4-Sulfenyl-2-carbamoyl-4-isoxazolin-3-ones: Biological Isostere to 4-Chloro-2-carbamoyl-4-isoxazolin-3-ones

Noriaki KUDO,* Takamitsu YONEDA, Kazuo SATO, Toyokuni HONMA, and Soji SUGAI

Agroscience Research Laboratories, Sankyo Co., Ltd., 1041 Yasu, Yasu-cho, Shiga 520-2342, Japan.

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4-Sulfenyl-2-carbamoyl-4-isoxazolin-3-ones (4) were designed on the basis of biological isosterism and prepared in four steps. Some of these compounds showed sufficient pre-emergent herbicidal activities against various kinds of weeds. Among the synthesized compounds, 2-(N-(4-chlorophenyl)-N-isopropylcarbamoyl)-4-ethylthio-5-methyl-4-isoxazolin-3-one (4cd) exhibited the most promising activity.

Key words biological isostere; herbicide; 4-isoxazolin-3-one; 3-hydroxyisoxazole; 2-sulfenyl- β -ketoester; cyclization

The introduction of a sulfur atom into compounds sometimes plays an important role in drugs and agrochemicals. In some aspects the chemical reactivity and property of sulfide resemble those of ether, but in other aspects they are very different.¹⁾ The sulfur atom potentially has the ability to undergo oxidation to the corresponding sulfoxide and sulfone. According to this property a sulfur atom acts distinctively. Metcalf reported that alkylthio-substituents in sulfur-containing cholinesterase inhibitors can be oxidized *in vivo* to the corresponding sulfoxide and sulfone to delay their endometabolic systemic properties.²⁾ The introduction of the alkylthio group in place of the chlorine atom sometimes brings about drastic changes in biological properties.³⁾ The chlorine atom of *s*-triazine herbicide **1**, so-called simazine,⁴⁾ had herbicidal activity but inflicted serious damage on transplanted rice. On the other hand, simetryne,⁵⁾ a compound **2** in which the chlorine atom was replaced with the methylthio group showed improved herbicidal activity and reduced rice injury (Chart 1). In simetryne, the methylthio group plays a biologically isosteric role, equal to that of a chlorine atom. This result indicates that the introduction of the alkylthio group instead of a chlorine atom on heterocyclic rings might increase herbicidal activity and decrease rice injury. The synthesis and herbicidal activities of 2-carbamoyl-4-chloro-4-isoxazolin-3-ones (**3**) have been reported.⁶⁾ These compounds showed effective herbicidal activity against harmful grass weed species such as barnyardgrass (*Echinochloa oryzicola* VASING), but they inflicted undesirable damage on transplanted rice. Thus, the discovery of the bioisosteric transformation³⁾ prompted us to synthesize 4-alkylthio-4-isoxazolin-3-one derivatives (**4**), in an effort to enhance the herbicidal activity and reduce undesired damage to rice (Chart 2). In this paper, we report synthesis of 4-alkylthio-2-carbamoyl-4-isoxazolin-3-ones and the herbicidal activity of these compounds in a paddy field.

The easiest way to synthesize the desired 4-alkylthio-2-carbamoyl-4-isoxazolin-3-ones was direct conversion of chlorine atom in 2-carbamoyl-4-chloro-4-isoxazolin-3-ones by alkanethiol. But it seemed that the substitution of chlorine atom attached to *sp*²-carbon of α -position of carbonyl group by alkanethiol hardly proceeded. Therefore, to synthesize the target compounds securely, incorporation of alkylthio group prior to forming isoxazoline ring was considered. According to the retro synthetic analysis, it was speculated that 4-alkylthio-2-carbamoyl-4-isoxazolin-3-ones could be selectively synthesized by carbamoylation of 4-alkylthio-3-hy-

droxyisoxazoles (**5**) at the nitrogen atom, and that **5** could be prepared through the regio-selective condensation of 2-alkylthio- β -ketoesters (**6**) and hydroxylamine (Chart 2).

A number of synthetic reactions of 2-alkylthio- β -ketoesters have been reported (Chart 3). Kay *et al.* reported that the introduction of methanesulfenyl group into **7** and subsequent reduction with zinc dust gave ethyl 2-methylthioacetate (**6a**) (Eq. 1).⁷⁾ Sasaki *et al.* reported the single step conversion of 2-chloroacetate (**7'**) to 2-arylthioacetate (**6p**) by treatment with arenethiol and triethylamine (Eq. 2).⁸⁾ Held *et al.* described the direct sulfenylation of β -ketoesters using benzenesulfenyl chloride (Eq. 3).⁹⁾ However, among the synthetic methods illustrated in Chart 3 (Eqs. 1–3), only a limited variety of β -ketoesters were available as starting materials, and the yields were low. Moreover, the pursuit of Kay's method did not proceed in good yield nor offer adequate generality for our purposes.¹⁰⁾ Clearly, a more efficient and general synthetic method for **6** was required for the preparation of various kinds of derivatives. From another viewpoint, Malleron *et al.* reported the synthesis of **6r** by deprotonation of ethyl 2-phenylthioacetate (**10**) followed by the

Chart 1

Chart 2

* To whom correspondence should be addressed.

Chart 3

Chart 4

addition of benzoyl chloride.¹¹ However, the benzoylation in this report was only exemplified and the yield of the product was a mere 10% (Eq. 4).¹¹ Given the wide range of acylating reagents that can be obtained commercially, and the easy accessibility of the starting materials, 2-alkylthioacetates (**13**), from thioglycolates (**11**) or 2-chloroacetates (**12**), we independently explored a similar preparation reaction of **6**. As a result, deprotonation of 2-alkylthioacetates (**13**) with lithium bis(trimethylsilyl)amide ($\text{LiN}(\text{TMS})_2$)¹² and subsequent treatment with acyl chlorides proved to be the best way to prepare **6**. Consequently, a variety of **6** could be prepared in good yields using this method. Details of these results are summarized in Table 1.

