Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 13 (2005) 237–255
Bioorganic & Medicinal Chemistry

# On the role of polarizability in QSAR

Rajeshwar P. Verma, Alka Kurup and Corwin Hansch*

*Department of Chemistry, Pomona College, Claremont, CA 91711, USA*

Received 1 August 2004; revised 22 September 2004; accepted 22 September 2004
Available online 12 October 2004

**Abstract**—The polarizability of a molecule, an important physical property, is currently attracting our attention particularly in the area of QSAR for chemical–biological interactions. In this report, the polarizability effects on ligand–substrate interactions has been discussed in terms of NVE (number of valence electrons) using additive values for valence electrons and the formulation of a total number of 51 QSAR. The QSAR model can be illustrated by Eq. I.

$$\log 1/C = a(\mathrm{NVE}) \pm \mathrm{constant} \quad \text{(I)}$$



## 1. Introduction

Although theoretically, one would expect polarizability to be important between the electrons in a ligand and a biological receptor, and we have been illustrating this via the Lorentz–Lorenz equation, our concern is about the dual nature of this expression. Pauling and Pressman[1] who attempted to understand its role in hapten–antibody interactions started our interest. We later found that their work only involved steric factors.[2]

The Lorentz–Lorenz equation A was formulated in 1880 before anyone had thought of electrons.

$$\mathrm{MR} = n^2 - 1/n^2 + 2(\mathrm{MW}/d) \quad \text{(A)}$$

In this expression, $n$ = refractive index of a liquid, $d$ = density, and MW = molecular weight. In the 20th century, Russian researchers routinely reported the values of $n$ and $d$ for new liquids and also for some solids by measuring at different concentrations in solution and then extrapolated the values for pure solid. We collected 1536 values for substituents. From these, Leo developed an algorithm for the calculation of CMR for the whole molecule similar to that he developed for Clog $P$. Both CMR and Clog $P$ are available from the Clog $P$ program.[3] In fact, our database of 11,600 bio QSAR has 2675 equations based on MR or CMR. Still it has bothered us as to the meaning of such equations since Eq. A has a volume component and a measure of polarizability. Recently,[4] with a few examples, we found that another approach to understanding polarizability was simply to add up the number of valence electrons (NVE) in a molecule, for example, H = 1, C = 4, N = 5, P = 5, O = 6, S = 6, and halogens = 7. A worrisome aspect of this approach is the use of 7 for all halogens regardless of their size. Our parameter NVE that is often superior to CMR does not depend on volume, as does CMR. This is most clear from the fact that all halogens have the same value for NVE.

Our first conformation of the fact that NVE works well for halogens came from a study by King.[5] In England, when a person dies from a drug overdose, commits suicide, or is accidentally killed, the government determines the concentration in the blood from which we formulated QSAR B.[4b]

$$\log 1/C = 0.61(\pm 0.17)\log P + 0.017(\pm 0.004)\mathrm{NVE} + 1.44(\pm 0.37)$$
$$n = 36, \quad r^2 = 0.850, \quad s = 0.438, \quad q^2 = 0.817$$
$$\text{outliers}: \ \text{morphine}, \ \text{theophylline}, \ CF_2Cl_2, \ \text{paraldehyde}, \ \text{halothane} \quad \text{(B)}$$

*Keywords*: Polarizability; NVE; QSAR; Enzymes; Receptors; Chemical–biological interaction.

* Corresponding author. Tel.: +1 909 621 8445; fax: +1 909 607 7726; e-mail: rverma@pomona.edu

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.09.039

The following halogens containing compounds were well fit: chlorpromazine, flurazepam, diazepam, chlormethiazole, tetrachloroethylene, $CCl_2F_2$, $CCl_4$, $CHCl_3$, $CH_2CCl_3$, $CFCl_3$, trichloroethylene, $CHF_2Cl$, $CHBrClCF_3$, $ClCH_2CH_2Cl$, $CH_2ClBr$, $CH_2Cl_2$, $C_2H_5Cl$.

Thus, we see that NVE holds for halogens regardless of size. King attempted to use log*P* to correlate the data but without success. We have two ways of dealing with polarizability, one dependent on volume, one independent of volume.

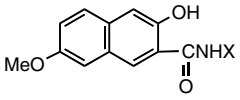
## 2. Materials and methods

All the data have been collected from the literature (see individual QSARs for respective references). *C* is the molar concentration of a compound and log1/*C* is the dependent variable that defines the biological parameter for QSAR equations. Physicochemical descriptors are auto-loaded, and multiregression analyses (MRA) to derive the QSAR are executed with the C-QSAR program.[3] NVE (number of valence electrons) is a parameter that is used as another approach to understand polarizability and calculated by simply summing up the valence electrons in a molecule, for example, H = 1, C = 4, N = 5, P = 5, O = 6, S = 6, and halogens = 7. In the QSAR equations, *n* is the number of data points, *r* is the correlation coefficient, $r^2$ is the goodness of fit, $q^2$ is the goodness of prediction, and *s* is the standard deviation. All the QSAR reported here are derived by us and were not given with the original data sets taken from the literature as referenced.

## 3. Results and discussion

### 3.1. Reactions involving enzymes

*$I_{50}$ of human cytomegalovirus DNA polymerase by **I***. Data from Vaillancourt et al.[6] (Table 1)




**I**

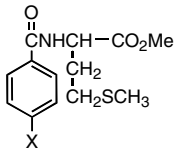
$$\log 1/C = 0.034(\pm 0.02)\mathrm{NVE} + 0.56(\pm 2.4)$$
$$n = 5, \quad r^2 = 0.925, \quad s = 0.168, \quad q^2 = 0.626 \qquad (1)$$

**Table 1.**

| No | X | log1/*C* (Eq. 1) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | 3-($CH_2$–(4-Cl–$C_6H_4$))–5-$C_2N_2S$ | 5.40 | 5.48 | −0.09 | 146 |
| 2 | 7-Cl–2-$C_7H_3NS$ | 5.19 | 4.94 | 0.25 | 130 |
| 3 | 5-(4-Cl–$C_6H_4$)–2-$C_3HNS$ | 5.22 | 5.28 | −0.06 | 140 |
| 4 | 4-Cl–2-$C_3HNS$ | 4.23 | 4.34 | −0.11 | 112 |
| 5 | 5-(3-$NO_2$–$C_6H_4$)–2-$C_3HNS$ | 5.62 | 5.62 | 0.00 | 150 |

The $q^2$ term is a bit low, but otherwise the statistics are good. This virus infects a large number of people and is associated with clinical syndromes in pneumonia and hepatitis.

*$I_{50}$ of farnesyltransferase by **II***. Data from Schlitzer et al.[7] (Table 2)

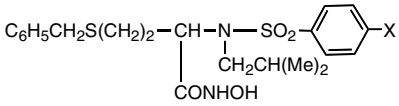



**II**

$$\log 1/C = 0.025(\pm 0.007)\mathrm{NVE} - 0.76(\pm 1.68)$$
$$n = 7, \quad r^2 = 0.939, \quad s = 0.115, \quad q^2 = 0.826 \qquad (2)$$
$$\text{outlier}: \ \mathrm{NHCOCH_2CH_2NHCO(CH_2)_{14}CH_3}$$

The authors were interested in blocking the farneslation of Ras proteins, which are important in cancer.

*$I_{50}$ of human matrix metalloproteinase-13 by **III***. Data from Hanessian et al.[8] (Table 3)

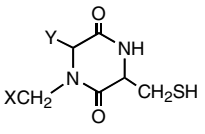



**III**

$$\log 1/C = 0.025(\pm 0.011)\mathrm{NVE} + 3.73(\pm 1.95)$$
$$n = 4, \quad r^2 = 0.980, \quad s = 0.058, \quad q^2 = 0.925 \qquad (3)$$

A surprisingly good fit for such complex ligands. The MMP enzymes are being intensely studied because of their role in proteolysis of the extra cellular matrix. At the moment we have 203 QSAR on this class of enzymes. These molecules contain a Zn atom that no doubt plays a role in polarizability.

*Inhibition of matrix metalloproteinase-1 by **IV***. Data from Szardenings et al.[9] (Table 4)




**IV**

$$\log 1/C = 0.038(\pm 0.011)\mathrm{NVE} + 1.85(\pm 1.22)$$
$$n = 6, \quad r^2 = 0.956, \quad s = 0.076, \quad q^2 = 0.887 \qquad (4)$$

It is not unexpected to find a metalloproteinase containing an SH group to react with the above type of compound, however one might not expect an NVE term. We have almost 191 QSAR on metalloproteinase QSAR but only 24 with an NVE term.

**Table 2.**

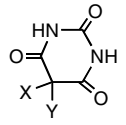
| No | X | log 1/*C* (Eq. 2) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1[a] | $NHCOCH_2CH_2NHCO(CH_2)_{14}CH_3$ | 5.43 | 5.09 | 0.34 | 232 |
| 2 | $NHCOCH_2NHCO(CH_2)_{13}CH_3$ | 4.92 | 4.79 | 0.13 | 220 |
| 3 | $NHCO(CH_2)_3NHCO(CH_2)_{13}CH_3$ | 4.88 | 5.09 | −0.21 | 232 |
| 4 | $NHCOCH_2CH_2CONH(CH_2)_{15}CH_3$ | 5.24 | 5.24 | 0.00 | 238 |
| 5 | $NHCO(CH_2)_3CONH(CH_2)_{14}CH_3$ | 5.27 | 5.24 | 0.03 | 238 |
| 6 | $CH_2NHCO(CH_2)_{15}CH_3$ | 4.05 | 4.08 | −0.04 | 192 |
| 7 | $CH_2NHCOCH_2NHCO(CH_2)_{14}CH_3$ | 5.12 | 5.09 | 0.03 | 232 |
| 8 | $CH_2NHCO(CH_2)_2NHCO(CH_2)_{13}CH_3$ | 5.14 | 5.09 | 0.05 | 232 |

[a] Outlier.

**Table 3.**

| No | X | log 1/*C* (Eq. 3) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | 4-OMe | 7.92 | 7.97 | −0.05 | 170 |
| 2 | 4-Br | 7.85 | 7.82 | 0.03 | 164 |
| 3 | $4\text{-}OC_6H_5$ | 8.49 | 8.52 | −0.03 | 192 |
| 4 | $4\text{-}C_6H_5$ | 8.42 | 8.37 | 0.05 | 186 |

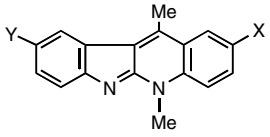
*Inhibition of matrix metalloproteinase-9 by **V***. Data from Foley et al.[10] (Table 5)




**V**

$$\log 1/C = 0.037(\pm 0.013)\mathrm{NVE} + 2.04(\pm 1.70)$$
$$n = 7, \quad r^2 = 0.911, \quad s = 0.318, \quad q^2 = 0.843$$
$$\text{outliers}: \ X = (CH_2)_5CH_3, \quad Y = C_6H_4\text{–}4\text{-}C_6H_5;$$
$$X = CH_3, \quad Y = C_6H_4\text{–}4\text{-}OC_6H_5 \qquad (5)$$

*Induced cleavage of calf thymus DNA by **VI***. Data from Kaczmarek et al.[11] (Table 6)




**VI**

$$\log 1/C = 0.038(\pm 0.011)\mathrm{NVE} + 1.85(\pm 1.22)$$
$$n = 6, \quad r^2 = 0.956, \quad s = 0.076, \quad q^2 = 0.807 \qquad (6)$$
$$\text{outlier}: \ X = Y = Me$$

Out of 27 QSAR on DNA we have only two examples on cleavage. The other is a very complex equation based on four terms. It is fascinating that QSAR 6 is so simple.

*Inhibition of phosphodiesterase by **VII***. Data from Keller et al.[12] (Table 7)

**Table 4.**

| No | X | Y | log 1/*C* (Eq. 4) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | $C_6H_{11}CH_2$ | $C_6H_{11}$ | 7.33 | 7.22 | 0.11 | 136 |
| 2 | $C_6H_{11}CH_2$ | 2-Quinolyl | 7.46 | 7.60 | −0.14 | 148 |
| 3 | $C_6H_{11}CH_2$ | $C_6H_4\text{–}4\text{-}OCH_3$ | 7.52 | 7.41 | 0.11 | 142 |
| 4 | $C_6H_5CH_2$ | $C_6H_4\text{–}4\text{-}OCH_3$ | 7.19 | 7.22 | −0.02 | 136 |
| 5 | $C_6H_5CH_2$ | $CH_2CH_2CH_2CH_3$ | 6.50 | 6.51 | −0.01 | 114 |
| 6 | $CH_2CH_2CH_2CH_3$ | $C_6H_{11}$ | 6.66 | 6.70 | −0.05 | 120 |

**Table 5.**

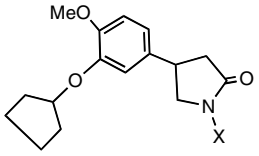
| No | X | Y | log 1/*C* (Eq. 5) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | $(CH_2)_5CH_3$ | $C_6H_5$ | 6.48 | 6.17 | 0.31 | 112 |
| 2 | $CH_3$ | $C_6H_5$ | 4.96 | 5.07 | −0.11 | 82 |
| 3[a] | $(CH_2)_5CH_3$ | $C_6H_4\text{–}4\text{-}C_6H_5$ | 6.06 | 7.21 | −1.14 | 140 |
| 4 | $CH_2CH_3$ | $C_6H_4\text{–}4\text{-}C_6H_5$ | 6.16 | 6.32 | −0.16 | 116 |
| 5[a] | $CH_3$ | $C_6H_4\text{–}4\text{-}OC_6H_5$ | 7.28 | 6.32 | 0.96 | 116 |
| 6 | $(CH_2)_5CH_3$ | $C_6H_4\text{–}4\text{-}OC_6H_5$ | 7.74 | 7.43 | 0.32 | 146 |
| 7 | $CH_2OCH_2C_6H_5$ | $C_6H_4\text{–}4\text{-}OC_6H_5$ | 7.77 | 7.80 | −0.03 | 156 |
| 8 | $CH_2CH_2OH$ | $C_6H_4\text{–}4\text{-}OC_6H_5$ | 6.93 | 6.76 | 0.17 | 128 |
| 9 | $CH_3$ | $CH_2C_6H_4\text{–}O(CH_2)_7CH_3$ | 6.79 | 7.28 | −0.49 | 142 |

[a] Outliers.

