66, 128577-92-4; 67, 128577-93-5; 68, 128577-94-6; 69, 128577-95-7; 70, 128577-96-8; 71, 117423-95-7; 72, 128577-97-9; 73, 128577-98-0; 74, 128577-99-1; 75, 128578-00-7; 76, 128578-01-8; 77, 117424-97-2; 78, 128578-02-9; 79, 128578-03-0; 80, 128578-04-1; 81, 117424-99-4; 82, 117425-00-0; 83, 128578-05-2; 84, 117423-74-2; 85, 128578-06-3; 86, 128599-34-8; 87, 128578-07-4; 88, 128578-08-5; 89, 128578-09-6; 90, 128578-10-9; 91, 128578-11-0; 92, 128578-12-1; 93, 117423-71-9; 94, 117425-07-7; 95, 117425-08-8; 96, 117425-02-2; 97, 117425-03-3; 98, 128599-35-9; 99, 128578-13-2; 100, 128578-14-3; 101, 128578-15-4; LTB_4, 71160-24-2; m-$EtO_2CC_6H_4COCl$, 67326-20-9; o-$MeOC_6H_4(CH_2)_2CO_2Et$, 70311-27-2; p-$MeOC_6H_4Br$, 104-92-7; $HC{\equiv}C(CH_2)_4OH$, 928-90-5; $EtO_2C(CH_2)_2CH_2Br$, 2969-81-5; PhSH, 108-98-5; PhOH, 108-95-2; $Ph_3P^+(CH_2)_4CO_2H{\cdot}Br^-$, 17814-85-6; PhCHO, 100-52-7; p-$MeOC_6H_4CHO$, 123-11-5; p-$MeSC_6H_4CHO$, 3446-89-7; m-$MeOC_6H_4CHO$, 591-31-1; o-$MeOC_6H_4CHO$, 135-02-4; p-ClC_6H_4CHO, 104-88-1; p-FC_6H_4CHO, 459-57-4; p-MeC_6H_4CHO, 104-87-0; p-HOC_6H_4CHO, 123-08-0; 2,4-dimethoxybenzaldehyde, 613-45-6.

A Free–Wilson/Fujita–Ban Analysis and Prediction of the Analgesic Potency of Some 3-Hydroxy- and 3-Methoxy-*N*-alkylmorphinan-6-one Opioids[1]

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Herein we describe a Free–Wilson/Fujita–Ban QSAR (quantitative structure–activity relationship) analysis of the analgesic potency of over 50 semisynthetic opioid narcotics. The 3-hydroxy- and 3-methoxy-*N*-alkylmorphinan-6-ones of B/C-cis and -trans stereochemistry include compounds exhibiting structural variation at five positions [*N*-methyl (C17), oxygen at C3, C4–C5 oxygen bridge, alkyl substituents at C7 and C8]. The pharmacological parameter correlated was the analgesic potency ($-\log ED_{50}$) exhibited on abdominal contractions produced by acetylcholine injection in mice. A satisfactory correlation was obtained only by assuming interdependent contributions of the substituents on C17 and O(C3), with which it was possible to explain 75% of the variance. Phenolic compounds (3-OH) behave somewhat differently from the methyl ethers (3-OCH_3), and in both series the substituents on C8 have a size-dependent negative contribution, implying steric hindrance at their contact point on the receptor. With use of this correlation the potency of five further members of the series was predicted. Subsequent testing fully confirmed the validity of the correlation since the measured potencies were, within experimental error, equal to those calculated. In a further refinement, phenolic compounds were considered separately from the ethers, and it was found that the contribution of the substituents on C17, C7, and C8 remained similar in sign and magnitude but not that of the furan oxygen. This analysis allows us to conclude that if both phenolic and nonphenolic members of this series act on the same receptor they must bind at different subsites or in alternate modes, supporting an earlier proposal in the literature.

Introduction

Opiate narcotics present a Janus-like double aspect: on the one hand their abuse and its consequences is one of this century's scourges, but on the other, their use in pharmacotherapy is essential and no adequate substitutes are known. For both reasons an understanding of their mechanism(s) of action at all levels, but specially at that of their receptor(s), is one of the great challenges in pharmacology today.

