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PROGRAM & ABSTRACTS

Synthesis of novel di-triazolyl-functionalised purine nucleosides

PO69

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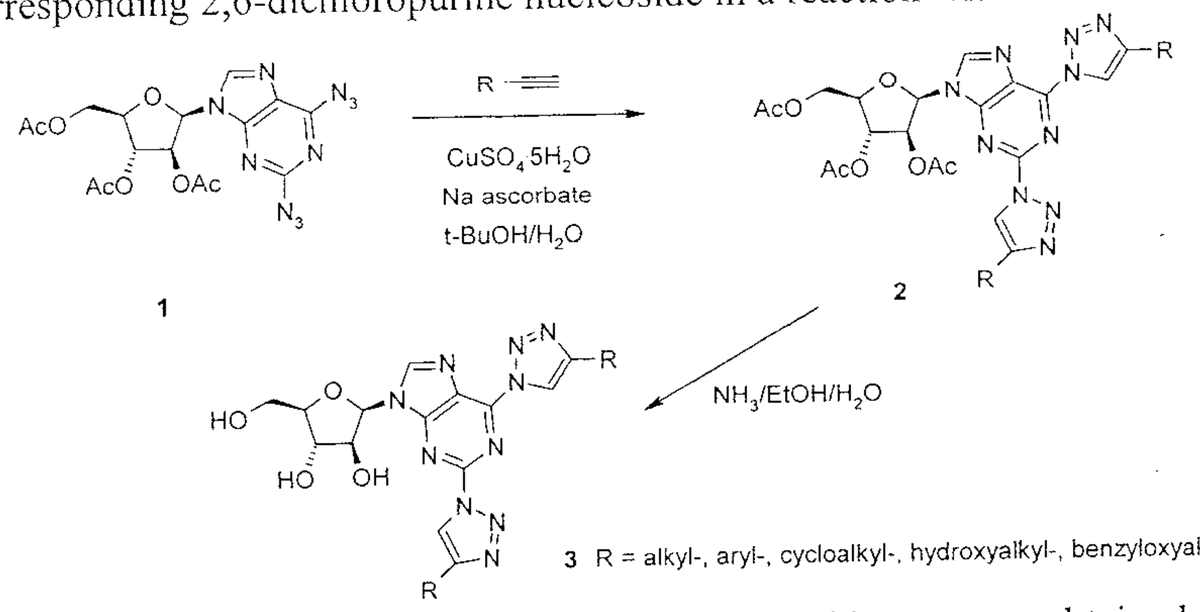
The synthesis of novel nucleoside analogs is of great importance because of their application in synthesis of antisense or antigene oligonucleotides and for their biological evaluation as antiviral and anticancer drug candidates [1]. One of the most powerful reactions for developing of new structures of nucleoside and oligonucleotide analogs is Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition [2]. We report here the synthesis of novel di-triazolyl-functionalised purine nucleosides. The key intermediate for synthesis of target compounds of type **3** is 9-(tri-*O*-acetyl-β-D-arabinofuranosyl)-2,6-diazidopurine (**1**), obtained from corresponding 2,6-dichloropurine nucleoside in a reaction with sodium azide.



Substituted 2,6-di-triazolylpurine arabinonucleosides were obtained in the reaction of diazide **1** with various terminal alkynes. Deprotection of **2** led to target nucleoside analogs **3.** Synthesis of similar triazolyl-functionalized nucleosides of *ribo* series is in progress.

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2. Kolb, H.C.; Finn, M.G.; Sharpless, K.B. *Angew. Chem. Int. Ed.*, **2001**, 40, 2004-2021.

