Drug Discovery Conference

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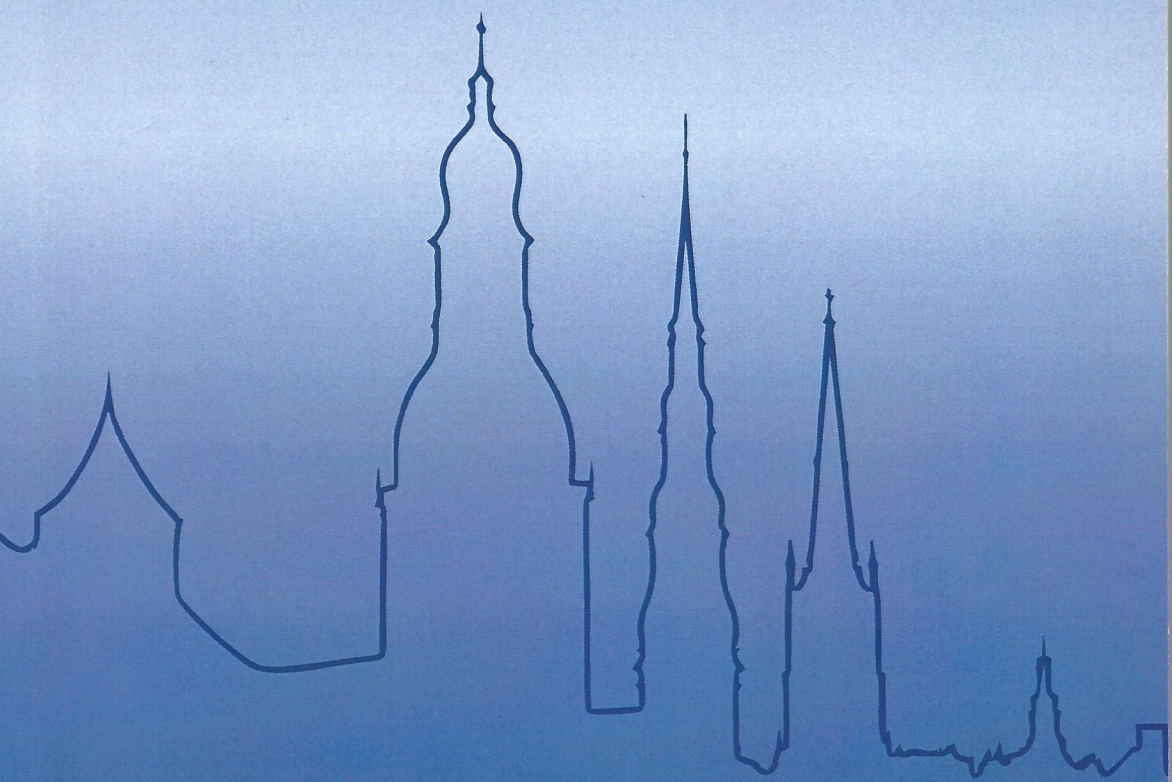

Abstract book

PP66. SYNTHESIS AND MMP-2 INHIBITION STUDIES OF NOVEL AZIRIDINE AND AZETIDINE DERIVATIVES

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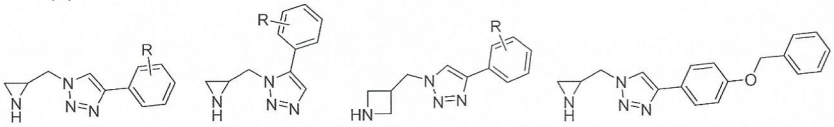
Matrix metalloproteinases (MMPs) are zinc-dipendent endopeptidases that are responsible for cleavage of extracellular matrix proteins such as collagen, gelatin, elastin and casein. Because of their effect on both physiological and pathological processes, MMPs have become interesting targets for treatment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

Previously, we have reported promising results for aziridines (±)-1 with 1,4-disubstituted 1,2,3-triazole in the side chain as a new class of MMP-2 inhibitors.2,3 The present work represents further investigation of these aziridine derivatives as well as new research among aziridines (±)-2 containing 1,5-disubtituted 1,2,3-triazole and azetidines 3 containing 1,4-disubstituted 1,2,3-triazole in the side chain.

Synthesis of the target compounds was realised by Huisgen 1,3-dipolar cycloaddition between 2-(azidomethyl)-1-tritylaziridine or 3-(azidomethyl)-1-terc-butyloxycarbonyl-azetidine and monosubstituted alkynes. 1,4-Disubstituted 1,2,3-triazoles containing N-protected aziridine or azetidine were obtained by Cu(I) catalysis reaching 88% and 99% yields respectively, while for analogues of 1,5-disubstituted 1,2,3-triazoles with yields up to 89% ruthenium complex Cp*RuCl(COD) catalyzed cycloaddition was employed. For aziridine derivatives deprotection was carried out by small excess of TFA in the presence of Et3SiH, but for azetidines the protecting group was cleaved by 4N HCl in dioxane.

Biological activity of compounds (±)-1, (±)-2 and 3 was investigated. For all aziridine derivatives (±)-1 high cytotoxicity was detected against tumour cell lines (IC50 = 10÷50 μM). Compound (±)-4, which selectively inhibits MMP-2, has been selected for futher research because of its high effect of cytotoxicity, especially on cell line HT-1080, and low basal cytotoxicity (LD50= 2083 mg/kg). In contrast, potencial MMPs inhibitors have not been determined among compounds (±)-2 and 3.



References:
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3. Romanchikova, N.; Trapencieris, P.; Zemītis, J.; Turks, M. J. Enzyme Inhib. Med. Chem. 2014, 29, 765-772.