$$n = \frac{\text{no. of plaques induced by the test compd}}{\text{no. of plaques in control}}$$

Mammary Tumor Growth Inhibition Tests. (a) DMBA-Induced, Hormone-Dependent Mammary Carcinoma of the SD Rat.[2] A single dose of 20 mg of DMBA (9,10-dimethyl-1,2-benzanthracene) was administered by gastric intubation to female SD (Sprague–Dawley) rats at an age of 50 days. After the appearance of tumors, about 4 weeks later, animals with at least one tumor with an area >140 mm^2 were classified in groups of ten. Compounds were administered in olive oil solution 6 times a week sc. The duration of treatment was 28 days. Measurement of tumor area was made twice weekly. The tumor area was defined by length × width of the tumor.

(b) Hormone-Dependent Human Mammary Carcinoma Serially Transplanted in Nude Mice.[7] Animals of a random-bred strain (NMRI nu/nu) at an age of 6 to 7 weeks were grafted with mammary carcinomas from premenopausal (female mice) and postmenopausal (castrated female or male mice) women. The premenopausal tumor was estrogen receptor positive and progesterone receptor negative; the postmenopausal tumor was estrogen receptor and progesterone receptor positive. Tumors were measured once a week by two diameters. Compounds were administered as olive oil solutions 6 times a week sc. The duration of treatment was 4–5 weeks. At the beginning of treatment, tumor size was defined as "1".

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Quantitative Structure–Activity Relationships of Aromatic Esters of 1-Methyl-4-piperidinol as Analgesics[1]

Chen-Yu Cheng,*[†] Einar Brochmann-Hanssen,[†] and James A. Waters[‡]

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94143, and Laboratory of Chemistry, NIAMDD, National Institutes of Health, Bethesda, Maryland 20014. *Received May 11, 1981*

Substituted benzoic acid esters of 1-methyl-4-piperidinol showed analgesic activity when assayed by the mouse hot-plate method, the more potent ones falling in the morphine–codeine range. To understand how substituents on the aromatic ring affect the analgesic potency, quantitative structure–activity correlations were carried out on a series of 44 derivatives. Among the various substituent parameters included in the study, L_{ortho} (length of ortho-substituents) and B_1 (minimal width of substituents) or E_s at meta and para positions gave negative correlation with the potency, while lipophilicity (especially π_{meta}) and the ability of being a hydrogen-bond acceptor enhanced the potency. Based on the QSAR results, a substitution pattern of the phenyl group was defined for optimal activity. Implications on drug–receptor interactions and the possible binding mode of these compounds were discussed.

Previous studies[2,3] have shown that substituted benzoic acid esters of 1-methyl-4-piperidinol possess analgesic activity by the hot-plate assay, with the more potent ones in the range of morphine and codeine, but, in general, they display no morphine-like physical dependence liability in monkeys.

These esters have the main structural features of many synthetic analgesics, namely, a benzene ring and a piperidine ring. However, they lack the quaternary phenyl substitution at C-4 of the piperidine ring, which is present in meperidine, prodine, and other 4-phenylpiperidine analgesics. Qualitative structure–activity correlations of some 3- and 4-substituted and 3,4-disubstituted benzoate esters were made with regard to substituent constants E_s[c] and π. No significant conclusions were drawn from this limited study,[3] and it became apparent that a quantitative study applying multiple-regression analysis would be necessary in order to gain insight into the involvement of the aromatic ring in determining the analgesic potency.

Over the years, several publications have appeared[4-9] on the quantitative structure–activity relationships of narcotic analgesics, but none has dealt extensively with the effects of substituents on the aromatic moiety.

Preliminary analysis of available compounds showed an insufficient spread of substituent parameter values. Therefore, additional monosubstituted compounds were synthesized based on Craig's plots,[10] as illustrated for para-substituted compounds in Figure 1. The structure and analgesic potency of all 48 benzoic acid esters of 1-methyl-4-piperidinol are shown in Table I. The analgesic potencies ranged from an average hot-plate ED_{50} of 3.9 to 74 mg/kg (0.012 to 0.23 mmol/kg), with the exception of a few which were marginally active or inactive at 100 mg/kg.

Results and Discussion

Among the various physicochemical parameters included in the study (cf. Experimental Section), those found to be significant in correlating the structure with activity are listed in Table I. The statistically significant regression equations are given below, where n is the number of compounds, r is the multiple regression coefficient, s is the standard deviation of the regression, and f is the value of

* Address correspondence to Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.
[†] University of California.
[‡] NIAMDD.

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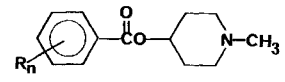
Table I. Hot-Plate Analgesic Potency and Physicochemical Parameters of Substituted Benzoic Acid Esters of 1-Methyl-4-piperidinol