A number of synthetic reactions of 3-hydroxyisoxazoles from β -ketoesters and hydroxylamine have been reported, but there is always a problem that the cyclization reaction affords a mixture of two regio-isomers. One promising procedure for regioselective preparation of 3-hydroxyisoxazoles was ketalization of β -ketoesters followed by the reaction of hydroxylamine and subsequent acid-hydrolysis.¹³ However, when this method was used for the preparation of 4-

alkylthio-3-hydroxyisoxazoles, the initial step to ketalize the 2-substituted β -ketoesters generally did not proceed smoothly.⁹ In our previous paper we reported that the desired 4-alkylthio-3-hydroxyisoxazoles (**5**) were produced in good yields by treating 2-alkylthio- β -ketoesters (**6**) with hydroxylamine in an alkaline solution at a temperature under -10°C without ketalization, immediately quenching the reaction mixture with concentrated HCl, and quickly heating at 80°C .¹⁰ Using this method, compounds **5** shown in Table 2 could be obtained without the appearance of regio-isomers. Condensation of difluoromethylthio substituted compound (**6l**) and hydroxylamine did not proceed under these conditions. Therefore, by simple treatment of the compound **6l** with trimethylorthoformate, the ketal **14l** was obtained and subsequent addition of hydroxylamine afforded hydroxamic acid, followed by the cyclization with hydrochloric acid to afford the desired **5l** in 45.0% yield efficiently (Chart 5).

3-Hydroxyisoxazoles (**5**) have two positions to be acylated. The reaction of 3-hydroxyisoxazoles with *N,N*-dialkylcarbamoyl chloride gave *O*-carbamoyled product, while the reaction with alkyl isocyanate gave *N*-carbamoyled product

Table 1

$$\begin{array}{ccccc}
 \text{HS-CH}_2\text{-C(=O)OEt} & \xrightarrow[\text{solvent}]{\text{R}_1\text{-Hal, base}} & \text{R}_1\text{S-CH}_2\text{-C(=O)OEt} & \xrightarrow[\text{THF}]{\text{R}_2\text{COCl, LiN(TMS)}_2} & \text{R}_2\text{-C(=O)-CH(SR}_1\text{)-C(=O)OEt} \\
 \mathbf{11} & & \mathbf{13} & & \mathbf{6 \text{ (R = Et)}}
 \end{array}$$

	R ₁ -Hal	R ₁	Base/solvent	13 yield (%)	R ₂	6 yield (%)
a	a)	Me			Me	74.2
b		Me			Et	81.2
c	EtI	Et	NaOEt/EtOH	70.4	Me	70.3
d		Et			Et	96.3
e		Et			<i>n</i> -Pr	65.3
f		Et			<i>iso</i> -Pr	64.0
g		Et			<i>tert</i> -Bu	93.4
h	<i>n</i> -PrI	<i>n</i> -Pr	NaOEt/EtOH	59.3	Me	68.6
i	<i>iso</i> -PrI	<i>iso</i> -Pr	NaOEt/EtOH	83.2	Me	76.4
j		<i>iso</i> -Pr			Et	57.2
k	<i>n</i> -BuI	<i>n</i> -Bu	NaH/THF	78.1	Me	61.9
l	CHF ₂ Cl	CHF ₂	NaOEt/EtOH	77.9	Me	48.8
m	MeOCH ₂ CH ₂ Cl	MeOCH ₂ CH ₂	NaH/THF	49.6	Me	57.2
n	HC≡CCH ₂ Br	HC≡CCH ₂	NaH/THF	37.8	Me	31.2
o	2,4-Cl ₂ C ₆ H ₃ CH ₂ Cl	2,4-Cl ₂ C ₆ H ₃ CH ₂	NaOEt/EtOH	76.2	Me	36.0

a) Compound 13a (R₁ = Me) was commercially available.

Table 2

5	R ₁	R ₂	Yield (%)
a	Me	Me	54.7
c	Et	Me	32.3
d	Et	Et	57.6
e	Et	<i>n</i> -Pr	72.0
f	Et	<i>iso</i> -Pr	32.3
g	Et	<i>tert</i> -Bu	71.0
h	<i>n</i> -Pr	Me	51.3
i	<i>iso</i> -Pr	Me	66.2
j	<i>iso</i> -Pr	Et	51.4
k	<i>n</i> -Bu	Me	35.4
m	MeOCH ₂ CH ₂	Me	41.6
n	HC≡CCH ₂	Me	32.6
o	2,4-Cl ₂ C ₆ H ₃ CH ₂	Me	22.6

Table 3

4	R ₁	R ₂	R ₃	R ₄	Yield (%)
ad	Me	Me	<i>iso</i> -Pr	4-ClC ₆ H ₄	53.5
ca	Et	Me	Me	4-ClC ₆ H ₄	65.9
cb	Et	Me	Et	4-ClC ₆ H ₄	65.9
cc	Et	Me	<i>n</i> -Pr	4-ClC ₆ H ₄	65.4
cd	Et	Me	<i>iso</i> -Pr	4-ClC ₆ H ₄	58.6
ce	Et	Me	<i>iso</i> -Pr	4-FC ₆ H ₄	63.1
cg	Et	Me	<i>iso</i> -Pr	4-MeC ₆ H ₄	74.7
ch	Et	Me	<i>iso</i> -Pr	2,4-Cl ₂ C ₆ H ₃	63.2
ci	Et	Me	<i>iso</i> -Pr	4-CNC ₆ H ₄	15.4
cj	Et	Me	<i>iso</i> -Pr	3-NO ₂ C ₆ H ₄	62.1
ck	Et	Me	<i>iso</i> -Pr	3-CF ₃ C ₆ H ₄	63.7
dd	Et	Et	<i>iso</i> -Pr	4-ClC ₆ H ₄	60.1
ed	Et	<i>n</i> -Pr	<i>iso</i> -Pr	4-ClC ₆ H ₄	15.1
fd	Et	<i>iso</i> -Pr	<i>iso</i> -Pr	4-ClC ₆ H ₄	62.8
gd	Et	<i>tert</i> -Bu	<i>iso</i> -Pr	4-ClC ₆ H ₄	5.5
hd	<i>n</i> -Pr	Me	<i>iso</i> -Pr	4-ClC ₆ H ₄	63.9
hf	<i>n</i> -Pr	Me	<i>iso</i> -Pr	2,4-F ₂ C ₆ H ₃	66.7
id	<i>iso</i> -Pr	Me	<i>iso</i> -Pr	4-ClC ₆ H ₄	50.1
jd	<i>iso</i> -Pr	Et	<i>iso</i> -Pr	4-ClC ₆ H ₄	48.1
ld	CF ₂ H	Me	<i>iso</i> -Pr	4-ClC ₆ H ₄	88.3
md	MeOCH ₂ CH ₂	Me	<i>iso</i> -Pr	4-ClC ₆ H ₄	52.3
nd	HC≡CCH ₂	Me	<i>iso</i> -Pr	4-ClC ₆ H ₄	57.2
od	2,4-Cl ₂ C ₆ H ₃ CH ₂	Me	<i>iso</i> -Pr	4-ClC ₆ H ₄	62.6

as reported earlier.¹⁴⁾ The latter reaction enabled us to produce *N*-carbamoyled compounds selectively, but this reaction could not be applied to *N,N*-dialkyl carbamoyled product. After some attempts were made to synthesize the *N,N*-dialkyl

