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Synthesis, Characterization and Biological Activities of Novel (*E*)-3-(1-(Alkyloxyamino)ethylidene)-1-alkylpyrrolidine-2,4-dione Derivatives

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Twenty novel tetramic acid derivatives (*E*)-3-(1-(alkyloxyamino)ethylidene)-1-alkylpyrrolidine-2,4-diones were synthesized by the reaction of 3-(1-hydroxyethylidene)pyrrolidine-2,4-diones with *O*-alkyl hydroxylamines. The title compounds were confirmed by IR, ^{1}H NMR, MS and elemental analysis. The structure of compound **6r** was further verified by X-ray diffraction crystallography. The bioassays showed that most of the title compounds exhibited noticeable herbicidal and fungicidal activities.

Key Words: Pyrrolidine-2,4-dione, Oxime ether, Synthesis, Crystal structure, Biological activity

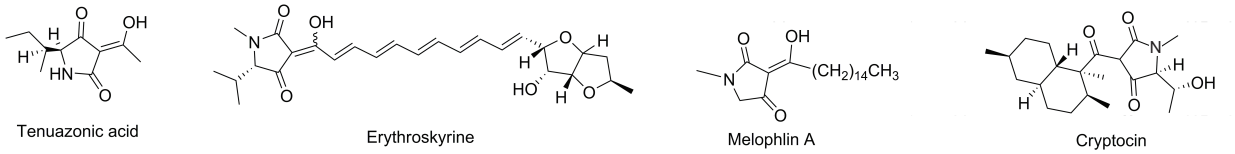
Introduction

To study the active material of natural products such as nicotine, toosendanin, pyrethrum, and essential oil of *Caesulia axillaris etc*.,[1-4] is very common in the field of medicinal chemistry. Pyrrolidine-2,4-dione (also known as tetramic acid) is one of the outstanding kinds of natural compounds, some naturally bioactive tetramic acids could be seen in Scheme 1.[5-8] Thereinto, tenuazonic acid (or TeA for short), a metabolic toxin from widely differing phytopathogenic fungi, has been found possessing herbicidal, antibacterial, and antitumor activities,[9-11] it has evoked many chemist's great interest. Up to now, multifarious tenuazonic acid derivatives have been synthesized to screen out new compounds with biological activity. For example, a series of 3-(*α*-hydroxy-benzylidene)pyrrolidine-2,4-dione derivatives were reported displaying high herbicidal activity,[12] another kind of tenuazonic acid derivatives with oxime ether moiety were presented showing obvious herbicidal and antifungal activities simultaneously.[13]

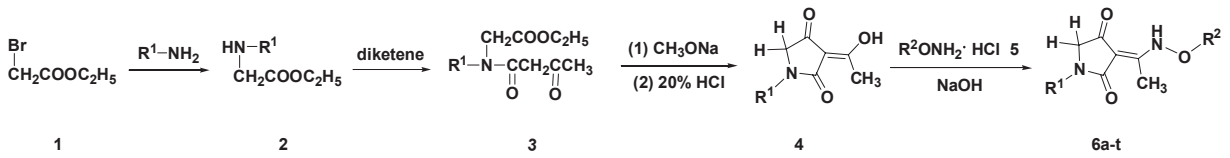
As an important kind of pesticides the oxime ether derivatives have been applied as insecticides, fungicides, and herbicides. Sulfoxime is a new insecticide with a structure of propiophenone oxime ether, having the characteristics of high activity, low toxicity, and low residue.[14] Cymoxan is the first oxime ether fungicide commercialized by DuPont.[15] And the first cyclohexanedione herbicide, alloxydim-sodium, with a oxime ether group, is a postemergence herbicide providing excellent control of a wide range of grass weeds.[16] In this article, alkyl and *cyclo*-alkyl were introduced to the 1-position of the heterocycle pyrrolidine-2,4-dione respectively, instead of substituted phenyl or hydrogen reported by Zhu,[13] to design and synthesize a series of novel tetramic acid derivatives with oxime ether moiety at 3-position. Moreover, these synthesized title compounds were tested to evaluate their herbicidal and fungicidal activities.

Results and Discussion

Synthesis. The title compounds **6a-t** were synthesized by the



Scheme 1. Some bioactive naturally existing tetramic acids



R^1: **6a-e** = *i*-C_3H_7, **6f-j** = *n*-C_4H_9, **6k-o** = *t*-C_4H_9, **6p-t** = *cyclo*-C_6H_{11}.
R^2: **6a**, **6f**, **6k**, **6p** = *n*-C_3H_7, **6b**, **6g**, **6l**, **6q** = *i*-C_3H_7, **6c**, **6h**, **6m**, **6r** = CH_2-CH=CH_2, **6d**, **6i**, **6n**, **6s** = *n*-C_4H_9, **6e**, **6j**, **6o**, **6t** = $CH_2C_6H_5$.

Scheme 2. The synthetic route and the structures of title compounds

reaction of 1-alkyl-3-(1-hydroxyethylidene)pyrrolidine-2,4-diones **4** with *O*-alkyl hydroxylamines **5** in the presence of sodium hydroxide. The detailed synthetic route and the structures of title compounds are shown in Scheme 2.

