Synthesis, Characterization, and Biological Activities of Novel (*Z*)-3-((*E*)-1-(Alkyloxyimino)ethyl)-5-arylidene-4-hydroxypyrroline-2-one Derivatives

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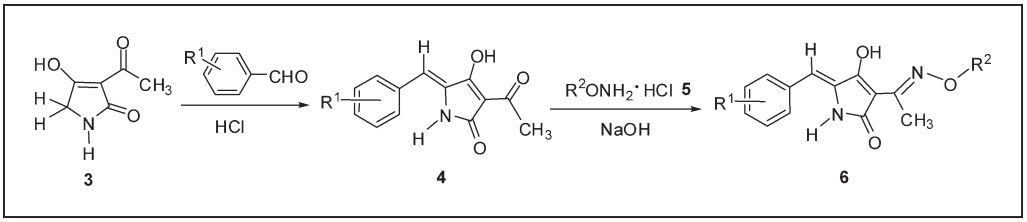

Twenty-four novel tetramic acid derivatives (*Z*)-3-((*E*)-1-(alkyloxyimino)ethyl)-5-arylidene-4-hydroxypyrroline-2-ones **6a–x** were synthesized by the reaction of (*Z*)-3-acetyl-5-arylidene-4-hydroxypyrroline-2-ones **4** with *O*-alkyl hydroxylamines **5** under reflux conditions in good yields (77.2–92.4%). Their structures were confirmed by IR, ^{1}H-NMR, MS, and elemental analysis. The preliminary bioassays showed that most of the title compounds exhibited noticeable fungicidal activities against *Colletotrichum orbiculare* and a certain degree of fungicidal activities against *Fusarium gramineaum* and *Rhizoctonia cerealis* at a concentration of 100 μg/mL.

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INTRODUCTION

Some hundreds of natural products containing the ring system pyrrolidine-2,4-dione (also known as tetramic acid) (Fig. 1) have been isolated from plants, fungi, and more recently from marine sponges [1–3]. The spectrum of biological activities displayed by these natural products is remarkable in its diversity [4–6]. An important representative of the tetramic acids is tenuazonic acid, which is a metabolite produced by some phytopathogenic fungi [7]. Since its isolation in 1957 from the culture filtrates of *Alternaria tenuis* [8], it has been found possessing antitumor, antiviral, antibacterial, and herbicidal activities [9–12]. Reutericyclin [13] is a typical 1,3-bisacyltetramic acid that is extracted from cells and culture filtrates of *Lactobacillus reuteri* and found to inhibit the growth of *Salmonella* and *Helicobacter*, the latter being the causative agent of stomach ulcers. The melophlins [14] are a class of *N*-methyl-3-acyltetramic acids recently isolated from the marine sponge *Melophlus sarassinorum*. Melophlin A and B displayed cytotoxic activity against HL60 cells at 0.2 and 0.4 μg/mL, respectively [15]. In 1971, Yuki *et al* synthesized a series of 5-subsitituted-3-(1-anilinoethylidene)pyrrolidine-2,4-dione derivatives and studied antitumor activities [16]. Zhu *et al* reported a series of 3-[(α-hydroxy-substituted)benzylidene]pyrrolidine-2,4-dione derivatives showing higher herbicidal activities [17].

Oxime ether derivatives have occupied an important position in medicinal and pesticide chemistry with a wide range of bioactivities [18]. As pesticides, they were used as insecticides, fungicides, and herbicides. Alloxydim [19], the first cyclohexanedione herbicide with an oxime ether group has been commercialized. The advantages of oxime ether derivatives, such as, high-activity against the target, low-toxicity toward the mammalians, and low-residue, have prompted chemists to design and synthesize more novel oxime ether derivatives [20].

In 1981, Tatsuaki *et al* synthesized thirteen 3-acetyl-5-subsititutedbenzylidenetetramic acids [21], the novel structures and infusive biological activities of which have aroused great interest to us. Herein, we introduced oxime ether groups into 3-acetyl-5-subsititutedbenzylidenetetramic acids to synthesize a series of novel (*Z*)-3-((*E*)-1-(alkyloxyimino)ethyl)-5-arylidene-4-hydroxy-pyrroline-2-one derivatives for the purpose of searching

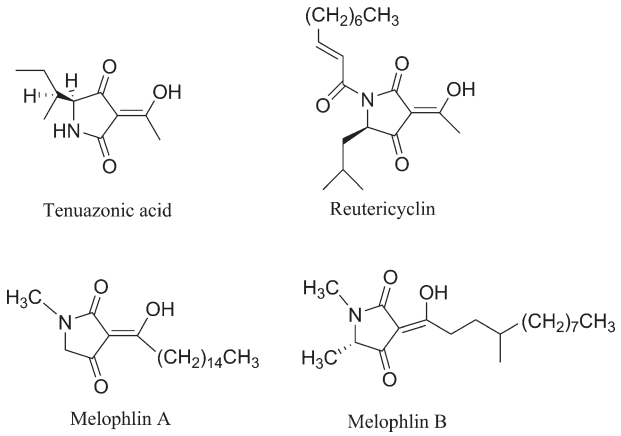


Figure 1. Some bioactive naturally occurring tetramic acids.

new potential pesticides with an excellent biological activities. The synthetic route is shown in Scheme 1.

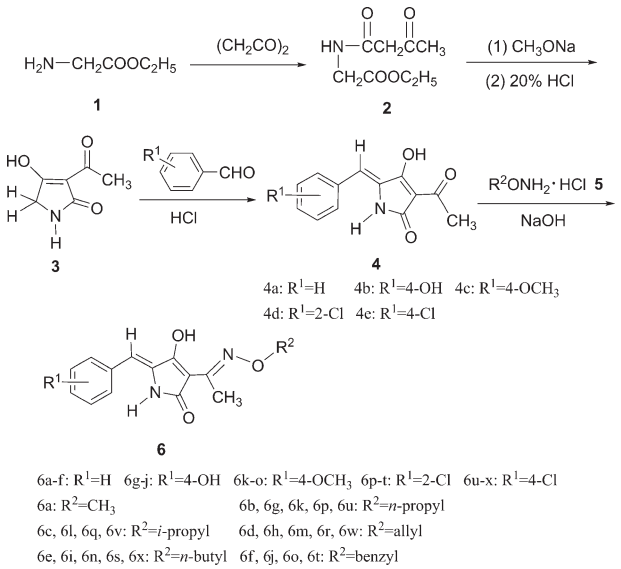
RESULTS AND DISCUSSION

Chemistry. The synthesis of compounds (*Z*)-3-acetyl-5-arylidene-4-hydroxypyrroline-2-ones **4** involved the condensation of **3** (1 equivalent) with substituted benzaldehydes (2 equivalent) in the presence of dry hydrochloride [21]. The dry hydrochloride as a key catalyst was obtained by the reaction of acetyl chloride with anhydrous ethanol. In the ^{1}H-NMR spectra of the compounds **4a**, **4c**, and **4e**, the protons of CH═ and NH showed the characteristic pair of signals, indicating these compounds in deuteriochloroform solution existed to a great extent as tautomers [22]. According to the literature based on a comparison of the ^{1}H-NMR chemical shift data for the vinyl proton signals at the region of 6.42–6.65 ppm with those of similar tetramates, the *Z* configuration of the compounds could be assigned, and this inference was consistent with crystal structure of **6e**.