Table 4. Spectral Data for Compounds 6, 5, and 4

Compound No.	¹ H-NMR	IR	MS
6d	4.42—4.01 (3H, m), 2.95—2.37 (4H, m), 1.45—0.98 (9H, m)	2980, 1735, 1705, 1580, 1230, 1025	204 (M ⁺), 158, 148, 102, 57 (base)
6e	4.42—4.02 (2H, m), 2.83—2.36 (4H, m), 1.82—0.81 (9H, m)	2970, 2940, 1710, 1580, 1235, 1220	218 (M ⁺), 148 (base), 120, 102, 71
6f	4.49—4.08 (2H, m), 3.29—2.40 (3H, m), 1.48—1.09 (6H, m), 1.15 (6H, d, <i>J</i> =7.2 Hz)	2980, 2950, 1740, 1710, 1580, 1240, 1150, 1225	218 (M ⁺), 172, 148, 102, 71 (base), 43
6g	4.19 (2H, q, <i>J</i> =7.1 Hz), 1.93—1.50 (2H, m), 1.26 (3H, t, <i>J</i> =7.1 Hz), 1.24 (9H, s)	2970, 2930, 1735, 1700, 1240, 1140, 1030	232 (M ⁺), 148, 120, 102, 85, 57 (base), 43
6j	4.26 (2H, q, <i>J</i> =7.4 Hz), 3.21—2.55 (3H, m), 1.47—0.99 (12H, m)	2970, 2860, 1710, 1570, 1230, 1025	218 (M ⁺), 172, 162, 130, 102, 57 (base)
6l	6.55 (1H, t, <i>J</i> =57.0 Hz), 4.27 (2H, q, <i>J</i> =7.1 Hz), 2.36 (3H, s), 1.33 (3H, t, <i>J</i> =7.1 Hz)	3000, 1590, 1240, 1050	212 (M ⁺), 166, 124 (base), 87
6m	4.43—4.07 (2H, m), 3.67—3.32 (2H, m), 3.32 (3H, s), 2.89—2.59 (2H, m), 2.34 (3H, s), 1.47—1.17 (3H, m)	3000, 2940, 1720, 1590, 1245	220 (M ⁺), 178, 174, 146, 144, 59 (base)
6n	4.28 (2H, q, <i>J</i> =7.1 Hz), 3.27 (2H, d, <i>J</i> =2.6 Hz), 2.40 (3H, s), 2.17 (1H, t, <i>J</i> =2.6 Hz), 1.37 (3H, t, <i>J</i> =7.1 Hz)	3300, 3000, 2110, 1715, 1590, 1240	200 (M ⁺), 158, 119, 91, 44 (base), 40
6o	7.36—7.02 (3H, m), 4.23 (2H, q, <i>J</i> =7.3 Hz), 3.77 (2H, s), 1.92 (3H, s), 1.34 (3H, t, <i>J</i> =7.3 Hz)	2980, 2930, 1710, 1580, 1240	320 (M ⁺), 159 (base), 87
5d	8.43 (1H, s), 2.95 (2H, q, <i>J</i> =7.0 Hz), 2.87 (2H, q, <i>J</i> =7.0 Hz), 1.45 (3H, t, <i>J</i> =7.0 Hz), 1.39 (3H, t, <i>J</i> =7.0 Hz)	2970, 2925, 1600	172 (M ⁺ - 1), 158, 102 (base), 57
5e	8.60—8.10 (1H, br s), 2.68 (2H, q, <i>J</i> =7.0 Hz), 2.58 (2H, t, <i>J</i> =7.0 Hz), 1.93—1.40 (2H, m), 1.20 (3H, t, <i>J</i> =7.0 Hz), 0.95 (3H, t, <i>J</i> =7.0 Hz)	2960, 2930, 1600	187 (M ⁺), 149, 102, 71 (base)
5f	8.97 (1H, br s), 3.18 (1H, septet, <i>J</i> =7.0 Hz), 2.88—2.44 (2H, m), 1.32 (2H, d, <i>J</i> =7.0 Hz), 1.22 (3H, t, <i>J</i> =7.8 Hz)	2980, 2940, 1675, 1595	187 (M ⁺), 149, 102, 71 (base)
5g	8.95 (1H, br s), 2.96—2.55 (2H, m), 1.45 (9H, s), 1.24 (3H, t, <i>J</i> =7.2 Hz)	2950, 2920, 1675, 1580	201 (M ⁺), 186, 142, 116, 84, 57 (base)
5j	10.45 (1H, s), 2.99 (1H, septet, <i>J</i> =7.0 Hz), 2.77 (2H, q, <i>J</i> =7.0 Hz), 1.27 (3H, t, <i>J</i> =7.0 Hz), 1.24 (6H, d, <i>J</i> =7.0 Hz)	3000, 2950, 1610	187 (M ⁺), 145, 130, 102, 89, 57 (base)
5l	9.49 (1H, s), 6.70 (1H, t, <i>J</i> =57.2 Hz), 2.47 (3H, s)	2940, 1720, 1610	181 (M ⁺), 158, 149, 71, 40 (base)
5m	8.36 (1H, s), 3.51 (2H, t, <i>J</i> =6.1 Hz), 3.36 (3H, s), 2.80 (2H, t, <i>J</i> =6.1 Hz), 2.37 (3H, s)	3000, 2940, 1610	189 (M ⁺), 163, 129, 73, 59, 44, 40 (base)