**Table 6.**

| No | X | Y | log 1/*C* (Eq. 6) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | H | OMe | 5.85 | 5.82 | 0.03 | 104 |
| 2 | Me | OMe | 6.00 | 6.05 | −0.05 | 110 |
| 3 | OMe | Me | 6.10 | 6.05 | 0.04 | 110 |
| 4 | OMe | OMe | 6.22 | 6.28 | −0.06 | 116 |
| 5 | OMe | H | 5.92 | 5.82 | 0.10 | 104 |
| 6 | H | H | 5.30 | 5.36 | −0.06 | 92 |
| 7[a] | Me | Me | 6.40 | 5.82 | 0.58 | 104 |

[a] Outlier.

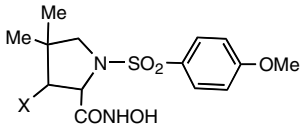



**VII**

$$\log 1/C = 0.021(\pm 0.005)\mathrm{NVE} + 2.71(\pm 0.82)$$
$$n = 12, \quad r^2 = 0.911, \quad s = 0.235, \quad q^2 = 0.872 \qquad (7)$$
outliers : 3-$OCOC_6H_5$–$C_6H_4$, (3-$OCH_2C_6H_5$, 5-$CO_2Me$)–$C_6H_3$

We have only two QSAR on phosphodiesterase, out of 11,600 QSAR. The other example is correlated with CMR that has a volume component in addition to polarizability. In this study, the authors were looking for better inhibitors of inflammation associated with asthma.

*Inhibition of matrix metalloproteinase-1 by **VIII***. Data from Hanessian et al.[13] (Table 8)




**VIII**

$$\log 1/C = 0.034(\pm 0.014)\mathrm{NVE} + 0.24(\pm 2.2)$$
$$n = 6, \quad r^2 = 0.922, \quad s = 0.239, \quad q^2 = 0.810 \qquad (8)$$
outliers : X = $CH_2SCH_2C_6H_5$

We have 197 QSAR on metalloproteinases but only this example is based on NVE.

*Inhibition of topoisomerase I by miscellaneous unsaturated fatty acids having various numbers of double bonds*. Data from Suzuki et al.[14] (Table 9)

**Table 7.**

| No | X | log 1/*C* (Eq. 7) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | H | 5.10 | 5.03 | 0.07 | 108 |
| 2 | $CH_2C_6H_5$ | 5.61 | 5.76 | −0.15 | 142 |
| 3 | $C_6H_5$ | 5.78 | 5.63 | 0.15 | 136 |
| 4 | 3-OH–$C_6H_4$ | 5.61 | 5.76 | −0.14 | 142 |
| 5 | 3,5-Di-$OCH_3$–$C_6H_3$ | 6.48 | 6.14 | 0.34 | 160 |
| 6[a] | 3-$OCOC_6H_5$–$C_6H_4$ | 7.23 | 6.57 | 0.66 | 180 |
| 7 | 3-$OCH_2C_6H_5$–$C_6H_4$ | 6.36 | 6.49 | −0.13 | 176 |
| 8[a] | (3-$OCH_2C_6H_5$, 5-$CO_2CH_3$)–$C_6H_3$ | 5.90 | 6.96 | −1.06 | 198 |
| 9 | (3-$OCH_2C_6H_5$, 5-COOH)–$C_6H_3$ | 6.55 | 6.83 | −0.28 | 192 |
| 10 | 3-(OCO–$C_7H_4$–4′-$OCH_3$)–$C_6H_4$ | 7.09 | 6.83 | 0.26 | 192 |
| 11 | 3-(NHCO–$C_6H_4$–4′-$OCH_3$)–$C_6H_4$ | 6.84 | 6.83 | 0.01 | 192 |
| 12 | 3-($OCH_2$–$C_6H_4$–3′-$OCH_3$)–$C_6H_4$ | 6.49 | 6.75 | −0.25 | 188 |
| 13 | 3-($OCH_2$–$C_6H_3$–3′-$OCH_3$)–5-COOH–$C_6H_3$ | 6.89 | 7.09 | −0.20 | 204 |
| 14 | 3-($OCH_2$–$C_6H_3$–3′-$OCH_3$)–5-$CONHN(CH_3)_2$–$C_6H_3$ | 7.80 | 7.47 | 0.32 | 222 |

[a] Outliers.

**Table 8.**

| No | X | log 1/*C* (Eq. 8) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1[a] | $CH_2SCH_2C_6H_5$ | 6.70 | 6.01 | 0.69 | 168 |
| 2 | $CH{=}CH_2$ | 4.59 | 4.77 | −0.18 | 132 |
| 3 | $CH_2OH$ | 5.06 | 4.84 | 0.21 | 134 |
| 4 | $CH_2SCH_2CH_2C_6H_5$ | 6.18 | 6.22 | −0.03 | 174 |
| 5 | $CH_2SCH_2$–$C_6H_4$-4-$OCH_3$ | 6.34 | 6.42 | −0.08 | 180 |
| 6 | $CH_2OCH_2C_6H_5$ | 5.79 | 6.01 | −0.22 | 168 |
| 7 | $CH(OH)CH_2SC_6H_5$ | 6.93 | 6.22 | 0.72 | 174 |

[a] Outlier.

**Table 9.**

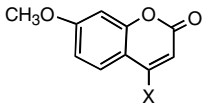
| No | Compound | log 1/C (Eq. 9) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | Oleic acid | 4.51 | 4.53 | −0.02 | 118 |
| 2 | Linoleic acid | 4.51 | 4.49 | 0.02 | 116 |
| 3 | Linolenic acid | 4.46 | 4.45 | 0.01 | 114 |
| 4 | Eicosanoic acid | 4.74 | 4.78 | −0.03 | 130 |
| 5 | Eicosadienoic acid | 4.80 | 4.74 | 0.06 | 128 |
| 6 | Eicosatrienoic acid | 4.70 | 4.69 | 0.00 | 126 |
| 7 | Eicosatetraenoic acid | 4.62 | 4.65 | −0.03 | 124 |
| 8[a] | Eicosapentaenoic acid | 4.37 | 4.61 | −0.25 | 122 |

[a] Outlier.

$$\log 1/C = 0.020(\pm 0.006)\mathrm{NVE} + 2.13(\pm 0.75)$$
$$n = 7, \quad r^2 = 0.936, \quad s = 0.037, \quad q^2 = 0.875 \qquad (9)$$
outlier : Eicosapentaenoic acid

There is an interest in inhibition of topoisomerases as anticancer drugs.

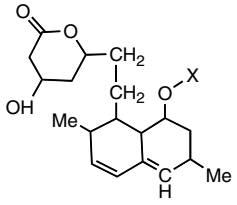
*Clearance values of cyp1A2-mediated O-dealkylation by human P-450 in insect cells of* ***IX***. Data from Venhorst et al.[15] (Table 10)




**IX**

$$\log V_{max}/K_m = 0.051(\pm 0.017)\mathrm{NVE} - 4.98(\pm 1.53)$$
$$n = 5, \quad r^2 = 0.969, \quad s = 0.101, \quad q^2 = 0.893$$
outlier : $X = CH_2N(Me)_2$
(10)

*Inhibition of HMG–COA reductase by* ***X***. Data from Lee et al.[16] (Table 11)




**X**

$$\log 1/C = 0.064(\pm 0.024)\mathrm{NVE} - 2.93(\pm 3.76)$$
$$n = 7, \quad r^2 = 0.902, \quad s = 0.329, \quad q^2 = 0.771 \qquad (11)$$
outliers : $CH_2C_6H_4$–4-Cl, $COCH_2CH{=}CH_2$

We have 42 QSAR on COX, of which two are based on NVE.

*COX-2 inhibition by* ***XI***. Shin et al.[17] (Table 12)

**Table 10.**

| No | X | log $V_{max}/K_m$ (Eq. 10) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | $CH_2NH_2$ | −1.04 | −0.97 | −0.07 | 78 |
| 2 | $CH_2NHCH_3$ | −0.67 | −0.67 | −0.01 | 84 |
| 3 | $CH_2NHC_2H_5$ | −0.22 | −0.36 | 0.13 | 90 |
| 4 | $CH_2NHC_3H_7$ | −0.02 | −0.05 | 0.03 | 96 |
| 5 | $CH_2NHC_4H_9$ | 0.17 | 0.26 | −0.09 | 102 |
| 6[a] | $CH_2N(CH_3)_2$ | 0.07 | −0.36 | 0.43 | 90 |

[a] Outlier.

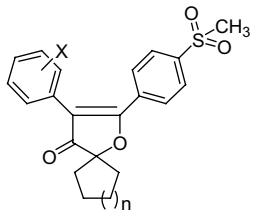
**Table 11.**

| No | X | log 1/C (Eq. 11) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | Me | 5.55 | 5.69 | −0.14 | 134 |
| 2 | $CH_2CH{=}CH_2$ | 6.43 | 6.34 | 0.09 | 144 |
| 3 | $CH_2C(Me){=}CH_2$ | 6.44 | 6.72 | −0.28 | 150 |
| 4 | $CH_2C_6H_5$ | 7.57 | 7.50 | 0.07 | 162 |
| 5[a] | $CH_2C_6H_4$–4-Cl | 6.77 | 7.88 | −1.11 | 168 |
| 6 | $CH_2C_6H_4$–4-F | 8.33 | 7.88 | 0.45 | 168 |
| 7 | COMe | 6.57 | 6.34 | 0.23 | 144 |
| 8[a] | $COCH_2CH{=}CH_2$ | 8.54 | 6.98 | 1.56 | 154 |
| 9 | $COCH_2C_6H_5$ | 7.72 | 8.14 | −0.42 | 172 |

[a] Outliers.

**Table 12.**

| No | X | n | log 1/C (Eq. 12) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | 3-F | 1 | 5.11 | 5.17 | −0.06 | 140 |
| 2 | 4-$CH(CH_3)_2$ | 1 | 6.91 | 6.86 | 0.06 | 152 |
| 3 | H | 2 | 5.28 | 5.17 | 0.11 | 140 |
| 4 | 3-$CH_3$ | 2 | 5.90 | 6.01 | −0.11 | 146 |




**XI**

**Table 13.**

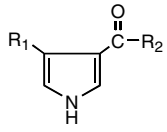
| No | $R_1$ | $R_2$ | log 1/*C* (Eq. 13) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1[a] | $C_6H_5$ | $C_6H_5$ | 5.22 | 5.76 | −0.54 | 92 |
| 2 | 2-Thiophene | $C_6H_5$ | 5.30 | 5.34 | −0.04 | 88 |
| 3 | 2-Thiophene | $C_6H_4$–Cl(4) | 6.00 | 5.97 | 0.03 | 94 |
| 4 | $C_6H_4$–Cl(4) | 2-Thiophene | 6.02 | 5.97 | 0.05 | 94 |
| 5 | $C_6H_4$–Cl(4) | 2-Thiophene–5-Cl | 6.57 | 6.60 | −0.03 | 100 |
| 6 | 2-Thiophene–5-Br | 2-Thiophene–5-Cl | 6.15 | 6.18 | −0.02 | 96 |

[a] Outlier.

$$\log 1/C = 0.14(\pm 0.06)\mathrm{NVE} - 14.55(\pm 7.96)$$
$$n = 4, \quad r^2 = 0.984, \quad s = 0.127, \quad q^2 = 0.912 \qquad (12)$$

Despite the three changes in X, a single parameter yields a good correlation. COX inhibitors might be used in the treatment of bone disease.

*COX-2 inhibition by **XII***. Data from Darnnhardt et al.[18] (Table 13)



**XII**

$$\log 1/C = 0.11(\pm 0.017)\mathrm{NVE} - 3.90(\pm 1.64)$$
$$n = 5, \quad r^2 = 0.992, \quad s = 0.047, \quad q^2 = 0.960 \qquad (13)$$
$$\text{outliers}: \ R_1 = R_2 = \mathrm{C6H5}$$

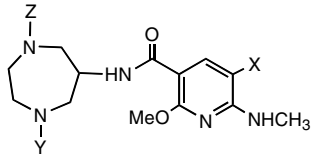
Despite some rather complicated variation in the inhibitors, a single parameter does a good job of rationalizing the data. Of the 27 QSAR on COX-2, 19 came from papers published in 2000–2003. This is rather unexpected since our large data contains 7743 QSAR published before 2000. This must be due to the type of chemicals studied. The first paper that was published was in 1994. Academic researchers are slow to see the value in this class of compound.

