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Synthesis and bioactivity of novel (*Z,E*)-1-(substituted phenyl)-3-[α-(alkyloxyimino)benzylidene]pyrrolidine-2,4-dione derivatives

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Abstract

A series of 1-(substituted phenyl)-3-[α-(alkyloxyimino)-benzylidene]pyrrolidine-2,4-dione derivatives as a mixture of two geometrical isomers of *Z*-configuration and *E*-configuration were synthesized by the reaction of the corresponding α-hydroxybenzylidene analogs with alkyloxyamine hydrochlorides. The target compounds were confirmed by IR, ^{1}H NMR, MS and elemental analysis. The title compounds exhibit inhibitory activity against *Echinochloa crusgalli* and *Brassica campestris*.

Keywords: herbicidal activity; oxime ether; synthesis; tetramic acid.

Introduction

As a metabolic toxin firstly isolated from the culture filtrates of *Alternaria tenuis*, tenuazonic acid [5-*sec*-butyl-3 -(1-hydroxyethylidene)pyrrolidine-2,4-dione, **A** in Figure 1] belongs to a class of natural tetramic acids containing a heterocyclic core of pyrrolidine-2,4-dione (Rosett et al., 1957). It exhibits a broad spectrum of bioactivities including antitumor, antibiotic, insecticidal, antiviral and herbicidal properties (Gitterman et al., 1964; Gitterman, 1965; Suzuki et al., 1967; La Croix et al., 1975; Janardhanan and Husain, 1984; Gallardo et al., 2004). It has attracted attention of many agrochemists because it is easily degraded (Zhou and Qiang, 2007). A number of other substituted pyrrolidine-2,4-diones have been designed and synthesized, and some compounds such as **B** in Figure 1 (Zhu et al., 2005a,b,c, 2007) and **C** in Figure 1 (Zhu et al., 2009, 2010) have been found to show noticeable bioactivities.

Oxime ether moieties have often been used in the molecular design of new pesticides. In fact, there are many compounds containing an oxime moiety that show significant insecticidal, herbicidal and fungicidal activities (Liu and Yao, 2004; Dai et al., 2008; Fan et al., 2008). Many commercial herbicides, such as clethodim, cycloxydim, propaquizafop and tepraloxydim have been applied in plant protection. In this article, alkyloxyamino groups were introduced at the 3-position of 3-(α-hydroxybenzylidene)pyrrolidine-2,4-diones to synthesize a series of novel tetramic acid derivatives containing an oxime ether moiety. The herbicidal activities of the synthesized compounds were also evaluated.

Results and discussion

Synthesis

The title compounds **5a–t** were synthesized by the reaction of 1-(substituted phenyl)-3-(α-hydroxybenzylidene)pyrrolidine-2,4-diones **3** with alkyloxyamine hydrochlorides **4** in the presence of sodium hydroxide. The synthetic route to the products **5** is shown in Scheme 1.

Compounds **3** were synthesized from aniline or substituted anilines, ethyl chloroacetate and ethyl benzoylacetate via a three-step procedure including substitution, condensation and cyclization (Fujinami et al., 1976; Zhu et al., 2005b). The alkyloxyamine hydrochlorides **4** were synthesized according to the reported methods (Du et al., 2004; Han et al., 2005; Lu, 2006).

Structure

The structure of the final compounds was confirmed by IR, ^{1}H NMR, MS and elemental analysis. The IR spectra showed peaks at 2916–2984 cm^{-1} due to C-H stretching vibration and peaks at 1676–1701 cm^{-1} for the carbonyl groups. The ^{1}H NMR spectra exhibited a singlet at δ 3.88–4.61 assigned to the protons of the NCH_2 group, and multiple signals at δ 6.88–8.02 assigned to aromatic protons. A molecular ion peak was observed in the mass spectra of all products. Moreover, the elemental analysis data matched the molecular formulas of title compounds.

