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3-D QSAR analysis of steroid/protein interactions: The use of difference maps

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SUMMARY

The approach to use difference maps depicting differences in 3-D QSAR coefficients of different biological activities to analyze and monitor selectivity is described.

INTRODUCTION

Quantitative structure-activity relationships (QSARs) have provided valuable aid in developing new therapeutic agents [1]. Recently, new three-dimensional (3-D) QSAR techniques have been introduced [2,3].

However, activity as such is only one interesting component in the drug development phase. Selectivity is often equally important. The sought-after compound should most likely fall within certain limits of a selectivity profile to be a really interesting candidate for further investigations.

This paper demonstrates the utilization of 3-D QSAR coefficient maps depicting differences in requirements between different biological activities. The example used is related to the affinities of human [4] and guinea-pig [5] CBG complexes with steroids.

METHOD OF CALCULATION

A short description of the technique will be given below. For a more detailed presentation of the methodology, conformational analysis and superimpositioning of structures etc., see Ref [6]. For a similar 3-D QSAR procedure (CoMFA), see Cramer et al. [3].

A three-dimensional (3-D) grid was spanned around the set of investigated compounds, with a

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TABLE I
NAMES OF STEROIDS 1–42

Compound No.	Name
1	11,17,21-trihydroxy-4-pregnene-3,20-dione
2	14α,17,21-trihydroxy-4-pregnene-3,20-dione
3	11β,17,21-trihydroxy-1,4-pregnadiene-3,20-dione
4	11β,17,21-trihydroxy-2α-methyl-4-pregnene-3,20-dione
5	11β,17,21-trihydroxy-2α-methyl-9α-fluoro-4-pregnene-3,20-dione
6	17,21-dihydroxy-4-pregnene-3,11,20-trione
7	11α,21-dihydroxy-4-pregnene-3,20-dione
8	11β,21-dihydroxy-4-pregnene-3,20-dione
9	17,21-dihydroxy-4-pregnene-3,20-dione
10	2α-hydroxy-4-pregnene-3,20-dione
11	6α-hydroxy-4-pregnene-3,20-dione
12	6β-hydroxy-4-pregnene-3,20-dione
13	11α-hydroxy-4-pregnene-3,20-dione
14	17-hydroxy-4-pregnene-3,20-dione
15	21-hydroxy-4-pregnene-3,20-dione
16	4-pregnene-3,20-dione
17	5-pregnene-3,20-dione
18	5β-pregnane-3,20-dione
19	3β-hydroxy-5-pregnen-20-one
20	3α-hydroxy-5β-pregnan-20-one
21	19-nor-4-pregnene-3,20-dione
22	9α-fluoro-16α-methyl-11β,17,21-trihydroxy-1,4-pregnadiene-3,20-dione
23	17,21-dimethyl-19-norpregna-4,9-diene-3,20-dione
24	17β-hydroxy-4-androsten-3-one
25	16α,17-dihydroxy-4-pregnene-3,20-dione
26	11β,21-dihydroxy-5β-pregnane-3,20-dione
27	16α-hydroxy-4-pregnene-3,20-dione
28	12α-hydroxy-5β-pregnane-3,20-dione
29	17-hydroxy-6α-methyl-4-pregnene-3,20-dione
30	17-hydroxy-16α-methyl-4-pregnene-3,20-dione
31	4-pregnene-3,11,20-trione
32	2α-methyl-4-pregnene-3,20-dione
33	6α-methyl-4-pregnene-3,20-dione
34	16α-methyl-4-pregnene-3,20-dione
35	17β-hydroxy-4-estren-3-one
36	3,17β-dihydroxy-1,3,5(10)-estratriene
37	17β,19-dihydroxy-4-androsten-3-one
38	11β,17,21-trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione
39	11β,17,21-trihydroxy-16α-methyl-4-pregnene-3,20-dione
40	11β-hydroxy-4-pregnene-3,20-dione
41	11β,17β-dihydroxy-17α-methyl-4-androsten-3-one
42	17,21-dihydroxy-1,4-pregnadiene-3,11,20-trione

