Application of the Free–Wilson Technique to Structurally Related Series of Homologues. Quantitative Structure–Activity Relationship Studies of Narcotic Analgetics

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A series of benzomorphans with ED_{50} values determined in vivo by the hot-plate method in mice is analyzed by the modified Free–Wilson method. The QSAR yields 36 substituent constants (a_i) with contributions to the overall activity in agreement with experimental data. Substituent constant values obtained for benzomorphans are used in calculating log $(1/C)$ values for six morphinans. An excellent correlation is obtained ($r = 0.95$) between the six calculated and observed activities. The possibility of extending the Free–Wilson approach from one series of homologues to another is demonstrated.

The mathematical model of Free and Wilson[1] (F–W) for quantitative structure–activity relationships (QSAR) has seen only moderate use since its introduction.[2-13] Recent studies, however, have demonstrated its utility, especially when combined with or followed by a Hansch[14-16] or Boĉek–Kopecký[17,18] analysis. The F–W technique is particularly suited to the case when hydrophobic, electronic, and steric parameters are not readily available. Experimental determination of such parameters for narcotic analgetics of the morphine, morphinan, and benzomorphan series would be a monumental task. However, lack of ample biological activity data and/or multiple occurrences for substituents in a series of drugs limits the applicability of the F–W method. These limitations might be surmounted if results from a F–W analysis of one series could be extended to a structurally similar homologous series of drugs. Therefore, we applied the F–W type QSAR to the structurally simple benzomorphans (see Table I for structure) and extrapolated the results from this series to the homologous, structurally more complex, morphinan series (see Table V for structure).

Methods. The F–W additivity model is based on the assumption that a particular substituent group which appears at the same position in the molecule will contribute a constant entity to (or subtract it from) the overall biological activity. This entity is quantitated as a substituent constant and is independent of physical parameters of the related compounds.

In our analysis the modified F–W approach developed by Cammarata and You[7] and Fujita and Ban[8] was used. This approach is based upon eq 1 where a_i = contribution

$$\log (1/C) = \sum_i a_i x_i + \mu \qquad (1)$$

of substituent i, with $a_H = 0$ (by definition), $x_i = 1$ or 0 depending upon the presence or absence of the ith substituent, and $\mu = \log (1/C)_{calcd}$ for the unsubstituted compound.[12] The compound bearing only hydrogens is entered into the matrix with biological activity = log $(1/C)$ and $x_i = 0$ for i = H at all substituted positions included in the analysis. No symmetry equations are required.[8] A standard multiple regression program, BMDO2R, that solves the input equations by matrix inversion was used. The F level for inclusion of variables was set equal to zero. Most of the relevant statistics, including the correlation coefficient (r), the standard deviation (s), the F statistic, and the correlation and covariance matrices are routinely computed with the program.

The benzomorphan biological test data were obtained from a NIH computer record system compiled by Jacobson and Kaufmann.[19,20] The data consist of ED_{50} values determined on Caesarian-derived general purpose mice[21] by the Eddy–Leimbach hot-plate technique.[22] Each compound was tested on at least 12 mice with the resulting ED_{50} in mg/kg determined by probit analysis. Morphinan biological test data were obtained from ref 23 and were determined by the same Eddy–Leimbach technique. All values were converted to the usual log $(1/C)$, where C = mol/kg of test animal.

Results

Ninety-nine benzomorphans substituted at five positions and possessing 36 different substituents are listed in Table I. Compounds **1–70** include the biologically more active levorotatory (–) isomers or racemic mixtures (±) and contain substituents with two or more occurrences. Compounds **71–86** are similar (–) isomers and racemates; however, they possess a substituent with one occurrence. Compounds **87–99** are the biologically less active dextrorotatory (+) isomers. All of these have their enantiomer present among compounds **1–70**. "Substituents" 37 and 38 distinguish between enantiomers.