It is worthy to point out that protons at the 5-position of the pyrrolidine-2,4-dione moiety and protons of the group R^4 each show two groups of signals with a similar

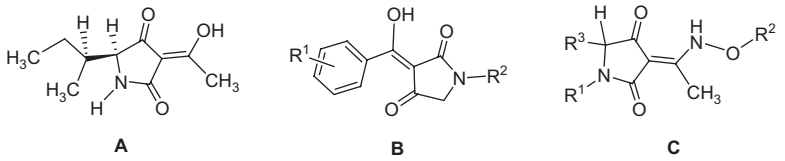
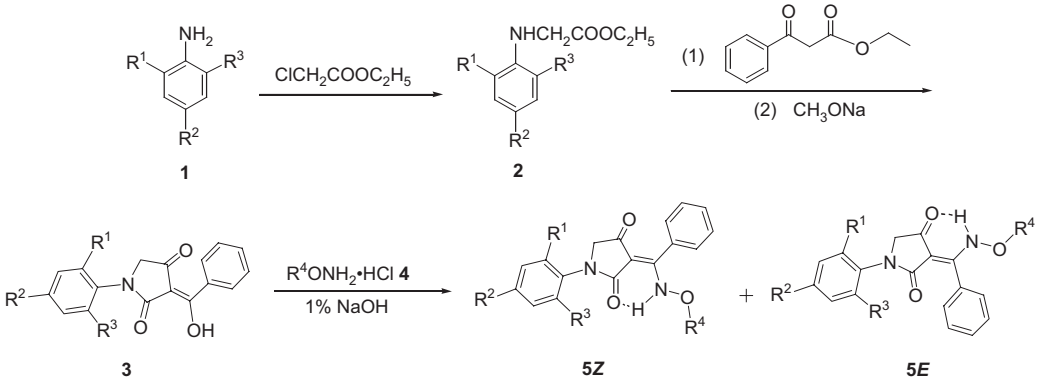


Figure 1 Structures of some bioactive tetramic acids.
A is a naturally occurring tetramic acid (tenuazonic acid), **B** and **C** are synthetic tetramic acids.



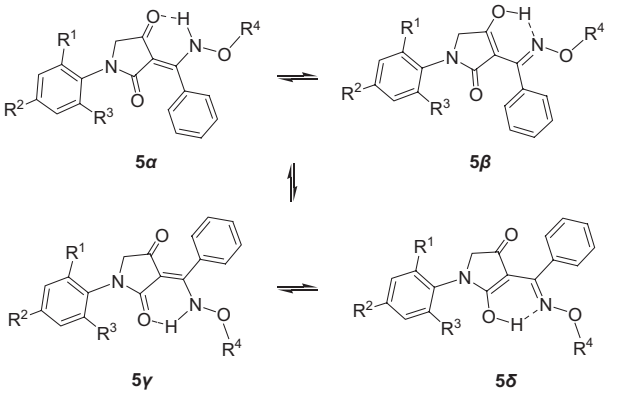
5a-e: $R^1=R^2=R^3=H$; **5f-j:** $R^1=CH_3$, $R^2=H$, $R^3=C_2H_5$; **5k-o**: $R^1=OC_2H_5$, $R^2=R^3=H$;
5p-s: $R^1=R^3=CH_3$, $R^2=H$; **5t:** $R^1=R^3=H$, $R^2=CH_3$.
5a, 5f, 5k, 5p, 5t: R^4=*n*-C_3H_7; **5b, 5g, 5l, 5q**: R^4=*i*-C_3H_7; **5c, 5h, 5m, 5r**: $R^4=CH_2CH=CH_2$;
5d, 5i, 5n, 5s: R^4=*n*-C_4H_9; **5e, 5j, 5o**: $R^4=CH_2C_6H_5$.

Scheme 1 Synthetic route to compounds **5** (a mixture of geometrical isomers).

ratio of integration area in ^{1}H NMR spectra. This result is consistent with the presence of two isomers for each final product **5**. Tetramic acid derivations can exist in four tautomeric forms (Athanasellis et al., 2001; Siegel et al., 2009), which for the corresponding structures of the products **5** is shown in Scheme 2. By using ^{15}N NMR spectroscopy, it has been shown that a related compound, 3-(1-anilinoethylidene)pyrrolidine-2,4-dione, exists primarily in two isomers, namely in *Z*-configuration and *E*-configuration of a ketoamine form (Yamaguchi et al., 1976). The X-ray diffraction crystallography studies have also shown that 3-(1-(propyloxyamino)ethylidene)-1-cyclohexylpyrrolidine-2,4-dione and 5-*sec*-butyl-3-(2,6-dimethylphenylamino)ethylidene-1*H*-pyrrolidine-2,4-dione exist in a ketoamine form (Wang et al., 2010; Zhu et al., 2010). It can be speculated that the target compounds exist in ketoamine form with two isomers of **5**α and **5**γ (Scheme 2). With target compound **5a** as a representative, its four isomers **5a**α, **5a**β, **5a**γ, and **5a**δ were calculated at the B3LYP/6-31+G* level and the respectively relative energies of 1.38, 12.73, 0.00 and 30.48 kJ/mol were obtained (Skylaris et al., 2003). This result suggests that **5a**γ (*Z*-configuration) and **5a**α (*E*-configuration) are the most stable isomers. Moreover, it can be suggested that the Z-isomer **5a**γ is the major product in the mixture. For all products **5** the intensities of the corresponding ^{1}H NMR signals tentatively assigned to the *Z* and *E* isomers are 60%–69% and 31%–40%, respectively.

