Synthesis, Crystal Structure, and Fungicidal Activity of Novel 1,5-Diaryl-1*H*-Pyrazol-3-Oxy Derivatives Containing Oxyacetic Acid or Oxy(2-thioxothiazolidin-3-yl)ethanone Moieties

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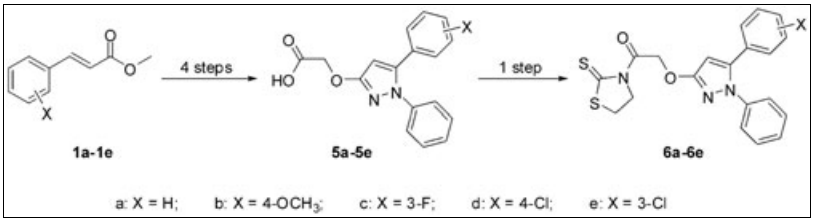

A series of novel 1,5-diaryl-1*H*-pyrazol-3-oxy derivatives containing oxyacetic acid or oxy(2-thioxothiazolidin-3-yl)ethanone moieties were prepared from methyl 3-arylacrylates *via* a serial of reactions included addition-cyclization, oxidation, substitution, hydrolysis, and condensation. Their structures were confirmed by ^{1}H-NMR, ^{13}C-NMR, IR, and elemental analysis. In addition, the crystal structure of the compound 2-(1,5-diphenyl-1*H*-pyrazol-3-yloxy)-1-(2-thioxothiazolidin-3-yl)ethanone was determined by single crystal X-ray diffraction analysis. Bioassay results indicated that the compound 2-(5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yloxy)-1-(2-thioxo-thiazolidin-3-yl)ethanone exhibited moderate inhibitory activity against *Gibberella zeae* at the dosage of 10 μg mL^{-1}.

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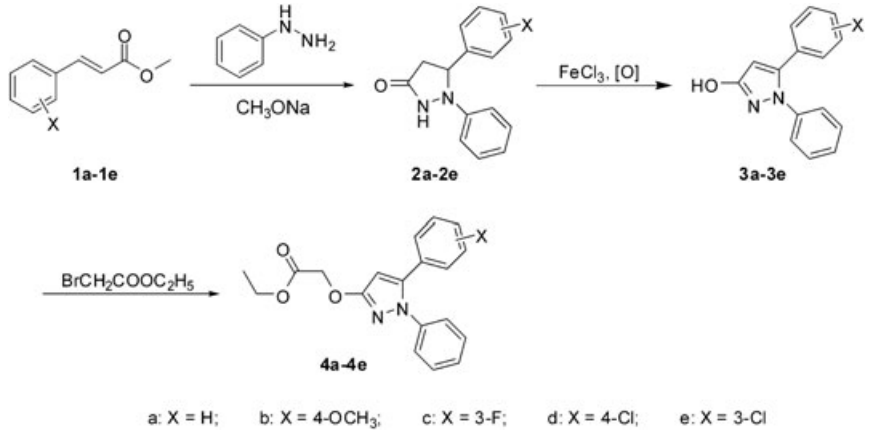
INTRODUCTION

As the discovery of the strobilurin fungicide pyraclostrobin by Baden Aniline and Soda Factory (BASF) scientists, 1*H*-pyrazol-3-oxy derivatives have attracted considerable attention in chemical and medicinal research because of their low mammalian toxicity and diverse bioactivities such as fungicidal [1–3], insecticidal [4], herbicidal [5], and plant growth regulatory activities [6]. Furthermore, several biological studies have also pointed out the value of alkyloxyacetate [7] and oxyacetic acid [8] as bioactive groups. Recently, focusing on incorporating alkyloxyacetate group with 1*H*-pyrazol-3-oxy derivatives in the hope of obtaining compounds of potential bioactivities, we reported the synthesis of novel 1,5-diaryl-1*H*-pyrazol-3-oxyacetates-containing alkyloxyacetate moiety and their good fungicidal activity [9]. However, very few representatives of bioactive 1,5-diaryl-1*H*-pyrazol-3-oxyacetic acids have hitherto been described in the literature.

