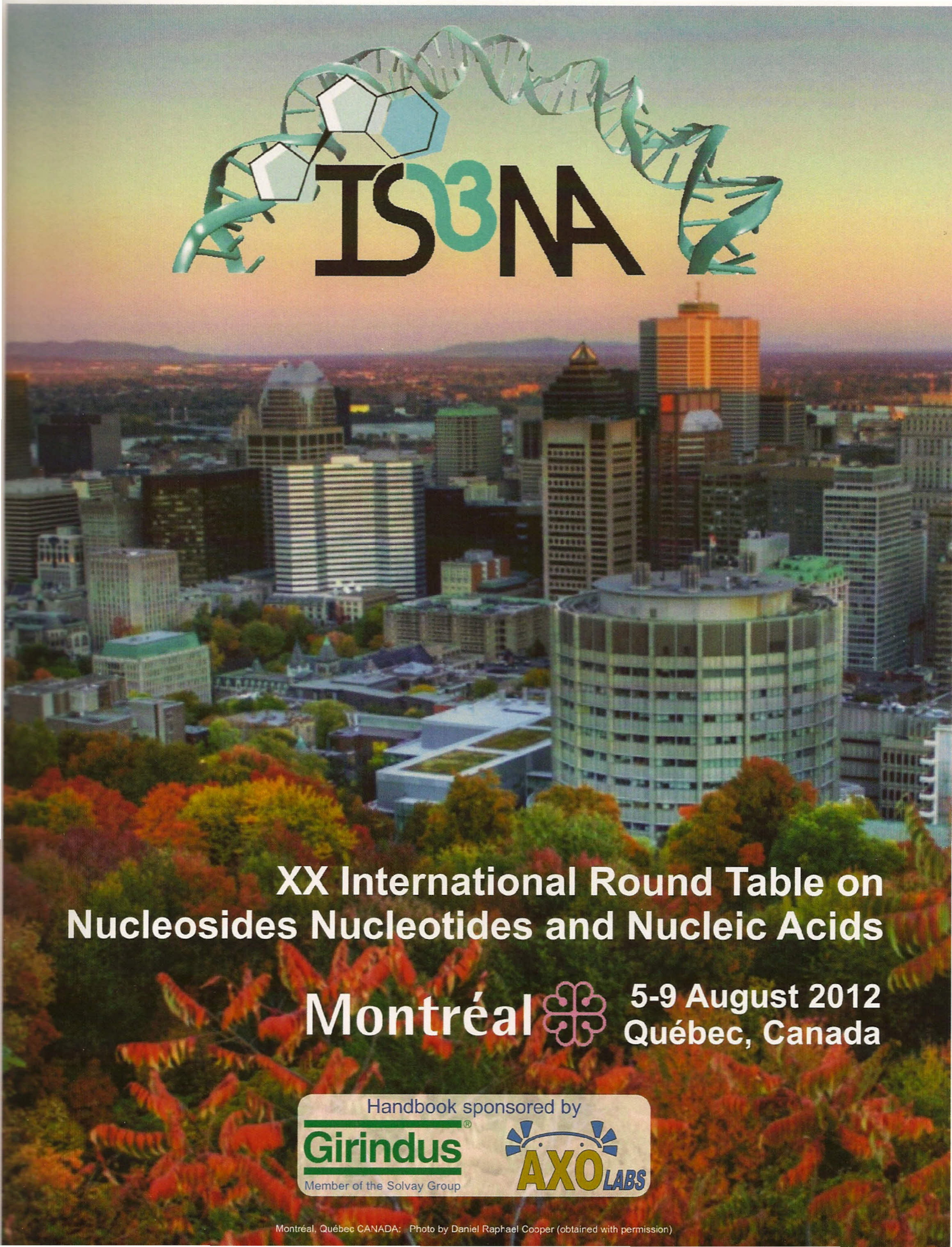

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REACTIVITY STUDIES OF 2,6-DITRIAZOLYLPURINE NUCLEOSIDES WITH NUCLEOPHILES

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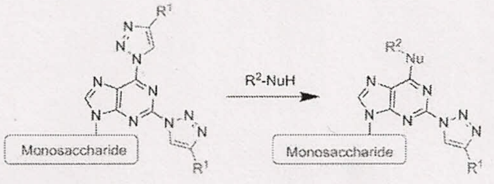
ABSTRACT

Reaction of 2,6-ditriazolylpurine nucleosides with nucleophiles is mild and efficient route to C6 derivatization of purine base. To explore scope and limitations of the method, we studied reactivity of various *N*- and *S*-nucleophiles as well as kinetics for selected reactions.

