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Quantitative Relationships between Steroid Structure and Binding to Putative Progesterone Receptors[1]

David L. Lee, Peter A. Kollman, Fred J. Marsh, and Manfred E. Wolff*

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, San Francisco, California 94143. *Received November 29, 1976*

Relationships between chemical structure of androst-4-en-3-one derivatives and their affinity for putative progesterone receptors are described. The binding affinity for 55 derivatives can be expressed by the equation log relative binding affinity (rabbit receptor) = 1.79 + 0.18 (±0.11) π_a + 1.45 (±0.21) π_b + 0.010 (±0.002) (surface area in hydrophobic pockets) − 0.012 (±0.003) (surface area out of hydrophobic pockets) − 0.99 (±0.21) MK − 0.33 (±0.08) (conformational changes). For this equation, r = 0.88. The equation successfully predicts the affinities of other compounds in the literature. The importance of the surface area terms is discussed.

A number of QSAR studies relating the structure of steroids to their pharmacological activity have appeared in recent years,[2-6] following our initial report in this area. Although there has been controversy regarding appropriate parameters to employ in such regressions, certainly the major difficulty in these studies has been their attempt to relate animal pharmacology to simple physiochemical vectors. Since animal results represent the sum of a number of part processes (receptor affinity, drug metabolism, drug distribution, and intrinsic activity), the coefficient for each variable in the regression will be the *net average* for the effect on *all* of these activities. The attempt to *average these very different contributions* is probably responsible, far more than the choice of a particular steric or hydrophobic parameter, for the scatter observed in the regressions.

There is a growing body of evidence which indicates that induction of protein synthesis mediates the action of steroid hormones on growth, differentiation, and metabolism in target tissues.[7] The initial events involve binding to a steroid-specific receptor protein and attachment of the resulting complex to the genome. Cytoplasmic receptors, characterized by specificity in binding steroid hormones with high affinity, have been demonstrated for all of the physiological steroids. Thus, in principle, it is possible to study a *single* part process, namely, drug–receptor affinity, in the case of the steroids.

The advantage of examining a single part process is seen in a brilliant study from Hansch's laboratory.[8-10] The enzyme affinities of over 1000 enzyme inhibitors were analyzed in terms of enzymic space around each substituent through the use of multiparameter regression techniques. Several important principles emerged from this monumental work. First, the usual qualitative relationships so familiar to the medicinal chemist could be expressed in quantitative fashion for hundreds of compounds. Second, there is difficulty in parameterizing the hydrophobic term by a single variable—enzymic space is better represented in terms of polar and nonpolar pockets. Third, the activity of a molecule can best be represented by setting up terms for *several positions* in the molecule.

Table I. Bondi Surface Area

Radical	Surface area, Å²		Surface area, Å²
-C-	0	-O-	10.0
-C-H	9.5	=CH-	17.9
$>CH_2$	22.4	$=CH_2$	30.9
$-CH_3$	35.2	-C≡	16.3
>C=CH-	23.1	≡CH	28.9
>C=O	27.6	Phenyl	88.5

As a result of our recent study on the thermodynamics of steroid–receptor interactions,[11] we have been able to approach these difficulties in parameterization from a somewhat different standpoint. We found[11] that binding forces for steroid–receptor interactions are primarily hydrophobic, except for specific polar interactions, and that it is possible to use surface area[12] as a parameter for hydrophobic bonding.[13] Second, the conformation of the A ring in glucocorticoids, which we have shown to be covariant with biological activity,[14] can be parameterized in the equation by the C-3 to C-17 distance. Third, a polar interaction term, analogous to the hydrophobic term, must be included.

In the present study, we describe the extension of these efforts to the progestational receptor system using the data of Kontula et al.[15]

Methods. Multiple regression analysis was accomplished with a stepwise regression program adapted for the PROPHET[16] time-sharing system. Octanol–water partition coefficients were taken from the compilations of Hansch and co-workers[17] and surface area of various substituents was taken from the work of Bondi[12] (Table I). The value used was the *net change* in surface area. Thus, for a 6α-methyl substituent, the net change is obtained by subtracting 22.4 Å², the value for the C-6 $-CH_2-$ group, and adding 9.4 Å² (C-6 –CH) plus 35.2 Å² (6α-CH_3), giving an

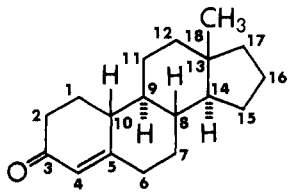

Figure 1. The parent ring system.

increase of 22.2 Å^2. The numbers in parentheses in the regression equations represent the standard errors of the regression coefficients. Unless otherwise indicated, all regression coefficients satisfied the t test[18] at the 99% confidence level. Given below each equation are n, the number of compounds; r the multiple correlation coefficient; s, the standard deviation of the regression; and F, the F test[18] for the significance of the regression.

Results and Discussion

In this series of studies, two main classes of steroids appeared most frequently—the progesterone derivatives and the 19-nonandrogens. The 19-norandrost-4-en-3-one system (Figure 1, common to both classes of compounds) was therefore employed as the parent structure.

In a previous study,[11] we showed that the most important contribution to steroid–receptor binding was hydrophobic. In the present case, a survey of the relationship between structure and binding revealed important patterns. Any change in the 3-keto group resulted in a loss of affinity. Presumably, the importance of this group is due to its interactions with a specific entity such as a hydrogen bond donor in the receptor. Polar substituents are deleterious to binding, substituents like hydroxyl, ether oxygen, and transformation of methylene to carbonyl being more detrimental than acetyl or acetoxy. This is consistent with the idea that the principal bonds between steroid and receptor are hydrophobic. Whether nonpolar groups have a favorable or unfavorable effect on the binding depends on their location in the steroid. For example, 7α-methylprogesterone has lower affinity for the receptor than progesterone, whereas 16α,17α-dimethylmethyleneprogesterone has higher affinity for the receptor relative to progesterone (in humans). This suggests the presence of hydrophobic pockets located in various specific positions in the receptor.

