QSAR Studies on Drugs Acting at the Central Nervous System

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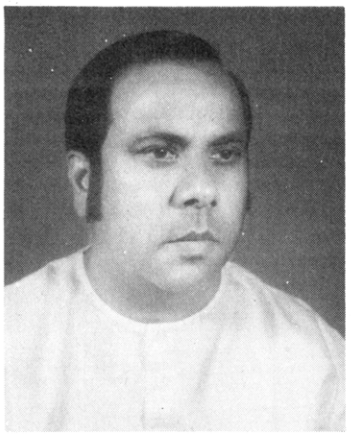

Satya P. Gupta is presently an Associate Professor at the Birla Institute of Technology and Science (BITS), Pilani, India. Born in 1945, he received his M.Sc. (Physical Chemistry) in 1967 and D.Phil. in 1971. For his D.Phil. he worked with Prof. Balkrishna on molecular orbital theory and developed a new technique known as the IOC-ω-technique (inclusion of overlap charges in the ω-technique). After his D.Phil., he spent a few years in the group of Prof. G. Govil at the Tata Institute of Fundamental Research (TIFR), Bombay, India, where he worked on conformational aspects of biomolecules such as phospholipids. At this stage, very little information was available on molecular conformations and packing of phospholipids. This work of Gupta et al. therefore became important in providing an understanding of the molecule organization of lipid bilayers and their static and dynamic properties. From TIFR, Gupta moved to BITS in 1973 and developed an interest in computer-aided drug design. For his significant contribution in this area, the National Academy of Sciences, India, made him its fellow in 1985.

I. Introduction

Drugs that exert their primary effects upon the central nervous system (CNS) comprise the most widely employed group of pharmacologically active agents. They influence the life of almost everyone everyday and produce specific physiological and psychological efects. They can relieve pain or fever, suppress disorders of movement, prevent epileptic seizures, induce sleep or arousal, reduce the desire to eat, and allay the tendency to vomit. Anxiety, mania, depression, schizophrenia, etc. can be easily treated by them without altering consciousness. Modern surgery would be impossible without general anesthetics. The introduction of potent psychotherapeutic agents over the past several years has had a dramatic impact on the basic concepts and treatment of mental illness. Socially acceptable stimulants and antianxiety agents produce stability, relief, and even pleasure for many. Addiction to these drugs, however, adversely affects lives.

With the use of CNS agents, pharmacologists try to understand the cellular and molecular basis of the enormously complex and varied functions of the brain. Using them, they can dissect the cellular and molecular mechanisms operating in the normal CNS and develop appropriate drugs to correct pathophysiological events in the abnormal CNS. However, the success of these studies is based on the knowledge of the sites and mechanisms of actions of these drugs, which requires a thorough study on their structure–activity relationships.

Long ago it was proposed that the biological activity of a compound is a function of its chemical structure. Today, biological activity is considered a function of physicochemical properties. With this concept, structure–activity relationships are developed when a set of physicochemical properties of a group of congeners is found to explain variations in biological responses of those compounds. This has resulted in the discovery, examination, and interpretation of structure–activity relationships in a more systematic way, which has led to the introduction of quantitative structure–activity relationships (QSAR).

The most widely used approach of QSAR continues to be the so-called Hansch approach,[1] where the variance in biological activity is explained by the variance of certain physicochemical and structural properties of molecules. The physicochemical properties include electronic characteristics, steric factors, and solvent-partitioning or hydrophobic effects. The merits and demerits of this approach have been discussed in detail in a recent review.[2] The aim of the present article is to review all QSAR studies made so far on CNS agents so that a broader perspective may be had to elucidate

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the mechanisms of their actions. For a particular class of CNS agents, the hallucinogens, QSAR studies have already proven their worth.[3]

II. Classification of CNS Drugs

For a systematic study of any kind on CNS drugs, some form of classification of these drugs is essential. The most appropriate way would obviously be according to their modes of action. However, at present we do not have adequate knowledge about their exact modes of action; hence it would not be possible to classify them on this basis.

CNS drugs are called specific and nonspecific, depending upon whether they produce the effects through an identifiable molecular mechanism unique to target cells that bear receptors for them or act by diverse molecular mechanisms affecting several different target cells. Drugs whose mechanisms currently appear to be general or nonspecific are classed according to whether they produce behavioral depression or stimulation, while specifically acting CNS drugs can be classed more definitively according to their locus of action or specific therapeutic usefulness. Thus we have broadly the following classification of CNS drugs.

A. General (Nonspecific) CNS Depressants. Drugs that have the ability to depress excitable tissue at all levels of the CNS by stabilization of neuronal membranes, leading to a decrease in the amount of transmitter released by the nerve impulse as well as to general depression of postsynaptic responsiveness and ion movement, fall in this category and include the anesthetic gases and vapors, aliphatic alcohols, and some hypnotic–sedative drugs.

B. General (Nonspecific) CNS Stimulants. Drugs that may stimulate the CNS by blocking inhibition or by direct neuronal excitation that involves increased transmitter release, more prolonged transmitter action, labilization of the postsynaptic membrane, or a decrease in synaptic recovery time are classified in this category. Members of this category are cerebral stimulants (xanthines), brainstem stimulants (picrotoxin, pentylenetetrazole), and spinal cord stimulants (strychnine).

C. Selective Modifiers of CNS Functions. These agents may produce depression, excitation, or both simultaneously on different systems. Some agents in this category may have little effect upon the level of excitability in doses that are used therapeutically. Drugs that can be put in this category are (a) anticonvulsants, (b) antiparkinsonism drugs, (c) narcotic analgetics, (d) analgetic antipyretics, (e) centrally acting muscle relaxants, and (f) psychopharmacological agents.

Certain drugs not considered to be centrally acting may sometimes produce profound effects on the CNS as part of their pharmacological actions. Many drugs administered for their peripheral action also produce side effects or toxic reactions that can be referred to the CNS. All such drugs can be placed in a separate class designated as miscellaneous.

It is now generally accepted that the CNS has excitatory and inhibitory chemical transmitters. The most probable of them are[4] acetylcholine, adrenaline, noradrenaline, dopamine, serotonin (5-hydroxytryptamine), histamine, L-glutamic acid and related amino acids, γ-aminobutyric acid (GABA), and glycine. Many drugs that modify the functions of the CNS have been demonstrated to affect the concentration of one or more of these substances in the central as well as peripheral nervous system. Apart from these neurochemicals, several endogenous peptides have been discovered in the brain.[4] They include enkephalin, endorphins, somatostatin, thyrotropin-releasing hormone (TRH), luteinizing hormone releasing hormone (LHRH), gastrin, cholecystokinin, oxytocin, and substance P. Drugs interfering with the release and action of these endogenous peptides may produce certain CNS effects.

III. QSAR Results and Discussion

A. General (Nonspecific) CNS Depressants

1. General Anesthetics

In this class of CNS drugs, general anesthetics have acquired the most important place. They affect vital functions of all types of cells, especially those of nervous tissue. The state of general anesthesia is a drug-induced absence of perception of all sensations. General anesthetics can depress the CNS to such an extent that sensitivity to pain is completely abolished. When used in surgery, they produce analgesia, loss of consciousness, and muscular relaxation.

General anesthetics are structurally nonspecific; i.e., they have no definite pattern of chemical structure. They are therefore classified on the basis of their method of administration. We have thus inhalation (or volatile) anesthetics and intravenous anesthetics. Inhalation anesthetics may be gases or volatile liquids. They vary greatly in potency, safety, and ability to induce analgesia and muscular relaxation. Intravenous are nonexplosive solids. They produce rapid loss of consciousness but insufficient anesthesia and muscular relaxation.

Since general anesthetics are structurally nonspecific, no unified theory has yet been proposed for the mechanism of their action. It is, however, admitted that they depress the CNS nonselectively by a physicochemical mechanism. Of the various theories that have been proposed, some are purely physical and some purely biochemical. Physical theories are based mainly on two physicochemical properties of anesthetics: polarizability and volume. The principal physical theories are[5-8] lipid theory, permeability theory, surface tension or adsorption theory, molecular size theory, neurophysiological theory, clathrate theory, and iceberg theory. Biochemical theories mainly include[5-8] inhibition of oxidation theory, interference with mitochondrial ATP formation theory, suppression of ion movement theory, and neurophysiological theory.

Among the physical theories, the most widely accepted one is the lipid theory advanced by Meyer[9] and Overton.[10] According to this theory, the potency of an anesthetic should be directly related to its olive oil–water partition coefficient. The Meyer–Overton view is that anesthetics bring about their action in a fatty phase of nerve tissue. Pauling[11] and Miller,[12] however, independently proposed that the critical action occurs in an aqueous phase and is better correlated to the tendency of anesthetics to form hydrates. In a thoughtful analysis of the facts, Miller et al.[13,14] suggested that the phase for anesthetics was nonaqueous. They also showed that there was a very high correlation

TABLE 1. Activity of Anesthetic Gases in Mice[13,14]

no.	gas	log (1/p)	log P	I
1	He	-2.28	0.28	0.0
2	H_2	-2.14	0.45	0.0
3	Ne	-1.94	0.28	0.0
4	N_2	-1.52	0.67	0.0
5	CH_4	-1.24	1.18	0.0
6	C_2F_6	-1.19	2.00	0.0
7	Ar	-1.18	0.74	0.0
8	SF_6	-0.75	1.68	0.0
9	CH_4	-0.66	1.09	0.0
10	Kr	-0.65	0.89	1.0
11	N_2O	-0.18	0.43	0.0
12	$CH_2{=}CH_2$	-0.15	1.13	0.0
13	C_2H_6	-0.11	1.81	0.0
14	Xe	0.02	1.28	0.0
15	C_3H_8	0.05	2.36	1.0
16	C_2H_2	0.15	0.37	0.0
17	CF_2Cl_2	0.40	2.16	0.0
18	$CH_3CH{=}CH_2$	0.40	1.77	0.0
19	c-C_3H_6	0.80	1.72	0.0
20	$CFCl_3$	0.82	2.53	1.0
21	CH_3F	0.85	0.51	1.0
22	CH_3Cl	0.85	0.91	1.0
23	CH_3I	1.15	1.51	1.0
24	C_2H_5Cl	1.40	1.43	1.0
25	C_2H_5Br	1.40	1.61	1.0
26	EtOEt	1.52	0.89	1.0
27	CH_2Cl_2	1.52	1.25	1.0
28	CH_3CHCl_2	1.59	1.79	1.0
29	$CHCl_3$	2.08	1.97	1.0
30	$CF_3CHClBr$	2.11	2.30	1.0
31	$Cl_2CHCF_2OCH_3$	2.66	2.21	1.0

between anesthetic pressure and olive oil–gas partition coefficient.[14]

The lipid theory does not explain the actual mechanism of action of general anesthetics. It simply expresses the direct parallelism between the lipid solubility and anesthetic action. However, it is this theory that has received extensive support from QSAR studies.

For the anesthetic gases (Table 1) for which Miller et al.[13,14] had shown the anesthetic pressure (p) to be related to the olive oil–gas partition coefficient, Hansch et al.[15] tried to correlate the potency with the octanol–water partition coefficient. As is obvious from eq 1, this partition coefficient could not fully account for

$$\log (1/p) = 1.193(\pm 0.59) \log P - 1.327(\pm 0.87) \quad (1)$$

$$n = 30,\ r = 0.613,\ s = 1.056$$

the variation in the anesthetic potency. In eq 1, n is the number of data points, r is the correlation coefficient, s is the standard deviation, and data within parentheses are 95% confidence intervals (such data without ± signs refer to standard errors of coefficients).

A significant correlation was, however, obtained when the polar character of the compounds was also taken into account. An indicator parameter I was defined to indicate the presence of a polar hydrogen atom in the molecule. The definition of a polar hydrogen atom was a phenomenological one. The compounds that contained an electronegative element (O, Cl, etc.) attached directly to a carbon atom were observed to be more potent anesthetics than those lacking such a hydrogen atom. I was given a value of 1 for such compounds and 0 for all others except HC≡CH and N_2O. It was assumed[15] that the C≡C function was electronegative enough to confer polar character on its hydrogens and that the hydrated form of N_2O was the active species.

TABLE 2. Anesthetic Activity of Aliphatic Ethers in Mice[17]

no.	ether	log (1/C)	log P	$^1\chi$
1	dimethyl ether	1.85	-0.23	1.414
2	methyl ethyl ether	2.22	0.27	1.914
3	divinyl ether	2.82		2.414
4	ethyl vinyl ether	2.82	1.04	2.414
5	methyl cyclopropyl ether	2.85	0.48	2.432
6	methyl isopropyl ether	2.70	0.57	2.270
7	diethyl ether	2.75	0.77	2.414
8	methyl propyl ether	2.90	0.77	2.414
9	ethyl cyclopropyl ether	3.10	0.98	2.932
10	ethyl isopropyl ether	3.00	1.07	2.770
11	methyl *tert*-butyl ether	3.00	0.80	2.561
12	methyl *sec*-butyl ether	3.04	1.04	2.808
13	methyl isobutyl ether	3.00	1.08	2.770
14	ethyl propyl ether	3.10	1.27	2.914
15	methyl butyl ether	3.15	1.27	2.914
16	diisopropyl ether	3.15	1.63	3.126
17	ethyl *tert*-butyl ether	3.15	1.56	3.061
18	ethyl *sec*-butyl ether	3.22	1.80	3.308
19	ethyl isobutyl ether	3.22	1.83	3.270
20	propyl isopropyl ether	3.26	1.83	3.270
21	methyl amyl ether	3.40	2.03	3.414
22	dipropyl ether	3.40	2.03	3.414
23	ethyl butyl ether	3.30	2.03	3.414
24	ethyl *tert*-amyl ether	3.40	2.08	3.561
25	ethyl isoamyl ether	3.45	2.35	3.846
26	ethyl amyl ether	3.45	2.53	3.914
27	di-*sec*-butyl ether	3.45	2.57	4.202
28	diisobutyl ether	3.30	2.64	4.260

Thus with the inclusion of this indicator parameter, the correlation obtained was

$$\log (1/p) = 1.166(\pm 0.25) \log P + 1.881(\pm 0.33)I - 2.106(\pm 0.39) \quad (2)$$

$$n = 30,\ r = 0.947,\ s = 0.438$$

In fact, the anesthetic potency was found to be better correlated with this indicator parameter describing the polar character of the molecule (eq 3) than with log P

$$\log (1/p) = 1.913(\pm 0.69)I - 0.596(\pm 0.45) \quad (3)$$

$$n = 30,\ r = 0.734,\ s = 0.909$$

(eq 1). From eq 1–3, however, one finds that the anesthetic potency of gases was not only governed by their hydrophobic property but also by their polar character. In the derivation of eq 1–3, compound 6 was not included, as it was misfit in the correlations.

Since Miller et al. had found an excellent correlation between the anesthetic potency and the olive oil–gas partition coefficient, Hansch et al.[15] assumed that the solubility of gases in olive oil must be determined by dispersion and polar forces (including hydrogen bonding) in such a way that olive oil models the effects of these forces in the critical lipophilic sites of action. However, according to Fujita et al.,[16] the indicator parameter I should be mostly attributed to the effect of association in solvents, octanol and water, which is not required to be considered for the correlation with log $P_{oil-gas}$. For the compounds for which eq 1–3 were derived, Fujita et al.[16] demonstrated that

$$\log P_{oil-gas} = \log P_{oct-H_2O} + 1.9HB + C \quad (4)$$

where HB is the hydrogen-bonding parameter.

The anesthetic potency of a series of aliphatic ethers (Table 2) studied by Marsh and Leake[17] in mice was found by Glave and Hansch[18] to depend only upon the octanol–water partition coefficient as shown by eq 5.

$$\log (1/C) = 1.038(\pm 0.19) \log P - 0.221(\pm 0.07)(\log P)^2 + 2.161(\pm 0.12) \quad (5)$$

$$n = 26,\ r = 0.966,\ s = 0.101,\ \log P_0 = 2.35$$

(In eq 5, C is the molar concentration for producing the desired effect. The term $\log (1/C)$ will be used in general for all kinds of activity measured in terms of concentration.) In the derivation of eq 5, mostly calculated $\log P$ values were used, and compounds 3 and 4 were not included. However, the measured value of $\log P$ for compound 4 was found to fit eq 5. No attempt was made to determine $\log P$ for compound 3.

Equation 5 represents a parabolic correlation between the potency and $\log P$, which expresses that the potency will reach an optimum and then decrease. The value of $\log P$ corresponding to the optimum activity ($\log P_0$) as obtained from eq 5 is 2.35.

For all 28 compounds of Table 2, Di Paolo[19] related the anesthetic potency with Kier's molecular connectivity index χ[20] (eq 6). This index signifies the degree

$$\log (1/C) = 1.865(\pm 0.13)(^1\chi) - 0.230(\pm 0.02)(^1\chi)^2 - 0.365(\pm 0.18) \quad (6)$$

$$n = 28,\ r = 0.986,\ s = 0.063,\ F_{2,25} = 449.1$$

of branching or connectivity in a molecule and is derived from the numerical extent of branching or connectivity in the molecular skeleton (hydrogen-suppressed graph). The term $^1\chi$ refers to the first-order simple connectivity index, which is calculated without taking into consideration the valency of the atoms.[20] The parameter F in eq 6 is the F ratio between the variances of calculated and observed activities and is highly significant here ($p < 0.001$).

Marsh and Leake[17] observed that, in general, there was an increase in the activity as the molecular weight or the molecular size increased. Further, within a group of compounds with the same total number of carbon atoms or the same molecular weight, the isomers with the longest straight chain or highest boiling point were found to be the most active. All these observations are very well accounted for by eq 6, as $^1\chi$ increases with increasing molecular size and is smaller for the more branched isomers in the group of compounds having the same number of carbon atoms. Equation 7, derived by Di Paolo,[19] was also found to be quite significant.

$$\log (1/C) = 4.376(\pm 0.05) - 3.729(\pm 0.15)/(^1\chi) \quad (7)$$

$$n = 28,\ r = 0.979,\ s = 0.076,\ F_{1,26} = 606.1$$

In eq 6, which represents a parabolic correlation, there were in fact only two compounds (compounds 27 and 28) past the optimum ($^1\chi_{op} = 4.05$, $\log (1/C) = 3.42$). Therefore, Di Paolo reexamined[21] the parabolic correlation using a new set of data (Table 3) of Jeppsson[22] where there were many measurements beyond the optimum point. This time he could not find any significant parabolic correlation but could derive eq 8,

$$\log (1/C) = 2.895(\pm 0.324) - 8.539(\pm 0.875)/(^1\chi) - 1.487(\pm 0.114)(^4\chi_p{}^v) \quad (8)$$

$$n = 27,\ r = 0.943,\ s = 0.170,\ F_{2,24} = 96.5$$

which expresses that $^1\chi$ is the important factor for smaller congeners up to a maximum and then the term $^4\chi_p{}^v$ becomes the main factor for larger congeners. The term $^4\chi_p{}^v$ describes a weighted count of all fragments or subgraphs consisting of four bonds joined as a path.[20] The superscript "v" refers to the fact that the valency of atoms has been taken into consideration in the calculation of this term.

TABLE 3. Anesthetic Activity of Hydrocarbons, Ethers, and Ketones in Mice[22]

no.	compd	log (1/C)	$^1\chi$	$^4\chi_p{}^v$
1	pentane	1.052	2.414	0.354
2	hexane	0.941	2.914	0.500
3	heptane	0.458	3.414	0.677
4	octane	0.391	3.914	0.854
5	nonane	0.428	4.414	1.030
6	decane	0.613	4.914	1.207
7	undecane	0.810	5.414	1.384
8	dodecane	1.124	5.914	1.561
9	tridecane	1.119	6.414	1.737
10	tetradecane	1.294	6.914	1.914
11	pentadecane	1.516	7.414	2.091
12	hexadecane	1.566	7.914	2.268
13	heptadecane	1.538	8.414	2.444
14	ethyl ether	1.036	2.414	0.204
15	propyl ether	0.305	3.414	0.391
16	butyl ether	0.104	4.414	0.595
17	pentyl ether	0.297	5.414	1.010
18	hexyl ether	0.535	6.414	1.364
19	heptyl ether	0.869	7.414	1.717
20	octyl ether	1.188	8.414	2.071
21	3-pentanone	0.657	2.808	0.250
22	4-heptanone	0.121	3.808	0.683
23	5-nonanone	−0.081	4.808	0.873
24	6-undecanone	0.076	5.808	1.269
25	7-tridecanone	0.978	6.808	1.623
26	8-pentadecanone	1.127	7.808	1.976
27	9-heptadecanone	1.455	8.808	2.330

Di Paolo also attempted[21] to correlate the activity data of Table 3 with $\log P$ and the molecular weight (MW). Parabolic correlations were obtained but they were much inferior to that expressed by eq 8 ($r = 0.814$ and 0.762 with $\log P$ and MW, respectively). However, good parabolic correlations with $\log P$ were found to exist when alkanes, ethers, and ketones were treated separately (eq 9–11).[22]

Alkanes

$$\log (1/C) = 0.76 \log P - 0.09(\log P)^2 + 0.74 \quad (9)$$

$$n = 12,\ r = 0.91,\ s = 0.192,\ \log P_0 = 4.33$$

Ethers

$$\log (1/C) = 0.64 \log P - 0.9(\log P)^2 + 1.67 \quad (10)$$

$$n = 7,\ r = 0.955,\ s = 0.450,\ \log P_0 = 3.56$$

Ketones

$$\log (1/C) = 0.49 \log P - 0.09(\log P)^2 + 2.18 \quad (11)$$

$$n = 7,\ r = 0.906,\ s = 0.309,\ \log P_0 = 2.70$$

The connectivity index was found to be related with the potency of gaseous anesthetics also.[23] Since χ cannot deal with atomic molecules, the noble gases of Table 1 were excluded in finding the correlation with it. Along with them H_2 and N_2 were also excluded, but C_3F_8, CH_3CHF_2, CH_3CClF_2, and $CHClF_2$ with $\log (1/p)$ values of −1.16, 0.35, 0.60, and 0.80, respectively, were added. For this modified set of compounds, Di Paolo et al.[23] then correlated the anesthetic potency with a zero-order valence connectivity index ($^0\chi^v$) as

$$\log (1/p) = 0.571(\pm 0.06)({}^0\chi^v) - 0.638(\pm 0.16) \quad (12)$$

$$n = 28,\ r = 0.881,\ s = 0.496,\ F_{1,26} = 90.4$$

The best correlation was, however, obtained when the parameter Q_H, describing the charge on the polar hydrogen, was added (eq 13). Since χ's have been shown[20]

$$\log (1/p) = 0.496(\pm 0.04)({}^0\chi^v) + 10.3(\pm 1.3)Q_H - 0.807(\pm 0.09) \quad (13)$$

$$n = 28,\ r = 0.966,\ s = 0.278,\ F_{2,25} = 173.3$$

to be related with log P, eq 13 has almost the same meaning as eq 2. However, just like eq 13, eq 14 was obtained[24] correlating the anesthetic potency of a large group of halogenated hydrocarbons with ${}^0\chi^v$ and Q_H, but for this series of compounds there was a parabolic correlation between the potency and log P and that too was not very significant (eq 15). The parameter I in

$$\log (1/C) = 1.026(\pm 0.044)({}^0\chi^v) + 1.054(\pm 0.053)Q_H - 5.229(\pm 0.171) \quad (14)$$

$$n = 45,\ r = 0.975,\ s = 0.27,\ F_{2,42} = 411$$

$$\log (1/C) = 0.88 \log P - 0.10(\log P)^2 + 0.51I + 0.18 \quad (15)$$

$$n = 45,\ r = 0.62,\ s = 0.49,\ \log P_0 = 4.4$$

eq 15 was used for compounds containing hydrogen that could participate in hydrogen bonding. The anesthetic data (in mice) on these halogenated hydrocarbons were collected by Davies et al.,[26] who themselves had tried to correlate them with a nonpolar factor (P_0) and the hydrogen bond donor ability of the molecules (eq 16).

$$\log (1/C) = 2.20(\pm 0.07)P_0 + \delta_1[0.64(\pm 0.05)H_{a1} - 0.43(\pm 0.10)] + \delta_2[0.49(\pm 0.07)H_{a2} - 0.16(\pm 0.15)] - 5.98(\pm 0.18) \quad (16)$$

$$n = 45,\ r = 0.988,\ s = 0.20$$

In eq 16, H_{ai} represents the total electron demand on the ith hydrogen and δ_i is equal to zero for $H_{ai} \leq 1.3$ and 1 for $H_{ai} > 1.3$. The nonpolar factor was derived from the partition coefficient.[26] From this equation, Davies et al.[26] proposed that the potency of a partially halogenated hydrocarbon may be accurately fitted to a simple phase distribution model based on van der Waals and hydrogen-bonding effects. Since van der Waals interactions and the hydrogen-bonding ability govern the boiling points of compounds, a parallelism between the anesthetic potency of halogenated hydrocarbons and their boiling point was also observed,[26] and a quantitative correlation obtained between the two was found (eq 17).[27] That the anesthetic potency is a

$$\log (1/C) = 0.035\text{bp} - 2.337 \quad (17)$$

$$n = 45,\ r = 0.892,\ s = 0.555,\ F_{1,43} = 81.98$$

function of polarizability of the molecule was also shown by Clements and Wilson.[28] Earlier, Pauling[11] had noted the dependence of anesthetic potency on molar refraction and thus concluded that any theory based on van der Waals attraction of anesthetics would be acceptable. Thus Pauling's observation was quite in accordance with Wulf and Featherstone's proposition[29] that anesthetic activity results from the molecular size of the compounds used. Wulf and Featherstone were able to show that anesthetic activity can be related with the van der Waals constants a and b appearing in the equation

$$(P + a/V^2)(V - b) = RT \quad (18)$$

The constant a is associated with the cohesive forces between molecules, and b is associated with their volumes. Wilson and co-workers[30,31] and later Kaufman and Koski[32] established a direct correlation between the anesthetic potency of compounds and the constant a that arises from the nature of forces operating between the molecules and the membrane. Kaufman and Koski[32] also concluded that in no case does the anesthetic potency appear to be governed by the geometrical structure or conformation of the anesthetics.