5n	8.69 (1H, s), 3.35 (2H, d, <i>J</i> =2.5 Hz), 2.45 (3H, s), 2.16 (1H, t, <i>J</i> =2.5 Hz)	3320, 1610	169 (M ⁺), 152, 126, 40 (base)
5o	9.04 (1H, s), 6.81—7.35 (3H, m), 3.88 (2H, s), 1.92 (3H, s)	2930, 1610	289 (M ⁺), 174, 159 (base), 149, 123
4ad	7.31 (4H, m), 4.65 (1H, septet, <i>J</i> =7.0 Hz), 2.36 (3H, s), 2.22 (3H, s), 1.24 (6H, d, <i>J</i> =7.0 Hz)	1710, 1615	340 (M ⁺), 293, 237, 196 (base), 154
4ca	7.23 (4H, s), 3.41 (3H, s), 2.62 (2H, q, <i>J</i> =7.1 Hz), 2.35 (3H, s), 1.12 (3H, t, <i>J</i> =6.9 Hz)	1710, 1615, 1490, 1320, 905	326 (M ⁺), 284, 211, 168, 140 (base), 111, 83
4cb	7.21 (4H, s), 3.78 (2H, q, <i>J</i> =6.9 Hz), 2.58 (2H, q, <i>J</i> =6.9 Hz), 2.30 (3H, s), 1.19 (3H, t, <i>J</i> =6.9 Hz), 1.10 (3H, t, <i>J</i> =6.9 Hz)	1715, 1620, 1490, 1380, 1280, 910	340 (M ⁺), 182 (base), 154, 40
4cc	7.19 (4H, s), 3.70 (2H, t, <i>J</i> =7.6 Hz), 2.59 (2H, q, <i>J</i> =7.6 Hz), 2.30 (3H, s), 1.67 (2H, sextet, <i>J</i> =7.6 Hz), 1.10 (3H, t, <i>J</i> =7.6 Hz), 0.90 (3H, t, <i>J</i> =7.6 Hz)	1700, 1620	354 (M ⁺), 239, 196, 169, 140 (base), 111, 70
4cd	7.19—7.33 (4H, m), 4.63 (1H, septet, <i>J</i> =7.0 Hz), 2.62 (2H, q, <i>J</i> =7.6 Hz), 2.32 (3H, s), 1.22 (6H, d, <i>J</i> =7.0 Hz), 1.13 (3H, t, <i>J</i> =7.6 Hz)	1715, 1620	354 (M ⁺), 196, 169, 154, 42 (base)
4ce	7.34—6.80 (4H, m), 4.59 (1H, septet, <i>J</i> =6.6 Hz), 2.61 (2H, q, <i>J</i> =7.1 Hz), 2.29 (3H, s), 1.20 (6H, d, <i>J</i> =6.6 Hz), 1.01 (3H, t, <i>J</i> =7.1 Hz)	1710, 1620, 1505, 1310, 910	338 (M ⁺), 180, 138, 57, 41 (base)
4cg	7.06 (4H, s), 4.57 (1H, septet, <i>J</i> =6.8 Hz), 2.61 (2H, q, <i>J</i> =7.2 Hz), 2.31 (3H, s), 2.25 (3H, s), 1.20 (6H, d, <i>J</i> =6.8 Hz), 1.11 (3H, t, <i>J</i> =7.2 Hz)	1705, 1615, 1310, 905	334 (M ⁺), 219, 176, 134 (base), 91, 41
4ch	7.53—7.09 (3H, m), 4.62 (1H, septet, <i>J</i> =6.9 Hz), 2.60 (2H, q, <i>J</i> =7.2 Hz), 2.33 (3H, s), 1.17 (6H, d, <i>J</i> =7.2 Hz), 1.11 (3H, t, <i>J</i> =7.2 Hz)	1700, 1610, 1460, 1375	388 (M ⁺), 230, 203, 188, 149 (base), 88, 57, 41
4ci	7.61 (2H, d, <i>J</i> =9.3 Hz), 7.32 (2H, d, <i>J</i> =9.3 Hz), 4.60 (1H, septet, <i>J</i> =6.6 Hz), 2.59 (2H, q, <i>J</i> =7.2 Hz), 2.31 (3H, s), 1.26 (6H, d, <i>J</i> =6.6 Hz), 1.10 (3H, t, <i>J</i> =7.2 Hz)	2230, 1700, 1615, 1460, 1380	345 (M ⁺), 187, 160, 145, 41 (base)
4cj	8.25—8.05 (2H, m), 7.63—7.48 (2H, m), 4.64 (1H, septet, <i>J</i> =6.9 Hz), 2.59 (2H, q, <i>J</i> =7.2 Hz), 2.33 (3H, s), 1.27 (6H, d, <i>J</i> =6.9 Hz), 1.10 (3H, t, <i>J</i> =7.2 Hz)	1680, 1590, 1490, 1430, 1350	365 (M ⁺), 185, 165 (base), 41
4ck	7.45 (4H, s), 4.62 (1H, septet, <i>J</i> =6.6 Hz), 2.53 (2H, q, <i>J</i> =6.9 Hz), 2.29 (3H, s), 1.23 (6H, d, <i>J</i> =6.6 Hz), 1.09 (3H, t, <i>J</i> =6.9 Hz)	1705, 1615, 1320, 1305, 1130, 900	388 (M ⁺), 230, 203, 188, 41 (base)
4dd	7.26 (4H, s), 4.61 (1H, septet, <i>J</i> =7.0 Hz), 2.89—2.45 (4H, m), 1.32—0.99 (6H, m), 1.23 (6H, d, <i>J</i> =7.0 Hz)	1710, 1610	368 (M ⁺), 196 (base), 169, 154, 57