The binding of the various acetates is also in accord with the proposed hydrophobic pockets. Esters diminish binding, but the magnitude of the effect depends on the location of the ester group. Thus, 21-acetoxyprogesterone has a relative binding affinity of 10 (progesterone = 100, in humans), whereas 17α-acetoxyprogesterone has a relative binding affinity of 67. The acetate group exerts its effect in two ways: the carboxylate portion has a normal polar effect and is detrimental to binding, whereas the methyl group, if located in a hydrophobic pocket, counteracts this effect by interacting favorably with the receptor.

At this stage a quantitative expression of steroid binding to the progesterone receptor would require four parameters: a polar term, a term to express the favorable hydrophobic bonding of nonhydroxyl groups with the receptor, a term to express the unfavorable interactions of nonhydroxyl groups with the receptor, and a "misplaced ketone" (MK) term. The MK term is an indicator variable which takes the value 0 except for compounds lacking a ketone at C-3, or possessing a ketone at any ring position other than C-3, when it has a value of 1. The presence of the MK term is required by the failure of the remaining parameters to account for the sharp decrease in binding

Table II. π Values Used in the Regression

Group	π	Group	π
OH (primary)	−1.16[a]	$-CH_2-$	0.5[a]
OH (secondary)	−1.39[a]	$-CH_2-$ (cyclic)	0.41[a]
OH (tertiary)	−1.43[a]	$-C\equiv CH$	0.48
OH (enolic)	−0.67[b]	$CO \rightarrow CH_2$	1.71[d]
-O-	−0.97[c]	$CH_2 \rightarrow CO$	−1.71[d]
$COCH_3$	−0.71[a]	$CO \rightarrow CHOH$	0.32[e]
$OCOCH_3$	−0.27[a]	Introduction of	−0.3[a]
F	−0.17[a]	double bond	
Cl	0.39[a]	Saturation of	0.3
CH_3	0.5[a]	double bond	

[a] From M. S. Tute, *Adv. Drug Res.*, 6, 77 (1971). [b] C. Hansch, A. Leo, S. H. Ungar, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, 16, 1207 (1973). [c] $[OCH_3] - [CH_3]$. [d] $[Me_2CO] - [n\text{-}C_3H_8]$. [e] $[Me_2CHOH] - [Me_2CO]$.

Table III. Location of Hydrophobic Pockets

	Location around steroid								
Animal species	6α	7α	10	11β	16α	17α	17β[a]	18[b]	21
Human/sheep	+	−	−	+	+	+	±	±	−
Rabbit	+	−	−	+	+	+	±	±	+
Guinea pig	+	−	−	+	−	−	±	±	+

[a] (+) for progesterone derivatives and (−) for androstane derivatives. [b] (+) for androstane derivatives and (−) for a progesterone derivatives. The difference in the bulk tolerance for the two classes of steroid can be rationalized in terms of a slightly different relationship between steroid and receptor after docking in each of the cases.

in compounds possessing such misplaced ketones. The π values (Table II) of polar substituents were employed directly as a measure of their polarity or as a measure of their disruptive effects on hydrophobic bonding between steroid and receptor. From our previous work,[11] the surface area of nonhydroxyl substituents was employed as a measure of hydrophobic bonding of relatively nonpolar groups. Below we compare the ability of π and surface area to analyze this effect. We consider all substituents other than hydroxyl groups as capable of hydrophobic bonding. Surface area was also employed as a measure of the unfavorable interactions of nonpolar groups not situated in a hydrophobic pocket of the receptor.

The locations of the pockets were determined by comparing the binding affinities of pairs of compounds differing in only one nonhydroxyl substituent. For example, the binding affinity of 17α-acetoxyprogesterone was 67 (progesterone = 100, in humans) whereas the binding affinity of 6α-methyl-17α-acetoxyprogesterone was 196. This indicates the presence of a hydrophobic pocket in the receptor in the vicinity of the 6 position of the steroid. The locations of the hydrophobic pockets for the various species of animals are shown in Table III.

A list of the steroids employed in this study is shown in Table IV. In Table V are the values employed for each of the previously discussed parameters for each of the steroids. The best equation incorporating the four parameters is eq 1.

Equation 1 (human): log relative binding affinity = 1.71 + 0.46 (±0.11) π + 0.011 (±0.003) (surface area in hydrophobic pockets) − 0.019 (±0.005) (surface area out of hydrophobic pockets) − 1.35 (±0.19) MK. n = 54, r = 0.86, s = 0.59, F = 34.

Many of the compounds with large deviations from the observed values had hydroxyl groups in the 17α, 20α, or 20β position of the steroid ring. This suggested that the polar effect of polar substituents in these positions should be weighted more heavily. Certain areas of the receptor

