Comparative QSAR: Angiotensin II Antagonists

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I. Introduction

The use of quantitative structure−activity relationships (QSAR) since their advent in 1962[1] has become increasingly helpful in understanding many aspects of chemical−biological interactions in drug and pesticide research as well as many areas of toxicology. With a properly designed set of congeners, carefully tested in almost any biological system, it has become easy to derive a QSAR by a steadily increasing number of computerized approaches. Getting a new QSAR no longer calls for rushing into print. What is called for is support for it from as many points of view as possible. In fact, there are so many fancy new programs that almost any set of chemicals acting on a given system can be correlated mathematically. Some wit has remarked that if you cannot derive a correlation equation it is a bad reflection on your library since there seems to be an almost unlimited selection of parameters. The real problem is to deduce when the result can be related to our general knowledge of chemistry and biology. For work in progress, one can test new molecules to check the equation, but for most published work, this is not possible. We are finding that lateral support is possible in a variety of ways.[2−10] From the beginning to present day, luck has played a major role in drug discovery.[11] This is illustrated by gross examples such as Viagra, designed as a heart drug, that is making billions selling for erectile dysfunction. Thalidomide developed as a sedative was a disaster causing terrible teratogenic problems. Today it is a promising drug in the treatment of leprosy. Diethylstilbestrol developed to prevent miscarriage by pregnant women caused cancer in their daughters. Finally, we know one of the best antitumor drugs of the 20th century (cisplatin) came from a physicist studying the growth of bacteria in an electric field! We need to make the best possible use of all that has been done in chemical−biological interactions to anticipate as many potential problems as possible.

The new subject of information science that depends so heavily on computers is in a rapid state of development with departments forming in many universities. We have been working on its development in chemical−biological reactions for some 30 years. We must be able to organize our experience so that we can readily keep track of what has happened in a given area and profit by it. Countless thousands of chemical−biological interaction studies have been made in the past century and are being made at an ever-increasing rate, but the vast majority of these reports say essentially the following: here are the structures and here are the activities and leave it to the reader to figure out what is happening.

Of course, to make a start on the problem one needs a common language.[5,12a] We still find Hammett constants to be the most helpful to account for electronic variation in the data and octanol/water partition coefficients for hydrophobic interactions. For steric problems, the sterimol parameters of Verloop and Tipker are very helpful for local steric effects. Now we have a good start on an information database that contains 15 600 QSAR of which 7300 pertain to chemical−biological interactions while the remainder are for pure chemical reactions for comparison. The database can be searched in thousands of different ways.[13] In the present report, we review nonpeptide angiotensin antagonists.

The vasoactive hormone angiotensin II produced by the renin−angiotensin system (RAS) plays an integral role in the pathophysiology of hypertension because it effects the regulation of fluid volume, electrolyte balance, and blood volume in mammals.[14,15] Renin is a proteolytic enzyme produced mainly in the juxtaglomerular apparatus of the kidney, which acts on the circulating α-globulin angiotensinogen produced by the liver (Figure 1).[16]

This enzymatic reaction results in the formation of angiotensin I (Ang I, a decapeptide) that has very little biological activity. Angiotensin-converting enzyme (ACE) then converts Ang I into physiologically active angiotensin II (Ang II), which is an octapep-

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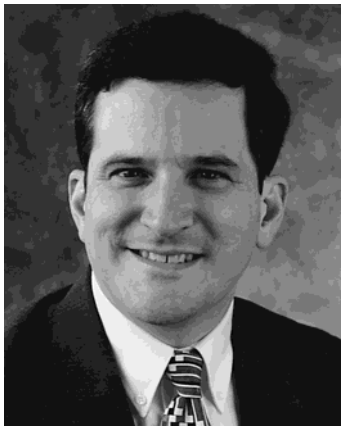
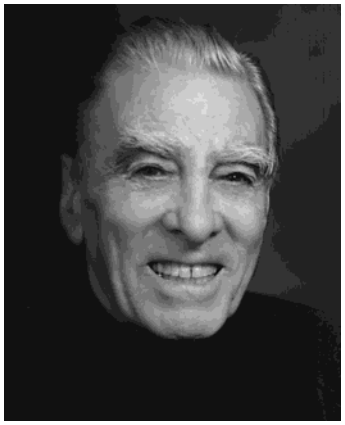
Alka Kurup received her undergraduate degree in Pharmacy in 1981 from Birla Institute of Technology and Science in Pilani, India. In 1988, she received her Masters degree from the College of Pharmacy in Manipal, India. For two years she assumed Inchargeship and Quality Control of the Pharmacy Manufacturing Wing at Kasturba Medical College in Manipal. In 1991, she joined Birla Institute of Technology and Science as a faculty member in the Department of Pharmacy. She completed her Ph.D. degree in 1997 under the supervision of Professor S. P. Gupta with her thesis regarding QSAR studies of anticancer drugs. She joined Professor Hansch's group in July 1998 to pursue postdoctoral research. Currently, she is involved in building the C-QSAR database. Her research interests include QSAR and computer-aided drug design.

Rajni Garg received her M.Sc. degree in Chemistry (1984) from Meerut University and M.Phil. (1988) degree from Delhi University, India. Her M.Phil. dissertation work was on peptide synthesis. She was a faculty member in the Chemistry Department of Birla Institute of Technology and Science, Pilani, India, from 1991 to 1996, where she taught organic and physical chemistry. She received her Ph.D. degree in 1996 under the supervision of Professor S. P. Gupta. Her doctoral work was on QSAR studies on anti-HIV agents. In February 1997, she joined Professor Corwin Hansch as a postdoctoral researcher, and she is currently involved in building a C-QSAR databank. Her research interests include QSAR and computer-assisted drug design.



Graduating with his B. S. in chemistry from R. P. I. in Troy, New York, in 1978, Dr. David J. Carini completed his Ph. D. degree in Organic Chemistry with Prof. Rick Danheiser at M. I. T. in 1982. His thesis was on the use of (trimethylsilyl)allenes in organic synthesis. In 1982 Dr. Carini joined Dupont as a medicinal chemist in drug discovery. He has work in the areas of cardiovascular diseases, cancer, and infectious diseases. Dr. Carini was part of the team at Dupont that discovered the first orally active angiotensin II antagonists for the treatment of hypertension. In 1997 he shared the American Chemical Society's Award for Team Innovation for his work on the angiotensin II antagonists.



Corwin Hansch received his undergraduate education at the University of Illinois and his Ph.D. degree in Organic Chemistry from New York University in 1944. After working with the DuPont Company, first on the Manhattan Project and then in Wilmington, DE, he joined the Pomona College faculty in 1946. He has remained at Pomona except for two sabbaticals: one at the Federal Institute of Technology in Zurich with Professor Prelog and the other at the University of Munich with Professor Huisgen. The Pomona group published the first paper on the QSAR approach relating chemical structure with biological activity in 1962. Since then, QSAR has received widespread attention. Dr. Hansch is an honorary fellow of the Royal Society of Chemistry and recently received the ACS Award for Computers in Chemical and Pharmaceutical Research for 1999.

tide. This is a potent vasoconstrictor agent. It also causes sympathetic activation and aldosterone secretion from adrenal glands. All of these actions contribute to the development of hypertension.[17−19] Interruption of the RAS has been shown to be an effective means for controlling hypertension in humans as evidenced by the commercially successful ACE inhibitors[20] Captopril[21] and Enalpril.[22] The antihypertensive action of these drugs is due to the decrease in plasma concentration of Ang II. However, angiotensin is not the only biologically important substrate for this enzyme. Studies of Erodes[23] and others have clearly demonstrated that ACE is identical to kinase II, one of the important enzymes involved in the inactivation of bradykinin (an inflammatory peptide), the final mediator of the kallikrein−kinin system (Figure 1). Hence, more of the major side effects associated with the clinical use of ACE inhibitors such as dry cough and rashes may be due to bradykinin potentiation.[24] Therefore, a need for more specific means of blocking the effects of Ang II arose.

Research in this area was sparked by patents of Takeda Chemical Industries in Japan in 1982.[25] At about the same time, DuPont began work on such an antagonist. This led to the discovery of the first important drug, Losartan, in 1986[26,27] that was very

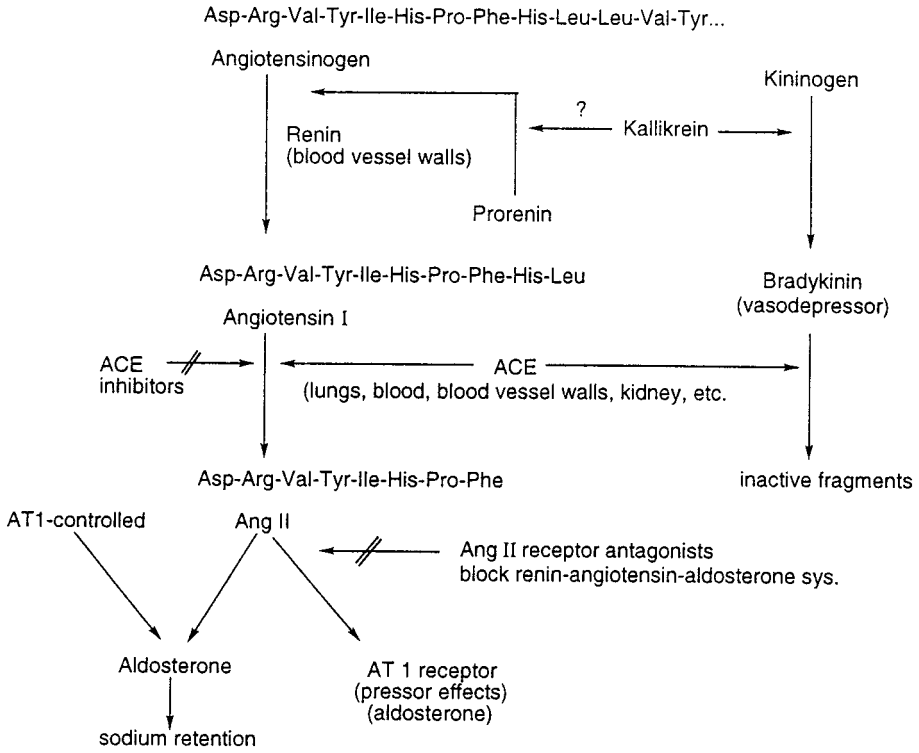
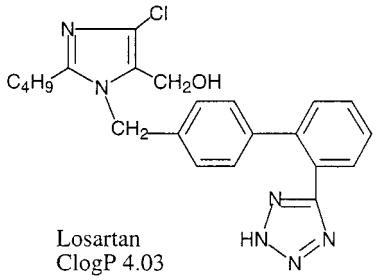


Figure 1. Stimulation of aldosterone secretion is another property of Ang II controlled through the AT1 receptor subtype.

successful in reducing blood pressure in patients suffering from hypertension.



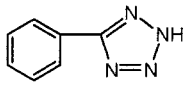
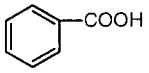
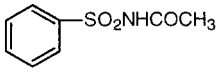
Losartan
ClogP 4.03

This drug functions by antagonizing the octapeptide hormone angiotensin II (Ang II).

Losarton has had a profound influence on the research for angiotensin antagonists as can be seen from the 39 QSAR in this report. Of these, all but three contain the central hydrophobic biphenyl unit. Carini et al.[28] listed many of the compounds that have been tested. A universal feature is an acidic moiety: tetrazole ring, −COOH, or $-SO_2NHCO-$. The pK_as of these vary considerably, see Chart 1.

The receptor site is a complex transmembrane unit for angiotensin II (AT I) that belongs to the superfamily of the seven transmembrane-domain receptors coupled with G-protein and the classic second messenger system. No doubt, it contains a variety of hydrophobic and hydrophilic regions. There is evidence that the ionic form of the acidic function of the inhibitor reacts with the positively charged Lys 199 residue in concert with His 256.[29] It suggests that acid isosteres that are significantly ionized at physiological pH should have higher affinity for the receptor. As noted above, the tetrazole moiety would be the most ionized of the three commonly employed.

Chart 1

acidic moiety	pKa	measured logP for unionized form
	2.3[a]	1.64
	4.2[b]	1.87
	4.7[c]	0.01 (calculated)

[a] taken from ref. 65a,[b] taken from ref. 65b,[c] taken from ref. 65c

II. Methods and Materials

The octanol/water Clog *P* values used as an assessment of hydrophobic effects are calculated values.[12c] π is the hydrophobic parameter for substituents usually measured for substituents attached to benzene. CMR is the calculated molar refractivity of the whole molecule; it is similar to molar volume but contains a small element for polarizability. Molar refractivity needs special consideration since CMR or MR appears in so many of the QSAR. It is defined as follows: $MR = (n^2 - 1)/(n^2 + 2)(MW/d)$. n is the refractive index and is a measure of the electron polarizability. MW stands for molecular weight, and d represents density. Since there is often little variation in n, MR is largely a measure of molar volume. Nevertheless, we have generally found that the MR or the calculated CMR gives better results than molar volume as calculated. Molar refractivity was first employed for biological correlation analysis by Pauling and Pressman[12d] and then extended by Agin et al.[12e] More recently we have discussed its

Table 1. I_{50} Data of Analogs of I for Rabbit Aorta[31]

		log 1/*C*						
no.	substituents	obsd	calcd (eq 1)	Δ	CMR	$B1_3$	$B1_4$	Clog P[b]
1	2-CF_3 [a]	9.96	−18.85	28.81	17.02	1.0	1.0	9.64
2	2-CF_3,4-NO_2	8.80	8.79	0.01	17.63	1.0	1.70	9.41
3	2-CF_3,4-NH_2	9.25	8.97	0.28	17.38	1.0	1.35	8.88
4	2-CF_3,4-$NHCOC_2H_5$	9.38	9.27	0.11	18.81	1.0	1.55	9.62
5	2-CF_3,4-$NHCH_2C_6H_5$	9.43	9.29	0.14	20.36	1.0	1.35	11.09
6	2-Cl,4-$CO_2C_2H_5$	8.85	9.18	−0.33	18.58	1.0	1.64	9.03
7	2-Cl,5-NO_2	9.39	9.54	−0.15	17.61	1.0	1.0	8.52
8	2-Cl,5-NH_2	9.25	9.33	−0.07	17.37	1.0	1.0	7.77
9	2-Cl,5-NHCOMe	10.28	9.85	0.43	18.33	1.0	1.0	7.03
10	2-Cl,5-$NHCOC_2H_5$	9.77	9.87	−0.10	18.79	1.0	1.0	7.25
11	2-Cl,5-NHC_3H_7 [a]	9.00	−19.14	28.14	18.76	1.0	1.0	7.78
12	2-Cl,5-NHCO-cy-C_3H_5	10.10	9.85	0.25	19.12	1.0	1.0	8.84
13	2-Cl,5-$NHCOCHMe_2$	9.75	9.83	−0.09	19.26	1.0	1.0	7.61
14	2-Cl,5-$NHCOC_3H_7$	9.96	9.83	0.13	19.26	1.0	1.0	8.09
15	2-Cl,5-$NHCOC_4H_9$	9.80	9.77	0.03	19.72	1.0	1.0	8.31
16	2-Cl,5-$NHCOCH_2CHMe_2$	9.96	9.77	0.19	19.72	1.0	1.0	8.84
17	2-Cl,5-$NHCOCMe_3$	9.80	9.77	0.03	19.72	1.0	1.0	8.71
18	2-Cl,5-$NHCOCH_2CMe_3$	9.68	9.70	−0.02	20.18	1.0	1.0	8.49
19	2-Cl,5-$NHCH_2C_6H_5$	9.52	9.67	−0.15	20.34	1.0	1.0	9.11
20	2-Cl,5-$NHCOC_6H_5$	9.39	9.67	−0.28	20.38	1.0	1.0	9.23
21	2-Cl,5-$NHCOCH_2C_6H_5$	9.92	9.59	0.33	20.84	1.0	1.0	8.74
22	2-Cl,5-$NHCO(CH_2)_2C_6H_5$	9.60	9.52	0.09	21.30	1.0	1.0	8.79
23	2-Cl,5-$NHCO_2C_3H_7$	9.59	9.81	−0.23	19.41	1.0	1.0	9.35
24	2-Cl,5-$NHCONHC_3H_7$	9.85	9.78	0.07	19.63	1.0	1.0	8.71
25	2-Cl,5-CO_2Me	9.60	9.80	−0.20	18.11	1.0	1.0	8.30
26	2-Cl,5-$CONHC_4H_9$	9.85	9.77	0.09	19.72	1.0	1.0	7.99
27	2-Cl,5-CON(Me)C_4H_9	9.20	9.70	−0.50	20.18	1.0	1.0	8.50
28	3-NO_2	7.51	7.76	−0.25	17.12	1.70	1.0	8.14
29	3-NH_2	8.24	8.12	0.12	16.87	1.35	1.0	7.05
30	3-$NHCOC_2H_5$	9.07	8.82	0.25	18.30	1.55	1.0	6.03
31	2-CF_3,5-$NHCOC_2H_5$	9.68	9.87	−0.19	18.81	1.0	1.0	6.80

[a] Data points not included in deriving equation. [b] Not included in the equation.

advantages and disadvantages.[12] B1, B5, and L are the sterimol parameters. B1 is primarily a width measurement of the first atom of a substituent. B5 is crude bulk measurement of the substituent, and L is the length of the substituent.[12a] The Hammett parameters for the electronic effect of substituents σ, σ^-, σ^+, σ^*, and σ_I have been discussed.[12a] The indicator variables *I* are assigned the value of 1 or 0 for special features with special effects that cannot be parametrized and has been explained wherever used. All of these parameters have been discussed and applications shown.[12a] For the reader interested in extensive discussion on parameters, see ref 12b.