no.	R_n	$\Sigma\pi$	π_m	π_o	L_o[a]	$B_{1,m}$[a]	$E_{s,m}$	$B_{1,p}$[a]	$E_{s,p}$	HB_o	HB_m	HB_p	log (1/C)[b] obsd	log (1/C)[b] calcd[c]	log (1/C)[b] Δ
1	3,4-$(OCH_3)_2$	0.08	0.04	0	0	0.35	−0.55	0.35	−0.55	0	1.128	1.128	1.91	1.84	0.07
2[d]	4-OC_2H_5	0.38	0	0	0	0	0	0.35	−0.62[e]	0	0	1.248	1.72	1.61	0.11
3	3-OCH_3	−0.02	−0.02	0	0	0.35	−0.55	0	0	0	1.128	0	1.67	1.63	0.04
4[d]	4-CN	−0.57	0	0	0	0	0	0.6	−0.51	0	0	1.898	1.65	1.62	0.03
5	3,4-(OCH_2O)	−0.05	−0.025	0	0	0.2[f]	−0.55	0.2	−0.55	0	1.128	0	1.61	1.65	−0.04
6[d]	4-O-*n*-C_4H_9	1.55	0	0	0	0	0	0.35	−0.94[g]	0	0	1.248	1.58	1.56	0.02
7[h]	2,4,6-$(CH_3)_3$	1.29	0	0.86	1.88	0	0	0.52	−1.24	0	0	0	1.55	1.11	−0.44
8	2,3-$(OCH_3)_2$	0.08	−0.02	−0.02	1.92	0.35	−0.55	0	0	1.128	1.128	0	1.55	1.49	0.06
9	3,5-$(OCH_3)_2$	0.08	0.08	0	0	0.7	−1.1	0	0	0	1.128	0	1.53	1.43	0.10
10[d]	2-CF_3	0.88	0	0.88	1.24	0	0	0	0	1.078	0	0	1.49	1.35	0.14
11	2-CH_3	0.56	0	0.56	0.94	0	0	0	0	0	0	0	1.48	1.37	0.11
12[d]	2-NO_2	−0.28	0	−0.28	1.38	0	0	0	0	1.918	0	0	1.48	1.34	0.14
13	2,4,6-$(OCH_3)_3$	0.06[i]	0	0.04	3.84	0	0	0.35	−0.55	0[j]	0	1.128	1.47	1.33	0.14
14	H	0	0	0	0	0	0	0	0	0	0	0	1.43	1.44	−0.01
15	4-OCH_3	−0.02	0	0	0	0	0	0.35	−0.55	0	0	1.128	1.43	1.62	−0.19
16	2-OCH_3	−0.02	0	−0.02	1.92	0	0	0	0	1.128	0	0	1.43	1.30	0.13
17	2-F	0.14	0	0.14	0.59	0	0	0	0	0	0	0	1.41	1.40	0.01
18	3-OCH_3, 4-CH_3	0.54	−0.02	0	0	0.35	−0.55	0.52	−1.24	0	1.128	0	1.4	1.44	−0.04
19[d]	3-CN	−0.57	−0.57	0	0	0.6	−0.51	0	0	0	1.898	0	1.39	1.48	−0.09
20	4-F	0.14	0.0	0	0	0	0	0.35	−0.46	0	0	0	1.38	1.37	0.01
21	2,5-$(CH_3)_2$	1.07[k]	0.56	0.56	0.94	0.52	−1.24	0	0	0	0	0	1.36	1.29	0.07
22	3,4,5-$(OCH_3)_3$	−0.6	−0.4	0	0	0.7	−1.1	0.35	−0.55	0	1.128	1.128	1.35	1.36	−0.01
23	3-F, 4-CH_3	0.7	0.14	0	0	0.35	−0.46	0.52	−1.24	0	0	0	1.32	1.07	0.25
24[d]	2-$CH_2C_6H_5$	2.01	0	2.01	1.57	0	0	0	0	0	0	0	1.28	1.32	−0.04
25	2,6-$(CH_3)_2$	1.07	0	1.07	1.88	0	0	0	0	0	0	0	1.27	1.30	−0.03
26	3-F	0.14	0.14	0	0	0.35	−0.46	0	0	0	0	0	1.26	1.26	0.00
27[d]	2-Cl	0.71	0	0.71	1.46	0	0	0	0	0	0	0	1.25	1.33	−0.08
28	3-OH	−0.67	−0.67	0	0	0.35	−0.55	0	0	0	1.0	0	1.21	1.24	−0.03
29[d]	2-Br	0.86	0	0.86	1.77	0	0	0	0	0	0	0	1.21	1.31	−0.10
30	4-CH_3	0.56	0	0	0	0	0	0.52	−1.24	0	0	0	1.17	1.25	−0.08
31	2,4,5-$(CH_3)_3$	1.5	0.56	0.56	0.94	0.52	−1.24	0.52	−1.24	0	0	0	1.17	1.10	0.07
32[d,h]	4-NO_2	−0.28	0	0	0	0	0	0.7	−2.52	0	0	1.918	1.14	1.31	−0.07
33	4-$C(CH_3)_3$	1.98	0	0	0	0	0	1.59	−2.78	0	0	0	1.13	1.01	0.12
34[d]	4-Cl	0.71	0	0	0	0	0	0.8	−0.97	0	0	0	1.11	1.29	−0.18
35	3,4-Cl_2	1.25	0.71	0	0	0.8	−0.97	0.8	−0.97	0	0	0	1.08	1.08	0.00
36	3,5-$(CH_3)_2$	1.07	1.07	0	0	1.04	−2.48	0	0	0	0	0	1.07	1.25	−0.18
37[d]	4-C_6H_5	1.96	0	0	0	0	0	2.11[l]	−3.82[l]	0	0	0	0.85	0.85	0.00
38[h]	2,6-$(OCH_3)_2$	0.08	0	0.08	3.84	0	0	0	0	0[j]	0	0	0.63	1.15	−0.52
39[d,h]	2-C_6H_5	1.96	0	1.96	4.22	0	0	0	0	0	0	0	1.52[n]	1.12	0.40
40	2-OC_6H_5	2.08	0	2.08	2.45	0	0	0	0	0[m]	0	0	1.24[n]	1.26	−0.02
41	2-OC_2H_5	0.38	0	0.38	2.86	0	0	0	0	1.248	0	0	1.18[n]	1.23	−0.05
42[d]	2-C_2H_5	1.02	0	1.02	2.05	0	0	0	0	0	0	0	1.15[n]	1.29	−0.14
43	3,4-$(CH_3)_2$	0.99	0.56	0	0	0.52	−1.24	0.52	−1.24	0	0	0	1.15[n]	1.17	−0.02
44[d]	2-$C_2H_4C_6H_5$	2.66	0	2.66	6.27	0	0	0	0	0	0	0	0.86[n]	0.97	−0.11
45[d]	2-CN	−0.57	0	−0.57	2.17	0	0	0	0	1.898	0	0	inact	1.27	
46	3-CH_3	0.56	0.56	0	0	0.52	−1.24	0	0	0	0	0		1.35	

47[d]	4-I	1.12	0	0	0	1.15	−1.4	0	0	0			1.23
48	2,3,5-I_3	3	2.00	1.12	2.17	2.3	−2.8	0	0	0	0	0	0.65

