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Synthesis, Fungicidal Activity, and QSAR of Pyridazinonethiadiazoles

XIA JUAN ZOU, GUI YU JIN,* AND ZU XING ZHANG

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

A series of novel 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-thiadiazoles, related to the fungicidal activity, were synthesized and tested in vivo against wheat leaf rust, *Puccinia recondita*. The preliminary bioassay indicated that they exhibited fungicidal activity and the activity was influenced by the nature of the substituents. A quantitative structure−activity relationship study showed that the hydrophobicity ($\sum\pi$) is a major positive parameter in affecting the activity; the electronic parameters ($\sum\sigma$, $\sum$F) are the major negative parameters in affecting the activity. Especially, introducing an ortho substituent with an inductively electron-donating property is favorable to the activity.

KEYWORDS: Synthesis; pyridazinonethiadiazoles; fungicides; wheat leaf rust; QSAR

1. INTRODUCTION

Pyridazine derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity. They are widely used in pharmaceuticals and agrochemicals (*1*, *2*). Several years ago, we became interested in the study of the chemistry and agrochemistry of 1-aryl-1,4-dihydro-6-methylpyridazin-4-one, in particular those substituted at the 3-position (*3*). Recently, we reported the fungicidal activity of novel diheterocyclic pyridazinonethiadiazoles (*4*).

Prompted by these results and in an attempt to establish the quantitative structure−activity relationships (QSAR) in this series and evaluate the modification of the fungicidal profile induced by the change of the substituents at the phenyl moiety, we designed and synthesized a series of 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-thiadiazoles with various substituents and measured their fungicidal activity.

2. MATERIALS AND METHODS

2.1. Synthetic Procedures. Melting points were measured on a Yanaco melting point apparatus and were uncorrected. Infrared spectra (IR) (potassium bromide) were recorded in a Shimadzu IR-435. ^{1}H NMR spectra were recorded on a JEOL FX-90Q spectrometer, and tetramethylsilane was used as an internal standard (chemical shifts are in δ values). A HP 5988 A spectrometer operating at 70 ev was used to obtain the mass spectra. Elemental (C, H, and N) analyses were carried out on a MT-3 analyzer.

5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-thiadiazoles (**3**). Substituted thiosemicarbazides (**2**; 0.5 mmol) were added in portions to concentrated sulfuric acid (5 mL) at 0 °C and stirred for 1 h maintaining the temperature at 0 °C. The reaction mixture was then allowed to stand for 20 h at room temperature and poured over crushed ice with stirring, and the separated solid was washed with water and recrystallized from ethanol/dimethylformamide (DMF). The physical constants and spectral analyses of these substituted 1,3,4-thiadiazoles are recorded in **Tables 1**−**3**.

2.2. Biological Assay. The antifungal activity was tested in vivo on wheat leaf rust, *Puccinia recondita*. The local susceptible cultivated Ming-Xian 169 wheat plants (10 germinating seeds) were grown under greenhouse conditions (T = 15−20 °C). The tested compounds were dissolved in water/DMF (5:1 by volume, containing Sorpal-144) to 0.001 M solutions, and these solutions were applied to the wheat leaves as foliar sprays using a hand-held spray gun.

The wheat leaves were inoculated with the uredospore and talcum powder (1:10 by volume) of *P. recondita* (the causal fungus of the wheat leaf rust). The plants were placed immediately in a moist chamber for 24 h. When the leaves were just dry, the solution containing tested compounds (10 mL) was sprayed into each pot. The plants were placed in a greenhouse. The percentage of disease control in the treated pots was compared to that of pots with a treatment in the absence of the tested compounds, and fungicidal activity was evaluated 10 days after treatment. Three replicates were included in the evaluation. For comparative purposes, the commercial fungicide Triadimefon was tested under the same condition as the title compounds (at concentrate 100 ppm, it gave 100% control). The activity was expressed in terms of D by the formula

$$D = \lg [a/(100 - a)] - \lg M_w$$

where a is the percentage of inhibition and M_w is the molecular weight of the tested compounds.

2.3. Physicochemical Parameters. Physicochemical parameters of the substituents on the phenyl moiety are listed in **Table 4**. For the hydrophobicity of the substituents, the π value of the substituents is defined by Hansch (*5*). $\sum\pi$ stands for the total hydrophobic effect of the substituents. Hammett σ constants were used for electronic parameters. $\sum\sigma$ was the summation of the σ values at the ortho, meta, and para position. For ortho substituents, the σ° value was taken to be equivalent to that σ_p of the corresponding para substituents (*6*) and the inductive constants (F) were used. $\sum F$ stands for the total inductive effect for ortho substituents. For the steric effect of the substituents, the Es parameter defined by Taft was used (*7*). $\sum$Es was the total steric effect of substituents.

