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Original article

Synthesis, antifungal activities and 3D-QSAR study of *N*-(5-substituted-1,3,4-thiadiazol-2-yl)cyclopropanecarboxamides

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ABSTRACT

A series of cyclopropanecarboxamide were prepared and tested for antifungal activity *in vivo*. The preliminary bioassays indicated that some compounds are comparable to the commercial fungicides. To further explore the comprehensive structure–activity relationship on the basis of fungicidal activity data, comparative molecular field analysis (CoMFA) was performed, and a statistically reliable model with good predictive power ($r^2 = 0.8$, $q^2 = 0.516$) was achieved. Based on the CoMFA, compound **7p** was designed and synthesized, which was found to display a good antifungal activity (79.38%) as **7g** and **7h**.
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1. Introduction

Cyclopropane derivatives, often as bioactive compounds, have been studied for years. At the end of 1960s, some cyclopropane compounds, such as pyrethroids [1], were marketed as low toxic pesticides. Also some pharmaceuticals contain cyclopropane group, such as ciprofloxacin monohydrochloride [2]. So synthesis of broader spectrum and highly bioactive substituted cyclopropane compounds, especially heterocycle substituted ones which are bioactive themselves, becomes the hot spot in the agricultural and medicinal chemistry field. Additionally, sulfur and nitrogen linked heterocyclic compounds received considerable attention in recent times because of their pharmacological and pesticidal importance [3–6]. 2-Amino-5-substituted-1,3,4-thiadiazoles are very useful starting materials for the synthesis of various bioactive molecules and applied in medicine and agriculture [7–10] (Fig. 1).

In our previous paper, we reported the synthesis of some cyclopropane derivatives which target herbicidal target KARI (ketol-acid reductoisomerase) [11–13]. As continued our work, a series of cyclopropanecarboxamide compounds were prepared, and their fungicidal activities were tested. The preliminary biological tests showed that some compounds exhibit good activity to *Sclerotinia sclerotiorum* (Lib.) de Bary, *Corynespora cassiicola*, *Botrytis cinerea*, *Fusarium oxysporum f.* sp. *cucumerinum*, *Cercospora arachidicola*, and *Rhizoctonia solanii*. The structure–activity relationship was also studied.

2. Results and discussion

2.1. Chemistry

The cyclopropane-1,1-dicarboxylic acid, prepared from 1,2-dichlorethane and diethyl malonate was cyclized for 16 h at refluxing temperature. In order to optimize the reaction time, microwave assistant irradiation was applied which shortened the reaction time to 40 min. The cyclopropane-1,1-dicarboxylic acid was obtained from the hydrolysis of diethyl cyclopropane-1,1-dicarboxylate, but the yield of this step is low, about 50%. Cyclopropanecarbonyl chloride was prepared from the cyclopropane dicarboxylic acid and $SOCl_2$, without isolation further reacted with 5-substituted-2-amino-1,3,4-thiadizoles at room temperature [12] as shown in Scheme 1. Several procedures are available for the one-step synthesis of 2-amino-5-substituted-1,3,4-thiadiazoles

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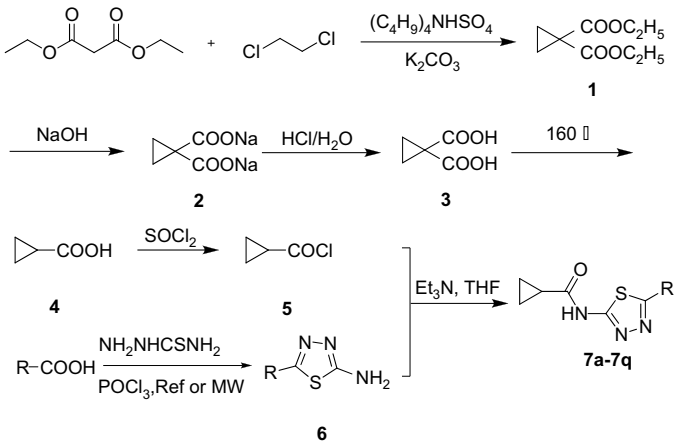

Scheme 1. The synthesis route of title compounds.

derivative. Yet the reaction of substituted aryl and alkyl acid with thiosemicarbazide in the presence of dehydrating agent $POCl_3$ affords a series of 2-amino-5-substituted-1,3,4-thiadiazoles under microwave irradiation.