Biological evaluation

The final products 5 were evaluated for herbicidal activities against *B. campestris* and *E. crusgalli in vitro* at the concentration of 100 mg/l (Luo and Yang, 2007). The results are summarized in Table 1. The data indicate that almost all compounds display certain inhibitory activities against the root of two tested plants, but no obvious bioactivity against the stem was found. Seven



Isomer **5**α: *E*-configuration
Isomer **5**γ: *Z*-configuration
Isomer **5**β: *s-trans* conformation
Isomer **5**δ: *s-syn* conformation

Scheme 2 Structures of four possible isomers of compounds **5**.

Table 1 Herbicidal activities of compounds **5a–t** against *B. campestris* and *E. crusgalli* (100 μg/ml, inhibitory rate percent).

Compounds	*B. campestris* root	*E. crusgalli* root	*E. crusgalli* stem
5a	50.0±3.2	6.8±1.6	-5.3±0.8
5b	21.8±1.4	32.2±3.2	7.5±1.2
5c	30.9±3.8	62.3±1.8	12.3±2.4
5d	41.6±0.9	52.6±1.6	-4.8±1.3
5e	51.5±3.5	5.5±0.9	2.2±1.5
5f	53.4±1.8	68.2±3.3	-15.1±2.7
5g	43.2±3.4	47.2±3.7	-10.2±3.8
5h	67.3±2.1	62.0±1.9	-8.9±1.4
5i	45.9±3.3	72.3±0.9	-26.6±2.8
5j	6.5±2.7	25.7±3.0	-20.9±3.2
5k	28.0±0.6	18.6±2.5	-13.6±4.2
5l	38.0±3.4	32.1±1.7	6.0±1.2
5m	7.3±1.9	22.4±1.3	7.3±3.7
5n	15.4±1.2	33.1±2.8	-1.7±2.4
5o	17.8±3.0	41.6±2.4	-10.2±1.7
5p	51.6±2.5	71.7±4.2	3.1±1.2
5q	54.6±3.2	59.8±4.1	-3.0±1.8
5r	27.6±2.7	76.5±1.3	17.8±2.2
5s	58.6±2.3	-9.2±1.5	6.3±2.6
5t	34.5±1.6	51.5±3.5	-3.8±1.0
TeA	92.6±1.0	97.8±0.4	43.1±2.9

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

compounds **5a**, **5e**, **5f**, **5h**, **5p**, **5q** and **5s** show moderate herbicidal activities against the root of *B. campestris*, with their inhibitory rates exceeding 50%. Nine compounds **5c**, **5d**, **5f**, **5h**, **5i**, **5p**, **5q**, **5r** and **5t** exhibit inhibitory rates of over 50% against the root of *E. crusgalli*.

Conclusions

A series of novel 3-benzylidene-substituted tetramic acid derivatives containing a substituted phenyl group at the 1-position and oxime ether group at the 3-position were synthesized. These compounds exist as a mixture of two geometrical E/Z isomers. The bioassay indicated that these compounds exhibit herbicidal activities against the root of *B. campestris* and *E. crusgalli* at the concentration of 100 μg/ml *in vitro*.

Experimental section

Melting points were determined on a WRS-1B digital melting-point apparatus and are not corrected. The IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer in KBr disks. Elemental analyses were performed on a Varian CHN analyzer. Mass spectra (electron impact) were recorded on a GC/MS-QP2010 spectrometer using direct injection technique. The ^{1}H NMR spectra were taken on a Mercury plus Varian-300 spectrometer at 300 MHz in $CDCl_3$ with TMS as the internal reference.

