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SYNTHESIS AND DNA CLEAVAGE ACTIVITY OF NOVEL SPIRO-[CYCLOBUTATHIAZOLE-4,4'-PYRAZOLE] DERIVATIVES

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Abstract – A facile and efficient synthesis of novel spiro pyrazole derivatives containing cyclobutathiazole moiety is described. The key substrate pyrazole-thiazolidine derivative as the building block for bis-heterocycles was formed *via* a Knoevenagel-type condensation of thiazolidinedione with pyrazol-3-one. Thermal treatment of the pyrazole-thiazolidine derivative with orthoesters in refluxing toluene caused an *C*-attack nucleophilic substitution, followed by an intramolecular cyclization/elimination sequence, giving the corresponding spiro[cyclobutathiazole-4,4'-pyrazole] derivatives. All the synthesized compounds were characterized by spectroscopic analysis and were tested for their DNA cleavage activity *in vitro*.

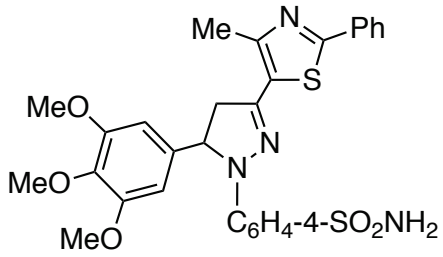
Dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday

Heterocyclic compounds are widely distributed in nature and are essential for life. Simple heterocyclic compounds have received considerable attention because of their important biological properties and their role as pharmacophores.[1] There are vast numbers of pharmacologically active heterocyclic compounds many of which are in regular clinical use. Among them, pyrazole and its derivatives are known to exhibit a wide spectrum of biological activities such as antipyretic, anti-inflammatory,[2] antiviral,[3] antibacterial,[4] hypoglycemic,[5] antihypertensive,[6] and antitumor[7] activities. Therefore, there have been many attempts to develop alternative methods for the synthesis of pyrazole derivatives.[8]

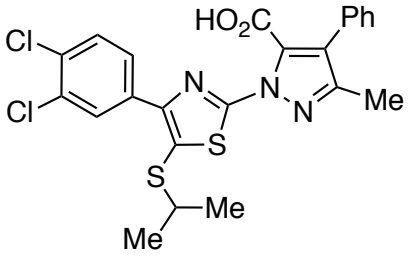
In medicinal chemistry, thiazole and related compounds have been very well known for their therapeutic applications. Thiazole moiety has been found as integral part of the structure of therapeutic agents and is widely used like sulfathiazole as antimicrobial agent, ravuconazole as antifungal agent, ritonavir as antiretroviral agent, and meloxicam as nonsteroidal anti-inflammatory drug.[9] In addition, thiazole

derivatives have wide-ranging collection of conventional biological activities, for example, antiallergic,[10] antioxidant,[11] anti-HIV,[12] anticancer,[13] antihypertensive,[14] and antidiabetic[15] activities. In this context, several synthetic methods used for the formation of thiazole derivatives have recently been reported in the literature.[16]

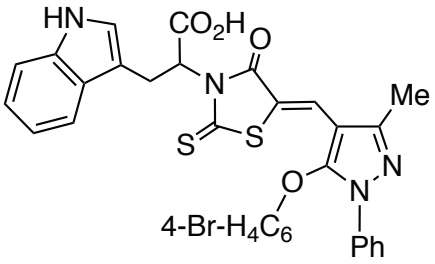
Based on these properties, it can be reasonably supposed that the development of synthetic strategies for some novel structures incorporating both the pyrazole and thiazole ring systems might provide additional lead molecules for drug discovery. Therefore, the preparation of some bioactive thiazole derivatives containing pyrazole moiety has been reported (Figure 1).[17]



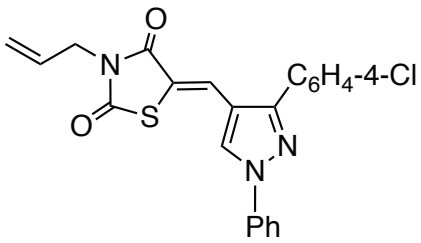
cyclooxygenase-2 inhibitor



antitumor agent



antimicrobial activity



neuroprotective agent

Figure 1. Selected bioactive thiazole and thiazolidine derivatives containing pyrazole moiety

