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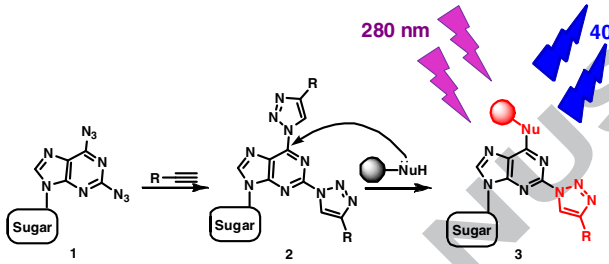

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1,2,3-Triazoles as leaving groups in purine chemistry: a three-step synthesis of N^6-substituted-2-triazolyl-adenine nucleosides and photophysical properties thereof

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ABSTRACT

A novel three-step approach for the synthesis of N^6-substituted-2-(1,2,3-triazol-1-yl)-adenine nucleosides is described. 2,6-Bis-(1,2,3-triazol-1-yl)purine nucleosides are obtained, which undergo regioselective nucleophilic aromatic substitution with amines at C(6). Thus, 1,2,3-triazoles are shown to be good leaving groups in purine chemistry. The title compounds exhibit interesting levels of fluorescence with quantum yields of up to 53%.

There are at least three distinct areas of application of purines: 1) anticancer therapy with antimetabolic purine nucleosides, which among others include fludarabine, thioguanine, clofarabine and cladribine;[1] 2) antiviral purine derivatives[2] with prominent examples being vidarabine, abacavir, entecavir and acyclovir; 3) agonists and antagonists of adenosine receptors. This last group contains agonists of the A_1 receptor that have provided clinical candidates for atrial arrhythmias, type 2 diabetes and insulin-sensitizing agents, pain management, and angina (tecadenoson, GW493838, TCPA, etc.).[3] Adenosine receptor A_{2A} agonists are excellent anti-inflammatory agents (apadenoson, regadenoson, binodenoson).[4] Also, selective activation of the adenosine receptor A_3 was demonstrated to be cardioprotective and cerebroprotective.[5] In the light of the aforementioned facts it is no surprise that active research on purine derivatives takes place.

Many chemical modifications of the purine system have been developed for the 2- and/or 6-positions. Nevertheless, significant improvements continue to appear.[6] We were intrigued by the possibility to use a 1,2,3-triazolyl moiety at C(6) of the purine as a leaving group. The use of 6-(1,2,4-triazol-4-yl)purines for this purpose was initiated by Robins' group[7] based on the earlier work of Divakar and Reese.[8] Indeed, 1,2,3- and 1,2,4-triazoles possess very similar acidities: pK_a 9.3 and 10.3, respectively.[9] Nevertheless, there are only limited known applications of 1,2,3-triazolyl moieties as potential leaving groups to date.[10] Additionally, regardless of the vast achievements in the field of 1,2,3-triazole–nucleoside conjugates,[11] there are only a few reports dealing with either 2- or 6-(1,2,3-triazol-1-yl)purine nucleosides or with 6-(1,2,3-triazol-4-yl)-purine nucleosides (Figure 1). These include 2-triazolyl derivatives as described by the groups of Van Calenbergh (**1a,b**),[12] Aldrich (**1c**)[13] and Lakshman (**1a**),[14] and 6-triazolyl derivatives as reported by Lakshman and co-workers (**2**)[15] and the group of Guieu and Parrain (**3**).[16] Grøtli has developed fluorescent 8-triazolyl adenosine **4** and demonstrated its substantial photophysical and base-mimicking properties in DNA.[17] Adenosine analogs **1** possess intrinsic similarity with **4** as both types of structures contain electron-donating amino and electron-withdrawing triazole[18] groups on the purine scaffold. The recent achievements and the general importance of the area of fluorescent nucleosides has been extensively reviewed.[19] Existing biological applications[12-14] and potential fluorescent properties of the target nucleosides **1** and their analogs prompted us to design a novel approach for their synthesis.