Table 4. (Continued)

Compound No.	¹ H-NMR	IR	MS
4ed	7.23 (4H, s), 4.61 (1H, septet, <i>J</i> =6.8 Hz), 2.82—2.47 (4H, m), 1.84—1.48 (2H, m), 1.28—0.94 (6H, m), 1.22 (6H, d, <i>J</i> =6.8 Hz)	1710, 1610	382 (M ⁺), 196, 169, 154, 71 (base)
4fd	7.36 (2H, d, <i>J</i> =9.0 Hz), 7.23 (2H, d, <i>J</i> =9.0 Hz), 4.62 (1H, quintet, <i>J</i> =6.9 Hz), 3.23 (1H, quintet, <i>J</i> =6.9 Hz), 2.64 (2H, q, <i>J</i> =7.3 Hz), 1.22 (6H, d, <i>J</i> =7.2 Hz), 1.12 (3H, t, <i>J</i> =7.3 Hz)	1710, 1605, 1490, 1305, 1245, 1095, 1015	382 (M ⁺), 312, 283, 196, 169, 154 (base), 71
4gd	7.22 (4H, s), 4.59 (1H, septet, <i>J</i> =6.6 Hz), 2.49 (2H, q, <i>J</i> =7.3 Hz), 1.33 (9H, s), 1.21 (6H, d, <i>J</i> =6.6 Hz), 1.12 (3H, t, <i>J</i> =7.3 Hz)	1710, 1580, 1310	396 (M ⁺), 196, 169, 149, 57 (base)
4hd	7.20—7.36 (4H, m), 4.65 (1H, septet, <i>J</i> =7.0 Hz), 2.58 (2H, t, <i>J</i> =7.6 Hz), 2.33 (3H, s), 1.47 (2H, qt, <i>J</i> =7.0, 7.6 Hz), 1.23 (6H, d, <i>J</i> =7.0 Hz), 0.94 (3H, t, <i>J</i> =7.0 Hz)	1710, 1615	368 (M ⁺), 294, 239, 196 (base), 169, 154, 144, 131, 111, 87
4hf	7.41—7.50 (1H, m), 6.81—6.92 (2H, m), 4.65 (1H, septet, <i>J</i> =7.0 Hz), 2.56 (2H, t, <i>J</i> =7.0 Hz), 2.34 (3H, s), 1.45 (2H, sextet, <i>J</i> =7.0 Hz), 1.23 (6H, br s), 0.92 (3H, t, <i>J</i> =7.0 Hz)	1710, 1615	370 (M ⁺), 198, 171, 156, 149, 131, 41 (base)
4id	7.20—7.35 (4H, m), 4.65 (1H, septet, <i>J</i> =6.4 Hz), 3.16 (1H, septet, <i>J</i> =6.4 Hz), 2.31 (3H, s), 1.23 (6H, d, <i>J</i> =6.4 Hz), 1.15 (6H, d, <i>J</i> =6.4 Hz)	1710, 1615	368 (M ⁺), 294, 239, 196, 169, 154 (base), 131, 111
4jd	7.11—7.47 (4H, m), 4.60 (1H, septet, <i>J</i> =7.0 Hz), 3.18 (1H, septet, <i>J</i> =7.0 Hz), 2.70 (2H, q, <i>J</i> =7.6 Hz), 1.23 (6H, d, <i>J</i> =7.0 Hz), 1.20 (3H, t, <i>J</i> =7.6 Hz), 1.15 (6H, d, <i>J</i> =7.0 Hz)	1705, 1600	382 (M ⁺), 326, 307, 283, 239, 196, 169, 154 (base), 145, 102, 57
4ld	7.08—7.40 (4H, m), 6.63 (1H, t, <i>J</i> =57.0 Hz), 4.60 (1H, septet, <i>J</i> =7.0 Hz), 2.37 (3H, s), 1.22 (6H, d, <i>J</i> =7.0 Hz)	1720, 1620	376 (M ⁺), 239, 223, 196 (base), 167, 154, 131, 111, 40
4md	7.19 (4H, s), 4.53 (1H, septet, <i>J</i> =7.0 Hz), 3.33 (2H, t, <i>J</i> =6.4 Hz), 3.20 (3H, s), 2.68 (2H, t, <i>J</i> =6.4 Hz), 2.24 (3H, s), 1.23 (6H, d, <i>J</i> =7.0 Hz)	1710, 1620	384 (M ⁺), 352, 293, 239, 196, 154, 111, 59, 41 (base)
4nd	7.00—7.40 (4H, m), 4.59 (1H, septet, <i>J</i> =7.0 Hz), 3.28 (2H, d, <i>J</i> =3.0 Hz), 2.35 (3H, s), 2.10 (1H, t, <i>J</i> =3.0 Hz), 1.20 (6H, d, <i>J</i> =7.0 Hz)	1710, 1620	364 (M ⁺), 294, 239, 196, 154, 111, 41 (base)
4od	7.32—7.39 (3H, m), 7.22—7.27 (2H, m), 7.05 (1H, dd, <i>J</i> =8.1, 2.3 Hz), 6.68 (1H, d, <i>J</i> =8.1 Hz), 4.64 (1H, septet, <i>J</i> =7.0 Hz), 3.82 (2H, s), 1.86 (3H, s), 1.23 (6H, d, <i>J</i> =7.0 Hz)	1710, 1610	484 (M ⁺), 325, 294, 239, 223, 196, 159 (base), 138, 111

Table 5. Physical Data for Compounds **5** and **4**

Compound No.	mp (°C)	Formula	Analysis (%)					
			Calcd			Found		
			C	H	N	C	H	N
5f	47—49	C ₈ H ₁₃ NO ₂ S	51.31	7.00	7.48	51.06	7.01	7.33
5g	83—88	C ₉ H ₁₅ NO ₂ S	53.70	7.51	6.96	53.47	7.44	6.95
5l	73—75	C ₅ H ₅ F ₂ NO ₂ S	33.15	2.78	7.73	33.10	2.80	7.84
4ad	131—134	C ₁₅ H ₁₇ ClN ₂ O ₃ S	52.86	5.03	8.22	52.22	4.87	8.49
4cb	Oil	C ₁₅ H ₁₇ ClN ₂ O ₃ S	52.86	5.03	8.22	52.64	4.96	8.23
4cd	64—65	C ₁₆ H ₁₉ ClN ₂ O ₃ S	54.16	5.40	7.89	54.12	5.36	7.90
4ce	61—62	C ₁₆ H ₁₉ FN ₂ O ₃ S	56.79	5.66	8.28	56.65	5.63	8.35
4ch	95—97	C ₁₆ H ₁₈ Cl ₂ N ₂ O ₃ S	49.36	4.66	7.20	49.43	4.61	7.22
4cj	111—112	C ₁₆ H ₁₉ N ₃ O ₃ S	52.59	5.24	11.50	52.30	5.17	11.39
4dd	Oil	C ₁₇ H ₂₁ ClN ₂ O ₃ S	55.35	5.74	7.59	55.09	5.69	7.80
4fd	Oil	C ₁₈ H ₂₃ ClN ₂ O ₃ S	56.46	6.06	7.32	56.22	6.02	7.30
4hd	52—54	C ₁₇ H ₂₁ ClN ₂ O ₃ S	55.35	5.74	7.59	55.34	5.67	7.74
4hf	47—48	C ₁₇ H ₂₀ F ₂ O ₃ S	55.12	5.44	7.56	55.22	5.67	7.51
4id	85—87	C ₁₇ H ₂₁ ClN ₂ O ₃ S	55.35	5.74	7.59	55.22	5.67	7.66
4ld	70—72	C ₁₅ H ₁₅ ClF ₂ N ₂ O ₃ S	47.81	4.01	7.43	47.99	3.95	7.55
4md	92—94	C ₁₇ H ₂₁ ClN ₂ O ₄ S	53.05	5.50	7.28	52.81	5.53	7.22