INTRODUCTION, RESULTS AND DISCUSSION, CONCLUSION

New methods for the synthesis of C6 purine derivatives have been intensively developed for decades. Search for new anticancer and antiviral agents, adenosine receptors agonists and antagonists prompted an renewed interest in purine chemistry, resulting in numerous synthetic methodologies [1,2]. Purines are excellent scaffolds for construction of bioprobes. To the best of our knowledge, di-(1,2,3-triazol-1-yl)purines were unexploited for the synthesis of C6 substituted purines.

We used click chemistry for the synthesis of series of 2,6-ditriazolylpurine nucleosides **1** from corresponding 2,6-diazidopurine derivatives. The observation that treatment of **1** with ammonia and amines gave fluorescent compounds, promted us to more detailed investigation of this reaction.



1 2

R^1 = alkyl, aryl R^2-NuH: *N*- or *S*-nucleophile

Monosaccharide: ribofuranose, arabinofuranose, arabinopyranose

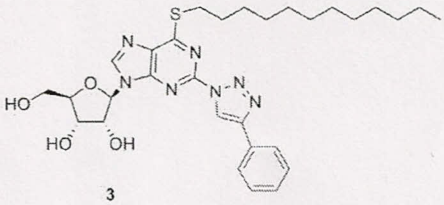
6-Methylamino-2-(1,2,3-triazol-1-yl)purine ribonucleosides were prepared earlier by a different method and investigated as selective adenosine A_3 receptor agonists or antagonists [2].

We report here reactions of 2,6-ditriazolylpurine nucleosides **1** with primary and secondary amines and hydrazines. The nucleophilic aromatic substitutions at C6 with amines, such as methyl- and dimethylamine, pyrrolidine, piperidine and other low molecular weight amines proceed smoothly at ambient temperature in water, water-THF or water-MeCN. Reaction times are from 30 min to 2 h. During these reaction conditions acetyl protecting groups were simultaneously removed from sugar moiety. Dipropylamine, dibenzylamine, morpholine required longer reaction time and/or elevated (40-50 ^{0}C) temperatures, and deprotection of sugar was carried out separately with NH_3/EtOH or CH_3NH_2/H_2O. All obtained N^6-modified 2-triazolylpurine derivatives **2** possess fluorescent properties. The only exception is 6-hydrazino derivative.

Further, we extended investigation to the reactions of amino acid esters as nucleophiles. Reaction of **1** with proline methyl ester is rather slow, however, we obtained product with bright blue fluorescence in UV light. Reactivity studies of **1** with amino acids are still in progress.

A number of 6-thioalkylated purines have interesting biological activity. For example, 6-mercaptopurine ribonucleoside is inhibitor of *de novo* purine biosynthesis.

To explore suitability of 2,6-ditriazolpurines as substrates for the synthesis of 6-thioalkylated purine nucleosides, we investigated reactions of **1** with thiols. Dodecanethiol was chosen for reaction kinetics studies. 6-Dodecylthio-2-triazolylpurine ribonucleoside **3** was obtained in 60-65% yield.



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In conclusion, we have demonstrated the versatility of 2,6-ditriazolylpurines as reactive intermediates suitable for C6 modifications.

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CLICK, SUBSTITUTE AND FLUORESCE: SYNTHESIS AND APPLICATIONS OF 2,6-DI-(1,2,3-TRIAZOLYL)-PURINE NUCLEOSIDES

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ABSTRACT

A novel class of ditriazolylpurine nucleosides were obtained from 2,6-diazido precursors via copper catalyzed azide-alkyne cycloaddition. These intermediates appeared to be very reactive towards *N*- and *S*-nucleophiles and thus selectively gave C(6)-substituted analogs with triazolyl moiety at C(2)-position. The latter products exhibit interesting fluorescence properties.

