Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 2775–2778

BIOORGANIC & MEDICINAL CHEMISTRY

Structure-Based 3-D-QSAR Analysis of Marine Indole Alkaloids

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Received 30 October 2001; accepted 29 January 2002

Abstract—A 3-D-QSAR study has been performed on these indole alkaloid derivatives to correlate their chemical structures with their observed antitumor activity against IGROV1. Due to the absence of information on their active mechanism, comparative molecular field analysis (CoMFA) has been applied. A model able to well correlate the antitumor activity with the chemical structures of mono and bis(indole) alkaloids **1**–**18** has been developed which is potentially helpful in the design of novel and more potent antitumor agents.

Introduction

Cancer remains a major threat to the public health. Natural products, especially marine indole alkaloids have been found to exhibit cytotoxic activity against human tumor cell lines.[1–6] In our previous publications, a series of eighteen marine mono(indole) or bis(indole) alkaloids analogues were reported and submitted to the National Cancer Institute for testing in vitro cytotoxicity against 60 tumor cell lines.[7–11] The majority of tested compounds were efficient antitumor agents showing GI_{50} values from 0.01 to 30.9 μM. Compound **8** was further screened by NCI for preliminary in vivo testing against tumor cells that were placed in the polyvinylidene fluoride (PVDF) hollow fibers of capsules and then implanted into the intraperitoneal or the subcutaneous compartment in mice. Compare computations were performed on the NCI screening data for all of the synthesized indole alkaloids, all of which were negative (Pearson correlation coefficients <0.6) against the NCI's Standard Agent database. This suggested that these compounds probably act a mechanism differing from those Standard Agents. Information on the structure requirements on marine indole alkaloids is still unknown. In a rational drug design, identification of the 3-D-QSAR analysis is one of the important steps, especially when the structure and properties of the bioreceptor remain unclear. In order to search for more potent analogues of indole alkaloids, 3-D-QSAR analyses have been performed on these 18 compounds by use of CoMFA method. Therefore, our aim in this paper is to elucidate the essential structural features for marine indole alkaloids.

Methods

Compounds and activities

The activity GI_{50} (the concentration of drug resulting in inhibition of cell growth to 50% of controls), equivalent to IC_{50} (the concentration of drug to reduce cell numbers to 50% of control cultures) values of the compounds, are cited from prior reports.[7–11] The structures of these 18 compounds and their activities value which are expressed as the PGI_{50} (the $-\log GI_{50}$) are listed in Table 1. Their antitumor activity was measured using IGROV1 tumor cell study. Compound **19** was excluded for the analysis because the exact activity of compound **19** was not determined ($GI_{50} < 0.01$ μM).

Computer modeling and structure alignment

The 3-D structures of 18 compounds were constructed using standard geometric parameters of molecular modeling software Sybyl 6.6. Atomic charges were calculated using the Gasteiger–Hückelprotocol. The search

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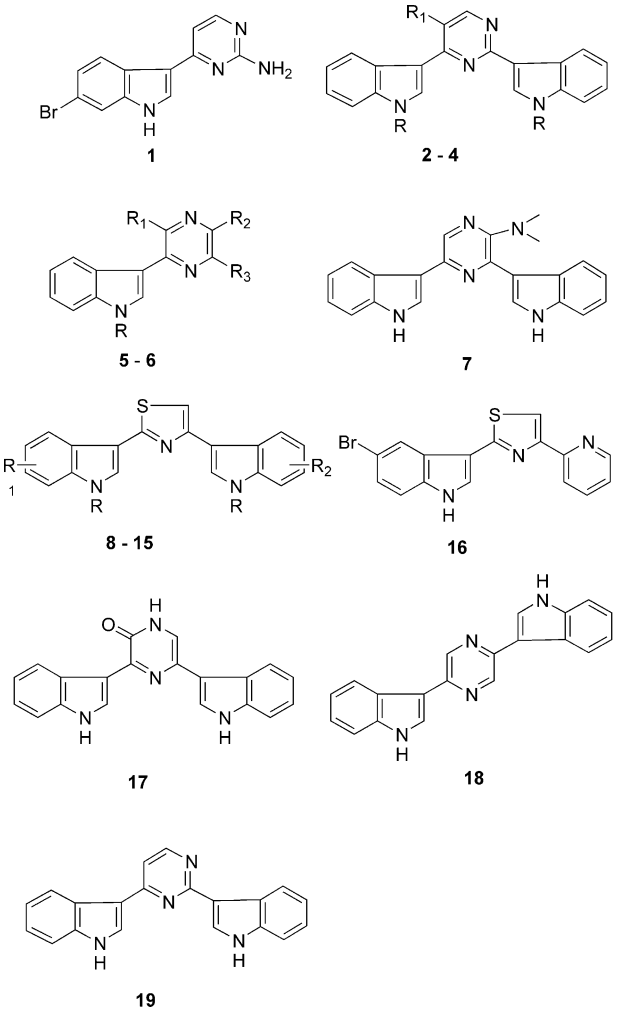
0968-0896/02/$ - see front matter
PII: S0968-0896(02)00057-3