distance of 1.5 Å between the grid points. The training set consisted of compounds 1–24 (see Table 1 for names) which had experimental affinities measured for both complexes. A methyl probe was used to evaluate the interactions of each grid point for two molecular fields represented by non-bonded interactions and charge-charge interactions. A third field related to the molecular lipophilicity potential (MLP) was also used. The three fields were then transformed so that each field represented the same scale by normalising the square root of the sum of variances of all points in each field, i.e., setting the square root sum of one field to unity, and scaling the remaining fields accordingly (block scaling). The scaling part differs from the methodology used in [6], where scaling was performed according to the extreme values of the three fields. Block scaling was applied so that the fields would contribute equally, and not be biased by the original numerical values. The relationship between each biological activity and field descriptors was analysed using PLS [7]. The number of significant principal components was determined with cross-validation by leaving one compound out of the analysis each round [8]. Following the statistical PLS analysis, a retransformation of the PLS loadings into ordinary regression coefficients was performed [9]. The results were depicted as stereo pictures of 3-D coefficient maps of the grid points corresponding to the difference between coefficients for human and guinea-pig CBG complexes (Figs. 1–4) of each field using CHEM-X [10]. For display purposes, the coefficients were transformed in such a way that the largest absolute value (i.e., ignoring the sign) was set to +100 or −100, depending on the sign, and the rest of the values were scaled accordingly. Figures 1–4 show coefficients with an absolute value larger than 45, as well as steroids 1–24 (hydrogens removed for clarity). Coefficient maps, structures, etc., are available from the author on request.

RESULTS AND DISCUSSION

Human CBG complexes

The PLS analysis resulted in four significant components with a 'predictive' r^2 value of 0.93. The calculated vs. experimental affinities are reported in Table 2 and depicted in Fig. 5. The affinities of compounds 25–37 were then predicted using the established relationship. The predictive ca-

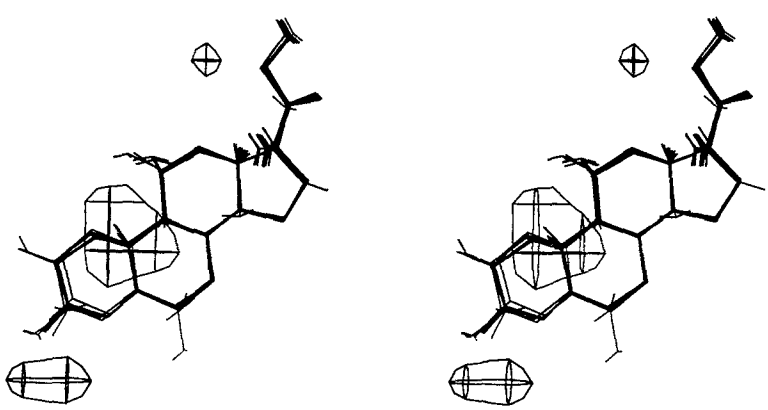


Fig. 1. Difference map of positive non-bonded interactions between human and guinea-pig CBG complexes. Contours are depicted at a level of 45.

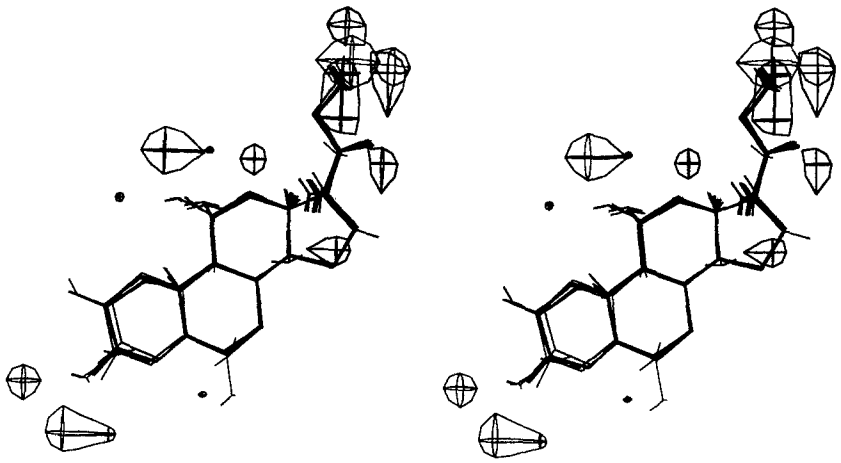


Fig. 2. Difference map of negative non-bonded interactions between human and guinea-pig CBG complexes. Contours are depicted at a level of −45.

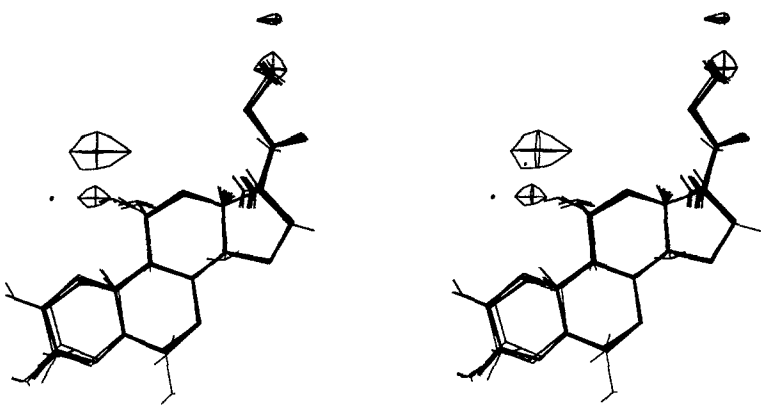


Fig. 3. Difference map of positive charge-charge interactions between human and guinea-pig CBG complexes. Contours are depicted at a level of 45.

