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Searching for Allosteric Effects Via QSARs

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Abstract—A study of our database of 7,000 QSARs involving chemical–biological interaction uncovered 11 examples where the QSARs all contain inverted parabolas based on molecular refractivity. That is, biological activity first decreases with increase in MR and then increases. Two of the examples are for enzymes: cyclooxygenase and trypsin. The others are for various receptors. The results seem to be best rationalized by the larger compounds inducing a change in a receptor unit that allows for a new mode of interaction.

Introduction

With the continuing growth of our database of QSARs, now composed of over 15,000 equations of which 7,000 are bio QSARs and 8,100 are from physical organic chemistry, we are becoming involved in chem-bioinformatics. This computerized system can be searched in hundreds of ways. It is simple of course to search for equations on a given system such as HIV inhibitors[1] or compounds binding to estrogen receptors,[2] but recently it has become more possible to make useful comparisons of chemical reactions with chemical–biological reactions.[3–5,16,18] We are now beginning to search for more complex comparisons.

In this report we consider QSARs of an unusual kind that we have encountered in the study of a variety of receptor interactions as well as two enzymes. These examples are very unusual in that correlation depends almost entirely on an inverted parabolic relationship on the calculated molecular refractivity (CMR). That is, at first potency decreases as CMR increases; then an inversion occurs, and potency begins to increase. One might assume that the larger molecules are touching some part of the receptor to increase potency or it is possible that an allosteric effect occurs and in some way the structure of the receptor is changed so that potency increases with size but also to some degree with polarizability (MR and molar volume are often collinear). Molecular refractivity is defined as:

$$\mathrm{MR} = \frac{n^2-1}{n^2+2}.\frac{MW}{d}$$

where n is the refractive index, MW is the molecular weight and d is the density. Often there is little variation in n so that MR is essentially a measure of volume. However, polarizability, which is related to refractive index, often yields better correlations than molar volume as calculated by the McGowan method ($MgVol$).[6] For each of the QSARs 1–11 we have compared molecular volume and molecular refractivity; in no case is molecular volume superior to MR.

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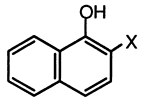
Results

The following equations based on the inverted CMR relationship have been formulated using data taken from the literature. We have concentrated on examples from studies on receptor inhibition with the exception of cyclooxygenase and trypsin. We have also found several examples with borderline statistics that have not been included. The QSARs have been arranged in order of increasing values of the inversion point.

I_{50} for inhibition of cyclooxygenase from bovine seminal vesicle by I (Table 1)[7]



I

$$\log 1/\mathrm{C} = -2.96(\pm 1.9)\mathrm{CMR} + 0.22(\pm 0.15)\mathrm{CMR}^2 + 14.7(\pm 6.0) \quad (1)$$

$n = 8$, $r^2 = 0.829$, $s = 0.206$, $q^2 = 0.587$
outliers: $CH_2C_6H_5$, $CH{=}CHCOOC_2H_5$, $(CH_2)_4COOH$
inversion point: 6.84 (6.5 to 8) r^2 $MgVol = 0.732$

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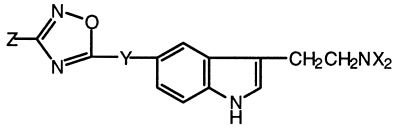
Table 1. I_{50} data for inhibition of cyclooxygenase from bovine seminal vesicle by I[7]

No.	Substituents	log 1/C			
		Obsd	Calcd eq (1)	Δ	CMR
1	H	5.70	5.77	−0.07	4.53
2	Me	5.52	5.35	0.17	4.99
3	CMe_3	4.43	4.66	−0.23	6.39
4	$CH_2CH{=}CH_2$	4.75	4.81	−0.07	5.90
5	$CH_2C_6H_5$[a]	5.47	4.72	0.75	7.51
6	$CH(Me)C_6H_5$	5.06	4.90	0.17	7.97
7	$CH{=}CHC_6H_5$	4.89	4.96	−0.07	8.10
8	$CH{=}CHCOOC_2H_5$[a]	4.96	4.67	0.29	7.32
9	$CH_2CH_2COOC_2H_5$	4.89	4.63	0.26	7.04
10	$(CH_2)_4COOC_2H_5$	4.75	4.89	−0.14	7.97
11	$(CH_2)_4COOH$[a]	3.14	4.63	−1.48	7.04

[a]Data points not used in deriving equation.