In the IR spectra of the title compounds **6**, there were medium or weak absorption bands for the enolic hydroxyl group (ν O—H) at around 3300 cm^{-1} and relatively strong absorption bands for the carbonyl at around 1680 cm^{-1}. The characteristic absorption peak of oxime ether group existed at around 1620 cm^{-1}. The main characteristic of the ^{1}H-NMR spectra of **6a–x** was the presence of high-frequency downfield broad singlet δ_H 7.53–9.72 presumably arising from the deshielded N—H proton linked to the carbonyl group. The singlet at δ_H 6.21–6.49 assigned to the C—H proton of CH═C and singlet at δ_H 2.32–2.57 assigned to the C—H protons of CH_3C═N. The signal of protons of OH group at the 4-position in NMR spectra was not been found, and this phenomena might be caused by the lability of these protons of compounds **4** and **6**, which involved in internal tautomerization in the enol form. Furthermore, the MS spectra of all the compounds **6** showed the molecular ion peak (M^+, 3–100%), and other fragmentation ions were consistent with their structures and could be clearly assigned.

In the crystal structure of compound **6e** (Fig. 2), the bond length C(5)—N(2) [1.295(3) Å] was close to the C═N double bond distance (1.34 Å). The bond lengths C(7)—C(9) and C(10)—C(11) were 1.354(3) Å and 1.338(3) Å, respectively, and they were close to the C═C double bond distance (1.34 Å). As a result, the benzene ring, C(10)—C(11), C(7)—C(9), C(5)—N(2), and C(8)═O(1) [1.237(2) Å] formed a large conjugated system. The bond length C(8)—N(1) [1.376(2) Å] was shorter than the normal C—N single bond (1.49 Å), suggesting the occurring of an electron density delocalization. The dihedral angle between benzene ring and pyrroline-2-one ring [N(1), O(1), O(2), C(7), C(8), C(9), C(10)] was 15.928(54)°. In addition, there was a weak π···π interaction between the parallel benzene rings (the

Scheme 1. General synthetic route for the target compounds **6a-x**.



4a: R^1=H 4b: R^1=4-OH 4c: R^1=4-OCH_3
4d: R^1=2-Cl 4e: R^1=4-Cl

6a-f: R^1=H 6g-j: R^1=4-OH 6k-o: R^1=4-OCH_3 6p-t: R^1=2-Cl 6u-x: R^1=4-Cl
6a: R^2=CH_3 6b, 6g, 6k, 6p, 6u: R^2=*n*-propyl
6c, 6l, 6q, 6v: R^2=*i*-propyl 6d, 6h, 6m, 6r, 6w: R^2=allyl
6e, 6i, 6n, 6s, 6x: R^2=*n*-butyl 6f, 6j, 6o, 6t: R^2=benzyl

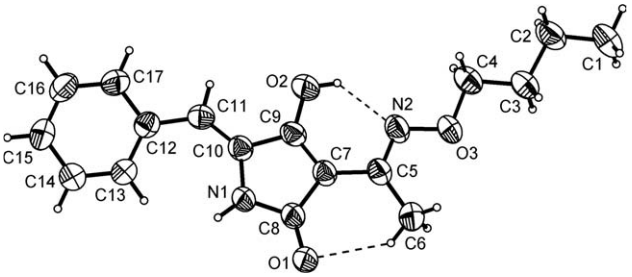


Figure 2. Molecular structure of compound **6e**.

Table 1

Antifungal activities of compounds **6a–x** (100 μg/mL, inhibitory rate percent).

Compound	R^1	R^2	Inhibitory rate[a] (%)		
			F. gramineaum	*R. cerealis*	*C. orbiculare*
6a	H	methyl	25.0 ± 1.5	50.9 ± 1.6	74.3 ± 0.9
6b	H	*n*-propyl	17.9 ± 2.3	30.3 ± 0.9	30.7 ± 2.7
6c	H	*i*-propyl	11.7 ± 3.5	45.4 ± 3.1	28.1 ± 2.4
6d	H	allyl	5.1 ± 2.7	7.8 ± 0.9	33.9 ± 3.1
6e	H	*n*-butyl	17.9 ± 3.5	37.8 ± 2.6	44.9 ± 3.1
6f	H	benzyl	5.6 ± 1.0	29.3 ± 3.0	33.3 ± 1.8
6g	4-OH	*n*-propyl	12.2 ± 2.3	14.8 ± 3.1	20.2 ± 4.0
6h	4-OH	allyl	4.6 ± 3.2	15.3 ± 0.9	39.6 ± 3.3
6i	4-OH	*n*-butyl	17.9 ± 3.2	29.8 ± 3.1	42.3 ± 3.3
6j	4-OH	benzyl	13.3 ± 0.9	28.8 ± 2.3	22.3 ± 4.0
6k	4-OCH_3	*n*-propyl	17.8 ± 1.7	38.4 ± 2.1	53.6 ± 3.6
6l	4-OCH_3	*i*-propyl	19.3 ± 2.3	30.8 ± 1.5	56.3 ± 4.1
6m	4-OCH_3	allyl	5.8 ± 1.7	N.A[b]	53.6 ± 0.9
6n	4-OCH_3	*n*-butyl	7.8 ± 2.3	45.5 ± 1.8	57.8 ± 4.1
6o	4-OCH_3	benzyl	9.3 ± 0.9	35.9 ± 3.1	20.3 ± 3.6
6p	2-Cl	*n*-propyl	9.8 ± 2.6	6.9 ± 3.1	73.4 ± 1.6
6q	2-Cl	*i*-propyl	N.A	7.4 ± 3.2	54.2 ± 0.9
6r	2-Cl	allyl	5.8 ± 2.3	N.A	23.4 ± 2.7
6s	2-Cl	*n*-butyl	9.3 ± 3.1	13.0 ± 1.5	19.3 ± 3.9
6t	2-Cl	benzyl	11.8 ± 2.3	17.0 ± 1.8	8.9 ± 1.8
6u	4-Cl	*n*-propyl	12.3 ± 3.1	16.5 ± 2.3	24.0 ± 3.9
6v	4-Cl	*i*-propyl	14.3 ± 2.4	16.9 ± 3.7	39.5 ± 2.7
6w	4-Cl	allyl	9.7 ± 2.1	32.4 ± 1.4	25.0 ± 1.7
6x	4-Cl	*n*-butyl	11.5 ± 1.4	42.3 ± 2.8	49.4 ± 3.0
Tenuazonic acid	–	–	10.0 ± 1.7	16.1 ± 3.1	14.5 ± 3.0
Propiconazole	–	–	98.4 ± 0.2	99.2 ± 0.1	95.1 ± 0.3