2.2. Fungicidal activities

The *in vivo* fungicidal results of all of the compounds against *S. sclerotiorum* (Lib.) de Bary, *R. solanii*, *F. oxysporum*, *C. cassiicola*, and *B. cinerea* were listed in Table 1. As shown in Table 1, Compounds **7b** and **7l** were found to display good fungicidal activities against *R. solanii*, *F. oxysporum*, *C. cassiicola*, and *B. cinerea*, compounds **7a**, **7c–f**, **7m–o** did not display obvious fungicidal activities against *S. sclerotiorum* (Lib.) de Bary, *R. solanii*, *F. oxysporum*, *C. cassiicola*, and *B. cinerea*. Compound **7k** have fair to good fungicidal activity with the commercial fungicide pyrimethanil against *F. oxysporum*. Among them, these compounds displayed the highest fungicidal activity against *B. cinerea*. All compounds did not exhibit good fungicidal activity against *S. sclerotiorum* (Lib.) de Bary at the concentration of 500 μg mL^{-1}.

2.3. Quantitative structure–activity relationship (3D-QSAR)

Molecular modeling was performed using SYBYL 6.91 software (Tripos, Inc.) [14]. Each structure was fully geometry-optimized using a conjugate gradient procedure based on the TRIPOS force field and Gasteiger and Hückel charges. Because these compounds share a common skeleton, 10 atoms marked with an asterisk were used for rms-fitting onto the corresponding atoms of the template structure (Figs. 2 and 3).

CoMFA steric and electrostatic interaction fields were calculated at each lattice intersection on a regularly spaced grid of 2.0 Å. The grid pattern was generated automatically by the SYBYL/CoMFA routine, and an sp^3 carbon atom with a van der Waals radius of 1.52 Å and a +1.0 charge was used as the probe to calculate the steric (Lennard-Jones 6–12 potential) field energies and electrostatic (Coulombic potential) fields with a distance-dependent dielectric at each lattice point. Values of the steric and electrostatic fields were truncated at 30.0 kcal/mol. The CoMFA steric and electrostatic fields generated were scaled by the CoMFA-STD method in SYBYL. The electrostatic fields were ignored at the lattice points with maximal steric interactions. A partial least-squares (PLS) approach was used to derive the 3D-QSAR, in which the CoMFA descriptors were used as independent variables, and ED values were used as dependent variables. The data were analyzed by CoMFA method and fungicidal activity against *B. cinerea* data (% *I*) at 500 μg mL^{-1} being converted to $ED = \log(I/((100 - I) \times MW))$ [15] as a dependent variable. The observed and calculated activity values for all the compounds are shown in Table 2, and the plots of the predicted versus the actual activity values for all the compounds are shown in Fig. 5.

The cross-validation with the leave-one-out (LOO) option and the SAMPLS program, rather than column filtering, was carried out to obtain the optimal number of components to be used in the final analysis. After the optimal number of components was determined, a non-cross-validated analysis was performed without column filtering. The modeling capability (goodness of fit) was judged by the correlation coefficient squared, r^2, and the prediction capability (goodness of prediction) was indicated by the cross-validated r^2 (q^2). The 3D-QSAR models gave a good q^2 (cross-validated r^2) = 0.516 and r^2 (non-cross-validated r^2) = 0.800, two components. The compound **7i** was illustrated to explain the field contributions of different properties obtained from the CoMFA analyses. The steric and electrostatic contribution contour maps of CoMFA are plotted in Fig. 4. As shown in Fig. 4a, green displays 2-positions or 3-position of benzene ring where a bulky group would be favorable for higher antifungal activity.[2] In contrast, yellow indicates 5-position of benzene ring where a decrease in the bulk of the target molecules is favored. For example, some compounds bearing 2-methyl, 3-methyl of benzene ring, such as **7h**, and **7i**, displayed higher antifungal activity against *B. cinerea*. As shown in Fig. 4b, the title compounds bearing an electron-donating group at the 2-position, 3-position or 4-position of benzene ring can improve the antifungal activity, such as **7h** and **7i**.

According to the above CoMFA analysis, compound **7p** (R = *p*-OMe Ph) was designed, synthesized and tested its antifungal activity against *B. cinerea*. The results indicated that the inhibition of compound **7p** is 79.38%, whose inhibition is as good as **7g** and **7h**.