Intermediates **4** were prepared according to the method including three steps. Firstly, ethyl bromoacetate was reacted with amine in ether to obtain ethyl 2-(alkylamino)acetate **2**. Then the treatment of compound **2** with diketene under low temperature formed ethyl 2-(*N*-alkyl-3-oxo-butyramido)acetate **3**, which was cyclized in the presence of sodium methoxide and acidified with hydrochloric acid to obtain intermediates **4**.[17] The intermediates **5** *O*-propyl, *O*-isopropyl, *O*-allyl, *O*-butyl, and *O*-benzyl hydroxylamine hydrochlorides were synthesized with starting materials ethyl acetate and hydroxylamine hydrochloride via a facile three-step procedure including acetylamination, etherification and hydrolyzation.[18,19]

Structure. In the IR spectra of the title compound **6** there were relatively strong absorption bands for the carbonyls at around 1680 cm^{-1} and 1635 cm^{-1} respectively. The stretching vibration absorption peak of N-H group existed at 3100 - 3182 cm^{-1}. In the ^{1}H NMR spectra of **6a-t**, the singlet at δ_H 3.57 - 3.76 assigned to the C-H proton of NCH_2 and singlet at δ_H 2.40 - 2.54 assigned to the C-H protons of $CH_3C{=}N$. Furthermore, the MS spectra of all the compounds **6** showed the molecular ion peak (M^+, 12 - 100%), and other fragmentation ions were consistent with their structures and could be clearly assigned. The data of measured elemental analyses were also consistent with the corresponding calculated ones.

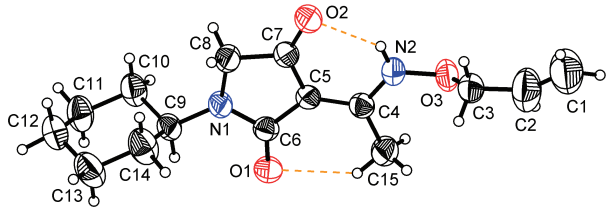


Figure 1. Molecular structure of compound **6r**.

In the crystal structure of compound **6r** (Figure 1), the bond C(4)-C(5) [1.395(4) Å], which was close to C=C double bond [1.38 Å], exhibited C=C double bond' property. The bond lengths C(4)-N(2) and C(6)-N(1) were [1.319(3) Å] and [1.367(3) Å] which were shorter than the normal C-N bond distance [1.47-1.50 Å]. The bond lengths C(5)-C(7) and C(5)-C(6) were [1.411 (4) Å] and [1.466(4)Å], they were shorter than C-C single bond distance [1.54 Å]. The bonds C(6)-O(1) and C(7)-O(2) [1.227 (4) Å and 1.236(4) Å, respectively], approaching to the normal C=O double bond distance [1.19 - 1.23 Å], displayed the property of C=O double bond. As a result, there was a electron delocalization between C(4)-C(5)-C(6)-N(1) and C(7), and a conjugated system was accordingly formed with C(6)=O(1), C(7)=O(2).

It is noteworthy that there existed intramolecular H-bondings between N(2)-H(2A)···O(2) and C(15)-H(15B)···O(1) to keep the balance of the molecular structure. In the packing diagram of compound **6r** (Figure 2), the molecules were connected each other through intermolecular H-bondings among N(2)-H(2A)···O(2), C(3)-H(3A)···O(1), and C(3)-H(3B)···O(2) to form a saw-toothed configuration. What's more, the molecular structure of compound **6r** showed *E* configuration of the ethylidene group and the dione structure of pyrrolidine. The crystal and refinement details of compound **6r** could be seen in Table 1.

The compounds containing the group of tetramic acid usually tautomerize their structures between ketone form and enol form.[20] The spectroscopic analysis especially X-ray diffraction crystallography revealed that the title compounds' structure belonged under ketone form. On contray to this, 3-(1-(alkyloxyimino)ethyl)-5-arylidene-4-hydroxypyrroline-2-one derivatives, another oxime ether of tetramic acid, exist in enol form.[21] By our recent research, it was found that there might be crucial relationship between tautomers and their biological activities, the title compounds exhibited noticeable herbicidal and fungicidal activities simultaneity, but above mentioned 4-hydroxypyrroline-2-one derivatives showed only fungicidal activity.[21] This deduction provided an important guidance for further studies on structural modification of tetramic acid derivatives.

