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Synthesis and Biological Activity of 2,6-Disubstituted 7-Deazapurine Ribonucleosides

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Several series of 2,6-disubstituted 7-deazapurine ribonucleosides were synthesized to investigate their biological activities. The key-intermediate chloronucleosides were prepared by an anion-base glycosylation with 2-amino-6-chloro-7-deazapurine. The target compounds were obtained by diazotation, either Suzuki and Sonogashira reactions in the case of 2-arylethynyl-6-hetaryl nucleosides or two consecutive Suzuki reactions in the case of 2,6-diaryl nucleosides. The sequence of diazotation and the first Suzuki reaction is flexible and can be changed depending on the target compounds. Some of the final nucleosides showed moderate cytotoxic activity against several cancer cell lines and low antagonistic activity against a panel of adenosine receptors.

Introduction

Nucleosides have many various biological functions and play a role in numerous cellular processes, so any modification in their structure can have a significant impact on their biological activity, which is however very difficult to predict. Thus, systematic studies are common in the nucleoside field. Among all modified nucleosides, modified 7-deazapurine (systematically pyrrolo[2,3-*d*]pyrimidine) ribonucleosides are a prominent class of compounds with a broad spectrum of biological activities. Simple 7-deazaadenosine (**Tubercidin**) is a well-known natural antibiotic,[1] whereas 7-substituted 3'-fluororibo-7-deazadenosines **1** and related nucleosides showed potent antiparazitic activity against *Trypanosoma brucei*[2] or *Leishmania*[3] as well as affinity for G protein-coupled receptors.[4] In our group, we reported 7-substituted-7-deazadenosines **2**[5] displaying interesting antiviral activity against several RNA viruses. We also discovered two classes of very potent and selective nucleoside cytostatics, **AB61**[6] and **PNH173**[7] (Figure 1) bearing a thiophen-2-yl group either at position 7 or at position 6. This difference has a huge impact on their mechanism of action. **AB61** is phosphorylated in cancer cells and then incorporated into both DNA causing DNA damage and apoptosis,[8] while **PNH173** is not incorporated into nucleic acids and its mechanism of action is not yet understood. Later on, we prepared several 2-substituted 7-deazapurine ribonucleosides **3** as analogues of **PNH173** bearing amino, methyl, chloro and fluoro substituents. These simple modifications at position 2 led to complete loss of the cytotoxic activity, but these compounds were found to be

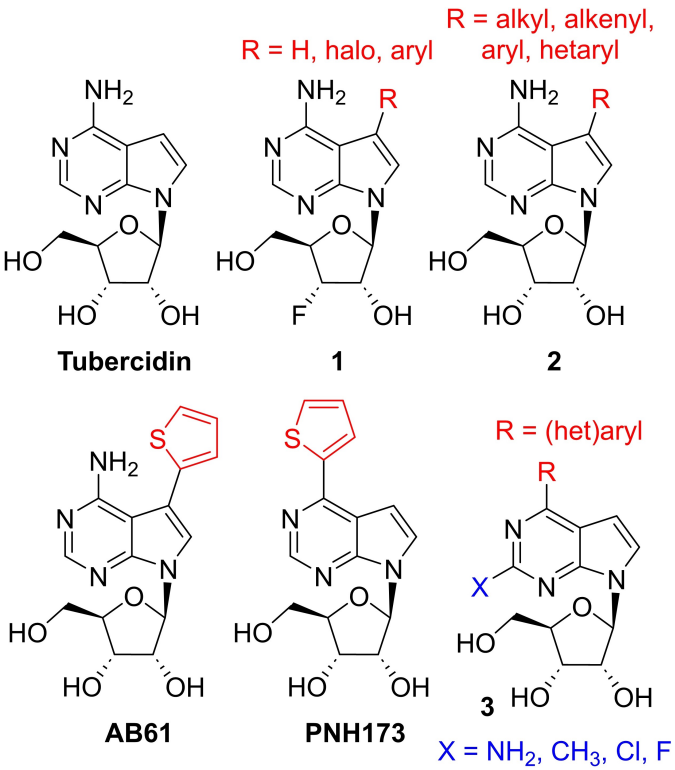

Figure 1. Examples of biologicaly active 7-deazapurine nucleosides.

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potent inhibitors of adenosine kinase from *Mycobacterium tuberculosis*.[9]

Modified adenines and adenosines are in principle a privileged class of compounds acting as modulators of all four adenosine receptors, which have been interesting drug targets for at least three decades.[10,11] From the numerous nucleoside derivatives investigated for their modulatory activity on adenosine receptors, there are several clinical candidates substituted in position 2 – e.g. adenosine derivatives Regadenoson[12] and Apadenoson[13] together with several others 2-arylethynyl derivatives like PENECA[14] and MRS5698[15] (Figure 2). All these derivatives have either amino or *N*-substituted amino group in position 6, there are no 7-deazapurine nucleosides bearing aryl substituent attached directly via C–C bond in position 6 and aryl or arylethynyl group in position 2 at the same time. Based on these findings, we decided to prepare a series of novel nucleosides bearing different size hetaryl groups in position 6 together with another aryl/arylethynyl group in position 2 (Figure 2) to better understand structure-activity relationship (SAR) and to study their cytostatic and antiviral activities together with their potential to modulate adenosine receptors.