[a] The listed values are the actual values minus the value for "H" so that the unsubstituted compound (14) can have zero value for all the parameters. [b] $C = ED_{50}$ (mmol/kg). Tested subcutaneously as water-soluble HCl salts by the hot-plate method; cf. A. E. Jacobson and E. L. May, *J. Med. Chem.*, 8, 563 (1965). [c] Derived from eq 12. [d] These derivatives were synthesized following the Craig's plot analysis. [e] $-0.62 = E_{s,OCH_3} + (E_{s,C_2H_5} - E_{s,CH_3}) = -0.55 + (-1.31 + 1.24)$. [f] Estimated from B_{1,OCH_3}. [g] $-0.94 = E_{s,OCH_3} + (E_{s,n\text{-}C_4H_9} - E_{s,CH_3}) = -0.55 + (-1.63 + 1.24)$. [h] Omitted in deriving eq 11. [i] $0.06 = \pi_{3,5\text{-}(OCH_3)_2} + \pi_{OCH_3} = 0.08 - 0.02$. [j] Assuming that a hydrogen bond cannot be formed because of unfavorable conformation forced by the di-ortho-substituents. [k] The value of $\pi_{3,5\text{-}(CH_3)_2}$ was used. [l] Because of the prefered perpendicular conformation of the biphenyl, maximum dimensions were used for the steric effect, i.e., E_s (L) and B_4 were used instead of E_s (S) and B_1. [m] Assuming the bulky phenyl group prevents "OC_6H_5" to be a hydrogen-bond acceptor. [n] Activity was observed in 4 to 5 out of 10 mice tested.

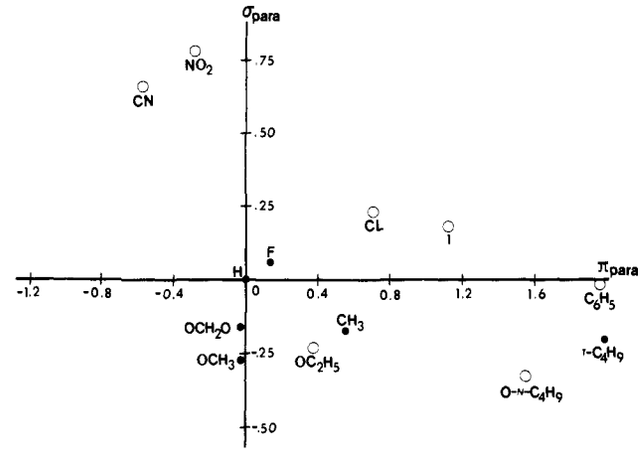


Figure 1. Application of Craig's plot for the selection of additional substituents. The purpose is to avoid the use of only those substituents which lie on or near a straight line, i.e., those which are highly correlated. Those marked by open circles are the substituents of additional compounds synthesized.

the F test. The number in parentheses under each coefficient is the value of Student's t test for that coefficient.

Four inactive compounds, namely, 2-cyano (**45**), 3-methyl (**46**), 4-iodo (**47**), and 2,3,5-triiodo (**48**) derivatives, are not included in the calculation, because no ED_{50} values can be assigned to them.

Since additivity cannot be readily assumed for many physicochemical parameters, i.e., multiple substituents might not exert an influence equal to the sum of the individual substituents, we decided to start the regression analysis with subgroups of monosubstituted compounds in order to simplify the process of selecting potential parameters. This approach might also minimize the risk of chance correlation[11] by reducing the number of variables screened in the last stage when all the compounds are included. Examples of subgrouping are not uncommon in the literature of QSAR.[12-15]

(A) Ortho-Substituted Derivatives (10–12, 14, 16, 17, 24, 25, 27, 29, 38-42, and 44). Equation 1 was obtained with the entire data set.

$$\log (1/C) = -\underset{(3.81)}{(0.14 \pm 0.037)}L_{ortho} + \underset{(2.14)}{(0.18 \pm 0.08)}HB_{ortho} + \underset{(2.08)}{(0.15 \pm 0.07)}\pi_{ortho} + 1.38 \quad (1)$$

$$n = 16;\ r = 0.77;\ s = 0.17;\ f = 5.84;\ f_{\alpha(1)=0.01,3,12} = 5.95$$

Examination of the residuals revealed that the calculated potency of the 2-phenyl derivative (**39**) was much lower than the observed potency, with a residual of 0.44. The reason for the higher observed potency of this compound is not clear, but this compound is unusual in that its activity is only marginal (footnote *n*, Table I) and toxicity was observed at 20 mg/kg.

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Table II. Squared Correlation Matrix for Variables of Equations 4 and 5

	$B_{1,m}$	$E_{s,m}$	π_m	HB_m	$HB_{m\text{-}ind}$
$B_{1,m}$	1.00	0.84	0.30	0.014	0.004
$E_{s,m}$		1.00	0.59	0.047	0.04
π_m			1.00	0.44	0.43
HB_m				1.00	0.85
$HB_{m\text{-}ind}$					1.00

Omission of compound **39** resulted in a much better correlation with the same parameters (eq 2).

$$\log (1/C) = -(0.16 \pm 0.02)L_{ortho} + (0.185 \pm 0.05)HB_{ortho} + (0.13 \pm 0.04)\pi_{ortho} + 1.41 \quad (2)$$
(7.25) (3.75) (2.91)

$n = 15$; $r = 0.93$; $s = 0.10$; $f = 21.77$; $f_{\alpha(1)=0.0005,3,11} = 13.7$

If all five marginally active ortho compounds (**39**, **40–42**, and **44**) were omitted from the regression, eq 3 was obtained in which the π_{ortho} term is no longer significant. It

$$\log (1/C) = -(0.21 \pm 0.03)L_{ortho} + (0.144 \pm 0.046)HB_{ortho} + 1.57 \quad (3)$$
(6.66) (3.13)

$n = 11$; $r = 0.93$; $s = 0.098$; $f = 27.32$; $f_{\alpha(1)=0.0005,2,8} = 22.7$

has been observed that HB_{ortho} can be replaced by $HB_{ortho\text{-}ind}$ in the above equations with little change in the statistics, since the two variables are highly correlated ($r^2 = 0.92$).