Table IV. Steroids Employed in Study

No.	Steroid
1	Progesterone
2	5α-Pregnane-3,20-dione
3	5β-Pregnane-3,20-dione
4	20α-Hydroxy-4-pregnen-3-one
5	20β-Hydroxy-4-pregnen-3-one
6	3β-Hydroxy-5-pregnen-20-one
7	11α-Hydroxy-4-pregnene-3,20-dione
8	17α-Hydroxy-4-pregnene-3,20-dione
9	19-Hydroxy-4-pregnene-3,20-dione
10	21-Hydroxy-4-pregnene-3,20-dione
11	11β,21-Dihydroxy-4-pregnene-3,20-dione
12	Cortisol
13	4-Pregnene-3,11,20-trione
14	4-Pregnene-3,12,20-trione
15	16α,17α-Epoxy-4-pregnene-3,20-dione
16	1,4-Pregnadiene-3,20-dione
17	7α-Methyl-4-pregnene-3,20-dione
18	16α-Ethyl-4-pregnene-3,20-dione
19	18-Methyl-4-pregnene-3,20-dione
20	16α,17α-(1′,1′-Dimethylmethylene)-4-pregnene-3,20-dione
21	17α-Hydroxy-4-pregnene-3,20-dione acetate
22	21-Hydroxy-4-pregnene-3,20-dione acetate
23	4,17α-Dihydroxy-4-pregnene-3,20-dione 17α-acetate
24	6α-Methyl-17α-hydroxy-4-pregnene-3,20 dione acetate
25	6-Methyl-17α-hydroxy-4,6-pregnadiene-3,20-dione acetate
26	6-Chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione acetate
27	19-Nor-4-pregnene-3,20-dione
28	20β-Hydroxy-19-nor-4-pregnene-3,20-dione
29	16α-Ethyl-21-hydroxy-19-nor-4-pregnene-3,20-dione
30	16α-Ethyl-21-fluoro-19-nor-4-pregnene-3,20-dione
31	16α-Ethyl-21-fluoro-19-nor-4,6-pregnadiene-3,20-dione
32	Norethisterone (17α-Ethynyl-17β-hydroxy-4-estren-3-one)
33	17α-Ethynyl-17β-hydroxy-5α-estran-3-one
34	17α-Ethynyl-4-estrene-3β,17β-diol
35	17α-Ethynyl-5α-estrane-3α,17β-diol
36	17α-Ethynyl-5α-estrane-3β,17β-diol
37	17α-Ethynyl-5β-estrane-3α,17β-diol
38	17α-Ethynyl-5β-estrane-3β,17β-diol
39	17α-Ethynyl-17β-hydroxy-4-estrene
40	17α-Ethynyl-4-estren-17β-ol acetate
41	7α-Methyl-17α-ethynyl-4-estren-17β-ol
42	17α-Ethynyl-5-estren-17β-ol
43	17α-Ethynyl-6-estrene-5α,17β-diol
44	11β-Chloro-17α-ethynyl-17α-hydroxy-4-estren-3-one
45	17α-Ethynyl-17β-hydroxy-5(10)-estren-3-one
46	7α-Methyl-17α-ethynyl-17β-hydroxy-5(10)-estren-3-one
47	17α-Ethynyl-17β-hydroxy-18-methyl-4-estren-3-one
48	17α-Ethynyl-17β-hydroxy-4-estren-3-one acetate
49	19-Nortestosterone
50	17α-Methyl-4-estren-17β-ol
51	4-Androstene-3,17-dione
52	Testosterone
53	17β-Hydroxy-5α-androstan-3-one
54	17α-Allyl-4-estren-17β-ol
55	17α-Hydroxy-4-pregnene-3,20-dione caproate
56	16α-Ethyl-21-hydroxy-19-nor-4-pregnene-3,20-dione phenylpropionate

presumably would be more hydrophobic than others and, therefore, the disruptive effects of a polar group on the hydrophobic binding process would be correspondingly different. Accordingly, the polar term was divided into two separate parts: one term (π_b) includes all polar groups

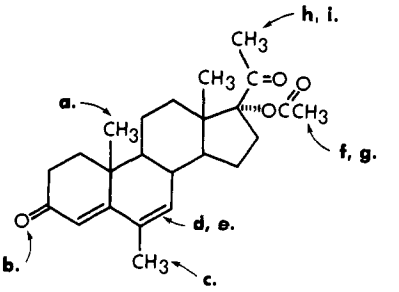

Figure 2. Derivation of parameter values for compound **24** for human receptor. a. C–H substituted by $-CH_3$ = (35.2 - 9.5) = 25 Å^2 increase in surface area out of hydrophobic pocket. b. MK = 0. c. CH_2 substituted by $-CH_3$ = [35.2 - (22.4 - 9.5)] = 22 Å^2 increase in surface area in hydrophobic pocket. d. Two-carbon hybridization change; conformational parameter = 2. e. Reduction of surface area in hydrophobic pockets by two hydrogens due to introduction of double bond = [(9.5 + 22.4) - 23.1] = 9 Å^2. f. CH substituted by $-OC(O)CH_3$ = [(10.0 + 27.6 + 35.2) - 9.5] = 63 Å^2 increase in surface area in hydrophobic pocket. g. Introduction of polar group in 17α position: $\pi_b = -0.27$. h. CH_2 substitution by $-C(=O)CH_3$ = [(27.6 + 35.2) - (22.4 - 9.5)] = 50 Å^2 increase in surface area in hydrophobic pocket. i. Introduction of polar group in the 17β position: $\pi_a = -0.71$.

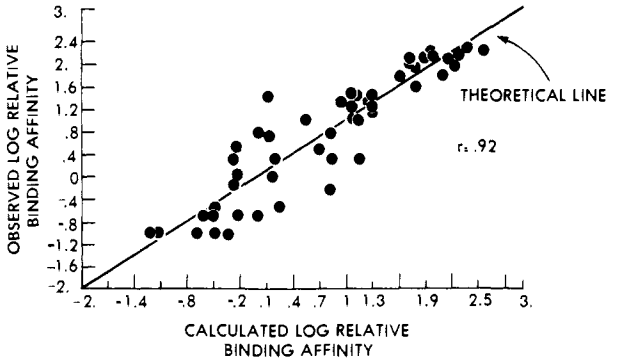

Figure 3. Graph of the observed (ref 15) vs. the calculated (eq 3) logarithm of the relative binding affinity of steroid derivatives to human receptor.

in the 17α, 20α, and 20β positions, whereas the other (π_a) encompasses all polar groups outside of those positions. Equation 2 relates these five parameters with the logarithm of the relative binding affinity.

Equation 2 (human): log relative binding affinity = 1.56 + 0.23 (±0.11) π_a + 1.19 (±0.19) π_b + 0.012 (±0.002) (surface area in hydrophobic pockets) - 0.017 (±0.004) (surface area out of hydrophobic pockets) - 1.60 (±0.17) MK. $n = 54$, $r = 0.90$, $s = 0.51$, $F = 41$.

Many of the compounds with the largest deviations from the observed values were conformationally different from 19-nor-4-androsten-3-one. These compounds possess an additional double bond at C-1 and C-2, lack a double bond at C-4 and C-5, or have some other carbon atom hybridization change. To compensate for conformational changes, a de novo parameter was added. The value of this conformational parameter is the sum of the number of carbon atoms with changes in hybridization from a 4-androsten-3-one base. For example, 1,4-pregnadiene-3,20-dione has two sp^2 carbon atoms which are sp^3 hybridized in 4-androsten-3-one. Therefore, an indicator value of 2 is assigned to this compound. An example of how values are assigned to one of the more complex cases is given in Figure 2. The best equation relating π_a, π_b, surface area in hydrophobic pockets, surface area out of hydrophobic pockets, and conformational changes with the logarithm of the relative binding affinity is eq 3 (Figure 3).