3. Conclusion

Using easily obtainable compounds **5**, we have prepared a new series of cyclopropanecarboxamide analogues **7** containing 1,3,4-thiadiazoles in good yields. Some of these compounds **7g**, **7h**, **7i**, **7p** exhibited excellent activity as displayed in Table 1. According to the CoMFA model, when R is substituted benzene groups, substituents at 2-position, 3-position or 4-position of the benzene ring are favored with electron-donating and bulky groups. Meanwhile, electron-withdrawing group is disfavored on these positions, such as NO_2 group.

4. Experimental section

4.1. Materials and methods

All reagents are analytical grade. Melting points were determined using a X-4 apparatus and were uncorrected. ^1H NMR spectra were measured on a Bruker AC-P500 instrument (300 MHz) using TMS as an internal standard and DMSO-d_6 as solvent. HRMS data was obtained on a FTICR-MS instrument (Ionspec 7.0T).

[2] For interpretation of the references to color in this text, the reader is referred to the web version of this article.

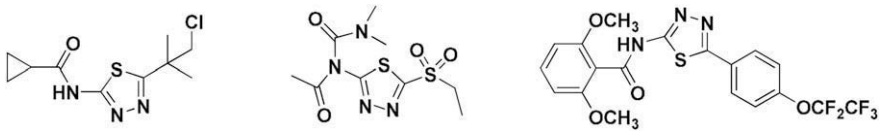

Fig. 1. The pesticides containing 1,3,4-thiadizole ring.

Table 1
The antifungal activities of compounds **7a**–**7q** *in vivo* at 500 μg mL^{-1}.

No.	*Sclerotinia sclerotiorum* (Lib.) de Bary	*Rhizoctonia solanii*	*Fusarium oxysporum*	*Corynespora cassiicola*	*Botrytis cinerea*
7a	24.00	37.00	17.00	22.52	83.73
7b	23.00	5.00	84.00	52.43	67.54
7c	51.70	23.00	10.00	49.66	32.09
7d	40.00	35.00	1.00	46.63	57.87
7e	47.70	11.00	20.00	29.30	41.98
7f	10.30	44.00	2.00	21.92	26.02
7g	24.00	9.00	16.00	17.43	80.53
7h	37.50	36.00	21.00	50.79	75.09
7i	20.00	39.00	11.00	8.38	90.67
7j	23.90	62.00	28.00	19.69	13.49
7k	25.50	44.00	91.00	21.45	35.11
7l	23.00	5.00	84.00	68.27	67.54
7m	43.06	16.00	13.00	18.56	30.27
7n	14.00	8.00	14.00	34.06	29.66
7o	5.00	0	0	15.73	38.76
7p	33.0	−9.00	12.00	33.26	79.38
7q	26.70	21.00	37.00	13.28	66.59
dimehachlon	96.70				
Jinggangmycin		92.10			
Thiophanate methyl			97.00		
Chlorothalonil				86.43	
Pyrimethanil					99.17

4.2. Synthesis

4.2.1. General procedure

4.2.1.1. Preparation of ***7a****.* The acid chloride was prepared according the reference [12]. Dropwised the acid chloride to substituted 2-amino-5-substituted-1,3,4-thiadiazoles (7.50 mmol), then vigorously stirred at ambient temperature for 4 h. The corresponding amide **7** precipitated immediately. The product was filtered, washed with THF, dried, and recrystallized from EtOH–H_2O to give the title compounds **7**.

7a: white crystal, yield 84.6%, m.p. 254–255 °C; ^{1}H NMR ($CDCl_3$) δ: 1.08–1.25 (m, 4H, cyclopropane–CH_2), 1.59 (s, 1H, Het-H), 2.29–2.35 (m, 1H, cyclopropane–CH), 8.78 (s, 1H, NH); FTICR-MS for $C_6H_7N_3OS$: found 168.0229, calcd. 168.0237.

7b: white crystal, yield 85.1%, m.p. > 300 °C; ^{1}H NMR ($CDCl_3$) δ: 1.05–1.19 (m, 4H, cyclopropane–CH_2), 1.55 (t, 3H, CH_3), 2.16–2.26 (m, 1H, cyclopropane–CH), 12.85 (s, 1H, NH); FTICR-MS for $C_7H_9N_3OS$: found 182.0395, calcd. 182.0394.

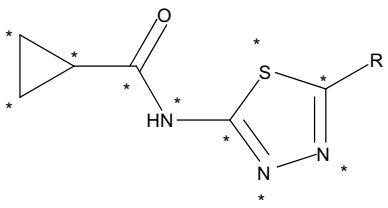

Fig. 2. The asterisk skeleton of title compounds.

