Fosfonianowe analogi kwasów amino(hydroksy)karboksylowych o potencjalnej aktywności biologicznej

The biological activity of L-glutamic acid derivatives has become an inspiration to design new compounds functionalized with a hydrophilic hydroxyl or amino group in the γ position. Phosphonic groups $P(O)(OH)_2$ have been introduced instead of the carboxyl functions. The phosphonic acid moiety may compete with a substrate having a carboxyl group for the active site of an enzyme or other cellular receptor. The introduction of additional amino and hydroxyl functional groups may change the physicochemical properties of these compounds and cause significant changes in the interaction with receptors. Since the designed compounds have two stereogenic centers, the synthesis of all possible stereoisomers should be considered, four enantiomers of (1-amino-3-hydroxypropane-1,3-diyl)diphosphonic acid and three enantiomers of (1,3-diaminopropane-1,3-diyl)diphosphonic acid.

The precursor for the synthesis of functionalized diphosphonic acids were enantiomerically pure tetraethyl (1-amino-3-oxopropyl)phosphonates, which have been converted into isomeric tetraethyl (1-amino-3-hydroxypropane-1,3-diyl)diphosphonates by Abramov's reaction with diethyl phosphite, and into tetraethyl (1,3-diaminopropane-1,3-diyl)diphosphonates by the Kabachnik-Fields reaction with triethyl phosphite and benzylamine. The obtained diastereoisomers of respective diphosphonates have been hydrolyzed to the corresponding diphosphonic acids. Enantiomerically pure tetraethyl (1-amino-3-oxopropyl)phosphonates have been obtained from (*S*)-*N*-(1-phenylethyl)-*C*-(diethoxyphosphoryl)nitrone according to the methodology previously developed in our research group. An alternative pathway for the synthesis of (*S*)-*N*-(1-phenylethyl)-*C*-(diethoxyphosphoryl)nitrone was developed using the oxidation of the appropriate amine with oxone.

Determination of the absolute configuration at C3 in (1-amino-3-hydroxypropane-1,3-diyl)diphosphonic esters and (1,3-diaminopropane-1,3-diyl)diphosphonic esters required their transformation into the respectively protected derivatives, and then analysis of ^{31}P NMR and ^{1}H NMR spectra, respectively.

Diphosphonic acids were examined for agonist activity towards metabotropic glutamatergic receptors: $mGluR_5$, $mGluR_7$, and $mGluR_8$. None of the tested compounds showed expected agonist activity.