ceptor homology model.

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15:30 Poster 6

Glycosylation reactions of natural poliphenolic compounds

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Due to their antioxidant potential, many naturally occurring phenolic compounds play an important role in the protection against various diseases. Their biological properties and mode of action may be affected by O-substituents, e.g. the presence of sugar residues. However, the O-glycosylation methods for low-nucleophilic or hindered phenolic compounds are not always satisfactory in term of yield as well as their regio- and stereoselectivity. In the present work, a variety of ribosylation approaches have been studied for two poliphenolic compounds, a biologically significant flavone, quercetin (**1**), and resveratrol (**2**), a compound occurring in the skin of grapes and red wine. Ribosylation of quercetin with 1,2,3,5-tetra-O-acetyl-β-d-ribofuranose in the presence of tin tetrachloride, i.e. under conditions which were successful in synthesis of genistein 4'-O-ribosides [1], failed completely. Similarly, the use of *p*-toluenesulfonic acid as a catalyst did not result in the formation of quercetin ribosides. Some promising results came from ribosylation experiments performed in the presence of boron trifluoride – diethyl etherate. The reactions yielded a mixture of α- and β-ribosides of quercetin, and the study on their structures, ratio and isolation are in progress. In the case of resveratrol, glycosylation with tetraacetylribose and tin tetrachloride gave a complicated mixture of compounds, from which an interesting product, 4-C-α,β-riboside could be isolated in a moderate yield. The application of boron trifluoride – diethyl etherate for ribosylation of resveratrol increases the yield of O-ribosides, as it has been judged from our preliminary experiments.

Acknowledgements: This work was supported by the network "Synthesis, structure and therapeutic properties of compounds and organic substances".

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15:30 Poster 7

2-(1-Arylsulfonylpiperidin-2-yl)ethyl derivatives as 5-HT$_7$ receptor ligands: synthesis and their affinity for 5-HT$_{1A}$/5-HT$_{2A}$/5-HT$_7$/D$_2$ receptors

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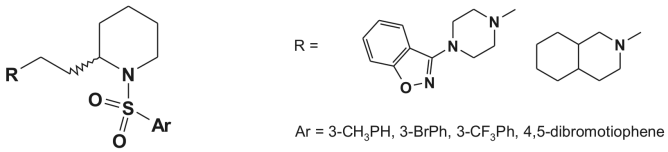
The affinity of several antidepressant and antipsychotic drugs for 5-HT$_7$ receptor, along with their distribution in CNS, suggested their involvement in the physiopathology of brain disorders. Indeed, some recent studies demonstrated direct involvement of 5-HT$_7$ receptors in depression, anxiety and mood diseases [1-3].

To better characterize the 5-HT$_7$ receptor, a new potent and selective compounds are required. Different research centers (among others our Department) are engaged in modeling, design, synthesis and structure-activity relationships studies of new 5-HT$_7$ ligands.

Here we present a series of 2-(1-arylsulfonylpiperidyn-2-yl)ethyl derivatives with various changes of aromatic substituent in arylsulfonylpiperidine moiety and modifications in terminal amine fragment.

In the competition binding studies of the investigated compounds, both selective 5-HT$_7$ receptor ligands and that with mixed 5-HT$_{2A}$/5-HT$_7$/D$_2$ pharmacological profile were found. The structure-affinity relationships for all the new derivatives are discussed.



