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The role of hydrophobic properties of chemicals in promoting allosteric reactions

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Abstract—An allosteric reaction has been found in a variety of instances where an inverted parabolic relationship between biological activity and hydrophobicity is apparent, that is the activity first decreases as hydrophobicity increases and after a certain point, activity begins to increase. This could be attributed to the ligands causing a change in the receptor structure. In this report, the role of hydrophobic properties of chemicals in promoting allosteric reactions have been discussed in term of hydrophobicity ($\log P$) by the formulation of a total number of 50 QSAR equations. The QSAR model of this type may be represented by Eq. I.

$$\log 1/C = -a\log P + b\log P^2 \pm \text{constant} \quad \text{(I)}$$

1. Introduction

We have been interested in understanding allosteric reactions in terms of QSAR.[1–6] Since the early work of Koshland[7] and Monod et al.,[8] an intense interest has been developed around this subject. A Google™ search on 'allosteric' makes 251,000 hits. The same search on 'QSAR' makes 176,000 hits. The early work on this subject has already been reviewed.[9,10]

In this report, our results will be limited to QSAR based on $\log P$. The allosteric reaction is uncovered when we have a result of the following type: $\log 1/C = -a\log P + b\log P^2$. At first, a defines the result. However, as $\log P$ increases in size, $b\log P^2$ takes over with the resulting curve being an inverted parabola. In the case of a normal parabolic effect, we have 936 QSAR. The allosteric effect is the result of a change in the structure of the receptor. Until we introduced the use of QSAR to uncover such reaction, establishing an allosteric reaction was a tedious process.

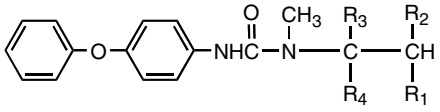
A single new QSAR standing alone, cannot be taken very seriously. One needs lateral validation. We have now reached this stage with Clog P and CMR in the study of allosteric reactions.

2. Methodology

Over the past 40 years we have made a strong effort to understand chemical–biological reactions by taking advantage of every data set that we could find in the literature. Our methodology, as well as all parameters, has been discussed in detail.[11,12] During the past 40 years, we have developed an excellent regression program (C-QSAR) that will autoload all parameters. We can normally develop a new QSAR from good literature data in an hour or so.

3. Results and discussion

Inhibition of ^{125}I-PYY binding to human neuropeptide Y5 (NPY5) by I. Data from Fotsch et al.[13] (Table 1)



I

Keywords: Allosteric reaction; Hydrophobicity; Quantitative structure–activity relationship (QSAR).
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Table 1. QSAR 1: Inhibition of [^{125}I]-PYY binding to human neuropeptide Y5 (NPYS) by I

No.	R_1	R_2	R_3	R_4	log 1/C			Clog P	E_s-R_3
					Obsd.	Pred.	Δ		
1	C_6H_5	OH(*S*)	Me(*R*)	H[a]	8.19	6.90	1.28	4.28	−1.24
2	C_6H_5	OH(*R*)	Me(*R*)	H	7.35	6.90	0.44	4.28	−1.24
3	C_6H_5	OH(*R*)	Me(*S*)	H	6.90	6.90	−0.01	4.28	−1.24
4	C_6H_5	OH(*S*)	Me(*S*)	H	6.29	6.90	−0.61	4.28	−1.24
5	C_6H_5	H	Me(*R*)	H[a]	8.51	5.27	3.24	5.24	−1.24
6	C_6H_5	H	Me(*S*)	H	5.30	5.27	0.04	5.24	−1.24
7	Me	H	Me(*R*)	H	7.62	7.17	0.45	4.20	−1.24
8	C_6H_5	H	H	H	7.46	7.28	0.18	5.01	0.00
9	C_6H_5	=O	Me(*R*)	H	5.02	5.85	−0.83	4.66	−1.24
10	C_6H_5	H	C_6H_5	H	8.10	8.34	−0.24	6.48	−1.01
11	C_6H_5	H	$CHMe_2$	H	6.42	6.06	0.36	6.17	−1.71
12	C_6H_5	H	Me	Me	5.88	5.55	0.34	5.64	−1.24
13	4-Cl–C_6H_4	H	Me	H[a]	9.05	6.16	2.88	5.95	−1.24
14	4-Pyridyl	H	Me	H	9.30	9.22	0.08	3.74	−1.24
15	Cy-C_6H_{11}	H	Me	H	7.15	7.34	−0.19	6.32	−1.24

[a] Data point not included in the equation.

$$\log 1/C = -18.52(\pm 5.64)\mathrm{C}\log P + 1.77(\pm 0.54)\mathrm{C}\log P^2 + 1.55(\pm 0.88)E_s - R_3 + 0.97(\pm 0.75)$$

$$n = 12,\ r^2 = 0.885,\ s = 0.479,\ q^2 = 0.690$$

inversion point: 5.24 (5.14–5.36)

outliers: C_6H_5, H, Me, H; C_6H_5, Me, H, H; 4-Cl-C_6H_4, H, Me, H (1)

Neuropeptide receptors are implicated in vasoconstriction, learning and memory. The above compounds were tested for such processes.

Inhibition of COX-2 in human whole blood by miscellaneous nonsteroidal anti-inflammatory drugs. Data from Dannhardt and Kiefer[14] (Table 2).

$$\log 1/C = -4.31(\pm 2.03)\mathrm{C}\log P + 0.78(\pm 0.33)\mathrm{C}\log P^2 + 10.45$$

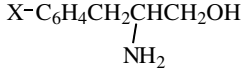
$$n = 11,\ r^2 = 0.871,\ s = 0.402,\ q^2 = 0.722 \quad (2)$$

inversion point: 2.77 (2.46–2.94)

outliers: Ketoprofen, sulindacsulfide, NS-398

COX-2 appears to play a role in angiogenesis and colon cancer. The authors note that the application of COX-2 inhibitors during the natural remission of inflammation could delay healing. Hence, inhibitors might be of practical value.

Inhibition of phenylamine t-RNA synthetase by



Data from Santi and Danenberg.[15] (Table 3)

Table 2. QSAR 2: Inhibition of COX-2 in human whole blood by miscellaneous nonsteroidal anti-inflammatory drugs

No.	Compound	log 1/C			Clog P
		Obsd.	Pred.	Δ	
1	Diclofenac	7.30	7.45	−0.14	4.73
2	Indomethacin	6.34	6.02	0.32	4.18
3	Ketorolac	6.07	5.50	0.56	1.62
4	Ketoprofen[a]	5.97	4.48	1.49	2.76
5	Tolmetin	5.15	4.72	0.43	2.21
6	Flurbiprofen	5.19	5.23	−0.03	3.75
7	Piroxicam	5.05	5.08	−0.04	1.89
8	Sulindacsulfide[a]	4.98	9.47	−4.49	5.31
9	Tenoxicam	4.85	5.53	−0.68	1.61
10	Naproxen	4.13	4.48	−0.34	2.82
11	Dup-697	7.22	7.08	0.14	4.60
12	NS-398[a]	6.33	4.61	1.71	3.20
13	SC-57125	5.65	5.91	−0.26	4.13
14	L-745337	5.01	4.96	0.05	3.56

[a] Data point not included in the equation.

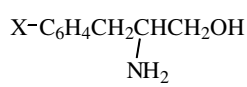
$$\log 1/K_i = -30.52(\pm 9.67)\mathrm{C}\log P + 14.89(\pm 4.95)\mathrm{C}\log P^2 + 14.8(\pm 4.53)$$

$$n = 8,\ r^2 = 0.945,\ s = 0.177,\ q^2 = 0.849 \quad (3)$$

inversion point: 1.03 (1.00–1.06)

outlier: X = 4-Cl

Table 3. QSAR 3: Inhibition of phenylamine t-RNA synthetase by



No.	X	log 1/K_i			Clog P
		Obsd.	Pred.	Δ	
1	2-Cl	−0.11	−0.25	0.14	1.22
2	3-Cl	0.15	0.24	−0.09	1.29
3	4-Cl[a]	−0.45	0.24	−0.69	1.29
4	2-Me	−0.91	−0.84	−0.07	1.03
5	3-Me	−0.60	−0.80	0.20	1.08
6	4-Me	−0.99	−0.80	−0.19	1.08
7	2-F	0.39	0.50	−0.11	0.72
8	3-F	0.43	0.50	−0.07	0.72
9	4-F	0.68	0.50	0.18	0.72

[a] Data point not included in the equation.

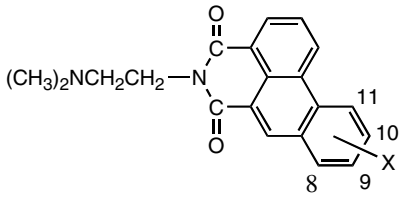
The authors were using these analogs to characterize the amino acid binding site of Phe-t-RNA. They noted a limiting hydrophobic binding site, but of course, had no idea of allosteric interactions.

Inhibition of HELA cells by X–N=C=S. Data from Horakova et al.[16] (Table 4)

$$\log 1/C = -2.09(\pm 2.04)\mathrm{C}\log P + 0.48(\pm 0.40)\mathrm{C}\log P^2 + 6.48(\pm 2.29)$$
$$n = 6,\ r^2 = 0.908,\ s = 0.206,\ q^2 = 0.697 \qquad (4)$$
inversion point: 2.20 (0.334–2.49)
outliers: C_6H_5, C_6H_4-4-Br

There are a number of natural isothiocyanates with strong antimicrobial activity. The authors were trying to find more potent inhibitors.

Inhibition of drug resistant non-small cell carcinoma (A459) by II. Data from Sami et al.[17] (Table 5)



II

$$\log 1/C = -11.31(\pm 5.60)\mathrm{C}\log P + 1.50(\pm 0.72)\mathrm{C}\log P^2 + 27.54(\pm 10.7)$$
$$n = 7,\ r^2 = 0.901,\ s = 0.263,\ q^2 = 0.758 \qquad (5)$$
inversion point : 3.77 (3.56–3.93)
outliers : 8-NO_2, 8-NH_2, 11-OH

The intention of this research was to find more potent anticancer compounds.

Inhibition of bacterial aryl amine N-acetyltransferase by III. Data from Brooke et al.[18] (Table 6)

Table 4. QSAR 4: Inhibition of HELA cells by X–N=C=S

No.	X	log 1/C			Clog P
		Obsd.	Pred.	Δ	
1	CH_3	4.69	4.69	0.00	1.17
2	$CH_2CH{=}CH_2$	4.22	4.21	0.01	1.94
3	$CH_2C_6H_5$	4.52	4.65	−0.13	3.20
4	$CH_2C_6H_4CL$(P)	5.38	5.58	−0.19	3.92
5	$CH_2CH_2C_6H_5$	4.77	4.71	0.06	3.26
6	$CH_2CH_2C_6H_4CH_3$(P)	5.60	5.33	0.26	3.76
7	C_6H_5[a]	3.14	4.76	−1.61	3.31
8	C_6H_4Br(P)[a]	3.41	6.29	−2.88	4.31

[a] Data point not included in the equation.

Table 5. QSAR 5: Inhibition of drug resistant non-small cell carcinoma by II

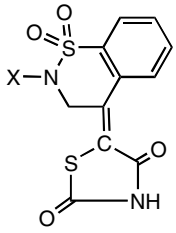
No.	X	log 1/C			Clog P
		Obsd.	Pred.	Δ	
1	H	6.66	6.27	0.39	3.97
2	8-NO_2[a]	6.81	6.21	0.61	3.76
3	8-NH_2[a]	6.55	7.41	−0.86	2.87
4	11-NO_2	6.02	6.21	−0.18	3.76
5	11-NH_2	7.43	7.41	0.02	2.87
6	8-Cl	7.66	7.52	0.14	4.70
7	8-OH	6.38	6.37	0.01	3.44
8	8-OMe	6.06	6.26	−0.20	3.97
9	11-Cl	7.35	7.52	−0.17	4.70
10	11-OH[a]	6.80	6.37	0.43	3.44

[a] Data point not included in the equation.

Table 6. QSAR 6: Inhibition of bacterial aryl amine N-acetyltransferase by III

No.	X	log 1/C			Clog P
		Obsd.	Pred.	Δ	
1	CH_2-2-naphthyl	4.11	4.14	−0.03	3.51
2	$CH_2CH(CH_2CH_3)_2$[a]	4.04	4.27	−0.23	3.08
3	$(CH_2)_7CH_3$	4.21	4.16	0.06	4.27
4	$(CH_2)_9CH_3$	4.66	4.71	−0.05	5.32
5	CH_2CH_2-cyclohexyl	4.09	4.11	−0.03	3.74
6	CH_2–C_6H_4–4-Br	4.19	4.22	−0.04	3.19
7	CH_2–(2-Cl-thiophen-5-Yl)	4.48	4.44	0.04	2.73
8	$CH_2C_6H_4CH{=}CHC_6H_5$	4.54	4.49	0.05	5.02
9	$CH_2C_6H_4$–4-C_6H_5[a]	4.70	4.15	0.55	4.22

[a] Data point not included in the equation.

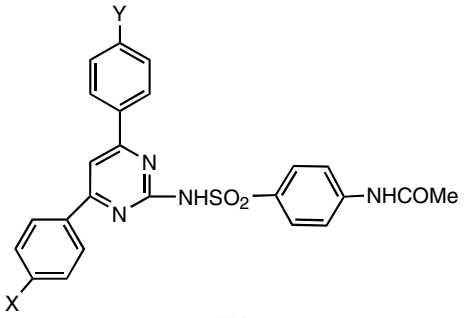


III

$$\log 1/C = -2.08(\pm 0.75)\mathrm{C}\log P + 0.27(\pm 0.09)\mathrm{C}\log P^2 + 8.10(\pm 1.47)$$
$$n = 7,\ r^2 = 0.961,\ s = 0.056,\ q^2 = 0.749$$
inversion point: 3.84 (3.65–3.97)
outliers: $CH_2CH(C_2H_5)_2$, $CH_2C_6H_4$-4-C_6H_5
(6)

Arylamine N-acetyltransferases (NATs) is a gene family of cytosolic 32–34 kDa enzymes that acetylate arylamines, *N*-aryl hydroxylamines and arylhydrazines via acetyl-CoA. These transferases are present in eukaryotes and prokaryotes. In humans, NAT-2 inactivates the anti-tubercular drug isonazid.

Inhibition of E. coli by IV. Data from Wasfy and Aly[19] (Table 7)



IV

$$\log 1/C = -6.36(\pm 1.73)\mathrm{C}\log P + 0.64(\pm 0.17)\mathrm{C}\log P^2 + 19.2(\pm 4.25)$$
$$n = 8,\ r^2 = 0.948,\ s = 0.042,\ q^2 = 0.842 \quad (7)$$
inversion point: 5.0 (4.93–5.07)
outliers: X = OMe, Y = H; X = Cl, Y = H; X = NO_2, Y = NO_2

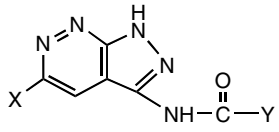
Table 7. QSAR 7: Inhibition of *E. coli* by IV

	X	Y	log 1/*C*			Clog *P*
			Obsd.	Pred.	Δ	
1	OMe	H[a]	3.59	3.39	0.19	4.56
2	Cl	H[a]	2.98	3.30	−0.32	5.23
3	NO_2	H	3.59	3.60	−0.02	4.27
4	OMe	Me	3.29	3.27	0.02	5.06
5	Cl	Me	3.60	3.61	−0.01	5.73
6	NO_2	Me	3.30	3.30	0.00	4.77
7	Me	OMe	3.29	3.27	0.02	5.06
8	OMe	OMe	3.30	3.37	−0.07	4.60
9	Cl	OMe	3.31	3.32	−0.01	5.28
10	NO_2	OMe	3.62	3.57	0.05	4.31
11	NO_2	NO_2[a]	3.34	3.88	−0.54	4.02

[a] Data point not included in the equation.