In this and the following QSARs, CMR is 0.1 of the calculated value. In each example, we have listed r^2 for *MgVol*, the correlation using the calculated value of molar volume.[6]

I_{50} for inhibition of 5-HT_{1D} receptor from pig caudate membrane by II (Table 2)[8]

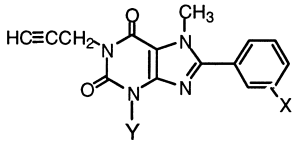


II

$$\log 1/C = -2.71(\pm 2.30)CMR + 0.18(\pm 0.13)CMR^2 + 18.0(\pm 10.3) \quad (2)$$

$n = 10$, $r^2 = 0.903$, $s = 0.282$, $q^2 = 0.773$
outliers: X = H, Y = —, Z = C_3H_7; X = H, Y = $(CH_2)_2$, Z = $CH_2C_6H_5$
inversion point: 7.65 (4.0 to 8.3) r^2 *MgVol* = 0.874

K_i for inhibition of adenosine receptor A1 from rat brain cortical membrane by III (Table 3)[9]



III

$$\log 1/K_i = -5.15(\pm 3.2)CMR + 0.28(\pm 0.17)CMR^2 + 29.3(\pm 14.8) \quad (3)$$

$n = 8$, $r^2 = 0.829$, $s = 0.051$, $q^2 = 0.536$
inversion point: 9.10 (8.8 to 9.24) r^2 *MgVol* = 0.693

Table 2. I_{50} data for inhibition of 5-HT_{1D} receptor from pig caudate membrane by II[8]

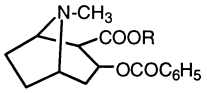
No.	Substituents			log 1/C			
	X	Y	Z	Obsd	Calcd eq. (2)	Δ	CMR
1	H,H	—	Me	8.00	7.75	0.25	6.87
2	H,H	—	C_3H_7[a]	8.10	7.64	0.46	7.80
3	H,H	—	$CH_2C_6H_5$	8.20	8.17	0.03	9.38
4	H,H	—	$CH_2C_6H_4$ (4-OMe)	9.10	8.62	0.48	10.0
5	H,H	—	$CH_2C_6H_4$ (4-NHCOMe)	9.30	9.30	0.00	10.71
6	H,H	—	$CH_2C_6H_4$ (4-$NHSO_2Me$)	9.50	9.73	−0.23	11.09
7	H,H	CH_2	Me	7.50	7.66	−0.16	7.33
8	H,H	CH_2	NH_2	7.70	7.67	0.03	7.24
9	Me,Me	CH_2	Me	7.30	7.71	−0.41	8.26
10	Me,Me	CH_2	NH_2	7.60	7.69	−0.09	8.17
11	Me,Me	$(CH_2)_2$	NH_2	7.90	7.81	0.09	8.63
12	H,H	$(CH_2)_2$	$CH_2C_6H_5$[a]	8.30	8.89	−0.59	10.31

[a]Data points not used in deriving equation.

Table 3. K_i data for inhibition of adenosine receptor A1 from rat brain cortical membranes by III[9]

No.	Substituents		log 1/K_i			
	X	Y	Obsd	Calcd eq. (3)	Δ	CMR
1	Br	Me	5.92	5.89	0.03	9.00
2	OMe	Me	5.89	5.91	−0.02	8.84
3	OMe	CH_2CH_2OH	5.98	5.93	0.06	9.46
4	Br	CH_2CH_2OH	5.89	5.97	−0.07	9.62
5	OMe	$CH_2CH_2CH_2OH$	6.05	6.08	−0.04	9.92
6	Br	$CH_2CH_2CH_2OH$	6.20	6.16	0.04	10.08
7	NH_2	Me	5.97	5.96	0.01	8.60
8	OH	Me	6.03	6.04	−0.01	8.38

I_{50} for inhibition of 5-HT transporter by cocaine analogues IV (Table 4)[10]

