), 7.56 (s, 2H, SO_3NH_2), 7.35 (m, 3H, naphthyl, NH_2), 7.20 (dd, J=2.4 Hz, J=8.8 Hz, 1H, naphthyl), 6.78 (d, $J_{1',2'}$=1.2 Hz, 1H, 1'-H), 5.68 (dd, $J_{2',1'}$=1.4 Hz, $J_{2',3'}$=6.2 Hz, 1H, 2'-H), 5.15 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.50 (dt, $J_{4',3'}$=2.1 Hz, $J_{4',5'}$=6.6 Hz, 1H, 4'-H), 4.08 (dd, $J_{5'a,4'}$=6.8 Hz, $J_{5'a,5'b}$=10.8 Hz, 2H, 5'a-H), 3.93 (m, 4H, 5'b-H, OCH_3), 1.60 and 1.41 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 157.79 (C-$6_{naphthyl}$), 152.84 and 151.45 (C-4, C-6), 139.66 (C-7a), 134.54, 134.13, 130.60, 130.00, 128.34, 126.72, 125.93, 125.32 and 118.98 (naphthyl, C-3a), 113.29 ($(CH_3)_2C$), 105.86 (naphthyl), 90.42 and 90.18 (C-1', C-7), 84.79 (C-4'), 83.48 (C-2'), 81.51 (C-3'), 67.61 (C-5'), 55.24 (OCH_3), 26.69 and 25.00 ($(CH_3)_2C$). HRMS $[M+H]^+$ calcd for $C_{24}H_{27}N_6O_7S$: 543.1656; found: 543.1668.

*4.2.31. General procedure for the preparation of compounds **17a**–**f***

To a solution of compound **16a**–**f** (contaminated with DMA) in MeCN (20 ml/mmol) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 equiv) and the mixture was stirred at room temperature for 15 min. In a separate flask 1,1'-carbonyldiimidazole (1.4 equiv) and salicylic acid (1.4 equiv) were dissolved in MeCN (20 ml/mmol of substrate) and the resulting solution was stirred at 60 ºC for 2 h, then it was cooled to room temperature. Both solutions were combined and stirred at room temperature overnight. After evaporation the residue was chromatographed on silica gel column with CH_2Cl_2-MeOH (98:2→9:1). Crude product obtained was rechromatographed on silica gel column using EtOAc to give pure **17a**–**f** as solid foam in 56-86% yield.

*4.2.32. 4-Amino-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-2,3-O-isopropylidene-β-D-ribofuranosyl}-6-phenyl-1H-[1,2,3]triazole[4,5-c]pyridine (**17a**)*

UV (MeOH): λ_{max} 246 nm (32500), 309.5 nm (13700). ^{1}H NMR (DMSO-d_6) δ 13.49 (s, 1H, OH), 8.12 (d, J=7.2 Hz, 2H, Ph), 7.77 (dd, J=1.8 Hz, J=8.2 Hz, 1H, sal), 7.66 (s, 1H, 7-H), 7.43 (m, 3H, Ph), 7.25 (m, 3H, NH_2, sal), 6.71 (m, 3H, sal, 1'-H), 5.59 (dd, $J_{2',1'}$=1.6 Hz, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.16 (dd, $J_{3',2'}$=6.2 Hz, $J_{3',4'}$=2.2 Hz, 1H, 3'-H), 4.47 (dt, $J_{4',3'}$=2.1 Hz, $J_{4',5'}$=6.5 Hz, 1H, 4'-H), 4.07 (dd, $J_{5'a,4'}$=7.0 Hz, $J_{5'a,5'b}$=11.0 Hz, 1H, 5'a-H), 3.91 (dd, $J_{5'b,4'}$=6.0 Hz, $J_{5'b,5'a}$=10.8 Hz, 1H, 5'b-H), 1.56 and 1.36 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 171.11 (CO), 160.69 (C-OH_{sal}), 152.76 and 151.43 (C-4, C-6), 139.41 (C-7a),

138.96 (Ph), 132.57 (sal), 130.67 (C-3a), 129.81 (sal), 128.65, 128.35 and 126.96 (Ph), 119.72, 117.50 and 116.52 (sal), 113.17 ($(CH_3)_2C$), 90.66 and 90.36 (C-1', C-7), 84.94 (C-4'), 83.31 (C-2'), 81.61 (C-3'), 67.18 (C-5'), 26.69 and 24.96 ($(CH_3)_2C$). HRMS $[M+H]^+$ calcd for $C_{26}H_{27}N_6O_8S$: 583.1606; found: 583.1607.