Novel chiral aziridine - triazole conjugates *PO70*

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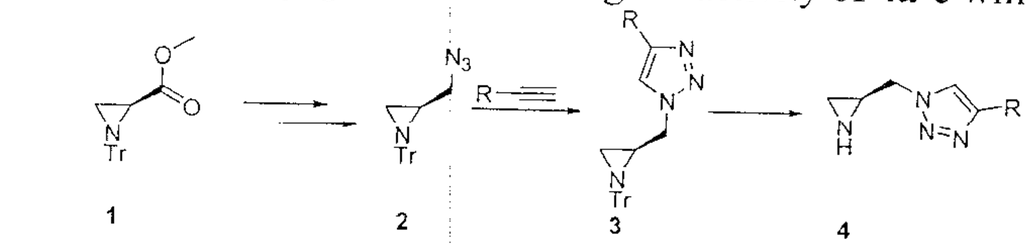
The pharmacological activity demonstrated by numerous aziridine derivatives[1] has been sufficient to promote our interest towards synthesis of novel aziridine – triazole conjugates. Hence, we modified aziridine derivatives with a 1,4-disubstituted 1,2,3-triazole unit[2] in the side chain, which due to its molecular dimensions is similar to an amide functionality in terms of distance and planarity.[3] Compounds of type **3** were reported by Harrity et. al. as intermediates for synthesis of triazolylalanine-type derivatives via aziridine ring opening.[4,5] Herein we report the synthesis of deprotected and water soluble homochiral aziridine-triazole conjugates **4a-e**. Biological activity of **4a-e** will be discussed.



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2. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596
3. Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674-1689
4. Jamookeeah, C. E.; Beadle, C. D.; Jackson, R. W. E.; Harrity J. A. P. *J. Org. Chem.* **2008**, *73*, 1128
5. Jamookeeah, C. E.; Beadle, C., Harrity J. A. P. *Synthesis* **2009**, *1*, 133

Application of nitromethyl monosaccharides in the synthesis of sugar-isoxazole conjugates

PO89

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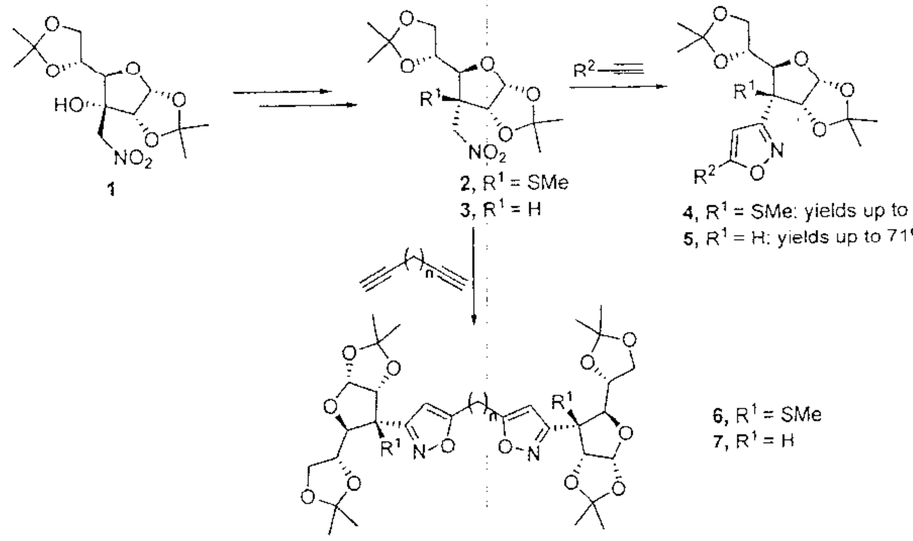
Isoxazoles as a subclass of azoles have gained a wide attraction due to their broad spectrum of biological activities. Recently, few intersting sugar-isoxazole conjugates were reported.[1] Thus, we decided to explore the possibilities of sugar-isoxazole conjugate synthesis via 1,3-dipolar cycloaddition of alkyne to nitrile oxide generated from nitro group.[2]

We started with the modification of D-glucose to synthesize nitro group containing alcohol **1** which was transformed into two different nitromethyl monosaccharides **2** and **3**.



Further, both compounds were successfully used as substrates for synthesis of sugar based isoxazole monomers **4** and **5** or dimers **6** and **7** in good to excellent yields.

