Journal of Computer-Aided Molecular Design, 6 (1992) 553–568
ESCOM

J-CAMD 174

Comparative molecular field analysis of CCK-A antagonists using field-fit as an alignment technique. A convenient guide to design new CCK-A ligands

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Received 3 March 1992
Accepted 3 July 1992

Key words: Cholecystokinin; CCK-A antagonists; Field-fit; Comparative molecular field analysis

SUMMARY

Comparative molecular field analysis (CoMFA) has been used as a three-dimensional quantitative structure–activity relationship (QSAR) method to correlate the affinities of several antagonists towards CCK-A receptors with their steric and electrostatic fields. In this publication, we describe, for the first time, a field-fit operation as an alignment technique. These results could serve as a guide for the design of new non-peptide antagonists.

INTRODUCTION

Cholecystokinin (CCK) is a gastrointestinal hormone peptide [1] that also functions as a neurotransmitter or neuromodulator [2]. The actions of CCK are mediated by two CCK receptor subtypes termed CCK-A and CCK-B [3]. CCK-A receptors are localized in tissue types such as pancreas, gall bladder and colon. The effects of CCK on pancreatic secretion, gut motility and satiety have been well studied [4,5]. Several studies have suggested the potential therapeutic use of antagonists and/or agonists of cholecystokinin and gastrin for conditions such as pancreatitis, ulcer disease, irritable bowel syndrome and eating disorders, as well as for the regulation of pain and amelioration of certain tumors [6,7].

A few receptors have been crystallized and their detailed three-dimensional structures were determined by X-ray diffraction techniques. Recent successes in quantifying ligand–enzyme binding by using steric and electrostatic fields in a perturbational treatment [8] prompted us to investigate

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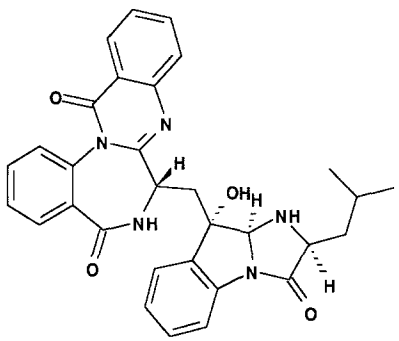
the possible use of CoMFA to describe the steric and electrostatic characteristics of CCK-A receptors. The aim of this study was, by using the CoMFA program, to map a three-dimensional quantitative structure–activity relationship by computing the measured-binding affinities with steric and electrostatic data of numerous antagonists previously described. We also tried to demonstrate that the CoMFA program could rapidly provide, with a limited quantity of molecules, a good idea of the structural and electrostatical requirements of CCK-A receptors and in this way could help in the design of new drugs.

One of the first known potent antagonists at CCK receptors is the natural product asperlicin **1** [9,10,11]. Study of the elements of the asperlicin structure that might be responsible for its modest CCK antagonist activity led to the discovery of the 3-[(2-indolylcarbony) amino]-1,4-benzodiazepine **2** (MK 329), which is the most potent CCK-A-selective antagonist known, with receptor affinity comparable to that of the native peptide itself [12].



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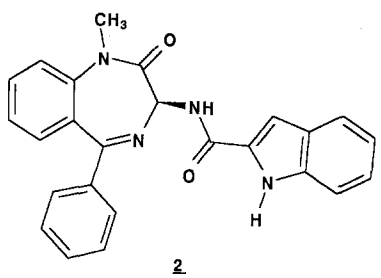
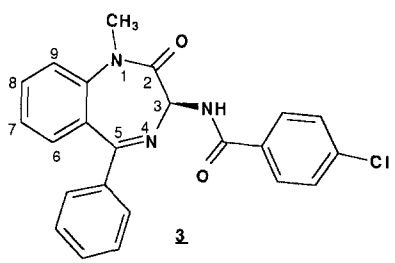


2

Further, the activity of **2** towards CCK-B receptors is over 1000-fold less than that towards CCK-A receptors. It must be pointed out that benzodiazepines with the indole ring replaced by an halogen-substituted phenyl ring (**3** for example) also possess an excellent affinity towards CCK-A



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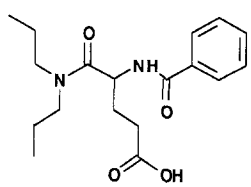


16

receptors [13]. These first results showed the importance of the benzodiazepine system, which must be considered as peptide-like in nature [14]. In consequence, in this study we selected 14 benzodiazepines (see Fig. 1) whose antagonist activities are described in several publications [12, 13,15].

Parallel to this study, the enhancement of the activity of proglumine **16** led to the creation of new glutamic acid derivatives which had good potency at CCK-A and CCK-B receptors [16]. Incorporating these molecules (see Fig. 2) in this study seemed to be interesting, assuming they would allow the exploration of new regions.