It should be noted that some 2,6-diaryl-,[16–20] 2,6-dialkynyl-[21,22] and alkynyl-aryl-purine[23] and –7-deazapurine heterocycles have been previously prepared by two consequent Suzuki-Miyaura, Stille or Sonogashira cross-coupling reactions of 2,6-dihalo-(7-deaza)purines and some exhibited cytostatic[21] and antimycobacterial effects[24] or interesting fluorescent properties.[18,25] However, the analogous 2,6-disubstituted 7-deazapurine nucleosides were unknown.

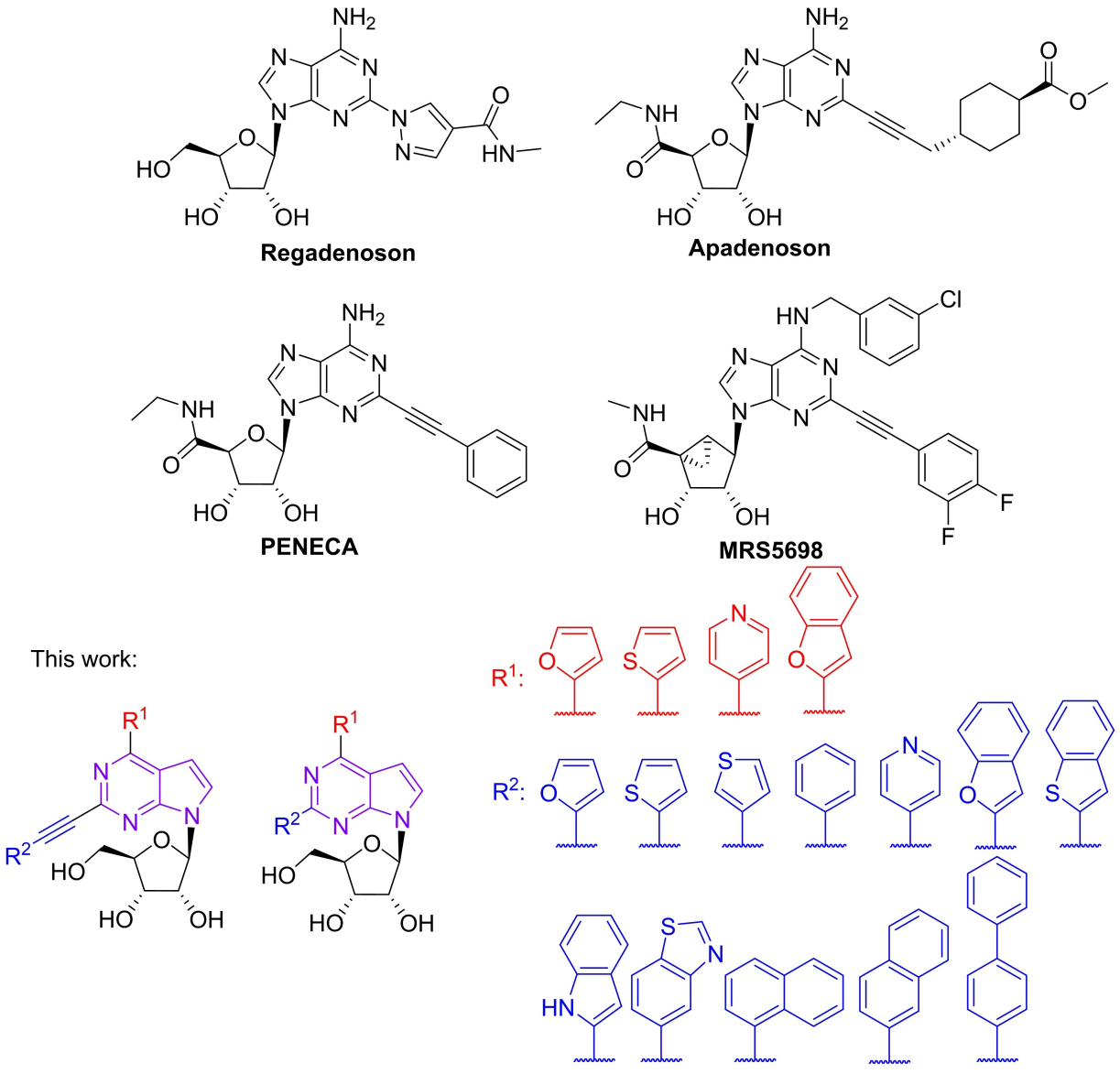

Figure 2. Known adenosine receptor modulators and target compounds of this study.

