Intramolecular Nonbonded S···O Interaction Recognized in (Acylimino)thiadiazoline Derivatives as Angiotensin II Receptor Antagonists and Related Compounds

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Abstract: The intramolecular nonbonded 1,5-type S···O interactions are recognized in the crystalline structures of the (acylimino)thiadiazoline derivatives (**1**−**3**) as angiotensin II receptor antagonists. The relative stability of the nonbonded 1,5-type S···O interaction was investigated using the X-ray crystallographic analyses and the ab initio MO calculations (HF/3-21G*, 6-31G*, and 6-311+G**) of the simplified model compounds (**6**, **7**, and **9**). The concept of mimic-fused bicyclic heterocycles consisting of fairly stable nonbonded S···O interaction seems to be an efficient approach toward the design and development of various drugs.

Introduction

Intramolecular nonbonded interaction between sulfur and oxygen (or nitrogen) atoms has been observed in a large number of organosulfur compounds controlling the conformation of small and large molecules.[1] In these molecules, the nonbonded S···O or S···N atoms' distances are significantly shorter than the sum of the corresponding van der Waals radii (3.32 or 3.35 Å) in the crystalline structure.[2] These kinds of interactions also can be classified into several categories such as 1−3, 1−4, 1−5, and 1−6 types with the size of the quasi-ring involving S···X (X = O, N, S, halogens, and other heteroatoms) moieties as shown in Figure 1.[1]

In the course of the development of new angiotensin II (AII) receptor antagonists,[3] we recognized a nonbonded 1,5-type S···O close contact in the crystalline structures of three representative (acylimino)thiadiazoline derivatives (**1**−**3**)[4] which have potent AII receptor antagonistic activities. On the basis of their X-ray crystallographic analyses, the nonbonded atom distances between the sulfur atom of the thiadiazoline moiety and the oxygen atom of the acyl moiety in the molecules of **1**−**3** were found to be 2.610(4), 2.588(3), and 2.542(7) Å, respectively (see dotted lines in Figure 2).

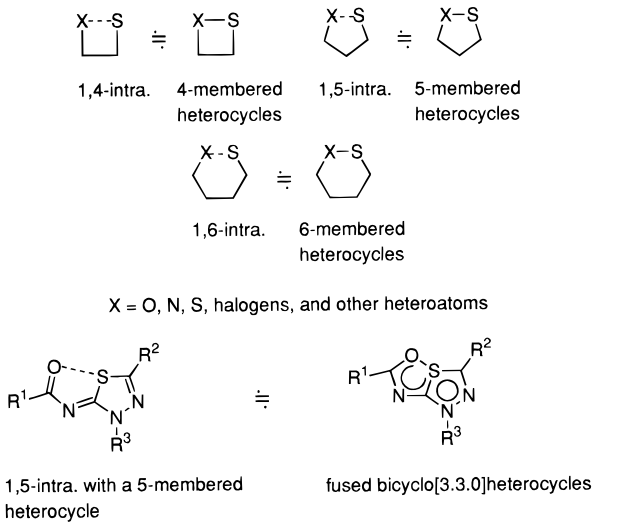

Figure 1. Equivalent mode to the heterocycles on the basis of S···X nonbonded interaction.

Recently, Goldstein and his colleagues have studied extensively the intramolecular nonbonded 1,4-type S···O interaction in the thiazole nucleoside analogues (vide infra) which play an important role on the mechanism of several biological effects

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[||] Rigaku Corporation.

(1) (a) Kucsman, A.; Kapovits, I. *Organic Sulfur Chemistry: Theoretical and Experimental Advances*, Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier Scientific Publishing Co.: Amsterdam, 1985; p 191−245. (b) Ohkata, K.; Ohsugi, M.; Yamamoto, K.; Ohsawa, M.; Akiba, K. *J. Am. Chem. Soc.* **1996**, *118*, 6355−6369.

(2) (a) L'abbe, G.; Meervelt, L. V.; Emmers, S.; Dehaen, W.; Toppet, S. *J. Heterocycl. Chem.* **1992**, *29*, 1765−1768. (b) Cohen-Addad, C.; Lehmann, M. S.; Becker, P.; Párkányi, L.; Kálmán, A. *J. Chem. Soc., Perkin Trans. 2* **1984**, 191−196. (c) Cohen-Addad, C.; Savariault, J.-M.; Lehmann, M. S. *Acta Crystallogr.* **1981**, *B37*, 1703−1706. (d) Kálmán, A.; Párkányi, L. *Acta Crystallogr.* **1980**, *B36*, 2372−2378.

(3) Wexler, R. R.; Greenlee, W. J.; Irvin, J. D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1996**, *39*, 625−656.

(4) (a) Hirata, T.; Nomiyama, J.; Sakae, N.; Nishimura, K.; Yokomoto, M.; Inoue, S.; Tamura, K.; Okuhira, M.; Amano, H.; Nagao, Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1469−1474. (b) Hirata, T.; Goto, S.; Tamura, K.; Okuhira, M.; Nagao, Y. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 385−388. (c) Tamura, K.; Okuhira, M.; Amano, H.; Inokuma, K.; Hirata, T.; Mikoshiba, I.; Hashimoto, K. *J. Cardiovasc. Pharmacol.* **1997**, *30*, 607−615.

