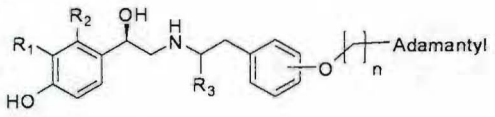


Fig. 1

Some compounds exhibit good potencies and duration of action in the reversion of acetylcholine-induced bronchoconstriction model in Guinea-Pig.

The effect of the adrenergic head, α-amino substitution and position of attachment of the adamantyl group on activity/duration will be discussed.

REFERENCES

1. J. Med. Chem. XXXX, *XXX*, 000-000. DOI: 10.1021/jm100068m
2. J. Med. Chem. XXXX, *XXX*, 000-000. DOI: 10.1021/jm100326d

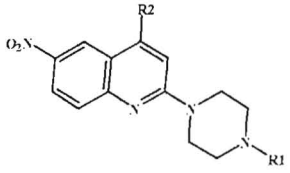
POSTER COMMUNICATIONS - **PC.389**

WHY *N*-4'-METHYLNITROQUIPAZINES POSSESS MUCH LOWER AFFINITY THAN NONMETHYLATED NITROQUIPAZINES

Z. Chilmonczyk[1,4], M. Jarończyk[1], I. Sylte[2], M. Gabrielsen[2], G. Nowak[3], A. J. Bojarski[3], A. P. Mazurek[1], G. Karpińska[1], F. Pluciński[1]

[1] National Medicines Institute, 30/34 Chełmska Street, 00-725 Warsaw, Poland. [2] Molecular Modelling Group, Medical Pharmacology and Toxicology, Institute of Medical Biology, Faculty of Health Sciences, University of Tromsø, N-9037 Tromsø, Norway. [3] Department of Medicinal Chemistry, Institute of Pharmacology Polish Academy of Sciences, Smętna 12 Street, 31-343 Kraków. [4] University of Rzeszow, Institute of Nursing and Obstetrics, Warzywna 1, 35-959 Rzeszów, Poland

Nitroquipazine (**1a**, R1 = R2 = H) possess much higher affinity to serotonin transporter (SERT) than quipazine (K_i = 0.17 nM and 30 nM, respectively [1]). That also concerns other derivatives of nitroquipazine bearing substituents at the aromatic rings and possessing nanomolar affinity to SERT [1,2] (for instance **1b**, R1 = H, R2 = Cl, K_i = 0.03 nM [2]). However, when methyl or ethyl substituent is introduced at N-4' nitrogen the affinity drops dramatically (**1c**. R1 = CH_3, R2 = Cl, K_i = 17 nM [2]; **1d**. R1 = CH_3, R2 = H, K_i = 1300 nM [3]; **1e**. R1 = C_2H_5, R2 = H, K_i = 86 nM [3]; **1f**. R1 = *n*-C_3H_7, R2 = H, K_i = 495 nM [3]).



1a-1f

To explain the impact of an alkylation on the SERT affinity we performed *ab initio* (Hartree-Fock 6-31** calculations on N-4'-protonated 6-nitroquipazine and N-4'-methyl-6-nitroquipazine. Two low energy conformations have been identified for each compound: with piperazine ring in a chair conformation and with piperazine ring in a boat conformation. In the latter conformation N-4'-hydrogen atom formed intramolecular hydrogen bonding with quinoline nitrogen atom. Calculations of molecular electrostatic potential for all conformations revealed substantial differences in charge distribution between methylated and nonmethylated compounds explaining different accessibility N-4'-hydrogen atom for binding with Asp98 residue in SERT. The results were confirmed by docking of the compounds to a SERT model.

This study was supported by a grant PNRF-103-AI-1/07 through the Norwegian Financial Mechanism.

REFERENCES

1. Lee B.S., Chu S., Lee B.C., Chi D.Y., Choe Y.S., Jeong K.J., Jin C. Synthesis and binding affinities of 6-nitroquipazine analogues for serotonin transporter. Part I. *Bioorg. Med. Chem. Lett.* **10**, 1559 (2000).
2. Moon B. S.,, Lee B. S., Chi D. Y. Synthesis and binding affinities of 6-nitroquipazine analogues for serotonin transporter. Part 4: 3-Alkyl-4-halo-6-nitroquipazines. *Bioorg. Med. Chem.* **13**, 4952-4959 (2005).
3. Chilmonczyk Z., *et al.* Unpublished results.

POSTER COMMUNICATIONS - **PC.390**

COMPUTER-AIDED DRUG DESIGN OF COMPETITIVE INHIBITORS OF L-DOPA-DECARBOXYLASE, A TARGET FOR THE TREATMENT OF PARKINSON'S DISEASE

Daidone F.[1], Montioli R.[2], Paiardini A.[1], Macchiarulo A.[3], Pascarella S.[1], Pellicciari R.[3], Bossa F.[1], Voltattorni C.[2]

[1] Department of Biochemical Sciences "A. Rossi Fanelli", University of Rome "La Sapienza"; [2] Department of Life and Reproduction Sciences, University of Verona; [3] Department of Drug Chemistry and Technology, University of Perugia

Parkinson's disease (PD) is a neurodegenerative condition involving the loss of dopaminergic neurons of the *substantia nigra*; its main symptoms are muscle rigidity, bradykinesia and akinesia (1).

Modern treatment of PD is based on the administration of l-DOPA, which is transformed by the pyridoxal-5'-phosphate (PLP)-dependent enzyme l-DOPA decarboxylase (DDC) into dopamine in dopaminergic neurons (1). However, only 1-5 % of l-DOPA reaches the brain, while the rest is metabolized by the peripheral DDC, causing various side effects. In order to increase central concentration of l-DOPA and prevent its side effects, a DDC-inhibitor (e.g. Carbidopa) that does not pass the blood-brain barrier, is co-administered (1). Unfortunately, Carbidopa is not selective for DDC, but reacts irreversibly with both free PLP-cofactor and other PLP-dependent enzymes, causing diverse side effects (2,3).