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Synthesis and Biological Activities of Novel Bis-heterocyclic Pyrrodiazole Derivatives

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ABSTRACT: *Novel structures of bis-heterocyclic pyrrodiazole derivatives containing pyrazole were designed and synthesized. The title compounds were characterized by ^{1}H NMR, IR, MS, and elemental analysis. Biological activities of three intermediate compounds and 25 pyrrodiazole derivatives were tested in vivo and in vitro. Some of the title compounds exhibited certain herbicidal activities against barnyardgrass and rape.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:21–27, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20369

INTRODUCTION

Research on the synthesis and biological activity of bis-heterocyclic compounds is an important research field for finding new pesticides. A lot of pesticides included a bis-heterocyclic structure, such as triabendazole [1], imidacloprid [2], and imazaquin [3]. Moreover, some structures with a pyrazole ring exhibited outstanding biological activities [4–7].

Plants contain numerous enzymes that are potential targets for herbicides. The enzymes involved in the biosynthesis of the branched-chain amino acids such as leucine, isoleucine, and valine are examples of such a pathway [8]. The first successful herbicides, targeting this pathway, were sulfonylureas [9] and imidazolinones [10], both of which inhibitacetohydroxyacid synthase in the first step of branched-chain amino acids biosynthesis pathway. Stimulated by the success of these herbicides, we have tried to find the inhibitors of other enzymes in this pathway. Ketol-acid reductoisomerase (KARI; EC 1.1.1.86) [12,13] is one such a case, which is the second enzyme in the biosynthesis of the branched-chain amino acids pathway [11].

On the basis of the reported 1.65 Å high-resolution crystal structure of spinach KARI complex [14], we obtained 279 molecules with low-binding energy toward KARI through the MDL/ACD 3D database, using the program DOCK 4.0 [15]. These potential structures provide more information for the design of new KARI herbicidal molecules, one of which is the title compounds that have low-binding energy. Considering the common bioactivity of bis-heterocyclic compounds and low-binding energy to KARI, we selected bis-heterocyclic derivatives to synthesize.

The title bis-heterocyclic derivatives were first synthesized, and the herbicidal activities of these compounds were tested in vivo and in vitro.

EXPERIMENTAL

Instruments

Melting points were determined using an uncorrected Yanaco MP-241 apparatus. Infrared spectra were recorded on a Bruker Equinox55 spectrophotometer as potassium bromide tablets. ^{1}H

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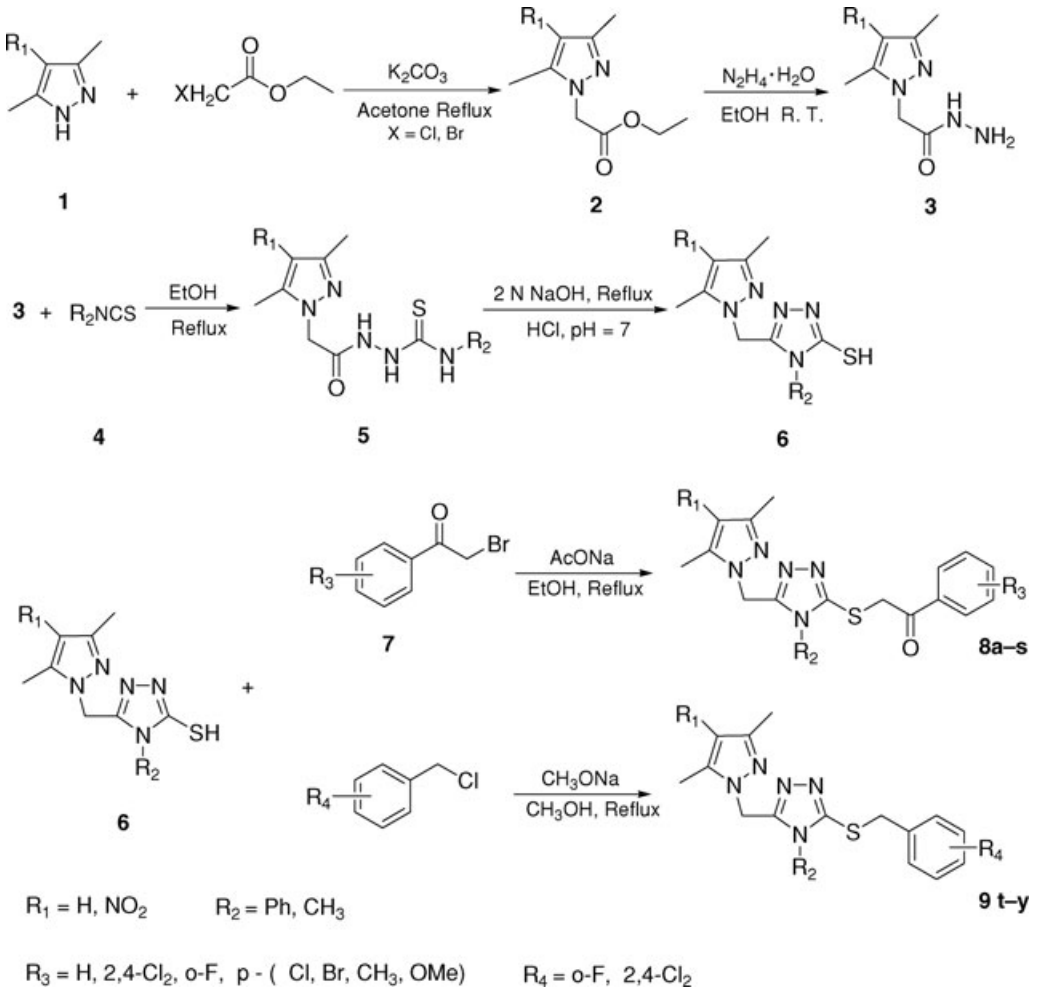