General procedure for the preparation of the title compounds 5a–t

A solution of aniline or substituted aniline **1** (0.05 mol), ethyl chloroacetate (0.06 mol) and sodium acetate (0.06 mol) in ethanol (100 ml) was heated under reflux for 8 h. After cooling, the mixture was treated with water (80 ml) and extracted with ether (3×25 ml). The combined organic layers were dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to give the presumed liquid product **2** (see Scheme 1). Then, a solution of the crude intermediate product **2** and ethyl benzoylacetate (0.06 mol) in dry xylenes (50 ml) was stirred for 24 h at 125–130°C. Then, a solution of sodium methoxide (0.12 mol) in methanol (40 ml) was added and the mixture was heated under reflux for 24 h. After cooling to room temperature, water was added (100 ml), and the aqueous layer was acidified to pH=2–3 with 20% hydrochloric acid. The mixture was extracted with chloroform (3×25 ml), and the combined organic layers were dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to obtain crude 1-(substituted phenyl)-3-(α-hydroxybenzylidene)-pyrrolidine-2,4-dione **3**, which was purified by crystallization from ethanol/chloroform, 4:1. To the solution of compound **3** (3 mmol) and *O*-substituted hydroxylamine hydrochloride **4** (3 mmol) in ethanol (25 ml) or chloroform (25 ml), a 1% solution of NaOH (4.4 ml) was added. The mixture was heated under reflux, and the progress of the reaction was monitored by TLC. Then the mixture was extracted with chloroform (3×25 ml), and the extract was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was crystallizated from ethanol/chloroform, 3:1 to afford the desired compound **5a–t**.

(*Z,E*)-1-Phenyl-3-[α-(propoxyamino)benzylidene]pyrrolidine-2,4-dione (5a): White powder; yield 30%; mp 160.0–160.2°C; ^{1}H NMR: δ for *Z*-isomer (65%) 0.78 (t, *J*=7.8 Hz, 3H, CH_3), 1.51–1.64 (m, 2H, CH_2CH_3), 3.86 (t, *J*=6.3 Hz, 2H, OCH_2), 4.23 (s, 2H, NCH_2), 7.10–7.64 (m, 10H, PhH); δ for *E*-isomer (35%) 1.03 (t, *J*=7.5 Hz, 3H, CH_3), 1.81–1.92 (m, 2H, CH_2CH_3), 4.36 (t, *J*=6.6 Hz, 2H, OCH_2), 4.45 (s, 2H, NCH_2), 7.10–7.64 (m, 10H, PhH); IR: 3065, 2965, 1696, 1580, 1500, 1477, 1307, 1225, 916 cm^{-1}; MS (EI) m/z: 336 (M^+), 278, 145, 105 (100), 77, 57, 45. Analysis: calculated for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.37; H, 5.84; N, 8.24.

(*Z,E*)-3-[α-(Isopropoxyamino)benzylidene)-1-phenylpyrrolidine-2,4-dione (5b): White powder; yield 36%; mp 167.1–169.3°C; ^{1}H NMR: δ for *Z*-isomer (69%) 1.16 [d, *J*=6.0 Hz, 6H, $CH(CH_3)_2$], 3.93–4.11 (m, 1H, OCH), 4.23 (s, 2H, NCH_2), 7.10–7.66 (m, 10H, PhH); δ for *E*-isomer (31%) 1.42 [d, *J*=6.0 Hz, 6H, $CH(CH_3)_2$], 4.62–4.75 (m, 1H, OCH), 4.45 (s, 2H, NCH_2), 7.10–7.66 (m, 10H, PhH); IR: 3455, 3061, 2972, 1698, 1585, 1500, 1433, 1378, 1229, 1177, 964 cm^{-1}; MS (EI) m/z: 336 (M^+), 276, 145, 105 (100), 77, 51, 45. Analysis: calculated for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.26; H, 5.87; N, 8.11.