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1. a) Wankhede, K. S.; Vaidya, V. V.; Sarang, P. S.; Salunkhe, M. M.; Trivedi, G. K. *Tetrahedron Lett.* **2008**, 49, 2069. b) Vaidya, V. V.; Wankhede, K. S.; Salunkhe, M. M.; Trivedi, G. K. *Can. J. Chem.* **2008**, 86, 138. c) Pérez-Balderas, F.; Hernández-Mateo, F.; Santoyo-González, F. *Tetrahedron.* **2005**, 61, 9338.
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Generation of new disaccharides via click chemistry

PO91

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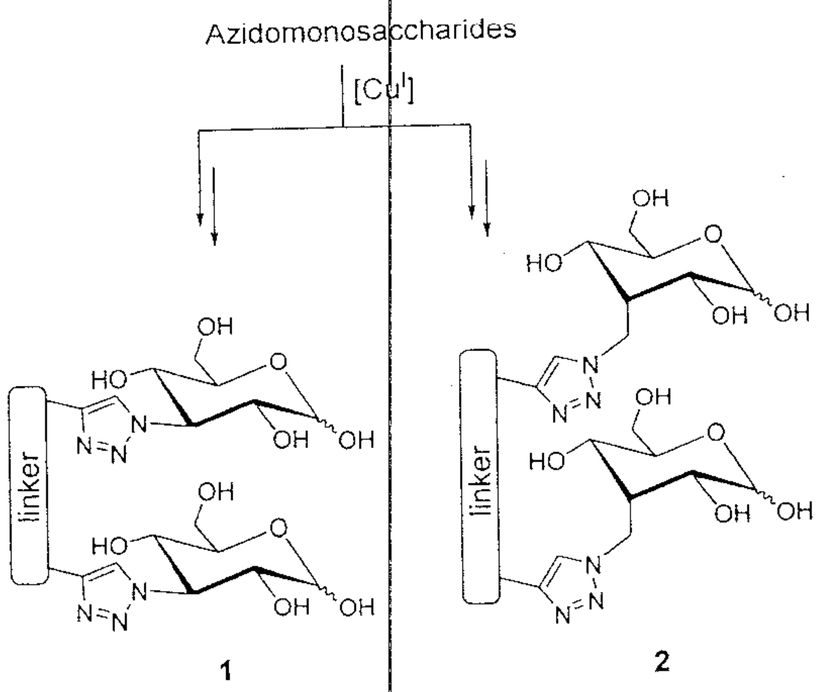
A series of novel carbohydrate conjugates were synthesized via click chemistry. Among the pharmaceutical uses, triazole-carbohydrate conjugates are known as inhibitors of the proliferation of leukemia cells[1] and glycosidases.[2]
Copper catalyzed 1,3-dipolar cycloadditon between azidomonosaccharides (D-glucose and D-galactose) and commercially available 1,n-diynes or "home-made" 2,2-dipropargyl dimedone and 5,5-dipropargyl Meldrum's acid gave the 1,4-substituted triazole-linked disaccharides. Two catalytic systems have been employed – $CuSO_4$/sodium ascorbate and CuI/DIPEA. Protecting groups were easily removed using acetic or trifluoroacetic acid.



1. El Akri, K.; Bougrin, K.; Balzarini, J.; Faraj, A.; Benhida, R. *Biorg. Med. Chem. Lett.* **2007**, 17, 6656.
2. a) Rossi, L. L.; Basu, A.; *Bioorg. Med. Chem. Lett.* **2005**, 15, 3596; b) Périon, R.; Ferrières, V.; García-Moreno, M. I.; Oritz Mellet, C.; Duval, R.; García Fernández, J. M.; Plusquellec, D. *Tetrahedron* **2005**, 61, 9118.

New method for derivatization and GC-analysis of polar and non-volatile products

PO105

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Silylation is a powerful tool used for increasing the volatility, thermal stability and chromatographic mobility of polar organic compounds.[1] In 2002, trimethylsilyl 2-methylprop-2-ene-1-sulfinate as new derivatization reagent was produced in sila-ene reaction between methallylsilane and sulfur dioxide in the presence of Lewis acid.[2,3,4] Obtained silyl sulfinate can be used in derivatization and qualitative and quantitative analysis of polyhydroxylated compounds.

Silyl sulfinate is a perspective reagent for derivatization of mixtures of polyhydroxylated compounds. One of the main accomplishments with the new reagent is the GC-MS analysis of silylated monosaccarides. This will be demonstrated on ribose and mannose as examples.