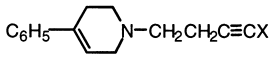


IV

$$\log 1/C = -10.0(\pm 6.3)CMR + 0.52(\pm 0.32)CMR^2 + 53.1(\pm 31.0) \quad (4)$$

$n = 8$, $r^2 = 0.842$, $s = 0.371$, $q^2 = 0.670$
outlier: $CH_2C_6H_5$
inversion point: 9.66 (9.06 to 9.92) $r^2\ MgVol = 0.841$

K_I for inhibition of dopamine D_2 receptor from rat striatal membrane by V (Table 5)[11]



V

Table 4. I_{50} data for inhibition of 5-HT transporter by cocaine analogues IV[10]

No.	Substituents	log 1/C			
		Obsd	Calcd eq. (4)	Δ	CMR
1	Me	5.98	5.96	0.03	8.10
2	C_2H_5	5.24	5.32	−0.08	8.56
3	C_3H_7	5.35	4.90	0.45	9.03
4	$CHMe_2$	4.60	4.90	−0.30	9.03
5	C_6H_5	4.47	4.81	−0.33	10.15
6	$CH_2C_6H_5$[a]	6.52	5.15	1.37	10.61
7	$(CH_2)_2C_6H_5$	6.21	5.72	0.49	11.07
8	$(CH_2)_3C_6H_5$	6.43	6.51	−0.08	11.54
9	$CH_2CH{=}CHC_6H_5$	6.43	6.61	−0.17	11.59

[a]Data point not used in deriving equation.

Table 5. K_i data for inhibition of dopamine D_2 transporter from rat striatal membrane by V[11]

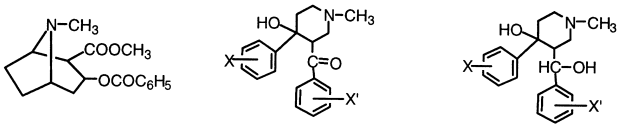
No.	Substituents	log 1/K_i				
		Obsd	Calcd eq. (5)	Δ	Clog P	CMR
1	C_6H_5	6.55	6.59	−0.05	4.95	9.41
2	4-OH-C_6H_4[a]	7.27	6.82	0.45	4.29	9.57
3	5-Indolyl	6.71	6.80	−0.08	4.94	10.53
4	4-Pyridinyl	7.50	7.45	0.04	3.46	9.20
5	3-Pyridinyl	7.43	7.45	−0.02	3.46	9.20
6	2-Pyridinyl[a]	6.87	7.39	−0.52	3.46	9.28
7	3-Quinolinyl	7.52	7.29	0.23	4.84	10.89
8	4-Isoquinolinyl	7.14	7.39	−0.25	4.63	10.89
9	4-NH_2-C_6H_4	7.32	7.03	0.29	3.73	9.78
10	3-NH_2-C_6H_4	7.06	7.03	0.03	3.73	9.78
11	2-NH_2-C_6H_4	6.74	7.03	−0.29	3.73	9.78
12	2-NH_2-5-Pyridinyl	7.48	7.36	0.12	3.13	9.57
13	3-NH_2-6-Pyridinyl	7.20	7.33	−0.13	3.13	9.65
14	4-OMe-C_6H_4	6.49	6.52	−0.03	4.87	10.03
15	3-O$(CH_2)_2$O-4-C_6H_3	6.90	6.77	0.13	4.88	10.47
16	5-Benzofuranyl	6.36	6.35	0.01	5.51	10.32

[a]Data points not used in deriving equation.