On the other hand, increasing attention has been devoted to the thiazole-based derivatives since the unique thiazole unit has been found in numerous pesticides such as thifluzamide [10], ethaboxam [11], and thiamethoxam [12]. Thiazolidine-2-thione, an excellent representative of thiazole derivatives, plays a significant role. Biological studies of the thiazolidine-2-thione have been shown to possess a variety of biological activities [13–15]. Therefore, we have reason to believe that the thiazolidine-2-thione can be used as an important skeleton in exploring novel bioactive molecules. Motivated by the aforementioned findings, we conceived that replacement of the active hydrogen of the thiazolidine-2-thione with an oxyacetic acid group forming an oxy(2-thioxothiazo-lidin-3-yl)ethanone moiety and then incorporating with 1*H*-pyrazol-3-oxy derivatives might result in new compounds with good biological activities.

Two common methods are known at present for the synthesis of these oxy(2-thioxothiazolidin-3-yl)ethanone compounds. One involves the following two steps: oxyacetyl chlorides were first prepared by the reaction of oxyacetic acids with thionyl chloride, which further proceeded dehydrochlorination with thiazolidine-2-thione [16–18]. The other involves the condensation of thiazolidine-2-thione with oxyacetic acids, using *N*,*N*′-dicyclohexylcarbodiimide (DCC) as dehydrating agent [19, 20] and 4-(dimethylamino)pyridine (DMAP) as catalyst. In contrast to thionyl chloride, DCC is an environmentally friendly and convenient reagent for the synthesis of heterocyclic acylamide compounds. Therefore, in this article, we report the synthesis of a series of novel 1,5-diaryl-1*H*-pyrazol-3-oxy derivatives containing oxy(2-thioxothiazolidin-3-yl)ethanone moiety (**6a**–**6e**) through the DCC condensation of thiazolidine-2-thione with 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)acetic acids (**5a**–**5e**), and the crystal structure of the compound 2-(1,5-diphenyl-1*H*-pyrazol-3-yloxy)-1-(2-thioxothiazolidin-3-yl)-ethanone (**6a**). Meanwhile the fungicidal activity of the

Scheme 1



compounds **4a**–**4e**, **5a**–**5e**, and **6a**–**6e** has been investigated with the aim of understanding the structure-activity relationships and developing new fungicides. A preliminary *in vitro* bioassay indicated that some of these newly synthesized compounds displayed fungicidal activity at the dosage of 10 μg mL^{-1}.

RESULTS AND DISCUSSION

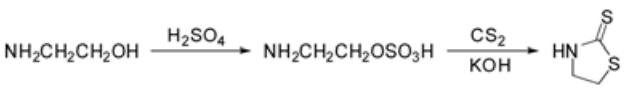
The key intermediates ethyl 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)acetates (**4a**–**4e**) were prepared according to the reported method from methyl 3-arylacrylates (**1a**–**1e**) *via* three steps including addition–cyclization, oxidation, and substitution (Scheme 1) [9]. Thiazolidine-2-thione (Scheme 2) was synthesized from 2-aminoethanol through two steps according to the reported procedure [21].

A previous report by Baraldi et al. described that alkaline hydrolysis of oxypyrazolecarboxylic acid esters in a mixture of methanol and sodium hydroxide solution could give the corresponding carboxylic acids [22]. Motivated by this finding, in our procedure, the hydrolysis of ethyl 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)acetates (**4a**–**4e**) was carried out in 95% ethanol in the presence of sodium hydroxide until the starting material was completely consumed as judged by thin-layer chromatography (TLC) (Scheme 3). The target products 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)acetic acids (**5a**–**5e**) were obtained by acidification with hydrochloric acid in moderate yield.