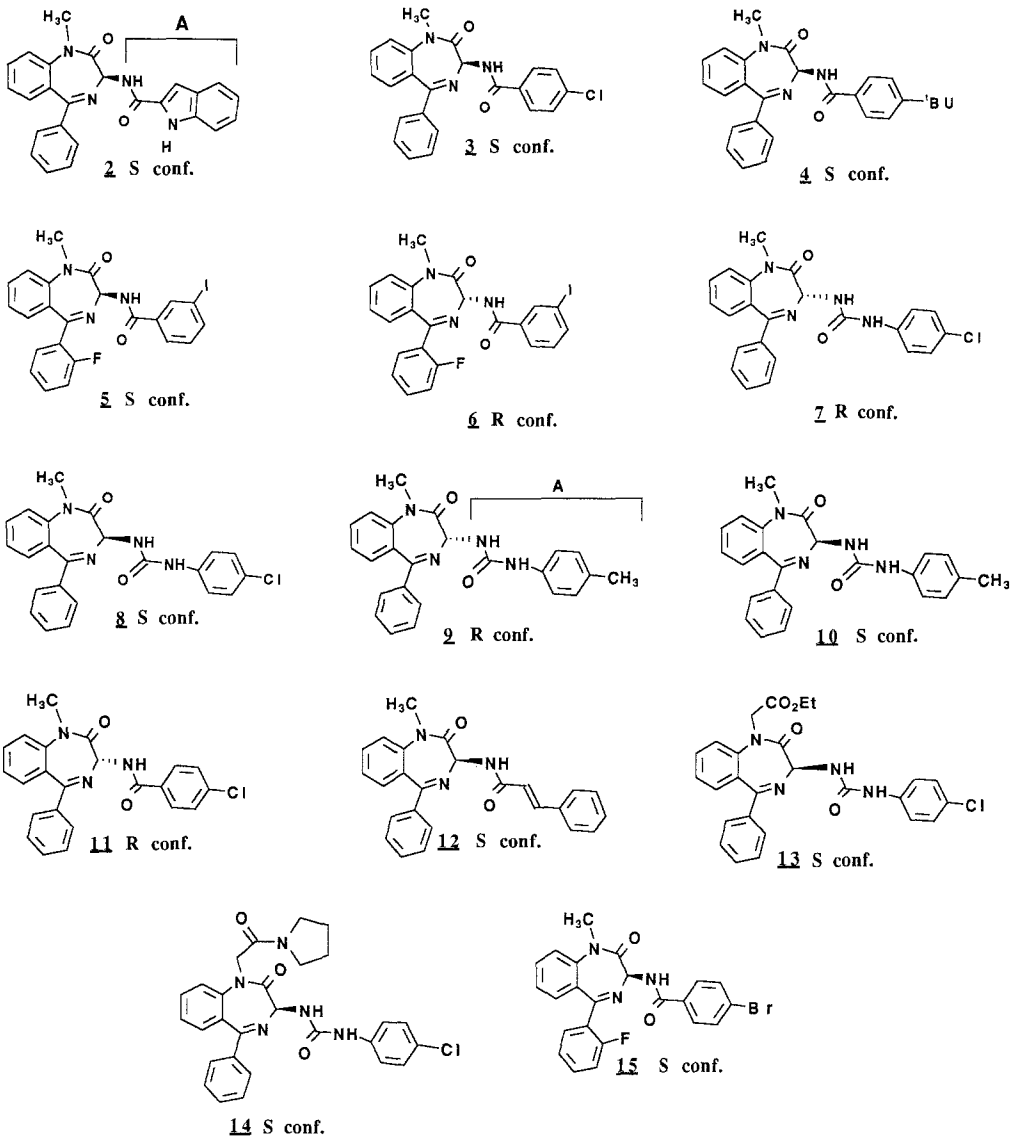


Fig. 1. The structures of the 14 benzodiazepine derivatives.

EXPERIMENTAL SECTION

1. Conformational analysis of antagonists to CCK-A receptors

Eighteen molecules (Figs. 1 and 2) were built with standard bond lengths and angles using the SYBYL 5.4 molecular modelling program [17]. The energy of each compound was then minimized (Maximin 2 with Simplex and Powell methods) with molecular mechanics [18,19] without consideration of electrostatic terms (Tripos force field).