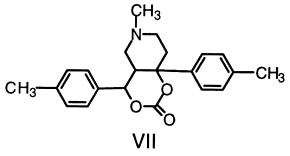
$$\log 1/K_i = -0.47(\pm 0.19)\text{Clog P} - 14.2(\pm 8.3)CMR + 0.72(\pm 0.41)CMR^2 + 78.5(\pm 41.7) \quad (5)$$

$n = 14$, $r^2 = 0.915$, $s = 0.186$, $q^2 = 0.665$
outliers: 4-OH-C_6H_4; 2-pyridinyl
inversion point: 9.85 (9.43 to 10.4) $r^2\ MgVol = 0.307$

K_i for inhibition of dopamine transporter ([^{3}H]-mazindole binding) by cocaine and cocaine antagonists VIA, VIB, and VII (Table 6)[12]



Cocaine VI A VI B



VII

$$\log 1/K_i = -10.2(\pm 3.5)CMR + 0.52(\pm 0.18)CMR^2 + 55.3(\pm 16.8) \quad (6)$$

$n = 8$, $r^2 = 0.938$, $s = 0.151$, $q^2 = 0.600$
outliers: X = X′ = 4-Me (VI A); X = X′ = 3,4-di-Cl(VI A)
inversion point: 9.86 (9.7 to 10.1) $r^2\ MgVol = 0.763$

K_i for inhibition of dopamine transporter ([^{3}H]-DA uptake) by cocaine and cocaine antagonists VIA, VIB, and VII (Table 7)[12]

$$\log 1/K_i = -9.29(\pm 2.9)CMR + 0.47(\pm 0.15)CMR^2 + 51.3(\pm 13.8) \quad (7)$$

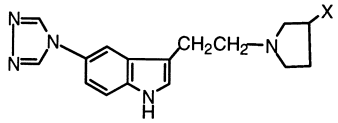
Table 6. K_i data for inhibition of dopamine transporter by cocaine antagonists VIA, VIB, and VII[12]

No.	Substituents X/X′	log 1/K_i			
		Obsd	Calcd eq. (6)	Δ	CMR
1	Cocaine	6.64	6.51	0.13	8.10
2	4-Me (VIA)[a]	6.31	4.90	1.41	9.75
3	H (VIA)	5.36	5.45	−0.10	8.83
4	4-F (VIA)	5.24	5.42	−0.18	8.86
5	3,4-di-Cl (VIA)[a]	7.96	5.34	2.62	10.79
6	2,4-di-Cl (VIA)	5.44	5.34	0.10	10.79
7	4-Me (VIB)	4.97	4.90	0.08	9.87
8	3,4-di-Cl (VIB)	5.38	5.46	−0.08	10.91
9	2,4-di-Cl (VIB)	5.36	5.46	−0.10	10.91
10	VII	5.09	4.93	0.16	10.11

[a]Data points not included in deriving equation.

$n = 8$, $r^2 = 0.961$, $s = 0.124$, $q^2 = 0.910$
outliers: X = X′ = 4-Me (VIA); X = X′ = 3,4-di-Cl (VIA)
inversion point: 9.99 (9.84 to 10.2) $r^2\ MgVol = 0.898$

I_{50} for displacement of [^{3}H]-5-HT from cloned human 5-HT_{1D} receptors expressed in CHO cells by VIII (Table 8)[13]

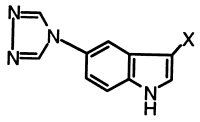


VIII

$$\log 1/C = -9.34(\pm 4.7)CMR + 0.47(\pm 0.23)CMR^2 + 53.8(\pm 23.5) \quad (8)$$

$n = 8$, $r^2 = 0.883$, $s = 0.233$, $q^2 = 0.700$
outliers: X = N(Me)$CH_2C_6H_5$(R); $CH_2N(Me)CH_2C_6H_5$(R)
inversion point: 10.02 (9.75 to 10.2) $r^2\ MgVol = 0.882$

I_{50} for displacement of [^{3}H]-5-HT binding to cloned human 5-HT_{1D} receptor in CHO cells by IX (Table 9)[14]



IX

$$\log 1/C = -6.63(\pm 2.2)CMR + 0.32(\pm 0.11)CMR^2 + 41.5(\pm 11.4) \quad (9)$$

$n = 10$, $r^2 = 0.878$, $s = 0.357$, $q^2 = 0.800$
outliers: X = $(CH_2)_2$-(3-$CH_2NHCH_2C_6H_5$-pyrrol-1-yl); $(CH_2)_3$-(3-oxo-N-$CH_2C_6H_5$-piperazin-4-yl)
inversion point: 10.4 (10.2 to 10.7) $r^2\ MgVol = 0.810$