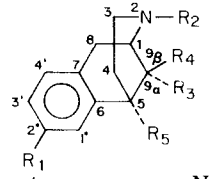
Substituent constants (a_i) resulting from the solution of three matrices consisting of compounds **1–99**, **1–86**, and **1–70** are presented in Table II. The a_i values derived in each analysis are all referenced to $a_H = 0$. Craig[9] has shown that differences between the additive constants at each position can be checked for statistical significance through t tests.[24] The absence of a significant t test for a certain a_i does not mean a lack of statistical significance for the particular a_i; it only means that the difference between the a_i and $a_H = 0$ is not significant.

Kubinyi and Kehrhahn have noted that the Fujita–Ban modification is a simple linear transformation of the classical F–W model.[12] In order to validate this for the standard multiple regression program used in our analysis, restrictive equations were incorporated into the matrix. The results of this analysis are found in Table II. Although the a_i and regression constant (μ) are different, subtraction of a_H at a position from the a_i of a substituent at that position will yield the a_i of the substituent when $a_H = 0$. Slight differences due to rounding are seen, but r, s, and F are identical. The statistics for the regressions are presented in Table III. They prove that the correlations obtained are significant at the 1% level. The explained variance (EV)[25] for the regression on compounds **1–70** was EV = 0.674.

Discussion and Application

For the matrix of 99 compounds, it is interesting to note the a_i values (Table II) for the (+) and (–) "substituents". The (+) a_i value of –0.968 is different from zero at the 5% level by the t test. This reflects the experimental finding that the dextro isomers are less active than the racemate or levo isomers in the benzomorphan series.[26] It is also known that the levo isomers are slightly more active than

Table I. Matrix of 6,7-Benzomorphans Included in Free-Wilson Type QSAR Studies



No.	Substituent	No.	Substituent	No.	Substituent	No.	Substituent
1	$R_1 = F$	11	$R_2 = CH_3$	21	$R_4 = CH_2CH_2CH_3$	31	$R_5 = CH_2(CH_2)_3CH_3$
2	$R_1 = OH$	12	$R_2 = CH_2CH_2(C_6H_5)$	22	$R_4 = CH_2OH$	32	$R_5 = CH_2(CH_2)_4CH_3$
3	$R_1 = OCOCH_3$	13	$R_2 = CH_2CH_2CO(C_6H_5)$	23	$R_3 = OCOCH_3$	33	$R_5 = C_6H_5$
4	$R_1 = OCOCH_2CH_3$	14	$R_2 = CH_2CH_2(2\text{-}C_4H_3S)$	24	$R_3 = CH_2CH_3$	34	$R_5 = OH$
5	$R_1 = OCOCH_2CH_2CH_3$	15	$R_2 = CH_2(C_3H_5)$	25	$R_3 = OH$	35	$R_5 = OCOCH_3$
6	$R_1 = OCOCH_2(CH_2)_2CH_3$	16	$R_2 = CH_2CHC(CH_3)_2$	26	$R_3 = CH_3$	36	$R_5 = OCOCH_2CH_3$
7	$R_1 = OCH_3$	17	$R_2 = CH_2(C_3H_3)=CH_2$	27	$R_5 = CH_3$	37	(+)
8	$R_1 = NO_2$	18[a]	$R_4 = CH_3$	28	$R_5 = CH_2CH_3$	38	(−)
9	$R_1 = OCOAr(3\text{-}C_5H_4N)$	19	$R_4 = CH_2CH_3$	29	$R_5 = CH_2CH_2CH_3$		
10	$R_1 = Cl$	20	$R_4 = OH$	30	$R_5 = CH_2(CH_2)_2CH_3$		

