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Studies of the New Herbicide KIH-6127. Part III. Synthesis and Structure–Activity Studies of Analogues of KIH-6127 against Barnyard Grass (*Echinochloa oryzicola*)*

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Abstract: The previously evaluated prototype, methyl 6-acetyl-2-[(4,6-dimethoxypyrimidin-2-yl)oxy]benzoate, was modified by the introduction of an oximino group. Further extensive synthetic modifications were then made to the 6-alkyl moiety (R^1), the ester moiety (R^2), the alkoxyimino moiety (R^3), the bridge-atom (X) and the 4,6-disubstituted-pyrimidine moiety (A, B, Z). Structure–activity relationships of the synthesized compounds were studied by examining their herbicidal activity against Barnyard grass (*Echinochloa oryzicola*) in paddy rice at various growth stages, including pre-emergence. The novel herbicide methyl 2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-6-[1-(methoxyimino)ethyl]benzoate, (KIH-6127) was found to be the most effective compound. The commercial development of this compound is currently in progress.

Key words: herbicide, barnyard grass, PS compound, KIH-6127, rice, acetolactate synthase (ALS)

1 INTRODUCTION

Our previous work reported that methyl 6-acetyl-2-[(4,6-dimethoxypyrimidin-2-yl)oxy]benzoate (Fig. 1, **I**) exhibited a good profile as a lead compound for the control of barnyard grass (*Echinochloa oryzicola* Frit.).

Most 6-substituted pyrimidin-2-yl salicylate compounds bearing an ester group showed reduced herbicidal and ALS inhibitory activities as compared with their 6-substituted carboxylic acid analogues.[2] This suggested that *ortho*-disubstitution is capable of preventing the metabolic hydrolysis of the ester moiety, by which pyrimidin-2-yl-salicylates are converted into the active carboxylic acid *in vivo*.[3]

As briefly discussed in Part II,[4] the 6-acyl pyrimidin-2-yl salicylates possess herbicidal activity, especially against barnyard grass, for a variety of ester moieties. For a series of 6-acyl compounds, only the 6-acetyl derivative **I** was sufficiently selective in rice whilst showing good control of barnyard grass.

Our optimization focused on the modification of the 6-acyl group. The introduction of an oximino group into the 6-acyl moieties was attempted to give a hypothetical bio-isosteric analogue of **I**. The methoxyimino group has a similar [σ_p] value ($CH_3O-N=CH-$: 0·30, $O=CH-$: 0·42)[5] value and a steric similarity to carbonyl, and the hydrophilicity of the oximino (R^3)

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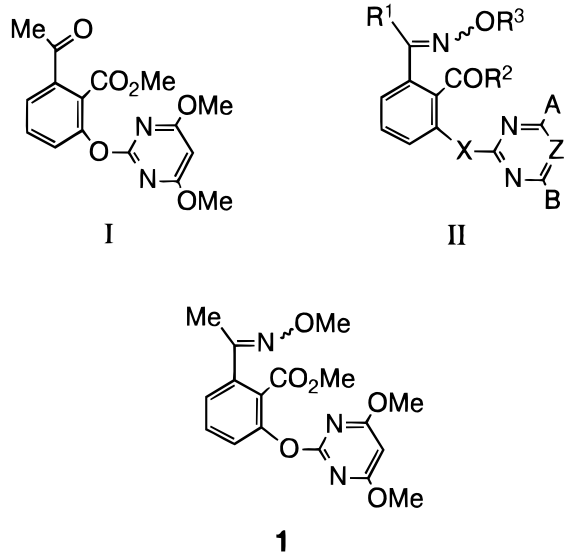


Fig. 1. Structures of compounds discussed. **I** Prototype compound. **II** General structure of test compounds. **1** KIH-6127.

moiety can be varied by alkylation or acylation. (Fig. 1, **II**).

This paper describes the modification of the alkyl (R^1), the ester (R^2), the oximino (R^3), the bridge (X) and the pyrimidine (A,B,Z) moieties **II** and the structure–activity profiles for barnyard grass control and rice safety.

2 MATERIALS AND METHODS

2.1 Synthesis of test compounds

[^{1}H] and [^{13}C]NMR spectra were recorded in deuterochloroform on a JEOL JMN-PMX-60Si and a JEOL JMN-GSX-400 with trimethylsilane as an internal standard, while IR spectra and mass spectra were measured on a Shimadzu IR-240 and a JEOL JMS-SX-102A spectrometer, respectively. All melting points are uncorrected. The structures of compounds were confirmed by NMR, IR and mass spectroscopies.

