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Design, synthesis and testing of new purple acid phosphatase inhibitors: Towards the development of anti-osteoporotic chemotherapeutics

Siti H Mohd-Pahmi, Gerhard Schenk and Ross P McGeary
The University of Queensland, Australia

Purple acid phosphatases (PAPs) are binuclear metallohydrolases that have been isolated from various mammals, plants, fungi and bacteria. They catalyse phosphoric ester hydrolysis under neutral to acidic conditions. In mammals, PAP activity is associated with bone resorption, which can lead to bone metabolic disorders such as osteoporosis. This therefore makes human PAP an attractive target to develop anti-osteopororotic drugs. Based on a previous lead compound and rational drug design, acyl derivatives of 1-amidophenylmethylphosphonic acid were designed as potential new potent PAP inhibitors. Docking studies have shown that the derivatives have high binding affinity due to the phosphonate moiety binding to the binuclear metal centre, which are as intended. Furthermore, the phenyl ring is predicted to occupy the space in a small pocket in the vicinity of the active site, and the acyl chain make favourable interactions with the surface of the enzyme; all of which contribute to the high binding affinity of the derivatives to the enzyme.

The derivatives were synthesised and tested as PAP inhibitors. Kinetic analysis showed that they are very potent pig PAP inhibitors with most of the derivatives having Ki values in the nanomolar range. The most potent pig PAP inhibitor within this series was the octadecyl-derivative with K_{ic} of 168 nM. This is the most potent pig PAP inhibitor to date.

Biography

Siti H Mohd-Pahmi is currently in her last month of her PhD at the University of Queensland, Australia. She completed her Bachelor of Biotechnology with Honors Class I in 2010 from the same university. As a young researcher, she has one publication that resulted from her honors year, and with many more to come from her PhD.