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Synthesis and QSAR studies of novel triazole compounds containing thioamide as potential antifungal agents

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Abstract—Eighteen novel triazole compounds containing thioamide were designed and synthesized. Their structures were confirmed by elemental analysis, ^{1}H NMR, IR, and MS. The title compounds exhibited certain antifungal activity. And the geometry structures of the title compounds were optimized by means of the density functional theory (DFT) method at B3LYP/6-31G* level. The quantitative structure–activity relationship (QSAR) of the title compounds was systematically investigated. A correlative equation between *FA* and DELH, *V* was well established by using the multiple linear regression (MLR).

1. Introduction

The fungicides containing triazole,[1,2] which have the most species and the quick development, are the germicides absorbed inside by plants. Basing on the high efficiency and the qualities of disinfecting and regulating the growth of plants widely, the kind of fungicides are concerned, such as triazolone, triazolol, and so on, which have become an important type of fungicides.[3–5] In addition, the fungicides containing triazole have high prevention and cure against fungi and have the function to increase the yield. The pyrrolamide and pyrrol thioacid amide containing thioacid amide have the protective effects on plants, which can protect the plants from the vegetable pathogenic microorganism.[6] *N*-(4-Pyridyl)-thioacid amide has the function to prevent and cure the harmful pest.

The thioacid amide groups were introduced to triazole molecule, which are favorable to increase the bio-activity and to generate new protective spectrum. So we have designed and synthesized 18 novel triazole compounds containing thioamide.

The series of new triazole compounds containing thioamide have been synthesized and the structures were characterized by IR analysis, elemental analysis, NMR analysis and MS analysis. There were little documents reporting about the QSAR studies of triazole compounds, and the QSAR studies of these species are favorable to the development of pesticides research fields, so in order to investigate the QSAR (quantitative structure–activity relationship) of this series of compounds deeply, we performed conformation analysis of the title compounds by using molecular mechanics. And the geometry structures of the 18 derivatives were optimized by means of the density functional theory (DFT) method. The QSAR equation of these compounds was established and discussed.

2. Results and discussion

2.1. Molecular descriptors and methods

Eighteen novel compounds were synthesized and the structures were characterized by IR analysis, elemental analysis, NMR analysis, and MS analysis, as shown in

Keywords: Triazole compounds; Thioamide; DFT; B3LYP/6-31G*; QSAR; SMR.
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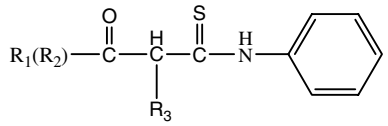


Figure 1. General structure of title compounds.

Table 1. Bioassay data of title compounds

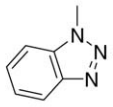
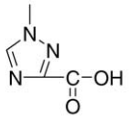
Compound	R_1/R_2	R_3	*FA*/50 μg/mL (%)
1	3,4-$Cl_2C_6H_3$		15.3
2	4-$MeOC_6H_4$		31.0
3	Ph–C_6H_4		20.5
4	2-F-4-MeC_6H_3		24.3
5	2-F-5-MeC_6H_3		20.3
6	C_6H_5		34.2
7	4-Ph–C_6H_4		45.5
8	4-$MeOC_6H_4$		34.7
9	4-ClC_6H_4		38.2
10	4-MeC_6H_4		30.3
11	4-$MeOC_6H_4$		27.3
12	C_6H_5		22.3
13	3,4-$Cl_2C_6H_3$		13.5
14	2,4-$Cl_2C_6H_3$		35.0
15	2-F-5-MeC_6H_3		13.7
16	4-FC_6H_4		9.1
17	2,4-$F_2C_6H_3$		9.1
18	2-F-4-MeC_6H_3		11.4

Figure 1 and Table 1. According to Disc paper method,[7] the antifungal trial was carried out against *wheat head blight*, the fungicidal activities (50 μg/ml) of title compounds for inhibition of *wheat head blight* (*FA*) are also listed in Table 1.

The three-dimensional structures of title compounds were built by the Chem3D package.[8] And the molecular mechanics MM2 force field containing MM2 section of Chem3D software was applied to search for lower energy conformations for each molecule[9] (step interval, 2.0 fs; frame interval, 10 fs; terminated step, 10000 steps; heating/cooling rate, 4.18 kJ/atom ps; target temperature, 300 K).

Basing on the lower energy conformations calculated by MM2 force field, the steady geometry structures of title compounds were optimized with DFT method at the hybrid functional B3LYP (Becke's three-parameter[10] functional employing the Lee, Yang, and Parr correlation functional[11]) and the medium-size basis set 6-31G* level. Through the frequency calculations for each optimized molecule at 298.15 K and 1 atm pressure, there were no imaginary frequencies appearing, which indicated that the stable structures optimized are reasonable and reliable. Then quantum-chemical descriptors were obtained as follows: the highest occupied molecular orbital energy (E_{HOMO}), the lowest unoccupied molecular orbital energy (E_{LUMO}), energy difference (DELH) between the frontier molecular orbitals (HOMO and LUMO) and dipole moments (μ). The quantum chemistry calculation was performed by Gaussian98 package on Pentium IV PC.

The molecular modeling system HYPERCHEM (Hypercube Inc., USA) software was further employed to calculate the following parameters from the energy-minimized structures: molecular volume (V), logarithm of *n*-octanol/water partition coefficient ($\log P$), molar refractivity (MR), and polarizability (P).

Balaban index (BIndx) and shape coefficient (Shpc) were calculated from the topology indices server of Chem3Dsoftware. The descriptors obtained on the ground are listed in Table 2.