The QSAR have been divided into four groups according to the test system: rabbit, rat, guinea pig, and human. Within each group these are arranged in order of decreasing potency (log 1/*C*) characterized by the range in log 1/*C*. However, it must be borne in mind that different quality of testing in the various laboratories will have an effect that cannot be estimated. First place is given by the largest log 1/*C* with the widest range. Also listed is the largest CMR value for each set. In general, positive hydrophobic effects characterized by Clog *P* are not important. Where log *P* is important, it is usually characterizing substitution at a single position. We have tested π for substituents at each position in attempts to ferret out local hydrophobic binding sites. One might conclude that since the biphenyl moiety is often present, this implies the presence of a hydrophobic site. This could be wrong. It could be a volume effect such as that represented by CMR. However, without variation in the hydrophobic character in this unit, no conclusion can be made on hydrophobicity.

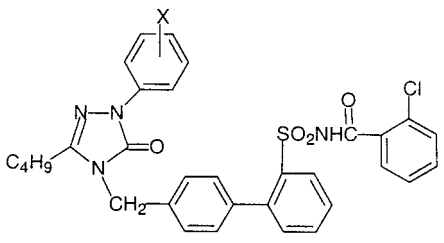
The inhibitory activities have been collected from the literature (see individual data for detailed references). All the QSAR reported in this study are derived by us and are not given in the original references. The physicochemical parameters are autoloaded from our C-QSAR database, and the QSAR regression analysis was executed with the C-QSAR program. The utility of the QSAR program in correlation analysis has been discussed.[6,13]

III. Results and Discussions

A. Rabbit Angiotensin Antagonists

The most popular test system has been the rabbit aorta ring. The following QSAR have been arranged according to the decreasing log 1/*C* range.

I_{50} rabbit aorta (Table 1)[31]



I

$$\log 1/C = 1.48(\pm0.64)\mathrm{CMR} - 1.64(\pm0.73)\log(\beta \times 10^{\mathrm{CMR}} + 1) - 1.85(\pm0.68)\mathrm{B1}_3 - 1.08(\pm0.48)\mathrm{B1}_4 - 13.2(\pm11.4) \quad (1)$$

$n = 29$, $r^2 = 0.856$, $s = 0.239$, $q^2 = 0.808$, log $1/C = 7.5-10.3$

opt. CMR = 18.6(±0.5)

highest CMR = 20.8

r^2 Clog P Vs CMR = 0.205

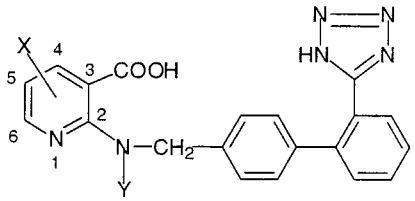
outliers: 2-CF_3; 2-Cl, 5-NHC_3H_7

Table 2. I_{50} Data of Analogs of II in Rabbit Aorta[32]

	substituents		log 1/C					
				calcd				Clog
no.	X	Y	obsd	(eq 2)	Δ	MR_6	$B5_5$	P^b
1	H	C_3H_7	10.10	9.60	0.50	0.10	1.0	5.12
2	4-Me	C_3H_7	9.64	9.60	0.04	0.10	1.0	5.32
3	5-Me	C_3H_7	8.80	8.81	−0.01	0.10	2.04	5.62
4	5-Cl	C_3H_7	9.07	9.00	0.08	0.10	1.80	5.87
5	5-F	C_3H_7	9.04	9.34	−0.30	0.10	1.35	5.30
6	5-I	C_4H_9	8.38	8.73	−0.35	0.10	2.15	6.81
7	5-C_6H_5	C_3H_7 [a]	8.91	8.00	0.91	0.10	3.11	7.01
8	5-NO_2	C_3H_7	8.33	8.51	−0.18	0.10	2.44	4.97
9	5-NH_2	C_3H_7 [a]	7.60	8.87	−1.27	0.10	1.97	4.84
10	5-NHCOMe	C_3H_7	7.90	7.63	0.28	0.10	3.61	5.00
11	6-Me	C_4H_9	8.15	8.30	−0.15	0.57	1.0	6.15
12	6-F	C_3H_7	9.63	9.63	0.0	0.09	1.0	5.30
13	6-OMe	C_3H_7	7.78	7.68	0.10	0.79	1.0	5.91

[a] Data points not included in deriving equation. [b] Not included in the equation.

I_{50} rabbit aorta (Table 2)[32]



II

$$\log 1/C = -2.81(\pm0.92)\mathrm{MR}_6 - 0.76(\pm0.26)\mathrm{B5}_5 + 10.65(\pm0.57) \quad (2)$$

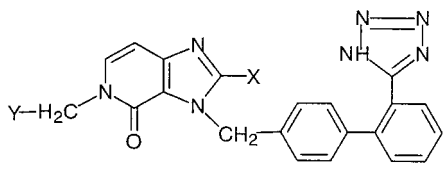
$n = 11$, $r^2 = 0.897$, $s = 0.276$, $q^2 = 0.744$, log $1/C = 7.6-10.1$

highest CMR = 14.2

r^2 Clog P Vs CMR = 0.566

outliers:
X = 5-C_6H_5, Y = C_3H_7; X = 5-NH_2, Y = C_3H_7

I_{50} rabbit aortic ring (Table 3)[33]



III

Table 3. I_{50} Data of Analogs of III in Rabbit Aortic Rings[33]

	substituents		log 1/C			
				calcd		
no.	X	Y	obsd	(eq 3)	Δ	Clog P
1	C_4H_9	COC_6H_5 [a]	8.40	−2.36	10.76	5.52
2	C_4H_9	$COCMe_3$	9.40	9.54	−0.14	5.43
3	C_4H_9	COOMe	9.70	9.83	−0.14	4.24
4	C_4H_9	COOH [a]	9.16	0.82	8.33	3.92
5	C_4H_9	$CONH_2$	9.40	9.54	−0.14	3.12
6	C_4H_9	$CONMe_2$	9.70	9.74	−0.04	3.81
7	C_3H_7	$CONMe_2$	10.00	9.59	0.41	3.28
8	C_2H_5	$CONMe_2$	9.52	9.43	0.09	2.76
9	cy-C_3H_5	$CONMe_2$	9.30	9.40	−0.10	2.67
10	C_4H_9	$CON(C_2H_5)_2$	10.10	9.84	0.26	4.87
11	C_2H_5	$CON(C_2H_5)_2$	9.52	9.74	−0.22	3.81
12	C_4H_9	CO-pyrrolidino	9.70	9.82	−0.12	4.17
13	C_2H_5	CO-piperidino	9.70	9.70	0.0	3.67
14	C_4H_9	CONHCMe	10.00	9.87	0.14	4.62
15	C_4H_9	$CONHC_6H_5$ [a]	9.00	−1.79	10.79	5.24
16	C_4H_9	$CON(Me)C_6H_5$	9.52	9.52	0.0	5.44
17	C_4H_9	$CON(C_6H_5)_2$	8.16	8.14	0.01	6.42

[a] Data points not included in deriving equation.

$$\log 1/C = 0.32(\pm0.19)\mathrm{Clog}\ P - 2.29(\pm0.72)\log(\beta \times 10^{\mathrm{Clog}\ P} + 1) + 8.56(\pm0.72) \quad (3)$$

$n = 14$, $r^2 = 0.862$, $s = 0.198$, $q^2 = 0.799$, log $1/C = 8.2-10.1$

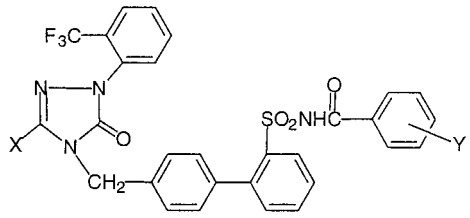
opt. Clog P = 4.5(±0.33)

highest CMR = 18.6

r^2 Clog P Vs CMR = 0.745

outliers: X = C_4H_9, Y = COC_6H_5; X = C_4H_9, Y = COOH; X = C_4H_9, Y = $CONHC_6H_5$

I_{50} rabbit aorta (Table 4)[34]



IV

$$\log 1/C = -0.63(\pm0.15)\mathrm{B5}_{Y,3} - 0.85(\pm0.30)\mathrm{B1}_{Y,4} - 0.13(\pm0.11)\mathrm{CMR} + 13.2(\pm2.1) \quad (4)$$

$n = 19$, $r^2 = 0.888$, $s = 0.181$, $q^2 = 0.832$, log $1/C = 7.7-10$

highest CMR = 19.5

r^2 Clog P Vs CMR = 0.069

outliers:
X = 5-C_4H_9, Y = 2-Cl; X = 5-C_4H_9, Y = 2,6-di-Me

Table 4. I_{50} Data of Analogs of IV in Rabbit Aorta[34]

	substituents		log 1/*C*						
no.	X	Y	obsd	calcd (eq 4)	Δ	$B5_{Y,3}$	$B1_{Y,4}$	CMR	Clog *P*[b]
1	5-C_4H_9	H	9.37	9.52	−0.15	1.00	1.00	16.52	9.69
2	5-C_4H_9	2-F	9.89	9.52	0.37	1.00	1.00	16.54	9.49
3	5-C_4H_9	4-F	9.17	9.22	−0.06	1.00	1.35	16.54	9.90
4	5-C_4H_9	2-Cl[a]	9.96	9.45	0.50	1.00	1.00	17.02	9.64
5	5-$(CH_2)_3CF_3$	2-Cl	9.44	9.45	0.0	1.00	1.00	17.06	9.05
6	5-C_4H_9	3-Cl	8.62	8.95	−0.33	1.80	1.00	17.02	10.47
7	5-C_4H_9	4-Cl	8.92	8.78	0.14	1.00	1.80	17.02	10.47
8	5-C_4H_9	2,3-di-Cl	9.14	8.89	0.26	1.80	1.00	17.51	10.26
9	5-C_4H_9	2,5-di-Cl	9.32	9.39	−0.07	1.00	1.00	17.51	10.38
10	5-C_4H_9	2-Br	9.40	9.42	−0.02	1.00	1.00	17.30	9.70
11	5-C_4H_9	2-CF_3	9.57	9.45	0.12	1.00	1.00	17.03	10.96
12	5-C_4H_9	3-CF_3	8.48	8.44	0.04	2.61	1.00	17.03	12.17
13	5-C_4H_9	4-CF_3	8.42	8.62	−0.20	1.00	1.99	17.03	12.17
14	5-C_4H_9	2-Me	9.25	9.46	−0.21	1.00	1.00	16.99	9.85
15	5-C_4H_9	2,6-di-Me[a]	8.23	9.40	−1.17	1.00	1.00	17.45	10.00
16	5-C_4H_9	2-C_6H_5	9.22	9.18	0.04	1.00	1.00	19.04	11.11
17	5-C_4H_9	2-$CH_2C_6H_5$	9.09	9.12	−0.03	1.00	1.00	19.50	11.41
18	5-C_4H_9	2-OMe	9.39	9.44	−0.05	1.00	1.00	17.14	9.84
19	5-C_4H_9	4-OMe	9.13	9.14	−0.01	1.00	1.35	17.14	9.91
20	5-C_4H_9	3,4,5-tri-OMe	7.68	7.68	0.0	3.07	1.35	18.38	9.19
21	5-C_4H_9	4-CN	9.12	8.95	0.17	1.00	1.60	17.00	9.29

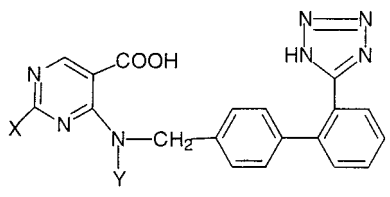
[a] Data points not included in deriving equation. [b] Not included in the equation.

Table 5. I_{50} Data of Analogs of V in Rabbit Aorta[32]

	substituents		log 1/*C*				
no.	X	Y	obsd	calcd (eq 5)	Δ	Clog *P*	L_X
1	H	H[a]	5.61	9.05	−3.44	3.96	2.06
2	Me	H[a]	7.50	8.78	−1.28	4.46	2.87
3	C_2H_5	H	8.30	8.29	0.01	4.99	4.11
4	C_3H_7	H	8.27	8.03	0.24	5.52	4.92
5	C_4H_9	H	7.91	7.54	0.38	6.05	6.17
6	C_5H_{11}	H	7.23	7.28	−0.05	6.58	6.97
7	CH_2CH_2OMe	H	6.81	7.15	−0.34	3.73	5.55
8	C_4H_9	Me	7.15	7.35	−0.20	5.44	6.17
9	Me	C_2H_5[a]	7.96	8.75	−0.79	4.39	2.87
10	Me	C_3H_7	9.60	8.92	0.68	4.91	2.87
11	Me	C_4H_9	8.81	9.08	−0.27	5.44	2.87
12	Me	C_5H_{11}	8.73	9.24	−0.51	5.97	2.87
13	Me	$CH_2CH{=}CH_2$	8.32	8.83	−0.51	4.63	2.87
14	Me	CH_2CHMe_2[a]	7.50	9.04	−1.54	5.31	2.87
15	Me	$CH_2CH_2CHMe_2$	8.85	9.20	−0.35	5.84	2.87
16	Me	CH_2CH_2OMe	8.50	8.54	−0.04	3.69	2.87
17	H	C_3H_7	9.68	9.19	0.49	4.42	2.06
18	H	C_4H_9	9.57	9.35	0.22	4.94	2.06
19	C_3H_7	C_3H_7	8.52	8.17	0.35	5.97	4.92
20	CF_3	C_3H_7	8.79	8.81	−0.02	5.32	3.30
21	SMe	C_4H_9	8.38	8.47	−0.09	5.90	4.30

[a] Data points not included in deriving equation.