(B) Meta-Substituted Derivatives (3, 9, 14, 19, 26, 28, and 36). The following equations were obtained:

$$\log (1/C) = (0.49 \pm 0.12)HB_{meta} - (0.95 \pm 0.24)B_{1,meta} + (0.61 \pm 0.18)\pi_{meta} + 1.46 \quad (4)$$
(4.1) (4.0) (3.3)

$n = 7$; $r = 0.94$; $s = 0.10$; $f = 7.08$; $f_{\alpha(1)=0.05,3,3} = 9.28$

$$\log (1/C) = (0.54 \pm 0.06)HB_{meta\text{-}ind} + (0.42 \pm 0.05)E_{s,meta} + (0.67 \pm 0.09)\pi_{meta} + 1.40 \quad (5)$$
(8.28) (8.34) (7.20)

$n = 7$; $r = 0.98$; $s = 0.05$; $f = 32.04$; $f_{\alpha(1)=0.01,3,3} = 29.5$

As shown in the squared correlation matrix (Table II), $B_{1,meta}$ and $E_{s,meta}$ are highly correlated ($r^2 = 0.84$) and so are HB_{meta} and $HB_{meta\text{-}ind}$ ($r^2 = 0.85$). It is, therefore, not surprising that a combination of either "$B_{1,meta}$, HB_{meta}, and π_{meta}" or "$E_{s,meta}$, $HB_{meta\text{-}ind}$, and π_{meta}" may be used to give significant correlation. Equation 5 is statistically superior to eq 4, although $E_{s,meta}$ and π_{meta} in eq 5 are marginally correlated ($r^2 = 0.59$), while $B_{1,meta}$ and π_{meta} in eq 4 show little correlation ($r^2 = 0.30$). Since three parameters are included with only seven data points, the possibility that eq 4 and 5 are the results of chance correlation cannot be excluded. However, the same parameters continue to give significant correlations in eq 7–13, where the number of meta-substituted derivatives is increased with the inclusion of multisubstituted compounds. There are 16 compounds with meta substituents in the combined data set.

(C) Para-Substituted Derivatives (2, 4, 6, 14, 15, 20, 30, 32–34, and 37). With the entire data set, eq 6 gave the best correlation.

$$\log (1/C) = (0.15 \pm 0.03)E_{s,para} + (0.25 \pm 0.07)HB_{para\text{-}in} + 1.41 \quad (6)$$
(4.52) (3.24)

$n = 11$; $r = 0.91$; $s = 0.123$; $f = 19.78$; $f_{\alpha(1)=0.001,2,8} = 18.5$

(D) Ortho- and/or Meta-Substituted Derivatives (8, 21, and Compounds from Sections A and B). Regression analysis on the complete data set gave eq 7.

$$\log (1/C) = -(0.14 \pm 0.03)L_{ortho} + (0.48 \pm 0.16)HB_{meta} + (-0.82 \pm 0.30)B_{1,meta} + (0.17 \pm 0.07)HB_{ortho} + (0.59 \pm 0.25)\pi_{meta} + (0.15 \pm 0.06)\pi_{ortho} + 1.40 \quad (7)$$
(4.44) (3.04) (2.67) (2.35) (2.33) (2.28)

$n = 24$; $r = 0.815$; $s = 0.155$; $f = 5.60$; $f_{\alpha(1)=0.0025,6,17} = 5.51$

As in eq 1, poor prediction was obtained for the 2-phenyl derivative (residual = 0.438). A much better correlation was obtained with the omission of this compound from the calculation:

$$\log (1/C) = -(0.17 \pm 0.02)L_{ortho} + (0.49 \pm 0.10)HB_{meta} - (0.87 \pm 0.20)B_{1,meta} + (0.18 \pm 0.047)HB_{ortho} + (0.62 \pm 0.17)\pi_{meta} + (0.12 \pm 0.04)\pi_{ortho} + 1.43 \quad (8)$$
(7.54) (4.66) (4.30) (3.78) (3.69) (2.88)

$n = 23$; $r = 0.925$; $s = 0.103$; $f = 15.73$; $f_{\alpha(1)=0.0005,6,16} = 7.74$

(E) Meta- and/or Para-Substituted Derivatives (1, 5, 18, 22, 23, 35, 43, and Compounds from Sections B and C). Equation 9 was obtained from regression analysis on the entire data set.

$$\log (1/C) = (0.39 \pm 0.07)HB_{meta} + (0.15 \pm 0.03)E_{s,para} - (0.70 \pm 0.14)B_{1,meta} + (0.25 \pm 0.05)HB_{para\text{-}ind} + (0.48 \pm 0.13)\pi_{meta} + 1.42 \quad (9)$$
(5.19) (5.14) (5.04) (4.51) (3.77)

$n = 24$; $r = 0.91$; $s = 0.117$; $f = 17.72$; $f_{\alpha(1)=0.0005,5,18} = 7.71$

(F) The Combined Data Set (1–44). Stepwise regression analysis on the complete data set including all the active compounds resulted in eq 10.

$$\log (1/C) = (0.14 \pm 0.03)E_{s,para} + (0.40 \pm 0.1)HB_{meta} - (0.72 \pm 0.18)B_{1,meta} + (0.25 \pm 0.07)HB_{para\text{-}ind} - (0.07 \pm 0.02)L_{ortho} + (0.51 \pm 0.17)\pi_{meta} + 1.44 \quad (10)$$
(4.04) (3.97) (3.88) (3.64) (3.35) (2.93)

$n = 44$; $r = 0.77$; $s = 0.166$; $f = 9.14$; $f_{\alpha(1)=0.0005,6,35} = 5.39$

The 2,4,6-trimethyl (**7**), 2,6-dimethoxy (**38**), and 2-phenyl (**39**) derivatives were poorly predicted, with residuals of 0.415, 0.536, and 0.381, respectively. The higher observed activity of compound **7** might be the result of a large increase in lipophilicity, which is not significant in the correlation due to predominant steric effects.