On the basis of the minimized geometries, conformational analysis, leading to the determina-

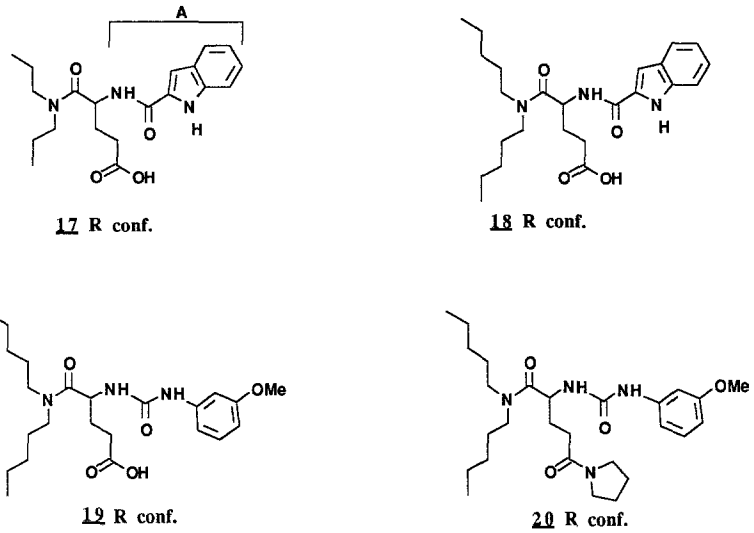


Fig. 2. The structures of the four glutamic acid derivatives

tion of the stables conformers for each compound, was carried out as follows:

a) The optimum conformations of the rings and the long chains (more than three rotatable bonds) were found by two methods:

1. The dynamic program [20]. The simulation was run under a constant temperature (800 K). The goal was to explore the conformational space available at this temperature and then to cool it down slowly to 300 K. The molecules were then settled into their natural conformations at this temperature. This procedure is known as simulated annealing.
2. The random search program [21]. This method is accomplished through a stochastic (Monte Carlo-like) approach (use a random element in exploring space). The stochastic searches generate starting geometries using random or pseudorandom variations of molecular geometry. The random method will cover all regions of conformational space, but only if the searches are unconstrained and allowed to run for a sufficiently long period of time. We only recorded the conformers with a total energy lower than the initial total energy. A boat conformation of the benzodiazepine rings was observed in all the cases.

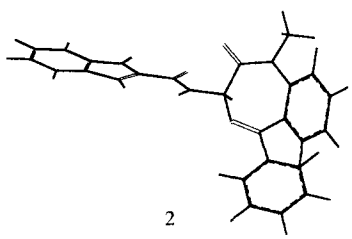
b) In the case of three or fewer rotatable bonds, the optimum conformations were determined by a systematic search with a rotation of these bonds from 0° to 360° and an increment of 5°. The resulting minimum energy structures from the conformational analysis were minimized once more with the Tripos force field without electrostatic terms. The conformations obtained for molecules **2**, **11**, **18** are presented in Fig. 3.

2. Comparative molecular field analysis (CoMFA)

The molecular fields were calculated with the CoMFA program [22,23] according to the following method:

First, a field-fit operation [22,23] was carried out comparing 18 molecules, one with another (Figs. 1 and 2). Three molecules were chosen as templates for three distinct structures (3S configu-

ration of benzodiazepines, 3R configuration of benzodiazepines and glutamic acid derivatives). For the glutamic acid derivatives, the molecule **18** (molecule close to **2** with an indole group and very active) was chosen as a template. For the benzodiazepine derivatives with a 3S configuration, molecule **2** (MK329, currently the most potent known CCK-A-selective antagonist) was chosen as a template and for the benzodiazepine derivatives with a 3R configuration, molecule **11** was chosen (it is the most active in this group). These field-fit operations were carried out on steric fields only. The steric field values were calculated at each lattice intersection, using a Tripos force field, as the sum of steric interactions between an artificial probe atom (Csp3), at that intersection, and each of the atoms in the target or template molecule (field-fit fields are identical to CoMFA fields). In the field-fit operation, the RMS difference in the sum of steric interaction energies, averaged across all lattice points between that of the molecule and that of the template molecule, is minimized with respect to the six rigid-body degrees of freedom (three rotational and three positional). Minimization is performed by the Simplex method [24] with step sizes such that individual atoms initially move no more than 0.2Å. Convergence occurs when successive function evalua-



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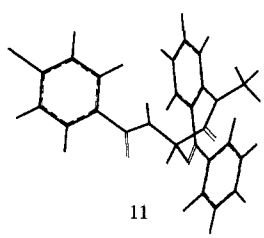

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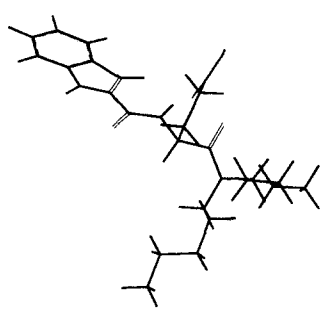

18

Fig. 3. Conformations of molecules **2**, **11**, **18**.

tions vary less than 1%. As with any minimization, field-fit is likely to be successful only if the final geometry is expected to closely resemble the starting geometry. The final energies were calculated with the field-fit turned off. At the end of this operation, these new conformers were compared with the most stable conformers to check that the differences in energy were less than 3 kcals/mol (probability of these conformers [25]). Then, the superimposition of these three distinct structures was chosen to be part A (Figs. 1 and 2) of each molecule.

