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Synthesis of 4*H*,6*H*-Furo[3,4-c]isoxazole Derivatives as New Potent Fungicides and Their Structure Activity Relationship

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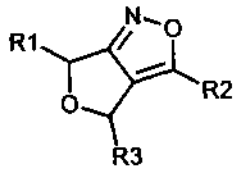
Received March 5, 1997

4*H*,6*H*-Furo[3,4-*c*]isoxazoles (**I-IV**), potential fungicides, have been designed and synthesized *via* intramolecular [2+3] cycloaddition of nitroalkyne **3** as a key step. The broad spectrum of fungicidal activities of furoisoxazoles (**I-IV**) were observed on plant pathogens at 250 ppm. Furoisoxazoles **II**, **III** with chlorophenyl at 6-position and methyl or alkylated oxime group at 3-position gave effective control of plant diseases. The furoisoxazole **IV** with a chlorophenyl group at 4-position also resulted in high fungicidal activities.

Introduction

In an effort to find a new lead compound as a plant fungicide, we were interested in the isoxazole derivatives. Many isoxazole derivatives show diverse medicinal and agricultural activities such as herbicidal, fungicidal, analgesic, anti-inflammatory, anti-microbial and CNS depression effect.[1-8] After consideration of synthetic aspect, we have designed furo[3,4-*c*]isoxazoles (**I-IV**), in which the fused isoxazole nucleus might provide potential fungicidal activity. Our preliminary research showed that furoisoxazoles **I** with *o*- or *p*-chlorophenyl substituent on 6-position and methyl on 3-position have a broad spectrum of fungicidal activities against representative six plant fungi.[9,10] Based on these results, we have continued further structural derivatization of furoisoxazole **I** to study structure activity relationship and eventually to enhance its fungicidal activity. Here, we report an efficient preparation of novel bicyclic isoxazole derivatives

I-IV with various substitutents on the 3-, 4- and 6-positions, and the substituent effect on their fungicidal activities.



I R^2=CH_3, R^3=H
II R^1=*o*-ClC_6H_4, R^3=H
III R^1=*p*-ClC_6H_4, R^3=H
IV R^2=CH_3, R^3=*o*-ClC_6H_4

Results and Discussion

Synthesis. Previously developed synthetic methodology was applied to the preparation of 6-aryl substituted 4*H*,6*H*-furo[3,4-*c*]isoxazole **I**: the intramolecular nitrile oxide-alkyne cycloaddition following the Michael addition of alkoxide to nitroolefin (Scheme 1).[10] Thus, various furoisoxazoles **Ia-l** were prepared from the corresponding aryl substituted nitroalkene **2** in good yields. Initially, 2-butyn-1-ol **1** was treated with *n*-BuLi in THF at low temperature, and then nitroalkene **2** was added. A subsequent acidic workup afforded nitro ether **3** in overall 95% yield. The ether **3** was readily cyclized into furoisoxazole **I** *via* a nitrile oxide intermediate **4** in the presence of phenyl isocyanate and a catalytic amount of Et_3N.[11] The nitroalkene **2** was easily formed by a condensation of the corresponding aldehyde (R^1-CHO) with nitromethane.[12]

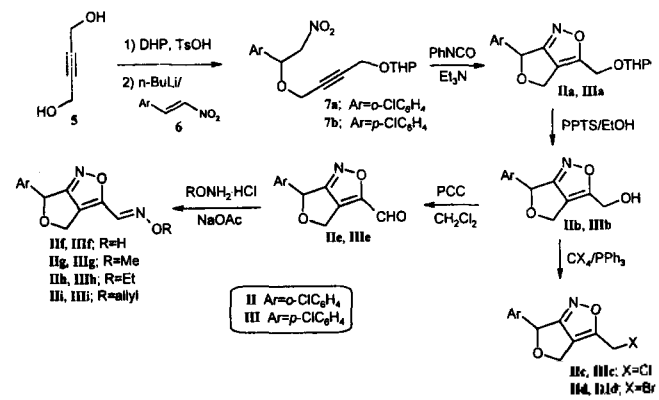
In order to introduce a variety of R^2 substitutents on the 3-position of furoisoxazole, 3-hydroxymethylfuroisoxazoles **IIb** and **IIIb** were prepared. After monoprotection of 2-butyn-1,4-diol **5** by reaction with dihydropyran under a usual reaction condition,[13] the Michael addition of its lithium alkoxide to the nitrostyrene **6** (Ar=*o*-ClC_6H_4 or *p*-ClC_6H_4) afforded the nitro ether **7** in good yield. Under the phenyl isocyanate mediated dehydration condition,[11] the nitro ether **7** was cyclized spontaneously to the furo[3,4-*c*]isoxazoles **IIa** and **IIIa** in high yields (see Scheme 2). Starting from furoisoxazoles **IIa** and **IIIa**, further functionalization of R^2 substituent on 3-position was proceeded smoothly to give furoisoxazoles **IIb-i** and **IIIb-i** as described in Scheme 2.

Tetrahydropyranyl ether of furoisoxazoles **IIa** and **IIIa** were deprotected by the reaction with pyridinium *p*-toluenesulfonate in ethanol[14] to afford the corresponding alcohols **IIb** and **IIIb** quantitatively. Subsequent oxidation of the alcoholes **IIb** and **IIIb** by using pyridinium chlorochromate in CH_2Cl_2 readily afforded the aldehydes (**IIe** and **IIIe**). The oximes (**IIf** and **IIIf**) or oxime ethers (**IIg-i** and **IIIg-i**) were prepared from the aldehydes (**IIe** and **IIIe**) by the reaction with the corresponding hydroxyl amine or various alkoxyamine hydrochlorides in the presence of an equimolar sodium acetate. The geometric isomers (*trans* and *cis*) of oximes **IIf-i** and **IIIf-i** were inseparable by silica gel column chromatography. Treatment of the alcohols (**IIb** and **IIIb**) with carbon tetrahalide in the presence of triphenyl phosphine readily gave halogen-substituted isoxazoles **II** and **III** (**c**, X=Cl; **d**, X=Br).

