EVALUATION OF ANTIDEPRESSANT- AND ANXIOLYTIC-LIKE ACTIVITY OF DUAL 5HT$_{1A}$/5-HT$_7$ RECEPTOR LIGANDS BASED ON PURINE-2,6-DIONE SCAFFOLD

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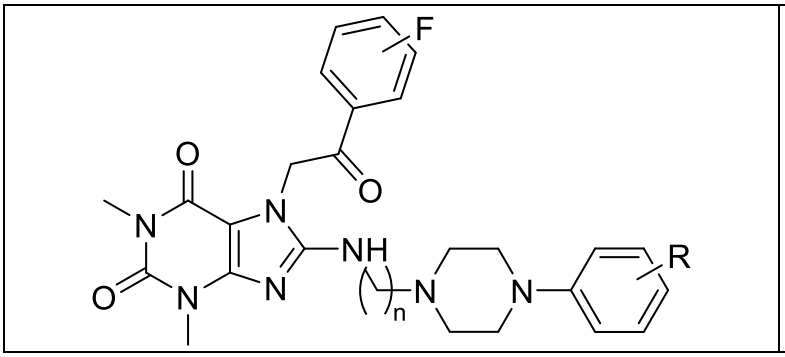
Fluorinated drugs constitute groups of atypical antipsychotics and antidepressants with a wide range of pharmacological mechanisms of action. The unique properties of fluorine, such as its high electronegativity, small size, and very low polarizability, impart various properties important in medicinal chemistry. Fluoro substitution will generally have enhanced physicochemical properties, binding interactions, and receptor selectivity of molecules. Our studies on a group of a long-chain arylpiperazines (LCAPs) class containing purine-2,6-dione scaffold as the terminal fragment revealed that some of them were 5-HT$_{1A}$/5-HT$_7$ receptor ligands with a diverse functional ago/antagonist profile [1, 2]. In the current study, we designed and synthesized a new series of derivatives containing fluorine substituent in a purine-2,6-dione scaffold. The new compounds were tested on affinity and intrinsic activity profiles for 5-HT$_{1A}$ and 5-HT$_7$ receptors.



2-F,3-F,4-F
n = 2-4
R = -H, 2-OCH$_3$, 3-Cl

The most active compound **Az-580** (7-(2-(3-fluorophenyl)-2-oxoethyl)-8-((4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)amino)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione) was a potent dual 5-HT$_{1A}$/5-HT$_7$ receptor ligand (K_i = 1.4 nM and 14.0 nM, respectively). In intrinsic activity studies, the compound showed antagonist properties, especially the 5-HT$_{1A}$ (K_b = 0.26nM) compared to the reference (NAN-190 K_b = 0.22nM). Compound **Az-580** in preclinical studies revealed antidepressant-like and anxiolytic-like properties. In FST compound was active at 10 mg/kg but in the Vogel test, at the dose of 3 mg/kg.

1. Partyka, A. et al. Antidepressant-like activity and safety profile evaluation of 1*H*-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione derivatives as 5-HT$_{1A}$ receptor partial agonists. *PLoS One*, 2020, 15, e0237196.
2. Zagórska, A. et al. Synthesis and biological evaluation of 2-fluoro and 3-trifluoromethyl-phenyl-piperazinylalkyl derivatives of 1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione as potential antidepressant agents. *J. Enzyme Inhib. Med. Chem.* 2016, 31, suppl. 3, 10-24.