Search for New MMP-2 Inhibitors Among Small Nitrogen Heterocycles Containing Disubstituted 1,2,3-Triazole in the Side Chain

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INTRODUCTION

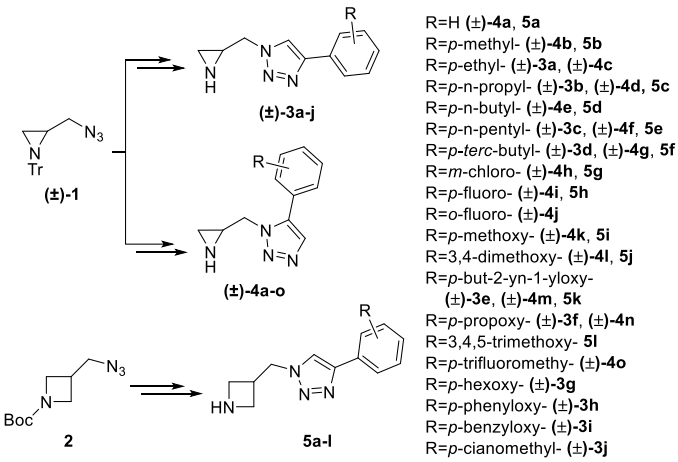
Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that are responsible for cleavage of extracellular matrix proteins such as collagen, gelatin, elastin and casein. Because of their effect on both physiological and pathological processes, MMPs have become interesting targets for treatment of cancer. In addition, it is known that MMP-2 has the most important impact to tumour growth.[1]

Previously, our research group has identified aziridine derivatives with 1,4-disubstituted 1,2,3-triazole in the side chain as a new class of MMP-2 inhibitors.[2,3] Herein we report futher investigation of these aziridine derivatives as well as new research among aziridines containing 1,5-disubstituted 1,2,3-triazole and azetidines containing 1,4-disubstituted 1,2,3-triazole in the side chain.

SYNTHESIS

Synthesis of target compounds was realised by metal catalyzed Huisgen 1,3-dipolar cycloaddition reactions between azide **(±)-1** or **2** and monosubstituted alkynes (Scheme 1). Derivatives of *N*-protected aziridine and azetidine containing 1,4-disubstituted 1,2,3-triazole were obtained using well established Cu(I) catalysis with reaction yields 61-88% and 62-99% respectively. Whereas for synthesis of *N*-protected aziridines containing 1,5-disubstituted 1,2,3-triazole ruthenium complex Cp*RuCl(COD) catalyzed azide-alkyne cycloaddition was employed with yields between 40 and 89%.

For aziridines *N*-protecting group was cleaved by small excess of TFA in the presence of Et_3SiH. Reaction proceeded in 64-85% yields for 1,4-disubstituted triazoles **(±)-3a-j** and 47-91% yields for 1,5-disubstituted triazoles **(±)-4a-o**. In contrast, for azetidines the deprotection was realised by 4N HCl in dioxane and isolated yields of **5a-l** varried between 53 and 74%.



Scheme 1. Approaches for synthesis of target compounds.

BIOLOGICAL ACTIVITY

For all compounds **(±)-3** high cytotoxicity was detected against tumour cell lines HT-1080 and MG-22A (IC_{50} = 10÷50 μM). Compound **(±)-3i** is selected for further research because of its high effect of cytotoxicity, especially on cell line HT-1080, and low basal cytotoxicity (LD_{50} = 2083 mg/kg). Most importantly, it inhibits MMP-2 selectively.

In contrast, potencial MMPs inhibitors have not been determined among compounds **(±)-4** and **5**.

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REFERENCES

[1] Zitka, O.; Kukacka, J.; Krizkova, S.; Huska, D.; Adam, V.; Masarik, M.; Prusa, R.; Kizek, R. *Curr. Med. Chem.* **2010**, *17*, 3751-3768.
[2] Kreituss, I.; Rozenberga, E.; Zemītis, J.; Trapencieris, P.; Romanchikova, N.; Turks, M. *Chem. Heterocycl. Compd.* **2013**, *49*, 1108-1117.
[3] Romanchikova, N.; Trapencieris, P.; Zemītis, J.; Turks, M. *J. Enzyme Inhib. Med. Chem.* **2014**, *29*, 765-772.