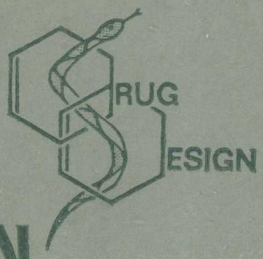

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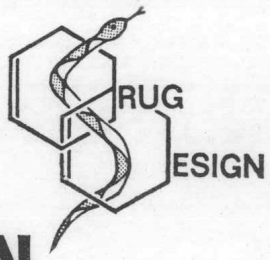

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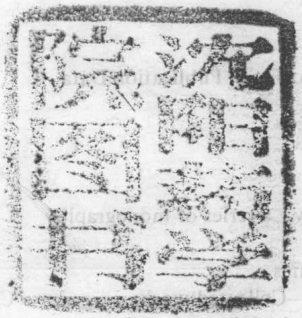

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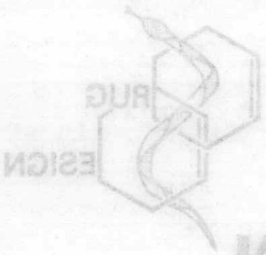

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Preface

Rapid progress in the field of drug design, especially in the physicochemical approach to the relationship of structure and mechanism of action and the applicability of the insight gained to drug design, makes a thorough review of this field a necessity for scientists involved in drug development.

This volume offers the reader a number of chapters dealing with recent, fundamental approaches to the development of bioactive compounds, specifically, the design of enzyme inhibitors based on the development of transition state analogs, the rationale for the combination of enzyme inhibitors (antimetabolites), and the physicochemical factors essential for drug distribution in the organ, including absorption and excretion. The chapter on operational schemes for analog synthesis, an approach ready for immediate use, is of particular interest. Chapters on the role of charge-transfer processes in the action of bioactive compounds and on physicochemical, quantum chemical, and related theoretical approaches to the understanding of compounds with action on the central nervous system open new perspectives for the future.

E. J. Ariëns

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Chapter 1 Utilization of Operational Schemes for Analog Synthesis in Drug Design

John G. Topliss and Yvonne C. Martin

I. Introduction

A very common problem in drug design is to find the optimum substitution on a benzene ring or on the benzenoid portion of a fused ring system in an active lead compound for maximization of drug potency. Since there are many possible substituents and several different ring positions, the number of possible compounds to consider containing up to, say, two substituents is very large. Thus, it would be highly advantageous to determine at an early stage which of these compounds might really be worth synthesizing.

Historically, approaches to this problem have been rather haphazard, depending for the most part on the particular experience and intuition of the medicinal chemist involved and the relative availability of the starting materials required for synthesis. With the advent (*11*) and subsequent development (*8*) of the Hansch method for structure–activity correlations,

a more rational approach to this problem became possible. Thus, a limited group of substituents which will give good discrimination between the physicochemical parameters π, σ, and E_s^c relating to hydrophobic, electronic, and steric effects, respectively, can be selected (*3*) and an initial group of 6–12 compounds synthesized. After performing a regression analysis, and assuming a worthwhile correlation is obtained, it should be possible to determine which parameters are influencing activity and to what relative degree. Knowing this, and having available a comprehensive list of possible substituents and their respective parameters, those compounds can be selected for synthesis with the highest indicated potency values commensurate with synthetic accessibility.

Since the regression analysis has been carried out with a minimum number of observations, the reliability of the correlation will not be high, but nevertheless the analysis will identify those compounds with the highest probability of enhanced potency based on the available data. When data on the second group of compounds become available, they can be combined with those of the first group. The correlations can thus be continuously refined as new data become available.

This procedure is suitable when the compounds are relatively easy to synthesize and a considerable time lag is encountered in obtaining activity data. However, it is less satisfactory under circumstances where synthesis is more difficult and test results are more readily forthcoming. In the latter case it would be desirable to proceed with every compound synthesized in the most probable direction toward greater potency. This maximizes the chances of finding the most potent compounds as early as possible.

Another problem in the utilization of the standard Hansch method is the reluctance on the part of some medicinal chemists to become involved with mathematics, statistical procedures, and computers. For these individuals a nonmathematical utilization of the Hansch approach might be of considerable interest.

In the context of the foregoing discussion the operational schemes (1 and 2) for aromatic substitution and side-chain problems discussed in the following sections may be considered (*26*). The π, σ (σ^*), and E_s^c values of the substituents are listed in Table I.