I_{50} rabbit aorta (Table 5)[32]



V

$$\log 1/C = 0.31(\pm 0.27)\text{Clog } P - 0.53(\pm 0.14)L_X + 8.91(\pm 1.32) \quad (5)$$

$n = 17$, $r^2 = 0.818$, $s = 0.375$, $q^2 = 0.722$,

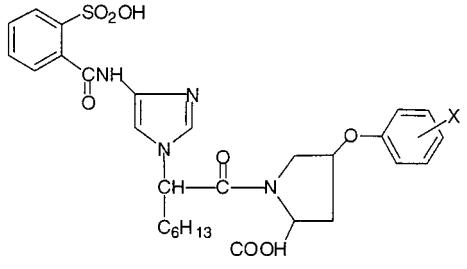
log 1/*C* = 5.6−9.7

highest CMR = 13.2

r^2 Clog *P* Vs CMR = 0.424

outliers: X = Y = H; X = Me, Y = H; X = Me, Y = C_2H_5; X = Me, Y = CH_2CHMe_2

I_{50} rabbit aorta (Table 6)[35]



VI

Table 6. I_{50} Data of Analog of VI in Rabbit Aorta[35]

		log 1/C					
no.	substituents	obsd	calcd (eq 6)	Δ	CMR	σ^+	Clog P^b
1	H	9.10	8.88	0.22	15.42	0	3.14
2	4-Me	8.96	8.74	0.23	15.89	−0.31	3.64
3	4-$CHMe_2$	7.60	7.55	0.06	16.81	−0.28	4.56
4	4-CMe_3	6.90	6.94	−0.04	17.28	−0.26	4.97
5	4-F	8.52	8.96	−0.43	15.44	−0.07	3.42
6	4-CF_3	7.46	7.39	0.08	15.93	0.61	4.27
7	4-C_6H_5 [a]	8.00	6.02	1.99	17.93	−0.18	5.03
8	4-OMe	9.36	9.21	0.15	16.04	−0.78	3.23
9	3-OMe	7.94	7.94	−0.01	16.04	0.12	3.23
10	2-OMe[a]	7.52	9.21	−1.69	16.04	−0.78	2.88
11	4-$OCHMe_2$	8.39	8.15	0.23	16.97	−0.85	4.07
12	3,4-di-OMe	7.80	8.28	−0.47	16.66	−0.66	2.87

[a] Data points not included in deriving equation. [b] Not included in the equation.

$$\log 1/C = -1.24(\pm 0.40)\text{CMR} - 1.41(\pm 0.58)\sigma^+ + 28.0(\pm 6.5) \quad (6)$$

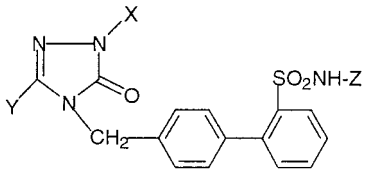
$n = 10$, $r^2 = 0.895$, $s = 0.292$, $q^2 = 0.807$, log 1/C = 6.9−9.4

highest CMR = 18

r^2 Clog P Vs CMR = 0.548

outliers: 4-C_6H_5; 2-OMe

I_{50} rabbit aorta (Table 7)[34]



VII

$$\log 1/C = 0.33(\pm 0.19)\text{CMR} + 0.86(\pm 0.19)\sigma^*_Z - 0.50(\pm 0.46)I_X + 1.26(\pm 2.84) \quad (7)$$

$n = 11$, $r^2 = 0.959$, $s = 0.248$, $q^2 = 0.867$, log 1/C = 5.9−9.4

highest CMR = 17

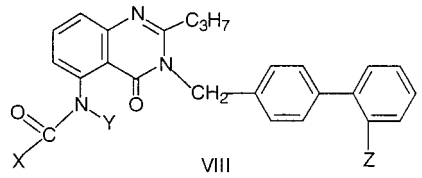
r^2 Clog P Vs CMR = 0.785

outlier:

X = 2-CF_3-C_6H_4, Y = C_4H_9, Z = COC_6H_5

I_X =1 for X = 2-CF_3-C_6H_4

I_{50} rabbit aorta (Table 8)[37]



VIII

$$\log 1/C = -0.52(\pm 0.26)\text{Clog } P + 12.8(\pm 2.0) \quad (8)$$

$n = 5$, $r^2 = 0.931$, $s = 0.163$, $q^2 = 0.698$, log 1/C = 8.1−9.4

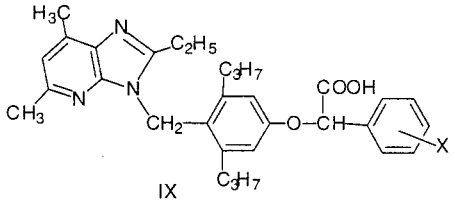
highest CMR = 21

r^2 Clog P Vs CMR = 0.739

outlier:

X = $NHCHMe_2$, Y = H, Z = $SO_2NHCOMe$

I_{50} rabbit aorta (Table 9)[38]



IX

$$\log 1/C = 0.75(\pm 0.55)\sigma - 0.56(\pm 0.15)L_4 + 10.2(\pm 0.40) \quad (9)$$

$n = 9$, $r^2 = 0.954$, $s = 0.130$, $q^2 = 0.868$, log 1/C = 7.7−9.3

highest CMR = 17.4

r^2 Clog P Vs CMR = 0.972

outliers: 3-C_6H_5; 4-OC_6H_5

Table 7. I_{50} Data of Analogs of VII in Rabbit Aorta[34]

	substituents			log 1/C						
no.	X	Y	Z	obsd	calcd (eq 7)	Δ	CMR	σ^*_Z	I_X	Clog P^b
1	2-Cl−C_6H_4	C_4H_9	CMe_3	5.89	6.10	−0.21	15.34	−0.30	0	7.45
2	2-Cl−C_6H_4	C_4H_9	H	6.09	6.16	−0.07	13.49	0.49	0	5.60
3	2-Cl−C_6H_4	C_4H_9	COC_6H_5	8.85	8.63	0.22	16.50	2.20	0	8.03
4	2-Cl−C_6H_4	C_4H_9	COMe	7.89	7.48	0.41	14.45	1.65	0	5.29
5	2-Cl−C_6H_4	C_4H_9	$COCF_3$	8.96	9.25	−0.29	14.50	3.70	0	7.40
6	2,6-di-Cl−C_6H_3	C_4H_9	COC_6H_5	8.59	8.79	−0.20	16.99	2.20	0	8.75
7	2-CF_3−C_6H_4	C_4H_9	COC_6H_5 [a]	9.37	8.14	1.23	16.52	2.20	1	9.69
8	2-$CHMe_2$	C_4H_9	COC_6H_5	8.16	8.09	0.07	14.89	2.20	0	6.39
9	2-CH_2CMe_3	C_4H_9	COC_6H_5	8.48	8.40	0.08	15.82	2.20	0	7.41
10	2-CF_3−C_6H_4	C_3H_7	COC_6H_5	7.89	7.98	−0.09	16.06	2.20	1	9.16
11	2-CF_3−C_6H_4	C_3H_7	COC_3H_5	7.75	−	−	14.80	−	1	6.77
12	2-CF_3−C_6H_4	$(CH_2)_3$−CF_3	COC_6H_5	8.26	8.15	0.11	16.57	2.20	1	9.10
13	2-CF_3−C_6H_4	CH_2−(cy-2-MeC_3H_4)	COC_6H_5	8.24	8.25	−0.01	16.85	2.20	1	9.59

[a] Data point not included in deriving equation. [b] Not included in the equation.

Table 8. I_{50} Data of Analogs of VIII in Rabbit Aorta[37]

	substituents			log 1/*C*			
no.	X	Y	Z	obsd	calcd (eq 8)	Δ	Clog *P*
1	C_6H_5	H	tetrazole	9.40	9.44	−0.04	6.37
2	C_6H_5	C_5H_{11}	tetrazole	8.82	8.66	0.17	7.88
3	C_6H_5	C_5H_{11}	$SO_2NHCOC_6H_5$	7.96	8.09	−0.13	8.97
4	C_6H_5	H	$SO_2NHCOC_6H_5$	9.00	8.87	0.13	7.46
5	$NHCHMe_2$	H	$SO_2NHCOMe$[a]	8.06	10.60	−2.54	4.14
6	$NHCHMe_2$	H	$SO_2NHCOC_6H_5$	9.05	9.18	−0.13	6.87

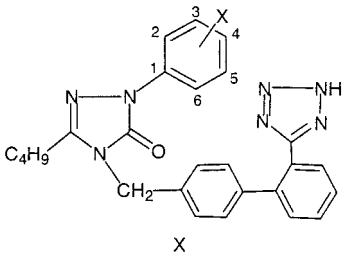
[a] Data point not included in deriving equation.

Table 9. I_{50} Data of Analogs of IX in Rabbit Aorta[38]

		log 1/*C*					
no.	substituents	obsd	calcd (eq 9)	Δ	σ	L_4	Clog *P*[b]
1	H	9.05	9.06	−0.01	0.00	2.06	7.86
2	2-Me	8.92	8.93	−0.01	−0.17	2.06	8.31
3	2-Cl	9.28	9.23	0.04	0.23	2.06	8.50
4	3-Me	9.13	9.01	0.12	−0.07	2.06	8.36
5	3-Cl	9.13	9.34	−0.21	0.37	2.06	8.57
6	3-OC_6H_5	9.33	9.25	0.08	0.25	2.06	9.96
7	3-C_6H_5[a]	8.17	9.11	−0.94	0.06	2.06	9.75
8	4-Me	8.40	8.48	−0.08	−0.17	2.87	8.36
9	4-Cl	8.55	8.41	0.14	0.23	3.52	8.57
10	4-C_2H_5	7.72	7.79	−0.07	−0.15	4.11	8.89
11	4-OC_6H_5[a]	8.28	7.66	0.63	−0.03	4.51	9.96

[a] Data points not included in deriving equation. [b] Not included in the equation.

I_{50} rabbit aorta (Table 10)[30]



X

$$\log 1/C = -0.27(\pm 0.17)\text{Clog } P - 0.37(\pm 0.27)\sigma + 1.78(\pm 0.33)B1_2 + 7.5(\pm 0.77) \quad (10)$$

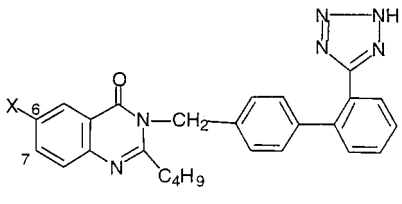
$n = 26$, $r^2 = 0.860$, $s = 0.246$, $q^2 = 0.788$,
$\log 1/C = 6.9-9.1$

highest CMR = 16

r^2 Clog *P* Vs CMR = 0.265

outliers: 4-OMe; 2-COOH; 2-NH_2

I_{50} rabbit aorta (Table 11)[39]



XI

Table 10. I_{50} Data of Analogs of X in Rabbit Aorta[30]

		log 1/*C*					
no.	substituents	obsd	calcd (eq 10)	Δ	Clog *P*	σ	$B1_2$
1	H	7.66	7.62	0.04	6.20	0	1.0
2	2-Me	8.39	8.48	−0.09	6.70	−0.17	1.52
3	2-Cl	8.62	8.76	−0.14	6.94	0.23	1.80
4	2-NO_2	9.07	8.64	0.44	5.99	0.78	1.70
5	2-OMe	8.18	8.36	−0.18	6.14	−0.27	1.35
6	3-Me	7.74	7.51	0.23	6.70	−0.07	1.0
7	3-Cl	6.92	7.29	−0.37	6.94	0.37	1.0
8	3-NO_2	7.37	7.41	−0.04	5.99	0.71	1.0
9	3-OMe	7.82	7.59	0.23	6.14	0.12	1.0
10	4-Me	7.80	7.55	0.25	6.70	−0.17	1.0
11	4-Cl	7.16	7.34	−0.18	6.94	0.23	1.0
12	4-NO_2	7.10	7.39	−0.29	6.00	0.78	1.0
13	4-OMe[a]	8.30	7.74	0.56	6.14	−0.27	1.0
14	4-C_2H_5	7.57	7.40	0.17	7.23	−0.15	1.0
15	4-F	7.68	7.55	0.13	6.37	0.06	1.0
16	4-COOMe	7.48	7.45	0.03	6.21	0.45	1.0
17	2-$CHMe_2$	8.85	8.90	−0.05	7.63	−0.15	1.90
18	2-C_6H_5	8.44	8.38	0.06	8.09	−0.01	1.71
19	2-$CH_2C_6H_5$	7.96	8.03	−0.07	8.27	−0.09	1.52
20	2-F	8.11	8.18	−0.07	6.37	0.06	1.35
21	2-Br	8.70	8.99	−0.29	7.09	0.23	1.95
22	2-CF_3	8.92	8.55	0.37	8.59	0.54	1.99
23	2-COOMe	8.25	8.59	−0.34	6.21	0.45	1.64
24	2-COOH[a]	6.94	8.59	−1.65	5.97	0.45	1.60
25	2-NH_2[a]	7.00	8.82	−1.82	4.98	−0.66	1.35
26	2-NMe_2	8.50	8.51	−0.01	6.37	−0.83	1.35
27	2,6-di-Cl	8.24	8.49	−0.25	7.66	0.46	1.80
28	2-NO_2,4-OMe	9.13	8.68	0.45	6.18	0.51	1.70
29	2,3,4,5,6-penta-F	7.77	7.78	−0.01	6.74	0.86	1.35

[a] Data points not included in deriving equation.

$$\log 1/C = -0.47(\pm 0.12)\text{Clog } P + 0.831(\pm 0.34)B1_X - 1.87(\pm 0.34)\sigma + 9.71(\pm 0.79) \quad (11)$$

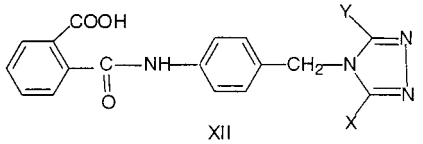
$n = 15$, $r^2 = 0.941$, $s = 0.141$, $q^2 = 0.910$,
$\log 1/C = 6.9-9$

highest CMR = 17.3

r^2 Clog *P* Vs CMR = 0.249

outliers: SOMe; OH; OMe-7-OMe (as can be seen in Table 11, a number of structures had to be omitted for lack of σ values)

I_{50} rabbit aorta pellets (Table 12)[40]



XII

Table 11. I_{50} Data of Analogs of XI in Rabbit Aorta[39]

		log 1/*C*					
no.	substituents	obsd	calcd (eq 11)	Δ	Clog *P*	$B1_X$	σ
1	H	8.22	8.12	0.10	5.17	1.00	0.00
2	Me	8.40	8.45	−0.05	5.67	1.52	−0.07
3	$CHMe_2$	8.30	8.28	0.02	6.59	1.90	−0.04
4	C_2H_5	8.40	8.20	0.19	6.19	1.52	−0.07
5	NO_2	7.55	7.46	0.09	4.99	1.70	0.71
6	SMe	8.16	8.10	0.06	5.87	1.70	0.15
7	SOMe[a]	9.00	8.05	0.95	3.96	1.40	0.52
8	SO_2Me	8.52	8.46	0.06	3.87	2.03	0.60
9	F	7.59	7.70	−0.11	5.35	1.35	0.34
10	Cl	7.54	7.75	−0.21	5.92	1.80	0.37
11	OH[a]	7.57	8.15	−0.58	5.25	1.35	0.12
12	$OCONHCHMe_2$ [b]	9.00	–	–	5.39	–	–
13	OMe	8.30	8.08	0.22	5.41	1.35	0.12
14	OMe,7-OMe[a]	7.89	8.63	−0.74	5.31	1.35	−0.15
15	NH_2	8.89	8.96	−0.07	4.64	1.35	−0.16
16	NHMe	8.70	8.68	0.02	5.43	1.35	−0.21
17	NMe_2	8.30	8.45	−0.15	5.72	1.35	−0.16
18	$NHSO_2CF_3$	6.92	6.95	−0.03	6.54	1.35	0.44
19	NHCOMe	8.05	8.18	−0.14	4.82	1.35	0.21
20	$NHCO(CH_2)_3CH_3$ [b]	8.70	–	–	–	–	–
21	$NHCO_2CH_2CHMe_2$ [b]	8.19	–	–	–	–	–
22	$NMeCO_2CH_2CHMe_2$ [b]	8.47	–	–	–	–	–
23	$NHCO_2CH_2C_6H_5$ [b]	8.37	–	–	–	–	–
24	$NMeCO_2CH_2C_6H_5$ [b]	9.08	–	–	–	–	–
25	$NHCONHCHMe_2$ [b]	9.13	–	–	–	–	–

[a] Data points not included in deriving equation. [b] Data points could not be included in deriving equation because of the lack of the σ and B_1 values.

Table 12. I_{50} Data of Analogs of XII in Rabbit Aorta Pellets[40]

	substituent		log 1/*C*				
no.	X	Y	obsd	calcd (eq 12)	Δ	CMR	Clog P^b
1	C_4H_9	C_6H_5	6.03	6.34	−0.31	13.07	3.97
2	SC_2H_5	C_6H_5	5.72	6.25	−0.53	12.95	3.47
3	SC_3H_7	C_6H_5	5.80	6.58	−0.78	13.41	4.00
4	C_4H_9	4-pyridyl	5.85	6.19	−0.34	12.86	2.57
5	C_4H_9	3-pyridyl	5.77	6.19	−0.42	12.86	2.57
6	C_4H_9	2-furyl	6.00	5.79	0.21	12.28	3.35
7	SC_2H_5	$CH_2C_6H_5$	6.00	6.58	−0.58	13.41	3.21
8	SC_3H_7	$CH_2C_6H_5$	6.42	6.90	−0.48	13.88	3.74
9	SC_3H_7	$CH_2CH_2C_6H_5$	7.12	7.22	−0.10	14.34	4.11
10	SC_3H_7	$(CH_2)_3C_6H_5$ [a]	6.49	7.55	−1.06	14.80	4.64
11	SC_3H_7	$CH_2SC_6H_5$ [a]	5.92	7.46	−1.54	14.68	4.03
12	SC_2H_5	CH_2OMe	5.28	5.26	0.03	11.52	1.15
13	SC_2H_5	CF_3	5.32	4.86	0.46	10.95	2.37
14	SC_3H_7	CF_3	5.68	5.18	0.50	11.41	2.90
15	C_4H_9	SCH_2COOMe	6.48	6.25	0.23	12.95	2.26
16	C_4H_9	$SCH_2CONHMe$	6.14	6.40	−0.26	13.16	1.25
17	C_4H_9	SCH_2CH_2OH	6.32	5.90	0.42	12.45	1.66
18	C_4H_9	SCHEtCOOMe	6.52	6.90	−0.38	13.87	3.31
19	C_4H_9	$SCH_2COC_6H_5$ [a]	6.72	7.57	−0.85	14.84	3.65
20	C_4H_9	SC_6H_5	7.22	6.90	0.32	13.88	4.48
21	C_4H_9	$SCH_2C_6H_5$	7.82	7.22	0.60	14.34	4.26
22	C_4H_9	$SCH_2CH_2C_6H_5$	7.15	7.55	−0.40	14.80	4.79
23	C_3H_7	$SCH_2C_6H_5$	6.92	6.90	0.02	13.88	3.74
24	C_4H_9	$SCH_2(2\text{-}Me\text{-}C_6H_4)$	7.85	7.55	0.30	14.80	4.71
25	C_4H_9	$SCH_2(3\text{-}Me\text{-}C_6H_4)$	7.49	7.55	−0.06	14.80	4.76
26	C_4H_9	$SCH_2(4\text{-}Me\text{-}C_6H_4)$	8.12	7.55	0.57	14.80	4.76
27	C_4H_9	$SCH_2(2\text{-}Cl\text{-}C_6H_4)$	7.52	7.57	−0.05	14.83	4.91
28	C_4H_9	$SCH_2(3\text{-}Cl\text{-}C_6H_4)$	7.59	7.57	0.02	14.83	4.98
29	C_4H_9	$SCH_2(4\text{-}Cl\text{-}C_6H_4)$	8.17	7.57	0.60	14.83	4.98
30	C_4H_9	$SCH_2(3\text{-}OMe\text{-}C_6H_4)$	7.68	7.65	0.03	14.96	4.18
31	C_4H_9	$SCH_2(4\text{-}OMe\text{-}C_6H_4)$	8.52	7.65	0.87	14.96	4.18
32	C_4H_9	$SOCH_2(4\text{-}OMe\text{-}C_6H_4)$	8.13	7.68	0.45	14.99	2.85
33	C_4H_9	$SCH_2(2\text{-}CN\text{-}C_6H_4)$	7.22	7.56	−0.34	14.82	3.84
34	C_4H_9	$SCH_2(4\text{-}CF_3C_6H_4)$	7.38	7.58	−0.20	14.85	5.15
35	C_4H_9	SCH_2-2-naphthyl[a]	7.31	8.40	−1.09	16.03	5.44
36	C_4H_9	$SCH(CO_2Me)C_6H_5$	8.21	8.00	0.21	15.46	3.67
37	C_4H_9	$SCH_2(2\text{-}CO_2Me\text{-}C_6H_4)$	7.85	8.00	−0.15	15.46	4.23
38	C_4H_9	$SCH_2(3\text{-}CO_2Me\text{-}C_6H_4)$	7.52	8.00	−0.48	15.46	4.23