7c: white crystal, yield 81.2%, m.p. 197–198 °C; ^{1}H NMR ($CDCl_3$) δ: 1.04–1.19 (m, 4H, cyclopropane–CH_2), 1.38 (t, 3H, CH_3), 2.21–2.26 (m, 1H, cyclopropane–CH), 3.02 (q, 2H, CH_2), 13.14 (s, 1H, NH); FTICR-MS for $C_8H_{11}N_3OS$: found 196.0556, calcd. 196.0550.

7d: white crystal, yield 84.5%, m.p. 175–176 °C; ^{1}H NMR ($CDCl_3$) δ: 1.02 (t, 3H, CH_3), 1.05–1.21 (m, 4H, cyclopropane–CH_2), 1.81 (m, 2H, CH_2), 2.25–2.31 (m, 1H, cyclopropane–CH), 2.98 (t, 2H, CH_2), 13.43 (s, 1H, NH); FTICR-MS for $C_9H_{13}N_3OS$: found 210.0704, calcd. 210.0707.

7e: white crystal, yield 84.5%, m.p. 127–128 °C; ^{1}H NMR ($CDCl_3$) δ: 0.92–0.96 (t, 3H, CH_3), 1.04–1.19 (m, 4H, cyclopropane–CH_2), 1.43 (m, 2H, CH_2), 1.56 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 2.19–2.22 (m, 1H, cyclopropane–CH), 13.00 (s, 1H, NH); FTICR-MS for $C_{10}H_{15}N_3OS$: found 210.0702, calcd. 210.0707.

7f: white crystal, yield 90.1%, m.p. 183–184 °C; ^{1}H NMR ($CDCl_3$) δ: 1.03–1.29 (m, 4H, cyclopropane–CH_2), 1.40 (d, 6H, CH_3), 2.26–2.28 (m, 1H, cyclopropane–CH), 3.33–3.40 (m, 1H, CH), 7.26–7.71 (m, 4H, Ar-H), 13.27 (s, 1H, NH); FTICR-MS for $C_9H_{13}N_3OS$: found 224.0865, calcd. 224.0863.

7g: white crystal, yield 86.5%, m.p. 249–251 °C; ^{1}H NMR ($CDCl_3$) δ: 1.11–1.26 (m, 4H, cyclopropane–CH_2), 2.35 (m, 1H, cyclopropane–CH), 7.47–7.92 (m, 5H, Ar-H), 13.33 (bs, 1H, NH); FTICR-MS for $C_{12}H_{11}N_3OS$: found 244.0550, calcd. 244.0550.

7h: white crystal, yield 82.6%, m.p. 216–218 °C; ^{1}H NMR ($CDCl_3$) δ: 1.04–1.25 (m, 4H, cyclopropane–CH_2), 2.39–2.45 (m, 1H, cyclopropane–CH), 2.56 (s, 3H, CH_3), 7.29–7.65 (m, 4H, Ar-H), 13.07 (bs, 1H, NH); FTICR-MS for $C_{13}H_{13}N_3OS$: found 260.0841, calcd. 260.0852.

7i: white crystal, yield 80.6%, m.p. 262–265 °C; ^{1}H NMR ($CDCl_3$) δ: 1.11–1.26 (m, 4H, cyclopropane–CH_2), 2.31–2.36 (m, 1H, cyclopropane–CH), 2.43 (d, 3H, CH3), 7.26–7.71 (m, 4H, Ar-H), 13.19 (s, 1H, NH); FTICR-MS for $C_{13}H_{13}N_3OS$: found 260.0841, calcd. 260.0852.

7j: white crystal, yield 84.6%, m.p. > 300 °C; ^{1}H NMR (DMSO) δ: 0.93–1.02 (m, 4H, cyclopropane–CH_2), 1.98–2.05 (m, 1H, cyclopropane–CH), 7.60 (d, J = 8.55 Hz, 2H, Ar-H), 7.95 (d, J = 8.54 Hz, 2H, Ar-H), 12.99 (bs, 1H, NH); FTICR-MS for $C_{12}H_{10}ClN_3OS$: found 280.0296, calcd. 280.0306.