According to Kaufman and Koski, the forces operating between the anesthetics and the membrane may arise from only the physicochemical properties of molecules such as charge distribution, ability to form hydrogen bonds, etc. Regarding the role of hydrogen bonds in anesthetic potency, the result of a recent NMR study[33] on some inhalation anesthetics containing acidic hydrogen can be mentioned as additional evidence.

As already mentioned, Pauling[11] and Miller[12] proposed that the critical action of an anesthetic occurs in the aqueous phase of the CNS and not in the lipid phase as propounded by Meyer and Overton. On the basis of their observation that certain inert gases, which were also anesthetics, formed hydrates, both authors had suggested that the function of an anesthetic agent was to increase the order of the aqueous phase of the neuron, thus lowering its conductance. To support this view, Haberfield and Kivuls[34] attempted to correlate the mole fraction of anesthetic gases (N) dissolved in water at their anesthetic pressure with the decrease in the entropy ($-\Delta S$) of the solution and found the following linear relationship:

$$-\Delta S = 7.08 \log (1/N) + 6.30$$

$$n = 15,\ s = 0.37,\ r \text{ not reported} \quad (19)$$

However, the thermodynamic observations made by Cammarata[35] for the potency of gaseous anesthetics were in support of only the oil–gas distribution study of Miller et al.[13]

Anesthesia in experimental animals can be reversed by application of moderate pressure.[36] One interpretation of this observation was that a large change of volume might be crucially associated with the fundamental action of anesthetics.[36] Recently, from a study of the mean excess volume of inhalation anesthetics, Mori et al.[37] concluded that the pressure reversal of anesthesia can be explained without assuming any specific receptor site for inhalation anesthetics. These authors found that the mean excess volume (the difference in anesthetic volume when transferred from the aqueous phase to the action site) of anesthetics dissolved in water was always negative and that incorporated into a phospholipid suspension was positive. Hence they proposed that inhalation anesthetics increase the volume of the total system when translocated from the aqueous phase into the membrane. Mullins' hypothesis was that anesthesia is a function of the volume of anesthetic present in the membrane,[38] and this view was supported by Davies et al.[39]

TABLE 4. Isonarcotic Activity of Esters, Alcohols, Ketones, and Ethers with Tadpoles[40]

no.	compd	log (1/C)	log P[a]
1	CH_3OH	0.30	-1.27
2	C_2H_5OH	0.50	-0.75
3	CH_3COCH_3	0.65	-0.73
4	$(CH_3)_2CHOH$	0.90	-0.36
5	$(CH_3)_3COH$	0.90	0.07
6	$CH_3CH_2CH_2OH$	1.00	-0.23
7	CH_3COOCH_3	1.10	-0.38
8	$C_2H_5COCH_3$	1.10	-0.27
9	$HCOOC_2H_5$	1.20	-0.38
10	$C_2H_5OC_2H_5$	1.20	0.59
11	$(CH_3)_2C(C_2H_5)OH$	1.20	0.59
12	$CH_3(CH_2)_3OH$	1.40	0.29
13	$(CH_3)_2CHCH_2OH$	1.40	0.16
14	$CH_3COOC_2H_5$	1.50	0.14
15	$C_2H_5COC_2H_5$	1.50	0.31
16	$CH_3(CH_2)_4OH$	1.60	0.81
17	$CH_3CH_2CH_2COCH_3$	1.70	0.31
18	$CH_3COOCH_2C_2H_5$	2.00	0.66
19	$C_2H_5COOC_2H_5$	2.00	0.66
20	$(CH_3)_2CHCOOC_2H_5$	2.20	1.05
21	$CH_3COOCH_2CH(CH_3)_2$	2.20	1.05
22	$CH_3COO(CH_2)_3CH_3$	2.30	1.18
23	$CH_3CH_2CH_2COOC_2H_5$	2.40	1.18
24	$CH_3(CH_2)_3COOC_2H_5$	2.70	1.70
25	$CH_3COO(CH_2)_4CH_3$	2.70	1.70
26	$C_6H_5COCH_3$	3.00	1.58
27	$CH_3(CH_2)_7OH$	3.40	2.37
28	$CH_3(CH_2)_3COO(CH_2)_3CH_3$	3.60	2.74

[a] Calculated value.[43]

TABLE 5. Tadpole Narcosis by Miscellaneous Compounds[41]

no.	compd	log (1/C)	log P
1	ethyl acetate	1.41	0.73[a]
2	ethyl propionate	2.10	1.23
3	ethyl butyrate	2.62	1.73
4	ethyl valerate	3.05	2.23
5	acetone	0.49	-0.21
6	2-butanone	1.02	0.29[a]
7	2-pentanone	1.57	0.79
8	chloroform	3.12	1.97[a]
9	nitromethane	0.85	-0.33[a]
10	ethyl ether	1.35	0.77[a]
11	methanol	-0.19	-0.66[a]
12	ethanol	0.26	-0.16
13	propanol	0.98	0.34[a]
14	butanol	1.77	0.84
15	hexanol	3.03	1.84
16	heptanol	3.60	2.34
17	octanol	4.05	2.84
18	methyl carbamate	0.59	-0.65
19	ethyl carbamate	1.46	-0.15[a]
20	propyl carbamate	2.33	0.35
21	isobutyl carbamate	2.49	0.65
22	isoamyl carbamate	3.00	1.15

[a] Experimentally determined values; all other values calculated.[44]

However, with all these diverse findings, the role of lipid solubility continues to be an important factor in narcotic effects of drugs. The data on tadpole narcosis obtained for groups of miscellaneous compounds by McGowan[40] (Table 4) and by Vernon[41] (Table 5) were found[43,44] to have a very high dependence on log P that ranged from -1.27 to 2.84 (eq 20 and 21). Equation 20 was obtained by Iwasa et al.[43] for the compounds of Table 4, and eq 21 was obtained by Hansch and Anderson[44] for the compounds of Table 5, excluding carbamates. The data for the carbamates were separately treated[44] and found to be as well related with log P (eq 22) as those of others. Similarly, the narcotic data of Meyer and Hemmi[42] for a small set of miscellaneous compounds were found by Hansch[1c] to be equally well correlated with log P (eq 23) over a sufficiently long range of the latter. Thus eq 20–23 show that there

$$\log (1/C) = 0.869 \log P + 1.242 \quad (20)$$

$$n = 28,\ r = 0.965,\ s = 0.229$$

$$\log (1/C) = 1.172(\pm 0.09) \log P + 0.685(\pm 0.12) \quad (21)$$

$$n = 17,\ r = 0.987,\ s = 0.204$$

$$\log (1/C) = 1.343(\pm 0.32) \log P + 1.611(\pm 0.22) \quad (22)$$

$$n = 5,\ r = 0.985,\ s = 0.192$$

$$\log (1/C) = 1.06(\pm 0.15) \log P + 0.81(\pm 0.20) \quad (23)$$

$$n = 12,\ r = 0.980,\ s = 0.212$$

exists a significant linear relationship between the narcotic effect and log P. A parabolic correlation was found to exist only in the case of some alcohols studied by Meyer and Hemmi[42] (eq 24).[1c,45] A bilinear model (eq 25) was also derived for these alcohols by Kubinyi.[46]

$$\log (1/C) = 1.49 \log P - 0.10(\log P)^2 + 0.50 \quad (24)$$

$$n = 10,\ r = 0.995,\ s = 0.215,\ \log P_0 = 7.6$$

$$\log (1/C) = 1.192(\pm 0.05) \log P - 6.131(\pm 19.14) \log (\beta P + 1) - 0.797(\pm 0.16) \quad (25)$$

$$n = 10,\ r = 1.0,\ s = 0.068$$

However, the narcotic effect of some alcohols studied in goldfish[47] was found to be only linearly related with log P (eq 26)[48] that ranged from -0.66 to 1.10. Similarly,

$$\log (1/C) = 1.148(\pm 0.020) \log P + 0.339 \quad (26)$$

$$n = 8,\ r = 0.985,\ s = 0.106$$

for various other systems and for varying groups of narcotics, only linear relationships were found to exist.[49] For a fairly large series of barbiturates studied for tadpole narcosis, the linear correlation obtained by Hansch et al.[50] was

$$\log (1/C) = 0.875(\pm 0.07) \log P + 0.108(\pm 0.10) \quad (27)$$

$$n = 28,\ r = 0.975,\ s = 0.182$$

Attempts were made to correlate the narcotic effects with other parameters also. Ostrenga related[51] the data of Table 4 with molar attraction constant F (eq 28), Kier et al.[52] related the Overton data[10] for a series of miscellaneous compounds with their connectivity index χ (eq 29), and Moriguchi and Kanada[53] related the still larger set of Overton's data[10] with van der Waals volume V_W and a hydrophilic parameter V_H (eq 30). As indicated by Ostrenga,[51] F is a good measure of relative hydrophobicity, and χ is well related with log P.[20]

$$\log (1/C) = 3.03 \times 10^{-3} F - 1.10 \quad (28)$$

$$n = 27,\ r = 0.968$$

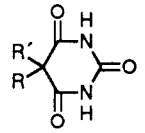
$$\log (1/C) = 0.922(\pm 0.049)(^1\chi) - 0.931(\pm 0.158) \quad (29)$$

$$n = 36,\ r = 0.956,\ s = 0.297$$

$$\log(1/C) = 2.940(\pm 0.243) V_W - 2.022(\pm 0.235) V_H + 0.390(\pm 0.246) \quad (30)$$

$$n = 53,\ r = 0.969,\ s = 0.290$$

TABLE 6. Hypnotic Activity of 5,5-Barbiturates[57]



no.	R	R′	log (1/C)	log P
1	ethyl	ethyl	3.09	0.65[a]
2	propyl	propyl	3.55	1.65
3	propyl	isopropyl	3.63	1.45
4	butyl	butyl	2.84	2.65
5	ethyl	isopropyl	3.30	0.95
6	ethyl	isobutyl	3.63	1.45
7	ethyl	butyl	3.72	1.65
8	ethyl	isoamyl	3.75	1.95
9	propyl	isoamyl	3.48	2.45
10	ethyl	phenyl	3.46	1.42[a]
11	ethyl	*sec*-butyl	3.63	1.45

[a] Experimentally determined values; all other values calculated.[44]

Further, the data that were used to derive eq 30 were already shown by Leo et al.[54] to be linearly well related with log P ($r^2 = 0.913$).

Murray et al.[55] related the narcotic effects of some alcohols with χ (eq 31), and Yalkowsky and Flynn[56]

$$\log (1/C) = 1.073(\pm 0.041)(^1\chi) - 1.167 \quad (31)$$

$$n = 15,\ r = 0.991,\ s = 0.141$$

observed a linear relationship with the chain length of alcohols. However, all these data were already shown to be well related with log P.[49] Thus the narcotic effect is found to be governed primarily by the lipid solubility of molecules. The existence of only a linear relationship with log P in tadpole narcosis suggests that the log P_0 for the maximum activity had not been reached among the points examined; hence all the points lay on the initial linear portion of the parabola.

2. Hypnotics and Sedatives

As a nonselective general depressant, a hypnotic drug produces drowsiness and sleep that resembles natural sleep and from which the recipient may be easily aroused. This effect is called hypnosis. On the other hand, a sedative drug, which also acts as a nonselective depressant, decreases activity, moderates excitement, and calms the recipient. These effects are known as sedation. The difference between hypnotic and sedative actions depends on dosage—a higher dose leads to hypnosis and a smaller dose to sedation. In fact, most hypnotic and sedative drugs, when used in high doses, can induce general anesthesia.

Barbiturates have been widely studied for their hypnotic effects, and structure–activity relationship studies have shown that, like general anesthesia, hypnosis is also a strong function of the lipid solubility of hypnotics. In an early QSAR study, Hansch and Anderson[44] correlated the hypnotic data of Shonle and Moment[57] on rabbits for a series of barbiturates (Table 6) with log P as

$$\log (1/C) = 2.092 \log P - 0.630(\log P)^2 + 1.918 \quad (32)$$

$$n = 11,\ r = 0.986,\ s = 0.139,\ \log P_0 = 1.66$$

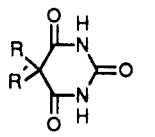
Later, Hansch et al.[58] made a wider QSAR study on the hypnotic effects of barbiturates, nonbarbiturates, and thiobarbiturates observed by various authors[59] in different experimental animals. The results obtained are shown in Table 7. Among the equations obtained for barbiturates, eq 33–37 were for series belonging to I, eq 38 for that belonging to II, and eq 39 for derivatives of III. Similarly, among those obtained for non-

TABLE 7. Activity and log P Correlations for Various Hypnotics

$$\log (1/C) = a \log P - b(\log P)^2 + c$$

exp animal	a	b	c	n	r	s	log P_0	eq no.
Barbiturates								
mice[a]	1.579	0.438	1.926	13	0.969	0.098	1.80	33
rabbits[b]	2.377	0.529	1.351	9	0.744	0.139	2.25	34
rats[c]	0.719	0.173	2.653	17	0.531	0.099	2.08	35
rats[d]	1.804	0.545	2.098	15	0.855	0.124	1.65	36
mice[e]	2.797	0.690	0.672	13	0.702	0.219	2.03	37
mice[f]	1.273	0.236	1.867	10	0.915	0.132	2.69	38
mice[g]	1.300	0.240	1.948	14	0.737	0.914	2.71	39
Nonbarbiturates								
mice[h]	0.864	0.219	2.501	6	0.858	0.178	1.97	40
mice[i]	2.451	0.686	0.724	8	0.965	0.058	1.79	41
mice[j]	2.134	0.510	0.857	8	0.944	0.105	2.09	42
mice[j]	2.099	0.675	1.663	8	0.947	0.082	1.56	43
rabbits[k]	1.020	0.231	1.516	11	0.826	0.114	2.21	44
guinea pigs[l]	1.589	0.414	1.322	13	0.805	0.130	1.92	45
mice[m]	0.999	0.314	1.983	6	0.913	0.108	1.59	46
mice[n]	0.599	0.177	1.893	14	0.918	0.079	1.69	47
Thiobarbiturates								
mice[o]	1.763	0.327	0.928	7	0.994	0.035	2.70	48
rats[p]	2.409	0.834	0.414	7	0.919	0.150	3.13	49
rabbits[q]	2.221	0.326	0.602	11	0.958	0.102	3.41	50

[a–q] Data from ref 59a–q, respectively.



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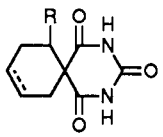

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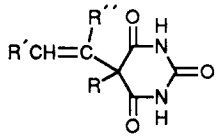

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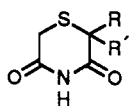

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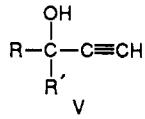

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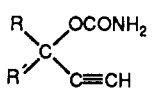

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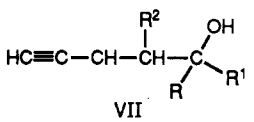
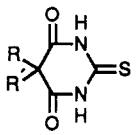


VII

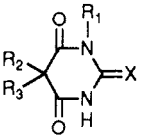


VIII

barbiturates, eq 40 was for the series of IV, eq 41 and 42 for the series of V, eq 43 for derivatives of VI, eq 44 for derivatives of VII, and eq 45–47 for tertiary alcohols, $(CH_3)_2C(SR)CONH_2$, and *N,N*-diacylureas, respectively, while all the equations obtained for thiobarbiturates belonged to different series of VIII. In all the series of compounds, the substituents were varying alkyl or alkenyl groups.

All the equations of Table 7, except eq 34, 35, and 39, express very significant correlations between the hypnotic activity and log P. Of those not expressing a high correlation, only eq 35 is not significant; the other two are reasonably good. The other commonality existing among all these equations, including eq 32, is that all of them represent parabolic correlations with not too different log P_0 values, even though they belong to a wide range of structurally dissimilar series of compounds acting on different kinds of animals. The mean

TABLE 8. Hypnotic Activity of Barbiturates



no. 1–15, X = O
no. 16, 17, X = S

no.	compd	R_1	R_2	R_3	log (1/C)	RI
1	barbituric acid	H	H	H		53
2	barbital	H	CH_2CH_3	CH_2CH_3	3.09	423
3	allobarbital	H	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	3.54	511
4	phenobarbital	H	CH_2CH_3	C_6H_5	3.32	523
5	metharbital	CH_3	CH_2CH_3	CH_2CH_3	3.12	532
6	aprobarbital	H	$CH_2CH{=}CH_2$	$CH(CH_3)_2$	3.60	552
7	butabarbital	H	CH_2CH_3	$CH(CH_3)CH_2CH_3$	3.63	600
8	cyclobarbital	H	CH_2CH_3	1-cyclohexenyl		604
9	butethal	H	CH_2CH_3	$CH_2CH_2CH_2CH_3$	3.72	610
10	butalbital	H	CH_2CH_3	$CH_2CH(CH_3)_2$	3.63	616
11	hexobarbital	CH_3	CH_3	1-cyclohexenyl	4.37	648
12	amobarbital	H	CH_2CH_3	$CH_2CH_2CH(CH_3)_2$	3.75	681
13	pentobarbital	H	CH_2CH_3	$CH(CH_3)CH_2CH_2CH_3$	4.05	686
14	secobarbital	H	$CH_2CH{=}CH_2$	$CH(CH_3)CH_2CH_2CH_3$	4.20	728
15	methohexital	CH_3	$CH_2CH{=}CH_2$	$CH(CH_3)C{=}CH_2$	4.74	776
16	thiopental	H	CH_2CH_3	$CH(CH_3)CH_2CH_2CH_3$	3.98	732
17	thiamylal	H	$CH_2CH{=}CH_2$	$CH(CH_3)CH_2CH_2CH_3$	4.15	760

log P_0 value found by Hansch et al.[58] was 1.98 ± 0.35. One assumes that drugs move by a random walk process to the receptor sites in the CNS. All the equations, therefore, strongly indicate that the diverse series of hypnotics have the same rate-determining step in producing CNS depression. This step may lie in the penetration of the inter- and/or intracellular membranes or one of the prior barriers such as the blood–brain barrier. The log P_0 of 2.0 ± 0.3 can be said to be the ideal lipophilic character to design into a neutral molecule for passive penetration in the CNS. Soloway et al.[60] injected solutions of benzeneboronic acids into mice and after 15 min analyzed for the concentration of boron in the mouse brain. For this solution, Hansch et al.[58] found log P_0 = 2.3.

Certain hypnotic data on barbiturates were also correlated with the molecular connectivity index (eq 51);[61] however, as this correlation was also parabolic and χ is well correlated with log P,[20] eq 51 does not present any different meaning than what we have discussed so far. However, in a few cases, as exhibited by eq 52 and 53, the hypnosis was found to have only a linear dependence on the lipid solubility of molecules. Equation

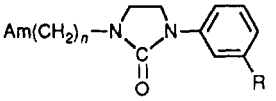
$$\log (1/C) = 1.782(^1\chi^v) - 0.129(^1\chi^v)^2 - 2.038 \quad (51)$$
$$n = 9,\ r = 0.883,\ F_{2,6} = 10.5$$

$$\log (1/C) = 2.42(\pm 0.12) + 0.55(\pm 0.09) \log P \quad (52)$$
$$n = 23,\ r = 0.943,\ s = 0.116$$

$$\log (1/C) = 1.36(\pm 0.03) + 0.0039(\pm 0.0006)\mathrm{RI} \quad (53)$$
$$n = 15,\ r = 0.875,\ F_{1,13} = 42.6$$

52 was derived[1c,49] for a series of arylalkylureas tested in mice,[62] and eq 53 was obtained[63] for a series of barbiturates as shown in Table 8. In eq 53, RI is the high-pressure liquid chromatography (HPLC) retention index, which parallels the octanol–water partition coefficient. These linear relationships indicate that probably in these cases the maximum activity had not been reached.

TABLE 9. CNS Depressant Activity of 2-Imidazolidinones[64]



no.	Am	n	R	log (1/C)[a]	log (1/C)[b]	log (1/C)[c]	log P[d]
1	pyrrolidinyl	2	Br	5.63	4.19		3.50
2	pyrrolidinyl	2	Cl	5.47	3.92	3.52	3.32
3	pyrrolidinyl	2	H	5.01	3.72	3.30	2.56
4	Et_2N	2	Br	5.42	4.19		3.58
5	Et_2N	2	Cl	5.33	4.39	3.82	3.40
6	EtMeN	2	Cl	5.37	3.81	3.45	2.90
7	EtMeN	2	H	5.09	3.92	3.44	2.14
8	EtMeN	2	Br	5.13	3.78		3.08
9	Me_2N	2	Cl	5.03	3.65	3.41	2.40
10	Me_2N	2	Br	4.89	3.72	3.37	2.58
11	Me_2N	2	SCH_3	4.67	3.65	3.31	2.26
12	Me_2N	2	OCH_3	4.64	3.42	3.20	1.76
13	Me_2N	2	CH_3	4.44	3.38		2.15
14	Me_2N	2	OH	4.05	2.96	2.95	1.15
15	Me_2N	2	H	3.84[e]	3.97[e]	3.13	1.64
16	Me_2N	3	Br	4.12[e]	3.64[e]	3.34	3.08
17	Me_2N	3	Cl	3.80[e]	3.76[e]	3.25	2.90
18	piperidinyl	2	Cl	4.88[e]	4.19	3.90	3.88
19	piperidinyl	2	H	4.23[e]	3.53	3.44	3.06
20	morpholinyl	2	Cl	4.07[e]	3.31	3.37	1.89
21	chlorpromazine			5.20	4.72	4.50	5.35

[a] Reduction of motor activity. [b] Ataxia. [c] Paralysis. [d] Calculated.[65] [e] Not used in regressions.

