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SIMVASTATIN INTENSIFY HEART RATE DEPRESSION AFTER METOPROLOL AND ATROPINE ADMINISTRATION IN NORMOCHOLESTEROLAEMIC RATS

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The use of statins has been for many years connected with significant clinical benefits due to cholestrerol synthesis inhibition and increase of LDL - lipoprotein expression. In recent years, growing attention is being paid to the pleiotropic properties of statins. The mechanisms responsible for blocking prenylation of small G proteins are the underlying explanation of the above mentioned properties of statins. The existence of an interaction on the intracellular signalling level between the simulation of beta - adrenergic receptors and statin administration has been demostrated. The aim of the study was heart rate and blood pressure evaluation after metoprolol administration in rats given normal diet and simastatin for two weeks. The study was performed on Wistar outbred rats. After a two days adaptation period, simvastatin in a dose 10 mg/kg was administered into the stomach for a period of two weeks. The last administration drug was on the day prior to the heart rate and blood pressure of the tests. Heart rate and blood pressure measurements were performed with the use of HSE Haemodyn equipment. Before immobilization on the operating table, the rats were anaesthesized with the use of penthobarbital administered intraperitoneally in a dose of 30 mg/kg. Need be, general anaesthesia was sustained by one administration of penthobarbital (10 mg/kg of body mass dose), until complete lack of response to pain was achieved. After parameter stabilization (approximately 15 minutes), metoprolol in a dose of 1.0 mg/kg, and atropine in dose of 0.5 mg/kg were given intraperitoneally. After the administration of metoprolol and atropine, evalution of parametres was performed for another 15 minutes. Heart rate, systolic, diastolic and mean blood pressure inital were similar. After metoprolol and atropine administration, heart rate in rats receiving simvastatine was significantly decrease compared to rats without simvastatin. Blood pressure (systolic, diastolic, mean) values, after metoprolol and atropine administration in both groups, were statistically insignificant. It seems that the basis of the above mentioned interaction is the influence of simvastatin on the autonomic nervous system or modulation of intracellular transmission.

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4,6-DISUBSTITUTED 2-(4-METHYL-1-PIPERAZINYL)PYRIDINES: SYNTHESIS AND THEIR BINDING TO SEROTONIN 5-HT$_{1A}$, 5-HT$_{2A}$, AND 5-HT$_7$ RECEPTORS

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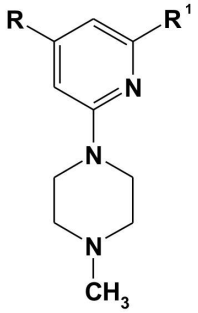
The role of the 5-HT$_7$ receptors in the CNS and the periphery has not been fully clarified since to date there are only limited number of the selective-active ligands. During screening of our compounds library against the 5-HT$_7$ receptor from rat hypothalamic membranes, it was found that a lot of agents, besides 5-HT$_{1A}$ and/or 5-HT$_{2A}$ receptors activity, displayed also a significant affinity towards 5-HT$_7$ sites. The 4-mono, and 4,6-disubstituted 2-(1-piperazinyl)pyridines were particularly interesting, since compounds of such structure have never been reported as 5-HT$_7$ receptor ligands.



R: Ph, 2-thienyl, 3-thienyl, 2-OCH_3-Ph, 3-OCH_3-Ph, 4-OCH_3-Ph
R^1: Ph, 2-thienyl, CH_3

Here we report the 5-HT$_7$ receptor affinity for some previously described 4,6-disubstituted 2-(1-piperazinyl)pyridines as well as a series of newly designed and synthesized analogues. The target compounds were synthesized using the benzotriazole-assisted Katritzky method. The affinity for three serotoninergic receptor subtypes (5-HT$_{1A}$, 5-HT$_{2A}$ and 5-HT$_7$) were determined and some structure-affinity relation-

ships are discussed.

In addition, an automated docking to homology model of 5-HT$_7$ receptor was performed, and it was found that in the best PMF-scored complexes ligands were placed between helices 2, 3 and 7, revealing a strong interaction formed by heteroatom and indole nitrogen of Trp7.40.

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STRUCTURAL MODIFICATIONS OF SOME ARYLPIPERAZINE LIGANDS TOWARDS IMPROVED SELECTIVITY FOR 5-HT$_7$ RECEPTORS

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The latest discovered subtype of serotonin receptors - 5-HT$_7$ - emerged as a new valuable therapeutic target. Based on its distribution and pharmacological studies, the 5-HT$_7$ receptors has been implicated in many different functions in CNS (like circadian rhythm, learning and memory, mood, endocrine regulation) as well as in the periphery. It was found that many of the previously described serotonin ligands showed a high level of 5-HT$_7$ receptor activity. The latter was observed for 5-HT$_{1A}$ agents, in particular in the group of long-chain arylpiperazine derivatives (LCAPs).

As part of our research program directed toward development of potent and selective 5-HT$_7$ receptor ligands, we synthesized a novel series of LCAPs analogues. The structural modifications included replacement of terminal amide fragment by aryl sulfonamide moiety and/or changes of aromatic substituent in arylpiperazine fragment.

All the new compounds were evaluated for affinity at 5-HT$_7$ and 5-HT$_{1A}$ receptors and preliminary structure-affinity relationships are presented.

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1-THIOSUGARS: SYNTHESIS AND BIOLOGICAL ACTIVITY AGAINST CSFV GLYCOPROTEINS.

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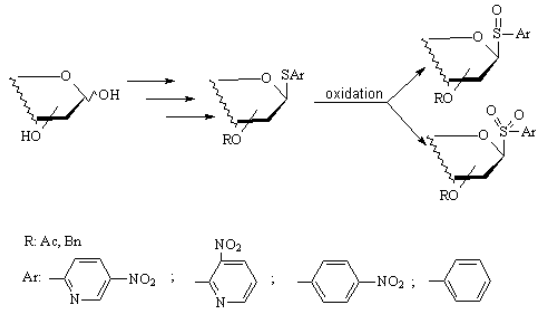
In search for effective inhibitors of sugar processing enzymes the *S*-glycosides and products of their oxidation attract constant attention as viable substrate analogs.

Along this line, we have reported a simple and efficient methodology for the synthesis of thioglycosides, derivatives of nitroaromatic halides, via aromatic nucleophilic substitution of halogen with 1-thiosugar derivatives [1,2]. Phenyl thioglycosides used in our study were prepared as described in literature, in reaction of acylglycosyl halides with thiophenol under phase transfer conditions [3].

The oxidation of glycosyl sulfides respectively to sulfoxides or sulfones was achieved using common oxidising agent [4]: *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 at room temperature. During oxidation to sulfoxides *m*-CPBA was added in equimolar amount in low temperature (-20 ^oC) to avoid sulfone formation.



Desired oxidation products were obtained in a good yield and their structures were confirmed by NMR spectra.

Biological studies with these inhibitors were divided into two parts. First, using the neutral red cytotoxicity assay, we established the optimal doses of inhibitors when the viability of swine kidney cells (SK6) was higher than 50%. In the next experiments, we examined the effect of concentration of inhibitors on penetration and propagation of classical swine fever virus (CSFV). The best results were observed for GP5 inhibitor. Even low doses of this inhibitor (5 μg/ml), when the