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Crystal and molecular structure of the phenylpiperazine derivative of 5-methyl-5-phenylhydantoin with activities towards GPCRs: α_1-adrenergic/serotonin 5-HT_{1A} and 5-HT_7

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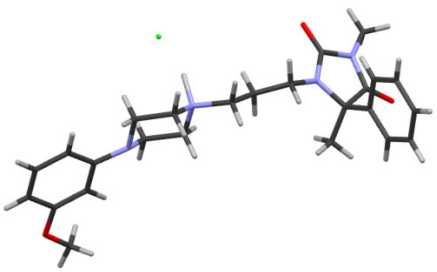
Recent studies have indicated a usage of α_1-adrenergic receptors (α_1-AR) antagonists in the treatment of arrhythmia, asthma or diabetes. The adrenergic receptors are the earliest identified of the G-protein coupled receptors (GPCRs).The serotonin 5-HT receptors are another group of GPCRs that participate in various physiological and pathophysiological processes within brain. 5-HT_{1A} receptor belongs to the largest class of 5-HT_1 receptors which are the earliest investigated group in the treatment of anxiety and depression. The 5-HT_7 receptor is involved in thermoregulation, circadian rhythm, learning, memory and sleep. This receptor may be a useful target in the treatment of depression [1].

Phenylpiperazine derivatives of hydantoin were previously identified as antiarrhythmic agents with moderate activity and low selectivity at α_1- and α_2-adrenoceptors. The interest in phenylpiperazine derivatives has increased for last two decades due to their interactions with α_1-adrenergic and serotonin 5-HT_{1A} and 5-HT_7 receptors, therefore their selectivity is a topic question.

In this report, we present results of the crystal structure analysis of 5-methyl-5-phenyl-1-(3′-(4-(3-methoxy-phenyl)piperazine)-propyl)-hydantoin. Crystals were obtained for hydrochloride of this compound. The nitrogen atom of piperazine is protonated and forms the hydrogen bond with chloride anion. The molecule of investigated compound adopts extended conformation. The crystal network in the studied structure can be characterized by C-H···O and C-H···N intermolecular interactions.



The geometry of this molecule was studied in the aspect of pharmacophore models in analysis of interactions with GPCRs: the Barbaro's model for phenylpiperazine antagonist of α_1-AR [2], the Lepalieur's model for an antagonist of 5-HT_{1A} [3] and model of 5-HT_7 antagonists elaborated by Bojarski's