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Results and Discussion

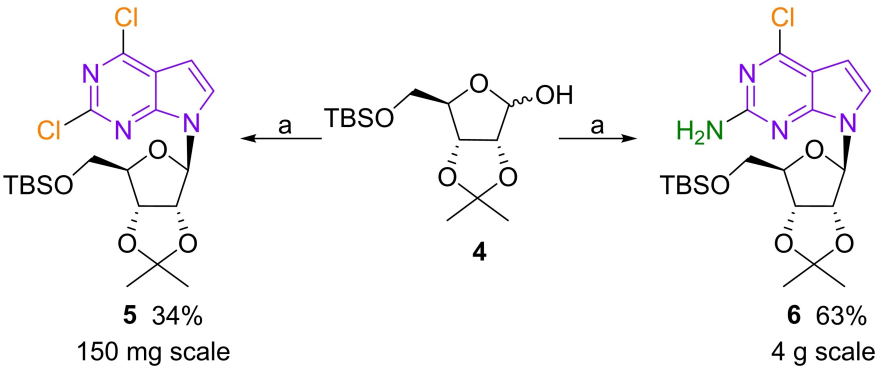
Chemistry

The key steps for synthesis of our target molecules are glycosylation of 2,6-disubstituted 7-deazapurine followed by two cross-coupling reactions (Suzuki or Sonogashira). First, we attempted to perform the anion base glycosylation of known protected halo-sugar, which was formed *in situ* from known protected ribose **4**[26] by reaction with CCl_4 and tris(dimethylamino)phosphine (HMPT) and then reacted with 2,6-dichloro-7-deazapurine using the standard conditions, KOH as a base in the presence of phase transfer catalyst TDA-1 in acetonitrile at r.t.[27] Although the reaction worked in a small scale (150 mg) and gave the desired nucleoside **5** in 34%, scale-up was unsuccessful and led only to decomposition of starting halogenose. Thus, we used 2-amino-6-chloro-7-deazapurine as a nucleobase and obtained the desired nucleoside **6** in much higher yield of 63%, which was reproducible even in a multi-gram scale (Scheme 1).

Although the Suzuki cross-coupling reactions of 2,6-dichloro-7-deazapurines are chemoselective with preferential reactivity at position 6, they can lead to formation of 2,6-disubstituted products.[17–19] To avoid that, we performed the Suzuki reaction with benzofuran-2-ylboronic acid on fully protected 2-amino-6-chloronucleoside **6** using $Pd(OAc)_2$ in a combination with the water-soluble ligand 3,3′,3′′-phosphanetriyltris(benzenesulfonic acid) trisodium salt (TPPTS) and obtained the nucleoside **7** in good yield of 75% (Scheme 2). Diazotation using excess of *tert*-butyl nitrite (TBN) and trimethylsilyl chloride (TMS–Cl) gave a mixture of fully protected and partially deprotected 2-chloro nucleosides **8** and **9** in excellent overall yield 91% (50% of **8**, 41% of **9**). The partial desilylation likely occurred during aqueous work-up. Deprotection of **8** with aqueous trifluoroacetic acid (TFA) gave the fully deprotected nucleoside **10** as a key intermediate. We decided to test different catalytic systems ($Pd(OAc)_2$, TPPTS, CuI, TEA and $Pd(PPh_3)_2Cl_2$, CuI, DIPEA) in both aqueous (water/MeCN) and organic solvents (DMF) on both key-intermediate nucleosides **9** and **10** and prepare a small series of nucleosides **11a–e** bearing arylethynyl groups of various sizes in position 2. All the target nucleosides **11a–e** were obtained in moderate yields (Table 1).

As both 2-chlorodeazapurine nucleosides **9** and **10** showed comparable reactivity in Sonogashira reaction, we decided to use the aqueous conditions and fully unprotected 2,6-dichloronucleoside **12** for synthesis of another series of 2-arylethynyl-6-(2-furyl)-7-deazapurine ribonucleosides **14a–e** (Scheme 3) and to investigate the effect of the size of hetaryl group in position 6. We also wanted to shorten the reaction sequence by switching the diazotation and coupling steps. Diazotation of 2-amino-6-chloronucleoside **6** gave the protected 2,6-dichloronucleoside **5** in 45% yield, which was deprotected by aqueous TFA to the 2,6-dichloronucleoside **12**. It was then used for chemoselective Suzuki coupling with (furan-2-yl)boronic acid using $Pd(OAc)_2$ in combination with water-soluble ligand TPPTS in a mixture of water and acetonitrile. Using only 1.1 equivalents of boronic acid and shortening the reaction time to only 10 min gave the desired key-intermediate 2-chloro-6-(furan-2-yl) nucleoside **13** in 84% yield (Scheme 3). The second aryl group was introduced into the molecule by Sonogashira reaction catalyzed again by combination of $Pd(OAc)_2$ with TPPTS together with CuI and TEA in a mixture of water and acetonitrile. All the target nucleosides **14a–e** were obtained in a moderate to good yields (34–62%, Scheme 3).