### 3.2. Reactions involving receptors

*Binding affinity of **XIII** to rat brain synaptic membrane*. Data from Hirokawa et al.[19] (Table 14)

**Table 14.**

| No | X | Y | Z | log 1/*C* (Eq. 14) | | | NVE |
|---|---|---|---|---|---|---|---|
| | | | | Obsd | Calcd | Δ | |
| 1 | Cl | Me | Me | 6.86 | 6.83 | 0.04 | 128 |
| 2 | Cl | $C_2H_5$ | $C_2H_5$ | 7.56 | 7.59 | −0.03 | 140 |
| 3 | Br | $C_2H_5$ | $C_2H_5$ | 7.68 | 7.59 | 0.09 | 140 |
| 4 | Br | Me | Cy–$C_3H_5$ (RS) | 7.33 | 7.46 | −0.14 | 138 |
| 5 | Br | $C_{25}$ | Cy–$C_3H_5$ (RS) | 7.89 | 7.85 | 0.04 | 144 |

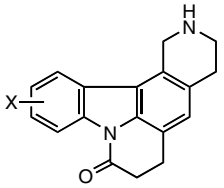


**XIII**

$$\log 1/C = 0.064(\pm 0.027)\mathrm{NVE} - 1.33(\pm 3.73)$$
$$n = 5, \quad r^2 = 0.950, \quad s = 0.102, \quad q^2 = 0.714 \qquad (14)$$

Variations have been made at three points in the complex parent compound, yet we obtain an excellent correlation with a single variable. Just how the electrons in these compounds line up with those in the receptor is of course, not known. NMR studies might be interesting to perform. The authors were searching for better drugs.

*Binding of **XIV** to human muscarinic-M4 receptors expressed in CHO cells*. Data from Gharagozloo et al.[20] (Table 15)



**XIV**

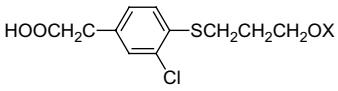
$$\log 1/C = 0.023(\pm 0.007)\mathrm{NVE} + 2.93(\pm 0.75)$$
$$n = 8, \quad r^2 = 0.927, s = 0.059, \quad q^2 = 0.879 \qquad (15)$$

**Table 15.**

| No | X | log 1/*C* (Eq. 15) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | H | 5.31 | 5.36 | −0.05 | 104 |
| 2 | 2-$CH_3$ | 5.71 | 5.64 | 0.07 | 116 |
| 3 | 2-OH | 5.56 | 5.50 | 0.06 | 110 |
| 4 | 2-$COOCH_3$ | 5.84 | 5.87 | −0.03 | 126 |
| 5 | 3-$OCH_3$ | 5.68 | 5.64 | 0.04 | 116 |
| 6 | 3-OH | 5.52 | 5.50 | 0.02 | 110 |
| 7 | 2,3-Di-$OCH_3$ | 5.90 | 5.92 | −0.02 | 128 |
| 8 | 8-$CH_3$ | 5.42 | 5.50 | −0.08 | 110 |

This is an excellent correlation for such a complex system. Usually one finds a $\log P$ term for reactions with cells but not in this instance.

*Inhibition of Peroxisome proliferators-activated receptor (ppar-alfa) by phenylacetic acids **XV***. Data from Santini et al.[21] (Table 16)




**XV**

$$\log 1/C = 0.097(\pm 0.047)\mathrm{NVE} - 9.28(\pm 7.69)$$
$$n = 6, \quad r^2 = 0.892, \quad s = 0.272, \quad q^2 = 0.788 \qquad (16)$$
$$\text{outlier}: \ (7\text{-}C_3H_7)\text{–}3\text{-}(CF_3)\text{–benzoxazo-6-yl}$$

In vivo lowering of glucose and triglyceride was attained.

*Inhibition of Peroxisome proliferators-activated receptor (ppar-delta) by phenylacetic acids **XV***. Data from Santini et al.[21] (Table 17)

$$\log 1/C = 0.017(\pm 0.007)\mathrm{NVE} + 5.27(\pm 1.08)$$
$$n = 5, \quad r^2 = 0.957, \quad s = 0.028, \quad q^2 = 0.840 \qquad (17)$$
$$\text{outliers}: \ C_6H_2\text{–}[2\text{-}C_3H_7, \ 3\text{-OH}, \ 4\text{-COMe}], \ (7\text{-}C_3H_7)\text{–}3\text{-}(CF_3)\text{–benzoxazo-6-yl}$$

*Binding of phenols to human estrogen receptor*. Data from Hu and Aizawa.[22] (Table 18)

**Table 18.**

| No | Compound | $\log 1/C$ (Eq. 18) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | 4-*n*-Nonylphenol | 5.02 | 5.42 | −0.40 | 90 |
| 2 | 4-*tert*-Octylphenol | 4.85 | 4.93 | −0.08 | 84 |
| 3 | 4,4′-Biphenyldiol | 3.97 | 3.80 | 0.18 | 70 |
| 4[a] | Bisphenol A | 3.96 | 5.26 | −1.30 | 88 |
| 5 | 4-Hydroxybiphenyl | 3.37 | 3.31 | 0.06 | 64 |
| 6 | 4-*sec*-Butylpphenol | 3.24 | 2.98 | 0.25 | 60 |
| 7 | 3-Hydroxybiphenyl | 3.21 | 3.31 | −0.10 | 64 |
| 8 | 2-Hydroxybiphenyl | 3.00 | 3.31 | −0.31 | 64 |
| 9 | 4-*tert*-Butylphenol | 3.00 | 2.98 | 0.01 | 60 |
| 10 | 2-*sec*-Butylphenol | 2.86 | 2.98 | −0.12 | 60 |
| 11 | 4-Ethylphenol | 2.77 | 2.01 | 0.76 | 48 |
| 12 | 3-*tert*-Butylphenol | 2.64 | 2.98 | −0.34 | 60 |
| 13 | 2-*tert*-Butylphenol | 2.63 | 2.98 | −0.36 | 60 |
| 14 | Phenol | 1.02 | 1.04 | −0.01 | 36 |
| 15[a] | Diethylstilbesterol | 8.22 | 6.55 | 1.67 | 104 |
| 16 | β-Estradiol | 7.64 | 6.88 | 0.76 | 108 |
| 17 | Estriol | 7.30 | 7.37 | −0.06 | 114 |
| 18 | Estrone | 6.48 | 6.72 | −0.24 | 106 |

[a] Outliers.

$$\log 1/C = 0.081(\pm 0.009)\mathrm{NVE} - 1.88(\pm 0.67)$$
$$n = 16, \quad r^2 = 0.964, \quad s = 0.363, \quad q^2 = 0.949 \qquad (18)$$
$$\text{outliers}: \ \text{Bisphenol A, diethylstilbesterol}$$

The authors were concerned with the environmental toxicity of industrial phenolic chemicals. We have many QSAR for the toxicity of phenols that depend on $\log P$.

*Binding of **XVI** to 5-HT-1A receptor*. Data from Mattson et al.[23] (Table 19)

**Table 16.**

| No | X | $\log 1/C$ (Eq. 16) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | $C_6H_2$–[2-($CH_2CH_2CH_3$), 3-OH, 4-$COCH_3$] | 5.80 | 5.88 | −0.08 | 156 |
| 2 | $C_6H_2$–[2-($CH_2CH_2CH_3$), 3-OH, 4-$COCH_2CH_3$] | 6.59 | 6.46 | 0.12 | 162 |
| 3 | $C_6H_2$–[2-($CH_2CH_2CH_3$), 3-OH, 4-C(=NOH)$CH_2CH_3$] | 7.13 | 7.05 | 0.08 | 168 |
| 4 | (7-$CH_2CH_2CH_3$)–3-($CH_2CH_3$)–Benzoxazo-6-yl | 6.61 | 6.27 | 0.34 | 160 |
| 5[a] | (7-$CH_2CH_2CH_3$)–3-($CF_3$)–Benzoxazo-6-yl | 6.90 | 7.43 | −0.53 | 172 |
| 6 | (7-$CH_2CH_2CH_3$)–3-($CH_2CH_3$)–Benzofuran-6-yl | 5.89 | 6.27 | −0.38 | 160 |
| 7 | (7-$CH_2CH_2CH_3$)–3-($C_6H_5$)–Benzofuran-6-yl | 7.74 | 7.82 | −0.08 | 176 |

[a] Outlier.

**Table 17.**

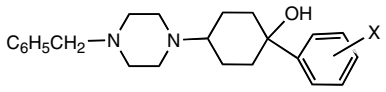
| No | X | $\log 1/C$ (Eq. 17) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1[a] | $C_6H_2$–[2-($CH_2CH_2CH_3$), 3-OH, 4-$COCH_3$] | 7.10 | 7.88 | −0.78 | 156 |
| 2 | $C_6H_2$–[2-($CH_2CH_2CH_3$), 3-OH, 4-$COCH_2CH_3$] | 8.00 | 7.98 | 0.02 | 162 |
| 3 | $C_6H_2$–[2-($CH_2CH_2CH_3$), 3-OH, 4-C(=NOH)$CH_2CH_3$] | 8.05 | 8.08 | −0.03 | 168 |
| 4 | (7-$CH_2CH_2CH_3$)–3-($CH_2CH_3$)–Benzoxazo-6-yl | 7.96 | 7.94 | 0.02 | 160 |
| 5[a] | (7-$CH_2CH_2CH_3$)–3-($CF_3$)–Benzoxazo-6-yl | 8.30 | 8.14 | 0.16 | 172 |
| 6 | (7-$CH_2CH_2CH_3$)–3-($CH_2CH_3$)–Benzofuran-6-yl | 7.92 | 7.94 | −0.02 | 160 |
| 7 | (7-$CH_2CH_2CH_3$)–3-($C_6H_5$)–Benzofuran-6-yl | 8.22 | 8.21 | 0.01 | 176 |

[a] Outliers.

**Table 19.**

| No | X | log 1/*C* (Eq. 19) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | 3-$OCH_2$-4 | 7.70 | 7.63 | 0.07 | 154 |
| 2 | 4-$OCH_3$ | 7.30 | 7.28 | 0.02 | 150 |
| 3 | 3-$OCH_3$ | 7.30 | 7.28 | 0.02 | 150 |
| 4 | 2-$OCH_3$ | 7.22 | 7.28 | −0.06 | 150 |
| 5[a] | 3,4-Di-$OCH_3$ | 6.85 | 8.33 | −1.47 | 162 |
| 6 | 4-F | 6.59 | 6.75 | −0.17 | 144 |
| 7 | $C_6H_5$ | 6.34 | 6.23 | 0.11 | 138 |

[a] Outlier.

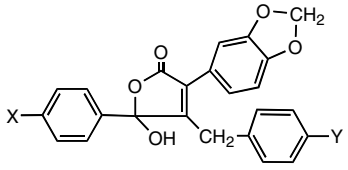



**XVI**

$$\log 1/C = 0.087(\pm 0.024)\mathrm{NVE} - 5.83(\pm 3.57)$$
$$n = 6, \quad r^2 = 0.962, \quad s = 0.111, \quad q^2 = 0.813 \qquad (19)$$
outlier : X = 3, 4-di-OMe

An object of this study was to find better antagonists on the neuronal firing in the rat dorsal raphé and on 5-HT-1A release in the raphé and hippocampus. We have often found NVE to be associated with reactions of nerves.

*Inhibition of Et-3 binding to rat cerebellum (Et-B) by* ***XVII***. Data from Doherty et al.[24] (Table 20)




**XVII**

$$\log 1/C = 0.081(\pm 0.039)\mathrm{NVE} - 6.77(\pm 6.12)$$
$$n = 6, \quad r^2 = 0.890, \quad s = 0.280, \quad q^2 = 0.783 \qquad (20)$$
outlier : X = 4-OMe, Y = 4-Me

Et is implicated in a number of diseases, for example, hypertension, congestive heart failure, renal failure. These problems motivated this study.

**Table 20.**

| No | X | Y | log 1/*C* (Eq. 20) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | 4-Cl | H | 5.28 | 5.33 | −0.04 | 150 |
| 2 | H | H | 4.66 | 4.84 | −0.19 | 144 |
| 3 | 4-OMe | H | 6.30 | 5.81 | 0.49 | 156 |
| 4 | 4-Me | H | 5.35 | 5.33 | 0.02 | 150 |
| 5 | 4-OMe | 4-Cl | 6.14 | 6.30 | −0.15 | 162 |
| 6 | 4-OMe | 4-OMe | 6.66 | 6.78 | −0.12 | 168 |
| 7[a] | 4-OMe | 4-Me | 5.35 | 6.30 | −0.95 | 162 |

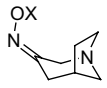
[a] Outlier.

**Table 21.**

| No | X | log 1/*C* (Eq. 21) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | $CH(CH_3)C{\equiv}CH$ | 6.08 | 6.08 | 0.00 | 76 |
| 2 | $CH_2C{\equiv}CCH_3$ | 6.05 | 6.08 | −0.03 | 76 |
| 3 | $CH_2CH_2CCH$ | 5.94 | 6.08 | −0.14 | 76 |
| 4 | $CH(C_2H_5)C{\equiv}CH$ | 6.63 | 6.49 | 0.15 | 82 |
| 5[a] | $CH_2C{\equiv}CCH_2CH_3$ | 6.01 | 6.49 | −0.47 | 82 |
| 6 | $CH_2CH_2C{\equiv}CH_3$ | 6.43 | 6.49 | −0.06 | 82 |
| 7 | $CH_2C{\equiv}CH$ | 5.75 | 5.67 | 0.09 | 70 |

[a] Outlier.

*Inhibition of [3H]-pirenzepine binding to rat cerebral cortex muscarinic-1 receptor by quinuclidinone o-alkynyloximes* ***XVIII***. Data from Somanadhan et al.[25] (Table 21)

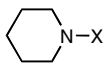



**XVIII**

$$\log 1/C = 0.068(\pm 0.03)\mathrm{NVE} + 0.895(\pm 2.44)$$
$$n = 6, \quad r^2 = 0.900, \quad s = 0.115, \quad q^2 = 0.694 \qquad (21)$$
outlier : $CH_2C{\equiv}CC_2H_5$

Cholinergic neurons in the brain are reduced early in the course of Alzheimer's disease. Muscarinic agonists are a possible treatment.