[a] Average of three replicates.
[b] N.A. = Not active.
Values are the mean ± S.D. of three replicates.

centroid-centroid distance was 4.36 Å) to pivotally maintain a 3D supramolecular network structure.

Furthermore, the crystal structure of compound **6e** simultaneously confirmed *E* configuration of 1-(alkyloxyimino)ethyl group and *Z* configuration of arylidene group, especially the enolic form at 4-position of the title compounds.

Biological activity. The results of fungicidal activities *in vitro* at a concentration of 100 μg/mL were listed in Table 1. Most of the compounds **6** exhibited notable fungicidal activities against *C. orbiculare*, thereby the inhibitory rates of the compounds **6a**, **6k**, **6l**, **6m**, **6n**, **6p**, and **6q** all exceeded 50%. Comparatively, the fungicidal activities against *R. oerealis* were moderate, but more than half of the compounds **6** were more active than tenuazonic acid. The preliminary estimation of structure-activity relationships indicated that the title compounds showed more remarkable fungicidal activities against *C. orbicular* when R^2 was saturated aliphatic alkyl, for example, the compound **6a** (R^1 was H and R^2 was CH_3) gave a best activity with EC_{50} value of 1.15 μg/mL (Table 2), indicating it was significant to further modify the structure of the title compounds.

Table 2

EC_{50} values of compounds **6a**, **6n**, and **6p** against *C. orbiculare*.

Compound	Regression eq.	EC_{50}[a](μg/mL)	r[b]
6a	$y = 0.36423x + 4.97749$	1.15	0.99
6n	$y = 0.92570x + 3.62689$	30.43	0.96
6p	$y = 0.50225x + 4.19465$	40.13	0.90

[a] Ec_{50} refer to median effect concentration.
[b] Refer to correlative coefficient.

It was worthy to clarify that the herbicidal activities of the title compounds were evaluated too. *Brassica campestris* and *Echinochloa crusgalli* (L.) *Beauv* were chosen as samples of annual dicotyledonous and monocotyledonous plants. But the herbicidal activities of all the title compounds were found to be quite weak.

CONCLUSIONS

A series of new tetramic acid derivatives containing oxime ether group at 3-position and arylidene group at 5-position were designed and synthesized by the

reaction of (*Z*)-3-acetyl-5-arylidene-4-hydroxypyrroline-2-ones with *O*-substituted hydroxylamine hydrochlorides. The data of IR, MS, ^{1}H-NMR spectra, and X-ray single-crystal structure diffraction confirmed the structures of the title compounds that contained enol structure and (3*E*, 5*Z*)-configuration. The bioassay results demonstrated that most of the title compounds, especially **6a**, possessed good activity against *C. orbiculare*. Further studies on structural modification are currently underway.

EXPERIMENTAL

The melting points of the products were determined on a WRS-1B digital melting-point apparatus and were uncorrected. IR was recorded on a Bruker Tensor 27 FT-IR spectrometer with KBr disk. Elemental analyses were performed on Elementar Vario-III CHN analyzer. Mass spectra were recorded on a GC/MS-QP2010 spectrometer using direct-injection technique. ^{1}H-NMR spectra was taken on a Mercury plus varian-300 spectrometer with TMS as the internal reference and DMSO-d_6 or $CDCl_3$ as the solvent. X-ray diffraction was performed with a Brucker Smart APEX II CCD diffractometer. All reagents were analytical-reagent grade or were chemically pure. The solvents were dried before use as needed.

Intermediate **3** was prepared according to the reported method [23]. The intermediates **5** *O*-allyl, *O*-methyl, and *O*-benzyl hydroxylamine hydrochlorides were synthesized starting from ethyl acetate and hydroxylamine hydrochloride via a facile three-step procedure including acetylamination, etherification, and hydrolyzation [24–26]. *O*-Propyl, *O*-isopropyl, and *O*-butyl hydroxylamine hydrochlorides were synthesized starting from hydroxylamine hydrochloride and phthalic anhydride in satisfactory yield according to the method reported by Han [27].

General procedure for the synthesis of intermediate (*Z*)-3-acetyl-5-arylidene-4-hydroxy-pyrroline-2-ones (4). To the solution of compound **3** (16 mmol) in ethanol (15 mL) added 8% HCl (18 mmol) in anhydrous ethanol and stirred until it dissolved, after that a substituted benzaldehyde (32 mmol) was added. The reaction mixture was refluxed for 3 h, and then cooled to give a red precipitate, which was filtered off and recrystallized from ethanol to afford the products **4a–e** in 35.2–60.8% yields.

(Z)-3-acetyl-5-benzylidene-4-hydroxypyrroline-2-one (4a). Red powder, mp 224.9–225.6°C; yield, 36.9%; IR (KBr, cm^{-1}) ν 3210, 1697, 1678, 1627, 1455, 1280, 1228, 1084, 936; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.58 (s, 3H, $COCH_3$), 6.67, 6.70 (s, s, 1H, CH=), 7.35–7.47 (m, 5H, PhH), 8.17, 8.54 (s, s, 1H, NH); Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.45; H, 4.92; N, 6.23.

(Z)-3-acetyl-4-hydroxy-5-(4-hydroxybenzylidene)-pyrroline-2-one (4b). Red powder, mp 262.3–263.1°C; yield, 45.2%; IR (KBr, cm^{-1}) ν 3373, 3174, 1682, 1606, 1575, 1449, 1357, 1228, 1087, 930; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 2.50 (s, 3H, $COCH_3$), 6.42 (s, 1H, CH=), 6.77 (d, 2H, PhH, J = 8.4 Hz), 7.49 (d, 2H, PhH, J = 8.4 Hz), 9.89 (s, 1H, NH), 10.33 (s, 1H, OH); Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 64.01; H, 4.61; N, 5.80.