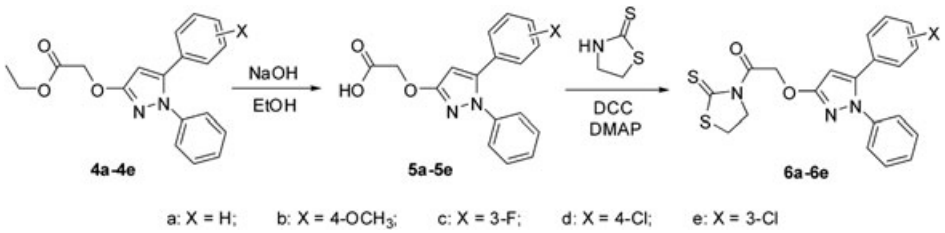
The DCC condensation of 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)acetic acids (**5a**–**5e**) with thiazolidine-2-thione was carried out in a molar ratio 1:1 in CH_2Cl_2 as solvent, using DMAP as catalyst according to a similar method [19], and was monitored by TLC. The most satisfactory results were obtained when the reactions were first stirred at 0°C for 3 h and then at room temperature for 12 h. The crude solids were purified *via* flash chromatography to furnish good yield of the desired products 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)-1-(2-thioxothiazolidin-3-yl)ethanones (**6a**–**6e**) (Scheme 3).

The structures of all synthesized compounds were confirmed by ^{1}H-NMR. Because of the difference of shielding effect between carboxyl and carbonyl-heteroaryl group, for compounds **5a**–**5e** and **6a**–**6e**, the chemical shift of the CH_2 in the oxy side chain appears at δ 4.74–4.92 ppm and δ 5.70–5.72 ppm, respectively, and the CH of the pyrazole ring appears at δ 6.04–6.24 ppm and δ 5.98–6.06 ppm, respectively. All these compounds showed a multiplet of aromatic protons in the range of δ 6.80–7.49 ppm. A single peak appearing at the lowest field of δ 9.48–12.92 ppm in the ^{1}H-NMR showed that the target compounds **5a**–**5e** have carboxyl hydrogen. For compounds **6a**–**6e**, the chemical shifts of the two CH_2 in thiazolidine-2-thione moiety appear at δ 4.60 ppm and δ 3.37 ppm, respectively. In addition, the results of single crystal X-ray diffraction analysis of 2-(1,5-diphenyl-1*H*-pyrazol-3-yloxy)-1-(2-thioxothiazolidin-3-yl)ethanone (**6a**) further validated the structure of the title compounds. Suitable crystals of **6a** were obtained by slow evaporation of ethyl acetate solutions at room temperature for about 10 days. Compound **6a** crystallizes in the monoclinic space group *P*21/*c* with unit cell parameters: a = 12.813(3) Å, b = 16.453(3) Å, c = 8.9470(18) Å, β = 97.68(3)°, Z = 4, D_c = 1.405 Mg m^{-3}, μ = 0.306 mm^{-1}, F(000) = 824. The detailed crystal data and structure refinement of **6a** are listed in Table 1. The molecular structure and the higher occupancy in the three-dimensional packing arrangement are shown in

Scheme 2



Scheme 3



Figures 1 and 2. The bond length of N1-C4 [1.408(5) Å] is longer than normal N-C amide bond (1.325–1.352 Å) [23]. The *C*-linked benzene ring A (C9-C14), *N*-linked benzene ring B (C15-C20), and thiazolidine-2-thione ring (N1/S1/C1-C3) are twisted 31.33°, 62.87°, and 82.71° from the plane of the bridge 1*H*-pyrazol ring (N2/N3/C6-C8), respectively. Rings A and B are, of course, planar and the dihedral angle between them is 72.16°. The intramolecular C-H**…**S hydrogen bond result in the formation of one nonplanar pseudoring (C5/H5B/S2/C3/N1/C4), in which it may be effective in the stabilization of the structure.