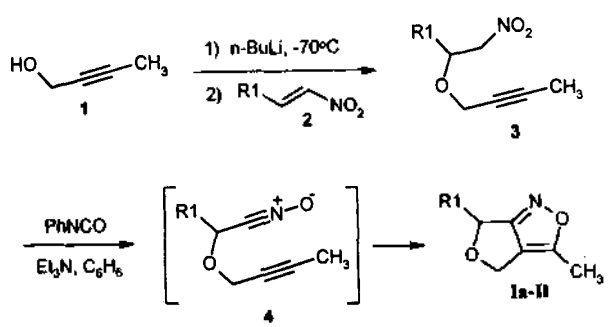
To prepare furoisoxazole **IV** with *o*-chlorophenyl on C-4 and methyl on C-3, we initially prepared the alkynol **8** from the reaction of 2-chlorobenzaldehyde with lithium acetylide followed by the methylation (*n*-BuLi/MeI). Treatment of the alkynol **8** with *n*-BuLi followed by the addition to nitrostyrene **6** gave the nitroalkyne **9**. The intramolecular cycloaddition of **9** using PhNCO/Et_3N readily furnished a bicyclic isoxazole **IV** (see Scheme 3).

Fungicidal activity. More than 60 furoisoxazoles **I-IV** were prepared and their antifungal activity was tested against the six plant fungal diseases such as rice blast (RCB; *Pyricularia oryzae*), rice sheath blight (RSB; *Rhizoctonia solani*), cucumber gray mold (CGM; *Botrytis cineria*), tomato late blight (TLB; *Phytophthora infestants*), wheat leaf rust (WLR; *Puccinia recondita*) and barley powdery mildew (BPM; *Erysiphe graminis*).[15] The selected examples and their results are summarized in the Table 1. The control values were calculated by the equation [1-(% of diseased area with treatment)/% of untreated diseased area)]×100. The structure activity relationship (SAR) of furoisoxazoles **I-IV** was studied on the level of fungicidal activity and disease selectivity.

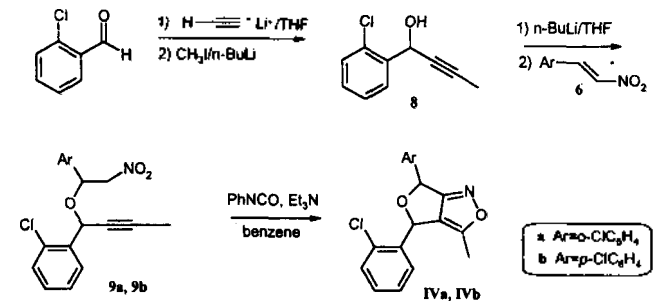
R^1 substituent effect. For the systematic examination of SAR of furoisoxazoles, the R^1 substituent was



Scheme 2.



Scheme 1.



Scheme 3.

Table 1. Substituent Effect on the Fungicidal Activities of Furoisoxazole Derivatives **I-IV**[a,b]

Compound[c]	R^1	R^2	R^3	RCB	RSB	CGM	TLB	WLR	BPM
Ia	isopropyl	CH_3	H	15	10	0	27	0	7
Ib	*o*-ClC_6H_4	CH_3	H	99	31	81	55	0	20
Ic	*m*-ClC_6H_4	CH_3	H	0	11	29	57	0	31
Id	*p*-ClC_6H_4	CH_3	H	0	20	90	0	0	0
Ie	*o,p*-$Cl_2C_6H_3$	CH_3	H	91	0	4	7	0	0
If	*m,p*-$Cl_2C_6H_3$	CH_3	H	0	5	57	27	0	0
Ig	*o*-FC_6H_4	CH_3	H	0	12	8	0	0	27
Ih	*p*-FC_6H_4	CH_3	H	0	15	23	24	0	0
Ii	*o*-$CF_3C_6H_4$	CH_3	H	0	32	89	81	0	0
Ij	*p*-$CF_3C_6H_4$	CH_3	H	0	25	10	15	0	0
Ik	*o*-$CH_3C_6H_4$	CH_3	H	7	24	38	0	0	16
Il	*p*-$CH_3C_6H_4$	CH_3	H	0	6	46	0	0	23
IIa	*o*-ClC_6H_4	CH_2OTHP	H	94	89	19	86	0	0
IIb	*o*-ClC_6H_4	CH_2OH	H	0	10	44	3	53	30
IIc	*o*-ClC_6H_4	CH_2Cl	H	0	45	11	10	0	63
IId	*o*-ClC_6H_4	CH_2Br	H	99	90	41	28	53	13
IIe	*o*-ClC_6H_4	CHO	H	50	0	8	27	73	6
IIf	*o*-ClC_6H_4	CH=NOH	H	91	65	80	43	0	96
IIg	*o*-ClC_6H_4	$CH=NOCH_3$	H	0	80	10	0	27	30
IIh	*o*-ClC_6H_4	CH=NOEt	H	0	15	14	0	27	98
IIi	*o*-ClC_6H_4	CH=NO-allyl	H	43	50	15	0	0	79
IIIa	*p*-ClC_6H_4	CH_2OTHP	H	0	25	0	73	68	35
IIIb	*p*-ClC_6H_4	CH_2OH	H	0	5	0	31	60	0
IIIc	*p*-ClC_6H_4	CH_2Cl	H	0	20	0	10	27	11
IIId	*p*-ClC_6H_4	CH_2Br	H	7	45	90	38	53	36
IIIe	*p*-ClC_6H_4	CHO	H	43	5	14	59	0	11
IIIf	*p*-ClC_6H_4	CH=NOH	H	75	50	15	48	53	34
IIIg	*p*-ClC_6H_4	$CH=NOCH_3$	H	0	55	20	38	0	96
IIIh	*p*-ClC_6H_4	CH=NOEt	H	0	40	12	0	0	49
IIIi	*p*-ClC_6H_4	CH=NO-allyl	H	7	50	4	0	0	61
Ib	*o*-ClC_6H_4	CH_3	H	99	31	81	55	0	27
IVa	*o*-ClC_6H_4	CH_3	*o*-ClC_6H_4	99	0	71	45	0	40
Id	*p*-ClC_6H_4	CH_3	H	0	20	90	0	0	0
IVb	*p*-ClC_6H_4	CH_3	*o*-ClC_6H_4	90	0	35	32	0	40