FIGURE 1 Synthetic route for compounds **8a–s** and **9t–y**.

NMR spectra were determined by Bruker AC-P500 (300 MHz), using tetramethylsilane as internal standard and $CDCl_3$ as solvent. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. Elemental analyses were determined on a Yanaco MT-3CHN elemental analyzer.

Synthesis of Compounds

The route shown in Fig. 1 was used for the synthesis of the title compounds. The yields were not optimized.

*2-(3,5-Trimethyl-1H-pyrazol-1-yl) acetohydrazide (**3a**) and 2-(3,5-Trimethyl-4-nitro-1H-pyrazol-1-yl) acetohydrazide (**3b**).* A mixture of acetylacetone (7.0 g, 0.12 mol) and hydrazine hydrate (7.0 g, 85%) was refluxed for 3 h in alcohol. Then, the alcohol was evaporated. Acetone (20 mL), ethyl chloroacetate (6.13 g, 122.55 mL), and K_2CO_3 (6.91 g), TBAB (Tetra Butyl Ammonium Bromide) as a catalyst, were added to the residue (**1a**; 3,5-dimethylpyrazole) and was refluxed for 18 h to give compound **2a**. After evaporating the solvent, hydrazine hydrate (1.34 g, 26.76 mmol) and alcohol (8 mL) were added and the mixture was stirred for 4 h at room temperature. Compound **3a** was obtained in 86.4% yield. The melting point was same as reported earlier [16].

3,5-Dimethyl-pyrazole reacted with nitric acid in acetic acid and acetic anhydride gave 3,5-dimethyl-4-nitro-pyrazole (**1b**). Same steps were followed for preparing **3b** as described for **3a**, except that ethyl chloroacetate was replaced by ethyl bromoacetate for **2b**. Compound **3b** was obtained in 74.0% yield. The melting point was 175–177°C.

*4-Methyl-5-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-4H-1,2,4-triazole-3-thiol (**6a**), 4-phenyl-5-((3,5-*

*dimethyl-1H-pyrazol-1-yl)methyl)-4H-1,2,4-triazole-3-thiol (**6b**), 4-Methyl-5-((3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)methyl)-4H-1,2,4-triazole-3-thiol (**6c**).* Compound **3** reacting with 1.5 g of substituted isothiocyanate gave compound **5** after 3-h refluxing in alcohol. Compound **5** was refluxed with 2 N NaOH for 3 h and was neutralized by diluted hydrochloric acid to give compound **6**. The yields of this step were quantitative. The melting points were above 260°C. ^{1}H NMR of **6a**: (300 MHz, $CDCl_3$) 11.25 (s, SH, 1H), 5.17 (s, N-CH_2, 2H), 3.78 (s, N-CH_3, 3H), 2.70 (s, Py-CH_3, 3H), 2.34 (s, Py-CH_3, 3H); ^{1}H NMR of **6b**: (300 MHz, $CDCl_3$) 12.78 (s, SH, 1H), 7.41–7.47 (m, PhH, 3H), 7.14 (d, $J = 6.7$, PhH, 2H), 5.68 (s, PyH, 1H), 5.05 (s, N-CH_2, 2H), 2.26 (s, Py-CH_3, 3H), 2.67 (s, Py-CH_3, 3H); ^{1}H NMR of **6c**: (400 MHz, $CDCl_3$) 10.15 (s, SH, 1H), 5.27 (s, N-CH_2, 2H), 3.69 (s, N-CH_3, 3H), 2.71 (s, Py-CH_3, 3H), 2.50 (s, Py-CH_3, 3H).