2.2. Statistical analysis

Multiple linear regression (MLR) analysis and correlation analysis were carried out by the statistics software SPSS 13.0 version, a program developed by the Apache Software Foundation. It is necessary to establish QSAR

Table 2. Physicochemical and topological parameters of title compounds

Compound	E_{HOMO}	E_{LUMO}	DELH	μ	V	$\log P$	MR	P	Bindx	Shpc
1	−0.22613	−0.10716	0.11897	4.6489	989.38	4.28	99.94	40.50	495483	1.00
2	−0.21565	−0.08634	0.12931	5.8344	981.96	2.99	96.80	39.12	507617	0.86
3	−0.21791	−0.09568	0.12223	5.8348	1116.60	4.93	115.47	46.31	868948	0.88
4	−0.21850	−0.08967	0.12883	5.5884	964.05	3.70	92.89	38.39	490134	1.00
5	−0.21907	−0.09109	0.12798	5.3624	964.43	3.70	92.89	38.39	484989	0.83
6	−0.21269	−0.09082	0.12187	5.5922	1020.23	4.19	105.75	43.92	562814	0.83
7	−0.21112	−0.09196	0.11916	6.0597	1232.01	5.87	130.89	53.58	1295248	0.88
8	−0.20967	−0.08135	0.12832	5.3133	1096.53	3.93	112.22	46.39	800435	0.86
9	−0.21605	−0.09762	0.11843	5.2653	1065.43	4.70	110.56	45.85	671203	1.00
10	−0.21904	−0.08728	0.13176	5.9720	1072.63	4.65	110.79	45.75	671203	1.00
11	−0.21934	−0.08567	0.13367	4.6844	1061.05	3.52	97.98	41.68	852968	0.86
12	−0.22333	−0.09454	0.12879	4.6695	985.62	3.77	91.52	39.21	592682	0.83
13	−0.23139	−0.01761	0.21378	4.5747	1070.75	4.80	101.13	43.06	835474	1.00
14	−0.23001	−0.01620	0.21381	3.6666	1066.57	4.80	101.13	43.06	827582	1.00
15	−0.22340	−0.01233	0.21107	4.7695	1047.53	4.38	96.78	40.95	819975	0.83
16	−0.22552	−0.01470	0.21082	4.2605	993.18	3.91	91.74	39.12	711159	1.00
17	−0.22650	−0.01453	0.21197	3.9425	1001.16	4.05	91.95	39.03	827582	1.00
18	−0.22280	−0.01209	0.21071	5.0676	1045.99	4.38	96.78	40.95	827582	1.00

Table 3. Pearson correlation matrix of the parameters used in this study

	FA	E_{HOMO}	E_{LUMO}	DELH	μ	*V*	log *P*	MR	*P*	Bindx	Shpc
FA	1.000										
E_{HOMO}	0.680	1.000									
E_{LUMO}	−0.556	−0.653	1.000								
DELH	−0.599	−0.733	0.994	1.000							
μ	0.493	0.796	−0.662	−0.712	1.000						
V	0.519	0.343	−0.045	−0.091	0.308	1.000					
log *P*	0.278	−0.015	0.097	0.090	0.119	0.806	1.000				
MR	0.687	0.575	−0.376	−0.422	0.567	0.901	0.748	1.000			
P	0.678	0.506	−0.265	−0.312	0.461	0.943	0.794	0.983	1.000		
Bindx	0.218	0.079	0.303	0.260	−0.017	0.884	0.710	0.625	0.709	1.000	
Shpc	−0.269	−0.528	0.374	0.414	−0.352	−0.076	0.247	−0.112	−0.085	−0.008	1.000

equation where the numbers of compounds exceed three times that of selected parameters.

In MLR analysis, the descriptors in the regression equation must be independent and the correlation of each one of the descriptors with each other and with *FA* was calculated and are presented by a Pearson correlation matrix in Table 3. To eliminate the inter-correlated parameters and minimize the information overlap in the models, the predictor variables with lower inter-correlation ($|r| < 0.5$) were only considered.[12] The equations containing the collinear descriptors were removed and the remaining multi-linear equations were established between *FA* and structural parameters following the forms: $FA = b_0 + b_1D_1 + b_2D_2 + \cdots + b_nD_n$, where *FA* represents the fungicidal activities of title compounds, $D_1, D_2, \ldots, D_n$ are the descriptors, the intercept (b_0) and the regression coefficients of the descriptors ($b_1, b_2, \ldots, b_n$) were determined by using the least squares method, and *n* is the number of the descriptors.

In the preliminary analysis by analyzing the correlation matrix (Table 3), it is observed that *FA* had the better relation with MR ($r = 0.687$), so the mono-parametric Eq. 1 was obtained with MR as independent and *FA* as dependent parameter.

2.3. Mono-parametric model

$$FA = -48.749(\pm 19.397) + 0.715(\pm 0.189)\mathrm{MR}$$
$$n = 18, \quad r = 0.687, \quad R^2_{\mathrm{A}} = 0.439, \quad \mathrm{SEE} = 8.17881,$$
$$F = 14.287. \qquad (1)$$

Here and hereafter, the figure within the parentheses indicates the standard error of each regression coefficient and the constant in the resultant equations at 95% confidence interval. Eq. 1 shows a better correlation coefficient ($r = 0.687$), and explained 43.9% of the variance in *FA* data only. So this model did not give an enough explanation for the relationship between *FA* and structure parameters.

The statistical quality[13] of the regression equations was gauged by parameters like correlation coefficient (*r*) or squared correlation coefficient (r^2), explained variance (R^2_{A}, i.e., adjusted R^2), standard error of estimate (SEE), and variance ratio (*F*).[14–16] The better regression models were selected on the basis of the higher *r*, *F* value (a statistic of assessing the overall significance) and the lower SEE.