[a]All activities were measured at 250 ppm against RCB (Rice Blast, *Pyricularia oryzae*), RSB (Rice Sheath Blight, *Rhizoctonia solani*), CGM (Cucumber Gray Mold, *Botrytis cinerea*), TLB (Tomato Late Blight, *Phytophthora infestants*), WLR (Wheat Leaf Rust, *Puccinia recondita*) and BPM (Barley Powdery Mildew, *Erysiphe graminis*). [b]Control values are calculated by the equation: [1-(percent of disease area in treatment)/(percent of disease area in untreated area)] × 100; 0 represents no activity and 100 means complete control of a disease. [c]The data for furoisoxazoles **Ia-l** are from the reference 9; for **IVa, b** from the reference 16.

varied after substituent R^2 was fixed with CH_3 group (**Ia-l**). As shown in the Table 1, relatively high fungicidal activity on RCB (>90% control) was observed by the substitution of chlorophenyl group for R^1 (**Ib**, **Ie**). Chlorine atom at *ortho* position of the phenyl ring at C-6 of a furoisoxazole was essential for high fungicidal activity. With *m*-ClPh group, the activity was decreased, especially against RCB as in case of isoxazole **Ic**. Other *ortho*-substituents on the phenyl ring at R^1 such as F (**Ig**), CF_3 (**Ii**) and CH_3 (**Ik**) were not effective at all against RCB. However, *o*-CF_3 group showed the high activity on CGM with ~90% control as in case of furoisoxazole (**Ii**). Substitution of alkyl group, instead of phenyl group, for R^1 in a furoisoxazole decreased the activity (**Ia**).

R^2 substituent effect. Because a chlorophenyl group at 6-position of furoisoxazole showed the best fungicidal activity, the R^1 substituent was fixed with *o*-ClPh or *p*-ClPh group as in isoxazoles **II** and **III**, respectively. Then, substituent R^2 was modified for SAR analysis as shown in the cases of **IIa-i** and **IIIa-i**. With *o*-ClPh as R^1 substituent, the R^2 substituents such as CH_3 (**Ib**), CH_2OTHP (**IIa**), CH_2Br (**IId**) and CH=NOH (**IIf**) showed more than 90% control against RCB. Considering the similar physicochemical properties of CH_2Br and CH_2Cl, different activities of isoxazoles **IIc** and **IId** were quite interesting. In contrast to the CH_2Br group (**IId**), the CH_2Cl substituent (**IIc**) gave lower activity than that of former isoxazole. It was initially assumed that this discrepancy was originated from the extent of proton-halogen exchange of allyl halide during the bioassay. Because the allyl bromide is chemically more reactive than allyl chloride, the isoxazole **IId** might be easily converted to the isoxazole **Ib**: thereby resulting in relatively high activity. However, it was not sufficient to explain different disease selectivity of isoxazoles **Ib** and **IId**: **Ib** was effective on RCB and CGM whereas **IId** was on RCB and RSB. The high activity by CH=NOH substituent (**IIf**) could

not be satisfactorily explained by hydrogen bonding. Because the CH_2OH group (**IIb**), being capable of acting as hydrogen bonding donor or acceptor like CH=NOH group, did not give high activity. The high fungicidal activity of isoxazole **IIa** was considered to be drived from the certain size of bulk of CH_2OTHP group. The size effect could explain well the high activities of isoxazoles **IIg-i** containing the substituent CH=N-OR. With CH=N-OEt group (**IIh**), the BPM was perfectly controlled at 250 ppm.

The similar R^2 substituent effect on the fungicidal activity was observed in cases of isoxazoles **IIIa-i** containing *p*-ClPh group as R^1 substituent. When R^2 was CH_2OTHP (**IIIa**), CH_2Br (**IIId**), CH=NOH (**IIIf**), and CH=NOMe (**IIIg**), the fungicidal activities of these isoxazoles were quite high. However, the disease selectivity of isoxazoles **IIIa-i** were different from that of isoxazoles **IIa-i** containing *o*-ClPh group as R^1 substituent. For instance, isoxazoles **IId** and **IIId** (both R^2=CH_2Br) were effective on TLB and RCB, respectively. Furoisoxazoles **IIg** and **IIIg** (both R^3=CH=$NOCH_3$) effectively controlled RSB and BPM, respectively depending on the R^1 substituent.

R^3 substituent effect. The R^3 substituent effect on the fungicidal activities of furoisoxazole derivatives was studied using the furoisoxazoles containing the ClPh and CH_3 groups as R^1 and R^2 substituents, respectively. Introduction of *o*-ClPh as R^3 substituent to the isoxazole **Ib** resulted in the similar fungicidal activity as shown in the case **IVa**. As shown in cases of isoxazoles **IVb** and **Id**, the substitution of *o*-ClPh for R^3 group shifted the high activity from CGM to RCB. In general, the *o*-ClPh group as R^3 substituent at 4-position of furoisoxazole gave high fungicidal activity on RCB.

In conclusion, we designed 4*H*,6*H*-furo[3,4-*c*]isoxazole, a novel fused heterocycle, as potent fungicide and developed efficient synthetic route for the diverse furoisoxazoles **I-IV** containing various substituents on the 3-, 4- and 6-positions. They exhibited *in vivo* fungicidal activity against six representative plant pathogens. The highest activity was observed with isoxazoles **Ib** and **Id** which controlled 50% of RCB and CGM even at 10 ppm, respectively.[9] The structure activity relationship of furoisoxazoles was also systematically studied. When the R^1 substituents of furoisoxazole were *ortho* or *para* substituted chlorophenyl groups, the high fungicidal activities were observed. The groups CH_3, CH_2Br and CH=N-OR were essential as a R^2 substituent for the high fungicidal activity. The groups *o*-ClPh or H as R^3 substituent, both gave similar fungicidal activities suggesting that the bulky *o*-chlorophenyl group is well accommodated by a biomolecule such as an enzyme or a receptor.[16]

Experimental Section

Chemical synthesis

Melting points are uncorrected. Mass spectra were recorded on a Shimatzu QP-1000 spectrometer using the electron impact mode at 25 eV. Infrared spectra were obtained on a Shimatzu IR-435 spectrophotometer. ^{1}H NMR were recorded in $CDCl_3$ at 60 or 200 MHz. Chemical shifts were reported in ppm (δ) relative to tetramethylsilane. Column chromatography was performed using Merck Kieselgel 60 (230-400 mesh) as the stationary phase.