*Antagonistic activity to muscarinic M3 receptor from guinea pig ileum of* ***XIX***. Data from Meier et al.[26] (Table 22)




**XIX**

$$\mathrm{pA2} = 0.030(\pm 0.009)\mathrm{NVE} + 3.82(\pm 0.78)$$
$$n = 10, \quad r^2 = 0.885, \quad s = 0.199, \quad q^2 = 0.819$$
outliers : X = $(CH_2)_3CH_2C_6H_5$; $(CH_2)_5$–$CH_2C_6H_5$ (22)

**Table 22.**

| No | X | pA2 (Eq. 22) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1[a] | $(CH_2)_3CH_2C_6H_5$ | 5.70 | 6.49 | −0.79 | 88 |
| 2 | $(CH_2)_4CH_2C_6H_5$ | 6.38 | 6.67 | −0.29 | 94 |
| 3[a] | $(CH_2)_5CH_2C_6H_5$ | 6.50 | 6.85 | −0.35 | 100 |
| 4 | $(CH_2)_2C{\equiv}CH$ | 5.38 | 5.52 | −0.14 | 56 |
| 5 | $(CH_2)_3CCH$ | 5.69 | 5.70 | −0.01 | 62 |
| 6 | $(CH_2)_4C{\equiv}CH$ | 6.16 | 5.88 | 0.28 | 68 |
| 7 | $(CH_2)_2C{\equiv}CC_6H_5$ | 6.47 | 6.37 | 0.10 | 84 |
| 8 | $(CH_2)_2CH{=}CH(CH_2)_2C_6H_5$ | 6.66 | 6.79 | −0.13 | 98 |
| 9 | $(CH_2)_2C{\equiv}C(CH_2)_2C_6H_5$ | 6.78 | 6.73 | 0.05 | 96 |
| 10 | $(CH_2)_2C{\equiv}C(CH_2)_3C_6H_5$ | 7.21 | 6.92 | 0.29 | 102 |
| 11 | $(CH_2)_3C{\equiv}CC_6H_5$ | 6.42 | 6.55 | −0.13 | 90 |
| 12 | $(CH_2)_3C{\equiv}C(CH_2)_2C_6H_5$ | 6.91 | 6.92 | −0.01 | 102 |

[a] Outliers.

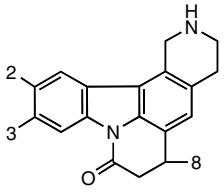
**Table 23.**

| No | X | log 1/*C* (Eq. 23) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | H | 5.57 | 5.44 | 0.13 | 104 |
| 2 | 2-$OCH_3$ | 6.05 | 6.17 | −0.12 | 116 |
| 3 | 2-OH | 5.81 | 5.81 | 0.00 | 110 |
| 4[a] | 2-$COOCH_3$ | 6.03 | 6.77 | −0.74 | 126 |
| 5 | 3-$OCH_3$ | 6.18 | 6.17 | 0.01 | 116 |
| 6 | 3-OH | 5.64 | 5.81 | −0.17 | 110 |
| 7 | 2,3-Di-$OCH_3$ | 6.97 | 6.89 | 0.08 | 128 |
| 8 | 8-$CH_3$ | 5.87 | 5.81 | 0.06 | 110 |
| 9[a] | 2,3-Di-$OCH_3$, 8-$CH_3$ | 6.70 | 7.25 | −0.55 | 134 |

[a] Outliers.

The authors were searching for a nonimidazole histamine $H_3$–receptor antagonist.

*Binding to NMS–liganded muscarinic–M2 receptors in CHO cells of **XX***. Data from Gharagozloo et al.[20] (Table 23)

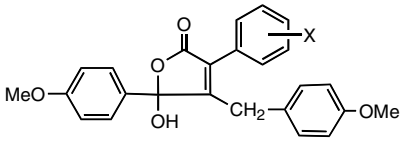


**XX**

$$\log 1/C = 0.060(\pm 0.016)\mathrm{NVE} - 0.84(\pm 1.81)$$
$$n = 7, \quad r^2 = 0.950, \quad s = 0.116, \quad q^2 = 0.846 \qquad (23)$$
outliers : 2-COOMe; 2, 3-di-OMe, 8-Me

Muscarinic receptors are targets for a variety of diseases such as asthma, intestinal motility, and Alzheimer's Disease.

*Inhibition of endothelin-A receptor by **XXI***. Data from Doherty et al.[24] (Table 24)



**XXI**

$$\log 1/C = 0.091(\pm 0.013)\mathrm{NVE} - 8.13(\pm 2.09)$$
$$n = 5, \quad r^2 = 0.994, \quad s = 0.041, \quad q^2 = 0.988 \qquad (24)$$
outlier : X = 3-$OCH_2O$-4

The potent vasoconstricter implicated in diseases such as hypertension, congestive heart failure, and ischemia have received much attention.

*Displacement of 5-HT1D from pig caudate membrane by **XXII***. Data from Street et al.[27] (Table 25)

**Table 24.**

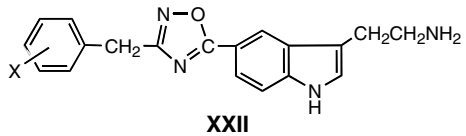
| No | X | log 1/*C* (Eq. 24) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1[a] | 3-$OCH_2O$-4 | 8.75 | 7.11 | 1.64 | 168 |
| 2 | H | 5.66 | 5.66 | 0.00 | 152 |
| 3 | 4-Cl | 6.15 | 6.20 | −0.05 | 158 |
| 4 | 4-OMe | 6.72 | 6.74 | −0.02 | 164 |
| 5 | 4-Me | 6.24 | 6.20 | 0.04 | 158 |
| 6 | 3,4-$Cl_2$ | 6.77 | 6.74 | 0.02 | 164 |

[a] Outlier.

**Table 25.**

| No | X | log 1/*C* (Eq. 25) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1[a] | 2-OMe | 7.80 | 9.00 | −1.20 | 132 |
| 2 | 3-OMe | 8.90 | 9.00 | −0.10 | 132 |
| 3 | 4-OMe | 9.10 | 9.00 | 0.10 | 132 |
| 4 | 4-NHCOMe | 9.30 | 9.30 | 0.00 | 142 |
| 5 | 4-NHSO2Me | 9.50 | 9.55 | −0.05 | 150 |
| 6 | 4-SO2NHMe | 9.60 | 9.55 | 0.05 | 150 |

[a] Outlier.

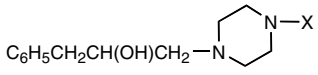


**XXII**

$$\log 1/C = 0.031(\pm 0.016)\mathrm{NVE} + 4.97(\pm 2.28)$$
$$n = 5, \quad r^2 = 0.924, \quad s = 0.091, \quad q^2 = 0.742 \qquad (25)$$
outlier : 2-OMe

Compounds of this type might have value in the treatment of migraines.

*Binding of **XXIII** to dopamine transporter rat striatal membranes.* Data from Kimura et al.[28] (Table 26)



**XXIII**

$$\log 1/C = 0.095(\pm 0.011)\mathrm{NVE} - 8.40(\pm 1.90)$$
$$n = 6, \quad r^2 = 0.993, \quad s = 0.042, \quad q^2 = 0.988$$
outliers : $CH(C_6H_4\text{–}4\text{-}F)_2$, $(CH_2)_4CH(C_6H_4\text{–}4\text{-}F)_2$ (26)

Dopamine transporters play an important role in the central nervous system. That is related to CNS disorders such as Parkinson's disease and depression.

*Reduction of action potential in grass frog nerves by miscellaneous alcohols*. Data from Hahin and Kondratiev.[29] (Table 27)

**Table 26.**

| No | X | log 1/*C* (Eq. 26) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1[a] | $CH(C_6H_4–4\text{-}F)_2$ | 7.70 | 6.99 | 0.71 | 162 |
| 2 | $CH_2CH(C_6H_4–4\text{-}F)_2$ | 7.55 | 7.56 | −0.01 | 168 |
| 3 | $CH_2CH_2CH(C_6H_4–4\text{-}F)_2$ | 8.15 | 8.13 | 0.03 | 174 |
| 4 | $CH_2CH_2CH_2CH(C_6H_4–4\text{-}F)_2$ | 8.70 | 8.70 | 0.00 | 180 |
| 5[a] | $CH_2CH_2CH_2CH_2CH(C_6H_4–4\text{-}F)_2$ | 8.22 | 9.27 | −1.05 | 186 |
| 6 | $CH_2CH_2CH{=}C(C_6H_4–4\text{-}F)_2$ | 8.47 | 8.51 | −0.04 | 178 |
| 7 | $CH_2CH_2OCH(C_6H_4–4\text{-}F)_2$ | 8.66 | 8.70 | −0.04 | 180 |
| 8 | $CH_2CH_2CH_2N(C_6H_4–4\text{-}F)_2$ | 8.76 | 8.70 | 0.06 | 180 |

[a] Outliers.

**Table 27.**

| No | Compound | log 1/*C* (Eq. 27) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | Methanol | −0.38 | −0.31 | −0.07 | 14 |
| 2 | Ethanol | 0.06 | 0.15 | −0.09 | 20 |
| 3 | *n*-Propanol | 0.63 | 0.60 | 0.03 | 26 |
| 4 | *n*-Butanol | 1.16 | 1.06 | 0.10 | 32 |
| 5 | *n*-Pentanol | 1.70 | 1.51 | 0.19 | 38 |
| 6 | *n*-Hexanol | 2.18 | 1.97 | 0.21 | 44 |
| 7 | *n*-Heptanol | 2.66 | 2.42 | 0.24 | 50 |
| 8[a] | Phenol | 2.09 | 1.36 | 0.73 | 36 |
| 9 | Benzyl alcohol | 1.70 | 1.82 | −0.12 | 42 |
| 10 | Phenethyl alcohol | 2.00 | 2.27 | −0.27 | 48 |
| 11 | 3-Phenyl-1-propanol | 2.51 | 2.72 | −0.22 | 54 |

[a] Outlier.

$$\log 1/C = 0.076(\pm 0.011)\mathrm{NVE} - 1.37(\pm 0.43)$$
$$n = 10, \quad r^2 = 0.969, \quad s = 0.192, \quad q^2 = 0.952 \qquad (27)$$
$$\text{outlier}: \ \text{Phenol}$$

The authors of this report were trying to get a better understanding of anesthesia. However, it is doubtful that such a simple procedure would be of much help.

*Minimum blocking concentration of miscellaneous compounds on frog muscles*. Data from Kamlet et al.[30] (Table 28)

$$\log 1/C = 0.083(\pm 0.008)\mathrm{NVE} - 1.41(\pm 0.33)$$
$$n = 20, \quad r^2 = 0.962, \quad s = 0.213, \quad q^2 = 0.955 \qquad (28)$$
$$\text{outlier}: \ CHCl_3$$

We have noticed a number of examples where toxicity to nerves is correlated with NVE.[4] This is an outstanding example.

*Inhibition of acid secretion from frog gastric mucosa by barbiturates*. Data from Dinno et al.[31] (Table 29)

$$\log K = 0.028(\pm 0.003)\mathrm{NVE} - 0.886(\pm 0.28)$$
$$n = 5, \quad r^2 = 0.996, \quad s = 0.018, \quad q^2 = 0.993 \qquad (29)$$
$$\text{outlier}: \ \text{Thiamylal}$$

**Table 28.**

| No | Compound | log 1/*C* (Eq. 28) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | Toluene | 2.00 | 1.60 | 0.40 | 36 |
| 2 | Methanol | −0.09 | −0.24 | 0.15 | 14 |
| 3 | Ethanol | 0.25 | 0.26 | −0.01 | 20 |
| 4 | Propanol | 0.60 | 0.76 | −0.16 | 26 |
| 5 | 2-Propanol | 0.45 | 0.76 | −0.31 | 26 |
| 6 | Butanol | 1.22 | 1.26 | −0.04 | 32 |
| 7 | Pentanol | 1.80 | 1.77 | 0.03 | 38 |
| 8 | Hexanol | 2.44 | 2.27 | 0.17 | 44 |
| 9 | Heptanol | 2.80 | 2.77 | 0.03 | 50 |
| 10 | Octanol | 3.16 | 3.27 | −0.11 | 56 |
| 11 | Acetone | 0.40 | 0.60 | −0.20 | 24 |
| 12 | Phenol | 2.00 | 1.60 | 0.40 | 36 |
| 13 | Thymol | 3.52 | 3.60 | −0.08 | 60 |
| 14 | Benzyl alcohol | 1.70 | 2.10 | −0.40 | 42 |
| 15 | Ether | 1.07 | 1.26 | −0.19 | 32 |
| 16[a] | $CHCl_3$ | 1.50 | 0.76 | 0.74 | 26 |
| 17 | Aniline | 1.70 | 1.60 | 0.10 | 36 |
| 18 | Nitrobenzene | 2.53 | 2.43 | 0.10 | 46 |
| 19 | 2-Naphthol | 3.00 | 3.10 | −0.10 | 54 |
| 20 | Pyridine | 1.23 | 1.10 | 0.13 | 30 |
| 21 | Quinoline | 2.70 | 2.60 | 0.10 | 48 |

[a] Outlier.

**Table 29.**

| No | Compound | log *K* (Eq. 29) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | Barbital | 1.15 | 1.15 | 0.00 | 72 |
| 2 | Diallylbarbituric acid | 1.38 | 1.38 | 0.00 | 80 |
| 3 | Phenobarbital | 1.58 | 1.60 | −0.02 | 88 |
| 4 | Pentobarbital | 1.68 | 1.66 | 0.02 | 90 |
| 5 | Secobarbital | 1.77 | 1.77 | 0.00 | 94 |
| 6[a] | Thiamylal | 1.89 | 1.77 | 0.12 | 94 |

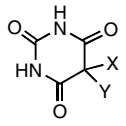
[a] Outlier.

