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Synthesis of Fluorinated Purine and 1-Deazapurine Glycosides as Potential Inhibitors of Adenosine Deaminase

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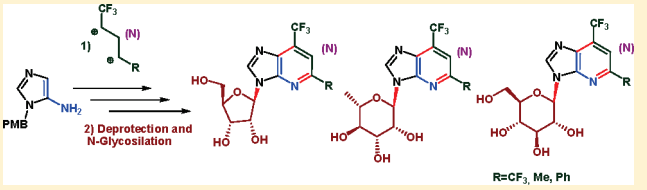
Supporting Information

ABSTRACT: The synthesis of 2- and 6-trifluoromethylated purines and 1-deazapurines was performed by formal [3 + 3]-cyclization reactions of 5-aminoimidazoles with a set of trifluoromethyl-substituted 1,3-CCC- and 1,3-CNC-dielectrophiles. The corresponding fluorinated nucleosides were synthesized by glycosylation of 9-unsubstituted purines and 1-deazapurines with peracetylated β-ribose, β-glucose, and rhamnose and subsequent deprotection. These scaffolds can be considered as potential inhibitors of adenosine deaminase (ADA) and inosine monophosphate dehydrogenase (IMPDH) enzymes.



The subject of the present paper is to report the synthesis of novel CF_3-containing purine and 1-deazapurine nucleosides as a platform for the design of adenosine deaminase (ADA) enzyme pitfalls. Deaminases are of particular interest since many of these enzymes represent potential drug targets for the design and synthesis of potent drugs for the treatment of various diseases, such as HIV and cancers. Adenosine deaminase (ADA) and RNA-specific adenosine deaminase (ADAR) play a very important role in medicine chemistry and drug design.[1] The inhibition of these enzymes has been reported to have substantial therapeutic potential and could be used for the treatment of cancer and genetic disorders.[1]

In general, imidazo[4,5-*b*]pyridines (1-deazapurines) are an important class of heterocyclic compounds that exhibit a wide range of activities.[2] 1-Deazapurine is a common structural motif found in numerous molecules which display antiviral, antifungal, antibacterial, and antiproliferative activities. The potent biological activity and the prevalence of 1-deazapurines in both natural products and pharmaceuticals have inspired significant interest in the synthesis of these heterocycles.[3]

Efforts to design potent and specific inhibitors of deaminases have been focused so far on molecules that mimic the transition state (TS) structure. Since the TS structure most likely resembles the hydrated intermediate, stable TS mimics containing a hydroxyl group attached to a tetrahedral carbon, located in a position analogous to the purine hydration site, were designed.[4,5] Alternatively, substrate analogues that undergo reversible covalent hydration may represent an even better strategy since the hydrated product has higher structural similarity to the TS structure and, therefore, would be expected to exhibit greater potency and specificity (Figure 1).[4,5]

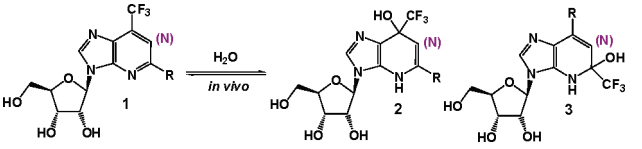


Figure 1. Concept: 2- and 6-trifluoromethyl-containing purines and 1-deazapurines as inhibitors of adenosine deaminase (ADA).

The electron-withdrawing CF_3 group in purine-like scaffolds **1** facilitates the addition of water to the 6-position of purine (purine isosteres)[6] and maintains the stability of the formed 6-hydrates **2** and **3** (Figure 1). Previously, a theoretical study has been carried out to establish 6-CF_3-substituted purine isosteres as promising inhibitors of ADA.[6] Since the CF_3 group is also isosterically close to the amino group,[4,7] the modification of the compounds, which mimic the putative transition state of ADA by isosterical change of the amino function to a CF_3 group, should not cause a problem of substrate recognition and can be expected to lead to enzyme inhibition (Figure 1).