The compounds **4a**–**4e**, **5a**–**5e**, and **6a**–**6e** were screened for activity against two fungi, namely *Gibberella zeae* and *Rhizoctonia cerealis*, at a concentration of 10 μg mL^{-1} according to a reported method [9, 24]. As a result, in Table 2, most of the compounds have weak fungicidal activity. Among these compounds, only compound **6d**, in which X is Cl group at the 4-position on the phenyl ring, exhibited moderate inhibitory activity against *Gibberella zeae*. This might imply that the introduction of oxy(2-thioxothiazolidin-3-yl)ethanone group to the 1*H*-pyrazol-3-oxy was important for improving its fungicidal activity. In terms of the 3-substituent, molecular structure containing an oxy(2-thioxothiazolidin-3-yl)ethanone moiety seems to have somewhat higher fungicidal activity. The sequence of fungicidal activity against *Gibberella zeae* is oxy(2-thioxothiazolidin-3-yl)ethanone moiety > alkyloxyacetate moiety > oxyacetic acid moiety. For example, compound **6d** showed better activity than **4d** and **5d**. In terms of the substituents X, compounds with electron-withdrawing substituents on the phenyl ring displayed higher fungicidal activity against *Gibberella zeae* than that with electron-donating substituents, as seen in the comparison of the compounds **4d**–**6d** (X = 4-Cl) and **4b**–**6b** (X = 4-OCH_3) with X at the 4-position on the phenyl ring, **4c**–**6c** (X = 3-F) and **4e**–**6e** (X = 3-Cl) with X at the 3-position on the phenyl ring. Moreover, according to the different position and electronic effect of the electron-withdrawing substituents on the phenyl ring, the sequence of fungicidal activity against *Gibberella zeae* is para-substituted > meta-substituted and fluoro-substituted > chloro-substituted. For example, within the series of X = -Cl derivatives, para-substituted **4d**–**6d** showed higher fungicidal activity than the corresponding meta-substituted **4e**–**6e** and **4c**–**6c**, while the fluoro-substituted **4c**–**6c** displayed better activity than the chloro-substituted **4e**–**6e**. However, most compounds showed no fungicidal activity against *Rhizoctonia cerealis* except the compounds **4a**, **4c**, and **4d** with weak activity.

Table 1

Crystal data and structure refinement for **6a**.

Empirical formula	$C_{20}H_{17}N_3O_2S_2$
CCDC No.	823885
Formula weight	395.49
Temperature	293(2)
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, *P*21/*c* (No. 14)
Unit cell dimensions	*a* = 12.813(3) Å α = 90.00°
	b = 16.453(3) Å β = 97.68(3)°
	c = 8.9470(18) Å γ = 90.00°
Volume	1869.2(7) $Å^3$
Z, Calculated density	4, 1.405 Mg m^{-3}
Absorption coefficient	0.306 mm^{-1}
F(000)	824
Crystal size	0.10 × 0.20 × 0.30 mm
Theta range for data collection	1.60° to 25.27°
Limiting indices	$-15 <= h <= 15, -19 <= k <= 0, 0 <= l <= 10$
Reflections collected/unique	3625/3391 [R_{int} = 0.024]
Max. and min. transmission	0.9701 and 0.9139
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3391/2/244
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0678, wR_2 = 0.1790
Largest diff. peak and hole	0.655 and –0.670 e $Å^{-3}$

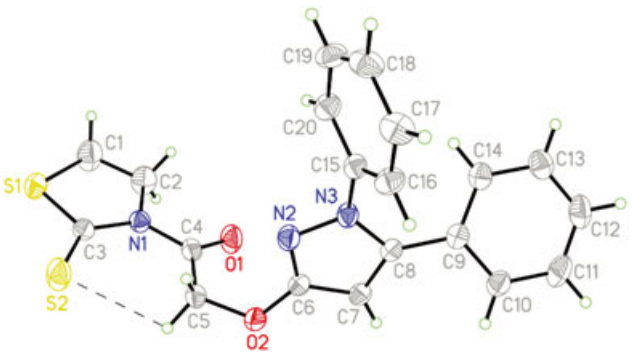


Figure 1. The molecular structure of **6a**.

