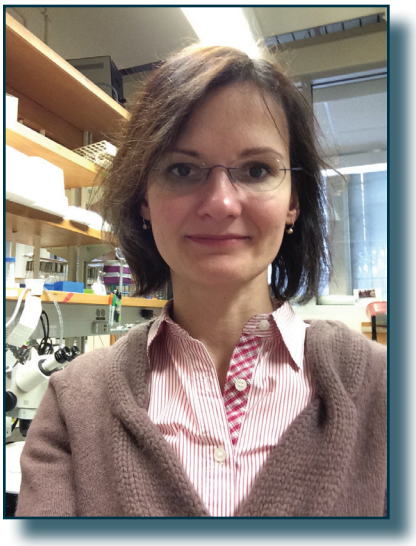
University of Minnesota
Driven to Discover℠

Department of Chemistry

Special Seminar

3:30 p.m. Monday, April 14 • 101J Smith Hall



Professor

Katarzyna Błażewska

Technical University of Lodz, Poland
Fulbright Scholar
Eranthie Weerapana's Laboratory, Boston College

Synthesis & Biological Characterization of Novel Phosphonocarboxylate RabGGTase Inhibitors

Abstract

Organophosphorus compounds are known as drugs used in the treatment of diverse medical conditions, such as bone diseases (osteoporosis, Paget's disease, bone metastasis), viral (smallpox, hepatisis) and bacterial infections.

Some of the most commonly used drugs of this class are bisphosphonates (BPs), which show anti-osteoporotic activity. Bisphosphonates of 2nd and 3rd generations are potent inhibitors of one of the mevalonate pathway enzyme, farnesyl pyrophosphate synthase (FPPS). During structure-activity relationship studies it was discovered that exchange of one of the phosphonic group in BP for carboxylic group resulted in the shift of activity towards different enzyme, Rab geranylgeranyl transferase (RGGT), responsible for post-translational modification of Rab proteins, implicated in a number of diseases.

Thus developed phosphonocarboxylates became the first compounds selectively targeting RGGT. Here it will be discussed how the novel phosphonocarboxylates were designed and made and if there is a correlation between SARs for bisphosphonates—FPPS and phosphonocarboxylates—RGGT. It will be also presented how the problem of highly ionic character of these compounds, potentially decreasing their bioavailability, was addressed.

Host: Professor Mark Distefano