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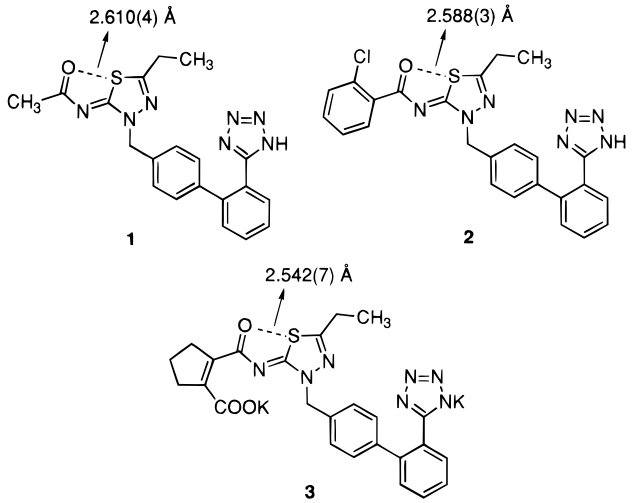


Figure 2. AII receptor antagonists (**1**−**3**) having an (acylimino)-thiadiazoline moiety.

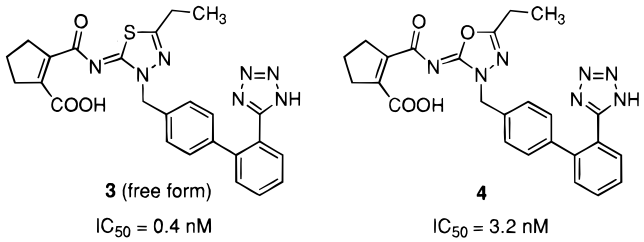


Figure 3. The binding affinities of (acylimino)thiadiazoline derivative (**3**) and (acylimino)oxadiazoline derivative (**4**).

such as antitumor activity and inhibition against inosine monophosphate dehydrogenase.[5]

Similarly, it can be speculated that the intramolecular nonbonded 1,5-type S···O interactions observed in the (acylimino)thiadiazoline derivatives (**1**−**3**) may influence not only the flat conformation of the (acylimino)thiadiazoline moiety of these compounds but also their antagonistic activities. In fact, the binding affinity of the oxadiazoline derivative (**4**: oxa analogue of **3**[6]) to the AII receptor (AT_1) was lower than that of the thiadiazoline derivative (**3**) as shown in Figure 3.[7] The results caused us to consider a hypothesis that this fairly stable S···O close contact might be one of important factors in causing the potent AII receptor antagonism of these thiadiazoline derivatives.

It is apparent that there are several heterocyclic drugs having potential for intramolecular nonbonded 1,4-, 1,5-, and 1,6-type S···O interactions (vide infra). With this in mind, coupled with our recent studies on the AII receptor antagonists, we envisage such kinds of intramolecular nonbonded S···X interaction (X = O, N, S, halogens, and other heteroatoms) providing a promising gateway for the design and development of new heterocyclic drugs. Specifically, the mimic heterocyclic moiety involving these intramolecular nonbonded 1,4-, 1,5-, and 1,6-types S···X interactions as shown in Figure 1 seems to be functionalized as the corresponding 4-, 5-, and 6-membered heterocycles consisting of both S and X atoms in the molecular recognition. To see how the (acylimino)thiadiazoline moiety of **1**−**3** can be available as a mimic-fused [3.3.0] heterocycle (Figure 1), we investigated the intramolecular nonbonded 1,5-type S···O interactions of some simplified model compounds by exploiting their X-ray crystallographic analyses and ab initio molecular orbital (MO) calculations.

Chemistry

We have reported the syntheses and biological properties of the three representative (acylimino)thiadiazoline derivatives (**1**−**3**).[4] The synthesis of oxadiazoline derivative (**4**) was carried out by the modified method in accordance with the preparation of **3**.[7]

The model compounds 5-ethyl-3-methyl-2-[(trifluoroacetyl)-imino]-1,3,4-thia(or oxa)diazoline (thia analogue, **7**, or oxa analogue, **9**) and 5-propyl-2-(trifluoroacetamido)-1,3,4-thiadiazole (**6**) were selected because of their good-quality crystals suited for X-ray crystallographic analysis and ease of MO calculation. Trifluoroacetamide derivatives (**5**, **6**, and **8**) were prepared by trifluoroacetylation of the corresponding 2-amino-1,3,4-thia(or oxa)diazole derivatives with trifluoroacetic anhydride. Regioselective methylation of 5-ethyl-2-(trifluoroacetamido)-1,3,4-thia(or oxa)diazole (**5** or **8**) with methyl iodide proceeded smoothly to afford the (trifluoroacetyl)imino derivative (**7** or **9**) (Scheme 1).[8]

Results and Discussion

1. Crystallographic Studies. Biologically active compounds (**1**−**3**) and model compounds (**6**, **7**, and **9**) were recrystallized from suitable solvents to obtain the corresponding crystals available for X-ray crystallographic analysis. The X-ray crystallographic data for **1**, **3**, **6**, **7**, and **9**, except for compound (**2**) reported earlier,[8] are summarized in Table 1.

The computer-generated drawings of the crystal structures of three (acylimino)thiadiazoline derivatives (**1**−**3**) are shown in Figure 4. In the represented structures, the part involving both the thiadiazoline ring and the acyl moiety adopts a plane conformation (see torsion angles) due to the S···O close contact (1,5-type intramolecular interaction) in each compound. This planarity was further investigated using the simple model compounds (**7** and **9**) as follows.