2-Imidazolidinones (Table 9) were studied[64] for their general depressant activity. Their potencies as measured in different tests were found[65] to be significantly related with log P as follows:

Reduction (50%) of motor activity of mice

$$\log (1/C) = 1.359 \log P - 0.163(\log P)^2 + 2.638 \quad (54)$$
$$n = 15,\ r = 0.91,\ s = 0.19,\ \log P_0 = 4.17$$

Inhibition of walk of mice (ataxia)

$$\log (1/C) = 0.403 \log P + 2.662 \quad (55)$$
$$n = 18,\ r = 0.91,\ s = 0.19$$

Paralysis in mice (inability of 50% of the test mice to remain on a 60° inclined screen)

$$\log (1/C) = 0.331 \log P + 2.552 \quad (56)$$
$$n = 17,\ r = 0.92,\ s = 0.14$$

The existence of linear relationships in the case of ataxia and paralysis tests led to the suggestion again that log P_0 for the maximum activity had not been reached. It was also suggested[65] that these compounds may be a different type of sedative hypnotic than those having log P_0 about 2, as they have log $P_0 > 4.0$ (eq 54). Exceptions in these correlations were attributed to chain steric factors. However, the muscle relaxant activity and acute lethal toxicity of some cyclohexanones etc. were found[66] to have a parabolic relation with log P as shown by eq 57 and 58, respectively, having log P_0 values comparable to those of barbiturates. Likewise, the acute lethal toxicity of a series of miscellaneous compounds (barbiturates, hydantoins, and imides) was also found to have a similar correlation (eq 59). In eq

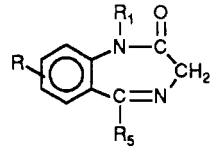
$$\log (1/C) = 1.601 \log P - 0.313(\log P)^2 - 0.276\mu \quad (57)$$
$$n = 8,\ r = 0.92,\ s = 0.21,\ \log P_0 = 2.56$$

$$\log (1/C) = 1.166 \log P - 0.217(\log P)^2 - 0.286\mu \quad (58)$$
$$n = 8,\ r = 0.85,\ s = 0.25,\ \log P_0 = 2.69$$

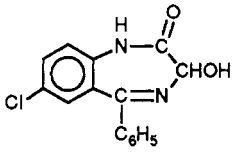
$$\log (1/C) = 0.80 \log P - 0.226(\log P)^2 - 0.361\mu \quad (59)$$
$$n = 10,\ r = 0.99,\ s = 0.11,\ \log P_0 = 1.77$$

57–59, however, there was an additional factor μ, the dipole moment of the compound. The negative coefficient of this factor suggests that if there is a polar moiety in the molecule, that would lead to a decrease in the CNS activity of the compound and that the more polar is the moiety, the less would be the activity.

1,4-Benzodiazepin-2-ones (IX) are a series of lactams including clinically employed drugs such as diazepam (IX, $R_1 = CH_3$, $R_5 = C_6H_5$, R = 7-Cl), nitrazepam (IX, $R_1 = H$, $R_5 = C_6H_5$, R = 7-NO_2), and oxazepam (X).



IX



X

Although several empirical rules have been established for the molecular design of these lactams with high CNS activity,[67] so far no mechanistic rationale has been provided to account for these rules. According to various authors,[68-72] geometrical factors play a major role in determining the chemical reactivity and resultant pharmacological activity of compounds containing lactam rings. The degree of nonplanarity of the amide group is thought to determine the lability of the lactam ring. However, if the geometry of the latter remains essentially constant in a series of compounds, then it is probable that electronic factors play an important role. This has been observed in a series of nine *N*-phenyl β-lactams having various phenyl substituents.[73] To substantiate this further, Blair and Webb[74] made CNDO/2 MO (molecular orbital) calculations on a series of substituted 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (IX, R_1 = H or CH_3, R_5 = substituted phenyl or pyridyl ring, R = variety of substituents) and tried to correlate the MO parameters with various CNS activities[67] of these compounds (eq 60–65).

Sedation and muscle relaxation in mice

$$\log (1/C) = 1.62(\pm 0.15) - 0.316(\pm 0.047)\mu \quad (60)$$
$$n = 45,\ r = 0.719,\ s = 0.429,\ F_{1,43} = 46.01$$

$$\log (1/C) = 9.1(\pm 6.3) - 0.298(\pm 0.048)\mu + 22.3(\pm 18.7)q_O \quad (61)$$
$$n = 45,\ r = 0.730,\ s = 0.427,\ F_{2,42} = 23.95$$

Sedation and muscle relaxation in cats

$$\log (1/C) = 4.24(\pm 0.19) - 0.481(\pm 0.067)\mu \quad (62)$$
$$n = 39,\ r = 0.761,\ s = 0.486,\ F_{1,37} = 51.03$$

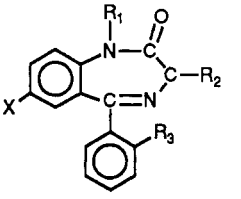
$$\log (1/C) = 18.3(\pm 11.9) - 0.389(\pm 0.103)\mu + 42.2(\pm 35.9)q_O \quad (63)$$
$$n = 39,\ r = 0.771,\ s = 0.483,\ F_{2,36} = 26.47$$

Taming activity (footshock test) in mice

$$\log (1/C) = 2.21(\pm 0.15) - 0.339(\pm 0.049)\mu \quad (64)$$
$$n = 39,\ r = 0.748,\ s = 0.386,\ F_{1,37} = 46.88$$

$$\log (1/C) = 9.57(\pm 10.6) - 0.293(\pm 0.082)\mu + 22.1(\pm 31.9)q_O \quad (65)$$
$$n = 39,\ r = 0.752,\ s = 0.388,\ F_{2,36} = 23.35$$

In eq 60–65, μ is the total dipole moment of the whole molecule and q_O is the net charge on the carbonyl oxygen. In these equations, only μ appears to be significant, and the charge on the oxygen hardly affects the correlation. There was a covariance also between μ and q_O, but with q_O the correlations were found[74] to be poorer than with μ. The inclusion of the hydrophobic parameter π was not found to improve the correlation. According to Blair and Webb,[74] the negative correlations with μ may be due to a binding process that involves dipole interaction removing the drug molecules from active service. However, since these correlations are not of very high degree, it still remains to be found what other physicochemical properties govern the activities of this class of CNS drugs. For another set of benzodiazepine analogues XI, Biagi et al.[75] measured



XI

X = Cl or NO_2
R_1 and R_2 = variety of substituents
R_3 = H, F, or Cl

the unspecific depressant effect by an exploratory behavior test in rats and the antianxiety effect by conflict behavior tests (punished and unpunished schedule) in them and correlated these effects with the measured chromatographic R_m values as follows:

Depressant effect

$$\log (1/C) = 2.912(\pm 1.076)R_m - 0.800(\pm 0.288)R_m^2 + 1.132(\pm 0.213)I_3 - 1.276(\pm 0.923) \quad (66)$$
$$n = 28,\ r = 0.855,\ s = 0.482,\ F_{3,24} = 21.81,\ R_{m,0} = 1.82$$

Antianxiety effect (punished)

$$\log (1/C) = 1.593(\pm 0.382)R_m + 0.803(\pm 0.162)I_3 - 1.195(\pm 0.648) \quad (67)$$

$$n = 17,\ r = 0.876,\ s = 0.330,\ F_{2,14} = 23.17$$

Antianxiety effect (unpunished)

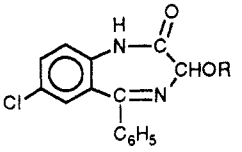
$$\log (1/C) = 1.107(\pm 0.454)R_m + 1.012(\pm 0.202)I_3 - 0.777(\pm 0.773) \quad (68)$$

$$n = 17,\ r = 0.845,\ s = 0.394,\ F_{2,14} = 17.54$$

In eq 66–68, I_3 is an indicator parameter with a value of unity for R_3 = Cl/F and zero for R_3 = H. Thus it indicates that halogen at the R_3 position may influence the activity by its electron-withdrawing effect. The parameter R_m was shown by Biagi et al.[75] to have a good correlation with log P, so a hydrophobic effect was elicited in the activity of benzodiazepines also. Similar conclusions were also recently drawn by Ray et al.[76] when they analyzed Biagi et al.'s data in relation to some structural parameters and log P. From the correlation between R_m and log P, $R_{m,0}$ = 1.82 in eq 66 was found to correspond to log P_0 = 2, the mean of log P_0 values obtained for the majority of barbiturates. Hence, it can be assumed that the depressant activity of benzodiazepines involves the same rate-limiting step as the hypnotic activity of barbiturates or others having log $P_0 = 2.0 \pm 0.3$.

Most of the drugs used to treat anxiety are either sedatives or at least have many properties in common with traditional sedatives such as barbiturates. Benzodiazepines share some of these properties when given in high doses. However, the wide diversity of compounds used to treat anxiety greatly complicates attempts to make any generalization about them.

Some authors[77] correlated the kinetic constant (k_1) of oxazepam esters XII, characterizing their appearance



XII

in the brain, with R_m values (eq 69), but since k_1 was also found to be correlated with the microsomal maximal hydrolysis rate, V_{max} (eq 70), and since R_m and V_{max} were strongly intercorrelated, the direct role of ester hydrophobicity in oxazepam appearance could not be explained.

$$\log k_1 = 2.52(\pm 2.33)R_m^2 - 3.25(\pm 1.42)R_m - 0.74$$

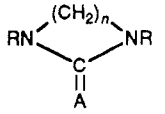
$$n = 10,\ r = 0.954,\ s = 0.205,\ R_{2,7} = 35.1 \quad (69)$$

$$\log k_1 = 0.60(\pm 0.14) \log V_{max} - 2.08$$

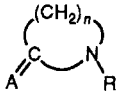
$$n = 10,\ r = 0.952,\ s = 0.195,\ F_{1,8} = 76.8 \quad (70)$$

Benzodiazepines possess a variety of CNS activities.[78] Lukovits and Lopata[79] intercorrelated the sedative, depressant, and anticonvulsant activities by principal component analysis, decomposing them into mutually independent components. Later, Lukovits[80] related one of the activities, the taming activity in mice (footshock test), with parameters obtained by principal component analysis on various electronic indices. These studies of Lukovits[80] and Lukovits and Lopata[79] were, however, of only predictive value within the data set examined and did not provide any insight into the mechanism of drug action.

TABLE 10. Acute Lethal Toxicity of Some Stimulants (Ureas, Thioureas, Lactams, Thiolactams, and γ-Thiobutyrolactone)[85-87]



no. 1–10

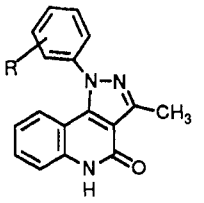


no. 13–21

no.	A	R	n	log (1/C)	log P[a]	μ[b]
1	S	CH_3	2	2.91	0.46	5.32
2	S	C_2H_5	2	2.72	1.46	5.32
3	S	H	3	2.32	−0.29	5.79
4	S	CH_3	3	3.12	0.83	5.63
5	S	C_2H_5	3	3.05	1.83	5.63
6	S	n-C_3H_7	3	2.72	2.83	5.63
7	O	H	4	1.60	−0.59	4.43
8	O	CH_3	4	2.31	0.53	3.75
9	S	H	4	2.78	0.13	5.36
10	S	CH_3	4	3.29	1.25	5.29
11	hexahydro-*o*-phenyleneurea			2.45	0.24	4.01
12	hexahydro-*o*-phenylenethiourea			3.30	1.01	5.60
13	S	H	3	2.28	−0.05	4.52
14	S	H	4	2.82	0.13	4.83
15	S	H	5	3.30	0.75	4.88
16	S	H	6	3.80	1.00	4.86
17	S	H	7	3.72	1.44	4.85
18	O	H	5	2.24	−0.19	3.88
19	O	H	6	2.67	0.24	3.86
20	O	H	7	2.88	0.67	3.85
21	O	H	11	1.72	1.72	3.64
22	γ-thiobutyrolactone			2.71	0.60	3.83

[a] Calculated.[85-87] [b] Measured; see ref 85–87.

Benzodiazepines are, however, supposed to act via a specific receptor mechanism, and therefore much attention has been paid toward the study of the nature of their binding with the receptors. In a recent study, Cecchi et al.[81-83] prepared a series of 1-aryl-3-methylpyrazolo[4,5-*c*]quinolin-4-ones (XIII) and studied their



XIII

ability to displace specific [^{3}H]flunitrazepam, a tritiated benzodiazepine from bovine brain membrane. The concentration of these compounds leading to 50% inhibition of specific [^{3}H]flunitrazepam binding was shown[84] to be significantly correlated with Taft's steric parameter, E_s, and Hansch's hydrophobic constant, π, of aryl substituents (eq 71), suggesting that binding of

$$\log (1/C) = 0.481(\pm 0.188)[E_s(2,6)] + 0.606(\pm 0.372)[\pi(3,5)] + 4.814 \quad (71)$$

$$n = 20,\ r = 0.87,\ s = 0.278\ F_{2,17} = 24.76$$

the compounds with benzodiazepine receptor involves strong hydrophobic interaction of the 3- and 5-substituents with dominant steric effects of the 2- and

6-substituents. The benzodiazepine receptor binding affinity of these compounds was, however, also noted to be correlated with the chemical shift of a carbon atom of the tricyclic system.[83]

B. General (Nonspecific) CNS Stimulants

Not many QSAR studies are available on this class of CNS drugs. Table 10 lists a series of stimulants consisting of ureas, thioureas, lactams, thiolactams, and γ-thiobutyrolactone. These stimulants were found[85-87] to possess widespread activities, as indicated by tremors, running fits, and convulsions. Therefore, the experimental observation of their respiratory stimulation was complicated, and acute lethal toxicity was determined. This lethal toxicity was then correlated with log P and the dipole moment (μ) as shown by eq 72–74.

$$\log (1/C) = 0.819 \log P - 0.291(\log P)^2 + 0.315\mu + 0.862 \quad (72)$$
$$n = 12,\ r = 0.942,\ s = 0.193,\ \log P_0 = 1.41$$

$$\log (1/C) = 1.336 \log P - 0.589(\log P)^2 + 0.584\mu - 0.012 \quad (73)$$
$$n = 10,\ r = 0.935,\ s = 0.240,\ \log P_0 = 1.13$$

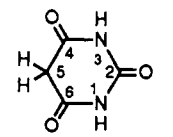
$$\log (1/C) = 1.010 \log P - 0.373(\log P)^2 + 0.227\mu + 1.405 \quad (74)$$
$$n = 22,\ r = 0.83,\ s = 0.31,\ \log P_0 = 1.35$$

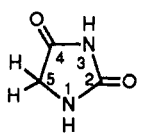
Equation 72 was obtained by Hussain and Lien[85] for ureas and thioureas (1–12), eq 73 by Lien et al.[86] for lactams and thiolactams (13–22), and eq 74 by Lien et al.[66] for all the compounds in Table 10. These equations exhibit that CNS stimulation also is a function of lipid solubility of stimulants. Further, since in all three equations, log P_0 values are in a similar range, all kinds of stimulants appear to have the same rate-limiting step. The positive dependence of the activity on μ further suggests that there may be some electrostatic interaction, most likely dipole–dipole interaction, of these stimulants with the peptide linkage of a protein or lipoprotein membrane.

C. Selective Modifiers of CNS Functions

1. Anticonvulsants

Anticonvulsants suppress epileptic seizures by depressing the central nervous sytem selectively without impairing the latter and without depressing respiration. There are many classes of drugs that are used as anticonvulsants. They include derivatives of barbiturate (XIV), hydantoin (XV), oxazolidine-2,4-dione (XVI), succinimide (XVII), benzodiazepine (XVIII), etc.


XIV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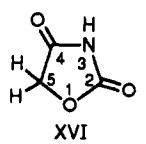
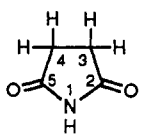

XVI


XVII

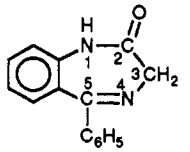

XVIII

TABLE 11. Activity of Some Anticonvulsants

(a) Miscellaneous Anticonvulsants Studied by Andrews[89]

no.	compd	log $(1/C)^a$	log P
1	3,5,5-trimethyloxazolidine-2,4-dione	2.16	−0.37
2	3,5-dimethyl-5-ethyloxazolidine-2,4-dione	2.59	0.13
3	5-ethyl-5-phenylhydantoin	3.72	1.53
4	5,5-diphenylhydantoin	4.40	2.47
5	5-phenylhydantoin	3.05	0.70
6	3-methyl-3-phenylsuccinimide	3.28	0.98
7	5-ethyl-5-phenylbarbituric acid	4.00	1.42
8	5,5-diethylbarbituric acid	3.00	0.65
9	3-ethyl-3-phenylsuccinimide	3.54	1.48
10	3,3-diphenylsuccinimide	3.74	2.25
11	3-phenylsuccinimide	2.77	0.48

(b) Miscellaneous Anticonvulsants Studied by Chen and Ensor[90]

no.	compd	log $(1/C)^b$	log $(1/C)^c$	log P
1	sodium diphenylhydantoin	4.06	4.38	2.47
2	3-methyl-5-phenyl-5-ethylhydantoin	4.49	3.69	2.09
3	5-phenyl-5-ethylhydantoin	4.16	3.74	1.53
4	sodium phenobarbital	4.43	3.99	1.42
5	*N*-methyl-5-phenyl-5-ethylbarbituric acid	4.01	3.84	1.98
6	phenylacetylurea	3.95	3.07	0.57
7	carbromal	3.79	2.92	1.04
8	5,5-diphenyl-2,4-dioxazolidinedione	2.75	2.16	1.61
9	3,5,5-trimethyloxazolidine-2,4-dione	2.41	2.16	−0.37

(c) Miscellaneous Anticonvulsants Studied by Swinyard[91]

no.	compd	log $(1/C)^d$	log P
1	3-methyl-5-ethyl-5-phenylhydantoin	3.60	2.09
2	phenobarbital	3.95	1.42
3	1-methyl-5-ethyl-5-phenylbarbituric acid	4.21	1.98
4	3,5,5-trimethyloxazolidine-2,4-dione	2.68	−0.37
5	3,5-dimethyl-5-ethyloxazolidine-2,4-dione	3.06	0.13
6	phenylacetylurea	2.95	0.57

[a] Antielectroshock activity in mice (supramaximal). [b] Antielectroshock activity in rats. [c] Antielectroshock activity in mice. [d] Pentylenetetrazole seizure protection.

Efforts were made to make QSAR studies on many of them. The data that were used in correlations were based on the measurement of effectiveness of drugs against pentylenetetrazole (metrazole) induced convulsion or minimal/maximal electroshock seizure in usually mice or rats.[88] Table 11 lists miscellaneous anticonvulsants studied by various authors.[89-91] Lien[92] made a QSAR study on them using calculated log P and obtained eq 75 for the data of Table 11a, eq 76 and 77 for the data of Table 11b, and eq 78 for the data of Table 11c. Equations 75–77 relate antielectroshock

$$\log (1/C) = 0.727 \log P + 2.521 \quad (75)$$
$$n = 11,\ r = 0.952,\ s = 0.214$$

$$\log (1/C) = 1.416 \log P - 0.403(\log P)^2 + 3.037 \quad (76)$$
$$n = 8,\ r = 0.946,\ s = 0.251,\ \log P_0 = 1.75$$

$$\log (1/C) = 0.718 \log P + 2.511 \quad (77)$$
$$n = 8,\ r = 0.928,\ s = 0.287$$

$$\log (1/C) = 0.529 \log P + 2.895 \quad (78)$$
$$n = 6,\ r = 0.886,\ s = 0.314$$

activity data, and eq 78 relates the data of the antipentylenetetrazole test. In the derivation of eq 76 and 77, compound 8 of Table 11b was not included. Its inclusion led to poorer correlations.

TABLE 12. Antielectroshock Activity of Some Cyclohexanones and Miscellaneous Compounds[93]

no.	compd	log (1/C)	log P	μ
	Cyclohexanones			
1	cyclohexanone	2.33	0.81	3.08
2	2-(2-tolyl)cyclohexanone	3.02	3.62	3.31
3	2-(*p*-aminophenyl)cyclohexanone	3.24	1.71	3.31
4	2-(α-hydroxy-*p*-chlorobenzyl)-cyclohexanone	2.95	2.62	3.64
5	2-(*p*-chlorobenzyl)cyclohexanone	3.00	4.14	3.31
6	α-cyclohexyl-*p*-chlorobenzyl alcohol	2.92	4.31	1.67
7	α-cyclohexyl-*p*-bromobenzyl alcohol	2.92	4.63	1.67
8	sodium phenobarbital	3.90	1.42	0.87
	Miscellaneous			
9	trimethadione	2.16	−0.37	1.74
10	paramethadione	2.59	0.13	1.69
11	5-ethyl-5-phenylhydantoin	3.72	1.53	1.74
12	diphenylhydantoin	4.40	2.47	1.74
13	5-phenylhydantoin	3.05	0.70	1.74
14	3-methyl-3-phenylsuccinimide	3.28	0.98	1.61
15	barbital	3.00	0.65	1.13
16	3-ethyl-3-phenylsuccinimide	3.54	1.48	1.61
17	3,3-diphenylsuccinimide	3.74	2.25	1.61
18	3-phenylsuccinimide	2.77	0.48	1.61

TABLE 13. Anticonvulsant Activity of Some Barbiturates, Hydantoins, and Imides[94]

no.	compd	log (1/C)[a]	log P	μ
1	phenobarbital	0.93	1.42	0.87
2	mephobarbital	0.99	1.98	0.87
3	metharbital	0.69	1.21	1.13
4	petharbital	0.76	2.78	1.13
5	mephenytoin	0.61	2.09	1.74
6	trimethadione	−0.65	−0.37	1.74
7	dimethadione	−0.76	−0.93	1.74
8	phensuximide	0.36	1.40	1.61
9	methsuximide	0.49	1.54	1.61
10	ethosuximide	0.02	0.01	1.47

[a] Anti-pentylenetetrazole-induced seizures.

While the dipole moment was shown not to play any role in this study, Lien et al. found that it had an effective role in another study.[66] Equations 79 and 80

$$\log (1/C) = 1.423 \log P - 0.267(\log P)^2 - 0.368\mu + 2.619 \quad (79)$$

$$n = 8,\ r = 0.89,\ s = 0.26,\ \log P_0 = 2.49$$

$$\log (1/C) = 1.153 \log P - 0.222(\log P)^2 - 0.368\mu + 2.994 \quad (80)$$

$$n = 18,\ r = 0.92,\ s = 0.24,\ \log P_0 = 2.59$$

were derived[66] for antielectroshock activity in mice of some cyclohexanes and miscellaneous compounds (Table 12) studied by Brodie et al.[93] While eq 79 related the data of only cyclohexanes, eq 80 related all the data of Table 12, including those of miscellaneous compounds. Similarly, the anti-pentylenetetrazole activity in mice of some barbiturates, hydantoins, and imides (Table 13)[94] was correlated[66] with log P and μ as shown by eq 81. The anti-pentylenetetrazole activity of an-

$$\log (1/C) = 0.588 \log P - 0.123(\log P)^2 - 0.597\mu + 0.825 \quad (81)$$

$$n = 10,\ r = 0.99,\ s = 0.12,\ \log P_0 = 2.39$$

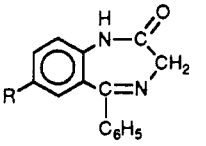
other series of miscellaneous compounds (Table 14)[95] was also found[96] to be related with log P and μ in the same fashion (eq 82). However, the antielectroshock

TABLE 14. Anticonvulsant Activities of Various Drugs[95]

no.	compd	log (1/C) MES[a]	log (1/C) MET[b]	log P	μ
1	pehnytoin	4.42		2.47	1.74
2	ethotoin	3.38	3.63	1.53	1.74
3	mephenytoin	3.56	3.86	2.09	1.74
4	phenobarbital	4.03	4.25	1.42	0.87
5	methabarbital	3.19	4.30	1.21	1.13
6	mephobarbital	3.86	4.02	1.98	0.87
7	primidone	4.28	3.57	2.10	1.35
8	trimethadione	2.36	2.68	−0.37	1.74
9	paramethadione	2.82	3.40	0.13	1.69
10	ethosuximide	<2.15	3.04	0.01	1.47
11	methsuximide	3.43	3.48	1.54	1.61
12	phensuximide	3.23	3.58	1.40	1.61
13	phenacemide	3.31	3.19	0.57	2.06

[a] Maximal electroshock seizure test. [b] The subcutaneous pentylenetetrazole seizure threshold test.