Compd no.	Substituent number																																		Log $(1/C)_{obsd}$[b]	Log $(1/C)_{pred}$[f]
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38		
1		1									1							1										1											3.92	2.94
2		1										1														1	1											1	3.83	3.22
3									1			1														1	1											1	3.68	3.93
4		1										1																1											3.66	3.15
5			1									1														1	1												3.61	3.16
6		1									1								1									1											1	3.51	3.16
7		1									1							1											1											3.45	2.86
8		1									1							1															1						1	3.26	3.04
9		1									1							1									1												1	3.22	2.81
10		1										1															1													3.21	3.02
11		1									1								1								1													3.07	3.04
12		1										1													1		1													2.99	2.21
13		1										1														1			1											2.92	3.27
14			1								1							1					1					1												2.82	2.80
15		1									1							1					1					1												2.78	2.86
16			1								1															1	1													2.72	2.47
17[c]		1									1															1	1											1	2.71	2.53
18			1								1							1					1				1													2.66	2.67
19							1					1														1	1											1	2.66	2.59
20		1									1																	1										1	2.62	2.45
21		1									1													1			1											1	2.62	2.36
22		1										1												1				1												2.61	3.18
23		1									1									1						1		1												2.61	2.24
24									1						1											1	1													2.59	2.34
25		1									1															1			1										1	2.57	2.58
26			1								1												1					1												2.53	2.31
27			1										1													1	1													2.49	2.70
28		1									1																		1										2.43	2.37
29			1								1													1				1												2.36	2.43
30[d]		1									1													1				1											1	2.35	2.49
31		1									1																1											1	2.16	2.32
32		1									1									1						1	1													2.15	2.12
33							1				1							1															1						1	2.14	2.40

34		1									1															1		1											2.06	2.66
35		1										1						1							1		1												2.05	2.70
36			1								1																1												1.98	2.26
37													1													1	1												1.93	1.72
38		1									1							1							1			1											1.89	2.13
39							1				1									1				1			1												1.87	1.31
40							1				1															1	1											1	1.87	1.89
41											1							1									1												1.82	1.83
42							1				1													1				1										1	1.81	1.85
43											1								1									1											1.80	2.18
44											1																						1					1	1.77	1.57
45											1							1											1										1.76	1.88
46		1									1																											1	1.72	2.21
47		1														1		1															1					1	1.70	1.87
48		1									1									1								1											1.67	2.04
49							1				1							1							1			1											1.65	1.49
50							1				1																1												1.64	1.69
51							1					1													1		1												1.58	1.58
52			1								1																												1.57	2.15
53		1														1										1	1											1	1.53	1.36
54							1				1									1						1	1												1.48	1.48
55							1				1												1					1											1.48	1.74
56											1															1			1										1.42	1.59
57											1												1				1												1.37	1.26
58		1													1											1	1												1.37	1.63
59											1																1												1.33	1.34
60																																							1.31	0.30
61											1																												1.30	1.23
62											1															1	1												1.27	1.54
63												1															1												1.26	2.04
64											1							1							1		1												1.16	1.02
65							1				1									1							1												1.14	1.28
66							1				1														1			1											0.99	1.01
67											1														1		1												0.97	0.53
68		1									1														1		1												0.90	1.51
69		1																1									1												0.88	1.89
70											1									1						1	1												0.68	1.13
71		1												1												1	1												4.04	4.04
72		1															1							1				1										1	3.70	3.70
73		1									1										1								1										2.88	2.88
74						1					1							1															1					1	2.78	2.78
75		1									1																			1									2.17	2.17
76				1							1																1												1.98	1.98
77		1									1																				1								1.96	1.96
78					1						1																1												1.92	1.92
79											1																								1				1.64	1.64
80		1									1											1					1												1.62	1.62
81									1		1													1				1											1.54	1.54
82		1									1																					1							1.53	1.53
83											1																									1			1.43	1.43
84	1										1															1	1												1.08	1.08
85										1	1															1	1												0.83	0.83
86											1																							1					0.75	0.75
87		1										1														1	1										1		2.05	2.11
88		1									1							1															1				1		1.99	2.07
89											1																						1				1		1.87	0.84

Table I (*Continued*)

Compd no.	Substituent number																												Log $(1/C)_{obsd}$[b]	Log $(1/C)_{pred}$[f]
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38		
90		1															1							1				1									1	1.79	2.18
91							1				1													1				1									1	1.62	0.92
92		1					1				1							1									1									1	1.60	1.62
93[e]		1									1													1		1									1	1.51	1.48
94		1									1															1			1						1	1.38	1.49
95		1									1								1									1								1	1.31	1.90
96		1									1																	1								1	1.22	1.09
97		1									1													1			1									1	1.20	1.31
98		1									1																1									1	1.04	1.20
99		1									1																	1								1	1.03	1.38