INTRODUCTION, RESULTS AND DISCUSSION, CONCLUSION

Application of copper catalyzed azide-alkyne 1,3-dipolar cycloaddition [1] in nucleoside, nucleotide and oligonucleotide chemistry was recently reviewed [2]. Since 2002 many different nucleoside and nucleotide derivatives containing 1,2,3-triazolyl moiety were synthesized and investigated. Nevertheless, only few literature reports deal with either 2- or 6-(1,2,3-triazol-1-yl)-purine nucleosides [3].

Here we report a straightforward way to 2,6-di-(1,2,3-triazol-1-yl)-purine nucleosides that represent a novel structural entity in nucleoside chemistry. Their synthesis from corresponding 2,6-diazidopurine nucleosides will be discussed. It was discovered that triazolyl moiety at C(6) of the purine base undergoes a facile nucleophilic aromatic substitution with amines, hydrazines and thiols (Fig. 1). This approach provides a versatile and user friendly method for the synthesis of various 6-amino-2-(1,2,3-triazol-1-yl)-purine nucleosides, including those that have been described earlier, albeit prepared by a longer synthetic sequence [3].

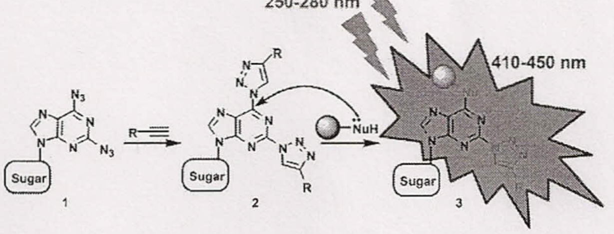

Figure 1. Synthesis of 2,6-di-(1,2,3-triazol-1-yl)-purine nucleosides **2** and their transformation into fluorescent derivatives **3**.

We have demonstrated that the aforementioned structures with general formula **3** posses fluorescent properties. 2,6-Ditriazolyl purine nucleosides **2a-d** were prepared in four distinct series. These include ribo-furanosyl- (**2a**), deoxyribo-furanosyl- (**2b**), arabino-furanosyl (**2c**) and arabino-pyranosyl nucleosides (**2d**) (Fig. 2.). Aromatic nucleophilic substitution proceeds equally well in all four series **2a-d**, giving a broad range of products **3**.

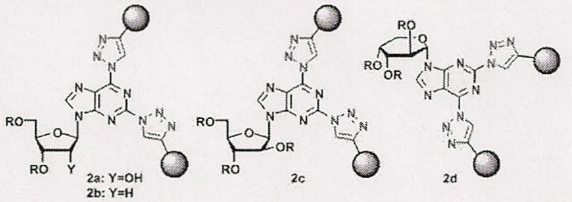

Figure 2. Four series of 2,6-di-(1,2,3-triazol-1-yl)-purine nucleosides.

All products with general formula **3** possess similar fluorescence properties with emission maxima between 410 and 450 nm (Fig. 3). The fluorescence is observed in various solvents (THF, MeCN, DMSO, H_2O). Emission properties of compounds **3** such as quantum yields and decay times are influenced by substitution pattern.

Potential applications of the discovered transformation **2→3** will be discussed.

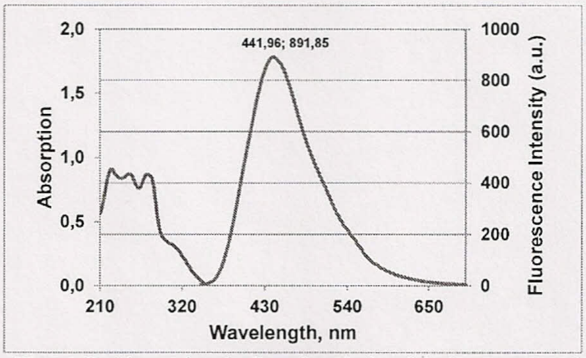

Figure 3. Absorption (red) and emission (blue) spectrum of 9-α-D-arabinopyranosyl-2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-trizol-1-yl)-6-pyrrolidin-1-yl-9*H*-purine ($7.7 \cdot 10^{-7}$ M) in water.

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