Table 1. Compounds used in the CoMFA analysis and their antitumor activity



Compound	R	R_1	R_2	R_3	Activity (μM)	PGI_{50}
1	—	—	—	—	23.7	4.62
2	Ts	MeO		—	2.08	5.68
3	H	Me		—	1.14	5.94
4	H	MeO		—	1.86	5.73
5	Ts	NH_2	H	Br	1.37	5.86
6	H	H	NH_2	MeO	19.6	4.71
7	—	—	—	—	3.24	5.49
8	H	H	H		8.14	5.09
9	H	6-Br	H		30.5	4.52
10	H	6-Br	6-Br		14.4	4.84
11	H	5-Br	5-Br		1.70	5.77
12	H	6-MeO	6-Br		4.61	5.34
13	H	5-Br	6-Br		2.43	5.61
14	H	5-Br	H		1.40	5.85
15	Me				27.0	4.57
16					19.9	4.70
17					2.93	5.53
18	H				30.9	4.51

routine of Sybyl 6.6 was employed for the systematic conformational search for the side chain of the compounds. When fully minimized by the tripos force field, the optimized configurations of these compounds were obtained and then aligned using fit atom protocol in Sybyl. CoMFA were then used to perform 3-D-QSAR analysis for these 18 compounds. All molecular modeling and QSAR-related calculations were carried out on a Silicon Graphics O2 workstation with molecular modeling software package Sybyl 6.6.

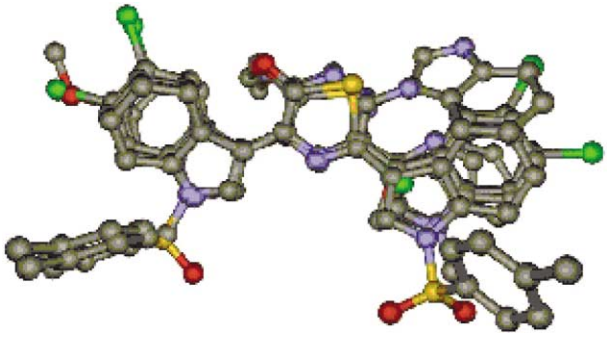


Figure 1. The alignment of the 17 indole alkaloid analogues.

PLS analysis

For the CoMFA calculation, steric and electronic field energies were calculated using a sp^3 carbon as the steric probe atom and a +1 charge for the electrostatic probe. Steric and electrostatic interactions were calculated using tripos force field with a distance-dependent dielectric constant. The cutoff was set to 30 kcal/mol. All models were investigated using full cross-validated particial least-squares (PLS) (leave one out) method with CoMFA standard options for scaling of variables. Minimum-sigma (column filtering) was set to 2.0 kcal/mol to improve the signal-to-noise ratio by omitting those lattice points whose energy variation is below this threshold (Fig. 1).

PLS analysis based on least-squares fit gave a correlation with a cross-validated q^2 of 0.584, with the maximum number of components four. Upon detailed examination of the residuals for this calculation it becomes apparent that compound **7** was at least partially responsible for the medium q^2. Omission with the compound **7** as an outlier from the aligned compounds and recalculation resulted in a much better q^2 of 0.674 at four components. After inspection of the structure of the compound **7**, we considered that the binding conformation of this compound may be different from the others because of the steric interference of the two methyl groups, which may have effect on the PLS results. The non-cross-validated PLS analysis of these 17 compounds was repeated with the optimum number of components, as determined by the cross-validated analysis, to give r^2 of 0.980. These values all indicate a good conventional statistical correlation and the CoMFA model has a fair predictive ability. The results of the analyses are shown in Table 2. The non-cross-validated predictions are shown in Table 3 and are graphically in Figure 2.

CoMFA contour map

The QSAR produced by CoMFA, with its hundreds or thousands of terms, was usually represented as a 3-D 'coefficient contour'. Colored polyhedra in the map represent those areas in 3-D space where changes in the field values of those compounds correlate strongly with concomitant change in activities. The CoMFA steric and electrostatic fields for the analysis based on alignments of these indole alkaloids are presented as contour plots in Figure 4. To aid in visualization the potent analogues **19** is also displayed in the maps. Figure 3 shows the atom ID of compound **19**.