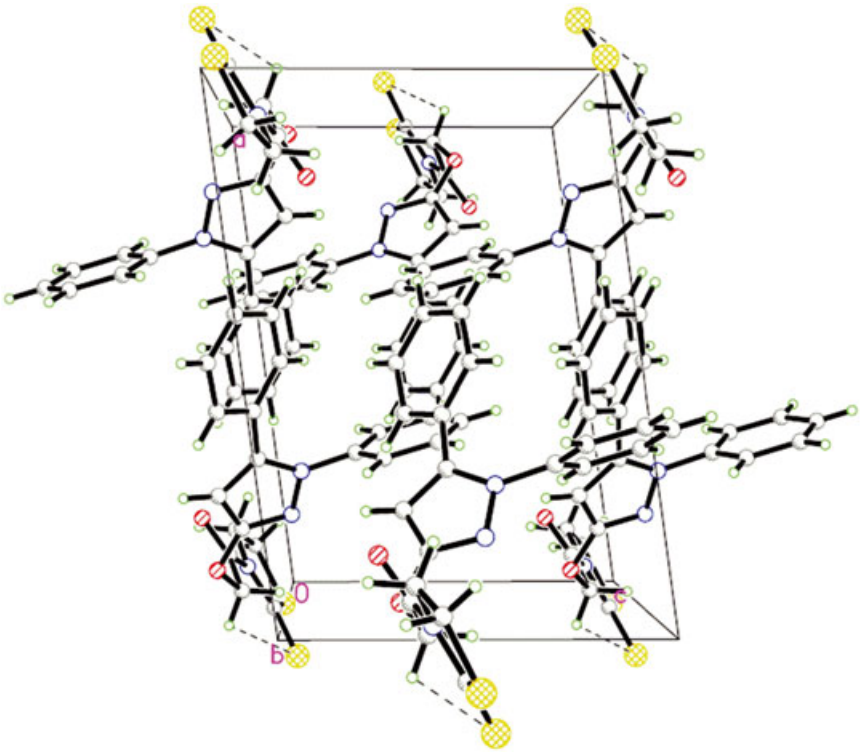


Figure 2. A partial packing diagram of **6a**.

EXPERIMENTAL

All reagents were of analytical reagent grade or were chemically pure. All solvents were dried by standard methods and distilled before use. Chromatographic purification of products was carried on flash silica gel (300–400 mesh). TLC was carried out using Merck Kieselgel 60 GF254 (230–400 mesh) fluorescent treated silica which were visualized under UV light (254 nm).

Table 2

Antifungal activity of newly synthesized compounds (% inhibition).

		10 μg mL^{-1}	
X	Compounds	*G. zeae*	*R. cerealis*
H	**4a**	21.29	18.44
	5a	–6.84	5.33
	6a	20.06	9.06
4-OCH_3	**4b**	1.14	4.92
	5b	–4.18	6.97
	6b	11.42	2.91
3-F	**4c**	30.25	17.15
	5c	16.36	9.39
	6c	30.56	0.97
4-Cl	**4d**	39.20	15.53
	5d	23.15	0.32
	6d	52.74	2.13
3-Cl	**4e**	23.38	8.54
	5e	13.27	8.41
	6e	28.66	0.72

Gibberella zeae and *Rhizoctonia cerealis* were obtained from Jiangsu Pesticide Research Institute, China.

Melting points were measured on an X-4 microscope electrothermal apparatus (Taike, China) and were uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AV-500 spectrometer at 500 MHz or a Bruker AV-300 spectrometer at 300 MHz using $CDCl_3$ or DMSO-d_6 as the solvent, with tetramethylsilane as an internal standard. IR spectra were recorded in KBr disk using a Nicolet 380 FTIR spectrophotometer and only diagnostic absorbances (λ_{max}) are reported. Elemental analyses were performed with a Flash EA-1112 elemental analyzer. X-Ray intensity data were recorded on a Bruker SMART 1000 charge coupled device (CCD) diffraction meter using graphite monochromated Mo Kα radiation (λ = 0.71073) Å.

Synthesis of compounds 4a–4e. The compounds **4a–4d** and new compound **4e** were synthesized from methyl 3-arylacrylates according to the reported procedure [9]. Spectral data of **4a–4d** match those previously reported [9, 25].