Spiro compounds are well known to possess varied biological activities.[18] Hence, their synthesis has always been a challenge and of attraction to organic chemists. Among them, in the literature there is not much research related to the synthesis of spiro pyrazole derivatives, *e.g.* compounds **A–D**[19] (Figure 2), even though they also have biological activities, such as antimicrobial, analgesic, and antitumor properties.[19b,20] Previously, we have reported some exciting synthetic strategies for the synthesis of this exclusive class of compounds **E–H**.[21] As part of our current studies on the development of new routes in the synthesis of spiro pyrazole derivatives, we herein wish to present the results of our investigation, a facile and efficient method for preparing novel spiro[cyclobutathiazole-4,4'-pyrazole] derivatives with DNA cleavage activity.

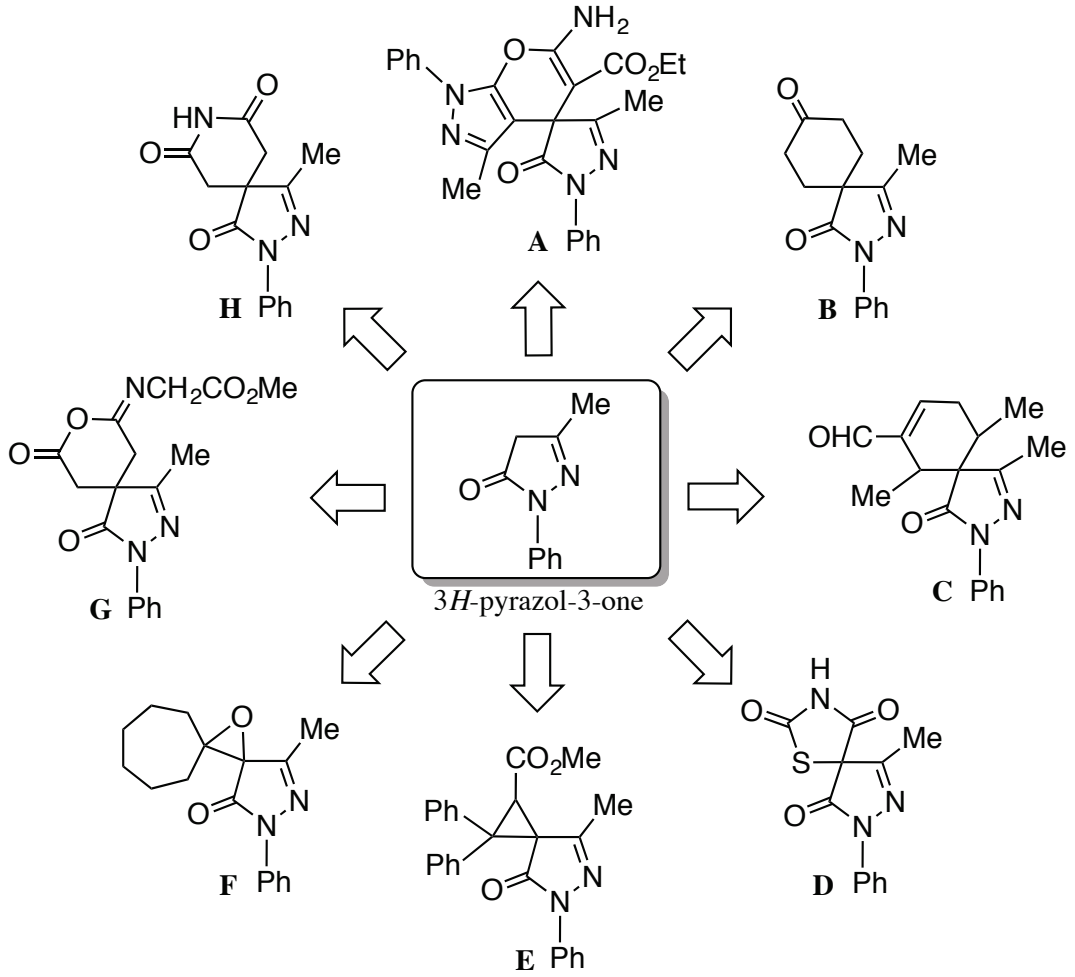
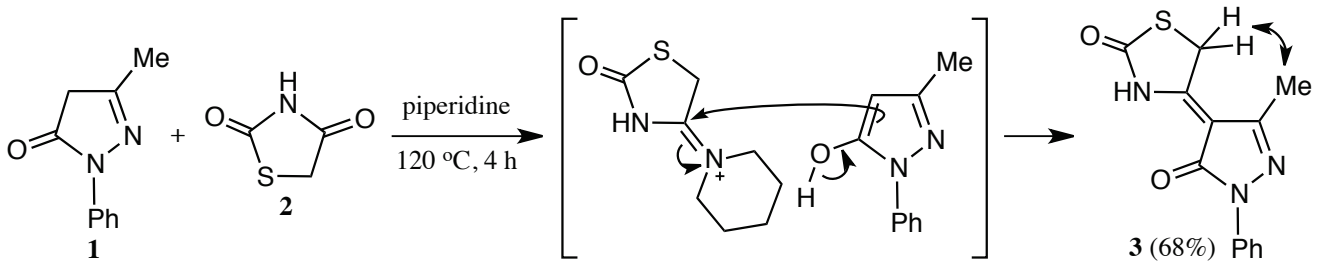