Figure 1.

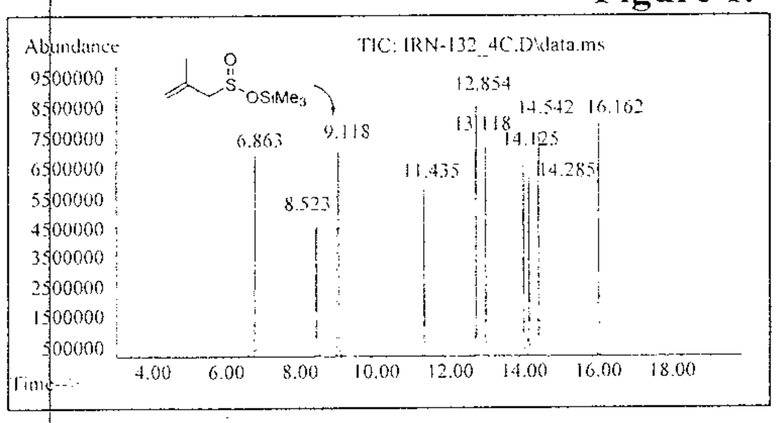
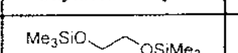
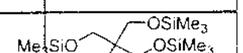
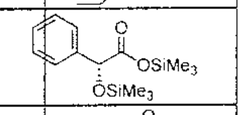
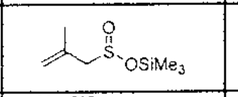
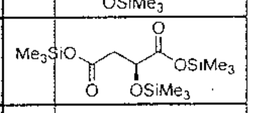
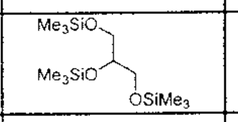
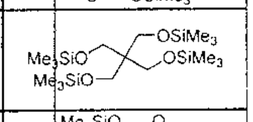
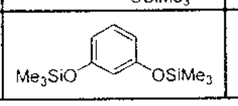
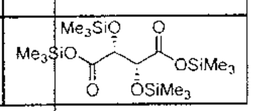


Table 1.

Retention time, min	Silylated analyte	Retention time, min	Silylated analyte
6.86		13.12	
8.52		14.13	
9.12		14.29	
11.44		14.54	
12.85		16.16	

A mixture of glycerol, ethylene glycol, 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, resorcinol, 2,2-dimethyl-1,3-propanediol, pentaerythritol, tartaric, mandelic, and malic acids was silylated and analyzed by GC-MS (**Fig.1, Table 1**).

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1. Halket, J. M.; Zaikin, V. G. *Eur. J. Mass Spectrom.* **2003**, 9, 1.
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Novel carbohydrate-triazole conjugates *PO129*