We also decided to prepare a series of 2,6-diarylsubstituted nucleosides, where both aryl groups are attached directly to the nucleobase. We employed the optimized synthetic strategy and used the unprotected 2,6-dichloronucleoside **12** as a starting material. The first aryl group was chemoselectively introduced into more reactive position 6 by Suzuki coupling using a combination of $Pd(OAc)_2$ with TPPTS ligand, Na_2CO_3 as a base in a mixture of acetonitrile and water. To achieve high regioselectivity, it is important to use only 1.1 equivalents of boronic acid and short reaction time (10 min). The second aryl group was introduced into the molecule using the same catalytic system, but higher excess of boronic acid (3 equivalents) and longer reaction time (1–2.5 hr). All the target nucleosides **17a–c**, **18b,d–g**, **19a,b** and **20e** were obtained in good to high yields (38–86%, Scheme 4, Table 2).



Scheme 1. a) 1: CCl_4 (1.5 equiv.), HMPT (1.5 equiv.), THF, −15 to −30 °C, 0.5–1 h; 2: Nucleobase (1.5 equiv.), KOH (2 equiv.), TDA-1 (1 equiv.), dry MeCN, 22 °C, overnight.

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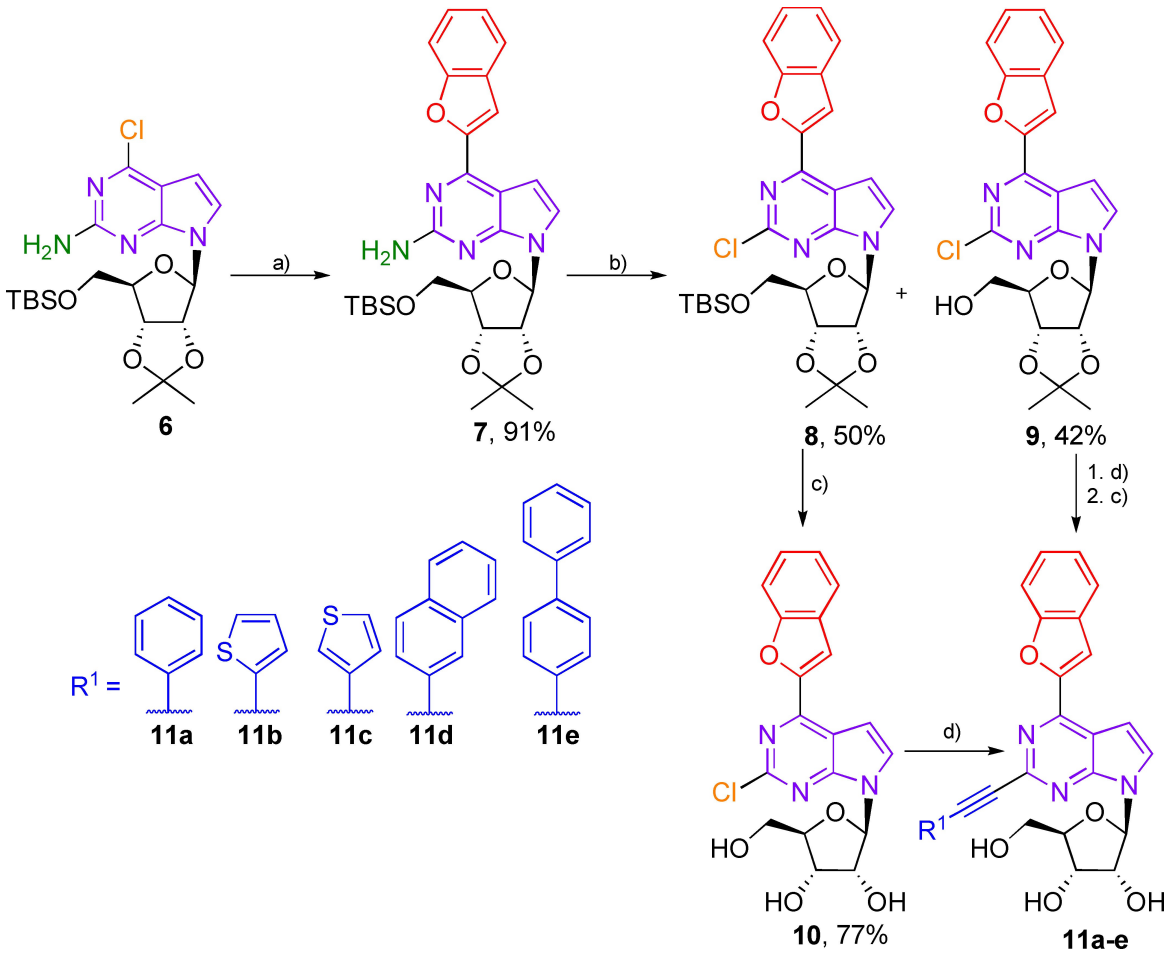
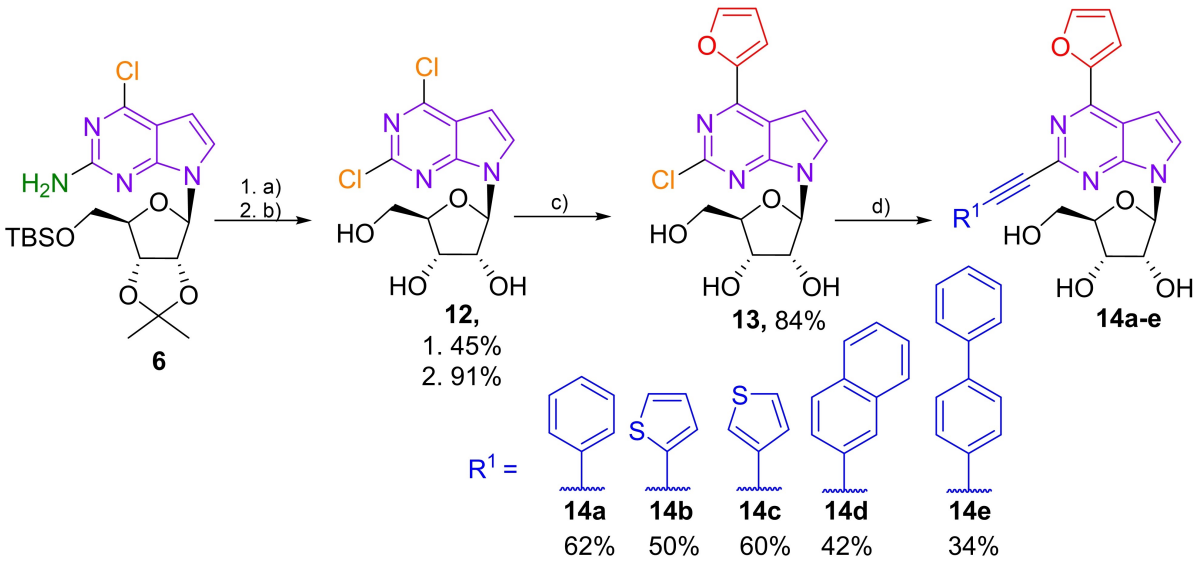