General procedure for the preparation of nitro ethers 3, 7 and 9. To a stirred solution of alkynol **1** (10 mmol) dissolved in THF (10 mL) was slowly added *n*-BuLi (6.3 mL of 1.6 M *n*-hexane solution, 10 mmol) at −78 °C. The reaction solution was allowed to warm to 0 °C and then treated dropwise with nitroalkene **2** (5 mmol) in THF (1 mL) and stirred for 4 h at rt. Aqueous acetic acid (12 mL of a 1 N solution) was added to the reaction mixture with stirring, and the resulting two layers were separated. The aqueous layer was extracted with Et_2O (2×10 mL), and the combined organic solution was washed with saturated NaCl solution (10 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel.

1-(2-Butynyloxy)-1-isopropyl-2-nitroethane (3a). Yield 96%: IR (neat) 1555, 1375 (NO_2) cm^{-1}; ^{1}H NMR 1.0 (d, 6H, $CH(CH_3)_2$), 1.8 (t, 3H, CC-CH_3), 1.9 (m, 1H, $CH(CH_3)_2$), 4.2 (m, 3H, $CHOCH_2$), 4.5 (m, 2H, CH_2NO_2).

1-(2-Butynyloxy)-1-(2-chlorophenyl)-2-nitroethane (3b). Yield 68%: IR (neat) 1555, 1370 (NO_2) cm^{-1}; ^{1}H NMR 1.8 (t, 3H, CH_3), 4.1 (m, 2H, OCH_2), 4.6 (m, 2H, CH_2NO_2), 5.8 (dd, 1H, OC*H*Ar), 7.4 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(3-chlorophenyl)-2-nitroethane (3c). Yield 25%: IR (neat) 1545, 1370 (NO_2) cm^{-1}; ^{1}H NMR 1.9 (t, 3H, CH_3), 4.0 (m, 2H, OCH_2), 4.6 (m, 2H, CH_2NO_2), 5.3 (dd, 1H, OCH), 7.3 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(4-chlorophenyl)-2-nitroethane (3d). Yield 60%: mp 72-74 °C; IR (CCl_4) 1540, 1370 (NO_2) cm^{-1}; ^{1}H NMR 1.8 (t, 3H, CH_3), 4.0 (m, 2H, OCH_2), 4.5 (m, 2H, CH_2NO_2), 5.2 (dd, 1H, OCH), 7.3 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(2,4-dichlorophenyl)-2-nitroethane (3e). Yield 87%: IR (neat) 1555, 1370 (NO_2) cm^{-1}; ^{1}H NMR 1.8 (t, 3H, CH_3), 4.1 (m, 2H, OCH_2), 4.5 (m, 2H, CH_2NO_2), 5.7 (dd, 1H, OC*H*Ar), 7.4 (m, 3H, Ar).

1-(2-Butynyloxy)-1-(3,4-dichlorophenyl)-2-nitroethane (3f). Yield 38%: IR (neat) 1545, 1370 (NO_2) cm^{-1}; ^{1}H NMR 1.9 (t, 3H, CH_3), 4.1 (m, 2H, OCH_2), 4.7 (m, 2H, CH_2NO_2), 5.5 (dd, 1H, OCH), 7.7 (m, 3H, Ar).

1-(2-Butynyloxy)-1-(2-fluorophenyl)-2-nitroethane (3g). Yield 67%: IR (neat) 1545, 1370 (NO_2) cm^{-1}; ^{1}H NMR 1.8 (t, 3H, CH_3), 4.1 (m, 2H, OCH_2), 4.6 (m, 2H, CH_2NO_2), 5.7 (dd, 1H, OCH), 7.3 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(4-fluorophenyl)-2-nitroethane (3h). Yield 55%: IR (neat) 1555, 1370 (NO_2) cm^{-1}; ^{1}H NMR 1.9 (t, 3H, CH_3), 4.1 (m, 2H, OCH_2), 4.6 (m, 2H, CH_2NO_2), 5.3 (dd, 1H, OCH), 7.3 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(2-trifluoromethylphenyl)-2-nitroethane (3i). Yield 54%: IR (neat) 1550, 1370 (NO_2) cm^{-1}; ^{1}H NMR 1.8 (t, 3H, CH_3), 3.0 (m, 2H, OCH_2), 4.4 (s, 1H, $CHHNO_2$), 4.5 (d, 1H, $CHHNO_2$), 5.8 (dd, 1H, OCH), 7.8 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(4-trifluoromethylphenyl)-2-nitroethane (3j). Yield 46%: IR (neat) 1540, 1370 (NO_2) cm^{-1}; ^{1}H NMR 1.8 (t, 3H, CH_3), 4.1 (m, 2H, OCH_2), 4.7 (m, 2H, CH_2NO_2), 5.5 (dd, 1H, OCH), 7.8 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(2-methylphenyl)-2-nitroethane (3k). Yield 70%: IR (neat) 1540, 1370 (NO_2) cm^{-1}; ^{1}H NMR 1.9 (t, 3H, CH_3), 2.5 (s, 3H, CH_3), 4.1 (m, 2H, OCH_2), 4.6 (m, 2H, CH_2NO_2), 5.7 (dd, 1H, OCH), 7.4 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(4-methylphenyl)-2-nitroethane (3l). Yield 83%: IR (neat) 1555, 1370 (NO_2) cm^{-1}; ^1H NMR 1.8 (t, 3H, CH_3), 2.4 (s, 3H, CH_3), 4.0 (m, 2H, OCH_2), 4.6 (m, 2H, CH_2NO_2), 5.3 (dd, 1H, OCH), 7.2 (m, 4H, Ar).

2-{4-[1-(2-Chlorophenyl)-2-nitroethoxy]-but-2-ynyl-oxy}-tetrahydrofuran (7a). Yield 63%: IR (neat) 1550, 1370 (NO_2) cm^{-1}; ^1H NMR 1.7 (m, 6H, $CH_2CH_2CH_2$), 3.7 (m, 2H, OCH_2CH_2), 4.2 (m, 4H, OCH_2CC and CH_2OTHP), 4.5 (d, 1H, OCHO), 4.6 (s, 1H, $CHHNO_2$), 4.8 (br s, 1H, $CHHNO_2$), 5.8 (dd, 1H, $OCHAr$), 7.3 (m, 4H, Ar).