This study was partly supported by the Ministry of Science and Higher Education (MNiSW), Grant No. N405 026 32/1743

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SAR studies of novel 5-HT$_7$R ligands with different spacers between aryl and amine moieties

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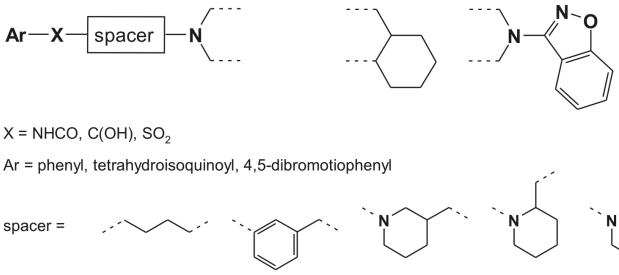
Since the discovery of the 5-HT_7 receptors and their potential therapeutic applications the search for potent and selective ligands has been initiated. More than 10 years of investigations resulted in finding a few selective antagonists like SB-269970-A and SB-656104-A. Several research groups and some pharmaceutical companies are active in this field, and a number of papers describing structure-activity relationship (SAR) [1] as well as some pharmacophoric models [2] have been published.

As a part of our research program directed towards the design and synthesis of potent and selective 5-HT_7 ligands we obtained new series of compounds with flexible and partly constrained spacer between aryl and amine fragment. Radioligand binding study showed that the investigated compounds reveal diverse affinity for 5-HT_7 receptor and selectivity over 5-HT_{1A}/5-HT_{2A}/D_2 sites. The structure-affinity relationships for all the new derivatives are discussed.



This study was partly supported by the Ministry of Science and Higher Education (MNiSW), Grant No. N405 026 32/1743

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15:30 Poster 9

The evaluation of tolterodine tartrate synthesis based on patent EP 0 325 574 B1.

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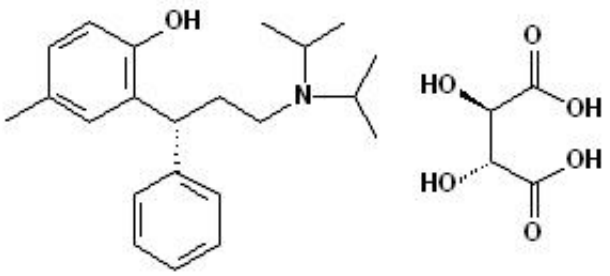
Tolterodine is used to relieve urinary difficulties, including frequent urination and inability to control urination. Tolterodine belongs to a class of medications called antimuscarinics. It acts by preventing bladder contraction. It is sold under the trade names Detrol and Detrusitol. DETROL Tablets are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

The chemical name of tolterodine is (R)-N,N-diizopropyl-3-(2-hydroxy-5-methylphenyl)- -3-phenylpropamine. It is delivered in pharmaceutical form as a tartrate. The empiric formula is $C_{26}H_{37}NO_7$ and the structural formula is represented below:



Synthesis of tolterodine tartrate was firstly revealed in patent EP 0325571 B1 published in 1989. It describes synthesis consisted of seven steps, which starts from p-cresol and trans-cinnamic acid. There is also a modification of first method. This alternative route contains eight synthetic steps. We found that patent description lacks a lot of very important information e.g. purity of intermediates or methods of their purification. It was not mentioned if products were obtained in crystalline, amorphous or oil form.

We decided to investigate both of synthetic routes to gain missing information and to evaluate their usefulness for application in industrial scale.

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Effect of selol on the opioids activity in vincristine induced hyperalgesia.

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The development of vincristine model of chemotherapeutic-induced painful toxic neuropathy provides an opportunity to investigate mechanisms involved in this form of neuropathic pain.

We examined (1) the effect of the opioid receptor agonists and (2) the effect of organoselenium compound (selol), on antinociceptive action of opioid agonists, morphine, fentanyl as well as ago-antagonist with potent analgesic activity, buprenorphine, - in vincristine neuropathic pain model. The changes in pain thresholds were determined using mechanical stimuli - the modification of the classic paw withdrawal test described by Randall-Selitto. Daily administration of VIN (70 μg/kg, iv) resulted in progressive decrease of pain threshold.

In conclusion, the results of present paper suggest, that selol significantly increases analgesic activity of opioids in vincristine model of chemotherapeutic-induced painful toxic neuropathy. This observation can be clinically relevant since selol possess anticancer activity. Therefore, concomitant administration of selenium and opioids may be benefitial in terminal neoplastic states.