It must be pointed out that before the field-fit operation we observed a very poor correlation between the molecular fields and the affinities (superimposition of part A):

Cross-validation groups = 9, components = 5:

run	comp 1	comp2	comp3	comp4	comp5
r^2	0.009	0.113	0.071	−0.013	0.046

We also tried other alignments (superimposition of benzodiazepine rings for instance) but only the field-fit gave a good correlation. This is the most crucial point of the whole method; the orientation rule determines the orientation of the corresponding molecular fields and, therefore, the whole comparative molecular field analysis. The atomic charges of these molecules were calculated by the Gasteiger and Marsili method [26].

The molecules were placed in a regular three-dimensional lattice and the molecular fields were calculated as follows. A probe atom with the Van der Waals properties of a sp3 carbon atom and a charge of +1 was placed at the various intersections of the regular three-dimensional lattice. The CoMFA grid spacing was 2 Å* in all three dimensions in the defined region [22]. The region was large enough to surround all the molecules in the analysis. The molecular steric and electrostatic fields were determined by the steric (Van der Waals) and electrostatic (Coulombic with 1/r dielectric) interactions between each of the compounds and the probe atoms. Wherever the probe atom experienced a steric repulsion greater than the 'cut-off' value (30 kcals/mol), the steric value was set at the 'cut-off' value and the electrostatic interaction was set at the mean of the other molecules' electrostatic interactions in the same location.

The biological activities were expressed as a logarithm of IC_{50}: i.e. the concentration (μM) of the compound required for half-maximal inhibition of the binding of [^{125}I] CCK-33 or [^{125}I] CCK-8 (+) to CCK receptors in rat pancreatic tissues [12,13,15,16].

The PLS methodology [27] was used in the QSAR calculations [28]. Cross-validation was used to obtain the optimum number of the components extracted in PLS. The final models were computed with the conventional r^2.

RESULTS

1. CoMFA of antagonists for CCK-A receptors

The data used in this analysis are presented in Table 1. The initial analyses were done with five

* Recently it was shown [22] that the effect of large changes in lattice spacings in the final CoMFA results is negligible. In this case, the cross-validated r^2 results suggest that, at least for steroids, the 2.0 Å spacing between lattice points was a good choice. We have run the CoMFA calculation with 1.0 Å spacing, but in our case we did not improve the quality of the results. The computing time for the calculation was very long with this spacing.

TABLE 1
BIOLOGICAL ACTIVITIES OF THE ANTAGONISTS TO CCK-A RECEPTORS [12, 13, 15, 16] AND ENERGIES OF THE CONFORMERS STUDIED

Compound	IC_{50} μM[a]	Log (IC_{50} μM)	Total energy[b][18,19] (Kcal/mol)
2	0.00019	−8.56	32.7
3	0.00039	−7.84	17.07
4	0.019	−3.96	21.1
5	0.00075	−7.19	18.7
6	0.015	−4.2	13.9
7	1.1	0.095	18.9
8	0.026	−3.64	20.7
9	0.280	−1.27	19.1
10	0.003	−5.80	21.8
11	0.0029	−5.84	13.8
12	0.0003	−8.11	17.8
13	0.22	−1.51	18.2
14	0.3	−1.20	27.7
15	0.0008	−7.13	17.2
17	1.1	0.095	27.8
18	0.0076	−4.87	28.8
19	0.0045	−5.40	18.1
20	0.12	−2.12	30.3

[a] The concentration (μM) of compound required for half-maximal inhibition of binding of [^{125}I] CCK-33 or [^{125}I] CCK-8 (+) binding to CCK receptors in rat pancreatic tissues.
[b] The total energies indicated here are only a measure of intramolecular strain relative to a hypothetical situation (Tripos force field). By themselves, these values have no physical meaning.

PLS components and nine cross-validation groups. This information was used to determine the optimum number of components. The analyses were then repeated without cross-validation and with boot-strapping procedures. The analysis of the CoMFA variables yielded the following:

Cross-validation groups = 9, components = 5, n = 18. (1)

r^2					
run	comp 1	comp 2	comp 3	comp 4	comp 5
	−0.014	0.207	0.424	0.413	0.451
F values					
run	comp 1	comp 2	comp 3	comp 4	comp 5
	0.000	0.626	1.769	1.687	1.969
Prob. of $r^2 = 0$					
run	comp 1	comp 2	comp 3	comp 4	comp 5
	1.000	0.683	0.194	0.212	0.156

The final CoMFA equation used for the predictions and CoMFA coefficient contour map cal-

culations is as follows:

Cross-validation groups = 0, components 5, $r^2 = 0.987$, F = 182, s = 0.387, n = 18. (2)

Cross-validation groups = 0, bootstrap samples = 9, components - 5,
$r^2 = 0.994 \pm 0.003$, s = 0.216 ± 0.0010, n = 18. (3)

Predicted activities and residuals obtained with Eq. 3 are in Table 2.