*4.2.33. 4-Amino-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-2,3-O-isopropylidene-β-D-ribofuranosyl}-6-(4-methylphenyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**17b**)*

UV (MeOH): λ_{max} 249.5 nm (31400), 309.5 nm (15900). ^{1}H NMR (DMSO-d_6) δ 13.49 (s, 1H, OH), 8.03 (d, J=8.4 Hz, 2H, Ph), 7.77 (dd, J=2.0 Hz, J=8.0 Hz, 1H, sal), 7.62 (s, 1H, 7-H), 7.24 (m, 5H, NH_2, sal, Ph), 6.72 (m, 2H, sal), 6.67 (d, $J_{1',2'}$=2.0 Hz, 1H, 1'-H), 5.58 (dd, $J_{2',1'}$=1.8 Hz, $J_{2',3'}$=6.2 Hz, 1H, 2'-H), 5.16 (dd, $J_{3',2'}$=6.2 Hz, $J_{3',4'}$=2.2 Hz, 1H, 3'-H), 4.46 (m, 1H, 4'-H), 4.06 (dd, $J_{5'a,4'}$=6.8 Hz, $J_{5'a,5'b}$=10.8 Hz, 1H, 5'a-H), 3.91 (dd, $J_{5'b,4'}$=6.4 Hz, $J_{5'b,5'a}$=10.8 Hz, 1H, 5'b-H), 2.35 (s, 3H, CH_3), 1.56 and 1.36 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 171.19 (CO), 160.72 (C-OH_{sal}), 152.80 and 151.38 (C-4, C-6), 139.49 (C-7a), 138.16 and 136.18 (Ph), 132.65 (sal), 130.60 (C-3a), 129.85 (sal), 129.01 and 126.89 (Ph), 119.72, 117.56 and 116.57 (sal), 113.21 ($(CH_3)_2C$), 90.67 and 89.84 (C-1', C-7), 84.94 (C-4'), 83.32 (C-2'), 81.63 (C-3'), 67.24 (C-5'), 26.71 and 24.98 ($(CH_3)_2C$), 20.82 (CH_3). HRMS $[M+H]^+$ calcd for $C_{27}H_{29}N_6O_8S$: 597.1762; found: 597.1760.

*4.2.34. 4-Amino-6-(4-fluorophenyl)-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-2,3-O-isopropylidene-β-D-ribofuranosyl}-1H-[1,2,3]triazole[4,5-c]pyridine (**17c**)*

UV (MeOH): λ_{max} 246.5 nm (33300), 311.5 nm (14400). ^{1}H NMR (DMSO-d_6) δ 13.47 (s, 1H, OH), 8.17 (m, 2H, Ph), 7.77 (dd, J=1.8 Hz, J=8.2 Hz, 1H, sal), 7.65 (s, 1H, 7-H), 7.27 (m, 5H, NH_2, sal, Ph), 6.72 (m, 2H, sal), 6.66 (d, $J_{1',2'}$=1.6 Hz, 1H, 1'-H), 5.58 (dd, $J_{2',1'}$=1.6 Hz, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.16 (dd, $J_{3',2'}$=6.2 Hz, $J_{3',4'}$=2.2 Hz, 1H, 3'-H), 4.47 (dt, $J_{4',3'}$=2.0 Hz, $J_{4',5'}$=6.2 Hz, 1H, 4'-H), 4.07 (dd, $J_{5'a,4'}$=6.6 Hz, $J_{5'a,5'b}$=10.6 Hz, 1H, 5'a-H), 3.92 (dd, $J_{5'b,4'}$=6.0 Hz, $J_{5'b,5'a}$=10.8 Hz, 1H, 5'b-H), 1.56 and 1.36 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 171.09 (CO), 162.60 (d, $J_{C,F}$=244.93 Hz, C-4_{Ph}), 160.68 (C-OH_{sal}), 151.65 and 151.42 (C-4, C-6), 139.38 (C-7a), 135.40 (d, $J_{C,F}$=2.18 Hz, C-1_{Ph}), 132.57 (sal), 130.60 (C-3a), 129.79 (sal), 129.04 (d, $J_{C,F}$=8.27 Hz, C-2_{Ph}, C-6_{Ph}), 119.71, 117.49 and 116.51 (sal), 115.14 (d, $J_{C,F}$=21.31 Hz, C-3_{Ph}, C-5_{Ph}), 113.20 ($(CH_3)_2C$), 90.75 and 90.18 (C-1', C-7), 84.87 (C-4'), 83.25 (C-2'), 81.52 (C-3'), 67.18 (C-5'), 26.69 and 24.95 ($(CH_3)_2C$). ^{19}F NMR (DMSO-d_6) δ -38.08. HRMS $[M+H]^+$ calcd for $C_{26}H_{26}N_6O_8SF$: 601.1511; found: 601.1518.