2-{4-[1-(4-Chlorophenyl)-2-nitroethoxy]-but-2-ynyl-oxy}-tetrahydrofuran (7b). Yield 60%: IR (neat) 1555, 1370 (NO_2) cm^{-1}; ^1H NMR 1.7 (m, 6H, $CH_2CH_2CH_2$), 3.7 (m, 2H, OCH_2CH_2), 4.1 (m, 4H, OCH_2CC and CH_2OTHP), 4.4 (m, 1H, OCHO), 4.6 (m, 1H, $CHHNO_2$), 4.8 (br s, 1H, $CHHNO_2$), 5.4 (dd, 1H, $OCHAr$), 7.4 (m, 4H, Ar).

1-(2-Chlorophenyl)-1-[1-(2-chlorophenyl)-2-nitro] ethoxy-but-2-yne (9a). Yield 65%: IR (neat) 1555, 1370 (NO_2) cm^{-1}; ^1H NMR 1.72 (d, 3H, CH_3), 4.44-4.57 (m, 2H, CH_2NO_2), 5.59 (q, 1H, OCHCC), 5.67 (dd, 1H, $OCHCH_2$), 7.23-7.38 (m, 6H, Ar), 7.60-7.68 (m, 2H, Ar).

1-(4-Chlorophenyl)-1-[1-(2-chlorophenyl)-2-nitro] ethoxy-but-2-yne (9b). Yield 57%: IR (neat) 1540, 1370 (NO_2) cm^{-1}; ^1H NMR 1.77 (d, 3H, CH_3), 1.90 (d, 3H, CH_3), 4.35-4.78 (m, 2H, CH_2NO_2), 5.15-5.77 (m, 2H, CHAr), 7.35-7.57 (m, 8H, ArH).

General procedure for the preparation of furoisoxazoles I, IIa, IIIa and IV. To a mixture of nitro ether **3** (5 mmol) and phenyl isocyanate (12.5 mmol) dissolved in dry benzene (30 mL) was added Et_3N (0.5 mmol), and the resulting mixture was stirred overnight at rt. Water (1 mL) was added, and the mixture was stirred for 2 h at which time the solids were removed by vacuum filtration. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using an *n*-hexane/EtOAc eluent.

6-Isopropyl-3-methyl-4*H*,6*H*-furo[3,4-c]isoxazole (Ia). Yield 70%: MS M^+ m/z 167; IR (neat) 1665, 1460, 1380 (isoxazole) cm^{-1}; ^1H NMR 1.0 (dd, 6H, $CH(CH_3)_2$), 2.0 (m, 1H, $CH(CH_3)_2$), 2.4 (s, 3H, CH_3), 4.8 (m, 3H, $CHOCH_2$).

6-(2-Chlorophenyl)-3-methyl-4*H*,6*H*-furo[3,4-c] isoxazole (Ib). Yield 86%: mp 88-89 °C; MS M^+ m/z 235, 237; IR (CCl_4) 1660, 1435, 1410 (isoxazole) cm^{-1}; ^1H NMR 2.4 (br s, 3H, CH_3), 4.9 (m, 2H, CH_2O), 6.4 (s, 1H, OCH), 7.3 (m, 4H, Ar).

6-(3-Chlorophenyl)-3-methyl-4*H*,6*H*-furo[3,4-c] isoxazole (Ic). Yield 64%: MS M^+ m/z 235, 237; IR (neat) 1660, 1465, 1410 (isoxazole) cm^{-1}; ^1H NMR 2.4 (s, 3H, CH_3), 4.9 (s, 2H, CH_2O), 6.0 (s, 1H, OCH), 7.3 (m, 3H, Ar), 7.5 (m, 1H, Ar).

6-(4-Chlorophenyl)-3-methyl-4*H*,6*H*-furo[3,4-c] isoxazole (Id). Yield 75%: mp 62-63 °C; MS M^+ m/z 235, 237; IR (CCl_4) 1660, 1485, 1400 (isoxazole) cm^{-1}; ^1H NMR 2.4 (s, 3H, CH_3), 4.9 (s, 2H, CH_2O), 6.0 (s, 1H, OCH), 7.3 (m, 4H, Ar).

6-(2,4-Dichlorophenyl)-3-methyl-4*H*,6*H*-furo[3, 4-c]isoxazole (Ie). Yield 55%: mp 106.5-107 °C; MS M^+ m/z 269, 271, 273; IR (CCl_4) 1660, 1460, 1430 (isoxazole) cm^{-1}; ^1H NMR 2.4 (s, 3H, CH_3), 4.9 (s, 2H, CH_2O), 6.2 (s, 1H,), 7.3 (m, 3H, Ar).

6-(3,4-Dichlorophenyl)-3-methyl-4*H*,6*H*-furo[3, 4-c]isoxazole (If). Yield 86%: MS M^+ m/z 269, 271, 273; IR (neat) 1660, 1465, 1415 (isoxazole) cm^{-1}; ^1H NMR 2.5 (s, 3H, CH_3), 4.9 (m, 2H, CH_2O), 6.0 (s, 1H, OCH), 7.5 (m, 2H,), 7.6 (m, 1H, Ar).

6-(2-Fluorophenyl)-3-methyl-4*H*,6*H*-furo[3,4-c] isoxazole (Ig). Yield 66%: MS M^+ m/z 219; IR (neat) 1660, 1480, 1415 (isoxazole) cm^{-1}; ^1H NMR 2.5 (m, 3H, CH_3), 5.0 (m, 2H, CH_2O), 6.3 (s, 1H, OCH), 7.3 (m, 4H, Ar).

6-(4-Fluorophenyl)-3-methyl-4*H*,6*H*-furo[3,4-c] isoxazole (Ih). Yield 87%: MS M^+ m/z 219; IR (neat) 1660, 1500, 1405 (isoxazole) cm^{-1}; ^1H NMR 2.4 (s, 3H, CH_3), 5.9 (s, 2H, CH_2O), 6.0 (s, 1H, OCH), 6.9-7.6 (m, 4H, Ar).

6-(2-Trifluoromethylphenyl)-3-methyl-4*H*,6*H*-furo[3,4-c]isoxazole (Ii). Yield 66%: MS M^+ m/z 269; IR (neat) 1660, 1415 (isoxazole) cm^{-1}; ^1H NMR 2.4 (s, 3H, CH_3), 5.0 (m, 2H, CH_2O), 6.4 (s, 1H, OCH), 7.5 (m, 4H, Ar).