Table 4. Regression and statistics parameters of bi-parametric models

Eq. no.	Parameters used	*r*	r^2	SEE	*F*
2	E_{HOMO}, *V*	0.745	0.555	7.75201	9.357
3	E_{HOMO}, log *P*	0.739	0.546	7.83341	9.008
4	E_{HOMO}, Bindx	0.700	0.490	8.30310	7.193
5	E_{LUMO}, *V*	0.744	0.554	7.76549	9.298
6	E_{LUMO}, log *P*	0.648	0.420	8.85025	5.433
7	E_{LUMO}, Bindx	0.688	0.473	8.43804	6.727
8	DELH, *V*	0.759	0.576	7.56346	10.208
9	DELH, log *P*	0.685	0.399	8.46505	6.637
10	DELH, Bindx	0.713	0.508	8.14896	7.755
11	μ, *V*	0.626	0.392	9.06222	4.835
12	μ, log *P*	0.540	0.292	9.78214	3.086
13	μ, Bindx	0.542	0.294	9.76711	3.119
14	E_{LUMO}, MR	0.758	0.574	7.58112	10.125
15	E_{LUMO}, *P*	0.782	0.611	7.24494	11.799
16	DELH, MR	0.767	0.588	7.46325	10.686
17	DELH, *P*	0.791	0.625	7.11316	12.521
18	E_{HOMO}, Shpc	0.559	0.313	9.63339	3.416
19	DELH, Shpc	0.559	0.359	9.30484	4.200
20	μ, Shpc	0.503	0.253	10.04501	2.539
21	*V*, Shpc	0.568	0.322	9.56616	3.569
22	log *P*, Shpc	0.446	0.199	10.40428	1.858
23	MR, Shpc	0.713	0.509	8.14312	7.776
24	*P*, Shpc	0.710	0.504	8.18140	7.634
25	Bindx, Shpc	0.345	0.119	10.90999	1.010

Through different combinations of two parameters which have no inter-correlation with each other, the series of equations were obtained, and the regression and statistical parameters are exhibited in Table 4. According to *r*, the best equation 8 was obtained.

2.4. Bi-parametric models

$$FA = -34.346(\pm 30.519) - 144.331(\pm 43.791)\mathrm{DELH}$$
$$+ 0.078(\pm 0.028)V \quad n = 18, \quad r = 0.759,$$
$$R^2_{\mathrm{A}} = 0.520, \quad \mathrm{SEE} = 7.56346, \quad F = 10.208. \qquad (8)$$

This bivariate combination of DELH and V showed good statistics ($r = 0.759$) and explained up to 52% of the variance in FA data. The SEE values were decreased

Table 5. Regression and statistics parameters of tri-parametric models

Model no.	Parameters used	r	r^2	SEE	F
26	E_{LUMO}, V, Shpc	0.745	0.555	8.02778	5.812
27	DELH, V, Shpc	0.759	0.576	7.82883	6.352
28	μ, log P, Shpc	0.637	0.405	9.27649	3.181
29	E_{LUMO}, log P, Shpc	0.664	0.441	8.99237	3.685
30	DELH, log P, Shpc	0.693	0.480	8.67421	4.309
31	μ, log P, Shpc	0.569	0.324	9.89321	2.233
32	E_{LUMO}, P, Shpc	0.785	0.617	7.44545	7.516
33	DELH, P, Shpc	0.792	0.628	7.33837	7.874
34	μ, P, Shpc	0.723	0.523	8.30684	5.120
35	E_{LUMO}, Bindx, Shpc	0.688	0.473	8.73337	4.188
36	DELH, Bindx, Shpc	0.714	0.509	8.42826	4.840
37	μ, Bindx, Shpc	0.551	0.303	10.04035	2.032
38	E_{LUMO}, MR, Shpc	0.762	0.581	7.78319	6.481
39	DELH, MR, Shpc	0.769	0.591	7.69149	6.749

to the extent as compared to Eq. 1. However, F value was 10.208 only. So there existed certain outliers which may be acting through different mechanism of action.

Different combinations of three-parameters which have no inter-correlation with each other were also discussed, and the regression parameters and statistics are shown in Table 5. According to r, the best equation 33 was obtained.

2.5. Tri-parametric models

$$FA = -16.596(\pm 30.127) - 105.186(\pm 48.809)\mathrm{DELH} + 1.509(\pm 0.474)P - 7.670(\pm 25.092)\mathrm{Shpc}$$
$$n = 18, \quad r = 0.792, \quad R^2_A = 0.548, \quad \mathrm{SEE} = 7.33837, \quad F = 7.874. \tag{33}$$

In view of the Shpc being significantly smaller than its standard deviation in the tri-parametric equation 33, the model had to be discarded. Such models are not allowed statistically.

According to Eq. 8, the compounds **1**, **3**, **14** exhibited the worse residuals between observed and predicted FA, −9.87633, −14.06744, and 17.52856, respectively. As indicated the compounds **1**, **3**, **14** may be acting through different mechanism to FA. After deletion of compounds **1**, **3**, and **14** from Eq. 8, Eq. 40 was obtained, and the value of correlation coefficient r was increased to 0.969, which exhibited excellent correlation between structure descriptors (DELH, V) and FA. Addition, the explained variance reached 93.9% and there was the lowest SEE (3.03495). So the best model Eq. 40 was obtained, where DC is deleted compound which behaves as outlier.

$$FA = -17.326(\pm 13.246) - 221.495(\pm 19.656)\mathrm{DELH} + 0.073(\pm 0.012)V$$
$$n = 15, \quad \mathrm{DC} = \mathbf{1}, \mathbf{3}, \mathbf{14} \quad r = 0.969, \quad R^2_A = 0.939, \quad \mathrm{SEE} = 3.03495, \quad F = 92.591. \tag{40}$$

The experimental, predicted FA by Eq. 40 and residual values are listed in Table 6 and the plot of observed FA versus predicted FA based on Eq. 40 is shown in Figure 2. Obviously, there is a close activity value.