The outlier is a thiobarbiturate. Thus, it is not surprising that it is poorly fit. Of course, barbiturates have been known for decades to inhibit many biological processes.

*Binding of barbiturates **XXIV** to bovine serum albumin*. Data from Goldbaum and Smith.[32] (Table 30)

**Table 30.**

| No | X | Y | log 1/*C* (Eq. 30) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | Et | Ethyl | 2.70 | 2.71 | −0.01 | 72 |
| 2 | Et | 1-Methylbutyl | 3.49 | 3.46 | 0.03 | 90 |
| 3 | Et | Phenyl | 3.39 | 3.38 | 0.01 | 88 |
| 4 | Allyl | 1-Methylbutyl | 3.60 | 3.63 | −0.03 | 94 |

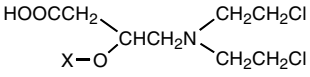


**XXIV**

$$\log 1/C = 0.042(\pm 0.008)\mathrm{NVE} - 0.31(\pm 0.68)$$
$$n = 4, \quad r^2 = 0.996, \quad s = 0.030, \quad q^2 = 0.938 \qquad (30)$$

We have 67 QSAR on albumin, of these 50 are simply correlated with log *P*. We have a surprising number of NVE QSAR from studies with various types of cells. Since a number of these are from cancer cells these will be considered first.

*Inhibition of human melanoma cells by **XXV***. Data from Faissat et al.[33] (Table 31)

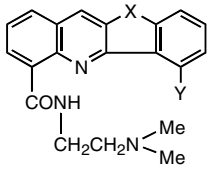


**XXV**

$$\log 1/C = 0.007(\pm 0.003)\mathrm{NVE} + 2.55(\pm 0.44)$$
$$n = 5, \quad r^2 = 0.927, \quad s = 0.078, \quad q^2 = 0.817 \qquad (31)$$

Since nitrogen mustards have long been known to be effective against cancer, this variation was studied.

*Inhibition of murine Lewis lung cancer cells by **XXVI***. Data from Chen et al.[34] (Table 32)



**XXVI**

**Table 32.**

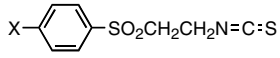
| No | X | Y | log 1/*C* (Eq. 32) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | CO | H | 7.04 | 7.07 | −0.03 | 130 |
| 2 | CO | $CH_3$ | 7.82 | 7.71 | 0.11 | 136 |
| 3 | NH | H | 6.54 | 6.64 | −0.10 | 126 |
| 4 | NH | $CH_3$ | 7.48 | 7.28 | 0.20 | 132 |
| 5[a] | $NCH_3$ | H | 6.85 | 7.28 | −0.43 | 132 |
| 6 | $NCH_3$ | $CH_3$ | 7.74 | 7.93 | −0.18 | 138 |

[a] Outlier.

$$\log 1/C = 0.11(\pm 0.06)\mathrm{NVE} - 6.91(\pm 7.90)$$
$$n = 5, \quad r^2 = 0.916, \quad s = 0.179, \quad q^2 = 0.709 \qquad (32)$$
$$\text{outlier}: \ \mathrm{X} = \mathrm{NCH_3}, \quad \mathrm{Y} = \mathrm{H}$$

Unfortunately, these compounds turned out to be not very effective.

*In a large study of various types of cancer cells, only one example could be related to toxicity by isothiocyanate derivative **XXVII***. Data from Miko et al.[35] (Table 33)



**XXVII**

$$\log 1/C = 0.026(\pm 0.014)\mathrm{NVE} + 2.36(\pm 1.21)$$
$$n = 5, \quad r^2 = 0.915, \quad s = 0.069, \quad q^2 = 0.775 \qquad (33)$$
$$\text{outlier}: \ 4\text{-N=C=S}$$

It is interesting that the outlier, having two –N=C=S functions, is much less active than predicted by QSAR 33.

**Table 33.**

| No | X | log 1/*C* (Eq. 33) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | H | 4.22 | 4.27 | −0.05 | 74 |
| 2 | 4-$OC_2H_5$ | 4.70 | 4.74 | −0.04 | 92 |
| 3 | 4-Cl | 4.40 | 4.43 | −0.03 | 80 |
| 4 | 4-Br | 4.52 | 4.43 | 0.10 | 80 |
| 5 | 4-$NO_2$ | 4.70 | 4.68 | 0.02 | 90 |
| 6[a] | 4-NCS | 3.80 | 4.63 | −0.84 | 88 |

[a] Outlier.

**Table 31.**

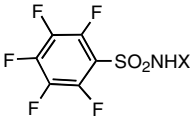
| No | X | log 1/*C* (Eq. 31) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | H | 3.06 | 3.10 | −0.04 | 84 |
| 2 | $COCH_2CH_3$ | 3.24 | 3.24 | 0.00 | 106 |
| 3 | $COC_7H_{15}$ | 3.39 | 3.44 | −0.05 | 136 |
| 4 | $COCH_2C_6H_5$ | 3.51 | 3.39 | 0.12 | 128 |
| 5 | $CO(CH_2)_3C_6H_4$–4-$N(CH_2CH_2Cl)_2$ | 3.71 | 3.74 | −0.03 | 182 |

**Table 34.**

| No | X/Compound | log 1/C (Eq. 34) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | 4-OMe–$C_6H_4$ | 7.54 | 7.35 | 0.19 | 124 |
| 2 | 5-Indolyl | 7.55 | 7.37 | 0.19 | 126 |
| 3[a] | 3,4-O$(CH_2)_2$O–Phenyl | 6.37 | 7.43 | −1.06 | 134 |
| 4 | 3,4-Di-Me–$C_6H_3$ | 6.92 | 7.35 | −0.43 | 124 |
| 5 | 4-$NMe_2$–$C_6H_4$ | 7.47 | 7.40 | 0.07 | 130 |
| 6 | Paclitaxel | 8.96 | 8.85 | 0.11 | 328 |
| 7 | Vinblastine | 8.64 | 8.76 | −0.12 | 316 |

[a] Outlier.

*Inhibition of MCF-7 cancer cells by*

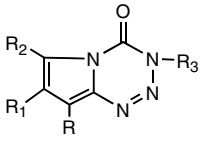



*plus Paclitaxel and Vinblastine*. Data from Medina et al.[36] (Table 34)

$$\log 1/C = 0.007(\pm 0.003)\mathrm{NVE} + 6.44(\pm 0.70)$$
$$n = 6, \quad r^2 = 0.906, \quad s = 0.268, \quad q^2 = 0.811 \qquad (34)$$
$$\text{outlier}: \ 3,4\text{-O}(\mathrm{CH_2})_2\mathrm{OC_6H_5}$$

The problem of multidrug resistant tumor initially inhibited by drug but then becoming resistant is serious. The authors were looking for drugs to solve. The cytotoxicity of these compounds was not affected by the multidrug resistant pump in these mostly multiresistant cells.

*Inhibition of UACC=257 Melanoma cell by* ***XXVIII***. Data from Diana et al.[37] (Table 35)

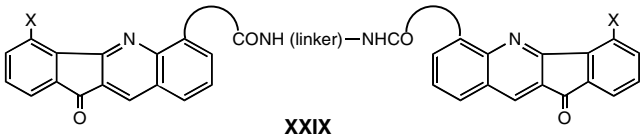



**XXVIII**

$$\log 1/C = 0.012(\pm 0.003)\mathrm{NVE} + 3.04(\pm 0.34)$$
$$n = 8, \quad r^2 = 0.948, \quad s = 0.077, \quad q^2 = 0.878$$
$$\text{outliers}: \ \mathrm{R = CN}, \quad \mathrm{R_1 = Me}, \quad \mathrm{R_2 = C_6H_5}, \quad \mathrm{R_3 = C_6H_4}\text{–4-Cl}; \quad \mathrm{R = CN}, \quad \mathrm{R_1 = C_6H_5}, \quad \mathrm{R_2 = Me}, \quad \mathrm{R_3 = C_6H_4}\text{–4-OMe} \qquad (35)$$

In screening this set of compounds against 23 cell lines, 11 sets were correlated by NVE a number of them had a σ term in addition to NVE.

*Inhibition of murine Lewis lung cancer cells by* ***XXIX***. Data from Deady et al.[38] (Table 36)

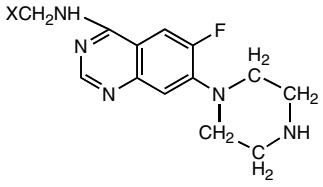



**XXIX**

$$\log 1/C = 0.046(\pm 0.011)\mathrm{NVE} - 3.59(\pm 2.70)$$
$$n = 10, \quad r^2 = 0.927, \quad s = 0.212, \quad q^2 = 0.870$$
$$\text{outliers}: \ \mathrm{X = H}, \ \text{Linker} = (\mathrm{CH_2})_2\mathrm{NMe}(\mathrm{CH_2})_2\mathrm{NMe}(\mathrm{CH_2})_2; \ \mathrm{X = H}, \ \text{Linker} = (\mathrm{CH_2})_3\mathrm{NH}(\mathrm{CH_2})_2\mathrm{NH}(\mathrm{CH_2})_3 \qquad (36)$$

The authors were following up leads from other laboratories that dimeric forms of chromophores joined by flexible lipophilic linker chains that were DNA-intercalating are effective anticancer compounds.

*Inhibition of CON-A stimulated mouse spleen cells by* ***XXX***. Data from Tobe et al.[39] (Table 37)



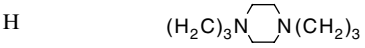

**XXX**

**Table 35.**

| No | R | $R_1$ | $R_2$ | $R_3$ | log 1/C (Eq. 35) | | | NVE |
|---|---|---|---|---|---|---|---|---|
| | | | | | Obsd | Calcd | Δ | |
| 1 | CN | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 4.51 | 4.51 | 0.00 | 120 |
| 2 | CN | $CH_3$ | $C_6H_5$ | $C_6H_4$–4-$OCH_3$ | 4.65 | 4.65 | 0.00 | 132 |
| 3[a] | CN | $CH_3$ | $C_6H_5$ | $C_6H_4$–4-Cl | 4.05 | 4.58 | 1.47 | 126 |
| 4 | CN | $CH_3$ | $C_6H_5$ | $C_6H_4$–3-Cl | 4.58 | 4.58 | 0.00 | 126 |
| 5 | CN | $CH_3$ | $C_6H_5$ | $C_6H_4$–4-$NO_2$ | 4.77 | 4.70 | 0.07 | 136 |
| 6[a] | CN | $C_6H_5$ | $CH_3$ | $C_6H_4$–4-$OCH_3$ | 4.07 | 4.65 | −0.58 | 132 |
| 7 | CN | $C_6H_5$ | $CH_3$ | $C_6H_4$–4-Cl | 4.45 | 4.58 | −0.13 | 126 |
| 8 | $COOC_2H_5$ | $CH_3$ | $C_6H_5$ | $C_6H_5$ | 1.81 | 4.76 | 0.06 | 140 |
| 9 | Mitozolomide | | | | 4.00 | 4.07 | −0.07 | 84 |
| 10 | Temozolomide | | | | 4.00 | 3.92 | 0.08 | 72 |

[a] Outliers.

**Table 36.**

| No | X | Linker | log 1/*C* (Eq. 36) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | H | $(CH_2)_2NH(CH_2)_2$ | 6.62 | 6.88 | −0.26 | 228 |
| 2 | H | $(CH_2)_3NMe(CH_2)_3$ | 7.92 | 7.70 | 0.22 | 246 |
| 3 | H | $(CH_2)_2NH(CH_2)_2NH(CH_2)_2$ | 7.85 | 7.70 | 0.15 | 246 |
| 4[a] | H | $(CH_2)_2NMe(CH_2)_2NMe(CH_2)_2$ | 7.48 | 8.25 | −0.77 | 258 |
| 5 | H | $(CH_2)_2NH(CH_2)_3NH(CH_2)_2$ | 8.33 | 7.98 | 0.35 | 252 |
| 6 | $CH_3$ | $(CH_2)_2NH(CH_2)_3NH(CH_2)_2$ | 8.30 | 8.53 | −0.23 | 264 |
| 7 | H | $(CH_2)_2NMe(CH_2)_3NMe(CH_2)_2$ | 8.57 | 8.53 | 0.04 | 264 |
| 8 | $CH_3$ | $(CH_2)_2NMe(CH_2)_3NMe(CH_2)_2$ | 9.16 | 9.08 | 0.08 | 276 |
| 9 | Cl | $(CH_2)_2NMe(CH_2)_3NMe(CH_2)_2$ | 8.96 | 9.08 | −0.12 | 276 |
| 10[a] | H | $(CH_2)_3NH(CH_2)_2NH(CH_2)_3$ | 6.26 | 8.25 | −1.99 | 258 |
| 11 | H |  | 8.62 | 8.71 | −0.09 | 268 |
| 12 | H | $(CH_2)_3NH(CH_2)_4$ | 7.57 | 7.70 | −0.13 | 246 |

[a] Outliers.

**Table 37.**

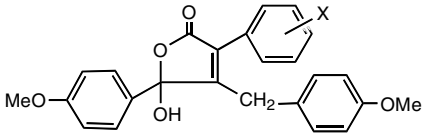
| No | X | log 1/*C* (Eq. 37) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | 3,4-Methylenedioxyphenyl | 5.29 | 5.30 | 0.00 | 144 |
| 2[a] | 3,4-Ethylenedioxyphenyl | 5.09 | 5.36 | −0.27 | 150 |
| 3 | Phenyl | 5.09 | 5.12 | −0.03 | 128 |
| 4 | 4-F–Phenyl | 5.21 | 5.19 | 0.02 | 134 |
| 5 | 3-Thienyl | 5.10 | 5.08 | 0.02 | 124 |
| 6 | 1-Napthy | 5.32 | 5.32 | 0.00 | 146 |

[a] Outlier.

$$\log 1/C = 0.011(\pm 0.004)\mathrm{NVE} + 3.74(\pm 0.53)$$
$$n = 5, \quad r^2 = 0.963, \quad s = 0.024, \quad q^2 = 0.906 \qquad (37)$$
$$\text{outlier}: \ 3,4\text{-ethylenedioxy phenyl}$$

One compound, number 6, showed anti-inflammatory effect in rats with adjuvant arthritis.