The authors were trying to develop more potent antibacterial agents.

Inhibition of human glycogen synthase kinase-3 by V. Data from Witherington et al.[20] (Table 8)

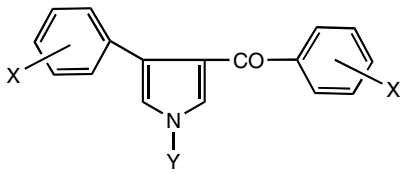


V

$$\log 1/C = -6.66(\pm 1.7)\mathrm{C}\log P + 1.35(\pm 0.33)\mathrm{C}\log P^2 + 16.2(\pm 2.1)$$
$$n = 10,\ r^2 = 0.932,\ s = 0.268,\ q^2 = 0.850$$
inversion point: 2.46 (2.35–2.57)
outliers: X = C_6H_5, Y = $(CH_2)_3CH_3$, X = 2,3-di-F-C_6H_3, Y = CH_2-piperidine-N-C_2H_5 (8)

The authors found that the introduction of a nitrogen into the 6-position of a set of pyrazolo[3,4-*b*]pyridine led to a great improvement in the inhibition of glycogen synthase kinase that is implicated in the control of several regulatory proteins.

Inhibition of COX-1 enzyme from bovine PMNLs by VI. Data from Dannhardt et al.[21] (Table 9)



VI

Table 8. QSAR 8: Inhibition of human glycogen synthase kinase-3 by V

No.	X	Y	log 1/*C*			Clog *P*
			Obsd.	Pred.	Δ	
1	C_6H_5	$CH_2CH_2CH_2CH_3$[a]	8.40	9.83	−1.43	3.62
2	C_6H_5	$(CH_2)_3N(CH_3)_2$	7.66	8.06	−0.40	2.67
3	C_6H_5	$(CH_2)_3$ Pyrrolidine	7.96	8.13	−0.17	2.77
4	C_6H_5	$(CH_2)_3$ Piperazin-*N*-CH_2CH_3	8.15	8.09	0.07	2.22
5	C_6H_5	$(CH_2)_3$ Morpholinyl	8.30	8.03	0.27	2.60
6	C_6H_5	4-Piperidin-*N*-CH_3	8.05	8.19	−0.14	2.10
7	C_6H_5	$(CH_2)_4$ Piperazinyl-*N*-CH_2CH_3	8.30	8.12	0.18	2.17
8	2,3-Di-F–C_6H_3	$(CH_2)_3N(CH_3)_2$	8.30	8.25	0.05	2.89
9	3-Pyridyl	Cyclopropyl	10.10	10.10	0.00	1.22
10	2,3-Di-F–C_6H_3	Cyclopentyl	9.96	10.17	−0.21	3.73
11	2,3-Di-F–C_6H_3	Piperidine-*N*-CH_2CH_3[a]	9.02	8.20	0.82	2.84
12	2,3-Di-F–C_6H_3	CH_2-Piperidine-*N*-CH_2CH_3	9.72	9.36	0.36	3.46

[a] Data point not included in the equation.

Table 9. QSAR 9: Inhibition of COX-1 enzyme from bovine PMNLs by VI

No.	X	Y	log 1/C			Clog P	$E_s - Y$
			Obsd.	Pred.	Δ		
1	H	H	5.48	5.48	0.00	4.08	0.00
2	2-Cl	H	5.32	5.32	0.00	5.09	0.00
3	4-OCH_3	H	5.48	5.49	0.00	4.06	0.00
4	4-F	H[a]	5.82	5.37	0.45	4.46	0.00
5	2-F	H[a]	5.17	5.50	−0.33	4.01	0.00
6	3-OCH_3	H[a]	5.00	5.49	−0.49	4.06	0.00
7	2-OCH_3	H	5.74	5.74	0.00	3.50	0.00
8	4-CF_3	H	5.44	5.51	−0.07	6.01	0.00
9	2-CF_3	H	5.59	5.51	0.07	6.01	0.00
10	H	CH_3	5.07	5.08	−0.01	4.32	−1.24
11	H	C_2H_5	5.01	4.98	0.02	4.85	−1.31
12	2-Cl	CH_3	5.00	5.01	−0.01	5.27	−1.24

[a] Data point not included in the equation.

$$\log 1/C = -1.88(\pm 0.80)\mathrm{C}\log P + 0.19(\pm 0.08)\mathrm{C}\log P^2 + 0.26(\pm 0.09)E_s - Y + 10.0(\pm 1.87)$$

$n = 9,\ r^2 = 0.981,\ s = 0.047,\ q^2 = 0.933$

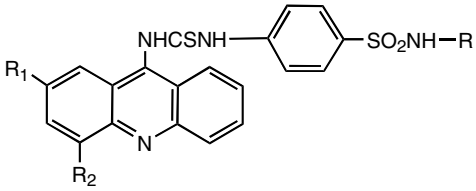
inversion point: 5.0 (4.87–5.19)

outliers: X = 4-F, Y = H; X = 2-F, Y = H; X = 3-OMe, Y = H

(9)

This represents a new class of COX-1 and COX-2 inhibitors. The COX-2 enzyme did not display an allosteric reaction.

Inhibition of prostate cancer cells (DU145) by VII. Data from Sondhi et al.[22] (Table 10)



VII

$$\log 1/C = -45.9(\pm 15.6)\mathrm{C}\log P + 5.80(\pm 2.0)\mathrm{C}\log P^2 + 94.8(\pm 30.2)$$

$n = 7,\ r^2 = 0.947,\ s = 0.181,\ q^2 = 0.846$

inversion point: 3.95 (3.91–4.01)

outlier: R_1 = Me, R_2 = H, R = 2-pyrimidinyl

(10)

The object of this study was to find new anti-inflammatory and anti-cancer drugs.

Inhibition of breast cancer cells (MCF7) by the same class of chemical used to derive QSAR 10. Data from Sondhi et al.[22] (Table 11)

$$\log 1/C = -39.54(\pm 16.4)\mathrm{C}\log P + 4.93(\pm 2.1)\mathrm{C}\log P^2 + 83.4(\pm 31.8)$$

$n = 7,\ r^2 = 0.942,\ s = 0.190,\ q^2 = 0.781$

inversion point: 4.01 (3.95–4.11)

outlier: $R_1 = CH_3$, R_2 = H, R = 2-pyrimidinyl

(11)

Table 10. QSAR 10: Inhibition of prostate cancer cells (BUIU5) by VII

No.	R_1	R_2	R	log 1/C			Clog P
				Obsd.	Pred.	Δ	
1	OCH_3	H	2-Thiazolyl	4.63	4.89	−0.27	4.29
2	H	H	2-Pyrimidinyl	6.10	6.13	−0.03	3.38
3	CH_3	H	2-Pyrmidinyl[a]	5.55	4.26	1.30	3.88
4	OCH_3	H	2-Pyrimidinyl	4.74	4.70	0.04	3.66
5	H	CH_3	2-Pyrimidinyl	4.30	4.26	0.05	3.88
6	CH_3	H	2-Pyrimidinyl (4-methyl)	5.24	5.28	−0.03	4.38
7	OCH_3	H	2-Pyrimidinyl (4-methyl)	4.50	4.48	0.01	4.16
8	H	CH_3	2-Pyrimidinyl (4-methyl)	5.51	5.28	0.23	4.38

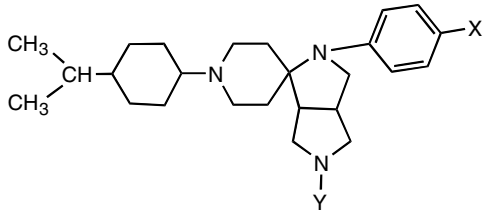
[a] Data point not included in the equation.

Table 11. QSAR 11: Inhibition of breast cancer cells (MCF7) by the same class of chemical used to derive QSAR 10

No.	R_1	R_2	R	log 1/C			Clog P
				Obsd.	Pred.	Δ	
1	OCH_3	H	2-Thiazolyl	4.56	4.58	−0.02	4.29
2	H	H	2-Pyrimidinyl	6.15	6.12	0.04	3.38
3	CH_3	H	2-Pyrimidinyl[a]	5.38	4.26	1.12	3.88
4	OCH_3	H	2-Pyrimidinyl	4.70	4.76	−0.05	3.66
5	H	CH_3	2-Pyrimidinyl	4.19	4.26	−0.07	3.88
6	CH_3	H	2-Pyrimidinyl (4-methyl)	4.60	4.86	−0.26	4.38
7	OCH_3	H	2-Pyrimidinyl (4-methyl)	4.48	4.30	0.18	4.16
8	H	CH_3	2-Pyrimidinyl (4-methyl)	5.05	4.86	0.19	4.38

[a] Data point not included in the equation.

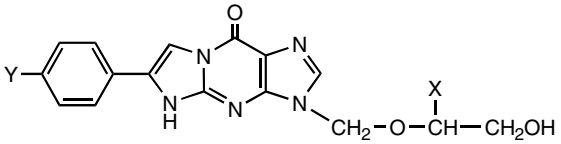
Interaction of VIII with the human opiod receptor. Data from Kolczewski et al.[23] (Table 12)



VIII

$$pK_i = -7.12(\pm 2.55)C\log P + 0.63(\pm 0.21)C\log P^2 + 25.8(\pm 7.5)$$
$$n = 8,\ r^2 = 0.959,\ s = 0.096,\ q^2 = 0.898$$
$$\text{outlier: X = H, Y = } CH_2C_6H_5(\pm) \quad (12)$$

Inhibition of human herpes simplex virus-2 in E6SM fibroblasts by IX. Data from Goslinski et al.[24] (Table 13)



IX

$$\log 1/C = -0.79(\pm 0.25)C\log P + 0.34(\pm 0.16)C\log P^2 + 6.35(\pm 0.11)$$
$$n = 9,\ r^2 = 0.939,\ s = 0.097,\ q^2 = 0.893$$
$$\text{inversion point: 1.17 (1.0–1.58)}$$
$$\text{outliers: X = H, Y = NHCOMe; X = H, Y = NHCOCH(Me)}_2\text{; X = H, Y = NHCONH}_2 \quad (13)$$

Table 12. QSAR 12: Interaction of VIII with the human opiod receptor

No.	X	Y	pK_i			Clog *P*
			Obsd.	Pred.	Δ	
1	H	Me(3AS, 6AR) (+)	5.67	5.59	0.08	5.36
2	H	Me(3AR, 6AS) (−)	5.63	5.59	0.04	5.36
3	H	$CH_2C_6H_5$ (±)[a]	6.04	7.01	−0.97	7.24
4	H	C_6H_5 (±)	6.66	6.55	0.11	6.98
5	H	$(CH_2)_3CH_3$ (±)	6.41	6.44	−0.03	6.91
6	H	$(CH_2)_2$-Morpholinyl (±)	5.53	5.52	0.01	5.77
7	F	CH_2–C_3H_5 (±)	5.97	6.08	−0.11	6.65
8	H	H (±)	5.75	5.86	−0.11	4.96
9	H	$(CH_2)_2OH$ (±)	6.03	6.00	0.03	4.82

[a] Data point not included in the equation.

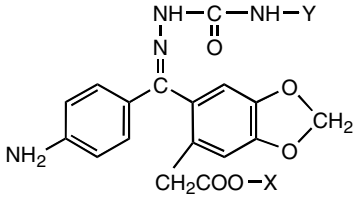
Table 13. QSAR 13: Inhibition of human herpes simplex virus-2 in E6SM fibroblasts by IX

No.	X	Y	log 1/*C*			Clog *P*
			Obsd.	Pred.	Δ	
1	H	OCOMe	6.70	6.57	0.13	−0.25
2	H	$OCOCHMe_2$	6.03	6.00	0.03	0.59
3	H	$OCOOC_6H_5$	6.08	6.10	−0.02	1.96
4	H	OH	6.43	6.58	−0.16	−0.27
5	H	NHCOMe[a]	4.60	6.92	−2.32	−0.58
6	H	$NHCOCHMe_2$[a]	5.33	6.17	−0.84	0.26
7	H	$MHCOOC_6H_5$	5.85	5.93	−0.08	1.53
8	H	$NHCONH_2$[a]	5.08	7.33	−2.25	−0.90
9	CH_2OH	OCOMe	6.73	6.69	0.04	−0.37
10	CH_2OH	$OCOCHMe_2$	6.06	6.05	0.01	0.46
11	CH_2OH	$OCOOC_6H_5$	6.11	6.04	0.07	1.84
12	CH_2OH	OH	6.68	6.71	−0.02	−0.39

[a] Data point not included in the equation.

The authors tested these compounds on two other herpes simplex virus, but those did not show an allosteric reaction.

A most unusual example of an allosteric reaction is that from the data of Micale et al.[25] (Table 14) for action on mice by X.



X

$$\log 1/K_g = -3.78(\pm 0.71)C\log P + 0.47(\pm 0.10)C\log P^2 + 11.2(\pm 1.3)$$
$$n = 9,\ r^2 = 0.979,\ s = 0.047,\ q^2 = 0.930$$
$$\text{inversion point: 4.00 (3.93–4.01)}$$
$$\text{outlier: X = } C_3H_7,\ \text{Y = Me} \quad (14)$$

Table 14. QSAR 14: Action on mice by X

No.	X	Y	log 1/Kg			Clog *P*
			Obsd.	Pred.	Δ	
1	Me	Me	4.55	4.53	0.02	2.66
2	C_2H_5	Me	4.02	3.99	0.03	3.19
3	C_3H_7	Me[a]	4.16	3.72	0.45	3.72
4	C_4H_9	Me	3.75	3.71	0.04	4.25
5	Me	C_2H_5	3.95	3.99	−0.05	3.19
6	C_2H_5	C_2H_5	3.64	3.72	−0.08	3.72
7	C_3H_7	C_2H_5	3.73	3.71	0.02	4.25
8	C_4H_9	C_2H_5	3.93	3.96	−0.03	4.78
9	Me	C_3H_7	3.75	3.72	0.03	3.72
10	Me	C_4H_9	3.73	3.71	0.02	4.25

[a] Data point not included in the equation.