Table 6. Observed, predicted FA and residual based on Eq. 40

Compound	Observed	Predicted	Residual
2	31.0	25.7851	5.21487
4	24.3	24.5827	−.28275
5	20.3	24.7988	−4.49879
6	34.2	30.2295	3.97052
7	45.5	46.3047	−.80468
8	34.7	34.3761	.32386
9	38.2	34.2942	3.90578
10	30.3	31.8678	−1.56780
11	27.3	30.5986	−3.29859
12	22.3	26.1677	−3.86775
13	13.5	13.5634	−.06339
15	13.7	12.4669	1.23306
16	9.1	8.5509	.54909
17	9.1	8.8793	.22071
18	11.4	12.4341	−1.03415

Eq. 40 gave important information at the molecular level as to the structure–activity relationship of this type of compounds. The negative coefficient of DELH in the equation showed that lower value corresponded to the greater FA. As it is indicated in Table 2, the least value of DELH for compounds **7** and **9**, which have the highest activity. On the contrary, the greater value of DELH for compound **13** was corresponded to the smaller FA. DELH represented energy difference between the frontier molecular orbitals. From the Pearson correlation matrix in Table 3, there was best correlation between DELH and E_{LUMO} ($r = 0.994$) and the plot of DELH versus E_{LUMO} of title compounds is shown in Figure 3, which indicated that E_{LUMO} had the greatest contributions to DELH. The smaller DELH, the lower E_{LUMO}. From the molecular orbital theory of chemical reactivity, LUMO, as an electron acceptor, represents the ability to obtain electron. And transition states are formed during interaction between LUMO (electron acceptor) and HOMO (electron donor) of the reacting

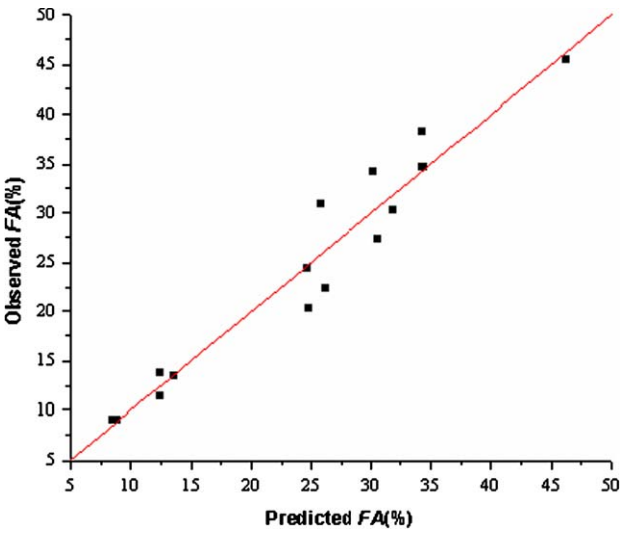


Figure 2. Plot of observed FA versus predicted FA based on Eq. 40.

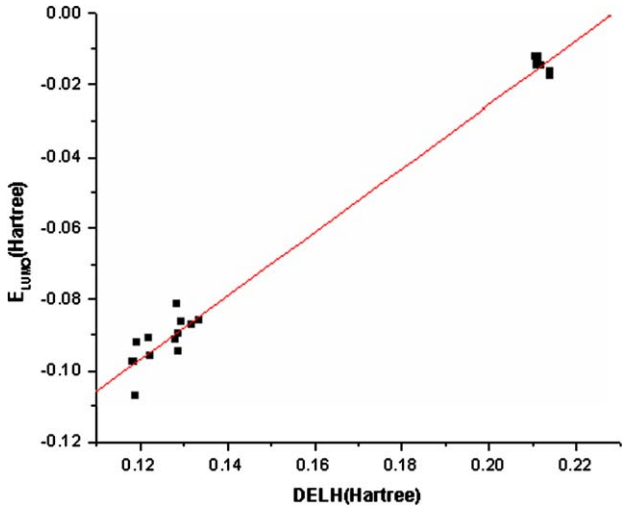


Figure 3. Plot of DELH versus E_{LUMO} of title compounds.

compound.[17] It becomes easier to obtain electron with the decreasing of E_{LUMO}, which led to the higher activities of molecule. The LUMO orbital energies and the 2D contours of the molecular electrostatic potential of the highest *FA* compounds **7** and **9** are represented in Figures 4 and 5, respectively. Through Figure 4, it is shown that the main activity sites of compounds **7** and **9** were carbonyl group and parts of benzene ring connected to C=O group directly. Besides, the higher electrostatic potentials are revealed around carbonyl group from Figure 5.

In addition, *V* was the other important factor to affect *FA* of title compounds. In germicide molecules, the substituting groups or structure units regarded as toxiphore had the main bactericidal effect, and the groups regarded as shaped charges can osmose the cell membrane of organism to prompt the effect of toxiphore. The difference of substituting groups or structure units of compounds led to the variance of molecule volume. That is, the variety of *V* had direct relations with the effect of toxiphore, which further affected *FA*. According to Eq. 40, the positive coefficient of *V* indicated an overall increase in size of molecules for improved *FA* of molecule. The greater *V* of title compounds was favorable to osmose the cell membrane of organism to enhance the effect of toxiphore, which increased the *FA* of the title compounds.

3. Conclusions

In summary, 18 novel triazole compounds were synthesized and confirmed by elemental analysis, ^{1}H NMR, IR, and MS. The title compounds exhibited certain antifungal activity. A correlative equation 40 between *FA* and DELH, *V* was well established by using the multiple linear regression (MLR). *FA* of the title compounds had negative correlative to DELH and had positive correlative to *V*.

4. Experimental

4.1. Synthesis and characterization of title compounds

The synthetic route of title compounds is shown in Figure 6.