In our opinion, purines and their isosteres bearing a perfluoroalkyl substituent at positions 2 and/or 6 should be also considered as potential inosine monophosphate dehydrogenase (IMPDH) inhibitors,[8a] due to the possibility of covalent binding of the Cys 331 moiety of the active side of the enzyme with the sufficiently strong electrophilic carbon atoms C-6 and C-2 to form stable Meisenheimer-type adducts. It was shown that, for example, the 6-chloro-substituted purine base[8] is dehalogenated

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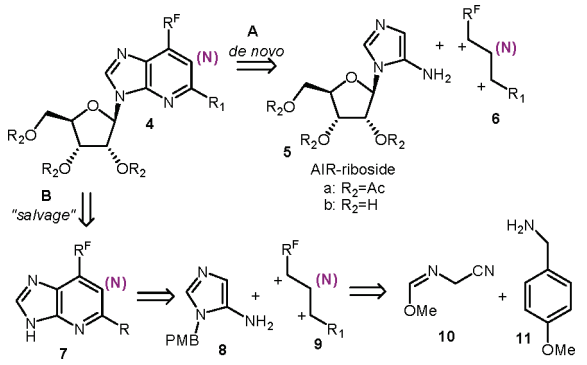
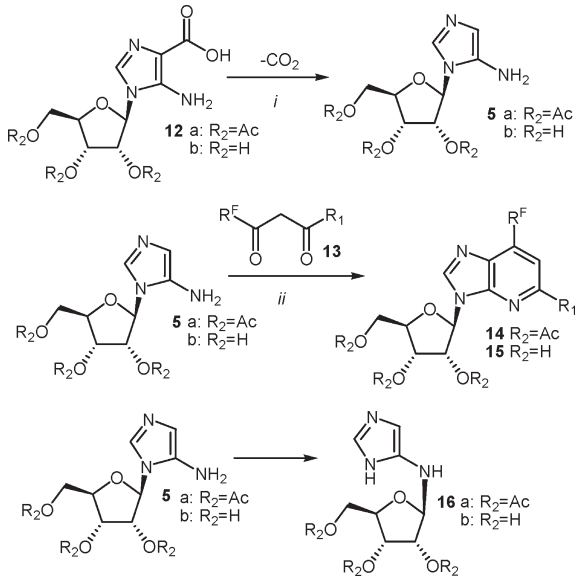


Figure 2. Retrosynthetic analysis.

Scheme 1[a]



[a] Reagents and conditions: (i) HOAc, absolute DMSO under argon, 60 to 80 °C; (ii) absolute DMF, under argon, 60 to 80 °C.

by IMPDH and a covalent bond is formed at position C-6 with Cys 331.

Retrosynthetically, the synthesis of our target molecules can be achieved by two different strategies. Following the (natural) biosynthetic pathways for the synthesis of purine nucleotides, we have called these strategies *de novo*[9] and *salvage*[10] (Figure 2). The first one is built on the regioselective electrophilic annulation of the pyridine and pyrimidine ring on the enamine moiety of the AIR-riboside[11] using diverse fluorine-containing 1,3-CCC- and 1,3-CNC-dielectrophiles. The second strategy relies on the initial assembly of the CF_3-containing purine/1-deazapurine framework starting with 5-aminoimidazole **8** which bears a *p*-methoxybenzyl (PMB) protecting group at position 9. Subsequent deprotection and glycosylation will furnish the desired scaffolds **9** (Figure 2).

Previously, we and others have developed several new strategies toward CF_3- and CF_2H-containing purines and purine isosteres (Scheme 1).[12,13]

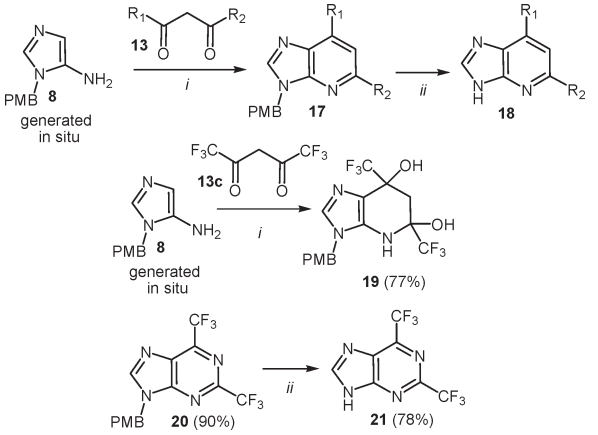
At the beginning of this project, we considered path **A** to be more efficient and easy to perform. AIR-riboside **5a** is a key substance in the de novo purine biosynthesis. Compound **5a**, as

Table 1. Synthesis of 1-Deazapurine Nucleosides 14 and 15

	R^F	R_1	**14**[a,b]	**14**[a,d]	**15**[a,c]	**15**[a,e]
a	CF_3	Me	10	4	5	3
b	CF_3	Ph	11	6	7	5
c	CF_3	CF_3	13	10	11	10
d	CF_2Cl	Me	10	7	10	8

[a] Yields of isolated products. [b] Reaction was performed using **5a**. [c] Reaction was performed using **5b**. [d] **5a** was generated in situ from **12a**. [e] **5b** was generated in situ from **12b**.