[a] Data points not included in deriving equation. [b] Not included in the equation.

$$\log 1/C = 0.70(\pm 0.12)\text{CMR} - 2.78(\pm 1.67) \quad (12)$$

$n = 34$, $r^2 = 0.812$, $s = 0.419$,
$q^2 = 0.787$, $\log 1/C = 5.3-8.5$

highest CMR = 16

r^2 Clog P Vs CMR = 0.564

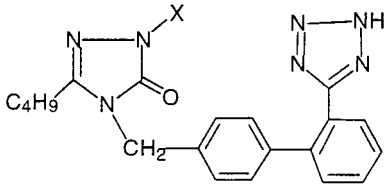
outliers: X = SC_3H_7, Y = $(CH_2)_3C_6H_5$;
X = SC_3H_7, Y=$CH_2SC_6H_5$; X=C_4H_9,
Y = $SCH_2COC_6H_5$; X = C_4H_9,
Y = SCH_2-2-naphthyl

Table 13. I_{50} Data of Analogs of XIII in Rabbit Aorta Rings[41]

		log 1/C			
no.	substituent	obsd	calcd (eq 13)	Δ	Clog P
1	H	7.38	7.53	−0.15	4.50
2	C_2H_5	7.66	7.62	0.04	4.69
3	$(CH_2)_2CH_3$	7.82	7.88	−0.05	5.22
4	$(CH_2)_3CH_3$	8.29	8.10	0.19	5.74
5	$(CH_2)_4CH_3$	8.25	8.25	0.0	6.27
6	$(CH_2)_5CH_3$	8.06	8.17	−0.11	6.80
7	$(CH_2)_7CH_3$	6.77	6.77	0.0	7.86
8	$CHMe_2$	7.70	7.77	−0.07	5.00
9	$CHMeCH_2CH_3$	8.00	8.01	−0.01	5.52
10	$CH_2CHMeCH_2CMe_3$	7.46	7.49	−0.03	7.47
11	CH_2−cy−C_3H_5	7.82	7.84	−0.01	5.13
12	CH_2CH_2−cy−C_6H_{11}	7.75	7.68	0.06	7.34
13	$CH_2COOCH_2CH_3$	8.05	7.72	0.32	4.90
14	$CH_2CO_2CMe_3$	7.80	8.13	−0.34	5.83
15	$(CH_2)_4COOCH_3$ [a]	8.36	−6.46	14.82	4.70
16	$(CH_2)_5COOCH_2CH_3$	8.01	8.11	−0.10	5.76
17	C_6H_5 [a]	7.23	−9.46	16.68	5.90
18	$CH_2C_6H_5$ [a]	7.80	−9.51	17.31	5.93
19	$CH_2CH_2C_6H_5$	8.51	8.25	0.26	6.25
20	$(CH_2)_3C_6H_5$ [a]	7.75	−11.28	19.02	6.63

[a] Data points not included in deriving equation.

I_{50} rabbit aorta rings (Table 13)[41]



XIII

$$\log 1/C = 0.50(\pm 0.19)\text{Clog } P - 3.0(\pm 0.83)\log(\beta \times 10^{\text{Clog } P} + 1) + 5.27(\pm 1.0) \quad (13)$$

$n = 16$, $r^2 = 0.849$, $s = 0.178$,
$q^2 = 0.793$, $\log 1/C = 6.8-8.5$

opt. Clog $P = 6.42(\pm 0.19)$

highest CMR = 14.5

r^2 Clog P Vs CMR = 0.568

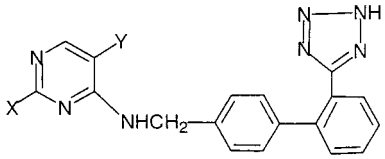
outliers:
$(CH_2)_4COOCH_3$; C_6H_5; $CH_2C_6H_5$; $(CH_2)_3C_6H_5$

Table 14. I_{50} Data of Analogs of XIV in Rabbit Aorta[32]

	substituents		log 1/C				
no.	X	Y	obsd	calcd (eq 14)	Δ	π_X	Clog P [b]
1	H	$CO_2C_2H_5$	6.24	6.14	0.10	0.0	3.82
2	Me	$CO_2C_2H_5$	7.13	7.26	−0.13	0.56	4.31
3	C_2H_5	$CO_2C_2H_5$	7.78	7.75	0.03	1.02	4.84
4	C_3H_7	$CO_2C_2H_5$	7.91	7.84	0.07	1.55	5.37
5	C_4H_9	$CO_2C_2H_5$	7.37	7.36	0.01	2.13	5.90
6	C_5H_{11}	$CO_2C_2H_5$	6.37	6.46	−0.09	2.63	6.43
7	CH_2CH_2OMe	$CO_2C_2H_5$ [a]	7.10	5.10	2.00	−0.37	3.58
8	Me	CH_2OH	7.12	7.26	−0.14	0.56	2.19
9	C_2H_5	CH_2OH	7.96	7.75	0.21	1.02	2.72
10	C_3H_7	CH_2OH	7.60	7.84	−0.24	1.55	3.25
11	C_4H_9	CH_2OH	7.53	7.36	0.17	2.13	3.78
12	CH_2CH_2OMe	CH_2OH [a]	6.41	5.10	1.31	−0.37	1.46

[a] Data points not included in deriving equation. [b] Not included in the equation.

I_{50} rabbit aorta (Table 14)[32]



XIV

$$\log 1/C = 2.50(\pm 0.56)\pi_X - 0.90(\pm 0.20)(\pi_X)^2 + 6.14(\pm 0.33) \quad (14)$$

$n = 10$, $r^2 = 0.941$, $q^2 = 0.853$,
$s = 0.165$, $\log 1/C = 6.2-8.0$

opt. $\pi_X = 1.38(1.29-1.47)$

highest CMR = 13.3

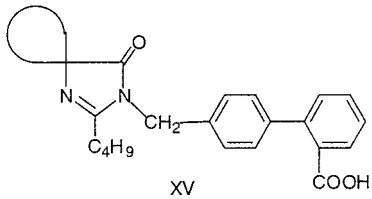
r^2 Clog P Vs CMR = 0.600

outliers: X = CH_2CH_2OMe, Y = $CO_2C_2H_5$;
X = CH_2CH_2OMe, Y = CH_2OH

Table 15. I_{50} Data of Analogs of XV in Rabbit Aorta[36]

		log 1/C			
no.	substituents	obsd	calcd (eq 15)	Δ	Clog P
1	$(CH_2)_2$	6.47	6.86	−0.39	4.54
2	$(CH_2)_3$	7.38	7.06	0.32	5.10
3	$(CH_2)_4$	7.20	7.26	−0.06	5.66
4	$(CH_2)_5$	7.42	7.46	−0.04	6.22
5	$(CH_2)_6$	7.92	7.66	0.26	6.78
6	$(CH_2)_2O(CH_2)_2$	6.70	6.60	0.10	3.82
7	$(CH_2)_2NH(CH_2)_2$	5.80	5.78	0.02	1.53
8	$(CH_2)_2CH(Me)(CH_2)_2$	7.41	7.64	−0.23	6.74

I_{50} rabbit aorta (Table 15)[36]



XV

$$\log 1/C = 0.36(\pm 0.13)\text{Clog } P + 5.23(\pm 0.71) \quad (15)$$

$$n = 8,\ r^2 = 0.877,\ s = 0.256,\ q^2 = 0.815,$$

$$\log 1/C = 5.8 - 7.9$$

$$\text{highest CMR} = 12.6$$

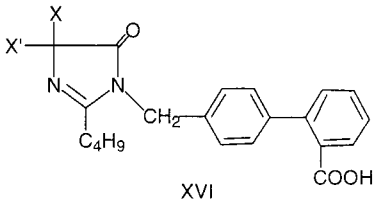
$$r^2 \text{ Clog } P \text{ Vs CMR} = 0.339$$

Table 16. I_{50} Data of Analogs of XVI in Rabbit Aorta[36]

		log 1/C				
no.	substituent X = X′	obsd	calcd (eq 16)	Δ	$L_{X+X'}$	Clog P[b]
1	Me[a]	6.92	7.73	−0.81	5.74	5.62
2	C_2H_5	6.57	6.85	−0.28	8.22	6.68
3	C_3H_7	6.32	6.27	0.05	9.84	7.74
4	$CHMe_2$	6.96	6.85	0.11	8.22	7.48
5	cy-C_3H_5	6.96	6.82	0.13	8.28	6.33
6	C_4H_9	5.40	5.38	0.02	12.34	8.79
7	CH_2CHMe_2 [a]	5.29	6.27	−0.98	9.84	8.53
8	C_6H_5	5.27	5.30	−0.04	12.56	7.90

[a] Data points not included in deriving equation. [b] Not included in the equation.

I_{50} rabbit aorta (Table 16)[36]



XVI

$$\log 1/C = -0.36(\pm 0.10)L_{X+X'} + 9.77(\pm 1.01) \quad (16)$$

$$n = 6,\ r^2 = 0.960,\ q^2 = 0.919,\ s = 0.167,$$

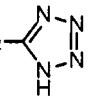
$$\log 1/C = 5.3 - 7.0$$

$$\text{highest CMR} = 15$$

$$r^2 \text{ Clog } P \text{ Vs CMR} = 0.648$$

$$\text{outliers: X = X′ = Me; X = X′ = } CH_2CHMe_2$$

In surveying QSAR 1−16, there are a number of common features of interest. All but three sets (6, 9, and 12) contain a biphenyl unit. The first eight most active sets (except 6) contain this moiety. All contain one of three acidic functions. The most common function being the tetrazole (2, 3, 5, 8, 10, 11, 13, and 14), four contain the COOH group (6, 9, 15, and 16) and four contain a $-SO_2N-$ unit (1, 4, 7, and 8). Those containing the COOH are among the least active. One with the $-SO_2NHCO-$ unit (1) is in the most active class. The receptor seems to be largely hydrophilic as all of the compounds contain ionizable groups; moreover, only five equations contain positive hydrophobic terms (3, 5, 13, 14, and 15). It must be remembered that Clog *P* is the calculated value, and the experimental value at pH 7.4 would be considerably lower. It would be valuable to measure some distribution coefficients at pH 7.4. None of the rabbit equations in contrast to the rat are for results in the whole animal. It is noteworthy that very little has been done to investigate the substituent effect on the distal (acidic group-bearing) ring of the biphenyl. This is probably because of the problem in synthesizing these derivatives. Some data appears in the work done by Duncia et al.[48] All of the acidic groups are sensitive to the electronic effects of substituents as shown by QSAR 17 and 18.

Ionization of X-C_6H_4-  in 50% ethanol 25 °C[42]

$$pK_a = -1.40(\pm 0.12)\sigma + 4.92(\pm 0.05) \quad (17)$$

$$n = 28,\ r^2 = 0.955,\ s = 0.129,\ q^2 = 0.946$$

Ionization of X−$C_6H_4SO_2NH_2$ in aqueous solution 20 °C[43]

$$pK_a = -0.63(\pm 0.09)\sigma^- - 0.76(\pm 0.32) \quad (18)$$

$$n = 18,\ r^2 = 0.954,\ s = 0.105,\ q^2 = 0.931$$

The sulfonamide group is not as sensitive. Ionization of benzoic acids is used to define σ; hence, the QSAR slope is 1. In the case of eq 17, the slope (ρ) is somewhat higher than it would be in water. For example, ρ for the ionization of benzoic acid in water is by definition −1 (we are speaking in terms of pK_a). In 50% ethanol, it is −1.40. Hence, the ρ in the case of the tetrazoles (eq 17) for water would probably be near −1. It would be interesting to place a strong electron-attracting substituent (e.g., CN) on the phenyl moiety para to the tetrazole unit and a strong electron-releasing group (e.g., NH_2) in the same position for comparison. If there is a significant difference, a QSAR could be developed to find the optimum electronic effect. This electronic effect would be beyond ionization in that it would effect the availability of the anions for interaction with electron poor centers.

Some facts must be remembered in the use of Clog *P*. Most important, it is calculated for the neutral form of all congeners that are partially ionized. Moreover, Clog *P* is the hydrophobic effect of the overall molecule. There may well be hydrophobic pockets that need to be searched for. In every instance we considered π values for all cases where structural variation was made in more than one position. Finally, Clog *P* is not yet the 'perfect' parameter. Note that it was necessary to use π in the case of QSAR 14; possibly the calculated Clog *P* is off the mark.

A point of interest is that of bulk tolerance of the receptor. To get some general impression of the problem we have calculated CMR for each data set and have listed the highest value. QSAR 1 that depends heavily on CMR can be used to calculate the optimum value of 18.6(±0.5). QSAR 3 is better fit by Clog *P*. Thus, it would seem that the large SO_2-$NHCOC_6H_4$−Cl moiety covered by QSAR 1 displaces binding of the congeners of QSAR 1, so that hydrophobic binding modeled by eq 3 is not apparent.

There are some positive hydrophobic binding sites as brought out by QSAR 3, 5, 13, 14, and 15, but most of the variance is associated with the sterimol parameters and the volume-polarizability parameter CMR. Relatively weak electronic terms are seen in QSAR 6, 7, 9, 10, and 11.

It appears to be very important to have the tetrazole, COOH, and sulfonamide groups in an ortho position that would twist the biphenyl groups out of planarity. A CH_2 or NCH_2 group joining the biphenyl unit also provides flexibility in every instance. QSAR 1−12 cover structures with considerable variation that have compounds active at 10^{-9} M or greater.

B. Rat Angiotensin Antagonists

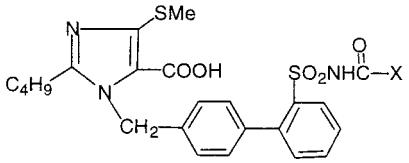
As with the data on rabbit angiotensin antagonists, the data for rats is ordered in terms of decreasing activity.

Table 17. I_{50} Data of Analogs of XVII in Rat Liver Membrane[44]

		log 1/*C*					
no.	substituent	obsd	calcd (eq 19)	Δ	Clog *P*	σ_I	I_X
1	NHMe	8.72	8.86	−0.14	4.83	0.13	1
2	NHC_2H_5	9.70	9.29	0.41	5.36	0.03	1
3	NHC_3H_7	9.52	9.59	−0.07	5.89	0.03	1
4	NHC_4H_9	9.70	9.90	−0.20	6.42	0.03	1
5	$N(C_2H_5)_2$ [a]	8.33	9.85	−1.52	6.30	0.02	1
6	OMe	9.05	8.93	0.12	4.73	0.27	0
7	OC_2H_5	9.05	9.22	−0.18	5.26	0.28	0
8	OC_4H_9	10.00	9.84	0.16	6.32	0.28	0
9	OCH_2CHMe_2	9.70	9.76	−0.06	6.19	0.28	0
10	Me	9.00	9.10	−0.10	4.41	−0.04	0
11	C_3H_7	9.70	9.68	0.02	5.47	−0.01	0
12	C_6H_5	10.05	10.04	0.01	6.34	0.12	0
13	$CH_2C_6H_5$	10.10	10.06	0.03	5.98	−0.08	0

[a] Data point not included in deriving equation.