4.1.1. Preparation of intermediates I.[18] According to the reported document,[18] seven intermediates (I) were obtained by the reaction between the seven kinds of

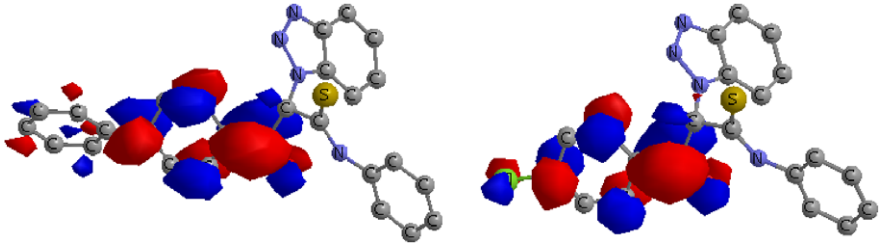


Figure 4. The LUMO orbital energy of compounds **7**, **9**.

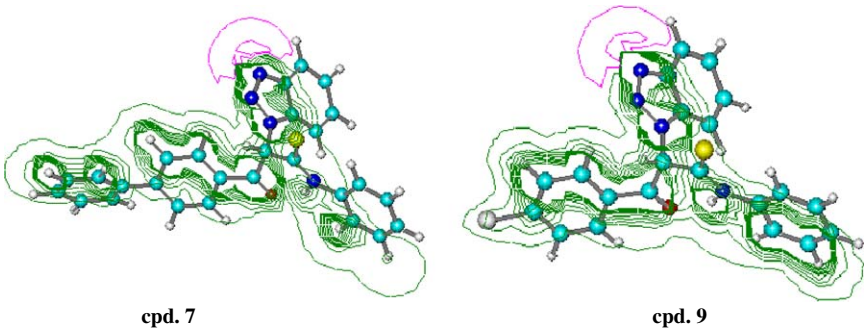


Figure 5. The 2D contours of the molecular electrostatic potential of compounds **7**, **9**.

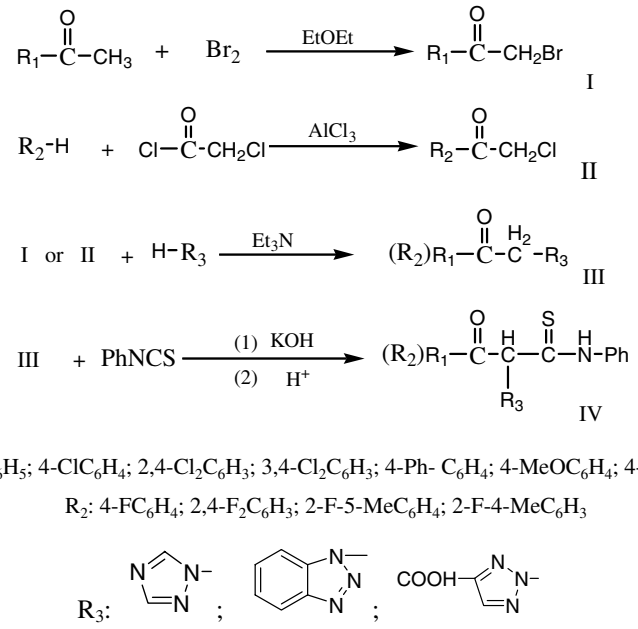


Figure 6. Synthetic route for the title compounds.

betone (the corresponding substituted group R_1) and bromine, which are listed in Table 7.

4.1.2. Preparation of intermediates II.[19] According to the reported document,[19] four intermediates (II) were obtained which are listed in Table 8.

4.1.3. Preparation of intermediates III.[20] According to the reported document,[20] 18 intermediates III were obtained by the reaction between intermediate I or II and R_3–H which are listed in Table 9.

4.1.4. Preparation of title compounds IV. The key intermediate III (3.72 g, 0.02 mol) was dissolved in 1,4-dioxane solution (40 ml), then a mixture of phenyl isothiocyanate (2.24 g, 0.02 mol) and the pulverous KOH (1.12 g, 0.02 mol) was added and it was stirred at room temperature for 1 h. The precipitated product added in acetone (20 ml) was washed, filtered, and dried to give kali salt. The kali salt was dissolved in 30 ml aqueous solution and stirred. One milliliter rortis chlorohydric acid was added dropwise to the stirred solution then heated to 60 °C. The precipitated product was separated out (about 3 h), then filtered to get the crude product, recrystallized with alcohols to gain the yellow solids, and purified by column chromatography (mineral ether/acetic ether, 2:1) to obtain yellow crystals. The 18 compounds of this series were prepared adopting the same above-mentioned procedures, which were performed by IR analysis, elemental analysis, NMR analysis, and MS analysis.

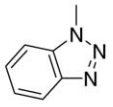
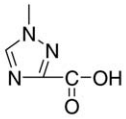
Table 7. The corresponding intermediates I

No.	R_1	Yield (%)	Mp (°C)
I_1	C_6H_5	77	50–51
I_2	4-ClC_6H_4	76	96–97
I_3	2,4-$Cl_2C_6H_3$	63.7	30–32
I_4	4-$MeOC_6H_4$	76.8	76–78
I_5	4-MeC_6H_4	63.1	51–52
I_6	4-PhC_6H_4	80.8	86–88
I_7	3,4-$Cl_2C_6H_3$	82.1	39–41

Table 8. The corresponding intermediates II

No.	R_1	Yield (%)	Mp (°C)
II_1	4-FC_6H_4	74.9	47–49
II_2	2, 4-$F_2C_6H_3$	63.1	53–55
II_3	2-F-4-MeC_6H_3	61.3	43–45
II_4	2-F-5-MeC_6H_3	36	46–48