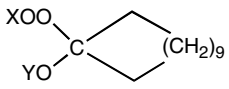
Table 15. QSAR 15: Antimalarial activity of XI against *Plasmodium falciparum*

No.	X	Y	log 1/*C*			Clog *P*
			Obsd.	Pred.	Δ	
1	CH_3	OCH_3	7.07	6.97	0.09	5.42
2	CH_2CH_3	OCH_2CH_3[a]	6.70	6.11	0.58	6.48
3	$CH_2CH_2CH_3$	$OCH_2CH_2CH_3$	5.74	5.78	−0.04	7.54
4	$CH_2CH_2CH_2CH_3$	$OCH_2CH_2CH_2CH_3$	5.68	5.98	−0.30	8.60
5	$CH_2CH{=}CH_2$	$OCH_2CH{=}CH_2$	5.80	5.90	−0.10	6.97
6	$CH_2C(CH_3){=}CH_2$	$OCH_2C(CH_3){=}CH_2$	5.82	5.78	0.04	7.77
7	CH_3	$OCH_2C(Me){=}CH_2$	5.89	6.05	−0.17	6.60
8	CH_3	$OCH_2CH_2CH_2CH_3$[a]	6.66	5.88	0.77	7.01
9	CH_3	$OCH_2CH_2CH_2C_6H_5$	6.00	5.79	0.21	7.90
10	CH_3	$O(CH_2)_6I$	6.13	5.87	0.26	8.31
11	CH_3	CH_3	7.10	7.13	−0.04	5.28
12	CH_2CH_3	CH_3	6.64	6.60	0.04	5.81
13	$CH_2CH_2CH_3$	CH_3	6.21	6.20	0.01	6.33

[a] Data point not included in the equation.

K_g is moles/kilogram that produces a standard audiogenic seizure in DBA2 mice. This equation implies that the chemicals find their way to the receptor without significant side reactions.

Antimalarial activity of XI against Plasmodium falciparum. Data from Hamada et al.[26] (Table 15)



XI

$$\log 1/C = -3.62(\pm 1.73)\mathrm{C}\log P + 0.24(\pm 0.13)\mathrm{C}\log P^2 + 19.7(\pm 5.84)$$

$n = 11,\ r^2 = 0.905,\ s = 0.178,\ q^2 = 0.723$

inversion point: 7.67 (7.34–8.62)

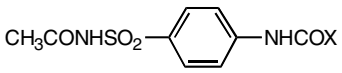
outliers: $X = C_2H_5,\ Y = OC_2H_5$;

$X = CH_3,\ Y = OC_4H_9$

(15)

This was an attempt to make more effective antimalarial drugs that was not successful.

Inhibition of human carbonic anhydrase II by XII. Data from Scozzafava et al.[27] (Table 16)



XII

$$\log 1/C = -0.61(\pm 0.19)\mathrm{C}\log P + 0.25(\pm 0.14)\mathrm{C}\log P^2 + 7.0(\pm 0.06)$$

$n = 7,\ r^2 = 0.979,\ s = 0.039,\ q^2 = 0.942$

inversion point: 1.21 (0.97–1.96)

outliers: C_6F_5, 4-CH_3-$C_6H_4SO_2NH$

(16)

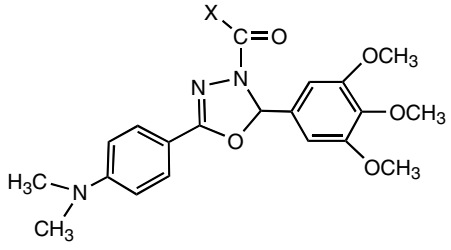
Table 16. QSAR 16: Inhibition of human carbonic anhydrase II by XII

No.	X	log 1/*C*			Clog *P*
		Obsd.	Pred.	Δ	
1	4-CH_3–C_6H_4–SO_2NH[a]	7.10	6.60	0.50	1.14
2	C_6F_5[a]	7.35	6.67	0.68	0.67
3	Nicotinoyl	7.10	7.08	0.02	−0.16
4	Isonicotinoyl	7.06	7.08	−0.02	−0.16
5	2,4-Di-Cl–C_6H_3	6.62	6.61	0.01	1.43
6	2-Thienyl	6.70	6.73	−0.03	0.48
7	$N(C_6H_5)_2$	6.60	6.61	−0.01	1.41
8	2-Cl–C_6H_4	6.72	6.67	0.06	0.69
9	4-F–C_6H_4	6.59	6.61	−0.03	0.95

[a] Data point not included in the equation.

The end point was the decrease of enzyme specific activity for the hydrolysis of 4-nitrophenylacetate. Antagonists of CAII might be of value in the treatment of ophthalmic infections.

Inhibition of NCI-H460 cells in culture by XIII. Data from Szczepankiewicz et al.[28] (Table 17)



XIII

$$\log 1/C = -16.13(\pm 6.58)\mathrm{C}\log P + 2.96(\pm 1.29)\mathrm{C}\log P^2 + 25.9(\pm 7.7)$$

$n = 8,\ r^2 = 0.930,\ s = 0.415,\ q^2 = 0.728$

inversion point: 2.73 (2.63–2.91)

outliers: CH_2OCOCH_3, CH_2OH

(17)

Table 17. QSAR 17: Inhibition of NCI-H460 cells in culture by XIII

No.	X	log 1/C			Clog P
		Obsd.	Pred.	Δ	
1	H	6.92	6.27	0.65	1.83
2	$COOC_2H_5$	4.48	4.64	−0.16	3.23
3	OMe	3.97	4.37	−0.40	3.13
4	CH_2OCOMe[a]	7.14	3.91	3.24	2.63
5	CH_2N_3	6.28	6.02	0.26	3.58
6	CH_2NMe_2	4.13	3.88	0.25	2.76
7	CH_2OH[a]	7.37	5.16	2.21	2.07
8	CH_2NH_2	6.18	6.34	−0.16	1.82
9	CH_2NHCHO	7.40	7.61	−0.21	1.61
10	$CH_2NHCOMe$	6.32	6.56	−0.24	1.78

[a] Data point not included in the equation.

The research was directed to using the H-460 cells to find more potent anticancer drugs. The authors data set 17 tested the same compounds on HCT-15 cells from which we formulated QSAR 18.

Data from Szczepankiewics et al.[28] (Table 18)

$$\log 1/C = -17.93(\pm 7.3)\mathrm{C}\log P + 3.33(\pm 1.43)\mathrm{C}\log P^2 + 28.0(\pm 8.6)$$

$$n = 8,\ r^2 = 0.920,\ s = 0.460,\ q^2 = 0.617$$

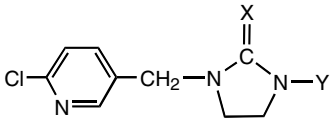
inversion point: 2.69 (2.61–2.85)

outliers: CH_2OCOCH_3, CH_2OH

(18)

The same compounds are outliers and inversion points are very similar.

Minimum lethal dose for American cockroaches of XIV. Data from Kiriyama et al.[29] (Table 19)



XIV

Table 18. QSAR 18: Inhibition of HCT-15 Gly by XIII

No.	X	log 1/C			Clog P
		Obsd.	Pred.	Δ	
1	H	7.02	6.37	0.65	1.83
2	$COOC_2H_5$	4.35	4.85	−0.50	3.23
3	OMe	4.40	4.52	−0.13	3.13
4	CH_2OCOMe[a]	7.72	3.89	3.83	2.63
5	CH_2N_3	6.82	6.48	0.34	3.58
6	CH_2NMe_2	4.10	3.90	0.20	2.76
7	CH_2OH[a]	7.59	5.18	2.41	2.07
8	CH_2NH_2	6.19	6.45	−0.26	1.82
9	CH_2NHCHO	7.46	7.83	−0.37	1.61
10	$CH_2NHCOMe$	6.74	6.68	0.06	1.78

[a] Data point not included in the equation.

Table 19. QSAR 19: Minimum lethal dose for American cockroaches of XIV

No.	X	Y	log 1/C			Clog P
			Obsd.	Pred.	Δ	
1	$CHNO_2$	H	9.59	9.82	−0.23	0.24
2	$CHNO_2$	Methyl[a]	7.77	8.55	−0.78	0.91
3	$CHNO_2$	Ethyl	7.98	7.92	0.06	1.44
4	$CHNO_2$	*n*-Propyl[a]	8.20	7.61	0.59	1.97
5	$CHNO_2$	*i*-Propyl	7.34	7.70	−0.36	1.75
6	$CHNO_2$	*n*-Butyl	7.55	7.63	−0.08	2.49
7	$CHNO_2$	*i*-Butyl	7.44	7.60	−0.16	2.36
8	$CHNO_2$	*n*-Pentyl	8.06	7.98	0.08	3.02
9	$CHNO_2$	Allyl	7.71	7.86	−0.15	1.52
10	$CHNO_2$	Propargyl	8.27	8.01	0.26	1.34
11	$CHNO_2$	Phenyl[a]	6.66	7.58	−0.92	2.25
12	$CHNO_2$	Benzyl	7.85	7.59	0.26	1.31
13	NNO_2	H	9.26	8.94	0.32	0.67

[a] Data point not included in the equation.

$$\log 1/C = -2.56(\pm 0.94)\mathrm{C}\log P + 0.58(\pm 0.28)\mathrm{C}\log P^2 + 10.4(\pm 0.72)$$

$$n = 10,\ r^2 = 0.906,\ s = 0.263,\ q^2 = 0.704$$

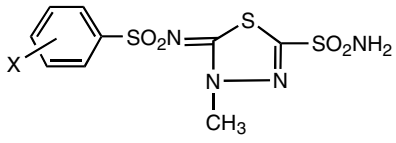
inversion point: 2.20 (1.94–2.80)

outliers: $X = CHNO_2$, $Y = CH_3$; $X = CHNO_2$, $Y = n\text{-}C_3H_7$; $X = CHNO_2$, $Y = C_6H_5$

(19)

In one example, $=CHNO_2$ was replaced with $=NNO_2$. This derivative was well fit by QSAR 19. Shortly after World War II, there was an enormous increase in the cockroach population in Japan and considerable effort was made to suppress it. We have 60 QSAR on the subject and found this equation as an allosteric effect.

Inhibition of bovine carbonic anhydrase IV by XV. Data from Supuran et al.[30] (Table 20)



XV

$$\log 1/K_i = -0.67(\pm 0.18)\mathrm{C}\log P + 0.60(\pm 0.16)\mathrm{C}\log P^2 + 8.37(\pm 0.12)$$

$$n = 12,\ r^2 = 0.896,\ s = 0.133,\ q^2 = 0.840$$

inversion point: 0.55 (0.45–0.67)

outliers: 4-Br, 2-NO_2, 2-COOH, 2,4,6-tri-CH_3

(20)

Of the outliers one would expect the COOH group to be misfit, since Clog *P* pertains to the unionized substituent.

Inhibition of E. coli by XVI. Data from Pernak et al.[31] (Table 21)

Table 20. QSAR 20: Inhibition of bovine carbonic anhydrase IV by XV

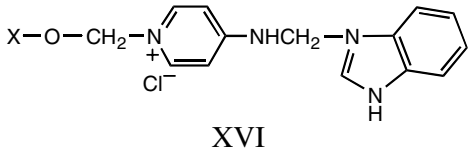
No.	X	log 1/K_i			Clog P
		Obsd.	Pred.	Δ	
1	4-Me	8.52	8.35	0.17	1.08
2	4-F	8.15	8.20	−0.05	0.72
3	4-Cl	8.30	8.51	−0.21	1.29
4	4-Br[a]	8.22	8.66	−0.44	1.44
5	4-I	9.00	8.98	0.02	1.70
6	4-OMe	8.30	8.19	0.11	0.50
7	4-NHCOMe	8.70	8.74	−0.04	−0.41
8	4-NH_2	9.10	9.06	0.04	−0.65
9	3-NH_2	9.10	9.06	0.04	−0.65
10	4-NO_2	8.22	8.22	0.00	0.32
11	3-NO_2	8.30	8.22	0.08	0.32
12	2-NO_2[a]	8.52	8.22	0.30	0.32
13	2-COOH[a]	9.30	8.22	1.08	0.32
14	2,4-Di-NO_2	8.10	8.33	−0.23	0.06
15	4-Cl–3-NO_2	8.30	8.25	0.05	0.88
16	2,4,6-Tri-Me[a]	8.05	9.58	−1.53	2.07

[a] Data point not included in the equation.

Table 21. QSAR 21: Inhibition of *E. coli* by XVI

No.	X	log 1/C			Clog P
		Obsd.	Pred.	Δ	
1	C_3H_7	3.42	3.50	−0.08	−0.38
2	C_4H_9	3.44	3.28	0.17	0.15
3	C_5H_{11}	3.16	3.14	0.02	0.68
4	C_6H_{13}	2.87	3.08	−0.21	1.21
5	C_7H_{15}	3.19	3.12	0.07	1.74
6	C_8H_{17}[a]	3.51	3.25	0.25	2.27
7	C_9H_{19}	3.52	3.47	0.05	2.80
8	$C_{10}H_{21}$[a]	3.54	3.78	−0.24	3.33
9	$C_{11}H_{23}$	4.16	4.18	−0.02	3.86
10	$C_{12}H_{25}$[a]	3.26	4.66	−1.40	4.39

[a] Data point not included in the equation.



XVI

$$\log 1/C = -0.40(\pm 0.33)\mathrm{C}\log P + 0.16(\pm 0.09)\mathrm{C}\log P^2 + 3.33(\pm 0.24)$$
$$n = 7,\ r^2 = 0.910,\ s = 0.147,\ q^2 = 0.745$$
inversion point: 1.25 (0.44–1.60)
outliers: C_8H_{17}, $C_{10}H_{21}$, $C_{12}H_{25}$

(21)

The authors were interested in the role of the charged N. Despite tests on a variety of bacteria, only *E. coli* displayed an allosteric reaction.

Displacement of [^{3}H]-Rauwolscine by miscellaneous alpha-2 adrenergic ligands. Data from Tian et al.[32] (Table 22)

Table 22. QSAR 22: Displacement of [^{3}H]-Rauwolscine by miscellaneous alpha-2 adrenergic ligands

No.	X	log 1/K_i			Clog P
		Obsd.	Pred.	Δ	
1	Epinephrine	7.35	7.30	0.05	−0.68
2	Deoxyepinephrine[a]	7.33	5.77	1.56	0.32
3	Norepinephrine	8.18	8.40	−0.22	−0.99
4	UK14304	8.32	8.02	0.29	1.49
5	Oxymetazoline[a]	7.92	35.45	−27.52	4.61
6	Synephrine	6.01	6.00	0.01	−0.09
7	Clonidine	7.54	7.81	−0.27	1.43
8	Norphenylephrine	7.21	6.52	0.69	−0.39
9	Phenylephrine	5.48	6.00	−0.52	−0.09
10	R(−)OH-3,4-(OH)2-Tolazooline	5.74	5.77	−0.02	0.28

[a] Data point not included in the equation.

$$\log 1/K_i = -0.94(\pm 0.67)\mathrm{C}\log P + 1.60(\pm 0.67)\mathrm{C}\log P^2 + 5.91(\pm 0.59)$$
$$n = 8,\ r^2 = 0.887,\ s = 0.438,\ q^2 = 0.715$$
inversion point: 0.30 (0.12–0.45)
outliers: Deoxyepinephrine, oxymetazoline

(22)

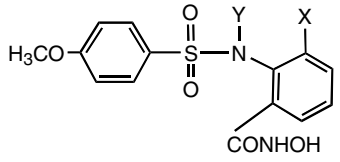
Clearance rate of polychlorinated biphenyls from Zebra fish. Data from Fox et al.[33] (Table 23)

$$\log k = -5.20(\pm 0.61)\log P + 0.36(\pm 0.05)\log P^2 + 16.9(\pm 2.0)$$
$$n = 28,\ r^2 = 0.972,\ s = 0.091,\ q^2 = 0.964$$
inversion point: 7.33 (7.24–7.45)

(23)

This is a rather amazing QSAR. No outliers and excellent statistics. The results imply a special receptor that is involved in elimination that worked more poorly as log P increased, but then began to increase. We have very few allosteric QSAR for whole animals or fish.