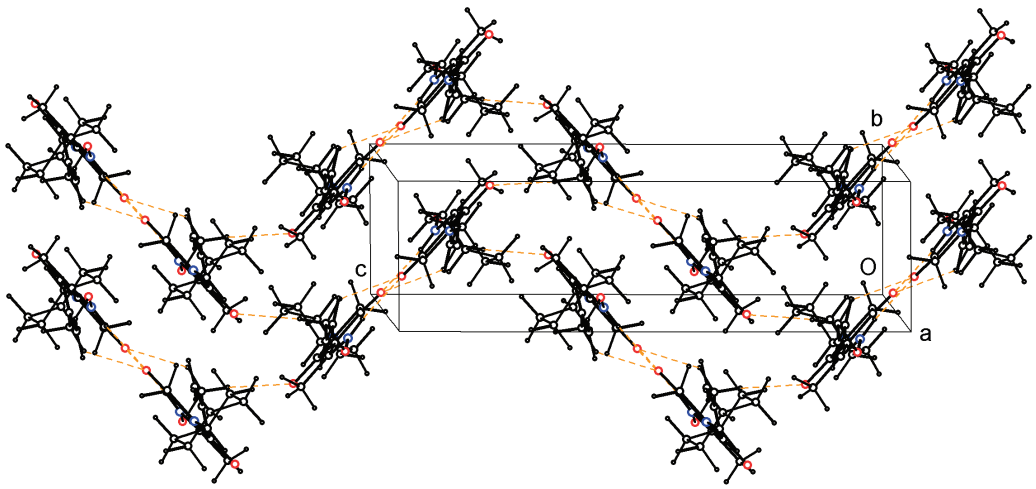


Figure 2. Packing diagram of compound **6r** showing the intermolecular interactions.

Table 1. Crystal data and refinement details for compound **6r**

Empirical formula	$C_{15}H_{22}N_2O_3$
Formula weight	278.350
Wavelength (Å)	0.71073
Temperature (K)	296(2)
Color, Shape	Colorless, Block
Crystal system	Monoclinic
space group	*C*2/*c*
a (Å)	32.778(9)
b (Å)	5.1948(14)
c (Å)	18.025(5)
α (°)	90.000
β (°)	102.734(3)
γ (°)	90.000
V (Å^3)	2993.7(14)
Z	8
D_{calc} (g cm^{-3})	1.235
F (000)	1200
μ (mm^{-1})	0.086
Crystal size (mm)	0.30 × 0.26 × 0.24
θ Range (°)	2.32-26.00
Reflection collected	10958
Independent reflections	2944
Data/restraints/parameters	2944/1/182
Goodness-of-fit on F^2	1.000
R indices (all data)	$R_1 = 0.0822$, $wR_2 = 0.1613$
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0678$, $wR_2 = 0.1565$

Experimental

The melting points of the products were determined on a WRS-1B digital melting-point apparatus and were not corrected. IR was recorded on a Bruker Tensor 27 FT-IR spectrometer with KBr disk. Elemental analyses were performed on a Elementar Vario-III CHN analyzer. Mass spectra was 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 $CDCl_3$ 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 prior to use as needed.

General procedure for the synthesis of 1-alkyl-3-(1-hydroxyethylidene)pyrrolidine-2,4-diones 4. The solution of amine (0.3 mol) in ether (50 mL) was cooled to 0 °C and ethyl bromoacetate was added gently in 2 h. Then the reaction mixture was stirred for 12 h at room temperature. After filtering and washing with ether, the filtrate was gradually removed by evaporation under vacuum to give the liquid product ethyl 2-(alkylamino)acetate.

Whereafter, ethyl 2-(alkylamino) acetate (0.12 mol) was dissolved in benzene (50 mL), cooled to 10 °C, added diketene (0.12 mol) slowly in 1 h and stirred for 10 h at room temperature. Then the solution of sodium methoxide (0.12 mol) in 40 mL methanol was added and refluxed for 4 h. By evaporation under vacuum the solvent was removed and 100 mL water was added, the impurities were extracted with ether (25 mL × 3) for three times, the aqueous layer was acidified to pH = 2 - 3 with 20% hydrochloric acid to obtain white solid, which was precipitated, filtered off, dried, recrystallized with ethyl acetate to get intermediates **4** in yield 43.2% - 62.1%.

3-(1-Hydroxyethylidene)-1-isopropylpyrrolidine-2,4-dione (4a): white solid; mp 75.8 - 76.7 °C; yield, 52.0%; IR (KBr, cm^{-1}) *v* 2977, 1716, 1636, 1468, 1381, 1247, 1229, 976; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (d, *J* = 6.6, 6H, $2CH_3$), 2.43 (s, 3H, $COCH_3$), 3.66 (s, 2H, CH_2), 4.47 - 4.56 (m, 1H, NCH); Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.35; H, 7.10; N, 7.72.

1-Butyl-3-(1-hydroxyethylidene)pyrrolidine-2,4-dione (4b): white solid; mp 28.6 - 29.3 °C; yield, 43.2%; IR (KBr, cm^{-1}) *v* 2961, 2871, 1714, 1630, 1481, 1378, 1247; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, *J* = 7.2, 3H, CH_2CH_3), 1.32 - 1.34 (m, 2 H, CH_2CH_3), 1.52 - 1.54 (m, 2H, CH_2CH_2), 2.42 (s, 3H, $COCH_3$), 3.42 (t, *J* = 7.2, 2H, NCH_2CH_2), 3.70 (s, 2H, CH_2); Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.53; H, 7.60; N, 7.19.

1-*tert*-Butyl-3-(1-hydroxyethylidene)pyrrolidine-2,4-dione (4c): white solid; mp 54.4 - 55.5 °C; yield, 62.1%; IR (KBr, cm^{-1}) *v* 2985, 1715, 1635, 1480, 1380, 1356, 1216; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H, 3 × CH_3), 2.42 (s, 3H, $COCH_3$), 3.77 (s, 2H, CH_2); Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.32; H, 7.59; N, 7.15.

