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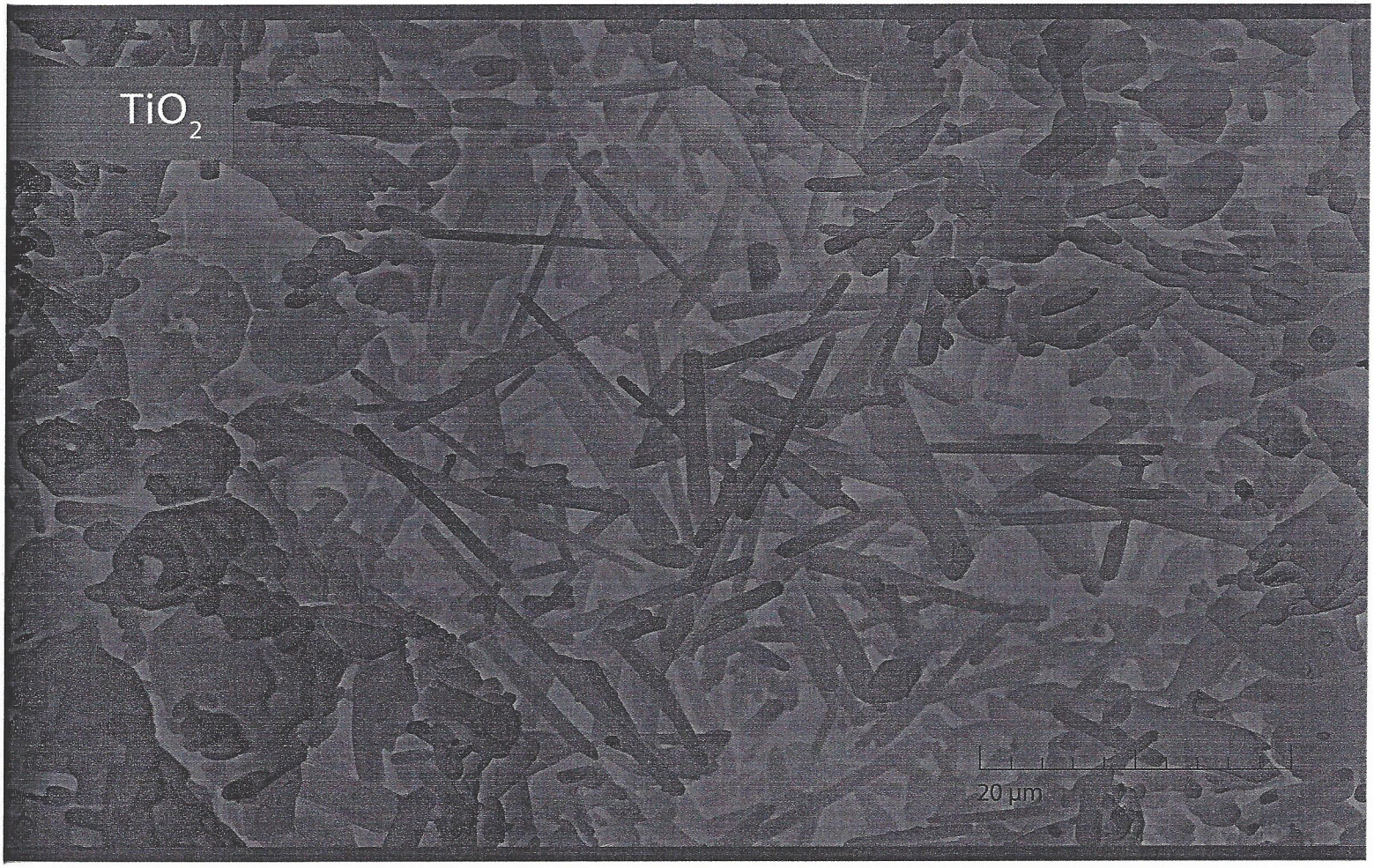


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# Synthesis and Properties of Triazolyl Purine Nucleosides