Table V. Parameters Employed for Linear Regression Analysis Relating Steroid Structure to Receptor Affinity in Humans and in Sheep

Compd	π_{a+b}	π_a	π_b	Surface area in hydrophobic pockets	Surface area out of hydrophobic pockets	M-Keto	Conformational changes	Log rel binding affinity (humans) Obsd	Log rel binding affinity (humans) Calcd[a]	Log rel binding affinity (sheep) Obsd	Log rel binding affinity (sheep) Calcd[b]
1	-0.71	-0.71	0	50	25	0	0	2	1.71	2	1.62
2	-0.71	-0.71	0	50	34	0	2	1.48	1.08	1.48	0.76
3	-0.71	-0.71	0	50	34	0	2	1.08	1.08	0.60	0.76
4	-0.39[c]	0	-0.39[c]	32	25	0	0	0.30	1.14	0	1.03
5	-0.39[c]	0	-0.39[c]	32	25	0	0	1	1.14	0.70	1.03
6	-0.39[d]	-0.39[d]	0	50	25	1	2	-0.69	-0.017		-0.018
7	-2.1	-0.71	-1.39	37	25	0	0	0.48	-0.26	-0.15	-0.61
8	-2.14	-0.71	-1.43	40	25	0	0	-0.15	-0.273	-0.30	-0.63
9	-1.87	-0.71	-1.16	50	22	0	0	-0.52	0.25	-0.52	-0.061
10	-1.87	-1.87	0	37	25	0	0	1.23	1.30	1.4	1.16
11	-3.26	-3.26	0	24	25	0	0	0.30	0.84	0	0.64
12	-4.69	-3.26	-1.43	14	25	0	0	-1	-1.14	-1.3	-1.61
13	-2.42	-2.42	0	50	25[f]	1	1	0	-0.23	-0.097	-0.43
14	-2.42	-2.42	0	50	25[f]	1	1	-0.69	-0.23	-1	-0.43
15	-1.68[g]	-0.71	-0.97[g]	27	25	0	0	0	0.17	-0.52	-0.086
16	-0.71	-0.71	0	40	25	0	2	1.48	1.13	1.2	0.83
17	-0.71	-0.71	0	50	47	0	0	1.43	1.30	1.32	1.20
18	-0.71	-0.71	0	94	25	0	0	1.98	2.23	1.87	2.103
19	-0.71	-0.71	0	50	47	0	0	1.43	1.30	1.04	1.20
20	-0.71	-0.71	0	89	25	0	0	2.11	2.17	1.9	2.05
21	-0.98	-0.71	-0.27	113	25	0	0	1.83	2.10	1.6	1.91
22	-0.98	-0.98	0	50	85	0	0	1	0.54	1	0.40
23	-1.65	-1.38	-0.27	100	25	0	0	1.62	1.80	1.2	1.58
24	-0.98	-0.71	-0.27	135	25	0	0	2.29	2.36	1.86	2.15
25	-0.98	-0.71	-0.27	125	25	0	2	1.94	1.79	1.51	1.36
26	-0.98	-0.71	-0.27	120	25	0	2	2.08	1.73	1.78	1.30
27	-0.71	-0.71	0	50	0	0	0	2.11	2.17	2.13	2.10
28	-0.39[c]	0	-0.39[c]	32	0	0	0	1.78	1.61	1.6	1.51
29	-1.87	-1.87	0	81	0	0	0	2.16	2.28	1.98	2.12
30	-0.71	-0.71	0	94	7	0	0	2.23	2.56	2.08	2.45
31	-0.71	-0.71	0	84	7	0	2	2.15	1.99	2.13	1.65
32	-1.43	-1.43	0	23	0	0	0	2.06	1.69	1.88	1.60
33	-1.43	-1.43	0	23	9	0	2	1.23	1.07	1	0.75
34	-1.43[d]	-1.43[d]	0	23	0	1	1	1.40	0.13	1	0.017
35	-1.43[d]	-1.43[d]	0	23	9	1	3	-1	-0.50	-1.52	-0.84
36	-1.43[d]	-1.43[d]	0	23	9	1	3	-0.70	-0.50	-1.3	-0.84
37	-1.43[d]	-1.43[d]	0	23	9	1	3	-1	-0.50	-2	-0.84
38	-1.43[d]	-1.43[d]	0	23	9	1	3	-0.52	-0.50	-0.7	-0.84
39	-1.43[e]	-1.43[e]	0	23	0	1	1	0.70	0.13	0.602	0.017
40	-0.27[e]	-0.27[e]	0	36	62	1	1	-0.70	-0.61	-1	-0.71
41	-1.43[e]	-1.43[e]	0	23	22	1	1	0.30	-0.28	0.301	-0.40
42	-1.43[e]	-1.43[e]	0	23	0	1	3	-1	-0.33	-0.7	-0.66
43	-2.86[e]	-2.86[e]	0	14	0	1	5	-1	-1.21	-2	-1.83
44	-1.43	-1.43	0	40	0	0	0	2.11	1.90	2.06	1.79
45	-1.43	-1.43	0	23	0	0	2	1.34	1.24	0.845	0.92
46	-1.43	-1.43	0	23	22	0	2	0.78	0.83	0.7	0.50
47	-1.43	-1.43	0	45	0	0	0	2.22	1.96	2	1.85
48	-0.27	-0.27	0	36	62	0	0	1.32	0.95	1.04	0.88
49	-1.39	-1.39	0	-11	0	0	0	1.14	1.30	1	1.24
50	-1.43	-1.43	0	13	0	1	1	0.78	0.0081	0.778	-0.093
51	-1.71	-1.71	0	0	26	1	1	-1	-0.70	-1	-0.81
52	-1.39	-1.39	0	-11	26	0	0	-22	0.82	0	0.74
53	-1.39	-1.39	0	-11	35	0	2	0.30	0.19	0	0.11
54	-1.43	-1.43	0	51	0	1	0	0.48	0.69	0.6	0.66
55	-0.98	-0.71	-0.27	113	25	0	0	1.88	2.06		
56	-0.98	-0.98	0	81	60	0	0	0.84	1.29		

[a] Derived from eq 3. [b] Derived from eq 7. [c] Value of π for the 17β-hydroxyethyl group obtained by summation of the π values of Et (1.0) and OH (-1.39). [d] A π value of +0.32 was employed for the change from a 3-keto group to a 3-hydroxyl group. [e] A π value of -1.71 was employed for the change from a methylene group to a carbonyl group. This value was obtained by comparing the π values of an acetyl group (-0.71) with an ethyl group (1.00). [f] No correction in surface area was made for the transformation of methylene to carbonyl, since the two groups have nearly identical surface areas. [g] A π value of -0.97 was employed for the ether oxygen, obtained by subtracting methyl (0.5) from methoxy (-0.47).