Inhibition of MMP-1 matrix metalloproteinase inhibition by XVII. Data from Levin et al.[34] (Table 24)



XVII

$$\log 1/C = -2.46(\pm 1.28)\mathrm{C}\log P + 1.09(\pm 0.68)\mathrm{C}\log P^2 + 7.29(\pm 0.33)$$
$$n = 7,\ r^2 = 0.921,\ s = 0.175,\ q^2 = 0.798$$
inversion point: 1.13 (1.01–1.52)
outliers: X = NO_2, Y = $CH_2C_6H_5$; X = CH_3, Y = $CH_2C_6H_5$

(24)

Table 23. QSAR 23: Clearance rate of polychlorinated biphenyls from Zebra fish

No.	Compound	log *K*			log *P*
		Obsd.	Pred.	Δ	
1	1,2,5-Di-Cl	−0.45	−0.31	−0.14	5.06
2	2,5,2′-Tri-Cl	−0.53	−0.59	0.05	5.24
3	2,5,4′-Tri-Cl	−1.06	−1.16	0.10	5.67
4	2,3,2′,5′-Tetra-Cl	−1.34	−1.26	−0.08	5.75
5	2,4,2′,5′-Tetra-Cl	−1.34	−1.36	0.03	5.85
6	2,5,2′,5′-Tetra-Cl	−1.41	−1.35	−0.06	5.84
7	2,6,2′,6′-Tetra-Cl	−0.41	−0.54	0.13	5.21
8	2,3′,4′,5′-Tetra-Cl	−1.55	−1.69	0.14	6.20
9	3,4,3′,4′-Tetra-Cl	−1.65	−1.81	0.16	6.36
10	2,3,4,2′,5′-Penta-Cl	−1.85	−1.76	−0.09	6.29
11	2,4,5,2′,3′-Penta-Cl	−1.90	−1.76	−0.14	6.29
12	2,4,5,2′,5′-Penta-Cl	−1.89	−1.82	−0.06	6.38
13	3,4,5,3′,4′-Penta-Cl	−2.00	−2.08	0.08	6.89
14	2,3,4,2′,3′,4′-Hexa-Cl	−2.07	−2.02	−0.05	6.74
15	2,3,6,2′,3′,6′-Hexa-Cl	−1.79	−1.71	−0.09	6.22
16	2,3,4,5,2′,4′-Hexa-Cl	−2.20	−2.06	−0.15	6.83
17	2,3,4,5,2′,5′-Hexa-Cl	−2.12	−2.05	−0.06	6.82
18	2,3,5,2′,5′,6′-Hexa-Cl	−1.92	−1.98	0.06	6.64
19	2,4,5,2′,4′,5′-Hexa-Cl	−1.98	−2.09	0.10	6.92
20	3,4,5,3′,4′,5′-Hexa-Cl	−2.12	−2.15	0.03	7.42
21	2,3,4,6,2′,4′,5′-Hepta-Cl	−2.06	−2.14	0.09	7.20
22	2,3,4,5,2′,5′,6′-Hepta-Cl	−2.17	−2.13	−0.04	7.11
23	2,3,4,5,2′,3′,4′,5′-Octa-Cl	−2.06	−2.07	0.01	7.80
24	2,3,4,5,6,2′,3′,4′-Octa-Cl	−2.15	−2.13	−0.02	7.56
25	2,3,4,5,6,2′,3′,5′-Octa-Cl	−2.11	−2.12	0.01	7.62
26	2,3,5,6,2′,3′,5′6′-Octa-Cl	−2.11	−2.15	0.03	7.24
27	2,3,4,5,6,2′,3′,4′,5′-Nona-Cl	−2.02	−1.95	−0.07	8.09
28	Deca-Cl	−1.88	−1.90	0.02	8.18

Table 24. QSAR 24: Inhibition of MMP-1 matrix metalloproteinase inhibition by XVII

No.	X	Y	log 1/*C*			Clog *P*
			Obsd.	Pred.	Δ	
1	H	$CH_2C_6H_5$	6.19	6.24	−0.04	1.68
2	CH_3[a]	$CH_2C_6H_5$	6.94	6.46	0.48	1.84
3	CH_3	CH_2–3-Pyridyl	6.84	6.57	0.27	0.34
4	OCH_3	$CH_2C_6H_5$	6.28	6.27	0.01	1.71
5	Cl	$CH_2C_6H_5$	6.40	6.37	0.03	1.78
6	NO_2[a]	$CH_2C_6H_5$	6.69	5.94	0.75	0.94
7	$OCH_2CONHOH$	$CH_2C_6H_5$	7.62	7.60	0.02	−0.12
8	$OC(CH_3)_2CONHOH$	$CH_2C_6H_5$	6.22	6.33	−0.11	0.50
9	CO_2CH_3	CH_2–3-Pyridyl	6.68	6.87	−0.18	0.19

[a] Data point not included in the equation.

We have 206 QSAR on metalloproteinases, but only one example of an allosteric reaction.

Binding of miscellaneous sulfonamides to serum albumin. Data from Nogami et al.[35] (Table 25)

$$\log k = -3.37(\pm 1.6)\mathrm{C}\log P + 1.68(\pm 0.62)\mathrm{C}\log P^2 + 5.10(\pm 0.89) \quad (25)$$

$n = 10,\ r^2 = 0.912,\ s = 0.287,\ q^2 = 0.717$

inversion point: 1.00 (0.80–1.12)

outliers: Sulfadiazine, *N*-4-acetylsulfadiazine, sulfaethidole

This study was undertaken to see if molecular absorption by carbon black would be a gold models for hydrophobicity. We have 51 QSAR that show hydrophobicity is important in albumin binding.

Inhibition of resistant L1210 leukemia cells by II. Data from Sami et al.[17] (Table 26)

$$\log 1/C = -10.22(\pm 4.14)\mathrm{C}\log P + 1.29(\pm 0.54)\mathrm{C}\log P^2 + 26.0(\pm 7.67) \quad (26)$$

$n = 7,\ r^2 = 0.935,\ s = 0.190,\ q^2 = 0.812$

inversion point: 3.96 (3.85–4.13)

outliers: H, 8-NO_2, 11-NO_2

Table 25. QSAR 25: Binding of miscellaneous sulfonamides to serum albumin

No.	Compound	log *K*			Clog *P*
		Obsd.	Pred.	Δ	
1	Sulfamonomethoxine	3.30	3.41	−0.11	1.05
2	*N*-4-Acetylsulfamonomethoxine	3.40	3.53	−0.13	1.27
3	Sulfadimethoxine	5.50	5.02	0.48	1.98
4	*N*-4-Acetylsulfadimethoxine	5.50	5.82	−0.32	2.20
5	Sulfadiazine[a]	2.90	4.78	−1.88	0.10
6	*N*-4-Acetylsulfadiazine[a]	3.30	4.20	−0.90	0.32
7	Sulfamerazine	3.70	3.68	0.02	0.60
8	Sulfisomidine	3.10	3.42	−0.32	1.10
9	*N*-Acetylsulfisomidine	3.70	3.57	0.13	1.32
10	Sufisomezole	3.70	3.73	−0.03	0.56
11	*N*-4-Acetylsulfisomezole	3.80	3.49	0.31	0.78
12	Sulfamethizole	4.30	4.31	−0.01	0.27
13	Sulfaethidole[a]	4.50	3.48	1.02	0.80

[a] Data point not included in the equation.

Table 26. QSAR 26: Inhibition of resistant L1210 leukemia cells by II

No.	X	log 1/*C*			Clog *P*
		Obsd.	Pred.	Δ	
1	H[a]	6.78	5.75	1.03	3.97
2	8-NO_2[a]	7.30	5.81	1.50	3.76
3	8-NH_2	7.27	7.27	−0.01	2.87
4	11-NO_2[a]	6.30	5.81	0.49	3.76
5	11-NH_2	7.30	7.27	0.03	2.87
6	8-Cl	6.29	6.47	−0.18	4.70
7	8-OH	5.87	6.10	−0.23	3.44
8	8-OMe	5.81	5.75	0.05	3.97
9	11-Cl	6.64	6.47	0.17	4.70
10	11-OH	6.27	6.10	0.17	3.44

[a] Data point not included in the equation.

Only two nitro substituents were tested and both are more active than predicted.

Inhibition of human carbonic anhydrase II by XV. Data from Supuran et al.[30] (Table 27)

Table 27. QSAR 27: Inhibition of human carbonic anhydrase II by XV

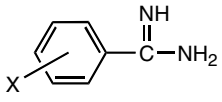
No.	X	log K_i			Clog *P*
		Obsd.	Pred.	Δ	
1	4-Me	8.52	8.50	0.02	1.08
2	4-F	8.40	8.38	0.02	0.72
3	4-Cl	8.52	8.65	−0.13	1.29
4	4-Br	8.70	8.79	−0.09	1.44
5	4-I	9.22	9.10	0.12	1.70
6	4-OMe	8.52	8.37	0.15	0.50
7	4-NHCOMe	9.15	8.98	0.18	−0.41
8	4-NH_2	9.22	9.31	−0.09	−0.65
9	3-NH_2	9.30	9.31	−0.01	−0.65
10	4-NO_2	8.40	8.42	−0.02	0.32
11	3-NO_2[a]	8.70	8.42	0.28	0.32
12	2-NO_2[a]	9.00	8.42	0.58	0.32
13	2-COOH[a]	9.70	8.42	1.28	0.32
14	2,4-Di-NO_2	8.40	8.54	−0.14	0.06
15	4-Cl–3-NO_2[a]	8.70	8.42	0.28	0.88
16	2,4,5-Tri-Me[a]	8.15	9.68	−1.52	2.07

[a] Data point not included in the equation.

$$\log 1/K_i = -0.73(\pm 0.19)\mathrm{C}\log P + 0.61(\pm 0.17)\mathrm{C}\log P^2 + 8.58(\pm 0.12)$$
$$n = 11,\ r^2 = 0.913,\ s = 0.125,\ q^2 = 0.815$$
inversion point: 0.60 (0.51–0.71)
outliers: 3-NO_2, 2-NO_2, 2-COOH, 4-Cl-3-NO_2, 2, 4, 6-tri-CH_3 (27)

Another example where NO_2 groups are poorly fit. The COOH is badly fit since Clog *P* is calculated for the neutral form. The authors were interested in the fact that carbonic anhydrases play critical roles in respiration and transport of CO_2/HCO_3 and secretion of electrolytes.

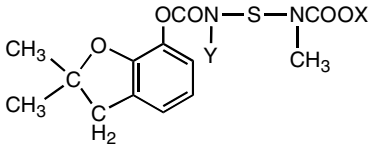
Inhibition of serum kallikerin by XVIII. Data from Markwardt et al.[36] (Table 28)



XVIII

$$\log 1/C = -1.10(\pm 0.29)\mathrm{C}\log P + 0.49(\pm 0.16)\mathrm{C}\log P^2 + 3.62(\pm 0.25)$$
$$n = 11,\ r^2 = 0.902,\ s = 0.257,\ q^2 = 0.823$$
inversion point: 1.12 (0.93–1.40)
outlier: 4-$NHCOCH_3$ (28)

LD_{50} of mouse by XIX. Data from Doyle et al.[37] (Table 29)



XIX

Table 28. QSAR 28: Inhibition of serum kallikerin by XVIII

No.	X	log 1/C			Clog P
		Obsd.	Pred.	Δ	
1	H	3.00	3.11	−0.11	0.65
2	4-NH_2	3.82	4.26	−0.43	−0.48
3	4-NHCOMe[a]	3.22	3.91	−0.69	−0.24
4	4-CH_2NH_2	4.52	4.14	0.39	−0.40
5	4-OMe	3.00	3.09	−0.09	0.71
6	3-OMe	3.00	3.09	−0.09	0.71
7	4-$OCH_2C_6H_5$	4.00	3.91	0.09	2.48
8	4-Me	3.30	3.00	0.30	1.14
9	4-Cl	3.15	3.08	0.08	1.51
10	3-Cl	3.10	3.08	0.02	1.51
11	3,4-Di-Cl	3.30	3.53	−0.23	2.16
12	4-$CH_2COCOOH$	5.22	5.15	0.08	−0.97

[a] Data point not included in the equation.

Table 29. QSAR 29: LD_{50} of mouse by XIX

No.	X	Y	log 1/C			Clog P
			Obsd.	Pred.	Δ	
1	Me	Me	3.88	3.85	0.03	3.15
2	Et	Me	3.69	3.72	−0.03	3.67
3	Pr	Me	3.62	3.61	0.02	4.20
4	I–Pr	Me[a]	3.85	3.65	0.20	3.98
5	Bu	Me	3.47	3.51	−0.04	4.73
6	Pentyl	Me	3.45	3.43	0.02	5.26
7	Heptyl	Me	3.38	3.33	0.06	6.32
8	Decyl	Me	3.27	3.29	−0.02	7.91
9	Et	Et	3.64	3.61	0.03	4.20
10	Et	I–Pr	3.49	3.55	−0.06	4.51

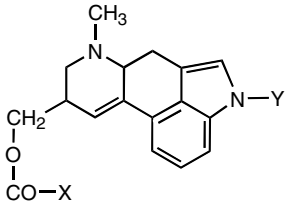
[a] Data point not included in the equation.

$$\log 1/C = -0.45(\pm 0.21)\mathrm{C}\log P + 0.03(\pm 0.02)\mathrm{C}\log P^2 + 4.95(\pm 0.55)$$
$$n = 9,\ r^2 = 0.951,\ s = 0.046,\ q^2 = 0.608$$
inversion point: 7.48 (6.65–10.9)
outlier: $X = CH(CH_3)_2,\ Y = CH_3$

(29)

The authors were using mice to check the toxicity of a potential pesticide. Our results would indicate that a particular receptor is involved.

Antagonist dissociation constant from A1-adrenoreceptors in rat aorta by XX. Data from Pertz et al.[38] (Table 30)



XX

Table 30. QSAR 30: Antagonist dissociation constant from A1-adrenoreceptors in rat aorta by XX

No.	X	Y	pA_2			Clog P
			Obsd.	Pred.	Δ	
1	Cy-C_3H_5	H	6.66	6.64	0.02	3.26
2	Cy-C_3H_5	$CHMe_2$	5.08	5.11	−0.03	4.42
3	Cy-C_4H_7	H[a]	5.52	6.09	−0.57	3.59
4	Cy-CH_7	$CHMe_2$	4.75	4.87	−0.12	4.75
5	Cy-C_5H_9	H	5.32	5.37	−0.05	4.15
6	Cy-C_5H_9	$CHMe_2$	4.57	4.66	−0.09	5.31
7	Cy-C_6H_{11}	H	5.05	4.89	0.16	4.71
8	Cy-C_6H_{11}	$CHMe_2$	4.77	4.69	0.08	5.87
9	Cy-C_7H_{13}	H	4.73	4.66	0.07	5.27
10	Cy-C_7H_{13}	$CHMe_2$	4.93	4.97	−0.04	6.43

[a] Data point not included in the equation.

$$\log \mathrm{PA}_2 = -4.35(\pm 0.85)\mathrm{C}\log P + 0.40(\pm 0.09)\mathrm{C}\log P^2 + 16.6(\pm 2.04)$$
$$n = 9,\ r^2 = 0.980,\ s = 0.102,\ q^2 = 0.948$$
inversion point: 5.51 (5.35–5.73)
outlier: $X = cyclo\text{-}C_4H_7,\ Y = H$

(30)

Inhibition of dihydrofolate reductase by miscellaneous 2,4-diamino-5-substituted-pyrimidines. Data from Otzen et al.[39] (Table 31)

$$\log 1/C = -12.67(\pm 5.29)\mathrm{C}\log P + 1.67(\pm 0.79)\mathrm{C}\log P^2 + 29.8(\pm 8.70)$$
$$n = 13,\ r^2 = 0.883,\ s = 0.405,\ q^2 = 0.701$$
inversion point: 3.80 (3.60–4.27)

(31)

This was a large study (11 QSAR) only one of which showed an allosteric reaction. We have 244 QSAR on DHFR and this is the only example showing a hydrophobic, allosteric reaction. This must be attributed to an unusual type of chemical.

