CONCLUSIONS

The dissertation thesis contributes to detail knowledge of the metabolism, transport and anticancer effects of classical taxanes (paclitaxel and docetaxel) as well as their novel synthetic analogs (SB-T-1103, SB-T-1214 and SB-T-1216). The most important results concerning studies on these anticancer drugs are summarized as follows:

- Detail metabolism of paclitaxel and docetaxel was estimated in human, rat, pig and minipig liver microsomes. The metabolism of docetaxel was the same in all four tested species. Drug was metabolized mainly to hydroxydocetaxel and two minor hydroxyoxazolidinones A and B. Despite various similarities between human and pig metabolism of paclitaxel, the profile of paclitaxel metabolites in the studied species was different and main human metabolite 6α-OHP remains uniquely human one. The other new metabolites of paclitaxel were revealed, specifically di-OHP in rats and a new hydroxypaclitaxel in rats, pigs and minipigs, where this metabolite is the main metabolic pathway of paclitaxel.

- The major enzymes responsible for oxidative metabolism of paclitaxel are CYP2C8 and CYP3A4 in humans and CYP3A1/2 in rats. Docetaxel is oxidatively metabolized by CYP3A family in humans as well as in rats. The oxidation metabolism of classical taxanes leads to detoxification of these chemicals and their excretion from organism.

- Metabolic profile and interspecies variability in the metabolism of three novel taxanes (SB-T-1103, SB-T-1214 and SB-T-1216) with higher activity toward tumour cells than classic taxanes. These new generation taxanes are potential drugs for more succesful cancer therapy. The major enzyme responsible for main metabolic pathways of novel taxanes was revealed to be CYP3A4.

- The inhibition of classical taxanes metabolism by phenolic antioxidants was estimated. Among tested antioxidants, stilbene resveratrol was the efficient inhibitor of paclitaxel metabolism. The formation of the main human paclitaxel metabolite 6α-OHP was also inhibited by fisetin, quercetin and morin. Metabolism of docetaxel was inhibited only slightly by quercetin.

- Cytotoxicity and transport of paclitaxel, docetaxel and novel taxanes SB-T-1103, SB-T-1214 and SB-T-1216 in adriamycin-sensitive (MDA-MB-435) and resistant

(NCI/ADR-RES) human breast cancer cells were investigated. Up to 6-fold higher paclitaxel and docetaxel levels were determined in MDA-MB-435 cells than in resistant NCI/ADR-RES cells, which show out different mRNA expression levels of P-gp involved in multidrug resistance. In contrast, both cell lines absorbed similar amounts of the novel taxanes. These new taxane analogs also show out much higher cytotoxicity against resistant NCI/ADR-RES cells than classical taxanes and they seem to be potential drugs for therapy of taxane-resistant tumours.

- Synthetic derivatives of naturally occurring flavonoids from the class of 4.6-dimethoxyaurons namely CB-284, CB-285 and CB-287 and 4-hydroxy-4-methoxyaurone (ML-50), proved to be efficient modulators of paclitaxel transport in P-gp highly expressing resistant human breast cancer cells. These agents might increase the efficiency of chemotherapy with paclitaxel in P-gp highly expressing and resistant breast tumours.

- Docetaxel was the efficient anticancer drug for T-cell lymphomas treatment upon repeated administration in rats. This drug was much more efficient than paclitaxel or the combined treatment with both drugs.
