AFFINITIES FOR α_1-AR/5-HT$_{1A}$ RECEPTORS AND WATER SOLUBILITY EVALUATION OF PHENYLPIPERAZINE PHENYTOIN DERIVATIVES

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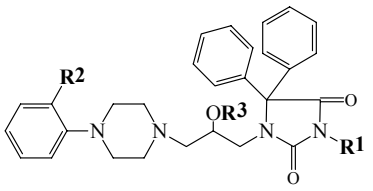
During our previous investigation to search for new antiarrhythmic agents, compound **AZ-99** was obtained (**Fig.1**, **R**^{1}=C_2H_5, **R**^{2}=H, **R**^{3}=H) as amine derivative of phenytoin [1].This compound possesses structural similarities to known α_1-adrenoceptor antagonists [2] and has shown hypotensive as well as antiarrhythmic activity in rats and significant affinities for α_1- and α_2-adrenoceptor. Bad water solubility of compound **AZ-99** restricted its pharmacological properties. As chemical modification of this, a series of new compounds were synthesized (**Fig.1**)



R1= CH 3, CH 2COOCH 3
R2=H, OC 2H5, F
R3=H, COCH 3

Fig.1

The obtained compounds were evaluated on their affinities for α_1- and α_2-adrenergic and 5-HT$_{1A}$ serotoninergic receptors in radioligand binding assays. Selected compounds were assessed on their affinity and selectivity for α_1-adrenoceptor subtypes in functional bioassays. Water solubility of the compounds was tested experimentally using UV-spectroscopy for evaluation of compounds concentration. Furthermore, theoretical prediction of the water solubility was carried out by the use of different computational methods. Results of theoretical and experimental determination of compounds solubility were compared and an influence of solubility on pharmacological properties was circumscribed and graphically displayed. The most promising compound (**Fig.1**, **R**^{1}=CH_3, **R**^{2}=OC_2H_5, **R**^{3}=H) with highest affinities for 5-HT$_{1A}$ and α_1-adrenergic receptors showed the highest water solubility, too.

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[1] Dyląg T., Zygmunt M., Maciąg D., Handzlik J., Bednarski M., Filipek B., Kieć-Kononowicz K., *Eur. J. Med. Chem*., **2004**, 39, 1013-1027.
[2] Bremner J.B., Cobam B., Griffith R., Groenewoud K. M., Yates B. F., *Bioorg.Med.Chem*., **2000**, 8, 201-214.