(Z)-3-acetyl-4-hydroxy-5-(4-methoxybenzylidene)-pyrroline-2-one (4c). Yellow powder, mp 239.3–240.1°C; yield, 60.8%; IR (KBr, cm^{-1}) ν 3239, 1673, 1668, 1588, 1522, 1519, 1383, 1240, 1032, 959; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.58 (s, 3H, $COCH_3$), 3.87 (s, 3H, $PhOCH_3$), 6.64, 6.66 (s, s, 1H, CH=), 6.97 (d, 2H, PhH, J = 6.9 Hz), 7.43 (d, 2H, PhH, J = 9.3 Hz), 7.76, 8.14 (s, s, 1H, NH); Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.56; H, 5.15 N, 5.48.

(Z)-3-acetyl-5-(2-chlorobenzylidene)-4-hydroxypyrroline-2-one (4d). White powder, mp 227.5–228.9°C; yield, 25.2%; IR (KBr, cm^{-1}) ν 3204, 1703, 1635, 1580, 1443, 1293, 1207, 1089, 938; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.57 (s, 3H, $COCH_3$), 6.89 (s, 1H, CH=), 7.32–7.48 (m, 4H, PhH), 7.97, 8.38 (s, s, 1H, NH); Anal. Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.57; H, 3.89; N, 5.42.

(Z)-3-acetyl-5-(4-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (4e). White powder, mp 238.3–240.9°C; yield, 40.2%; IR (KBr, cm^{-1}) ν 3185, 1705, 1624, 1586, 1493, 1420, 1247, 1089, 929; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.58 (s, 3H, $COCH_3$), 6.60, 6.62 (s, s, 1H, CH=), 7.35–7.41 (m, 4H, PhH), 7.84, 8.11 (s, s, 1H, NH); Anal. Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.68; H, 3.75; N, 5.23.

General procedure for the preparation of the title compounds 6a–x. To a solution of (*Z*)-3-acetyl-5-arylidene-4-hydroxypyrroline-2-one **4** (1.5 mmol) and *O*-substituted hydroxylamine hydrochloride **5** (1.6 mmol) in ethanol (25 mL) was added 0.2 mol/L NaOH (8 mL). Then, the reaction mixture was refluxed for 3 h. After cooling to room temperature, the mixture was poured into water (30 mL), and the precipitate was filtered. The filtrate was extracted with chloroform and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a yellow solid. Finally, the solid was collected together and recrystallized from ethanol or ethyl acetate to give title compounds **6a–x**.

(Z)-5-benzylidene-4-hydroxy-3-((E)-1-(methoxyimino)ethyl)-pyrroline-2-one (6a). Yellow powder, mp 188.5–189.1°C; yield, 90.1%; IR (KBr, cm^{-1}) ν 3344, 3215, 3028, 2940, 1698, 1655, 1620, 1455, 1058, 903; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.51 (s, 3H, CH_3C=N), 3.93 (s, 3H, OCH_3), 6.5 (s, 1H, CH=), 7.32–7.43 (m, 5H, PhH), 7.59 (s, 1H, NH); MS *m*/*z* (%): 258(M^+, 14), 167(26), 149(84), 81(46), 69(100), 57(94); Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.62; H, 5.49; N, 10.76.

(Z)-5-benzylidene-4-hydroxy-3-((E)-1-(propoxyimino)ethyl)-pyrroline-2-one (6b). Yellow powder, mp 165.9–166.4°C; yield, 92.3%; IR (KBr, cm^{-1}) ν 3332, 3211, 3029, 2967, 1687, 1615, 1566, 1450, 1384, 1245, 1050, 925; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.00 (t, 3H, CH_2CH_3, J = 7.2 Hz), 1.71–1.83 (m, 2H, CH_2CH_3), 2.55 (s, 3H, CH_3C=N), 4.00 (t, 2H, OCH_2, J = 6.3 Hz), 6.49 (s, 1H, CH=), 7.30–7.43 (m, 5H, PhH), 7.74 (s, 1H, NH); MS *m*/*z* (%): 286(M^+, 92), 228(100), 212(18), 149(16), 117(70), 82(56), 45(40); Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 66.71; H, 6.43; N, 9.68.

(Z)-5-benzylidene-4-hydroxy-3-((E)-1-(isopropoxyimino)ethyl)-pyrroline-2-one (6c). Yellow powder, mp 163.1–64.1°C; yield, 87.2%; IR (KBr, cm^{-1}) ν 3297, 3160, 3019, 2975, 1682, 1611, 1572, 1497, 1375, 1241, 1102, 909; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.34 (d, 6H, $CH(CH_3)_2$, J = 6.3 Hz), 2.57 (s, 3H, CH_3C=N), 4.22–4.30 (m, 1H, OCH), 6.49 (s, 1H, CH=),

7.30–7.45 (m, 5H, PhH), 7.78 (s, 1H, NH); MS *m*/*z* (%): 286(M^+, 100), 244(28), 225(78), 172(34), 149(32), 117(60), 82(82), 58(22); Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.48; H, 6.47; N, 9.70.

(Z)-3-((E)-1-(allyloxyimino)ethyl)-5-benzylidene-4-hydroxypyrroline-2-one (6d). Red powder, mp 170.2–171.3°C; yield, 85.3%; IR (KBr, cm^{-1}) ν 3328, 3218, 3030, 2936, 1681, 1621, 1564, 1452, 1269, 1088, 1005, 936; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.52 (s, 3H, $CH_3C{=}N$), 4.54 (d, 2H, OCH_2, J = 6.3 Hz), 5.40–5.48 (m, 2H, $CH{=}CH_2$), 5.95–6.08 (m, 1H, $CH{=}CH_2$), 6.49 (s, 1H, CH=C), 7.31–7.42 (m, 5H, PhH), 7.56 (s, 1H, NH); MS *m*/*z* (%): 284(M^+, 24), 267(10), 213(18), 167(28), 149(100), 81(66), 69(68), 57(36); Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.14; H, 5.72; N, 9.80.