Biological data on narcotic analgesics[2] include both antinociceptive potencies in whole animals and receptor-binding assays: the correlation between them is generally good for closely related analogues[3-5] but not for very different structures.[6] In addition to countless SAR (structure–activity relationship) studies over more than a century, in the last 20 years several QSAR (quantitative structure–activity relationship) analyses have also been described. Kutter et al.[7] showed that lipophilicity was not decisive for their analgesic potency but determined their transport into and concentration in the brain. Jacobson et al.[8] found it necessary to include both receptor affinity and log *P* terms to obtain an acceptable correlation for a structurally diverse group. Johnson in a wide ranging study[9] of receptor affinities and using a Free–Wilson-related fragment approach concluded that the use of molecular hydrophobicity and steric bulk parameters did not give satisfactory correlations and emphasized the need to consider the substituents' location in the molecule. Lien et al.[10] found for a series of 14-hydroxycodeinones that quadratic log *P* and separate molar refraction terms for substituents were necessary to give a satisfactory correlation. Katz et al.[11] found a parabolic dependence on log *P* for agonists and antagonists in their affinity for receptors in the guinea pig ileum; the best correlation equation required both affinity and log *P* terms and was not statistically significant at the 0.95 level. In a later paper Katz et al.,[12] using the Free–Wilson/Fujita–Ban (FW/FB) method to analyze a series of benzomorphans, could explain 80% of the variance using only structural contribu-

(1) Taken from the M.S. Thesis in Pharmacology of Z.H.-G., C.I.E.A.-I.P.N., 1989. Presented in part at the XII Congreso Nacional de Farmacología, Pátzcuaro, Michoacán, November 27–30, 1988; Abstracts p. 119.
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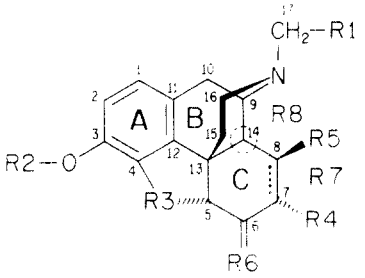

R1	n′	n	R2	n′	n
H	18	14	H	21	15
c-C_3H_5	13	13	CH_3	28	26
c-C_4H_7	18	14			
R3	**n′**	**n**	**R4**	**n′**	**n**
H,H	34	26	H	38	32
-O-	15	15	CH_3	11	9
R5	**n′**	**n**	**R6**	**n′**	**n**
H	21	17	H,H	1*	0
CH_3	20	16	$=CH_2$	1*	0
C_2H_5	5	5	=O	47	41
n-C_3H_7	3	3			
R7	**n′**	**n**	**R8**	**n′**	**n**
H,H	47	41	B/C-cis	45	41
=	2*	0	B/C-trans	4*	0

Figure 1. Common structure of the 49 morphinans. R1–R8 are the structural variants considered and n' is the number of times they were present. The asterisked compounds were initially excluded, leaving 41 morphinan-6-ones in the basis set in which the indicated substituents occur n times at R1–R5. Note that R3 represents the presence or absence of a furan oxygen ether linkage and c = cyclo.

tions; they were also able to predict the potencies of a related series of morphinans. Mager[13] has also published a multivariate analysis of diverse opioids which, however, did not include any of the morphinan series.

The research summarized above indicates that simple Hansch-type relations are not to be found for this type of compound.

The availability in our laboratories of uniform analgesic potency determinations (partly unpublished) on over 50 structurally related morphinans[14-18] prompted us to attempt their OSAR analysis. The presence in all of them of the same functional groups, limited type of substituent, and thus their predictably similar physicochemical properties led us to choose a de novo analysis instead of a Hansch-type approach.

Basis Set. Of the 49 compounds on which potency data were available (Figure 1), eight were excluded, four because they had B/C-trans stereochemistry and two because they had a double bond between C7 and C8, on the basis that they differ structurally too much from the remaining compounds. Also eliminated was one compound with an exocyclic methylene at R6 and one with two hydrogens there, because of their singular occurrence; these variants are listed in Figure 1 under R6, R7, and R8. This left the 41 compounds with structural variations at R1–R5 identified in Table I. Compound **25**, bearing hydrogens at all these positions, was chosen as the reference structure; its potency corresponds exactly to the average of the set, a fortunate happenstance. The basis set displays a 160-fold potency range (2.20 log units) and is symmetrically distributed about a midpotency of log AP (analgesic potency) = 6.0, corresponding to an ED_{50} of 1.0 μmol/kg, close to that of morphine.

