Chapter 30. Quantitative Structure-Activity Relationships in Drug Design

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Introduction - This review covers new developments concerning the methodological aspects of quantitative structure-activity relationships (QSAR), the physicochemical/structural parameters employed, applications of QSAR approaches to various problems and the significance of the results in drug design. Particular emphasis has been placed on uses of QSAR approaches. Expansion of activity in this field has continued since the last Annual Reports review two years ago. The proceedings of two symposia have been published[1,2] and the second Gordon Conference on QSAR was held in 1977. The most widely used approach continues to be the linear-free energy related model.[3]

Methods - Several newer methods for correlating biological activities such as cluster analysis,[4] pattern recognition[5,6] and Fibonacci numbers[7] have been discussed. The DARC-PELCO[8] and the sequential simplex[9] procedures have been advanced as possible means of more rapidly approaching the most active drug congener. Molecular orbital (MO) indices[10] and calculations of lowest energy conformations have continued to draw interest.[11]

A set of molecular connectivity parameters was derived and used in correlating various molecular and physical properties. Biological data were also correlated and parabolic relationships between molecular connectivity parameters and biological activities were formulated. The method has the advantage that experimentally measured physico-chemical constants are not required.[12] To date, however, only one study has dealt with testing the correlations.[13]

The Free-Wilson (F-W) model and the modified version of Fujita and Ban has been carefully analyzed. The method has been extended to include combinations of continuous parameters (e.g. π, π^2, etc.) and F-W parameters, a concept that is equivalent to Hansch's idea of using indicator variables.[14] The F-W model has been limited by its inability to predict activities of congeners having substituents not present in the matrix. This limitation was due to the usually imprecise correlation of "de novo" constants with experimentally measured constants. Kubinyi has shown that a multiparameter correlation can be used to extend the applicability of the F-W model.[15]

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The theory of linear equations has been reviewed and difficulties in application to QSAR examined.[16] A method has been proposed for incorporating drug ionization in QSAR equations.[17] A bilinear model was formulated whereby lower activity congeners were related by a linear equation and the higher activity congeners by an asymptotic rather than a parabolic equation.[18,19] A method for applying the Hansch approach without the use of a computer was described. The procedure involves comparison of the potency order of a small initial set of compounds with that calculated for various parameter dependencies.[20] One limitation of the Hansch approach has been its inability to deal with different activities of stereoisomers. However, a means of incorporating stereoisomers into one equation has been devised whereby the physico-chemical constants of the groups on the chiral center are treated as independent variables.[21,22] Progress has also been made in reply to the criticism that the validity of regression equations are not evaluated by the synthesis and testing of new compounds.[23-25]

Parameters - Hansch and coworkers have updated their 1973 compilation of substituent parameters by adding 48 new substituents.[26] σ^0 values for 190 substituents have been determined from infrared spectroscopy.[27] Steric constants for 161 groups have been compiled.[28] Molar refraction (MR) and its use has been reviewed.[29] Some newer parameters were proposed as alternatives to log P in correlating biological data (e.g. solubility,[30] distribution,[31] and chromatographic R[32]). A hydrogen-bonding parameter was discussed.[33] Photoionization potential was used as an index for correlating the brain levels of psychotropic drugs.[34]

Log P continued as the important parameter. The most recent Pomona College output has over 10,000 measured log P's. Chromatographic techniques[35,36] and a solvent extraction method[37] for determining log P's were described. Methods for estimating log P were developed. The SCAP model predicted octanol-water log P with an average absolute deviation of 9%.[38] The hydrophobic fragmental constant, f, its derivation and additive nature was described.[39,40] Deviations between calculated and experimental values were attributed to conformational differences[41] or dimer formation.[42] The relationship of log P to surface area,[43] molecular volumes[44] and van der Waals volume[45] was discussed.