Figure 2. Structures of reported spiro compounds containing pyrazol-3-one moiety

Initially, a Knoevenagel-type condensation of 3*H*-pyrazol-3-one **1** and thiazolidinedione **2** was examined (Scheme 1). We carried out several experiments on pyrazole-thiazolidine derivative **3**, testing different reaction conditions, for example, substrate/base molar ratio, solvent, reaction temperature, and reaction time. Best result was obtained when a mixture of **1** and **2** in the presence of a catalytic amount of piperidine under the solvent-free was stirred at 120 ˚C for 4 h. Indeed, the expected pyrazole-thiazolidine derivative **3** was isolated as a geometrical single isomer of *Z* configuration in 68% yield.

This product **3** gave satisfactory elemental analysis and spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and MS) consistent with their assigned structures (see experimental section). For example, IR spectrum of **3** displays a band at 3350 cm^{-1} because of an amido group and two bands at 1713 and 1662 cm^{-1} because of two carbonyl groups. The ^{1}H NMR spectrum of **3** in $CDCl_3$ exhibits a three-proton singlet at δ 2.34 assignable to the methyl protons, a two-proton singlet at δ 4.59 assignable to the methylene protons, and a D_2O exchangeable one-proton broad singlet at δ 11.21 assignable to the amido proton. The ^{13}C NMR spectrum of **3** in $CDCl_3$ shows a signal at δ 16.2 because of the methyl carbon, a signal at δ 34.0 because of the methylene carbon, and two signals at δ 163.9 and 172.2 because of two carbonyl carbons. In

addition, a clear nuclear Overhauser effect for **3** was observed between the methyl protons and methylene protons of *Z* configuration.

