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Original article

3D-QSAR studies on the inhibitors of AP-1 and NF-κB mediated transcriptional activation

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ABSTRACT

Comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) were performed on a series of 68 inhibitors of AP-1 and NF-κB mediated transcriptional activations. The CoMFA model produced statistically significant results with the cross-validated q^2 of 0.594 and the conventional correlation coefficient r^2 of 0.968. The best CoMSIA model was obtained by the combination use of steric, electrostatic, hydrogen-bond donor and acceptor fields. The corresponding q^2 and r^2 of CoMSIA model were 0.703 and 0.932, respectively. From the cross-validated results, it can be seen that the CoMSIA model has a better predictive ability than CoMFA model due to the importance of the hydrogen bonds for the activity of these inhibitors. The predictive abilities of the two models were further validated by a test set of 15 compounds. The models gave predicted correlation coefficient r^2_{pred} of 0.891 for CoMFA model and 0.810 for CoMSIA model. Based on the above results, we identified the key structural features that may help to design potent inhibitors with improved activities: (1) the NH linker at the position R_4 acts as important hydrogen-bond donor and any group on phenyl or 2-thienyl ring of R_1 substituent decreases inhibitory activity, (2)further structural modification of compound **50** on the phenyl ring of the quinazoline ring considering steric, electrostatic and hydrogen-bond acceptor properties will influence the inhibitory activity.

1. Introduction

In certain autoimmune diseases and chronic inflammatory states, the continuous activation of T-lymphocytes (T-cells) leads to a self-perpetuating destruction of normal tissues or organs [1]. This activation initiates a cascade of events that result in the over-production of certain transcription factors [2] and proinflammatory cytokines [3,4]. Two important transcription factors, nuclear factor-κ binding (NF-κB) and activator protein-1 (AP-1), control the production of many cytokines and are relevant to immunoinflammatory diseases [5–8]. Therefore, modulation of either one or both of these transcription factors should lead to suppression of cytokine levels and represent attractive targets for the prevention of immunoinflammatory diseases [9]. As these two transcription factors are regulated by distinct signaling pathway involving several proteins, many key factors involved in their activation pathway can be the targets for drug design [10]. There are many reports about inhibitors of NF-κB or AP-1 transcriptional activation [11–17], but very few compounds are known to inhibit both the AP-1 and NF-κB mediated transcriptional activation [10]. Recently, Palanki et al. designed a series of novel compounds (Table 1) and tested their activity in the transfected human Jurkat T-cells [18–22]. These compounds could interfere with cyclosporin-resistant CD28 co-stimulation as well as CD3-mediated signaling pathway [10], which were required both for the transcriptional activation of AP-1 and NF-κB [23]. In order to design more compounds with desired activity, it is very necessary and useful to investigate the quantitative structure–activity relationships (QSARs) of these known inhibitors that can both inhibit the transcriptional activation of AP-1 and NF-κB.

Nowadays, three-dimensional quantitative structure–activity relationship (3D-QSAR) approaches, such as comparative molecular field analysis (CoMFA) [24] and comparative molecular similarity analysis (CoMSIA) [25,26] have been widely used in drug design [27–29]. The contour maps obtained from these models could not only help us to understand the quantitative relationship between the molecular structures and their activity but also can help to design new potent inhibitors with desired activity. In this work, 3D-QSAR models were built based on a series inhibitors of AP-1 and NF-κB mediated transcriptional activation [22,23] using CoMFA and CoMSIA methods.

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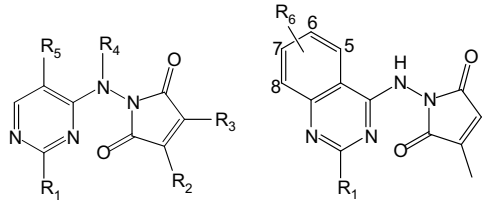
Table 1
Structures and biological activities of the compounds used in training and test sets.