General Procedure for Preparation of **8a–s** *and* **9t–y**

*2-(5-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-4-methyl-4H-1,2,4-triazol-3-ylthio)-1-phenylethanone (**8a**).* Compound **6** was refluxed with substituted α-bromoacetophenone, sodium acetate, and alcohol for 1 h to give compound **8a**. The compound was obtained in 67.1% yield as a white crystal; mp 119–121°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.98 (d, $J = 8.3$, ArH, 2H), 7.59 (t, $J = 7.2$, ArH, 1H), 7.47 (t, $J = 7.6$, ArH, 2H), 5.81 (s, PyH, 1H), 5.38 (s, Py-CH_2, 2H), 4.88 (s, S-CH_2, 2H), 3.65 (s, N-CH_3, 3H), 2.77 (s, Py-CH_3, 3H), 2.19 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1681, 1595, 1552, 1474, 1445, 1187. MS (ESI), *m/z*: 438 (M − 1), 271, 220. Elemental Anal. (%), Calcd.: C, 59.71; H, 5.71; N, 20.56; Found: C, 59.80; H, 5.61; N, 20.51.

*2-(5-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)-1-phenylethanone (**8b**).* The compound was obtained in 73.5% yield as a white crystal; mp 138–139°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 8.00 (d, $J = 8.6$, ArH, 2H), 7.59 (t, $J = 7.6$, N-PhH, 1H), 7.42–7.51 (m, N-PhH and ArH, 5H), 7.10 (d, $J = 7.4$, N-PhH, 2H), 5.68 (s, PyH, 1H), 5.21 (s, Py-CH_2, 2H), 4.91 (s, S-CH_2, 2H), 2.05 (s, Py-CH_3, 3H), 2.04 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1681, 1595, 1559, 1488, 1438, 1187. MS (ESI), *m/z*: 404 (M + 1), 387, 310, 189. Elemental Anal. (%) Calcd.: C, 65.48; H, 5.19; N, 17.21; Found: C, 65.49; H, 5.25; N, 17.36.

*1-(4-Chlorophenyl)-2-(5-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio) ethanone (**8c**).* The compound was obtained in 62.5% yield as a white crystal; mp 161–163°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.96 (d, $J = 8.5$, ArH, 2H), 7.43–7.54 (m, N-PhH and ArH, 5H), 7.12 (d, $J = 7.7$, N-PhH, 2H), 5.69 (s, PyH, 1H), 5.21 (s, Py-CH_2, 2H), 4.86 (s, S-CH_2, 2H), 2.06 (s, Py-CH_3, 6H). IR (KBr), ν (cm^{-1}): 1681, 1595, 1545, 1495, 1438, 1216. MS (ESI), *m/z*: 436 (M + 1), 385, 340, 313, 267, 239. Elemental Anal. (%), Calcd.: C, 60.21; H, 4.59; N, 16.00; Found: C, 60.34; H, 4.60; N, 15.99.

*2-(5-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)-1-(4-fluorophenyl) ethanone (**8d**).* The compound was obtained in 67.6% yield as a white crystal; mp 166–167°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 8.03–8.06 (m, ArH, 2H), 7.43–7.52 (m, N-PhH, 3H), 7.10–7.16 (m, N-PhH and ArH, 4H), 5.68 (s, PyH, 1H), 5.21 (s, Py-CH_2, 2H), 4.86 (s, S-CH_2, 2H), 2.04 (s, Py-CH_3, 6H). IR (KBr), ν (cm^{-1}): 1667, 1595, 1552, 1495, 1438, 1159. MS (ESI), *m/z*: 422 (M + 1), 342, 256, 179. Elemental Anal. (%), Calcd: C, 62.84; H, 4.61; N, 16.86; Found: C, 62.69; H, 4.78; N, 16.62.

*2-(5-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-4-methyl-4H-1,2,4-triazol-3-ylthio)-1-(4-fluorophenyl) ethanone (**8e**).* The compound was obtained in 80.0% yield as a white crystal; mp 180–181°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 8.02–8.07 (m, ArH, 2H), 7.16 (t, $J = 8.4$, ArH, 2H), 5.81 (s, PyH, 1H), 5.37 (s, Py-CH_2, 2H), 4.85 (s, S-CH_2, 2H), 3.66 (s, N-CH_3, 3H), 2.28 (s, Py-CH_3, 3H), 2.19 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1674, 1595, 1538, 1481, 1431, 1151. MS (ESI), *m/z*: 458 (M − 1), 339, 325, 267, 222. Elemental Anal. (%), Calcd: C, 56.66; H, 5.18; N, 19.28; Found: C, 56.81; H, 5.05; N, 19.49.