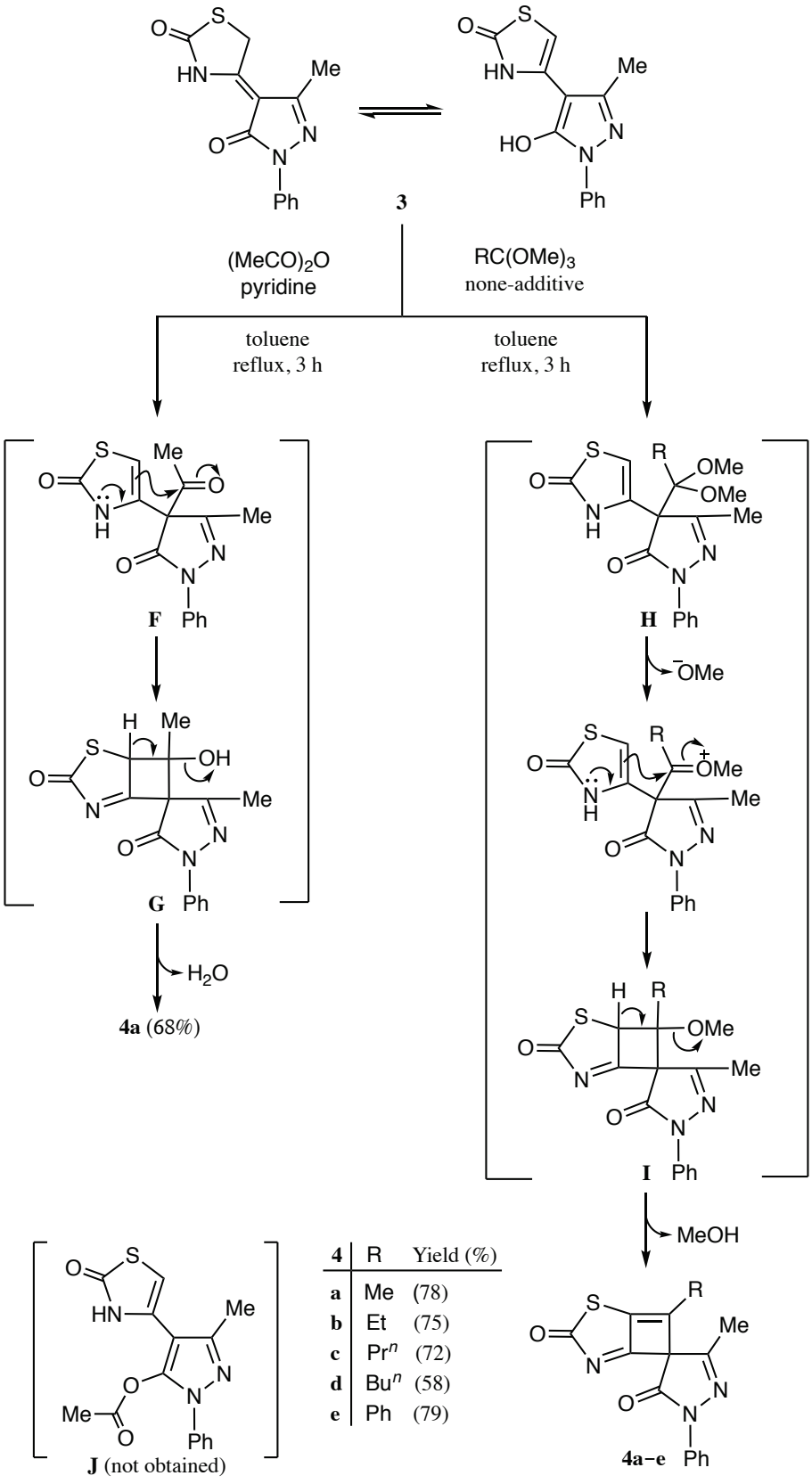


Scheme 1

In our next studies, to check something about reactivity of pyrazole-thiazolidine **3**, we examined an acetylation of **3** in detail. Interestingly, thermal treatment of **3** with acetic anhydride in the presence of pyridine in refluxing toluene for 3 h caused an *C*-acetylation/intramolecular cyclization sequence, followed by a dehydration reaction of **G**, giving the spiro[cyclobutathiazole-4,4'-pyrazole] derivative **4a** as the only isolated product in 68% yield (Scheme 2). The key step of this reaction is an efficient intramolecular cyclization reaction of *C*-acetylated intermediate **F**. In this case, *O*-acetylated product like **J** could not be detected at all. The IR spectrum of **4a** displays two bands at 1698 and 1626 cm^{-1} because of two carbonyl groups. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ exhibits two three-proton singlets at δ 2.64 and 2.70 assignable to two methyl protons. The ^{13}C NMR spectrum of **4a** in $CDCl_3$ shows two signals at δ 14.0 and 20.0 because of two methyl carbons, a signal at δ 100.6 because of the spiro carbon, and two signals at δ 165.5 and 181.8 because of two carbonyl carbons. By comparison of one- and two-dimensional (1D and 2D) NMR, MS, and elemental analysis of **4a** it seems that the structural assignments given to this compound is correct.

