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NOVEL DERIVATIVES OF 2-AMIDOCYCLOHEX-1-ENE CARBOXYLIC ACID AS HCA_1, HCA_2, AND HCA_3 RECEPTOR AGONISTS

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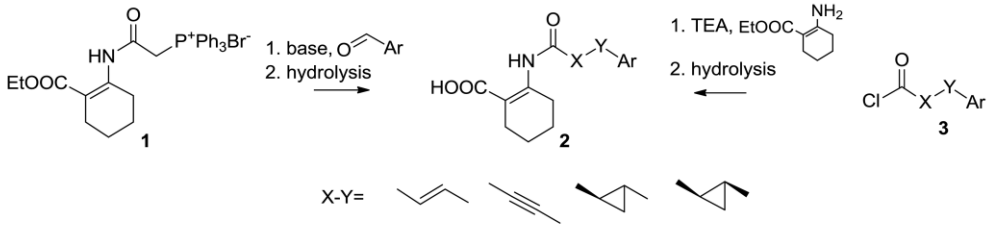
Hydroxy-carboxylic acid (HCA_1, HCA_2 and HCA_3) receptors are G-protein-coupled receptors which are expressed in adipocytes. HCA_2 and HCA_3 receptors are also expressed in a variety of immune cells. HCA_2 receptor is the supposed target of antidyslipidemic drug nicotinic acid. HCA receptors represent promising drug targets for metabolic disorders, inflammatory, immune and other diseases [1].

A variety of synthetic ligands for HCA receptors have been developed. The series of 2-propanamidocyclohex-1-enecarboxylic acid moiety containing compounds **2** (X-Y = $-CH_2CH_2-$) were designed at Merck as HCA_2 agonists and several compounds were identified as more active than nicotinic acid and with better pharmacokinetic properties [2, 3]. Because the incorporation of rigidity elements in the linker X-Y could help to pre-organize the molecule in a favorable bioactive conformation, we synthesized cyclohex-1-enecarboxylic acid derivatives **2** with linkers X-Y as well as various aryl groups (Ar) [4].



To evaluate the possible agonist properties of the synthesized compounds towards human HCA_1, HCA_2, and HCA_3 receptors, forskolin-stimulated cAMP accumulation assays were arranged. Our studies showed that incorporation of rigid linkers X-Y such as *E*-double bond or triple bond increase activity and selectivity of 2-naphtalenyl and 6-hydroxy-2-naphtalenyl derivatives. It was established that activity and selectivity is critically dependent on the aromatic part of the molecule.

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