*1-(4-Chlorophenyl)-2-(5-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-4-methyl-4H-1,2,4-triazol-3-ylthio) ethanone (**8f**).* The compound was obtained in 85.3% yield as a white crystal; mp 185–187°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.95 (d, $J = 8.5$, ArH, 2H), 7.45 (d, $J = 8.6$, ArH, 2H), 5.82 (s, PyH, 1H), 5.39 (s, Py-CH_2, 2H), 4.84 (s, S-CH_2, 2H), 3.66 (s, N-CH_3, 3H), 2.28 (s, Py-CH_3, 3H), 2.19 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1681, 1588, 1552, 1481, 1431, 1080. MS (ESI), *m/z*: 376 (M + 1), 360. Elemental Anal. (%), Calcd: C, 54.19; H, 4.80; N, 18.76; Found: C, 54.32; H, 4.83; N, 18.63.

*2-(5-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)-1-(4-methoxyphenyl)ethanone (**8g**).* The compound was obtained in 77.3% yield as a white crystal; mp 128–129°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 8.01 (d, $J = 8.5$, ArH,

2H), 7.44–7.54 (m, N-PhH, 3H), 7.12 (d, $J = 8.1$, N-PhH, 2H), 6.96 (d, $J = 8.5$, ArH, 2H), 5.70 (s, PyH, 1H), 5.23 (s, Py-CH_2, 2H), 4.90 (s, S-CH_2, 2H), 3.89 (s, N-CH_3, 3H), 2.07 (s, Py-CH_3, 3H), 2.06 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1660, 1588, 1545, 1502, 1431, 1180. MS (ESI), *m/z*: 434 (M + 1), 360, 179. Elemental Anal. (%), Calcd: C, 63.51; H, 5.27; N, 16.16; Found: C, 63.72; H, 5.35; N, 16.15.

*2-(5-((3,5-Dimethyl-4-nitro-1H-pyrazol-1-yl) methyl)-4-methyl-4H-1,2,4-triazol-3-ylthio)-1-phenylethanone (***8h***)*. The compound was obtained in 91.6% yield as a white crystal; mp 212–214°C; ^{1}H NMR (DMSO-d_6, 300 MHz), δ: 8.00 (d, $J = 7.3$, ArH, 2H), 7.68 (t, $J = 6.9$, ArH, 1H), 7.55 (t, $J = 7.5$, ArH, 2H), 5.58 (s, Py-CH_2, 2H), 4.86 (s, S-CH_2, 2H), 3.59 (s, N-CH_3, 3H), 2.62 (s, Py-CH_3, 3H), 2.38 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1674, 1552, 1481, 1452, 1202. MS (ESI), *m/z*: 387 (M + 1), 310, 247. Elemental Anal. (%), Calcd: C, 52.79; H, 4.73; N, 21.81; Found: C, 52.84; H, 4.70; N, 21.75.

*2-(5-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)-1-(4-nitrophenyl) ethanone (***8l***)*. The compound was obtained in 69.0% yield as a white crystal; mp 179–183°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.86 (d, $J = 8.5$, ArH, 2H), 7.62 (d, $J = 8.5$, ArH, 2H), 5.81 (s, PyH, 1H), 5.37 (s, Py-CH_2, 2H), 4.82 (s, S-CH_2, 2H), 3.65 (s, N-CH_3, 3H), 2.27 (s, Py-CH_3, 3H), 2.19 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1681, 1574, 1481, 1416, 1194. MS (ESI), *m/z*: 449 (M + 1), 404. Elemental Anal. (%), Calcd: C, 48.40; H, 4.45; N, 16.50; Found: C, 48.58; H, 4.32; N, 16.66.

*1-(4-Bromophenyl)-2-(5-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio) ethanone (***8m***)*. The compound was obtained in 81.4% yield as a white crystal; mp 101–102°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.64 (d, $J = 8.4$, ArH(6), 1H), 7.44 (d, $J_{ac} = 1.9$, ArH(3), 1H), 7.32 (dd, $J_{ab} = 8.4$, $J_{ac} = 1.9$, ArH(5), 1H), 5.82 (s, PyH, 1H), 5.36 (s, N-CH_2, 2H), 4.67 (s, S-CH_2, 2H), 3.64 (s, N-CH_3, 3H), 2.28 (s, Py-CH_3, 3H), 2.20 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1681, 1581, 1545, 1488, 1459, 1101. MS (ESI), *m/z*: 483 (M + 1), 447, 430, 354, 284. Elemental Anal. (%), Calcd: C, 49.72; H, 4.02; N, 17.30; Found: C, 49.76; H, 4.18; N, 17.07.