* To whom correspondence should be addressed. Tel: 086-010-62757520. Fax: 086-010-62751725. E-mail: zouxj@mdl.ipc.pku.edu.cn.

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Table 1. Physical Data of New Compounds

compd	R_1	R_2	yield (%)	mp (°C)	molecular	analysis (%, calcd) C	H	N
3a	*o*-Cl	*m*-CF_3	95	>300	$C_{20}H_{13}ClF_3N_5OS$	51.60 (51.77)	2.84 (2.80)	15.15 (15.16)
3b	*o*-Cl	*o*-F	94	>300	$C_{19}H_{13}ClFN_5OS$	54.95 (55.12)	3.11 (3.14)	16.99 (16.99)
3c	*o*-Cl	H	93	>300	$C_{19}H_{14}ClN_5OS$	57.52 (57.62)	3.46 (3.53)	17.70 (17.76)
3d	H	*o*-F	95	>300	$C_{19}H_{14}FN_5OS$	59.99 (60.12)	3.71 (3.69)	18.63 (18.54)
3e	H	*m*-CF_3	95	297–298	$C_{20}H_{14}F_3N_5OS$	55.78 (55.92)	3.26 (3.26)	16.28 (16.38)
3f	2,6-Cl_2	*m*-CF_3	95	>300	$C_{20}H_{12}Cl_2F_3N_5OS$	48.15 (48.19)	2.57 (2.41)	14.10 (14.11)
3g	2,6-Cl_2	*o*-F	95	>300	$C_{19}H_{12}Cl_2FN_5OS$	50.65 (50.88)	2.72 (2.67)	15.63 (15.69)
3h	*p*-Cl	*m*-CF_3	95	>300	$C_{20}H_{13}ClF_3N_5OS$	51.55 (51.77)	2.81 (2.80)	15.25 (15.16)
3i	*p*-Cl	*o*-F	95	298–300	$C_{19}H_{13}ClFN_5OS$	55.45 (55.15)	3.11 (3.14)	16.98 (16.99)
3k	2,4,5-Cl_3	*o*-F	96	280–282	$C_{19}H_{11}Cl_3FN_5OS$	47.15 (47.25)	2.28 (2.27)	14.50 (14.57)
3l	2,4,5-Cl_3	*m*-CF_3	95	>300	$C_{20}H_{11}Cl_3F_3N_5OS$	45.08 (45.07)	1.91 (2.06)	12.95 (13.20)
3m	2,4-2CH_3	*m*-CF_3	95	>300	$C_{22}H_{18}F_3N_5OS$	59.27 (59.25)	3.90 (4.04)	15.73 (15.79)
3n	2,4-2CH_3	*o*-F	94	275–276	$C_{21}H_{18}FN_5OS$	61.60 (61.88)	4.46 (4.42)	16.93 (17.26)
3o	2,4-Cl_2	*o*-F	96	254–255	$C_{19}H_{12}Cl_2FN_5OS$	50.59 (50.88)	2.94 (2.67)	15.40 (15.69)
3p	2,4-Cl_2	*m*-CF_3	95	>300	$C_{20}H_{12}Cl_2F_3N_5OS$	47.90 (48.19)	2.38 (2.41)	14.04 (14.11)
3q	2,4-Cl_2	H	95	273–274	$C_{19}H_{13}Cl_2N_5OS$	53.23 (53.01)	3.15 (3.02)	16.60 (16.47)

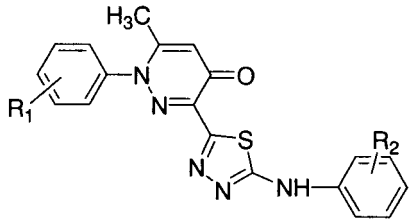
Table 2. MS Data of Some Compounds

compd	*m*/*z* (%)
3a	463 (43), 444 (2), 274 (12), 263 (1), 246 (34), 218 (63), 203 (24), 193 (43), 178 (83), 152 (100), 145 (40), 125 (18), 111 (52), 95 (12), 75 (53)
3i	413 (41), 394 (52), 354 (3), 263 (3), 246 (21), 229 (12), 201 (18), 193 (34), 178 (78), 168 (61), 164 (45), 152 (89), 136 (21), 111 (100), 95 (19), 75 (95), 51 (18)
3q	429 (54), 227 (22), 212 (50), 201 (7), 186 (50), 150 (100), 135 (15), 76 (17)

