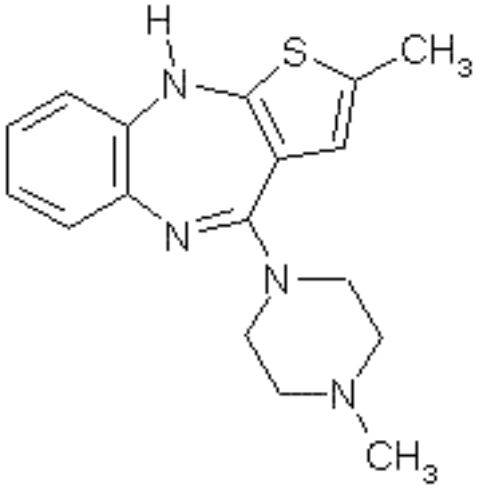

I

is an atypical antipsychotic drug with a high affinity for serotonin ($5HT_{2A/2C}$), dopamine (D_{1-4}), muscarinic (M_{1-5}), histamine H_1, and adrenergic α_1 receptors [1- 2]. Olanzapine is indicated for the treatment of patients with schizophrenia and psychosis of a schizoaffective nature.

We have developed a sensitive and selective HPLC method with electrochemical detection to determine the concentration of olanzapine in human plasma. The analysis was carried out on a reversed-phase column (Symmetry C18, 150 x 4.6 mm I.D., 5 µm) using a mixture of 0.06 M ammonium acetate (pH 5.90), acetonitrile and methanol (40:41:37, v/v/v) as the mobile phase. The flow rate was 0.69 mL/min. The detection voltage was + 0.6 V and the cell and column temperature were 36°C. The drug and internal standard (clozapine) were isolated from plasma using liquid-liquid extraction with ethyl acetate. The mean recovery of olanzapine and internal standard were about 90% and 82%, respectively. Ascorbic acid was added to the samples to inhibit degradation of olanzapine during extraction and storage. The lower limit of quantitation for the assay was established at 0.313 ng/mL. Repeatability, intermediate precision and accuracy were satisfactory.

The method for the assay of olanzapine in human plasma is sufficiently sensitive to apply during the pharmacokinetic and bioequivalence studies of this drug.

[1] J. T. Callaghan, R. F. Bergstrom, L. R. Ptak, C. M. Beasley, Clin.Pharmacokinet., 37 (1999) 177.

[2] O. V. Olesen, K. Linnet, Ther.Drug Monit., 21 (1999) 87

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New serotonin receptors ligands in the group of 8-acylamide derivatives of 1,3-dimethyl-7-[(4-phenyl- piperazin-1-yl)-alkyl]-1H-purine-2,6-(3H,7H)-dione

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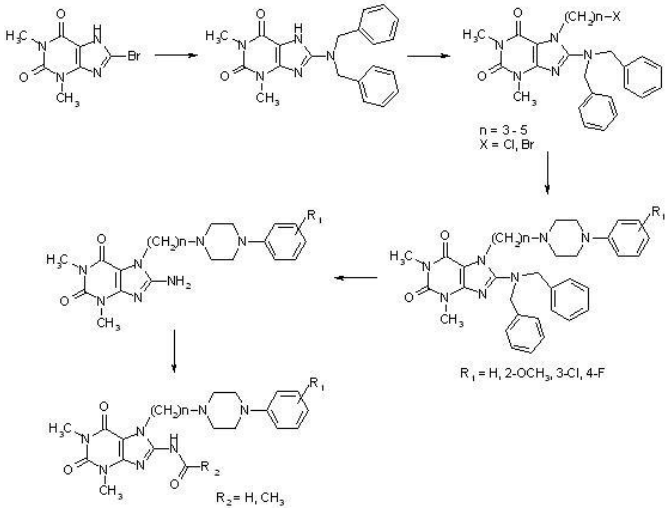
It is known, that many serotonin receptors ligands, especially 5-HT1A and $5\text{-}HT_{2A}$, posses antidepressant, anxiolitic and antipsychotic activity. As we reported in our previous paper [1] several 8-alkoxy derivatives of 1,3-dimethyl-7-[(4-phenylpiperazin-1-yl)-alkyl]-1*H*-purine-2,6(3*H*,7*H*)-dione have shown moderate to high affinity for $5\text{-}HT_{1A}$ (K_i = 11-19 nM), $5\text{-}HT_{2A}$ (K_i = 15-253 nM) and $5\text{-}HT_7$ (K_i = 51-83 nM) receptors, depending on the structure of moiety in the 7 position of 1*H*-purine-2,6(3*H*,7*H*)-dione. In our further studies in a group of 8-amino derivatives of 1,3-dimethyl-7-[(4-phenylpiperazin-1-yl) -alkyl]-1*H* -purine -2,6(3*H*,7*H*) -dione we have found out, that replacing the alkoxy substituent in the 8 position with amino substituent strongly decreases affinity for $5\text{-}HT_{2A}$ and $5\text{-}HT_7$ receptors, but enhances affinity and selectivity for 5-HT1A ones. In order to determine the influence of moiety in 8 position of 1*H*-purine- 2,6(3*H*,7*H*)-dione on the affinity for serotonin receptors we designed and synthesized 1,3-dimethyl-7 -[(4-phenylpiperazin-1-yl) -alkyl]-1*H*-purine -2,6(3*H*,7*H*)-dione derivatives possessing 8-acylamide substituent (Scheme 1).



The new 8-acylamide analogues are under pharmacological trials. The structure-activity relationship will be discussed.

[1] G. Chłoń-Rzepa, P. Żmudzki, P. Zajdel, A.J. Bojarski, B. Duszyńska, A. Nikiforuk, E. Tatarczyńska, M. Pawłowski: Bioorg. Med. Chem. 2007, 15, 5239-5250

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Synthesis and serotonin receptors activity of new purine-2,6-dione derivatives with arylpiperazinylalkoxy moieties

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For several years much attention has been focused on the functional importance of serotonin receptors in the pathogenesis of neuropsychiatric and other diseases. Among many classes of serotonin recep-