Scheme 2[a]



[a] Reagents and conditions: (i) CH_2Cl_2, under argon, reflux, 2 h; (ii) TFA, 20 °C, 24−72 h.

well as its acylated derivative **5b**, is unstable and very difficult to prepare.[11] We have synthesized the corresponding nucleosides **5** and studied their reactions with the fluorinated 1,3-diketones **13**. Starting this investigation, we have focused on the development of optimal reaction conditions for the pyridine ring annulation. Unfortunately, extremely low yields were obtained using various solvents (AcOH, CH_3OH, CH_3CN, H_2O). The employment of acidic catalysts, such as *p*-toluenesulfonic acid (PTSA), or ion-exchange resins did not allow improved yields. The best yields of 1-deazapurine nucleosides **14** and **15** were obtained using dry DMF and conducting the reaction under inert atmosphere. Unfortunately, the products were isolated only in the range of 13% yield.

The main reason for the low yields lies in the fact that, in the case of compounds **5**, a Dimroth rearrangement takes place with formation of product **16**.[11] We have also used a decarboxylation reaction of **12**[11c,14] to generate **5** in situ in the presence of 1,3-diketones. The reactions were carried out in absolute DMF under argon atmosphere at 60−80 °C[11b] and delivered the corresponding protected and unprotected 1-deazapurine nucleosides **14** and **15** with yields in the range of 3−10% (Table 1).

With these unsatisfactory results in hand, we next focused our attention on path **B**. As a source for the in situ generation of 5-aminoimidazole **8**, we have used the reaction of imidate **10** with *p*-methoxybenzyl amine **11**. The subsequent reaction of **8** with a number of 1,3-CCC-dielectrophiles afforded 1-deazapurines **17** in good yields (Scheme 2; Table 2). Under the mild reaction conditions, we have succeeded in isolating the corresponding intermediate **19** and have proved its structure by 2D NMR methods. Hydrate **19** is relatively stable and was dehydrated

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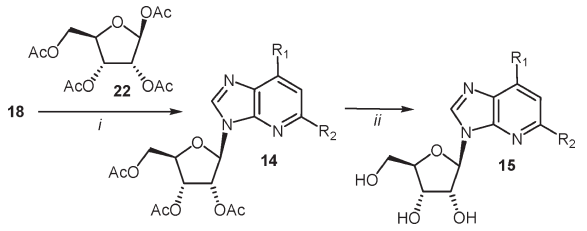
Table 2. Synthesis 1-Deazapurines 17 and 18

	R_1	R_2	17[a]	18[a]
a	CF_3	Me	77	65
b	CF_3	Ph	71	60
c	CF_3	CF_3	55	74
d	CF_2Cl	Me	80	75
e	CO_2Me	Me	66	81

[a] Yields of isolated products.

Scheme 3[a]



[a] Reagents and conditions: (i) BSA (*O,N*-bis(trimethylsilyl)acetamide), TMSOTf; (ii) MeOH, NH_3, 20 °C, 24 h.

Table 3. Synthesis of 1-Deazapurine Nucleosides 14 and 15

	R_1	R_2	14[a]	15[a]
a	CF_3	Me	61	98
b	CF_3	Ph	45	99
c	CF_3	CF_3	67	98
d	CF_2Cl	Me	75	99
e	CO_2Me	Me	77	*b*