Table 9. The corresponding intermediates III

No.	R_1/R_2	R_3	Yield (%)	Mp (°C)
III_1	3,4-$Cl_2C_6H_3$		78	155–156
III_2	4-$MeOC_6H_4$		68	104–106
III_3	Ph–C_6H_4		85	123–125
III_4	2-F-4-MeC_6H_3		62	138–139
III_5	2-F-5-MeC_6H_3		43	141–143
III_6	C_6H_5		50	128–129
III_7	Ph–C_6H_4		38	183–185
III_8	4-$MeOC_6H_4$		48	132–133
III_9	4-ClC_6H_4		46	173–175
III_{10}	4-MeC_6H_4		41	178–180
III_{11}	4-$MeOC_6H_4$		63	123–125
III_{12}	C_6H_5		38.5	119–120
III_{13}	3,4-$Cl_2C_6H_3$		68	130–131
III_{14}	2,4-$Cl_2C_6H_3$		48.3	167–169
III_{15}	2-F-5-MeC_6H_3		46	159–161
III_{16}	4-FC_6H_4		37.6	161–163
III_{17}	2,4-$F_2C_6H_3$		72	135–136
III_{18}	2-F-4-MeC_6H_3		69	156–157

4.1.4.1. 3-(3,4-Dichlorophenyl)-3-oxo-*N*-phenyl-2-(1*H*-1,2,4-triazol-1-yl)propanethioamide (1). Mp: 153–155 °C; IR (KBr) cm^{-1}: 1700, 1493, 1117, 3434; MS (70 eV): *m*/*z* (%) 256, 227, 173, 147, 136, 109, 75; ^1H NMR (300 MHz): δ_h 6.90 (s, 1H, CH), 7.00–7.60 (m, 8H, Ar–H), 8.00 (s, 1H, Tr–H), 8.8 (s, 1H, Tr–H), 12.30 (s, 1H, N–H); Elem. Anal.: Found % (Calcd %) C 52.20 (52.18), H 3.12 (3.09), N 14.30 (14.32).

4.1.4.2. 3-(4-Methoxyphenyl)-3-oxo-*N*-phenyl-2-(1*H*-1,2,4-triazol-1-yl)propanethioamide (2). Mp: 155–156 °C; IR (KBr) cm^{-1}: 1685, 1057, 1138, 3433; MS (70 eV): *m*/*z* (%) 217, 189, 137, 109, 135, 104, 91, 77, 51; ^1H NMR (300 MHz): δ_h 1.20 (s, 3H, CH_3), 3.84 (s, 1H, CH), 7.09–8.00 (m, 9H, Ar–H), 8.07 (s, 1H, Tr–H), 8.80 (s, 1H, Tr–H), 12.55 (s, 1H, N–H); Elem. Anal.: Found % (Calcd %) C 61.30 (61.35), H 4.60 (4.58), N 15.88 (15.90).

4.1.4.3. 3-(Biphenyl-4-yl)-3-oxo-*N*-phenyl-2-(1*H*-1,2,4-triazol-1-yl)propanethioamide (3). Mp: 175–177 °C; IR (KBr) cm^{-1}: 1697, 1500, 1130, 3432; MS (70 eV): *m*/*z* (%) 263, 181, 158, 104, 77, 55, 135, 91; ^1H NMR (300 MHz): δ_h 4.15 (s, 1H, CH), 7.20–7.80 (m, 14H, Ar–H), 8.00 (s, 1H, Tr–H), 8.24 (s, 1H, Tr–H), 12.55 (s, 1H, N–H); Elem. Anal.: Found % (Calcd %) C 69.30 (69.33), H 4.52 (4.55), N14.08 (14.06).

4.1.4.4. 3-(2-Fluoro-4-methylphenyl)-3-oxo-*N*-phenyl-2-(1*H*-1,2,4-triazol-1-yl)propanethioamide (4). Mp: 168–170 °C; IR (KBr) cm^{-1}: 1686, 1512, 1132, 3436; MS (70 eV): *m*/*z* (%) 220, 192, 137, 109, 75, 55, 135, 91; ^1H NMR (300 MHz): δ_h 1.29 (s, 3H, CH_3), 6.42 (s, 1H, CH), 7.07–7.34 (m, 8H, Ar–H), 7.66 (s, 1H, Tr–H), 8.43 (s, 1H, Tr–H), 12.58 (s, 1H, N–H); Elem. Anal.: Found % (Calcd %) C 61.03 (61.00), H 4.25 (4.27), N 15.80 (15.81).

4.1.4.5. 3-(2-Fluoro-5-methylphenyl)-3-oxo-*N*-phenyl-2-(1*H*-1,2,4-triazol-1-yl)propanethioamide (5). Mp: 166–167 °C; IR (KBr) cm^{-1}: 1698, 1513, 1131, 3435; MS (70 eV): *m*/*z* (%) 219, 192, 136, 91, 77, 55; ^1H NMR (300 MHz): δ_h 2.34 (s, 3H, Ph–CH_3), 7.04 (s, 1H, CH), 7.05–8.08 (m, 8H, Ar–H), 7.71 (s, 1H,Tr–H), 8.35 (s, 1H, Tr–H), 13.58 (s, 1H, N–H); Elem. Anal.: Found % (Calcd %) C 61.03 (61.00), H 4.25 (4.27), N 15.80 (15.81).

4.1.4.6. 2-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3-oxo-*N*,3-diphenylpropanethioamide (6). Mp: 156–158 °C; IR (KBr) cm^{-1}: 1699, 1518, 1082, 3403; MS (70 eV): *m*/*z* (%) 255, 178, 150, 136, 1118, 104, 93, 77, 51; ^1H NMR (300 MHz): δ_h 7.01 (s, 1H, CH), 7.01–7.97 (m, 14H, Ar–H), 12.83 (s, 1H, N–H); Elem. Anal.: Found % (Calcd %) C 67.70 (67.72), H 4.34 (4.33), N 15.06 (15.04).

4.1.4.7. 2-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3-(biphenyl-4-yl)-3-oxo-*N*-phenylpropanethioamide (7). Mp: 156–158 °C; IR (KBr) cm^{-1}: 1693, 1507, 1049, 3370; MS (70 eV): *m*/*z* (%) 331, 254, 177, 150, 136, 118, 104, 93, 77; ^1H NMR (300 MHz): δ_h 7.05(s, 1H, CH), 7.17–7.36 (m, 18H, Ar–H), 13.83(s, 1H, N–H); Elem. Anal.: Found % (Calcd %) C 72.32 (72.30), H 4.52 (4.49), N 12.45 (12.49).