All test compounds were obtained by the reactions (Methods A, B, C and D) summarized as shown in Fig. 2. Compounds **10**, **12**, **13**, **15** and **16** were synthesized by Methods E and F as shown in Figs 3 and 4, respectively. The synthetic intermediates for the test compounds were obtained by our reported method.[1,4,6–9] Other starting compounds, such as the corresponding alkoxy amines, were prepared by standard procedures[10,11] or were commercially available. Typical examples of synthetic procedures are as follows:

2.1.1 Method A

2.1.1.1 Synthesis of methyl 2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-6-[1-(methoxyimino)propyl]benzoate (**3**). Methyl 2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-6-propionylbenzoate[1,4] (0·62 g, 1·79 mmol), methoxylamine hydrochloride (0·45 g, 5·40 mmol) and potassium acetate (0·53 g, 5·40 mmol) were added to methanol (80 ml), and the mixture was heated at reflux for 6 h. The precipitate was filtered off, and the filtrate was evaporated. The residue was added to water and extracted with ethyl acetate. The organic layer was washed with water, separated and dried. The solvent was evaporated and the mixture purified using a silica-gel column with hexane + ethyl acetate (7 + 3 by volume) as eluent and crystallized from isopropyl ether/ethyl acetate to give **3** (0·6 g; 85·9%); m.p. 75–77°C, [^{1}H]NMR δ: 1·06 (t, J = 7 Hz, 3H), 2·73 (q, J = 7 Hz, 2H), 3·73 (s, 3H), 3·83 (s, 6H), 3·92 (s, 3H), 5·86 (s, 1H), 7·00–7·63 (m, 3H) ppm:

2.1.1.2 Synthesis of methyl 6-[1-(allyloxyimino)ethyl]-2-[(4,6-dimethoxypyrimidin-2-yl)oxy]benzoate (**34**). Compound **I** (1·0 g, 0·30 mmol), allyloxyamine hydrochloride (1·0 g, 0·92 mmol) and potassium acetate (0·9 g, 0·92 mmol) were added to methanol (30 ml), and the mixture was heated at reflux with stirring for 5 h. The reaction mixture was then poured into cold water and extracted with ethyl acetate. The organic layer was washed in turn with dilute hydrochloric acid, then with aqueous sodium hydrogen carbonate and water. The organic layer was dried, concentrated, and the oily

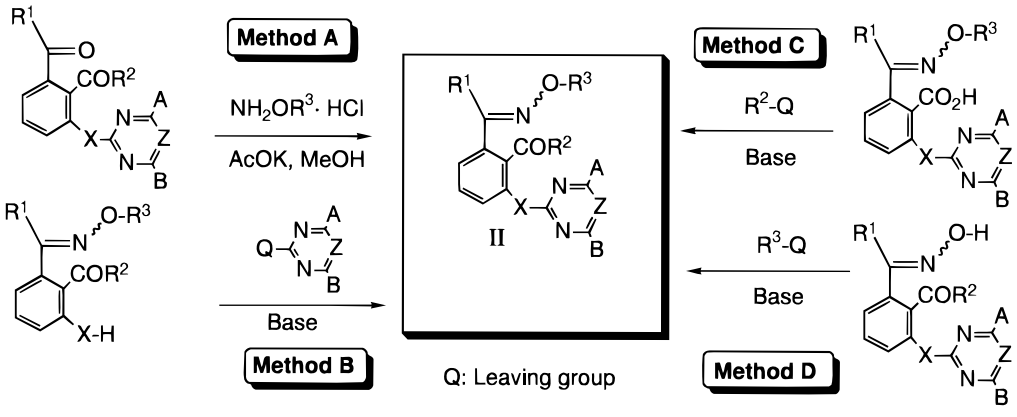


Fig. 2. General synthetic schemes (Methods A, B, C & D) for compounds **II**.