Herein, we describe a *de novo* synthetic methodology towards N^6-substituted-2-triazolyl adenine nucleosides and investigations of their fluorescent properties. Our approach includes the use of 2,6-bis-(triazolyl)purine intermediates with a 1,2,3-triazolyl moiety as the leaving group in heteroaromatic nucleophilic substitution reactions. To the best of our knowledge, the latter chemical entities and mechanistic approach have not been reported previously.

The starting materials were obtained *via* Vorbrüggen glycosylation[20] of 2,6-diazidopurine[21] (**6**). Nucleoside type structures **7** and **9** were obtained in 90% and 65% yields, respectively (Scheme 1). Both these diazides are rather unstable in daylight and at elevated temperatures, but can be stored for a long period of time in the dark below 5 °C.

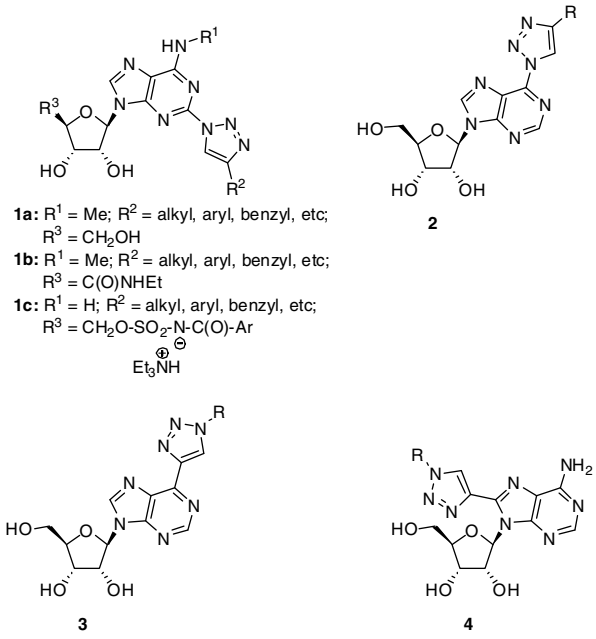
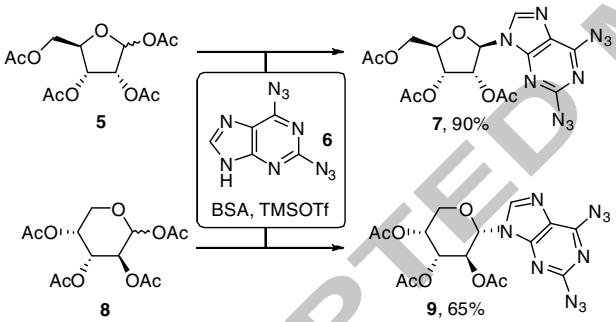


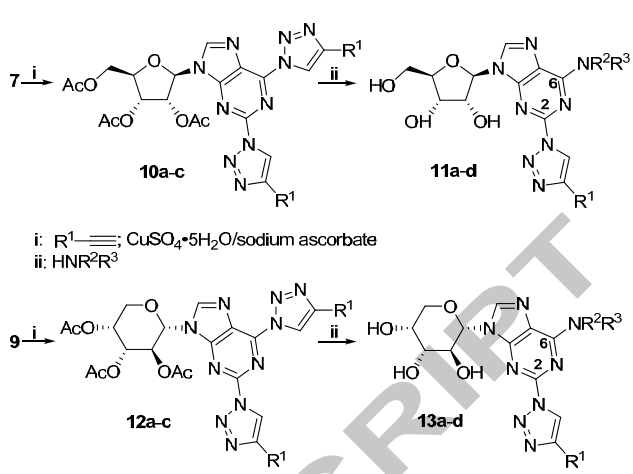
Figure 1. Nucleoside analogs with triazolyl-purine bases.

With the required substrates in hand, we demonstrated the scope of our approach which does not require the use of naturally occurring nucleosides as the key starting materials.



