SHORT COMMUNICATIONS

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An example of successful prediction of cholinesterase inhibitory potency from regression analysis

In studies of quantitative correlation techniques including the mathematical models of BRUICE *et al.*[1], FREE AND WILSON[2], BOČEK *et al.*[3] and KOPECKÝ *et al.*[4], or the free-energy related models of HANSCH AND FUJITA[5] or ZAHRADNÍK AND CHVAPIL[6], one of the primary goals is to predict accurately the biological or biochemical activity of a compound before it is even synthesized. Published examples of successful predictions are rare. FULLER *et al.*[7], however, have successfully predicted the inhibitory potency of two *N*-(phenoxyethyl)cyclopropylamine derivatives against monoamine oxidase (EC 1.4.3.4) using a modification of the HANSCH[8] model. This study reports a successful prediction of cholinesterase inhibitory potency of 1-decyl-3-(*N*-ethyl-*N*-methylcarbamoyl)piperidine hydrobromide using a mathematical model.

An application of the method of FREE AND WILSON[2] to the observed I_{50} (molarity of the compound effecting 50% inhibition) values of 12 alkyl substituted 3-carbamoylpiperidines has been previously published[9,10]. The inhibitory potencies of these moieties were measured against butyrylcholinesterase (acylcholine acylhydrolase, EC 3.1.1.8)[11,12], and the I_{50} values for 36 similarly substituted homologs in the series were calculated from the regression analysis.

In order to test the utility of this method of selecting compounds for synthesis and evaluation, a specific derivative was chosen for further study. It can be seen from Table I of refs. 9 and 10 that the most desirable choice of previously unsynthesized homologs from an inhibitory potency point of view is 1-decyl-3-(*N*-ethyl-*N*-methylcarbamoyl)piperidine hydrobromide, since all of the other 1-decyl derivatives had been synthesized and evaluated. Therefore, this compound was synthesized from nicotinic acid and methylethylamine using a sequence of reactions and procedures as previously described[11]; the product was crystallized from abs. ethanol and had a m.p. 160.5–161.5°. (Analysis. Found: C, 58.04; H, 10.16; Br, 20.58; N, 6.90. $C_{19}H_{39}BrN_2O$ requires: C, 58.30; H, 10.04; Br, 20.41; N, 7.16 (Analysis by Galbraith Laboratories, Knoxville, Tenn.).) The compound was evaluated for its cholinesterase inhibitory potency by the manometric method of BEASLEY *et al.*[11] at 37° using human plasma cholinesterase (Sigma Chemical Co., Type II: Pseudo)* and acetylcholine chloride as substrate. The I_{50} value for 1-decyl-3-(*N*-ethyl-*N*-methylcarbamoyl)-piperidine hydrobromide was found to be $0.98 \cdot 10^{-5} \pm 0.03 \cdot 10^{-5}$ M.

The I_{50} value of this compound may be calculated from Table II of refs. 9 and 10, and by using the expression

$$I_{50} = \mu + \Sigma \text{ group contributions}$$

The substitutions are $\mu^{**} = 70.84 \cdot 10^{-5}$ M, *N*-decyl group contribution at position

* This preparation was shown experimentally to possess identical enzymodynamic properties to Cholase (Cutter Laboratories, Berkeley, Calif.) which had been used in some of our earlier inhibition studies.

** The contribution to the activity from the parent part of the molecule; also, the overall average of the activities.

$R_1 = -70.51 \cdot 10^{-5}$ M, methyl group contribution at position $R_2 = 0.68 \cdot 10^{-5}$ M, and ethyl group contribution at position $R_3 = -0.23 \cdot 10^{-5}$ M. The calculated (predicted) I_{50} value is $0.78 \cdot 10^{-5}$ M (ref. 10) which is in good agreement with the observed value of $0.98 \cdot 10^{-5} \pm 0.03 \cdot 10^{-5}$ M.

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Department of Medicinal Chemistry,
College of Pharmacy,
University of Tennessee Medical Units,
Memphis, Tenn. 38103 (U.S.A.)

JAMES G. BEASLEY
WILLIAM P. PURCELL

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