Ethyl 2-(5-(3-chlorophenyl)-1-phenyl-1H-pyrazol-3-yloxy) acetate (4e). White crystal; mp 95–96°C; yield: 3.07 g (86%); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.28–7.03 (m, 9H, Ar-H), 6.05 (s, 1H, CH), 4.87 (s, 2H, CH_2), 4.28 (q, *J* = 7.5 Hz, 2H, CH_2), 1.30 (t, *J* = 7.5 Hz, 3H, CH_3); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 168.9, 162.3, 142.9, 139.6, 134.4, 132.2, 129.6, 128.9, 128.6, 128.5, 127.1, 126.9, 124.9, 94.3, 65.4, 61.2, 14.2; IR (KBr, v, cm^{-1}): 3130, 3064, 2983, 2941, 1752, 1638, 1593, 1551, 1500, 1468, 1412, 1377, 1269, 1212, 1153, 1085, 794, 771, 700; Anal. Calcd. for $C_{19}H_{17}ClN_2O_3$: C 63.96, H 4.80, N 7.85; found C 63.87, H 4.81, N 7.82.

Synthesis of compounds 5a–5e. ***General Procedure.*** To a solution of **4a–4e** (10 mmol) in 95% ethanol (40 mL), sodium hydroxide (0.42 g, 10.5 mmol) was added. The mixture was then

stirred at room temperature until the starting material had been completely consumed as judged by TLC analysis. The solvent was evaporated under reduced pressure and water (10 mL) was added with good stirring. The aqueous layer was extracted with ethyl acetate and then acidified with hydrochloric acid, allowed to stand, and filtered. The precipitate that formed was filtered off and dried to furnish the desired compounds **5a**–**5e** that required no further purification.

2-(1,5-Diphenyl-1H-pyrazol-3-yloxy)acetic acid (5a). White crystal; mp 105–106°C; yield: 1.88 g (64%); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.91 (s, 1H, OH), 7.39–7.17 (m, 10H, Ar-H), 6.20 (s, 1H, CH), 4.76 (s, 2H, CH_2); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 173.4, 162.1, 144.9, 139.7, 130.3, 128.8, 128.7, 128.6, 128.5, 127.0, 125.0, 93.8, 65.2; IR (KBr, ν, cm^{-1}): 3419, 2913, 2774, 2664, 2575, 1744, 1595, 1548, 1503, 1421, 1310, 1257, 1207, 1152, 1081, 918, 759, 696; Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C 69.38, H 4.79, N 9.52; found C 69.46, H 4.80, N 9.49.

2-(5-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-3-yloxy)acetic acid (5b). White crystal; mp 167–168°C; yield: 2.14 g (66%); ^{1}H-NMR (500 MHz, DMSO-d_6) δ 12.82 (s, 1H, OH), 7.38–6.90 (m, 9H, Ar-H), 6.11 (s, 1H, CH), 4.74 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) δ 169.9, 162.0, 159.3, 143.9, 139.7, 129.7, 128.9, 126.9, 124.7, 122.2, 114.0, 93.0, 64.7, 55.1; IR (KBr, ν, cm^{-1}): 3432, 2923, 1745, 1601, 1553, 1510, 1475, 1422, 1258, 1203, 1153, 1078, 819, 765, 697; Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C 66.66, H 4.97, N 8.64; found C 66.72, H 4.96, N 8.67.

2-(5-(3-Fluorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)acetic acid (5c). White crystal; mp 141–142°C; yield: 1.91 g (61%); ^{1}H-NMR (500 MHz, DMSO-d_6) δ 12.86 (s, 1H, OH), 7.39–7.17 (m, 9H, Ar-H), 6.20 (s, 1H, CH), 4.75 (s, 2H, CH_2); ^{13}C-NMR (300 MHz, DMSO-d_6) δ 169.9, 163.6, 162.0, 143.0, 139.4, 130.7, 130.6, 129.0, 127.1, 126.4, 124.8, 115.7, 115.4, 93.7, 64.8; IR (KBr, ν, cm^{-1}): 3415, 3064, 2912, 2772, 2665, 2574, 1747, 1591, 1551, 1504, 1423, 1257, 1150, 1083, 865, 767, 696; Anal. Calcd. for $C_{17}H_{13}FN_2O_3$: C 65.38, H 4.20, N 8.97; found C 65.45, H 4.21, N 8.94.