Inhibition of A_1A-adrenergenic receptor in rat vas deferens prostatic portion by miscellaneous tetrahydroacridines quinazoline and quinoline. Data from Rosini et al.[40] (Table 32)

$$\mathrm{p}K_\mathrm{i} = -7.15(\pm 2.49)\mathrm{C}\log P + 0.95(\pm 0.35)\mathrm{C}\log P^2 + 19.47(\pm 4.25)$$
$$n = 8,\ r^2 = 0.927,\ s = 0.329,\ q^2 = 0.802$$
inversion point: 3.78 (3.58–4.07)
outliers: see Table 32

(32)

The authors were seeking better drugs for prostate cancer.

Table 31. QSAR 31: Inhibition of dihydrofolate reductase by miscellaneous 2,4-diamino-5-substituted-pyrimidines

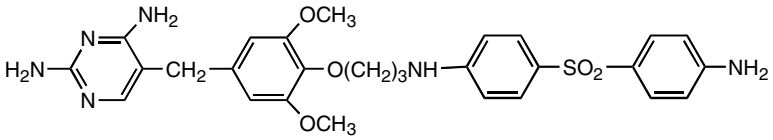
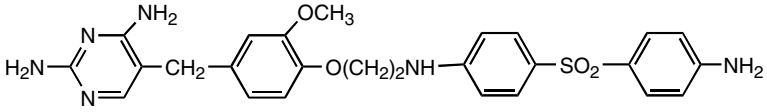
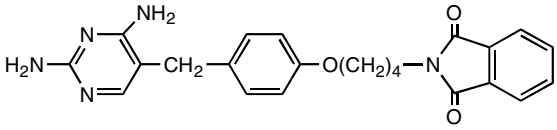
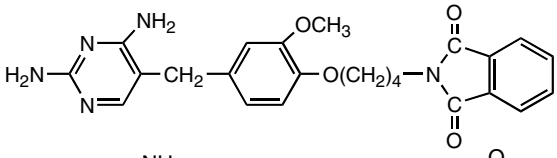
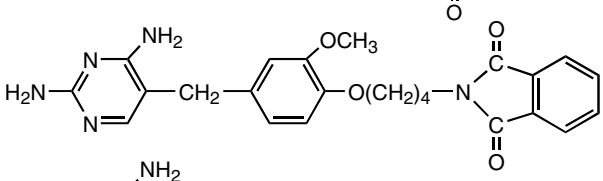
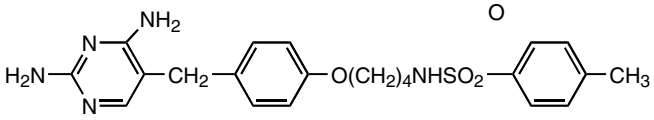
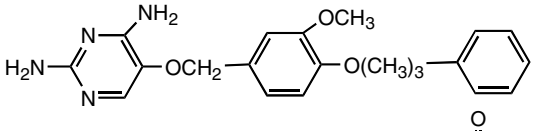
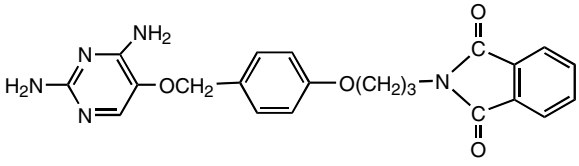
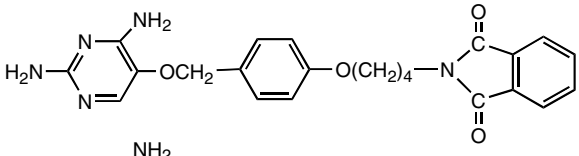
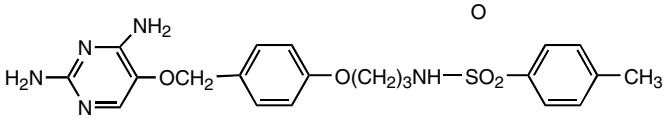
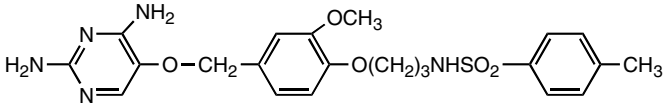
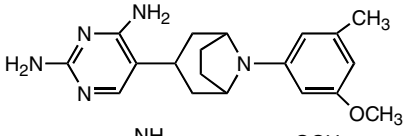
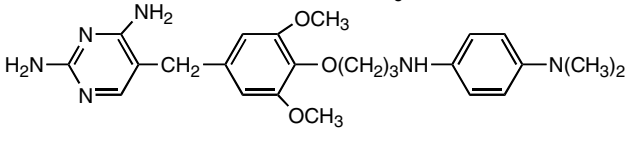
No.	Compound	log 1/*C*			Clog *P*
		Obsd.	Pred.	Δ	
1		7.40	7.33	0.07	2.81
2		6.66	7.58	−0.92	2.74
3		5.79	5.88	−0.09	3.48
4		6.94	6.27	0.66	3.22
5		6.30	6.27	0.03	3.22
6		6.11	6.00	0.11	3.38
7		6.07	6.13	−0.06	4.30
8		5.50	5.73	−0.23	3.68
9		5.70	5.76	−0.06	3.96
10		5.80	5.71	0.08	3.81
11		6.01	5.81	0.20	3.55
12		9.62	9.19	0.43	2.35
13		6.69	6.91	−0.22	2.95

Table 32. QSAR 32: Inhibition of A_1A-adrenergenic receptor in rat vas deferens prostatic portion by miscellaneous tetrahydroacridines, quinazoline and quinoline

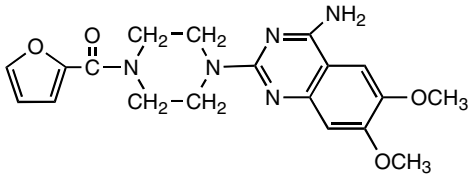
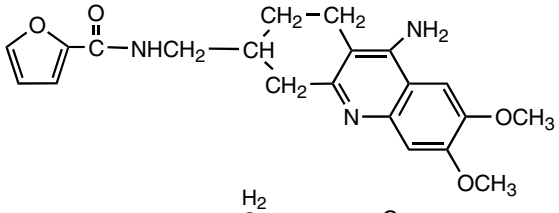
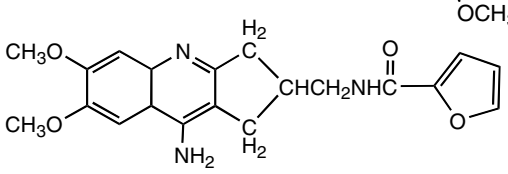
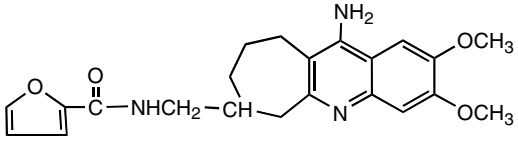
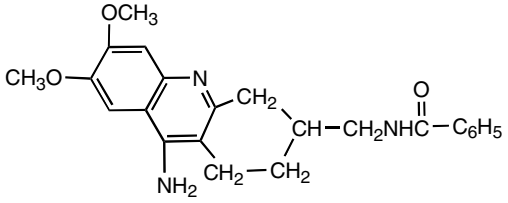
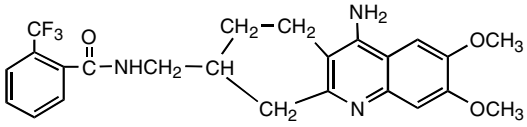
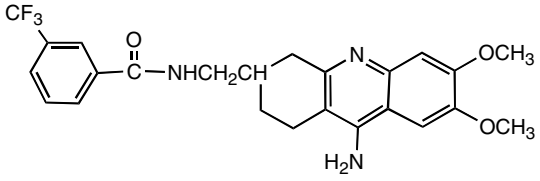
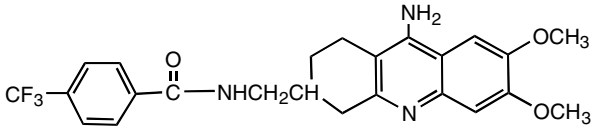
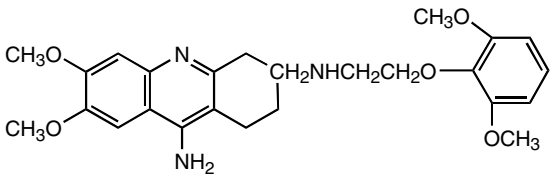
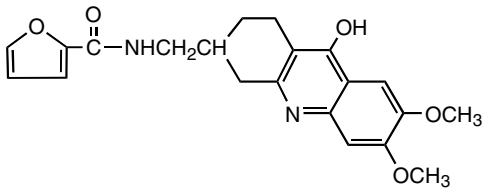
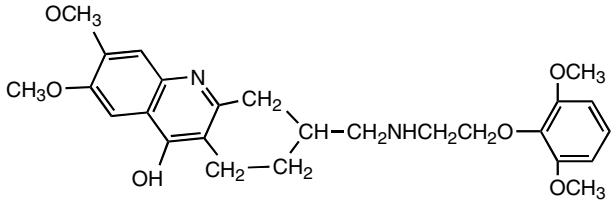
No.	Compound	pK_I			Clog P
		Obsd.	Pred.	Δ	
1		8.93	8.85	0.08	2.03
2		6.52	6.76	−0.24	2.85
3[a]		6.26	8.04	−1.78	2.29
4		6.34	6.08	0.26	3.41
5[a]		6.67	5.96	0.71	3.68
6		6.47	5.96	0.51	3.70
7		7.16	7.17	−0.01	4.91
8[a]		6.08	7.17	−1.09	4.91
9		5.70	5.95	−0.25	3.76

Table 32 (*continued*)

No.	Compound	pK_I			Clog *P*
		Obsd.	Pred.	Δ	
10		5.76	6.04	−0.28	3.47
11		6.24	6.30	−0.06	4.38

Inhibition of recombinant dihydrofoate reductase from Plasmodium falciparum by miscellaneous chemicals. Data from Rastelli et al.[41] (Table 33)

$$\log 1/K_i = -1.99(\pm 0.72)\mathrm{C}\log P + 0.43(\pm 0.13)\mathrm{C}\log P^2 + 6.77(\pm 0.91)$$

$n = 9,\ r^2 = 0.947,\ s = 0.118,\ q^2 = 0.917$

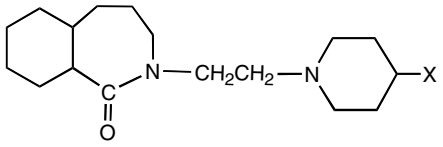
inversion point: 2.31 (2.08–2.46)

outliers: see Table 33

(33)

The effort in this research was directed toward finding better anti-malarial drugs.

Binding to the 5-HT-2A receptor by XXI. Data from Forbes et al.[42] (Table 34)



XXI

$$pK_i = -6.30(\pm 4.0)\mathrm{C}\log P + 1.14(\pm 0.63)\mathrm{C}\log P^2 + 15.0(\pm 6.04)$$

$n = 12,\ r^2 = 0.882,\ s = 0.296,\ q^2 = 0.795$

inversion point: 2.76 (2.24–2.93)

outliers: OC_6H_4-4-Cl; COC_6H_4-4-F; 5-F-1H-benzotriazol-1-yl; 5-F-1, 3-dihydro-indol-2-one-1-yl

(34)

The object of this research was to compare 5-HT_7 and 5-HT-2A receptors. The 5-HT_7 receptor does not show an allosteric effect. This would seem to be desirable.

Inhibition of growth of non small cell lung cancer (HOP-92) by miscellaneous heterocycles. Data from El-Sherbeny.[43] (Table 35)

$$\log 1/C = -5.40(\pm 2.77)\mathrm{C}\log P + 0.58(\pm 0.31)\mathrm{C}\log P^2 + 17.13(\pm 6.12)$$

$n = 8,\ r^2 = 0.889,\ s = 0.106,\ q^2 = 0.647$

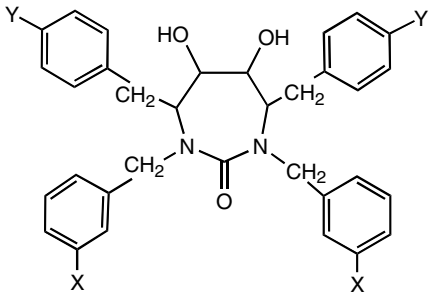
inversion point: 4.70 (4.57–5.00)

outliers: see Table 35

(35)

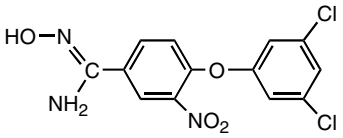
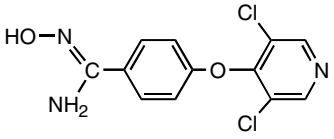
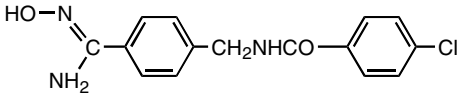
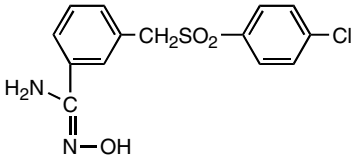
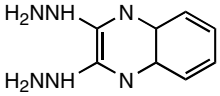
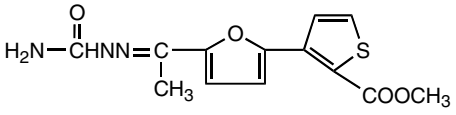
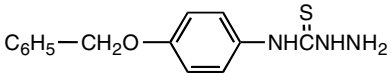
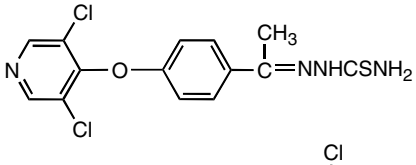
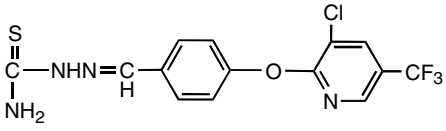
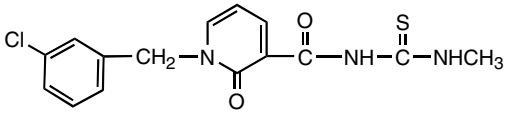
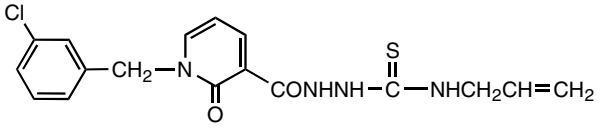
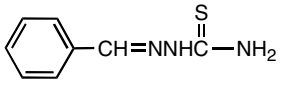
The researchers were looking for better antiviral and antitumor agents. Out of six QSAR from six sets of data, only one showed an allosteric reaction. One needs a receptor that can undergo such reactions and chemicals fit to produce such response.

