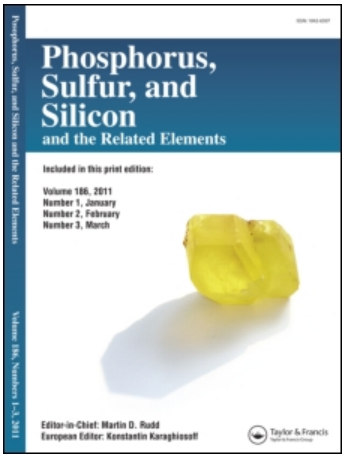

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Design and Enantioselective Synthesis of Phosphonates as Enzyme Inhibitors

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DESIGN AND ENANTIOSELECTIVE SYNTHESIS OF PHOSPHONATES AS ENZYME INHIBITORS

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The serine proteases [1] form an important group of hydrolytic enzymes essential to a variety of biological activities ranging from food digestion to blood clotting. However their uncontrolled activity is also known to be implicated in a number of pathological conditions including emphysema, cystic fibrosis, cancer and myocardial infarction. Their selective control is therefore an important goal and could offer a basis for the rational design of therapeutic agents.

Recent studies [2] involving the phosphonate analogues of peptidyl amino acids have shown that the diphenyl esters behave as potent specific irreversible inactivators of targeted members of the serine protease group e.g. chymotrypsin and elastase. We have also more recently prepared fluoro- and chloro- substituted phenyl esters of these analogues and have found considerable enhancement in inhibitory activity over the unsubstituted analogues, (e.g. m-chlorophenyl esters show k_i/K_i values up to 10^3x greater than the corresponding phenyl esters).

We have also successfully extended our synthetic approach to the preparation of a number of basic amino acid analogues e.g. cbz-Orn^P(OPh)$_2$, cbz-Lys^P(OPh)$_2$ etc.,[3] and using a guanidation reaction elaborated these to arginine and related analogues e.g. cbz-Arg^P(OPh)$_2$ and cbz-*homo*-Arg^P(OPh)$_2$ etc. These have been targeted as inhibitors of trypsin and trypsin-like serine proteases. Preliminary biological results suggest they are selective for these and also show specificity towards individual members of the trypsin group.

The dependence of biological interactions on absolute configuration imposes limitations on results obtained using racemic materials. As a result we have developed a convenient enantioselective synthesis for individual isomers of a wide range of α-aminophosphonous and phosphonic acids [4] and the corresponding phenyl esters. The biological properties of these compounds are currently being investigated.

Referances

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