I_{50} rat liver membrane (Table 17)[44]



XVII

$$\log 1/C = 0.58(\pm 0.20)\text{Clog } P - 1.18(\pm 1.1)\sigma_I - 0.29(\pm 0.29)I_X + 6.49(\pm 1.1) \quad (19)$$

$n = 12$, $r^2 = 0.861$, $s = 0.201$,
$q^2 = 0.700$, log $1/C = 8.3-10.1$

highest CMR = 16

r^2 Clog *P* Vs CMR = 0.484

outlier: $N(C_2H_5)_2$

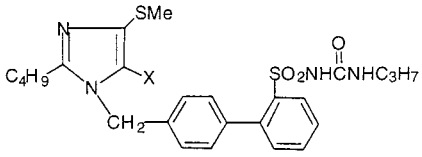
$I_X = 1$ for N-alkyl derivatives

Table 18. I_{50} Data of Analogs of XVIII in Rat Liver Membrane[44]

		log 1/*C*				
no.	substituent	obsd	calcd (eq 20)	Δ	Clog *P*	CMR
1	COOH[a]	9.52	8.62	0.91	5.38	14.67
2	CH_2OH	8.35	8.52	−0.18	4.93	14.64
3	H	8.59	8.55	0.04	5.97	14.02
4	$COOCH_2C_6H_5$	10.00	9.73	0.27	6.77	17.65
5	$COOCMe_3$	9.22	9.51	−0.29	7.28	16.53
6	$COOC_2H_5$	9.40	9.11	0.29	6.57	15.60
7	CONHMe	8.68	8.68	−0.01	4.72	15.35
8	CONHCH(COOH) $CH(Me)CH_2CH_3$	9.52	9.74	−0.21	6.50	17.86
9	$CONH_2$ [a]	9.00	8.49	0.51	4.39	14.89
10	$CONHCH_2COOMe$	9.10	9.00	0.10	4.72	16.47
11	$CONHCH_2COOH$	8.82	8.83	0	4.51	16.00
12	CONHCOMe	8.77	8.79	−0.02	4.53	15.85
13	$CONHSO_2C_6H_5$[a]	9.10	9.80	−0.70	6.22	18.27

[a] Data points not included in deriving equation.

I_{50} rat liver membrane (Table 18)[44]



XVIII

$$\log 1/C = 0.19(\pm 0.17)\text{Clog } P + 0.28(\pm 0.15)\text{CMR} + 3.43(\pm 2.3) \quad (20)$$

$n = 10$, $r^2 = 0.855$, $s = 0.216$,
$q^2 = 0.687$, log $1/C = 8.4-10.0$

highest CMR = 18.3

r^2 Clog *P* Vs CMR = 0.223

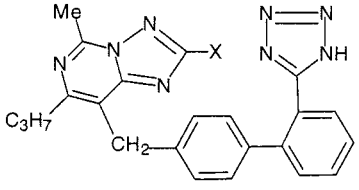
outliers: COOH; $CONH_2$; $CONHSO_2C_6H_5$

Table 19. K_i Data of Analogs of XIX in Rat Adrenal Membrane[47]

		log 1/K_i					
no.	substituent	obsd	calcd (eq 21)	Δ	CMR	I_X	Clog *P*[b]
1	OH	7.62	7.64	−0.02	11.98	0	5.30
2	OMe	7.57	7.44	0.13	12.44	0	5.62
3	$SCH_2CO_2C_2H_5$	7.00	6.51	0.49	14.67	0	6.03
4	SMe	6.76	7.17	−0.41	13.09	0	5.94
5	SO_2NMe_2	6.73	6.80	−0.06	13.99	0	4.02
6	SO_2NH_2 [a]	7.96	7.18	0.78	13.06	0	4.02
7	SO_2NHMe	6.86	6.99	−0.13	13.53	0	4.87
8	NH_2	9.00	8.61	0.39	12.19	1	4.67
9	NHMe	8.30	8.42	−0.12	12.65	1	5.49
10	$NHCH_2CO_2C_2H_5$	7.50	7.76	−0.27	14.23	1	5.77

[a] Data point not included in deriving equation. [b] Not included in the equation.

K_i rat adrenal membrane (Table 19)[47]



XIX

$$\log 1/K_i = -0.42(\pm 0.31)\text{CMR} + 1.07(\pm 0.59)\text{I}_\text{X} + 12.6(\pm 4.1) \quad (21)$$

$n = 9$, $r^2 = 0.855$, $s = 0.338$, $q^2 = 0.599$,
log $1/C = 6.8-9.0$

highest CMR = 12.5

r^2 Clog P Vs CMR = 0.015

outlier: SO_2NH_2

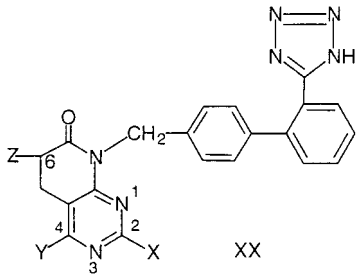
$I_X = 1$ for X = NHR

Table 20. I_{50} Data of Analogs of XX in Rat Liver Membrane[46]

	substituent			log 1/C				
no.	X	Y	Z	obsd	calcd (eq 22)	Δ	Clog P	$B1_Y$
1	Me	Me	H	8.28	8.04	0.25	3.40	1.52
2	Me	CF_3	H	7.61	7.46	0.15	3.87	1.99
3	Me	Me	Me	8.50	8.49	0.01	3.92	1.52
4	Me	C_2H_5	H	8.64	8.50	0.14	3.93	1.52
5	Me	$CHMe_2$	H	7.89	8.05	−0.16	4.33	1.90
6	Me	C_3H_7	H	8.75	8.96	−0.22	4.46	1.52
7	C_2H_5	Me	H	8.89	8.50	0.39	3.93	1.52
8	$CHMe_2$	Me	H	8.66	8.85	−0.19	4.33	1.52
9	C_3H_7	Me	H	8.87	8.96	−0.09	4.46	1.52
10	Me	CH_2OH	H[a]	7.64	6.70	0.94	1.86	1.52
11	Me	CHO	H	7.30	7.41	−0.11	2.87	1.60
12	CH_2OH	Me	H	6.55	6.70	−0.16	1.86	1.52

[a] Data point not included in deriving equation.

I_{50} rat liver membrane (Table 20)[46]



XX

$$\log 1/C = 0.87(\pm 0.21)\text{Clog } P - 2.11(\pm 0.97)B1_\text{Y} + 8.28(\pm 1.64) \quad (22)$$

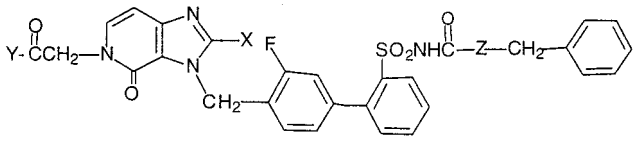
$n = 11$, $r^2 = 0.929$, $s = 0.224$,
$q^2 = 0.844$, log $1/C = 6.6-8.9$

highest CMR = 12.5

r^2 Clog P Vs CMR = 0.522

outlier: X = Me, Y = CH_2OH, Z = H

I_{50} rat adrenal gland (Table 21)[45]



XXI

$$\log 1/C = -0.23(\pm 0.09)\text{CMR} - 0.08(\pm 0.03)L_\text{Y} + 0.24(\pm 0.15)B1_\text{Y} + 12.89(\pm 1.68) \quad (23)$$

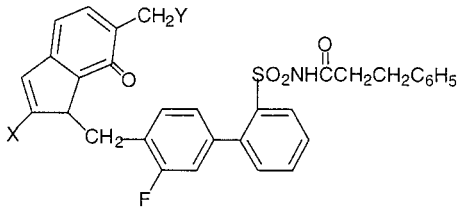
$n = 15$, $r^2 = 0.927$, $s = 0.064$,
$q^2 = 0.821$, log $1/C = 7.8-8.6$

highest CMR = 20.4

r^2 Clog P Vs CMR = 0.759

outlier: X = C_4H_9, Y = NH_2, Z = CH_2

I_{50} rat adrenal gland (Table 22)[45]



XXII

Table 21. I_{50} Data of Analogs of XXI in Rat Adrenal Gland[45]

	substituent			log 1/C						
no.	X	Y	Z	obsd	calcd (eq 23)	Δ	L_Y	$B1_Y$	CMR	Clog P[b]
1	C_4H_9	$NHCH_2CHMe_2$	CH_2	8.24	8.28	−0.04	6.07	1.35	19.32	6.07
2	C_4H_9	NHC_3H_7	CH_2	8.44	8.38	0.06	6.07	1.35	18.86	5.67
3	C_4H_9	$NHCMe_3$	CH_2	8.41	8.37	0.04	4.83	1.35	19.32	5.85
4	C_4H_9	$NHCH_2C_6H_5$	CH_2	7.94	7.85	0.09	8.24	1.35	20.44	6.18
5	C_4H_9	NC_5H_{10}	CH_2	8.40	8.34	0.06	6.17	1.91	19.61	5.96
6	C_4H_9	$N(C_2H_5)_2$	CH_2	8.30	8.37	−0.07	4.83	1.35	19.32	6.10
7	C_4H_9	NH_2	CH_2[a]	8.54	8.96	−0.42	2.78	1.35	17.47	4.21
8	C_3H_7	NHC_5H_{11}	CH_2	8.06	8.12	−0.06	8.13	1.35	19.32	6.20
9	C_3H_7	NHC_4H_9	CH_2	8.34	8.32	0.02	6.88	1.35	18.86	5.67
10	C_3H_7	NHC_3H_7	CH_2	8.57	8.49	0.08	6.07	1.35	18.39	5.14
11	C_3H_7	$NHCH_2CH_2CHMe_2$	CH_2	8.20	8.21	0.01	6.88	1.35	19.32	6.07
12	C_3H_7	$NHCH_2CH_2CH_2CHMe_2$	CH_2	7.84	7.89	−0.06	9.60	1.35	19.78	6.60
13	C_3H_7	$NHCMe_3$	CH_2	8.43	8.48	−0.05	4.83	1.35	18.86	5.32
14	C_3H_7	NC_5H_{10}	CH_2	8.44	8.44	0.00	6.17	1.91	19.14	5.43
15	C_4H_9	NC_5H_{10}	O	8.33	8.41	−0.08	6.17	1.91	19.30	6.30
16	C_3H_7	NC_5H_{10}	O	8.54	8.52	0.02	6.17	1.91	18.83	5.77

[a] Data point not included in deriving equation. [b] Not included in the equation.

Table 22. I_{50} Data of Analogs of XXII in Rat Adrenal Gland[45]

	substituent		log 1/*C*					
no.	X	Y	obsd	calcd (eq 24)	Δ	π_Y	L_Y	Clog *P*[b]
1	C_4H_9	$CONMe_2$	8.51	8.50	0.01	−1.51	4.77	5.12
2	C_3H_7	$CONMe_2$	8.57	8.50	0.07	−1.51	4.77	4.59
3	C_2H_5	$CONMe_2$	8.42	8.50	−0.08	−1.51	4.77	4.06
4	C_4H_9	C_6H_5	7.46	7.61	−0.16	1.96	6.28	7.12
5	C_4H_9	COC_6H_5	7.52	7.39	0.13	1.05	4.57	6.83
6	C_4H_9	$CH_2COC_6H_5$	7.41	7.41	0.0	1.01	4.57	7.04
7	C_4H_9	COMe[a]	7.06	7.86	−0.80	−0.55	4.06	5.28
8	C_4H_9	$COCMe_3$	7.77	7.64	0.13	0.69	4.87	6.73
9	C_4H_9	COC_4H_9	8.08	8.21	−0.13	1.04	6.92	6.86
10	C_4H_9	$COOC_2H_5$	8.36	8.09	0.27	0.51	5.95	6.07
11	C_4H_9	COOH	7.47	7.72	−0.25	−0.32	3.91	5.22

[a] Data point not included in deriving equation. [b] Not included in the equation.

$$\log 1/C = -0.41(\pm 0.13)\pi_Y + 0.35(\pm 0.17)L_Y + 6.23(\pm 0.89) \quad (24)$$

$n = 10$, $r^2 = 0.892$, s = 0.170, $q^2 = 0.783$, log $1/C = 7.1-8.6$

highest CMR = 20.1

r^2 Clog *P* Vs CMR = 0.720

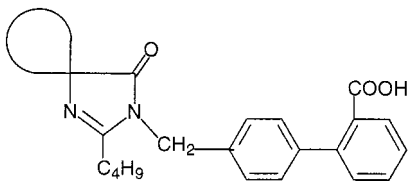
outlier: X= C_4H_9, Y = COMe

Table 23. I_{50} Data of Analogs of XXIII in Rat Liver Membrane[36]

		log 1/*C*			
no.	substituent	obsd	calcd (eq 25)	Δ	Clog *P*
1	$(CH_2)_2$	6.59	7.26	−0.68	4.54
2	$(CH_2)_3$	7.42	7.49	−0.07	5.10
3	$(CH_2)_4$	8.00	7.72	0.28	5.66
4	$(CH_2)_5$	8.14	7.95	0.20	6.22
5	$(CH_2)_6$	8.06	8.18	−0.12	6.78
6	$(CH_2)_2O(CH_2)_2$	7.33	6.97	0.36	3.82
7	$(CH_2)_2NH(CH_2)_2$	6.05	6.03	0.03	1.53
8	$(CH_2)_2CH(Me)(CH_2)_2$[a]	7.18	8.16	−0.98	6.74

[a] Data point not included in deriving equation.

I_{50} rat liver membrane (Table 23)[36]



XXIII

$$\log 1/C = 0.41(\pm 0.23)\text{Clog } P + 5.40(\pm 1.16) \quad (25)$$

$n = 7$, $r^2 = 0.811$ $s = 0.381$, $q^2 = 0.722$, log $1/C = 6.1-8.1$

highest CMR = 12.6

r^2 Clog *P* Vs CMR = 0.037

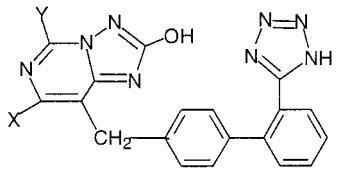
outlier: $(CH_2)_2CH(Me)(CH_2)_2$

Table 24. K_i Data of Analogs of XXIV in Rat Adrenal Membrane[47]

	substituent		log 1/K_i			
no.	X	Y	obsd	calcd (eq 26)	Δ	Clog *P*
1	C_3H_7	Me[a]	7.62	6.90	0.73	5.88
2	C_2H_5	Me	7.46	7.23	0.22	5.35
3	cy-C_3H_5	Me	7.09	7.29	−0.20	5.27
4	C_3H_7	H	7.34	7.21	0.12	5.38
5	C_3H_7	C_2H_5	6.65	6.56	0.09	6.41
6	C_3H_7	C_3H_7	6.18	6.22	−0.04	6.94
7	C_3H_7	CH_2OMe	7.04	7.36	−0.32	5.16
8	C_3H_7	CH_2OH	8.00	7.88	0.12	4.34

[a] Data point not included in deriving equation.

