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Mini Review

Why the xanthine derivatives are used to study of P-glycoprotein-mediated multidrug resistance in L1210/VCR line cells

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Abstract. There is generally well known that various xanthines occur frequently in natural products, e.g. black coffee, black tea, green tea, natural dyes etc. Xanthine molecules are good tolerated and metabolised by organisms. Moreover, natural xanthines and/or sythesized xanthines may recall a lot positive affects (hemorheologic properties, anti-inflammatory properties, tracheal smooth muscle relaxant, positive chronotropic and central nervous system-stimulating, etc.) and may even induce a quantity of changes on the molecular level (inhibition of cyclic nucleotide phosphodiesterases, inhibition of the synthesis of tumor necrosis factor (TNF-α), cellular Ca^{2+} homeostasis, etc.). In our previous paper we showed that some xanthine derivatives (pentoxifylline and its derivatives) depress P-glycoprotein (P-gp) mediated multidrug resistance of the mouse leukemic cells. Other authors, first of all Sadzuka and co-workers, confirm this usefulness of long side substituted xanthines as biochemical modulators. However, the mechanism of molecular action of xanthine derivatives has not been clarified. One of the possible ways to chemosensitize the cancer cells is direct competiting in defence mechanism – inhibition of efflux pump (P-gp). Interaction of xanthine derivatives with binding site of P-gp is a question which could be solved by experiment; although, molecular modelling may clear up this matter. But, each dynamic and static program for molecular simulation of P-gp action is dividing on input variable, considering mechanistic view of insight drug transport.

Usefulness of substituted xanthines in reversal of multidrug resistance

Xanthine (3,7-dihydro-purine-2,6-dione) is a purine base found in most human body tissues and fluids and in other organisms. Substituted xanthines are compounds based on alkylated positions of the purine skeleton at N1, N3, N7 and C8 (Figure 1). Namely: caffeine, theophylline, theobromine, isobutylmethylxanthine (IBMX) and pentoxifylline (PTX), are favourite and often used in various experiments, moreover, they are very good tolerated by organisms.

These alkyl-xanthine derivatives were used in diverse applications, e.g. as: inhibitors of metabolism in sea urchin eggs (Nath and Rebhun 1976), suppressor of cytokine-induced NO production *via* inhibition of the expression of inducible NO-synthase mRNA in macrophages (Trajkovic et al. 1997), hemorheologic agents (Porter et al. 1982), improvers of circulatory failure in murine models of endotoxaemia (Wu et al. 1999), anti-inflammatory agents (Rao et al. 2005), nonspecific inhibitors of cyclic nucleotide phosphodiesterases (Nicholson et al. 1991). Moreover, alkyl-xanthine derivatives constitute nonspecific phosphodiesterase inactivators – they increase the cyclic adenosine monophosphate (cAMP) level in the cells thus inhibiting the synthesis not only of TNF-α, but also of IL-1L, IL-6, and IL-8 (Han et al. 1990; Semmler et al. 1993; Zabel et al. 1993; Neuner et al. 1994). However, other authors describe that xanthines have long been known for their effects on cellular Ca^{2+} homeostasis (Huddart and Syson 1975; Peterson et al. 1979; Deth et al. 1981; Jiang et al. 1984).

Xanthine derivatives have some pharmacological actions such as tracheal smooth muscle relaxant, positive chronotropic and central nervous system-stimulating ones, which widely varied with the xanthine skeleton substituents (Takagi et al. 1988; Miyamoto et al. 1989, 1992, 1993, 1995; Sakai et al. 1992; Sanae et al. 1995). Sadzuka and co-workers (1993, 1995, 1998, 1999, 2000, 2002, 2004) tested xanthine derivatives based on 1,7-alkylated-3-n-propyl xanthine skeleton as