*1-(2,4-Dichlorophenyl)-2-(5-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)ethanone (***8n***)*. The compound was obtained in 75.9% yield as a white crystal; mp 137–138°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.91 (d, $J = 8.2$, ArH, 2H), 7.26–7.52 (m, N-PhH and ArH, 5H), 7.10 (d, $J = 7.2$, N-PhH, 2H), 5.68 (s, PyH, 1H), 5.22 (s, N-CH_2, 2H), 4.91 (s, S-CH_2, 2H), 3.42 (s, ArCH_3, 3H), 2.06 (s, Py-CH_3, 3H), 2.04 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1741, 1700, 1648, 1544, 1511, 1467, 1400, 1063. MS (ESI), *m/z*: 472 (M + 1), 329, 179. Elemental Anal. (%), Calcd: C, 65.97; H, 5.54; N, 17.01; Found: C, 66.16; H, 5.55; N, 16.77.

*1-(4-Bromophenyl)-2-(5-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-4-methyl-4H-1,2,4-triazol-3-ylthio)-ethanone (***8o***)*. The compound was obtained in 61.3% yield as a white crystal; mp 133–134°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.97 (d, $J = 8.9$, ArH, 2H), 6.93 (d, $J = 8.9$, ArH, 2H), 5.79 (s, PyH, 1H), 5.35 (s, N-CH_2, 2H), 4.83 (s, S-CH_2, 2H), 3.87 (s, OCH_3, 3H), 3.63 (s, N-CH_3, 3H), 2.26 (s, Py-CH_3, 3H), 2.17 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1661, 1602, 1457, 1413, 1245. MS (ESI), *m/z*: 422 (M + 1), 351, 329, 256, 179. Elemental Anal. (%), Calcd: C, 58.22; H, 5.72; N, 18.99; Found: C, 58.20; H, 5.70; N, 18.85.

*1-(2,4-Dichlorophenyl)-2-(5-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-4-methyl-4H-1,2,4-triazol-3-ylthio)ethanone (***8p***)*. The compound was obtained in 86.7% yield as a white crystal; mp 206–208°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.90 (d, $J = 8.2$, ArH, 2H), 7.28 (d, $J = 8.2$, ArH, 2H), 5.40 (s, Py-CH_2, 2H), 4.88 (s, S-CH_2, 2H), 3.74 (s, N-CH_3, 3H), 2.75 (s, Py-CH_3, 3H), 2.49 (s, Py-CH_3, 3H), 2.43 (s, ArCH_3, 3H). IR (KBr), ν (cm^{-1}): 1675, 1566, 1486, 1202. MS (ESI), *m/z*: 410, 142, 414 (M + 1). Elemental Anal. (%), Calcd: C, 53.71; H, 5.09; N, 21.00; Found: C, 53.99; H, 5.03; N, 20.99.

*2-(5-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)-1-p-tolylethanone (***8r***)*. The compound was obtained in 62.3% yield as a white crystal; mp 122–123°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.65 (d, $J = 8.4$, ArH(6), 1H), 7.45 (d, $J_{ac} = 1.9$, ArH(3), 1H), 7.34 (dd, $J_{ab} = 8.4$, $J_{ac} = 2.0$, ArH(5), 1H), 5.39 (s, Py-CH_2, 2H), 4.71 (s, S-CH_2, 2H), 3.73 (s, N-CH_3, 3H), 2.75 (s, Py-CH_3, 3H), 2.49 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1674, 1567, 1495, 1409, 1187. MS (ESI), *m/z*: 418 (M + 1). Elemental Anal. (%), Calcd: C, 44.62; H, 3.60; N, 18.42; Found: C, 44.84; H, 3.54; N, 18.46.

*2-(5-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-4-methyl-4H-1,2,4-triazol-3-ylthio)-1-(4-methoxyphenyl)ethanone (***9t***)*. The compound was obtained in 87.4% yield as a white crystal; mp 93–95°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.44–7.49 (m, ArH and N-PhH, 2H), 7.38 (t, $J = 7.6$, N-PhH, 2H), 7.32 (d, $J_{ac} = 1.9$, ArH(3), 1H), 7.13 (dd, $J_{ab} = 8.4$, $J_{ac} = 1.9$, ArH(5),

1H), 6.91 (d, $J = 7.7$, N-PhH, 2H), 5.67 (s, PyH, 1H), 5.17 (s, Py-CH_2, 2H), 2.04 (s, Py-CH_3, 6H). IR (KBr), ν (cm^{-1}): 1741, 1700, 1648, 1544, 1511, 1467, 1400, 1063. MS (ESI), *m/z*: 372 (M + 1), 256, 179. Elemental Anal. (%), Calcd: C, 56.50; H, 4.57; N, 15.51; Found: C, 56.76; H, 4.31; N, 15.76.