Table 3. Spectral Analyses of New Compounds

compd	IR (ν/cm^{-1})	NMR (δ/DMSO-d_6, ppm)
3a	1604.7 (C═O), 3261.0 (NH)	2.20 (s, 3H, CH_3), 6.96 (s,1H, pyridazinone), 7.15–8.44 (m, 8H, 2C_6H_4), 11.04 (bs, NH)
3b	1612.2 (C═O), 3282.1 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 6.90–8.48 (m, 8H, 2C_6H_4)
3c	1613.5 (C═O), 3213.0 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 6.84–8.00 (m, 9H, C_6H_5, C_6H_4), 10.40 (bs, NH)
3d	1603.6 (C═O), 3271.3 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 7.04–8.48 (m, 9H, C_6H_5, C_6H_4)
3e	1608.3 (C═O), 3228.0 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 7.20–8.32 (m, 9H, C_6H_5, C_6H_4)
3f	1622.3 (C═O), 3264.0 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 7.20–8.40 (m, 7H, C_6H_3, C_6H_4), 10.40 (bs, NH)
3g	1623.4 (C═O), 3246.5 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 7.04–8.48 (m, 7H, C_6H_3, C_6H_4)
3h	1605.1 (C═O), 3255.0 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 7.36–8.40 (m, 8H, 2C_6H_4), 10.88 (bs, NH)
3i	1619.1 (C═O), 3235.5 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 7.04–8.48 (m, 8H, 2C_6H_4)
3k	1619.1 (C═O), 3261.0 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 7.04–8.48 (m, 7H, C_6H_3, C_6H_4)
3l	1609.8 (C═O), 3279.0 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 7.20–8.40 (m, 6H, C_6H_2, C_6H_4), 10.88 (bs, NH)
3m	1599.8 (C═O), 3273.2 (NH)	2.12 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 6.96 (s,1H, pyridazinone), 7.36–8.64 (m, 7H, C_6H_3, C_6H_4), 10.96 (bs, NH)
3n		2.04 (s, 6H, 2CH_3), 2.40 (s, 3H, CH_3), 6.68 (s,1H, pyridazinone), 7.04–8.40 (m, 7H, C_6H_3, C_6H_4)
3o	1603.6 (C═O), 3268.0 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 7.04–8.48 (m, 7H, C_6H_3, C_6H_4)
3p	1603.6 (C═O), 3240.5 (NH)	2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 7.20–8.32 (m, 7H, C_6H_3, C_6H_4)
3q		2.20 (s, 3H, CH_3), 6.80 (s,1H, pyridazinone), 6.88–8.00 (m, 8H, C_6H_3, C_6H_5), 10.40 (bs, NH)

Table 4. Fungicidal Activity and Physicochemical Properties



			electronic params		hydrophobic params	steric params	inhibition	D	
compd	R_1	R_2	$\sum\sigma$	$\sum F$	$\sum\pi$	$\sum$Es	%	obsvd	calcd
3a	*o*-Cl	*m*-CF_3	0.66	0.79	1.59	−1.21	70	−2.30	−2.4938
3b	*o*-Cl	*o*-F	0.29	0.07	0.85	−1.43	10	−3.57	−2.9009
3c	*o*-Cl	H	0.23	0.41	0.71	−0.97	10	−3.16	−2.9570
3d	H	*o*-F	0.06	−0.34	0.14	−0.46	50	−2.58	−2.7883
3e	H	*m*-CF_3	0.43	0.38	0.88	−0.24	60	−2.46	−2.3813
3f	2,6-Cl_2	*m*-CF_3	0.89	1.19	2.30	−2.18	50	−2.70	−2.5971
3g	2,6-Cl_2	*o*-F	0.52	0.47	1.56	−2.40	30	−3.01	−3.004
3h	*p*-Cl	*m*-CF_3	0.66	0.79	1.59	−1.21	60	−2.44	−2.4938
3i	*p*-Cl	*o*-F	0.29	0.07	0.85	−1.43	50	−2.67	−2.9009
3k	2,4,5-Cl_3	*o*-F	0.75	0.41	2.27	−3.37	60	−2.50	−2.6770
3l	2,4,5-Cl_3	*m*-CF_3	1.12	0.89	3.01	−3.15	70	−2.36	−2.0454
3m	2,4-2CH_3	*m*-CF_3	0.09	1.61	2.00	−2.72	90	−1.69	−1.7477
3n	2,4-2CH_3	*o*-F	−0.28	0.30	1.26	−2.94	90	−1.66	−1.6028
3o	2,4-Cl_2	*o*-F	0.52	−0.42	1.56	−2.40	80	−2.05	−2.1715
3p	2,4-Cl_2	*m*-CF_3	0.89	0.48	2.30	−2.18	90	−1.74	−1.9328
3q	2,4-Cl_2	H	0.46	1.20	1.42	−1.94	20	−3.23	−3.4251

3. RESULTS

3.1. Synthesis. In our previous paper, we reported the synthesis of hydrazide **1** (*8*) and thiosemicarbazide **2** (*9*). Treatment of compound **2** with concentrated sulfuric acid yielded the corresponding 1,3,4-thiadiazoles (**Scheme 1**).

