Abstract:
The aim of the present study was to investigate the influence of classic and atypical neuroleptics on the activity of rat CYP2A measured as a rate of testosterone 7α-hydroxylation. The reaction was studied in control liver microsomes in the presence of neuroleptics, as well as in microsomes of rats treated intraperitoneally (ip) 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 in vitro. Most of the neuroleptics added in vitro to control liver microsomes decreased the activity of the rat CYP2A. Chlorpromazine ($K_i = 11$ µM) was the most potent inhibitor of the rat CYP2A among the studied drugs, whose effect was more pronounced than that of the other tested phenothiazines ($K_i = 41–83$ µM), haloperidol ($K_i = 190$ µM) or sertindole ($K_i = 78$ µM). Risperidone was not active in this respect. The investigated neuroleptics when given to rats in vivo for one day or two weeks – did not produce any indirect inhibitory effect on CYP2A via other mechanisms. The obtained results show direct inhibitory effects of phenothiazine neuroleptics on the activity of CYP2A in rat liver, which may be of physiological importance for the metabolism of testosterone, considering simultaneous inhibition of CYP2C11 and CYP3A by those drugs.

Key words: phenothiazines, haloperidol, risperidone, sertindole, CYP2A, testosterone 7α-hydroxylation, liver microsomes, rat, in vitro study, chronic treatment