II. Operational Scheme for Aromatic Substitution

For Scheme 1, which covers aromatic substitution, the assumption is made that the starting compound is the unsubstituted phenyl compound and that its biological activity has been measured. Since many systems are $+\pi$-dependent, i.e., activity increases with increasing π values, the *p*-chloro

TABLE I

SUBSTITUENT CONSTANT VALUES

Aromatic

Substituent	π^a	σ^b	E_s^{cc}
H	0.00	0.00	1.24
4-Cl	0.70	0.23	0.27
3-Cl	0.76	0.37	0.27
3-CF_3	1.07	0.43	−1.16
4-NO_2	0.24	0.78	−1.28
4-CF_3	1.07	0.54	−1.16
4-Br	1.19	0.23	0.08
4-I	1.43	0.28	−0.16
2-Cl	0.76	0.23	0.27
4-CH_3	0.60	−0.17	0.00
4-$C(CH_3)_3$	1.68	−0.20	−.154
3-CH_3	0.51	−0.07	0.00
4-$OCH(CH_3)_2$	0.76[f]	−0.45	—
4-OCH_2Ph	2.09[f]	−0.42	—
4-OPh	1.59[f]	−0.32	—
3-Br	0.94	0.39	0.08
3-I	1.15	0.35	−0.16
3-NO_2	0.11	0.71	−1.28
2-CH_3	0.84	−0.17	0.00
2-OCH_3	−0.33	−0.27	0.69
4-CN	−0.32	0.66	—
4-$COCH_3$	−0.37	0.50	—
4-SO_2CH_3	−1.26	0.72	—
4-$CONH_2$	−1.49	0.40	—
4-SO_2NH_2	−1.82	0.57	—
4-F	0.15	0.06	0.78
3-$N(CH_3)_2$	0.18	−0.21	—
3-NH_2	−1.23	−0.16	0.63
4-OCH_3	−0.04	−0.27	0.69
4-$N(CH_3)_2$	0.18[f]	−0.83	—
4-NH_2	−1.23	−0.66	0.63
4-OH	−0.61	−0.37	0.69

Side chain

Substituent	π^a	σ^{*d}	E_s^{ce}
CH_3	0.50	0.00	0.00
i-C_3H_7	1.30	−0.19	−1.08
cyclo-C_5H_9	2.14	−0.20	−1.12
cyclo-C_6H_{11}	2.51	−0.15	−1.40
CH_2Ph	2.63	0.22	−0.69
$(CH_2)_2Ph$	3.13	0.08	−0.69

(*Continued*)

TABLE I (*Continued*)

Side chain			
Substituent	π[a]	σ^*[d]	E_s[c,e]
cyclo-C_4H_7	1.80[f]	−0.20[f]	−0.67
CH_2-cyclo-C_3H_5	1.80[f]	−0.13[f]	—
tert-C_4H_9	1.98[g]	−0.30	−2.46
C_2H_5	1.00	−0.10	−0.38
$CHCl_2$	1.15[f]	1.92	−2.15
CF_3	1.07[f]	2.76[f]	−2.08
CH_2CF_3	1.57[f]	0.92	—
CH_2SCH_3	0.77[f]	0.44[f]	−0.64
Ph	2.13	0.60	—
H	0.00	0.49	0.32
CH_2OH	−0.66[f]	0.56	—
CH_2CH_2OH	−0.16[f]	0.20[f]	—
CH_2OCH_3	0.02[f]	0.64	−0.50
$CH_2CH_2OCH_3$	0.52[f]	0.23[f]	−1.08
$CH_2SO_2CH_3$	−0.76[f]	1.32	—

[a] From Fujita *et al.* (*5*), Iwasa *et al.* (*15*), Miller and Hansch (*24*), and Leo *et al.* (*22*).

[b] From Hine (*14*) and Jaffé (*16*). The σ values relate to an electronic effect at the point of attachment of the phenyl group to some other moiety. It is possible that in some situations the electronic effect of a substituent may be important with respect to another position on the phenyl group. However, for the most part the arguments presented will not be materially affected.

[c] From Kutter and Hansch (*20*).

[d] From Taft (*25*).

[e] Obtained from values taken from Taft (*25*) and corrected according to Hancock *et al.* (*7*).

[f] Estimated.

[g] From Hansch and Coats (*10*).

analog is a good first choice, particularly since the ease of synthesis, relative to other substituted phenyl compounds, is generally favorable.

For the purposes of this analysis the potency of the 4-chloro compound can be classified as greater than, equal to, or less than the activity of the parent compound. If the potency is increased, this can be attributed most probably to a $+\pi$ effect, a $+\sigma$ effect (activity increases with increasing σ values), or to a combination of $+\pi$ and $+\sigma$. In this event the 3,4-dichloro compound would be selected for synthesis next since this would result in both larger $+\pi$ and $+\sigma$ values when summed for the two substituents.

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