INTERMOLECULAR π-π INTERACTIONS IN STRUCTURES OF ORGANIC COMPOUNDS WITH THEOPHYLLINE FRAGMENT

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Non-covalent interactions between aromatic rings play a significant role in the crystal structure stabilisation, formation of protein-ligand complexes or intercalation of ligands into DNA [1]. Commonly observed types of interaction are π-π and stacking interactions. They occur when the contribution to the energy of the π electrons and σ electron framework attractive interactions exceeds the contribution of the π electron cloud repulsion of both interacting π systems [2]. Stacking is a specific type of π-π interaction, propagating continuously along the defined crystallographic direction, which is perpendicular to the surface of the interacting aromatic rings. Both types of interaction require a proper mutual arrangement of aromatic fragments. The most common arrangement is one consisting of parallel rings separated by a distance of about 3.2 - 3.5 Å [3].

Theophylline (Fig. 1) and its derivatives are one of the most common drugs used in the treatment of asthma and chronic obstructive pulmonary disease (COPD). The explanation for the observed therapeutic effect is still uncertain, however many molecular mechanisms were already proposed. Theophylline is responsible for the non-selective inhibition of cyclic nucleotide phosphodiesterases, which causes an increased concentration of the cyclic nucleotides: AMP and GMP. This results in a relaxation of the airway smooth muscle and an anti-inflammatory effect, but also unwanted side effects such as: nausea, headache or cardiac arrhythmia. Theophylline is also known as an adenosine receptor antagonist, presumably indirectly taking part in prevention of bronchoconstriction. Cardiac arrhythmia and stimulation of the central nervous system are the side effects of the mentioned antagonism [4].

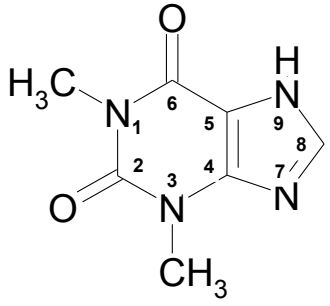

Fig. 1. Scheme of the theophylline molecule.

In our investigation on selected C-8 and N-9 substituted theophylline derivatives, crystals of three compounds were obtained and their structures were determined. During the structure analysis it was observed, that the main forces stabilising each crystal structure are π electron interactions between the theophylline fragments as well as weak hydrogen bonds. Each of the investigated theophylline derivatives contain an additional aromatic fragment: 3-chloro, 4-fluoro or 2-metoxy monosubstituted phenyl ring. Despite of the molecular similarities among selected compounds, different π-π

interaction motives were observed in the crystal structures. Formation of those π-π motives can be correlated to the specific electronic properties of the substituents attached to the above mentioned phenyl ring. In the crystal structure of the compound with metoxy group as substituent, the dimer is observed, formed by two π-π interacting theophylline fragments. In the two other structures, containing electron withdrawing halogen substituent attached to the phenyl ring, a more complex π-π motives are observed. Similar theophylline dimers are also formed, but this system additionally interacts, on both sides, with the phenyl ring of neighbouring molecules. In case of compound with chlorine substituted phenyl ring, the described interaction is enriched by the weak C-H···Ph hydrogen bond, closing the whole motive on both sides.

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