Equation 3 (human): log relative binding affinity = 1.74 + 0.22 (±0.10) π_a + 1.30 (±0.17) π_b + 0.012 (±0.002) (surface area in hydrophobic pockets) - 0.018 (±0.004) (surface area out of hydrophobic pockets) - 1.34 (±0.17) MK - 0.23 (±0.06) (conformational changes). $n = 54$, $r = 0.92$, $s = 0.45$, $F = 45$.

This equation satisfies the "F test"[18] and is statistically significant at the 0.99 confidence level, $F_{6,47} = 45$; $F_{6,47,\alpha=0.01} = 3.21$. A squared correlation matrix of the parameters employed in the final equations, 3, 4, and 7-11, showed no coefficient that exceeded 0.30, indicating that all of the variables are essentially independent. The thermodynamic

contribution of each parameter can be calculated from regression equations which relate binding affinity or ΔG to physical properties.[19] By transforming eq 3 to eq 4,[20] the coefficient for surface area is found to be 15 cal/Å^2. This value is in a reasonable range for such a hydrophobic interaction.[13]

Equation 4 (human): $\Delta G_{association}$ = −11 505 − 275 (±120) π_a − 1628 (±218) π_b −15 (±2) (surface area in hydrophobic pockets) + 23 (±5) (surface area out of hydrophobic pockets) + 1673 (±211) MK + 286 (±78) (conformational changes) cal. n = 54, r = 0.92, s = 566, F = 45.

Hansch[9] has commented on the problem of parameterizing such hydrophobic and polar interactions. He has suggested that these hydrophobic interactions are best modeled by π with a coefficient of 0.4–1.2 whereas the polar interactions are better modeled by molar refractivity (MR). Here, we see that the hydrophobic interactions are well modeled by a simple surface area term. Substituents in hydrophobic pockets are considered to add to the binding, whereas substituents *not* in such favorable receptor space exert a corresponding decrease on the binding. Polar substituents present a more complex relationship. In these progestational steroids, the addition of *any* polar group decreases binding. Our results suggest the value of using a surface area term for hydrophobic interactions and retaining the π term for polar interactions.

We tested our premise that surface area is a better measure of hydrophobic interactions than π in deriving equations such as 3. A linear regression relating π_a, π_b, π_c (summation of π values of nonhydroxyl substituents located in hydrophobic pockets), π_d (summation of π values of nonhydroxyl substituents situated out of hydrophobic pockets), MK, and conformational changes with the logarithm of the relative binding affinity was made, where π_c and π_d are analogous to the surface area terms employed in eq 3. The best equation relating these five parameters with binding affinity is eq 5. The correlation is poorer when one employs π rather than surface area for the hydrophobic terms; π_a π_c, and π_d do not meet the F test at the 0.01 level.

Equation 5: log relative binding affinity = 2.08 + 0.28 (±0.14) π_a + 1.33 (±0.26) π_b − 0.01 (±0.10) π_c − 0.31 (±0.28) π_d − 1.53 (±0.25) MK − 0.19 (±0.09) (conformational changes). n = 54, r = 0.82, s = 0.67, F = 16.

We also tested the proposal[9] that polar interactions be modeled by molar refractivity (MR) in eq 6, in which π_a and π_b have been replaced by MR_a and MR_b, the molar refractivity values for these polar groups. Only a poor correlation was achieved; all terms except MK failed the F test at the 0.01 level.

Equation 6 (human): log relative binding affinity = 1.56 − 0.014 (±0.027) MR_a + 0.047 (±0.033) MR_b + 0.09 (±0.14) π_c − 0.48 (±0.36) π_d − 0.15 (±0.14) (conformation changes) − 1.47 (±0.32) MK. n = 54, r = 0.70, s = 0.84, F = 7.

At this point the six parameter equation (eq 3) was selected as the most general model. Equation 3 was further examined for its ability to correlate the binding affinities of steroids to the receptor obtained from sheep, rabbit, and guinea pig. In rabbit and guinea pig receptor, the location of the various hydrophobic pockets differs from human receptor. This difference offers a test of our hypothesis that (1) hydrophobic bonding can occur in only particular pockets, (2) hydrophobic bonding is proportional to the surface area of the substituents residing in a pocket, and (3) detrimental nonpolar interactions are proportional to the surface areas of substituents out of a pocket.

A list of the steroids in the linear regression analysis relating π_a, π_b, surface area in hydrophobic pockets, surface area out of hydrophobic pockets, MK, and conformational changes with the logarithm of the relative binding affinity for each species is shown in Tables V and VI. Equations 7–9 were obtained.

Equation 7 (sheep): log relative binding affinity = 1.74 + 0.27 (±0.10) π_a + 1.50 (±0.19) π_b + 0.01 (±0.002) (surface area in hydrophobic pockets) − 0.019 (±0.004) (surface area out of hydrophobic pockets) − 1.25 (±0.19) MK − 0.34 (±0.07) (conformational changes). n = 53, r = 0.92, s = 0.49, F = 43.

Equation 8 (rabbit): log relative binding affinity = 1.90 + 0.21 (±0.12) π_a + 1.42 (±0.21) π_b + 0.011 (±0.002) (surface area in hydrophobic pockets) − 0.017 (±0.005) (surface area out of hydrophobic pockets) − 0.97 (±0.22) MK − 0.34 (±0.08) (conformational changes). n = 53, r = 0.89, s = 0.55, F = 29.