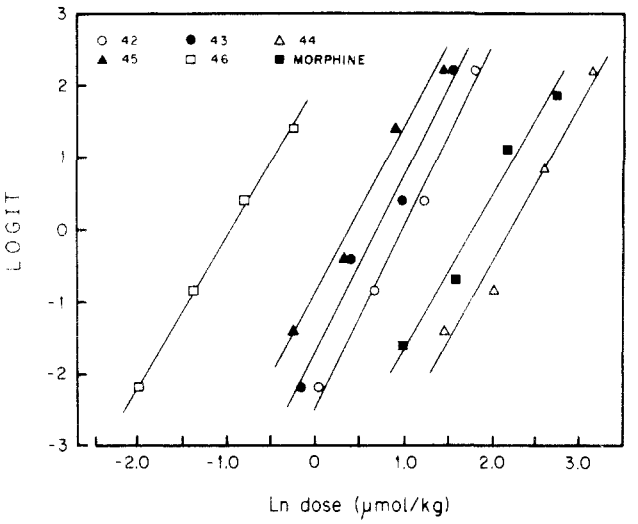

Figure 2. Logit dose–response curves for the compounds in the test series. The compounds are identified in Table II.

Test Set. To test the predictive power of the derived equations, samples of five additional analogues of this series whose analgesic potency in the acetylcholine (AcCh) induced mouse writhing test was unknown were obtained and tested. These structures (Table II) represent novel combinations of the same substituents included in the basis set.

Results and Discussion

Analgesic Potency of the Test Compounds. The results of the analgesic assays are shown in Figure 2 and Table III. They include those obtained for morphine, which served as a control in the bioassay; our result (ED_{50} = 6.13 μmol/kg, log AP = 5.21) agrees satisfactorily with that previously determined in these laboratories (log AP = 5.27). The ln dose vs logit regressions were straight lines in all cases and were parallel statistically (t test, $p < 0.05$), strongly implying interaction of these analgesics with a common receptor. The potencies of these five compounds were evenly spread about their mean (log AP = 5.7), which was similar to that of the basis set (6.0) and within its potency span. The ratio of potencies within the test set was only 24 but included compounds both weaker and stronger than morphine.

Results of the Free-Wilson/Fujita-Ban Analyses. A. Basis Set. The initial attempt, in which independent contributions from all substituents at all varied positions were assumed, resulted in a nonsignificant correlation (n = 41, r = 0.57, s = 0.54, F = 1.95, p = 0.86). To examine if the substituents at R2 and R3 contribute interdependently, another attempt was made combining them into a fictitious fragment R(2,3), with no improvement. In a subsequent analysis (FW/FB #1) a mutual dependence of the contributions at R1 and R2 was assumed. When

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Table I. Designation and Structures of the Compounds in the Basis Set[a]

