MTD Calculations on Quantitative Structure-Activity Relationships of Steroids Binding to the Progesterone Receptor

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The minimal topological difference (MTD) method is used to describe quantitative structure-activity relationships (QSAR) for the progesterone-receptor binding affinity including 59 progestational steroids. Multiple correlation coefficients of $r = 0.962$ and $r = 0.955$ are obtained by use of the MTD variable and a measure of hydrophobicity for the series of progesterone and ethisterone derivatives, respectively. Hydrophobic effects are found to strongly influence receptor binding. In accordance with the hydrogen bonding concept, the optimized MTD receptor maps indicate cavity vertices in the regions of oxygen functions at C3 and in the 17β position. Receptor wall vertices are attributed in the areas of 4, 10β, and 13β substituents of 4-en-3-one steroids while 17α side chains additionally contain receptor cavity vertices. A comparison of corresponding receptor maps suggests in accord with X-ray crystal structure data that progesterone and ethisterone derivatives are bound in somewhat different orientations relative to the receptor surface.

Introduction

Recent developments of computer hardware, powerful computer-graphic systems, and calculation procedures for large molecules make it feasible to theoretically treat the interaction between drugs and biopolymers. However, one necessary precondition to perform such computations is some knowledge of the atomic binding-site structure of these interaction systems. A piece of information to model such binding sites is provided by the amino-acid sequence of the proteins involved. In the case of steroid hormone receptors, the human estrogen receptor [1] and the human glucocorticoid receptor sequence [2] have been recently determined. But this knowledge needs completion from other sources of binding site mapping, *e.g.* statistical analyses using crystallographic data of a series of drugs or quantitative structure-activity relationships (QSAR) studies.

To this end, the minimal topological difference (MTD) method [3, 4] has proved to be especially useful among the QSAR techniques since it is capable to provide a consistent and comprehensive characteristic of the drug-biopolymer interaction surface geometry in general. In the field of steroid research, the MTD scheme has been applied for cardiotonic steroids [5–7], glucocorticoids [3], and estrogens [3, 8]. The present MTD study includes 59 progestational steroids of both the progesterone and the ethisterone type from which the relative binding affinities for the rabbit-uterine progesterone receptor are available. For progestins, various QSAR analyses have demonstrated that hydrophobic interactions markedly influence progestational activity (Clauberg assay) and receptor binding [9–15]. Therefore, an explicit measure of hydrophobicity at all substitution sites except at those of C3 and C17β is additionally taken into account in the present MTD investigation. The exceptions are made since both regions are strongly supposed to be involved in hydrogen bonding to the receptor rather than in hydrophobic interactions. We expect that the findings due to orientational restrictions of those hydrogen bonds concluded from X-ray data superpositions [16–20] and the present MTD receptor maps as well as further results on molecular receptor structure (*e.g. cf.* [21]) will be valuable contributions to an appropriate receptor modelling when the progesterone-receptor protein sequence is disposable and by further help of protein conformational investigations.

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Table I. Data of the progesterone series.