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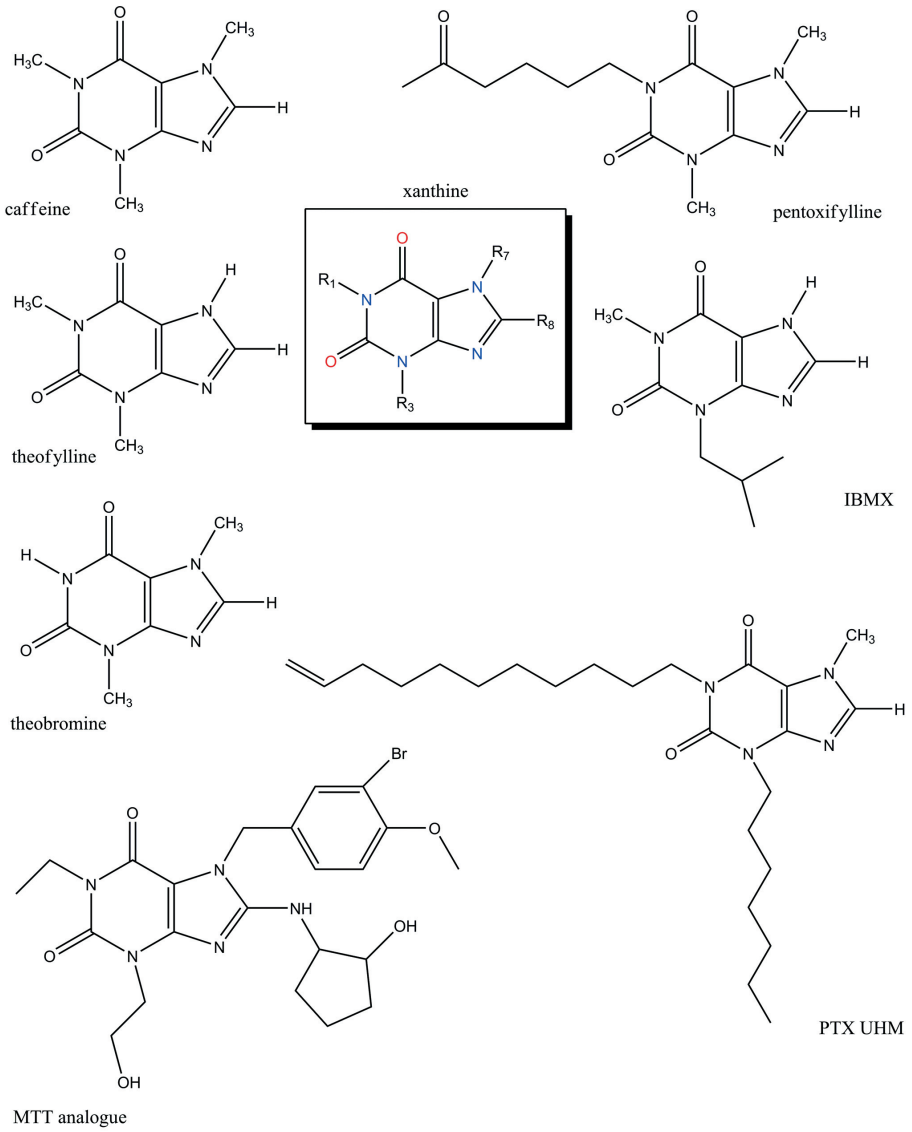

Figure 1. Xanthine skeleton (in the middle) and selected derivatives – substituted position R1, R3, R7 and R8. PTX-UHM, 1-undecylenyl-3-heptyl-7-methyl xanthine – compound with aliphatic carbohydrate chains; MTT analogue, 1-ethyl-3-(2-hydroxyethyl)-7-(2-bromo-4-methoxy-benzyl)-8-(2-hydroxy-cyclopenthylamino) xanthine – compound with non-aliphatic substituents.

biochemical modulators of DOX at P388 (leukaemic) and P388/DOX (resistance) cells, but the mechanism of action of these xanthine derivatives have not been clarified. Radiosensitization of lung carcinoma cells by IBMX were compared with other alkyl-xanthines (Malki et al. 2006). IBMX was more potent than the derivatives without 3-isobutyl substituent (Figure 1) in radiosensitization of normal lung epithelial cells and the lung carcinoma cells stably transfected with wild-type p53. IBMX increased p53 protein level more than caffeine in lung carcinoma cells stably transfected with wild-type p53. This suggests that 3-isobutyl-methylxanthine might function through a p53-dependent mechanism.

