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FROM PHOTOFLUORINATION TO SUICIDE-SUBSTRATE ENZYME INHIBITORS

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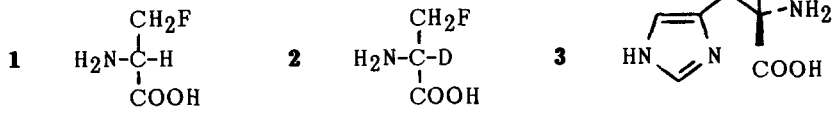
The fundamental idea of our approach for design of novel drugs rests on 'isogeometric modification' of metabolites of key importance to biochemistry of disease processes. 'Isogeometric transformation' aims to alter a metabolite maximally with respect to chemical character but without substantial distortion of its geometry. 'C-Fluorination,' that is transformation of one or more C-X bonds of the metabolite into C-F bonds, is the means to realize isogeometric transformation. 'Photofluorination' and 'fluorodehydroxylation' are our synthetic methods developed for C-fluorination. To date, two general classes of fluorine compounds were developed in this framework, namely the β-fluoro-α-amino acids (that is, β-fluoroalanine and its α-substituted variants) and the β-fluoro-α-amines.



3-Fluoro-D-alanine **1** was designed on the basis of consideration of molecular physiology of bacteria, specifically to interfere with biosynthesis of the bacterial cell wall. It represents the first instance of design of an entirely novel type of an effective antibacterial. Its α-deuterated variant **2** (generic name fludalanine MK-641), in combination with a 'pro-drug' of cycloserine (MK-642) is presently undergoing clinical evaluation as a perorally active wide-spectrum antibacterial. **1** and **2** were shown to be suicide-substrate enzyme inhibitors of bacterial alanine racemase. (S)-α-Fluoromethylhistidine **3** represents a further development along this line. It was designed to be a suicide-substrate enzyme inhibitor of the mammalian enzyme histidine decarboxylase, the enzyme involved in the exclusive biosynthetic pathway in formation of histamine. **3** represents the first truly selective and highly active inhibitor of this enzyme. It is under extensive biochemical and pharmacological study in evaluation as a potential new approach for treatment of diseases associated with excessive levels of histamine.