No.	Steroid designation	Ref.	A^{exp}	A^{theor}	MTD	f	Vertex occupation
1.	17α-Me-P	[22]	2.67	2.20	2	0.52	1, 5, 8, 13, 19, 20, 21
2.	17α-Me-19-nor-P	[23]	2.50	2.49	1	0.00	1, 8, 13, 19, 20, 21
3.	6α-Me-17α-OAc-P	[24]	2.49	2.55	1	0.08	1, 3, 5, 8, 13, 14, 15, 16, 19, 20, 21
4.	16α-Et-21-OH-19-nor-P	[25]	2.38	2.20	2	0.52	1, 8, 11, 12, 19, 20, 21, 22
5.	19-nor-P	[26]	2.36	2.04	1	−0.52	1, 8, 19, 20, 21
6.	6α-Me-P	[27]	2.06	2.20	2	0.52	1, 3, 5, 8, 19, 20, 21
7.	P	–	2.00	1.76	2	0.00	1, 5, 8, 19, 20, 21
8.	16α-Et-P	[28]	1.98	1.92	3	1.04	1, 5, 8, 11, 12, 19, 20, 21
9.	18-Me-19-nor-P	[22]	1.96	1.76	2	0.00	1, 8, 9, 19, 20, 21
10.	6α-Cl-P	[22]	1.88	1.65	2	−0.13	1, 3, 5, 8, 19, 20, 21
11.	17α-F-P	[22]	1.86	1.44	2	−0.37	1, 5, 8, 13, 19, 20, 21
12.	17α-OMe-P	[22]	1.80	1.81	1	−0.79	1, 5, 8, 13, 14, 19, 20, 21
13.	17α-Br-P	[22]	1.78	2.07	2	0.36	1, 5, 8, 13, 19, 20, 21
14.	17α-OAc-P	[26]	1.78	2.11	1	−0.44	1, 5, 8, 13, 14, 15, 16, 19, 20, 21
15.	6α-F-17α-OAc-P	[27]	1.76	1.55	1	−1.10	1, 3, 5, 8, 13, 14, 15, 16, 19, 20, 21
16.	7α-Me-P	[28]	1.61	1.48	3	0.52	1, 4, 5, 8, 19, 20, 21
17.	21-F-P	[22]	1.57	1.76	2	0.00	1, 5, 8, 19, 20, 21, 22
18.	21-I-P	[22]	1.52	1.76	2	0.00	1, 5, 8, 19, 20, 21, 22
19.	18,19-dinor-P	[22]	1.52	1.60	1	−1.04	1, 19, 20, 21
20.	18-Me-P	[28]	1.51	1.48	3	0.52	1, 5, 8, 9, 19, 20, 21
21.	16α-Me-P	[22]	1.42	1.48	3	0.52	1, 5, 8, 11, 19, 20, 21
22.	21-OH-P	[28]	1.40	1.76	2	0.00	1, 5, 8, 19, 20, 21, 22
23.	4-Me-P	[22]	1.36	1.48	3	0.52	1, 2, 5, 8, 19, 20, 21
24.	3-deoxy-P	[22]	1.04	1.04	3	0.00	5, 8, 19, 20, 21
25.	6α-Me-17α-OH-P	[27]	0.85	1.04	2	−0.84	1, 3, 5, 8, 13, 19, 20, 21
26.	11β,21-diOH-P	[28]	0.60	0.35	2	−1.65	1, 5, 6, 8, 19, 20, 21, 22
27.	20-deoxy-P	[22]	0.60	1.04	3	0.00	1, 5, 8, 19, 21
28.	6α-OH-P	[22]	0.48	0.35	2	−1.65	1, 3, 5, 8, 19, 20, 21
29.	17α-OH-P	[29]	−0.05	0.60	2	−1.36	1, 5, 8, 13, 19, 20, 21
30.	18-OH-P	[22]	−0.16	−0.37	3	−1.65	1, 5, 8, 9, 19, 20, 21
31.	7α-OH-P	[22]	−0.16	−0.37	3	−1.65	1, 4, 5, 8, 19, 20, 21
32.	16α-OH-P	[22]	−0.16	−0.37	3	−1.65	1, 5, 8, 11, 19, 20, 21
33.	4-OH-P	[22]	−0.30	−0.13	3	−1.36	1, 2, 5, 8, 19, 20, 21
34.	11β,17α,21-triOH-P	[28]	−1.00	−0.82	2	−3.02	1, 5, 6, 8, 13, 19, 20, 21, 22

P: progesterone; Me: methyl; Et: ethyl; OH: hydroxy; OMe: methoxy; OAc: acetoxy; F: fluoro; Cl: chloro; Br: bromo; I: iodo.