*Inhibition of endothelin-A from rabbit renal artery vascular smooth muscle cells by* ***XXXI***. Data from Doherty et al.[24] (Table 38)




**XXXI**

$$\log 1/C = 0.068(\pm 0.015)\mathrm{NVE} - 4.69(\pm 2.43)$$
$$n = 5, \quad r^2 = 0.985, \quad s = 0.048, \quad q^2 = 0.968 \qquad (38)$$
$$\text{outlier}: \ 3,4\text{-OCH}_2\text{O-}$$

The potent vasoconstrictor endothelin-A is implicated in several human diseases such as hypertension, isochemia, and cerebral vasospasms.

*Stability of human leukocyte enzyme in human blood* $T^{1/2}$ *in minutes by* ***XXXII***. Data from Desai et al.[40] (Table 39)

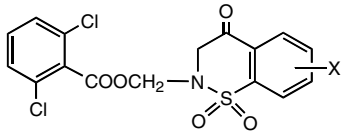
**Table 38.**

| No | X | log 1/*C* (Eq. 38) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1[a] | 3,4-$OCH_2O$ | 8.05 | 6.77 | 1.27 | 168 |
| 2 | H | 5.70 | 5.68 | 0.02 | 152 |
| 3 | 4-Cl | 6.02 | 6.09 | −0.07 | 158 |
| 4 | 4-Ome | 6.51 | 6.50 | 0.01 | 164 |
| 5 | 4-Me | 6.12 | 6.09 | 0.04 | 158 |
| 6 | 3,4-$Cl_2$ | 6.51 | 6.50 | 0.01 | 164 |

[a] Outlier.

**Table 39.**

| No | X | log $T_{1/2}$ (Eq. 39) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | 4-$OCH_2CH_3$ | 1.00 | 1.05 | −0.05 | 142 |
| 2 | 4,6-Di-$OCH_2CH_3$ | 1.99 | 2.03 | −0.04 | 160 |
| 3 | 4,6-Di-$OCH_3$ | 1.48 | 1.37 | 0.10 | 148 |
| 4 | 6-$OCH_3$ | 0.70 | 0.72 | −0.02 | 136 |




**XXXII**

$$\log T^{1/2} = 0.055(\pm 0.021)\mathrm{NVE} - 6.74(\pm 3.04)$$
$$n = 4, \quad r^2 = 0.985, \quad s = 0.085, \quad q^2 = 0.916 \qquad (39)$$

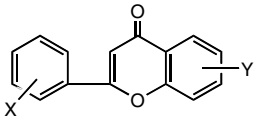
Human leukocyte elastase has been implicated in pulmonary disease: emphysema, cystic fibrosis, bronchitis.

*Inhibition of nitric oxide in lipopolysaccharide-activated-mouse peritoneal macrophages by flavones* ***XXXIII***. Data from Matsuda et al.[41] (Table 40)

**Table 40.**

| No | X | Y | log 1/C (Eq. 40) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | H | H | 4.28 | 4.35 | −0.06 | 82 |
| 2 | 4-OH | H | 4.47 | 4.44 | 0.03 | 88 |
| 3 | 5,7-Di-OH | H | 4.51 | 4.54 | −0.03 | 94 |
| 4 | 5-OH–7-$OCH_3$ | H | 4.64 | 4.63 | 0.01 | 100 |
| 5[a] | 7-OH | 4′-OH | 4.85 | 4.54 | 0.32 | 94 |
| 6 | H | 4′-Di-OH | 4.64 | 4.54 | 0.10 | 94 |
| 7 | 7-OH | 3′,4′-Di-OH | 4.59 | 4.63 | −0.05 | 100 |
| 8 | 5-OH | 3′-OH, 4′-$OCH_3$ | 4.96 | 4.91 | 0.05 | 118 |
| 9 | 5-OH–7-$OCH_3$ | 3′,4′-Di-$OCH_3$ | 4.96 | 5.01 | −0.05 | 124 |

[a] Outlier.

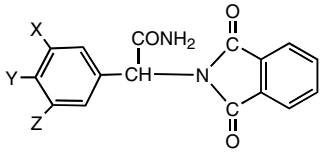


**XXXIII**

$$\log 1/C = 0.016(\pm 0.004)\mathrm{NVE} + 3.06(\pm 0.40)$$
$$n = 8, \quad r^2 = 0.941, \quad s = 0.061, \quad q^2 = 0.883 \qquad (40)$$
$$\text{outlier}: \ \mathrm{X} = \text{7-OH}, \quad \mathrm{Y} = 4'\text{-OH}$$

NO has been implicated in various processes such as ischema, inflammation, and reperfusion.

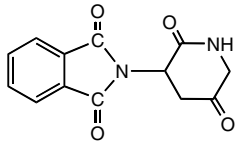
*Inhibition of tumor factor-alpha in human PBMC by **XXXIV***. Data from Muller et al.[42] (Table 41)



**XXXIV**

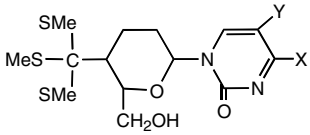
$$\log 1/C = 0.049(\pm 0.012)\mathrm{NVE} - 1.60(\pm 1.40)$$
$$n = 8, \quad r^2 = 0.946, \quad s = 0.142, \quad q^2 = 0.897 \qquad (41)$$
$$\text{outliers}: \ \mathrm{X} = \mathrm{H}, \quad \mathrm{Y} = \mathrm{OC_3H_7}, \quad \mathrm{Z} = \mathrm{OC_3H_7};$$
$$\mathrm{X} = \mathrm{OMe}, \quad \mathrm{Y} = \mathrm{H}, \quad \mathrm{Z} = \mathrm{OMe}$$

The study of these molecules was inspired from the fact that thalidomide **XXXV** was found to be effective in the treatment of leprosy, bone marrow transplantation, and rheumatoid arthritis.



**XXXV**

*Inhibition of plasmocytoma murine cell line by **XXXVI** (antiviral activity) versus HSV-1*. Data from Mugnaini et al.[43] (Table 42)



**XXXVI**

$$\log 1/C = 0.100(\pm 0.025)\mathrm{NVE} - 9.51(\pm 3.31)$$
$$n = 6, \quad r^2 = 0.968, \quad s = 0.063, \quad q^2 = 0.903 \qquad (42)$$
$$\text{outliers}: \ \mathrm{X} = \mathrm{OH}, \quad \mathrm{Y} = \mathrm{F}(\text{L-}\beta); \quad \mathrm{X} = \mathrm{OH},$$
$$\mathrm{Y} = \mathrm{Me}(\text{D-}\beta)$$

*Inhibition of S. aureus by **XXXVII***. Data from Pernak et al.[44] (Table 43)

**Table 41.**

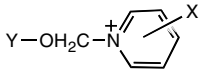
| No | X | Y | Z | log 1/C (Eq. 41) | | | NVE |
|---|---|---|---|---|---|---|---|
| | | | | Obsd | Calcd | Δ | |
| 1 | H | H | H | 3.59 | 3.55 | 0.04 | 104 |
| 2 | H | H | CN | 4.05 | 3.94 | 0.11 | 112 |
| 3 | H | CN | H | 3.82 | 3.94 | −0.12 | 112 |
| 4 | H | H | $OCH_3$ | 3.92 | 4.14 | −0.22 | 116 |
| 5 | H | $OCH_3$ | H | 4.21 | 4.14 | 0.07 | 116 |
| 6 | H | $OCH_3$ | $OCH_3$ | 4.92 | 4.73 | 0.19 | 128 |
| 7 | H | $OC_2H_5$ | $OC_2H_5$ | 5.25 | 5.33 | −0.08 | 140 |
| 8[a] | H | $OC_3H_7$ | $OC_3H_7$ | 4.26 | 5.92 | −1.66 | 152 |
| 9 | H | Cl | Cl | 4.15 | 4.14 | 0.01 | 116 |
| 10[a] | $OCH_3$ | H | $OCH_3$ | 4.41 | 4.73 | −0.33 | 128 |

[a] Outliers.

**Table 42.**

| No | X | Y | log 1/C (Eq. 42) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | OH | H(L-β) | 3.40 | 3.45 | −0.05 | 130 |
| 2[a] | OH | F(L-β) | 3.64 | 4.05 | −0.41 | 136 |
| 3 | OH | $CH_3$(L-β) | 3.98 | 4.05 | −0.07 | 136 |
| 4 | $NH_2$ | H(L-β) | 3.42 | 3.45 | −0.03 | 130 |
| 5 | OH | H(D-β) | 3.48 | 3.45 | 0.03 | 130 |
| 6 | OH | F(D-β) | 4.11 | 4.05 | 0.07 | 136 |
| 7[a] | OH | $CH_3$(D-β) | 3.56 | 4.05 | −0.49 | 136 |
| 8 | $NH_2$ | H(D-β) | 3.49 | 3.45 | 0.05 | 130 |

[a] Outliers.



**XXXVII**

$$\log 1/C = 0.024(\pm 0.006)\mathrm{NVE} + 0.88(\pm 0.91)$$
$$n = 9, \quad r^2 = 0.925, \quad s = 0.207, \quad q^2 = 0.875$$
$$\text{outliers}: \ \mathrm{X} = 3\text{-}\mathrm{CONH_2}, \quad \mathrm{Y} = \mathrm{C_{11}H_{23}}; \quad \mathrm{X} = 3\text{-}\mathrm{CONHCH_2OCH_2OC_{10}H_{21}}; \quad \mathrm{Y} = \mathrm{C_{10}H_{21}} \tag{43}$$

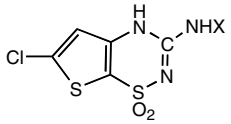
This was an attempt to find more potent drugs.

*Inhibition of housefly mitochondria by salicylanilides and miscellaneous*. Data from Williamson and Metcalf.[45] (Table 44)

$$\log 1/C = 0.056(\pm 0.008)\mathrm{NVE} + 1.01(\pm 0.91)$$
$$n = 15, \quad r^2 = 0.952, \quad s = 0.342, \quad q^2 = 0.935$$
$$\text{outlier}: \ 4,5,6,7\text{-tetra-Cl}, \ 2\text{-}\mathrm{CF_3}\text{–benzimidizide} \tag{44}$$

This is a superb correlation, the outlier does not belong to the salicylanilide family of compounds.

*Inhibition of glucose stimulated insulin release in wistar rat islets by **XXXVIII***. Data from Nielsen et al.[46] (Table 45)



**XXXVIII**

$$\log 1/C = 0.125(\pm 0.027)\mathrm{NVE} - 4.54(\pm 2.52)$$
$$n = 10, \quad r^2 = 0.932, \quad s = 0.256, \quad q^2 = 0.906 \tag{45}$$
$$\text{outlier}: \ \mathrm{X} = \mathit{cyclo}\text{-}\mathrm{C_5H_9}$$

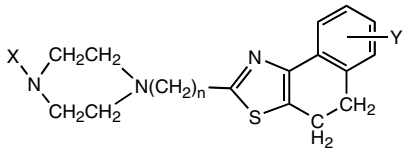
The authors were interested in finding a drug for diabetes.

*Inhibition of keto aldehyde formation by XN=C=S*. Data from Guo et al.[47] (Table 46)

$$\log 1/C = 0.063(\pm 0.029)\mathrm{NVE} + 2.94(\pm 1.86)$$
$$n = 5, \quad r^2 = 0.939, \quad s = 0.173, \quad q^2 = 0.856 \tag{46}$$
$$\text{outlier}: \ (\mathrm{CH_2})_6\mathrm{C_6H_5}$$

The authors were investigating the inhibition of 4-(methylnitrosa amino)-1-(3-pyridyl)-1-butanone induced tumorigenesis in mouse lung microsomes.

*Inhibition of [3H] 8-OH-DPAT binding to rat brain by **XXXIX***. Data from Perrone et al.[48] (Table 47)



**XXXIX**

$$\log 1/C = 0.053(\pm 0.015)\mathrm{NVE} - 0.71(\pm 2.31)$$
$$n = 10, \quad r^2 = 0.897, \quad s = 0.246, \quad q^2 = 0.853$$
$$\text{outliers}: \ \mathrm{X} = \mathrm{C_6H_5}, \quad \mathrm{Y} = \mathrm{H}, \quad n = 2; \quad \mathrm{X} = \mathrm{C_6H_5}, \quad \mathrm{Y} = 6\text{-}\mathrm{OMe}, \quad n = 4; \quad \mathrm{X} = \mathrm{C_6H_4}\text{–}2\text{-}\mathrm{OMe}, \quad \mathrm{Y} = 7\text{-}\mathrm{OMe}, \quad n = 4 \tag{47}$$

**Table 43.**

| No | X | Y | log 1/C (Eq. 43) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | 3-$CONH_2$ | $C_{10}H_{21}$ | 4.02 | 3.79 | 0.23 | 119 |
| 2[a] | 3-$CONH_2$ | $C_{11}H_{23}$ | 4.64 | 3.94 | 0.70 | 125 |
| 3 | 3-$CONH_2$ | $C_{12}H_{25}$ | 4.36 | 4.08 | 0.27 | 131 |
| 4 | 3-$CONH_2$ | $C_{12}H_{25}$ | 3.75 | 4.04 | −0.28 | 129 |
| 5 | 3-$CONHCH_2OCH_2OC_7H_{15}$ | $C_7H_{15}$ | 5.05 | 4.97 | 0.08 | 167 |
| 6 | 3-$CONHCH_2OCH_2OC_8H_{17}$ | $C_8H_{17}$ | 5.40 | 5.26 | 0.14 | 179 |
| 7 | 3-$CONHCH_2OCH_2OC_9H_{19}$ | $C_9H_{19}$ | 5.40 | 5.55 | −0.15 | 191 |
| 8[a] | 3-$CONHCH_2OCH_2OC_{10}H_{21}$ | $C_{10}H_{21}$ | 3.63 | 5.85 | −2.22 | 203 |
| 9 | 4-$CONH_2$ | $C_{10}H_{21}$ | 3.73 | 3.79 | −0.06 | 119 |
| 10 | 4-$CONH_2$ | $C_{11}H_{23}$ | 3.74 | 3.94 | −0.20 | 125 |
| 11 | 4-$CONH_2$ | $C_{12}H_{25}$ | 4.06 | 4.08 | −0.03 | 131 |

[a] Outliers.