(Z)-5-benzylidene-3-((E)-1-(butoxyimino)ethyl)-4-hydroxypyrroline-2-one (6e). Yellow crystal, mp 158.9–159.5°C; yield, 82.3%; IR (KBr, cm^{-1}) ν 3328, 3215, 3028, 2957, 2874, 1679, 1655, 1624, 1451, 1367, 1092, 1048, 973; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.97 (t, 3H, CH_2CH_3, J = 7.2 Hz), 1.41–1.54 (m, 2H, CH_2CH_3), 1.69–1.78 (m, 2H, OCH_2CH_2), 2.56 (s, 3H, $CH_3C{=}N$), 4.05 (t, 2H, OCH_2, J = 6.3 Hz), 6.50 (s, 1H, CH=), 7.33–7.48 (m, 5H, PhH), 7.98 (s, 1H, NH); MS *m*/*z* (%): 300(M^+, 82), 228(100), 210(22), 172(20), 117(64), 90(48), 82(42), 45(46); Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.25; H, 6.60; N, 9.43.

(Z)-5-benzylidene-3-((E)-1-(benzyloxyimino)ethyl)-4-hydroxypyrroline-2-one (6f). Yellow powder, mp 201.7–202.5°C; yield, 90.5%; IR (KBr, cm^{-1}) ν 3349, 3207, 3008, 2932, 1698, 1657, 1622, 1455, 1367, 1096, 995; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.45 (s, 3H, $CH_3C{=}N$), 5.07 (s, 2H, OCH_2), 6.50 (s, 1H, CH=), 7.30–7.42 (m, 10H, 2PhH), 7.50 (s, 1H, NH); MS *m*/*z* (%): 334(M^+, 18), 228(74), 210(14), 117(20), 115(26), 91(100), 77(22), 45(34); Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 72.19; H, 5.49; N, 8.30.

(Z)-3-((E)-1-(propoxyimino)ethyl)-4-hydroxy-5-(4-hydroxybenzylidene)-pyrroline-one (6g). Yellow powder, mp 225.2–226.5°C; yield, 80.0%; IR (KBr, cm^{-1}) ν 3378, 3346, 3156, 2967, 1661, 1601, 1580, 1513, 1233, 1148, 1067, 935; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 0.90 (t, 3H, CH_2CH_3, J = 7.2 Hz), 1.57–1.69 (m, 2H, CH_2CH_3), 2.35 (s, 3H, $CH_3C{=}N$), 4.00 (t, 2H, OCH_2, J = 6.3 Hz), 6.21 (s, 1H, CH=), 6.73 (d, 2H, PhH, J = 8.4 Hz), 7.43 (d, 2H, PhH, J = 8.1 Hz), 9.71 (s, 1H, NH), 9.78 (s, 1H, OH); MS *m*/*z* (%): 302(M^+, 4), 244(100), 227(22), 133(22), 84(38), 55(20); Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.37; H, 6.08; N, 9.20.

(Z)-3-((E)-1-(allyloxyimino)ethyl)-4-hydroxy-5-(4-hydroxybenzylidene)-pyrroline-2-one (6h). Red powder, mp 231.2–232.4°C; yield, 83.3%; IR (KBr, cm^{-1}) ν 3363, 3348, 3159, 2982, 1662, 1598, 1513, 1274, 1234, 1152, 1065, 958; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 2.33 (s, 3H, $CH_3C{=}N$), 4.60 (d, 2H, OCH_2, J = 5.7 Hz), 5.28–5.40 (m, 2H, $CH{=}CH_2$), 5.93–6.07 (m, 1H, $CH{=}CH_2$), 6.24 (s, 1H, CH=C), 6.74 (d, 2H, PhH, J = 8.4 Hz), 7.44 (d, 2H, PhH, J = 8.1 Hz), 9.72 (s, 1H, NH), 9.81 (s, 1H, OH); MS *m*/*z* (%): 300(M^+, 4), 271(14), 244(100), 226(22), 137(24), 84(52), 57(88); Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.55; H, 5.29; N, 9.40.

(Z)-3-((E)-1-(butoxyimino)ethyl)-4-hydroxy-5-(4-hydroxybenzylidene)-pyrroline-2-one (6i). Yellow powder, mp 210.2–211.2°C; yield, 85.5%; IR (KBr, cm^{-1}) ν 3386, 3351, 3189, 3026, 2959, 1695, 1665, 1587, 1457, 1255, 1098, 913; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 0.88 (t, 3H, CH_2CH_3, J = 7.2 Hz), 1.31–1.44 (m, 2H, CH_2CH_3), 1.55–1.65 (m, 2H, OCH_2CH_2), 2.35 (s, 3H, $CH_3C{=}N$), 4.04 (t, 2H, OCH_2, J = 6.3 Hz), 6.21 (s, 1H, CH=), 6.73 (d, 2H, PhH, J = 8.4 Hz), 7.43 (d, 2H, PhH, J = 7.8 Hz), 9.71 (s, 1H, NH), 9.78 (s, 1H, OH); MS *m*/*z* (%): 316(M^+, 3), 244(100), 227(22), 155(19), 137(25), 84(34), 55(15); Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.16; H, 6.45; N, 8.80.

(Z)-3-((E)-1-(benzyloxyimino)ethyl)-4-hydroxy-5-(4-hydroxybenzylidene)-pyrroline-2-one (6j). Yellow crystal, mp 240.3–241.9°C; yield, 78.8%; IR (KBr, cm^{-1}) ν 3359, 3349, 3169, 3018, 2796, 1658, 1601, 1579, 1561, 1272, 1056, 956; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 2.32 (s, 3H, $CH_3C{=}N$), 5.13 (s, 2H, OCH_2), 6.21 (s, 1H, CH=), 6.73 (d, 2H, PhH, J = 8.7 Hz), 7.33–7.45 (m, 7H, PhH), 9.71 (s, 1H, NH), 9.80 (s, 1H, OH); MS *m*/*z* (%): 350(M^+, 5), 244(100), 227(24), 133(17), 105(13), 84(33), 55(15); Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.92; H, 5.25; N, 8.08.

(Z)-4-hydroxy-5-(4-methoxybenzylidene)-3-((E)-1-(propoxyimino)ethyl)-pyrroline-2-one (6k). Yellow powder, mp 174.0–175.7°C; yield, 86.8%; IR (KBr, cm^{-1}) ν 3321, 3216, 2964, 2874, 1680, 1602, 1514, 1249, 1117, 1054, 1037, 928; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.99 (t, 3H, CH_2CH_3, J = 7.5 Hz), 1.71–1.80 (m, 2H, CH_2CH_3), 2.53 (s, 3H, $CH_3C{=}N$), 3.84 (s, 3H, $PhOCH_3$), 4.00 (t, 2H, OCH_2, J = 7.2 Hz), 6.46 (s, 1H, CH=), 6.93 (d, 2H, PhH, J = 8.7 Hz), 7.36 (d, 2H, PhH, J = 8.7 Hz), 7.53 (s, 1H, NH). MS *m*/*z* (%): 316(M^+, 6), 258(100), 202(22), 179(19), 137(25), 83(34), 45(15); Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.89; H, 6.45; N, 8.94.