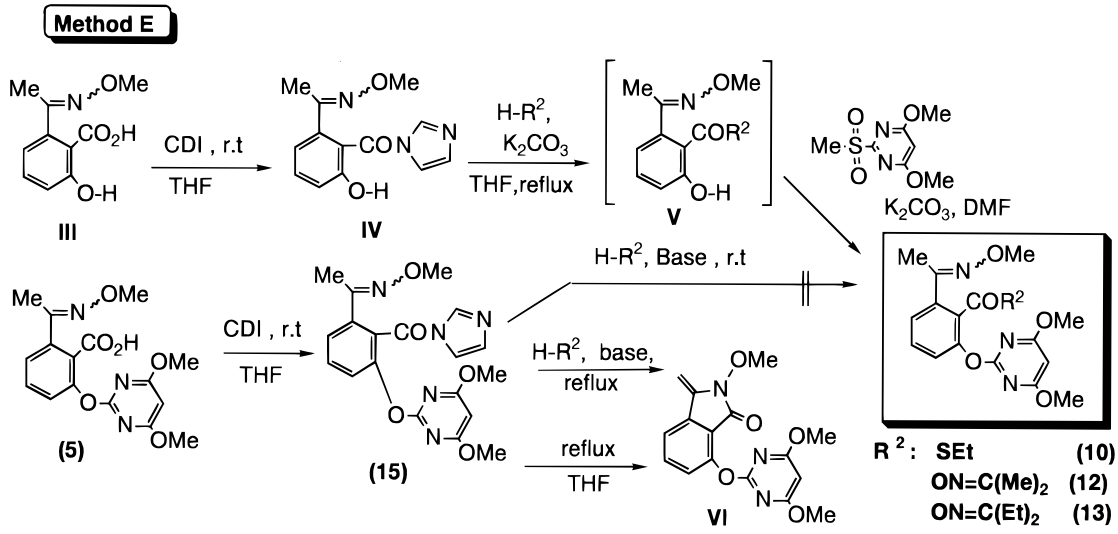


Fig. 3. Introduction of the R^2 moiety in the presence of CDI (*N,N'*-carbonyl diimidazole).

residue purified by silica-gel column chromatography using hexane + isopropyl ether (10 + 1 by volume) as eluent to give **34** as colourless crystals (0·54 g; 46%); m.p. 76–78°C, [^{1}H]NMR δ: 2·20 (s, 3H), 3·66 (s, 3H), 3·79 (s, 6H), 4·60 (d, J = 6 Hz, 2H), 5·0–5·60 (m, 2H), 5·69 (s, 1H), 5·75–6·15 (m, 1H), 7·0–7·50 (m, 3H) ppm.

2.1.2 *Method B*

2.1.2.1 Synthesis of methyl 2-[(4,6-dimethoxypyrimidin-2-yl)oxy-6-[1-(methoxyimino)ethyl]benzoate (**1**). Methyl 6-[1-(methoxyimino)ethyl]salicylate (1·15 g, 5·0 mmol), 4,6-dimethoxy-2-methanesulfonylpyrimidine (DMSP) (1·12 g, 5·1 mmol) and potassium carbonate (0·71 g, 5·65 mmol) were added to *N,N*-dimethylformamide (DMF; 50 ml), and the mixture was heated at 100°C for 2 h. After cooling, the reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated to give **1** as a crude solid, which was then washed with isopropyl ether to give pure **1** (1·35 g; 73%); m.p. 105–106°C, [^{1}H]NMR δ: 2·17 (s, 3H), 3·76 (s, 3H), 3·82 (s, 6H), 3·96 (s, 3H), 5·73 (s, 1H), 7·16–7·50 (m, 3H) ppm.

2.1.2.2 Synthesis of methyl 2-[(4,6-dimethoxypyrimidin-2-yl)-N-formylamino-6-[1-methoxyimino)ethyl]benzoate (**26**). Methyl 2-formylamino-6-[1-(methoxyimino)ethyl] benzoate (10 g, 0·04 mol) was added to a suspension of sodium hydride (1·0 g, 0·04 mol) in benzene (100 ml), and the resultant mixture was stirred at room temperature for 10 min. DMSP (8·7 g, 0·04 mol) was then added and the mixture heated at reflux for 6 h. After cooling, the reaction mixture was poured into ice/water, and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated. The residue was purified by silica-gel column chromatography as in Section 2.1.1.2 to give **26** (8·3 g; 54%); m.p. 147–149°C. [^{1}H]NMR δ: 2·15 (s, 3H), 3·59 (s, 3H), 3·73 (s, 6H), 3·85 (s, 3H), 5·69 (s, 1H), 7·15–7·59 (m, 3H), 10·15–10·30 (brs, 1H) ppm.