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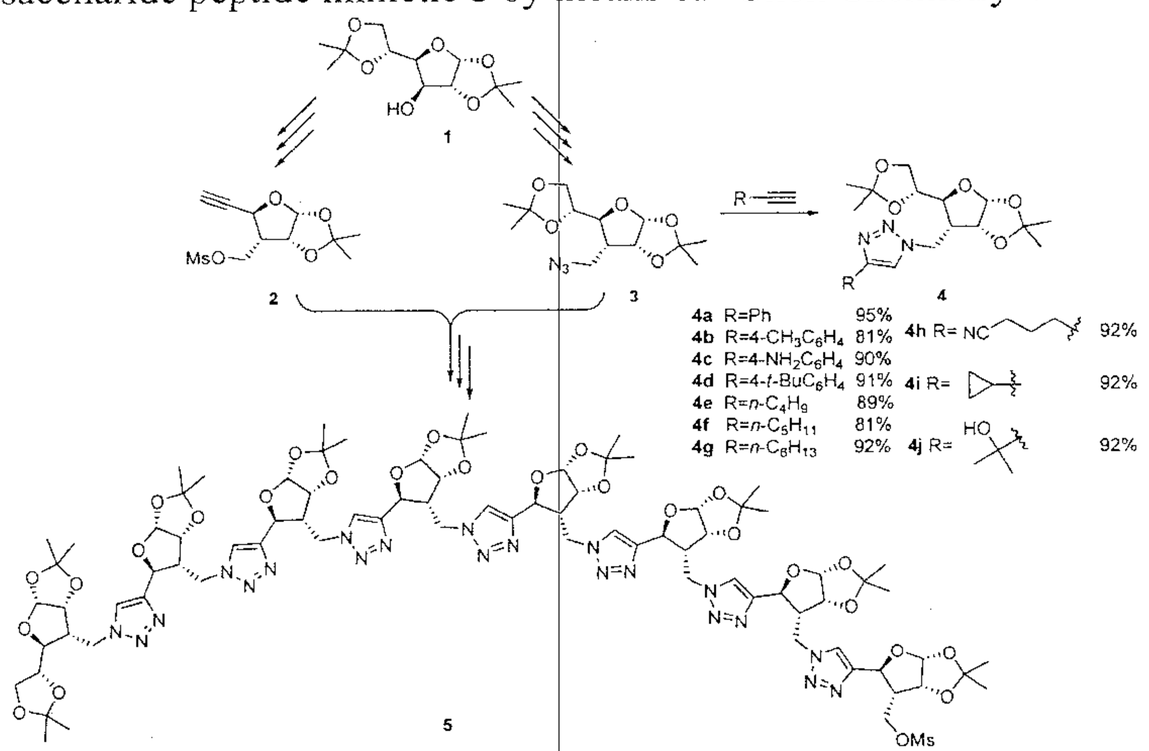
Recently carbohydrate-triazole conjugates were closely investigated as glycosidase inhibitors, *trans*-sialidase inhibitors, and glycogen phosphorylase inhibitors.[1] On the other hand, 1,2,3-triazoles are isosteric to the amides and are often used as latter in biologically active compounds.[2]
Hence, we report synthesis of 1,2,3-triazole-carbohydrate conjugates **4a-j** as well as octasaccharide peptide mimetic **5** by means of "Click Chemistry".[3]



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3-Aminomethyl allose as a platform for the synthesis of *N*-heterocyclic sugar derivatives

PO130

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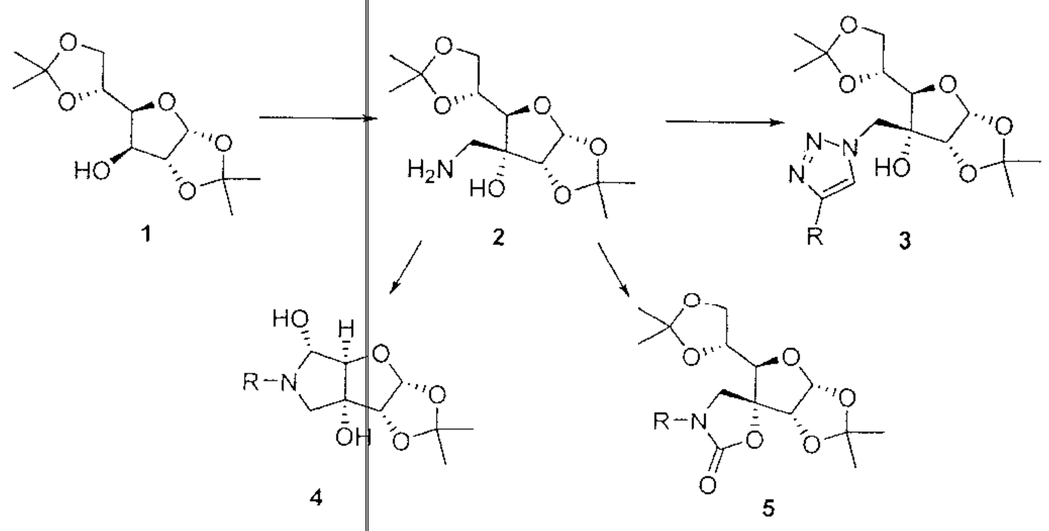
Due to their versatility, sugars proved to be excellent highly chiral platforms for combinatorial chemistry[1]. In particular, low price and high availability of D-glucose makes it attractive for both scientific and industrial applications.