TABLE 15. Anticonvulsant Activities of 1,4-Benzodiazepinones[67]



compd	R	log (1/C)[a]	log (1/C)[b]	log (log/C)[c]	π	σ
1	H	<2.47[d]	3.89	3.49	0.00	0.00
2	F	<2.50[d]	2.92[d]	3.40	0.14	0.06
3	Cl	4.65	4.03	3.32	0.71	0.23
4	Br	5.20	4.90[d]	3.20	0.86	0.23
5	CN	5.31	3.89	2.59[d]	−0.57	0.66
6	NO_2	5.60	3.97	2.90[d]	−0.28	0.78
7	CF_3	5.48	4.78	4.16	0.88	0.54
8	CH_3	3.16[d]	3.22	<2.54[d]	0.56	−0.17
9	$N(CH_3)_2$	3.85	2.88	2.62	0.18	−0.83
10	SCH_3	4.15	3.93	2.97	0.61	0.00
11	SC_2H_5	3.57	3.07[d]	2.69	1.07	0.03
12	SC_4H_9	3.81	3.21	2.66	2.07	0.03
13	$SOCH_3$	4.07	3.52	2.99	−1.58	0.49
14	SO_2CH_3	2.72[d]	2.60	<2.60[d]	−1.63	0.72
15	C_6H_5	<2.60[d]	<2.59[d]	<2.59[d]	1.96	−0.01

[a] Anti-pentylenetetrazole test. [b] Antielectroshock (maximal) test. [c] Antielectroshock (minimal) test. [d] Not included in regression (reasons not mentioned).

activity of the same series was found to be well related with molecular weight only (eq 83).[96] So far as the

$$\log (1/C) = 0.852 \log P - 0.301(\log P)^2 - 0.629\mu + 4.139 \quad (82)$$

$$n = 12,\ r = 0.915,\ s = 0.227$$

$$\log (1/C) = 7.776 \log \mathrm{MW} - 14.438 \quad (83)$$

$$n = 13,\ r = 0.941,\ s = 0.241$$

electronic effect is concerned, in the case of certain benzodiazepines (Table 15),[67] the Hammett constant σ was used and the following correlations were obtained:[96]

Anti-pentylenetetrazole test

$$\log (1/C) = 0.144\pi - 0.307\pi^2 + 1.291\sigma + 4.558 \quad (84)$$

$$n = 10,\ r = 0.867,\ s = 0.470$$

Antielectroshock (maximal) test

$$\log (1/C) = 0.361\pi - 0.258\pi^2 + 0.954\sigma + 3.660 \quad (85)$$

$$n = 11,\ r = 0.824,\ s = 0.418$$

Antielectroshock (minimal) test

$$\log (1/C) = 0.081\pi - 0.220\pi^2 + 0.984\sigma + 3.262 \quad (86)$$

$$n = 10,\ r = 0.827,\ s = 0.326$$

However, for a larger series of benzodiazepines, the dipole moment was an important factor in their anti-pentylenetetrazole activity in mice (eq 87).[74] The hydrophobic parameter π was not found to be important here. An attempt to improve the correlation by including the net charge at the carbonyl oxygen (q_O) was not successful (eq 88). For a small series of benzodiazepines, the anti-pentylenetetrazole activity was found to be related with the rate of borohydride reduction of molecules (k_2) (eq 89),[97] suggesting a possible involvement of the carbonyl group at the receptor site. In another series of benzodiazepines, the same activity was shown to have a highly significant correlation with the electron density in the π-orbital at the aromatic carbon adjacent to the amide function.[98]

$$\log (1/C) = 0.081\pi - 0.220\pi^2 + 0.984\sigma + 3.262 \quad (86)$$

$$n = 10,\ r = 0.827,\ s = 0.326$$

$$\log (1/C) = 3.26(\pm 0.29) - 0.500(\pm 0.089)\mu \quad (87)$$

$$n = 52,\ r = 0.621,\ s = 0.866,\ F_{1,50} = 31.32$$

$$\log (1/C) = 11.6(\pm 14.6) - 0.458(\pm 0.12)\mu + 24.9(\pm 43.8)q_O \quad (88)$$

$$n = 52,\ r = 0.624,\ s = 0.872,\ F_{2,49} = 15.61$$

$$C = 2.40 - 0.88 \log k_2 \quad (89)$$

$$n = 11,\ r = 0.995$$

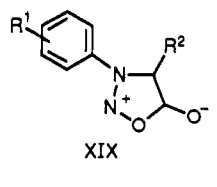
In some cases, the steric factors were also found to be important. For example, the antielectroshock activities of some hydantoins (Table 16) tested in mice and rats[99] were found[66] to be related with log P and Taft's steric parameter E_s of the N_1 substituent as shown by eq 90 and 91, while the anti-pentylenetetrazole activities of a small series of sydnones (XIX) tested in mice were found to be related with π and E_s of the substituent in the phenyl ring as shown by eq 92.[100] Equation 93 was, however, derived[101] for a series of phenylsuccinimides (XX) to show again the effect of the electronic factor in anticonvulsant activity (electroshock test). In eq 93, the electronic factor F is the Swain–Lupton field parameter.[102]

$$\log (1/C)^{\text{mice}} = 0.490 \log P + 0.525E_s + 2.286 \quad (90)$$

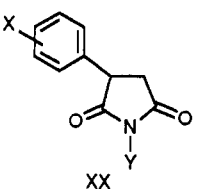
$$n = 11,\ r = 0.92,\ s = 0.26$$

$$\log (1/C)^{\text{rats}} = 1.124 \log P - 0.330(\log P)^2 + 0.540E_s + 2.330 \quad (91)$$

$$n = 11,\ r = 0.96,\ s = 0.14,\ \log P_0 = 1.70$$



XIX



XX

$$\log (1/C) = 0.71\pi(\mathrm{R}^1) - 0.64E_s(\mathrm{R}^1) \quad (92)$$

$$n = 7,\ r = 0.983,\ s = 0.079$$

$$\log (1/C) = 1.025(\pm 0.229)\pi_X - 0.350(\pm 0.127)\pi_X^2 - 0.170(\pm 0.138)F + 3.233(\pm 0.070) \quad (93)$$

$$n = 15,\ r = 0.970,\ s = 0.079,\ F_{3,11} = 58.45$$

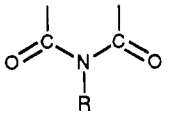
TABLE 16. Antielectroshock Activities of Hydantoins[99]

no.	hydantoin	log $(1/C)^a$	log $(1/C)^b$	log P	E_s
1	1-methyl-5-α-thienyl	2.76	2.86	0.58	0.00
2	1-ethyl-5-α-thienyl	2.91	3.13	1.08	−0.07
3	1-n-propyl-5-α-thienyl	2.72	3.14	1.58	−0.36
4	1-isopropyl-5-α-thienyl	2.94	3.01	1.38	−0.47
5	1-allyl-5-α-thienyl	2.90	3.19	1.28	−0.36
6	1-n-butyl-5-α-thienyl	2.59	2.81	2.08	−0.39
7	5-phenyl	3.04	3.36	0.34	1.24
8	diphenyl	4.44	3.95	2.47	1.24
9	5-α-thienyl	2.75	2.99	0.03	1.24
10	5,5-di-α-thienyl	3.82	3.84	1.84	1.24
11	5-phenyl-5-α-thienyl	3.92	3.83	2.15	1.24

[a] In mice. [b] In rats.

Andrews[89] analyzed the anticonvulsant activity of some compounds (see Table 11a) in relation to atomic charges of the so-called "biologically active center" and the dipole moment of the molecule. No significant correlation was obtained, and the hydrogen-bonding atoms, although common to all the compounds studied, could not be proved to be responsible for variation in the activity. Thus electronic factors are not found to play any definite role in anticonvulsant activities, and consequently the hydrophobic constant remains the prime factor in anticonvulsant action, too. The existence of only linear correlations between activity and log P (or π) (eq 75, 77, 78, 90, 92, etc.) in some cases simply suggests that log P (or π) values were not great enough in such cases to establish the upper limit for the rate of penetration.

Many conformational studies were also made on anticonvulsant drugs.[103-106] Weintraub,[103] in his conformational study on barbiturates, hydantoins, and succinimides, where the group shown by XXI is common,



XXI

found that steric, conformationally dependent, effects were important in these compounds. The relative accessibility of two of the carbonyl groups appeared to be related to the anticonvulsant activity of drugs. Weintraub also found that his charge calculations were in agreement with those of Andrews[89] in that there was no evidence of a relationship between partial atomic charges or hydrogen-bonding ability of compounds and their anticonvulsant activity. However, in a latter study on the stereochemistry and electronic structure of compounds belonging to the series of barbiturates, hydantoins, and succinimides, Andrews and Defina[105] found the existence of a common electrostatic potential field. The principal features of this potential were a positive potential region surrounding hydrocarbon substituents, negative potentials associated with carbonyl groups, and a positive potential about an imide nitrogen. These authors also noted the possibility of hydrogen bonding of compounds with the biological receptor through their carbonyl and imide nitrogen system. Their calculations also showed that anticonvulsants adopt a common preferred conformation. Thus, both stereochemical and electronic features were

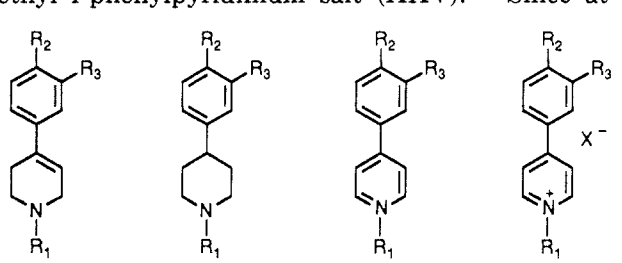
found by Andrews and Defina to play an important role in anticonvulsant actions of drugs.

The conformational analysis of convulsant and anticonvulsant barbiturates made by Andrews and Jones[104] revealed that barbiturates should have fully extended conformations with the side chains essentially perpendicular to the barbiturate ring. However, a recent conformational study by Wong et al.[106] on a series of ureides did not reveal an exclusive conformation that could account for their anticonvulsant activity. However, on the basis of their study, Wong et al.[106] proposed a general model for anticonvulsant activity comprising two aromatic rings or their equivalent in a favored orientation and a third region, usually a cyclic ureide, consisting of a number of hydrogen-bond-forming functional groups. The hydrogen-bonding groups in this region, however, appeared to be less important than the correct conformational arrangement of the hydrophobic elements.

2. Antiparkinsonism Drugs

Parkinson's disease, first described by James Parkinson in 1817 as paralysis agitans, is usually characterized by four major clinical features: tremor, bradykinesia, rigidity, and a disturbance of posture. It is independent of specific etiology and appears in the later part of life, producing a slowly increasing disability in movement. A parkinsonism-like syndrome may arise from several causes.[107,108] The untoward effect of certain drugs is one of them. The other most common causes are atherosclerosis and viral encephalitis. Drugs that produce parkinsonism have in common the capacity to prevent the action of dopamine in the basal ganglia of the brain.[109] In patients suffering from parkinsonism, it has been observed that dopamine was largely absent from their striatum and substantia nigra.[110,111] Hence, compounds that would maintain the dopamine level in basal ganglia may be useful as antiparkinsonism drugs. Though there have been studies on antiparkinsonism drugs, hardly any QSAR study is available on them.

A recent QSAR study was, however, made[112] on drugs that may lead to parkinsonism. the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, XXIIa) was found to possess the nigrostriatal neurotoxic effect causing irreversible parkinsonism in humans and primates by selective destruction of neurons in the substantia nigra.[113,114] In order to find out whether the toxic effects of MPTP in humans is related to the formation and/or clearance of metabolites, Gessner et al.[115] studied some hydroxylated derivatives of 4-phenyl-1,2,3,6-tetrahydropyridine (XXII), 4-phenylpiperidine (XXIII), 4-phenylpyridine (XXIV), and 1-methyl-4-phenylpyridinium salt (XXV). Since at



XXIIa, $R_1 = CH_3$, $R_2 = R_3 = H$ XXIII XXIV XXV

present no simple model exists to evaluate the neurotoxic effects of such compounds, they were tested[115] in vitro as inhibitors of the enzyme dihydropteridine reductase (DHPR). DHPR catalyzes the conversion of dihydrobiopterin to tetrahydrobiopterin, the required cofactor for enzymatic hydroxylation of L-tyrosine to L-dopa. Hence, DHPR plays an important role in the biosynthesis of dopamine. The inhibition activities of compounds were studied against DHPR of human liver and rat striatal synaptosomes. These inhibition potencies were found[112] to be significantly correlated with the van der Waals volume (V_W) and the Hammett constant (σ) of the R_2 substituent (eq 94 and 95). The

$$\log (1/C)(\text{hum liv}) = 5.25(\pm 1.31)V_{W,2} - 1.54(\pm 0.37)V_{W,2}^2 - 4.05(\pm 1.14)\sigma_2 - 0.89(\pm 0.45)I - 0.19 \quad (94)$$

$$n = 26,\ r = 0.968,\ s = 0.44,\ F_{4,21} = 75.28$$

$$\log (1/C) = 4.63(\pm 1.67)V_{W,2} - 1.38(\pm 0.47)V_{W,2}^2 - 4.26(\pm 1.45)\sigma_2 - 0.81(\pm 0.57)I + 0.20 \quad (95)$$

$$n = 20,\ r = 0.947,\ s = 0.56,\ F_{4,21} = 43.64$$

parameter I used in eq 94 and 95 indicates a difference between the derivatives of XXIII and those of XXII, XXIV, and XXV. It was given a value of 1 for the former and zero for the latter. The negative value of I in both eq 94 and 95 showed that a completely hydrogenated nitrogen-containing ring will reduce the activity. Equations 94 and 95 further suggest that the size and electron-donating capability of the R_2 substituent will govern the DHPR inhibition potency of the compounds (an increase in the negative value of σ increases the electron-donating capability of the substituent). However, on the basis of this single QSAR study, not much light can be thrown on the mechanism of DHPR inhibition.

3. Analgetics

Drugs that are used to relieve pain, without impairing consciousness, are known as analgetics or analgesics. They are selective central nervous system depressants. According to Lim et al.,[116] they can be grouped into (a) peripherally acting, nonnarcotic (e.g., salicylates); (b) centrally acting, nonnarcotic (e.g., *d*-proxyphene); and (c) centrally acting, narcotic (e.g., morphine and meperdine).

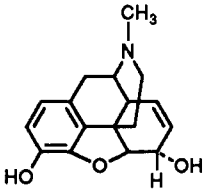
The major sites of action of centrally acting, narcotic analgetics are the cerebrum and medulla.[117] Therefore, their ability to pass the blood–brain barrier is extremely important. Consequently, the lipophilicity, molecular weight, molar refraction, and steric constants of drugs may affect their analgetic potency. Drugs that usually act as analgetics are morphine and its relatives, morphinans, benzomorphans, phenylpiperidines, diphenylpropylamines, phenothiazines, etc. All these analgetics have several common structural features,[117] e.g., a quaternary carbon atom, a phenyl or isostere ring attached to this carbon atom, a tertiary amino group two carbon atoms removed, and a phenolic hydroxyl group in the meta position relative to the point of attachment to the quaternary carbon atom if the tertiary nitrogen is part of a six-membered ring. It therefore becomes apparent that the electronic characteristics of molecules will also play important roles in their analgesic potency.

TABLE 17. Morphine-like Analgetics and Their Potencies

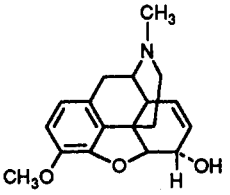
no.	compd	log P	log (C_{iventr}/C_{iv})[a]	log ($1/C$)[b]	log ($1/EC_{50}$)[c]
1	etorphine	0.15	−0.78	5.67	0.52
2	fentanyl	1.29	−0.76	4.55	0.00
3	furyl derivative	0.25	−0.48		
4	levorphanol	−2.04	−1.04	3.33	0.15
5	methadone	1.65	−0.79	2.64	−1.30
6	ketobemidone	−3.06	−1.34	2.67	−0.30
7	hydromorphone	−4.00	−2.74	3.28	0.00
8	pethidine	0.53	−0.92	1.78	−2.85
9	dihydromorphine	−5.00	−2.76	2.56	−0.48
10	morphine	−5.00	−2.95	2.44	−0.48
11	nonmorphine	−5.00	−3.47	1.21	−0.60

[a] Ratio of intraventricular and Intravenous analgetic potencies.[118] [b] Analgetic potency in mice.[119] [c] Receptor binding affinity in rats.[119]

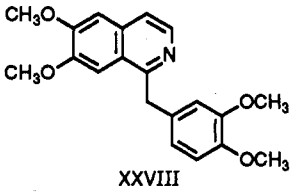
Morphine (XXVI) is an opium alkaloid. Certain other alkaloids such as codeine (XXVII) and papaverine (XXVIII) can also be extracted from opium. All these



XXVI



XXVII



XXVIII

alkaloids, including morphine, are, however, theoretically derivable from benzylisoquinoline. Since they were primarily derived from opium, they were once called opiates. Many semisynthetic congeners of morphine were also given this name. However, now all drugs, natural or synthetic, showing morphine-like actions are called opioid.

There have been some QSAR studies of analgetics. For a series of morphine-like analgetics (Table 17), Kutter et al.[118] related the ratio of activities obtained by intraventricular and intravenous application in rabbits with log P as

$$\log (C_{iventr}/C_{iv}) = 0.036(\pm 0.20) \log P - 0.090(\pm 0.05)(\log P)^2 - 0.673(\pm 0.30) \quad (96)$$

$$n = 11,\ r = 0.97,\ s = 0.297$$

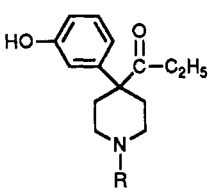
Since this ratio of activities eliminated from the equation the affinity of various analgetics for the narcotic receptor, eq 96 simply verified that the ability of molecules to reach the receptor site would be a function of log P. The two activities separately were not found to be related with log P. To show that the receptor binding affinity and lipophilicity together would determine the analgetic potency, Jacobson et al.[119] tried to correlate the analgetic potency of these compounds, determined in their laboratory for mice,[119] with log P and the receptor binding affinity (K) measured in terms of the concentration required to inhibit 50% of the stereospecific binding of [^{3}H]dihydromorphine in rat brain homogenate and obtained the equation

$$\log (1/C) = 4.254(\pm 0.699) + 1.107(\pm 0.528) \log (1/K) + 0.317(\pm 0.184) \log P \quad (97)$$

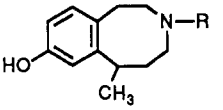
$$n = 10,\ r = 0.91,\ s = 0.62$$

The correlation expressed by eq 97 is highly significant and hence expresses that lipophilicity should be combined with receptor binding affinity for explaining in vivo analgetic activity. Further, it may be assumed that the narcotic receptor is the same or very similar in mice and rats, as the analgetic effect was determined in mice and the binding affinity in rats.

The receptor binding affinity was found to play a major role in some cases; e.g., for a small series of N-alkylnorketobemidones (XXIX),[120] for certain N-alkylnorbenzazocines (XXX),[121] and for a small group of prodine-type compounds (XXXI),[122] significant linear



XXIX



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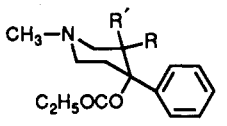
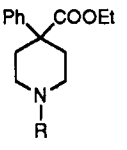


XXXI



XXXII

correlations were found to exist between the analgetic potency and the receptor binding affinity with r values of 0.951, 0.945, and 0.990, respectively. Similarly, for a series of alkyl homologues of meperdine (XXXII), the analgetic potency was shown by Pert et al.[123] to be linearly related with the receptor binding affinity with a value of $r = 0.927$. In this case, however, the binding data used were those assayed in the presence of sodium, while those used for N-alkylketobemidones (XXIX) were the ones assayed in the same laboratory in the absence of sodium. The binding data for ketobemidones[120] assayed in the presence of sodium and those for meperdines[123] assayed in the absence of sodium were found to be less significantly related with analgetic potency. In either case the binding affinity was measured against [^{3}H]naloxone binding in mouse or rat brain homogenate. This discrepancy of ketobemidones and meperdines is attributed to the difference in their abilities to bind with the receptor.[123] Ketobemidones bind more strongly with the receptor than meperdines. The sodium makes up this weakness of meperdines but reduces the ketobemidones' affinity for receptor due to some conformational change.[124]

Several qualitative observations were also made to suggest that analgetic potencies are strong functions of receptor binding affinities of drugs.[125-127] The discovery of the opiate receptor has enabled measurement of the receptor-mediated events. The opioids interact with the opiate receptor and produce several effects in vivo. Almost all opioids have been shown[128] to have some antagonist effect in addition to an agonist or opioid effect. They also have side effects in vivo, such as tolerance, dependence of the opiate type, some nausea, cough suppressant effect, respiratory depressant effect, etc. The side effects and the narcotic antagonist effects may be mediated by the same receptor. However, there

exists the possibility of a number of receptors with which the opioids and their antagonists can interact; e.g., morphine-type opioids interact with μ-receptors, agonist–antagonists such as *N*-allylnormetazocine with σ-receptors, and ketocylazocine-like compounds with κ-receptors.[129,130] There may be some other types of receptor also.

To explain the structure–activity relationships of agonists and antagonists, Snyder and co-workers[131] proposed a model of opiate receptor in which the receptor was assumed to exist in two different conformations: the antagonist conformation (a sodium-binding form) and the agonist conformation (non-sodium-binding form). Kolb[132] proposed that only one conformation of the receptor is needed for binding of both agonists and antagonists. In Kolb's model, there are two distinct, spatially fixed, amine-binding sites: one agonist amine-binding site and one antagonist amine-binding site. Agonists and antagonists interact with their respective amine-binding sites via the lone-pair electrons on their nitrogen atoms. The binding through the lone pair of nitrogen has been proposed to involve proton transfer from the nitrogen to the receptor.[133–135] However, the cationic region around the nitrogen has been shown to be relatively unaffected by varying N substituents,[136] and the main cause of differing receptor binding and interaction with active site has been attributed to the conformational behavior of the N substituents.[136,137] The positive charge on protonated nitrogen has not been found to be completely localized but delocalized over many of the neighboring atoms,[136,138,139] and morphine and morphine-like opioids have been suggested to have delocalized interaction with a diffused anionic receptor site.[139–141]

Several investigators have suggested that effective receptor interactions depend upon the drug assuming a conformation in which the key aromatic ring and the basic nitrogen exhibit a spatial relationship similar to that of morphine.[131,137,142–144] In certain classes of opioids, the presence of an allyl or cyclopropylmethyl substituent on the basic nitrogen causes the drug to act as a morphine antagonist or a mixed agonist–antagonist. Antagonists reverse the effects of μ-agonists by interaction with a separate recognition site that is coupled to the μ-opioid receptor.[145]

On the basis of the geometry and the electronic structure of some analgetic benzamide amines, obtained by using molecular mechanics and quantum mechanical methods, Cheney et al.[146] proposed that three factors play a significant role in receptor binding: (1) membrane–water partitioning, (2) the capacity of the aromatic ring and amine N substituent to act as electron acceptors, and (3) the conformational energy required to attain the binding configuration.

However, the initial data on receptor binding assayed in rat brain homogenate for ketobemidones,[120] meperdines,[123] and other morphine-like opioids[127,147] were not found[148] to be related with bulk lipophilicity of molecules. For in vitro binding to specific receptors, the bulk lipophilicity in fact should not be expected to adequately define affinities that are normally based upon steric distribution of molecular binding regions. Therefore, Johnson[148] correlated the binding affinities with only lipophilicity of some regional fragments of molecules. For regional fragments, the molecular weight and molar refraction were also found to be well correlated with the binding data.[148] However, since the pattern of choosing the fragments was quite arbitrary, little could be said about the modes of participation of molecules in the binding.

For a series of enkephalin derivatives of general structure H-Tyr-D-Ala-Gly-X-Y-NH_2, where X and Y are variable amino acid residues, the opiate receptor binding affinity was found to be related with hydrophobic, electronic, and steric constants of well-defined X and Y fragments.[149] For potencies to depress the contractions of electrically stimulated guinea pig ileum (gpi) and mouse vas deferens (mvd) preparations, the correlations obtained were[149]

$$\log (1/C)_{gpi} = 8.103 - 0.411(\pm 0.13)(\pi_X + \pi_Y) - 0.694(\pm 0.13)S_X + 0.146(\pm 0.05)(\upsilon_X + \upsilon_Y) \quad (98)$$

$$n = 12,\ r = 0.979,\ s = 0.128,\ F = 62.8$$

$$\log (1/C)_{mvd} = 9.685 - 0.667(\pm 0.07)(\pi_X + \pi_Y) - 0.629(\pm 0.04)S_X + 0.076(\pm 0.03)(\upsilon_X + \upsilon_Y) \quad (99)$$

$$n = 8,\ r = 0.998,\ s = 0.049,\ F = 845$$

$$\log (1/C)_{gpi} = 8.186 - 0.382(\pm 0.18)(\pi_X + \pi_Y) - 0.659(\pm 0.11)S_X + 0.129(\pm 0.08)(\upsilon_X + \upsilon_Y) \quad (100)$$

$$n = 8,\ r = 0.992,\ s = 0.134,\ F = 90.8$$

where π_X and π_Y refer to the hydrophobic constants of the side chains (R) of X and Y, respectively, and were obtained by the equation

$$\pi(R) = \log P(\text{amino acid}) - \log P(\text{glycine}) \quad (101)$$

and S_X refers to the electronic parameter of the side chain of X, defined as

$$S = pK_a(RCOOH) - pK_a(HCOOH) \quad (102)$$

The steric parameter υ for the side chain was calculated from its van der Waals volume, V, as

$$\upsilon(R) = [V(R) - V(H)]/V(CH_2) \quad (103)$$

These correlations exhibit a negative effect of hydrophobicity in receptor binding. Since $(\upsilon_X + \upsilon_Y)$ is shown to produce a positive effect, a van der Waals type of interaction may be assumed to be involved in the receptor binding. Since S_X, which is a function of pK_a, is also shown to produce a negative effect, it can be said that for a better binding the X moiety should be highly dissociated.