6-(4-Trifluoromethylphenyl)-3-methyl-4*H*,6*H*-furo[3,4-c]isoxazole (Ij). Yield 69%: MS M^+ m/z 269; IR (neat) 1660, 1405 (isoxazole) cm^{-1}; 2.4 (s, 3H, CH_3), 4.9 (s, 2H, CH_2O), 6.1 (s, 1H, OCH), 7.6 (m, 4H, Ar).

6-(2-Methylphenyl)-3-methyl-4*H*,6*H*-furo[3,4-c] isoxazole (Ik). Yield 81%: mp 48-49 °C; MS M^+ m/z 215; IR (neat) 1660, 1455, 1410 (isoxazole) cm^{-1}; ^1H NMR 2.4 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 5.9 (m, 2H, CH_2O), 6.2 (s, 1H, OCH), 7.2 (m, 4H, Ar).

6-(4-Methylphenyl)-3-methyl-4*H*,6*H*-furo[3,4-c] isoxazole (Il). Yield 89%: mp 44-46.5 °C; MS M^+ m/z 215; IR (CCl4) 1660, 1505, 1405 (isoxazole) cm^{-1}; ^1H NMR 2.3 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 4.9 (s, 2H, CH_2O), 6.0 (s, 1H, OCH), 7.2 (m, 4H, Ar).

6-(2-Chlorophenyl)-3-(tetrahydropyran-2-yloxy-methyl)-4*H*,6*H*-furo[3,4-c]isoxazole (IIa). Yield 95%: MS M^+ m/z 335, 337; IR (neat) 1660, 1460, 1435 (isoxazole) cm^{-1}; ^1H NMR 1.6 (m, 6H, $CH_2CH_2CH_2$), 3.6 (m, 2H, OCH_2CH_2), 4.7 (m, 3H, CH_2OTHP and OCHO), 5.0 (s, 2H, OCH_2), 6.4 (s, 1H, $OCHAr$), 7.3 (m, 4H, Ar).

6-(4-Chlorophenyl)-3-(tetrahydropyran-2-yloxy-methyl)-4*H*,6*H*-furo[3,4-c]isoxazole (IIIa). Yield 90%: MS M^+ m/z 335, 337; IR (neat) 1660, 1460, 1435 (isoxazole) cm^{-1}; ^1H NMR 1.6 (m, 6H, $CH_2CH_2CH_2$), 3.7 (m, 2H, OCH_2CH_2), 4.8 (m, 3H, CH_2OTHP and OCHO), 5.0 (s, 2H, OCH_2), 6.0 (s, 1H, $OCHAr$), 7.5 (m, 4H, Ar).

6-(2-Chlorophenyl)-3-hydroxymethyl-4*H*,6*H*-furo [3,4-c]isoxazole (IIb). The mixture of **IIa** (28.70 g, 85.5 mmol) and TsOH hydrate (813 mg, 4.28 mmol) in ethanol (20 mL) was stirred overnight at 50 °C. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (n-hexane/EtOAc, 2:1) to give **IIb** (19.15 g, 89% yield): mp 85-86 °C; MS M^+ m/z 251, 253; IR (CCl_4) 2905 (OH), 1660, 1480, 1415 (isoxazole) cm^{-1}; ^1H NMR 2.6 (s, 1H, OH), 4.8 (m, 2H, CH_2OH), 5.0 (m, 2H, OCH_2), 6.4 (s, 1H, $OCHAr$), 7.3 (m, 4H, Ar).

3-Chloromethyl-6-(2-chlorophenyl)-4*H*,6*H*-furo [3,4-c]isoxazole (IIc). The mixture of **IIb** (605 mg, 2.40 mmol) and Ph_3P (1.89 g, 7.21 mmol) dissolved in dry CCl_4 (10 mL) was refluxed for 30 min. After being cooled, the

reaction mixture was filtered and the filtrated was purified by column chromatography (*n*-hexane/EtOAc, 4 : 1) to give **IIc** as a white solid (421 mg, 65% yield): mp 55-55.5 °C; MS M^+ m/z 269, 271, 273; IR (CCl_4) 1665, 1430 (isoxazole) cm^{-1}; ^1H NMR 4.6 (m, 2H, CH_2Cl), 5.1 (m, 2H, OCH_2), 6.5 (s, 1H, OC*H*Ar), 7.4 (m, 4H, Ar).

3-Bromomethyl-6-(2-chlorophenyl)-4*H*,6*H*-furo[3,4-c]isoxazole (IId). To a stirred mixture of **IIb** (620 mg, 2.46 mmol) and Ph_3P (1.94 g, 7.39 mmol) dissolved in dry CH_2Cl_2 (5 mL) at 0 °C was added portionwise CBr_4 (1.14 g, 7.39 mmol), and the mixture was stirred for 2 h at rt. Et_2O (5 mL) was added and the mixture was filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (*n*-hexane/EtOAc, 4 : 1) to give **IId** as a solid (505 mg, 65% yield): mp 90-91 °C; MS M^+ m/z 313, 315, 317; IR (CCl_4) 1660, 1435 (isoxazole) cm^{-1}; ^1H NMR 4.5 (s, 2H, CH_2Cl), 5.1 (s, 2H, OCH_2), 6.5 (s, 1H, OC*H*Ar), 7.4 (m, 4H, Ar).

6-(2-Chlorophenyl)-4*H*,6*H*-furo[3,4-c]isoxazole-3-carboaldehyde (IIe). To a stirred solution of **IIb** (6.98 g, 27.80 mmol) in CH_2Cl_2 (30 mL) was added portionwise PCC (8.99 g, 41.70 mmol) and the mixture was stirred for 2 h at rt. Et_2O (30 mL) was added, the supernatant liquid was decanted, and the insoluble residue was washed with Et_2O (3×10 mL). The combined organic solution was passed through a short pad of Florisil. The solvent was evaporated and the crude product was purified by column chromatography (*n*-hexane/EtOAc, 4 : 1) to give **IIe** as an oil (3.28 g, 48% yield): MS M^+ m/z 249, 251; IR (neat) 1690 (C=O) cm^{-1}; ^1H NMR 5.2 (m, 2H, OCH_2), 6.5 (s, 1H, OCHAr), 7.5 (m, 4H, Ar), 9.9 (s, 1H, CHO).