Scheme 2. a) 2-BenzofurylB(OH)$_2$ (1.1 equiv.), Pd(OAc)$_2$ (0.025 equiv.), TPPTS (0.06 equiv.), Na$_2$CO$_3$ (1.5 equiv.), H$_2$O/MeCN, 90 °C, 1.5 h; **b)** TMS–Cl (35 equiv.), TBN (70 equiv.), dry DCM, 22 °C, 1 h; **c)** 75% TFA, 22 °C, 1 h; **d)** R^1-acetylene (2 equiv.), Pd(OAc)$_2$ (0.15 equiv.), TPPTS (0.75 equiv.), CuI (0.3 equiv.), TEA (2 equiv.), H$_2$O/MeCN, 120 °C, 1.5 h, MW or R-acetylene (2 equiv.), Pd(PPh$_3$)$_2$Cl$_2$ (0.05 equiv.), CuI (0.05 equiv.), DIPEA (3 equiv.), DMF, 130 °C, 1 h, MW.



Scheme 3. a) TMS–Cl (9 equiv.), TBN (20 equiv.), dry DCM, 22 °C, 1 h; **b)** 75% TFA, 22 °C, 1 h; **c)** 2-FurylB(OH)$_2$ (1.1 equiv.), Pd(OAc)$_2$ (0.025 equiv.), TPPTS (0.06 equiv.), Na$_2$CO$_3$ (1.5 equiv.), H$_2$O/MeCN, 100 °C, 10 min; **d)** R^1-acetylene (2 equiv.), Pd(OAc)$_2$ (0.15 equiv.), TPPTS (0.75 equiv.), CuI (0.3 equiv.), TEA (3 equiv.), H$_2$O/MeCN, 90 °C, overnight.