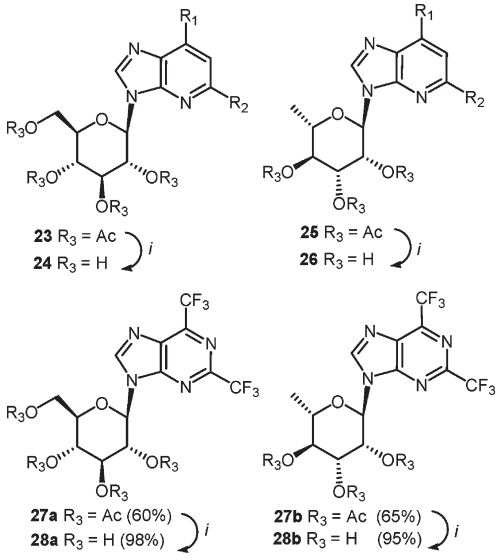
[a] Yields of isolated products. [b] See Scheme 5.

under acidic conditions or by prolonged reflux in CH_2Cl_2. The stability of **19** supports our concept (Figure 1). Purine **21** was prepared by inverse electron demand Diels–Alder reaction of **8** with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine which proceeded smoothly to give **20**. Subsequently, the PMB group was cleaved to give **21** (Scheme 2).

To obtain various 9-sugar-modified 6-CF_3 purines and their 1-deaza analogues, we chose tetraacetyl-ribose **22** as a model compound and have studied the direct glycosylation of 1-deazapurines **18**. During the optimization, several conditions were tried for the glycosylation. They include a diverse set of Lewis acid catalysts ($SnCl_4$, $TiCl_4$, $TiBr_4$, Me_2O-BF_3), base catalysts (NaH, $NaNH_2$, TMEDA, DBU), and solvents (CH_3CN, DCM, C_6H_6, toluene, 1,2-dichloroethane, DMF). The best results were found to be the so-called silyl-Hilbert–Johnson reaction conditions.[13−15] The glycosylations were performed in acetonitrile under reflux in inert atmosphere, using *O,N*-bis(trimethylsilyl)acetamide for the initial silylation of the heterocyclic moiety. As a catalyst for the next glycosylation step, TMSOTf was used. The deprotection of the sugar group was carried out in a concentrated solution of ammonia in methanol to give the correspondent unprotected ribosides **15** in quantitative yields (Scheme 3; Table 3).

Using a previously elaborated strategy, the α-L-rhamnose and β-D-glucose moieties can be swiftly introduced into purine and

Scheme 4[a]



[a] Reagents and conditions: (i) MeOH, NH_3, rt, 24 h.

1-deazapurine core structures by glycosylation of **18** and **21** with peracetylated rhamnose and β-D-glucose which deliver the correspondent peracetylated α-L-rhamnosides **23** and **27a** and β-D-glucosides **25** and **27b**. The latter compounds were treated with a 7 M solution of ammonia in methanol to remove the acetyl protective groups and to give the desired α-L-rhamnosides and β-D-glucosides **24**, **26**, and **33** (Scheme 4; Table 4).

To better understand the structure of the products obtained, we attempted to grow crystals of all 1-deazapurine nucleosides suitable for X-ray diffraction analysis. The X-ray crystal structure analysis of **26b** proved that the glycosylation reaction occurred at position 9 of the 1-deazapurine framework. The anomeric carbon atom possesses a α-configuration (Figure 1 in Supporting Information).[16]

As an extension of our current study, we have decided to introduce a carboxylic acid group at position 6 of the 1-deazapurines and synthesize the correspondent 9-sugar-modified derivatives. Compound **18e** was prepared from **17e** and easily converted to the desired riboside **14e**, glycoside **30**, and rhamnoside **32** by direct N-glycosylation. Subsequent deprotection was carried out with ammonia. At the same time, we observed the transformation of the ester function into an amide, and the resulting products proved to be 9-glycosylated 5-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxamides **29**, **31**, and **33** (Scheme 5).

In conclusion, we have developed a new and general strategy for the assembly of 6-CF_3-1-deazapurines bearing a ribose, rhamnose, and glucose moiety at position 9. The synthesized scaffolds constitute a platform for the mechanism-based design and synthesis of adenosine deaminase (ADA) and inosine monophosphate dehydrogenase (IMPDH) enzyme inhibitors.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Compounds 14a–e. To a suspension of 1.33 mmol of deprotected imidazo-[4,5-*b*]-pyridine (1 equiv) in 6 mL of dry acetonitrile was added 1.2 equiv of BSA under argon atmosphere. The obtained clear solution was refluxed for 20 min and then was left to cool to room temperature. Afterward, the solution of corresponding acetylated sugar (1.2 equiv) in dry acetonitrile