K_i rat adrenal membrane (Table 24)[47]



XXIV

$$\log 1/K_i = -0.64(\pm 0.26)\text{Clog } P + 10.7(\pm 1.5) \quad (26)$$

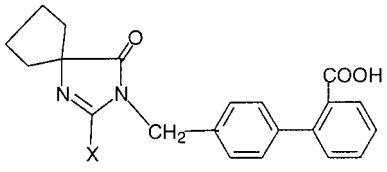
$n = 7$, $r^2 = 0.886$, $s = 0.216$ $q^2 = 0.816$, log $1/C = 6.2-8.0$

highest CMR = 12.9

r^2 Clog *P* Vs CMR = 0.253

outlier: X = C_3H_7, Y = Me

I_{50} rat liver membrane (Table 25)[36]



XXV

Table 25. I_{50} Data of Analogs of XXV in Rat Liver Membrane[36]

		log 1/*C*				
no.	substituent	obsd	calcd (eq 27)	Δ	L_X	Clog *P*[b]
1	H	5.00	4.70	0.30	2.06	3.55
2	Me	5.16	5.21	−0.05	2.87	4.43
3	C_3H_7[a]	7.57	6.50	1.07	4.92	5.49
4	C_3F_7	5.00	–	–	–	6.92
5	C_4H_9	8.00	7.28	0.72	6.17	6.01
6	C_5H_{11}	7.62	7.79	−0.17	6.97	6.54
7	cy−C_5H_9	6.39	6.48	−0.10	4.90	5.81
8	C_6H_5 [a]	5.28	7.35	−2.07	6.28	5.86
9	$CH_2C_6H_5$	5.60	6.31	−0.71	4.62	6.20

[a] Data points not included in deriving equation. [b] Not included in the equation.

$$\log 1/C = 0.63(\pm 0.35)L_X + 3.40(\pm 1.74) \quad (27)$$

$n = 6$, $r^2 = 0.859$, $s = 0.535$ $q^2 = 0.713$,

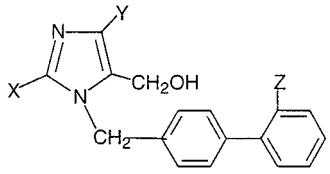
log 1/*C* = 5−8

highest CMR = 12.8

r^2 Clog *P* Vs CMR = 0.611

outliers: C_3H_7; C_6H_5, value of L for C_3F_7 lacking

I_{50} rat adrenal cortex (Table 26)[26]



XXVI

$$\log 1/C = 10.71(\pm 8.84)\text{CMR} - 0.45(\pm 0.40)(\text{CMR})^2 + 0.63(\pm 0.46)I_Z - 56.31(\pm 49.37) \quad (28)$$

$n = 15$, $r^2 = 0.852$, $s = 0.293$, $q^2 = 0.794$,

log 1/*C* = 4.6−7.9

opt. CMR = 11.86(11.41 − 16.81)

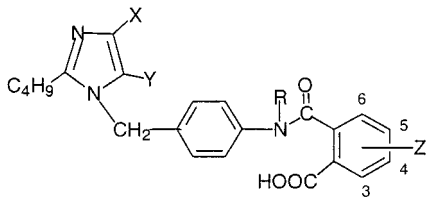
highest CMR = 12.39

r^2 Clog *P* Vs CMR = 0.185

outliers: X = C_5H_{11}, Y = Cl, Z = COOH; X = C_6H_{13}, Y = Cl, Z = COOH; X = C_6H_5, Y = Cl, Z = COOH

$I_Z = 1$ for Z = tetrazole group

I_{50} rat adrenal cortex (Table 27)[48]



XXVII

$$\log 1/C = 1.34(\pm 0.56)B1_{6,Z} + 5.23(\pm 0.75) \quad (29)$$

$n = 8$, $r^2 = 0.852$, $s = 0.218$, $q^2 = 0.714$,

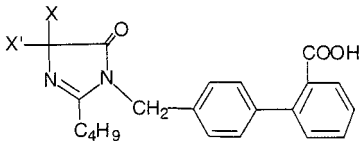
log 1/*C* = 5.2−7.8

highest CMR = 13.8

r^2 Clog *P* Vs CMR = 0.118

outliers: R = H, X = Cl, Y = CH_2CO_2Me, Z = 3,4,5,6-tetra-F; R = Me, X = Cl, Y = CH_2OMe, Z = 3,6-di-Cl

I_{50} rat liver membrane (Table 28)[36]



XXVIII

Table 26. I_{50} Data of Analogs of XXVI in Rat Adrenal Cortex[26]

	substituents			log 1/*C*					
no.	X	Y	Z	obsd	calcd (eq 28)	Δ	CMR	I_Z	Clog *P*[b]
1	C_2H_5	Cl	COOH	5.77	5.75	0.02	10.08	0	2.91
2	C_3H_7	Cl	COOH	6.80	6.40	0.40	10.55	0	3.44
3	C_4H_9	Cl	COOH	6.64	6.86	−0.22	11.01	0	3.97
4	C_5H_{11}	Cl	COOH[a]	6.01	7.12	−1.11	11.47	0	4.50
5	C_6H_{13}	Cl	COOH[a]	5.89	7.18	−1.30	11.94	0	5.03
6	*trans*-CH=$CHCH_2CH_3$	Cl	COOH	7.10	6.89	0.20	11.06	0	3.89
7	C_6H_5	Cl	COOH[a]	4.62	7.17	−2.55	11.67	0	4.21
8	C_4H_9	Br	COOH	7.05	7.04	0.01	11.30	0	4.05
9	C_4H_9	I	COOH	7.22	7.18	0.03	11.82	0	3.88
10	C_4H_9	H	COOH	6.57	6.37	0.20	10.52	0	3.32
11	C_4H_9	CF_3	COOH	7.21	6.87	0.34	11.03	0	4.30
12	C_4H_9	NO_2	COOH	6.59	6.94	−0.36	11.13	0	3.12
13	C_3H_7	Me	COOH	5.75	6.37	−0.62	10.52	0	3.01
14	C_4H_9	Cl	tetrazole	7.72	7.78	−0.06	11.58	1	3.37
15	C_4H_9	Br	tetrazole	7.72	7.81	−0.09	11.86	1	3.45
16	C_4H_9	I	tetrazole	7.70	7.69	0.01	12.39	1	3.28
17	C_4H_9	H	tetrazole	7.54	7.54	0.00	11.08	1	2.72
18	C_4H_9	CF_3	tetrazole	7.92	7.78	0.14	11.59	1	5.16

[a] Data points not included in deriving the equation. [b] Not included in the equation.

Table 27. I_{50} Data of Analogs of XXVII in Rat Adrenal Cortex[48]

	substituents				log 1/*C*				
no.	R	X	Y	Z	obsd	calcd (eq 29)	Δ	$B1_{6,Z}$	Clog P^b
1	H	Cl	$CH2CO_2Me$	H	6.85	6.68	0.17	1.0	3.41
2	H	CH_2CO_2Me	Cl	H	6.38	6.42	−0.04	1.0	3.51
3	H	Cl	CH_2OMe	H	6.55	6.42	0.13	1.0	3.51
4	H	Cl	CH_2CO_2Me	3,4,5,6-tetra-F[a]	6.10	7.14	−1.04	1.35	3.31
5	H	Cl	CH_2CO_2Me	$3\text{-}NO_2$	6.40	6.68	−0.28	1.0	2.83
6	H	Cl	CH_2CO_2Me	6-OMe	7.10	7.14	−0.04	1.35	3.39
7	H	Cl	CH_2CO_2Me	6-Me	7.50	7.36	0.13	1.52	3.51
8	H	Cl	CH_2CO_2Me	3,6-di-Cl	7.75	7.73	0.02	1.80	3.49
9	H	Cl	CH_2OMe	3,6-di-Cl	7.38	7.47	−0.09	1.80	3.59
10	Me	Cl	CH_2OMe	3,6-di-Cl[a]	5.24	7.47	−2.22	1.80	5.15

[a] Data points not included in deriving the equation. [b] Not included in the equation.

Table 28. I_{50} Data of Analogs of XXVIII in Rat Liver Membrane[36]

		log 1/*C*				
no.	substituent X = X′	obsd	calcd (eq 30)	Δ	CMR	Clog P^b
1	Me	7.46	7.66	−0.21	10.91	5.62
2	C_2H_5	7.25	7.13	0.12	11.84	6.68
3	C_3H_7	6.82	6.60	0.23	12.76	7.74
4	$CHMe_2$ [a]	7.70	6.60	1.10	12.76	4.48
5	cy-C_3H_5	7.10	6.76	0.34	12.49	6.33
6	C_4H_9	5.77	6.07	−0.30	13.69	8.79
7	CH_2CHMe_2	5.68	6.07	−0.39	13.69	8.53
8	C_6H_5	5.52	5.32	0.21	15.00	7.90

[a] Data point not included in deriving equation. [b] Not included in the equation.

$$\log 1/C = -0.57(\pm 0.25)\text{CMR} + 13.9(\pm 3.2) \quad (30)$$

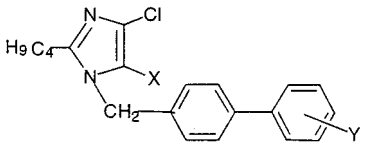
$n = 7$, $r^2 = 0.876$, $s = 0.319$, $q^2 = 0.753$,
$\log 1/C = 5.5-7.7$

highest CMR = 15

r^2 Clog *P* Vs *CMR* = 0.648

outlier: $X = X' = CHMe_2$

I_{50} rat adrenal cortex (Table 29)[26]



XXIX

$$\log 1/C = -1.23(\pm 0.48)\text{CMR} + 1.88(\pm 0.58)I_{2,Y} + 19.9(\pm 5.37) \quad (31)$$

$n = 10$, $r^2 = 0.895$, $s = 0.271$, $q^2 = 0.809$,
$\log 1/C = 5.0-7.7$

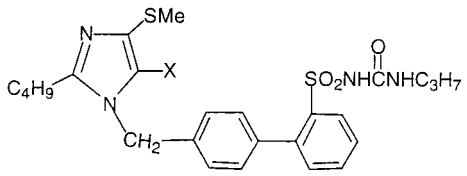
highest CMR = 12.9

r^2 Clog *P* Vs CMR = 0.663

outliers: $X = CH_2OH$, Y = 4-COOH;
$X = CH_2OH$, Y = 2-tetrazole, 5-CN

$I_{2,Y} = 1$ for 2-tetrazolyl derivative

I_{50} pithed rat (Table 30)[44]



XXX

$$\log 1/C = 7.79(\pm 2.08)\text{CMR} - 0.24(\pm 0.06)(\text{CMR})^2 - 55.6(\pm 16.8) \quad (32)$$

$n = 12$, $r^2 = 0.893$, $s = 0.157$, $q^2 = 0.816$,
$\log 1/C = 5.8-7.5$

Table 29. I_{50} Data of XXIX in Rat Adrenal Cortex[26]

	substituents		log 1/*C*					
no.	X	Y	obsd	calcd (eq 31)	Δ	CMR	$I_{2,Y}$	Clog P^b
1	CH_2OH	2-tetrazole	7.72	7.57	0.16	11.58	1	3.37
2	CH_2OMe	$2\text{-}CH_2$-tetrazole	6.52	6.43	0.10	12.50	1	3.85
3	CH_2OMe	2-CONH-tetrazole	6.16	5.93	0.22	12.91	1	2.03
4	CHO	2-tetrazole	7.70	7.71	−0.01	11.46	1	4.28
5	CH_2OH	2-COOH	6.64	6.38	0.26	11.01	0	3.97
6	CH_2OH	3-COOH	6.31	6.38	−0.07	11.01	0	4.85
7	CH_2OH	4-COOH[a]	4.96	6.38	−1.42	11.01	0	4.85
8	CH_2OH	2-COOH,3-Me	5.72	5.81	−0.09	11.47	0	4.47
9	CH_2OH	2-COOH,6-OMe	5.52	5.62	−0.10	11.63	0	3.55
10	CH_2OH	2-tetrazole,4-OMe	6.24	6.81	−0.57	12.19	1	3.28
11	CH_2OH	2-tetrazole,5-OMe	6.92	6.81	0.11	12.19	1	3.28
12	CH_2OH	2-tetrazole,5-CN[a]	6.29	6.98	−0.69	12.05	1	2.80

[a] Data points not included in deriving equation. [b] Not included in the equation.

Table 30. I_{50} Data of Analogs of XXX in Pithed Rat[44]

no.	substituent	log 1/*C* obsd	log 1/*C* calcd (eq 32)	Δ	CMR	Clog *P*[b]
1	COOH	6.62	6.52	0.11	14.67	5.39
2	CH_2OH	6.40	6.49	−0.09	14.64	4.93
3	H	5.86	5.97	−0.12	14.02	5.97
4	$COOCH_2C_6H_5$	6.50	6.40	0.11	17.65	7.87
5	$COOCMe_3$	6.78	6.95	−0.17	16.53	7.28
6	$COOC_2H_5$	6.86	6.94	−0.09	15.60	6.57
7	CONHMe[a]	7.45	6.87	0.58	15.35	4.73
8	CONHCH(COOH) $CH(Me)CH_2CH_3$	6.25	6.23	0.03	17.86	6.51
9	$CONH_2$	6.96	6.65	0.31	14.89	4.41
10	$CONHCH_2COOMe$	7.09	6.96	0.13	16.47	4.74
11	$CONHCH_2COOH$	7.00	6.99	0.01	16.00	4.53
12	CONHCOMe	6.81	6.98	−0.17	15.85	4.54
13	$CONHSO_2C_6H_5$	5.77	5.83	−0.06	18.27	6.22

[a] Data point not included in deriving equation. [b] Not included in the equation.

opt. CMR = 16.1(15.9−16.2)

highest CMR = 18.3

r^2 Clog *P* Vs CMR = 0.223

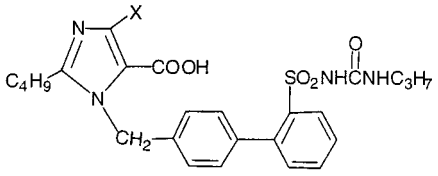
outlier: CONHMe

Table 31. I_{50} Data of XXXI in Rat Liver Membrane[44]

no.	substituent	log 1/*C* obsd	log 1/*C* calcd (eq 33)	Δ	Clog *P*
1	SMe	6.62	6.41	0.21	5.38
2	SC_6H_5	5.96	5.66	0.30	7.16
3	S-2-thienyl	5.48	5.71	−0.23	7.03
4	$S(CH_2)_3OH$	6.73	6.66	0.07	4.77
5	$S(CH_2)_4OH$	6.70	6.58	0.13	4.98
6	$S(CH_2)_4OCOMe$	6.03	6.18	−0.15	5.92
7	$SCH_2CF_2CF_2CH_2OH$	5.91	6.19	−0.28	5.91
8	SCF_3[a]	6.74	5.94	0.79	6.49
9	$SCHF_2$[a]	6.92	6.22	0.70	5.82
10	SCH_2CF_3	5.88	5.87	0.02	6.67
11	SOMe	6.60	6.55	0.06	5.04
12	SO_2Me	6.98	7.08	−0.10	3.77
13	Cl	6.52	6.54	−0.02	5.06

[a] Data points not included in deriving equation.

I_{50} rat liver membrane (Table 31)[44]



XXXI

$$\log 1/C = -0.42(\pm 0.13)\text{Clog } P + 8.66(\pm 0.73) \quad (33)$$

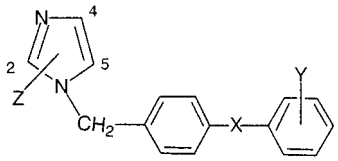
$n = 11$, $r^2 = 0.858$, $s = 0.188$, $q^2 = 0.767$,
log 1/*C* = 5.5−7.0

highest CMR = 17.2

r^2 Clog *P* Vs CMR = 0.185

outliers: SCF_3; $SCHF_2$

I_{50} rat adrenal cortex (Table 32)[50]



XXXII

$$\log 1/C = -0.54(\pm 0.14)\text{Clog } P - 8.83(\pm 1.92)B1_{2,Z} - 1.62(\pm 1.22)B1_{5,Z} + 24.66(\pm 4.20) \quad (34)$$

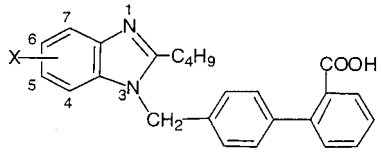
$n = 17$, $r^2 = 0.904$, $s = 0.197$, $q^2 = 0.785$,
log 1/*C* = 4.9−6.9

highest CMR = 13.81

r^2 Clog *P* Vs CMR = 0.095

outliers: X = −, Y = 3-COOH, Z = 2-C_4H_9, 5-CH_2OH; X = *trans*-CH=CH, Y = 2-COOH, Z = 2-C_4H_9, 4-Cl, 5-CH_2OH

I_{50} rat lung (Table 33)[49]



XXXIII

$$\log 1/C = -0.65(\pm 0.28)MR_4 + 0.37(\pm 0.28)MR_6 + 0.25(\pm 0.24)\pi_7 + 6.17(\pm 0.16) \quad (35)$$

$n = 14$, $r^2 = 0.830$, $s = 0.169$ $q^2 = 0.552$,
log 1/*C* = 5.2−6.7

highest CMR = 15

r^2 Clog *P* Vs CMR = 0.655

Table 32. I_{50} Data of Analogs of XXXII in Rat Adrenal Cortex[50]

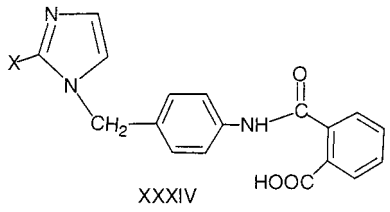
	substituents			log 1/*C*					
no.	X	Y	Z	obsd	calcd (eq 34)	Δ	Clog *P*	$B1_{2,Z}$	$B1_{5,Z}$
1	NHCO	2-COOH	2-C_4H_9,4-Cl,5-CH_2COOCH_3	6.85	6.93	−0.08	3.41	1.52	1.52
2	−	3-COOH	2-C_4H_9,4-Cl,5-CH_2OH	6.31	6.16	0.16	4.85	1.52	1.52
3	−	3-COOH	2-C_4H_9,5-CH_2OH[a]	5.96	6.50	−0.54	4.20	1.52	1.52
4	−	3-COOH	2-C_4H_9,4-Cl,5-CH_2OCOMe	5.60	5.69	−0.09	5.70	1.52	1.52
5	−	3-COOH	2-C_4H_9,4-Cl,5-CH_2OMe	5.54	5.72	−0.18	5.66	1.52	1.52
6	CO	2-COOH	2-C_4H_9,4-Cl,5-CH_2OH	6.80	6.90	−0.10	3.46	1.52	1.52
7	CO	2-COOH	2-C_4H_9,4-CH_2OH,5-Cl	6.47	6.39	0.08	3.56	1.52	1.80
8	CO	2-COOH	2-C_4H_9,4-CH_2OCOMe,5-Cl	5.85	5.93	−0.08	4.42	1.52	1.80
9	CO	2-COOH	2-C_4H_9,4-Cl,5-CH_2OMe	6.82	6.46	0.36	4.28	1.52	1.52
10	O	2-COOH	2-C_4H_9,4-Cl,5-CH_2OH	6.40	6.27	0.13	4.63	1.52	1.52
11	S	2-COOH	2-C_4H_9,4-Cl,5-CH_2OH	6.40	6.29	0.11	4.60	1.52	1.52
12	OCH_2	2-COOH	2-C_4H_9,4-Cl,5-CH_2OH	6.04	6.26	−0.23	4.65	1.52	1.52
13	OCH_2	2-COOH	2-C_4H_9,5-CH_2OH	6.51	6.61	−0.10	4.00	1.52	1.52
14	OCH_2	2-COOH	2-C_4H_9,4-Cl,5-CH_2OCOMe	5.75	5.80	−0.06	5.50	1.52	1.52
15	OCH_2	2-COOH	2-C_4H_9,4-Cl,5-CH_2OMe	5.92	5.82	0.10	5.46	1.52	1.52
16	OCH_2	2-COOH	2-C_3H_7S,5-CH_2OH	5.23	4.93	0.30	4.16	1.70	1.52
17	OCH_2	2-COOH	2-C_2H_5S,5-CH_2OH	4.92	5.22	−0.30	3.64	1.70	1.52
18	trans-CH=CH	2-COOH	2-C_4H_9,4-Cl,5-CH_2OH[a]	5.27	5.94	−0.67	5.25	1.52	1.52
19	NHCONH	2-$NHSO_2CF_3$	2-C_4H_9,4-Cl,5-CH_2OMe	5.62	5.63	−0.01	5.82	1.52	1.52

[a] Data points not included in deriving the equation.