**Table 44.**

| No | Compound | log 1/C (Eq. 44) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | Salicylanilide | 4.97 | 5.51 | −0.54 | 80 |
| 2 | 3-OH–2-Naphth.Carbanilide | 6.44 | 6.52 | −0.08 | 98 |
| 3 | 5-Cl–2′Cl–4′$NO_2$–Salicylanilide | 7.59 | 7.09 | 0.50 | 108 |
| 4 | 5-Cl–3-PH–2′5′DICl–Salicylanilide | 7.91 | 8.10 | −0.20 | 126 |
| 5 | 5-Cl–3-PH–3′4′-DICl–Salicylanilide | 8.03 | 8.10 | −0.07 | 126 |
| 6 | 5-Cl–3-(P–Cl–PH)–4′Cl–Salicylanilide | 8.03 | 8.10 | −0.07 | 126 |
| 7 | 5-Cl–3-PH–2′4′5′Cl–Salicylanilide | 8.42 | 8.44 | −0.02 | 132 |
| 8 | 5-Cl–3-PH–3′Cl–4′$NO_2$–Salicylanilide | 8.56 | 8.66 | −0.10 | 136 |
| 9 | 5-Cl–3(PCLPH)–2′Cl, 5′$NO_2$–Salicylanilide | 8.75 | 9.00 | −0.25 | 142 |
| 10 | 5Cl–3(PCLPH)–2′4′5′TRICl–Salicanilide | 8.76 | 8.78 | −0.02 | 138 |
| 11 | 5Cl–3(P–Cl–PHE)–2′Cl–4′CN–Salicylanilide | 8.85 | 8.55 | 0.30 | 134 |
| 12 | 5Cl–3(P–Cl–PHE)–2′Cl–4′$CF_3$–Salicylanilide | 9.08 | 9.45 | −0.37 | 150 |
| 13 | 2,4-DNP | 4.72 | 4.83 | −0.11 | 68 |
| 14 | 4,6-$NO_2$–*o*-Cresol | 5.50 | 5.17 | 0.33 | 74 |
| 15 | 5Cl–3(*t*-Butyl)–2′Cl–4′$NO_2$–salicylanilide | 9.14 | 8.44 | 0.70 | 132 |
| 16[a] | 4,5,6,7-Tetra-Cl, 2–$CF_3$–benzimidizide | 7.06 | 6.13 | 0.93 | 91 |

[a] Outlier.

**Table 45.**

| No | X | log 1/C (Eq. 45) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | $(CH_2)_2CH_3$ | 6.15 | 6.46 | −0.31 | 88 |
| 2 | $CHMe_2$ | 6.74 | 6.46 | 0.28 | 88 |
| 3 | $CH(Me)CH_2CH_3$, (*R*) | 7.22 | 7.21 | 0.01 | 94 |
| 4 | $CH(Me)CH_2CH_3$, (*S*) | 7.15 | 7.21 | −0.06 | 94 |
| 5 | $CMe_3$ | 7.22 | 7.21 | 0.01 | 94 |
| 6 | $C(Me)_2CH_2CH_3$ | 7.70 | 7.96 | −0.26 | 100 |
| 7 | Cy–$C_4H_7$ | 7.30 | 6.96 | 0.34 | 92 |
| 8[a] | Cy–$C_5H_9$ | 6.36 | 7.71 | −1.36 | 98 |
| 9 | Cy–(1-Me–$C_3H_4$) | 6.68 | 6.96 | −0.28 | 92 |
| 10 | Cy–(1-Me–$C_4H_6$) | 8.00 | 7.71 | 0.29 | 98 |
| 11 | Diazoxide | 4.69 | 4.71 | −0.02 | 74 |

[a] Outlier.

**Table 46.**

| No | X | log 1/C (Eq. 46) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | $CH_2C_6H_5$ | 6.10 | 6.09 | 0.01 | 50 |
| 2 | $CH_2CH_2C_6H_5$ | 6.40 | 6.47 | −0.07 | 56 |
| 3 | $(CH_2)_4C_6H_5$ | 7.22 | 7.22 | 0.00 | 68 |
| 4[a] | $(CH_2)_6C_6H_5$ | 7.26 | 7.98 | −0.72 | 80 |
| 5 | $(CH_2)_4$–(3-Pyridyl) | 7.46 | 7.22 | 0.23 | 68 |
| 6 | $(CH_2)_3CO$–(3-Pyridyl) | 7.30 | 7.47 | −0.17 | 72 |

[a] Outlier.

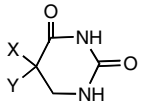
A problem in the development of antipsychotics is that of avoiding extrapyramidal side effects (EPS). The best affinity for 5-$HT_{1A}$ receptors was obtained for 1-(2-methoxyphenyl) piperazine derivatives. Thus, study toward these compounds might yield better drugs.

*Narcosis of mice by barbiturates* ***XXXX***. Data from Hansch et al.[49] (Table 48)

**Table 47.**

| No | X | Y | *n* | log 1/C (Eq. 47) | | | NVE |
|---|---|---|---|---|---|---|---|
| | | | | Obsd | Calcd | Δ | |
| 1 | $C_6H_5$ | H | 1 | 6.40 | 6.25 | 0.15 | 132 |
| 2[a] | $C_6H_5$ | H | 2 | 7.38 | 6.57 | 0.81 | 138 |
| 3 | $C_6H_5$ | H | 3 | 6.77 | 6.88 | −0.12 | 144 |
| 4 | $C_6H_5$ | 7-OMe | 3 | 7.17 | 7.52 | −0.34 | 156 |
| 5 | $C_6H_5$ | H | 4 | 7.16 | 7.20 | −0.04 | 150 |
| 6 | $C_6H_5$ | 7-OMe | 4 | 7.47 | 7.83 | −0.37 | 162 |
| 7[a] | $C_6H_5$ | 6-OMe | 4 | 8.39 | 7.83 | 0.55 | 162 |
| 8 | $C_6H_5$ | 5-OMe | 4 | 8.00 | 7.83 | 0.17 | 162 |
| 9[a] | $C_6H_4$–2-OMe | 7-OMe | 4 | 7.92 | 8.47 | −0.55 | 174 |
| 10 | $C_6H_4$–2-OMe | 6-OMe | 4 | 8.49 | 8.47 | 0.03 | 174 |
| 11 | $C_6H_4$–2-OMe | 5-OMe | 4 | 8.42 | 8.47 | −0.05 | 174 |
| 12 | 2-Pyridinyl | 7-OMe | 4 | 8.15 | 7.83 | 0.32 | 162 |
| 13 | 2-Pyridinyl | 5-OMe | 4 | 8.09 | 7.83 | 0.25 | 162 |

[a] Outliers.




**XXXX**

$$\log 1/C = 0.034(\pm 0.011)\mathrm{NVE} + 0.30(\pm 1.0)$$
$$n = 11, \quad r^2 = 0.847, \quad s = 0.095, \quad q^2 = 0.782$$
$$\text{outliers}: \ \mathrm{X} = \mathrm{CH(Me)_2}, \quad \mathrm{Y} = \mathrm{MeCH{=}C(Et)}\text{–};$$
$$\mathrm{X} = \mathrm{C_2H_5}, \quad \mathrm{Y} = \mathrm{EtCH{=}C(Me)}\text{–};$$
$$\mathrm{X} = \mathrm{CH(Me)_2}, \quad \mathrm{Y} = \mathrm{EtCH{=}C(Me)}\text{–} \qquad (48)$$

We have often found instances where chemicals acting on nerves are correlated by NVE.[4,5]

*Total elimination rate constant from rabbit of barbiturates*. Data from Watari et al.[50] (Table 49)

**Table 48.**

| No | X | Y | log 1/C (Eq. 48) | | | NVE |
|---|---|---|---|---|---|---|
| | | | Obsd | Calcd | Δ | |
| 1 | Et | EtCH=C(Pr)– | 3.75 | 3.72 | 0.03 | 100 |
| 2 | Er | BuCH=C(Me)– | 3.75 | 3.72 | 0.03 | 100 |
| 3[a] | I–Pr | MeCH=C(Et)– | 3.72 | 3.52 | 0.20 | 94 |
| 4[a] | Et | EtCH=C(Me)– | 3.65 | 3.31 | 0.34 | 88 |
| 5 | Et | PrCH=C(Me)– | 3.64 | 3.52 | 0.12 | 94 |
| 6 | Pr | EtCH=C(Me)– | 3.56 | 3.52 | 0.04 | 94 |
| 7 | Pr | MeCH=C(Et)– | 3.42 | 3.52 | −0.10 | 94 |
| 8 | Et | MeCH=C(Et)– | 3.40 | 3.31 | 0.09 | 88 |
| 9 | Me | BuCH=C(Me)– | 3.38 | 3.52 | −0.14 | 94 |
| 10 | Me | PrCH=C(Me)– | 3.27 | 3.31 | −0.04 | 88 |
| 11 | Me | EtCH=C(Me)– | 3.21 | 3.11 | 0.10 | 82 |
| 12 | Me | I–PrCH=C(Me)– | 3.20 | 3.31 | −0.11 | 88 |
| 13 | Me | MeCH=C(Et)– | 3.06 | 3.11 | −0.05 | 82 |
| 14[a] | I–Pr | EtCH=C(Me)– | 3.98 | 3.52 | 0.46 | 94 |

[a] Outliers.

**Table 49.**

| No | Compound | log K (Eq. 49) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | Hexobarbital | 0.17 | 0.00 | 0.17 | 92 |
| 2 | Pentobarbital | −0.01 | −0.14 | 0.13 | 90 |
| 3 | Cyclobarbital | −0.05 | 0.00 | −0.06 | 92 |
| 4 | Amobarbital | −0.35 | −0.14 | −0.21 | 90 |
| 5 | Allobarbaital | −0.92 | −0.84 | −0.09 | 80 |
| 6[a] | Phenobarbital | −1.60 | −0.28 | −1.33 | 88 |
| 7 | Barbital | −1.34 | −1.40 | 0.06 | 72 |

[a] Outlier.

$$\log K = 0.070(\pm 0.025)\mathrm{NVE} - 6.45(\pm 2.13)$$
$$n = 6, \quad r^2 = 0.940, \quad s = 0.163, \quad q^2 = 0.866 \qquad (49)$$
outlier : Phenobarbital

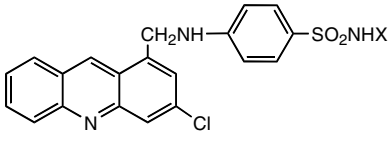
*Concentration that produced no effect on sheepshead minnow of miscellaneous compounds*

Data from Sabljic.[51] (Table 50)

$$\log 1/C = 0.078(\pm 0.013)\mathrm{NVE} - 1.09(\pm 0.56)$$
$$n = 18, \quad r^2 = 0.914, \quad s = 0.307, \quad q^2 = 0.895 \qquad (50)$$
outlier : 1, 2, 4-Trichlorobenzene

No doubt these chemical were operating on the nervous system of fish.

*Minimum inhibitory concentration of* ***XXXXI*** *on candida albicans*. Data from Safwat et al.[52] (Table 51)




**XXXXI**

**Table 50.**

| No | Compound | log 1/C (Eq. 50) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1 | Chlorobenzene | 4.26 | 3.91 | 0.35 | 36 |
| 2 | 1,3-Dichlorobenzene | 4.54 | 4.38 | 0.16 | 42 |
| 3 | 1,4-Dichlorobenzene | 4.42 | 4.38 | 0.04 | 42 |
| 4[a] | 1,2,4-Trichlorobenzene | 4.08 | 4.85 | −0.77 | 48 |
| 5 | 1,2,3,5-Tetrachlorobenzene | 5.33 | 5.33 | 0.00 | 54 |
| 6 | 1,2,4,5-Tetrachlorobenzene | 5.86 | 5.33 | 0.53 | 54 |
| 7 | Pentachlorobenzene | 5.92 | 5.80 | 0.12 | 60 |
| 8 | 1,2-Dichloroethane | 2.88 | 3.13 | −0.25 | 26 |
| 9 | 1,1,1-Trichloroethane | 3.49 | 3.60 | −0.11 | 32 |
| 10 | Pentachloroethane | 3.83 | 4.54 | −0.71 | 44 |
| 11 | Hexachloroethane | 5.37 | 5.01 | 0.36 | 50 |
| 12 | 1,3-Dichloropropane | 3.43 | 3.60 | −0.17 | 32 |
| 13 | Dichloromethane | 2.82 | 2.66 | 0.16 | 20 |
| 14 | 1-Chloronaphthalene | 5.13 | 5.33 | −0.20 | 54 |
| 15 | 4-Chlorophenol | 4.60 | 4.38 | 0.22 | 42 |
| 16 | 2,4,5-Trichlorophenol | 5.30 | 5.33 | −0.03 | 54 |
| 17 | 2,3,5,6-Tetrachlorophenol | 5.37 | 5.80 | −0.43 | 60 |
| 18 | 1,1-Eichloroethylene | 3.08 | 2.97 | 0.11 | 24 |
| 19 | Tetrachloroethylene | 3.76 | 3.91 | −0.15 | 36 |

[a] Outlier.