Applications of QSAR Approaches - Hansch and coworkers correlated the inhibition of dihydrofolate reductase (DHFR) from different organisms with physicochemical parameters in three compound series. These studies represented attempts to discern variations in enzyme characteristics. An indicator variable merged parallel sets of DHFR inhibition by dihydrotriazines from two distinct tumor cells.[46] Two equations were nec-

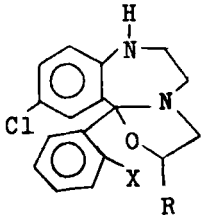
essary for correlating the inhibitory activities of pyrimidines, possibly because of species variations and because two separate sets of pyrimidines were investigated.[47,48] Two quinazoline QSAR equations differ significantly from each other in that the bacterial DHFR equation shows no dependence on substituent properties at position 6. These two quinazoline equations can be quantitatively compared since common congeners were used in the two enzyme studies.[48,49] Based on these results, a map of the active site of DHFR was constructed and specific areas of the map were described as hydrophobic, polar and sterically sensitive. The X-ray structure of methotrexate-bound DHFR was determined[50] and its characteristics differ from the map proposed by Hansch.

As with DHFR, interest in chymotrypsin centered on characterizing the active site environment. A single equation correlated the binding constants of stereoisomeric D- and L-amides acting as inhibitors and substrates, respectively, with MR terms.[22] The presence of the MR terms allowed the identification of three "pockets" as polar and not lipophilic areas. Further support for these descriptions was elaborated in an extensive study where sets of esters and amides were related to MR and not π.[51]

Studies on the binding of two sets of ligands to papain, another hydrolytic enzyme, demonstrated the importance of MR.[52] The X-ray structure, however, showed a bank of lipophilic amino acids near the cleft in papain. A separate set of substrates were designed to specifically explore this area, care being taken to ensure orthogonality between π and MR. The QSAR for this new set of substrates was related to lipophilicity and not MR. The three equations, taken together, clearly define a lipophilic and a polar pocket for papain.[53]

Tumor cells exhibit abnormal levels of certain enzymes. The enzymes are involved in DNA synthesis, proteolysis or cellular oxidations. QSAR summarized in a consistent way, the bulk of the data gathered by Baker and his group. Inhibitory potencies of the various compound series were related to MR and/or π. Indicator variables were used to parameterize major structural variations.[47,54] QSAR studies on malate dehydrogenase,[55] thymidylate synthetase[56] and ribonucleotide diphosphate reductase[57] were reported. Electronic and hydrophobic factors were involved in the inhibition of cholinesterase by carbamates[58] and displacement of vinblastine from tubulin by Vinca alkaloids.[59] Size (E_s) and hydrophilicity ($-\pi$) of substituents were important in the uncoupling of mitochondrial oxidative phosphorylations by dicoumarol derivatives.[60]

Applications of QSAR approaches have been quite numerous



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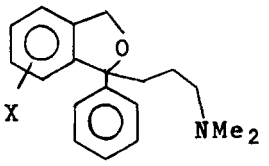

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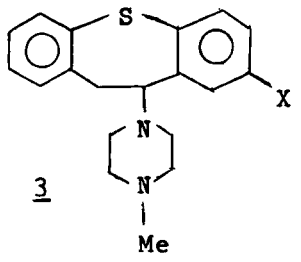