carbamoyled product, 2-chlorocarbonyl-4-isoxazolin-3-ones (**15**) generated from 3-hydroxyisoxazoles and phosgene were proved to be satisfactory intermediates. Accordingly, treatment of 3-hydroxyisoxazole derivatives (**5**) with 4 eq of phosgene in toluene gave 2-chlorocarbonyl-4-isoxazole-3-one derivatives (**15**), selectively. After evaporating the solvent and excess amount of phosgene, a mixture of aniline derivatives and triethylamine was added to the solution of the

crude residue in tetrahydrofuran (THF) to afford the desired 2-carbamoyl-4-isoxazolin-3-ones (**4**) in good yields. Two strong absorptions observed in the IR spectrum ($\nu_{\max}$ cm⁻¹: 1700—1715 and 1600—1620) strongly suggested the existence of two carbonyl groups in the molecule. Taking this result into consideration, these structures were determined to be *N*-carbamoyled products rather than *O*-carbamoyled products. Our results are summarized in Table 3.

Table 6. Herbicidal Activity of Compounds 4

4	g/a	EO	LP	SJ	EA	CS	EK	OS
ca	25	5	4	4	4	5	5	1
cb	10	5	4	5	4	5	5	2
cc	10	5	5	5	4	5	5	1
cd	25	5	5	5	5	5	5	1
cd	10	5	5	5	5	5	5	0
ce	25	5	5	5	5	5	5	3
cg	10	5	2	5	4	5	5	0
ch	10	5	4	5	4	5	5	0
ci	10	5	4	5	4	5	5	3
cj	10	5	4	5	4	5	5	1
ck	10	5	3	4	2	5	5	0
dd	25	5	4	4	4	5	5	2
dd	10	5	3	3	3	4	5	0
hd	25	5	5	5	5	5	5	2
hd	10	5	3	5	5	5	5	0
hf	10	5	5	5	5	5	5	1
id	25	5	5	5	4	5	5	2
id	10	5	3	5	3	5	5	0
jd	25	5	3	5	3	5	5	0
ld	10	5	3	5	5	5	5	1
md	25	5	3	5	4	5	5	1
md	10	5	2	5	3	5	5	0
nd	25	5	4	5	3	5	5	2
nd	10	5	3	5	3	5	5	0

EO: *Echinochloa oryzicola*, LP: *Lindernia procumbens*, SJ: *Scirpus juncoides*, EA: *Eleocharis acicularis*, CS: *Cyperus serotinus*, EK: *Eleocharis kuroguwai*, OS: transplanted rice.

Biological Results

The comparative herbicidal activity of the synthesized compounds was measured at the whole plant level *via* a greenhouse assay. Table 6 shows the results of herbicidal evaluations of the synthesized compounds. Structures and activity relationships strongly resembled those of 4-chloro-4-isoxazolin-3-one derivatives (3).⁶ The substitution of a chlorine atom at the 4-position of the 4-isoxazolin-3-one ring with the alkylthio groups maintains herbicidal activity. In this series, an alkylthio group seemed to act as a biological isostere to a chlorine atom. All tested compounds showed good activity against *Echinochloa oryzicola* VASING (EO), *Cyperus serotinus* ROTB. (CS), and *Eleocharis kuroguwai* OHWI (EK). In general, lower activity was accompanied by a change from methylthio to longer alkylthio substituents at the 4-position (R₁S) of the 4-isoxazolin-3-one ring. Introduction of an alkoxyalkylthio group (4md) or alkynylthio group (4nd) gave disappointing results. Compared with the more bulky isopropyl group (4cd), a small alkyl group such as a methyl (4ca) or ethyl group (4cb) at the nitrogen atom in the carbamoyl group slightly decreased herbicidal activity and increased injury toward transplanted rice. Electron withdrawing groups such as a nitro (4cj) or trifluoromethyl group (4ck) on an aryl group (R₄) decreased the activity, and the introduction of a cyano group (4ci) increased the unwanted damage to transplanted rice.

In summary, the novel 4-isoxazolin-3-ones (4) presented in this paper showed good to excellent herbicidal activity and rice selectivity. In this series, the alkylthio group played a biological isosteric role to a chlorine atom. Among the synthesized compounds, 2-(*N*-(4-chlorophenyl)-*N*-isopropylcarbamoyl)-4-ethylthio-5-methyl-4-isoxazolin-3-one (4cd) exhibited the best herbicidal activity against all tested weeds.

While several compounds were investigated more fully in the greenhouse, none of them seemed to show adequate potential to merit detailed field evaluation.

Experimental

Synthesis All melting points (mp) are uncorrected. IR spectra were measured on a Jasco A-102 spectrometer or Perkin-Elmer 1600 spectrometer. ¹H-NMR spectra were recorded at 60 MHz on a Varian 360A spectrometer, at 200 MHz on a Varian Gemini 200 spectrometer, or at 270 MHz on a JOEL GX 270 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HR-MS) were obtained with a JEOL JMS-D300 mass spectrometer and a VG Auto Spec M mass spectrometer.

Ethyl 2-Ethylthioacetate (13c) Sodium ethoxide (12.76 g, 188 mmol) was added to a solution of ethyl thioglycolate (11) (15 g, 125 mmol) in ethanol (150 ml) and the resulting mixture was stirred at room temperature for 5 min. Then, ethyl iodide (30 ml, 0.356 mmol) was added and the resulting mixture was refluxed for 1 h. The reaction mixture was concentrated to one-third volume, diluted with water, and extracted with ether (2×). The combined extracts were washed with brine (1×), dried over Na₂SO₄, and evaporated *in vacuo*. The residue was distilled under reduced pressure (bp 85 °C (20 mmHg)) to yield 13.04 g (70.4%) of 13c as oil.