*4.2.35. 4-Amino-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-2,3-O-isopropylidene-β-D-ribofuranosyl}-6-(4-trifluoromethylphenyl)-1H-[1,2,3]triazole[4,5-c]pyridine (**17d**)*

UV (MeOH): λ_{max} 243.5 nm (45100), 312 nm (17200). ^{1}H NMR (DMSO-d_6) δ 13.47 (s, 1H, OH), 8.34 (d, J=8.4 Hz, 2H, Ph), 7.79 (m, 4H, Ph, 7-H, sal), 7.41 (s, 2H, NH_2), 7.24 (m, 1H, sal), 6.71 (m, 3H, sal, 1'-H), 5.57 (dd, $J_{2',1'}$=2.0 Hz, $J_{2',3'}$=6.0 Hz, 1H, 2'-H), 5.17 (dd, $J_{3',2'}$=6.2 Hz, $J_{3',4'}$=2.2 Hz, 1H, 3'-H), 4.49 (dt, $J_{4',3'}$=2.1 Hz, $J_{4',5'}$=6.2 Hz, 1H, 4'-H), 4.09 and 3.95 (2×dd, $J_{5',4'}$=6.3 Hz, $J_{5'a,5'b}$=10.9 Hz, 2H, 5'-H), 1.57 and 1.36 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 171.15 (CO), 160.69 (C-OH_{sal}), 151.62 and 150.91 (C-4, C-6), 142.81 (Ph), 139.20 (C-7a), 132.60 (sal), 131.08 (C-3a), 129.80 (sal), 128.74 (q, $J_{C,F}$=31.80 Hz, C-4_{Ph}), 127.60 (Ph), 125.28 (q, $J_{C,F}$=3.77 Hz, C-3_{Ph}, C-5_{Ph}), 124.37 (q, $J_{C,F}$=272.19 Hz, CF_3), 119.70, 117.52 and 116.53 (sal), 113.27 ($(CH_3)_2C$), 91.65 and 90.97 (C-1', C-7), 84.87 (C-4'), 83.27 (C-2'), 81.44 (C-3'), 67.22 (C-5'), 26.71 and 24.96 ($(CH_3)_2C$). ^{19}F NMR (DMSO-d_6) δ 14.78. HRMS $[M+H]^+$ calcd for $C_{27}H_{26}N_6O_8SF_3$: 651.1479; found: 651.1479.

*4.2.36. 4-Amino-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-2,3-O-isopropylidene-β-D-ribofuranosyl}-6-(naphth-2-yl)-1H-[1,2,3]triazole[4,5-c]pyridine (**17e**)*

UV (MeOH): λ_{max} 251 nm (29600), 317.5 nm (9400). ^{1}H NMR (DMSO-d_6) δ 13.50 (s, 1H, OH), 8.70 (s, 1H, naphthyl), 8.29 (dd, J=1.6 Hz, J_2=8.4 Hz, 1H, naphthyl), 7.98 (m, 3H, naphthyl), 7.84 (s, 1H, 7-H), 7.77 (m, 1H, sal), 7.54 (m, 2H, naphthyl), 7.36 (s, 2H, NH_2), 7.24 (m, 1H, sal), 6.72 (m, 3H, sal, 1'-H), 5.62 (dd, $J_{2',1'}$=1.6 Hz, $J_{2',3'}$=6.4 Hz, 1H, 2'-H), 5.18 (dd, $J_{3',2'}$=6.2 Hz, $J_{3',4'}$=2.2 Hz, 1H, 3'-H), 4.50 (m, 1H, 4'-H), 4.09 (dd, $J_{5'a,4'}$=6.8 Hz, $J_{5'a,5'b}$=10.8 Hz, 1H, 5'a-H), 3.94 (dd, $J_{5'b,4'}$=6.0 Hz, $J_{5'b,5'a}$=10.8 Hz, 1H, 5'b-H), 1.58 and 1.37 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 171.14 (CO), 160.70 (C-OH_{sal}), 152.54 and 151.51 (C-4, C-6), 139.47 (C-7a), 136.39, 133.10 and 132.98 (naphthyl), 132.58 (sal), 130.79 (C-3a), 129.81 (sal), 128.50, 127.76, 127.47, 126.43, 126.33, 126.08 and 124.96 (naphthyl) 119.72, 117.50 and 116.52 (sal), 113.19 ($(CH_3)_2C$), 90.85 and 90.78 (C-1', C-7), 84.94 (C-4'), 83.27 (C-2'), 81.59 (C-3'), 67.19 (C-5'), 26.71 and 24.97 ($(CH_3)_2C$). HRMS $[M+H]^+$ calcd for $C_{30}H_{29}N_6O_8S$: 633.1762; found: 633.1767.