*2-(5-((3,5-Dimethyl-4-nitro-1H-pyrazol-1-yl) methyl)-4-methyl-4H-1,2,4-triazol-3-ylthio)-1-p-tolylethanone (***9u***)*. The compound was obtained in 52.4% yield as a white crystal; mp 79–80°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.15–7.22 (m, ArH, 2H), 6.91–7.00 (m, ArH, 2H), 5.79 (s, PyH, 1H), 5.32 (s, Py-CH_2, 2H), 4.33 (s, S-CH_2, 2H), 3.34 (s, N-CH_3, 3H), 2.27 (s, Py-CH_3, 3H), 2.16 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1741, 1700, 1648, 1544, 1511, 1467, 1400, 1063. MS (ESI), *m/z*: 401 (M + 1), 3372, 351, 256, 179. Elemental anal. (%), Calcd: C, 57.94; H, 5.70; N, 21.31; Found: C, 57.99; H, 5.47; N, 21.13.

*1-(4-Chlorophenyl)-2-(5-((3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)methyl)-4-methyl-4H-1,2,4-triazol-3-ylthio)ethanone (***9v***)*. The compound was obtained in 45.2% yield as a white crystal; mp 168–169°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.18–7.26 (m, ArH, 2H), 6.92–7.00 (m, ArH, 2H), 5.36 (s, Py-CH_2, 2H), 4.37 (s, S-CH_2, 2H), 3.45 (s, N-CH_3, 3H), 2.74 (s, Py-CH_3, 3H), 2.46 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1559, 1488, 1452, 1416, 1230. MS (ESI), *m/z*: 421 (M + 1), 372, 351, 256, 179. Elemental Anal. (%), Calcd: C, 50.84; H, 4.55; N, 22.29; Found: C, 51.05; H, 4.55; N, 22.33.

*1-(2,4-Dichlorophenyl)-2-(5-((3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)methyl)-4-methyl-4H-1,2,4-triazol-3-ylthio)ethanone (***9w***)*. The compound was obtained in 82.3% yield as a white crystal; mp 128–129°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.36 (d, $J_{ac} = 2.1$, ArH(3), 1H), 7.26 (d, $J = 7.7$, ArH(6), 1H), 7.06 (dd, $J_{ab} = 8.4$, $J_{ac} = 2.1$, ArH(5), 1H), 5.81 (s, PyH, 1H), 5.33 (s, Py-CH_2, 2H), 4.41 (s, S-CH_2, 2H), 3.40 (s, N-CH_3, 3H), 2.29 (s, Py-CH_3, 3H), 2.18 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1741, 1700, 1648, 1544, 1511, 1467, 1400, 1063. MS (ESI), *m/z*: 453 (M − 1), 408, 222. Elemental Anal. (%), Calcd: C, 50.39; H, 4.29; N, 17.88; Found: C, 50.27; H, 4.48; N, 18.32.

*2-(5-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-4-methyl-4H-1,2,4-triazol-3-ylthio)-1-p-tolylethanone (***9y***)*. The compound was obtained in 67.2% yield as a white crystal; mp 152–153°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.36 (d, $J_{ac} = 2.0$, ArH(3), 1H), 7.33 (d, $J = 8.3$, ArH(6), 1H), 7.08 (dd, $J_{ab} = 8.4$, $J_{ac} = 2.0$, ArH(5), 1H), 5.37 (s, Py-CH_2, 2H), 4.45 (s, S-CH_2, 2H), 3.49 (s, N-CH_3, 3H), 2.76 (s, Py-CH_3, 3H), 2.48 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1559, 1493, 1464, 1413, 1129. MS (ESI), *m/z*: 356 (M + 1), 256, 179. Elemental Anal. (%), Calcd: C, 44.76; H, 3.69; N, 19.66; Found: C, 44.97; H, 3.77; N, 19.67.

*3-(2,4-Dichlorobenzylthio)-5-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-4-methyl-4H-1,2,4-triazole (***8q***)*. The compound was obtained in 84.8% yield as a white crystal; mp 181–182°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.95 (d, $J = 8.6$, ArH, 2H), 7.46 (d, $J = 8.6$, ArH, 2H), 5.39 (s, Py-CH_2, 2H), 4.84 (s, S-CH_2, 2H), 3.74 (s, N-CH_3, 3H), 2.75 (s, Py-CH_3, 3H), 2.48 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1681, 1574, 1488, 1414, 1202. MS (ESI), *m/z*: 382, 384, 386 (M + 1), 310, 296. Elemental Anal. (%), Calcd: C, 48.29; H, 4.14; N, 19.89; Found: C, 48.51; H, 4.07; N, 19.97.

*3-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-5-(2-fluorobenzylthio)-4-phenyl-4H-1,2,4-triazole (***8s***)*. The compound was obtained in 86.4% yield as a white crystal; mp 133–134°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.90 (d, $J =$ 8.1, ArH, 2H), 7.27 (d, $J = 8.1$, ArH, 2H), 5.80 (s, PyH, 1H), 5.36 (s, Py-CH_2, 2H), 4.86 (s, S-CH_2, 2H), 3.64 (s, N-CH_3, 3H), 2.42 (s, Py-CH_3, 3H), 2.27 (s, Py-CH_3, 3H), 2.19 (s, ArCH_3, 3H). IR (KBr), ν (cm^{-1}): 1667, 1610, 1552, 1474, 1194. MS (ESI), *m/z*: 394 (M + 1). Elemental Anal. (%), Calcd: C, 60.71; H, 6.03; N, 19.93; Found: C, 60.82; H, 5.95; N, 19.70.