The unusual behavior of the 2-phenyl derivative (**39**) has been observed in eq 1 and 10. Omission of compounds **7** and **39** from the regression resulted in eq 11.

$$\log (1/C) = (-0.10 \pm 0.02)L_{ortho} + (0.15 \pm 0.03)E_{s,para} + (0.28 \pm 0.05)HB_{para\text{-}ind} + (0.39 \pm 0.08)HB_{meta} - (0.70 \pm 0.14)B_{1,meta} + (0.51 \pm 0.13)\pi_{meta} + (0.11 \pm 0.05)HB_{ortho} + 1.42 \quad (11)$$
(5.73) (5.44) (5.36) (5.05) (4.75) (3.84) (2.31)

$n = 42$; $r = 0.88$; $s = 0.128$; $f = 16.51$; $f_{\alpha(1)=0.0005,7,30} = 5.31$

Table III. Squared Correlation Matrix for Variables of Equation 12

	L_o	HB_o	$B1_m$	HB_m	π_m	$E_{s,p}$	$HB_{p\text{-}ind}$
L_o	1.00	0.08	0.11	0.06	0.00	0.12	0.02
HB_o		1.00	0.03	0.00	0.00	0.06	0.03
$B1_m$			1.00	0.22	0.18	0.01	0.01
HB_m				1.00	0.20	0.02	0.00
π_m					1.00	0.01	0.03
$E_{s,p}$						1.00	0.03
$HB_{p\text{-}ind}$							1.00

The correlation here is much better than in eq 10, but the 2,6-dimethoxy derivative (**38**) is still poorly predicted, with a residual value of −0.408. The low activity of this compound is probably due to the steric effects of its di-ortho-substituents. It appears that this effect cannot be approximated by twice the steric effect of a single substituent (in Table I, $L_{ortho,2,6\text{-}(OCH_3)_2} = 2 \times L_{ortho,2\text{-}OCH_3}$).

Omission of compound **38** from the calculation gave eq 12. Replacing HB_{meta} and $B_{1,meta}$ in eq 12 with $HB_{meta\text{-}ind}$

$$\log (1/C) = \underset{(6.72)}{(0.15 \pm 0.02)}E_{s,para} + \underset{(6.04)}{(0.40 \pm 0.07)}HB_{meta} - \underset{(5.86)}{(0.72 \pm 0.12)}B_{1,meta} + \underset{(5.77)}{(0.26 \pm 0.04)}HB_{para\text{-}ind} - \underset{(4.85)}{(0.08 \pm 0.02)}L_{ortho} + \underset{(4.53)}{(0.52 \pm 0.11)}\pi_{meta} + 1.44 \quad (12)$$

$n = 41$; $r = 0.89$; $s = 0.110$; $f = 21.43$; $f_{\alpha(1)=0.0005,6,30} = 5.66$

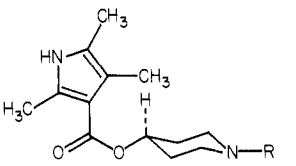
and $E_{s,meta}$ resulted in a similar correlation. However, addition of the HB_{ortho} (or $HB_{ortho\text{-}ind}$) term to the equation resulted in slight improvement of the correlation (eq 13).

$$\log (1/C) = \underset{(6.63)}{(0.15 \pm 0.02)}E_{s,para} + \underset{(6.32)}{(0.27 \pm 0.04)}HB_{para\text{-}ind} + \underset{(6.18)}{(0.39 \pm 0.06)}HB_{meta} - \underset{(5.80)}{(0.68 \pm 0.12)}B_{1,meta} - \underset{(5.34)}{(0.08 \pm 0.02)}L_{ortho} + \underset{(4.63)}{(0.50 \pm 0.11)}\pi_{meta} + \underset{(2.15)}{(0.09 \pm 0.04)}HB_{ortho} + 1.42 \quad (13)$$

$n = 41$; $r = 0.90$; $s = 0.105$; $f = 21.00$; $f_{\alpha(1)=0.0005,7,30} = 5.31$

Equation 12 was used to give the calculated log $(1/C)$ values listed in Table I. Table III shows the squared correlation matrix for the variables of eq 12. The small numbers indicate that these variables are reasonably independent. It was observed that the two parameters for the hydrogen-bonding effect, HB and HB_{ind}, can be interchanged in the above equations with little change in the statistics. The indicator variable HB_{ind} has been used successfully for the hydrogen-bonding effect in QSAR studies,[15-17] although the real situation is conceivably more complicated. No earlier attempts have been made to use a continuous parameter for this stereospecific interaction. Our effort to partially quantitize it by the HB parameter did not result in significantly better equations. We also observed the correlation between the B_1 parameter and the E_s parameter. This correlation has been discovered as a general phenomenon,[18,37c] and where the minimum width of substituents is important, the choice between these parameters seems to depend on the specific congeneric series at hand.[18]

Table IV. 2,4,5-Trimethylpyrrole-3-carboxylic Acid Esters of N-Substituted 4-Piperidinol



R	L,[a] Å	ED_{50},[b] mg/kg	formula	log $(1/C)$[c]
CH_3	3.0	4.9	$C_{14}H_{22}N_2O_2 \cdot F_3CCOOH$	1.871
$CH_2C_6H_5$	3.63	6.3	$C_{20}H_{26}N_2O_2 \cdot HCl \cdot H_2O$	1.781
CH_2CH_3	4.11	10.4	$C_{15}H_{24}N_2O_2 \cdot F_3CCOOH$	1.561
$CH_2CH_2C_6H_5$	8.33	20 (marginal)	$C_{21}H_{28}N_2O_2 \cdot F_3CCOOH$	1.356

[a] Length of R. [b] From ref 26. [c] ED_{50} in millimoles per kilogram.

In QSAR studies, in order to discover a meaningful correlation, oftentimes a large number of independent variables have to be screened. However, as the number of variables becomes large, as compared to the number of observations, the risk of obtaining a chance correlation will be substantial. This phenomenon has been observed by Topliss et al.,[11,19] based on simulated QSAR studies employing random numbers. In our study, 30 variables (cf. Experimental Section) were screened for possible inclusion in the correlation. Taking into account the high correlation between E_s and B_1 and that between the two hydrogen-bonding parameters, the actual number of independent variables reduces to 24. In eq 12, six independent parameters were entered with a total of 41 observations. According to Figure 7, in ref 11, with 24 variables and 41 observations, the probability of encountering a chance correlation with $r^2 \geq 0.7$ is 1% or less. It is, therefore, safe to conclude that the correlation represented by eq 12 is not spurious. A correlation coefficient of 0.89, i.e., about 80% of the total variance explained, is generally considered reasonable for QSAR studies based on in vivo data.

Of the four inactive derivatives (**45–48**), only the 2,3,5-triiodo derivative was correctly predicted to have very low potency. The reasons for the inactivity of the other three compounds are not clear at this moment. The 2-cyano substituent might make the ester linkage in compound **45** less stable through its strong electron-withdrawing effect, while the 4-iodo substituent might impart some special property to compound **47**. The inactivity of the 3-methyl derivative (**46**) was rather surprising because the 3,5-dimethyl derivative (**36**) showed activity, but the possibility of an experimental error cannot be excluded.