(*Z,E*)-3-[α-(Allyloxyamino)benzylidene]-1-phenylpyrrolidine-2,4-dione (5c): White powder; yield 30%; mp 144.5–144.9°C; ^{1}H NMR: δ for *Z*-isomer (66%) 4.25 (s, 2H, NCH_2), 4.38 (d, *J*=6.0 Hz, 2H, OCH_2), 5.24–5.50 (m, 2H, $CH=CH_2$), 5.78–5.91 (m, 1H, $CH=CH_2$), 7.05–7.64 (m, 10H, PhH); δ for *E*-isomer (34%) 4.40 (s, 2H, NCH_2), 4.85 (d, *J*=6.0 Hz, 2H, OCH_2), 5.24–5.50 (m, 2H, $CH=CH_2$), 6.09–6.18 (m, 1H, $CH=CH_2$), 7.05–7.64 (m, 10H, PhH); IR: 3451, 3053, 2916, 1698, 1573, 1501, 1439, 1377, 1227, 1158, 924 cm^{-1}; MS (EI) m/z: 334 (M^+), 276, 145, 105 (100), 77, 57, 45.

Analysis: calculated for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 70.97; H, 5.86; N, 8.52.

(*Z,E*)-3-[α-(Butoxyamino)benzylidene]-1-phenylpyrrolidine-2,4-dione (5d): White powder; yield 30%; mp 144.5–144.9°C; ^{1}H NMR: δ for *Z*-isomer (67%) 0.81 (t, *J*=7.2 Hz, 3H, CH_3), 1.15–1.22 (m, 2H, CH_2CH_3), 1.47–1.58 (m, 2H, OCH_2CH_2), 3.88 (t, *J*=5.4 Hz, 2H, OCH_2), 4.20 (s, 2H, NCH_2), 7.09–7.65 (m, 10H, PhH); δ for *E*-isomer (33%) 0.99 (t, *J*=7.2 Hz, 3H, CH_3), 1.36–1.41 (m, 2H, CH_2CH_3), 1.77–1.95 (m, 2H, OCH_2CH_2), 4.39 (t, *J*=6.9 Hz, 2H, OCH_2), 4.43 (s, 2H, NCH_2), 7.09–7.65 (m, 10H, PhH); IR: 3457, 3039, 2933, 1701, 1583, 1500, 1439, 1303, 1223, 1177, 960 cm^{-1}; MS (EI) m/z: 350 (M^+), 276, 145, 105 (100), 77, 56, 45. Analysis: calculated for $C_{21}H_{22}N_2O_3$: C, 71.89; H, 6.33; N, 7.99. Found: C, 71.97; H, 6.26; N, 7.72.

(*Z,E*)-3-[α-(Benzyloxyamino)benzylidene]-1-phenylpyrrolidine-2,4-dione (5e): White powder; yield 40%; mp 177.0–177.8°C; ^{1}H NMR: δ for *Z*-isomer (60%) 4.21 (s, 2H, NCH_2), 4.89 (s, 2H, OCH_2), 7.04–7.76 (m, 15H, PhH); δ for *E*-isomer (40%) 4.39 (s, 2H, NCH_2), 5.39 (s, 2H, OCH_2), 7.04–7.76 (m, 15H, PhH); IR: 3063, 2926, 1701, 1585, 1501, 1442, 1379, 1230, 1178, 954 cm^{-1}; MS (EI) m/z: 384 (M^+), 276, 145, 105 (100), 77, 52. Analysis: calculated for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.97; H, 5.26; N, 7.63.

(*Z,E*)-1-(2-Ethyl-6-methylphenyl)-3-[α-(propoxyamino)benzylidene]pyrrolidine-2,4-dione (5f): Pink powder; yield 23%; mp 155.9–157.5°C; ^{1}H NMR: δ for *Z*-isomer (61%) 0.77 (t, *J*=7.8 Hz, 3H, CH_2CH_3), 1.22 (t, *J*=6.0 Hz, 3H, $PhCH_2CH_3$), 1.51–1.62 (m, 2H, CH_2CH_3), 2.20 (s, 3H, $PhCH_3$), 2.49–2.60 (m, 2H, $PhCH_2$), 3.85 (t, *J*=6.3 Hz, 2H, OCH_2), 3.99 (s, 2H, NCH_2), 7.11–7.73 (m, 8H, PhH); δ for *E*-isomer (39%) 0.93 (t, *J*=7.5 Hz, 3H, CH_2CH_3), 1.22 (t, *J*=6.0 Hz, 3H, $PhCH_2CH_3$), 1.85–1.94 (m, 2H, CH_2CH_3), 2.20 (s, 3H, $PhCH_3$), 2.49–2.60 (m, 2H, $PhCH_2$), 4.19 (s, 2H, NCH_2), 4.36 (t, *J*=6.3 Hz, 2H, OCH_2), 7.11–7.73 (m, 8H, PhH); IR: 3450, 3023, 1681, 1582, 1500, 1475, 1372, 1227, 1157, 960 cm^{-1}; MS (EI) m/z: 378 (M^+, 100), 319, 146, 132, 77, 58, 45. Analysis: calculated for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.87; H, 6.88; N, 7.51.