														log AP		
no.	1	2	3	4	5	6	7	8	9	10	11	12	13	obs[b]	calcd[c]	calcd[d]
1	1	0	0	0	1	0	1	1	0	0	1	0	0	5.45	5.67	5.62
2	1	0	0	1	0	0	1	1	0	0	1	0	0	6.03	5.58	5.78
3	0	1	0	0	1	0	1	1	0	0	1	0	0	5.16	5.82	5.73
4	1	0	0	0	1	0	1	1	0	0	0	1	0	5.72	5.48	5.39
5	0	0	1	0	1	0	1	1	0	0	1	0	0	5.26	5.35	5.25
6	1	0	0	0	1	1	0	1	0	0	1	0	0	5.87	5.96	6.09
7	1	0	0	1	0	1	0	1	0	0	1	0	0	5.32	5.86	5.69
8	1	0	0	0	1	1	0	1	0	1	0	0	0	5.84	6.16	6.29
9	0	0	1	1	0	0	1	1	0	0	1	0	0	6.41	6.32	6.54
10	0	1	0	0	1	0	1	1	0	1	0	0	0	6.20	6.03	5.93
11	1	0	0	0	1	1	0	0	1	0	1	0	0	5.95	5.73	5.76
12	1	0	0	0	1	0	1	1	0	1	0	0	0	5.54	5.88	5.82
13	1	0	0	1	0	0	1	1	0	1	0	0	0	5.95	5.78	5.95
14	0	0	1	0	1	0	1	1	0	1	0	0	0	5.58	5.55	5.45
15	0	1	0	0	1	0	1	1	0	0	0	1	0	5.18	5.63	5.50
16	0	1	0	1	0	0	1	1	0	1	0	0	0	5.37	5.04	5.26
17	0	1	0	0	1	1	0	1	0	0	1	0	0	6.59	6.11	6.21
18	0	1	0	1	0	1	0	1	0	0	1	0	0	4.81	5.12	5.00
19	0	0	1	1	0	0	1	1	0	1	0	0	0	6.49	6.53	6.72
20	0	0	1	1	0	1	0	0	1	0	1	0	0	6.95	6.61	6.46
21	0	0	1	0	1	1	0	1	0	0	1	0	0	5.99	5.63	5.72
22	1	0	0	0	1	0	1	1	0	0	0	0	1	4.87	4.60	4.49
23	1	0	0	0	1	0	1	0	1	1	0	0	0	5.71	5.65	5.49
24	0	0	1	0	1	1	0	1	0	1	0	0	0	6.09	5.84	5.92
25	1	0	0	1	0	1	0	1	0	1	0	0	0	5.99	6.07	5.87
26	0	1	0	0	1	1	0	1	0	1	0	0	0	6.87	6.31	6.41
27	0	0	1	1	0	1	0	1	0	1	0	0	0	6.45	6.81	6.63
28	0	1	0	1	0	1	0	1	0	1	0	0	0	5.16	5.32	5.17
29	0	1	0	0	1	1	0	0	1	1	0	0	0	5.97	6.08	6.08
30	0	0	1	0	1	1	0	0	1	1	0	0	0	5.16	5.60	5.59
31	1	0	0	0	1	1	0	1	0	0	0	1	0	5.93	5.76	5.86
32	1	0	0	0	1	1	0	1	0	0	0	0	1	4.90	4.89	4.96
33	0	1	0	1	0	1	0	0	1	1	0	0	0	5.24	5.09	5.15
34	0	0	1	1	0	1	0	0	1	1	0	0	0	6.71	6.58	6.60
35	0	1	0	0	1	1	0	1	0	0	0	1	0	5.91	5.91	5.98
36	0	1	0	0	1	1	0	1	0	0	0	0	1	4.76	5.04	5.08
37	0	0	1	0	1	1	0	0	1	0	1	0	0	5.25	5.40	5.39
38	0	1	0	0	1	1	0	0	1	0	1	0	0	6.15	5.87	5.88
39	0	0	1	0	1	1	0	1	0	0	0	1	0	5.47	5.44	5.49
40	0	0	1	1	0	1	0	0	1	0	1	0	0	6.23	6.37	6.43
41	0	0	1	1	0	1	0	1	0	0	1	0	0	6.60	6.61	6.46

[a] The contents of columns 1–13 indicate the presence (1) or absence (0) at the positions (R) of the substituents indicated below (see Figure 1). At R3, –O– indicates the presence and H,H the absence of the furan ring; *c* = cyclo.

1: R1 = H
2: R1 = *c*-C_3H_5
3: R1 = *c*-C_4H_7
4: R2 = H
5: R2 = CH_3
6: R3 = H,H
7: R3 = –O–
8: R4 = H
9: R4 = CH_3
10: R5 = H
11: R5 = CH_3
12: R5 = C_2H_5
13: R5 = *n*-C_3H_7

[b] log AP values were computed from information supplied by Dr. J. E. Villarreal. [c] Calculated log AP values by FW/FB #1. [d] Calculated log AP values by FW/FB #1A and #1B.

Table II. Structures and Analgesic Potencies of the Compounds in the Test Set[a]

					log AP		
no.	R1	R2	R4	R5	measured	predicted[b]	dif
42	H	H	CH_3	H	5.56	5.83	–0.27
43	H	CH_3	CH_3	C_2H_5	5.69	5.53	0.16
44	*c*-C_4H_7	CH_3	CH_3	C_2H_5	5.04	5.20	–0.16
45	*c*-C_4H_7	H	CH_3	C_2H_5	5.82	6.18	–0.36
46	*c*-C_4H_7	H	H	CH_3	6.41	6.61	–0.20
morphine					5.21		

[a] For all R3 = H,H; please refer to Figure 1. [b] Predicted log AP values by FW/FB #1.