The behavior of different N-substituents on the piperidine ring was also examined by regression analysis. A correlation was obtained between analgesic potency [log $(1/C)$] and the length of N-substituents measured by Verloop's sterimol value of L (eq 14).

$$\log (1/C) = \underset{(3.15)}{-(0.087 \pm 0.028)}L + 2.06 \quad (14)$$

$n = 4$; $r = 0.912$; $s = 0.116$; $f = 9.89$; $f_{\alpha(1)=0.10,1,2} = 8.53$

(16) C. Hansch, A. Vittoria, C. Silipo and P. Y. C. Jow, *J. Med. Chem.*, 18, 546 (1975).
(17) T. Fujita, T. Nishioka, and M. Nakajima, *J. Med. Chem.*, **20**, 1071 (1977).
(18) A. Verloop, W. Hoogenstraaten, and J. Tipker, in "Drug Design", Vol. II, E. J. Ariens, Ed., Academic Press, New York, 1976, p 165.
(19) J. G. Topliss and R. J. Costello, *J. Med. Chem.*, 15, 1066 (1972).

Although the data are from substituted pyrrolecarboxylates (Table IV) instead of benzoates, it is apparent from previous work that a suitable heterocyclic or aromatic ring can be interchanged in esters of this type.[2]

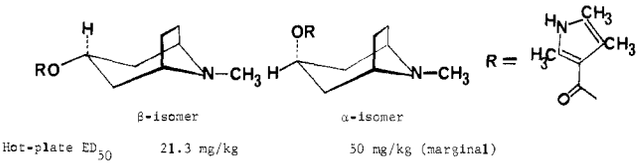
The QSAR results may be summarized as follows: (1) Increasing the length of ortho substituents results in a decrease of potency. (2) Substituents capable of accepting a hydrogen bond tend to increase potency. A hydrogen-bond acceptor can function at all three positions on the phenyl ring, but the energy contribution is the greatest at the meta position. (3) The meta and para positions are sensitive to steric hindrance, which may be represented by either the minimal width (B_1) or the E_s parameter of a substituent. (4) Sensitivity to increase in lipophilicity, which enhances the potency, is observed at meta and ortho positions, but the effect is less significant at the ortho position, possibly due to the predominant steric effect. (5) There appears to be a steady trend toward decreasing potency with increasing length of N-substituents.

Based on the QSAR, we can define a desirable substitution pattern of the phenyl ring for this type of benzoate. A compound of optimal potency should have (1) no ortho substitution, (2) meta and para substituents of good hydrogen-bond accepting ability but of minimal width to minimize steric hindrance, (3) good lipophilicity associated with the meta substituent, and (4) an N-substituent not bulkier than a methyl group.

The most potent derivative synthesized so far in this series, namely, the 3,4-dimethoxybenzoic acid ester of 1-methyl-4-piperidinol (1), seems to have met the above criteria, and further modification of the phenyl ring is unlikely to generate compounds of higher potency.

Since the regression analysis was done on data from in vivo assays, an interpretation of the structure–activity relationships should preferably include events in both the pharmacokinetic phase (absorption, distribution, metabolism, and excretion of the drug) and the pharmacodynamic phase (molecular interaction of the active agent with its specific site of action). Good correlations between opiate receptor affinity and analgesic potency have been reported for homologous series of meperidines,[20-22] prodines,[23] *N*-alkylnorbenzazocines,[24] and *N*-alkylketobemidones.[25] This suggests that the observed differences in potency among homologous compounds of the 4-phenylpiperidine type are mainly due to receptor-related events rather than differential access to the receptor,[20] and the in vivo ED_{50} potencies appear to provide a fair approximation of the relative receptor affinities.[21] On the other hand, it has been shown,[5] with a group of structurally diverse analgesics, that lipophilicity combined with receptor binding affinity are adequate for explaining in vivo antinociceptive activity. Our QSAR results have demonstrated that the overall lipophilicity ($\sum\pi$) is not significant in correlating the in vivo hot-plate potency, indicating that these aromatic esters of 4-piperidinol might behave like other homologous 4-phenylpiperidines. Thus, we shall try to rationalize our QSAR results, a priori, in terms of drug–receptor interactions. There are two ways by which

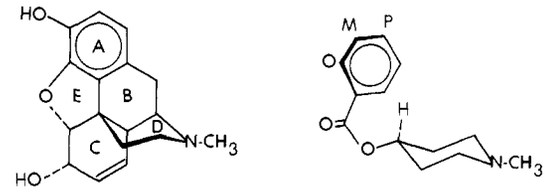
Chart I. 3-Tropanol 2,4,5-Trimethylpyrrole-3-carboxylate



β-isomer α-isomer

Hot-plate ED_{50} 21.3 mg/kg 50 mg/kg (marginal)

Chart II. Proposed Binding Conformation of Aromatic Esters of 1-Methyl-4-piperidinol Approximates A, D, and E Rings of the Morphine Molecule



the length of an ortho substituent can decrease the potency: one is through unfavorable steric interaction with the receptor and the other is through intramolecular steric hindrance, which creates an energy barrier to the adoption of a favorable binding conformation with the receptor. The latter appears to be more likely because the length of adjacent meta substituents is not significant in correlating the activity. In order to visualize this intramolecular steric interaction, it is necessary to determine whether the ester linkage prefers the equatorial or the axial position. Previous work[26] with aromatic esters of 3α- and 3β-tropanol (Chart I), where the orientation of the ester linkage is fixed by a two-carbon bridge between C-2 and C-6, showed that the activity resides mainly in the β isomer, in which the ester group is in the equatorial position, assuming a chair conformation of the piperidine ring. It is therefore reasonable to assume that the preferred binding conformation of the benzoic acid esters of 4-piperidinol also has the ester group in the equatorial position. The steric hindrance exerted by the ortho substituent may be caused by the phenyl ring tilting up toward the piperidine ring in such a way that the dihedral angle formed by C-4 of the piperidine ring, the oxygen atom, the carbonyl carbon, and C-1 of the benzene ring approaches 0°. This would result in a conformation approaching that assumed by rings A, D, and E of the morphine molecule (Chart II), although a complete overlap cannot be achieved due to steric interactions between ortho hydrogens or other ortho substituents on the benzene ring and hydrogen atoms on the piperidine ring. Therefore, the ortho position on the phenyl ring of the 4-piperidinol benzoates does not correspond to the phenolic position in morphine.