Table 33. I_{50} Data of Analogs of XXXIII in Rat Lung[49]

		log 1/*C*						
no.	substituent	obsd	calcd (eq 35)	Δ	MR_4	MR_6	π_7	Clog *P*[b]
1	H	6.40	6.14	0.26	0.10	0.10	0.0	6.09
2	4-Me	5.92	5.84	0.08	0.57	0.10	0.0	6.59
3	5-Me	5.92	6.14	−0.22	0.10	0.10	0.0	6.59
4	6-Me	6.07	6.31	−0.24	0.10	0.57	0.0	6.59
5	7-Me	6.32	6.28	0.04	0.10	0.10	0.56	6.59
6	4-NH_2	5.77	5.86	−0.09	0.54	0.10	0.0	5.55
7	5-NH_2	6.09	6.14	−0.05	0.10	0.10	0.0	5.55
8	6-NH_2	6.27	6.30	−0.03	0.10	0.54	0.0	5.55
9	7-NH_2	5.97	5.83	0.14	0.10	0.10	−1.23	5.55
10	4-NHCOMe	5.24	5.24	0.0	1.49	0.10	0.0	5.73
11	5-NHCOMe	6.34	6.14	0.20	0.10	0.10	0.0	5.73
12	6-NHCOMe	6.74	6.65	0.09	0.10	1.49	0.0	5.73
13	7-NHCOMe	5.74	5.90	−0.16	0.10	0.10	−0.97	5.73
14	5-NHCONH-cy-C_6H_{11}	6.10	6.14	−0.04	0.10	0.10	0.0	7.82

I_{50} rat adrenal cortex (Table 34)[48]



XXXIV

$$\log 1/C = 1.29(\pm 0.44)\mathrm{CMR} - 7.85(\pm 3.70)\log(\beta \times 10^{\mathrm{CMR}} + 1) - 7.83(\pm 4.45) \quad (36)$$

$n = 11$, $r^2 = 0.880$, $s = 0.371$, $q^2 = 0.781$,
$\log 1/C = 4.0 - 6.6$

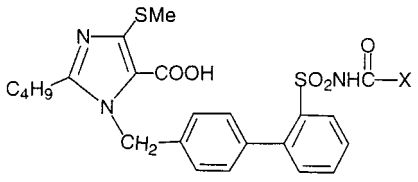
opt. CMR = 11.64(±0.27)

highest CMR = 12.51

r^2 Clog *P* Vs CMR = 0.789

outlier: CH_2(4-OMe-C_6H_4)

I_{50} pithed rat (Table 35)[44]



XXXV

$$\log 1/C = 0.50(\pm 0.16)\mathrm{CMR} - 1.24(\pm 1.24) \quad (37)$$

$n = 9$, $r^2 = 0.881$, $s = 0.120$, $q^2 = 0.803$,
$\log 1/C = 5.0 - 6.4$

highest CMR = 15.9

r^2 Clog *P* Vs CMR = 0.787

outliers: NHMe; OC_2H_5; $CH_2C_6H_5$

Table 34. I_{50} Data of Analogs of XXXVI in Rat Adrenal Cortex[48]

		log 1/*C*				
no.	substituents	obsd	calcd (eq 36)	Δ	CMR	Clog *P*[b]
1	H	4.00	3.71	0.29	8.91	1.23
2	Me	4.00	4.30	−0.30	9.38	1.50
3	C_2H_5	5.07	4.89	0.18	9.84	2.03
4	$(CH_2)_2CH_3$	5.43	5.46	−0.03	10.31	2.56
5	$(CH_2)_3CH_3$	6.21	5.98	0.23	10.77	3.08
6	$(CH_2)_4CH_3$	6.62	6.35	0.27	11.23	3.61
7	$(CH_2)_5CH_3$	6.46	6.35	0.11	11.70	4.14
8	$(CH_2)_6CH_3$	5.96	5.64	0.32	12.16	4.67
9	$(CH_2)_2C_6H_5$	5.03	5.08	−0.05	12.35	3.44
10	CH_2(4-OMe−C_6H_4)[a]	5.60	−89.76	95.37	12.51	3.21
11	$CH_2-C_6H_{11}$	5.55	6.02	−0.47	11.98	4.15
12	$CHMe_2$	4.92	5.46	−0.54	10.31	2.43

[a] Data point not included in deriving equation. [b] Not included in the equation.

Table 35. I_{50} Data of Analogs of XXXV in Pithed Rat[44]

		log 1/*C*			
no.	substituent	obsd	calcd (eq 37)	Δ	CMR
1	NHMe[a]	5.02	5.56	−0.54	13.74
2	NHC_2H_5	5.68	5.78	−0.10	14.21
3	NHC_3H_7	6.13	6.01	0.12	14.67
4	$NHCH_2CH=CH_2$	5.98	6.00	−0.02	14.65
5	NHC_4H_9	6.43	6.25	0.18	15.14
6	OMe	5.53	5.45	0.08	13.52
7	OC_2H_5 [a]	6.15	5.68	0.47	13.99
8	OC_4H_9	5.97	6.14	−0.17	14.92
9	OCH_2CHMe_2	6.12	6.14	−0.02	14.92
10	Me	5.40	5.37	0.03	13.38
11	C_3H_7	5.75	5.83	−0.08	14.30
12	$CH_2C_6H_5$ [a]	5.52	6.61	−1.09	15.89

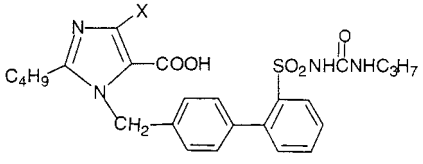
[a] Data points not included in deriving equation.

Table 36. I_{50} Data of Analogs of XXXVI in Rat[44]

		log 1/*C*				
no.	substituents	obsd	calcd (eq 38)	Δ	CMR	Clog *P*[b]
1	SMe	6.13	5.87	0.26	14.67	5.38
2	$S(CH_2)_3OH$	5.01	5.19	−0.18	15.75	4.77
3	$S(CH_2)_4OH$	4.79	4.89	−0.10	16.22	4.98
4	$SCH_2CF_2CF_2CH_2OH$	5.11	4.85	0.26	16.28	5.91
5	SCH_2SMe[a]	5.33	5.07	0.27	15.94	5.60
6	SCF_3	5.67	5.84	−0.17	14.72	6.49
7	$SCHF_2$	5.90	5.85	0.05	14.70	5.82
8	SCH_2CF_3	5.43	5.55	−0.12	15.18	6.67
9	Cl[a]	5.24	6.37	−1.13	13.89	5.06

[a] Data points not included in deriving equation. [b] Not included in the equation.

I_{50} rat (Table 36)[44]



XXXVI

$$\log 1/C = -0.64(\pm 0.31)\text{CMR} + 15.2(\pm 4.7) \quad (38)$$

$n = 7$, $r^2 = 0.849$, $s = 0.210$, $q^2 = 0.670$,

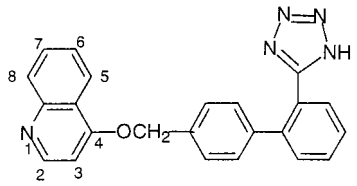
$\log 1/C = 4.8-6.1$ highest CMR = 16.*3*

r^2 Clog *P* Vs CMR = 0.184

outliers: SCH_2SMe; Cl

C. Guinea Pig Angiotensin Antagonists

I_{50} guinea pig adrenal membrane (Table 37)[51]



XXXVII

$$\log 1/C = -1.17(\pm 0.59)B1_6 - 0.43(\pm 0.26)L_7 - 0.94(\pm 0.28)B5_8 - 1.0(\pm 0.48)\sigma + 10.7(\pm 1.30) \quad (39)$$

$n = 20$, $r^2 = 0.853$, $s = 0.312$, $q^2 = 0.766$,

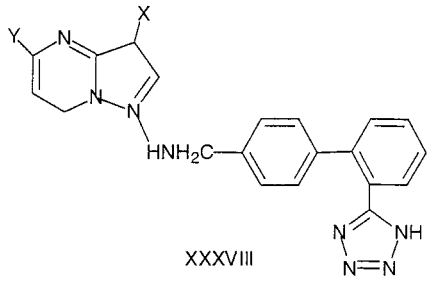
$\log 1/C = 5.7-8.2$ highest CMR = 13.6

r^2 Clog *P* Vs CMR = 0.316

outliers: 2,6-di-Me; 2-C_2H_5, 6-COOMe

D. Human Angiotensin Antagonists

K_i human recombinant AT1 receptor (Table 38)[52a]



XXXVIII

$$\log 1/K_i = 14.88(\pm 6.35)\text{CMR} - 0.65(\pm 0.26)(\text{CMR})^2 + 1.33(\pm 0.75)B1_X - 77.69(\pm 39.14) \quad (40)$$

$n = 17$, $r^2 = 0.902$, $s = 0.352$, $q^2 = 0.812$,

$\log 1/C = 6.0-9.8$

opt. CMR = 11.47(10.8 − 11.8)

highest CMR = 13.98

r^2 Clog *P* Vs CMR = 0.861

outliers: X = H, Y = H; X = H, Y = NMe_2

Table 37. I_{50} Data of Analogs of XXXVII in Guinea Pig Adrenal Membrane[51]

		log 1/*C*							
no.	substituent	obsd	calcd (eq 39)	Δ	$B1_6$	L_7	$B5_8$	σ^b	Clog P^d
1	2-Me	7.80	7.66	0.13	1.0	2.06	1.0	0.0	5.50
2	2-C_2H_5	7.51	7.66	−0.16	1.0	2.06	1.0	0.0	6.03
3	2-C_2H_5,5-Me	7.89	7.73	0.15	1.0	2.06	1.0	−0.07	6.53
4	2-C_2H_5,5-Cl	6.92	7.30	−0.37	1.0	2.06	1.0	0.37	6.76
5	2-C_2H_5,5-CN	7.22	7.11	0.12	1.0	2.06	1.0	0.56	5.56
6	2,6-di-Me[a]	6.33	7.23	−0.90	1.52	2.06	1.0	−0.17	6.00
7	2-Me,6-Cl	5.92	6.50	−0.58	1.80	2.06	1.0	0.23	6.23
8	2-C_2H_5,6-CN	6.44	6.31	0.14	1.60	2.06	1.0	0.66	5.56
9	2-C_2H_5,6-CF_3	6.07	5.97	0.10	1.99	2.06	1.0	0.54	6.97
10	2-C_2H_5,6-COOMe[a]	7.18	6.47	0.71	1.64	2.06	1.0	0.45	6.06
11	2-C_2H_5,6-OMe	7.66	7.53	0.13	1.35	2.06	1.0	−0.27	6.30
12	2-C_2H_5,6-$OCHMe_2$	7.59	7.55	0.04	1.35	2.06	1.0	−0.29	7.13
13	2-C_2H_5,6-OCH_2CH_2F	8.16	7.55	0.61	1.35	2.06	1.0	−0.29[c]	6.55
14	2-C_2H_5,6-OCH_2CF_3	7.59	7.55	0.04	1.35	2.06	1.0	−0.29[c]	7.58
15	2-C_2H_5,7-Me	6.85	7.39	−0.53	1.0	2.87	1.0	−0.07	6.53
16	2-C_2H_5,7-Cl	6.80	6.67	0.13	1.0	3.52	1.0	0.37	6.76
17	2-C_2H_5,7-CN	6.34	6.17	0.17	1.0	4.23	1.0	0.56	5.56
18	2-C_2H_5,7-OMe	6.66	6.72	−0.06	1.0	3.98	1.0	0.12	6.30
19	2-Me,8-Me	6.51	6.85	−0.35	1.0	2.06	2.04	−0.17	6.00
20	2-C_2H_5,8-Cl	6.85	6.68	0.17	1.0	2.06	1.80	0.23	6.76
21	2-C_2H_5,8-CF_3	5.70	5.61	0.09	1.0	2.06	2.61	0.54	6.97
22	2-C_2H_5,8-OMe	6.02	5.98	0.04	1.0	2.06	3.07	−0.27	6.30

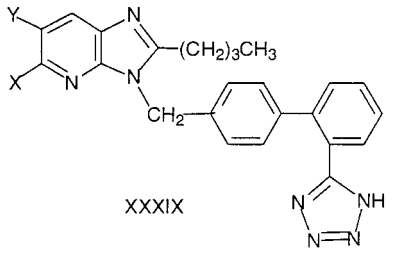
[a] Data points not included in deriving equation. [b] σ values for 2 position are essentially constant so they have not been parametrized. [c] Estimated values of σ. [d] Not included in the equation.

Table 38. K_i Data of Analogs of XXXVIII for Human Recombinant AT 1 Receptor[52a]

			log 1/K_i					
	substituents			calcd				Clog
no.	X	Y	obsd	(eq 40)	Δ	CMR	$B1_X$	P^c
1	H	C_2H_5	9.51	8.99	0.52	11.47	1.00	3.88
2	Me	Me	9.70	9.67	0.03	11.47	1.52	3.62
3	Me	C_2H_5	9.59	9.53	0.05	11.94	1.52	4.15
4	C_2H_5	Me	9.14	9.53	−0.40	11.94	1.52	4.15
5	C_2H_5	C_2H_5	9.62	9.12	0.51	12.40	1.52	4.68
6	C_3H_7	C_2H_5	8.89	8.42	0.47	12.87	1.52	5.21
7	C_6H_5	C_2H_5	5.96	5.83	0.13	13.99	1.71	5.77
8	OMe	C_2H_5	9.05	9.20	−0.15	12.09	1.35	4.15
9	Cl	C_2H_5	9.77	9.89	−0.12	11.97	1.80	4.60
10	$CO_2C_2H_5$	C_2H_5	7.77	8.21	−0.44	13.05	1.64	4.43
11	H	H[b]	7.40	8.43	−1.03	10.55	1.00	2.85
12	H	Me	9.02	8.85	0.18	11.01	1.00	3.35
13	H	C_3H_7	9.19	8.84	0.34	11.94	1.00	4.41
14	H	C_6H_5	7.00	7.36	−0.36	13.06	1.00	4.95
15	H	Cl	8.59	8.86	−0.28	11.04	1.00	3.57
16	H	OMe	8.80	8.92	−0.13	11.16	1.00	3.64
17	H	OC_2H_5	8.89	8.97	−0.08	11.63		4.17
18	H	SMe	8.64	8.91	−0.27	11.82	1.00	3.99
19	H	NMe_2 [b]	7.66	8.90	−1.24	11.84	1.00	3.57

[b] Data points not included in deriving equation. [c] Not included in the equation

I_{50} human recombinant AT1 receptor (Table 39)[52b]



XXXIX

$$\log 1/C = -0.30(\pm 0.10)L_X + 0.24(\pm 0.16)\text{CMR} + 0.91(\pm 0.43)\text{Clog } P - 1.39(\pm 0.49)\log(\beta \times 10^{\text{Clog } P} + 1) + 3.99(\pm 2.94) \quad (41)$$

$$n = 27,\ r^2 = 0.899,\ s = 0.111,\ q^2 = 0.849,$$

$$\log 1/C = 7.9 - 9.4$$

$$\text{opt. Clog } P = 3.80(\pm 0.61)$$

$$\text{highest CMR} = 16.28$$

$$r^2 \text{ Clog } P \text{ Vs CMR} = 0.067$$

outliers: X = Me, Y = 5-Me-pyridin-2-yl; X = Me, Y = 4-Me-pyridin-2-yl; X = C_2H_5, Y = pyridin-2-yl; X = COMe, Y = 1-oxo-pyridin-2-yl; X = COMe, Y = pyridin-2-yl

In looking through QSAR 19−38 for rat angiotensin receptor, it is observed that all sets contain the biphenyl moiety except 27 and 34. Three acid functions are also present: tetrazole, COOH, and $-SO_2NH$. Only five QSAR (19, 20, 22, 25, and 35) contain modest positive hydrophobic terms. The range of activity is narrow except for QSAR 22, where the pyrimidine ring appears to be well positioned for hydrophobic interactions. Most of the activity is associated with overall bulk (CMR) or specific steric effects modeled by sterimol parameters.