*4.2.37. 4-Amino-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-2,3-O-isopropylidene-β-D-ribofuranosyl}-6-(6-methoxynaphth-2-yl)-1H-[1,2,3]triazole[4,5-c]pyridine (**17f**)*

UV (MeOH): λ_{max} 247 nm (58700), 323.5 nm (27300). ^{1}H NMR (DMSO-d_6) δ 13.48 (s, 1H, OH), 8.61 (s, 1H, naphthyl), 8.25 (dd, J=1.8 Hz, J=8.6 Hz, 1H, naphthyl), 7.90 (dd, 2H, naphthyl), 7.77 (m, 2H, 7-H, sal), 7.33 (m, 3H, NH_2, naphthyl), 7.25 (m, 1H, sal), 7.19 (dd,

J=2.6 Hz, 1H, naphthyl), 6.71 (m, 3H, sal, 1'-H), 5.61 (dd, $J_{2',1'}$=1.8 Hz, $J_{2',3'}$=6.2 Hz, 1H, 2'-H), 5.18 (dd, $J_{3',2'}$=6.0 Hz, $J_{3',4'}$=2.0 Hz, 1H, 3'-H), 4.49 (dt, $J_{4',3'}$=2.3 Hz, $J_{4',5'}$=6.3 Hz, 1H, 4'-H), 4.09 (dd, $J_{5'a,4'}$=6.8 Hz, $J_{5'a,5'b}$=10.8 Hz, 1H, 5'a-H), 3.93 (m, 4H, 5'b-H, OCH_3), 1.58 and 1.37 (2×s, 6H, $C(CH_3)_2$). ^{13}C NMR (DMSO-d_6) δ 171.17 (CO), 160.71 (C-OH_{sal}), 157.76 (C-$6_{naphthyl}$), 152.78 and 151.45 (C-4, C-6), 139.51 (C-7a), 134.52 and 134.14 (naphthyl), 132.62 (sal), 130.68 (C-3a), 130.08, 129.84, 128.38, 126.69, 125.99, 125.44, 119.72, 118.89, 117.54 and 116.54 (sal, naphthyl), 113.22 ($(CH_3)_2C$), 105.83 (naphthyl), 90.80 and 90.28 (C-1', C-7), 84.89 (C-4'), 83.25 (C-2'), 81.59 (C-3'), 67.22 (C-5'), 55.24 (OCH_3), 26.73 and 24.98 ($(CH_3)_2C$). HRMS $[M+H]^+$ calcd for $C_{31}H_{31}N_6O_9S$: 663.1868; found: 663.1870.

*4.2.38. General procedure for the preparation of compounds **6a**–**f***

Compound **17a**–**f** was treated with cooled 80% aq trifluoroacetic acid (10 ml/mmol) and, if necessary to dissolve the starting material, MeOH was added. The resulting mixture was stirred at 5 ºC until deprotection was complete. Then it was evaporated and co-evaporated several times with MeOH. The residue was chromatographed on silica gel column with EtOAc-MeOH-Et_3N (90:10:0.5→70:30:0.5) to obtain product **6a**–**f** as triethylammonium salt (solid foam, 65-75% yield).

*4.2.39. 4-Amino-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-β-D-ribofuranosyl}-6-phenyl-1H-[1,2,3]triazole[4,5-c]pyridine triethylammonium salt (**6a**)*

UV (MeOH): λ_{max} 245.5 nm (37700), 309 nm (16200). UV (H_2O): λ_{max} 245 nm (30800), 303.5 nm (12700). Fluorescence emission in MeOH: λ_{max} 419 nm, Φ_F = 0.37; in H_2O: λ_{max} 433 nm, Φ_F = 0.0015. ^{1}H NMR (DMSO-d_6) δ 13.57 (s, 1H, OH), 9.09 (brs, 1H, Et_3NH^+), 8.16 (m, 2H, Ph), 7.79 (dd, J=2.0 Hz, J=7.6 Hz, 1H, sal), 7.57 (s, 1H, 7-H), 7.39 (m, 3H, Ph), 7.25 (m, 3H, NH_2, sal), 6.72 (m, 2H, sal), 6.27 (d, $J_{1',2'}$=5.2 Hz, 1H, 1'-H), 5.62 (d, $J_{2'\text{-}OH,2'\text{-}H}$=6.0 Hz, 1H, 2'-OH), 5.46 (d, $J_{3'\text{-}OH,3'\text{-}H}$=5.2 Hz, 1H, 3'-OH), 4.71 (m, 1H, 2'-H), 4.36 (m, 1H, 3'-H), 4.25 (m, 2H, 4'-H, 5'a-H), 4.16 (m, 1H, 5'b-H), 3.04 (brs, 6H, $(CH_3CH_2)_3NH^+$), 1.15 (t, J=7.4 Hz, 9H, $(CH_3CH_2)_3NH^+$). ^{13}C NMR (DMSO-d_6) δ 170.92 (CO), 160.67 (C-OH_{sal}), 152.47 and 151.45 (C-4, C-6), 139.05 (C-7a), 138.88 (Ph), 132.57 (sal), 130.89 (C-3a), 129.83 (sal), 128.58, 128.33 and 127.07 (Ph), 119.85, 117.51 and 116.55 (sal), 90.48 and 90.33 (C-1', C-7), 82.97 (C-4'), 73.03 (C-2'), 70.55 (C-3'), 68.66 (C-5'), 45.71 ($(CH_3CH_2)_3NH^+$), 8.62 ($(CH_3CH_2)_3NH^+$). HRMS $[M-H]^-$ calcd for $C_{23}H_{21}N_6O_8S$: 541.1147; found: 541.1141.

