Synthesis of NK-1 antagonists

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NK-1 receptor antagonists are represented so far by only one drug, Aprepitant, which is available on the market for prevention of chemotherapy-induced nausea and vomiting. Nevertheless, it is assumed that NK-1 antagonists will be able to participate in treatment of migraine, rheumatoid arthritis, asthma, pain, inflammatory bowel disease, Parkinson's disease, anxiety and depression in future.

This thesis is concerned with asymmetric synthesis of derivatives of 2-amino-4*H*-pyran, which thanks their substitutions are in accordance with structure of pharmacophore of NK-1 antagonists.

As a starting material for their preparation has been used commercial methyl *p*-tolyl sulfone and (*R*)-methyl *p*-tolyl sulfoxide, which was synthesized from menthyl-(*S*)-*p*-toluenesulfinate by nucleophilic substitution.

These compounds were subjected to reaction with ethyl 2-picolinate. From prepared *β*-ketosulfoxide and *β*-ketosulfone were obtained 2-amino-4*H*-pyrans by Michael addition.

The derivatives proceeding from *β*-ketosulfoxide were subjected to reduction of the sulfoxide and trifluoroacetylation of the amine group on the carbon 2 of the pyran ring. Prepared derivatives had agonistic activity at NK-1 receptor, what showed us importance of at least one oxygen on sulfur and also importance of non-substituted amine group in position 2. Moreover derivatives with sulfone group had higher antagonistic activity than derivatives with sulfoxide group.