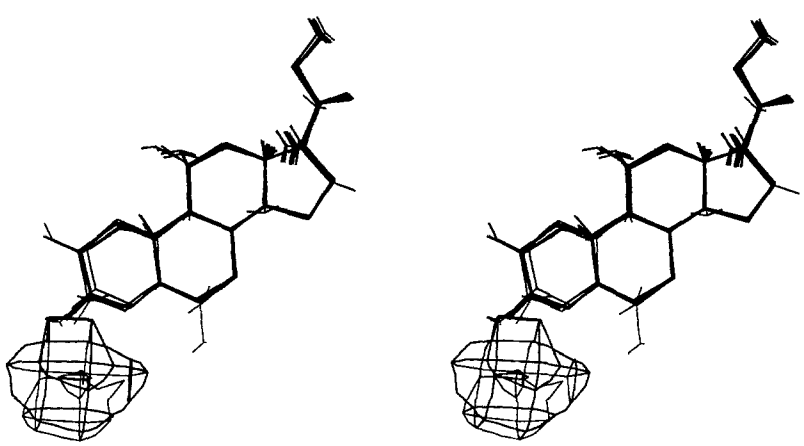


Fig. 4. Difference map of negative charge-charge interactions between human and guinea-pig CBG complexes. Contours are depicted at a level of −45.

TABLE 2
EXPERIMENTAL[a] AND CALCULATED AFFINITIES OF HUMAN AND GUINEA PIG CBG COMPLEXES[b]

Compound no.	Human CBG complex		Guinea pig CBG complex	
	Exp.	Calc.	Exp.	Calc.
1	8.85	8.51	7.44	6.83
2	6.85	6.62	5.00	4.89
3	8.57	8.75	6.78	6.59
4	8.78	8.84	6.95	6.93
5	6.23	6.63	4.53	4.97
6	7.70	7.49	6.20	6.48
7	8.15	8.38	5.70	6.38
8	8.98	9.10	7.26	7.30
9	8.81	8.69	6.58	6.53
10	8.43	8.03	5.82	5.25
11	7.15	7.27	4.61	4.69
12	6.49	6.54	4.18	4.59
13	8.00	8.01	5.48	5.33
14	8.80	8.46	6.20	5.54
15	8.83	9.30	6.49	7.04
16	8.77	8.82	6.20	5.84
17	8.11	8.10	5.20	4.80
18	7.62	7.72	5.60	5.21
19	5.70	5.91	3.95	4.37
20	6.36	6.43	4.28	4.55
21	7.70	7.27	4.85	4.91
22	5.59	5.67	4.08	4.02
23	6.70	6.96	5.45	5.45
24	7.70	7.32	5.34	5.68
25	6.85	7.54		
26	7.70	7.67		
27	7.00	8.03		
28	6.00	6.34		
29	7.41	8.26		
30	7.69	7.74		
31	7.57	7.50		
32	8.53	9.38		
33	7.85	8.60		
34	8.04	7.96		
35	6.70	6.05		
36	4.90	4.71		
37	6.70	5.09		
38			5.56	6.40
39			6.95	5.84
40			7.11	6.17
41			4.95	5.79
42			5.04	6.76

[a] Human CBG complexes, see Ref 4.
Guinea pig CBG complexes, see Ref 5.
[b] The affinity values are given in $\log(K_a)$, M^{-1} units.