Equation 9 (guinea pig): log relative binding affinity = 1.78 + 0.15 (±0.10) π_a + 1.49 (±0.18) π_b + 0.007 (±0.002) (surface area in hydrophobic pockets) − 0.016 (±0.003) (surface out of hydrophobic pockets) − 1.35 (±0.18) MK − 0.29 (±0.07) (conformational changes). n = 53, r = 0.92, s = 0.47, F = 43. π_a is significant at the 0.90 level but not at the 0.99 level.

As can be seen from eq 3, 7, and 8 which correspond to the regression analysis for the human, sheep, and rabbit, there is good agreement in the regression coefficients for the various parameters. This is remarkable considering the many compounds employed in this study and that the location of the various hydrophobic pockets differs from species to species.

There are inherent limitations to these equations; for example, they contain no substituent size limitation term and predict that an infinitely large hydrophobic group located in a hydrophobic pocket would have an infinitely large binding affinity for the receptor. Two compounds, 16α-ethyl-21-hydroxy-19-nor-4-pregnene-3,20-dione phenylpropionate and 17α-hydroxy-4-pregnene-3,20-dione caproate, were excluded from the previous studies due to the excessive size of the ester groups and due to the paucity of such compounds in this study. There are indications, though, from biological activity studies that the methyl group is the largest substituent tolerated in most positions of the steroid nucleus, with the exception of the 16, 17, and 21 positions. There appears to be a cleft or opening in the receptor in the proximity of the 17 position (with the exception of the guinea pig receptor) that can accommodate fairly large groups such as caproate. From the present data, it appears that binding affinity of a steroid for the receptor reaches a plateau for substitution in the 17α position with the acetoxy group eliciting the greatest binding affinity per Å^2 response. Further substituent size increases in this position have little effect on the binding affinity and there is no subsequent decrease in binding affinity. Owing to the lack of additional data, it can only be stated that the hydrophobic pocket in the 16α position is at least the size of an ethyl group and the hydrophobic pocket in the 21 position is at least the size of an acetoxy group. In principle, our basic six-parameter equations (eq 3 and 7–9) are able to handle any substituent, even those which surpass the size of any one hydrophobic pocket. If a substituent were larger than its hydrophobic pocket, none of it would reside in the pocket, and the surface area of that substituent would be placed in the "surface area out of a hydrophobic pocket" parameter. Proceeding in this manner, the two aforementioned compounds which were previously excluded were now included into the basic

Table VI. Parameters Employed for Linear Regression Analysis Relating Steroid Structure to Receptor Affinity in Rabbits and in Guinea Pigs

Compd	π_a	π_b	Surface area in hydrophobic pockets (rabbit)	Surface area out of hydrophobic pockets (rabbit)	Surface area in hydrophobic pockets (pig)	Surface area out of hydrophobic pockets (pig)	M-Keto	Conformational changes	Log rel binding affinity (rabbit) Obsd	Log rel binding affinity (rabbit) Calcd[a]	Log rel binding affinity (pig) Obsd	Log rel binding affinity (pig) Calcd[b]
1	−0.71	0	50	25	50	25	0	0	2	1.87	2	1.64
2	−0.71	0	50	34	50	34	0	2	1.74	1.10	1.4	0.92
3	−0.71	0	50	34	50	34	0	2	1.08	1.10	0.7	0.92
4	0	−0.39[c]	32	25	32	25	0	0	1.01	1.24	0	1.03
5	0	−0.39[c]	32	25	32	25	0	0	0.778	1.24	0.6	1.03
6	−0.39[d]	0	50	25	50	25	1	2	−0.301	0.28	−0.52	−0.24
7	−0.71	−1.39	37	25	37	25	0	0	0.301	−0.29	−0.097	−0.52
8	−0.71	−1.43	40	25	40	25	0	0	−0.097	−0.31	−0.52	−0.56
9	−0.71	−1.16	37	25	37	25	0	0	−0.301	0.047	−0.22	−0.18
10	−1.87	0	37	25	37	25	0	0	1.4	1.52	1.146	1.37
11	−3.26	0	24	25	24	25	0	0	0.02	1.12	0.447	1.07
12	−3.26	−1.43	14	25	14	25	0	0	−1	1.05	−1	−1.13
13	−2.42	0	50	25[f]	50	25[f]	1	1	0.301	0.23	0	−0.25
14	−2.42	0	50	25[f]	50	25[f]	1	1	−0.221	0.23	−0.52	−0.25
15	−0.71	−0.97[g]	27	25	27	25	0	0	−0.097	0.22	−0.046	0.027
16	−0.71	0	40	25	40	25	0	2	1.3	1.11	1.64	0.99
17	−0.71	0	50	47	50	47	0	0	1.61	1.59	1.67	1.29
18	−0.71	0	94	25	50	69	0	0	1.98	2.33	1.08	0.94
19	−0.71	0	50	57	50	47	0	0	1.5	1.59	1.63	1.29
20	−0.71	0	89	25	50	64	0	0	2.38	2.27	1	1.02
21	−0.71	−0.27	113	25	50	87	0	0	1.72	2.13	−0.7	0.25
22	−0.98	0	109	25	109	25	0	0	1.69	2.43	1.34	2.05
23	−1.38	−0.27	100	25	37	87	0	0	1.77	1.87	−0.4	0.048
24	−0.71	−0.27	135	25	72	87	0	0	2	2.36	1.11	0.41
25	−0.71	−0.27	125	25	63	87	0	2	2	1.68	−0.3	−0.24
26	−0.71	−0.27	120	25	58	87	0	2	2.16	1.55	−0.097	−0.28
27	−0.71	0	50	0	50	0	0	0	2.41	2.18	2.06	2.05
28	0	−0.39[c]	32	0	32	0	0	0	1.76	1.56	1.43	1.44
29	−1.87	0	81	0	37	44	0	0	2.44	2.29	1.4	1.07
30	−0.71	0	101	0	57	44	0	0	2.36	2.71	1.6	1.39
31	−0.71	0	92	0	48	44	0	2	2.24	1.96	1.17	0.74
32	−1.43	0	23	0	−11	34	0	0	2.23	1.76	0.95	0.94
33	−1.43	0	23	9	−11	43	0	2	1.23	1.00	0.3	0.21
34	−1.43[d]	0	23	0	−11	34	1	1	1.3	0.45	−0.22	−0.71
35	−1.43[d]	0	23	0	−11	43	1	3	−1	−0.32	−2	−1.43
36	−1.43[d]	0	23	9	−11	43	1	3	−0.52	−0.32	−2	−1.43
37	−1.43[d]	0	23	9	−11	43	1	3	−1	−0.32	−2	−1.43
38	−1.43[d]	0	23	9	−11	43	1	3	−1	−0.32	−1.09	−1.43
39	−1.43[e]	0	23	0	−11	34	1	1	1.11	0.45	−0.52	−0.709
40	−0.27[e]	0	36	62	0	95	1	1	0	0.023	−2	−1.43
41	−1.43[e]	0	23	22	−11	56	1	1	0.954	0.17	−0.7	−1.06
42	−1.43	0	23	0	−11	34	1	3	−0.523	−0.21	−1.15	−1.29
43	−2.86[e]	0	14	0	−20	34	1	5	−1	−1.22	−2	−2.15
44	−1.43	0	40	0	6	34	0	0	2.32	1.94	1.48	1.06
45	−1.43	0	23	0	−11	34	0	2	1.56	1.11	3	0.35
46	−1.43	0	23	22	−11	56	0	2	0.903	0.83	−0.4	0.0001
47	−1.43	0	45	0	11	34	0	0	2.62	1.99	1.43	1.10
48	−0.27	0	36	62	0	95	0	0	2.05	1.34	0.78	0.21
49	−1.39	0	−11	0	−11	0	0	0	1	1.42	1.6	1.49
50	−1.43[e]	0	13	0	−11	26	1	1	1.3	0.34	0.3	−0.58
51	−1.71[e]	0	0	26	0	26	1	1	−1	−0.17	−0.7	−0.54
52	−1.39	0	−11	26	−11	26	0	0	−0.22	1.09	0	1.071
53	−1.39	0	−2	26	−2	26	0	2		1.18		0.56
54	−1.43	0	−2	26	−11	60	1	0	1.08	0.19	−0.7	−0.84
55	−0.71	−0.27	113	25			0	0	1.88	2.13		
56	−0.98	0	81	160			0	0	0.845	0.46		