**Table 51.**

| No | X | log 1/C (Eq. 51) | | | NVE |
|---|---|---|---|---|---|
| | | Obsd | Calcd | Δ | |
| 1[a] | C(=NH)$NH_2$ | 8.35 | 8.65 | −0.30 | 152 |
| 2 | Acetyl | 8.65 | 8.65 | 0.00 | 152 |
| 3[a] | 2-Pyridyl | 7.18 | 8.68 | −1.50 | 164 |
| 4 | 2-Pyrimidinyl | 8.69 | 8.68 | 0.00 | 164 |
| 5 | 4-Me–2-Pyrimidinyl | 8.70 | 8.70 | 0.00 | 170 |
| 6 | 2-Thiazolyl | 8.69 | 8.67 | 0.02 | 160 |
| 7 | H | 8.61 | 8.61 | −0.01 | 136 |
| 8 | 1-PH–5-Pyrazolyl | 8.74 | 8.74 | 0.00 | 188 |
| 9 | 3,4-$(Me)_2$–5-Isoxazolyl | 8.70 | 8.70 | 0.00 | 172 |
| 10 | 4,6-$(Me)_2$–2-Pyrimidinyl | 8.71 | 8.71 | 0.00 | 176 |
| 11 | $CONH_2$ | 8.65 | 8.65 | 0.00 | 152 |

[a] Outliers.

$$\log 1/C = 0.003(\pm 0.00)\mathrm{NVE} + 8.27(\pm 0.06)$$
$$n = 9, \quad r^2 = 0.972, \quad s = 0.007, \quad q^2 = 0.954 \qquad (51)$$
outliers : X = C(=NH)$NH_2$; 2-pyridyl

A good correlation for a very miscellaneous set of derivatives. The coefficient with NVE is extremely small nevertheless $q^2$ is excellent.

## 4. Summary

Polarizability has long been a subject of great interest to chemists. We have clearly found two important ways to deal with it; the Lorentz–Lorenz equation and using the sum of the valence electrons (NVE). The results with CMR cannot be replaced with NVE or vise versa. The volume component of CMR must have something to do with changing the geometry of receptors to provide better access to the ligand. In examples where NVE is ideal, it would seem that the receptor is more flexible. In the present study we have considered only cases where a single parameter suffices to yield a good correlation. We have many examples where one or more terms are needed in addition to NVE. We plan to review these at a later date. At the moment, we have 706 QSAR that contain an NVE term. In some instances NVE has a negative coefficient indicating electron repulsion between ligand and receptor. We have not included any of these in this report.

## References and notes


1. Pauling, L.; Pressman, D. *The Nature of the Chemical Bond*; Cornell University Press: Berlin, 1960; p 607.
2. Kutter, E.; Hansch, C. *Arch. Biochem. Biophys.* **1969**, *135*, 626.
3. Clog*P* and C-QSAR program, BioByte Corp. 201 W. Fourth St., Suit 204, Claremont, CA 91711. www.biobyte.com.
4. (a) Hansch, C.; Steinmetz, W. E.; Leo, A. J.; Mekapati, S. B.; Kurup, A.; Hoekman, D. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 120; (b) Hansch, C.; Kurup, A. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 1647.
5. King, LA. *Meeting of International Association of Forensic Toxicologists, August 23–30, 1985*; Brandeberger: Rigi, Switzerland, 1987.
6. Vaillancourt, V. A.; Cudahy, M. M.; Staley, S. A.; Brideau, R. J.; Conrad, S. J.; Knechtel, M. L.; Cudahy, M. M.; Staley, S. A.; Brideau, R. J.; Conrad, S. J.; Knechtel, M. L.; Oien, N. L.; Wieber, J. L.; Yagi, Y.; Wathen, M. W. *Bioorg. Med. Chem.* **2000**, *10*, 2079.
7. Schlitzer, M.; Bohm, M.; Sattler, I. *Bioorg. Med. Chem.* **2000**, *8*, 2399.
8. Hanessian, S.; Moitessier, N.; Gauchet, C.; Viau, M. *J. Med. Chem.* **2001**, *44*, 3066.
9. Szardenings, A. K.; Harris, D.; Lam, S. L.; Shi, L.; Tien, D.; Wang, Y.; Patel, D. V.; Campbell, D. A. *J. Med. Chem.* **1998**, *41*, 2194.
10. Foley, L. H.; Palermo, R.; Dunten, P.; Wang, P. *Bioorg. Med. Chem.* **2001**, *11*, 969.
11. Kaczmarek, L.; Pecyzynska-Czoch, W.; Osiadacz, J.; Mordarski, M.; Sokalski, W. H.; Boratynski, J.; Marcinkowska, E.; Glazman-Kusnierczyk, H.; Radzikowski, C. *Bioorg. Med. Chem.* **1999**, *7*, 2457.
12. Keller, T. H.; Bray-French, K.; Demnitz, F. W. J.; Muller, T.; Pombo-Villar, E.; Walker, C. *Chem. Pharm. Bull.* **2001**, *49*, 1009.
13. Hanessian, S.; MacKay, D. B.; Moitessier, N. *J. Med. Chem.* **2001**, *44*, 3074.
14. Suzuki, K.; Shono, F.; Kai, W.; Uno, T.; Uydea, M. *J. Enzyme Inhib.* **2000**, *15*, 357.
15. Venhorst, J.; Onderwater, R. C. A.; Meerman, J. H. M.; Commandeur, J. N. M.; Vermeulen, N. P. E. *Drug Metab. Dispos.* **2000**, *28*, 1524.
16. Lee, T.-J.; Holtz, W. L.; Smith, R. L.; Alberts, A. W.; Gilfillan, J. L. *J. Med. Chem.* **1991**, *34*, 2474.
17. Shin, S. S.; Byun, Y.; Lim, K. M.; Choi, J. K.; Lee, K.-W.; Moh, J. H.; Kim, J. K.; Jeong, Y. S.; Kim, J. Y.; Choi, Y. H.; Koh, H.-J.; Park, Y.-H.; Oh, Y. I.; Noh, M.-S.; Chung, S. *J. Med. Chem.* **2004**, *47*, 792.
18. Darnnhardt, G.; Kiefer, W.; Kramer, G.; Machrlein, S.; Nowe, U.; Fiebich, B. *Eur. J. Med. Chem.* **2000**, *35*, 499.
19. Hirokawa, Y.; Fujiwara, I.; Suzuki, K.; Harada, H.; Yoshikawa, T.; Yoshida, N.; Kato, S. *J. Med. Chem.* **2003**, *46*, 702.
20. Gharagozloo, P.; Lazateno, S.; Miyauchi, M.; Popham, A.; Birdsall, N. H. M. *J. Med. Chem.* **2002**, *45*, 1259.
21. Santini, C.; Berger, G. D.; Han, W.; Mosley, R.; MacNaul, K.; Berger, J.; Doebber, T.; Wu, M.; Moller, D. E.; Tolman, R. L.; Sahoo, S. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1277.
22. Hu, J.-Y.; Aizawa, T. *Water Res.* **2003**, *37*, 1213.
23. Mattson, R. J.; Catt, J. D.; Sloan, C. P.; Gao, Q.; Carter, R. B.; Gentile, A.; Mahle, C. D.; Matos, F. F.; McGovern, R.; Vandermaelen, C. P.; Yocca, F. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 285.
24. Doherty, A. M.; Patt, W. C.; Edmunds, J. J.; Berryman, K. A.; Reisdrop, B. R.; Plummer, M. S.; Shahripour, A.; Lee, C.; Cheng, X.-M.; Walker, D. M.; Haleen, S. J.; Keiser, J. A.; Flynn, M. A.; Welch, K. M.; Hallak, H.; Taylor, D. G.; Reynolds, E. E. *J. Med. Chem.* **1995**, *38*, 1259.
25. Somanadhan, B.; Loke, W.-K.; Sim, M.-K.; Go, M. L. *Bioorg. Med. Chem.* **2002**, *10*, 207.
26. Meier, G.; Ligneau, X.; Pertz, H. H.; Ganellin, C. R.; Schwartz, J.-C.; Shunack, W.; Stark, H. *Bioorg. Med. Chem.* **2002**, *10*, 2535.
27. Street, L. J.; Baker, R.; Castro, J. L.; Chambers, M. S.; Guiblin, A. R.; Hobbs, S. C.; Matassa, V. G.; Reeve, A. J.; Beer, M. S.; Middlemiss, D. M.; Noble, A. J.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J. *J. Med. Chem.* **1993**, *36*, 1529.
28. Kimura, M.; Masud, T.; Yamada, K.; Mitani, M.; Kubota, N.; Kawakatsu, N.; Kishii, K.; Inazu, M.; Kiuchi, Y.; Oguchi, K.; Namiki, T. *Bioorg. Med. Chem.* **2003**, *11*, 1621.
29. Hahin, R.; Kondratiev, A. *J. Membr. Biol.* **2001**, *180*, 137.
30. Kamlet, M. J.; Doherty, R. M.; Abraham, M. H.; Taft, R. W. *Quant. Struct.–Act. Relat.* **1988**, *7*, 71.
31. Dinno, M. A.; Holloman, T. L.; Schwartz, M. *Proc. Soc. Exptl. Biol. Med.* **1972**, *141*, 397.
32. Goldbaum, L. R.; Smith, P. K. *J. Pharmacol. Exp. Ther.* **1954**, *111*, 197.
33. Faissat, L.; Martin, K.; Chavis, C.; Montero, J.-L.; Lucas, M. *Bioorg. Med. Chem.* **2003**, *11*, 325.
34. Chen, J.; Deady, L. W.; Kaye, A. J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *Bioorg. Med. Chem.* **2002**, *10*, 2381.
35. Miko, M.; Uher, M.; Flock, L. *Biologia (Bratislava)* **1980**, *35*, 861.
36. Medina, J. C.; Shan, B.; Beckmann, H.; Farrell, K. P.; Clarks, D. L.; Learned, R. M.; Roche, P.; Li, A.; Baichwal, V.; Case, C.; Baeuerle, P. K.; Rosen, T.; Jaen, J. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2653.

37. Diana, P.; Barraja, P.; Lauria, A.; Montalbano, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G. *Bioorg. Med. Chem.* **2003**, *11*, 2371.
38. Deady, L. W.; Desneres, J.; Kaye, A. J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *Bioorg. Med. Chem.* **2000**, *8*, 977.
39. Tobe, M.; Isobe, I.; Tomizawa, H.; Nagasaki, T.; Obara, F.; Hayashi, H. *Bioorg. Med. Chem.* **2003**, *11*, 609.
40. Deasi, R. G.; Dunlap, R. P.; Farrell, R. P.; Ferguson, E.; Franke, C. A.; Gordon, R.; Hlasta, D. J.; Talomite, T. G. *Bioorg. Med. Chem.* **1995**, *5*, 105.
41. Matsuda, H.; Morikawa, T.; Ando, S.; Toguchida, I.; Yoshikawa, M. *Bioorg. Med. Chem.* **2003**, *11*, 1995.
42. Muller, G. W.; Corral, L.; Shire, M. G.; Wang, H.; Moreira, A.; Kaplan, G.; Stirling, D. *J. Med. Chem.* **1996**, *39*, 3238.
43. Mugnaini, C.; Botta, M.; Coletta, M.; Corell, L. F.; Focher, F.; Marrini, S.; Renzulli, M. L.; Verri, A. *Bioorg. Med. Chem.* **2003**, *11*, 357.
44. Pernak, J.; Kalewska, J.; Ksycinska, H.; Cybulski, J. *Eur. J. Med. Chem.* **2001**, *36*, 899.
45. Williamson, R. L.; Metcalf, R. L. *Science* **1967**, *158*, 1694.
46. Nielsen, F. E.; Bodvarsdottir, T. B.; Worsaae, A.; MacKay, P.; Stidsen, C. E.; Boonen, H. C. M.; Pridal, L.; Arkhammer, P. O. G.; Wahl, P.; Ynddal, L.; Junager, F.; Dragsted, N.; Tagmose, T. M.; Mogensen, J. P.; Koch, A.; Treppendahl, S. P.; Hansen, J. B. *J. Med. Chem.* **2002**, *45*, 4171.
47. Guo, Z.; Smith, T. J.; Wang, E.; Eklind, K. I.; Chung, F.-L.; Yang, C. S. *Carcinogenesis* **1993**, *14*, 1167.
48. Perrone, R.; Berardi, F.; Colabufo, N. A.; Tortorella, V.; Fornaretto, M. G.; Caccia, C.; McArthur, R. A. *Eur. J. Med. Chem.* **1997**, *32*, 739.
49. Hansch, C.; Steward, A. R.; Anderson, S. M.; Bentley, D. *J. Med. Chem.* **1968**, *11*, 1.
50. Watari, N.; Sugiyama, Y.; Kaneniwa, N.; Hiura, M. *J. Pharmacokinet. Biopharm.* **1988**, *16*, 279.
51. Sabljic, A. *Bull. Environ. Contam. Toxicol.* **1983**, *30*, 80.
52. Safwat, H. M.; Ragalo, F. H.; Ed, N. M.; El Aba, A. M. *Egypt. J. Pharm. Sci.* **1988**, *29*, 151.