The computer-generated drawings of the crystal structures of (trifluoroacetyl)imino derivatives (**7** and **9**) are shown in Figure 5. Selected atom distances, bond angles, and torsion angles of **7** and **9** are listed in Table 2. Significant close contact (2.670(4) Å) between sulfur (S1) and oxygen (O1) atoms and planarity of the S1−C2−N3−C6−O1 moiety (see torsion angles) were recognized in the molecule of thiadiazoline derivative (**7**) like those of the (acylimino)thiadiazoline derivatives (**1**−**3**). Surprisingly, similar close contact (2.740(4) Å) between two oxygen atoms, O1 and O2, and planarity of the O1−C2−N3−C6−O2 moiety were also recognized in the oxadiazoline (**9**) as shown in Figure 5 and Table 2.

It is remarkable that the bond lengths of C2−N3 and N3−C6 are the same and the bond angles of S1−C2−N3 and N3−C6−O1 are almost the same in the case of **7** as shown in Table 2. This clearly indicates that the conjugate (quasi) ring system (S1−C2−N3−C6−O1) due to the fairly stable nonbonded 1,5-

(5) (a) Franchetti, P.; Cappellacci, L.; Grifantini, M.; Barzi, A.; Nocentini, G.; Yang, H.; O'Connor, A.; Jayaram, H. N.; Carrell, C.; Goldstein, B. M. *J. Med. Chem.* **1995**, *38*, 3829−3837. (b) Goldstein, B. M.; Li, H.; Hallows, W. H.; Langes, D. A.; Franchetti, P.; Cappellacci, L.; Grifantini, M. *J. Med. Chem.* **1994**, *37*, 1684−1688. (c) Li, H.; Hallows, W. H.; Punzi, J. S.; Marquez, V. E.; Carrell, H. L.; Pankiewicz, K. W.; Watanabe, K. A.; Goldstein, B. M. *Biochemistry* **1994**, *33*, 23−32. (d) Goldstein, B. M.; Takusagawa, F.; Berman, H. M.; Srivastava, P. C.; Robins, R. K. *J. Am. Chem. Soc.* **1983**, *105*, 7416−7422.

(6) Compound **3** shows the strongest angiotensin II antagonistic activity in vitro and in vivo among a series of (acylimino)thiadiazoline derivatives. This compound referred to KRH-594 is now under clinical trial as a antihypertensive agent in Japan.

(7) Synthesis and detailed biological activity of (acylimino)oxadiazoline derivative **4** will be reported elsewhere.

(8) Hirata, T.; Shiro, M.; Nagao. Y. *Heterocycles* **1997**, *44*, 133−138.

Scheme 1

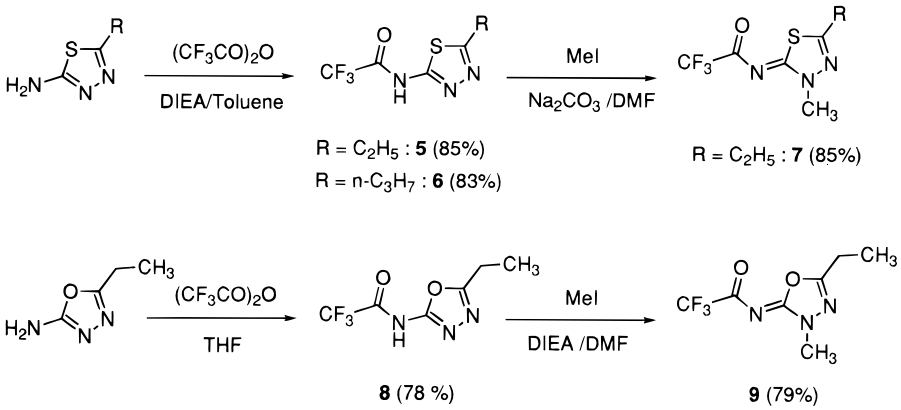


Table 1. Summary of X-ray Crystallographic Analyses of Compounds **1**, **3**, **6**, **7**, and **9**

	1	**3**	**6**	**7**	**9**
formula	$C_{20}H_{19}N_7OS$	$C_{25}H_{21}K_2N_7O_3S$	$C_7H_8F_3N_3OS$	$C_7H_8F_3N_3OS$	$C_7H_8F_3N_3O_2$
formula weight	405.48	577.74	239.21	239.21	223.15
crystal description	colorless prism	colorless needle	colorless prism	colorless prism	colorless prism
crystal system	monoclinic	triclinic	triclinic	triclinic	monoclinic
space group	$P2_1/n$	$\bar{P}1$	$\bar{P}1$	$\bar{P}1$	$P2_1/c$
lattice constants					
a, Å	10.691(5)	11.724(3)	10.188(4)	5.002(3)	6.988(2)
b, Å	11.060(3)	16.794(4)	10.884(4)	12.049(7)	13.996(1)
c, Å	17.399(6)	7.372(3)	4.898(1)	9.592(7)	10.200(1)
α, deg		102.52(3)	91.50(3)	111.75(5)	
β, deg	104.64(3)	106.53(3)	99.60(3)	106.47(6)	94.13(2)
γ, deg		105.86(2)	69.50(3)	82.72(6)	
volume, Å^3	1990(1)	1268.5(8)	501.3(3)	514.7(6)	994.9(3)
Z	4	2	2	2	4
density (calcd), g/cm^3	1.353	1.512	1.585	1.543	1.490
residual *R*, R_W	0.041, 0.059	0.066, 0.072	0.062, 0.091	0.044, 0.068	0.064, 0.098
GOF	1.22	1.71	1.65	1.33	1.45
p[a]	0.0325	0.0150	0.0500	0.0455	0.0645

[a] See the Experimental Section.