4.1.4.8. 2-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3-(4-methoxyphenyl)-3-oxo-*N*-phenylpropanethioamide (8). Mp: 136–138 °C; IR (KBr) cm^{-1}: 1685, 1494, 1129, 3446; MS (70 eV): *m*/*z* (%) 273, 165, 136, 118, 105, 91, 77, 55; ^1H NMR (300 MHz): δ_h 1.09 (s, 3H, CH_3), 7.04 (s, 1H, CH), 7.04–7.29 (m, 13H, Ar–H), 11.83 (s, 1H, N–H); Elem. Anal.: Found % (Calcd %) C 64.62 (64.60), H 4.63 (4.65), N 14.34 (14.35).

4.1.4.9. 2-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3-(4-chlorophenyl)-3-oxo-*N*-phenylpropanethioamide (9). Mp: 137–139 °C; IR (KBr) cm^{-1}: 1591, 1485, 1079, 3425; MS (70 eV): *m*/*z* (%) 290, 168, 148, 136, 118, 104, 93, 77; ^1H NMR (300 MHz): δ_h 6.05 (s, 1H, CH), 7.01–7.80 (m, 13H, Ar–H), 12.13 (s, 1H, N–H); Elem. Anal.: Found % (Calcd %) C 61.95 (61.99), H 3.75 (3.72), N 13.75 (13.77).

4.1.4.10. 2-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3-oxo-*N*-phenyl-3-*p*-tolylpropanethioamide (10). Mp: 146–147 °C; IR (KBr) cm^{-1}: 1701, 1498, 1131, 3433; MS (70 eV): *m*/*z* (%) 269, 178, 150, 136, 119, 104, 91, 77, 55; ^1H NMR (300 MHz): δ_h 1.24 (m, 3H, CH_3), 4.94 (m, 1H, CH), 7.28–7.89 (m, 13H, Ar–H), 13.33 (s, 1H, N–H); Elem. Anal.: Found % (Calcd %) C 68.39 (68.37), H 4.70 (4.69), N 14.45 (14.48).

4.1.4.11. 1-(1-(4-Methoxyphenyl)-1-oxo-3-(phenylamino)-3-thioxopropan-2-yl)-1*H*-1,2,4-triazole-3-carboxylic acid (11). Mp: 179–181 °C; IR (KBr) cm^{-1}: 1595, 1493, 1137, 3446; MS (70 eV): *m*/*z* (%) 261, 231, 215, 187, 136, 119, 91, 77, 55; ^1H NMR (300 MHz): δ_h 1.41 (s,3 H, CH_3), 4.90–5.01 (s, 1H, CH), 7.25–7.35 (m, 9H, Ar–H), 7.58 (s, 1H, Tr–H), 13.83 (s, 1H, N–H), 11.2 (s, 1H, O–H); Elem. Anal.: Found % (Calcd %) C 57.60 (57.57), H 4.02 (4.06), N 14.12 (14.13).

4.1.4.12. 1-(1-Oxo-1-phenyl-3-(phenylamino)-3-thioxopropan-2-yl)-1*H*-1,2,4-triazole-3-carboxylic acid (12). Mp: 192–194 °C; IR (KBr) cm^{-1}: 1699, 1496, 1160, 3432; MS (70 eV): *m*/*z* (%) 231, 186, 169, 136, 119, 91, 77, 55; ^1H NMR (300 MHz): δ_h 4.61 (s, H, CH), 4.91 (s, 1H, CH), 7.26–7.43 (m, 10H, Ar–H), 7.72 (s, 1H, Tr–H), 13.23 (s, 1H, N–H), 11.2 (s,1H,O–H); Elem. Anal.: Found % (Calcd %) C 59.02 (59.00), H 3.82 (3.85), N 15.27 (15.29).

4.1.4.13. 1-(1-(3,4-Dichlorophenyl)-1-oxo-3-(phenylamino)-3-thioxopropan-2-yl)-1*H*-1,2,4-triazole-3-carboxylic acid (13). Mp: 159–161 °C; IR (KBr) cm^{-1}: 1684, 1471, 1117, 3430; MS (70 eV): *m*/*z* (%) 300, 283, 256, 176, 148, 136, 119, 93, 77; ^1H NMR (300 MHz): δ_h 4.14 (s, 1H, CH), 7.18–7.35 (m, 8H, Ar–H), 7.57 (s, 1H, Tr–H), 11.50 (s, 1H, N–H), 9.2 (s, 1H, O–H); Elem. Anal.: Found % (Calcd %) C 49.68 (49.67), H 2.80 (2.78), N 12.85 (12.87).

4.1.4.14. 1-(1-(2,4-Dichlorophenyl)-1-oxo-3-(phenylamino)-3-thioxopropan-2-yl)-1*H*-1,2,4-triazole-3-carboxylic acid (14). Mp: 186–188 °C; IR (KBr) cm^{-1}: 1593, 1493, 1138, 3437; MS (70 eV): *m*/*z* (%) 301, 283, 256, 177, 147, 136, 118, 91, 77; ^1H NMR (300 MHz): δ_h 3.02 (s, 1H, CH), 6.92–7.43 (m, 8H, Ar–H), 7.69 (s, H,

Tr–H), 13.50 (s, 1H, N–H), 12.2 (s, 1H, O–H); Elem. Anal.: Found % (Calcd %) C 49.68 (49.67), H 2.80 (2.78), N 12.85 (12.87).

