XHE-III-74 was the first alpha 4 selective GABAA receptor modulator investigate by our collaborators and us in respect to asthma. Yocum et al showed airway smooth muscle relaxation of XHE-III-74 in mouse and human *ex vivo* preparation. It was also active as an aerosol reducing airway hyperresponsiveness. However, its different metabolic stability in mice than in human impedes the development of XHE-III-74. In addition, high levels of XHE-III-74 were observed in brain, which caused CNS effects at dosages of 40 mg/kg and higher.

XHE-III-74EE is an alternative derivative of XHE-III74, bearing an ethyl ester instead of a t-butyl ester. The compound was stable in presence of mouse or human liver microsomes. When given ip, XHE-III-74EE protected against airway hyperresponsiveness in a murine model of asthma. It also attenuated smooth muscle relaxation *ex vivo*. In respect to inflammation, XHE-III-74EE reduced the expression of IL-2 in Jurkat cells and increased negative membrane potential *in vitro*. Unfortunately, XHE-III-74EE was not persistent *in vivo* with a short life time of 16 minutes in blood. Pronounced CNS effects were observed at 40 mg/kg ip and more.

XHE-III-74A was investigated due to metabolism of XHE-III-74EE to its corresponding acid. XHE-III-74A is alpha 4 selective GABAA receptor modulator although less potent than XHE-III-74EE. It did not cause any CNS effects and reduced eosinophilia in the mouse lung. In addition, it reduces the expression of IL-2 in Jurkat cells and significantly decreases the concentration of [Ca2+] in activated T-cells. XHE-III-74A relaxed precontracted tracheal rings *ex vivo*. However, the pharmacokinetics of XHE-III-74A are not optimal with a half-life of 13 minutes in blood due to rapid excretion.

MRS-II-66, a dimethylamide analog of XHE-III-74, was shown to relax airway smooth muscle *ex vivo* and reduce airway hyperresponsiveness in a murine asthma model when given ip. Although MRS-II-66 is stable in the presence of mouse and human liver microsomes, it has inadequate pharmacokinetics. The half-life was less than 10 minutes and conversion to the mono methylamide but not the carboxylic acid was observed *in vivo*.

RJ-II-50 is a phenolic analog of XHE-III-74EE that has shown relaxation in smooth muscle and alleviated airway hyperresponsiveness in a murine model of asthma when given orally. In addition, it has anti-inflammatory properties reducing the number of CD4+ T-cells in bronchoalveolar lavage fluid. CD4+ T-cell directly responded to RJ-II-50 with an increase of negative current. High stability and long half-life was observed *in vivo*, making it an excellent drug candidate for asthma.

SH-053-2’F-R-CH3 acid is an analog of alpha 5 selective GABAA receptor modulator SH-053-2’F-R-CH3. In contrast to SH-053-2’F-R-CH3, SH-053-2’F-R-CH3 acid was not crossing the BBB and therefore induced no CNS effect. It is stable in the presence of mouse and liver microsomes and has very good pharmacokinetic parameters. SH-053-2’F-R-CH3 acid relaxed airway smooth muscle and attenuated airway hyperresponsiveness in a murine model of asthma. SH-053-2’F-R-CH3 acid also relaxed precontracted human smooth muscle. Finally, the acid had also anti-inflammatory properties due to the reduction of eosinophils and leukocytes. Overall, protic alpha 5 selective GABAA receptor modulators are excellent drug candidates for asthma.