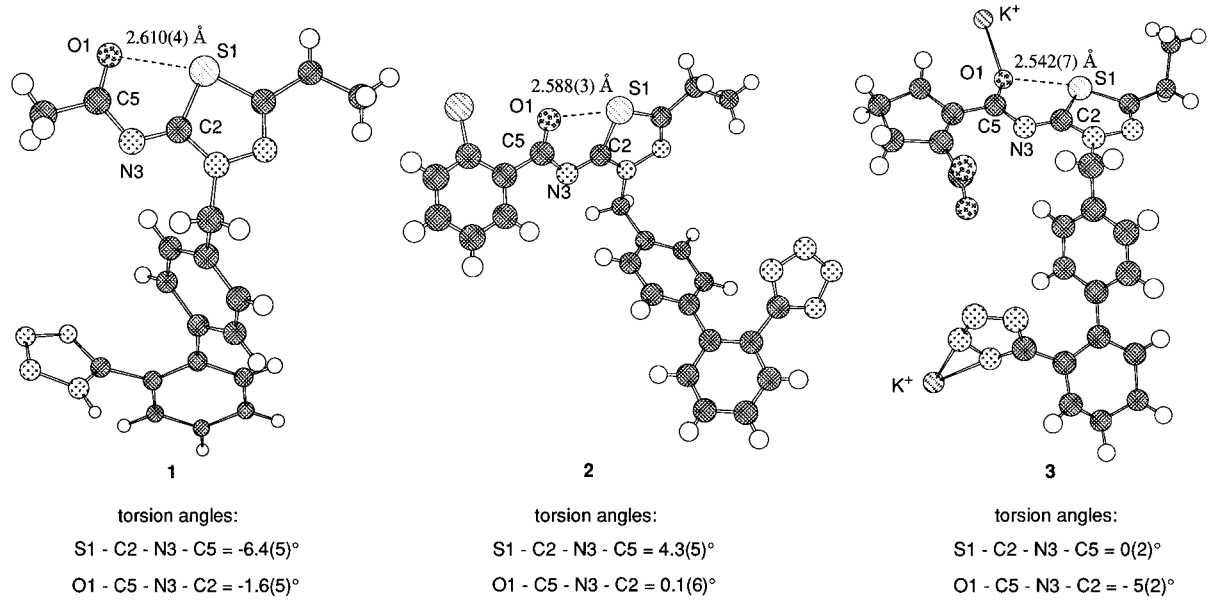


Figure 4. Computer-generated drawings of the compounds (**1**, **2**, and **3**) derived from the X-ray coordinates. Dotted lines show the S···O close contacts.

type S···O interaction (vide infra) is formed. Here, we particularly emphasize that the part involving both the thiadiazoline ring and the acylimino moiety has not only the plane conformation but also the novel character which we call the "mimic-fused bicyclic heterocycle". Considering that the antagonistic activity of the thiadiazoline derivative (**3**) is stronger than that of the oxadiazoline derivative (**4**), the formation of this stable or unstable mimic-fused heterocycle system may be a considerable factor in causing the activity of **3** or **4**.

The flexibility of the (acylimino)thiadiazoline moiety is restricted due to the double bond of the imine part. Hence, to further examine this remarkable intramolecular, nonbonded 1,5-

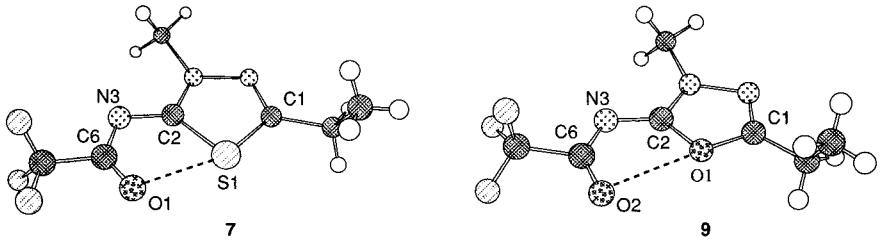


Figure 5. Computer-generated drawings of the compounds (**7** and **9**) derived from the X-ray coordinates. Dotted lines show the S···O or O···O close contact.

Table 2. Selected Atom Distances, Bond Angles, and Torsion Angles of Model Compounds **7** and **9**

thiadiazoline derivative **7**		oxadiazoline derivative **9**	
	Atom Distances (Å)		
S1−O1	2.670(4)	O1−O2	2.740(4)
	3.32[a]		3.04[a]
C2−N3	1.327(5)	C2−N3	1.294(4)
N3−C6	1.328(6)	N3−C6	1.329(4)
C6−O1	1.225(5)	C6−O2	1.207(4)
	Bond Angles (deg)		
S1−C2−N3	129.6(3)	O1−C2−N3	128.3(3)
C2−N3−C6	115.4(4)	C2−N3−C6	120.5(2)
N3−C6−O1	129.4(4)	N3−C6−O2	131.6(3)
C1−S1−C2	88.3(2)	C1−O1−C2	105.1(3)
	Torsion Angles (deg)		
S1−C2−N3−C6	−1.4(6)	O1−C2−N3−C6	0.1(5)
O1−C6−N3−C2	7.2(8)	O2−C6−N3−C2	−7.5(6)

[a] Sum of the corresponding van der Waals radii (S and O or O and O).

type S···O interaction between sulfur of the heterocycles and oxygen of the acyl part, the X-ray crystallographic analysis of the (acylamino)thiadiazole derivative (**6**) was investigated as another simple model compound bearing some steric flexibility. The computer-generated drawing of the crystal structure of **6** is shown in Figure 6. The S···O close contact (2.646(4) Å) between thiadiazole S1 and O1 of the trifluoroacetamide moiety, indicating the intramolecular nonbonded 1,5-type S···O interaction, was also recognized in the crystal structure of the (acylamino)thiadiazole derivative (**6**) as we anticipated. It can be understandable that the nonbonded S···O interaction controls the conformation of the low molecular weight compound.