Materials and Methods

The MTD study is performed for a series of 34 progesterone derivatives (Table I) as well as for a series of 25 testosterone derivatives (Table II). As experimental data of biological activities A^{exp}, relative binding affinities (RBA) for the progesterone receptor of rabbit uteri are used in terms of logarithms of per-cent RBA values (progesterone = 100%). All activity data which can be found in Tables I and II are taken from [22–32] or determined in this work due to competition experiments described in detail elsewhere [33]. In brief, rabbit uterus cytosol was incubated with [^{3}H]progesterone and suitable concentrations of the competitor at 0 °C for 20 h, followed by charcoal-dextran separation and counting of bound [^{3}H]. Relative binding affinities were calculated from the concentrations of 50% inhibition using progesterone as reference.

Literature data of $\delta\Delta G^\circ$ have been transformed according to the equation: $RBA = \exp(-\delta\Delta G^\circ/RT) \cdot 100\%$. The hypermolecule covering all the 59 steroids employed is given in Fig. 1. A justification of using common vertices for the 17β progesterone-like side chain atoms can be derived from both experimental and theoretical investigations [34–36] which indicate that the conformation described by a torsional angle C16–C17–C20–O20 between 0° and −46° is preferred in almost all cases. Compounds with additional unsaturated bonds in the steroid backbone are excluded from consideration because

Table II. Data of the testosterone series.

No.	Steroid designation	Ref.	A^{exp}	A^{theor}	MTD	f	Vertex occupation
1.	18-Me-NE	[31]	2.55	2.32	1	0.31	1, 8, 9, 13, 18, 19
2.	11 = CH_2-18-Me-NE	[30]	2.54	2.42	1	0.47	1, 7, 8, 9, 13, 18, 19
3.	7α,17α-diMe-NT	[23]	2.33	2.45	1	0.52	1, 4, 8, 13, 19
4.	11β-Cl-NE	[28]	2.32	1.91	1	−0.33	1, 6, 8, 13, 18, 19
5.	NE	[23]	2.19	1.99	1	−0.21	1, 8, 13, 18, 19
6.	17α-Me-NT	[26]	2.00	2.12	1	0.00	1, 8, 13, 19
7.	17α-CH_2Cl-NT	(§)	1.93	2.22	1	0.16	1, 8, 13, 14, 19
8.	17α-Et-NT	[27]	1.89	2.45	1	0.52	1, 8, 13, 14, 19
9.	18-Et-NE	[23]	1.86	1.56	2	0.83	1, 8, 9, 10, 13, 18, 19
10.	17α-Pr-18-nor-T	[27]	1.83	1.69	2	1.04	1, 5, 13, 14, 15, 19
11.	17α-CH = CH_2-NT	[32]	1.81	2.22	1	0.16	1, 8, 13, 14, 19
12.	17α-CH_2CMe = CH_2-NT	[32]	1.68	1.79	2	1.19	1, 8, 13, 14, 15, 16, 19
13.	18-Me-NT	[23]	1.53	1.03	2	0.00	1, 8, 9, 19
14.	7α-Me-NT	[25]	1.34	1.03	2	0.00	1, 4, 8, 19
15.	3-deoxy-17α-Me-NT	[28]	1.30	1.03	2	0.00	8, 13, 19
16.	E	[32]	1.28	1.23	2	0.31	1, 5, 8, 13, 18, 19
17.	3-deoxy-11 = CH_2-18-Me-NE	[30]	1.20	1.33	2	0.47	7, 8, 9, 13, 18, 19
18.	3-deoxy-7α-Me-NE	[28]	0.95	1.23	2	0.31	4, 8, 13, 18, 19
19.	3-deoxy-NE	[25]	0.85	0.90	2	−0.21	8, 13, 18, 19
20.	NT	[32]	0.78	0.70	2	−0.52	1, 8, 19
21.	18-Et-NT	[23]	0.65	0.27	3	0.52	1, 8, 9, 10, 19
22.	4-Cl-17α-Me-T	(§)	0.11	0.37	3	0.68	1, 2, 5, 8, 13, 19
23.	T	[28]	−0.22	−0.06	3	0.00	1, 5, 8, 19
24.	17α-CH_2CN-T	(§)	−0.52	−0.33	3	−0.42	1, 5, 8, 13, 14, 17, 19
25.	4-Cl-11β-OH-17α-Me-T	(§)	−1.00	−0.68	3	−0.97	1, 2, 5, 6, 8, 13, 19