2.1.2.3 Synthesis of methyl 2-[(4,6-dimethoxypyrimidin-2-yl)amino]-6-[1-(methoxyimino)ethyl]benzoate (**27**). Concentrated hydrochloric acid (1 ml) was added to a

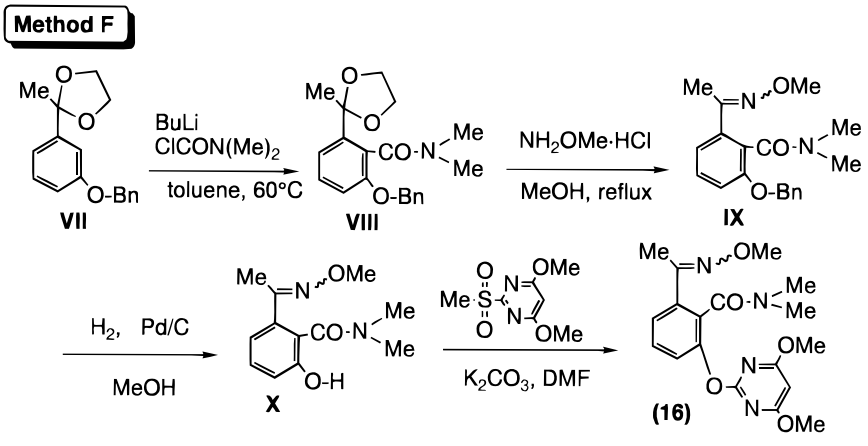


Fig. 4. Synthesis of *N,N*-dimethyl-2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-6-[1-(methoxyimino)ethyl]benzamide (**16**).

solution of **26** (1·34 g, 3·45 mmol) in methanol (50 ml). The mixture was allowed to stand overnight at room temperature, poured onto ice/water, and then extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogen carbonate and then with water, dried and concentrated. The residue was purified by silica-gel column chromatography as in Section 2.1.1.2 to give **27** (0·87 g; 70%) m.p. 82–84°C, [^{1}H]NMR δ: 2·15 (s, 3H), 3·85 (s, 3H), 3·90 (s, 9H), 5·56 (s, 1H), 6·92 (d, J = 7 Hz, 1H), 7·39 (t, J = 7 Hz, 1H), 8·56 (d, J = 7 Hz, 1H), 8·90–9·20 (brs, 1H) ppm.

2.1.3 *Method C*

2.1.3.1 Synthesis of ethyl 2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-6-[1-(methoxyimino)ethyl]benzoate (**6**). Sodium hydride (0·14 g, 6·0 mmol) was added to a solution of **5** (2 g, 6·0 mmol) in DMF (50 ml) with stirring at room temperature. After the generation of hydrogen had finished, ethyl bromide (0·76 g, 7·0 mmol) was added. The resultant mixture was stirred for 1 h at 60°C, and then poured into cold water, and the oily product thus formed extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated, and the residue purified by silica-gel column chromatography as in Section 2.1.1.2 to obtain **6** (1·5 g; 69%) m.p. 65–68°C, [^{1}H]NMR δ: 1·26 (t, J = 7 Hz, 3H), 2·23 (s, 3H), 3·73 (s, 6H), 3·81 (s, 3H), 4·07 (q, J = 7 Hz, 2H), 5·76 (s, 1H), 7·15–7·60 (m, 3H) ppm.

2.1.4 *Method D*

2.1.4.1 Synthesis of methyl 6-[1-(acetyloxyimino)ethyl]-2-[(4,6-dimethoxypyrimidin-2-yl)oxy]benzoate (**39**). Triethylamine (0·434 g, 4·3 mmol) was added to a solution of **28** (1·5 g, 4·3 mmol) in acetone (20 ml) below 0°C. Acetyl chloride (0·34 g, 4·3 mmol) was added dropwise to the resultant mixture below 5°C, and the mixture stirred at 5–10°C for 2 h. The reaction mixture was then poured onto ice/water, extracted with ethyl acetate, and the organic layer washed with water, dried and concentrated below 30°C. The residue was purified by silica-gel column chromatography as in Section 2.1.1.2 to give **39** as a colourless oil (0·86 g; 52%); n_D^{20}: 1·5510, [^{1}H]NMR δ: 2·16 (s, 3H), 2·26 (s, 3H), 3·66 (s, 3H), 3·76 (s, 6H), 5·73 (s, 1H), 7·08–7·73 (m, 3H) ppm.

2.1.5 *Method E*

2.1.5.1 Synthesis of O-[*2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-6-[1-(methoxyimino)ethyl]benzoyl*]-N-(*3-pentylidene)hydroxyamine* (**13**). A solution of **III** (2·6 g, 12·4 mmol) and 1,1′-carbonyldiimidazole (CDI; 2·0 g, 12·4 mmol) in tetrahydrofuran (20 ml) was stirred at room temperature for 1 h. Pentane-3-one oxime (1·25 g, 12·4 mmol) and potassium carbonate (0·85 g, 12·4 mmol) were added to the resultant mixture (**IV**), and the mixture was heated at reflux for 1 h. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated to give crude **V** in 80% yield. According to Method B, a mixture of crude **V** (2·9 g, 9·9 mmol), DMSP (2·2 g, 1·0 mmol) and potassium carbonate (1·38 g, 10 mmol) in DMF (20 ml) was stirred at 90°C for 1 h to give **13** (51%); m.p. 103–105°C, [^{1}H]NMR δ: 1·00 (t, J = 7 Hz, 3H), 1·13 (t, J = 7 Hz, 3H), 1·20–2·50 (m, 4H), 2·26 (s, 3H), 3·79 (s, 6H), 4·10 (s, 1H), 5·79 (s, 1H), 7·15–7·85 (m, 3H) ppm.