2. Computational Studies. The ab initio geometry optimization at the HF/3-21G* level[9] was first performed on the (trifluoroacetyl)imino derivatives (**7** and **9**) to examine the relative energy of their three conformers as shown in Scheme 2 using the Gaussian 92[10] programs. The geometrical parameters were obtained from the structural data of their X-ray analyses. The results are summarized in Scheme 2 on the basis of the energy (0 kcal/mol) of **7-CT**[11] and **9-CT**[11] at $\chi = 180°$ (torsion angle of the C═N−C−CF_3 moiety).

The ab initio computation defined that the conformers (**7-CT** and **9-CT**)[11] observed in their X-ray crystallographic analysis are most stable among the three conformers of the compounds (**7** and **9**). The energy gap between **7-CT** and **7-CC**[11] or **7-CT** and **7-TT**[11] in the thiadiazoline derivative (**7**) was much larger than that between **9-CT** and **9-CC**[11] or **9-CT** and **9-TT**[11] in the oxadiazoline derivative (**9**). It is characteristic that the energy gap between **7-CT** and **7-TT** in **7** is quite large ($\Delta E^* = +9.06$ kcal/mol) in comparison with that ($\Delta E^* = +1.05$ kcal/mol) between **9-CT** and **9-TT** in oxadiazoline derivative **9**. This can be accounted for by the consideration that the intramolecular nonbonded 1,5-type S···O interaction most likely stabilizes the **7-CT** conformer in molecule **7**. Thus, **7-CT** is regarded as a stable mimic-fused bicyclic heterocycle rather than a monocyclic one. The computational studies of **7** and **9** led us to encourage the construction of such a system in this series of derivatives. This consideration is consistent with the results of X-ray analyses as described above. The existence of the stable mimic-fused bicyclic heterocycle may be regarded as one of important reasons why the (acylimino)thiadiazoline (**3**) exhibited the higher AII receptor antagonism in comparison with its oxa analogue (**4**).

To characterize further the energy level of this interesting interaction, another model compound (**6**) was precisely calculated. Compound **6** was submitted to the ab initio geometry optimizations at the HF/3-21G*, 6-31G*,[12] and 6-311+G** levels.[13] The results are shown in Figure 7 and Table 3.

In conformers A (torsion angle: 0°) and B (torsion angle: 180°), the difference of the relative energy should be remarkable at any calculation levels, namely, the torsion angle 180° conformer is fairly stable in a range of −8.16 to −8.74 kcal/mol in comparison with the conformer with 0° torsion angle. The X-ray crystallographic structure of **6** reflects the results of this calculation, indicating that the intramolecular nonbonded 1,5-type S···O interaction can regulate the conformation of the free rotatory molecule **6**. Thus, we realized that the formation of the stable intramolecular nonbonded 1,5-type S···O interaction is possible even in a molecule **6** more flexible than **7**.

There have been a few reports on the intramolecular, nonbonded S···O interaction exploiting modern computational methods.[14] Csizmadia and his colleagues carried out a quantum chemical study of the intramolecular 1,5-type S···O interaction by the ab initio SCF-MO method in which they clarified the relative energy levels of the interaction.[15] Employing the ab initio MO and semiempirical (MNDO) computation, Goldstein and his colleagues have disclosed the nature and magnitude of the 1,4-type S···O interaction between the thiazole sulfur and

(9) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939−947.

(10) The ab initio calculations were performed using Gaussian 92 programs: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkly, J. S.; Gonzales, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Steward, J. J. P.; Pople, J. A., *Gaussian 92*; GAUSSIAN, Inc.: Pittsburgh, 1993.

(11) CC, CT, and TT conformers of **7** and **9** mean the cis(heteroring C═N−)-s-cis(CF_3CO−N═), cis(heteroring C═N−)-s-trans(CF_3CO−N═), and trans(heteroring C═N−)-s-trans(CF_3CO−N═) arrangements, respectively.

(12) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213−222.

(13) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650−654.

(14) (a) Becker, P.; Cohen-Addad, C.; Delly, B.; Hirshfeld, F. L.; Lehmann, M. S. A Theoretical Study of Short S-O "Non-bonded" Interaction. In *Applied Quantum Chemistry*; Smith, V. H., Jr., Schaefer, H. F., III, Morokuma, K., Eds.; D. Reidel: Boston, 1986; pp 361−373. (b) Barbieri, G.; Benassi, R.; Taddei, F. *J. Mol. Struct.* **1989**, *184*, 269−276.

(15) Ángyán, J. G.; Poirier, R. A.; Kucsman, Á.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1987**, *109*, 2237−2245.