[a] R_4 is presented before R_3 to maintain an initial numbering system. [b] Log $(1/C)_{obsd}$ values were computed on a molar basis using salt form information supplied by Dr. A. E. Jacobson. [c] Average of 7907 (log $1/C = 2.85$) and 7569 (log $1/C = 2.57$), which are the same compound but different salt forms. [d] Average of 8178 (log $1/C = 2.40$) and 8320 (log $1/C = 2.30$) (different salt forms). [e] Average of 8194 (log $1/C = 1.58$) and 8323 (log $1/C = 1.43$) (different salt forms). [f] Predicted log $1/C$ values calculated from eq 1 using a_i of **99** compound set from Table II.

the racemate, and this is seen in the a_i value of the (-) "substituent" (0.173 referenced to $a_{(\pm)} = 0$). Since 13 pairs of enantiomers are included in this matrix, double weighting of substituents 1–**36** could lead to distortion of their a_i values. Inclusion of compounds **71**–**86**[27] (Table I) could result in misleading statistics since they yield single-point determinations.

A matrix of 70 compounds is obtained when dextro isomers (**87**–**99**) and compounds with single-occurring substituents (**71**–**86**) are deleted from the original 99-compound matrix. Examination of the a_i values at the individual positions reveals the interesting points outlined below.

For substituent R_1 it is known that the order of analgesic activity is $H < OCH_3 < OCOCH_3 \simeq OH$. Our a_i values bear out this relationship: $a_H = 0$, $a_{OCH_3} = 0.349$, $a_{OCOCH_3} = 0.923$, and $a_{OH} = 0.984$.[28] The t tests indicate that the a_{OH} and a_{OCOCH_3} are different from the a_{OCH_3} at the 5 and 10% level, respectively: $t_{OH} = 2.22$, $t_{0.05}^{(43)} = 2.01$, $t_{OCOCH_3} = 1.92$, $t_{0.10}^{(18)} = 1.73$. Experimental ED_{50} values suggest that the nicotinolyloxy substituent is less active than a free hydroxyl. Although this is not reflected in our a_i, a t test established no difference between the $a_{OCOAr(3\text{-}C_5H_4N)}$ and the a_{OH} at the 10% level: $t_{OCOAr(3\text{-}C_5H_4N)} = 0.46$, $t_{0.10}^{(33)} = 1.69$. This indicates the desirability of performing a statistical test before drawing conclusions about substituents with few occurrences.

For substituent R_2 there are three a_i values significantly different from zero. The order of activity at this position is $H < CH_3 \simeq CH_2CH_2CO(C_6H_5) < CH_2CH_2(C_6H_5)$.[26] This order is reflected by our values: $a_H = 0$, $a_{CH_3} = 0.924$, $a_{CH_2CH_2CO(C_6H_5)} = 1.10$, and $a_{CH_2CH_2(C_6H_5)} = 1.62$. In spite of multiple occurrences for CH_3 and $CH_2CH_2(C_6H_5)$, a t test did not establish a difference between $a_{CH_2CH_2(C_6H_5)}$ and a_{CH_3} at the 10% level: $t_{CH_2CH_2(C_6H_5)} = 0.91$, $t_{0.10}^{(60)} = 1.67$.

Positions R_3 (9α) and R_4 (9β) can be examined together. Compounds with alkyl substituents at C-9 oriented away from nitrogen (9α) are generally less effective than those in which the same substituent is oriented toward the N ring (9β).[26] This relationship is observed here, as at R_3, $a_{CH_3} = 0.204$, $a_{CH_2CH_3} = 0.0350$, while at R_4 $a_{CH_3} = 0.486$, $a_{CH_2CH_3} = 0.172$.

