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Synthesis of highly functionalized fluorocyclopropanes. Applications to the synthesis of constrained amino-acids analogs

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Synthesis of biologically active peptides is a central goal in medicinal chemistry. However, major drawbacks in this area are their low metabolic stability and poor ligand-receptor interactions eroding the bioavailability of peptide-based drugs. To overcome these disadvantages, considerable interest has been devoted to synthesize peptidomimetics by modifying the natural sequence of amino acids of bioactive peptides.

In our ongoing project, we decided to focus on the design of peptidomimetics including a fluorinated cyclopropane moiety. Incorporation of a three-membered ring influences the secondary structure, leading to conformationally constrained peptide chains. Thus, the ligand affinity for the enzyme binding site would be improved, as well as the orientation of amino acid side chains. Moreover, many studies show that the presence of a fluorine atom induces modifications of various parameters (lipophilicity, acidity/basicity, electronic distribution or bond lengths).

We report here an efficient, general, asymmetric synthesis of highly functionalized fluorinated cyclopropanes and especially the synthesis of fluorinated cyclopropyl analogs of four natural amino acids (methionine, leucine, arginine and lysine), and the incorporation of these scaffolds in peptides. We also report the diastereoselective synthesis of glutamic acid analogs and the evaluation of their agonist activity towards metabotropic glutamate receptor sub-type 4 (mGluR4). Finally the synthesis of fluorinated analog of TMC 435 (which incorporates within its structure a cyclopropyl amino-acid unit), a NS3/4A serine protease inhibitor for HCV treatment will be described.