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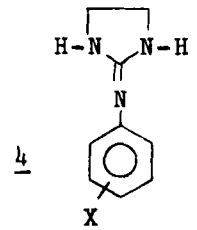
in the CNS field. Electronic indices seemed to be a major factor in a number of studies. Correlations were observed between various CNS activities of benzodiazepines (minor tranquilizers) and calculated total molecular dipole moment.[61] QSAR for benzodiazepinooxazoles 1, also of interest as minor tranquilizers, demonstrated the significance of the field effect, as measured by F, for nine biological test systems. These equations did not identify factors for selectivity of action.[62] Hansch and F-W analyses for a series of 1-aryl-1-[3-(di- and monoalkylamino)propyl]phthalans 2 possessing potent selective 5-HT uptake inhibiting properties appeared to demonstrate an impact of F of the aromatic substituents on drug-receptor interaction.[63] The monoamine oxidase inhibitory potencies of N-isopropylaryl hydrazides related to the antidepressant drug iproniazide were found to correlate with the electron withdrawing capacity of the aryl ring substituents.[69] This result along with previously published data on other classes of MAO inhibitors[65] led to a proposal of a general model for the inhibitor pharmacophore. A relationship was established between log P, steric bulk in the *para* position and the ability to stimulate serotonin receptors in an *in-vitro* sheep umbilical artery preparation for a series of psychotomimetic phenylethylamine derivatives. The log P and steric bulk terms for the *para* substituents were interpreted as indicating directional hydrophobicity. The relative activity in man of a group of four compounds was successfully predicted using this model.[66] An equation correlating potency with three connectivity terms and permitting an interpretation of SAR was found. The equation gave reasonable predictions of potencies for amphetamines not in the list as well as mescalines and tryptamines.[13] Electronic (σ) and molar volume terms were used to correlate the ataxic activities of 10-piperazinodibenzo[b,f]thiepins 3.[67] The role of hydrophobic and electronic factors in the binding of eleven tricyclic tranquilizers and antidepressants to human serum albumin was studied. The results indicated that the major factor influencing binding is the ability of the drugs to form a strong charge transfer complex with the tryptophan residue of HSA, with hydrophobicity playing only a minor role.[68] Conformations of the tri-

cyclic and butyrophenone type neuroleptics have been compared to the trans conformation of dopamine. The need to consider neuroleptic conformations other than those found experimentally, in drawing conclusions about the correlation between antipsychotic activity and similarity to portions of the dopamine structure, was stressed.[11]

In the cardiovascular field QSAR studies were reported for antihypertensive agents and β-blockers. In a series of clonidine analogs 4, differing in the aromatic ring substitution, a QSAR analysis showed the critical dependence of the α-mimetic activity in the pithed rat on a steric effect in the



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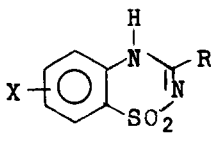

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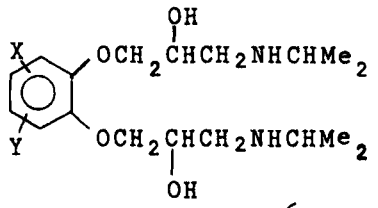

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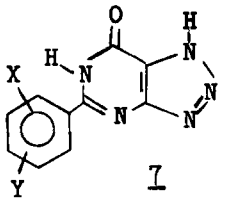
ortho positions. The resulting equation allowed the accurate prediction of the activities of three subsequently synthesized highly active compounds. However, no significant correlation between physicochemical parameters and central hypotensive activity, for the seven analogs having such activity, was found.[69] Another study of 26 clonidine analogs successfully correlated hypotensive activity with steric, electronic and lipophilic factors. An ingenious approach was developed in which "kinetic" aspects of the compounds were separated out allowing drug activity at the central α-adrenoreceptor level to be related to molecular structural characteristics of the compounds. The results were used to construct an interesting speculative working model for drug-receptor interactions in this series.[70] The activities of a series of antihypertensive substituted benzothiadiazine derivatives 5 has been correlated with their binding energies to a receptor model calculated using the monopole bond polarizability method.[71] This compound series had been previously analyzed using MO, Hansch and F-W methods.[72] A parabolic relationship between hydrophobicity, measured by octanol-water partition coefficients, and the non-specific antiarrhythmic and cardiodepressant actions of a series of β-adrenergic blocking drugs, determined in the isolated frog heart, guinea pig and cat models was established. Thus, the hydrophobicity of β-adrenergic blocking drugs should be a useful predictor of their non-specific activities.[73] A similar parabolic dependence of the non-specific activities of a small series of alkyl substituted 1,1'-(o-phenylenedioxy)bis(3-isopropylamino-2-propanols) 6 on hydrophobicity was noted. Tracheal β-adrenergic blocking activity correlated with the steric parameter E_s whereas affin-

ity to right atrial β-adrenoreceptors was dependent on both E_s and π.[74]