6-(2-Chlorophenyl)-3-(hydroxyimino)methyl-4*H*,6*H*-furo[3,4-c]isoxazole (IIf). The mixture of **IIb** (392 mg, 1.57 mmol), $HONH_2$ HCl (164 mg, 2.36 mmol) and NaOAc (193 mg, 2.36 mmol) dissolved in EtOH (10 mL) was stirred for 8 h at rt and then filtered. The filtrate was concentrated and the crude product was purified by column chromatography (*n*-hexane/EtOAc, 4 : 1) to give **IIf** (400 mg, 96% yield) as an isomeric mixture (*trans* : *cis*=7 : 1): MS M^+ m/z 264, 266; IR (CCl_4) 3150 (OH) cm^{-1}; ^1H NMR ($CDCl_3$ +DMSO-d_6) 2.7 (br, 1H, OH), 5.2 and 5.3 (m, 2H, OCH_2), 6.5 (s, 1H, OC*H*Ar), 7.4 (m, 4H, Ar), 7.6 and 8.2 (s, 1H, C*H*=NOH).

6-(2-Chlorophenyl)-3-(methoxyimino)methyl-4*H*,6*H*-furo[3,4-c]isoxazole (IIg) was prepared from **IIb**, $MeONH_2$ HCl and NaOAc in a same manner to that described for **IIf**. Yield 95%: mp 107-115 °C; MS M^+ m/z 278, 280; IR (KBr) 1650, 1435 (isoxazole) cm^{-1}; ^1H NMR 4.1 and 4.2 (s, 3H, OCH_3), 5.1 and 5.2 (s, 2H, OCH_2), 6.6 (s, 1H, OC*H*Ar), 7.4 (m, 4H, Ar), 7.6 and 8.1 (s, 1H, C*H*=NOMe).

6-(2-Chlorophenyl)-3-(ethoxyimino)methyl-4*H*,6*H*-furo[3,4-c]isoxazole (IIh) was prepared from **IIb**, $EtONH_2$ HCl and NaOAc in a same manner to that described for **IIf**. Yield 93%: MS M^+ m/z 292, 294; IR (neat) 1650, 1460, 1435 (isoxazole) cm^{-1}; ^1H NMR 1.4 and 1.45 (t, 3H, CH_2CH_3), 4.4 and 4.5 (q, 2H, OCH_2CH_3), 5.3 and 5.4 (s, 2H, OCH_2), 6.6 (s, 1H, OC*H*Ar), 7.5 (m, 4H, Ar), 7.6 and 8.2 (s, 1H, C*H*=NOEt).

3-(2-Allyloxyimino)methyl-6-(2-chlorophenyl)-4*H*,6*H*-furo[3,4-c]isoxazole (IIi) was prepared from **IIb**, CH_2=$CHCH_2ONH_2$ HCl and NaOAc in a same manner to that described for **IIf**. Yield 95%: MS M^+ m/z 304, 306; IR (neat) 1650, 1450 (isoxazole) cm^{-1}; ^1H NMR 4.8 (m, 2H, OCH_2CH), 5.1 and 5.2 (s, 2H, OCH_2), 5.5 (m, 2H, CH=CH_2), 5.8-6.2 (m, 1H, C*H*=CH_2), 6.5 (s, 1H, OC*H*Ar), 7.4 (m, 4H, Ar), 7.6 and 8.2 (s, 1H, C*H*=$NOCH_2$).

6-(4-Chlorophenyl)-3-hydroxymethyl-4*H*,6*H*-furo[3,4-c]isoxazole (IIIb) was prepared from **IIIa** in a same manner to that described for **IIb**. Yield 91%: MS M^+ m/z 251, 253; IR (neat) 3370 (OH) 1660, 1485, 1400 (isoxazole) cm^{-1}; ^1H NMR 2.7 (s, 1H, OH), 4.8 (m, 2H, CH_2OH), 5.0 (m, 2H, OCH_2), 6.1 (s, 1H, OC*H*Ar), 7.4 (m, 4H, Ar).

3-Chloromethyl-6-(4-chlorophenyl)-4*H*,6*H*-furo[3,4-c]isoxazole (IIIc) was prepared from **IIIb** in a same manner to that described for **IIc**. Yield 61%: MS M^+ m/z 269, 271, 273; IR (neat) 1665, 1430 (isoxazole) cm^{-1}; ^1H NMR 4.6 (m, 2H, CH_2Cl), 5.1 (m, 2H, OCH_2), 6.1 (s, 1H, OC*H*Ar), 7.4 (m, 4H, Ar).

3-Bromomethyl-6-(4-chlorophenyl)-4*H*,6*H*-furo[3,4-c]isoxazole (IIId) was prepared from **IIIb** in a same manner to that described for **IId**. Yield 60%: MS M^+ m/z 313, 315, 317; IR (neat) 1660, 1485 (isoxazole) cm^{-1}; ^1H NMR 4.6 (s, 2H, CH_2Br), 5.0 (s, 2H, OCH_2), 6.0 (s, 1H, OCHAr), 7.4 (m, 4H, Ar).

6-(4-Chlorophenyl)-4*H*,6*H*-furo[3,4-c]isoxazole-3-carboaldehyde (IIIe) was prepared from **IIIb** in a same manner to that described for **IIe**. Yield 48%: MS M^+ m/z 249, 251; IR (neat) 1695 (C=O) cm^{-1}; ^1H NMR 5.2 (m, 2H, OCH_2), 6.1 (s, 1H, OC*H*Ar), 7.5 (m, 4H, Ar), 10.0 (s, 1H, CHO).

6-(4-Chlorophenyl)-3-(hydroxyimino)methyl-4*H*,6*H*-furo[3,4-c]isoxazole (IIIf) was prepared from **IIIe** in a same manner to that described for **IIf**. Yield 85%: MS M^+ m/z 264, 266; mp 134-140 °C; IR (KBr) 3100 (OH) cm^{-1}; ^1H NMR 2.8 (br, 1H, OH), 5.1 and 5.2 (m, 2H, OCH_2), 6.1 (s, 1H, OC*H*Ar), 7.5 (m, 4H, Ar), 7.6 and 8.2 (s, 1H, C*H*=NOH).

