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NIJAGAN CHAI-NGAM : STUDY OF THE EFFECT OF ACETOPHENONE ANALOGS ON BILE SECRETION IN RATS. THESIS ADVISOR: PAWINEE PIYACHATURAWAT, Ph.D., CHAIVAT TOSKULKAO, Ph.D., PRAYAD KOMARATAT, Ph.D., APICHART SUKSAMRARN, Ph.D. 144 p. ISBN 974-589-362-5

It has previously been reported that phloracetophenone or 2,4,6-trihydroxy acetophenone is effective in stimulating bile secretion. In relation to the abundance of naturally occurring acetophenone analogs and the fact that hepatobiliary secretion of xenobiotics depend upon chemical structure of the compounds, it is of interest to investigate the relationship between the chemical structure of acetophenone analogs and derivatives and their choleretic activities (SAR). In the present study, the choleretic activities of twenty compounds varying in substituent of H-atoms on the benzene ring of the acetophenone molecule and replacement of the keto group with other functional groups, were examined in adult male rats. Each compound was intraduodenally administered at a dose 50 mg/kgBW and bile samples were collected via a bile fistula for analysis of bile flow rate and bile acid, cholesterol and phospholipid concentration and output. Acetophenone analogs with hydroxy substituents induced hydrocholeresis with less cholesterol and phospholipid secretion. The increases in bile flow rate and bile salt secretion by the hydroxylated analogs were directly related to the number and position of hydroxy group on the benzene ring. In contrast to hydroxylated analogs, acetophenone analogs with methoxy and chloro substituents which had low to moderate choleretic activities produced more biliary lipid secretion, and the bile had a high lithogenic index. Likewise, the derivatives in which the keto group was replaced by either aldehyde or carboxylic acid, also had moderate choleretic activity. Among hydroxylated acetophenone analogs, 4-hydroxy-acetophenone and 2,4-dihydroxyacetophenone and 2,4,6-trihydroxyacetophenone induced the most potent hydrocholeresis, a high bile flow rate and low lithogenic index. Meanwhile the choleretic action of 2,6-dihydroxyacetophenone and 2,4,6-trihydroxyacetophenone were accompanied by decreases of plasma cholesterol.These hydroxylated compounds may have potential for development as therapeutic agents for treatment of cholestasis, dissolving gallstone, and lowering plasma cholesterol, respectively.

A relationship between choleretic action and hydrophobicity of the compounds was not found. However, the analogs which had free hydroxy groups and were more hydrophilic, induced more bile flow as compared to other analogs in the same group. These free hydroxy groups are suggested to be essential for hepatic biotransformation of compounds and also for choleretic activity. The results from this investigation provide a rational basis for selection, as well as development, of compounds, for therapeutic use to improve hepatic function.