One of the advantages of the 3D-QSAR, produced by a comparative molecular field analysis, is the possibility of representing the equation as a three-dimensional 'coefficient contour' map. Figures 4 and 5 show views of such maps, for the steric and electrostatic aspects of CCK-A CoMFA QSARs.

2. Description of the three-dimensional 'coefficient contour' map

From the CoMFA plots of the steric and electrostatic coefficients, we were able to determine some fundamental aspects of CCK-A receptors. The field distribution histograms for the steric and electrostatic coefficients are presented in Figs. 6 and 7.

For this description of the map, three contour levels were graphed from the steric coefficients of CoMFA (Figs. 8, 13 and 15) and two contour levels were graphed from the electrostatic coefficients (Figs. 11 and 12). The superimposition of these two types of contour level is useful to define

TABLE 2
PREDICTED ACTIVITIES AND RESIDUAL VALUES FROM EQUATION 3

Compound	Real activities log ($IC_{50}\mu M$)	Predicted activities[a] log ($IC_{50}\mu M$)	Residual values[a]
2	−8.56	−8.10	−0.460
3	−7.84	−8.06	0.228
4	−3.96	−4.014	0.054
5	−7.19	−7.09	−0.10
6	−4.2	−4.39	0.19
7	0.095	0.383	−0.288
8	−3.64	−3.996	−0.356
9	−1.27	−0.796	−0.474
10	−5.80	−5.54	−0.255
11	−5.84	−5.81	0.023
12	−8.11	−8.07	−0.04
13	−1.51	−1.59	0.083
14	−1.20	−1.001	−0.199
15	−7.13	−7.10	−0.03
17	0.095	0.383	−0.288
18	−4.87	−5.02	0.151
19	−5.40	−5.3	−0.10
20	−2.12	−2.13	0.011

[a] Results obtained with the boot-strapping procedure.

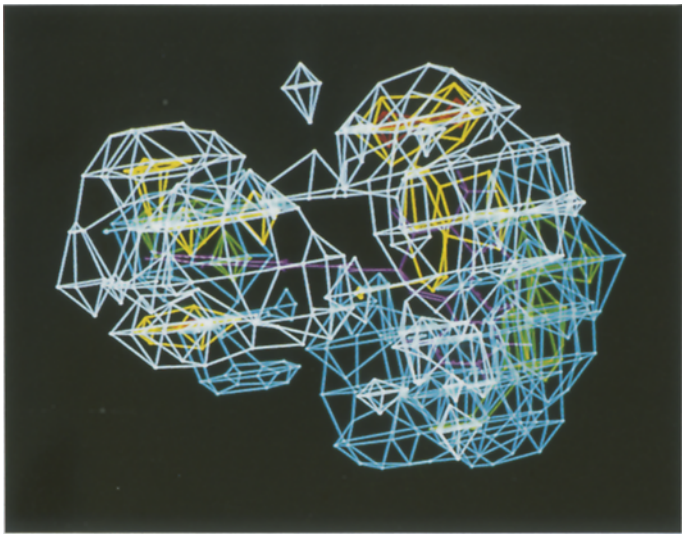

Fig. 4. Steric coefficient CoMFA map (Actual value – Auto mode). Field values are divided into six different ranges, colored from low to high as blue, green, cyan, white, yellow and red (see coefficient field histogram (Fig. 6)). In this map, the molecule **2** is in magenta.

the electrostatic character of the most important steric regions of the theoretical receptor. It must be said that CoMFA is only capable of revealing those structural requirements that can be deduced from existing test data. There may be other important features in regions where all the tested molecules are very similar.

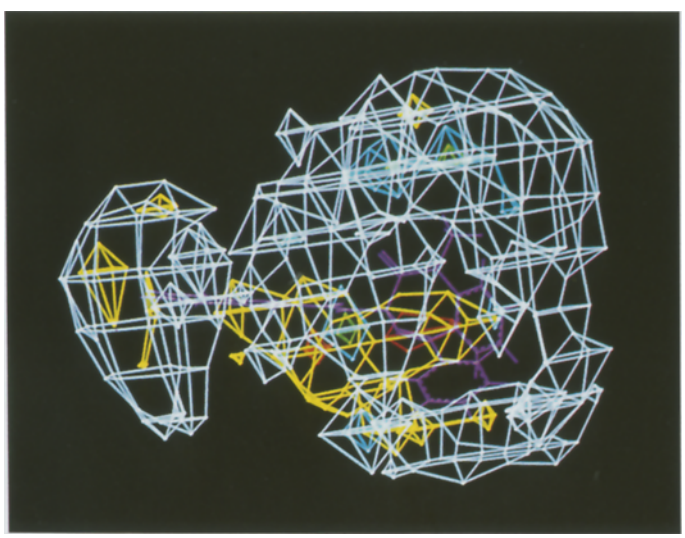

Fig. 5. Electrostatic coefficient CoMFA map (Actual value – Auto mode). Same representation as for the steric coefficient CoMFA map (see electrostatic field histogram (Fig. 7)).