However, the notable point that has emerged from this correlation study is that both bioassays have been correlated significantly with structural parameters in identical fashion. Hence, it appears that in both systems the receptor binding sites are structurally similar. However, for another series of enkephalin-like peptides, Zaslavsky et al.[150] found that peptides do not behave in the same way in guinea pig ileum (gpi) and mouse vas deferens (mvd) or rat brain homogenate (rbh), as their activities for the latter two were significantly correlated with their bulk hydrophobicity (eq 104 and 105) but those for the former were not. In eq 104 and

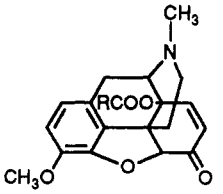
$$\log (1/C)_{mvd} = 5.806 + 0.329n^{CH_2} \quad (104)$$

$$n = 13,\ r = 0.863,\ s = 0.55$$

$$\log (1/C)_{rbh} = 7.065 + 0.345n^{CH_2} \quad (105)$$

$$n = 12,\ r = 0.996,\ s = 0.044$$

TABLE 18. Esters of 14-Hydroxycodeinone and Their Analgetic Activity



compd	R	log P	log (RA)[a]
1	CH_3	1.40	0.60
2	C_2H_5	1.90	1.27
3	n-C_3H_7	2.40	1.46
4	n-C_4H_9	2.90	1.59
5	n-C_5H_{11}	3.40	1.67
6	n-C_6H_{13}	3.90	1.78
7	n-C_7H_{15}	4.40	0.71
8	n-C_9H_{19}	5.40	0.05
9	n-$C_{11}H_{23}$	6.40	−1.47
10	$C_6H_5CH_2$	3.36	1.72
11	$C_6H_5CH_2CH_2$	3.86	2.06
12	C_6H_5CH=CH	3.66	2.25
13	CH_3CH=$CHCO$	2.20	1.49

[a] Analgetic activity relative to morphine in tail clip assay.[151]

105, n^{CH_2} refers to the hydrophobicity as the multiple of that of the CH_2 group. The hydrophobicity was measured by studying the partition coefficient in an aqueous polymeric Ficoll–dextran biphasic system.

Though it appears from eq 104 and 105 that peptides behave in a similar way in mouse vas deferens and rat brain homogenate, it was not so. The hydrophobicity values used to derive eq 104 and 105 were measured in different ionic strengths of biphasic systems. Therefore, it follows that the σ-receptor characterized in the mouse vas deferens interacts with opioid peptides under conditions entirely different, in regard to ionic composition at the membrane and/or the ionizable state of the receptor site, from those in rat brain homogenate.

However, the QSAR results of Fauchère[149] and those of Zaslavsky et al.[150] were based on insufficient data; hence no generalizations regarding opioid–receptor binding in different biosystems can be made. The hydrophobicity has also not been found in these studies to play any uniform role.

The role of hydrophobicity may thus be undecided in drug–receptor interaction, but the in vivo analgetic effects have been shown to be a strong function of log P. This is in fact not unexpected, as all narcotic analgetics have to cross the blood–brain barrier to reach the major sites of their actions in the brain, and their ability to do so will depend upon their hydrophobic nature. Therefore, the analgetic data of Buckett[151] on esters of 14-hydroxycodeinone (Table 18) were found to be highly correlated with log P (eq 106).[152,153] Similarly, the analgetic affect of meperdines (Table 19) studied by Pert et al.[123] was found to have a reasonably good correlation with log P (eq 107).[152,153] However, in the case of meperdines, the steric factor was also found to play a significant role. Consequently, when Hancock's corrected steric parameter (E_s^c)[154] for the N substituent was included in the correlation, a significant improvement to eq 107 was obtained (eq 108).[152,153]

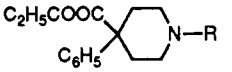
$$\log (RA) = 2.193 \log P - 0.339(\log P)^2 - 1.745 \quad (106)$$

$$n = 13,\ r = 0.960,\ s = 0.307,\ \log P_0 = 3.23$$

$$\log (1/C) = 1.681 \log P - 0.275(\log P)^2 - 2.515 \quad (107)$$

$$n = 9,\ r = 0.864,\ s = 0.239,\ \log P_0 = 2.90$$

TABLE 19. *N*-Alkylnormeperidines and Their Analgetic and Opiate Receptor Activities[123]



compd	R	log P	E_s^c(R)	analgesia[a] log (1/C)	receptor affinity[b] log (1/C)[c]	log (1/C)[d]
1	CH_3	1.28	0.00	4.48	6.30	4.40
2	C_2H_5	1.56	−0.38	4.39	5.30	4.30
3	n-C_3H_7	1.85	−0.67	4.34	5.40	4.00
4	n-C_4H_9	2.13	−0.70	4.70	6.05	4.52
5	n-C_5H_{11}	2.41	−0.71	5.00	6.40	4.82
6	n-C_6H_{13}	2.78	−0.71	5.30	6.70	5.70
7	n-C_7H_{15}	3.06	−0.71	5.30	7.26	6.19
8	n-C_8H_{17}	3.43	−0.71	5.00	7.52	6.10
9	n-C_9H_{19}	3.71	−0.71	4.82	6.82	5.10

[a] Hot-plate test in mice. [b] Inhibition of [^{3}H]naloxone binding in rate brain homogenate. [c] In the absence of Na. [d] In the presence of Na.

$$\log (1/C) = 5.041 \log P - 0.854(\log P)^2 + 2.246E_s^c - 0.563 \quad (108)$$

$$n = 9,\ r = 0.994,\ s = 0.051,\ \log P_0 = 2.95$$

The positive coefficient of E_s^c in eq 108 indicates that the analgetic effects of meperdines would be greatly hindered by a larger substituent at the nitrogen. This steric hindrance may be due to the limited bulk tolerance at the active site of the receptor. In fact, the in vitro receptor affinities of meperdines in the absence and presence of sodium both were shown,[152,153] though having a reasonably good dependence on log P (eq 109 and 110), to be greatly affected by the steric factor (eq 111 and 112).

$$\log (1/C)_{no\ Na} = 0.333 \log P + 0.077(\log P)^2 + 5.078 \quad (109)$$

$$n = 9,\ r = 0.798,\ s = 0.528$$

$$\log (1/C)_{Na} = 1.787 \log P - 0.207(\log P)^2 + 1.997 \quad (110)$$

$$n = 9,\ r = 0.794,\ s = 0.568$$

$$\log (1/C)_{no\ Na} = 7.015 \log P - 1.075(\log P)^2 + 4.471E_s^c - 1.043 \quad (111)$$

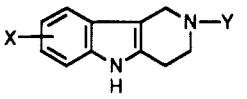
$$n = 9,\ r = 0.959,\ s = 0.271,\ \log P_0 = 3.26$$

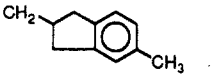
$$\log (1/C)_{Na} = 8.698 \log P - 1.398(\log P)^2 + 4.622E_s^c - 4.333 \quad (112)$$

$$n = 9,\ r = 0.947,\ s = 0.328,\ \log P_0 = 3.11$$

In eq 109–112, the square term of log P does not appear to be significant, and it is logical that a parabolic relation with log P should not be expected for in vitro measurements.

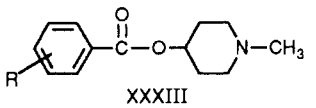
TABLE 20. Analgetic Potencies (Hot-Plate Test) of Carbolines[158]



compd	X	Y	σ_R	$E_{s,p}$	$E_{s,8}$	log $(1/C)^a$
1	6-CH_3	$(CH_2)_3COC_6H_4$-*p*-F	−0.14	−0.46	0.00	1.917
2	5-CH_3, 8-F	$(CH_2)_3COC_6H_4$-*p*-F	−0.32	−0.46	−0.46	1.745
3	8-CN	$(CH_2)_3COC_6H_4$-*p*-F	1.00	−0.46	−0.55	2.167
4	H	$(CH_2)_3COC_6H_4$-*p*-F	0.00	−0.46	0.00	1.627
5	8-CF_3	$(CH_2)_3COC_6H_4$-*p*-F	0.61	−0.46	−2.40	1.491
6	8-OCH_3	$(CH_2)_3COC_6H_4$-*p*-F	−0.43	−0.46	−0.55	1.400
7	8-Br	$(CH_2)_3COC_6H_4$-*p*-F	−0.16	−0.46	−1.10	1.377
8	8-CH_3	$(CH_2)_3COC_6H_4$-*p*-F	−0.14	−0.j6	−1.20	1.372
9	8-F	$(CH_2)_3COC_6H_5$	−0.32	0.00	−0.46	1.441
10	8-F	H	−0.32	0.00	−0.46	1.124
11	8-F	$CH_2C_6H_5$	−0.32	0.00	−0.46	0.926
12	8-Cl	H	−0.18	0.00	−0.98	1.134
13	8-F	$(CH_2)_4C_6H_4$-*p*-F	−0.32	−0.46	−0.46	1.528
14	8-F	$(CH_2)_4COCH_4$-*p*-F	−0.32	−0.46	−0.46	1.417
15	8-F	$(CH_2)_3CN$	−0.32	0.00	−0.46	0.805
16	8-F		−0.32	−0.55	−0.46	1.426
17	8-F	$(CH_2)_3CHOHC_6H_4$-*p*-F	−0.32	−0.46	−0.46	1.449
18	8-F	$(CH_2)_3COC_6H_4$-*p*-F	−0.32	−0.46	−0.46	1.589

[a] Hot-plate test.

The steric and hydrophobic parameters were also found to play equally good roles in the analgetic potency (hot plate) of a large series of substituted benzoic acid esters of 1-methyl-4-piperidinol (XXXIII) (eq 113).[155]



XXXIII

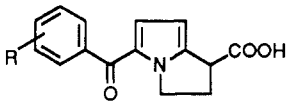
$$\log (1/C) = 0.15(\pm0.12)E_{s,p} - 0.72(\pm0.12)B_{1,m} - 0.08(\pm0.02)L_o + 0.52(\pm0.01)\pi_m + 0.40(\pm0.07)(HB)_m + 0.26(\pm0.04)(HB)_{ind,p} + 1.44 \quad (113)$$

$$n = 41,\ r = 0.89,\ s = 0.11,\ F = 21.43$$

In eq 113, $E_{s,p}$ refers to Taft's steric parameter of the para substituent, $B_{1,m}$ the minimal width of the meta substituent, and L_o the length of the ortho substituent. All three parameters therefore show that there would be steric hindrance in the activity from all positions of the phenyl ring. The hydrophobic constant π_m shows that there may be stereospecific hydrophobic interaction from the meta position.

In this case, however, the hydrogen-bonding ability of the substituents also appears to play an additional role. In eq 113, the positive coefficients of $(HB)_m$ (quantitized hydrogen-bonding parameter indicating the ability of the meta substituent to form a hydrogen bond) and $(HB)_{ind,p}$ (a parameter used to indicate the involvement of the para substituent in the hydrogen bonding) express that hydrogen bonding of the meta and para substituents with the receptor may enhance the activity of molecules. The substituents on the phenyl ring were of a varied nature.

The hydrogen-bonding and steric effects were also found[156] to play significant roles in a large series of acyl-1,2-dihydro-3*H*-pyrrolo[1,2-α]pyrrolecarboxylic acids (XXXIV). The potency relative to aspirin (RA) of the mouse writhing assay[156] was shown to be related with the hydrogen-bonding and steric parameters as expressed by eq 114, where D_h is a hydrogen-bonding



XXXIV

$$\log (RA) = 0.63(\pm0.26) - 1.09(\pm0.62)\bar{D}_h^3 - 0.67(\pm0.45)\bar{D}_h^4 - 0.79(\pm0.50)\bar{B}_3^3 - 0.47(\pm0.27)(\bar{L}^2)^2 - 0.13(\pm0.09)(\bar{L}^4)^2 - 0.70(\pm0.36)(\bar{B}_6^4)^2 \quad (114)$$

$$n = 39,\ r = 0.860,\ s = 0.54,\ F = 15.14$$

parameter equal to 1 for hydrogen bond acceptor substituents and zero for others, and B_3 and L are Verloop steric parameters.[157] Superscripts refer to the position of the substituents, and the bar denotes that for each parameter the mean has been subtracted in order to reduce the collinearities. In this case, the steric parameter appears to be effective from all positions of the phenyl ring, and the hydrogen-bonding ability is from the meta and para positions only. In this case too, the substituents were of a varied nature.

In this case, however, the hydrophobic parameter was not found to play any role. It was also not found[158] to play any role in the case of a series of γ-carbolines (Table 20). The steric parameter did show its effect by being correlated,[158] along with an electronic parameter showing the resonance effect (σ_R), with the analgetic potency (hot-plate test) as shown by eq 115, where

$$\log (1/C) = 1.39 + 0.52\sigma_R - 0.86E_{s,p} + 0.26E_{s,8} \quad (115)$$

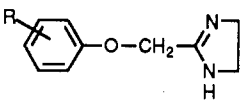
$$n = 18,\ r = 0.878,\ s = 0.17$$

$E_{s,p}$ refers to the steric constant of the para substituent at the phenyl ring of the side chain Y and $E_{s,8}$ to that of the X substituent at the 8-position of carboline. The σ_R values were taken only for X substituents at the 6- and 8-positions in carboline. Now eq 115 shows that while the steric effect of the substituent in Y will in-

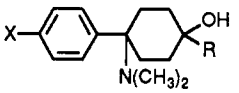
crease the activity, the same effect of the substituent in the carboline ring at the 8-position will decrease the activity. Additionally, substituents in carboline at the 6- and 8-positions will also produce a resonance effect. The hydrogen-bonding effect was not examined in this case.

Though eq 115 apparently expresses a good correlation and accounts for 77% ($r^2 = 0.77$) of the variance in the activity, it was, however, not found to correctly predict the activity of any of the compounds later synthesized in the series.[158] Hence, the correlation appears to be only a chance correlation and warrants reexamination.

Notwithstanding the above two examples, the hydrophobic nature of analgetics continues to be an important factor for their activity. Certain imidazolines (XXXV) and a group of 4-amino-4-arylcyclohexanols (XXXVI), when subjected to QSAR analysis, showed



XXXV



XXXVI

a significant dependence of their potency on hydrophobic constants of the substituents. Equation 116 was

$$\log (1/C) = 1.850\pi - 0.945\pi^2 - 7.90E_{HOMO} + 5.117 \quad (116)$$

$$n = 6,\ r = 0.975$$

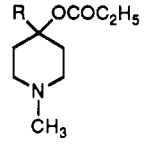
$$\log (1/C) = 1.200\pi_R + 1.633\pi_X + 0.543 \quad (117)$$

$$n = 16,\ r = 0.926,\ s = 0.615$$

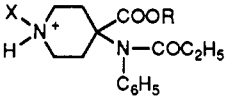
$$\log (1/C) = 1.213\pi_R + 1.205\pi_X + 0.861 \quad (118)$$

$$n = 16,\ r = 0.926,\ s = 0.598$$

derived for the mouse writhing assay of imidazolines,[159] and eq 117 and 118 were obtained for mouse tail flick and writhing assays, respectively, of the derivatives of XXXVI.[160] In eq 116, there is, however, one additional term, E_{HOMO}, which denotes the energy of the highest occupied molecular orbital in a quantum mechanical treatment of a π-electron system. The involvement of this term refers to a charge-transfer phenomenon taking place in a drug–receptor interaction. However, since eq 116 is based on an insufficient number of data points, one should not rely much upon it. However, a charge-transfer phenomenon was shown to play a major role in the analgetic action of some prodine analogues (XXXVII; R = 3-thienyl, 2-pyridyl, 3-pyridyl, 1-naphthyl, 2-naphthyl, and 3-quinolyl) when Sabih et



XXXVII



XXXVIII

al. plotted their potency versus E_{HOMO} and found a straight line.[161] Quantitatively, the relationship was expressed, without any statistical parameter, as[161]

$$\log (1/C) = 0.04 - 2.2E_{HOMO} \quad (119)$$

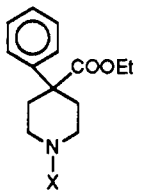
Using the hydrophobic fragment constants (f),[162] Yang et al.[163] derived eq 120 for the analgetic potency

$$\log (1/C) = 1.114f_X - 0.230f_X^2 - 1.069f_R + 3.300 \log (MW)_X - 0.399 \quad (120)$$

$$n = 60,\ r = 0.861,\ s = 0.488,\ f_{X0} = 2.25$$

of a very large series of fentanyl derivatives (XXXVIII). In eq 120, however, the molecular weight of the X substituent also appears as a governing factor; hence it is difficult to say what is the actual nature of binding—polar or hydrophobic—of X substituents with the receptor. That f_R is the only parameter appearing for the R group suggests, because of having a negative coefficient, that binding of the R group would be in a polar region.

For a series of norpethidines (XXXIX), the analgetic effect was shown qualitatively to increase with increasing chain length of the X substituent to a maximum, after which the activity fell off at a similar rate.[164]



XXXIX

The maximum activity was found when X consisted of 6 or 7 carbon atoms. This is clearly an effect of the hydrophobic nature of the X group, which increased with the chain length. In four different series, the X groups were alkyl, ω-hydroxyalkyl, ethoxyalkyl, and tetrahydro-2-furylalkyl.

4. Psychopharmacological Agents

Psychopharmacological agents are selective modifiers of the central nervous system that are used for the treatment of psychiatric disorders. They are also called psychoactive or psychotropic agents and include those drugs that either depress or stimulate selectively mental activity. They have been broadly classified into the following groups.

(*i*) *Antipsychotic Agents.* Drugs that produce calm in severely disturbed psychiatric patients and relieve them of the symptoms of their disease are called antipsychotic or neuroleptic agents. Unlike hypnotics and sedatives, they do not cloud consciousness or depress vital centers, nor do they produce coma and anesthesia even at large doses. They are used in the treatment of patients with psychotic disorganization of thought and behavior and in relief of severe emotional tension. Their main application is, in fact, in the treatment of functional psychoses, especially schizophrenia. They produce effects on the extrapyramidal system. However, they are not curative, their action being primarily palliative, as the causative factor of functional psychoses is unknown.

(*ii*) *Antianxiety Agents.* They are those psychopharmacological agents that are used to control neuroses and stress. They are also called minor tranquilizers, anxiolytics, or tensiolytics. In large doses they may be helpful in the treatment of severe psychomotor excitability such as delirium tremens. They can also be used in certain symptoms of toxic psychoses.

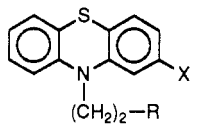
(*iii*) *Antidepressants.* Drugs that are used to restore mentally depressed patients to an improved mental status are called antidepressants. They decrease the

intensity of the patient's symptoms, reduce his tendency to suicide, accelerate the rate of his improvement, and promote his mental well being.

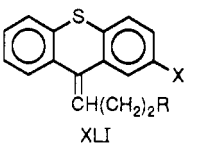
(*iv*) *Hallucinogens.* Hallucinogens commonly refer to drugs that act at the CNS to produce changes in thought, perception, and mood, sense of time and place, memory, and accustomed patterns of the outer and inner universe of "normal" individuals. Such drugs have also been called psychedelic (mind manifesting) agents to express the general activation of psychic phenomena without connotation of negative or morbid components. Another term commonly used for these CNS agents is "psychotomimetic", which implies disturbances of memory, hyperexcitability, deep depressive withdrawal, or even violent behavior resembling psychoses. However, since the extraordinary, unexpected, colorful, world encompassing, or frightening visions conjured up by these agents are comparable to autogeneous hallucinations, the term "hallucinogen" appears to be the most appropriate for them.

Hallucinogens are the most widely studied class of psychopharmcological agents. They are well studied not only experimentally but also theoretically. Many QSAR studies are available on them.[3] Antidepressants have also been well studied theoretically as well as experimentally. QSAR studies are available on them also.[2] A few QSAR studies are available on antipsychotics, too, but antianxiety agents have hardly been subjected to any QSAR study. The QSARs available on hallucinogens, antidepressants, and antipsychotics are presented here.

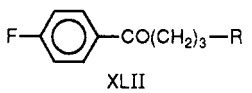
Antipsychotics. Drugs that have been found to act as antipsychotics belong to the series of phenothiazines (XL), thioxantheses (XLI), butyrophenones (XLII), and Rauwolfia alkaloids or miscellaneous compounds.



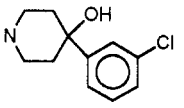
XL



XLI



XLII



XLIII

Among these, the phenothiazines and butyrophenones with chlorpromazine (XL, R = $CH_2N(CH_3)_2$, X = Cl) and haloperidol (XLII with R as XLIII) as their prototypes, respectively, are the most widely used drugs in medical practice.

Antipsychotic drugs are thought to modulate catecholamine functions in the CNS by blocking dopamine receptors.[165] There have been found good correlations between the antipsychotic potencies of butyrophenones and phenothiazines and their affinities to compete for in vitro binding of [^{3}H]haloperidol to dopamine receptors in calf and rat striatum.[166,167] Atypical neuroleptics such as benzamide derivatives have also been shown to be selective neuroleptic agents.[168] At relatively high concentrations, neuroleptics have been reported to alter neurotransmitter release from rat striatum via nonreceptor mechanisms,[169,170] and for a series of phenothiazines and benzamide derivatives, it was recently shown[171] that their ability to enhance the striatal dopamine release had a linear relationship (r = 0.727) with a lipophilic character determined by reversed-phase thin liquid chromatography. This was in fact consistent with the fact that neuroleptics are potent surface-active agents.[172]

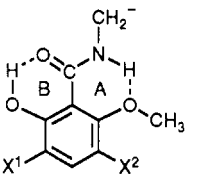
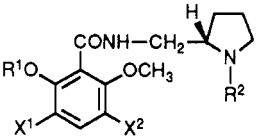


Figure 1. Formation of pseudorings in derivatives of XLIV.