Also of interest is the negative coefficient of OH at both the 9α and 9β positions. The 9α a_{OH} is significantly different from zero at the 5% level, $t_{9\alpha\text{-}OH} = 3.98$, $t_{0.05}^{(85)} = 1.99$, but the 9β a_{OH} is significantly different from zero only at the 10% level, $t_{9\beta\text{-}OH} = 1.94$, $t_{0.10}^{(85)} = 1.67$. The negative effect of the 9α- or 9β-OH on analgesic activity has been documented.[26,29,30]

Three alkyl and one phenyl group are substituted on R_5. None of their a_i values are significantly different from zero at the 5% level.

As previously described by Craig[31] the range of a_i at each position can help identify those positions most sensitive to change in substituent. By studying the range of a_i at R_1–R_5, we note that the nitrogen position (R_2) and aromatic ring position (R_1) are the sites most sensitive to substitution, followed by the 9β (R_4) and 9α (R_3) positions. It appears that the C-5 position (R_5) is the least sensitive to the effect of substitution on biological activity. The major importance of R_2 and R_1 in the determination of biological activity has been well documented.[32]

Data allowing an evaluation of the qualitative value of single-occurring substituents (compounds 1–**86** in Table II) are presented in Table IV. The a_i values obtained are parallel to the experimental parameter, Δ

$$\Delta = \log (1/C)_{\text{obsd (single-point compound)}} - \log (1/C)_{\text{obsd (analogous H compound)}}$$

Table II. Substituent Constants (a_i)

Position	No.	Substituent	Compds 1-99		Compds 1-86		Compds 1-70			Compds 1-70 using restrictive eq	
			a_i	n[a]	a_i	n	a_i	n	Range[b]	a_i	n
R_1	9	$OCOAr(3\text{-}C_5H_4N)$	1.49[c]	2	1.69[c]	2	1.694[c]	2		1.02[c]	2
	3	$OCOCH_3$	0.869[c]	8	0.923[c]	8	0.923[c]	8		0.246[c]	8
	2	OH	0.803[c]	51	0.984[c]	40	0.984[c]	33		0.307[c]	33
	4	$OCOCH_2CH_3$	0.612	1	0.641	1					
	5	$OCOCH_2CH_2CH_3$	0.552	1	0.581	1					
	6	$OCOCH_2(CH_2)_2CH_3$	0.367	1	0.729	1					
	7	OCH_3	0.239	13	0.349	12	0.349	12		−0.328	12
		H	0	19	0	18	0	15		−0.676	15
	8	NO_2	−0.108	1	0.036	1					
	1	F	−0.454	1	−0.463	1					
	10	Cl	−0.704	1	−0.713	1			1.69		
R_2	14	$CH_2CH_2Ar(2\text{-}C_4H_3S)$	2.54[c]	1	2.44[c]	1					
	12	$CH_2CH_2(C_6H_5)$	1.58[c]	13	1.62[c]	12	1.62[c]	12		0.658[c]	12
	17	$CH_2\text{-}c\text{-}(C_3H_3)CH_2$	1.53[c]	2	2.14[c]	1					
	13	$CH_2CH_2CO(C_6H_5)$	1.11[c]	2	1.10[c]	2	1.10[c]	2		0.136[c]	2
	11	CH_3	0.835[c]	75	0.924[c]	64	0.924[c]	50		−0.039	50
	15	$CH_2\text{-}c\text{-}(C_3H_5)$	0.133	2	0.022	2	0.022	2		−0.941	2
		H	0	2	0	2	0	2		−0.963	2
	16	$CH_2CHC(CH_3)_2$	−0.414	2	−0.242	2	−0.242	2	1.86	−1.20	2
R_3	26	CH_3	0.166	26	0.204	24	0.204	21		0.250	21
	24	CH_2CH_3	0.103	12	0.035	8	0.035	6		0.081	6
		H	0	46	0	39	0	28		0.046	28
	23	$OCOCH_3$	−0.037	6	−0.078	6	−0.078	6		−0.032	6
	25	OH	−0.729[c]	9	−0.809[c]	9	−0.809[c]	9	1.01	−0.762[c]	9
R_4	21	$CH_2CH_2CH_3$	0.586	1	0.507	1					
	19	CH_2CH_3	0.518	4	0.712[c]	3	0.712[c]	3		0.612[c]	3
	18	CH_3	0.433[c]	19	0.486[c]	17	0.486[c]	16		0.385[c]	16
		H	0	67	0	57	0	44		−0.100	44
	20	OH	−0.318	7	−0.412	7	−0.412	7	1.12	−0.512	7
	22	CH_2OH	−0.552	1	−0.703	1					
R_5	33	C_6H_5	0.552	7	0.336	5	0.336	4		0.180	4
	35	$OCOCH_3$	0.385	1	0.411	1					
	28	CH_2CH_3	0.290	26	0.239	21	0.239	19		0.083	19
	29	$CH_2CH_2CH_3$	0.236	8	0.160	7	0.160	6		0.004	6
	36	$OCOCH_2CH_3$	0.175	1	0.201	1					
	27	CH_3	0.114	47	0.110	43	0.110	37	0.336	−0.046	37
	30	$CH_2(CH_2)_2CH_3$	0.112	1	−0.043	1					
		H	0	5	0	4	0	4		−0.156	4
	31	$CH_2(CH_2)_3CH_3$	−0.098	1	−0.253	1					
	34	OH	−0.505	1	−0.479	1					
	32	$CH_2(CH_2)_4CH_3$	−0.528	1	−0.683	1					
Isomer[d]	37	(+)	−0.968	13							
		(±)	0	65							
	38	(−)	0.173	21							