2-(5-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)acetic acid (5d). White crystal; mp 159–160°C; yield: 2.01 g (61%); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.92 (s, 1H, OH), 7.44–7.18 (m, 9H, Ar-H), 6.24 (s, 1H, CH), 4.75 (s, 2H, CH_2); ^{13}C-NMR (300 MHz, DMSO-d_6) δ 169.7, 162.0, 143.9, 139.3, 133.3, 130.1, 129.0, 128.6, 128.0, 127.2, 124.8, 93.7, 65.0; IR (KBr, ν, cm^{-1}): 3412, 3063, 2781, 1747, 1600, 1549, 1504, 1427, 1239, 1089, 1062, 1017, 838, 768, 696; Anal. Calcd. for $C_{17}H_{13}ClN_2O_3$: C 62.11, H 3.99, N 8.52; found C 62.19, H 3.98, N 8.55.

2-(5-(3-Chlorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)acetic acid (5e). White crystal; mp 172–173°C; yield: 2.07 g (63%); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H, OH), 7.32–7.03 (m, 9H, Ar-H), 6.04 (s, 1H, CH), 4.92 (s, 2H, CH_2); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 173.5, 162.1, 143.2, 139.4, 134.4, 132.0, 130.0, 129.7, 129.0, 128.7, 127.3, 126.9, 125.0, 94.2, 65.0; IR (KBr, ν, cm^{-1}): 3411, 3064, 2911, 2771, 2666, 2573, 1747, 1591, 1551, 1501, 1421, 1256, 1085, 919, 865, 767, 696; Anal. Calcd. for $C_{17}H_{13}ClN_2O_3$: C 62.11, H 3.99, N 8.52; found C 62.21, H 3.40, N 8.55.

Synthesis of compounds 6a–6e. ***General Procedure.*** Compounds **5a**–**5e** (1.0 mmol) was dissolved in a solution of DCC (0.22 g, 1.05 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred at 0°C for 1 h. Then thiazolidine-2-thione (0.12 g, 1.0 mmol) and DMAP (0.01 g, 0.1 mmol) was added. The solution was stirred at 0°C for 2 h and then at room temperature for 12 h. The white precipitate was filtered off, and the solvent was evaporated under reduced pressure. The residue was then purified by flash column chromatography over silica gel (50 g) eluting with petroleum ether/ethyl acetate 3:1 to gain the target compounds **6a**–**6e**.

2-(1,5-Diphenyl-1H-pyrazol-3-yloxy)-1-(2-thioxothiazolidin-3-yl)ethanone (6a). Yellow crystal; mp 187–188°C; yield: 0.28 g (71%); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30–7.20 (m, 10H, Ar-H), 6.04 (s, 1H, CH), 5.71 (s, 2H, CH_2), 4.60 (t, J = 7.5 Hz, 2H, CH_2), 3.37 (t, J = 7.5 Hz, 2H, CH_2); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 201.1, 170.4, 162.2, 144.5, 140.0, 130.6, 128.7, 128.6, 128.4, 126.7, 124.8, 94.0, 69.7, 55.5, 29.7; IR (KBr, ν, cm^{-1}): 3154, 3054, 2948, 1699, 1594, 1550, 1503, 1471, 1361, 1276, 1223, 1178, 1145, 1073, 964, 914, 875, 756, 696; Anal. Calcd. for $C_{20}H_{17}N_3O_2S_2$: C 60.74, H 4.33, N 10.62; found C 60.66, H 4.34, N 10.66.