Certain alkoxybenzamide derivatives (XLIV) were, however, recently characterized as potent and selective dopamine blocking agents.[173-177] They were tested for



XLIV

anti-dopamine activity in vivo by their ability to inhibit the apomorphine syndrome in rat and in vitro by their ability to displace [^{3}H]spiperone from striatal preparations of the rat brain. An analogue of haloperidol, the spiperone is one of the most potent neuroleptics discovered so far. The in vitro activity data (concentrations leading to 50% blockade of [^{3}H]spiperone binding) of a large group of these compounds studied by de Paulis et al.[176,177] were found to be correlated with the hydrophobic and electronic properties of the X^1 substituent (eq 121).[178] In eq 121, D_1 is a dummy parameter used for the R^1 substituent. The R^1 substituent was either an alkyl group or simply a hydrogen atom. D_1 was given a value of unity for the alkyl group and zero for the hydrogen. Thus eq 121, which expresses a very significant correlation, suggests that an OH group at the 2-position must be preferred. The alkylation of this group will reduce the activity. This reduction in activity due to alkylation of the OH group at the 2-position is presumed to be due to the steric hindrance produced by the alkyl group in the formation of a coplanar six-membered pseudoring through the hydrogen bonding between the amide nitrogen and the 6-methoxy group (ring A in Figure 1).[176,177] The formation of this pseudoring is presumed to be an essential structural requirement for the in vitro antidopamine activity of compounds belonging to XLIV.[176,177] The presence of an OH group at the 2-position stabilizes this planar arrangement by forming another six-membered pseudoring through the hydrogen bonding between the phenolic and carbonyl groups (ring B in Figure 1).[176,177]

$$\log (1/C) = 2.502(\pm 0.560)\pi_{X^1} - 1.013(\pm 0.353)\pi_{X^1}{}^2 - 1.283(\pm 0.543)\sigma_{X^1} - 2.238(\pm 0.319)D_1 + 6.855 \quad (121)$$

$$n = 47,\ r = 0.942,\ s = 0.414,\ F_{4,42} = 78.59$$

Equation 121 further suggests that while the hydrophobic nature of the X^1 substituent is important for the in vitro anti-dopamine activity of alkoxybenzamide derivatives, it also puts a limit on the activity. This optimization of the in vitro activity by hydrophobicity can be attributed to a limited steric bulk tolerance at the active site of the receptor. The optimum π_{X^1} value

is 1.24. So far as the role of the electronic character of the X^1 substituent is concerned, eq 121 shows that the electron-donating substituent will favor binding of compounds with the receptor. Therefore, it was suggested that along with the hydrophobic binding of the X^1 substituent with the receptor, there can be a charge-transfer phenomenon also in which the X^1 group may act as an electron donor to some electron-acceptor site of the receptor.[178] de Paulis and Hall,[179] however, found in their QSAR study on a similar series of compounds that a large lipophilic substituent at the 3-position (X^1 substituent) with little or no electronic properties was beneficial for in vitro anti-dopamine activity. Gupta et al.,[178] too, noted that there were no roles of any electronic property of the X^1 substituent in the in vivo actions of these compounds. The best correlations that were obtained for their in vivo activities (against two apomorphine syndromes, motor hyperactivity and stereotypies)[176,177] were as shown by eq 122 and 123, where only the hydrophobic effect of the X^1 substituent and the steric effect of the R^1 group had surfaced.

$$\log (1/C)_{\text{antihyper}} = 0.970(\pm 0.461)\pi_{X^1} - 0.712(\pm 0.400)D_1 + 5.732 \quad (122)$$

$$n = 34,\ r = 0.704,\ s = 0.507,\ F_{2,31} = 14.76$$

$$\log (1/C)_{\text{antistereo}} = 0.788(\pm 0.357)\pi_{X^1} - 0.792(\pm 0.313)D_1 + 5.418 \quad (123)$$

$$n = 34,\ r = 0.770,\ s = 0.395,\ F_{2,31} = 21.84$$

This difference in correlations of in vitro and in vivo activities had, however, led Gupta et al. to suggest that benzamides might have slightly different mechanisms for their in vitro and in vivo actions.[178]

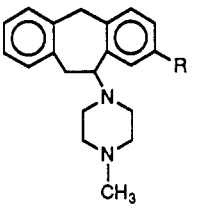
Certain quantum mechanical calculations have indicated that the neuroleptic potency of chlorpromazine-like drugs may depend upon their electron-donating character,[180,181] the folding of the tricyclic ring system along the heteroatom N axis,[182] and the conformation of the side chain.[183,184] Many conformational similarities were found between the dopamine and tricyclic neuroleptics,[185-188] and De Mol[189] suggested the relevance of charge-transfer complexes as a model for receptor interactions in which phenothiazines may act as electron donor. De Mol[189] studied the effect of some phenothiazines including chlorpromazine on the oxidation of the catecholamine neurotransmitters—noradrenaline and dopamine—catalyzed by human ceruplasmin and found that the effect was related to the electron-donating property of molecules. For example, he showed that k_{NA}/k_{NA_0}, the ratio of the pseudo-first-order rate constants for oxidation of noradrenaline (NA) in the presence and the absence of phenothiazine, was well correlated with the Hammett constant σ of the X substituent (XL) (eq 124). The values of σ used here were those used for the para substituents.

$$\log (k_{NA}/k_{NA_0}) = 0.275 - 0.302\sigma_X \quad (124)$$

$$n = 10,\ r = 0.943$$

There are, however, few Hansch-type QSAR studies on neuroleptics. The only other example that we could cite was the study of Tollenaere et al.[190] on a series of 10-piperazinodibenzo[*b*,*f*]thiepins (Table 21). For this series of neuroleptics, Tollenaere et al.[190] were able to correlate their in vivo activity (rotating-rod test in mice) with the electronic and steric parameters of the R substituent as

TABLE 21. The Neuroleptic 10-(4-Methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepins and Their Activity in the Rotating-Rod Test in Mice (in Vivo)[190]



compd	R	σ_p	E_s	V, mL	log (1/C)
1	c-Pe	−0.020	−0.51	77.4	0.096
2	*t*-Bu	−0.197	−1.54	67.5	0.154
3	OH	−0.370	0.69	5.4	0.508
4	NH_2	−0.660	0.63	17.2	0.667
5	H	0.000	1.24	3.1	0.728
6	*i*-Pr	−0.151	−0.47	51.4	0.744
7	Me	−0.170	0.00	19.2	0.869
8	F	0.062	0.78	7.4	0.935
9	Br	0.232	0.08	17.7	0.958
10	CH_2OH	0.000	0.03	21.5	1.013
11	SMe	0.000	0.17	34.7	1.026
12	Et	−0.151	−0.07	35.3	1.055
13	CF_3	0.540	−1.16	32.1	1.065
14	Cl	0.227	0.27	13.2	1.221
15	OMe	−0.268	0.69	24.7	1.309
16	CN	0.660	0.16	13.2	1.387
17	COMe	0.502	0.44	34.6	1.795

$$\log (1/C) = 0.698\sigma_p + 0.347E_s + 0.0458V - 0.00059V^2 + 0.297 \quad (125)$$

$$n = 17,\ r = 0.965,\ s = 0.128,\ F = 40.4$$

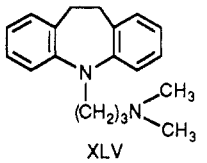
where V is the molar volume of R. In this study also, the role of the electronic parameter has surfaced, but since the coefficient of σ_p is positive, it suggests that the electron-withdrawing nature and not the electron-donating nature of the substituent will enhance the activity. The positive coefficient of E_s suggests that small R substituents would be preferred, and a parabolic correlation in V indicates that though larger substituents may lead to steric hindrance, small ones would lead to enhanced activity by involving themselves in dispersion interactions with the receptor site. This point was not well explained by Tollenaere et al. The V optimizes the activity, and its value corresponding to the optimum activity was calculated as 38.8 mL. The hydrophobic parameter was found not to be important in this study.

The opposite roles of σ_p in eq 124 and 125 are now questionable. In fact all neuroleptics are flexible molecules, and such flexible molecules are not amenable to QSAR study, as their conformations studied in the solid state or solution may not correspond to those required to express the effect at the receptor site. Therefore, the most useful information of this type would result from studies on conformationally restricted molecules having specific neuroleptic properties.

Another pitfall in the study of Tollenaere et al.[190] is that the rotating-rod test is a measure of ataxia, which is neither specific for neuroleptics nor generally seen in all classes of neuroleptics. Hence, unless sufficient QSAR studies are available on specific neuroleptics, no

convincing conclusion can be drawn regarding their modes of actions.

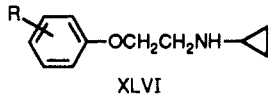
Antidepressants. The antidepressant agents mainly fall into two groups: (i) the monoamine oxidase (MAO) inhibitors, a structurally heterogeneous class of substances, and (ii) tricyclic compounds structurally related to the phenothiazine class of antipsychotic agents, the prototype of which is imipramine (XLV). No QSAR



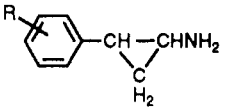
XLV

studies are available on the latter class of antidepressants but sufficient studies are available on MAO inhibitors, which have been systematically compiled and critically analyzed in a recent review.[2] Since they have already been discussed in detail, we present them here summarily and discuss their important implications.

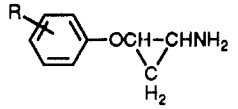
MAO is an insoluble enzyme located on the outer membrane of the mitochondrion[191] and probably forms an intrinsic part of the structure of this membrane.[192] It plays an important role in the inactivation of both exogenously and endogenously formed amines.[193] Excessive biological inactivation of neurotransmitters such as noradrenaline, dopamine, and serotonin by MAO becomes the cause of mental depression. Since the discovery that the antidepressant activity of iproniazid is due to its high in vivo MAO inhibition,[194] several series of MAO inhibitors have been studied. Some of the known MAO inhibitors[195,196] include (arylalkyl)hydrazines, aryl hydrazides, arylpropargylamines, arylcyclopropylamines, (aryloxy)cyclopropylamines, *N*-cyclopropyl(aryloxy)ethylamines, β-carbolines, and α-methylated arylalkylamines. Those on which QSAR studies were discussed are *N*-(phenoxyethyl)cyclopropylamines (XLVI), phenyl- and phenoxycyclopropylamines (XLVIIa,b), (arylalkyl)hydrazines (XLVIIIa–c), arylhydrazides [$ArCONHNHCH(CH_3)_2$], (aryloxy)acetohydrazides (XLIX), α-methyltryptamines (L), β-carbolines (LI), tetrahydro-β-carbolines (LII), and pargylines (LIII) and their analogues. The most significant QSAR equations obtained in each case are as follows.



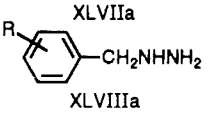
XLVI



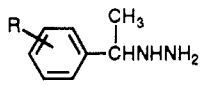
XLVIIa



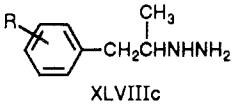
XLVIIb



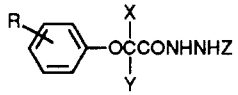
XLVIIIa



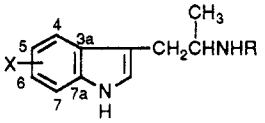
XLVIIIb



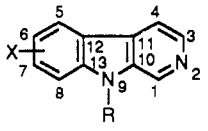
XLVIIIc



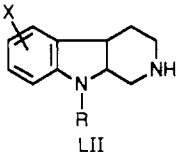
XLIX



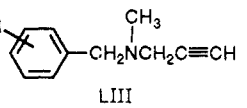
L



LI



LII



LIII

N-(Phenoxyethyl)cyclopropylamines (XLVI)[197]

Rat MAO (in vitro)

$$\log (1/C) = 0.702(\pm 0.20)E_s + 1.640(\pm 0.50)\sigma + 0.198(\pm 0.27)\pi + 4.153(\pm 0.42) \quad (126)$$

$$n = 18,\ r = 0.945,\ s = 0.342$$

Human MAO (in vitro)

$$\log (1/C) = 1.030(\pm 0.39)E_s + 1.089(\pm 1.2)\sigma + 0.398(\pm 0.76)\pi + 4.541(\pm 0.88) \quad (127)$$

$$n = 9,\ r = 0.955,\ s = 0.435$$

trans-Phenylcyclopropylamines (XLVIIa) against rat MAO (in vivo)[198]

$$\log (1/C) = 5.180(\pm 0.276) - 0.746(\pm 0.614)\pi + 1.858(\pm 1.370)\sigma_2 + 0.502(\pm 0.211)E_{s,3} \quad (128)$$

$$n = 10,\ r = 0.939,\ s = 0.179$$

Phenoxycyclopropylamines (XLVIIb) against rat MAO (in vivo)[198]

$$\log (1/C) = 3.743(\pm 1.176) - 0.489(\pm 1.306)\pi + 0.411(\pm 2.041)\sigma_1 + 0.986(\pm 1.253)E_{s,4} \quad (129)$$

$$n = 6,\ r = 0.936,\ s = 0.241$$

Benzylhydrazines (XLVIIIa) against guinea pig MAO (in vitro)[198]

$$\log (1/C) = 5.832(\pm 0.209) - 0.545(\pm 0.125)\pi + 1.638(\pm 0.271)\sigma_2 + 0.516(\pm 0.161)E_{s,3} \quad (130)$$

$$n = 0,\ r = 0.996,\ s = 0.062$$

α-Phenethylhydrazines (XLVIIIb) against mouse MAO (in vitro)[198]

$$\log (1/C) = 3.343(\pm 0.898) + 0.606(\pm 0.464)\pi + 0.933(\pm 0.980)E_{s,4} \quad (131)$$

$$n = 7,\ r = 0.876,\ s = 0.214$$

(Phenylisopropyl)hydrazines (XLVIIIc) against mouse MAO (in vitro)[198]

$$\log (RA) = 1.671(\pm 1.168)E_{s,4} - 0.675(\pm 0.761)\pi - 0.268(\pm 1.008) \quad (132)$$

$$n = 7,\ r = 0.894,\ s = 0.220$$

(RA is the activity relative to iproniazid)

Arylhydrazides [$ArCONHNHCH(CH_3)_2$] against rat MAO (in vivo)[199]

$$MI = 13491 - 9511(\pm 1125)Q_0 \quad (133)$$

$$n = 20,\ r = 0.894,\ s = 30,\ F = 71.5$$

$$MI = 83.37 + 88.25(\pm 23.09)\sigma \quad (134)$$

$$n = 10,\ r = 0.804,\ s = 31.4,\ F = 14.6$$

(Q_0 is the π-electron density at the carbonyl oxygen, and MI is the marsilid index, defined as the ratio of the increase in serotonin in rat brain produced by a substance, in amount equimolar to 100 mg/kg, to the increase in serotonin produced by 100 mg of marsilid, i.e., iproniazid).

(Aryloxy)acetohydrazides (XLIX) against rat MAO (in vitro)[200,201]

$$\log (1/C) = 5.46 - 26.5E_{1/2} - 0.634(\Delta pK_a) + 0.307E_{s,6} \quad (135)$$

$$n = 24,\ r = 0.962,\ s = 0.163$$

$$\log (1/C) = -5.2 - 29E_{1/2} - 0.82(^2\chi) + 1.8(^3\chi^v) \quad (136)$$

$$n = 24,\ r = 0.941,\ s = 0.201$$

($E_{1/2}$ is the polarographic half-wave potential, ΔpK_a is a measure of the relative basicity of nitrogen, $^2\chi$ is the second-order simple connectivity index, and $^3\chi^v$ is the third-order valence connectivity index[20])

α-Methyltryptamines (L) against guinea pig MAO (in vitro)[198]

$$\log (1/C) = 3.152(\pm0.4) - 1.085(\pm0.620)\pi_{4,6} + 1.251(\pm0.714)\sigma_{7a} + 1.071(\pm0.439)E_{s,5} \quad (137)$$

$$n = 15,\ r = 0.862,\ s = 0.231$$

β-Carbolines (LI) against beef MAO (in vitro)[198]

$$\log (1/C) = 2.777(\pm0.503) + 0.590(\pm0.191)\pi_{6,8} + 0.720(\pm0.814)\sigma_{12} + 0.731(\pm0.290)E_{s,6,8} + 0.361(\pm0.230)D \quad (138)$$

$$n = 12,\ r = 0.979,\ s = 0.144$$

(D is a dummy variable equal to 1 for R = NCH_3 and 0 for R = H)

Tetrahydro-β-carbolines (LII) asgainst beef MAO (in vitro)[198]

$$\log (1/C) = 2.586(\pm0.511) + 0.525(\pm0.515)\pi_{6,8} + 0.730(\pm0.417)E_{s,6} + 1.030(\pm0.392)D \quad (139)$$

$$n = 15,\ r = 0.909,\ s = 0.341$$

Pargylines (LIII) against rat MAO (in vitro)[198]

$$\log (1/C) = 5.547(\pm0.588) + 0.389(\pm0.39)\pi + 1.192(\pm0.734)\sigma_2 + 0.764(\pm0.435)E_{s,4} \quad (140)$$

$$n = 11,\ r = 0.937,\ s = 0.271$$

Another series of pargylines against rat MAO (in vitro)[202]

$$\log (1/C) = 4.38(\pm1.38)pK_a - 0.35(\pm0.10)(pK_a)^2 + 0.25(\pm0.19)\pi + 1.02(\pm0.45)D' \quad (141)$$

$$n = 47,\ r = 0.87,\ s = 0.58$$

(D' is a dummy variable to account for the presence of the substituent at the 2-position of the aromatic ring).

A close look at these equations suggests that MAO inhibition is predominantly governed by electronic and steric factors. Except for eq 131, 132, and 139, all other equations have some kind of electronic parameter. Similarly, except for eq 133, 134, and 141, all other equations have steric factors. In the majority of cases, steric factors appear to produce their effects from the 3- or 4-position of the aromatic ring. Wherever σ appears as the electronic factor, its coefficient is positive, indicating that electron-withdrawing substituents may increase the MAO inhibition potency.

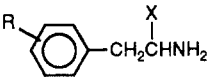
Though the hydrophobic parameter appears in several cases, its role is not consistent. In many equations, e.g., eq 128–130, 132, and 137, its coefficient is negative, and in others, positive. With a negative coefficient, the negative role of π on activity may be attributed to the fact that since hydrophobicity is related to the bulkiness of the group, substituents would be producing steric hindrance instead of leading to any hydrophobic interaction. Since in many cases π was not found to play any role, it can be assumed that an increase in activity due to hydrophobicity would be possible only when the hydrophobic substituents of the molecules would be properly oriented with respect to the hydrophobic site of the enzyme.

Since the inhibition of MAO will lead to an increase in the availability of noradrenaline (NA) or serotonin (5-hydroxytryptamine (5-HT)), the question arises if all antidepressants elicit their effects by increasing the availability of NA or 5-HT. The clinical efficacy of tricyclic antidepressants and MAO inhibitors was discovered by chance in the 1950s. Since then, the unraveling of the mechanism(s) of action of antidepressants has been a tantalizing goal. It has been, however, generally accepted that at least part of the therapeutic action of antidepressant drugs may be the consequence of an increased availability of NA or 5-HT at a postsynaptic receptor site.[203] A further discussion on the commonality of the mechanism(s) of the action of antidepressants has been made by Sugrue.[204] According to him, a major limitation in attempting to comprehend the mechanism(s) of antidepressant therapies is the complete lack of appropriate models for monitoring central neurotransmitter functioning in humans. Therefore, pharmacological studies on animals play an important role in attempting to understand how antidepressants work.

The tricyclic antidepressant desipramine is supposed to be associated with the induction of subsensitive central presynaptic α_2-adrenoceptors in both man and rodents.[204] However, neurochemical, behavioral, and electrophysiological studies have indicated that this property is not possessed by all forms of antidepressant therapies. Hence, it cannot be concluded that such an action accounts for the primary mechanism of action of antidepressants. It has been proposed that the efficacy of antidepressants might be related to their ability to induce supersensitive central α_1-adrenergic and serotoninergic receptors.[205] However, since depression is not a homogeneous entity as indicated by both diagonistic[206] and biochemical criteria[207] and since complex interconnections exist among central putative neurotransmitter and modulatory systems because one monoaminergic system can be modified by changes in another system, it is not possible to attribute unequivocally a common mechanism of action to all forms of antidepressants. In light of the complexity of the brain, one can assume not only that there exist multiple intervention sites into the central neuronal circuitry but also that chronic antidepressant therapies possess different intervention sites.[204]

Hallucinogens. As already mentioned, this class of CNS drugs has been extensively studied. In a separate

TABLE 22. Hallucinogenic Activity and Related Electronic and Physicochemical Parameters for Phenylalkylamines[a]

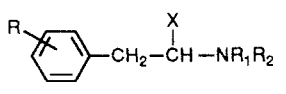


compd	R	X	MU	E_{HOMO}, au	IP, eV	log P
1	3,4,5-$(OCH_3)_3$	H	1	−0.5226		1.18
2	2,4,5-$(OCH_3)_3$	H	1			1.44
3	3-OCH_3-4,5-(OCH_2O)	H	1			1.38
4	4-OCH_3	CH_3	5	−0.5262	8.16	1.77
5	2,4-$(OCH_3)_2$	CH_3	5	−0.5194	7.91	1.75
6	2,5-$(OCH_3)_2$	CH_3	8	−0.5012	7.70	1.88
7	3,4,5-$(OCH_3)_3$	CH_3	2.2	−0.5218	8.16	1.48
8	2,4,5-$(OCH_3)_3$	CH_3	17	−0.5001	7.66	1.74
9	2,3,5-$(OCH_3)_3$	CH_3	4	−0.5026		1.61
10	2,3,6-$(OCH_3)_3$	CH_3	13	−0.5112		1.73
11	2,4,6-$(OCH_3)_3$	CH_3	10	−0.5217	7.76	1.57
12	3,4-(OCH_2O)	CH_3	3		8.01	1.68
13	3-OCH_3-4,5-(OCH_2O)	CH_3	2.7			1.80
14	2-OCH_3-4,5-(OCH_2O)	CH_3	12			2.42
15	2-OCH_3-3,4-(OCH_2O)	CH_3	10			2.04
16	2,3-(OCH_2O)-4-OCH_3	CH_3	3			1.72
17	2,5-$(OCH_3)_2$-3,4-(OCH_2O)	CH_3	12			2.16
18	2,3-$(OCH_3)_2$-4,5-(OCH_2O)	CH_3	5			2.54
19	2,3,4,5-$(OCH_3)_4$	CH_3	6	−0.5126		1.48
20	2,5-$(OCH_3)_2$-4-OC_2H_5	CH_3	15			2.24
21	2,5-$(OCH_3)_2$-4-CH_3	CH_3	80	−0.4929	7.62	2.08
22	2,5-$(OCH_3)_2$-4-C_2H_5	CH_3	100			2.81
23	2,5-$(OCH_3)_2$-4-(*n*-C_3H_7)	CH_3	80			3.31
24	2,5-$(OCH_3)_2$-4-(*n*-C_4H_9)	CH_3	36			3.81
25	2,5-$(OCH_3)_2$-4-(*n*-C_5H_{11})	CH_3	10			4.31
26	2,5-$(OCH_3)_2$-4-Br	CH_3	400		7.94	2.58
27	3,4-$(OCH_3)_2$	CH_3	<1	−0.5238	8.03	1.00
28	2,3,4-$(OCH_3)_3$	CH_3	<2	−0.5274	8.09	1.36
29	3-OCH_3-4,5-(OC_2H_4O)	CH_3	<1			
30	2-OC_2H_5-4,5-$(OCH_3)_2$	CH_3	<7			
31	2,4-$(OCH_3)_2$-5-OC_2H_5	CH_3	<7			
32	3,4,5-$(OCH_3)_3$	C_2H_5	<2			
33	4-OCH_3	H	<1			
34	3,4-$(OCH_3)_2$	H	<0.2			
35	2-OCH_3-3,4-(OCH_2O)	H	<5			

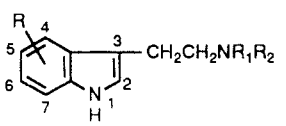
[a] See ref 3.

review, we have compiled all available QSAR studies on hallucinogens and discussed their importance in detail.[3] We mention here some of the important QSARs and discuss the possible mechanisms of hallucinations.

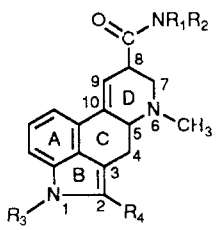
Presently, several compounds are known that cause psychoses.[208] However, the true hallucinogens, which have been used deliberately to produce psychosis and which have been extensively studied, belong to the following chemical classes: (a) phenylalkylamines (LIV), (b) indolealkylamines (LV), and (c) lysergic acid derivatives (LVI). QSARs have been accordingly arranged around them.



LIV
mescaline, R = 3,4,5-$(OCH_3)_3$
X = H, $NR_1R_2 = NH_2$



LV
serotonin, $R_1 = R_2 = H$
R = 5-OH



LVI
LSD, $R_1 = R_2 = C_2H_5$
$R_3 = R_4 = H$

(*a*) *Phenylalkylamines.* Phenylalkylamines are the most widely studied class of hallucinogens. They have been studied for a variety of actions such as hallucinogenic activity in humans, direct interaction with serotonin receptors, and hyperthermic potency in rabbits. Attempts were made to correlate these activities with the electronic, topological, and physicochemical properties of molecules.

(*i*) *Hallucinogenic Activity.* Shulgin et al.[209] compiled the human data of hallucinogenic activity for a fairly large number of phenylalkylamines (Table 22). The activity was expressed in terms of mescaline units (MU). Mescaline [3,4,5-(trimethoxyphenyl)ethylamine] is an effective hallucinogen and hence is used as a reference compound. MU refers to the ratio of the effective dose of mescaline to that of drug. When doses were expressed in moles, MU was replaced by mMU. From the data in Table 22, the following correlations were obtained.