[a] Derived from eq 8. [b] Derived from eq 9. [c] Value of π for the 17β-hydroxyethyl group obtained by summation of the values of Et (1.0) and OH (−1.39). [d] A π value of 0.32 was employed for the change from a 3-keto group to a 3-hydroxyl group. This was required because the parent ring system is a 3-keto derivative. [e] A π value of −1.71 was employed to the change from a methylene group to a carbonyl group. This value was obtained by subtracting the π value of Et (1.0) from MeCO (−0.71). [f] No correction in surface area was made for the transformation of methylene to carbonyl, since the two groups have nearly identical surface areas. [g] A π value of −0.97 was employed for the ether oxygen, obtained by subtracting methyl (0.5) from methoxy (−0.47).

six-parameter equations. The parameters for these two compounds are shown in Table VI. The size of the individual hydrophobic pockets is as defined in Table VII. Substituents in the 17α position which were larger than acetoxy were treated equivalent to acetoxy. The basic six-parameter equations derived in this manner for the human and the rabbit are shown in eq 10 and 11, respectively.

Equation 10 (human): log relative binding affinity = 1.77 + 0.23 (±0.09) π_a + 1.29 (±0.17) π_b + 0.011 (±0.002)

Table VII. Maximum Substituent Size Allowable in Hydrophobic Pockets

Location of pocket	Max substituent size, A²
6α	22
7α	0
10	0
11β	22
16α	45
17α	Indeterminate
18	22 for progesterone derivatives 0 for androgen derivatives
21	63

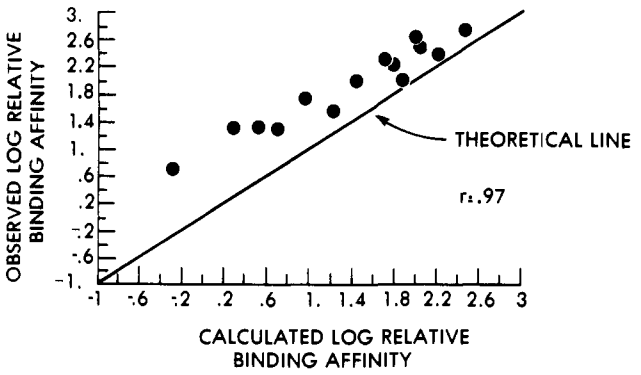

Figure 4. Graph of the observed (ref 21) vs. the predicted (eq 11) logarithm of the relative binding affinity of steroid derivatives to rabbit receptor.

(surface area in hydrophobic pockets) − 0.020 (±0.003) (surface area out of hydrophobic pockets) − 1.34 (±0.17) MK − 0.22 (±0.06) (conformational changes). $n = 56$, $r = 0.92$, $s = 0.45$, $F = 46$.

Equation 11 (rabbit): log relative binding affinity = 1.79 + 0.18 (±0.11) π_a + 1.45 (±0.21) π_b + 0.010 (±0.002) (surface area in hydrophobic pockets) − 0.012 (±0.003) (surface area out of hydrophobic pockets) − 0.99 (±0.21) MK − 0.33 (±0.08) (conformational changes). $n = 55$, $r = 0.88$, $s = 0.54$, $F = 29$. π_a is significant at the 0.95 level but not at the 0.99 level.

Another limitation of these equations is in assessing the effects of various conformational changes on the binding affinity. The conformational change parameter of eq 3 and 7–11 expresses the *average* binding affinity loss for conformational changes in the C-1, -2, -3, -4, -5, -6, -7, -11, and -12 positions of the parent steroid nucleus. Conformational changes in specific positions of the steroid nucleus may not be adequately represented by this parameter. Steroids with unnatural configurations, retroprogesterone, dydrogesterone, 14α,17α,19-nor-4-pregnene-3,20-dione, 9α,10α,17α-ethynyl-4-oestren-17α-ol, and *A*-nor-3-pregnene-2,20-dione, were excluded from this study because of difficulties in fully parameterizing these configurational changes. The compound, 4,16-pregnadiene-3,20-dione, was also excluded from this study since the Δ^{16} double bond not only induced a conformational change in the steroid nucleus but also drastically affected the position of the 17β-acetyl side chain which plays a very important role in binding for the progesterone derivatives. Attempts to factor the MK term into separate terms did not improve the correlation.

