Abstract
The aim of the present study was to investigate the influence of classic and atypical neuroleptics on the activity of rat CYP2C6 measured as a rate of warfarin 7-hydroxylation. The reaction was studied in control liver microsomes in the presence of neuroleptics, as well as in microsomes of rats treated intraperitoneally for one day or two weeks (twice a day) with pharmacological doses (mg/kg) of the drugs (promazine, levomepromazine, thioridazine, perazine 10, chlorpromazine, haloperidol 0.3, risperidone 0.1, sertindole 0.05), in the absence of the neuroleptics \textit{in vitro}. Some of the neuroleptics added \textit{in vitro} to control liver microsomes decreased the activity of CYP2C6. Sertindole and levomepromazine ($K_i = 25$ and $31$ µM, respectively) were the most potent inhibitors of the rat CYP2C6 among the drugs studied. Their effects were more pronounced than those of the other phenothiazines tested: thioridazine and chlorpromazine ($K_i = 88$ and $91$ µM, respectively), promazine and perazine ($K_i = 322$ and $341$ µM, respectively), risperidone ($K_i = 414$ µM) or haloperidol ($K_i = 606$ µM). The investigated neuroleptics – when given to rats \textit{in vivo} for one day or two weeks – did not produce any indirect effect on CYP2C6 via other mechanisms, except for levomepromazine, which increased the activity of the enzyme after 24-h exposure. Therefore, the direct inhibitory effect of levomepromazine on CYP2C6 may be attenuated by an indirect mechanism at the beginning of the neuroleptic therapy. In summary, the obtained results show direct inhibitory effects of some phenothiazine neuroleptics and sertindole on the activity of CYP2C6 \textit{in vitro} in rat liver microsomes. Considering relatively high pharmacological doses and therapeutic concentrations of phenothiazines, it seems that the inhibitory effect of levomepromazine (and other phenothiazines with $K_i$ values below 100 µM) found \textit{in vitro} may be of physiological and pharmacological importance \textit{in vivo}.

Key words: phenothiazines, haloperidol, risperidone, sertindole, CYP2C6, warfarin 7-hydroxylation, liver microsomes, rat, \textit{in vitro} study, chronic treatment