Field Source type: PLS Coefficient
Field Energy type: Steric
Total number of points: 1728 Number of valid points: 1710
Field value range: -0.007 to 0.010
Field value stats: Average = -0.007; St.Dev. = 0.010
**** Field Histogram ****

-0.00749 :	5
-0.00552 :*	30
-0.00355 :	25
-0.00157 :**********	1532
0.000396:**	73
0.00237 :	26
0.00434 :	12
0.00631 :	5
0.00828 :	1
0.0103 :	1

Fig. 6. The field distribution histogram for the steric CoMFA.

2.1 Steric contour level of −0.005

The graph (Fig. 8) of this steric coefficient gave a good idea of the regions responsible for the nanomolar potency. We clearly saw three regions, named **B C, D**, centered on three points, named b, c, d, respectively. The respective positions of these points are described in Fig. 9.

The region **B** could be occupied by a halogen, such as chlorine, or by an aromatic ring. The regions **C** and **D** are occupied by aromatic rings.

Field Source type: PLS Coefficient
Field Energy type: Electrostatic
Total number of points: 1728 Number of valid points: 1707
Field value range: -0.070 to 0.054
Field value stats: Average = -0.070; St.Dev. = 0.054
**** Field Histogram ****

-0.0699 :	2
-0.0562 :	2
-0.0424 :	2
-0.0286 :	16
-0.0148 :**********	328
-0.00106:**********	1324
0.0127 :	23
0.0265 :	7
0.0403 :	2
0.054 :	1

Fig. 7. The field distribution histogram for the electrostatic CoMFA.

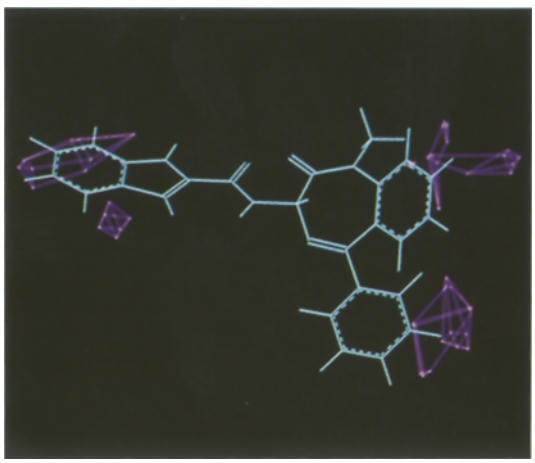

Fig. 8. Steric coefficient CoMFA map (User specified – contour level of −0.005). The white molecule **2** is bound to these three regions.

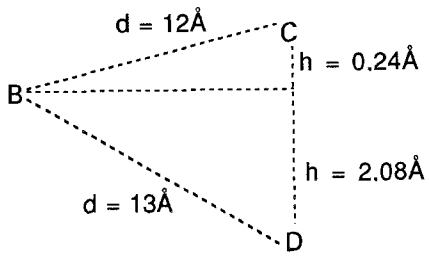

Fig. 9. Respective positions of points B, C and D.

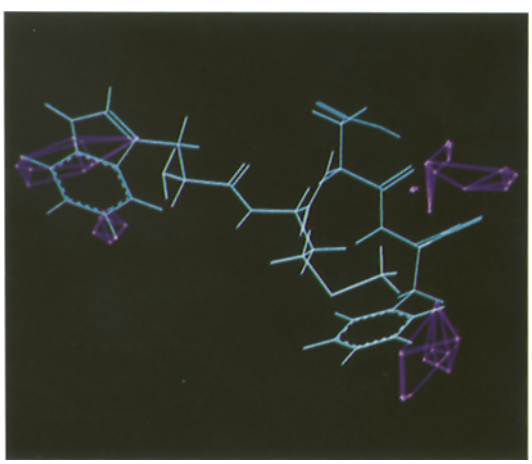

Fig. 10. CCK-4 peptide (in white) in the steric coefficient CoMFA map (User specified – contour level of −0.005).

