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Small Nitrogen Heterocycles Containing 1,2,3-Triazoles in the Side Chain

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Introduction

There are several enzymes that are interesting as targets for the treatment of cancer. Enzymes such as matrix metalloproteinases (MMP) have an effect on both physiological and pathological processes, including cancer. MMPs are zinc-dependent endopeptidases that are implicated in cleavage of extracellular matrix protein such as collagen, elastin, gelatin and casein [1].

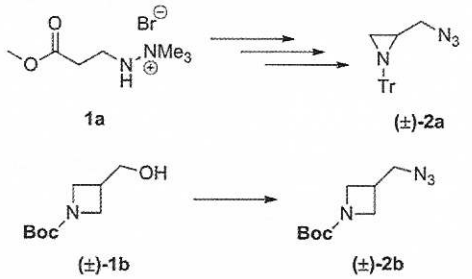
An easy and fast way to discover and develop new pharmacophores is click chemistry that allows to connect two functionalities through 1,2,3-triazole ring by undergoing metal catalyzed Huisgen 1,3-dipolar cycloaddition [2].

Previously our research group has identified aziridine-triazole conjugates as a new class of MMP-2 inhibitors [3]. Aziridines as well as azetidines constitute an important class of aza heterocycles with useful properties and applications widely used in drug design.

Results and Discussions

Herein we report synthesis of a series of 1,4- and 1,5-disubstituted aziridine-triazole and azetidine-triazole conjugates. The products are obtained by well-established Cu(I) catalyzed azide-alkyne cycloaddition (CuAAC) and recently explored Ru(II) catalyzed azide-alkyne cycloaddition (RuAAC) reactions.

The starting material for synthesis of target compounds by Cu(I) and Ru(II) catalyzed cycloaddition is aziridine derived azide **(±)-2a** which was prepared from commercially available hydrazinium salt **1a** in five steps [4]–[5]. In the case of azetidine, the starting material is azide **(±)-2b** which was prepared from commercially available primary alcohol **1b** in two steps (Scheme 1).



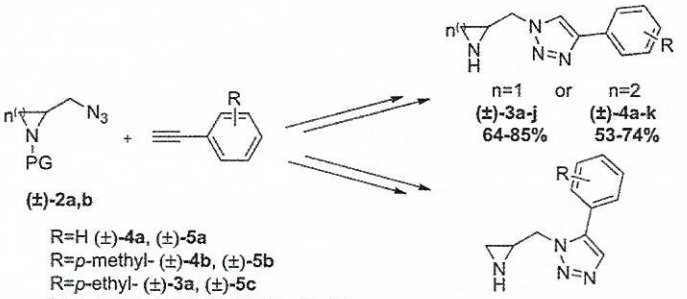
Scheme 1. Synthesis of aziridine and azetidine derived azides.

The further synthesis is based on Huisgen 1,3-dipolar cycloaddition between azide and terminal alkyne. In order to get both possible regioisomers both CuAAC and RuAAC were employed (Scheme 2).

CuAAC was carried out in acetone and water mixture at room temperature and $CuSO_4 \cdot 5H_2O$/sodium ascorbate was used as a catalytic system. Reaction yields for azetidine and aziridine derivatives were 62 % – 99 % and 60% – 88 %, respectively.

RuAAC was carried out in anhydrous toluene and in most of the cases at room temperature. Reaction was catalyzed by Cp*RuCl(COD). Catalyst loading varied between 3 mol-% and 6 mol-%. Reaction yields were 40 % – 89 %.

Aziridine deprotection was realized in anhydrous DCM by TFA in the presence of Et_3SiH. Reaction proceeded in 64 % – 85 % yields for 1,4-disubstituted triazoles and 80 % – 89 % yields for 1,5-disubstituted triazoles. In contrast, for azetidines the protecting group was cleaved by 4N HCl in dioxane and isolated yields of **(±)-4a-k** varried between 53 and 74%.



R=H (±)-**4a**, (±)-**5a**
R=*p*-methyl- (±)-**4b**, (±)-**5b**
R=*p*-ethyl- (±)-**3a**, (±)-**5c**
R=*p*-n-propyl- (±)-**3b**, (±)-**4c**, (±)-**5d**
R=*p*-*n*-butyl- (±)-**4d**, (±)-**5e**
R=*p*-*n*-pentyl (±)-**3c**, (±)-**4e**, (±)-**5f**
R=*p*-*terc*-butyl- (±)-**3d**, (±)-**4f**, (±)-**5g**
R=*m*-chloro- (±)-**4g**, (±)-**5h**
R=*p*-fluoro- (±)-**4h**, (±)-**5i**
R=*o*-fluoro- (±)-**5j**
R=*p*-methoxy- (±)-**4i**, (±)-**5k**
R=3,4-dimethoxy- (±)-**4j**, (±)-**5l**
R=3,4,5-trimethoxy- (±)-**4k**
R=*p*-propoxy- (±)-**3e**, (±)-**5m**
R=*p*-hexoxy- (±)-**3f**
R=*p*-phenyloxy- (±)-**3g**
R=*p*-benzyloxy- (±)-**3h**
R=*p*-cianometyl- (±)-**3i**
R=*p*-but-2-yn-1-yloxy- (±)-**3j**

Scheme 2. Synthesis of target compounds.

Biological activity of target compounds will be discussed.

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