[a] Number of occurrences. [b] The range is computed by subtracting the lowest a_i at a position from the highest a_i at that position; the ranges shown refer to a_i derived from compounds 1-70. [c] These values denote a significant difference (5% level) between an a_i value and the a_H value at that position. [d] Just as hydrogen is eliminated as a substituent at each position in the matrix in Table I, the (±) "substituent" is eliminated and $a_{(\pm)}$ is set equal to zero.

Table III. Statistics from Free-Wilson Analysis of 6,7-Benzomorphans

Compds analyzed	No. of compds n	Correlation coeff r	Standard deviation s	Regression constant μ[a]	F statistic from regression	Critical F at 1% level
1-99	99	0.893	0.466	0.420	6.23	$F_{38,60} = 1.95$
1-86	86	0.909	0.457	0.305	6.45	$F_{36,49} = 2.09$
1-70	70	0.879	0.457	0.305	8.35	$F_{20,49} = 2.27$
1-70[b]	70	0.8	0.457	2.15	8.35	$F_{20,49} = 2.27$

[a] Computed from the expression $\mu = \log (1/C)_{\text{obsd mean}} - \Sigma_{i=1}^{q} a_i \bar{x}_i$, where a_i = substituent constant for substituent x_i, $\bar{x}_i$ = mean value for substituent x_i, and q = number of substituents. With the modified Free-Wilson, $\bar{x}_i$ = (number of occurrences)/(number of compounds); when restrictive equations are used $\bar{x}_i = 0$. [b] Using restrictive equations.

Table IV. Evaluation of a_i for Single-Point Substituents

Substituent position	Compd no.	Single-point substituent	Δ[a,b]	Substituent constant
R_1	76[c]	$OCOCH_2CH_3$	0.65	0.64
	78[c]	$OCOCH_2CH_2CH_3$	0.59	0.58
	84[d]	F	−0.19	−0.46
	85[d]	Cl	−0.44	−0.71
R_4	73[e]	$CH_2CH_2CH_3$	0.45	0.51
R_5	79[f]	$OCOCH_3$	0.34	0.41
	83[f]	$OCOCH_2CH_3$	0.13	0.20
	86[f]	OH	−0.55	−0.48

[a] $\Delta = \log (1/C)_{\text{obsd}}$(single-point compound) − $\log (1/C)_{\text{obsd}}$(hydrogen analogue) (where the hydrogen analogue refers to replacement of the single-occurring substituent by hydrogen). [b] Δ values for single-occurring substituents [$R_1 = OCOCH_2(CH_2)_2CH_3$, NO_2; $R_2 = CH_2CH_2(2\text{-}C_4H_3S)$, $CH_2\text{-}c\text{-}(C_3H_3)CH_2$; $R_4 = CH_2OH$; $R_5 = CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_3CH_3$, $CH_2(CH_2)_4CH_3$] cannot be calculated due to lack of a hydrogen reference compound. [c] Compound 59 used as reference. [d] Compound 62 used as reference. [e] Compound 28 used as reference. [f] Compound 61 used as reference.

for all single-point substituents from this table.