*3-(2,4-Dichlorobenzylthio)-5-((3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)methyl)-4-methyl-4H-1,2,4-triazole (***9x***)*. The compound was obtained in 53.2% yield as a white crystal; mp 111–112°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 6.96–7.47 (m, N-PhH and ArH, 7H), 6.90 (d, $J = 7.2$, N-PhH, 2H), 5.68 (s, PyH, 1H), 5.19 (s, Py-CH_2, 2H), 4.43 (s, S-CH_2, 2H), 2.05 (s, Py-CH_3, 3H), 2.03 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1741, 1700, 1648, 1544, 1511, 1467, 1400, 1063. MS (ESI), *m/z*: 427 (M + 1), 372, 318, 274, 179. Elemental Anal. (%), Calcd: C, 63.99; H, 4.85; N, 17.80; Found: C, 64.10; H, 5.12; N, 17.80.

*3-(2,4-Dichlorobenzylthio)-5-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazole (***8i***)*. The compound was obtained in 47.5% yield as a white crystal; mp 165–166°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 8.33 (d, $J = 8.8$, ArH, 2H), 8.20 (d, $J = 8.8$, ArH, 2H), 7.44–7.56 (m, N-PhH, 3H), 7.14 (d, $J = 7.8$, N-PhH, 2H), 5.70 (s, PyH, 1H), 5.21 (s, Py-CH_2, 2H), 4.86 (s, S-CH_2, 2H), 2.06 (s, Py-CH_3, 6H). IR (KBr), ν (cm^{-1}): 1741, 1700, 1648, 1544, 1511, 1467, 1400, 1063. MS (ESI), *m/z*: 444, 446, 447 (M + 1), 434, 360, 179. Elemental Anal. (%), Calcd:

TABLE 1 Herbicidal Activity Data and KARI Activity Data of Compounds (% Inhibition)

					Rape Root Test		*Barnyardgrass Cup Test*		*KARI Activity*
Compound	R_1	R_2	R_3	R_4	*10 μg mL⁻¹*	*100 μg mL⁻¹*	*10 μg mL⁻¹*	*100 μg mL⁻¹*	*200 μg mL⁻¹*
8a	H	CH_3	H		0	26.2	14.9	27.4	0.0
8b	H	Ph	H		7.4	33.8	15.3	47.0	37.1
8c	H	Ph	4-Cl		0	13.1	30.5	45.7	–[a]
8d	H	Ph	4-F		0	2.3	9.7	14.3	7.5
8e	H	CH_3	4-F		0	0	14.3	37.2	23.2
8f	H	CH_3	4-Cl		0	7.6	14.5	36.8	–
8g	H	Ph	4-OCH_3		10.8	50.8	2.6	47.3	–
8h	NO_2	CH_3	H		0	0	24.4	36.4	–
8i	H	Ph	4-NO_2		0	0	20.7	50.6	11.7
8j	H	Ph	4-Br		0	43.6	16.8	63.5	40.9
8k	H	Ph	2,4-Cl_2		13.7	33.8	11.3	52.1	20.1
8l	H	CH_3	4-Br		0	61.1	0	28.5	0
8m	H	CH_3	2,4-Cl_2		0	0	0	5.7	–
8n	H	Ph	4-CH_3		0	0	26.5	52.5	–
8o	H	CH_3	4-OCH_3		0	82.5	16.3	61.5	0
8p	NO_2	CH_3	4-CH_3		0	77.5	2.5	32.6	0
8q	NO_2	CH_3	4-Cl		0	0	0	26.7	–
8r	NO_2	CH_3	2,4-Cl_2		4.1	76.8	11.3	62.2	23.0
8s	H	CH_3	4-CH_3		0	0	21.8	28.0	–
8t	H	CH_3		2,4-Cl_2	0	0	6.5	31.3	–
8u	H	Ph		2-F	5.2	64.4	8.9	39.2	3.5
8v	NO_2	CH_3		2,4-Cl_2	0	61.1	17.8	41.8	0
8w	H	Ph		2,4-Cl_2	0	12.8	29.1	48.7	–
8x	H	CH_3		2-F	0	8.2	21.8	48.4	–
8y	NO_2	CH_3		2-F	0	43.0	26.5	51.2	–

[a]– indicates that the compound cannot be resolved in our test solution. So, no data were obtained.

C, 58.70; H, 4.68; N, 18.72; Found: C, 58.92; H, 4.49; N, 18.74.