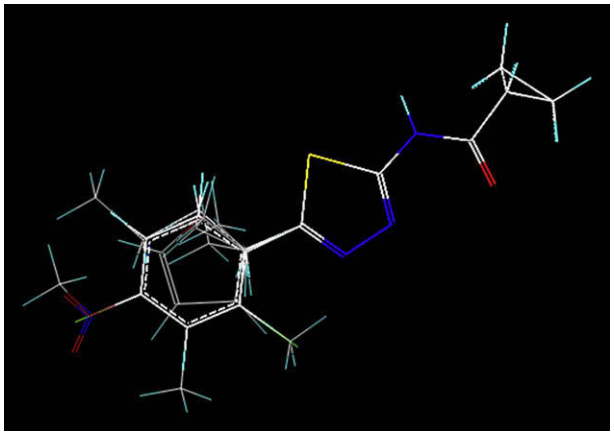

Fig. 3. Superposition modes of compounds.

Table 2
The structures, activities and total score of compounds.

No.	R^1	ED	ED″	Residue
7a	H	−1.51	−1.89	0.38
7b	Me	−1.94	−1.92	−0.02
7c	Et	−2.62	−2.23	−0.39
7d	Pr	−2.19	−2.27	0.08
7e	Iso-Pr	−2.46	−2.4	−0.06
7f	Bu	−2.8	−2.35	−0.45
7g	Ph	−1.77	−2.46	0.69
7h	*o*-Me Ph	−1.93	−1.9	−0.03
7i	*m*-Me Ph	−1.42	−1.54	0.12
7j	*p*-Cl Ph	−2.71	−2.75	0.04
7k	*o*-Cl Ph	−2.1	−2.13	0.03
7l	*o*-F Ph	−2.82	−2.46	−0.36
7m	*p*-NO_2 Ph	−2.83	−2.67	−0.16
7n	Py	−2.77	−2.48	−0.29
7o	Furan	−2.57	−2.57	0

ED = experimental value, ED″ = predictive value of ED.

7k: white crystal, yield 88.4%, m.p. 253–255 °C; ^{1}H NMR (DMSO) δ: 0.93–1.02 (m, 4H, cyclopropane–CH_2), 1.98–2.05 (m, 1H, cyclopropane–CH), 7.68 (d, J = 7.29 Hz, 2H, Ar-H), 8.08 (d, J = 7.73 Hz, 2H, Ar-H), 12.99 (bs, 1H, NH); FTICR-MS for $C_{12}H_{10}ClN_3OS$: found 280.0296, calcd. 280.0306.

7l: white crystal, yield 83.6%, m.p. > 300 °C; ^{1}H NMR (DMSO) δ: 0.73–1.16 (m, 4H, cyclopropane–CH_2), 1.94–2.03 (m, 1H, cyclopropane–CH), 7.39–7.69 (m, 3H, Ar-H), 8.25 (m, 1H, Ar-H), 13.00 (bs, 1H, NH); FTICR-MS for $C_{12}H_{10}FN_3OS$: found 264.0597, calcd. 264.0601.

7m: white crystal, yield 85.4%, m.p. > 300 °C; ^{1}H NMR (DMSO) δ: 0.94–0.99 (m, 4H, cyclopropane–CH_2), 1.98–2.02 (m, 1H, cyclopropane–CH), 8.18 (d, J = 8.83 Hz, 2H, Ar-H), 8.32 (d, J = 8.81 Hz, 2H, Ar-H), 13.11 (bs, 1H, NH); FTICR-MS for $C_{12}H_{10}N_4O_3S$: found 289.0392, calcd. 289.0401.

7n: white crystal, yield 89.7%, m.p. 238–239 °C; ^{1}H NMR (DMSO) δ: 0.92–0.98 (m, 4H, cyclopropane–CH_2), 1.98–2.01 (m, 1H, cyclopropane–CH), 7.54 (m, 1H, Py-H), 8.29 (m, 1H, Py-H), 8.66 (m, 1H, Py-H), 9.01 (m, 1H, Py-H), 13.03 (bs, 1H, NH); FTICR-MS for $C_{11}H_{10}N_4OS$: found 247.0637, calcd. 247.0648.

7o: white crystal, yield 86.5%, m.p. 272–273 °C; ^{1}H NMR ($CDCl_3$) δ: 1.01–1.25 (m, 4H, cyclopropane–CH_2), 2.24–2.26 (m, 1H, cyclopropane–CH), 6.56 (d, J = 1.68 Hz, 1H, furan-H), 7.03 (d, J = 3.43 Hz, 1H, furan-H), 7.58 (s, 1H, furan-H), 13.00 (s, 1H, NH); FTICR-MS for $C_{10}H_9N_3O_2S$: found 236.0483, calcd. 236.0488.