Single-occurring substituents $CH_2CH_2(2\text{-}C_4H_3S)$ and $CH_2\text{-}c\text{-}(C_3H_3)CH_2$ are statistically different from zero at the 5% level. Although analogous hydrogen compounds are not available for reference, the extreme activity of $CH_2CH_2(2\text{-}C_4H_3S)$ has been noted.[26]

We attempted to extend the use of a_i values determined from compounds in the benzomorphan series to the morphinan series. We identified a group of morphinans (Table V) with substituents at R_1 and R_2 for which a_i values were obtained in the benzomorphan series. The activity contribution of the cyclohexyl ring formed from $C_{5\text{-}8,13,14}$ was approximated with the a_i values of ethyl groups at R_3 and R_5 in benzomorphans. The extension was made by comparing observed activities with calculated activities for morphinans. Calculated activities are computed using eq 2. A sample morphinan activity

$$\log (1/C)_{\text{calcd (morphinan)}} = \sum_i a_{i\,\text{(benzomorphan)}} + \mu_{\text{benzomorphan}} \quad (2)$$

calculation is given in eq 3 for compound **3′** (Table V) using benzomorphan a_i (compounds **1–86**, Table II); μ is taken from the regression on compounds **1–86** (Table III). Log

$$\log (1/C)_{\text{calcd (morphinan)}} = a_{R_1=OH} + a_{R_2=CH_3} + a_{R_3=CH_2CH_3} + a_{R_4=H} + a_{R_5=CH_2CH_3} + \mu = 0.984 + 0.924 + 0.035 + 0 + 0.239 + 0.305 = 2.49 \quad (3)$$

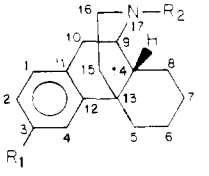
$(1/C)$ values calculated this way for morphinans **3′** and **4′** are identical with log $(1/C)$ values calculated for benzomorphans **30** and **22**, respectively, from Table I. For morphinans **1′**, **2′**, **5′**, and **6′** we could not identify corresponding benzomorphans with known analgesic activity. Therefore, the above calculations were based on the assumption that identical substituents at R_1 and R_2 in benzomorphans and morphinans possess very similar contributions to the biological activity.

A plot of observed activities vs. calculated activities is shown in Figure 1. The regression equation (eq 4) correlating log $(1/C)_{\text{obsd}}$ with log $(1/C)_{\text{calcd}}$ for the six morphinans was obtained from Figure 1. The correlation is

$$\log (1/C)_{\text{obsd}} = 0.769\ (\pm 0.351) \log (1/C)_{\text{calcd}} + 4.05\ (\pm 1.019) \quad (4)$$
$$n = 6,\ r = 0.95,\ s = 0.254$$

significant at the 1% level with $F = 37.1$ and EV = 0.878. The presence of a positive intercept in Figure 1 could be due to the introduction of $a_{CH_2CH_3}$ at R_3 and R_5 which underestimates the activity contribution of the cyclohexyl ring.[33]

Table V. Comparison of Morphinan Log $(1/C)_{\text{obsd}}$ with Biological Activities Calculated by Use of Benzomorphan, a_i



Compd no.	Substituents[a] R_1	R_2	Log $(1/C)_{\text{calcd}}$[b]	Log $(1/C)_{\text{obsd}}$[c]	Log $(1/C)_{\text{pred}}$[d]
1′	OH	$CH_2CH{=}C(CH_3)_2$	1.33	5.32	5.07
2′	OCH_3	$CH_2CH_2(C_6H_5)$	2.56	5.72	6.02
3′	OH	CH_3	2.49	5.73	5.96
4′	OH	$CH_2CH_2(C_6H_5)$	3.19	6.49	6.50
5′	$OCOCH_3$	$CH_2CH_2(C_6H_5)$	3.13	6.64	6.46
6′	OH	$CH_2CH_2(2\text{-}C_4H_3S)$	4.01	7.27	7.13