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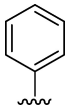
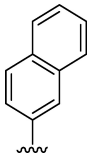
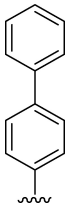
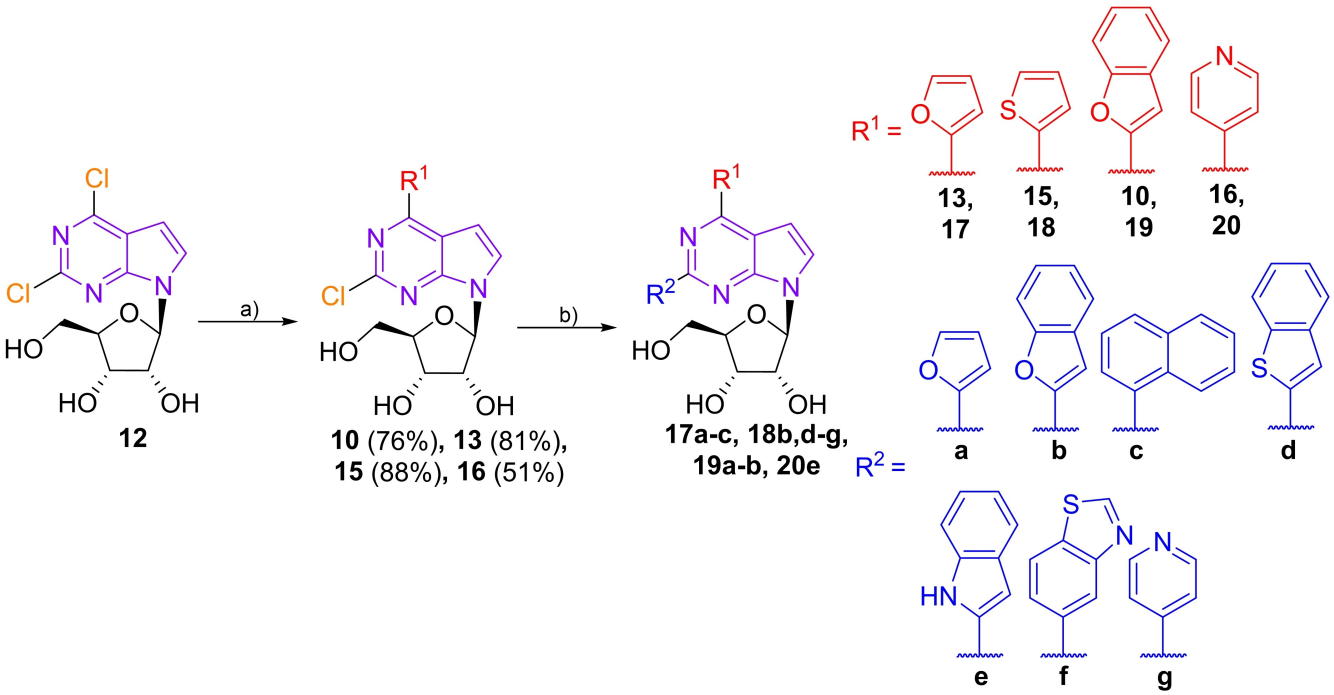
Table 1. Sonogashira coupling reaction conditions used for synthesis of compounds **11 a-e**.

Compound	Starting Material	R^1	Sonogashira coupling conditions	Yield [%]
11 a	**10**		$Pd(OAc)_2$, TPPTS, CuI, TEA, H_2O/MeCN	29
11 b	**9**		$Pd(PPh_3)_2Cl_2$, CuI, DIPEA, DMF	24
11 c	**10**		$Pd(PPh_3)_2Cl_2$, CuI, DIPEA, DMF	46
11 d	**9**		$Pd(OAc)_2$, TPPTS, CuI, TEA, H_2O/MeCN	32
11 e	**9**		$Pd(PPh_3)_2Cl_2$, CuI, DIPEA, DMF	40



Scheme 4. a) R^1–$B(OH)_2$ (1.1 equiv.), $Pd(OAc_2)$ (0.025 equiv.), TPPTS (0.06 equiv.), Na_2CO_3 (1.5 equiv.), H_2O/MeCN, 100 °C, 10 min; **b)** R^2–$B(OH)_2$ (3 equiv.), $Pd(OAc_2)$ (0.05 equiv.), TPPTS (0.12 equiv.), Na_2CO_3 (3 equiv.), H_2O/MeCN, 100 °C, 1–2.5 h.

