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COMBO: NEW PRINCIPLES AND NEW METHODS FOR ANALYZING SYNERGISTIC AND ANTAGONISTIC DRUG COMBINATIONS IN ANTIVIRAL THERAPY.
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Our interest in the analysis of drug combinations arose from the work of this laboratory on synergistic interactions of dipyridamole and dideoxynucleosides (Szebeni, et al., PNAS 86:3842, 1989). We began by exploring enzyme kinetics-based models for drug interaction and derived a number of them that are particularly useful for analyzing this class of data. We then developed a computer program package (COMBO) for non-linear, weighted least squares fitting of experimental data to these models. In addition to formulations for pure synergy and antagonism (the "Robust Synergy" and "Robust Antagonism" models), COMBO permits analysis of simultaneous antiviral and toxic effects (the "Eff-Tox" model). COMBO operates in the MLAB (Civilized Software, Inc., Bethesda, MD) computing environment. Parameters reflecting synergy, potentiation, antagonism, and therapeutic index are obtained. Confidence limits and p-values on the parameters are obtained by a Monte Carlo algorithm. The approach programmed in COMBO has several additional useful features: (1) global parameters for potentiation, synergy, and antagonism are obtained; (2) the choice of data models is flexible; (3) all data points can generally be used (without censoring); (4) constant drug dose ratios are not necessary; (5) the choice of error structures is flexible; (6) statistical criteria for selection of outliers are generated. In the philosophy of its organization, COMBO can be thought of as a computer "tool box" for analysis of drug combinations. We have used it to evaluate data from several laboratories on different combinations active against HIV-1 (Bunow and Weinstein, Annals N.Y. Acad. Sci., in press). We gratefully acknowledge the advice of Dr. Larry R. Muenz on statistical aspects of this work.

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Antipicornavirus Activity of R 77975, a New Analog of R 61837 With Improved Spectrum and Potency

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The discovery and analysis of two groups of rhinoviruses exhibiting differential susceptibility to antiviral compounds allowed us to identify 17 screening serotypes, representative for all 100 serotypes. This development of a rational screening system contributed to the discovery of R 77975, or ethyl 4-[2-[1-(6-methyl-3-pyridazinyl)-4-piperidinyl] ethoxy] benzoate. The MICs required for R 77975 to inhibit the cytopathic effect (by 50%) of 8 (47%) or 12 (70%) of the 17 screening serotypes were 0.002 µg/ml (5.4 nM) and 0.020 µg/ml, respectively. The concentration needed to achieve 50% inhibition of logarithmic cell growth was 8.0 µg/ml. Overall, R 77975 is approximately 1000 times more active than its predecessor R 61837 against the human rhinoviruses. While R 61837 only displays its activity against rhinoviruses from antiviral group B, R 77975 is highly active against rhinoviruses of both antiviral groups. R 77975 also inhibits 50% of 15 enteroviruses at 0.7 µg/ml, whilst R 61837 was generally inactive against the same viruses. Like R 61837, R 77975 is a capsid-binding antiviral agent, neutralizing susceptible serotypes in a time- and concentration- dependent way. In case of rhinovirus Hank's, the serotype used in clinical trials, the original infectivity can only be regained using several rounds of organic solvent extraction to remove the drug bound to the viral particles.