Compounds 13d–13o were synthesized in the same manner. (Compound 13a is commercially available.)

Ethyl 2-Ethylthioacetoacetate (6c) A 1.0 M solution of LiN(TMS)₂ in THF (7.08 ml, 7.08 mmol) was gradually added to a solution of ethyl 2-ethylthioacetate (13c) (500 mg, 3.37 mmol) in THF (10 ml) at a temperature below –50 °C and after 30 min a solution of acetyl chloride (0.32 g, 4.08 mmol) in THF (5 ml) was added at –50 °C. The resulting mixture was stirred at –50 °C for 50 min, at –20 °C for 1 h, at 0 °C for 40 min, and at room temperature for 30 min. The reaction mixture was quenched by the addition of saturated aqueous solution of NH₄Cl and 1 N hydrochloric acid and then extracted with ether (3×). The combined extracts were washed with brine (1×), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford 451 mg of 6c (70.3%) as oil.

Compounds 6a, 6b, 6d–6n were synthesized in the same manner.

Ethyl 2-Ethylthio-3-oxopentanoate (6d): Oil, HR-MS Calcd for C₉H₁₆O₃S: 204.0820. Found: 204.0821.

Ethyl 2-Ethylthio-3-oxohexanoate (6e): Oil, HR-MS Calcd for C₁₀H₁₈O₃S: 218.0977. Found: 218.0975.

Ethyl 2-Ethylthio-4-methyl-3-oxopentanoate (6f): Oil, HR-MS Calcd for C₁₀H₁₈O₃S: 218.0977. Found: 218.0976.

Ethyl 4,4-Dimethyl-2-ethylthio-3-oxopentanoate (6g): Oil, HR-MS Calcd for C₁₁H₂₀O₃S: 232.1133. Found: 232.1132.

Ethyl 2-Isopropylthio-3-oxopentanoate (6j): Oil, HR-MS Calcd for C₁₀H₁₈O₃S: 218.0977. Found: 218.0977.

Ethyl 2-Difluoromethylthioacetoacetate (6l): Oil, HR-MS Calcd for C₇H₁₀F₂O₃S: 212.0319. Found: 212.0317.

Ethyl 2-(2-Methoxyethylthio)acetoacetate (6m): Oil, HR-MS Calcd for C₉H₁₆O₄S: 220.0769. Found: 220.0770.

Ethyl 2-(2-Propynylthio)acetoacetate (6n): Oil, HR-MS Calcd for C₉H₁₂O₃S: 200.0507. Found: 200.0508.

Ethyl 2-(2,4-Dichlorobenzylthio)acetoacetate (6o) A 1.0 M solution of LiN(TMS)₂ in THF (62.24 ml, 62.24 mmol) was gradually added to a solution of ethyl 2-(2,4-dichlorobenzylthio)acetate (13o) (8.69 g, 31.1 mmol) and acetyl chloride (2.6 g, 31.1 mmol) in THF (200 ml) at a temperature below –50 °C and the resulting mixture was stirred at –50 °C for 1 h. The reaction mixture was quenched by the addition of saturated aqueous solution of NH₄Cl and 1 N hydrochloric acid and then extracted with ether (3×). The combined extracts were washed with brine (1×), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford 3.6 g of 6o (36.0%) as oil. HR-MS Calcd for C₁₃H₁₄Cl₂O₃S: 320.0041. Found: 320.0042.

4-Ethylthio-3-hydroxy-5-methylisoxazole (5c) 6c (2.60 g, 13.7 mmol) was added to a solution of potassium hydroxide (0.90 g, 13.6 mmol) in water (16 ml) and methanol (32 ml) at 0 °C and the mixture was stirred for 30 min. An aqueous solution (16 ml) of potassium hydroxide (2.70 g, 40.9 mmol) and hydroxylamine hydrochloride (2.85 g, 41.0 mmol) was added at –30 °C. After 1.5 h acetone (20 ml) was added to the mixture and the stirring was continued for an additional 10 min. After adding concentrated hydrochloric acid (7 ml) and stirring at 90 °C for 45 min, the mixture was diluted with water and extracted with ether (3×). The combined extracts were washed with brine (1×) and then extracted with 1 N aqueous solution of sodium hy-

dioxide (2×). The aqueous extracts were acidified with 6N hydrochloric acid and extracted with ether (3×), then the combined extracts were washed with brine (1×), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford 713 mg of **5c** (32.3%) as amorphous.

Compounds **5a**, **5d**—**5k**, **5m**—**5o** were synthesized in the same manner.

5-Ethyl-4-ethylthio-3-hydroxyisoxazole (**5d**): Oil, HR-MS Calcd for C₇H₁₁NO₂S: 173.0511. Found: 173.0509.

4-Ethylthio-3-hydroxy-5-propylisoxazole (**5e**): Oil, HR-MS Calcd for C₈H₁₃NO₂S: 187.0667. Found: 187.0668.

5-Ethyl-3-hydroxy-4-isopropylthioisoxazole (**5j**): Oil, HR-MS Calcd for C₈H₁₃NO₂S: 187.0667. Found: 187.0666.

3-Hydroxy-4-(2-methoxyethylthio)-5-methylisoxazole (**5m**): Oil, HR-MS Calcd for C₇H₁₁NO₃S: 189.0460. Found: 189.0461.

3-Hydroxy-5-methyl-4-(2-propynylthio)isoxazole (**5n**): mp 105—110 °C, HR-MS Calcd for C₇H₇NO₂S: 169.0198. Found: 169.0199.

4-(2,4-Dichlorobenzylthio)-3-hydroxy-5-methylisoxazole (**5o**): mp 136—137 °C, HR-MS Calcd for C₁₁H₉Cl₂NO₂S: 288.9731. Found: 288.9730.