Biological Profiling

All the final nucleosides **11 a–e**, **14 a–e**, **17 a–c**, **18 b,d–g**, **19 a,b** and **20 e** were tested for their *in vitro* cytotoxic activity. The following cancer cell lines were used for the study: A549 (lung cancer), CCRF-CEM (acute T-lymphoblastic leukemia), HCT116 and HCT116p53$^-$ (colon carcinoma, parental and p53 deficient), K562 (chronic myelogenous leukemia), U2OS (bone osteosarco-

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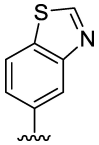
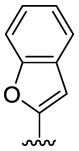
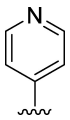
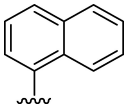
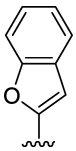
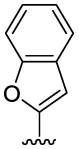
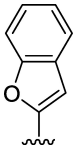
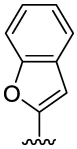
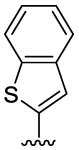
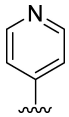
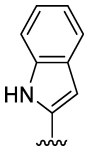
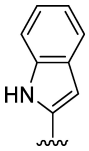
Table 2. 2,6-Diaryl 7-deazapurine ribonucleosides – yields of 2nd Suzuki coupling.

Compound	R^1	R^2	Yield [%]	Compound	R^1	R^2	Yield [%]
17a			86	**18f**			65
17b			83	**18g**			67
17c			83	**19a**			82
18b			80	**19b**			72
18d			47	**20e**			38
18e			79				

ma) using a colorimetric MTS assay.[28] Additionally, HeLa (cervical cancer), HepG2 (hepatocellular liver carcinoma) and HL60 (acute promyelocytic leukemia) cell lines were tested using the luminescent CellTiter-Glo assay. For comparison, non-malignant fibroblast cell lines (BJ and MRC-5) were included in the MTS assay, while non-cancerous human dermal fibroblasts (NHDF) were assessed with the CellTiter-Glo assay.[29] Initial screenings were done at 50 μM concentration for the MTS assay and 10 μM for the CellTiter-Glo assay. All the results are summarized in Table 3.

In general, none of the target nucleosides showed significant cytotoxic activity. In the series of 2-arylethynyl nucleosides **11a–e** and **14a–e**, there is a clear trend showing that nucleosides **14a–e** bearing smaller furanyl ring at position 6 are more potent and display cytotoxic activities against all tested cell lines (including non-malignant fibroblasts BJ, MRC-5 and NHDF) in single-digit micromolar range. 6-Benzofuranyl nucleosides **11a–e** are on the other hand less potent, but are not cytotoxic to non-malignant fibroblasts BJ and MRC-5 at the maximum tested concentration. Nucleoside **11b** bearing thiophen-2-yl group at position 2 is the most potent in this series with single-digit micromolar activities against CCRF-CEM, HCT116, HCT116p53 and U2OS cell lines. Interestingly, thiophen-3-yl analogue **11c** is significantly less potent as well as nucleosides **11a**, **11d** and **11e** with more bulky substituents.

We wanted to study the effect of size and orientation of (het)aryl substituents together with the impact of heteroatoms in the series of 2,6-diaryl substituted nucleosides. Surprisingly, all three nucleosides **17a–c** bearing furan-2-yl group at position 6 are completely inactive, whilst analogous nucleosides **18b**,**d**,**e** bearing thiophen-2-yl at position 6 show moderate cytotoxic activities against whole panel of tested cell lines with no selectivity against fibroblasts. SAR at position 2 shows that benzofuran-2-yl analogues **18b** and **19b** are the most potent, however, their activity is still weak. Analysis of nucleosides **18** suggests that size of the hetaryl group is not the most important as benzofuranyl nucleoside **18b** is the most active compound, whereas pyridinyl analogue **18g** is less potent. Heteroatoms play a significant role in cytotoxic activity, changing O with S in **18d** or with NH group in indole derivative **18e** led to significant drop in cytotoxic activity, adding second heteroatom in benzothiazol derivative **18f** led to complete loss

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Table 3. Cytotoxic activities of 2,6-disubstituted 7-deazapurine nucleosides **11a–e**, **14a–e**, **17a–c**, **18b,d–g**, **19a–b**, **20e**.