Table 7. K_i data for inhibition of dopamine transporter by cocaine and cocaine antagonists VIA, VIB, and VII[12]

		log 1/K_i			
No.	Substituents X/X′	Obsd	Calcd eq. (7)	Δ	CMR
1	Cocaine	6.56	6.55	0.02	8.10
2	4-Me (VIA)[a]	6.44	4.91	1.53	9.75
3	H (VIA)	5.59	5.51	0.07	8.83
4	4-F (VIA)	5.38	5.48	−0.10	8.86
5	3,4-di-Cl (VIA)[a]	7.29	5.19	2.10	10.79
6	2,4-di-Cl (VIA)	5.23	5.19	0.04	10.79
7	4-Me (VIB)	4.80	4.89	−0.09	9.87
8	3,4-di-Cl (VIB)	5.38	5.28	0.09	10.91
9	2,4-di-Cl (VIB)	5.12	5.28	−0.16	10.91
10	VII	5.02	4.89	0.13	10.11

[a]Data points not included in deriving equation.

Table 8. I_{50} data for displacement of human 5-HT_{1D} receptors expressed in CHO cells by VIII[13]

		log 1/C			
No.	Substituents	Obsd	Calcd eq. (8)	Δ	CMR
1	H	8.47	8.38	0.09	8.30
2	$OCH_2C_6H_5$(R)	8.20	7.94	0.26	11.43
3	OH(R)	8.05	8.15	−0.10	8.45
4	$OCH_2C_6H_5$(S)	7.70	7.94	−0.24	11.43
5	N(Me)$CH_2C_6H_5$(R)[a]	7.43	9.06	−1.63	12.11
6	$CH_2OCH_2C_6H_5$(R)	8.64	8.65	−0.01	11.89
7	CH_2OH(R)	7.59	7.57	0.01	8.92
8	$CH_2N(Me)CH_2C_6H_5$ (R)[a]	9.16	10.06	−0.90	12.57
9	$CH_2NHCH_2C_6H_5$(R)	9.30	9.05	0.25	12.11
10	$CH_2NHCH_2C_6H_5$(S)	8.80	9.05	−0.25	12.11

[a]Data points not included in deriving equation.

Table 9. I_{50} data for displacement of human 5-HT_{1D} receptors expressed in CHO cells by IX[14]

		log 1/C			
No.	Substituents	Obsd	Calcd eq. (9)	Δ	CMR
1	$(CH_2)_2NMe_2$	9.52	9.60	−0.08	7.55
2	$(CH_2)_2$-Pyrrol-1-yl	8.51	8.41	0.10	8.30
3	$(CH_2)_2$-(3-$CH_2NHCH_2C_6H_5$-Pyrrol-1-yl)[a]	9.22	7.87	1.35	12.11
4	$(CH_2)_2$-(N-Me-Piperazin-4-yl)	6.87	7.50	−0.63	9.13
5	$(CH_2)_3$-(N-Me-Piperazin-4-yl)	7.48	7.19	0.29	9.60
6	$(CH_2)_3$-Morpholin-4-yl	8.06	7.69	0.36	8.92
7	$(CH_2)_3$-Pyrazin-1-yl	7.62	7.43	0.19	9.23
8	$(CH_2)_4$-(N-Me-Piperazin-4-yl)	6.68	7.01	−0.33	10.06
9	$(CH_2)_3$-(2-Oxo-N-$CH_2C_6H_5$-piperazin-4-yl)	8.18	7.91	0.27	12.14
10	$(CH_2)_3$-(2-Oxo,N-$CH_2CH_2C_6H_5$-piperazin-4-yl)	8.28	8.48	−0.20	12.61
11	$(CH_2)_3$-(3-Oxo-N-$CH_2C_6H_5$-piperazin-4-yl)[a]	6.76	7.91	−1.15	12.14
12	$(CH_2)_3$-(2-Thio-N-$CH_2C_6H_5$-piperazin-4-yl)	9.10	9.08	0.02	13.00

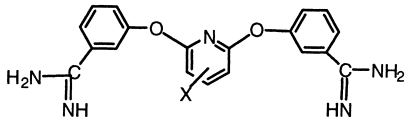
[a]Data points not included in deriving equation.