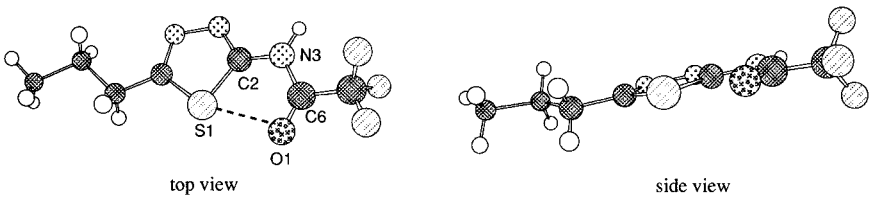
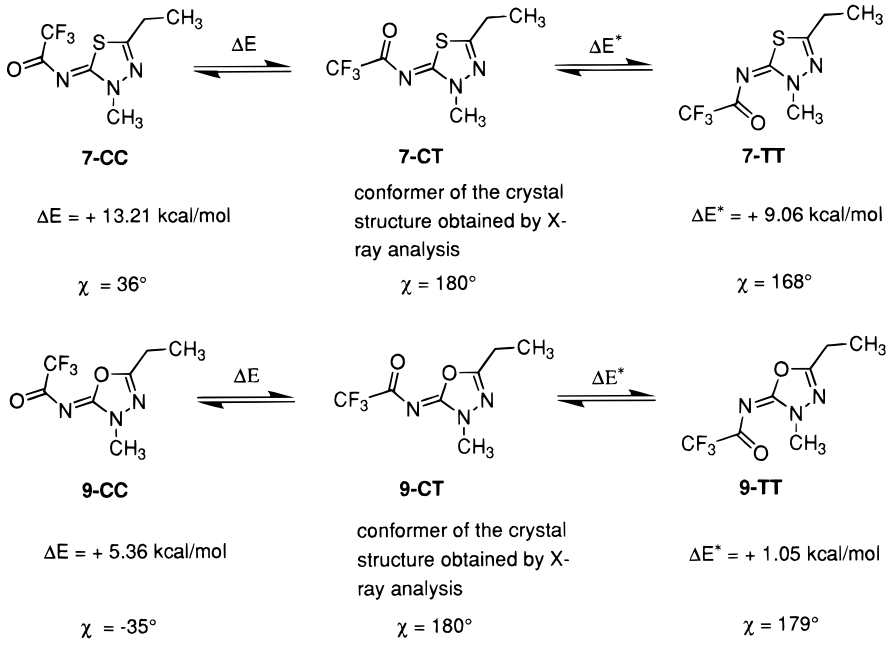


Figure 6. Computer-generated drawing of the model compound (**6**) derived from the X-ray coordinates. Dotted line shows the S···O close contact.

Scheme 2



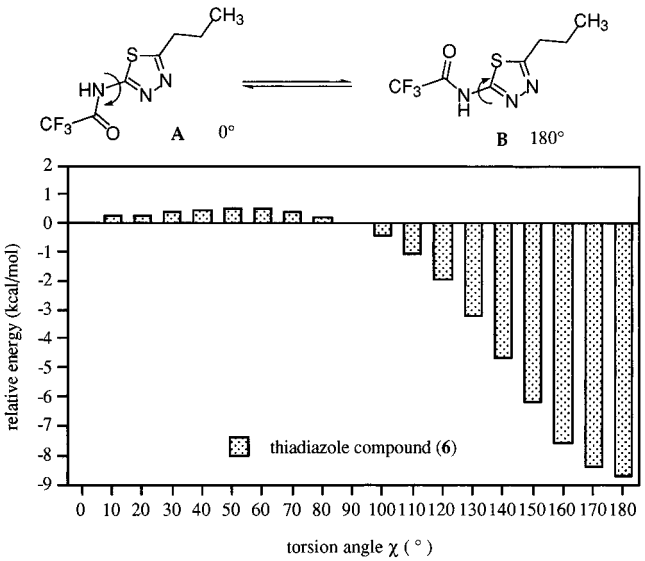
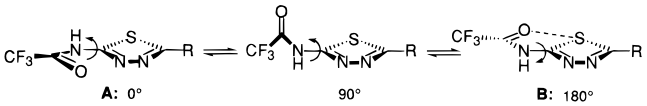


Figure 7. Ab initio calculation of the model compound (**6**) at the HF/3-21G* level.

the furanose oxygen in a thiazole nucleoside, tiazofurin (**10**).[16] To our knowledge, our result described above is the first example to determine the relative energy of the stable conformer due to the nonbonded, intramolecular 1,5-type S···O interaction in the (acylimino)thiadiazoline and (acylamino)thiadiazole concerned with biological activity.

(16) Burling, F. T.; Goldstein, B. M. *J. Am. Chem. Soc.* **1992**, *114*, 2313−2320.

Table 3. Ab Initio Calculations of Model Compound **6** at the Various Calculation Levels



6 : R = *n*-C_3H_7

	relative energy (kcal/mol)[a]		
χ (deg)	HF/3-21G*	HF/6-31G*	HF/6-311+G**
0	0.00	0.00	0.00
90	0.01	−2.25	−2.75
180	−8.74	−8.16	−8.17

[a] Each relative energy is the calculation value based on the corresponding 0° torsion angle conformer (0 kcal/mol).

Conclusion

In conclusion, clear evidence for the intramolecular, nonbonded 1,5-type S···O interactions in the (acylimino)thiadiazolines (**1**, **2**, **3**, and **7**) and the (acylamino)thiadiazole (**6**) was obtained from their X-ray crystallographic analyses. A possibility of the similar nonbonded 1,5-type O···O interaction in the (acylimino)oxadiazoline (**9**) was also suggested on the basis of its X-ray crystallographic analysis. The satisfactory relative stability of the conformer having this 1,5-type S···O interaction among possible ones of the simple compounds (**6**

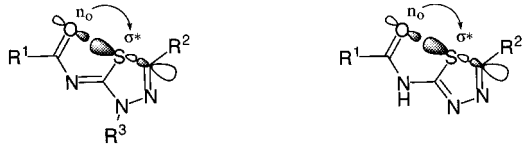


Figure 8. Possible explanation of the nonbonded 1,5-type S···O interaction due to $n_o \rightarrow \sigma^*$ orbital overlap effect.

and **7**) was demonstrated by exploiting the ab initio MO calculations at the HF/3-21G*, 6-31G*, and 6-311+G** levels. The relative stability of the conformer having a similar nonbonded 1,5-type O···O interaction in molecule **9** proved to be unremarkable in comparison with that of the other two corresponding conformers. Although no quantitative data has yet emerged, the stability of a particular 1,5-type S (with electron-withdrawing groups)···O (with electron-donating groups) and O···O interactions may be due to n_o (C═O) $\rightarrow \sigma^*$ (C−S and C−O) as shown in Figure 8.