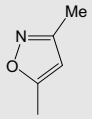
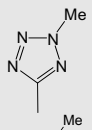
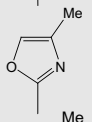
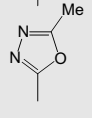
Compound	R_1	R_2	R_3	R_4	R_5	R_6	pIC_{50}
1[a]	CF_3	Me	H	H	CO_2Et		6.000
2	Me	Me	H	H	CO_2Et		4.796
3	Et	Me	H	H	CO_2Et		5.000
4[a]	*t*-Bu	Me	H	H	CO_2Et		6.000
5	SMe	Me	H	H	CO_2Et		6.699
6	Phenyl	Me	H	H	CO_2Et		7.000
7	2-Thienyl	Me	H	H	CO_2Et		7.699
8[a]	4-Pyridyl	Me	H	H	CO_2Et		5.222
9	2,6-Dichloro-4-Pyridyl	Me	H	H	CO_2Et		5.699
10	3-Quinolinyl	Me	H	H	CO_2Et		5.222
11	4-(2-Methyl)-thiazolyl	Me	H	H	CO_2Et		5.097
12	1-(3,5-Dimethyl)-pyrazolyl	Me	H	H	CO_2Et		5.000
13[a]	4-Methoxy-phenyl	Me	H	H	CO_2Et		6.046
14	3-Methoxy-phenyl	Me	H	H	CO_2Et		5.301
15	4-Fluoro-phenyl	Me	H	H	CO_2Et		6.155
16[a]	4-Chloro-phenyl	Me	H	H	CO_2Et		6.523
17	4-Trifluoro-methyl-phenyl	Me	H	H	CO_2Et		6.398
18[a]	3-Bromo-phenyl	Me	H	H	CO_2Et		6.155
19	3-Nitro-phenyl	Me	H	H	CO_2Et		5.155
20	3-Thienyl	Me	H	H	CO_2Et		7.000
21[a]	5-Methyl-2-thienyl	Me	H	H	CO_2Et		6.699
22	5-Chloro-2-thienyl	Me	H	H	CO_2Et		6.523
23	2-Benzo-thienyl	Me	H	H	CO_2Et		5.398
24	2-Furanoyl	Me	H	H	CO_2Et		6.699
25	Cyclopropyl	Me	H	H	CO_2Et		6.000
26	2-(Cyclo-hex-2-enyl-methyl)	Me	H	H	CO_2Et		5.699
27	3,5-Dichloro-phenyl	Me	H	H	CO_2Et		6.523
28[a]	Benzyl	Me	H	H	CO_2Et		5.155
29	Phenoxy	Me	H	H	CO_2Et		4.824
30	2-Phenyl-thio	Me	H	H	CO_2Et		6.000
31	2-Phenyl-sulfonyl	Me	H	H	CO_2Et		5.000
32	Phenyl	Me	H	Me	CO_2Et		5.699
33[a]	Phenyl	Me	H	Ac	CO_2Et		5.398
34	2-Thienyl	Me	H	Me	CO_2Et		6.000
35	4-Fluoro-phenyl	Me	H	Me	CO_2Et		5.523
36	Et	Me	H	Me	CO_2Et		5.000
37	CF_3	Me	Me	H	CO_2Et		5.000
38	CF_3	Phenyl	H	H	CO_2Et		4.699
39[a]	CF_3	H	H	H	CO_2Et		5.000
40	2-Thienyl	Me	H	H			6.523
41	2-Thienyl	Me	H	H	CN		5.301
42	2-Thienyl	Me	H	H			6.699
43[a]	2-Thienyl	Me	H	H			6.699
44	2-Thienyl	Me	H	H			6.523

Table 1 (*continued*)

Compound	R_1	R_2	R_3	R_4	R_5	R_6	pIC_{50}
45	2-Thienyl	Me	H	H			6.699
46	2-Thienyl						7.222
47	Phenyl						7.000
48[a]	CF_3						7.000
49	2-Thienyl					5-OMe	8.097
50	2-Thienyl					6-OMe	8.523
51[a]	2-Thienyl					7-OMe	7.699
52	2-Thienyl					8-OMe	7.301
53	2-Thienyl					6,7-Di-OMe	7.301
54	2-Thienyl					6,7,8-Tri-OMe	7.398
55	2-Thienyl					5-F	7.301
56	2-Thienyl					6-Cl	7.699
57[a]	2-Thienyl					5-Me	7.699
58	2-Thienyl					7-(*N*-morpholyl)	6.699
59	2-Thienyl					7-(NMe_2)	7.398
60	CF_3					5-OMe	8.000
61	CF_3					6-OMe	7.523
62	CF_3					5-Me	6.398
63	CF_3					6-SMe	7.097
64	CF_3					6-SOMe	6.000
65	CF_3					6-SO_2Me	5.046
66	CF_3					6-OH	7.000
67[a]	CF_3					7-(1-Piperidyl)	6.699
68	CF_3					7-(NMe_2)	7.699

[a] Test set compound.

2. Materials and methods

2.1. Data sets

In this study, the involved 68 compounds were taken from the works of Palanki et al. [22,23] and their structures were listed in Table 1. The in vitro inhibitory activity (IC_{50}) was transformed to negative logarithmic units marked as pIC_{50} in the CoMFA and CoMSIA analysis. The data set was divided into a training set (53 compounds) to generate the 3D-QSAR models and a test set (the rest 15 compounds) to evaluate the predictive ability of the developed models (shown in Table 1). In addition, the compounds in the test set were considered to cover the wide range of the activity in the whole data set (Fig. 1).

2.2. Molecular modeling and alignment

Molecular modeling and statistical analysis were performed using the molecular modeling package SYBYL 6.9 [30]. Energy minimization of the molecular structure was performed using the Powell gradient algorithm with the Tripos force field [31] and Gasteiger–Hückel charge [32]. The lowest energy conformation was used to perform 3D-QSAR calculations.

Because the bioactive conformations of these inhibitors were not known, the most potent compound **50** was chosen as the template for alignment. The reference atoms in the compound **50** for alignment are shown in Fig. 2A. Each compound was aligned to the template using the Align Database function due to its easy implementation and effectiveness. The aligned compounds are displayed in Fig. 2B.

2.3. CoMFA and CoMSIA models

The CoMFA descriptors, steric (Lennard–Jones 6–12 potential) and electrostatic (Coulomb potential) fields energies between the probe