Although we examined the reaction of **3** with the other acylating agent, such as benzoyl chloride and 4-chlorobenzoyl chloride, our attempts were unacceptable with respect to yield. The reaction was not clean. To confirm about the reactivity of **3** and the structure of **4a**, the behavior of the other reagent such as orthoesters was also investigated. Thus, pyrazole-thiazolidine **3** was reacted with trimethyl orthoacetate in refluxing toluene for 3 h to provide the desired **4a** (78%), which was shown to be identical with the authentic sample prepared from **3** with acetic anhydride on the basis of a comparison of the melting point, IR, and NMR spectrum. Based on this result, we carried out the reactions of **3** with orthoesters such as trimethyl orthopropionate, trimethyl orthobutyrate, trimethyl orthovalerate, and trimethyl orthobenzoate. Indeed, the expected spiro[cyclobutathiazole-4,4'-pyrazole] derivatives **4b–e** were obtained in moderate to good yields. The results and a plausible mechanism for the formation of **4a–e** are illustrated in Scheme 2. Thus, the reaction of **3** with orthoesters is assumed to proceed through the formation of the intermediate acetals **H**, which undergo an intramolecular cyclization with an elimination of MeOH to

result in the formation of **I**. Furthermore, an elimination of MeOH from **I** easily occurs and then **4a–e** would be produced. These products **4** were characterized by spectroscopic analyses (see experimental section).



4	R	Yield (%)
a	Me	(78)
b	Et	(75)
c	Pr^n	(72)
d	Bu^n	(58)
e	Ph	(79)

Scheme 2

Finally, we have tested *in vitro* DNA cleavage activity of the synthesized compounds **3** and **4a–e**. The values obtained for activity were based on the remaining amounts of covalently closed circular duplex DNA, namely ccc-DNA, of plasmid pBR322 (see references[22]). The data of DNA cleavage activity is summarized in Table 1. Indeed, in the absence of Cu^{2+}, all the tested compounds showed no DNA cleavage activity. These activities of compounds **3** and **4b**, however, were obviously accelerated by the addition of 1 mM Cu^{2+} (entries 2 and 4). Furthermore, it was found that compounds **4c** and **4d** have moderate activity with Cu^{2+} (entries 5 and 6).

Table 1. DNA cleavage by **3** and **4a–e** in the absence and/or presence of Cu^{2+}

Entry	Compound	DNA type	Relative amounts of DNA (%)	
			Without Cu^{2+} [a]	With Cu^{2+} [b]
1	Control[c]	ccc- oc- linear-	100 0 0	100 0 0
2	**3**[d]	ccc- oc- linear-	100 0 0	0 48 52
3	**4a**[d]	ccc- oc- linear-	100 0 0	100 0 0
4	**4b**[d]	ccc- oc- linear-	100 0 0	37 63 0
5	**4c**[d]	ccc- oc- linear-	100 0 0	76 24 0
6	**4d**[d]	ccc- oc- linear-	100 0 0	71 29 0
7	**4e**[d]	ccc- oc- linear-	100 0 0	100 0 0

[a] Incubation for 3 h. [b] Incubation for 1 h. [c] Amount: 0 mM. [d] Amount: 10 mM.
As activity was accelerated upon addition of Cu^{2+}, the quantity of compounds and the incubation time were minimized until differences in activity could be observed.

