ASYMMETRIC SYNTHESIS OF NEUROTROPIC DRUGS – GABA ANALOGS USING Ni(II)-CATALYZED MICHAEL ADDITION

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γ -Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. Addition of malonates or β -ketophosphonates to nitroolefins is good approach to the key precursors of GABA-derived drugs [(R)-fenotrotil, (R)-baclofen, (R)-phenibut, (R)-rolipram, (S)-pregabalin] and chiral substituted γ -aminophosphonic acids – a potent GABAergic compounds. Except anticonvulsant (S)-pregabalin these drugs were commercialized in its racemic forms, it has been reported that its biological activity resides predominantly in (R)-enantiomer of aryl GABA derivatives. Use of non-racemic pharmaceutical substances will allow to lower a dosage of drugs and to increase efficiency of nervous diseases therapy. There are many methods available in the literature on the synthesis of enantiomerically pure GABA derivatives. However, these methods suffer from disadvantages such as the low overall yields, the need of separation of precursor diastereomers and the use of expensive chiral reagents in stoichiometric amounts. In this context, a more performance approach for the synthesis of enantiomerically pure GABA derivatives and analogs is highly desirable.

Herein we report the efficient atom-economic technology of the synthesis of GABA analogs based on metal complexes catalyzed asymmetric Michael addition. Enantioselectivity of the reactions of various Michael donors with nitroolefins were studied in the presence of Ni, Co, Mn, Fe, Cu complexes with chiral N-ligands (substituted (S,S)-cyclohexane-1,2-diamines, (S,S)-1,2-diphenylethane-1,2-diamines, L-proline and (S)-camphor derivatives). We showed that activation by Et₃N of a Ni(II) complexes with one chiral diamine ligand is possible. It gives the chance to reduce quantity of a chiral ligand. As result we have developed performance catalytic system with minimal content of chiral component, which provide high yield of the Michael adducts with up to 99% ee at concentration of the catalyst 0.2 mol.%. Hydrogenation of the chiral adducts and subsequent hydrolysis leads to 3-substituted GABA.

The proposed approach was successfully used for development of the production process of non-racemic pharmaceutical substances of (R)-fenotrotil, (R)-baclofen, (R)-phenibut, (R)-rolipram and (S)-pregabalin.