2.1.6 *Method F*

2.1.6.1 Synthesis of N,N-*dimethyl-2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-6-[1-(methoxyimino)ethyl]benzamide* (**16**). *n*-Butyllithium (9 g, 20·4 mmol: 14% hexane solution) was added dropwise to a solution of 3-benzyloxyacetophenone ethylene ketal[1,4] **VII**; (5 g, 18·5 mmol) in toluene (25 ml) with stirring at 6–7°C for 10 min. The mixture was stirred at room temperature for a further 30 min, and *N*,*N*-dimethylcarbamoyl chloride (1·98 g, 18·5 mmol) added dropwise at room temperature. This mixture was gradually heated to 60°C, and maintained for 2 h, then poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated. The residue was purified by silica-gel column chromatography as in Section 2.1.1.2 to give **VIII** (43%); m.p. 85–87°C, [^{1}H]NMR δ: 1·76 (s, 3H), 2·83 (s, 3H), 3·09 (s, 3H), 3·66–4·10 (m, 4H), 5·13 (s, 2H), 6·85–7·62 (m, 3H), 7·43 (s, 5H) ppm.

A solution of **VIII** (1·5 g, 4·46 mmol) and methoxyammonium chloride (1·2 g, 14 mmol) in methanol (15 ml) was heated at reflux for 1 h to give **IX** (0·9 g, 2·76 mmol), which was then catalytically hydrogenated in the presence of Pd/C under standard conditions to give **X** quantitatively (0·68 g, 2·87 mmol). According to the procedure of Method B, **X** was converted into **16** (72%); n_D^{20}: 1·5491, [^{1}H]NMR δ: 2·20 (s, 3H), 2·83 (s, 3H), 3·00 (s, 3H), 3·79 (s, 6H), 3·86 (s, 3H), 5·73 (s, 1H), 7·15–7·43 (m, 3H) ppm.

2.1.7 *Syntheses of other compounds*

2.1.7.1 Synthesis of methyl 6-[1-(methoxyimino)ethyl] salicylate. According to Method A, methyl 6-acetylsalicylate[8] was converted to methyl 6-[1-(methyoxyimino)ethyl]salicylate (83%); n_D^{20}: 1·5423, [^{1}H]NMR δ: 2·07 (s, 3H), 3·83 (s, 3H), 3·86 (s, 3H), 6·53–7·53 (m, 3H), 10·66–11·00 (brs, 1H) ppm.

2.1.7.2 Synthesis of 6-[1-(methoxyimino)ethyl]salicylic acid (**III**). A solution of methyl 6-[1-(methoxyimino) ethyl]salicylate (25·4 g) in aqueous potassium hydroxide (200 g litre^{-1}; 100 ml) was stirred at 80°C for 1 h to give 6-[1-(methoxyimino)ethyl]salicylic acid (**III**). The reaction mixture was acidified with citric acid, then extracted with ethyl acetate. The organic layer was

washed with water, dried and concentrated, and the residue triturated with isopropyl ether + hexane (1 + 1 by volume) and recrystallized from isopropyl ether to give **III** as yellow crystals (31·4% yield); m.p. 110·5–112°C, [^{1}H]NMR δ: 1·85 (s, 3H), 3·53 (s, 3H), 6·17–7·17 (m, 3H), 8·50–9·56 (brs, 1H) ppm.

2.2 Stereochemistry

All reaction product oxime derivatives obtained by the present synthetic methods were *E*/*Z* mixtures. Usually one isomer was major, forming >90% of the mixture. The isomers were easily separated by silica-gel (Wakogel C-300) column chromatography using hexane + ethyl acetate (10 + 1 to 6 + 1 by volume) as eluent and with subsequent recrystallization. Each compound was found to have greater than 98% purity by HPLC. The stereochemistry of *E*/*Z* isomers in typical compounds was confirmed by high resolution NMR spectroscopy, with the major isomer being *E*, as discussed in Section 3.1.