(Z)-4-hydroxy-3-((E)-1-(isopropoxyimino)ethyl)-5-(4-methoxybenzylidene)-pyrroline-2-one (6l). Yellow powder, mp 206.8–208.0°C; yield, 91.0%; IR (KBr, cm^{-1}) ν 3320, 3207, 2979, 2835, 1687, 1602, 1517, 1253, 1187, 1115, 1036, 980; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ:1.34 (d, 6H, $CH(CH_3)_2$, J = 6.0 Hz), 2.55 (s, 3H, $CH_3C{=}N$), 3.84 (s, 3H, $PhOCH_3$), 4.24–4.28 (m, 1H, OCH), 6.47 (s, 1H, CH=), 6.93 (d, 2H, PhH, J = 8.7 Hz), 7.36 (d, 2H, PhH, J = 8.1 Hz), 7.56 (s, 1H, NH). MS *m*/*z* (%): 316(M^+, 5), 279(16), 202(36), 167(35), 149(100), 69(53), 57(56), 45(66); Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.82; H, 6.31; N, 8.77.

(Z)-3-((E)-1-(allyloxyimino)ethyl)-4-hydroxy-5-(4-methoxybenzylidene)-pyrroline-2-one (6m). Yellow powder, mp 168.7–169.7°C; yield, 90.0%; IR (KBr, cm^{-1}) ν 3323, 3202, 2981, 2835, 1677, 1602, 1568, 1514, 1255, 1183, 1037, 931; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.51 (s, 3H, $CH_3C{=}N$), 3.85 (s, 3H, $PhOCH_3$), 4.55 (d, 2H, OCH_2, J = 6.0 Hz), 5.40–5.47 (m, 2H, $CH{=}CH_2$), 5.95–6.06 (m, 1H, $CH{=}CH_2$), 6.51 (s, 1H, CH=C), 6.94 (d, 2H, PhH, J = 9.0 Hz), 7.36 (d, 2H, PhH, J = 8.7 Hz), 7.69 (s, 1H, NH). MS *m*/*z* (%): 314(M^+, 7), 258(100), 241(19), 148(20), 132(24), 83(18), 45(21); Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 64.51; H, 5.72; N, 8.98.

(Z)-3-((E)-1-(butoxyimino)ethyl)-4-hydroxy-5-(4-methoxybenzylidene)-pyrroline-2-one (6n). Yellow powder, mp 166.3–167.0°C; yield, 87.6%; IR (KBr, cm^{-1}) ν 3319, 3186, 2956, 1685, 1604, 1514, 1253, 1176, 1067, 956; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.95 (t, 3H, CH_2CH_3, J = 7.5 Hz), 1.39–1.52 (m, 2H, CH_2CH_3), 1.67–1.76 (m, 2H, OCH_2CH_2), 2.52 (s, 3H, $CH_3C{=}N$), 3.84 (s, 3H, $PhOCH_3$), 4.04 (t, 2H, OCH_2, J =

6.6 Hz), 6.45 (s, 1H, CH=), 6.92 (d, 2H, PhH, J = 8.4 Hz), 7.37 (d, 2H, PhH, J = 8.7 Hz), 7.66 (s, 1H, NH). MS m/z (%): 330(M^+, 5), 258(100), 202(25), 147(24), 132(37), 83(24), 45(19); Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.94; H, 6.76; N, 8.40.

(Z)-3-((E)-1-(benzyloxyimino)ethyl)-4-hydroxy-5-(4-methoxybenzylidene)-pyrroline-2-one (6o). Yellow powder, mp 205.8–206.7°C; yield, 77.2%; IR (KBr, cm^{-1}) ν 3322, 3212, 2924, 2837, 1692, 1618, 1601, 1513, 1252, 1180, 1036, 990; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.43 (s, 3H, CH_3C=N), 3.84 (s, 3H, $PhOCH_3$), 5.08 (s, 2H, OCH_2), 6.40 (s, 1H, CH=), 6.92 (d, 2H, PhH, J = 9.0 Hz), 7.34–7.40 (m, 7H, PhH), 7.56 (s, 1H, NH); MS m/z (%): 364(M^+, 4), 258(100), 243(22), 147(13), 132(14), 83(23), 45(18); Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.58; H, 5.42; N, 7.60.

(Z)-5-(2-chlorobenzylidene)-4-hydroxy-3-((E)-1-(propoxyimino)ethyl)-pyrroline-2-one (6p). Yellow powder, mp 164.7–165.9°C; yield, 82.3%; IR (KBr, cm^{-1}) ν 3336, 3222, 2965, 2874, 1695, 1654, 1620, 1442, 1369, 1244, 1091, 989; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.00 (t, 3H, CH_2CH_3, J = 7.2 Hz), 1.74–1.81 (m, 2H, CH_2CH_3), 2.55 (s, 3H, CH_3C=N), 4.00 (t, 2H OCH_2, J = 6.6 Hz,), 6.72 (s, 1H, CH=), 7.23–7.47 (m, 4H, PhH), 7.60 (s, 1H, NH); MS m/z (%): 320(M^+, 3), 285(31), 227(100), 210(73), 115(17), 83(16), 55(19); Anal. Calcd for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73. Found: C, 61.23; H, 5.39; N, 8.83.

(Z)-5-(2-chlorobenzylidene)-4-hydroxy-3-((E)-1-(isopropoxyimino)ethyl)-pyrroline-2-one (6q). Yellow powder, mp 187.7–189.2°C; yield, 85.7%; IR (KBr, cm^{-1}) ν 3340, 3224, 2977, 2944, 1683, 1618, 1442, 1396, 1246, 1087, 1041, 985; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.35 (d, 6H, $CH(CH_3)_2$, J = 6.0 Hz), 2.56 (s, 3H, CH_3C=N), 4.22–4.31 (m, 1H, OCH), 6.72 (s, 1H, CH=), 7.22–7.46 (m, 4H, PhH), 7.56 (s, 1H, NH); MS m/z (%): 320(M^+, 5), 285(100), 243(32), 227(43), 198(34), 89(46), 45(20); Anal. Calcd for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73. Found: C, 61.35; H, 5.45; N, 8.78.