2-(5-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-3-yloxy)-1-(2-thioxothiazolidin-3-yl)ethanone (6b). Yellow crystal; mp 162–163°C; yield: 0.29 g (68%); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.27–6.80 (m, 9H, Ar-H), 5.98 (s, 1H, CH), 5.70 (s, 2H, CH_2), 4.60 (t, J = 7.6 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.37 (t, J = 7.6 Hz, 2H, CH_2); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 201.1, 170.4, 162.1, 159.7, 144.4, 140.1, 130.0, 128.6, 126.5, 124.8, 123.0, 113.8, 93.5, 69.7, 55.5, 55.2, 29.7; IR (KBr, ν, cm^{-1}): 3033, 2928, 2854, 1712, 1602, 1553, 1510, 1476, 1448, 1378, 1263, 1228, 1161, 1073, 967, 765, 697; Anal. Calcd. for $C_{21}H_{19}N_3O_3S_2$: C 59.27, H 4.50, N 9.87; found C 59.36, H 4.49, N 9.90.

2-(5-(3-Fluorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)-1-(2-thioxothiazolidin-3-yl)ethanone (6c). Yellow crystal; mp 121–122°C; yield: 0.29 g (70%); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31–6.91 (m, 9H, Ar-H), 6.06 (s, 1H, CH), 5.72 (s, 2H, CH_2), 4.60 (t, J = 7.6 Hz, 2H, CH_2), 3.37 (t, J = 7.6 Hz, 2H, CH_2); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 201.1, 170.3, 164.1, 162.2, 143.2, 139.7, 132.5, 130.1, 128.8, 127.1, 124.9, 124.5, 115.9, 115.6, 94.4, 69.8, 55.5, 29.7; IR (KBr, ν, cm^{-1}): 3063, 2928, 2854, 1710, 1590, 1553, 1502, 1447, 1368, 1279, 1228, 1172, 1059, 864, 779, 696, 671; Anal. Calcd. for $C_{20}H_{16}FN_3O_2S_2$: C 58.09, H 3.90, N 10.16; found C 58.18, H 3.91, N 10.12.

2-(5-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)-1-(2-thioxothiazolidin-3-yl)ethanone (6d). Yellow crystal; mp 132–133°C; yield: 0.30 g (71%); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.49–7.18 (m, 9H, Ar-H), 6.03 (s, 1H, CH), 5.71 (s, 2H, CH_2), 4.60 (t, J = 7.6 Hz, 2H, CH_2), 3.37 (t, J = 7.6 Hz, 2H, CH_2); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 201.1, 170.3, 162.3, 143.0, 139.7, 134.2, 131.0, 129.9, 128.9, 127.2, 126.7, 124.9, 94.4, 69.8, 55.5, 29.7; IR (KBr, ν, cm^{-1}): 2926, 2855, 1705, 1671, 1611, 1548, 1505, 1459, 1402, 1369, 1325, 1265, 1222, 1159, 1087, 1054, 916, 814, 749, 696; Anal. Calcd. for $C_{20}H_{16}ClN_3O_2S_2$: C 55.87, H 3.75, N 9.77; found C 55.75, H 3.76, N 9.74.

2-(5-(3-Chlorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)-1-(2-thioxothiazolidin-3-yl)ethanone (6e). Yellow crystal; mp 143–144°C; yield: 0.31 g (73%); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30–7.05 (m, 9H, Ar-H), 6.05 (s, 1H, CH), 5.72 (s, 2H, CH_2), 4.60 (t, J = 7.6 Hz, 2H, CH_2), 3.37 (t, J = 7.6 Hz, 2H, CH_2); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 201.1, 170.3, 162.3, 143.0, 139.7, 134.4, 132.3, 129.7, 128.9, 128.7, 128.6, 127.1, 127.0, 124.9, 94.4, 69.8, 55.5, 29.7; IR (KBr, ν, cm^{-1}): 3128, 3060, 2927, 2851, 1706, 1594, 1549, 1501, 1468, 1441, 1368, 1279, 1224, 1187, 1054, 879, 767, 695, 672; Anal. Calcd. for $C_{20}H_{16}ClN_3O_2S_2$: C 55.87, H 3.75, N 9.77; found C 55.78, H 3.74, N 9.80.

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