[a] For the purpose of calculating activities $R_3 = CH_2CH_3$, $R_4 = H$, and $R_5 = CH_2CH_3$ in all morphinans listed (see eq 2). [b] Calculated by use of eq 3. [c] Values taken from ref 23. [d] Calculated by use of regression eq 4.

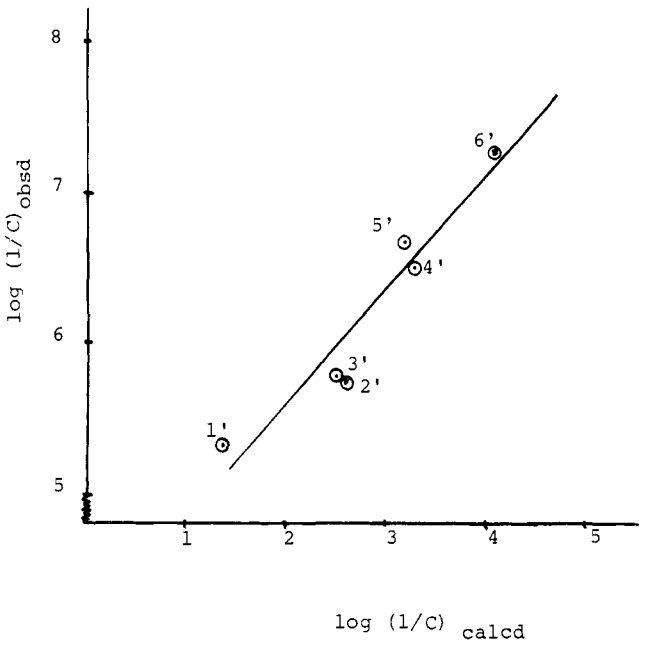


Figure 1. Observed activities vs. Free–Wilson-derived calculated activities for six morphinans.

It appears from above that, in vivo, the contribution of the cyclohexyl ring is a constant entity for the morphinans studied. An average "cyclohexyl" = 3.41 has been calculated from data in Table V. This "apparent" substituent constant value could be used to further the extension to an additional homologous series (i.e., morphines).

Hansch implies that two classes of compounds have similar modes of action if they yield comparable regression equations.[34],[35] Our study suggests that if a_i determined from one series of compounds can be successfully extended to another series, then the two series may act similarly at the molecular level. A lack of correlation may indicate a dissimilar mode of action.

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(25) EV is calculated according to the expression EV = $[\Sigma d^2/(n - k)]/[\Sigma y^2/(n - 1)]$ where $d = \log (1/C)_{obsd} - \log (1/C)_{calcd}$, $y = \log (1/C)_{obsd} - \log (1/C)_{mean\ obsd}$, k = number of parameters (including μ), and n = number of compounds. For further details see ref 24.
(26) Reference 23, p 141.
(27) Compound **72** contains substituent 17 at R_2. This substituent is also present in compound **90**, which is a dextro isomer. Deletion of the dextro isomers will then lead to a single-point determination for substituent 17.
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(33) We wish to thank one reviewer for his remarks, summarized below. The form of correlation eq 4 suggests that the morphinans are neither substituted benzomorphans nor a new series. They appear to be somewhere in between. From eq 4 we have $\log (1/C)_{obsd(morph)} = 0.769 \log (1/C)_{calcd(benz)} + 4.05$. Thus the coefficient for a given substituent on a morphinan is only 0.769 of the coefficient for the same substituent on a benzomorphan. If the $a_i - s$ were the same then the cyclohexyl would be "just another substituent"; if there was no collinearity the series would be unrelated. The 0.769 being significantly different from 1.0 indicates the "in between" character. The authors may have a tool for describing degrees of "similarity" or "congenericity.".
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