(Z)-3-((E)-1-(allyloxyimino)ethyl)-5-(2-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (6r). Yellow powder, mp 194.1–196.5°C; yield, 86.0%; IR (KBr, cm^{-1}) ν 3331, 3195, 3027, 2911, 1705, 1660, 1623, 1440, 1347, 1249, 1097, 1044, 993; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.51 (s, 3H, CH_3C=N), 4.54 (d, 2H, OCH_2, J = 6.9 Hz), 5.41–5.48 (m, 2H, $CH=CH_2$), 5.95–6.08 (m, 1H, $CH=CH_2$), 6.71 (s, 1H, CH=C), 7.22–7.48 (m, 4H, PhH), 7.76 (s, 1H, NH); MS m/z (%): 318(M^+, 7), 283(27), 227(100), 210(68), 115(10), 89(15), 45(19); Anal. Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.01; H, 4.82; N, 8.64.

(Z)-3-((E)-1-(butoxyimino)ethyl)-5-(2-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (6s). Yellow powder, mp 165.7–166.9°C; yield, 88.7%; IR (KBr, cm^{-1}) ν 3285, 3200, 2958, 2872, 1685, 1652, 1624, 1441, 1369, 1246, 1049, 976; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.96 (t, 3H, CH_2CH_3, J = 7.2 Hz), 1.40–1.52 (m, 2H, CH_2CH_3), 1.67–1.77 (m, 2H, OCH_2CH_2), 2.50 (s, 3H, CH_3C=N), 4.05 (t, 2H, OCH_2, J = 7.5 Hz), 6.69 (s, 1H, CH=), 7.21–7.50 (m, 4H, PhH), 7.57 (s, 1H, NH); MS m/z (%): 334(M^+, 5), 299(25), 227(100), 210(88), 114(13), 89(17), 45(22); Anal. Calcd for $C_{17}H_{19}ClN_2O_3$: C, 60.99; H, 5.72; N, 8.37. Found: C, 61.30; H, 5.81; N, 8.42.

(Z)-3-((E)-1-(benzyloxyimino)ethyl)-5-(2-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (6t). Yellow crystal, mp 205.0–205.5°C; yield, 91.3%; IR (KBr, cm^{-1}) ν 3331, 3236, 3029, 2930, 1698, 1620, 1565, 1442, 1369, 1095, 1041, 995; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.42 (s, 3H, CH_3C=N), 5.08 (s, 2H, OCH_2), 6.67 (s, 1H, CH=), 7.21–7.50 (m, 9H, PhH), 7.56 (s, 1H, NH); MS m/z (%): 368(M^+, 2), 308(14), 153(100), 127(65), 98(74), 63(25), 50(11); Anal. Calcd for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.54; H, 4.72; N, 7.52.

(Z)-5-(4-chlorobenzylidene)-4-hydroxy-3-((E)-1-(propoxyimino)ethyl)-pyrroline-2-one (6u). Yellow powder, mp 222.2–223.8°C; yield, 89.5%; IR (KBr, cm^{-1}) ν 3336, 3208, 3024, 2968, 1685, 1656, 1617, 1433, 1385, 1275, 1093, 1010, 968; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.00 (t, 3H, CH_2CH_3, J = 7.8 Hz), 1.74–1.81 (m, 2H, CH_2CH_3), 2.56 (s, 3H, CH_3C=N), 4.00 (t, 2H, OCH_2, J = 6.6 Hz), 6.44 (s, 1H, CH=), 7.32–7.40 (m, 4H, PhH), 7.47 (s, 1H, NH); MS m/z (%): 320(M^+, 4), 262(100), 206(19), 152(30), 116(15), 89(32), 58(23), 45(26); Anal. Calcd for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73. Found: C, 60.14; H, 5.42; N, 8.66.

(Z)-5-(4-chlorobenzylidene)-4-hydroxy-3-((E)-1-(isopropoxyimino)ethyl)-pyrroline-2-one (6v). Yellow powder, mp 231.3–233.6°C; yield, 81.2%; IR (KBr, cm^{-1}) ν 3331, 3194, 3030, 2978, 1674, 1655, 1618, 1430, 1368, 1154, 1090, 985; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ:1.34 (d, 6H, $CH(CH_3)_2$, J = 6.3 Hz), 2.57 (s, 3H, CH_3C=N), 4.21–4.30 (m, 1H, OCH), 6.42 (s, 1H, CH=), 7.34–7.41 (m, 4H, PhH), 8.16 (s, 1H, NH); MS m/z (%): 320(M^+, 10), 262(100), 206(48), 151(42), 129(32), 89(48), 58(63), 45(60); Anal. Calcd for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; N, 8.73. Found: C, 59.47; H, 5.27; N, 8.61.

(Z)-3-((E)-1-(allyloxyimino)ethyl)-5-(4-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (6w). Yellow powder, mp 209.2–209.9°C; yield, 80.2%; IR (KBr, cm^{-1}) ν 3327, 3205, 3028, 2919, 1694, 1655, 1619, 1430, 1365, 1266, 1092, 1010, 993; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.51 (s, 3H, CH_3C=N), 4.54 (d, 2H, OCH_2, J = 6.9 Hz), 5.41–5.47 (m, 2H, $CH=CH_2$), 5.95–6.08 (m, 1H, $CH=CH_2$), 6.41 (s, 1H, CH=C), 7.34–7.41 (m, 4H, PhH), 8.05 (s, 1H, NH); MS m/z (%): 318(M^+, 3), 262(100), 210(10), 152(25), 116(15), 83(32), 55(19), 45(31); Anal. Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.02; H, 4.70; N, 8.87.

(Z)-3-((E)-1-(butoxyimino)ethyl)-5-(4-chlorobenzylidene)-4-hydroxy-pyrroline-2-one (6x). Yellow crystal, mp 203.3–207.2°C; yield, 92.4%; IR (KBr, cm^{-1}) ν 3294, 3201, 3019, 2957, 1708, 1679, 1617, 1431, 1367, 1276, 1092, 1010, 974; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.96 (t, 3H, CH_2CH_3, J = 7.5 Hz), 1.40–1.52 (m, 2H, CH_2CH_3), 1.68–1.77 (m, 2H, OCH_2CH_2), 2.55 (s, 3H, CH_3C=N), 4.04 (t, 2H, OCH_2, J = 6.9 Hz), 6.44 (s, 1H, CH=), 7.33–7.40 (m, 4H, PhH), 7.70 (s, 1H, NH); MS m/z (%): 334(M^+, 6), 262(100), 206(42), 152(45), 113(28), 84(59), 57(46), 45(88); Anal. Calcd for $C_{17}H_{19}ClN_2O_3$: C, 60.99; H, 5.72; N, 8.37. Found: C, 60.55; H, 5.79; N, 8.52.