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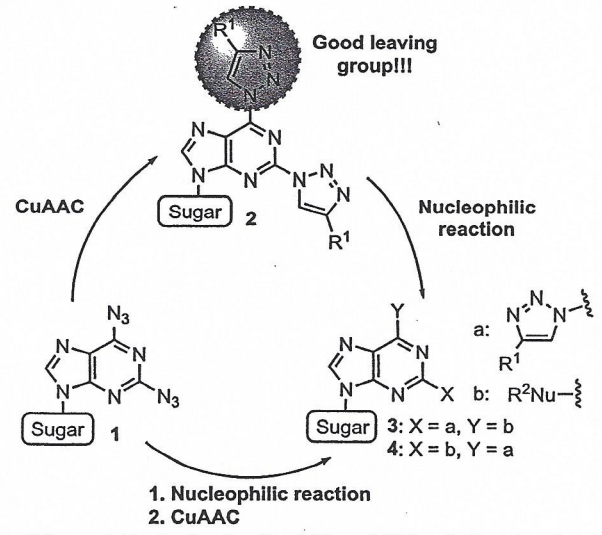
## Introduction

Modified purine nucleosides possess antiviral, anticancer and antimycobacterial activities. They also bind to purinergic and adenosine receptors. Thence, the synthesis of novel purine nucleoside analogues continues to develop.

Purine nucleoside azole conjugates represent a distinct class of nucleoside analogues [1]. To the best of our knowledge, only scarce amount of purine-triazole conjugates are described thus far.

## Results and Discussions

A novel method for the synthesis of C(2) and C(6) modified purine nucleoside analogues has been developed. Firstly, we used 1,3-dipolar cycloaddition reactions between 2,6-diazidopurine nucleosides **1** and different terminal alkynes, forming bis-triazolylderivatives **2** [2], which have subsequently been substituted with different *N*- and *S*-nucleophiles, forming monotriazolyl compounds **3** [2–3]. Secondly, the nucleophilic substitution reactions between 2,6-diazidopurine nucleosides **1** and different nucleophiles and subsequent CuAAC reactions were made, resulting in products **3** and **4** [3–4]. The regioselectivity of these reactions depends on the nature of the nucleophile. Thereby, the reactivity between bis-triazolylpurine nucleosides **2** and 2,6-diazidopurine nucleosides **1** were compared. It was found that, 2,6-bis-triazolylpurine derivatives **2** are faster reacting in the nucleophilic substitutions (Scheme 1, Table I).




**Scheme 1.** Synthesis of purine C(2)- and C(6)-substituted analogues.

$CuSO_4 \cdot 5H_2O$ and sodium ascorbate was the best catalytic system for 1,3-dipolar cycloaddition reactions (**1**→**2**), which were carried out in *tert*-butanol-water solvent system. The reaction rate was increased with addition of 10 mol-% AcOH. We exploited the terminal alkynes with alkyl, aryl and heterocyclic substituents in the structure of product **2**.

In aromatic nucleophilic substitution reactions we successfully used different amines as *N*-nucleophiles, such as methylamine, dimethylamine, piperidine and pyrrolidine. The reactions were carried out in amine-water solution at 30 °C – 40°C temperatures for 30 min to 6 h. Butanethiol, cyclohexanethiol, benzylthiol, octanethiol, dodecanethiol, thiophenol, 4-chlorothiophenol, 4-bromothiophenol and others were used as *S*-nucleophiles. The reactions were accelerated in the presence of the base (eg., $K_2CO_3$, NaH, $Et_3N$, etc.). DMF or THF can be used as solvents.

TABLE I
Results of C(2)- and C(6)-Triazolyl Purine Nucleosides 2-4.

| Product | $R^1$- | $R^2Nu$- | Yield, % |
|---|---|---|---|
| Sugar = 2',3',5'-Tri-*O*-acetyl-β-D-ribofuranosyl- | | | |
| **2a** | $C_6H_5$- | - | 83 |
| **3a** | | 4-Br-$C_6H_4S$- | 90 |
| **4a** | | $C_6H_5CH_2S$- | 91 |
| Sugar = β-D-Ribofuranosyl- | | | |
| **3b** | $C_6H_5$- |  | 96 |

To summarize, a novel class of bis-triazolyl purine nucleosides **2** was obtained and triazolyl moiety at C(6) of the purine base undergoes a facile nucleophilic heteroaromatic substitution with *N*- and *S*-nucleophiles. Some compounds have interesting photophysical and biological properties.

*Supervisor: Dr. chem. Ē. Bizdēna, Dr. chem. M. Turks*

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