T: testosterone; NT: 19-nortestosterone; E: ethisterone; NE: 19-norethisterone; Me: methyl; Et: ethyl; Pr: propyl; OH: hydroxy; Cl: chloro; CN: cyano; $=CH_2$: methylene; (§): this work.

of the non-imposability in the hypermolecule construction. The 4,9-dien-3-one steroids, *e.g.*, are known to favourably adopt an inverted A-ring conformation which has significantly altered atomic locations compared to the normal conformation found in the case of 10-methyl and 19-nor steroids as employed in this study [33].

Hydrophobicity of all substituents other than in the 17β position and the 3-ketonic oxygen is taken into account by a sum of the corresponding hydrophobic fragmental constants f including relevant proximity corrections [37]. For electronegative substituents close to hydrogen bonding areas (3-one, 17β side chain), only half of the proximity effect

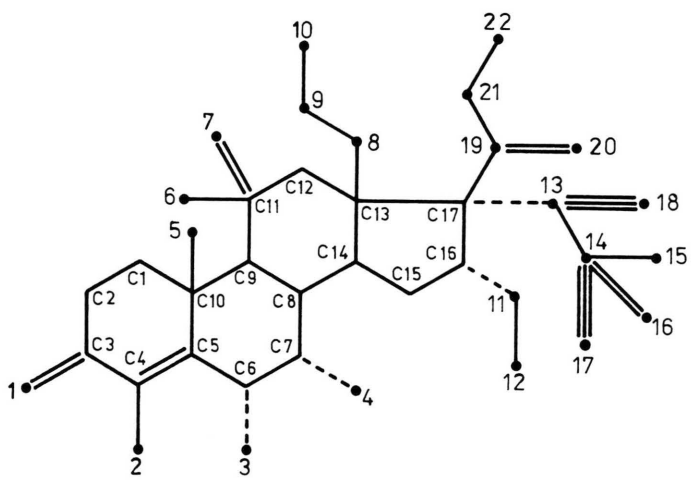

Fig. 1. Schematic representation of the hypermolecule with numerotation of vertices and steroid-skeleton carbon atoms.

referring to hydrophobic interaction is applied accounting for the fact that the hydrophobicity interference is restricted to only one direction.

Since the MTD technique is described in detail elsewhere [3–7] only the strategy in the MTD optimization should be mentioned: An initial receptor map (set of ε_j attributions) has been obtained by means of a Free-Wilson treatment using the whole data set. On the basis of the corresponding MTD parameter values and the hydrophobicity f data, a first linear correlation coefficient is calculated. From monosubstitutions of ε_j values for each of the j vertices, that corrected receptor map is selected which improves the correlation coefficient (r) best. The optimized receptor map S^* is found if no further increase in the r value can be achieved by ε_j changes.

Results and Discussion

The following optimized receptor map and the related regression equation are obtained for the series of progesterone derivatives:

$$S_P^* \begin{cases} j\ (\varepsilon = -1)\text{: } 1, 14, 20 \\ j\ (\varepsilon = \ \ 0)\text{: } 3, 6, 8, 12, 13, 15, 16, 22 \\ j\ (\varepsilon = +1)\text{: } 2, 4, 5, 9, 11 \end{cases}$$