The relative energy contribution from hydrogen bonding, in the order of meta, para, and ortho, indicates that in the preferred binding conformation, hydrogen-bond accepting substituents at the meta position are more favorably oriented to accept a hydrogen bond, whereas hydrogen-bond acceptors at the para or ortho position, being less favorably oriented, can only form weaker hydrogen bonds.

The relatively high values of the regression coefficient associated with the π_{meta} term might indicate the presence of a hydrophobic area in the vicinity of the meta position when these aromatic esters are bound to the receptor. Hypothetical models[27-30] of the opiate receptor propose a

(20) P. S. Portoghese, *Acc. Chem. Res.*, 11, 21 (1978).
(21) D. L. Larson and P. S. Portoghese, *J. Med. Chem.*, 19, 16 (1976).
(22) C. B. Pert, S. H. Snyder, and P. S. Portoghese, *J. Med. Chem.*, 19, 1248 (1976).
(23) M. A. Iorio and W. A. Klee, *J. Med. Chem.*, 20, 309 (1977).
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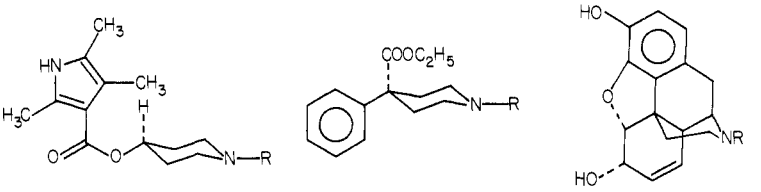
(25) R. Wilson, M. Rogers, C. B. Pert, and S. H. Snyder, *J. Med. Chem.*, 18, 240 (1975).
(26) J. A. Waters, *J. Med. Chem.*, 20, 1094 (1977).

Table V. Relative Analgesic Activity[a] of N-Substituted Homologues of Aromatic Esters of 4-Piperidinol, Meperidine, and Morphine



R	N-substituted 4-piperidinol pyrrolecarboxylate[b]	N-substituted normeperidine[c]	N-substituted normorphine[c]
Me	1.0	1.0	1.0
$C_6H_5CH_2$	0.8	<0.5	<0.1
Et	0.5	0.5	<0.1
$C_6H_5(CH_2)_2$	0.3	2.6	6
$C_6H_5(CH_2)_4$		2.8	~0.3[d]
$C_6H_5CH=CHCH_2$		40	<0.1

[a] Activity relative to the *N*-methyl homologue in each series. [b] From Table IV. [c] From Table II in ref 29. [d] The activity of the morphinan analogue was used.

planar area or a lipophilic site on the receptor to accommodate the aromatic ring of morphine-like compounds. The negative correlation with the B_1 (or E_s) parameter of a meta or para substituent indicates steric hindrance to such an interaction.

Variation of N-substituents has been used as a means of comparing modes of drug–receptor interaction of several classes of opiates.[29] Table V shows the relative analgesic potency of N-substituted analogues of the aromatic ester, meperidine, and morphine. At first glance, the variation of activity in the aromatic ester series does not resemble that of either the meperidine homologues or the morphine homologues. However, if the trend shown in eq 14 is extrapolated, i.e., if the activity continues to decrease with further increase in the length of the N-substituent, then the behavior of N-substituents of the aromatic esters appears to resemble that of morphine derivatives more than that of meperidine derivatives. In the meperidine series, the potency is dramatically increased when the *N*-methyl group is replaced by bulky aralkyl groups, e.g., phenylbutyl and cinnamyl, while the potency of morphine derivatives is greatly reduced.

A nonopiate type receptor was previously proposed for these aromatic acid esters of nonquaternary C-4 piperidinol[2,3] because of their atypical behavior in the testing for physical dependence liability and their marginal binding affinity toward the opiate receptor in rat brain homogenate. However, the QSAR results presented thus far seem to favor a binding mode approximating that of morphine-like compounds, at least in binding to the μ receptor which mediates heat-antinociception,[31] with morphine being a prototype agonist. The marginal binding affinity of these flexible esters to the opiate receptor may be compensated by their rapid and efficient penetration into the CNS, as has been shown to be the case with 4-phenylpiperidines.[21,32] Further receptor studies in rat brain homogenates and other systems are in progress using tritiated **14**.[33]

Table VI. Derivation of the HB Parameter

substituent[a]	$K_{25\,°C}$,[b] L/mol	$-\Delta G_{25\,°C}$,[c] kcal/mol	HB[d]
OH	0.74	−0.178	1.000
OC_6H_5	0.79	−0.14	1.038
CF_3	0.84	−0.1[e]	1.078
OCH_3	0.92	−0.05	1.128
OC_2H_5	1.04	0.07	1.248
CN	3.4	0.72	1.898
NO_2	3.5	0.74	1.918

[a] Substituents capable of accepting a hydrogen bond. [b] Equilibrium constant of hydrogen bonding between substituted benzene and phenol as a hydrogen-bond donor in carbon tetrachloride. Values from the compilation by Joesten and Schaad.[36] [c] $-\Delta G_{25\,°C} = RT \ln K_{25\,°C}$. [d] The numbers were obtained by adding 1.178 to each of the $-\Delta G$ terms. [e] $\Delta G_{CF_3} \simeq \Delta G_{CH_2F} = \Delta G_{CH_2Cl} + (\Delta G_{C_6H_{13}F} - \Delta G_{C_6H_{13}Cl}) = 0.4 + (0.372 - 0.673) = 0.4 + -0.3 = 0.1$.

Experimental Section

Biological Data. Analgesic activity was measured by the mouse hot-plate method[2,3] and the ED_{50} is expressed in millimoles per kilogram.

QSAR Methods. The calculation was performed with the MULREG program, which carries out an unweighted stepwise multiple regression analysis and is available in the PROPHET system, a time-sharing computer resource sponsored by the National Institutes of Health.