One of the purposes of developing QSAR equations like equations 3 and 7–11 is to provide a predictive base for future synthesis. Recently, we became aware of a study which offered a chance to test this aspect of our work. Raynaud et al.[21] reported the rabbit receptor affinities for a series of 14 steroids obtained by total synthesis. Of these, four compounds were also used in the Kontula study.

Table VIII. Steroid Employed in Work of Raynaud et al.[21]

No.	Compd	π_a	π_b	Surface area in hydrophobic pockets	Surface area out of hydrophobic pockets	M-Keto	Conformational changes	Obsd log rel binding affinity	Calcd[a] log rel binding affinity	Residuals	% error
1	Progesterone	−0.71	0	50	25	0	0	2	1.87	0.13	6.6
27	19-Norpregn-4-ene-3,20-dione	−0.71	0	50	0	0	0	2.41	2.18	0.23	9.54
32	17α-Ethynyl-17β-hydroxy-4-estren-3-one	−1.43	0	23	0	0	0	2.23	1.76	0.47	20.8
47	17α-Ethynyl-17β-hydroxy-18-methyl-4-estren-3-one	−0.71	0	45	0	0	0	2.62	1.99	0.63	23.8
57	19-Norpregna-4,9-diene-3,20-dione	−0.71	0	41	0	0	2	2	1.43	0.57	28.5
58	19-Norpregna-4,9,11-triene-3,20-dione	−0.71	0	32	0	0	4	1.3	0.68	0.62	47.4
59	17α-Methyl-19-norpregn-4-ene-3,20-dione	−0.71	0	76	0	0	0	2.7	2.45	0.25	9.2
60	17α-Methyl-19-norpregn-4,9-diene-3,20-dione	−0.71	0	67	0	0	2	2.3	1.70	0.60	25.9
61	17α-Methyl-19-norpregna-4,9,11-triene-3,20-dione	−1.43	0	58	0	0	4	1.74	0.95	0.79	45
62	17α-Ethynyl-17-hydroxy-18-ethyl-4-estren-3-one	−1.43	0	23	45	0	0	1.54	1.20	0.34	21.8
63	17α-Ethynyl-17-hydroxy-4,9,11-estratrien-3-one	−1.43	0	5	0	0	4	1.3	0.27	1.04	80
64	17α-Ethynyl-17-hydroxy-18-methyl-4,9,11-estratrien-3-one	−1.43	0	27	0	0	4	1.3	0.50	0.81	61.7
65	17α-Ethynyl-17-hydroxy-18-ethyl-4,9,11-estratrien-3-one	−1.43	0	5	45	0	4	0.7	−0.29	0.99	141.8
66	17α,21-Dimethyl-19-norpregna-4,9-diene-3,20-dione	−0.21	0	89	0	0	2	2.48	2.02	0.46	18.4

[a] As determined from eq 11.

Equation 11 was used to predict the activities of this series. The results are shown in Table VIII and Figure 4. A satisfactory prediction of binding affinities is obtained, certainly of sufficient accuracy to guide a synthetic program. The scatter observed is probably due to the use of data from a different laboratory.

A linear regression analysis incorporating both Kontula's and Raynaud's work results in eq 12.

Equation 12 (rabbit): log relative binding affinity = 1.92 + 0.21 (±0.11) π_a + 1.5 (±0.20) π_b + 0.009 (±0.002) (surface area in hydrophobic pockets) − 0.013 (±0.003) (surface area out of hydrophobic pockets) − 1.27 (±0.17) MK − 0.21 (±0.05) (conformational changes). $n = 65$, $r = 0.88$, $s = 0.53$, $F = 35$.

Our results thus represent a QSAR approach having predictive value and indicate that surface area is a logical and useful parameter to model hydrophobic binding. Like the work of Hansch, they show also that receptor mapping can be effectively carried out through QSAR techniques.

References and Notes

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A Model for the Prostaglandin Synthetase Cyclooxygenation Site and Its Inhibition by Antiinflammatory Arylacetic Acids

Peter Gund* and T. Y. Shen

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065. *Received December 20, 1976*

Conformational analysis of indomethacin and other nonsteroidal antiinflammatory drugs leads to formulation of a hypothetical complementary receptor site model. The same model can serve to describe the prostaglandin cyclooxygenase active site, and, indeed, arachidonic and other polyunsaturated fatty acids could be folded on the model in a manner which rationalizes their stereospecific transformation to cyclic *endo*-peroxides (PGG). The model rationalizes the structure–activity relationships of enzyme substrates and inhibitors and appears to be in agreement with biochemical studies of the enzyme.

Over 10 years ago, on the basis of observed in vivo structure–activity relationships for indomethacin (1) analogues, an antiinflammatory receptor site was hypothesized[1,2] to consist of two noncoplanar hydrophobic regions and a cationic center. After the 1971 discovery[3-5] that indomethacin and other antiinflammatory drugs inhibit prostaglandin (PG) synthesis, this receptor was equated to the PG synthetase active site.[6] A related hypothetical receptor site was proposed from the shape of some antiinflammatory benzoic acid derivatives.[7]

We have modeled the three-dimensional structures of some antiinflammatory arylacetic acids and found common spatial features. We have hypothesized a complementary receptor site model, which can also accommodate some polyunsaturated fatty acids in a conformation which rationalizes their stereospecific conversion into cyclic *endo*-peroxides.

It is now well established that prostaglandins and their metabolites are involved in the inflammatory process and that many antiinflammatory drugs inhibit the PG synthetase enzyme complex at physiological concentrations.[7-10] While prostaglandin synthesis is a complex, multistep process[11-15] (Scheme I), we only concern ourselves here with the initiation step—substrate binding by fatty acid dioxygenase—since this is the step inhibited by aspirin,[16] indomethacin, and other antiinflammatory agents.[12]

Modeling Methods. Molecular structures were generated from standard bond lengths and angles, or from crystallographic coordinates where available, and viewed interactively on a Tektronix 4010 display terminal.[17] Conformational energies were calculated by quantum mechanical (CNDO/2[18]) and classical mechanical (MODBUILDER[19]) methods. Favored conformations were