In conclusion, we have demonstrated the reactions of the key substrate pyrazole-thiazolidine with acetic anhydride and/or orthoesters. This methodology offers significant advantages with regard to the supply of spiro[cyclobutathiazole-4,4'-pyrazole] derivatives, which may be important building blocks in organic synthesis and for the preparation of biologically active compounds with interest in medicinal chemistry. In this present work, we have found that pyrazole-thiazolidine **3** and spiro[cyclobutathiazole-4,4'-pyrazole] **4b** showed high DNA cleavage activity *in vitro* with Cu^{2+}. In addition, **4c** and **4d** exhibited

moderate DNA cleavage activity. Further synthetic applications for novel spiro pyrazole derivatives are in progress.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-A500 spectrometer at 500.00 and 125.65 MHz or with a JEOL JNM-ECZ600R/S1 spectrometer at 600.17 and 150.91 MHz, respectively. The ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to TMS as internal standard. Positive FAB MS spectra were obtained on a JEOL JMS-700T spectrometer. Elemental analyses were performed on YANACO MT-6 CHN analyzer.

The preparation of pyrazole-thiazolidine 3 from 1 and 2 in the presence of piperidine. A mixture of 3*H*-pyrazol-3-one **1** (1.740 g, 10 mmol), thiazolidinedione **2** (1.171 g, 10 mmol), and piperidine (0.085 g, 1 mmol) was stirred at 120 °C for 4 h. The resulting mixture was recrystallized from $CHCl_3$/petroleum ether to give (*Z*)-4-(1,5-dihydro-3-methyl-5-oxo-1-phenyl-4*H*-pyrazol-4-ylidene)-2-thiazolidinone (**3**): this compound was obtained as pale yellow needles (1.850 g, 68%), mp 196–198 °C (dec.); IR (KBr): ν 3350 (NH), 1713, 1662 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, Me), 4.59 (s, 2H, CH_2), 7.17–7.20 (m, 1H, Ph-H), 7.38–7.42 (m, 2H, Ph-H), 7.92–7.95 (m, 2H, Ph-H), 11.21 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 16.2 (Me), 34.0 (CH_2), 104.7 (pyrazole C-4), 118.8, 125.1, 128.9, 138.2 (Ph-C), 146.4 (pyrazole C-3), 155.5 (thiazole C-4), 163.9 (pyrazole C-5), 172.2 (thiazole C-2); MS: *m/z* 274 $[M+H]^+$. Anal. Calcd for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37. Found: C, 57.18; H, 4.10; N, 15.39.

The preparation of spiro compound 4a from 3 and acetic anhydride in the presence of pyridine. A mixture of **3** (0.273 g, 1 mmol), Ac_2O (0.510 g, 5 mmol), and pyridine (0.400 g, 5 mmol) in toluene (5 mL) was refluxed for 3 h. The solvent was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to afford 3',7-dimethyl-1'-phenyl-2-thia-4-azaspiro[bicyclo[3.2.0]heptane-6,4'-pyrazole]-1(7),4-diene-3,5'(1'*H*)-dione (**4a**): this compound was obtained as pale yellow needles (0.201 g, 68%), mp 211–213 °C (dec.) ($CHCl_3$/petroleum ether); IR (KBr): ν 1698, 1626 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.64 (s, 3H, 7-Me), 2.70 (s, 3H, 3'-Me), 7.41–7.44 (m, 1H, Ph-H), 7.54–7.57 (m, 2H, Ph-H), 7.81–7.83 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 14.0 (3'-Me), 20.3 (7-Me), 100.6 (C-6), 121.0 (Ph-C), 123.6 (C-1), 128.0, 129.6, 136.5 (Ph-C), 146.6 (C-3'), 148.7 (C-7), 151.1 (C-5), 165.5 (C-5'), 181.8 (C-3); MS: *m/z* 298 $[M+H]^+$; high-resolution MS: Calcd for $C_{15}H_{12}N_3O_2S$ 298.0650, Found 298.0644. Anal. Calcd for $C_{15}H_{11}N_3O_2S \cdot 0.2H_2O$: C, 59.87; H, 3.82; N, 13.96. Found: C, 59.88; H, 3.81; N, 13.99.

