Poster Sessions

MS31.P25

Inhibition of MMP-1, 3, and 13 by Same Inhibitor – Structure Based Design Study
Bobby L. Barnett, Michelle Dunaway, Longin Chen, Tim Rydel, Mike Natchus, Fei Gu, "Department of Chemistry, U. of Cincinnati, Cincinnati, OH (USA)." Procter & Gamble Co., Cincinnati, OH (USA). E-mail: bobby.barnett@uc.edu

Matrix metalloproteinase (MMP) inhibitors are potential therapeutic agents for various diseases including cancer and osteoarthritis. Recent data from clinical trials with MMP inhibitors indicate that there is a great need for selective inhibitors. X-ray crystallography [1], [2], [3] has been used as a tool to help understand specific binding interactions of inhibitors to various MMPs. Large conformational changes have been noted when comparing the structures of the active MMP-3 catalytic domain and the one inhibited by a hydroxamic acid inhibitor. Both soaking and co-crystallization methods were used to generate the MMP-3 inhibitor complex crystals for data collection. The same inhibitor has also been co-crystallized with MMP-1 and MMP-13. Comparisons of the structures of three inhibited enzymes, MMP-1, 3, and 13 show that MMP-3 and 13 are extremely similar. There are major differences in the binding pockets, especially in the S1’ pocket between MMP-1 and MMP-3/13. These structural studies have helped design more selective inhibitors that can be used as therapeutic agents with improved safety profile.

Keywords: osteoarthritis, drug design

MS31.P27

Regioslective deacetylation based on teicoplanin-complexed Orf2* crystal structure
Hsiu-Chien Chan, Tsung-Lin Li, "Genomics Research Center, Academia Sinica, Taipei, (Taiwan)." Institute of Bioinformatics and Structural Biology, National Tsing Hua University, Hsinchu, (Taiwan). E-mail: sandra120976@gmail.com.

Lipoglycopeptide antibiotics are more effective than vancomycin against MRSA as they carry an extra aliphatic acyl side chain on glucosamine (Glm) at residue 4 (r4)[1]. The biosynthesis of the r4 N-acetyl Glc moiety at teicoplanin (Tei) or A40926 has been elucidated, in which the primary amine nucleophile of Glm is freed from the r4 GlcNac pseudo-Tei precursor by Orf2* for the subsequent acylation reaction to occur[2]. In this report, two Orf2* structures in complex with -D-octyl glucoside or Tei were solved. Of the complexed structures, the substrate binding site and a previously unknown hydrophobic cavity were revealed, wherein r4 GlcNac acts as the key signature for molecular recognition and the cavity allows substrates carrying longer acyl side chains in addition to the acetyl group. On the basis of the complexed structures, a triple-mutation mutant S98A/V121A/F193Y is able to regioslectively deacetylate r6 GlcNac pseudo-Tei instead of that at r4. Thereby, novel analogs can be made at the r6 sugar moiety.

Keywords: regioselective, glycopeptide antibiotic, deacetylase.