It is worth noticing that the ability of xanthine derivatives with long carbohydrate sidechain on N1 or/and N3 (e.g. PTX, PTX-UHM, Figure 1) to interfere in multidrug resistance (MDR) is not common for all tested xanthine derivatives (Dočolomanský et al. 2005) and could not be explained on the basis of known biological activities of substituted xanthines (such as inhibition of phosphodiesterase activity, inhibition of TNF-α synthesis, activation of calcium-induced calcium repase channels, etc.). MDR is a phenomenon when cancer cells became resistant to wide range of structurally and functionally various unrelated anticancer agents (Ling 1997). The MDR phenotype is observed in rodent and human

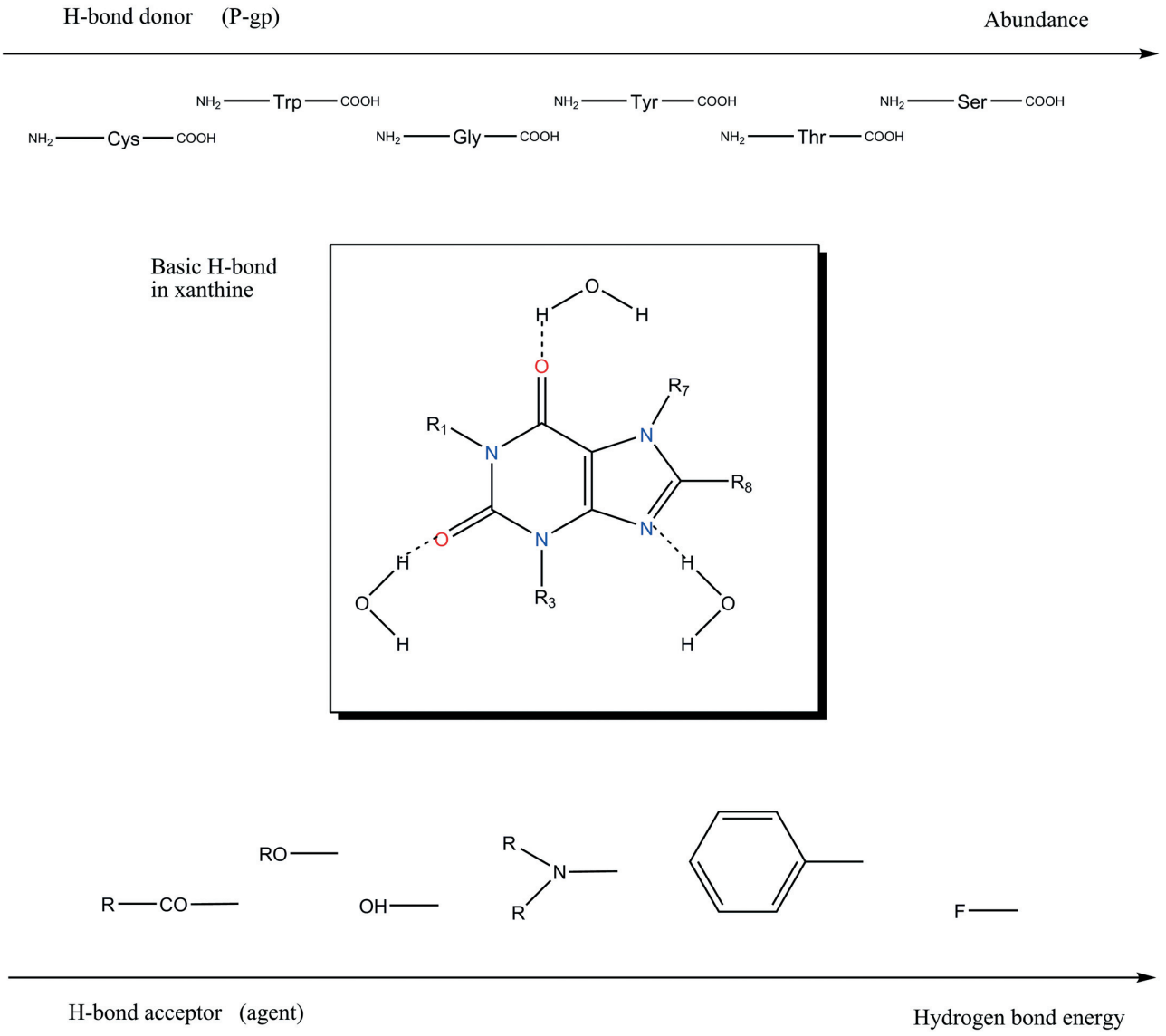

Figure 2. H-bond groups in substituted xanthine. Upper line: donor groups found in transmembrane amino acid sequences of P-gp in order of abundance. Lower line: acceptor groups in order of H-bond strength, in the middle is structure of possible H-bond in xanthine skeleton.