$$A^{\text{theor}} = 3.209 - 0.725 \cdot \text{MTD} + 0.854 \cdot f \qquad (1)$$

$$n=34 \ \ r=0.962 \ \ s=0.262 \ \ F_{2,31}=194.6 \ \ \alpha<0.001$$

Moreover, the receptor map S_P^* is illustrated in Fig. 2. In view of the fact that experimental activity data from very different sources are combined, the standard deviation (s) is quite reasonable. The cavity vertices found for the carbonyl oxygens at C3 ($j=1$) and C20 ($j=20$) correspond to hydrogen-bonding facilities generally assumed in progesterone-receptor binding. The attributions of receptor wall vertices for $j=2$ (C4), $j=4$ (C7α) and of sterically irrelevant vertices for $j=3$ (C6α), $j=22$ (C21) are in full agreement with the findings and conclusions of Seeley *et al.* [22] and of Raynaud *et al.* [38] due to receptor binding and of Zeelen [39] due to progestational activity. The steric hindrance of the 10-methyl group ($j=5$) has also been deduced in [22, 33, 39].

The wall vertex $j=9$ is consistent with the result derived in [22] that the receptor binding site surface is close to C18 but indicates, on the other hand, that the separation from the receptor surface in this region is somewhat greater than that in the A-ring area. Some conflicting conclusions have been drawn for 11β substituents. While Seeley *et al.* [22] proposed a hydrogen acceptor function at this site, v.d. Broek *et al.* [40] stressed the role of steric factors in 11β alkyl substitutions for oral Clauberg-test activities. The present MTD receptor map suggests some kind of receptor pocket in the 11β region. This is in agreement with recent model concepts based on RBA data of anti-progestational steroids [41].

The assignment of a receptor wall vertex for $j=11$ (C16α) is in accord with a strong activity-reducing contribution of the 16α-methyl substituent in the oral Clauberg assay [39] but contrasts with the A-ring binding/D-ring acting model proposed by Duax *et al.* [42] and with the conclusions in [22]. In the former model by Duax *et al.*, no tight contact between the receptor protein and the steroid D-ring region is postulated. This model is also in contradiction with the assumption of hydrophobic interactions from 17α substituents [15, 22].

In addition to hydrophobic bonding, 17α side chains provide further sources of a receptor-binding energy increase due to the cavity vertex $j=14$ of the optimized MTD receptor map. This vertex manifests the only exception from the single-connected network rule generally applied in MTD investigations [3, 4]. This may be explained by intra- or intermolecular influences on conformational properties (*e.g.* on the 17β side-chain orientation) or by a lack of complementarity in the three-dimensional structure of the receptor protein in the $j=13$ region.

In the case of testosterone derivatives, the 17α substituent is also found to contain the only cavity vertex in addition to hydrogen bonding centres at C3 and C17β. Likewise, an almost 3-fold enhanced binding affinity caused by the 17α-methyl substitution was observed for the progesterone receptor from rat placenta [14].

The complete MTD results of the testosterone series are:

$$S_T^* \begin{cases} j\ (\varepsilon = -1)\text{: } 1, 13 \\ j\ (\varepsilon = \ \ 0)\text{: } 4, 6, 7, 9, 14, 16, 18 \\ j\ (\varepsilon = +1)\text{: } 2, 5, 8, 10, 15, 17 \end{cases}$$

$$A^{\text{theor}} = 3.213 - 1.092 \cdot \text{MTD} + 0.636 \cdot f \qquad (2)$$

$$n=25 \ \ r=0.955 \ \ s=0.294 \ \ F_{2,22}=114.0 \ \ \alpha<0.001$$

The concentration of wall vertices attached to C13 in the optimized receptor map S_T^* also shown in Fig. 2 is in accord with the displacement from the progesterone receptor site in the distribution maps of a correspondence analysis when the 13β side chain is lengthened [43].