Inhibition of antiviral activity of cells infected with HIV by XXII. Data from Patel et al.[44] (Table 36)



XXII

Table 33. QSAR 33: Inhibition of recombinant dihydrofolate reductase from *Plasmodium falciparum* by miscellaneous chemicals

No.	Compound	log 1/*C*			Clog *P*
		Obsd.	Pred.	Δ	
1[a]		4.49	5.71	−1.23	4.01
2		4.56	4.53	0.03	2.70
3		4.44	4.51	−0.07	2.63
4		4.46	4.58	−0.12	1.79
5[a]		5.01	4.47	0.54	2.15
6		4.80	4.81	−0.01	3.20
7		4.58	4.52	0.06	1.95
8		5.82	5.82	0.01	4.08
9[a]		5.03	5.71	−0.68	4.01
10		4.71	4.50	0.21	2.03
11		4.97	4.95	0.02	1.25
12		4.43	4.55	−0.12	1.87

[a] Outliers.

Table 34. QSAR 34: Binding to the 5-HT-2A receptor by XXI

No.	X	pK_I			Clog *P*
			PRED	DEV	
1	OC_6H_5	6.81	6.86	−0.05	3.45
2	OC_6H_4-4-F	7.50	7.10	0.40	3.59
3	OC_6H_4-4-Cl[a]	7.13	8.56	−1.43	4.16
4	OC_6H_4-4-CH_3	7.26	7.57	−0.31	3.80
5	COC_6H_4-4-F[a]	7.77	6.41	1.36	3.04
6	COC_6H_4-4-Cl	7.11	7.15	−0.04	3.61
7	1*H*-Indol-3-Yl	8.77	8.41	0.36	4.11
8	1*H*-Indol-1-Yl	7.71	8.05	−0.34	3.99
9	1*H*-Benzotriazol-1-Yl	6.57	6.42	0.15	2.45
10	1,3-Dihydro-indol-2-one-1-Yl	6.65	6.72	−0.07	2.16
11	3*H*-Benzooxazol-2-one-3-Yl	6.01	6.40	−0.39	2.47
12	5-F-1*H*-Indol-1-Yl	8.16	8.16	0.00	4.03
13	5-F-1*H*-Benzotriazol-1-Yl[a]	7.31	6.34	0.97	2.59
14	5-F-1,3-Dihydro-indol-2-one-1-Yl[a]	7.37	6.55	0.82	2.30
15	1,3-Dihydro-benzoimidazol-2-one-5-Yl	6.52	6.55	−0.03	3.21
16	5-F-3*H*-Benzooxazol-2-one-3-Yl	6.73	6.40	0.33	2.47

[a] Data point not included in the equation.

$$\log 1/K_i = -10.21(\pm 2.83)C\log P + 0.79(\pm 0.21)C\log P^2 + 39.1(\pm 9.39)$$
$$n = 11,\ r^2 = 0.930,\ s = 0.189,\ q^2 = 0.865$$
inversion point: 6.5 (6.4–6.6)
outliers: X = H, Y = OH; X = 3-(1H)pyrazole, Y = OCH_3; X = 3-(1H)pyrazole, Y = $O(CH_2)_2$-morpholinyl; X = 3-(1H)pyrazole, Y = $O(CH_2)_2NMe_2$

(36)

The authors were looking for new HIV drugs.

Binding to hemoglobin in wistar rats in vivo by nitrobenzenes. Data from Sabbioni.[45] (Table 37)

$$\log HBI = -11.1(\pm 5.64)C\log P + 1.97(\pm 1.0)C\log P^2 + 1.51(\pm 1.0)B1_4 + 3.62(\pm 1.44)\sigma^+ + 14.2(\pm 7.86)$$
$$n = 14,\ r^2 = 0.874,\ s = 0.507,\ q^2 = 0.743$$
inversion point: 2.82 (2.61–3.10)
outlier: 2,4-di-F

(37)

Aromatic nitro compounds are a potential environmental pollutants resulting from the manufacturing for use in pesticides.

Binding of RN=C to human alpha subunit of hemoglobin. Data from Reisberg and Olson.[46] (Table 38)

$$\log k = -0.77(\pm 0.44)C\log P + 0.35(\pm 0.23)C\log P^2 - 1.72(\pm 0.44)B1 + 4.76(\pm 0.78)$$
$$n = 12,\ r^2 = 0.949,\ s = 0.188,\ q^2 = 0.833$$
inversion point: 1.11 (0.853–1.74)
outlier: $CH_2CH(CH_3)_2$

(38)

*B*1 is a steric parameter for the first atom of the substituent.[11] This report was to study the kinetics of binding of chemicals to hemoglobin.

Binding to rat brain membrane by analogues of nicotine. Data from Wang et al.[47] (Table 39)

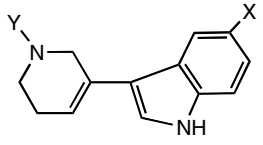
$$\log 1/K_i = -5.15(\pm 2.0)C\log P + 1.12(\pm 0.55)C\log P^2 - 1.26(\pm 0.60)I + 12.51(\pm 1.66)$$
$$n = 14,\ r^2 = 0.891,\ s = 0.344,\ q^2 = 0.761$$
inversion point: 2.29 (2.08–2.83)
outliers: (*R*)-nicotine, (*R*,*S*)-*cis*-3′-Me-nicotine, (*R*,*S*)-*trans*-5′-Me-nicotine

(39)

I = 1 for *cis*/*trans* substituents.

This study was an attempt to better understand the action of nicotine. It suggests a very specific binding site for nicotine that might be applicable to humans.

Binding to serotonin by XXIII. Data from Dahlgren et al.[48] (Table 40)

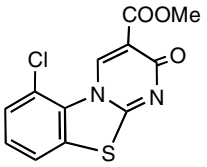
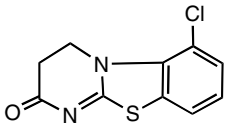
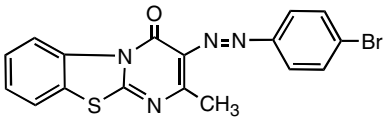
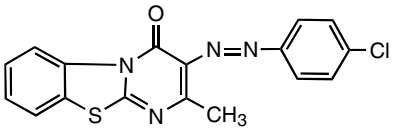
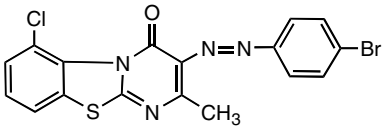
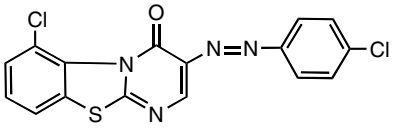
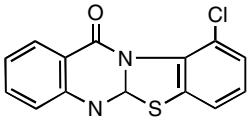
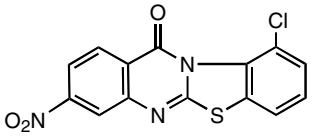
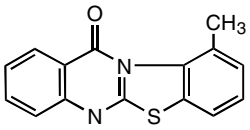
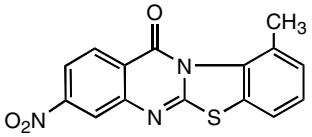


XXIII

$$\log 1/K_i = -3.17(\pm 0.79)C\log P + 0.49(\pm 0.13)C\log P^2 - 0.56(\pm 0.21)I - Y + 12.04(\pm 1.17)$$
$$n = 22,\ r^2 = 0.873,\ s = 0.183,\ q^2 = 0.811$$
inversion point: 3.24 (3.11–3.39)
outliers: X = H, Y = CH_3; X = OH, Y = CH_3; X = Br, Y = C_3H_7; X = $CONH_2$, Y = C_3H_7

(40)

Table 35. QSAR 35: Inhibition of growth of non small cell lung cancer (HOP-92) by miscellaneous heterocycles

No.	Compound	log 1/*C*			Clog *P*
		Obsd.	Pred.	Δ	
1[a]		4.12	6.65	−2.54	2.74
2[a]		4.37	8.39	−4.01	2.08
3		4.52	4.44	0.08	4.70
4		4.52	4.46	0.06	4.55
5		4.72	4.73	−0.02	5.41
6		4.60	4.63	−0.03	5.26
7		4.60	4.70	−0.09	4.03
8		4.81	4.93	−0.12	3.77
9		4.87	4.89	−0.02	3.82
10		5.33	5.19	0.14	3.56

[a] Data point not included in the equation.

Table 36. QSAR 36: Inhibition of antiviral activity of cells infected with HIV by XXII

No.	X	Y	$\log 1/K_i$			Clog *P*
			Obsd.	Pred.	Δ	
1	H	H	6.10	6.37	−0.27	7.24
2	3-(1*H*)Pyrazole	H	7.25	6.95	0.30	7.63
3	H	OH[a]	6.74	6.22	0.51	5.90
4	3-(1*H*)Pyrazole	OH	5.87	5.97	−0.10	6.30
5	H	OMe	6.22	6.20	0.02	7.08
6	3-(1*H*)Pyrazole	OMe[a]	8.00	6.68	1.32	7.47
7	H	OCH_2CH_2OH	7.11	7.02	0.09	5.33
8	3-(1*H*)Pyrazole	OCH_2CH_2OH	6.34	6.42	−0.08	5.72
9	H	OCH_2-Pyridin-4-Yl	7.00	6.92	0.08	7.62
10	3-(1*H*)Pyrazole	OCH_2-Pyridin-4-Yl	7.74	7.74	0.01	8.01
11	H	$O(CH_2)_2$-Morpholinyl	6.64	6.46	0.18	7.31
12	3-(1*H*)Pyrazole	$O(CH_2)_2$-Morpholinyl[a]	5.99	7.09	−1.10	7.71
13	3-(1*H*)Pyrazole	OCH_2-Pyridin-3-Yl	7.49	7.74	−0.24	8.01
14	H	$O(CH_2)_2NHMe$	6.10	6.08	0.02	6.09
15	3-(1*H*)Pyrazole	$O(CH_2)_2NMe_2$[a]	5.27	7.01	−1.74	7.67

[a] Data point not included in the equation.

Table 37. QSAR 37: Binding to hemoglobin in wistar rats in vivo by nitrobenzenes

No.	X	log HBI			σ^+	Clog *P*	$B1_4$
		Obsd.	Pred.	Δ			
1	4-Me	−0.37	0.08	−0.44	−0.31	2.38	1.52
2	4-C_2H_5	−0.92	−0.25	−0.67	−0.30	2.91	1.52
3	4-C_6H_5	2.25	2.24	0.01	−0.18	3.77	1.71
4	H	1.78	1.76	0.01	0.00	1.89	1.00
5	4-F	1.60	1.55	0.05	−0.07	2.03	1.35
6	4-Cl	2.33	1.74	0.59	0.11	2.60	1.80
7	4-Br	2.35	2.02	0.33	0.15	2.75	1.95
8	2-Me	−0.14	−0.56	0.41	−0.31	2.30	1.00
9	2-C_2H_5	−0.59	−1.05	0.46	−0.30	2.83	1.00
10	3-Me	0.01	0.16	−0.15	−0.07	2.38	1.00
11	3,5-Me_2	−0.20	−0.46	0.26	−0.14	2.88	1.00
12	2-Cl	0.32	0.79	−0.46	0.11	2.40	1.00
13	3-Cl	1.73	1.48	0.26	0.37	2.60	1.00
14	3-Cl-4-F	1.00	1.66	−0.66	0.30	2.74	1.35
15	2,4-F_2[a]	0.36	1.84	−1.48	−0.14	1.87	1.35

[a] Data point not included in the equation.

Table 38. QSAR 38: Binding of RN=C to human alpha subunit of hemoglobin

No.	R	log *K*			Clog *P*	$B1_4$
		Obsd.	Pred.	Δ		
1	Me	2.59	2.55	0.04	−0.44	1.52
2	C_2H_5	2.15	2.08	0.07	0.09	1.52
3	C_3H_7	1.60	1.80	−0.19	0.62	1.52
4	C_4H_9	1.77	1.71	0.06	1.15	1.52
5	C_5H_{11}	1.92	1.82	0.10	1.68	1.52
6	C_6H_{13}	2.08	2.12	−0.05	2.21	1.52
7	$CHMe_2$	1.08	1.24	−0.16	0.40	1.90
8	CH_2CHMe_2[a]	0.87	1.71	−0.85	1.02	1.52
9	(+)$CHMeC_2H_5$	1.00	1.07	−0.07	0.93	1.90
10	(−)$CHMeC_2H_5$	1.00	1.07	−0.07	0.93	1.90
11	CMe_3	0.08	−0.11	0.19	0.80	2.60
12	Cy-C_6H_{11}	0.89	1.12	−0.23	1.59	1.91
13	$CH_2C_6H_5$	2.04	1.73	0.31	1.33	1.52

[a] Data point not included in the equation.

Table 39. QSAR 39: Binding to rat brain membrane by analogues of nicotine

No.	Compound	$\log 1/K_i$			Clog *P*	I
		Obsd.	Pred.	Δ		
1	(*S*)-Nicotine	9.00	8.78	0.22	0.90	0
2	(*R*)-Nicotine[a]	8.00	8.78	−0.78	0.90	0
3	(*R*,*S*)-Nicotine	8.52	8.78	−0.26	0.90	0
4	(*R*,*S*)-2′-Me-Nicotine	8.70	8.62	0.08	0.96	0
5	(*R*,*S*)-*cis*-3′-Me-Nicotine[a]	7.40	5.86	1.54	1.62	1
6	(*R*,*S*)-*trans*-3′-Me-Nicotine	7.52	7.36	0.16	0.96	1
7	(*R*,*S*)-*cis*-5′-Me-Nicotine	5.70	5.86	−0.16	1.62	1
8	(*R*,*S*)-*trans*-5′-Me-Nicotine[a]	8.00	5.86	2.14	1.62	1
9	(*R*,*S*)-2′-C_2H_5-NOR-Nicotine	7.00	7.35	−0.35	1.49	0
10	(*R*,*S*)-*N*′-C_2H_5-Nornicotine	8.00	7.44	0.56	1.43	0
11	(*R*,*S*)-*N*′-C_3H_7-NOR-Nicotine	6.96	6.74	0.22	1.96	0
12	(*R*,*S*)-$CHMe_2$-NOR-Nicotine	6.76	6.95	−0.20	1.74	0
13	(*R*,*S*)-C_4H_9-Nornicotine	6.80	6.66	0.14	2.49	0
14	(*R*,*S*)-CH_2-C_6H_5-Nornicotine	6.77	6.99	−0.22	2.87	0
15	(*R*,*S*)-CH_2CHF_2-Nornicotine	6.82	7.36	−0.53	1.48	0
16	(*R*,*S*)-CH_2-CR_3-Nornicotine	7.00	6.62	0.38	2.19	0
17	(*R*,*S*)-$CH_2CH{=}CH_2$-Nornicotine	7.00	7.04	−0.04	1.68	0

[a] Outliers.