Table 2. Summary of CoMFA results and statistics

Methods	Cross-validated		Conventional		
	q^2	Optimal no. of components	r^2	s	F
CoMFA	0.674	4	0.972	0.106	104.164

Table 3. Experimental activities arid predictive activities of CoMFA

Compd	Experimental activities	Predictive activities
1	4.62	4.52
2	5.68	5.67
3	5.94	5.90
4	5.73	5.70
5	5.86	5.95
6	4.71	4.78
8	5.09	5.04
9	4.52	4.73
10	4.84	4.74
11	5.77	5.79
12	5.34	5.32
13	5.61	5.72
14	5.85	5.66
15	4.57	4.58
16	4.70	4.67
17	5.53	5.59
18	4.51	4.54

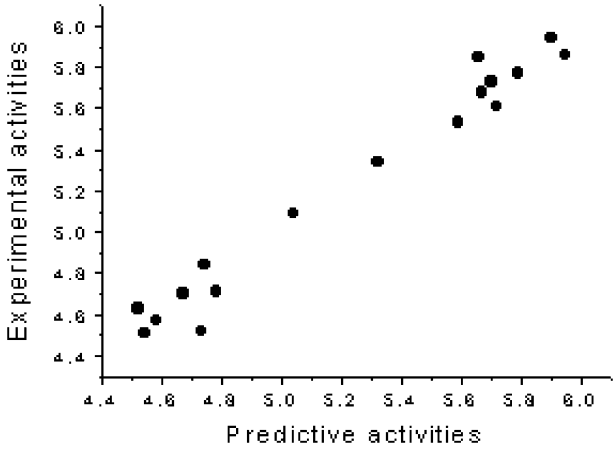


Figure 2. Experimental activities versus predictive values for the CoMFA model.

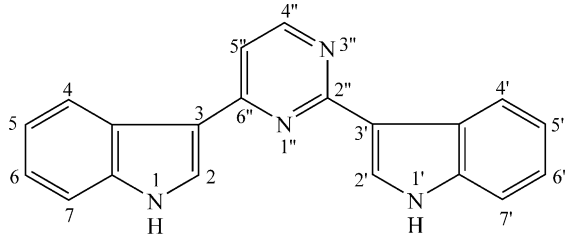


Figure 3. The atom ID of compound **19**.

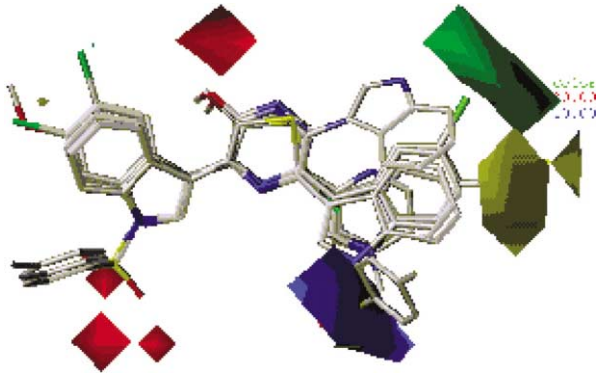


Figure 4. Contour maps from the CoMFA analysis in combination with all compounds. Hydrogen is omitted for clarity.

Results and Discussion

The CoMFA steric contour map indicates that areas in which molecular steric bulk might have a favorable (green) or disfavorable (yellow) effect on the activity of an analogue. As shown in Figure 4, the green contour surrounding the 5′-substituted group in indole reflects the increase in activity found by introducing steric bulk in this region. In contrast, a yellow contour at the end of the 6′-substituted group of these analogues indicates that steric occupancy with bulk groups in this region will decrease activity. This can well explained why the 5′and 5 substituted analogues **11** (1.70 μM) **13** (2.43 μM) and **14** (1.40 μM) are more potent than 6′ and 6 substituted compounds **9** (30.5 μM), **10** (14.4 μM) and **12** (4.61 μM).

The CoMFA electrostatic map indicates red contours in regions where high electron density might play a favorable role in activity, and blue contours in areas in which the negative charge is predicted to decrease activity. With the bis(indole) alkaloid series, there is only a major blue contour located around the nitrogen atom on the 1′ position. This indicates that more positive charge is favored in this region. In addition, some red polyhedrals focus on the nitrogen atoms of the 2′ and 5″ positions, which shows that negative interactions for this analogues are favored in this regions. This conclusion is well consistent with the experiments that introducing negative group such as hydroxyl and amino group in the 5″ position may increase the activities, such as **2** (2.08 μM), **4** (1.86 μM) and **17** (2.93 μM).

In summary, the CoMFA model described herein gave us very critical information about the three dimensional interaction of bis(indole) alkaloid derivatives with the receptor and proved a good predictive ability, and described the steric, electrostatic and hydrophobic requirements for recognition forces of the receptor site. This study offers structural insight to aid the development of novel and more potent antitumor agents.

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