4.1.4.15. 1-(1-(2-Fluoro-5-methylphenyl)-1-oxo-3-(phenylamino)-3-thioxopropan-2-yl)-1*H*-1,2,4-triazole-3-carboxylic acid (15). Mp: 189–191 °C; IR (KBr) cm^{-1}: 1735, 1494, 1172, 3463; MS (70 eV): *m*/*z* (%) 264, 246, 218, 136, 119, 91, 77, 55; ^1H NMR (300 MHz): δ_h 2.31 (s, 3H, Ph–CH_3), 7.09–8.12 (m, 8H, Ar–H), 8.83 (s, 1H, Tr–H), 13.33 (s, 1H, N–H), 12.23 (s, 1H, O–H); Elem. Anal.: Found % (Calcd %) C 57.25 (57.28), H 3.80 (3.79), N 12.89 (12.87).

4.1.4.16. 1-(1-(4-Fluorophenyl)-1-oxo-3-(phenylamino)-3-thioxopropan-2-yl)-1*H*-1,2,4-triazole-3-carboxylic acid (16). Mp: 182–184 °C; IR (KBr) cm^{-1}: 1703, 1500, 1162, 3432; MS (70 eV): *m*/*z* (%) 249, 232, 204, 136, 123, 118, 95, 77, 55; ^1H NMR (300 MHz): δ_h 4.42 (m, 1H, CH), 7.08–7.89 (m, 9H, Ar–H), 7.68 (s, 1H, Tr–H), 13.13 (s, 1H, N–H), 10.87 (s, 1H, O–H); Elem. Anal.: Found % (Calcd %) C 56.26 (56.24), H 3.40 (3.41), N 14.56 (14.58).

4.1.4.17. 1-(1-(2,4-Difluorophenyl)-1-oxo-3-(phenylamino)-3-thioxopropan-2-yl)-1*H*-1,2,4-triazole-3-carboxylic acid (17). Mp: 224–225 °C; IR (KBr) cm^{-1}: 1699, 1513, 1108, 3470; MS (70 eV): *m*/*z* (%) 267, 251, 223, 142, 136, 118, 93, 77, 55; ^1H NMR (300 MHz): δ_h 3.42 (m, 1H, CH), 7.18–7.59 (m, 8H, Ar–H), 7.68 (s, 1H, Tr–H), 13.13 (s, 1H, N–H), 10.87 (s, 1H, O–H); Elem. Anal.: Found % (Calcd %) C 53.75 (53.73), H 3.03 (3.00), N 13.88 (13.92).

4.1.4.18. 1-(1-(2-Fluoro-4-methylphenyl)-1-oxo-3-(phenylamino)-3-thioxopropan-2-yl)-1*H*-1,2,4-triazole-3-carboxylic acid (18). Mp: 177–179 °C; IR (KBr) cm^{-1}: 1698, 1503, 1131, 3445; MS (70 eV): *m*/*z* (%) 263, 246, 218, 136, 118, 93, 75, 55, 51; ^1H NMR (300 MHz): δ_h 1.31 (s, 3H, Ph–CH_3), 7.09–8.12 (m, 8H, Ar–H), 8.83 (s, 1H, Tr–H), 15.47 (s, 1H, N–H), 11.73 (s, 1H, O–H); Elem. Anal.: Found % (Calcd %) C 57.26 (57.28), H 3.80 (3.79), N 14.05 (14.06).

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References and notes

1. Xu, L. Z.; Jian, F. F.; Shi, J. G.; Sun, P. P.; Jiao, K. *Chin. J. Chem.* **2004**, *22*, 698.
2. Xu, L. Z.; Jian, F. F.; Shi, J. G.; Li, L. *Chin. J. Chem.* **2004**, *22*, 1308.
3. Cao, K. G.; Wang, Z. W.; Zhao, X. Q.; Fang, T. *Chin. J. Org. Chem.* **2003**, *23*, 1411 (in Chinese).
4. Eto, M. *Organic and Biological Chemistry: Organophosphorus Pesticides*; CRC Press: Cleveland, 1974.
5. Lin, B. D. *Pesticide* **1983**, *22*, 31 (in Chinese).
6. Erdelen, C.; Heil, M.; Kleefeld, G.; Bretschneider, T. DE19625263, 1998; *Chem. Abstr*. **1998**, *128*, 88784d.
7. Li, Y. C.; Yue, M. X.; Dong, J. H.; Yu, W. Q.; Han, Y. F.; Li, B. W.; Li, S. Z. *Acta Agric. Boreali-Sinica* **1999**, *14*, 79 (in Chinese).
8. CambridgeSoft corp., 100 Cambrige Park, MA 02140-2317, USA.
9. Xu, L. S.; He, Y. P.; Li, Z. H. *Acta Chim. Sinica* **2002**, *60*, 1784.
10. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
11. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
12. De, K. et al. *Bioorg. Med. Chem.* **2004**, *12*, 3323–3332.
13. Snedecor, G. W.; Cochran, W. G. *Statistical Methods*; Oxford and IBH: New Delhi, 1967, pp. 381–418.
14. Chatterjee, S.; Hadi, A. S.; Price, B. *Regression Analysis by Examples*, 3rd ed.; Wiley VCH: New York, 2000.
15. *QSPR/QSAR Studies for Molecular Descriptors*; Diudea, M. V., Ed.; Nova Science: Huntingdon, New York, 2000.
16. Bikash, D.; Shovanlal, G.; Subrata, B.; Soma, S.; Tarun, J. *Bioorg. Med. Chem.* **2003**, *11*, 5493.
17. Fukui, K. In *Theory of Orientation and Stereoselection*; Springer: New York, 1975; pp 34–39.
18. Bicke, F. F.; Burckhalter, J. H. *J. Am. Chem. Soc.* **1942**, *64*, 451.
19. Morley, J. O. *Synthesis* **1977**, 54.
20. Shi, Y. N.; Fang, J. X. *Chin. J. Appl. Chem.* **1995**, *12*, 28 (in Chinese).