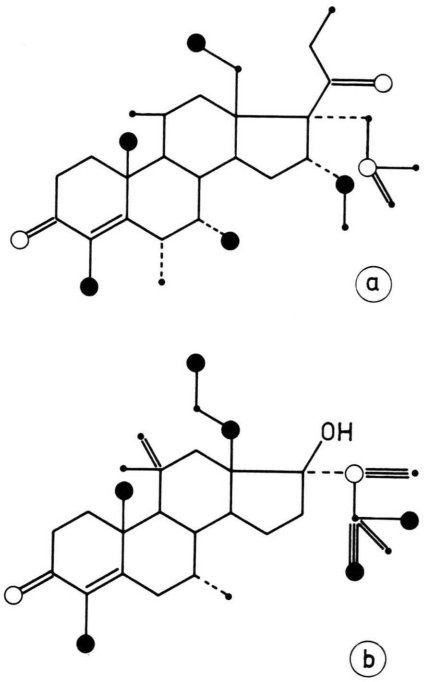

Fig. 2. Results of the MTD receptor map for the (a) progesterone series and (b) testosterone series (○ receptor cavity

Interestingly, there are substantial differences in the MTD receptor maps of the testosterone and progesterone series. A fusion of both series would result in a strongly decreased correlation coefficient. Therefore, it might be assumed that pregnene and androstene analogues are bound in slightly different arrangements relative to the receptor surface. This is likely if both types of steroids form hydrogen bonds in the 17β region with similar orientational specificity. Fig. 3 shows a superposition of X-ray single-crystal data of progesterone and norethisterone performed by a least-squares fit technique in a way which permits common hydrogen bonding patterns. In close agreement with the MTD findings, the superposition of Fig. 3 indicates almost equivalent interactions from the ring A in both cases. Major differences can be found for D-ring substituents. The shift of testosterone-type compounds toward the β side compared to progesterone derivatives corresponds to the fact that a wall vertex is closer to C13 for testosterone analogues ($j=8$). Furthermore, this shift in the relative steroid-receptor complex geometry could bring the 7α substituent apart from a close receptor contact as it is seen in the MTD results for vertex $j=4$. The interpretation of 17α vertices is much more complicated since conformation degrees of freedom are also to be taken into account. However, the receptor cavity vertex $j=13$ in the testosterone series can be explained as it occupies a position approaching C17 of progesterone which is assumed to have a cavity-vertex skeleton (*cf.* Fig. 3).

In conclusion, there is some evidence from the MTD results evaluated as well as from crystallographic data of Fig. 3 that 17β-hydroxy compounds bind to the progesterone receptor with a steroid-skeleton orientation being slightly different from that of 17β-acetyl analogues. Thus, both types of progesterone-receptor binding steroids are able to form hydrogen bonds which are almost equivalent in geometry. According to Zeelen [46], different geometrical arrangements up to a certain extent might be accommodated by the progesterone receptor in which the steroid-complementary cleft is not inherent but is formed due to protein flexibility when the steroid-receptor interaction takes place (induced fit model).

In full agreement with the concept of Zeelen and with other QSAR findings [9–15] but in contrast with the model by Duax *et al.* [42], the MTD investigation presented confirms the substantial role of hydrophobic contacts to the receptor in wide regions of the steroid-backbone surface including the D-ring area. The strong influence of hydrophobicity upon RBA data can be taken from both Eqn. (1) and Eqn. (2). In the case of progesterone derivatives, the hydrophobic effects are computed to be even dominating over the steric factor expressed as MTD. Accord-

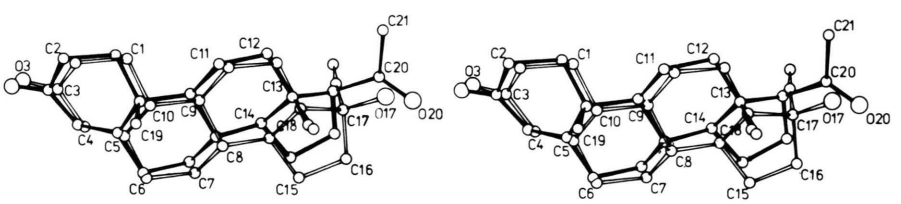

Fig. 3. Crystal structure of progesterone [44] superimposed with that of norethisterone [45] in stereoscopic view.

ingly, future calculations on progestin-receptor interactions should prefer receptor models which represent fairly complete surroundings of progestational steroid hormones.

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