3.2. Fungicidal Activity. Table 4 summarizes the fungicidal screening results of the studied compounds. The results indicated that the fungicidal activity was different with the substituents of phenyl moiety.

Among compounds in which the R_1 substituents were fixed and the R_2 was further substituted, the higher the hydrophobicity of R_2 was, the higher the fungicidal activity was. That is, *m*-CF_3 > *o*-F > H. The preferred substituent for R_1 was the 2,4-2CH_3 group. Although the above observations are not straightforward, they at least suggest a great importance for the molecular hydrophobicity and electronic effects of substituents in the structure−activity pattern.

3.3. QSAR Analyses. Of the combination of the parameters described above as independent variables, eq 1 gave the best correlation.

$$D = 2.8021\ (\pm 0.4499)\sum\pi - 3.2753\ (\pm 0.5335)\sum\sigma + 0.9950\ (\pm 0.2138)\sum\mathrm{Es} - 0.9355\ (\pm 0.2097)\sum F - 2.8445\ (\pm 0.0703) \quad n = 16,\ r = 0.9017,\ s = 0.2812 \quad (1)$$

In this equation, *n* is the number of compounds, *s* is the standard deviation, *r* is the multiple correlation coefficient, and the numbers in parentheses are the 95% confidence intervals. The development of eq 1 and the squared correlation matrix for the variables considered is shown in **Tables 5** and **6**, respectively. The fungicidal activity values calculated by eq 1 are listed in **Table 4**.

4. DISCUSSION

The above quantitative analyses indicate that the activity in terms of *D* gave a better correlation. In eq 1, the $\sum\pi$ term was a major positive parameter affecting the activity. The activity increases linearly with the increase in the molecular hydrophobicity, $\sum\pi$, when other factors are separated and substitution patterns are appropriate.

Scheme 1

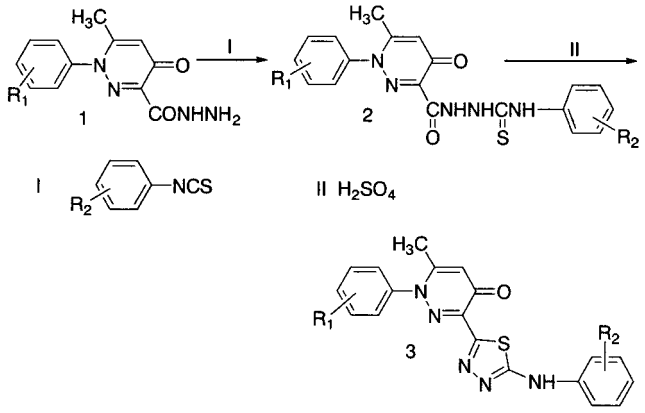


Table 5. Development of QSAR of Eq 1

intercept	$\sum\pi$	$\sum\sigma$	$\sum$Es	$\sum$F	*s*	*r*	*F*
−2.9440	0.2875				0.5330	0.3814	2.3832
−3.0147	0.6742	−1.0899			0.4731	0.6123	3.8992
−2.8876	1.3278	−1.8178	0.4099		0.4513	0.6892	3.6188
−2.8445	2.8021	−3.2753	0.9950	−0.9355	0.2812	0.9017	11.9645

Table 6. Squared Correlation Matrix for Variables Used in Eq 1

	$\sum\pi$	$\sum\sigma$	$\sum$Es	$\sum F$
$\sum\pi$	1.0000			
$\sum\sigma$	0.5340	1.0000		
$\sum$Es	0.5759	0.0569	1.0000	
$\sum F$	0.3205	0.0769	0.0886	1.0000

For the electronic parameters, $\sum\sigma$, $\sum F$ was significant, which improved the correlation greatly. The coefficient of the $\sum\sigma$ and $\sum F$ is negative. This indicates that the higher the electron-donating field effect of the ortho substituents is, the higher the fungicidal activity is.

In conclusion, the higher the hydrophobicity of the title compounds was, the higher the fungicidal activity against wheat leaf rust was. Introducing an ortho substituent with an inductively electron-donating property was favorable to the activity.

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