Table III. Analgesic Bioassay Data of the Test Set

no.	ED_{50}, μmol/kg	95% CI[a]	no.	ED_{50}, μmol/kg	95% CI[a]
42	2.75	2.08–3.62	**45**	1.52	0.97–2.37
43	2.03	1.53–2.68	**46**	0.39	0.26–0.58
44	9.18	6.49–13.0	morphine	6.13	4.87–7.70

[a] 95% confidence interval.

combined into a fictitious fragment R(1,2), a highly significant correlation emerged (Table IV, second column). This implicitly divides the basis set into two classes: phenols and methyl ethers (see below).

In Table I are listed the measured and calculated potencies. The residuals, with an average absolute value of 0.23, were randomly distributed about a mean of zero. The correlation between measured and calculated values (not shown) had an intercept of 0 and slope = 1.00 for $n = 41$, with $r = 0.87$ and $s = 0.29$.

The FW/FB #1 model explains 75% of the variance. It should be noted that the terms for the interdependence of R1 and R2 are not negligible. The first three contributions at R5 for the sequence H, CH_3, C_2H_5, and *n*-C_3H_7 are linear ($r^2 \approx 1$) with their Moriguchi volume terms,[19] suggesting steric hindrance at their point of interaction with the receptor. Upon reaching *n*-C_3H_7, the potency falls

(19) Moriguchi, I.; Kanada, Y.; Komatsu, K. *Chem. Pharm. Bull.* **1976**, *24*, 1799.

Table IV. Results of the FW/FB Analyses

fragment	contribution[c] FW/FB #1 (R2 = H or CH_3)	FW/FB #1A (R2 = H)	FW/FB #1B (R2 = CH_3)
μ	6.066[a]	5.866[a]	6.292[b]
R1 = c-C_3H_5, R2 = H	−0.742*	−0.694*	
R1 = c-C_4H_7, R2 = H	+0.745*	+0.764*	
R1 = H, R2 = CH_3	+0.096		
R1 = c-C_3H_5, R2 = CH_3	+0.243		+0.114
R1 = c-C_4H_7, R2 = CH_3	−0.230		−0.372*
R3 = −O−	−0.283*	+0.087	−0.474*
R4 = CH_3	−0.232	−0.027	−0.329*
R5 = CH_3	−0.205*	−0.175*	−0.198*
R5 = C_2H_5	−0.399*		−0.430*
R5 = n-C_3H_7	−1.274*		−1.329*
n	41	15	26
r	0.87	0.94	0.83
s	0.34	0.28	0.34
F	9.14	13.91	5.72
p	<0.001	<0.001	<0.005

[a] Compound **25** was taken as the reference structure. [b] Compound 8 was taken as the reference structure. [c] An asterisk indicates a value significantly different ($p < 0.05$) vs zero (H). 95% CI were ca. 0.4 for all contributions; they are not shown since they are not very informative in FW analyses (see ref 26).

abruptly (Table I, compounds **22**, **32**, **36**), confirming the qualitative conclusions reached earlier.[14,15]

The FW/FB #1 model suggests that the best substituents for high potency would be cyclobutyl at R1, hydrogen at R2 (phenol), lack of the furan oxygen bridge at R3, and hydrogens at R4 and R5. Precisely this substitution pattern is shown by **27**, which, while not the most potent, is very potent (log AP = 6.45). The lowest potency is predicted for R1 = c-C_3H_5, R2 = H, R3 = −O−, R4 = CH_3, and R5 = n-C_3H_7, but this could not be verified since this compound is not found in the basis set.

In order to refine the analysis, the basis set was divided into two subsets comprising the phenols (FW/FB #1A) and the methyl ethers (FW/FB #1B), for which R2 is, respectively, H and CH_3. By analyzing them separately we sought to examine how the contributions from the remaining variants (R3, R4, R5) compared in these two families. As shown in Table IV, the correlation improved slightly for the phenols but deteriorated for the methyl ethers. Where comparisons were possible, the contributions remained essentially the same, although a few changed sign. When these equations were used separately to calculate the potencies of the basis set, only a marginal improvement was achieved (average absolute difference = 0.22).