The physicochemical parameters included in the regression analysis are described briefly as follows. (1) Electronic effects: σ, Hammett's constant for substituents on an aromatic ring; F and R, values for inductive and resonance effects, respectively, according to Swain and Lupton.[34] (2) Steric effects: E_s, Taft's steric parameter;[35] MR, the molar refractivity of the substituent; L, B_1, and B_4, Verloop's sterimol values (in angstroms) for the length, the smallest width, and the largest width, respectively, of a substituent.[18] (3) Hydrophobic effects: π, the logarithm of the octanol–water partition coefficient for a substituent ($\pi_X = \log P_{C_6H_5X} - \log P_{C_6H_6}$). (4) Hydrogen bonding: HB_{ind}, the indicator variable. Substituents capable of accepting a hydrogen bond are

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(28) K. W. Bentley, A. Cowan, and J. W. Lewis, *Annu. Rev. Pharmacol.*, 11, 241 (1971).
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(31) M. B. Tyers, *Br. J. Pharmacol.*, **69**, 503 (1980).
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(33) S. H. Snyder, F. Bruns, J. Daly, and J. A. Waters, personal communication.
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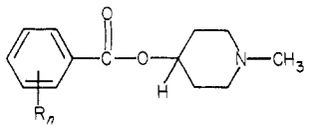
(35) R. W. Taft, *J. Am. Chem. Soc.*, **74**, 3120 (1952).
(36) M. D. Joesten and L. J. Schaad, "Hydrogen Bonding", Marcel Dekker, New York, 1974.

Table VII. 1-Methyl-4-piperidinol Esters



no.	R_n	mp,[a] °C	formula	recrystn solvent[b]	yield, %	anal.[c]
2	4-OC_2H_5	228-229	$C_{15}H_{21}NO_3 \cdot HCl$	C	58	C, H, N
4	4-CN	247-249	$C_{14}H_{16}N_2O_2 \cdot HCl$	C	37	C, H, N
6	4-O-*n*-C_4H_9	215-216	$C_{17}H_{25}NO_3 \cdot HCl$	C	61	C, H, N
10	2-CF_3	213-214	$C_{14}H_{16}F_3NO_2 \cdot HCl$	C	19	C, H, N
12	2-NO_2	172-175	$C_{13}H_{16}N_2O_2 \cdot HCl$	C	20	C, H, N
19	3-CN	239-241	$C_{14}H_{16}N_2O_2 \cdot HCl$	A	45	C, H, N
24	2-$CH_2C_6H_5$	193-200	$C_{20}H_{23}NO_2 \cdot HCl$	C	26	H, N; C[d]
27	2-Cl	175-176	$C_{13}H_{16}ClNO_2 \cdot HCl$	C	37	C, H, N
29	2-Br	190-193	$C_{13}H_{16}BrNO_2 \cdot HCl$	C	61	C, H, N
32	4-NO_2	215-217	$C_{13}H_{16}N_2O_4 \cdot HCl \cdot 1.5H_2O$	B	25	C, H, N
34	4-Cl	229-229.5	$C_{13}H_{16}ClNO_2 \cdot HCl$	C	64	C, H, N
37	4-C_6H_5	272-275	$C_{19}H_{21}NO_2 \cdot HCl$	D	48	C, H, N
42	2-C_2H_5	179.5-180.5	$C_{15}H_{21}NO_2 \cdot HCl$	C	26	C, H, N
45	2-CN	195-197	$C_{14}H_{16}N_2O_2 \cdot HCl$	C	3	C, H, N
47	4-I	267-268.5	$C_{13}H_{16}INO_2 \cdot HCl$	E	83	C, H, N

[a] Melting points were taken on a Kofler hot stage and are corrected. [b] A = acetone; B = EtOH; C = acetone-EtOH; D = EtOH-H_2O; E = acetone-EtOH-H_2O. [c] Analytical results obtained within ±0.4% of the theoretical values, unless otherwise noted. [d] C: calcd, 69.45; found, 70.00.

given a value of 1 and those unable to form a hydrogen bond are given a value of 0. HB, a thermodynamically derived parameter indicating the relative hydrogen-bond accepting ability of a substituent. The development of the HB parameter is shown in Table VI.

With the exception of the HB parameter, all parameter values are obtained from or estimated according to the literature.[37] The analgesic activity is represented as log $(1/C)$, where C is the hot-plate ED_{50} in millimoles per kilogram (Table I).

Synthetic Methods. 1-Methyl-4-piperidinol Esters. Forty-eight substituted benzoic acid esters of 1-methyl-4-piperidinol are presented in Table I. Compounds **2, 4, 6, 10, 12, 19, 24, 27, 29, 32, 34, 37, 39, 42, 45,** and **47** were synthesized for this study by the general procedure outlined below, the details of which are summarized in Table VII. The remaining esters in Table I were synthesized previously.[2,3]

A solution of 22.5 mmol of the carboxylic acid in 45 mL of thionyl chloride was refluxed for 30 min. The excess thionyl chloride was then removed in vacuo, and the residue was mixed with dry benzene (over 3 Å molecular sieves) and evaporated. To the crude acid chloride was added 15 mmol of 1-methyl-4-piperidinol in 60 mL of dry pyridine, and the mixture was refluxed for 5 h.

Compounds **6, 37,** and **47** were isolated by addition of 30 mL of benzene to the cooled reaction mixture, removal of the solid by suction filtration, and recrystallization as designated in Table VII.

Compounds **27, 34,** and **42** were obtained by evaporation of the pyridine in vacuo from the reaction mixture, followed by boiling of the crude residue with 50 mL of acetone for 5 min. After the solution cooled, the solid was removed by suction filtration and recrystallized.

Esters **2, 4, 10, 12, 24, 37,** and **45** were obtained by removal of the pyridine in vacuo, converting the crude ester hydrochloride to the free base (75 mL of 5% Na_2CO_3; extraction with 200 mL of ether), and then reforming the ester HCl by addition of ethereal HCl to the dried ethereal solution of the free base. Compounds **10, 12, 24, 39,** and **45** were then further purified, prior to recrystallization, by column chromatography on 100 g of silica gel; elution was with 2–8% MeOH in $CHCl_3$.

Esters **19, 29,** and **32** were obtained by direct column chromatography of the crude reaction mixture (pyridine removed) as described above. Homogenous fractions, in all cases, as indicated by TLC ($CHCl_3$/MeOH, 9:1; silica gel GF), were combined and recrystallized from the appropriate solvent(s) as indicated in Table VII.

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