1-Cyclohexyl-3-(1-hydroxyethylidene)pyrrolidine-2,4-dione (4d): white solid; mp 106.0 - 106.8 °C; yield, 51.1%; IR (KBr, cm^{-1}) *v* 2939, 2859, 1717, 1640, 1472, 1374, 1251; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 - 1.88 (m, 10H, C_6H_{10}), 2.44 (s, 3H, $COCH_3$), 3.68 (s, 2H, NCH_2), 4.04 - 4.16 (m, 1H, NCH); Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.11; H, 7.58; N, 6.37.

General procedure for the preparation of the title ompounds 6a-t. To the compound **4** (1.5 mmol) and *O*-substituted hydroxylamine hydrochloride **5** (2.1 mmol) in ethanol (25 mL) was added 2% NaOH (4.4 mL). Then the solution was refluxed and monitored on TLC. After the reaction completed, water (50 mL) was added, the organic layer was extracted with ethyl acetate, dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. Recrystallization from ether afforded the corresponding compounds **6a-t**.

(*E*)-1-Isopropyl-3-(1-(propoxyamino)ethylidene)pyrrolidine-2,4-dione (6a): colorless crystal; mp 31.0 - 32.4 °C; yield, 86.2%; IR (KBr, cm^{-1}) *v* 3156, 2971, 2878, 1680, 1633, 1577, 1453, 1402, 1237, 1063 ; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.13 (d, *J* = 6.3 Hz, 6H, $CH(CH_3)_2$), 1.69 - 1.76 (m, 2H, OCH_2CH_2), 2.54 (s, 3H, CH_3C=), 3.63 (s, 2H, NCH_2), 3.92 (t, *J* = 6.7 Hz, 2H, OCH_2), 4.48 - 4.51 (m, 1H, $CH(CH_3)_2$); MS *m*/*z* (%): 240(M^+, 75), 225(100), 166(58), 139 (31), 124(18), 84(25), 56(46); Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 60.42; H, 8.30; N, 11.76.

(*E*)-3-(1-(Isopropoxyamino)ethylidene)-1-isopropylpyrrolidine-2,4-dione (6b): damask viscous liquid; yield, 91.2%; IR (KBr, cm^{-1}) *v* 3156, 2975, 2933, 1681, 1633, 1578, 1454, 1238, 1113, 1063; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, *J* = 6.6 Hz,

6H, NCH(C*H*$_3$)$_2$), 1.28 (d, *J* = 6.6 Hz, 6H, OCH(C*H*$_3$)$_2$), 2.52 (s, 3H, CH_3C=), 3.61 (s, 2H, NCH_2), 4.10 - 4.14 (m, 1H, OC*H*(CH$_3$)$_2$), 4.45 - 4.48 (m, 1H, NC*H*(CH$_3$)$_2$); MS *m*/*z* (%): 240(M^+, 70), 225(42), 183(100), 139(23), 124(18), 70(20), 56(34); Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 60.32; H, 8.45; N, 11.74.

(*E*)-3-(1-(Allyloxyamino)ethylidene)-1-isopropylpyrrolidine-2,4-dione (6c): colorless powder; mp 45.3 - 46.2 °C; yield, 75.4%; IR (KBr, cm^{-1}) *v* 3102, 2972, 2930, 1680, 1633, 1574, 1452, 1400, 1238, 1127; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 2.51 (s, 3H, CH_3C=), 3.63 (s, 2H, NCH_2), 4.44 - 4.50 (m, 3H, NC*H*(CH$_3$)$_2$ + OC*H*$_2$), 5.38 - 5.44 (m, 2H, CH=C*H*$_2$), 5.89 - 6.02 (m, 1H, C*H*=CH$_2$); MS *m*/*z* (%): 238 (M^+, 100), 223(83), 167(98), 139(62), 124(33), 84(31), 56 (82); Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.21; H, 7.53; N, 11.81.

(*E*)-3-(1-(Butoxyamino)ethylidene)-1-isopropylpyrrolidine-2,4-dione (6d): colorless powder; mp 48.0 - 48.9 °C; yield, 81.6%; IR (KBr, cm^{-1}) *v* 3162, 2966, 2874, 1682, 1643, 1577, 1453, 1401, 1238, 1064; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, *J* = 7.3 Hz, 3H, CH_2CH_3), 1.13 (d, *J* = 6.9 Hz, 6H, CH(C*H*$_3$)$_2$), 1.37 - 1.48 (m, 2H, C*H*$_2$CH$_3$), 1.62 - 1.72 (m, 2H, OCH$_2$C*H*$_2$), 2.53 (s, 3H, CH_3C=), 3.63 (s, 2H, NCH_2), 3.92 (t, *J* = 6.7 Hz, 2H, OCH_2), 4.44 - 4.52 (m, 1H, C*H*(CH$_3$)$_2$); MS *m*/*z* (%): 254 (M^+, 78), 239(100), 167(44), 149(82), 139(32), 69(30), 57(36); Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.01; H, 8.65; N, 11.09.