(*Z,E*)-1-(2-Ethyl-6-methylphenyl)-3-[α-(isopropoxyamino)benzylidene]pyrrolidine-2,4-dione (5g): White powder; yield 22%; mp 159.4–163°C; ^{1}H NMR: δ for *Z*-isomer (64%) 1.14 [d, *J*=6.0 Hz, 6H, $CH(CH_3)_2$], 1.22 (t, *J*=5.1 Hz, 3H, $PhCH_2CH_3$), 2.20 (s, 3H, $PhCH_3$), 2.49–2.61 (m, $PhCH_2$), 3.99 (s, 2H, NCH_2), 4.68–4.77 (m, 1H, OCH), 7.08–7.77 (m, 8H, PhH); δ for *E*-isomer (36%) 1.22 (t, *J*=7.5 Hz, 3H, $PhCH_2CH_3$), 1.43 [d, *J*=6.3 Hz, 6H, $CH(CH_3)_2$], 2.20 (s, 3H, $PhCH_3$), 2.49–2.61 (m, 2H, $PhCH_2$), 4.19 (s, 2H, NCH_2), 4.49–4.55 (m, 1H, OCH), 7.08–7.77 (m, 8H, PhH); IR: 3451, 3030, 2978, 1686, 1580, 1500, 1389, 1221, 1178, 981 cm^{-1}; MS (EI) m/z: 378 (M^+, 100), 319, 146, 132, 77, 45. Analysis: calculated for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.92; H, 6.76; N, 7.62.

(*Z,E*)-3-[α-(Allyloxyamino)benzylidene]-1-(2-ethyl-6-methylphenyl)pyrrolidine-2,4-dione (5h): White powder; yield 19%; mp 168.5–169.1°C; ^{1}H NMR: δ for *Z*-isomer (68%) 1.20 (t, *J*=7.5 Hz, 3H, $PhCH_2CH_3$), 2.20 (s, 3H, $PhCH_3$), 2.49–2.62 (m, 2H, $PhCH_2$), 4.05 (s, 2H, NCH_2), 4.76 (d, *J*=7.5 Hz, 2H, OCH_2), 5.25–5.51 (m, 2H, $CH=CH_2$), 5.79–5.91 (m, 1H, $CH=CH_2$), 7.12–7.75 (m, 8H, PhH); δ for *E*-isomer (32%) 1.20 (t, *J*=7.5 Hz, 3H, $PhCH_2CH_3$), 2.20 (s, 3H, $PhCH_3$), 2.49–2.62 (m, 2H, $PhCH_2$), 4.39 (s, 2H, NCH_2), 4.88 (d, *J*=6.3 Hz, 2H, OCH_2), 5.25–5.51 (m, 2H, $CH=CH_2$), 5.95–6.19 (m, 1H, $CH=CH_2$), 7.12–7.75 (m, 8H, PhH); IR: 3023, 2971, 1686, 1581, 1470, 1418, 1216, 1185, 987 cm^{-1}; MS (EI) m/z: 376 (M^+), 318, 146, 132, 105, 69, 57 (100), 45. Analysis: calculated for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 72.96; H, 6.88; N, 7.57.