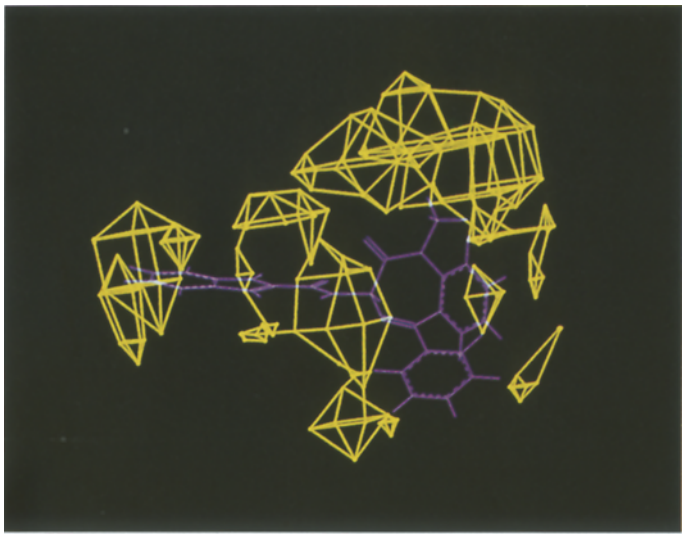

Fig. 11. Electrostatic coefficient CoMFA map (User specified – Contour level of −0.01).

2.1.1 Remark

The CCK-4 peptide (Trp-Met-Asp-Phe) was built from X-ray data [29]. It exhibits a low affinity for CCK-4 receptors. However, when we placed this molecule in the steric map, we observed (Fig. 10) that the indole group (Trp) and the phenyl group (Phe) fitted very well with the **B** and **D** regions, respectively. This result confirms the importance of these two regions. The low activity will be explained further by the strong interaction of CCK-4 with region **H** defined below.

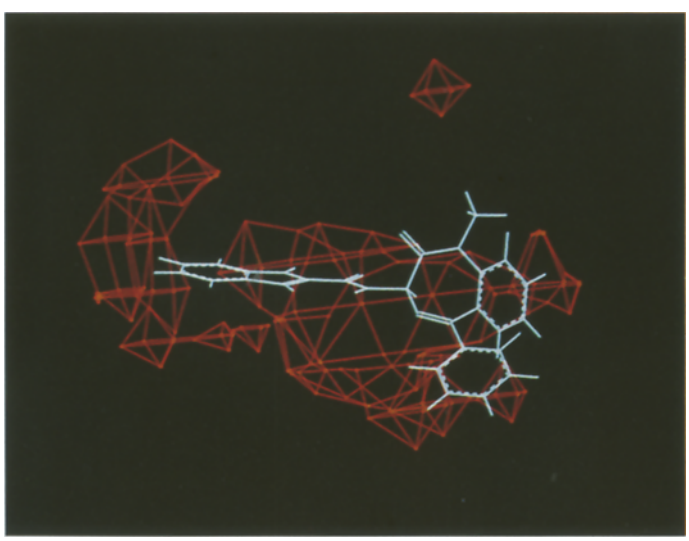

Fig. 12. Electrostatic coefficient CoMFA map (User specified – Contour level of 0.01).

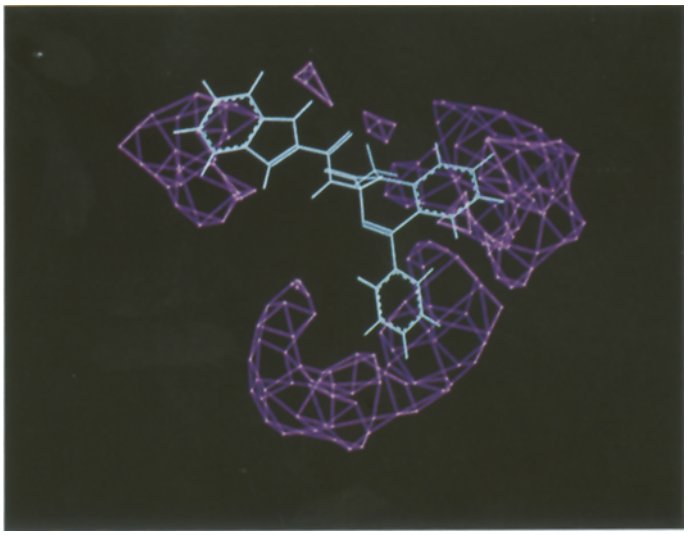

Fig. 13. Steric coefficient CoMFA map (User specified – Contour level of −0.002).

2.1.2 Electrostatic characteristics of these regions (electrostatic contour level of −0.01 and 0.01 (Figs. 11 and 12))

The center of the region **B** was found to be negative and its borders positive. The region **C** was positive, and the region **D** was neutral (neutral means no important electrostatic interaction) or lightly negative (contour level of −0.005).

2.2 Steric contour level of −0.002

With this graph (see Fig. 13), we could see an extension of the steric regions described above. This extension showed the possible steric interaction of the antagonists with other new regions named **E** and **F**, which could enhance the activities of some compounds (for example, comparisons between the activities of **17** and **18**).

The respective position of these new regions in comparison to **B** is represented as above in Fig. 14. This graph also shows a small region which underlines the importance of the methyl group on N^1 diazepine nitrogen.

