QUANTITATIVE STRUCTURE-ACTIVITY STUDY OF INHIBITION OF BLOOD PLATELET AGGREGATION BY ASPIRIN DERIVATIVES

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The platelet-aggregation inhibitory abilities of aspirin and twenty-three ring-substituted derivatives have been investigated in vivo in the rabbit. Aggregation was examined in the Bryston HU aggregometer, using rabbit tendon collagen as aggregating agent, at one hour after oral dosing and at maximal inhibition. Lipophilicities were determined chromatographically at pH 1.1 on polyamide plates (Dearden, Patel & Tubby, 1974). It was found that the one-hour results could be fitted reasonably well by a quadratic equation:

$$\log (1/ED50) = 3.565 - 9.063\ R_M - 28.767\ R_M^2$$

$$n = 15,\ r = 0.846,\ s = 0.227$$

Inclusion of electronic and steric terms did not improve the correlation. Those compounds with log P values above about 2.5 showed no detectable inhibitory activity after one hour.

Maximal inhibition was investigated in order to test the computer model prediction (Dearden & Townend, 1976) that maximal potency should approach a maximum asymptotically as lipophilicity increases. It was found that the inhibitory effect increased to a maximum and then fell slightly as lipophilicity increased. This fall may be caused by one or more of a number of factors: (i) increased metabolism with increased in vivo residence time; we have found that salicylic acid is about 1000 times less active than is aspirin in inhibiting platelet aggregation; (ii) competition of the corresponding salicylic acid for the binding site; we have found that the more lipophilic the salicylic acid derivative, the more effectively does it prevent aspirin from inhibiting platelet aggregation (cf. Lefort & Vargaftig, 1977); (iii) poor aqueous solubility of the more lipophilic derivatives (cf. Flynn & Yalkowsky, 1972); (iv) preferential storage of lipophilic derivatives in adipose tissue.

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