(*Z,E*)-3-[α-(Butoxyamino)benzylidene]-1-(2-ethyl-6-methylphenyl)pyrrolidine-2,4-dione (5i): Pink powder; yield 33%; mp 142.8–145.2°C; ^{1}H NMR: δ for *Z*-isomer (64%) 0.82 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.23 (t, *J*=6.6 Hz, 3H, $PhCH_2CH_3$), 1.33–1.60 (m, 4H, CH_2CH_2), 2.21 (s, 3H, $PhCH_3$), 2.56 (q, *J*=6.6 Hz, 2H, $PhCH_2$), 3.88 (s, 2H, NCH_2), 4.21 (t, *J*=6.0 Hz, 2H, OCH_2), 7.12–7.73 (m, 8H, PhH); δ for *E*-isomer (36%) 0.99 (t, *J*=6.6 Hz, 3H, CH_2CH_3), 1.23 (t, *J*=7.5 Hz, 3H, $PhCH_2CH_3$), 1.68–1.93 (m, 4H, CH_2CH_2), 2.21 (s, 3H, $PhCH_3$), 2.56 (q, *J*=7.5 Hz, 2H, $PhCH_2$), 4.00 (s, 2H, NCH_2), 4.41 (t, *J*=6.3 Hz, 2H, OCH_2), 7.12–7.73 (m, 8H, PhH); IR: 3023, 2963, 1691, 1582, 1471, 1417, 1216, 1183, 976 cm^{-1}; MS (EI) m/z: 392 (M^+), 319, 174, 146 (100), 104, 77, 56. Analysis: calculated for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.23; H, 7.09; N, 7.32.

(*Z,E*)-3-[α-(Benzyloxyamino)benzylidene]-1-(2-ethyl-6-methylphenyl)pyrrolidine-2,4-dione (5j): White powder; yield 36%; mp 171.3–177.0°C; ^{1}H NMR: δ for *Z*-isomer (63%) 1.22 (t, *J*=6.9 Hz, 3H, $PhCH_2CH_3$), 2.19 (s, 3H, $PhCH_3$), 2.48–2.59 (m, 2H, $PhCH_2$), 4.02 (s, 2H, NCH_2), 4.88 (s, 2H, OCH_2), 7.12–7.76 (m, 13H, PhH); δ for *E*-isomer (37%) 1.22 (t, *J*=7.5 Hz, 3H, $PhCH_2CH_3$), 2.19 (s, 3H, $PhCH_3$), 2.48–2.59 (m, 2H, $PhCH_2$), 4.15 (s, 2H, NCH_2), 5.41 (s, 2H, OCH_2), 7.12–7.76 (m, 13H, PhH); IR: 3032, 2971, 1695, 1581, 1469, 1391, 1213, 1178, 971 cm^{-1}; MS (EI) m/z: 426 (M^+), 320, 146, 132, 108, 91 (100), 51. Analysis: calculated for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.14; N, 6.57. Found: C, 76.14; H, 6.16; N, 6.44.

(*Z,E*)-1-(2-Ethoxyphenyl)-3-[α-(propoxyamino)benzylidene]-pyrrolidine-2,4-dione (5k): White powder; yield 36%; mp 152.4–153.5°C; ^{1}H NMR: δ for *Z*-isomer (68%) 0.77 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.40 (t, *J*=7.5 Hz, 3H, OCH_2CH_3), 1.52–1.60 (m, 2H, CH_2CH_3), 3.83 (t, *J*=6.3 Hz, 2H, OCH_2), 4.06 (q, *J*=6.9 Hz, 2H, OCH_2CH_3), 4.45 (s, 2H, NCH_2), 6.91–7.70 (m, 9H, PhH); δ for *E*-isomer (32%) 0.93 (t, *J*=7.5 Hz, 3H, CH_2CH_3), 1.40 (t, *J*=6.9 Hz, 3H, OCH_2CH_3), 1.67–1.75 (m, 2H, CH_2CH_3), 4.06 (q, *J*=7.5 Hz, 2H, OCH_2CH_3), 4.19 (t, *J*=6.3 Hz, 2H, OCH_2), 4.58 (s, 2H, NCH_2), 6.91–7.70 (m, 9H, PhH); IR: 3045, 2953, 1680, 1608, 1502, 1391, 1229, 1167, 914 cm^{-1}; MS (EI) m/z: 380 (M^+), 320, 120 (100), 103, 77, 65, 45. Analysis: calculated for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.32; H, 6.53; N, 7.28.