*4.2.40. 4-Amino-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-β-D-ribofuranosyl}-6-(4-methylphenyl)-1H-[1,2,3]triazole[4,5-c]pyridine triethylammonium salt (**6b**)*

UV (MeOH): λ_{max} 250 nm (33700), 311.5 nm (16400). UV (H_2O): λ_{max} 249.5 nm (27400), 306.5 nm (14000). Fluorescence emission in MeOH: λ_{max} 412 nm, Φ_F = 0.06; in H_2O: λ_{max} 433 nm, Φ_F = 0.0018. ^{1}H NMR (DMSO-d_6) δ 13.56 (s, 1H, OH), 8.06 (d, J=8.0 Hz, 2H, Ph), 7.80 (dd, J=1.8 Hz, J=7.8 Hz, 1H, sal), 7.52 (s, 1H, 7-H), 7.24 (m, 5H, Ph, sal, NH_2), 6.72 (m, 2H, sal), 6.25 (d, $J_{1',2'}$=5.6 Hz, 1H, 1'-H), 5.61 (d, $J_{2'OH,2'H}$=6.0 Hz, 1H, 2'-OH), 5.46 (d, $J_{3'OH,3'H}$=5.2 Hz, 1H, 3'-OH), 4.70 (m, 1H, 2'-H), 4.35 (m, 1H, 3'-H), 4.24 (m, 2H, 4'-H, 5'a-H), 4.17 (m, 1H, 5'b-H), 3.02 (m, 6H, $(CH_3CH_2)_3NH^+$), 2.32 (s, 3H, CH_3), 1.15 (t, J=7.2 Hz, 9H, $(CH_3CH_2)_3NH^+$). ^{13}C NMR (DMSO-d_6) δ 171.37 (CO), 160.64 (C-OH_{sal}), 152.15 and 151.27 (C-4, C-6), 139.02 (C-7a), 138.01 and 135.81 (Ph), 132.48 (sal), 130.74 (C-3a), 129.79 (sal), 128.93 and 126.93 (Ph), 119.84, 117.43 and 116.48 (sal), 90.34 and 90.06 (C-1', C-7), 82.96 (C-4'), 72.97 (C-2'), 70.51 (C-3'), 68.63 (C-5'), 45.50 ($(CH_3CH_2)_3NH^+$), 20.73 (CH_3), 8.46 ($(CH_3CH_2)_3NH^+$). HRMS $[M-H]^-$ calcd for $C_{24}H_{23}N_6O_8S$: 555.1304; found: 555.1294.

*4.2.41. 4-Amino-6-(4-fluorophenyl)-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-β-D-ribofuranosyl}-1H-[1,2,3]triazole[4,5-c]pyridine triethylammonium salt (**6c**)*