6-(4-Chlorophenyl)-3-(methoxyimino)methyl-4*H*,6*H*-furo[3,4-c]isoxazole (IIIg) was prepared from **IIb**, $MeONH_2$ HCl and NaOAc in a same manner to that described for **IIf**. Yield 94%: mp 77-80 °C; MS M^+ m/z 278, 280; IR (CCl_4) 1650, 1480 (isoxazole) cm^{-1}; ^1H NMR 4.0 and 4.1 (s, 3H, OCH_3), 5.1 and 5.2 (s, 2H, OCH_2), 6.1 (s, 1H, OCHAr), 7.4 (m, 4H, Ar), 7.6 and 8.1 (s, 1H, C*H*=NOMe).

6-(4-Chlorophenyl)-3-(ethoxyimino)methyl-4*H*,6*H*-furo[3,4-c]isoxazole (IIIh) was prepared from **IIIe**, $EtONH_2$ HCl and NaOAc in a same manner to that described for **IIf**. Yield 94%: MS M^+ m/z 292, 294; IR (neat) 1650, 1485, 1435 (isoxazole) cm^{-1}; ^1H NMR 1.3 and 1.4 (t, 3H, CH_2CH_3), 4.2 and 4.3 (q, 2H, OCH_2CH_3), 5.1 and 5.2 (s, 2H, OCH_2), 6.1 (s, 1H, OC*H*Ar), 7.4 (m, 4H, Ar), 7.6 and 8.1 (s, 1H, C*H*=NOEt).

3-(2-Allyloxyimino)methyl-6-(4-chlorophenyl)-4*H*,6*H*-furo[3,4-c]isoxazole (IIIi) was prepared from **IIIe**, CH_2=$CHCH_2ONH_2$ HCl and NaOAc in a same manner to that described for **IIf**. Yield 94%: MS M^+ m/z 304, 306; IR (neat) 1650, 1485 (isoxazole) cm^{-1}; ^1H NMR 4.8 (m, 2H, OCH_2CH), 5.1 and 5.2 (s, 2H, OCH_2), 5.2-5.6 (m, 2H, CH=CH_2), 5.8-6.1 (m, 1H, CH=CH_2), 6.1 (s, 1H, OC*H*Ar),

7.4 (m, 4H, Ar), 7.6 and 8.2 (s, 1H, C*H*=NOCH$_2$).

4,6-Bis(2-chlorophenyl)-3-methyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (IVa). Yield 75%: MS M$^+$ m/z 345, 347, 349; IR (CCl_4) 1660, 1435, 1410 (isoxazole) cm^{-1}; ^{1}H NMR 2.32 (s, 3H, CH_3), 6.16 (s, 1H, ArC*H*), 6.20 (s, 1H, ArC*H*), 7.25-7.58 (m, 8H, Ar).

4-(2-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-4*H*,6*H*-furo[3,4-c]isoxazole (IVb). Yield 70%: MS M$^+$ m/z 345, 347, 349; IR (CCl_4) 1660, 1485, 1400 (isoxazole) cm^{-1}; ^{1}H NMR 2.35 (s, 3H, CH_3), 6.38 (s, 1H, ArC*H*), 6.60 (s, 1H, ArC*H*), 7.32-7.60 (m, 8H, Ar).

Biological tests

All the test furo[3,4-*c*]isoxazole (**I-IV**) compounds (12.5 mg) were readily dispersed in a standard formulation of 5 mL of acetone and 45 mL of Tween 20 solution (250 ppm). The resulting solution was evenly sprayed onto plants while rotated on a turntable, and all tests were run in two-pot replicates.

Test 1. Evaluation of activity against rice blast was done by foliage spray onto rice plants (second leaf stage) grown in 5-cm pots. After the spray deposit had dried, the plants were inoculated with a suspension of conidia in water (1×10^6 spores/mL) and placed in a dew chamber at 25 °C for 24 h. For inoculum preparation, rice blast fungus (*Pyricularia oryzae*) was incubated on rice polish agar medium at 26 °C for 2 weeks and then scratched aerial mycelia with rubber and irradiated with near UV light for 2 d. The plants were then held in lighted growth chamber (26±2 °C) for an additional 5 d and rated on the disease severity.

Test 2. Evaluation of activity against rice sheath blast was done by foliage spray onto rice plants (third leaf stage) grown in 5-cm pots. After the spray deposit had dried, the treated plants were inoculated by injecting inoculum (incubated in wheat bran medium at 25 °C for 7 d). The plants were then held in lighted dew chamber (28 °C) for 5 d and rated on the disease severity.

Test 3. Evaluation of activity against cucumber gray mold was done by foliage spray onto cucumber plants (first leaf stage) grown in 5-cm pots. After the spray deposit had dried for 1 day, the treated cucumber foliage was inoculated with conidia (1×10^6 spores/mL) of *Botrytis cinerea* (incubated on potato dextrose agar medium at 25 °C for 15 d) by leaf spray all sides until just before runoff. The plants were then held in lighted dew chamber (20±2 °C) for an additional 4-5 d and rated on the disease severity.

Test 4. Evaluation of activity against tomato late blight was done by foliage spray to run off onto 14-day-old tomato plants grown in 5-cm polyvinyl pots. After the spray deposit had dried for 1 day, the treated plants were inoculated by spraying with a suspension of zoosporangia (1×10^5 zoosporangia/mL; incubated on V-8 juice agar medium at 20 °C for 2 weeks). The plants were then held in lighted dew chamber (20±2 °C) for an additional 4 d and rated on the disease severity.

Test 5. Evaluation of activity against wheat leaf rust was made by foliage spray of the first leaf of wheat (cultivar; Chokwang) grown in polyvinyl pots (diameter, 5 cm) for 7 d. fter the spray deposit dried, plants were dusted with a uredospores colonied on the second leaf and placed in a moist chamber at 20 °C for 24 h. One day after inoculation, plant were moved to the plant growth chamber (20 °C , 70% relative humidity) to induce disease. The plants were then held in growth chamber (20±2 °C) for an additional 10 d and rated on the disease severity.

Test 6. Evaluation of activity against barley powdery mildew was done by foliage spray onto the first leaf of 7-day-old barley (cultivar, Allbori) grown in 5-cm polyvinyl pots. After spray deposit had dried for 1 day, the treated plants were dusted with conidia of *Erysiphe graminis* (formed on the primary leaf of barley). The inoculated plants were then placed in a growth chamber (20±2 °C) for an additional 7 day and rated on the disease severity.

Acknowledgment. We are grateful to the CNU Research Foundation for partial support of this research and thank the Agrochemical Screening Center of KRICT for the bioassay.

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