A compelling example of activity enhancement using the Hansch approach for a series of substituted 8-azapurines 7 having anti-allergic properties was reported. Through a series of stages in which predictive use of the Hansch technique played a major role, the activity of the original lead compound was enhanced over 10^5 times.[75] Also in the allergy field a quantitative linear relationship was obtained between the activity of a series of substituted oxalinic acids 8 in preventing the release of mediators of immediate hypersensitivity from the rat mast cell and the energy of a low-lying anti-bonding π orbital localized in the phenyl ring. A theoretical basis for the correlation involving a charge-transfer interaction in which the drug acts as an electron acceptor was proposed.[76]



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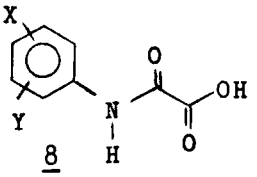

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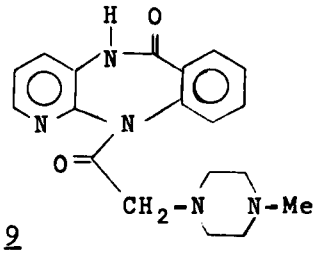

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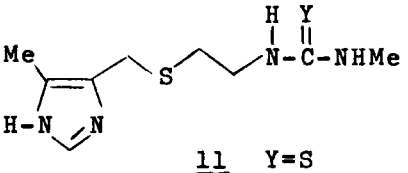
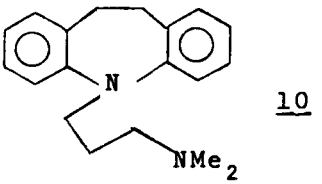


11 Y=S
12 Y=NCN



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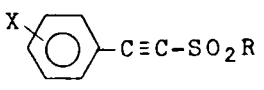
That partitioning characteristics can have a profound effect on the pharmacological activity of a compound is illustrated by pirenzepine 9, a new type of anti-ulcer drug. Despite structural similarities with psychotropic tricyclic compounds, pirenzepine is devoid of any central activity. In rats it does not penetrate the blood brain barrier and produces no CNS effects after intracerebral administration. The inability of the compound to pass the blood brain barrier and to activate the psychotropic receptors was attributed to thermodynamic factors relating to its low partition coefficient, log P 0.10 compared to 4.80 for imipramine 10.[77] The pharmacological equivalence of the thiourea and cyanoguanidine groupings in the antiulcer H_2 receptor antagonists metiamide 11 and cimetidine 12 respectively, was linked to the close correspondence in the physicochemical properties of these groupings with regard to acidity, hydrophobicity, dipole moment and geometry. Thiourea and cyanoguanidine are therefore established as bioisosteres and the development of cimetidine from

metiamide is an excellent example of the use of the concept of bioisosterism in drug design.[78]

Conformational analysis of antiinflammatory arylacetic acids was used to hypothesize a detailed model for the active site of the fatty acid dioxygenase unit of the PG synthetase enzyme and the mechanism of PGG formation was interpreted in terms of this model. The model rationalizes observed structure-activity relationships among enzyme substrates and inhitors, including several nonsteroidal antiinflammatory drugs and is of potential utility in designing novel specifically acting antiinflammatory drugs.[79] The antiinflammatory effects of a series of 4-benzyloxyarylacetic acids substituted in the 3-position showed a parabolic dependence on the lipophilicity of the variable substituents and a positive relationship with the electron withdrawing effect of substituents in the meta position with respect to the acetic acid chain. The activity of a compound synthesized after the analysis had been completed was consistent with the regression equation.[80]