Equation 39 for angiotensin receptor in guinea pig adrenal membrane shows steric interactions of the ligand with the receptor. Bulky groups on the left-hand side of the biphenyl moiety reduce the activity. However, this is only one example for this system; still it is consistent with other systems and QSARs obtained for them.

Results with the human AT 1 receptor (eqs 40 and 41) are of interest because here in eq 41 we find the

Table 39. I_{50} Data of Analogs of XXXIX for Human Recombinant AT 1 Receptor[52b]

	substituents		log 1/*C*					
no.	X	Y	obsd	calcd (eq 41)	Δ	L_X	Clog *P*	CMR
1	CH_2OH	1-oxo-pyridin-2-yl	9.09	9.04	0.04	3.97	3.50	15.10
2	CH_2OH	pyridin-2-yl	9.09	8.91	0.18	3.97	4.16	14.95
3	Me	1-oxo-pyridin-2-yl	8.85	8.89	−0.03	2.87	5.03	14.95
4	$CH(OMe)_2$	pyridin-2-yl	8.81	8.72	0.09	4.78	4.70	16.03
5	COOMe	1-oxo-pyridin-2-yl	8.75	8.94	−0.19	4.73	3.54	15.60
6	COOMe	pyridin-2-yl	8.73	8.79	−0.06	4.73	4.20	15.45
7	$CH(OMe)_2$	1-oxo-pyridin-2-yl	8.84	8.99	−0.16	4.78	4.04	16.18
8	$CH(OMe)_2$	pyridin-4-yl	8.87	8.80	0.07	4.78	4.49	16.03
9	CH_2OH	1-oxo-pyridin-4-yl	9.07	9.01	0.05	3.97	3.29	15.10
10	CH_2OH	pyridin-4-yl	8.98	8.96	0.01	3.97	3.95	14.95
11	Me	1-oxo-pyridin-4-yl	9.04	8.98	0.06	2.87	4.82	14.95
12	Me	pyridin-4-yl	8.61	8.64	−0.03	2.87	5.49	14.80
13	Me	1-oxo-pyridin-3-yl	8.98	8.98	0.0	2.87	4.82	14.95
14	Me	pyridin-3-yl	8.59	8.64	−0.05	2.87	5.49	14.80
15	Me	1-oxo,5-Me-pyridin-2-yl	8.83	8.77	0.07	2.87	5.53	15.41
16	Me	5-Me-pyridin-2-yl[a]	8.67	3.84	4.83	2.87	6.20	15.26
17	Me	1-oxo,4-Me-pyridin-2-yl	8.79	8.77	0.03	2.87	5.53	15.41
18	Me	4-Me-pyridin-2-yl[a]	9.43	3.84	5.59	2.87	6.20	15.26
19	H	1-oxo-pyridin-2-yl	8.88	9.11	−0.23	2.06	4.83	14.49
20	H	pyridin-2-yl	8.87	8.77	0.10	2.06	5.50	14.33
21	Me	1-oxo-6-Me-pyridin-2-yl	8.68	8.77	−0.09	2.87	5.53	15.41
22	Me	6-Me-pyridin-2-yl	8.60	8.42	0.18	2.87	6.20	15.26
23	CH_2SO_2Me	1-oxo-pyridin-2-yl	8.72	8.73	−0.01	4.92	2.66	16.29
24	CH_2SO_2Me	pyridin-2-yl	9.05	8.98	0.06	4.92	3.33	16.13
25	$CHCH_2$	pyridin-2-yl	7.90	7.99	−0.09	4.29	6.22	15.31
26	C_2H_5	1-oxo-pyridin-2-yl	8.30	8.38	−0.08	4.11	5.56	15.41
27	C_2H_5	pyridin-2−yl[a]	8.67	3.45	5.22	4.11	6.23	15.26
28	CH_2OMe	1-oxo-pyridin-2-yl	8.85	8.76	0.09	4.78	4.31	15.57
29	COMe	1-oxo-pyridin-2-yl[a]	8.10	4.09	4.01	4.06	5.00	15.45
30	COMe	pyridin-2-yl[a]	8.75	3.74	5.01	4.06	5.67	15.30
31	$CHMe_2$	1-oxo-pyridin-2-yl	8.35	8.30	0.05	4.11	5.96	15.88
32	$CHMe_2$	pyridin-2-yl	7.90	7.95	−0.05	4.11	6.62	15.72

[a] Data points not included in deriving equation.

Clog *P* is important and that an optimum of 3.80 can be established. This is near to the value of 4.1 for the drug losartan. As for eq 40, we kept it with CMR as it gave a better QSAR, but it should be noted that the mutual correlation between Clog *P* and CMR is high ($r^2 = 0.861$).

Equation 20 suggests that modest increase in activity might be obtained by increased bulk. Just how much is not clear. The log *P* term in this QSAR is of marginal value. The highest log 1/*C* for any of the QSAR is 10.1. This is probably close to the limit. However, what is completely lacking is some idea of what the optimum log *P* would be for results in whole animals. It is known that $-COO^-$ has a π value of about 4 log units lower than −COOH. No data is available for the tetrazole or sulfonamides. What needs to be done is to measure some log *P* values at pH 7.4. Compounds XX without 4-substituents would be a good place to start. Bioavailability is clearly dependent on log *P*. For this reason, we have included Clog *P* values in every set even though they do not sometimes appear in the QSAR (the instances are marked) so that some feeling can be estimated for whole animal studies.

IV. Conclusions

Carini et al.[26] proposed Figure 2, based on their following observations. The presence of biphenyl group enhanced the oral activity, but the presence

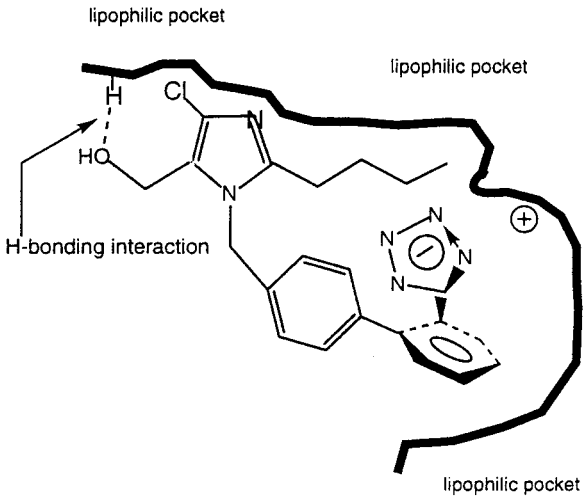


Figure 2.

of a linker chain between the two phenyl moieties reduces the activity. The acidic isostere imparts highest activity to the drug molecule when present at the ortho position. A short alkyl chain at the 2 position of imidazole or the fused imidazole ring is needed for efficient binding to the receptor. The imidazole ring is required as an acceptor in a hydrogen-bonding interaction with the receptor.

It appears that all the molecules designed to study AT 1 receptor antagonistic activity are based on this model as all the molecules have these pharmaco-

phores i.e., a nitrogen atom in the imidazole/hetrocyclic ring, an alkyl side chain, and an acidic moiety and these are connected through the biphenyl group as spacer. We could derive 39 QSARs from the data reported in the literature as referenced with each QSAR. To summarize our general thoughts about all of the QSAR derived by us, we conclude as follows.

The 39 QSAR derived by us provide an overview of the structure−activity relationships for a variety of compounds in various systems. To our knowledge, these are the first QSAR for angiotensin antagonists. None of the data sets are ideally designed, but they do offer ideas for further work.

The most important conclusion is the lack of importance for hydrophobic interactions with the receptors. We cannot say anything about the area where the biphenyl unit binds. Out of the 39 QSAR, only 11 equations contain positive log *P* or π terms (3, 5, 13, 14, 15, 19, 20, 22, 25, 35, and 41). Of these, the term in eqs 5, 20, and 35 are of marginal importance. Equation 3 has a small positive term and then a large linear negative term. There is little variation in X so that Y has the greatest influence. Since the CH_2 linker unit provides considerable flexibility, it is not clear where Y is binding. We have the same problem with eq 13. Where X binds is not clear, but it could be in the same area as Y in eq 3. Equation 14 is also similar where Y does not contact hydrophobic space but X does. Equation 40 is the most interesting in that it defines an optimum log *P* not too far from that of eq 3 and that is near that of losartan. However, in QSAR 3 and 41, only small limited regions of the receptor are being explored. Negative hydrophobic terms are found in QSAR 8, 10, 11, 24, 26, 33, and 34. Clearly the receptors are largely polar in character. The most commonly occurring parameter is CMR or MR (eqs 1, 2, 4, 6, 7, 12, 20, 21, 23, 28, 30, 31, 32, 35, 36, 37, 38, 40, and 41). Sometimes these terms are positive and sometimes negative.

A point for confusion here is the fact that all but five QSAR (6, 9, 12, 29, and 36) contain a biphenyl moiety and in these cases other bulky units are present. Although the biphenyl unit is clearly strongly hydrophobic, from the data in hand we cannot conclude that its role is hydrophobic or simply a CMR-type effect. Since there *can* be considerable collinearity (r^2 Clog *P* Vs CMR > 0.7) between Clog *P* or π and CMR or MR that might hide hydrophobic effects, we have indicated the degree of collinearity between these parameters for each QSAR, and it needs further investigation.

We need to examine the instances where optimum hydrophobic terms can be established.

QSAR	opt. log *P*	highest log 1/*C*
3	4.5	10.1
13	6.4	8.5
40	3.8	9.4

Two of these values are near 4.03, the Clog *P* for the drug losartan. The reason for the one high value is not obvious. There are four examples where the optimum CMR values are found.

Chart 2

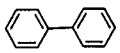
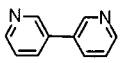
drug	acidic group	ClogP	CMR
losartan	tetrazole	4.03	11.64
valsartan	tetrazole	5.08	12.20
irbesartan	tetrazole	6.04	12.31
candesartan	terazole	5.43	12.12
eprosartan	COOH	5.05	11.88
telmisartan	COOH	7.46	15.47
tasosartan	tetrazole	3.06	11.61
saprisartan	$NHSO_2CF_3$	6.28	13.87

QSAR	opt. CMR	highest log 1/*C*
1	18.6	10.3
28	11.8	7.9
32	16.1	7.5
36	11.6	6.6

Potency roughly follows the optimum CMR. The CMR for losartan is 11.7. In the one instance where we might have expected to find an optimum Clog *P*, eq 32, for a whole animal, we find only CMR terms. In this example collinearity between Clog *P* and CMR is very low.

Considering examples where the hydrophobic terms are quite significant, positive, and linear (eq 13, 14, 15, 19, 22, and 25), some insight can be obtained about parts of the receptor that are hydrophobic. QSAR 13, 14, and 15 indicate that the heterocyclic moiety attached to the left side of the biphenyl unit can have substituents that clearly contact hydrophobic space. QSAR 19 shows that substituents on the sulfonamido group can reach hydrophobic space. Equations 22 and 25 have the same properties as 13, 14, and 15. It is of interest to compare QSAR 15 with 16 and 25 with 30. In these two sets when the loop is present (eqs 15 and 25) a modest hydrophobic effect is seen but when this is split (eqs 16 and 30) only a negative steric effect is present. Thus, a very restricted hydrophobic site is uncovered.

A crucial point is getting some perspective on the so often used biphenyl moiety. A comparison with the bipyridyl moiety would help to define the nature of the receptor.

	ClogP	CMR
	4.01	5.2
	1.5	4.8

If hydrophobicity is important, it will clearly show by comparison with the bipyridyl analogue.

The calculated log *P* for the drugs already in the market are given in Chart 2. We have also included

CMR values and the acidic group present in these drugs.

Sterimol parameters occur in QSAR 1, 2, 4, 5, 9, 10, 11, 16, 22, 23, 24, 27, 29, 34, 39, 40, and 41. Most of these molecules have short alkyl chains (Me, Et, Pr, Bu) attached to the carbon next to the nitrogen in the hetrocylic ring (imidazole, pyrimidine, quinazoline, etc). Looking at QSAR 2, 5 and 16, 34, the negative coefficient of the sterimol parameters indicate that the bulkier and bigger groups cannot be tolerated at these positions.

Interestingly, eq 14 can be rederived as eq 42

$$\log 1/C = 2.34(\pm 0.50)L_X - 0.25(\pm 0.06)L_X^2 + 2.49(\pm 1.06) \quad (42)$$

$$n = 10,\ r^2 = 0.945,\ s = 0.159,\ q^2 = 0.874$$

$$\text{Opt. } L_X = 4.26(4.73-4.79)$$

$$r^2\ L_X \text{ Vs } \pi_X = 0.993$$

This suggests that the substituents have a parabolic interaction in terms of L, i.e., length. Likewise the other equations also suggest steric interactions with the receptor, either positive or negative. The negative coefficient indicates larger groups at the specific positions decrease the activity. As seen in the eqs 4 and 9, the negative coefficient for L and B1 for the substituents on the phenyl ring, attached to the acidic isostere, indicate that bigger groups at the para position decrease the activity. The positive coefficients of the sterimol parameter shows that there is positive steric interaction of the substituents with the receptor (eqs 10, 11, 23, 24, 27, and 29).

Electronic terms are present in eqs 6, 7, 9, 10, 11, 19, and 39 only. For most of the other equations (eqs 3, 8, 12, 13, 14, 15, 16, 20, 21, 23, 24, 25, 26, 28, 30, 32, 33, 38, 40, and 41), electronic effects could not be evaluated, either because of the lack of parameter values for unusual substituents or because of lack of variation in substituents (e.g., all alkyl groups). Most researchers still do not consider the importance of having substituent variation in hydrophobic, electronic, and steric properties for which known parameter values are available (see Chapter 13 in refs 12a,b). For eqs 2, 4, 5, 27, 34, and 36, the substituents are in positions where steric interactions appear to be more important than electronic effects. For eqs 8, 28, and 31, the groups attached to the biphenyl moiety do not have much variation. They are one of the three acidic isosteres. Equation 29 is ambivalent because of the −COOH group present ortho to the −CONR− linker chain attached to the phenyl ring.

It is most interesting that in six of the seven examples the σ term has a negative coefficient regardless of position. The term in QSAR 9 may be related to the ionization of the nearby COOH function. Insight on this can be gained from the following QSAR for the ionization of $X-C_6H_4COOH$ in aqueous solution from the work of Dippy et al.[53]

$$pK_a = -0.59(\pm 0.01)\sigma + 4.31(\pm 0.04) \quad (43)$$

$$n = 5,\ r^2 = 0.991,\ s = 0.019,\ q^2 = 0.977$$

Using the ionization constant instead of pK_a yields a slope of 0.59 close to that in eq 9.

The fact that almost regardless of position ρ with σ is negative is of interest. MR was first used to account for molecular polarizability via the refractive index terms.[12d] There are two shortcomings to this process: collinearity with volume and the directional nature of polarizability.[54] The latter may mean that unless the electronic properties of the receptor and ligand are in suitable alignment the polarizability factor may be missed. In such cases MR is simply a measured volume and correlation with volume will be found. We believe that since ρ is generally negative from various positions, this is associated with polarizability.

We have found CMR and MR (for substituents) to be quite valuable parameters in QSAR. At present our database contains 1287 QSAR that require these terms. Very recently, CMR has enabled us to uncover a number of QSAR that identify allosteric interactions between ligands and receptors.[56]

Finally, we mention that we could not include some of the data sets in this report because we could not derive a statistically significant correlation.[57−62] Also, some studies reporting 3D QSAR[63] or conformational analysis[61,62,64] could not be used to derive QSAR via our approach for comparative purpose.

V. Acknowledgment

This research was supported by Grant #R01 ES 07595 from NIEHS.

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