B. Test Set. With use of the derived correlation equation the potencies of the five test compounds were predicted. These were subsequently measured, and an excellent agreement between them was found (Table II). The absolute average value of the residuals was 0.23, identical with that of the test series.

A new FW/FB analysis was carried out on the combined basis and test sets, and the results when compared to those in Table IV, remained essentially the same ($n = 46$, $r = 0.87$, $s = 0.32$, $F = 10.8$, $p < 0.001$). Also the separate addition of three further phenols to FW/FB #1A and of two methyl ethers to FW/FB #1B did not change the results.

The extremely accurate prediction made by this simple method emphasizes once again the utility of de novo analysis provided it is applied to an appropriately chosen group of structures.

C. Excluded Compounds. Having derived a robust regression, it seemed of interest to apply it to the compounds initially excluded (asterisked entries in Figure 1; Table V). For the des-6-keto analogue (**47**) the predicted potency was 1.49 units higher than that measured, justifying its exclusion from the basis set and indicating that the 6-keto function definitely enhances potency. For the 6-*exo*-methylene analogue (**48**), that predicted was 0.54 units higher than that measured, also justifying its exclusion. For the two compounds with a double bond between C7 and C8 (**49** and **50**), the residuals were 0.29 and −0.26, respectively, which can be taken to mean that this structural variation is unimportant and that they should not have been excluded. On the other hand, the four B/C-trans analogues (**51**–**54**) had residuals of 0.45, −0.86, −0.93, and −0.89, 2–4 times the average of the basis set, which clearly indicates that they differ sufficiently from the included analogues to justify their exclusion.

D. Structure–Activity Relationships. The derived relationships explain a good fraction of the variance and have excellent predictive value. Although the R(1,2) combination resulted in a viable model, implying their mutual interaction, this is unlikely. We note that the contributions of R4 and R5 remain essentially constant in both series, while the contribution of R1 and R3 are different in both sign and magnitude. We interpret this as implying an unchanging position of the R4 and R5 substituents on the receptor for both families but small differences in the positions of the substituents on the nitrogen and the oxygen. Furthermore we suggest that these molecules when bound to the receptor pivot about the C-ring region, with which the atoms on O3 and C17 alternate between two subsites on the receptor, each capable of inducing the analgesic response when occupied.

It has been suggested that in this type of compound O-demethylation is necessary and that only the free phenols display strong agonistic activity. This is not supported by our data since our activity estimates were obtained 15–17 min after sc administration, a period too short for metabolic transformation. Furthermore, for five such pairs (**6**/**7**, **10**/**16**, **17**/**18**, **26**/**28**, and **29**/**33**) the methyl ethers were more potent than the phenols, whereas the opposite was true in another 10 pairs (Table I).

Several of the compounds studied here bear cyclopropylmethyl and cyclobutylmethyl groups on the nitro-

Table V. Structures and Analgesic Potencies of the Excluded Compounds[a]

no.	R1	R2	R4	R5	R6	R7	R8	log AP measured	log AP predicted[b]
47	H	H	H	CH_3	H,H	H,H	cis	5.12	6.61
48	c-C_4H_7	H	H	CH_3	CH_2	H,H	cis	6.07	6.61
49	H	CH_3	H	H	O	=	cis	6.45	6.16
50	H	CH_3	CH_3	H	O	=	cis	5.67	5.93
51	H	H	H	CH_3	O	H,H	trans	6.32	5.86
52	c-C_4H_7	H	H	CH_3	O	H,H	trans	5.75	6.61
53	c-C_4H_7	CH_3	CH_3	H	O	H,H	trans	4.68	5.60
54	c-C_4H_7	H	H	H	O	H,H	trans	5.92	6.81

[a] See Figure 1; for all R3 = H,H. [b] Predicted log AP values by FW/FB #1.

gen, substituents that are frequently associated with narcotic antagonist activity. Although it is possible that the potencies of compounds with these substituents are the net effect of both agonistic and antagonistic activity, this is unlikely since previous work[17] established that they do not show strong mixed agonist–narcotic antagonist activity. Furthermore, our results (Table IV) show that the calculated contribution of these groups show no consistent pattern.