cell lines selected for resistance to a single anticancer drug (Litiman et al. 2001). This type of resistance is often caused by activity of drug efflux of ATP-dependent pump, called P-glycoprotein (P-gp, product of *mdr1* and *mdr3* genes). P-gp is an integral membrane protein (170 kDa) located in the cell plasma membrane and exports structurally diverse groups of substances out of cytoplasm (Kvačkajová-Kišucká et al. 2001; Wiese et al. 2001). However, the mechanism of MDR depression through partial or full suppression of P-gp transport activity by agents called chemosensitizers is not clear (Breier et al. 2005). Most chemosensitizers bind with transmembrane domain in P-gp, but steroids and flavonoids are new recently introduced chemosensitizers, which inhibit these transport proteins by binding with nucleotide-binding domain (Dayan et al. 1997; Consell et al. 1998).

Structure-activity relationship between substituted xanthines and target transporter

Structure-activity relationship studies attempt to identify complementary spatial features in ligand-receptor or xanthines-transporter interaction. The pharmacophore is defined as critical functional group in the ligand that is

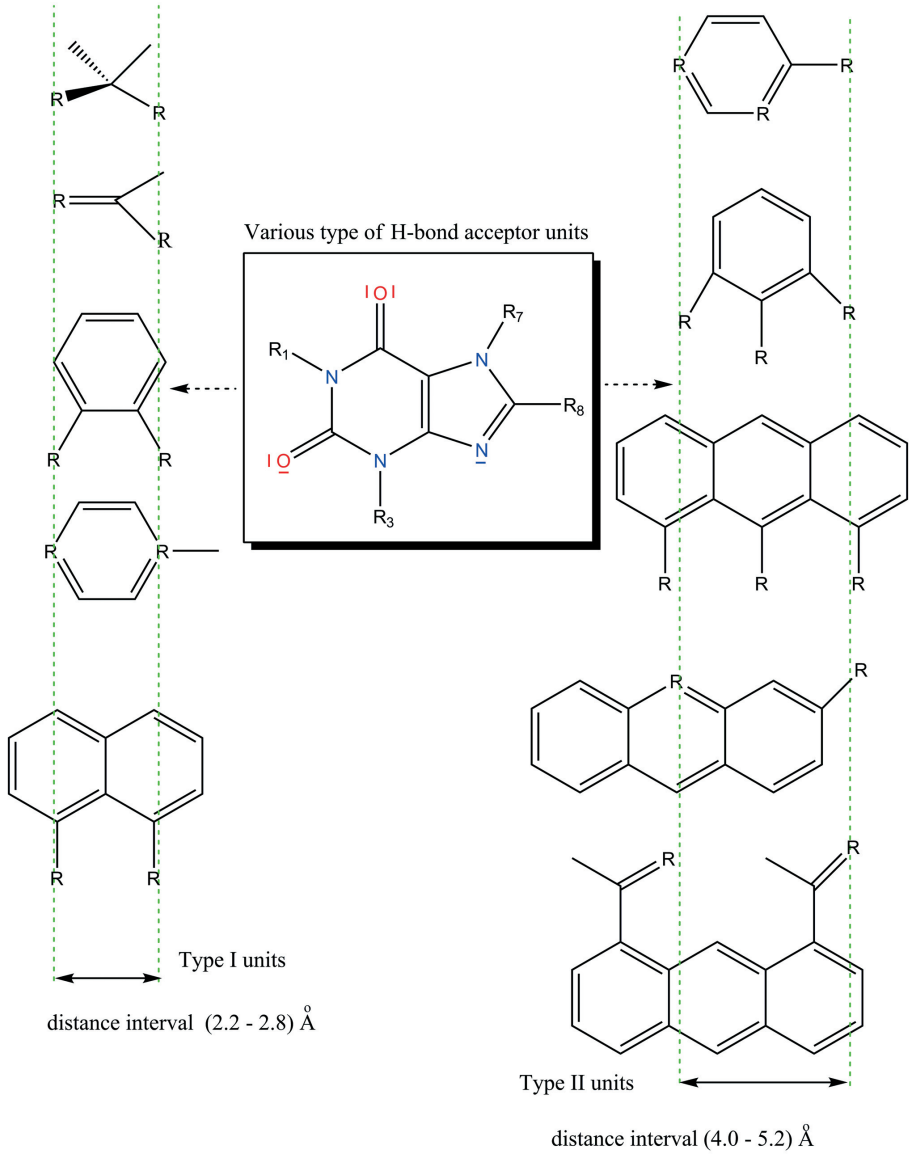

Figure 3. H-bond acceptor patterns observed in P-gp substrates. In the middle: substituted xanthine skeleton with possible free electron pairs could satisfy type I or type II. Type I (2.5 ± 0.3Å), two electron donor units; type II (4.6 ± 0.6Å, outer groups), three electron donor units; R, heteroatoms or substituents.

responsible for creating biological response (Stouch et al. 2002). A lot of information on substrate and P-gp interactions has been gathered in the late 1970's and they are based on multiple linear regression using a variable number of descriptors, e.g. lipophilicity (Penzotti et al. 2002), H-bond ability (Klopman et al. 1997; Ecker et al. 1999), molecular weight, size, and surface area (Eytan et al. 1999; Lentz et al. 2000; Kupsáková et al. 2004), unsaturated rings (Zamora et al. 1988), etc.

Various attempts have been made to find a common set of structural features required for substrate to interact with P-gp. First, some experiments suggested the requirement of a basic nitrogen atom and two planar aromatic domains (Pearce et al. 1989). However, later observation showed that basic nitrogen is not essential. The nitrogen occurs in imines (-N=, pyroles, imidazoles and pyrimidines) and in substituted amines (-NR2) or amides; but, only tertiary and quaternary amines and N-methyl amides seem to be involved in an interaction with P-gp. The second, cluster of electron donor groups (H-bond acceptors) were observed in compounds, which are known to be substrates or modulators of P-gp (e.g. electronegative atoms O, N, S, or F, Cl;