Thus, the positive introduction of the mimic-fused bicyclic heterocycle system consisting of the intramolecular nonbonded S···O interaction into the designed bioactive compounds proves encouraging for the development of new drugs such as our AII receptor antagonists (**1**−**3**) and other sulfur-containing heterocyclic agents (**10**[5], **11**,[17] **12**,[18] etc.[17a]) as shown in Figure 9. Studies on the extension of this concept to an intermolecular S···O interaction are in progress. The intermolecular nonbonded S···O (e.g., oxygen of peptide bond: −CONH−) interactions between the sulfur-containing bioactive compounds and the receptors (or enzymes) are anticipated to be a new pharmacophore bonding.

Experimental Section

All melting points were determined on a Yanagimoto micro apparatus and are uncorrected. The infrared (IR) spectra were recorded on a JASCO J-0085 or a Perkin-Elmer 1720 infrared fourier transform spectrometer. The proton nuclear magnetic resonance (^{1}H NMR, 200 MHz) spectra were recorded on a JEOL-FX-200. Chemical shifts are given in δ values (ppm) using tetramethylsilane as an internal standard. Electron impact (EI) mass spectra (MS) were obtained on a JEOL-SX-102A instrument. Elementary combustion analyses were within ±0.4% of theoretical values. Column chromatography was performed using Merck silica gel 60 N (70−230 mesh). 2-Amino-5-ethyl-1,3,4-thiadiazole was purchased from Aldrich Chemical Co., Ltd. 2-Amino-5-propyl-1,3,4-thiadiazole and 2-amino-5-ethyl-1,3,4-oxadiazole were prepared by the procedure described in the literature.[19] Ethyl acetate, tetrahydrofuran, and *N*,*N*-dimethylformamide are abbreviated as AcOEt, THF, and DMF, respectively.

5-Ethyl-2-(trifluoroacetamido)-1,3,4-thiadiazole (5). To a suspension of 2-amino-5-ethyl-1,3,4-thiadiazole (2.0 g, 15.5 mmol) in toluene (50 mL) and diisopropylethylamine (2.8 mL, 16.1 mmol) was added trifluoroacetic anhydride (2.4 mL, 17.0 mmol) at 0 °C, and then the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water, and extracted with AcOEt. The organic layer was washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo afforded **5** (2.95 g, 85%) as colorless solids: mp 124−126 °C (EtOH); ^{1}H NMR ($CDCl_3$) 1.34 (t, J = 7.6 Hz, 3 H), 3.07 (q, J = 7.6 Hz, 2 H); IR (KBr) 1642 cm^{-1} (C═O); EI-MS *m*/*z* 225 M$^+$. Anal. Calcd for $C_6H_6F_3N_3OS$: C, 32.00; H, 2.69; N, 18.66. Found: C, 32.27; H, 2.74; N, 18.86.

5-Propyl-2-(trifluoroacetamido)-1,3,4-thiadiazole (6). Compound **6** was prepared by the similar method described above (83%): mp 169−171 °C (hexane−AcOEt); ^{1}H NMR ($CDCl_3$) 1.06 (t, J = 7.3 Hz, 3 H), 1.79−1.91 (m, 2 H), 3.01 (t, J = 7.6 Hz, 2 H); IR ($CHCl_3$) 1651 cm^{-1} (C═O); EI-MS *m*/*z* 239 M$^+$. Anal. Calcd for $C_7H_8F_3N_3OS$: C, 35.15; H, 3.37; N, 17.57. Found: C, 35.35; H, 3.40; N, 17.55.

5-Ethyl-3-methyl-2-[(trifluoroacetyl)imino]-1,3,4-thiadiazoline (7). To a suspension of **5** (1.33 g, 5.91 mmol) and Na_2CO_3 (332 mg, 3.16 mmol) in DMF (15 mL) was added methyl iodide (0.50 mL, 8.03 mmol), and then the mixture was stirred for 31 h at room temperature. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and dried over anhydrous $MgSO_4$. After evaporation of the solvent in vacuo, the residue was purified by column chromatography (hexane−AcOEt, 5:1) to give **7** (1.20 g, 85%) as colorless prisms: mp 53−54 °C (CH_2Cl_2−hexane); ^{1}H NMR ($CDCl_3$) 1.39 (t, J = 7.5 Hz, 3 H), 2.95 (q, J = 7.5 Hz, 2 H), 4.02 (s, 3H); IR ($CHCl_3$) 1642 cm^{-1} (C═O); EI-MS *m*/*z* 239 M$^+$. Anal. Calcd for $C_7H_8F_3N_3OS$: C, 35.15; H, 3.37; N, 17.57. Found: C, 35.08; H, 3.40; N, 17.62.

5-Ethyl-2-(trifluoroacetamido)-1,3,4-oxadiazole (8). To a suspension of 2-amino-5-ethyl-1,3,4-oxadiazole (2.0 g, 17.7 mmol) in THF (30 mL) was added trifluoroacetic anhydride (2.8 mL, 19.9 mmol) at 0 °C followed by stirring for 30 min. The reaction mixture was poured into aqueous $NaHCO_3$ solution (containing 1.80 g of $NaHCO_3$) and extracted with AcOEt. The organic layer was washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo afforded **8** (2.89 g, 78%) as colorless solids: mp 105−106 °C (hexane−AcOEt); ^{1}H NMR ($CDCl_3$) 1.40 (t, J = 7.5 Hz, 3 H), 2.87 (q, J = 7.5 Hz, 2 H); IR ($CHCl_3$) 1667, 1596 cm^{-1} (C═O, C═N); EI-MS *m*/*z* 209 M$^+$. Anal. Calcd for $C_6H_6F_3N_3O_2$: C, 34.46; H, 2.89; N, 20.09. Found: C, 34.75; H, 2.92; N, 20.25.