This interpretation of our analysis provides independent evidence for the validity of the multiple modality concept proposed by Portoghese for the phenol-binding subsite on the analgesic receptor.[20,21]

In conclusion, the successful de novo analysis of this extensive group of analgesic morphinan derivatives shows that meaningful QSAR's can be obtained in which the potency of a given member can be predicted from the contributions to it of the molecular fragments it contains.

Experimental Section

Compounds. The semisynthetic opioid analgesics (substituted morphinan-6-ones) in Tables I, II, and IV were prepared by Miles Laboratories (Elkhart, IN) and SISA, Inc. (Cambridge, MA).[14-18] The analgesic activity of most of them was determined by Dr. J. E. Villarreal and Mr. Luis Salazar in the Instituto Miles de Terapéutica Experimental (México, D.F.) as described in unpublished reports, using a method similar to that published.[15] Samples of the compounds in Table II, whose analgesic potency was determined in the present work, were generously provided by Dr. J. E. Villarreal (now at Sección de Terapéutica Experimental, Departamento de Farmacología y Toxicología, C.I.E.A.-I.P.N., México, D.F.).

Analgesic Potency Determination. Swiss female white mice (6–7 weeks, 20–25 g) were selected 1 day before testing and kept in a separate room at constant temperature (ca. 25 °C), where they were allowed unrestricted access to food and water. Each group of mice was tested previously with AcCh and accepted if at least 9/10 showed signs of pain and abdominal contractions. A solution of AcCh (Sigma, St. Louis, MO) of 0.32 mg/mL was prepared and 0.1 mL were injected ip per 10 g of body weight, corresponding to a dose of 3.2 mg/kg. The analgesics were dissolved in water (if available as a soluble salt) or suspended in 0.2% methylcellulose when present as the free base. They were administered sc, 15 min before the animals were challenged with AcCh. Complete analgesia was assumed when the mouse showed no writhing within the first 2 min after AcCh injection. Besides the control groups, four dose levels were tested, each with 10 mice. Because of limited sample size, only one dose–response determination was made for each of the five compounds in the test set and for morphine as an additional control. The ED_{50} was calculated by a simple logit method[22] and transformed into mole/kilogram, and the negative logarithm was taken as the measure of analgesic potency (log AP).

Free–Wilson/Fujita–Ban Analysis. For the QSAR analysis we used the method of Free and Wilson[23] as modified by Fujita and Ban[24] implemented in a computer program written expressly for this purpose.[25] It is based on the equation

$$\log (1/C)_i = \mu + \sum_{j=1}^{r} \sum_{k=1}^{mj} b_{ijk} z_{jk}$$

where $\log (1/C)_i$ is the potency of the ith compound and μ is that calculated by the regression for the hydrogen-substituted reference structure (for which $z_{jH} = 0$), r is the number of substitution sites, m_j is the number of variable fragments or substituents at site j, z_{jk} is the contribution of fragment jk (substituent k at position j), and b_{ijk} is an indicator variable which takes the value of 1 in the presence and 0 in the absence of substituent jk in compound i. The computer program was tested with the data of Free and Wilson[23] and Kubinyi[26] and gave exactly the same results as reported by these authors.

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Registry No. 1, 128526-61-4; 2, 128526-62-5; 3, 128526-63-6; 4, 128526-64-7; 5, 128526-65-8; 6, 128548-78-7; 7, 128548-79-8; 8, 125-70-2; 9, 128526-66-9; 10, 128526-67-0; 11, 128548-80-1; 12, 3990-01-0; 13, 427-00-9; 14, 128526-68-1; 15, 128526-69-2; 16, 128526-70-5; 17, 128526-71-6; 18, 128548-81-2; 19, 128526-72-7; 20, 128575-78-0; 21, 128548-82-3; 22, 128526-73-8; 23, 128548-83-4; 24, 128574-62-9; 25, 77-07-6; 26, 14725-17-8; 27, 4163-26-2; 28, 4163-15-9; 29, 128526-74-9; 30, 128526-75-0; 31, 128526-76-1; 32, 128526-77-2; 33, 128526-78-3; 34, 128526-79-4; 35, 14725-17-8; 36, 128548-84-5; 37, 128548-85-6; 38, 128548-86-7; 39, 128526-80-7; 40, 128526-81-8; 41, 128526-82-9; 42, 128526-83-0; 43, 128526-84-1; 44, 128575-77-9; 45, 128599-18-8.

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