I_{50} for displacement of [^{3}H]-5-HT binding to cloned human 5-HT_{1B} receptor in CHO cells by VIII (Table 10)[13]

$$\log 1/C = -4.88(\pm 2.1)CMR + 0.24(\pm 0.10)CMR^2 + 31.9(\pm 10.4) \quad (10)$$

$n = 8$, $r^2 = 0.881$, $s = 0.139$, $q^2 = 0.652$
outliers: OH(R); N(Me)$CH_2C_6H_5$(R)
inversion point: 10.4 (10.2 to 10.6) $r^2\ MgVol = 0.881$

K_i for inhibition of bovine trypsin by X (Table 11)[15]



X

$$\log 1/K_i = -3.02(\pm 1.2)CMR + 0.14(\pm 0.05)CMR^2 + 0.46(\pm 0.25)B1_4 \quad (11)$$

$n = 22$, $r^2 = 0.837$, $s = 0.131$, $q^2 = 0.772$
outlier: 3-NHCO-gly-NH_2
inversion point: 10.8 (10.2 to 11.1) $r^2\ MgVol = 0.691$

Discussion

We have used the word 'allosteric' for our discussion, although at present we do not know exactly what all this implies. Obviously a change in mechanism is occurring as the slope of the QSAR changes from negative to positive. If we had only 1 or 2 such examples we would not take the results very seriously, but simply set them aside for future consideration. Especially since

Table 10. I_{50} data for displacement of human 5-HT_{1B} receptors expressed in CHO cells by VIII[13]

		log 1/C			
No.	Substituents	Obsd	Calcd eq. (10)	Δ	CMR
1	H	7.55	7.55	0.01	8.30
2	$OCH_2C_6H_5$(R)	6.84	6.77	0.07	11.43
3	OH(R)[a]	7.03	7.40	−0.37	8.45
4	$OCH_2C_6H_5$(S)	6.56	6.77	−0.21	11.43
5	N(Me)$CH_2C_6H_5$(R)[a]	6.68	7.21	−0.53	12.11
6	$CH_2OCH_2C_6H_5$(R)	7.07	7.05	0.03	11.89
7	CH_2OH(R)	7.03	7.03	0.00	8.92
8	$CH_2N(Me)CH_2C_6H_5$(R)	7.50	7.63	−0.14	12.57
9	$CH_2NHCH_2C_6H_5$(R)	7.33	7.21	0.12	12.11
10	$CH_2NHCH_2C_6H_5$(S)	7.33	7.21	0.12	12.11

[a]Data points not used in deriving equation.

Table 11. K_i data for inhibition of bovine trypsin by X[15]

		log 1/K_i				
No.	Substituents	Obsd	Calcd eq. (11)	Δ	CMR	$B1_4$
1	H	5.96	5.97	−0.01	9.85	1.0
2	3,5-di-Cl	5.68	5.84	−0.17	10.84	1.0
3	3,5-di-F	5.92	5.96	−0.04	9.89	1.0
4	3,5-di-F,4-Me	6.09	6.11	−0.02	10.35	1.52
5	3,5-di-F,4-OMe	5.96	6.02	−0.06	10.50	1.35
6	3-NH_2	5.89	5.89	0.00	10.22	1.0
7	3-NHCOMe	5.92	5.86	0.06	11.19	1.0
8	3-$NHSO_2Me$	5.72	5.92	−0.20	11.56	1.0
9	3-$NHCONHC_6H_5$	7.00	6.94	0.06	13.60	1.0
10	3-NHCONHMe	6.08	5.92	0.15	11.55	1.0
11	3-$NHCOC_6H_5$	6.59	6.67	−0.09	13.23	1.0
12	3-NHCO-gly-NH_2[a]	6.55	5.92	0.63	11.55	1.0
13	3-CF_3	6.11	5.87	0.24	10.36	1.0
14	3-$CONH_2$	5.92	5.84	0.08	10.72	1.0
15	3-CONHMe	5.85	5.86	−0.01	11.19	1.0
16	3-$CONMe_2$	6.11	5.95	0.16	11.65	1.0
17	3-CO-gly-NH_2	5.70	5.86	−0.17	11.19	1.0
18	3-$COOC_2H_5$	6.04	5.90	0.14	11.43	1.0
19	3-COOH	5.66	5.85	−0.20	10.51	1.0
20	4-$CONH_2$	6.11	6.07	0.03	10.72	1.50
21	4-CONHMe	6.13	6.11	0.01	11.19	1.54
22	4-$COOC_2H_5$	6.10	6.19	−0.10	11.43	1.64
23	4-COOH	6.24	6.13	0.11	10.51	1.60