Scheme 1. Synthesis of 2,6-diazidopurine nucleosides **7** and **9**.

Thus we proceeded to investigate the bis-triazole formation. Diazides **7** and **9** underwent copper-catalyzed 1,3-dipolar cycloaddition reactions with different terminal alkynes.[22] Various Cu(I) sources were screened including the well-established $CuSO_4$•$5H_2O$/sodium ascorbate system, $Cu^0/CuSO_4$ and CuI. Additionally, various solvent systems (acetone/water, CH_2Cl_2/water, *tert*-butanol/water, THF) and temperature regimes (20-80 °C) were explored. A compromise between low reactivity ($t_{1/2}$ ~ 16-20 h at ambient temperature) and the thermal stability of the diazides had to be found. Addition of dilute acetic acid accelerated the cycloaddition reactions at ambient or slightly elevated temperatures in 1-4 hours.[23] The best reaction conditions for the double cycloaddition reaction included mixing of **7** or **9** with the alkyne in *t*-BuOH/acetone/water in the presence of $CuSO_4$•$5H_2O$/sodium ascorbate and dilute acetic acid. Bis-triazolyl-nucleosides **10** and **12** were, after work-up, isolated by silica gel column chromatography. The isolated yields of the chromatographically homogeneous products ranged from 60% to 83% (Scheme 2, Table 1).



Scheme 2. Synthesis of 2,6-bis-triazolylpurine nucleosides (β-D-ribofuranosyl and α-D-arabinopyranosyl series) and their substitution with amines at C(6) (see Table 1).

To our delight, the envisaged nucleophilic aromatic substitution with amines at C(6) of the purine in compounds **10** and **12** took place easily and this was combined with cleavage of the acetate protecting groups. *N*-Nucleophiles such as ammonia, methylamine, pyrrolidine and piperidine were successfully used and N^6-substituted-2-triazolyl-riboadenosine derivatives **11** and their arabinopyranosyl analogs **13** were isolated in good to excellent yields (Table 1). Both the regioselectivity of the azide 1,3-dipolar cycloaddition yielding 1,4-disubstituted 1,2,3-triazoles and the C(6)-regioselectivity of the nucleophilic heteroaromatic substitution in the purine moiety was proved by isolation of product **11a,** which was found to be identical to that described by Van Calenbergh.[12] The expected elimination of 4-phenyl-1*H*-[1,2,3]triazole was confirmed by HPLC and ^{1}H-NMR analysis of the reaction mixtures in the cases where bis-triazolyl purines **10a** and **12a** were treated with amines.

We found that compounds **11** and **13** fluoresce when exited at 280 nm. This previously unreported property of N^6-substituted-2-triazolyl adenine derivatives opens up a new field of investigation for these compounds.

All the products possessed similar fluorescence properties with emission maxima around 400 nm and quantum yields of up to 53%, which is comparable with 8-triazolyladenosine analogs (64% for compound **4**: R = Bn).[17a] The spectra are shown in Figure 2, and the photophysical characterization (absorption and fluorescence properties) of the products are given in Table 1.

In summary, we have disclosed here a novel three-step approach for the synthesis of N^6-substituted-2-triazolyl adenine nucleosides which uses 2,6-diazidopurine and a monosaccharide of choice as the starting materials and therefore can be described as being convergent.[24] The second step of the sequence involves the double click reaction and provides new structural entities, 2,6-bis-(1,2,3-triazol-1-yl)purine nucleosides, which readily undergo regioselective nucleophilic aromatic substitution with amines. The total yields of the title compounds reach 67% over three steps starting from 2,6-diazidopurine. Our approach competes well with the previously reported methods that give rise to, e.g. **11a** or its analogs either from guanosine or from O^6-allyl-2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)guanosine in five steps and a maximum yield of 27%. The described synthetic route demonstrates the use of 1,2,3-triazoles as excellent nucleofuges in purine chemistry. It reveals also an excellent price/performance ratio or step economy in the synthesis of N^6-substituted-2-triazolyl adenine nucleosides when relatively cheap