A number of applications of QSAR were reported for chemotherapeutic agents. An interesting example was the use of QSAR in studying the mode of action of tuberculostatic drugs of the isonicotinic acid hydrazide type. Antibacterial activity and rate constants for the quaternization of 2-substituted pyridines with methyl iodide showed a similar dependence on the steric and electronic effects of the substituents. These correlations provided evidence that the reactivity of the pyridine nitrogen atom is essential for the biological activity of 2-substituted isonicotinic acid hydrazides and support the hypothesis that isonicotinic acid derivatives are incorporated into an NAD analogue.[81] In a similar vein QSAR studies of antifungal 1-alkylsulfonyl-2-arylacetylenes 13 supported a mechanism of action based on a reaction of the compounds with nucleophiles present in the fungal cells which was confirmed by kinetic studies with a model nucleophile. A compound designed for high activity based on the regression equation was synthesized but was far less active than predicted.[82] A high inverse correlation was found between antibacterial activity against a dental plaque forming organism and the size of the substituents as measured by MR, in the 5-position of a series of 5-substituted 8-hydroxyquinolines.[83] A QSAR analysis, based on the Hansch model, of the antibacterial properties of a series of long chain aliphatic monoamines related activity principally to the surface active parameter, critical micelle concentration.[84] The in-vitro antibacterial activity of a series of 1-phenyl-4,6-diamino-1,2-dihydro-2,2-dimethyl-s-triazines 14 showed a parabolic dependence on partition with no significant contribution from electronic or steric terms. That no in-vivo activity was observed was attributed to strong non-specific binding in view of the high value of the optimum

partition for the series.[85]



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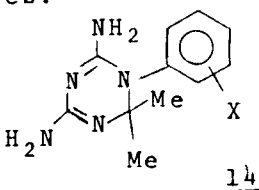

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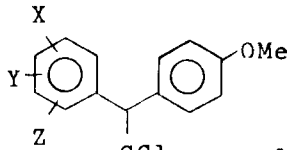

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In a well designed test of the practical worth of the method of physicochemical-activity relationships, a series of substituted 2-aryl-2-(p-methoxyphenyl)-1,1,1-trichloroethanes 15 were selected to obtain well-spread sets of minimally correlated physicochemical parameter values. The compounds were then synthesized and tested for toxicity towards houseflies. A statistically significant regression equation was obtained indicating that toxicity increases with lipophilic character and donation of electrons to the benzene ring by resonance, and decreases by the introduction of bulky substituents in the benzene ring particularly at the ortho positions. The regression equation obtained forecast the activity of eight further members of the series sufficiently well so that by a statistical test the hypothesis that the same function applies to all members of the series could not be rejected.[86]

The method of discriminant analysis was used to analyze structure-activity relationships in a series of antitumor 1-phenyl-3-benzyl-3-methyltriazenes. The analysis classified 11 of 13 compounds correctly.[87] Antileukemic activity (L-1210) for three series of homologous dialkanesulfonic esters was correlated with a binomial expression in lipophilic-hydrophilic balance. Since the sulfonyloxy function is strongly hydrophilic considerable latitude is available for the introduction of various lipophilic moieties in alkylating agents with sulfonate esters as leaving groups.[88] In a study on the delivery of a variety of antitumor agents to the central nervous system brain level measurements indicated that most drugs, even those with very low log P values, have some accessibility to the CNS. In addition to the well known considerations of lipid solubility, degree of ionization and protein binding, molecular size plays an important role in determining penetration of the blood brain barrier.[89] Absorption of antitumor rhodium II carboxylates by cells is governed primarily by the compound's hydrophobic character. Optimum activity was obtained in the pentanoate.[90]

In the hormone field a detailed QSAR study of androst-4-en-3-one derivatives and their affinity for putative progesterone receptors led to the derivation of a six variable regression equation which satisfactorily predicted the affinities of other literature compounds. A novel feature of the analysis was the use of a surface area parameter for non-

hydroxyl substituents as a measure of hydrophobic bonding of relatively nonpolar groups.[91] In a comprehensive QSAR study of thyroid hormone analogs correlations between in-vivo anti-goiter activities and in-vitro nuclear receptors support the idea that binding to nuclear receptors is the first step in initiating events leading to subsequent hormonal effects. Factors that need to be considered in designing new analogues were identified.[92]

Finally an impressive case of the use of molecular models in conjunction with knowledge of the structure of the receptor site to design compounds which should bind to and stabilize the deoxy conformation of human haemoglobin has been described. The compounds so designed were not closely related to the natural starting substance but had the expected property of promoting oxygen liberation and their relative potencies were in the predicted sequence. This example illustrates the potential of drug design when the receptor site is understood in sufficient detail and may well be a portent of a future era in quantitative drug design.[93]

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