UV (MeOH): λ_{max} 246 nm (39800), 308.5 nm (16000). UV (H_2O): λ_{max} 245 nm (30000), 304.5 nm (13400). Fluorescence emission in MeOH: λ_{max} 420 nm, Φ_F = 0.11; in H_2O: λ_{max} 442 nm, Φ_F = 0.002. ^{1}H NMR (DMSO-d_6) δ 13.56 (s, 1H, OH), 8.21 (m, 2H, Ph), 7.79 (m, 1H, sal), 7.56 (s, 1H, 7-H), 7.23 (m, 5H, NH_2, Ph, sal), 6.72 (m, 2H, sal), 6.26 (d, $J_{1',2'}$=5.6 Hz, 1H, 1'-H), 5.61 (d, $J_{2'\text{-}OH,2'H}$=6.4 Hz, 1H, 2'-OH), 5.46 (d, $J_{3'\text{-}OH,3'\text{-}H}$=4.8 Hz, 1H, 3'-OH), 4.70 (m, 1H, 2'-H), 4.36 (m, 1H, 3'-H), 4.24 (m, 2H, 4'-H, 5'a-H), 4.18 (m, 1H, 5'b-H), 3.08 (m, 6H, $(CH_3CH_2)_3NH^+$), 1.17 (t, J=7.4 Hz, 9H, $(CH_3CH_2)_3NH^+$). ^{13}C NMR (DMSO-d_6) δ 170.90 (CO), 162.56 (d, $J_{C,F}$=244.88 Hz, C-4_{Ph}), 160.65 (C-OH_{sal}), 151.45 and 151.35 (C-4, C-6), 138.93 (C-7a), 135.33 (Ph), 132.57 (sal), 130.85 (C-3a), 129.81 (sal), 129.18 (d, $J_{C,F}$=8.42 Hz, C-2_{Ph}, C-6_{Ph}), 119.82, 117.50 and 116.54 (sal), 115.06 (d, $J_{C,F}$=21.47 Hz, C-3_{Ph}, C-5_{Ph}), 90.43 and 90.37 (C-1', C-7), 83.07 (C-4'), 72.92 (C-2'), 70.49 (C-3'), 68.65 (C-5'), 45.68 ($(CH_3CH_2)_3NH^+$), 8.60 ($(CH_3CH_2)_3NH^+$). ^{19}F NMR (DMSO-d_6) δ -38.30. HRMS $[M-H]^-$ calcd for $C_{23}H_{20}N_6O_8SF$: 559.1053; found: 559.1051.

*4.2.42. 4-Amino-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-β-D-ribofuranosyl}-6-(4-trifluoromethylphenyl)-1H-[1,2,3]triazole[4,5-c]pyridine triethylammonium salt (**6d**)*

UV (MeOH): λ_{max} 244 nm (46900), 310 nm (18700). UV (H_2O): λ_{max} 244 nm (46900), 309 nm (18000). Fluorescence emission in MeOH: λ_{max} 409 nm, Φ_F = 0.32; in H_2O: λ_{max} 422 nm, Φ_F = 0.0019. ^{1}H NMR (DMSO-d_6) δ 13.54 (s, 1H, OH), 8.39 (d, J=8.4 Hz, 2H, Ph), 7.76 (m, 4H, Ph, sal, 7-H), 7.37 (s, 2H, NH_2), 7.24 (m, 1H, sal), 6.71 (m, 2H, sal), 6.28 (d, $J_{1',2'}$=6.0 Hz, 1H, 1'-H), 5.62 (d, $J_{2'\text{-OH},2'\text{-H}}$=6.4 Hz, 1H, 2'-OH), 5.47 (d, $J_{3'\text{-OH},3'\text{-H}}$=5.2 Hz, 1H, 3'-OH), 4.69 (m, 1H, 2'-H), 4.36 (m, 1H, 3'-H), 4.24 (m, 3H, 4'-H, 5'-H), 3.09 (m, 6H, $(CH_3C\mathit{H}_2)_3NH^+$), 1.17 (t, J=7.2 Hz, 9H, $(C\mathit{H}_3CH_2)_3NH^+$). ^{13}C NMR (DMSO-$d_6$) δ 171.00 (CO),160.66 (C-OH_{sal}), 151.64 and 150.57 (C-4, C-6), 142.67 (Ph), 138.62 (C-7a), 132.55 (sal), 131.35 (C-3a), 129.78 (sal), 128.62 (q, $J_{C,F}$=32.12 Hz, C-4_{Ph}), 127.70 (Ph), 125.17 (q, $J_{C,F}$=3.85 Hz, C-3_{Ph}, C-5_{Ph}), 124.39 (q, $J_{C,F}$=276.08 Hz, CF_3), 119.77, 117.46 and 116.52 (sal), 91.84 and 90.67 (C-1', C-7), 83.27 (C-4'), 72.92 (C-2'), 70.43 (C-3'), 68.65 (C-5'), 45.68 ($(CH_3\mathit{C}H_2)_3NH^+$), 8.60 ($(\mathit{C}H_3CH_2)_3NH^+$). ^{19}F NMR (DMSO-$d_6$) δ 14.74. HRMS $[M-H]^-$ calcd for $C_{24}H_{20}N_6O_8SF_3$: 609.1021; found: 609.1013.