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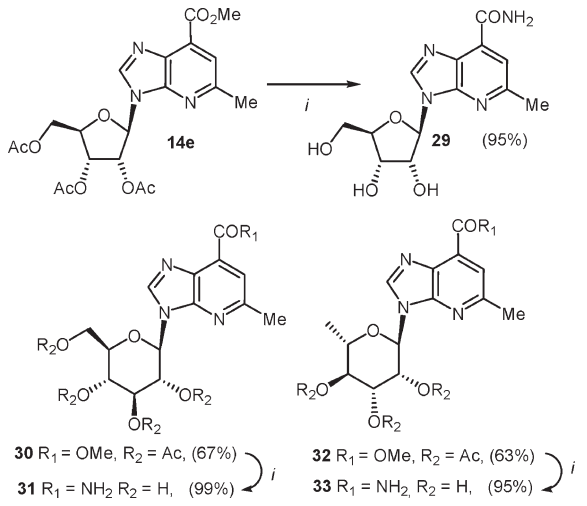
Scheme 5[a]



[a] Reagents and conditions: (i) MeOH, NH_3, 20 °C, 24 h.

Table 4. Synthesis of 1-Deazapurine Nucleosides 22, 23, 24, and 25

	R_1	R_2	22[a]	23[a]	24[a]	25[a]
a	CF_3	Me	61	96	75	95
b	CF_3	Ph	45	97	79	94
c	CF_3	CF_3	67	97	66	93

[a] Yields of isolated products.

and TMSOTf (0.25 equiv) was added, and the reaction mixture was refluxed for 2 h (until the color of the solution became yellow-orange). The solvent and liquid byproducts were evaporated to dryness, and the residue was purified by column chromatography (EtOAc/heptane = 1:2, then 1:1) to give the desired glycosylated product as white oil.

Spectral Data for the Compound 1-(2,3,5-Tri-*O*-acetyl-*β*-D-ribofuranosyl)-7-(trifluoromethyl)-5-phenyl-3*H*-imidazo-[4,5-*b*]pyridine (14b): White oil, yield 45%, R_f (EtOAc/heptane, 1:1) = 0.55; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ = 1.93 (s, 3H, Ac), 2.12 (s, 3H, Ac), 2.18 (s, 3H, Ac), 4.34 (dd, 1H, $-CH_2-$, J_1 = 6.0 Hz, J_2 = 3.0 Hz), 4.47 (br m, 2H, $-CH_2-$, H-5′), 5.85 (t, 1H, H-4′, ^3J = 5.1 Hz), 6.21 (t, 1H, H-3′, ^3J = 5.1 Hz), 6.31 (d, 1H, H-2′, ^3J = 4.8 Hz), 7.54 (br m, 3H, Ph), 7.98 (s, 1H, H-5), 8.10 (d, 2H, Ph, ^3J = 9.3 Hz), 8.90 (s, 1H, H-2); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 20.4 (CH_3—CO), 20.5 (CH_3—CO), 20.5 (CH_3—CO), 62.6 ($-CH_2-$), 70.1 (C-5′), 73.1 (C-4′), 79.9 (C-3′), 87.3 (C-2′), 112.8 (C-5, t, $^3J_{(C-F)}$ = 3.0 Hz), 122.6 (CF_3, q, $^1J_{(C-F)}$ = 272.4 Hz), 127.5 (C-4″), 129.1 (C-3″, C-5″), 129.6 (C-2″, C-6″), 129.8 (C-4, q, $^2J_{(C-F)}$ = 29.1 Hz), 131.0 (C-1″), 138.2 (C-6), 144.7 (C-2), 147.6 (C-3a), 154.1 (C-7a), 169.4 (C═O), 169.5 (C═O), 170.4 (C═O); MS (GS) 521 (32) [$(M + H)^+$], 306 (10), 259 (79), 244 (10), 157 (14), 139 (100), 97 (42), 43 (78); HRMS (ESI) calcd for $C_{24}H_{23}F_3N_3O_7$ $(M + H)^+$ 521.1489, found 522.1485; IR (ATR) ν = 1721, 1630, 1589, 1463, 1402, 1359, 1242, 1056, 761, 623 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information. Synthetic procedures, compound characterization, copies of NMR spectra, X-ray structure. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) X-ray crystallographic data (excluding structure factors) for the structure **26b**, reported in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 805544 for **26b** and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.