ANTI-INFLAMMATORY POTENCIES OF SOME ASPIRIN DERIVATIVES: A QUANTITATIVE STRUCTURE-ACTIVITY STUDY

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Although hundreds of aspirin derivatives must have been synthesised and tested over the years, no quantitative study of the variation of anti-inflammatory potency with structure appears to have been made. We have examined aspirin and twenty-seven ring-substituted derivatives for anti-inflammatory potency in the rat-paw oedema test (Winter et al, 1962), and have measured the octanol-aqueous buffer, pH 1.1 partition coefficients on the AKUFVE apparatus (Davis & Elson 1974). Derivatives were carefully selected to give a wide range of physico-chemical properties, and all four substituent positions were utilised. A correlation of anti-inflammatory potency with lipophilicity gave:

$$\log(1/ED50) = 1.822 + 1.032 \log P - 0.195 (\log P)^2 \quad (1)$$

$$n = 28 \quad r = 0.812 \quad s = 0.243$$

It was noted, however, that the eight compounds containing 4-substituents showed low potency, and in fact appeared to lie on a second parabola displaced vertically from that on which all the other compounds lay. Removing such compounds from the correlation gave:

$$\log(1/ED50) = 1.958 + 1.029 \log P - 0.195 (\log P)^2 \quad (2)$$

$$n = 20 \quad r = 0.951 \quad s = 0.118$$

The eight 4-substituted compounds gave the equation:

$$\log(1/ED50) = 1.580 + 1.034 \log P - 0.207 (\log P)^2 \quad (3)$$

$$n = 8 \quad r = 0.934 \quad s = 0.146$$

which differs appreciably from equation (2) only in the constant term; this indicates that both groups of compounds (i.e. with and without 4-substituents) act at the same site, with some anomaly of 4-substitution giving rise to lower potency. It was considered likely that this effect was a steric reduction of drug-receptor interaction, and inclusion of the Verloop steric parameters L and B_2 for 4-substituents only gave the following correlation:

$$\log(1/ED50) = 2.285 + 1.031 \log P - 0.195 (\log P)^2 - 0.045 L_{(4)} - 0.244 B_{2(4)} \quad (4)$$

$$n = 28 \quad r = 0.966 \quad s = 0.113$$

Other workers have noted the difference in anti-inflammatory potency between 4- and 5-substituted salicylic acids (e.g. Hannah et al 1977) and have ascribed this to enhanced potency of the 5-derivative. However, our results, which were obtained using a range of compounds in which all substituent positions were utilised, make it clear that it is not 5-substitution that enhances potency, but rather it is 4-substitution that lowers potency, relative to all other substitution. This study thus emphasises the importance, from an interpretative point of view, of examining a carefully selected range of compounds rather than one or two.

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