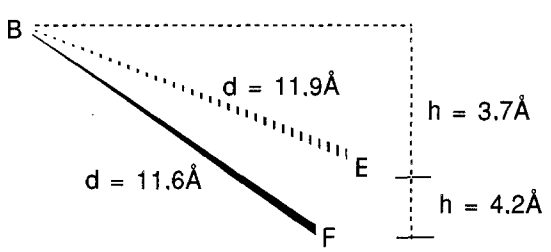

Fig. 14. Respective positions of points B, E and F.

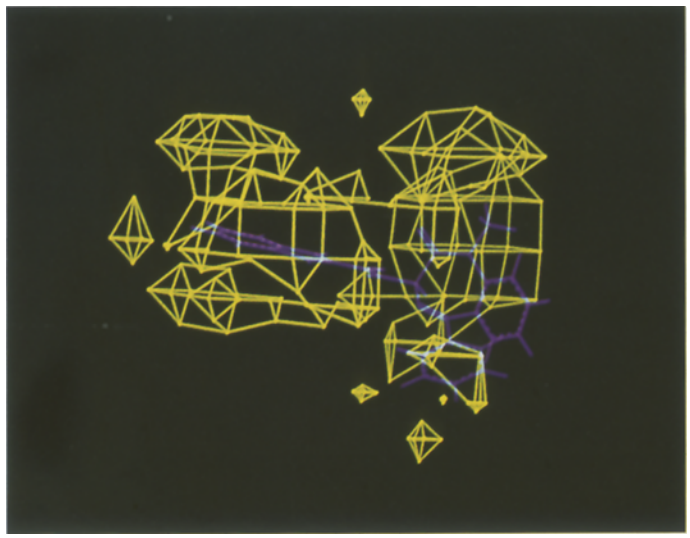

Fig. 15. Steric coefficient CoMFA map (User specified – Contour level of 0.002). The magenta molecule **2** is in fact weakly bound to these two regions.

2.2.1 Electrostatic characteristics of these new regions (electrostatic contour level of −0.01 and 0.01)

The regions **E** and **F** are neutral.

2.3 Steric contour level of 0.002

This graph (Fig. 15) represents the regions where all interactions decrease activity. In this case,

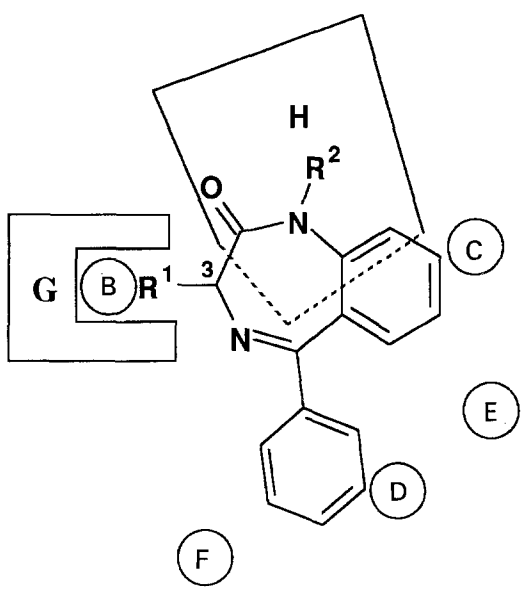

Fig. 16. Representation of regions G and H and approximative comparison with the position of regions B, C, D, E, F.

two important regions **G** around **B**, and **H** around the benzodiazepine carboxamide can be distinguished (Fig. 16). The region **H** explains the importance of the configuration at C^3, which conditions the position of the benzodiazepine ring system. The enantiomers with 3S configuration have their benzodiazepine ring systems situated outside the region **H**, enantiomers with a 3R configuration occupy an important part of region **H**, leading to a strong decrease in affinity. The position of this region can also explain the loss of affinity observed with a bulky substituent R^2 at N^1. Further, the influences of the length, the geometry and the bulk on R^1 are clearly defined by region **G**.

2.3.1 Electrostatic characteristics of regions **G** *and* **H** *(electrostatic contour level of −0.01 and 0.01)*

Region **H** is negative and region **G** is mostly positive; however region **G** possesses a negative character at its extremity.

CONCLUSION

This study shows that a relation can be established between the steric and electrostatic characteristics of CCK-A antagonists with measured affinity constants in vitro. The results clearly show the importance of the 3R or 3S configurations of the benzodiazepine system and correspond to those of previous papers, which have shown the importance of the chiral carbon atom at position 3 of the diazepine ring in terms of BDZ-receptor interactions [30]. This study could be enriched with new structures. Nevertheless, in its present configuration, this map can be used as a guide to predict the affinity of new potential ligands. Work on CCK-B receptors is now in progress.

ACKNOWLEDGEMENTS

Support from Adir & Cie is gratefully acknowledged. We thank Marie Paule Foloppe for her help.

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