Ethyl 2-Difluoromethylthio-3,3-dimethoxybutyrate (14l) 95% sulfuric acid (0.2 ml) was added to a mixture of **6l** (16.47 g, 77.6 mmol) and trimethyl orthoformate (10.2 ml, 93.2 mmol) in methanol (20 ml) and the resulting mixture was refluxed for 15 h. After neutralizing the reaction mixture with a solution of potassium hydroxide in methanol and filtering it, the filtrate was concentrated *in vacuo* to give 12.72 g of **14l** (63.5%) as a crude oil, which was subjected to the next reaction without further purification. ¹H-NMR (CDCl₃) δ: 6.85 (1H, t, *J*=56.7 Hz), 4.20 (2H, q, *J*=7.0 Hz), 4.09 (1H, s), 3.25 (6H, s), 1.50 (3H, s), 1.28 (3H, t, *J*=7.0 Hz); IR ν_{max} cm⁻¹ (KBr): 3000, 1730, 1160, 1110, 1040; MS (*m/z*): 243 (M⁺ - 15), 227 (base), 213, 132, 99, 89.

5-Difluoromethylthio-3-hydroxy-5-methylisoxazole (5l) Compound **5l** was prepared from **14l** as the compound **5c**.

2-[N-(4-Chlorophenyl)-N-isopropylcarbamoyl]-4-ethylthio-5-methyl-4-isoxazolin-3-one (4cd) A 2.26 M solution of phosgene in toluene (89 ml, 201 mmol) was added to **5c** (6.25 g, 39 mmol) and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* and diluted again with toluene (50 ml). A solution of *N*-isopropyl-4-chloroaniline (6.97 g, 41 mmol) and triethylamine (6.7 ml, 48.1 mmol) in toluene (30 ml) was added to the solution and the resulting mixture was stirred at room temperature for 35 min. The reaction mixture was diluted with ether, washed with 1N hydrochloric acid (1×), aqueous solution of NaHCO₃ (1×), and brine (1×), dried over Na₂SO₄, and evaporated. The residue was subjected to silica gel column chromatography to give 8.15 g of **4cd** (58.6%) as a light yellow powder.

A series of compounds **4** listed in Table 3 were synthesized by the same method.

2-[N-(4-Chlorophenyl)-N-methylcarbamoyl]-4-ethylthio-5-methyl-4-isoxazolin-3-one (4ca): Oil, HR-MS Calcd for C₁₄H₁₅ClN₂O₃S: 326.0492. Found: 326.0493.

2-[N-(4-Chlorophenyl)-N-propylcarbamoyl]-4-ethylthio-5-methyl-4-isoxazolin-3-one (4cc): mp 82—83 °C, HR-MS Calcd for C₁₆H₁₉ClN₂O₃S: 354.0805. Found: 354.0806.

4-Ethylthio-2-[N-isopropyl-N-(4-methylphenyl)carbamoyl]-5-methyl-4-isoxazolin-3-one (4cg): mp 60—61 °C, HR-MS Calcd for C₁₇H₂₂N₂O₃S: 334.1351. Found: 334.1352.

2-[N-(3-Cyanophenyl)-N-isopropylcarbamoyl]-4-ethylthio-5-methyl-4-isoxazolin-3-one (4ci): mp 108—109 °C, HR-MS Calcd for C₁₇H₁₉N₃O₃S: 345.1147. Found: 345.1147.

4-Ethylthio-2-[N-isopropyl-N-(3-trifluoromethylphenyl)carbamoyl]-5-methyl-4-isoxazolin-3-one (4ck): Oil, HR-MS Calcd for C₁₇H₁₉F₃N₂O₃S: 388.1068. Found: 388.1067.

2-[N-(4-Chlorophenyl)-N-isopropylcarbamoyl]-4-ethylthio-5-propyl-4-isoxazolin-3-one (4ed): Oil, HR-MS Calcd for C₁₈H₂₃ClN₂O₃S: 382.1118. Found: 382.1117.

5-tert-Butyl-2-[N-(4-chlorophenyl)-N-isopropylcarbamoyl]-4-ethylthio-4-

isoxazolin-3-one (4gd): Oil, HR-MS Calcd for C₁₉H₂₅ClN₂O₃S: 396.1274. Found: 396.1274.

2-[N-(4-Chlorophenyl)-N-isopropylcarbamoyl]-5-ethyl-4-isopropylthio-4-isoxazolin-3-one (4jd): mp 74—76 °C, HR-MS Calcd for C₁₈H₂₃ClN₂O₃S: 382.1118. Found: 382.1121.

2-[N-(4-Chlorophenyl)-N-isopropylcarbamoyl]-5-methyl-4-(2-propynylthio)-4-isoxazolin-3-one (4nd): mp 52—54 °C, HR-MS Calcd for C₁₇H₁₇ClN₂O₃S: 364.0648. Found: 364.0645.

2-[N-(4-Chlorophenyl)-N-isopropylcarbamoyl]-4-(2,4-dichlorobenzylthio)-5-methyl-4-isoxazolin-3-one (4od): mp 96.5—98.5 °C, HR-MS Calcd for C₂₁H₁₉Cl₂N₂O₃S: 484.0182. Found: 484.0183.

Herbicide Tests Plastic pots (surface area=100 cm²) were filled with a clay loam soil and kept in a greenhouse. The test plants were five narrowleaf weeds [*Echinochloa oryzicola* VASING., *Scirpus juncoideus* ROXB var. *ohwianus* T. KOYAMA, *Eleocharis acicularis* (L.) ROEM. et SCHULT. var. *longiseta* SVEN., *Cyperus serotinus* ROTTB., and *Eleocharis kuroguwai* OHWI] and one broadleaf weed [*Lindernia pyxidaria* L.], and *Sagittaria pygmaea* Miq., and *Oryza sativa* L. A predetermined number of seeds of each weed were placed on top of the soil. An additional 1 cm of soil was placed over the seeds, and then seedlings of *Oryza sativa* L. that had reached the two-leaf stage were transplanted. For the herbicidal test, wettable powders were prepared by mixing the compounds (10%) with Emulgen 810 (surfactant; 0.5%), Demol N (surfactant; 0.5%), Kunilite 210 (diatomaceous earth; 20%), and Dieclite CA (clay; 69%). The wettable powders formulated from the compounds were applied 3 d after the seeds had been sown. Approximately 3 weeks after treatment, the herbicidal activity of each compound was judged by visual observation of the symptoms of the treated plants in comparison with untreated controls. Using the following criteria, the herbicidal potency was scaled from 0 to 5 according to the extent of the injury shown by the plants: 5, >91% growth inhibition; 4, 71—90% growth inhibition; 3, 51—70% growth inhibition; 2, 31—50% growth inhibition; 1, 11—30% growth inhibition; 0, <10% growth inhibition.

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References and Notes

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