MTS, IC_{50} (μM)									XTT, IC_{50} (μM)			
Compd	BJ	MRC-5	A549	CCRF-CEM	HCT116	HCT116p53-	K562	U2OS	HeLa	HepG2	HL60	NHDF
11a	>50	>50	>50	28	34	38	>50	>50	>10	>10	>10	>10
11b	>50	40	23	8.6	2.4	3.7	>50	6.2	>10	>10	>10	>10
11c	>50	>50	>50	20	>50	29	>50	>50	>10	>10	>10	>10
11d	>50	29	31	28	>50	33	>50	29	>10	>10	>10	>10
11e	>50	>50	42	21	30	32	40	29	>10	>10	>10	>10
14a	9.4	5.1	12	3.8	5.3	7.0	7.0	5.9	9.3	7.6	7.5	-
14b	2.2	1.2	2.5	0.9	1.2	1.4	1.7	1.6	4.4	3.5	3.1	13
14c	8.9	5.0	14	4.3	5.2	7.1	6.1	6.5	11	8.5	8.1	-
14d	20	8.4	26	5.6	9.5	11	19	9.8	>10	-	-	>10
14e	>50	10	44	4.7	9.4	13	25	18	>10	>10	14	>10
17a	>50	>50	>50	>50	>50	>50	>50	>50	>10	>10	>10	>10
17b	>50	>50	>50	17	>50	>50	>50	>50	>10	>10	>10	>10
17c	>50	>50	>50	38	>50	>50	26	>50	>10	>10	>10	>10
18b	19	19	19	1.8	5.3	2.8	4.4	3.5	5.5	2.5	6.5	-
18d	20	21	26	11	27	24	8.0	15	19	13	18	-
18e	17	23	24	11	21	17	16	14	>10	10	>10	25
18f	>50	>50	>50	>50	>50	>50	>50	>50	>10	>10	>10	>10
18g	>50	>50	>50	17	30	33	37	>50	>10	10	9.3	>10
19a	25	27	30	8.0	25	26	16	16	20	>10	16	>10
19b	6.4	6.8	5.5	2.6	3.5	3.6	11	1.9	6.6	9.4	21	6.3
20e	>50	>50	>50	6.9	30	20	28	32	>10	5.9	>10	>10

The data used for analysis were obtained from three independent experiments.

of activity. To conclude, none of the tested compounds showed cytostatic activity below 1 μM concentrations and thus are much less active than the parent **PNH173** compound.

Modified nucleosides can potentially modulate the activity of adenosine receptors. Therefore, all the target nucleosides were tested for their agonistic and antagonistic activities on all four adenosine receptor subtypes (A_1AR, A_{2A}AR, A_{2B}AR, and A_3AR) using an aequorin functional assay.[30] None of the compounds showed any agonistic activity on any of the adenosine receptors. Screening for antagonistic activity identified only 3 compounds, nucleosides **11a–e** from the series of 2-arylethynyl-6-(benzofuran-2-yl), that showed weak antagonistic activity on A_1AR, A_{2A}AR and A_3AR (Table 4). All the active nucleosides have only a monoaryl group (**11a–c**) attached via an ethynyl linker at position 2. Nucleosides with bulkier aryl groups at position 2, such as the naphthyl **11d** and the biphenyl derivative **18e**, were completely inactive. On the other hand, a bulkier substituent at position 6 appears to enhance antagonistic activity.

Table 4. Antagonistic activities of compounds **11a–c**.

IC_{50} (μM)				
Compd	A_1AR	A_{2A}AR	A_{2B}AR	A_3AR
11a	16	17	>50	>50
11b	13	>50	>50	41
11c	10	>50	>50	49

The data used for analysis were obtained from three independent experiments.

Conclusions

This work is a part of our systematic research of base-modified 7-deazapurine nucleosides and their biological activities. We synthesized several series of 2,6-disubstituted 7-deazapurine ribonucleosides to study their anticancer activity and potential modulation of adenosine receptors. Two series of 2-arylethynyl-6-hetaryl nucleosides were prepared using two different synthetic strategies, which both rely on two consecutive cross-coupling reactions. First, a hetaryl substituent was introduced into position 6 by Suzuki reaction, followed by the introduction of an arylethynyl group at position 2 by Sonogashira coupling. Both reactions were catalyzed by $Pd(OAc)_2$ in combination with the water-soluble ligand TPPTS in a mixture of water and acetonitrile. The starting nucleoside was prepared by anion-base glycosylation, which worked better (higher yield and multi-gram scale) with 2-amino-6-chloro-7-deazapurine than with 2,6-dichloro-7-deazapurine. Another key-step in the synthesis was diazotation to 2-chloronucleosides, performed either

after the first Suzuki coupling to avoid any potential issues with disubstitution during coupling, or just after glycosylation. In that case, it gave 2,6-dichloronucleoside, which was first deprotected by aqueous TFA and used for both cross-coupling reactions. The regioselectivity can be controlled by using only 1.1 equivalents of boronic acid and short reaction time (only 10 min), then the reaction proceeds selectively in position 6. The same synthetic strategy starting from 2,6-dichloro-7-deazapurine ribonucleoside was used also for synthesis of 2,6-diaryl derivatives.

Biological evaluation of the final nucleosides showed that most compounds exhibited only moderate to low cytotoxic activity and no selectivity against non-malignant fibroblasts. Compared to the parent 2-unsubstituted 6-hetaryl-7-deazapurine ribonucleosides,[7] the cytotoxic activity of the synthesized compounds was significantly lower. This suggests that the presence of bulky aryl or arylethynyl substituent in position 2 may block the interaction with the biological target. Target compounds also did not significantly affect adenosine receptors, with the exception of three nucleosides from the series of 2-arylethynyl-6-benzofuran-2-yl nucleosides **11a–c**, which showed weak antagonistic effects on A_1AR, A_{2A}AR and A_3AR.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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