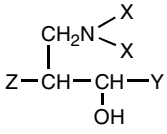
Table 40. QSAR 40: Binding to serotonin by XXIII

No.	X	Y	log K_i			Clog P	I–Y
			Obsd.	Pred.	Δ		
1	H	CH_3[a]	6.58	7.00	−0.41	2.83	0
2	CH_3	CH_3	7.14	6.92	0.22	3.32	0
3	F	CH_3	6.91	6.92	−0.01	3.14	0
4	Cl	CH_3	6.95	7.02	−0.08	3.71	0
5	Br	CH_3	7.30	7.10	0.20	3.86	0
6	OCH_3	CH_3	7.10	7.07	0.03	2.68	0
7	OH	CH_3[a]	6.84	7.48	−0.65	2.16	0
8	CN	CH_3	6.89	7.08	−0.19	2.65	0
9	$COCH_3$	CH_3	7.04	7.13	−0.09	2.57	0
10	CO_2CH_3	CH_3	6.99	6.96	0.03	2.93	0
11	$CONH_2$	CH_3	8.42	8.34	0.08	1.53	0
12	$NHCOCH_3$	CH_3	7.80	7.86	−0.07	1.84	0
13	H	C_2H_5	6.67	6.92	−0.25	3.35	0
14	CH_3	C_2H_5	7.38	7.10	0.27	3.85	0
15	F	C_2H_5	6.85	7.01	−0.16	3.67	0
16	Cl	C_2H_5	7.33	7.41	−0.08	4.24	0
17	Br	C_2H_5	7.62	7.56	0.06	4.39	0
18	OCH_3	C_2H_5	7.15	6.93	0.22	3.38	0
19	CN	C_2H_5	6.73	6.92	−0.19	3.18	0
20	H	C_3H_7	6.25	6.56	−0.31	3.88	1
21	Br	C_3H_7[a]	6.72	7.74	−1.02	4.91	1
22	OCH_3	C_3H_7	6.65	6.57	0.07	3.90	1
23	CN	C_3H_7	6.52	6.46	0.06	3.71	1
24	CO_2CH_3	C_3H_7	6.67	6.77	−0.10	4.16	1
25	$CONH_2$	C_3H_7[a]	8.33	6.56	1.77	2.59	1
26	$NHCOCH_3$	C_3H_7	6.69	6.41	0.28	2.90	1

[a] Data point not included in the equation.

Y is an indicator variable that takes the value of 1 for $Y = C_3H_7$. There are seven such examples. This was a theoretical study to better understand the receptor structure.

Equilibrium dissociation constant between [^{3}H] imipramine and human serotonin transporter of XXIV. Data from Carlier et al.[49] (Table 41)



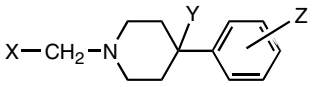
XXIV

$$\log K_D = -4.40(\pm 2.34)C\log P + 0.53(\pm 0.36)C\log P^2 - 0.52(\pm 0.36)B5 - Z + 11.70(\pm 3.53)$$
$$n = 11,\ r^2 = 0.957,\ s = 0.254,\ q^2 = 0.886$$
inversion point: 4.12 (3.71–6.0)
outlier: X = H; Y = 1,3,5-tri-C_6H_2; Z = C_6H_5

(41)

The compounds might be useful antidepressants.

Inhibition of CA+2 currents in primary rat cerebrocortical neurons by XXV. Data from Annaoura et al.[50] (Table 42)



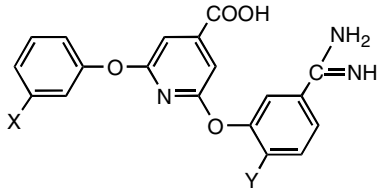
XXV

$$\log 1/C = -1.51(\pm 0.93)C\log P + 0.14(\pm 0.08)C\log P^2 + 0.42(\pm 0.16)CMR + 4.80(\pm 3.40)$$
$$n = 10,\ r^2 = 0.943,\ s = 0.076,\ q^2 = 0.778$$
inversion point: 5.46 (4.80–5.72)
outlier: X = CH = CHC_6H_5, Y = H, Z = 4-O-cy-C_5H_9; X = COC_6H_5, Y = OH, Z = 4-OC_6H_5

(42)

These compounds are calcium channel blockers with reduced affinity for dopamine D_2 receptors.

Binding affinity to inhibit the activity of Trypsin by XXVI. Data from Phillips et al.[51] (Table 43)



XXVI

Table 41. QSAR 41: Equilibrium dissociation constant between [^{3}H] imipramine and human serotonin transporter of XXIV

No.	X	Y	Z	log KD			Clog P	$B5-Z$
				Obsd.	Pred.	Δ		
1	H	C_6H_5	C_6H_5	3.48	3.27	0.21	2.07	3.11
2	H	Cy-C_6H_{11}	4-OMe-C_6H_4	1.88	1.92	−0.04	2.83	3.11
3	H	1,3,5-Tri-Me-C_6H_2	C_6H_5[a]	2.07	1.26	0.81	3.47	3.11
4	H	CMe_3	C_6H_5	3.04	3.17	−0.13	2.12	3.11
5	H	CMe_3	2-Naphthyl	0.79	0.77	0.01	3.29	4.31
6	H	C_6H_5	2-Naphthyl	0.79	0.82	−0.02	3.24	4.31
7	Me	C_6H_5	C_6H_5	1.68	1.80	−0.12	2.92	3.11
8	Me	Cy-C_6H_{11}	4-OMe-C_6H_4	1.48	1.14	0.34	3.68	3.11
9	Me	1,3,5-Tri-C_6H_2	C_6H_5	0.93	1.05	−0.12	4.31	3.11
10	Me	CMe_3	C_6H_5	1.60	1.74	−0.14	2.97	3.11
11	Me	CMe_3	2-Naphthyl	0.08	0.41	−0.33	4.14	4.31
12	Me	C_6H_5	2-Naphthyl	0.75	0.41	0.34	4.09	4.31

[a] Data point not included in the equation.

Table 42. QSAR 42: Inhibition of CA + 2 currents in primary rat cerebrocortical neurons by XXV

No.	X	Y	Z	log 1/C			Clog P	CMR
				Obsd.	Pred.	Δ		
1	CH=CHC$_6$H$_5$	H	4-OC$_6$H$_5$	6.10	6.04	7.09	0.06	11.82
2	CH=CHC$_6$H$_5$	H	4-CH$_2$-(4-F-C$_6$H$_4$)	6.22	6.23	7.20	−0.01	12.14
3	CH=CHC$_6$H$_5$	H	4-O-cy-C$_5$H$_9$[a]	5.30	5.63	6.38	−0.33	11.45
4	CH=CHC$_6$H$_5$	OH	4-OC$_6$H$_5$[a]	5.77	5.73	5.45	0.04	11.97
5	CH=CHC$_6$H$_5$	OH	4-CH$_2$-(4-F-C$_6$H$_4$)[a]	5.82	5.87	5.56	−0.05	12.30
6	CH=CHC$_6$H$_5$	OH	3-F,4-C$_6$H$_5$	5.72	5.68	5.39	0.04	11.83
7	COC$_6$H$_5$	H	4-OC$_6$H$_5$	5.49	5.57	6.30	−0.07	11.34
8	COC$_6$H$_5$	H	4-CH$_2$-(4-F-C$_6$H$_4$)	5.64	5.70	6.29	−0.06	11.66
9	COC$_6$H$_5$	H	4-O-cy-C$_5$H$_9$	5.39	5.31	5.59	0.07	10.97
10	COC$_6$H$_5$	OH	4-OC$_6$H$_5$[a]		5.65	4.55		11.49
11	COC$_6$H$_5$	OH	4-CH$_2$-(4-F-C$_6$H$_4$)	5.82	5.76	4.66	0.07	11.82
12	COC$_6$H$_5$	OH	3-F,4-C$_6$H$_5$	5.52	5.61	4.48	−0.08	11.35

[a] Data point not included in the equation.

Table 43. QSAR 43: Binding affinity to inhibit the activity of Trypsin by XXVI

No.	X	Y	log 1/C			Clog P	I
			Obsd.	Pred.	Δ		
1	(CH$_2$)$_4$CH$_3$	H	6.24	6.30	−0.05	6.11	0.00
2	(CH$_2$)$_4$CH$_3$	OH	6.28	6.18	0.11	5.30	0.00
3	CONMe$_2$[a]	H	6.14	6.49	−0.35	1.96	0.00
4	CONMe$_2$	OH	6.82	6.76	0.06	1.15	0.00
5	NMe$_2$	OH	6.12	6.01	0.11	2.85	1.00
6	Imidazol-1-Yl[a]	OH	5.92	6.32	−0.40	2.63	0.00
7	2-Me-Imidazol-1-Yl	OH	6.24	6.27	−0.04	2.89	0.00
8	4-Me-Imidazol-1-Yl[a]	OH	6.80	6.27	0.52	2.89	0.00
9	1-Me-Imidazol-2-Yl	OH	6.19	6.32	−0.14	2.63	0.00
10	1,4-Di-Me-Imidazol-2-Yl	OH	6.33	6.27	0.06	2.90	0.00
11	4,5-Di-hydro-1*H*-imidazol-2-Yl	OH	5.85	5.96	−0.10	3.19	1.00
12	4,5-Di-hydro-1-Me-imidazol-2-Yl	OH	6.66	6.73	−0.07	0.59	1.00
13	4-4-Di-Me-4,5-di-hydro-1*H*-imidazol-2-Yl	OH	5.85	5.87	−0.02	4.23	1.00
14	H$_2$NC≡CNMH$_2$	OH	6.46	6.38	0.08	1.47	1.00

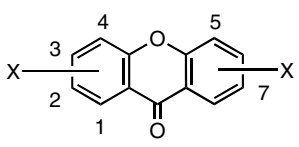
[a] Data point not included in the equation.

$$\log 1/K_i = -0.52(\pm 0.18)\mathrm{C}\log P + 0.06(\pm 0.03)\mathrm{C}\log P^2 - 0.27(\pm 0.16)I + 7.28(\pm 0.29)$$
$$n = 11,\ r^2 = 0.913,\ s = 0.104,\ q^2 = 0.770$$
inversion point: 4.44 (3.9–5.5)
outliers: CONMe$_2$, H; Imidazol-1-yl, OH; 4-CH$_3$-Imidazol-1-yl, OH

(43)

$I = 1$ for the presence of basic N. The authors were interested in developing new anticoagulants. Factor Xa plays an important role in the coagulation of blood.

Inhibition of renal cancer cells (TK-10) by XXVII. Data from Pedro et al.[52] (Table 44)



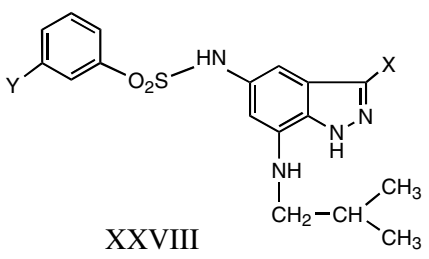
XXVII

$$\log 1/C = -4.53(\pm 1.52)\mathrm{C}\log P + 0.85(\pm 0.28)\mathrm{C}\log P^2 + 0.21(\pm 0.11)I + 0.56(\pm 0.13)I_1 + 9.85(\pm 2.0)$$
$$n = 17,\ r^2 = 0.902,\ s = 0.081,\ q^2 = 0.710$$
inversion point: 2.65 (2.58–2.72)
outliers: 1-OH; 4-OH; 3,5-di-OH; 3-OCH$_3$, 4-OH

(44)

Indicator variable $I = 1$ for only dihydroxy compounds; $I_1 = 1$ for the presence of one hydroxy and one methoxy in the molecule. Xanthones have been used in many cancer studies. They also have value as anti-inflammatory drugs.

Binding affinity of XXVIII to s-adenosyl homocysteine/methylthioadenosine nucleosidase. Data from Li et al.[53] (Table 45)



XXVIII

Table 44. QSAR 44: Inhibition of renal cancer cells (TK-10) by XXVII

No.	X	log1/C			Clog P	I	I_1
		Obsd.	Pred.	Δ			
1	1-OH[a]	4.16	4.63	−0.47	3.61	0	0
2	3-OH	3.90	3.85	0.05	2.71	0	0
3	4-OH[a]	4.27	3.85	0.42	2.71	0	0
4	1-OCH_3	3.97	4.01	−0.03	3.08	0	0
5	2-OCH_3	3.93	4.01	−0.08	3.08	0	0
6	3-OCH_3	4.03	4.01	0.02	3.08	0	0
7	1,2-Di-OH	4.18	4.20	−0.02	3.06	1	0
8	1,7-Di-OH	4.22	4.20	0.02	3.06	1	0
9	2,3-Di-OH	4.21	4.22	−0.01	2.23	1	0
10	3,4-Di-OH	4.23	4.22	0.01	2.23	1	0
11	3,5-Di-OH[a]	3.99	4.27	−0.28	2.16	1	0
12	2,3-Di-OCH_3	3.76	3.86	−0.10	2.77	0	0
13	3,4-Di-OCH_3	3.89	3.86	0.02	2.77	0	0
14	1-OCH_3,2-OH	4.45	4.44	0.02	2.49	0	1
15	3-OH,5-OCH_3	4.30	4.42	−0.11	2.70	0	1
16	3-OCH_3,4-OH[a]	4.14	4.44	−0.30	2.49	0	1
17	3-OCH_3,5-OH	4.51	4.42	0.09	2.70	0	1
18	2-CH_3-1,3-Di-OH	4.46	4.40	0.06	3.46	0	0
19	2,3-Di-OH-4-OCH_3	4.12	4.22	−0.10	2.00	0	0
20	1-CHO,4-OH,3-OCH_3	4.14	4.00	0.14	2.24	0	0
21	2-CHO,3-OH,4-OCH_3	3.89	3.85	0.04	2.61	0	0

[a] Data point not included in the equation.