*4.2.43. 4-Amino-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-β-D-ribofuranosyl}-6-(napht-2-yl)-1H-[1,2,3]triazole[4,5-c]pyridine triethylammonium salt (**6e**)*

UV (MeOH): λ_{max} 251 nm (46300), 315 nm (14800). UV (H_2O): λ_{max} 250 nm (48200), 311.5 nm (13600). Fluorescence emission in MeOH: λ_{max} 412 nm, Φ_F = 0.38; in H_2O: λ_{max} 420 nm, Φ_F = 0.0025. ^{1}H NMR (DMSO-d_6) δ 13.58 (s, 1H, OH), 8.73 (s, 1H, naphthyl), 8.34 (dd, J=1.8 Hz, J=8.6 Hz, 1H, naphthyl), 8.06 (m, 1H, naphthyl), 7.92 (m, 2H, naphthyl), 7.80 (dd, J=1.8 Hz, J=7.8 Hz, 1H, sal), 7.74 (s, 1H, 7-H), 7.51 (m, 2H, naphthyl), 7.32 (s, 2H, NH_2), 7.24 (m, 1H, sal), 6.72 (m, 2H, sal), 6.30 (d, $J_{1',2'}$=6.0 Hz, 1H, 1'-H), 5.64 (d, $J_{2'OH,2'H}$=6.0 Hz, 1H, 2'-OH), 5.48 (d, $J_{3'OH,3'H}$=5.2 Hz, 1H, 3'-OH), 4.75 (m, 1H, 2'-H), 4.38 (m, 1H, 3'-H), 4.28 (m, 2H, 4'-H, 5'a-H), 4.20 (m, 1H, 5'b-H), 3.07 (brs, 6H, $(CH_3C\mathit{H}_2)_3NH^+$), 1.16 (t, J=7.2 Hz, 9H, $(C\mathit{H}_3CH_2)_3NH^+$). ^{13}C NMR (DMSO-$d_6$) δ 170.98 (CO), 160.68 (C-OH_{sal}), 152.22 and 151.51 (C4, C6), 139.02 (C-7a), 136.29, 133.05 and 133.01 (naphthyl), 132.52 (sal), 131.01 (C-3a), 129.83 (sal), 128.65, 127.68, 127.33, 126.34, 126.14, 126.05 and 125.11 (naphthyl), 119.82, 117.46 and 116.51 (sal), 90.92 and 90.40 (C-1', C-7), 83.05 (C-4'), 72.92 (C-2'), 70.53 (C-3'), 68.63 (C-5'), 45.65 ($(CH_3\mathit{C}H_2)_3NH^+$), 8.62 ($(\mathit{C}H_3CH_2)_3NH^+$). HRMS $[M-H]^-$ calcd for $C_{27}H_{23}N_6O_8S$: 591.1304; found: 591.1295.

*4.2.44. 4-Amino-1-{5-O-[N-(2-hydroxybenzoyl)sulfamoyl]-β-D-ribofuranosyl}-6-(6-methoxynapht-2-yl)-1H-[1,2,3]triazole[4,5-c]pyridine triethylammonium salt (**6f**)*

UV (MeOH): λ_{max} 247.5 nm (47000), 322.5 nm (21200). UV (H_2O): λ_{max} 243 nm (26600), 318.5 nm (12600). Fluorescence emission in MeOH: λ_{max} 418 nm, Φ_F = 0.5; in H_2O: λ_{max} 425 nm, Φ_F = 0.007. ^{1}H NMR (DMSO-d_6) δ 13.57 (s, 1H, OH), 8.65 (d, J=1.6 Hz, 1H, naphthyl), 8.30 (dd, J=1.8 Hz, J=8.6 Hz, 1H, naphthyl), 7.96 (d, J=8.8 Hz, 1H, naphthyl), 7.82 (m, 2H, naphthyl, sal), 7.68 (s, 1H, 7-H), 7.27 (m, 4H, naphthyl, sal, NH_2), 7.15 (dd, J=2.6 Hz, J=9.0 Hz, 1H, naphthyl), 6.72 (m, 2H, sal), 6.29 (d, $J_{1',2'}$=6.0 Hz, 1H, 1'-H), 5.64 (d, $J_{2'OH,2'H}$=6.0 Hz, 1H, 2'-OH), 5.48 (d, $J_{3'OH,3'H}$=5.2 Hz, 1H, 3'-OH), 4.74 (m, 1H, 2'-H), 4.38 (m, 1H, 3'-H), 4.24 (m, 3H, 4'-H, 5'-H), 3.89 (s, 3H, OCH_3), 3.04 (q, J=7.2 Hz, 6H, $(CH_3CH_2)_3NH^+$), 1.16 (t, J=7.4 Hz, 9H, $(CH_3CH_2)_3NH^+$). ^{13}C NMR (DMSO-d_6) δ 171.01 (CO), 160.69 (C-OH_{sal}), 157.68 (C-$6_{naphthyl}$), 152.47 and 151.45 (C-4, C-6), 139.05 (C-7a), 134.46 and 134.08 (naphthyl), 132.56 (sal), 130.90 (C-3a), 130.23 (naphthyl), 129.85 (sal), 128.42, 126.61, 125.94 and 125.59 (naphthyl), 119.83 (sal), 118.69 (naphthyl), 117.49 and 116.53 (sal), 105.70 (naphthyl), 90.41 and 90.35 (C-1', C-7), 83.05 (C-4'), 72.89 (C-2'), 70.53 (C-3'), 68.66 (C-5'), 55.20 (OCH_3), 45.62 ($(CH_3CH_2)_3NH^+$), 8.71 ($(CH_3CH_2)_3NH^+$). HRMS $[M-H]^-$ calcd for $C_{28}H_{25}N_6O_9S$: 621.1409; found: 621.1402.