2.3 Biological tests

Each test compound was formulated as a 100 g kg^{-1} wettable powder, containing 'Emalgen' 810 (5·0 g kg^{-1}; Kao Ltd), 'Demoln' (5·0 g kg^{-1}, Kao Ltd), Kunilite 250 (diatomaceous earth; 180 g kg^{-1}), Carplex No/80 (white carbon; 60 g kg^{-1}) and Zeeklite (clay). The wettable powder was diluted with water to the desired concentration. Plastic pots (square, 100 cm^2 in surface area) were packed with clay loam soil (organic matter 1·44%, pH 5·6) and water was added up to 3 cm in depth. *E. oryzicola* (Ec) was seeded at a depth of 0·5 cm 1 day after puddling and fertilization. Rice seedlings (*Oryza sativa*, two-leaf growth stage) (Or) were transplanted in depths of 3 cm in the same pot. One day after seeding, or when *E. oryzicola* reached the desired leaf-growth stage, a diluted suspension (10 ml) of wettable powder was poured into the pots, individually. The test pots were maintained at 20–35°C and the water temperature at 15–30°C during the test period. No artificial light was used. A water depth of 3 cm was maintained during the test period. Three weeks later (DAT 21), the herbicidal activity and rice injury ratings were visually evaluated on a percentage scale, where 0% = no control or crop injury and 100% = complete mortality. ED_{90} and ED_{10} values were calculated as the amounts of active ingredient (g ha^{-1}) required for 90% control of barnyard grass, and 10% injury of rice, respectively.

3 RESULTS AND DISCUSSION

The herbicidal activities and physical properties of the test compounds are shown in Tables 1 and 2 respectively.

3.1 Stereochemistry

The condensation of crude methyl 6-[1-(methoxyimino) ethyl]salicylate with DMSP gave a mixture of **1E** (*E*-isomer) and **1Z** (*Z*-isomer) in a >9 : 1 (*E*/*Z*) ratio. The isomers were separated by silica-gel column chromatography and [^{1}H] and [^{13}C]NMR spectra recorded to confirm their stereochemistry. The chemical shifts are summarized as shown in Table 3.

According to the resonances of [^{1}H] and [^{13}C]NMR spectra, both proton and carbon chemical shifts for the 3-position of **1E** were observed to be more downfield than those of **1Z**. Conversely, those for the 1-position of **1E** were more upfield than those of **1Z** in accordance with the literature.[12,13] A weak NOE spectrum was observed between the 1-position and the 3-position of **1E**, but no NOE spectrum was observed for **1Z**. Consequently, the major isomer was tentatively assigned as being the *E*-isomer.

3.2 Synthesis of test compounds

Four synthetic schemes for PS compounds (Methods A, B, C and D) were developed and employed for the preparation of a variety of compounds of general structure **II** (Fig. 1). The target ethylthio (**10**), alkylidene iminooxy (**12** and **13**) ester and amide (**16**) derivatives required alternative approaches (Figs 3 and 4).

When a mixture of **5** and ethylmercaptan was treated at room temperature in the presence of 1,1′-carbonyl diimidazole (CDI) only starting material was recovered. A second attempt under reflux conditions and with the addition of potassium carbonate gave undesired **VI**. The latter compound was also obtained quantitatively by heating **15** at reflux in tetrahydrofuran.

It would appear that the bulky *ortho* pyrimidine ring of **15** tends to enhance undesirable cyclization to give **VI**.

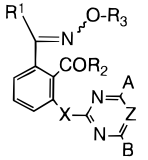
We then performed a similar reaction on the analogous compound lacking the bulky pyrimidine moiety. Thus, a mixture of **IV** and ethylmercaptan or ketone oximes was reacted under reflux in the presence of potassium carbonate to give the desired intermediates (**V**), which were subsequently transformed into **10**, **12** and **13**.

Figure 4 shows the preparation of the amide (**16**) derivative. In the first step, we performed an *ortho*-lithiation reaction in toluene with the addition of *N*,*N*-dimethylcarbamoyl chloride. Reaction occurred only above 60°C, and when the mixture was maintained at this temperature for 2 h, **VIII** was obtained in 43% yield. Subsequent treatment of **VIII**,[8] afforded **X** and **16** without problem.