The effective and convenient route towards substituted carbohydrate conjugates (**3** - **5**) was developed. These types of molecular architectures are known to exhibit wide range of biological activities, such as leukemia cell proliferation[2] and glycosidase[3,4] inhibition. The improved procedure for synthesis of strategic aminomethyl derivative **2** from readily available diacetone-D-glucose (**1**) will be discussed.

References:

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3. Rossi, L.L.; Basu, A.; *Bioorg. Med. Chem. Lett.*, **2005**, 15, 3596.
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An easy entry to 4-*N*-derivatized tetrahydroindazoles via Ritter reaction

PO146

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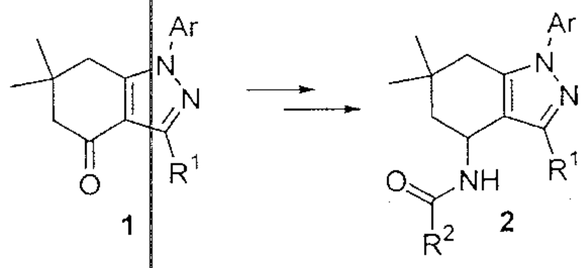
Tetrahydroindazoles (THIs), as a group of fused-pyrazoles have experienced significant renaissance in the last decade. This is explained by the fact that the above mentioned molecular scaffold can be perfectly derivatized to create a broad spectrum of distinct biological activities. Thus, different derivatives of THIs exhibit properties that allow to consider them as potential herbicides, anti-inflammatory drugs, anticancer substances, etc.
Hence, we have proceeded to the synthesis of 4-*N*-derivatized tetrahydroindazoles **2**. The synthesis starts with tetrahydroindazol-4-one **1** which is reduced to the corresponding pseudobenzylic alcohol. The Ritter reaction on the latter in a strongly protonating medium provides THIs decorated with amide side chain.



Deacylation procedures and further functionalization possibilities of 4-amino-tetrahydroindazoles will be discussed.

A straightforward way to chiral 7-amino-tetrahydroindazol-4-ones

PO147

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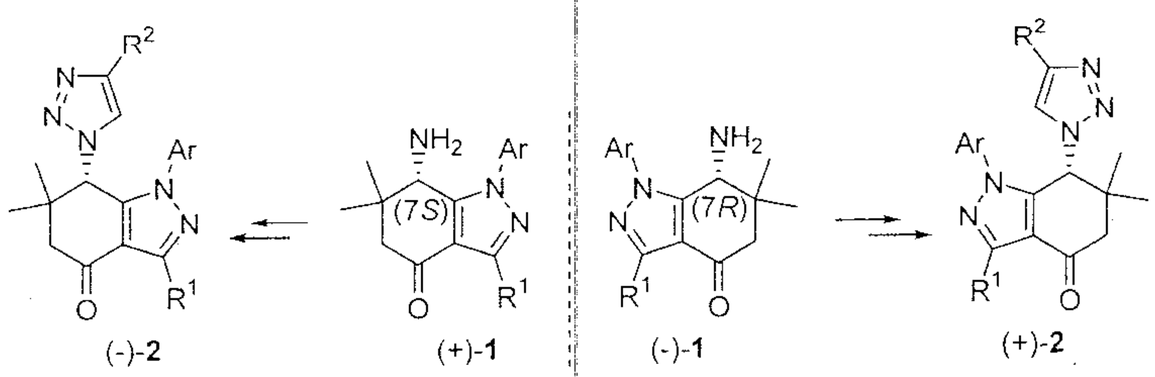
Recently, we have reported the synthesis of racemic 7-triazolyl functionalized 4,5,6,7-tetrahydroindazoles (THIs).[1] In order to dimerize these building blocks and/or to conjugate them with products coming from natural chiral pool, both enantiopure forms of 7-azido-THIs are required.
The key step in their synthesis is a chiral resolution of 7-amino-THIs **1**. Thus, enantiopure forms of (+)-1 and (-)-1 were obtained. The thorough X-ray data comparison of the above mentioned enantiomers versus racemate showed several interesting phenomena that will be discussed.