4.3. MbtA Enzyme Assay

MbtA was expressed in *E. coli* and purified as described. MbtA concentration was determined by active site titration with **2** as described [34]. The inhibition assays were performed as reported in duplicate under initial velocity conditions. In brief the reaction was initiated by adding 10 µL [^{32}P]PP_i with 7 nM MbtA in 90 µL reaction buffer (278 µM salicylic acid, 11.1 mM ATP, 1.11 mM PPi, 83.3 mM Tris-HCl, pH 7.5, 11.1 mM $MgCl_2$, 2.22 mM DTT) at 37 °C in the presence of eight different concentrations of the inhibitor (1.5-fold dilution from 100 nM down to 8.78 nM and a 3-fold dilution to 2.93 nM). The reaction was terminated at 20 min by the addition of 200 µL of quenching buffer (350 mM $HClO_4$, 100 mM PPi, 1.8 % *w/v* activated charcoal). The charcoal was pelleted by centrifugation and washed once with 500 µL H_2O and analyzed by liquid scintillation counting as described. Fractional initial velocities were fit by nonlinear regression analysis to the Morrison equation (eq 1) using GraphPad Prism 5.0

$$\frac{v_i}{v_0} = 1 - \frac{([E]+[I]+K_i^{app}) - \sqrt{([E]+[I]+K_i^{app})^2 - 4[E][I]}}{2[E]} \qquad \text{(eq 1)}$$

where, I represents the concentration of inhibitor, K_i^{app} is the apparent inhibition constant, E is

the active enzyme concentration (determined by active-site titration), v_i is the initial rate at each [*I*], and v_0 is the initial rate of the DMSO control. A fitted curve for compound **6e** is shown (Fig. 3) as an example.

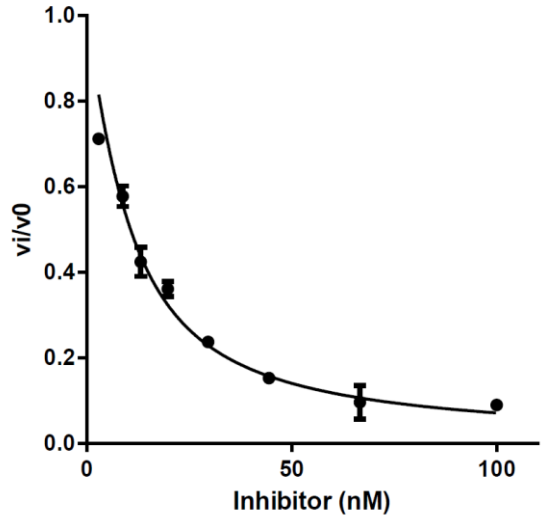


Figure 3. Dose-response of fractional initial velocity of [^{32}P]-ATP formation catalyzed by MbtA as a function of inhibitor **6e** concentration.

4.4. M. tuberculosis H37Rv MIC Assay

All compounds minimum inhibitory concentrations (MICs) were experimentally determined as previously described. MICs were determined in triplicate in iron-deficient GAST according to the broth microdilution method using compounds from DMSO stock solutions or with control wells treated with an equivalent amount of DMSO. Isoniazid was used as a positive control while DMSO was employed as a negative control. All measurements reported herein used an initial cell density of 10^4–10^5 cells/assay and growth monitored at 10–14 days, with the untreated and DMSO-treated control cultures reaching an OD_{620} 0.2–0.3. Plates were incubated at 37 °C (100 µL/well) and growth was recorded by measurement of optical density at 620 nm.

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Supplementary data

Supplementary data associated with this article can be found in the online version at

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2-Aryl-8-aza-3-deazaadenosine Analogues of 5'-*O*-[*N*-(Salicyl)sulfamoyl]adenosine: Nucleoside Antibiotics that Block Siderophore Biosynthesis in *Mycobacterium tuberculosis*

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