The intermediate lithium salt of **VII** was sufficiently stable to require carbamoylation at the unusually high temperature of 60°C.[14]

TABLE 1

Effects of Substituents on the Herbicidal Activity against *Echinochloa oryzicola* (Ec) and *Oryza sativa* (Or)



II

Compd. No.	R^1	R^2	R^3	*A*	*B*	*X*	*Z*	*Pre-emergence* $Ec[ED_{90}]^a$ ($g\ ha^{-1}$)	*Pre-emergence* $Or[ED_{10}]^b$ ($g\ ha^{-1}$)	*Selectivity* ($Ec: ED_{90}/Or:ED_{10}$)	*3-leaf growth stage* $Ec[ED_{90}]^a$ ($g\ ha^{-1}$)
2	H	OMe	Me	OMe	OMe	O	CH	16	63	4	NT[c]
1	Me	OMe	Me	OMe	OMe	O	CH	16	250	16	32
3	Et	OMe	Me	OMe	OMe	O	CH	63	63	1	NT
4	Pr	OMe	Me	OMe	OMe	O	CH	>1000	63	<1/16	NT
5	Me	OH	Me	OMe	OMe	O	CH	16	<4	<1/4	NT
6	Me	OEt	Me	OMe	OMe	O	CH	63	63	1	NT
7	Me	OPr	Me	OMe	OMe	O	CH	250	63	1/4	NT
8	Me	*i*-OPr	Me	OMe	OMe	O	CH	250	63	1/4	NT
9	Me	OCH_2Ph	Me	OMe	OMe	O	CH	250	63	1/4	NT
10	Me	SEt	Me	OMe	OMe	O	CH	250	250	1	NT
11	Me	OCH_2SPh	Me	OMe	OMe	O	CH	250	250	1	NT
12	Me	$ON{=}C(Me)_2$	Me	OMe	OMe	O	CH	16	<4	<1/4	NT
13	Me	$ON{=}C(Et)_2$	Me	OMe	OMe	O	CH	63	<4	<1/16	NT
14	Me	O-Propargyl	Me	OMe	OMe	O	CH	63	<4	<1/16	NT
15	Me	1-Imidazoyl	Me	OMe	OMe	O	CH	1000	63	1/16	NT
16	Me	$N(Me)_2$	Me	OMe	OMe	O	CH	1000	>1000	>1	NT
17	Me	OMe	Me	OMe	$OCHF_2$	O	CH	63	1000	16	NT
18	Me	OMe	Me	Me	Cl	O	CH	1000	>1000	>1	NT
19	Me	OMe	Me	OMe	Me	O	CH	250	>1000	>4	NT

TABLE 1 *Continued*

Compd. No.	R^1	R^2	R^3	*A*	*B*	*X*	*Z*	*Pre-emergence* $Ec[ED_{90}]^a$ ($g\ ha^{-1}$)	*Pre-emergence* $Or[ED_{10}]^b$ ($g\ ha^{-1}$)	*Selectivity* ($Ec: ED_{90}/Or:ED_{10}$)	*3-leaf growth stage* $Ec[ED_{90}]^a$ ($g\ ha^{-1}$)
20	Me	OMe	Me	OEt	OEt	O	CH	>1000	>1000	>1	NT
21	Me	OMe	Me	Me	Me	O	CH	>1000	>1000	>1	NT
22	Me	OMe	Me	OMe	Cl	O	CH	250	1000	4	NT
23	Me	OMe	Me	OMe	$N(Me)_2$	O	N	250	250	1	NT
24	Me	OMe	Me	OMe	OMe	O	N	250	>1000	>4	NT
25	Me	OMe	Me	OMe	OMe	S	CH	63	250	4	NT
26	Me	OMe	Me	OMe	OMe	NCHO	CH	1000	250	1/4	NT
27	Me	OMe	Me	OMe	OMe	NH	CH	>1000	>1000	1	NT
28	Me	OMe	H	OMe	OMe	O	CH	16	4	1/4	125
29	Me	OMe	Et	OMe	OMe	O	CH	16	250	16	63
30	Me	OMe	Pr	OMe	OMe	O	CH	16	250	16	63
31	Me	OMe	*i*-Pr	OMe	OMe	O	CH	16	63	4	125
32	Me	OMe	Bu	OMe	OMe	O	CH	16	63	4	>250
33	Me	OMe	CH_2Ph	OMe	OMe	O	CH	63	>1000	>16	>250
34	Me	OMe	Allyl	OMe	OMe	O	CH	16	250	16	63
35	Me	OMe	Proparyl	OMe	OMe	O	CH	63	250	4	63
36	Me	OMe	$CH_2CH{=}CHCl$	OMe	OMe	O	CH	63	63	1	NT
37	Me	OMe	CH_2CH_2Cl	OMe	OMe	O	CH	16	1000	62	63
38	Me	OMe	$CH_2CH_2CH_2Cl$	OMe	OMe	O	CH	63	63	1	63
39	Me	OMe	COMe	OMe	OMe	O	CH	16	16	1	NT
40	Me	OMe	COPh	OMe	OMe	O	CH	16	16	1	NT
41	Me	OMe	$COCF_3$	OMe	OMe	O	CH	63	63	1	NT

[a] Rate (g ha^{-1}) required for 90% control of *Echinochloa oryzicola* (Ec).
[b] Rate (g ha^{-1}) required for 10% injury of *Oryza sativa* (Or).
[c] NT: not tested.