(-)-**2** (+)-**1** (-)-**1** (+)-**2**

Further functionalization of chiral amines **1** lead to corresponding enantioenriched triazole derivatives **2** in good to excellent yields. Examples include, *inter alia*, different monosaccharide conjugates (R^2 = monosaccharide residue).

References:

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Synthesis of enantiopure triazole-modified homoalanine derivatives

PO148

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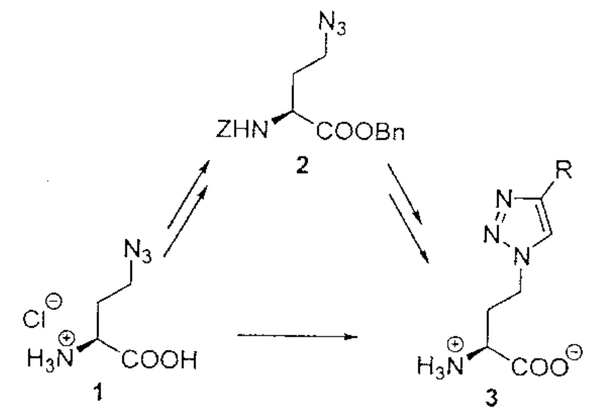
Since the discovery of efficient catalysis of the Huisgen dipolar cycloadditions between alkynes and azides,[1] this reaction has become important in the field of derivatization of different molecular scaffolds. Moreover, triazoles themselves possess interesting biological activities.[2]

Recently, serine derived triazole derivatives were synthesized and checked as probes to investigate ligand-protein binding interactions of the neutral amino acid transporter SN1.[3] Hence, we report here on the synthesis of series of homologs of the above mentioned triazole-modified alanines. Our synthetic route starts from commercially available exotic amino acid – L-azidohomoalanine (**1**). Synthetic scheme includes either a direct click approach or goes via protected intermediate **2**. A broad range of triazole-substituted homoalanine derivatives **3** were obtained.



References:

1. a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004. b) for a recent, see: Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51.

2. For a recent example, see e.g.: Kamal, A.; Shankaraiah, N.; Devaiah, V.; Laxma Reddy, K.; Juvekar, A.; Sen, S.; Kurian, N.; Zingde, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1468-1473 and references therein.

3. Gajewski, M.; Seaver, B.; Sean Esslinger, C.-S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4163.

Synthesis and X-ray analysis of 7-bromoarbidol, an impurity standard of arbidol

PO153

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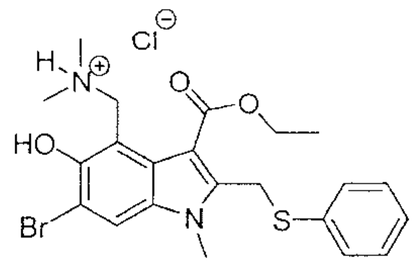
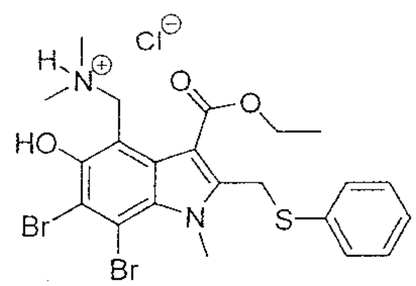
Since the use of *Tyrian purple* (6,6'-dibromoindigo) the mankind has shown a certain interest in the use of bromoindole derivatives. Indeed, there is a plethora of naturally occurring biologically active bromoindole derivatives, most of them arising from differently brominated tryptophans[1]. In the recent years, synthetic agent arbidol (**1**) has emerged as a representative broad spectrum antiviral medicament from the group of bromoindoles. According to one of the hypotheses it acts as an interferon inducer,[2] whereas other studies suggest that it blocks viral fusion.[3]



Arbidol (**1**)



7-Bromoarbidol (**2**)

7-Bromoarbidol (**2**) has proved to be as one of the standard impurities of pharmaceutically active ingredient. Synthesis and X-ray analysis of the latter will be discussed.

References:

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4. Miller, L.; Bergeron, R. *J. Chrom. A* **1994**, *658*, 489.