Crystal structure determination. The single crystal of **6e** was selected and glued on the tip of a glass fiber. Both cell dimensions and intensities were measured on a Bruker Smart APEX CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at 296(2) K. θ_{max} = 25.99; 6205 measured reflections; 3113 independent reflections (R_{int} = 0.0385) of which 2421 had $I > 2\delta$ (I). Data was corrected for Lorentz and polarization effects and absorption (T_{min} = 0.9781, T_{max} = 0.9831). Crystal structure was solved by direct methods using the SHELXS-97 program [28]. All nonhydrogen

atoms were refined anisotropically. The C—H hydrogen atoms were positioned geometrically and refined using a riding model. The hydrogen atoms linked to nitrogen and oxygen were located from the difference Fourier map and were set as isotropic. Full-matrix least squares refinement based on F^2 using the weight of $1/[\sigma^2(F_o^2) + (0.1206P)^2 + 0.0717P]$ gave final values of $R = 0.0575$, $\omega R = 0.1770$, and GOF(F) = 1.044. The maximum and minimum difference peaks and holes were 0.352 and –0.381 e $Å^{-3}$, respectively.

The crystallographic data have been deposited with Cambridge crystallographic data center, CCDC No. 734371. Copies of this information can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; or E-mail: deposit@ccdc.cam.ac.uk).

Fungicidal assay. Inhibition effects of the title compounds **6a–x** on phytopathogenic fungi (*Fusarium gramineaum*, *Colletotrichum orbiculare*, and *Rhizoctonia cerealis*) were tested using a radial growth inhibition technique according to literature [29]. Each compound was diluted with 0.5 mL DMF and added to potato sucrose agar medium (PSA), respectively to obtain a concentration of 100 μg/mL immediately before pouring into the petri dishes. Each concentration was tested in triplicate. Parallel controls were maintained with 0.5 mL DMF mixed with PSA medium. The discs of mycelial felt (0.5 cm diameter) of fungi were transferred aseptically to the center of Petri dishes. The treatments were incubated at 25°C in the dark. The diameter of the mycelium was measured after the fungal growth in the control treatments had covered two-thirds of the Petri dishes. The growth inhibition rates were calculated with the following equation: $I = [(C - T)/C] \times 100\%$. Here, I was the growth inhibition rate (%), C was the control settlement radius (mm), and T was the treatment group fungi settlement radius (mm).

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REFERENCES AND NOTES

[1] Royles, B. J. L. Chem Rev 1995, 95, 1981.

[2] Meronuck, R. A.; Steele, J. A.; Mirocha, C. J.; Christensen, C. M. Appl Microbiol 1972, 23, 613.

[3] Satan, U.; Wada, S. I.; Matsunagas, S.; Watabe, S.; Vansoest, R. W. M.; Fusetanin, N. J Org Chem 1999, 64, 2331.

[4] Hopmann, C.; Kurz, M.; Bronstrup, M.; Wink, J.; LeBeller, D. Tetrahedron Lett 2002, 43, 435.

[5] Aoki, S.; Higuchi, K.; Ye, Y.; Satari, R.; Kobayashi, M. Tetrahedron 2000, 56, 1833.

[6] Ohta, E.; Ohta, S.; Ikegami, S. Tetrahedron 2001, 57, 4699.

[7] Motta, S. D.; Soares, L. M. V. Food Chem 2000, 71, 111.

[8] Rosett, B. T.; Sankhala, R. H.; Stickings, C. E.; Taylor, M. E. U.; Thomas, R. Biochem J 1957, 67, 390.

[9] Yuki, H.; Kariya, K.; Hashimoto, Y. Chem Pharm Bull 1967, 15, 727.

[10] Gallardo, G. L.; Pen, N. I.; Chacana, P.; Terzolo, H. R.; Cabrera, G. M. World J Microbiol Biotechnol 2004, 20, 609.

[11] Lebrun, M. H.; Duvert, P.; Gaudemer, F.; Gaudemer, A.; Deballon, C. J Inorg Biochem 1985, 24, 167.

[12] Wan, Z. X.; Qiang, S.; Xu, S. C.; Shen, Z. G.; Dong, Y. F. Chi J Biol Cont 2001, 17, 10.

[13] Gänzle, M. G.; Hoeltzel, A.; Walter, J.; Jung, G.; Hammes, W. P. Appl Environ Microbiol 2000, 66, 4325.

[14] Biersack, B.; Diestel, R.; Jagusch, C.; Sasse, F.; Schobert, R. J Inorg Biochem 2009, 103, 72.

[15] Rainer, S.; Carsten, J. Tetrahedron 2005, 61, 2301.

[16] Yuki, H.; Kaizu, Y.; Yoshida, S.; Higuchi, S.; Honda, S.; Takiure, K. Chem Pharm Bull 1971, 19, 1664.

[17] Zhu, Y. Q.; Zou, X. M.; Hu, F. Z.; Yao, C. S.; Liu, B.; Yang, H. Z. J Agric Food Chem 2005, 53, 9566.

[18] Dai, H.; Li, Y. Q.; Du, D.; Qin, X.; Zhang, X.; Yu, H. B.; Fang, J. X. J Agric Food Chem 2008, 56, 10805.

[19] Liu, A. P.; Yao, J. R. Chi J Pesitic 2004, 43, 196.

[20] Fan, L.; Cui, J. G.; Wei, Y. L.; Huang, Y. M. Mod Agrochem 2008, 7, 6.

[21] Tatsuaki, Y.; Seisuke, Y.; Sadao, H.; Yohko, S.; Kimitoshi, S.; Hidetaka, Y. Pharm Soc Jpn 1981, 101, 125.

[22] Giorgos, A.; Efstathios, G.; Olga, I. M. J Heterocycl Chem 2001, 38, 1203.

[23] Harris, S. A.; Fisher, L. V.; Folkers, K. J Med Chem 1965, 8, 478.

[24] Du, Z. T.; Yue, G. R.; Ma, J. Y.; Wu, T. X.; Pan, X. F. Chem Reagents 2004, 26, 117.

[25] Wu, Y. X.; Dai, L.Y. Chi J Pestic 2004, 43, 113.

[26] Lu, J. The synthesis of a series of O-substituted hydroxylamines. M. Sc. Dissertation, Zhejiang University, China, 2006.

[27] Han, S. D.; Wang, G. C.; Li, F. Zhejiang Chemical Industry 2005, 36, 14.

[28] Sheldrick, G. M. SHELXS-97, Program for crystal structure solution; University of Göttingen: Göttingen, Germany, 1997.

[29] Chen, X.; Yang, C. L. J Agric Food Chem 2009, 57, 2441.