General procedure for the preparation of spiro compounds 4a–e from 3 and orthoesters. A mixture of **3** (0.273 g, 1 mmol) and trimethyl orthoacetate (0.360 g, 3 mmol), trimethyl orthopropionate (0.403 g,

3 mmol), trimethyl orthobutyrate (0.445 g, 3 mmol), trimethyl orthovalerate (0.487 g, 3 mmol), or trimethyl orthobenzoate (0.547 g, 3 mmol) in toluene (5 mL) was refluxed for 3 h. The resulting mixture was recrystallized from toluene/petroleum ether to yield **4a–e**.

3',7-Dimethyl-1'-phenyl-2-thia-4-azaspiro[bicyclo[3.2.0]heptane-6,4'-pyrazole]-1(7),4-diene-3,5'(1'*H*)-dione (4a): Pale yellow needles (0.233 g, 78%); it was shown to be identical with the authentic sample prepared from **3** with Ac_2O on the basis of a comparison of the melting point, IR, and NMR spectrum.

7-Ethyl-3'-methyl-1'-phenyl-2-thia-4-azaspiro[bicyclo[3.2.0]heptane-6,4'-pyrazole]-1(7),4-diene-3,5'(1'*H*)-dione (4b): Pale yellow needles (0.235 g, 75%), mp 204–205 °C (dec.); IR (KBr): ν 1697, 1620 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 1.28 (t, J = 7.6 Hz, 3H, CH_2*Me*), 2.57 (s, 3H, 3'-Me), 2.87 (q, J = 7.6 Hz, 2H, C*H*$_2$Me), 7.42–7.44 (m, 1H, Ph-H), 7.57–7.61 (m, 2H, Ph-H), 7.82–7.85 (m, 2H, Ph-H); ^{13}C NMR (DMSO-d_6): δ 11.0 (CH_2*Me*), 14.2 (3'-Me), 27.9 (*C*H_2Me), 100.9 (C-6), 121.1 (C-1), 121.5, 128.5, 130.3, 136.7 (Ph-C), 145.7 (C-3'), 152.0 (C-5), 155.5 (C-7), 166.0 (C-5'), 181.4 (C-3); MS: *m*/*z* 312 $[M+H]^+$. Anal. Calcd for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.61; H, 4.26; N, 13.49.

7-Propyl-3'-methyl-1'-phenyl-2-thia-4-azaspiro[bicyclo[3.2.0]heptane-6,4'-pyrazole]-1(7),4-diene-3,5'(1'*H*)-dione (4c): Pale yellow needles (0.235 g, 72%), mp 202–203 °C (dec.); IR (KBr): ν 1696, 1618 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 0.94 (t, J = 7.6 Hz, 3H, CH_2CH_2*Me*), 1.76 (sext, J = 7.6 Hz, 2H, CH_2C*H*$_2$Me), 2.58 (s, 3H, 3'-Me), 2.84 (t, J = 7.6 Hz, 2H, C*H*$_2CH_2$Me), 7.42–7.45 (m, 1H, Ph-H), 7.58–7.61 (m, 2H, Ph-H), 7.82–7.84 (m, 2H, Ph-H); ^{13}C NMR (DMSO-d_6): δ 13.9 (CH_2CH_2*Me*), 14.2 (3'-Me), 20.3 (CH_2*C*H_2Me), 36.1 (*C*H_2CH_2Me), 101.0 (C-6), 121.6 (Ph-C), 122.0 (C-1), 128.5, 130.3, 136.7 (Ph-C), 145.7 (C-3'), 152.1 (C-5), 154.5 (C-7), 166.0 (C-5'), 181.4 (C-3); MS: *m*/*z* 326 $[M+H]^+$. Anal. Calcd for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91. Found: C, 62.54; H, 4.52; N, 12.90.