(*E*)-3-(1-(Benzyloxyamino)ethylidene)-1-isopropylpyrrolidine-2,4-dione (6e): colorless crystal; mp 111.3 - 112.2 °C; yield, 83.5%; IR (KBr, cm^{-1}) *v* 3182, 3035, 2968, 2925, 1664, 1624, 1575, 1454, 1398, 1320, 1176; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (d, *J* = 6.3 Hz, 6H, CH(C*H*$_3$)$_2$), 2.43 (s, 3H, CH_3C=), 3.65 (s, 2H, NCH_2), 4.43 - 4.51 (m, 1H, C*H*(CH$_3$)$_2$), 4.95 (s, 2H, OCH_2), 7.39 (m, 5H, PhH); MS *m*/*z* (%): 288 (M^+, 17), 167(43), 106(20), 91(100), 77(33), 56(17); Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.18; H, 6.85; N, 9.87.

(*E*)-1-Butyl-3-(1-(propoxyamino)ethylidene)pyrrolidine-2,4-dione (6f): damask viscous liquid; yield, 93.5%; IR (KBr, cm^{-1}) *v* 3149, 2962, 2930, 2872, 1682, 1636, 1577, 1457, 1238, 1065; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 - 0.95 (m, 6H, 2 × CH_2CH_3), 1.22 - 1.69 (m, 6H, 3 × CH_2), 2.49 (s, 3H, CH_3C=), 3.30 (t, *J* = 6.6 Hz, 2H, NC*H*$_2$CH$_2$), 3.57 (s, 2H, NCH_2), 3.80 (t, *J* = 6.3 Hz, 2H, OCH_2); MS *m*/*z* (%): 254 (M^+, 57), 211(54), 169(100), 153(25), 112(26), 69(10), 57(9); Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.83; H, 8.86; N, 10.92.

(*E*)-1-Butyl-3-(1-(isopropoxyamino)ethylidene)pyrrolidine-2,4-dione (6g): damask viscous liquid; yield, 84.6%; IR (KBr, cm^{-1}) *v* 3162, 2963, 2930, 1680, 1635, 1578, 1458, 1375, 1239, 1112; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.23 (d, *J* = 6.0 Hz, 6H, CH(C*H*$_3$)$_2$), 1.24 - 1.50 (m, 4H, 2 × CH_2), 2.47 (s, 3H, CH_3C=), 3.30 (t, *J* = 6.3 Hz, 2H, NC*H*$_2$CH$_2$), 3.58 (s, 2H, NCH_2), 4.04 - 4.14 (m, 1H, OC*H*(CH$_3$)$_2$); MS *m*/*z* (%): 254 (M^+, 65), 211(51), 169(100), 153(34), 112(28), 45(21); Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.02; H, 8.81; N, 10.95.

(*E*)-3-(1-(Allyloxyamino)ethylidene)-1-butylpyrrolidine-2,4-dione (6h): damask viscous liquid; yield, 85.1%; IR (KBr, cm^{-1}) *v* 3121, 2960, 2932, 1684, 1636, 1575, 1457, 1368, 1239, 1026; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.25 - 1.38 (m, 2H, C*H*$_2$CH$_3$), 1.46 - 1.55 (m, 2H, NCH_2CH_2), 2.52 (s, 3H, CH_3C=), 3.34 (t, *J* = 6.6 Hz, 2H, NC*H*$_2$CH$_2$), 3.70 (s, 2H, NCH_2), 4.44 (d, *J* = 6.3 Hz, 2H, OCH_2), 5.24 - 5.45 (m, 2H, CH=C*H*$_2$), 5.90 - 6.03 (m, 1H, C*H*=CH$_2$); MS *m*/*z* (%): 252 (M^+, 50), 209(62), 153(100), 149(71), 112(26), 69(62), 57(78); Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.39; H, 7.85; N, 10.97.

(*E*)-3-(1-(Butoxyamino)ethylidene)-1-butylpyrrolidine-2,4-dione (6i): damask viscous liquid; yield, 89.7%; IR (KBr, cm^{-1}) *v* 3111, 2960, 2931, 1684, 1637, 1577, 1457, 1371, 1268, 1070; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 - 0.95 (m, 6H, 2 × CH_3), 1.26 - 1.70 (m, 8H, 4 × CH_2), 2.51 (s, 3H, CH_3C=), 3.32 (t, *J* = 7.2 Hz, 2H, NC*H*$_2$CH$_2$), 3.66 (s, 2H, NCH_2), 3.91 (t, *J* = 6.7 Hz, 2H, OCH_2); MS *m*/*z* (%): 268 (M^+, 53), 225(100), 195(25), 153 (77), 112(23), 84(22), 57(28); Anal. Calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01; N, 10.44. Found: C, 62.22; H, 8.90; N, 10.41.

(*E*)-3-(1-(Benzyloxyamino)ethylidene)-1-butylpyrrolidine-2,4-dione (6j): colorless powder; mp 52.9 - 53.9 °C; yield, 92.4%; IR (KBr, cm^{-1}) *v* 3141, 3032, 2958, 2930, 1680, 1635, 1573, 1455, 1367, 1239; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.25 - 1.37 (m, 2H, C*H*$_2$CH$_3$), 1.45 - 1.55 (m, 2H, NCH_2CH_2), 2.43 (s, 3H, CH_3C=), 3.32 (t, *J* = 7.2 Hz, 2H, NC*H*$_2$CH$_2$), 3.68 (s, 2H, NCH_2), 4.95 (s, 2H, OCH_2), 7.39 (m, 5H, PhH); MS *m*/*z* (%): 302 (M^+, 12), 196(10), 153 (26), 91(100), 77(24); Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.24; H, 7.40; N, 9.31.