Table 1. Synthesis of 2,6-bis-triazolyl nucleosides **10** and **12** and their nucleophilic substitution products **11** and **13** and the photophysical characterization of the latter

Entry	Starting material	R^1	Product **10/12** (yield, %)[a]	NR^2R^3	Product **11/13** (yield, %)[b]	λ_{max}(abs), (nm) (DMSO)	λ_{max}(emis), (nm) (DMSO)	Quantum yield (%)
1				-NHMe	**11a** (92)	257/300	398	32
2	**7**	Ph	**10a** (83)		**11b** (86)	257/271	402	50
3	**7**	CH_2OH	**10b** (64)		**11c** (89)	255/278	394	38
4	**7**	CMe_2OH	**10c** (70)		**11d** (86)	255/296	394	33
5					**13a** (88)	257/271	401	51
6	**9**	Ph	**12a** (78)		**13b** (88)	257/267	404	53
7				-NHMe	**13c** (73)	258/299	396	33
8				$-NMe_2$	**13d** (91)	258/266	402	50
9	**9**	CMe_2OH	**12b** (75)		**13e** (69)	255/275	393	34
10				$-NMe_2$	**13f** (74)	255/275	392	30
11	**9**	n-C_5H_{11}	**12c** (60)		**13g** (71)	255/275	394	36
12				$-NH_2$	**13h** (83)	-	-	-

[a] Experimental conditions: diazide (1 equiv.), alkyne (5 equiv.), $CuSO_4$ (5.5 mol%), sodium ascorbate (9.2 mol%), 10% $AcOH_{aq}$/*t*-BuOH/water, from ambient temperature to 40 °C.

[b] Experimental conditions: amine (excess) in water or water/THF, from ambient temperature to 40 °C.

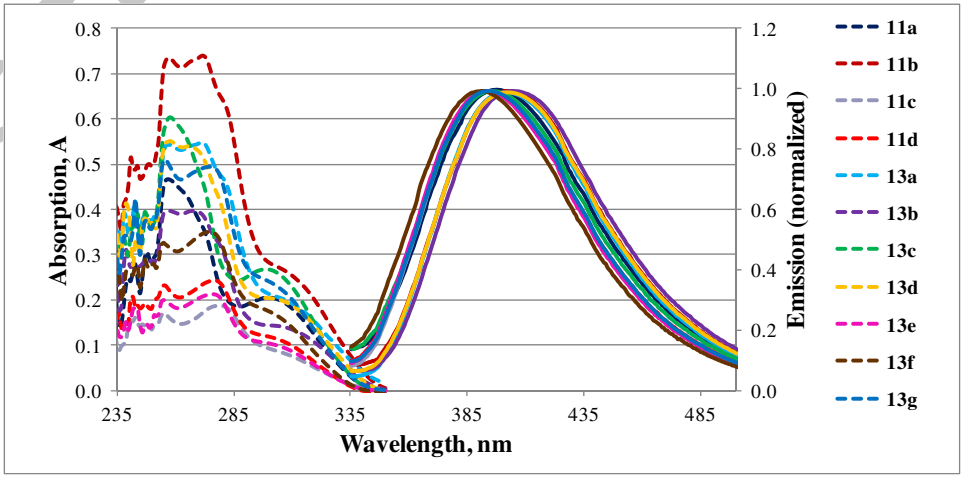


Figure 2. Absorption (dashed lines) and emission (solid lines) spectra of compounds **11a-d** and **13a-g**.

and commercially available terminal alkynes are used for the synthesis of the bis-triazolyl intermediates.

Finally, we discovered that the title compounds showed useful levels of fluorescence. Detailed investigations on the susceptibility of 2,6-bis-(1,2,3-triazol-1-yl)purine derivatives towards various *N*-, *S*- and *O*-nucleophiles are underway in our laboratory and will be reported elsewhere, together with a full account on the photophysical properties of the obtained products.

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Supplementary Material

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