TABLE 2
Physical Properties of Test Compounds and Synthetic Procedure Employed

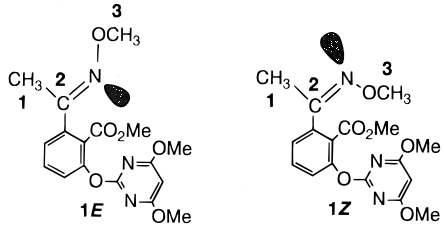
Compound number	*m.p.* [°C] n_D^{20}	*Method*[a]	*Compound number*	*m.p.* [°C] n_D^{20}	*Method*[a]
1	105–106	B	**22**	110–113	A
2	78–79	A	**23**	1·5378	A
3	75–77	A	**24**	131–135	B
4	1·5343	A	**25**	1·5709	A
5	125–127	C	**26**	147–149	B
6	65–68	C	**27**	82–84	B
7	1·5449	C	**28**	131–132	A
8	1·5301	C	**29**	93–95	A
9	1·5545	A	**30**	73–76	A
10	73–88	E	**31**	74–75	A
11	1·5687	C	**32**	1·5374	A
12	1·5355	E	**33**	1·5681	A
13	103–105	E	**34**	76–78	A
14	95–98	C	**35**	77–80·5	A
15	194–199	E	**36**	1·5588	A
16	1·5491	F	**37**	1·5540	A
17	1·5221	A	**38**	1·5539	A
18	1·5587	A	**39**	1·5510	D
19	126–129	A	**40**	121–125	D
20	1·5342	A	**41**	110–111	D
21	79·80	A			

[a] See Section 2 and Figs 2, 3, 4.

3.3 Structure–activity of test compounds

Comparing the effects of acyl moieties (R^1) (Table 1), these compounds exhibited herbicidal activity in the order: CH_3 (**1**), H (**2**) > C_2H_5(**3**) ⩾ C_3H_7(**4**). The hydrogen derivative (**2**) showed poor selectivity in rice. Clearly, increasing chain length in R^1 led to a reduction in herbicidal activity.

TABLE 3
[^{1}H] and [^{13}C]NMR Chemical Shifts of 1*E* & 1*Z* KIH-6127



	Chemical shifts[a]				
	[^1H]*NMR*		[^{13}C]*NMR*		
Compound	*1*	*3*	*1*	*2*	*3*
1*E*	2·185	3·929	14·80	154·27	62·00
1*Z*	2·252	3·724	21·84	154·33	61·45

[a] δ [ppm] from trimethylsilane as an internal standard in deuterochloroform.

In the 6-acetyl series, the effects of the ester moiety (R^2) can be observed. Only the methyl ester derivative (**1**) exhibited both potent barnyard grass control activity and selectivity. The carboxylic acid (**5**) and oxime ester (**12**) also showed potent activity against barnyard grass but were less selective.

The esters **10**–**13** had been prepared with the objective of improving selectivity by reducing metabolic activation *in vivo*.

In contrast to the esters, the amides (**15**) and (**16**) were very weakly active. It seems probable that the ester linkage of this series is converted to an activated substance by an esterase in the metabolic pathway to the target site (ALS)[15] in barnyard grass.

The introduction of other pyrimidine substitution patterns (**17**–**22**), or triazine analogues (**23**, **24**) and thio (**25**) or nitrogen bridged compound (**26**, **27**) led to less herbicidally active compounds than **1**.

Table 1 also shows the effects of changing the imino (R^3) moiety. The pre-emergence activity of the test compounds (**1**, **28**–**41**) was not very sensitive to changing R^3 and all of compounds retained activity.

The introduction of bulky substituents (**31**–**33**) decreased the three-leaf growth-stage activity. The hydroxy (**28**) and acyloxy (**39**–**41**) derivatives were much less selective than the alkoxyimino esters.

In conclusion, the structure–activity study has shown that the methyl ester group was critical for selective pre-emergence control of barnyard grass in rice. The novel

herbicide KIH-6127[6,16] (**1**) was found to be the most effective compound.

The herbicidal activity of KIH-6127* has also been evaluated in paddy fields in Japan since 1990 and shown a remarkable herbicidal activity at low dose (30 g AI ha^{-1}) applications.[16]

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* The name pyriminobac-methyl for this compound, has been approved by ISO.