[a]Data point not used in deriving equation.

rather few data points have been employed in most cases and the structural changes are complex. However, in all examples, data points on both sides of the inversion point allow us to place good 95% confidence limits on each of the inversion points. All of the results are from studies in the period 1990 to 2000, as ever more receptor studies are being published.

There is high collinearity between CMR and volume (*MgVol*, McGowan molar volume). However, more than simple volume must be involved, since in each example we have calculated r^2 for the use of molar volume. In no case does *MgVol* yield a better correlation than CMR. The polarizability portion (n^2-1/n^2+2) is not a satisfactory way to assess polarizability since it cannot account for the directional, three-dimensional nature of the effect of electron movement. The refractive index is simply a rough measure. Still, it is clearly important in a number of our QSARs.

Unfortunately, the substituent changes are generally rather complex and this does not help interpretation. It does bring out the very nonspecific type of ligand interaction. In examples 1, 3, 5, and 6, the relatively low values of r^2 for *MgVol* suggest that polarizability does play a significant role. MR was first used by Pauling and Pressman[17] for a biological process (haptan antibody interaction) and we have discussed its history.[16] An interesting facet of the present study was our inability to find terms in addition to MR that could improve the correlation except in QSARs 5 and 11. It is especially noteworthy that no positive hydrophobic terms have shown up. This must be due in part to the type of derivatives used in the investigation. Often we had no means other than the use of general parameters Clog P, CMR and *MgVol*. Also number of data points determined was low. Despite these handicaps we have found an interesting pattern of chemical–biological interaction from recent publications that have provided the necessary data. Only in data published in the 1990s have we found useful data and most of it was associated with receptors rather than isolated enzymes or in whole animals.

Despite the terrible complexity of sets of congeners interacting with the extremely complex machinery of biological systems we are finding increasing numbers of examples where lateral validation provides encouraging evidence that valuable insight can be obtained via comparative QSAR studies.

For lack of a better understanding of just what is occurring at the molecular level, we have used the term allosteric to classify our results. How well this fits in with what Monod, Wyman and Changeux[19] first describe as an allosteric process is unknown. Changeux and Edelstein have recently reviewed the progress in this field.[20] However, they gave little attention to the Koshland, Nemethy, Filmer model.[21] These two models focus on changes in protein-receptors containing subunits. It seems possible to us that a change might be induced in a receptor that could open another mode of binding. In our case, a single receptor or enzyme. Their term ''allostery'' from Greek origin, means ''another shape''. This has recently been illustrated for single receptors or enzymes.[22] It is this mechanism that appeals the most to us.

At the moment, our database has 1,056 QSARs on various types of receptors and enzymes. From this rather large number, we have the ability to identify only these eleven cases plus a few borderline possibilities, where not enough congeners were identified to define the upside of the curve with confidence.

We have 38 QSARs on trypsin, but only in the case of QSAR 11 with the highly polar amidines have we been able to find the inverted parabola. In this example, with more 'normal' substituents, we have only one outlier in 23 congeners. In some of the other sets with rather gross substituents, it is not surprising that a higher percentage of outliers is found.

Very recently Bender et al. have inferred an allosteric interaction via QSARs.[23] To our knowledge this is the first attempt to use QSARs in this fashion. Their results for a very complex set of molecules yield a good normal parabolic relationship with molecular volume. In searching our database we find 60 examples of QSAR parabolic in terms of CMR and 27 cases having parabolic relationships with *MgVol*. At present it is not clear if any of the results involve allosteric effects.

Conclusion

In conclusion, we hope that our results will encourage the many others working with receptors to check for the possibility of allostery and the role of QSARs in rationalizing such results.

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