(*E*)-1-*tert*-Butyl-3-(1-(propoxyamino)ethylidene)pyrrolidine-2,4-dione (6k): damask viscous liquid; yield, 84.5%; IR (KBr, cm^{-1}) *v* 3164, 2969, 2934, 1680, 1630, 1579, 1445, 1366, 1229, 1065; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.39 (s, 9H, $(CH_3)_3C$), 1.65 - 1.78 (m, 2H, C*H*$_2$-CH_3), 2.44 (s, 3H, CH_3C=), 3.70 (s, 2H, NCH_2), 3.83 - 4.87 (t, *J* = 6.6 Hz, 2H, OCH_2); MS *m*/*z* (%): 254 (M^+, 92), 239(100), 180(51), 139(95), 111(40), 83(42), 70(736), 57(48); Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.64; H, 8.60; N, 11.06.

(*E*)-1-*tert*-Butyl-3-(1-(isopropoxyamino)ethylidene)pyrrolidine-2,4-dione (6l): colorless powder; mp 100.4 - 101.2 °C; yield, 85.6%; IR (KBr, cm^{-1}) *v* 3100, 2975, 2939, 1656, 1622, 1570, 1361, 1322, 1233, 1058; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (d, *J* = 6.3 Hz, 6H, CH(C*H*$_3$)$_2$), 1.41 (s, 9H, $(CH_3)_3C$), 2.50 (s, 3H, CH_3C=), 3.73 (s, 2H, NCH_2), 4.10 - 4.17 (m, 1H, C*H*(CH$_3$)$_2$); MS *m*/*z* (%): 254(M^+, 47), 239(56), 181(81), 156(73), 139(100), 70(56), 45(95); Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.48; H, 8.76; N, 10.95.

(*E*)-3-(1-(Allyloxyamino)ethylidene)-1-*tert*-butylpyrrolidine-2,4-dione (6m): colorless crystal; mp 72.1 - 73.2 °C; yield, 81.9%; IR (KBr, cm^{-1}) *v* 3109, 2974, 2926, 1679, 1630, 1576, 1443, 1365, 1228, 1162, 1052; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H, $(CH_3)_3C$), 2.47 (s, 3H, CH_3C=), 3.76 (s, 2H, NCH_2), 4.43 (m, 1H, CH=C*H*$_2$), 5.36 (d, 2H, *J* = 6.3 Hz, OCH_2), 5.88 - 6.02 (m, 1H, C*H*=CH$_2$); MS *m*/*z* (%): 252 (M^+, 44), 237(53), 181(100), 155(31), 84(43), 70(66), 57(81); Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 62.07; H, 8.06; N, 10.97.

(*E*)-3-(1-(Butoxyamino)ethylidene)-1-*tert*-butylpyrrolidine-

Table 2. Herbicidal and antifungal activities of compounds **6a-t** (100 μg/mL, inhibitory rate percent)

compd.	*Ratio*(%)					
	B. campestris	*E. crusgalli*		*F. graminearum*	*R. cerealis*	*C. orbiculare*
	Root	Root	Stem			
6a	40.8 ± 4.8	64.1 ± 2.6	2.6 ± 3.4	14.8 ± 1.5	34.1 ± 2.4	27.5 ± 1.9
6b	29.4 ± 1.5	26.0 ± 3.2	8.2 ± 1.7	18.6 ± 0.5	35.8 ± 1.4	31.7 ± 2.6
6c	44.2 ± 3.2	85.5 ± 1.8	14.3 ± 2.4	14.8 ± 1.3	39.2 ± 2.3	42.1 ± 0.4
6d	39.0 ± 3.5	88.1 ± 1.6	0	26.7 ± 0.2	59.1 ± 1.8	52.1 ± 1.5
6e	41.5 ± 4.9	69.4 ± 0.9	0	29.1 ± 0.8	46.6 ± 1.6	50.0 ± 2.3
6f	61.8 ± 5.3	41.7 ± 3.3	0	42.9 ± 1.2	47.4 ± 0.8	57.5 ± 2.2
6g	60.0 ± 5.1	36.8 ± 3.7	0	23.8 ± 2.6	42.7 ± 2.0	37.1 ± 1.2
6h	52.4 ± 2.0	75.7 ± 1.9	0	29.1 ± 0.4	44.0 ± 1.4	67.5 ± 0.9
6i	73.5 ± 0.5	85.1 ± 0.9	0	31.4 ± 2.5	55.2 ± 0.7	55.0 ± 1.8
6j	45.4 ± 2.1	48.9 ± 3.0	0	50.5 ± 3.6	57.8 ± 2.8	68.8 ± 1.5
6k	46.8 ± 4.7	47.2 ± 2.5	0	12.3 ± 0.5	41.1 ± 4.3	45.0 ± 2.4
6l	28.9 ± 4.5	54.8 ± 1.7	0	10.3 ± 1.3	26.0 ± 3.1	62.5 ± 2.6
6m	45.7 ± 3.5	70.5 ± 1.3	0	16.4 ± 0.5	53.4 ± 2.6	70.0 ± 2.7
6n	67.0 ± 1.3	54.5 ±2.8	8.3 ± 4.1	12.3 ± 1.9	63.0 ± 1.2	63.0 ± 1.0
6o	44.2 ± 5.6	41.6 ± 2.4	8.6 ± 3.6	22.6 ± 1.5	58.0 ± 2.4	66.0 ± 4.2
6p	74.7 ± 2.0	80.5 ± 4.2	0	19.6 ± 1.8	42.8 ± 3.1	44.0 ± 3.6
6q	54.2 ± 2.5	66.8 ± 4.1	0	20.4 ± 5.2	20.9 ± 0.8	30.7 ± 2.9
6r	57.3 ± 3.9	80.7 ± 1.3	0	15.0 ± 2.7	28.4 ± 1.6	63.9 ± 5.1
6s	78.1 ± 4.0	85.2 ± 2.5	0	31.4 ± 3.2	48.3 ± 4.1	52.7 ± 2.6
6t	37.0 ± 2.9	16.4 ± 3.5	0	43.6 ± 2.0	23.9 ± 1.3	50.2 ± 1.6
TeA	92.3 ± 2.1	97.8 ± 0.4	43.1 ± 2.9	10.0 ± 1.7	16.1 ± 3.1	14.5 ± 3.0