7-Butyl-3'-methyl-1'-phenyl-2-thia-4-azaspiro[bicyclo[3.2.0]heptane-6,4'-pyrazole]-1(7),4-diene-3,5'(1'*H*)-dione (4d): Pale brown needles (0.195 g, 58%), mp 175–177 °C (dec.); IR (KBr): ν 1701, 1621 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 0.86 (t, J = 7.6 Hz, 3H, $CH_2CH_2CH_2$*Me*), 1.35 (sext, J = 7.6 Hz, 2H, CH_2CH_2C*H*$_2$Me), 1.71 (quint, J = 7.6 Hz, 2H, CH_2C*H*$_2CH_2$Me), 2.57 (s, 3H, 3'-Me), 2.85 (t, J = 7.6 Hz, 2H, C*H*$_2CH_2CH_2$Me), 7.42–7.45 (m, 1H, Ph-H), 7.58–7.61 (m, 2H, Ph-H), 7.79–7.86 (m, 2H, Ph-H); ^{13}C NMR (DMSO-d_6): δ 14.1 ($CH_2CH_2CH_2$*Me*), 14.2 (3'-Me), 22.0 (CH_2CH_2*C*H_2Me), 28.6 (CH_2*C*H_2CH_2Me), 33.9 (*C*$H_2CH_2CH_2$*Me*), 100.9 (C-6), 121.5 (Ph-C), 121.9 (C-1), 128.5, 130.3, 136.7 (Ph-C), 145.7 (C-3'), 152.0 (C-5), 154.7 (C-7), 165.9 (C-5'), 181.4 (C-3); MS: *m*/*z* 340 $[M+H]^+$. Anal. Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.50; H, 4.99; N, 12.32.

3'-Methyl-1',7-diphenyl-2-thia-4-azaspiro[bicyclo[3.2.0]heptane-6,4'-pyrazole]-1(7),4-diene-3,5'(1'*H*)-dione (4e): Pale yellow needles (0.282 g, 79%), mp 231–232 °C (dec.); IR (KBr): ν 1706, 1610

cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 2.62 (s, 3H, 3'-Me), 7.44–7.48 (m, 1H, Ph-H), 7.60–7.67 (m, 5H, Ph-H), 7.89–7.94 (m, 4H, Ph-H); ^{13}C NMR (DMSO-d_6): δ 14.2 (3'-Me), 100.9 (C-6), 121.1 (C-1), 121.7, 128.5, 128.6, 130.1, 130.3, 131.1, 132.7, 136.7 (Ph-C), 146.0 (C-3'), 148.7 (C-7), 151.9 (C-5), 166.7 (C-5'), 181.9 (C-3); MS: *m/z* 360 $[M+H]^+$. Anal. Calcd for $C_{20}H_{13}N_3O_2S$: C, 66.84; H, 3.65; N, 11.69. Found: C, 66.71; H, 3.69; N, 11.62.

Reaction of plasmid pBR322 with compounds 3 and 4a–e. The method of assaying the DNA cleavage activity, using a covalently closed circular duplex DNA (ccc-DNA) of plasmid pBR322 as a substrate, was described in our previous investigation.[22] The results are listed in Table 1. The reaction mixture (100 μL) containing 1 μg of ccc-DNA of plasmid pBR322, 10 mM of **3** and **4a–e**, and 50 mM Tris-HCl buffer (pH 7.4), was incubated at 37 ˚C. At interval, 20 μL of the reaction was mixed with 2 μL of 10 × Loading Buffer (TAKARA BIO INC. Shiga, Japan). The resulting mixture was directly by 1.0% agarose gel electrophoresis. After electrophoresis, the gels were stained with ethidium bromide (0.5 μg/mL) for 20 min. Under these conditions the order of anodal migration for the tree topological forms of the DNA was ccc-DNA, full-length linear duplex DNA (linear-DNA), and nicked open circular duplex DNA (oc-DNA). The ccc-DNA produced oc-DNA after single strand scission and linear-DNA after double-strand scission. They were all detected as clearly separated bands in agarose gels. The stained DNA bands were made visible using BioDoc-It™ Imaging Systems (UVP, Upland, CA) and then took the JPEG image file. For quantitative analysis of DNA on the gels, densitometric analyses of the images file were carried out using QuantiScan densitometry software (BIOSOFT, Cambridge, U.K.). The area under the ccc-DNA was multiplied by a factor of 1.42 to correct for its reduced binding of ethidium bromide as indicated by Lloyd and coworkers.[22a]

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