Table 45. QSAR 45: Binding affinity of XXVIII to s-adenosyl homocysteine/methylthioadenosine nucleosidase

No.	X	Y	log 1/C			Clog P	I
			Obsd.	Pred.	Δ		
1	Cl	C_6H_3-3-Cl,4-F	8.47	8.16	0.30	7.46	1.0
2	Cl	C_6H_4-4-Cl	7.90	8.07	−0.17	7.31	1.0
3	Cl	C_6H_3-3,4-Di-Cl	8.80	8.49	0.30	7.91	1.0
4	Cl	C_6H_3-3,4-Di-F	8.09	7.81	0.29	6.82	1.0
5	Cl	3-Quinolinyl	7.97	7.70	0.27	6.54	1.0
6	Cl	2-CH_3-Pyrimidin-6-Yl	7.44	7.48	−0.04	4.95	1.0
7	CH_3	2-CH_3-Pyrimidin-6-Yl	6.72	6.66	0.06	4.35	0.0
8	Cl	4-C_6H_3N-3-CH_3	7.55	7.48	0.06	5.68	1.0
9	Cl	4-Pyridyl	7.28	7.46	−0.18	5.18	1.0
10	CH_3	4-Pyridyl	6.62	6.60	0.02	4.59	0.0
11	Cl	C_6H_3-3-CH_3, 4-Cl	8.41	8.42	−0.01	7.81	1.0
12	Cl	C_6H_4-3-CF_3	7.96	8.18	−0.23	7.49	1.0
13	CH_3	C_6H_4-3-CF_3[a]	7.70	6.91	0.79	6.92	0.0
14	Cl	C_6H_3-3-CH_3-4-F	7.84	8.03	−0.19	7.24	1.0
15	Cl	C_6H_4-4-CF_3	7.89	8.18	−0.30	7.49	1.0
16	Cl	C_6H_4-3-SCH_3	7.77	7.98	−0.22	7.17	1.0
17	Cl	C_6H_4-3-CH_3[a]	7.44	7.94	−0.50	7.09	1.0
18	CH_3	C_6H_4-3-CH_3	7.00	6.73	0.27	6.50	0.0
19	Cl	C_6H_5[a]	7.03	7.71	−0.68	6.59	1.0
20	CH_3	C_6H_5	6.30	6.59	−0.28	6.00	0.0
21	Cl	C_6H_4-3-CH_2CH_2OH	7.60	7.49	0.11	5.78	1.0
22	CH_3	C_6H_4-3-CH_2CH_3	6.90	6.96	−0.06	7.03	0.0

[a] Data point not included in the equation.

$$\log 1/C = -1.64(\pm 1.40)\mathrm{C}\log P + 0.15(\pm 0.11)\mathrm{C}\log P^2 + 0.94(\pm 0.29)I + 10.89(\pm 4.24)$$

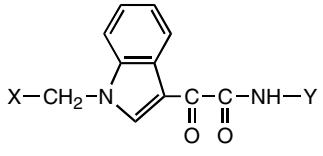
$n = 19,\ r^2 = 0.900,\ s = 0.231,\ q^2 = 0.846$

inversion point: 5.33 (2.84–5.80)

outliers: X = CH_3, Y = C_6H_4-3-CF_3;
X = Cl, Y = C_6H_4-3-CH_3;
X = Cl, Y = C_6H_5

(45)

The authors were seeking new antibacterial agents SAH/MTA occurs in many bacteria and hence is a good target.



XXIX

Inhibition of human breast cancer cells (MCF-7) by XXIX. Data from Li et al.[54] (Table 46)

$$\log 1/C = -5.94(\pm 3.62)\mathrm{C}\log P + 0.64(\pm 0.49)\mathrm{C}\log P^2 + 0.57(\pm 0.28)\mathrm{CMR} + 12.85(\pm 7.81)$$

$n = 12,\ r^2 = 0.889,\ s = 0.216,\ q^2 = 0.785$

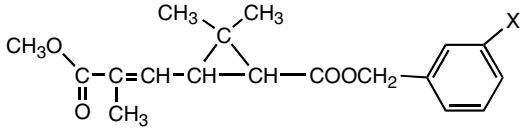
inversion point: 4.61 (4.16–7.53)

outliers: X = Thiophen-3-yl, Y = 3-Me-isothiazol-5-yl; X = isoxazol-5-yl, Y = 3-Me-isothiazol-5-yl; X = thiazol-4-yl, Y = 6-quinolinyl

(46)

An attempt to find better anticancer drugs.

MLD for American cockroaches of XXX. Data from Nishimura et al.[55] (Table 47)



XXX

$$\log 1/C = -1.63(\pm 1.3)\mathrm{C}\log P + 0.20(\pm 0.15)\mathrm{C}\log P^2 + 0.25(\pm 0.13)B5\text{-}3 + 9.77(\pm 3.0)$$

$n = 17,\ r^2 = 0.866,\ s = 0.271,\ q^2 = 0.740$

inversion point: 3.98 (2.65–4.42)

outliers: $CH_2C_6H_5$

(47)

*B*5-3 is the sterimol parameter for the width of a substituent. After World War II there was a terrible epidemic of cockroaches in Japan. A large effort was made to find suitable pesticides. This is another allosteric reaction on cockroaches.

Inhibition of TNF-alpha production in human peripheral blood mononuclear cells by XXXI. Data from Tobe et al.[56] (Table 48)

$$\log 1/C = -4.73(\pm 1.88)\mathrm{C}\log P + 0.65(\pm 0.28)\mathrm{C}\log P^2 - 1.26(\pm 0.18)\sigma_4^+ + 14.80(\pm 3.16)$$

$n = 10,\ r^2 = 0.987,\ s = 0.048,\ q^2 = 0.936$

inversion point: 3.62 (3.52–3.83)

outlier: $R_1 = H,\ R_2 = H,\ R_3 = H$

(48)

Table 47. QSAR 47: MLD for American cockroaches of XXX

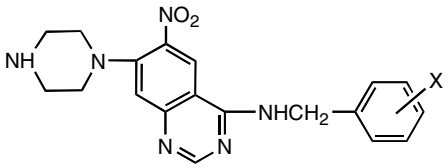
No.	X	log 1/*C*			Clog *P*	*B*5-3
		Obsd.	Pred.	Δ		
1	H	7.11	6.80	0.31	4.24	1.00
2	F	7.28	6.91	0.37	4.39	1.35
3	Cl	6.92	7.18	−0.26	4.96	1.80
4	Br	7.06	7.29	−0.23	5.11	1.95
5	I	7.56	7.47	0.09	5.37	2.15
6	Me	7.03	7.17	−0.14	4.74	2.04
7	Et	7.29	7.68	−0.39	5.27	3.17
8	CH_2PH[a]	8.57	9.17	−0.60	6.31	6.02
9	CH_2OPH	7.92	8.20	−0.28	5.93	3.53
10	OMe	7.23	7.32	−0.09	4.16	3.07
11	OEt	7.35	7.49	−0.14	4.69	3.36
12	OPr(I)	8.11	7.79	0.32	5.00	4.10
13	OPH	9.35	9.17	0.18	6.34	5.89
14	OCH_2PH	8.48	8.20	0.28	5.93	3.50
15	COPH	8.34	8.40	−0.06	5.28	5.98
16	NO_2	7.40	7.15	0.25	3.99	2.44
17	CN	6.82	6.96	−0.14	3.68	1.60
18	SO_2Me	7.63	7.73	−0.10	2.60	3.17

[a] Data point not included in the equation.

Table 46. QSAR 46: Inhibition of human breast cancer cells (MCF-7) by XXIX

No.	X	Y	log 1/*C*			Clog *P*	CMR
			Obsd.	Pred.	Δ		
1	Furan-3-yl	3-Me-Isothiazol-5-yl	6.02	5.66	0.36	3.40	9.94
2	Thiophen-3-yl	3-Me-Isothiazol-5-yl[a]	6.02	5.45	0.57	3.90	10.53
3	Thiophen-2-yl	3-Me-Isothiazol-5-yl	5.17	5.45	−0.29	3.90	10.53
4	2-Furyl	3-Me-Isothiazol-5-yl	5.44	5.66	−0.21	3.40	9.94
5	Isoxazol-5-yl	3-Me-Isothiazol-5-yl[a]	5.58	8.21	−2.63	2.20	9.72
6	3-Me-Isoxazol-5-yl	3-Me-Isothiazol-5-yl	7.14	7.14	0.00	2.70	10.19
7	3-CH_2CH_3-Isoxazol-5-yl	3-Me-Isothiazol-5-yl	6.20	6.33	−0.13	3.30	10.65
8	3-$CHMe_2$-Isoxazol-5-yl	3-Me-Isothiazol-5-yl	6.08	6.03	0.05	3.70	11.12
9	3-C_6H_5-Isoxazol-5-yl	3-Me-Isothiazol-5-yl	6.02	6.18	−0.15	4.30	12.24
10	4-CN-C_6H_4	3-Me-Isothiazol-5-yl	6.22	6.05	0.17	3.70	11.20
11	Furan-2-yl	6-Quinolinyl	5.90	5.78	0.12	4.10	11.35
12	Thiophen-2-yl	6-Quinolinyl	5.92	5.98	−0.06	4.60	11.95
13	Thiazol-4-yl	6-Quinolinyl[a]	5.51	6.96	−1.45	3.30	11.73
14	Thiophen-3-yl	6-Quinolinyl	6.13	5.98	0.16	4.60	11.95
15	3-Me-Isoxazol-5-yl	6-Quinolinyl	7.04	7.05	−0.02	3.20	11.60

[a] Data point not included in the equation.



XXXI

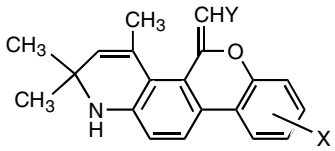
Table 48. QSAR 48: Inhibition of TNF-alpha production inhuman peripheral blood mononuclear cells by XXXI

No.	X	log1/*C*			Clog *P*	σ_4^+
		Obsd.	Pred.	Δ		
1	4-Cl	6.15	6.15	0.00	3.86	0.11
2	2-F	6.30	6.32	−0.02	3.29	0.00
3	3-F	6.40	6.32	0.08	3.29	0.00
4	4-F	6.40	6.41	−0.01	3.29	−0.07
5	2,4-Di-F	6.30	6.36	−0.06	3.44	−0.07
6	2,4-Di-F	6.40	6.38	0.02	3.37	−0.07
7	H[a]	6.05	6.39	−0.35	3.15	0.00
8	4-CF_3	5.62	5.60	0.02	4.03	0.61
9	4-NO_2	5.62	5.60	0.02	2.89	0.79
10	4-CN	6.10	6.12	−0.02	2.58	0.66
11	4-$COOC_6H_5$	5.60	5.65	−0.05	3.65	0.48

[a] Data point not included in the equation.

Tumor necrosis factor (TNF) plays an important role in the protective immune response of the host versus bacterial and viral infections. On the other hand, it is associated with arthritis and septic shock. σ^+ is often important in radical reactions.

Binding to human progesterone receptor by XXXII. Data from Zhi et al.[57] (Table 49)



XXXII

$$\log 1/K_i = -12.55(\pm 5.9)\mathrm{C}\log P + 0.70(\pm 0.35)\mathrm{C}\log P^2 - 1.94(\pm 0.44)\sigma_Y^- + 64.64(\pm 25.0)$$

$$n = 18,\ r^2 = 0.875,\ s = 0.236,\ q^2 = 0.770$$

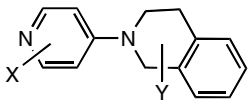
inversion point: 8.96 (8.75–9.46)

outliers: X = 9-F, Y = 2-OMe-C_6H_4;
X = 9-F, Y = 2-SMe-C_6H_4

(49)

The role of σ^- is not clear, but it does imply the importance of increasing the electron density on the phenyl ring. These compounds might have some value in inhibiting cancer.

*Binding to N-methyl-*D*-aspartate receptor of XXXIII*. Data from Buttelmann et al.[58] (Table 50)



XXXIII

Table 49. QSAR 49: Binding to human progesterone receptor by XXXII

No.	X	Y	log 1/K_i			Clog *P*	σ_Y^-
			Obsd.	Pred.	Δ		
1	H	2-Me-C_6H_4	9.18	9.19	−0.01	8.15	−0.17
2	7-F	C_6H_5	9.21	9.15	0.07	7.93	0.00
3	7-F	3-F-C_6H_4	8.26	8.31	−0.04	8.07	0.34
4	7-F	4-F-C_6H4	9.15	9.02	0.13	8.07	−0.03
5	7-F	2-Me-C_6H_4	8.82	8.93	−0.11	8.43	−0.17
6	9-F	C_6H_5	9.21	9.15	0.06	7.93	0.00
7	9-F	2-Me-C_6H_4	9.26	8.93	0.33	8.43	−0.17
8	9-F	2-CH_2CH_3-C_6H_4	8.64	8.78	−0.14	8.96	−0.19
9	9-F	2-$(CH_2)_2CH_3$-C_6H_4	8.80	8.72	0.08	9.49	−0.06
10	9-F	2-$CHMe_2$-C_6H_4	8.72	8.83	−0.11	9.36	−0.16
11	9-F	2-OMe-C_6H_4[a]	8.42	9.78	−1.36	7.85	−0.26
12	9-F	2-SMe-C_6H_4[a]	9.23	8.44	0.78	8.49	0.06
13	9-F	F-C_6H_4	9.21	9.02	0.19	8.07	−0.03
14	9-F	2-Cl-C_6H_4	7.65	8.11	−0.46	8.64	0.19
15	9-F	2-Br-C_6H_4	7.79	7.94	−0.15	8.79	0.25
16	9-F	2-CN-C_6H_4	7.94	8.25	−0.31	7.36	1.00
17	9-F	2-CHO-C_6H_4	8.59	8.37	0.21	7.28	1.03
18	9-F	2-OCF_3-C_6H_4	8.19	7.88	0.31	8.96	0.27
19	9-F	2-NMe_2-C_6H_4	8.92	9.16	−0.24	8.09	−0.12
20	9-F	2-CF_3-C_6H_4	7.34	7.16	0.18	8.81	0.65

[a] Data point not included in the equation.

Table 50. QSAR 50: Binding to *N*-methyl-D-aspartate receptor of XXXIII

No.	X	Y	$\log 1/K_i$			Clog *P*	I
			Obsd.	Pred.	Δ		
1	H	H	8.10	8.04	0.05	2.69	0
2	H	1-CH_3(rac)	5.25	5.79	−0.54	3.21	1
3	H	4-CH_3(rac)[a]	7.60	5.79	1.81	3.21	1
4	H	5-Cl	8.10	7.37	0.73	3.41	1
5	H	6-Cl	6.64	7.37	−0.73	3.41	1
6	H	7-Cl	7.43	7.37	0.06	3.41	1
7	H	8-Cl	7.59	7.37	0.22	3.41	1
8	H	6,7-Di-OCH_3	4.55	4.28	0.27	2.35	1
9	6′-CH_3,2′-$NHCH_2CH_2OH$	H	8.70	8.44	0.26	2.90	0
10	2′-CH_3	H[a]	8.10	9.89	−1.79	3.19	0
11	2′-NH_2	H	8.70	8.46	0.24	2.37	0
12	2′NH_2,6′-CH_3	H	8.40	8.34	0.06	2.86	0
13	6′-CH_3,2′-$NHCOCOOC_2H_5$	H	8.10	8.09	0.01	2.53	0
14	2′-$NHCOCH_2OH$,6′-CH_3	H	7.82	8.44	−0.61	2.37	0

[a] Data point not included in the equation.

$$\log 1/K_i = -31.82(\pm 22.9)C\log P + 6.04(\pm 4.1)C\log P^2 - 4.23(\pm 1.2)I + 50.0(\pm 32)$$
$$n = 12,\ r^2 = 0.897,\ s = 0.498,\ q^2 = 0.625$$
$$\text{inversion point: } 2.64\ (2.23\text{–}2.74)$$
$$\text{outliers: } X = H,\ Y = 4\text{-}CH_3(rac);\ X = 2'\text{-}CH_3,\ Y = H \quad (50)$$

$I = 1$ for the presence of any substituent in Y. Overactivity of the *N*-methyl-D-asparate receptor can play a role in a variety of neurodegenerative disorders, therefore it is important to be able to control this reaction.

4. Summary

It is of interest to note that 33 out of 50 sets are for work done in the 21st century. This could be due to two possible factors, more complicated receptors and less work with very simple compounds. Ten QSAR came from studies on cancer cells of various kinds. This might suggest that cancer cells are more susceptible to allosteric reactions. We have 220 QSAR from studies with cancer cells.

Understanding allosteric reactions can be very helpful in drug development. Until one understands the inverted parabolic relationship, it could be difficult to see which congener to make next. It is rather surprising to find two examples with mice in which the chemicals are able to find receptors without being influenced by the many other possible hydrophobic interactions. We have 320 QSAR on mice that contain log *P* terms.

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