The values are expressed as means ± SD of the replicates; n = 3 for all groups.

2,4-dione (6n): damask viscous liquid; yield, 93.8%; IR (KBr, cm^{-1}) *v* 3127, 2961, 2934, 1680, 1630, 1578, 1444, 1365, 1228, 1069; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 1.40 (s, 9H, $(CH_3)_3C$), 1.33 - 1.40 (m, 2H, CH_2-CH_3), 1.59 - 1.66 (m, 2H, OCH_2CH_2), 2.50 (s, 3H, CH_3C=), 3.67 (s, 2H, NCH_2), 3.90 (t, *J* = 6.2 Hz, 2H, OCH_2); MS *m*/*z* (%): 268 (M^+, 65), 253(100), 149(84), 139(73), 70(64), 57(73); Anal. Calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01; N, 10.44. Found: C, 63.07; H, 9.06; N, 10.52.

(*E*)-3-(1-(Benzyloxyamino)ethylidene)-1-*tert*-butylpyrrolidine-2,4-dione (6o): colorless crystal; mp 98.6 - 99.5 °C; yield, 95.3%; IR (KBr, cm^{-1}) *v* 3142, 3084, 2969, 2934, 1680, 1630, 1579, 1445, 1366, 1229, 1065; ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.42 (s, 9H, $(CH_3)_3C$), 2.40 (s, 3H, CH_3C=), 3.76 (s, 2H, NCH_2), 4.96 (s, 2H, OCH_2), 7.38 (m, 5H, PhH); MS *m*/*z* (%): 302 (M^+, 18), 287(10), 181(14), 91(100), 77(11); Anal. Calcd for $C_{17}H_{22}$-N_2O_3: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.93; H, 7.40; N, 9.32.

(*E*)-1-Cyclohexyl-3-(1-(propoxyamino)ethylidene)pyrrolidine-2,4-dione (6p): colorless powder; mp 71.3 - 72.1 °C; yield, 76.7%; IR (KBr, cm^{-1}) *v* 3177, 2972, 2855, 1663, 1624, 1574, 1456, 1397, 1326, 1233, 1068; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.25 - 1.37 (m, 2H, OCH_2CH_2), 1.61 - 1.73 (m, 10H, 5 × CH_2), 2.50 (s, 3H, CH_3C=), 3.60 (s, 2H, NCH_2), 3.87 (t, *J* = 6.5 Hz, 2H, OCH_2), 4.00 - 4.10 (m, 1H, NC*H*); MS *m*/*z* (%): 280 (M^+, 42), 221(56), 149(69), 113(33), 81(47), 69(54), 45(100); Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.63; H, 8.50; N, 10.05.

(*E*)-1-Cyclohexyl-3-(1-(isopropoxyamino)ethylidene)pyrrolidine-2,4-dione (6q): colorless crystal; mp 68.8 - 69.6 °C; yield, 86.3%; IR (KBr, cm^{-1}) *v* 3118, 2981, 2930, 1666, 1634, 1575, 1450, 1336, 1264, 1222, 1118, 1011; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, *J* = 6.3 Hz, 6H, $CH(CH_3)_2$), 1.35 - 1.80 (m, 10H, 5 × CH_2), 2.52 (s, 3H, CH_3C=), 3.63 (s, 2H, NCH_2), 4.02 - 4.12 (m, 2H, NC*H* + C*H*$(CH_3)_2$); MS *m*/*z* (%): 280 (M^+, 86), 221(100), 156(48), 139(72), 112(12), 81(25), 55(47); Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.69; H, 8.69; N, 10.06.