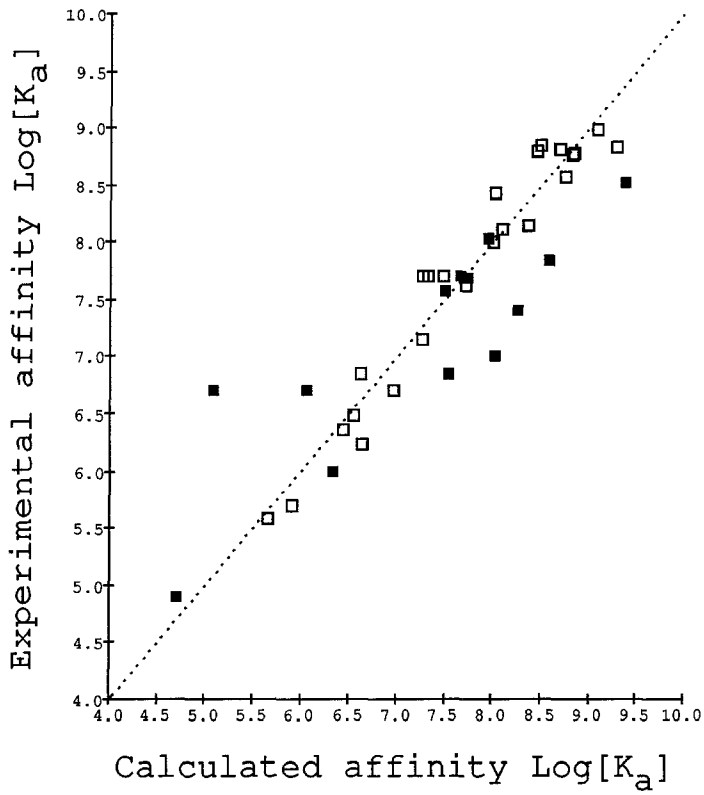


Fig. 5. Calculated vs. experimental affinities for human CBG complexes with steroids. □, training set; ■, predicted compounds.

pability is good, except for compound 37, the only compound with a hydroxy group in position 19.

Guinea-pig CBG complexes

The PLS analysis resulted in three significant components with a 'predictive' r^2 value of 0.87. The calculated vs. experimental affinities are reported in Table 2 and depicted in Fig. 6. The predicted affinities of 38–41 is fair. Compound 42 is significantly overestimated; this compound is, however, the only structure with a carbonyl group in position 11.

Difference maps

The difference maps show differences in coefficients between human and guinea-pig CBG complexes. Figures 1–4 depict the positive and negative difference maps for the non-bonded and charge-charge interaction fields at an absolute level of 45. The molecular-lipophilic-potential field (not shown) did not display any differences at the 45 level. One may, with these maps, identify areas that are important for selectivity, and vice versa. One may also, together with ordinary coefficient maps (not depicted), further analyze the possibilities to modify existing lead structures (or create new leads) to obtain the desired activity as well as selectivity.

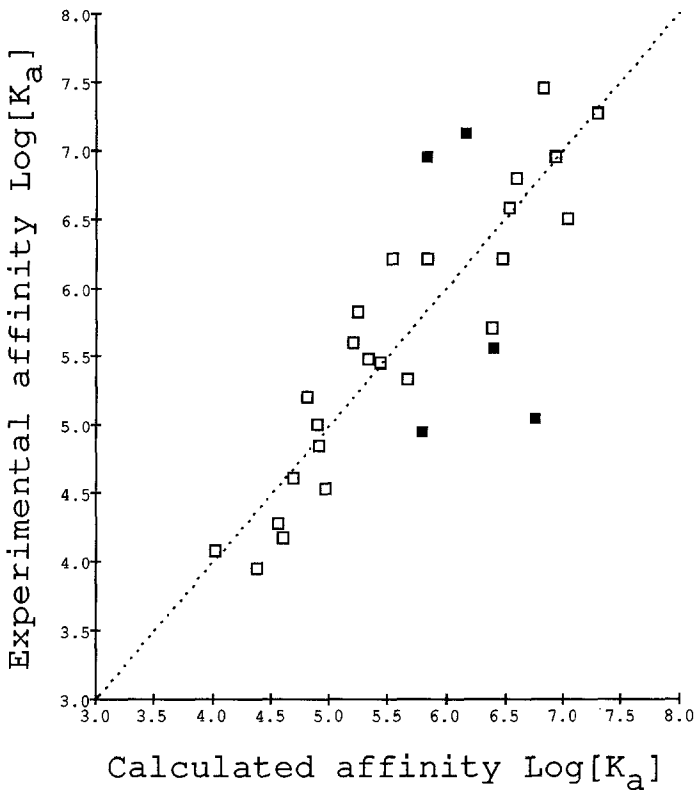
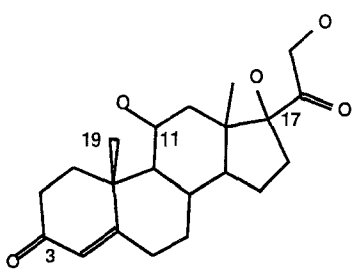


Fig. 6. Calculated vs. experimental affinities for guinea-pig CBG complexes with steroids. □, training set; ■, predicted compounds.



The non-bonded difference maps indicate that the presence of a substituent in position 10 and a smaller side chain at position 17 is favorable for the selectivity of human vs. guinea-pig CBG complexes (Figs. 1, 2).

The main differences in electronic characteristics of the two types of complexes are centered around position 3. An electronegative atom attached to that position (for instance, a carbonyl group) promotes the selectivity for human CBG complexes (Figs. 3, 4).

CONCLUSIONS

The difference maps represent valuable tools with which one may, in conjunction with ordinary coefficient maps, analyze and identify areas of interest with respect to activity and selectivity.

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