Kang and Green[210]

$$\log (MU) = 19.07 + 35.65E_{HOMO} \quad (142)$$

$$n = 13,\ r = 0.753,\ F_{1,11} = 14.36$$

$$\log (mMU) = 18.07 + 35.10E_{HOMO} \quad (143)$$

$$n = 13,\ r = 0.756,\ F_{1,11} = 14.62$$

(E_{HOMO} is the energy of the highest occupied molecular orbital obtained by the INDO method[211])

Domelsmith and Houk[212,213]

$$\log (\text{mMU}) = 19.53 - 2.37\text{IP} \quad (144)$$

$$n = 11,\ r = 0.86$$

$$\log (\text{mMU}) = 11.15 - 1.48\text{IP} + 0.78 \log P \quad (145)$$

$$n = 11,\ r = 0.94$$

(IP is the ionization potential measured by photoelectron spectroscopy[214])

Bailey and Verner[215] (compounds 4–8 and 28)

$$\log (\text{MU}) = 0.038\lambda - 9.96 \quad (146)$$

$$n = 6,\ r = 0.94,\ F_{1,4} = 28.15$$

$$\log (\text{MU}) = 0.000213\epsilon + 0.176 \quad (147)$$

$$n = 6,\ r = 0.94,\ F_{1,4} = 27.92$$

(λ is the UV absorption maximum and ϵ is the molar absorptivity)[215]

Sung and Parker[216] (compounds 4–6, 8, and 10–12)

$$\text{MU} = 7.918K - 3.798 \quad (148)$$

$$r = 0.97,\ F = 101.03$$

(K is the association constant for the complex formed between the drug and 1,4-dinitrobenzene, an electron acceptor used as a serotonin receptor model)[216]

Barfknecht et al.[217] (compounds 1–26)

$$\log (\text{MU}) = 3.15(\pm 1.33) \log P - 0.50(\pm 0.25)(\log P)^2 - 3.17(\pm 1.61) \quad (149)$$

$$n = 26,\ r = 0.79,\ s = 0.41,\ \log P_0 = 3.14$$

Kier and Hall[218] (compounds 4–26)

$$\log (\text{mMU}) = 45.16(\pm 7.30)/({}^3\chi_p) + 1.288(\pm 0.20)({}^6\chi_p) - 4.298(\pm 0.19)/({}^4\chi_{pc}{}^v) - 5.592(\pm 2.32) \quad (150)$$

$$n = 23,\ r = 0.920,\ s = 0.251,\ F_{3,19} = 35.0$$

(χ's are the molecular connectivity indices and quantitate the number and types of atoms, branching, cyclization, and bond types in a molecule. With different orders m and types t, different ${}^m\chi_t$'s quantitate these structural features of the molecule in quite diverse ways. Moreover, ${}^m\chi_t{}^v$ terms take into consideration the valence of the atoms, while ${}^m\chi_t$ terms do not. Thus the use of such different χ terms in a single equation makes the interpretation of the result difficult.)

Di Paolo et al.[219] (compounds 4–20)

$$\log (\text{MU}) = 0.31E - 0.89 \quad (151)$$

$$n = 17,\ r = 0.73,\ s = 0.21,\ F_{1,15} = 16.70$$

$$\log (\text{MU}) = 0.28E - 0.26I_{3,4} - 0.63 \quad (152)$$

$$n = 17,\ r = 0.83,\ s = 0.17,\ F_{2,14} = 15.50$$

(E is the calculated interaction energy of compounds with 3-methylindole used as a receptor model.[219] $I_{3,4}$ is an indicator variable depicting the presence of substituents at positions 3 and 4 of the ring)

Glennon et al.[220] (for a small series of mescaline analogues)

$$\text{MU} = 129({}^3\chi_c{}^v) - 4.45({}^4\chi_p) - 14.54 \quad (153)$$

$$n = 10,\ r = 0.97,\ s = 3.02$$

Gupta et al.[221] (same series as used by Glennon et al.)

$$\log (\text{MU}) = 0.758({}^1\chi^v) - 2.70 \quad (154)$$

$$n = 6,\ r = 0.962,\ s = 0.209,\ F_{1,4} = 49.20$$

$$\log (\text{MU}) = 0.668({}^1\chi^v) - 1.298 \quad (155)$$

$$n = 8,\ r = 0.951,\ s = 0.251,\ F_{1,6} = 57.05$$

(ii) Rabbit Hyperthermia and LSD-like Effects in Animals. The rabbit hyperthermia assay has been found to have an excellent correlation with human potencies of hallucinogens.[222–225] However, Anderson et al.[224] reported that hyperthermic potency could be correlated neither with E_{HOMO} nor with log P, the two important parameters for hallucinogenic activity. Gupta et al.[225] analyzed the data obtained by Aldous et al.[222] for some phenylisopropylamines and found that the hyperthermic potencies of those derivatives that resembled DOM [1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane, compound 21 in Table 22] with variation only at the 4-position were well correlated with $\sum\pi$ (sum of π values of substituents) (eq 156 and 157).

$$\log (\text{HT}_1) = 2.456(0.523)\sum\pi - 1.563(0.282)(\sum\pi)^2 - 0.566 \quad (156)$$

$$n = 10,\ r = 0.906,\ s = 0.468,\ F_{2,7} = 16.00$$

$$\log (\text{HT}_2) = 2.543(0.646)\sum\pi - 1.679(0.348)(\sum\pi)^2 - 0.600 \quad (157)$$

$$n = 10,\ r = 0.884,\ s = 0.578,\ F_{2,7} = 12.55$$

HT_1 and HT_2 refer to hyperthermic potencies obtained by two different methods[222] relative to DOM. For this small set of compounds, the LSD-like effect observed by Aldous et al.[222] was also found to be related with $\sum\pi$ but in combination with the steric parameter of the 4-substituent (eq 158).

$$\log (1/C) = 2.386(0.914)\sum\pi - 0.682(0.664)(\sum\pi)^2 - 1.383(1.047)E_{s,4} + 0.556 \quad (158)$$

$$n = 8,\ r = 0.813,\ s = 0.572$$

(iii) Activity with Serotonin Receptors. Phenylalkylamines have been found to have a direct action on serotonin receptors. However, QSAR studies have been made only in a very few cases. For a small series, the agonist activity on the serotonin receptors of an isolated umbilical artery preparation was shown by Nichols et al.[226] to be related with log P and an indicator parameter I_4 for the 4-substituent as

$$\log (\text{RBR}) = 0.595 \log P - 0.539I_4 - 0.265 \quad (159)$$

$$n = 17,\ r = 0.926,\ s = 0.23,\ F_{2,14} = 42.05$$

I_4 had a value from 0 to 2, depending upon the length of the chain. The same data were correlated with χ by Kier and Glennon[227] as

$$\log (\text{RBR}) = 11.07({}^3\chi_p{}^v) - 2.78({}^3\chi_p{}^v)^2 + 6.89({}^4\chi_p{}^v) - 21.19 \quad (160)$$

$$n = 17,\ r = 0.95,\ s = 0.196,\ F_{3,13} = 39.6$$

The term RBR stands for relative biological response and represents the ratio of ED_{50} of mescaline to that of compound.

Certain data reported by Glennon et al.[228] on serotonin receptor binding affinity (pA_2) for some phenylalkylamines were found[229] to be related with the van der Waals volume (V_W) and with molar refraction (MR) as

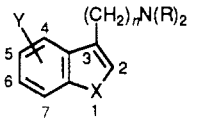
$$pA_2 = 2.174(0.378)\sum V_W + 5.196 \quad (161)$$

$$n = 9,\ r = 0.909,\ s = 0.265,\ F_{1,7} = 33.15$$

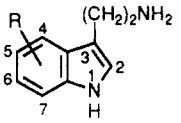
$$pA_2 = 0.079(0.013)\sum(MR) + 5.316 \quad (162)$$

$$n = 9,\ r = 0.912,\ s = 0.260,\ F_{1,7} = 34.70$$

(*b*) *Indolealkylamines.* Indolealkylamines are the least studied for their hallucinogenic activity, but they are, however, comparatively well studied for their actions on serotonin receptors. Most of the binding affinity data have been subjected to QSAR studies. However, an attempt by Glennon and Gessner[230a] to correlate the pA_2 data[230] of a series belonging to LVII



LVII



LVIII

with molecular orbital (MO) parameters gave no conclusive correlation, but an analysis of Vane's data[231] on the activity of tryptamines (LVIII) on isolated rat fundus strip by Green and co-workers[232,233] in relation to MO parameters and hydrophobic constant produced many statistically significant correlations, of which the one professed to be the most meaningful[233] was as shown by eq 163, where f_1^E and q_1 are the electrophilic

$$\log(1/C) = 18.09f_1^E - 74.77q_1 + 1.182\pi_7 - 13.067 \quad (163)$$

$$n = 15,\ r = 0.962,\ s = 0.288,\ F_{3,11} = 59.4$$

frontier orbital electron density and the net total charge, respectively, at the 1-position (the ring nitrogen) calculated by the CNDO/2 method.

Serotonin uptake inhibition activity of tryptamines was also studied[234] and correlated with the total orbital energy (TOE) and log *P* by Kumbar et al.[234] and with V_W by Gupta et al.[235] The data set was divided into two groups, one possessing higher ED_{50} values and one possessing lower ED_{50} values. For the higher group, correlations obtained were as shown by eq 164 and 165, and those for the lower group were as shown by eq 166 and 167.

$$\log(ED_{50}) = 3.368(\pm0.939)\log(TOE) - 0.055(\pm0.094)\log P - 3.581 \quad (164)$$

$$n = 12,\ r = 0.856,\ s = 0.190$$

$$\log(ED_{50}) = 0.928V_W + 0.826 \quad (165)$$

$$n = 12,\ r = 0.791,\ s = 0.164$$

$$\log(ED_{50}) = 2.324(\pm0.842)\log(TOE) + 0.226(\pm0.092)\log P - 3.275(\pm0.033) \quad (166)$$

$$n = 11,\ r = 0.938,\ s = 0.109$$

$$\log(ED_{50}) = 1.093V_W - 0.244 \quad (167)$$

$$n = 11,\ r = 0.890,\ s = 0.152$$

Tryptamines and some other drugs were found to displace specifically bound [^{3}H]serotonin and [^{3}H]LSD from rat cerebral cortex membranes,[236] and their displacement potencies were found to be correlated with log *P* as[237]

$$\log(1/C) = 1.391\log P - 0.330(\log P)^2 + 6.181 \quad (168)$$

$$n = 14,\ r = 0.873,\ s = 0.766$$

$$\log(1/C) = 1.222\log P - 0.182(\log P)^2 + 5.265 \quad (169)$$

$$n = 16,\ r = 0.906,\ s = 0.613$$

Equation 168 was for [^{3}H]serotonin displacement, and eq 169 was for [^{3}H]LSD displacement. Some other data obtained by Green et al.[238] and by Bennett and Aghajanian[239] on [^{3}H]LSD displacement by tryptamines and related compounds were shown[212] to be related with the first and second ionization potentials of molecules (eq 170 and 171, respectively).

$$\log(1/C) = 47.78 - 3.81IP_1 - 1.64IP_2 \quad (170)$$

$$n = 10,\ r = 0.85$$

$$\log(1/C) = 43.26 - 2.79IP_1 - 1.93IP_2 \quad (171)$$

$$n = 7,\ r = 0.97$$

A small set of data available on the hallucinogenic activity of tryptamines was found, along with those of LSD and mescaline, to be related with E_{HOMO} (eq 172).[240]

$$\log(MU) = 5.956 - 10.259E_{HOMO} \quad (172)$$

$$n = 6,\ r = 0.972,\ s = 0.327,\ F_{1,4} = 68.81$$

(*c*) *Lysergic Acid Derivatives.* Lysergic acid derivatives or LSD analogues have been comparatively well studied for their anti-serotonin and hallucinogenic activities, and the data available have been subjected to QSAR studies. For the series of LSD and LSD analogues given in Table 23, the anti-serotonin (anti-S) and hallucinogenic (H) activities were found to be correlated with TOE as shown by eq 173 and 174[241,242] and with V_W as shown by eq 175 and 176.[243]

$$\log(\text{anti-S}) = 10.2838\log(TOE) - 16.2811 \quad (173)$$

$$n = 15,\ r = 0.889,\ s = 0.271$$

$$\log(H) = 7.3951\log(TOE) - 11.8596 \quad (174)$$

$$n = 12,\ s = 0.40$$

$$\log(\text{anti-S}) = 2.536(0.388)V_W(NR_1R_2) + 1.120(0.581)V_W(R_3) - 0.056 \quad (175)$$

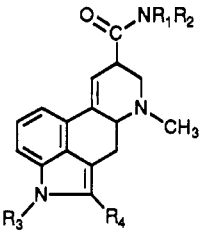
$$n = 15,\ r = 0.916,\ s = 0.283,\ F_{2,12} = 31.17$$

$$\log(H) = 2.474(0.503)V_W(NR_1R_2) + 1.267(0.477)V_W(R_3) - 0.716 \quad (176)$$

$$n = 10,\ r = 0.916,\ s = 0.218,\ F_{2,7} = 18.14$$

In agreement with the findings of Gupta et al.,[243] some of the Cereletti and Doepfner data on anti-serotonin activity of LSD analogues that had variation only in the

TABLE 23. Anti-Serotonin and Hallucinogenic Activities and the Hückel Total MO Energy of LSD and Its Analogues[a]



compd	NR_1R_2	R_3	R_4	anti-S[b]	H[b]	TOE, β
1	$N(C_2H_5)_2$	H	H	100	100[d]	58.250
2	$N(C_2H_5)_2$	H	Br	150	7.2,[d] <2	61.294
3	NH_2	H	H	4.3	0	42.292
4	$NH[CH(C_2H_5)CH_2OH]$	CH_3	H	400	0.6	63.294
5	$NHCH_3$	H	H	6.3		46.188
6	$N(CH_3)_2$	H	H	23.2	10[d,e]	50.262
7	NHC_2H_5	H	H	11.9	5,[d] 3.4[e]	50.180
8	NHC_2H_5	CH_3	H	835[c]	4,[d] 5[e]	54.228
9	NHC_2H_5	$COCH_3$	H	39	7[d,e]	59.756
10	$NH(i\text{-}C_3H_7)$	H	H	22.2		51.024
11	$N(C_2H_5)_2$	CH_3	H	368	36,[d] 40[e]	62.294
12	$N(C_2H_5)_2$	OCH_3	H	58.9	66[d,e]	63.718
13	$N(C_2H_5)_2$	$COCH_3$	H	210	100,[d] 91[e]	67.824
14	$N(C_2H_5)_2$	H	I	57.4		59.516
15	$N(C_2H_5)_2$	CH_3	Br	533	<1	65.352
16	$N(-C_4H_8-)$	CH_3	H	130	<5	62.502
17	$N(-C_4H_8-)$	H	H	4.7[c]	5.3,[d] 10[e]	58.440
18	$N(-CH_2CH{=}CHCH_2-)$	H	H	4.1[c]	10[d,e]	52.968
19	$N(-C_5H_{10}-)$	H	H	8.5[c]		62.442
20	$N(-C_2H_4OC_2H_4-)$	H	H	8.0[c]	11[d,e]	62.728

[a] See ref 3. [b] Relative to that of LSD taken as 100. [c] Not included in the regression analysis. [d] Used to obtain eq 174. [e] Used to obtain eq 176.

NR_1R_2 group (R_1 = H, R_2 = alkyl) were shown to be related with the number of carbon atoms (N) in the alkyl substituent as[242]

$$\text{anti-S} = 1/(0.01185 + 0.2207e^{-N}) \quad (177)$$

The same data were found to be correlated with V_W as[243]

$$\log(\text{anti-S}) = 1.789(0.173)V_W(NR_1R_2) + 0.282 \quad (178)$$

$$n = 7,\ r = 0.977,\ s = 0.113,\ F_{1,5} = 106.38$$

However, adding to this series a few dialkyl side chain (NR_1R_2) substituted analogues, Dunn and Bederka[244] correlated the anti-S data with log P (eq 179), while Glennon and Kier[245] correlated the anti-S data with χ (eq 180). In eq 179, D is a dummy variable used to account for the amide nitrogen being enclosed in a ring system.

$$\log(\text{anti-S}) = 0.84(\pm0.35)\log P - 0.14(\pm0.08)(\log P)^2 - 0.74(\pm0.28)D - 0.54(\pm0.32) \quad (179)$$

$$n = 14,\ r = 0.94,\ s = 0.20$$

$$\log(\text{anti-S}) = 24.94(\pm3.9) - 0.835(\pm0.033)(^2\chi) - 0.917(\pm0.083)(^6\chi_p) - 1/0.0072(\pm0.004)(^0\chi^v) \quad (180)$$

$$n = 16,\ r = 0.94,\ s = 0.196$$

From all these correlations on hallucinogens relating their hallucinogenic, anti-serotonin, and hyperthermic potencies with a variety of parameters, one still cannot derive an unequivocal mechanism of hallucination. The basic postulate regarding the mode of interaction of hallucinogens was that these drugs exert their biological effects through the formation of charge-transfer complexes with the receptors.[210,232,246-248] In agreement with this were eq 142–148, 151, and 152 correlating the hallucinogenic activity with electronic parameters related to the charge-transfer ability of molecules or the strength of the charge-transfer complex formed. However, since direct interaction of compounds with serotonin receptors was not found to be related with any such electronic parameters, the idea of the formation of charge-transfer complexes was shaken. The assumption is that hallucinogens might act in the brain as antimetabolites of serotonin.[249,250] Although [^{3}H]-serotonin and [^{3}H]LSD displacement data of some tryptamines were found to be related with ionization potentials (eq 170 and 171), they were not found to have any direct relation with hallucinogenic activity.

Furthermore, the hallucinogenic activity that was correlated with electronic parameters depicting the formation of charge-transfer complexes belonged to only one class of hallucinogens, i.e., the phenylalkylamines. Hence, the idea of the formation of charge-transfer complexes cannot be generalized for all kinds of hallucinogens. Equation 172 correlating the hallucinogenic activity of LSD, mescaline, and some tryptamines is hardly of any significance, as it uses a very small number of data points. Similarly, eq 164, 166, 173, and 174 correlating different activities with TOE throw hardly any light on the mechanism of drug–receptor interaction, as no particular significance has been attached to this quantum mechanical parameter.

As correlations have shown (eq 159–162 for phenylalkylamines, eq 165 and 167–169 for tryptamines, and eq 175 and 177–180 for LSD analogues), the anti-serotonin activity has a greater dependence on log P, bulk of substituents, and the steric parameters. log P was also found to be related with hallucinogenic activity (eq

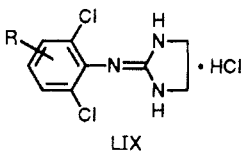
149). Equation 176, which correlated the hallucinogenic activity of LSD analogues with V_W, indicates the dependence of activity only on hydrophobicity, since V_W in this case would be related with log P as there is variation of only the alkyl group in the substituent. The rabbit hyperthermia and LSD-like effects of phenylalkylamines were also shown to be related with hydrophobic constants (eq 156–158). It was therefore argued[3] that while drug action may be ultimately related to chemical or electronic factors, distribution or transport to the receptor may also be important in determining the activity of hallucinogens, and that steric factors may simultaneously hinder the interaction. Correlations of activities with χ sometimes accounted for steric effects. In general, they have been more useful in their predictive value than in providing any understanding of the mechanism of drug–receptor interaction. As already pointed out, the use of different χ terms in a single equation, as in eq 150, 160, and 180, makes the interpretation of the results difficult.

Thus it is found that at the molecular level, the electronic, hydrophobic, and steric factors play a dominant role in the various biological and pharmacological actions of hallucinogenic drugs. Since the subjective nature of hallucinogenic activity in man leads to 20–25% error in the measurement[209] and the in vitro data are not completely free from errors, certain anomalies, discrepancies, and deviations in the correlations were but natural. For a detailed discussion of QSAR studies on hallucinogens, readers may refer to a previous review.[3]

D. Miscellaneous

1. Drugs Interacting with Central α-Adrenoceptors

The possibility that α-adrenoceptors might exist in the brain and the fact that drugs such as clonidine, guanfacine, and α-methyl-DOPA exert hypotensive activity via a primary influence on the CNS[251] aroused interest in structure–activity relationships of drugs interacting with α-adrenoceptors. Like β-adrenoceptors, α-adrenoceptors are also subdivided into α_1 and α_2 types. The terms α_1 and α_2 indicate only the preference of the receptors for agonists and antagonists and not the localization with respect to the nerve ending and the synapse.[251] The acute blood pressure lowering effect of α-adrenoceptor agonists has been attributed to the participation of the α_2 type.[252-255] The structure–activity relationship studies of α-adrenoceptor drugs that display central hypotensive activity has been mainly concerned with clonidine and related imidazolidines (LIX).



LIX

Clonidine, 2-[(2,6-dichlorophenyl)imino]imidazolidine hydrochloride (LIX, R = H), has been introduced into clinical medicine under the name of catapresan or catapres as an effective hypotensive drug. The hypotensive activity of clonidine-like derivatives and some related compounds has been correlated in a more or less quantitative manner with the binding affinity for [^{3}H]clonidine binding sites in brain tissue with various degrees of success.[256-260]

TABLE 24. Hypotensive Potency and α-Adrenoceptor Binding Affinities of Structurally Dissimilar α-Adrenoceptor Agonists[261]

no.	compd[a]	pC_{25}	$pIC_{50}(\alpha_1)$	$pIC_{50}(\alpha_2)$	log P
1	44-549	2.77	1.22	2.80	2.02
2	Bay-a 6781	2.32	−0.13	2.22	1.39
3	lofexidine	2.09	0.18	2.60	0.73
4	clonidine	2.04	−0.08	2.51	0.85
5	Bay-c 6014	1.96	−0.57	2.00	1.28
6	UK-14, 304	1.55	−0.38	2.44	0.31
7	B-HT 920	1.43	−2.70	1.60	1.09
8	naphazoline	0.95	0.39	2.32	−0.52
9	St-871	0.84	−0.10	2.19	2.31
10	tiamenidine	0.69	−0.69	2.04	−0.17
11	St-1913	0.68	0.27	2.17	−0.53
12	KUM 32	0.63	−0.53	1.32	2.12
13	xylazine	0.62	−1.79	0.85	1.34
14	tramazoline	0.55	−0.04	1.80	−0.62
15	xylometazoline	0.26	0.24	1.64	0.40
16	St-739	−0.02	−0.15	1.19	2.51
17	B-HT 933	−0.14	−2.97	0.73	0.05
18	tetryzoline	−0.16	−0.20	1.52	−0.90
19	St-889	−1.02	−1.04	0.65	2.80
20	St-404	−1.31	−1.72	0.23	−0.34
21	St-1967	0.88	0.00	1.38	1.36

[a] For structures of compounds, see ref 253.

Timmermans et al.[253] determined the hypotensive activity for a series of structurally dissimilar α-adrenoceptor agonists (Table 24) in anesthetized normotensive rats. The activity was quantitated by C_{25}, the dose in micromoles per kilogram required to induce a 25% decrease in mean arterial pressure. It was then correlated[261] with the in vitro binding affinities of compounds for α_1- and α_2-adrenoceptors measured as the molar concentrations (IC_{50}) inhibiting the specific [^{3}H]prazosin (0.2 nM) and [^{3}H]clonidine (0.4 nM) binding, respectively.[261] The activity (pC_{25}) was found not to be so well correlated with $pIC_{50}(\alpha_1)$ (eq 181) as with $pIC_{50}(\alpha_2)$ (eq 182), confirming that the central

$$pC_{25} = 0.436(\pm 0.45)[pIC_{50}(\alpha_1)] + 1.063 \quad (181)$$

$$n = 21,\ r = 0.422,\ s = 0.894,\ F = 4.1$$

$$pC_{25} = 1.265(\pm 0.38)[pIC_{50}(\alpha_2)] - 1.342 \quad (182)$$

$$n = 21,\ r = 0.846,\ s = 0.578,\ F = 48.0$$

hypotensive activity of α-adrenoceptor agonists depends primarily upon α_2-adrenoceptor binding and not upon α_1-adrenoceptor binding. The correlation expressed by eq 182 was further improved when the apparent partition coefficient was also included (eq 183). Thus eq

$$pC_{25} = 1.125(\pm 0.24)[pIC_{50}(\alpha_2)] + 0.863(\pm 0.31)\ \log P - 0.368(\pm 0.15)(\log P)^2 - 1.120 \quad (183)$$

$$n = 21,\ r = 0.952,\ s = 0.350,\ F = 55.3$$

183 showed that the penetration ability of compounds, which parabolically depends upon lipophilicity, greatly influences the central hypotensive activity. Equation 184 correlating pC_{25} with log P only shows that 39% of

$$pC_{25} = 0.943 + 1.163(\pm 0.75)\ \log P - 0.565(\pm 0.36)(\log P)^2 \quad (184)$$

$$n = 21,\ r = 0.622,\ s = 0.873,\ F = 5.7$$

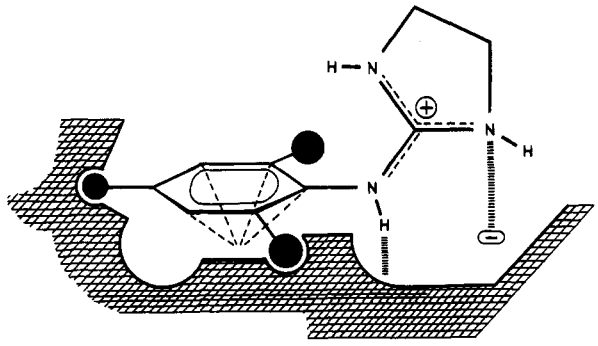


Figure 2. Timmermans' hypothetical model of interactions of imidazolidines with central α-adrenoceptor.

the variance in the activity can be explained by log P alone.