*3-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-5-(2-fluorobenzylthio)-4-methyl-4H-1,2,4-triazole (***8j***).* The compound was obtained in 87.3% yield as a white crystal; mp 161–162°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.89 (d, $J = 8.6$, ArH, 2H), 7.63 (d, $J = 8.6$, ArH, 2H), 7.43–7.55 (m, N-PhH, 3H), 7.12 (d, $J = 6.8$, N-PhH, 2H), 5.70 (s, PyH, 1H), 5.23 (s, Py-CH_2, 2H), 4.86 (s, S-CH_2, 2H), 2.07 (s, Py-CH_3, 3H), 2.06 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1581, 1558, 1474, 1431. MS (ESI), *m/z*: 332 (M + 1), 256, 179. Elemental Anal. (%), Calcd: C, 54.62; H, 4.32; N, 14.42; Found: C, 54.78; H, 4.18; N, 14.52.

*3-((3,5-Dimethyl-4-nitro-1H-pyrazol-1-yl)methyl)-5-(2-fluorobenzylthio)-4-methyl-4H-1,2,4-triazole (***8k***).* The compound was obtained in 90.1% yield as a white crystal; mp 103–104°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.69 (d, $J = 8.3$, ArH(6), 1H), 7.44–7.55 (m, ArH and PhH, 4H), 7.34 (dd, $J_{ab} = 8.4$, $J_{ac} = 2.0$, ArH(5), 1H), 7.10 (d, $J = 6.9$, PhH, 2H), 5.70 (s, PyH, 1H), 5.20 (s, Py-CH_2, 2H), 4.66 (s, S-CH_2, 2H), 2.07 (s, Py-CH_3, 3H), 2.05 (s, Py-CH_3, 3H). IR (KBr), ν (cm^{-1}): 1688, 1581, 1545, 1502, 1445, 1416, 1202. MS (ESI), *m/z*: 377 (M + 1), 355, 329, 273, 179. Elemental Anal. (%), Calcd: C, 55.97; H, 3.93; N, 14.85; Found: C, 55.94; H, 4.05; N, 14.83.

The Herbicidal Activities

Inhibition for the Root-Growth of Rape (Brassica campestris). The tested compounds were made into an emulsion. Rapeseeds were soaked in distilled water for 4 h before being placed on a filter paper in a 6-cm-diameter Petri dish, to which 2 mL of tested solution had been added in advance. The control one was treated with 2 mL of distilled water alone. Fifteen seeds were used on each dish. The dish was incubated in a dark room, and seeds were allowed to germinate for 65 h at 28 ± 1°C. Lengths of 10 selected rape roots from each plate were measured. The inhibitive rates were calculated from the root length.

Inhibition of the Seedling Growth of Barnyardgrass (Echinochloa crusgalli). The tested compounds were made into an emulsion. Ten barnyardgrass seeds were placed in a 50-mL cup covered with a layer of glass beads and a piece of filter paper at the bottom, to which 5 mL of tested solution had been added in advance. The control one was treated with 5 mL of distilled water alone. The cup was placed in

an illumination incubator, and seeds were allowed to germinate for 65 h at 28 ± 1°C. The heights of the aboveground plant parts from each cup were measured. The inhibitive rates were calculated from the plant heights.

KARI Activity Tests

Gerwick et al. [17] reported that the inhibition for *Escherichia coli* KARI was time dependent. To characterize the steady-state inhibition constant, *E. coli* KARI was preincubated for 10 min with NADPH, Mg^{2+}, and the title compound. Then, the reaction was initiated with hydroxypyruvate. Under these conditions, the change in A340 was found to be linear with time.

RESULTS AND DISCUSSION

Synthesis

Compound **1b** was first prepared by the reported method [18]. In our experiments, we found that the direct nitration by nitric acid was incomplete and was difficult for purification. So, we prepared compound **1b** by reacting with nitric acid in acetate acid/acetic anhydride. **1b** could be easily purified by extraction with ethyl acetate. With a nitryl group in pyrazole, **1b** was difficult to react with ethyl chloroacetate for preparing compound **2**. In this step, ethyl bromoacetate was used to replace ethyl chloroacetate. The yield of compound **2** was relatively high.

Compounds **8a–8y** were identified by ^{1}H NMR. The measured elemental analyses were also consistent with the corresponding calculated ones.

Herbicidal Activities In Vivo and In Vitro

The herbicidal activities of the title compounds were determined with KARI inhibition, roots of rape, and the barnyardgrass cup test. The results are shown in Table 1. Most of the compounds showed weak herbicidal activities in vivo and in vitro. Compounds **8t, 8u**, and **8w** showed higher inhibition abilities of rape root at 100 μg/mL. KARI inhibition activities of some compounds could not tested because of their poor solubility in the test solution.

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