(*E*)-3-(1-(Allyloxyamino)ethylidene)-1-cyclohexylpyrrolidine-2,4-dione (6r): colorless crystal; mp 83.0 - 84.1 °C; yield, 82.4%; IR (KBr, cm^{-1}) *v* 3116, 2929, 2852, 1670, 1626, 1578, 1448, 1392, 1318, 1179, 1071; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (m, 10H, 5 × CH_2), 2.53 (s, 3H, CH_3C=), 3.73 (s, 2H, NCH_2), 4.03 - 4.04 (m, 1H, NCH), 4.03 (t, *J* = 6.3 Hz, 2H, OCH_2), 5.40 - 5.46 (m, 2H, CH=CH_2), 5.90 - 6.03 (m, 1H, C*H*=CH_2); MS *m*/*z* (%): 278 (M^+, 44), 222(76), 179(87), 140(10), 124(31), 83(55), 55(76); Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 65.01; H, 8.04; N, 10.16.

(*E*)-3-(1-(Butoxyamino)ethylidene)-1-cyclohexylpyrrolidine-2,4-dione (6s): colorless crystal; mp 67.4 - 68.2 °C; yield, 89.0%; IR (KBr, cm^{-1}) *v* 3154, 2932, 2855, 1666, 1626, 1577, 1452, 1393, 1328, 1231, 1068; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 1.28 - 1.80 (m, 14H, 7 × CH_2), 2.53 (s, 3H, CH_3C=), 3.65 (s, 2H, NCH_2), 3.92 (t, *J* = 6.0 Hz, 2H, OCH_2), 4.03 - 4.07 (m, 1H, NCH); MS *m*/*z* (%): 294 (M^+, 68), 221(100), 179(43), 139(68), 112 (26), 83(31), 55(52); Anal.

Calcd for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90; N, 9.52. Found: C, 64.91; H, 8.84; N, 9.46.

(*E*)-3-(1-(Benzyloxyamino)ethylidene)-1-cyclohexylpyrrolidine-2,4-dione (6t): colorless crystal; mp 121.4 - 122.5 °C; yield, 90.6%; IR (KBr, cm^{-1}) *v* 3172, 3036, 2927, 2853, 1667, 1620, 1574, 1449, 1396, 1261, 1228, 1059; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 - 1.80 (m, 10H, 5 × CH_2), 2.42 (s, 3H, CH_3C=), 3.64 (s, 2H, NCH_2), 4.00 - 4.05 (m, 1H, NCH), 4.94 (s, 2H, OCH_2), 7.38 (m, 5H, PhH); MS *m*/*z* (%): 328 (M^+, 13), 222(51), 179(86), 140(81), 91(95), 77(100), 51(46); Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.05; H, 7.41; N, 8.42.

Biological Evaluation

The title compounds were evaluated for their herbicidal activities in Petri plates against *Echinochloa crusgalli* and *Brassica campestris* according to a modified method.[22] The results as shown in Table 2 indicated that all the compounds displayed obvious inhibition activities against the roots of two tested plants at the concentration of 100 μg/mL. The inhibitory rates of the compounds **6i**, **6p** and **6s** against the root of *B. campestris* exceeded 70%, and the inhibitory rate of the compounds **6c**, **6d**, **6i**, **6p**, **6r** and **6s** against the root of *E. crusgalli* were over 80%.

In addition, the fungicidal activities of the title compounds in vitro against *Fusarium graminearum*, *Rhizoctonia cerealis* and *Colletotrichum orbiculare* were tested by using a mycelia growth inhibition technique according to the literature.[23] As Table 2 shown, almost all the compounds exhibited higher fungicidal activities than TeA at the concentration of 100 μg/mL. Thereinto, the compound **6j** presented best fungicidal activities with inhibition ratios of more than 50% against all the tested pathogenic fungi.

Comparing the title compounds containing alkyl or *cyclo*-alkyl at 1-position with the similar kind of oxime ether compounds containing substituted phenyl or hydrogen at 1-position, the former presented better inhibiting effect against the weed root and nearly same bioactivity against fungi, but almost lost their inhibition activity against the weed stem.[13] It is interesting that another pyrrolidine-2,4-dione derivatives with schiff base group at 3-position also exhibited remarkably herbicidal activities and fungicidal activities simultaneity.[24] It indicated that it is feasible and promising to further modify the structure against 3-position of pyrrolidine-2,4-dione to design and screen new pesticides.

Conclusions

In summary, a series of novel tetramic acid derivatives containing oxime ether group at 3-position were designed and synthesized. All these compounds were confirmed by IR, MS, ^{1}H NMR spectra and elemental analysis. Especially X-ray single crystal structure diffraction to the compound **6r** made sure the pyrrolidine-2,4-dione moiety and *E* configuration of the title compounds. According to the preliminary bioassays most of the title compounds exhibited noticeable herbicidal activities especially against the root of *E. crusgalli* and higher fungicidal activities than the leading compound TeA. Further studies on structural modification and the relationship between structures and biological activities are currently underway.

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Supplementary Material. Crystallographic data for the structure analysis of the compound **6r** have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 753455. Copies of these information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk or URL: http:// www.ccdc.cam.ac.uk).

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