7p: white crystal, yield 84.5%, m.p. 264–267 °C; ^{1}H NMR (DMSO) δ: 0.95–0.99 (m, 4H, cyclopropane–CH_2), 1.98–2.02 (m, 1H, cyclopropane–CH), 3.84 (s, 3H, CH_3), 7.15 (d, 2H, Ar-H), 7.90 (d, 2H, Ar-H), 12.88 (bs, 1H, NH); FTICR-MS for $C_{13}H_{13}N_3O_2S$: found 276.0781, calcd. 276.0801.

7q: white crystal, yield 84.4%, m.p. 194–196 °C; ^{1}H NMR ($CDCl_3$) δ: 1.02–1.18 (m, 8H, cyclopropane–CH_2), 2.17–2.02 (m, 1H, cyclopropane–CH), 2.29–2.32 (m, 1H, cyclopropane–CH), 12.97 (s, 1H, NH); FTICR-MS for $C_9H_{11}N_3OS$: found 210.0690, calcd. 210.0696.

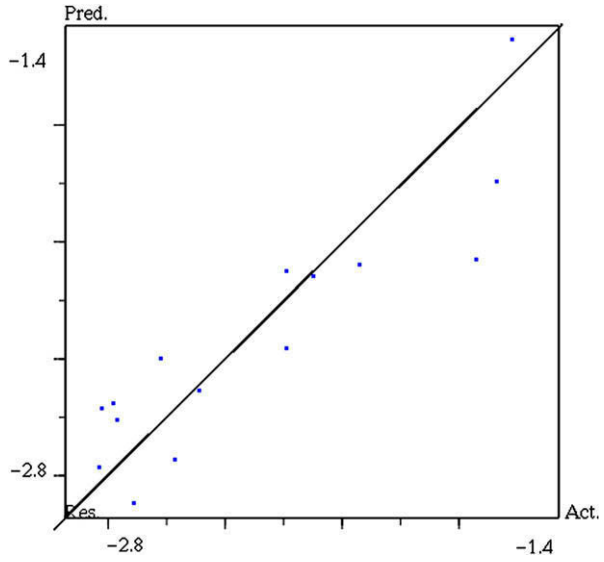

Fig. 5. CoMFA predicted as experimental *p*ED values.

4.3. Antifungal activity

Fungicidal activities of compounds of series **7** against *S. sclerotiorum* (Lib.) de Bary, *R. solanii*, *F. oxysporum*, *C. cassiicola*, and *B. cinerea* were evaluated using pot culture test according to reference [16]. The culture plates were cultivated at (24 ± 1) °C. Fungicidal activities of commercial fungicides dimehachlon, jinggangmycin, Thiophanate methyl, chlorothalonil, pyrimethanil as a control against above mentioned five fungi were evaluated at the same condition. The relative inhibition rate of the circle mycelium compared to blank assay was calculated via the following equation:

$$\text{Relative inhibition rate } (\%) = \frac{d_{ex} - d'_{ex}}{d_{ex}} \times 100\%$$

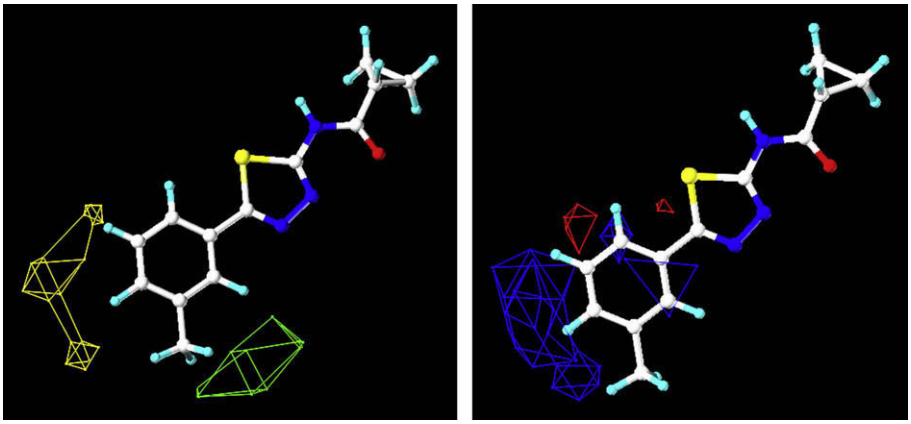

Fig. 4. Steric and electrostatic contribution contour maps of CoMFA.

where d_{ex} is the extended diameter of the circle mycelium during the blank assay; and d'_{ex} is the extended diameter of the circle mycelium during testing.

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