unshared electron pair; or unsaturated system with a π-electron orbital) (Seelig et al. 2003) (Figure 2). The third, spatial distances among various electron donors (Seeleig 1998; Pajeva et al. 2002; Penzotti et al. 2002; Globisch et al. 2006) are resulted into two types of pattern. The type I units are formed by two H-bond acceptor groups with a spatial separation 2.5 ± 0.3Å. Type II units are formed either by three H-bond acceptor groups separated from each other by 2.5 ± 0.3Å, with a spatial separation of the outer two acceptor groups of 4.6 ± 0.6 Å; or by only two H-bond acceptor groups with a spatial separation 4.6 ± 0.6 Å (Figure 3). Calculated spatial distances among electron donor groups in the selected xanthine derivatives homologate them to the type of a pattern I unit and II unit (Dočolomanský et al. 2009). Recently, a 2.5 nm resolution structure of P-gp was obtained by electron microscopy and single-particle image analysis (Rosenberg et al. 1997). In the P-gp molecule there is a large central pore, ~5 nm in diameter, which is closed at the inner (cytoplasmic) side of the plasma membrane (Bosch and Croop 1996). The aim of research is to reveal the putative role of the interaction of some chemosensitizers with the lipid phase in the mechanism of drug resistance reversal caused by these compounds. The interactions of MDR modulators with phospholipid liposomes and multilamellar lipid structures were studied using fluorescence spectroscopy, absorption spectroscopy and differential scanning microcalorimetry (Ford et al. 1989).

The interactions of transported drugs with the lipid bilayer and P-gp through a solvation exchange mechanism (Omote and Al-Shawi 2006) were postulated by molecular dynamic (MD) simulation and drug transport was illustrated in detail. Using MD simulation they predict important parameters (H-bond interaction energies) that are not directly measurable and provide a compelling link between the rate of transport and the H-bonding potential of the substrates. However, this model goes beyond descriptive and provides new mechanistic insight into drug transport (Seelig 2006).

Substituted xanthines by long aliphatic side chain fulfill above constellate molecular model as modulators or chemosensitizers, but mechanism of multidrug resistance influencing is not resolved yet.

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