5-Ethyl-3-methyl-2-[(trifluoroacetyl)imino]-1,3,4-oxadiazoline (9). To a suspension of **8** (367 mg, 1.75 mmol) and diisopropylethylamine (0.36 mL, 2.07 mmol) in DMF (5 mL) was added methyl iodide (0.15 mL, 2.41 mmol) followed by stirring for 23 h at room temperature. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and dried over anhydrous $MgSO_4$. After evaporation of the solvent in vacuo, the residue was purified by column chromatography (hexane−AcOEt, 5:1 to 3:1) to give **9** (310 mg, 79%) as colorless prisms: mp 33−35 °C (CH_2Cl_2−hexane); ^{1}H NMR ($CDCl_3$) 1.37 (t, J = 7.5 Hz, 3 H), 2.81 (q, J = 7.5 Hz, 2 H), 3.65 (s, 3H); IR ($CHCl_3$) 1681, 1641, 1600 cm^{-1} (C═O, C═N); EI-MS *m*/*z* 223 M$^+$. Anal. Calcd for $C_7H_8F_3N_3O_2$: C, 37.68; H, 3.61; N, 18.83. Found: C, 37.61; H, 3.63; N, 18.94.

X-ray Studies. Crystallographic data for **1**, **3**, **6**, **7**, and **9** are summarized in Table 1. Rigaku AFC7R diffractometer employing Ni-filtered Cu Kα radiation was used. Three standard reflections monitored every 150 reflections showed no significant changes during data collection. An empirical absorption correction based on azimuthal scans of several reflections was applied for **6** and **9**, but not for the others. Structures were solved by directed methods[20] and refined by full-matrix least-squares technique to minimize $\Sigma (w|\Delta F|^2)$. The weighting scheme was based on counting statistics and included a factor, p, to down-weight the intense reflections: $w = [\sigma^2(F_o) + p^2|F_o|)^2]^{-1}$. All calculations were performed using teXsan[21] crystallographic software package. Full details of the crystallographic data are deposited in the Supporting Information.

Computational Studies. All calculations were carried out using the CONVEX-3440 of Computer Center in University of Tokushima. The ab initio calculations were performed using the Gaussian 92 system of programs at the RHF level of the theory using 3-21G*, 6-31G*, and 6-311+G**.

The geometry of (acylimino)thiadiazoline (**7**) and (acylimino)-oxadiazoline (**9**) was optimized at the ab initio HF/3-21G* level. The global energy minimum for each compound was normalized to 0 kcal/mol. As the result of the computation, each CT (*cis*-*s*-*trans*)[11]

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(21) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation, 1996.

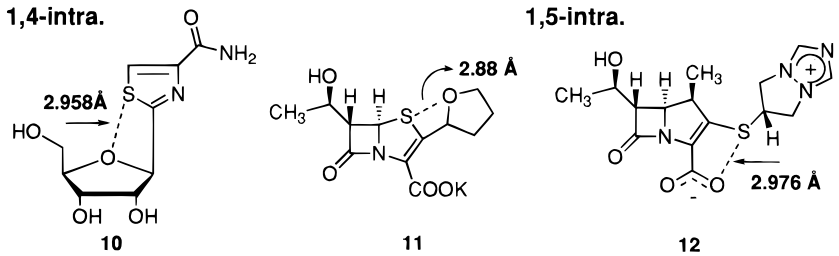

Figure 9. Examples of the S···O close contact recognized in the heterocyclic agents (**10**−**12**).

conformer referred to that of the crystallographic structure (X-ray analysis) indicated the minimum energy. The relative energies of CC (*cis-s-cis*)[11] and TT (*trans-s-trans*)[11] conformers were computed, and the optimized torsion angles χ (C═N−C−CF_3) of the CC and TT conformers were determined. The results are shown in Scheme 2.

The geometry of the model (acylamino)thiadiazole (**6**) was optimized at the ab initio HF/3-21G*, 6-31G*, and 6-311+G** levels. In the case of the HF/3-21G* calculation, several energy values as a function of torsion angles χ (N═C−N−CO) are calculated in the range 0−180° (χ). The selected torsion angle χ is defined by the S1−C2−N3−C6 atom arrangements for the (acylamino)thiadiazole (**6**). The $\chi = 0°$ conformer refers to the conformation in which the carbonyl oxygen is antiperiplanar relation to the sulfur of the thiadiazole ring, and the energy of this conformer was normalized to 0 kcal/mol. The χ value was incremented in 10° steps and fixed. The geometry at $\chi = 180°$ of the (acylamino)thiadiazole derivative **6** was based on the X-ray crystallographic analysis. The results are summarized in Figure 7. In the case of the HF/6-31G* or 6-311+G** calculation, each relative energy was calculated for the corresponding conformer at 0°, 90°, and 180° (χ values). The data are indicated in Table 3.

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Supporting Information Available: Detailed crystallographic and structural data (bond lengths, bond angles, and torsion angles) for **1**, **3**, **6**, **7**, and **9** (106 pages). See any current masthead page for ordering and Web access instructions.

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