However, for a series of imidazolidines (LIX), the central hypotensive activity (pC_{30}) was found to be correlated[262] with only steric and electronic parameters (eq 185 and 186). In eq 185 and 186, $\sum E_s$ refers to the

$$pC_{30} = 8.026 - 1.771(\pm 0.56)\sum E_s - 0.401(\pm 0.12)(\sum E_s)^2 + 1.898(\pm 1.09)\sum R + 5.129(\pm 1.67)E_{HOMO}(P) + 6.771(\pm 1.96)EE(P) \quad (185)$$

$$n = 27,\ r = 0.941,\ s = 0.326,\ F = 32.20$$

$$pC_{30} = 34.122 - 2.347(\pm 0.54)\sum E_s - 0.555(\pm 0.11)(\sum E_s)^2 - 0.590(\pm 0.19)\sum F - 48.694(\pm 40.01)q_{C_8}(P) + 1.432(\pm 0.52)EE(P) \quad (186)$$

$$n = 27,\ r = 0.935,\ s = 0.340,\ F = 29.35$$

overall steric factor, $\sum R$ to the resonance contribution of the substituents, $E_{HOMO}(P)$ to the energy of the highest occupied MO of the protonated species, EE(P) to the excitation energy of the protonated species, $\sum F$ to the inductive component of the substituents, and $q_{C_8}(P)$ to the π-electron charge density at the guanidine carbon atom of the protonated species.

Equations 185 and 186 are both highly significant; therefore it is difficult to say whether the charge-transfer phenomenon, as E_{HOMO} indicates, or some kind of electrostatic interaction, as q_{C_8} indicates, is involved in the drug–receptor interaction. With q_{C_8}, E_{HOMO} was not found to be relevant in the correlation. The partial correlation of the first excitation energy, EE(P), related to the intramolecular promotion of an electron from the highest occupied MO to the lowest unoccupied MO, is somewhat difficult to interpret. However, in this case it was related to $E_{HOMO}(P)$. Similarly, the occurrence of $\sum R$ in one equation and $\sum F$ in the other is difficult to justify.

Regarding the steric effects, it is, however, observed from both equations that up to a point the bulk of the substituents will lead to an increase in the activity (the larger the substituent, the more negative is its E_s value). Since, except two compounds, all others in the series were ortho and para substituted, it can be assumed that the substituents at these positions might be helping the molecule come into proper orientation with respect to the active sites of the receptors and that they themselves might be involved in the interaction. The nature of the interaction between them and the receptor may be of the van der Waals type. A hypothetical working model of the interactions of imidazolidines with the receptor proposed by Timmermans and van Zwieten[262] is shown in Figure 2. The van der Waals type of interaction (or dispersion interaction) was also indicated by Lee and Lien,[263] when they found the [^{3}H]clonidine displacement activity of a mixed series of α-agonists on rat brain membrane to be related with their molecular weight (eq 187).

$$\log (1/K_i) = 9.869(\pm 3.511)MW - 15.028(\pm 3.511) \quad (187)$$

$$n = 18,\ r = 0.830,\ s = 0.684$$

However, regarding the interactions of imidazolidines and related compounds with the receptor, Timmemans et al.[264] concluded the following on the basis of their QSAR studies:

(i) The aromatic phenyl ring of the imidazolidine possibly interacts by means of electron donation with an electron-deficient area of the receptor.

(ii) A positively charged nitrogen of the imidazolidine nucleus interacts with a negatively charged site at the receptor.

(iii) A third type of interaction is based upon the formation of a hydrogen bond with the bridge nitrogen, although this type of interaction is probably less important quantitatively.

From a steric point of view it seems likely that one side of the substituted phenyl nucleus determines the fitting with the receptor (Figure 2).

For a small series of arylquinolizines, Huff et al. recently demonstrated[265] the existence of significant correlations between α-adrenoceptor affinities of compounds and the lipophilicity of their aryl portion (eq 188 and 189). Equation 188 was derived for the

$$\log (1/K_i) = 1.08(\pm 0.28)\log P + 5.13(\pm 0.36) \quad (188)$$

$$n = 8,\ r = 0.84,\ s = 0.622,\ F_{1,6} = 14.83$$

$$\log (1/K_i) = 1.17(\pm 0.24)\log P + 5.47(\pm 0.31) \quad (189)$$

$$n = 8,\ r = 0.89,\ s = 0.532,\ F_{1,6} = 23.67$$

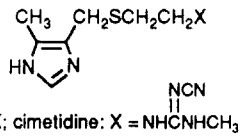
[^{3}H]prazosin displacement data (α_1-adrenoceptor affinity) and eq 189 was derived for the [^{3}H]clonidine displacement data (α_2-adrenoceptor affinity). This correlation study led Huff et al. to suggest that the structure of the aromatic ring in arylquinolizines plays an important role in determining their α-adrenoceptor affinity and exerts its influence primarily through the hydrophobic interactions.[265]

2. Drugs Interacting with Histamine Receptors

Evidence has recently accumulated to suggest that histamine, which is primarily active in the peripheral nervous system, might be a central neutrotransmitter.[266,267] Histamine has two types of receptor, H_1 and H_2. The H_1 type is blocked selectively by classical antihistamines[268] and the H_2 type by H_2-blocking drugs.[269] Certain CNS drugs such as LSD and 2-bromo-LSD (BrLSD) have been suggested to interact with H_2 receptors.[270] However, the contribution that the blockade of H_2-receptors makes to the behavioral effects of LSD and BrLSD is not known. Another drug, cimetidine, a well-known H_2-receptor antagonist, has been found to produce rare idiosyncratic responses that may be revealing of a central function. Cimetidine normally does not enter the brain[271] and is used in the treatment of duodenal ulcer, but there are reports of mental

confusion in patients after they are administered cimetidine. The patients were described as agitated, delirious, and disoriented, but all symptoms rapidly reversed when the drug was withdrawn.[272]

Histamine activates adenylate cyclase in some brain regions of some species.[273,274] The histamine H_2 receptor linked to adenylate cyclase in the brain is not distinguishable from that in guinea pig heart, rat uterus, or parietal cells of the stomach.[272] Therefore the cyclase system and peripheral systems can be studied as a target of psychotropic drugs. Both LSD and BrLSD are competitive antagonists of histamine at the H_2 receptor linked to adenylate cyclase in guinea pig hippocampus and cortex. However, no detailed structure–activity relationship study has been made on any H_2 antagonist; hence the nature of the interaction of drugs with H_2 receptors is not known. For certain cimetidine analogues (LX), a reasonable relationship



LX; cimetidine: X = $NHCNHCH_3$

between in vitro H_2 antagonist activity (determined on histamine-stimulated guinea pig right atrium) and lipophilicity was observed.[275,276] Later Young et al.[277] found that activity might be optimized by combining a dipole moment (μ) with high lipophilicity (eq 190).

$$\log (1/K) = 1.08(\pm 0.85) \log P + 0.23(\pm 0.17)\mu + 2.74(\pm 2.30) \quad (190)$$

$$n = 7,\ r = 0.910,\ s = 0.426$$

However, since there were certain anomalies for eq 190, the dipole moment term was replaced by the dipole moment orientation term ($\cos \theta$) and eq 191 was obtained,[277] which was quite significant even for a larger data set.

$$\log (1/K) = 0.600(\pm 0.458) \log P + 9.12(\pm 2.93) \cos \theta - 2.71(\pm 2.64) \quad (191)$$

$$n = 13,\ r = 0.906,\ s = 0.409$$

The dependence of activity on dipole moment orientation (and not on magnitude) (eq 191) led Young et al.[277] to suggest that the amidine-type moiety in this series of compounds has an orientational function rather than an involvement in direct dipole–dipole or dipole–charge interactions at the receptor. The cyanoguanidine group has been shown to be an effective hydrogen-bond donor from its ability to interact with the imidazole ring nitrogen (N_π) in cimetidine.[278] Young et al.[277] therefore assumed that the cyanoguanidine and related moieties interact with H_2 receptor by hydrogen bonding and that the strength of interaction is determined by the dipole's ability to align with the receptor.

The significance of log P in eq 191 suggests that lipophilicity also plays some role in H_2 antagonist activity. According to Young et al.,[277] since molecules are very polar, the log P parameter may represent a hydrophobic effect; if so, this might suggest the involvement of desolvation effects at the receptor. It was envisaged that the drug molecules in aqueous solution are in a water solvent shell and have to undergo desolvation in order to fully realize the hydrogen-bonding and dipolar interactions at the receptor.[277]

However, these studies do not provide any deeper insight into the mechanism of interactions of H_2 antagonists with the receptor, nor does the study on guinea pig right atrium ensure an identical mechanism of interaction with brain H_2 receptor.

3. Cholinergic and Anticholinergic Drugs

Evidence has accumulated to support the presence of acetylcholine and cholinergic synapses at certain sites of the CNS. In biochemical studies, acetylcholine has been recovered from central nerve terminals.[279] It appears to fulfil a transmitter function at the collaterals of motor axons and the Renshaw cells of the anterior horn of the cord as well as in certain cortical, thalamic, and hippocampal areas and possibly even in the caudate nucleus.[280,281] Therefore, both cholinergic and anticholinergic drugs, when administered to man and animals, cause marked behavioral effects.[282] Pilocarpine, muscarine, and arecoline evoke a characteristic cortical arousal or activation response in cats following the intravenous injection of relatively small doses, similar to that produced by acetylcholine or anticholinesterases. The arousal response to all these drugs is reduced or blocked by atropine and related anticholinergics.[283] In the CNS, cholinergic transmission appears to be predominantly nicotinic in the spinal cord and both muscarinic acid nicotinic at the subcortical and cortical levels in the brain.[284] Accordingly, many or most of the CNS effects of atropine-like drugs at ordinary doses are probably attributable to their central anticholinergic actions. At high or toxic doses, the central effects of atropine or related drugs consist, in general, of stimulation followed by depression. Such effects are probably due to a combination of antimuscarinic and other actions. One would have gathered a deeper insight into the mechanism of cholinergic and anticholinergic drugs if there had been QSAR studies on them. No QSAR studies are available on any group of cholinergic or anticholinergic drugs with reference to their CNS effects. However, without reference to any CNS effects, the cholinesterase inhibition activity of many anticholinesterases has been extensively subjected to QSAR analysis.[2] Anticholinesterases are cholinergics in nature and, if they cross the blood–brain barrier, stimulate cholinergic receptor sites (primarily muscarinic) leading to depression.

IV. An Overview

It seems appropriate to judge all QSAR studies on the following points: (1) Do QSARs indicate any physicochemical, electronic, steric, or structural feature essentially common to all CNS agents? (2) How far have QSAR studies been consistent with experimental observations, and how much have they supplemented knowledge on the mechanisms of actions of CNS drugs? (3) How much have they helped find the nature of the receptors and map the active site at the receptors?

As to the first point, one would find that the fundamental property of the molecules that is overwhelmingly involved in the activity of CNS drugs is hydrophobicity. The greatest contribution of QSAR studies is that they have provided a systematic and fairly complete understanding in quantitative terms of the role of hydrophobicity in drug design. All CNS agents

have to cross the physiological "blood–brain barrier" to reach the brain tissues and elicit their effects. This barrier is an important boundary between the peripheral and central nervous systems in the form of a permeability barrier to the passive diffusion of substances from the bloodstream into various regions of the CNS. Thus the transport of small molecules from the blood to neuronal tissues becomes largely a function of the properties of the cell membrane. Hence, only the lipophilic molecules that can be dissolved in the lipid phase of the membrane would be able to reach the brain sites. However, highly lipophilic molecules might become trapped in the cell membrane and thus may never reach the binding site. Consequently, in most situations, the drug activity has a parabolic dependence on log P.

Hydrophobicity is related not only to penetration and distribution phenomena but also to the interaction with the receptor sites. The critical role of hydrophobicity in in vitro activity has provided valuable information about receptor sites. So far as in vivo activity is concerned, we have seen that the primary factor governing the potency of general nonspecific CNS depressants and stimulants both is log P. However, while all the correlations obtained for stimulants (eq 72–74), though fewer in number, were essentially of parabolic nature in log P with an average log P_0 value of 1.30, those obtained for depressants were of varied nature. For hypnotics and sedatives most of the correlations (eq 32–50) were parabolic, having an optimum lipophilicity near 2. These correlations were concerned with the hypnotic activity of the barbiturate series. Equations 57–59, relating the muscle relaxant activity and lethal toxicity of cyclohexanones and some miscellaneous series, were also parabolic in log P with a log P_0 value near 2. The parabolic dependence of the depressant effect of benzodiazepines on chromatographic R_m values (eq 66) signifies only the dependence on log P with log P_0 around 2. All such parabolic correlations with log P indicate that all diverse series of hyponotics and some general depressants have probably the same rate-determining step in producing CNS effects. This step may lie in the penetration of the inter- and/or intracellular membranes or one of the prior barriers such as the blood–brain barrier. The log P_0 of 2.0 ± 0.3 can be said to be the ideal lipophilic character to design into a neutral molecule for passive penetration into the CNS.[58,285] Equations showing only a linear relationship of hypnotic or depressant activity with log P (eq 52, 55, and 56) or with parameters related to log P (eq 53, 67, and 68) may be interpreted as indicating a situation where the maximum activity had not been reached.

For stimulants the average log P_0 of 1.30 indicates that they have a different rate-determining step than the hypnotics or sedatives; the high log P_0 value (>4) for 2-imidazolidines suggests that these hypnotics are of a totally different nature.

Anesthesia and narcosis were also found to primarily depend upon lipophilicity. However, for anesthesia, there were also many other parameters, such as the ability to form hydrogen bonds, charge distribution, and polarizability, that greatly affected it. Among the selective modifiers of CNS functions, the anticonvulsants and analgetics have largely based their activity on log P. However, while, as discussed in section III.C.1, log P was a prime factor in anticonvulsant activity, it should be combined with receptor binding affinity for explaining in vivo analgetic activity (eq 97). The in vivo hallucinogenic activity in man of phenylalkylamines, though discussed to primarily depend upon the charge-transfer phenomenon, was shown to have significant correlation with log P (eq 149). The central hypotensive activity of α-adrenoceptor agonists and the potency of histamine H_2 antagonists were also shown to depend upon log P (eq 183 and 191). Thus lipophilicity is found to be an essential factor common to almost all kinds of CNS agents.

Electronic parameters, indicative of dipole–dipole or charge–dipole interactions, charge-transfer phenomena, hydrogen-bond formation, etc., are another important factor governing the activity of most CNS agents. Equations 2–4 and 13–16 show the importance of hydrogen bonding in anesthesia produced by gases and halogenated hydrocarbons, and eq 57–65 show the effect of the dipole moment of molecules in sedation produced by different kinds of drugs. The dipole moment was also found to govern the anticonvulsion produced by a variety of anticonvulsants (eq 79–82 and 88). However, in both sedation and anticonvulsion the effect of the dipole moment was negative. This negative effect of μ was attributed by Blair and Webb[74] to a binding process that involves the dipole interaction removing the drug molecules from active service. The positive effect of μ in the case of stimulants (eq 72–74), however, led to the suggestion of the involvement of dipole–dipole interaction between the molecules and the receptors.

The ability of compounds to form hydrogen bonds was found to be important in some analgetics (eq 113 and 114). However, for other selective modifiers of CNS functions, the major electronic factor influencing the activity has been the Hammett constant σ, which represents the effect of charge–charge or charge–dipole interactions of compounds with the receptors. The DHPR inhibition leading to parkinsonism (eq 94 and 95), actions of neuroleptics (eq 121 and 125), and the MAO inhibition by various kinds of antidepressants (eq 126–130, 134, 137, 138, and 140) were shown to have a significant dependence on σ. Except in DHPR inhibition, in the other two cases, there was a uniform positive role of σ, indicating the effect of electron-withdrawing substituents in the molecules.

Hallucinogens have been a typical class of psychopharmacological agents whose activity has been primarily governed by their ability to form charge-transfer complexes with the receptors. That is why the hallucinogenic activity in man of the prime class of hallucinogens, phenylalkylamines, has been related to parameters indicative of the ability of molecules to form charge-transfer complexes with the receptors (eq 142–148, 151, and 152). E_{HOMO} in eq 142 and IP (ionization potential) in eq 143–145 define the electron-donating capability of molecules in charge-transfer phenomena, and λ in eq 146, ϵ in eq 147, K in eq 148, and E in eq 151 and 152 refer to the stability of the complexes formed. The hallucinogenic activity of a small group of miscellaneous hallucinogens was also found to be related with E_{HOMO} (eq 172) and the [^{3}H]LSD displacement activity of some tryptamines with IP (eq 170 and 171).

The steric effects, however, were not found so common among the CNS-active drugs. In the case of general (nonspecific) CNS drugs, there were virtually no steric effects. Only the benzodiazepine receptor binding affinity (in vitro) of some compounds was found to involve a steric effect (eq 71). However, more often than not, steric factors appeared in the case of selective modifiers of CNS functions. They made a significant contribution to the activities of analgetics (eq 108 and 111–115), antidepressants (MAO inhibitors) (eq 126–132 and 137–140), and hallucinogens (eq 158–160, 165, and 180) and affected the action of some anticonvulsants such as hydantoins and sydnones (eq 90–92) and that of certain neuroleptics (eq 121–123 and 125). Since analgetics, antidepressants (MAO inhibitors), and hallucinogens act on well-defined receptors, the steric influence in them can be attributed to the limited bulk tolerance by the receptors at the active sites. Further, in the case of these CNS agents the parabolic correlations of their in vitro activities with log P speak of nothing but the limited bulk tolerance at the active sites of the receptors.

As far as the knowledge derived from QSAR studies about the nature of the receptors and their active sites for these CNS drugs is concerned, we have already discussed (see section III.C.3) that the discrepancy in binding of ketobemidones and meperdines with opiate receptors in the absence and presence of sodium led Snyder and co-workers[131] to propose a model of opiate receptor in which the receptor was assumed to exist in two different conformations: the antagonist conformation (a sodium-binding form) and the agonist conformation (non-sodium-binding form). Kolb[132] proposed that only one conformation of receptor is needed for binding of both agonists and antagonists. In Kolb's model, there are two distinct, spatially fixed, amine-binding sites: an agonist amine-binding site and an antagonist amine-binding site. Agonists and antagonists interact with their respective amine-binding sites via the lone-pair electrons on their nitrogen atoms. On the basis of the geometry and the electronic structure of some analgetic benzamide amines obtained by molecular mechanics and quantum mechanical methods, Cheney et al.[146] proposed that three factors play a significant role in receptor binding: (1) membrane–water partitioning, (2) the capacity of the aromatic ring and the amine N substituent to act as electron acceptors, and (3) the conformational energy required to attain the binding configuration. It was the difference in SAR analysis of agonists and antagonists that led to the suggestion of the existence of a number of opiate receptors.[129,130]

Neuroleptics were suggested to be surface active. QSAR studies on MAO inhibitors have shown remarkable similarity in electronic and steric effects. Knoll[286] described two main forms of mitochondrial MAO: MAO-A and MAO-B. MAO-A is specialized for binding and metabolizing the ethylamine side chain of a substrate if it is attached to a 5-hydroxyindole ring, and MAO-B is specialized for reorganizing and metabolizing phenylethylamine.[287–289] Therefore, the essential structural requirements of an MAO inhibitor are an aromatic ring, an amine group, a short carbon chain between them, and a proper "enzyme-killing" group.[2] A model of inhibitor–enzyme binding fully consistent

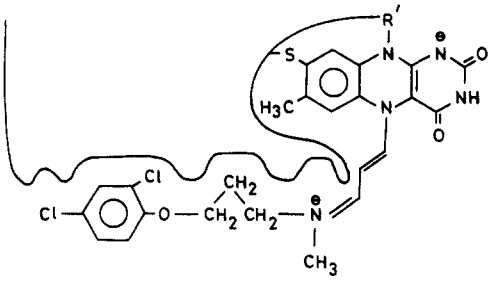


Figure 3. Knoll's model of binding of clorgyline to MAO-A.

with QSAR findings has been proposed by Knoll[288] (Figure 3) in which the binding site for the nitrogen is in the vicinity of the covalently bound flavin group of the enzyme. This model, although shown for the inhibition of MAO-A by clorgyline, a potent inhibitor of MAO-A, is also applicable for the inhibition of MAO-B by deprenyl, a potent inhibitor of MAO-B. The essential positive charge on the nitrogen will be increased by electron withdrawal by the substituents, and thus the interaction of nitrogen with the anionic site of the enzyme will be enhanced. Hence, the occurrence of σ with a positive sign in almost all the correlation equations is well substantiated. The small carbon chain between the phenyl ring and the nitrogen appears to hydrophobically bind with the enzyme.

In the case of hallucinogens, QSAR studies were not able to predict the exact nature of drug–receptor interactions.[3] While hydrophobicity and steric factors appear to be important in all types of hallucinogenic drugs, the electronic properties seem to be important in the case of only phenylalkylamines. With this background, it is difficult to assume that all types of hallucinogens have an exactly identical mode of action. It was, however, assumed[3] that there can be two receptor sites for hallucinogens, so that structurally and conformationally different molecules would interact with different receptor sites and binding at one site might involve totally electronic interaction while binding at the other site might involve totally hydrophobic interaction.

It was a QSAR study (eq 182) that confirmed that the central hypotensive activity of α-adrenoceptor agonists depends primarily upon α_2-adrenoceptor binding, and on the basis of a QSAR study only, it was assumed that cyanoguanidine and related moieties in cimetidine analogues interact with the H_2 receptor by hydrogen bonding and that the strength of the interaction is determined by the dipole's ability to align with the receptor (eq 191).

For anticonvulsants, it was discussed (see section III.C.1) that stereochemical and electronic features of molecules were important for their anticonvulsant actions. This suggests that their receptors also should possess a special stereochemical and electronic feature.

All general (nonspecific) CNS drugs have been shown to base their activity on lipophilicity, i.e., their ability to cross the cell membrane. Consequently, benzodiazepines, which act on a well-defined receptor,[290] elicit their depressant activity through the same mechanism as do the barbiturates in producing their hypnotic activity (see section III.A.2).

As far as common structural features among the CNS drugs are concerned, there is hardly any commonality in general nonspecific drugs. However, in specific

modifiers of CNS functions, where physicochemical, electronic, steric, and topographical, i.e., all sorts of properties, have played some roles, there must be designed a common structural model. Specific topographical arrangements for analgetics, hallucinogens, anticonvulsants, antidepressants, and antipsychotics have been already proposed.[291,292] According to Andrews and Lloyd,[291,292] in all CNS drugs the aromatic ring and the nitrogen moieties are the primary binding groups whose topographical arrangement is fundamental to the activity of drugs. On the basis of this hypothesis, Lloyd and Andrews[293] using five semirigid CNS active drugs—morphine, strychnine, LSD, apomorphine, and mianserine—recently defined a four-point model for a common pharmacophore. Two of the points of the model represent hydrogen bonding between the nitrogen and the receptor, and the other two the possible hydrophobic interactions between the aromatic group and the receptor. This common model was found to be an appropriate basis for the action of nine other CNS drugs, each being a key representative of a different CNS-active drug class or neurotransmitter system. Kaufman and Koski concluded[32,294] after several physicochemical, quantum mechanical, and other theoretical studies that the pharmacological effectiveness of CNS agents is governed by lipophilicity and by topographical and electronic structures of the pharmacophore.

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VI. References

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