(*Z,E*)-1-(2-Ethoxyphenyl)-3-[α-(isopropoxyamino)benzylidene]-pyrrolidine-2,4-dione (5l): White powder; yield 34%; mp 153.0–153.9°C; ^{1}H NMR: δ for *Z*-isomer (64%) 1.17 [d, *J*=6.0 Hz, 6H, $CH(CH_3)_2$], 1.45 (t, *J*=6.3 Hz, 3H, OCH_2CH_3), 4.06 (q, *J*=6.9 Hz, 2H, OCH_2CH_3), 4.25 (s, 2H, NCH_2), 4.68 (m, 1H, OCH), 6.92–7.73 (m, 9H, PhH); δ for *E*-isomer (36%) 1.29 [d, *J*=6.3 Hz, 6H, $CH(CH_3)_2$], 1.45 (t, *J*=6.9 Hz, 3H, OCH_2CH_3), 4.06 (q, *J*=6.3 Hz, 2H, OCH_2CH_3), 4.47 (s, 2H, NCH_2), 4.74 (m, 1H, OCH), 6.92–7.73 (m, 9H, PhH); IR: 3450, 3033, 2976, 1677, 1610, 1500, 1389, 1229, 1173, 925 cm^{-1}; MS (EI) m/z: 380 (M^+), 320, 120 (100), 103, 77, 45. Analysis: calculated for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.35; H, 6.50; N, 7.21.

(*Z,E*)-3-[α-(Allyloxyamino)benzylidene]-1-(2-ethoxyphenyl)-pyrrolidine-2,4-dione (5m): White powder; yield 33%; mp

136.0–137.7°C; ^{1}H NMR: δ for *Z*-isomer (65%) 1.39 (t, *J*=6.9 Hz, 3H, OCH_2CH_3), 4.05 (q, *J*=6.9 Hz, 2H, OCH_2CH_3), 4.45 (s, 2H, NCH_2), 4.75 (d, *J*=6.3 Hz, 2H, OCH_2), 5.20–5.33 (m, 2H, $CH=CH_2$), 5.75–5.99 (m, 1H, $CH=CH_2$), 6.92–8.02 (m, 9H, PhH); δ for *E*-isomer (35%) 1.47 (t, *J*=6.9 Hz, 3H, OCH_2CH_3), 4.14 (q, *J*=6.9 Hz, 2H, OCH_2CH_3), 4.59 (s, 2H, NCH_2), 4.89 (d, *J*=6.0 Hz, 2H, OCH_2), 5.35–5.51 (m, 2H, $CH=CH_2$), 6.07–6.20 (m, 1H, $CH=CH_2$), 6.92–8.02 (m, 9H, PhH); IR: 3452, 3025, 2982, 1676, 1606, 1501, 1391, 1229, 1102, 924 cm^{-1}; MS (EI) m/z: 378 (M^+), 320, 120, 103 (100), 77, 57. Analysis: calculated for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.81; H, 5.67; N, 7.25.

(*Z,E*)-3-[α-(Butoxyamino)benzylidene]-1-(2-ethoxyphenyl)-pyrrolidine-2,4-dione (5n): White powder; yield 43%; mp 157.6–158.1°C; ^{1}H NMR: δ for *Z*-isomer (64%) 0.82 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.22–1.50 (m, 4H, CH_2CH_2), 1.42 (t, *J*=7.5 Hz, 3H, OCH_2CH_3), 3.88 (t, *J*=6.3 Hz, 2H, OCH_2), 4.15 (q, *J*=6.9 Hz, 2H, OCH_2CH_3), 4.26 (s, 2H, NCH_2), 6.92–7.70 (m, 9H, PhH); δ for *E*-isomer (36%) 0.93 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.44 (t, *J*=7.5 Hz, 3H, OCH_2CH_3), 1.53–1.84 (m, 4H, CH_2CH_2), 4.03 (t, *J*=6.3 Hz, 2H, OCH_2), 4.46 (q, *J*=7.5 Hz, 2H, OCH_2CH_3), 4.61 (s, 2H, NCH_2), 6.92–7.70 (m, 9H, PhH); IR: 3441, 3023, 2955, 1683, 1610, 1502, 1391, 1230, 1121, 924 cm^{-1}; MS (EI) m/z: 394 (M^+), 279, 167, 149, 81, 69 (100), 53. Analysis: calculated for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.92; H, 6.67; N, 7.23.

(*Z,E*)-3-[α-(Benzyloxyamino)benzylidene]-1-(2-ethoxyphenyl)-pyrrolidine-2,4-dione (5o): White powder; yield 47%; mp 162.8–162.9°C; ^{1}H NMR: δ for *Z*-isomer (69%) 1.34 (t, *J*=7.5 Hz, 3H, OCH_2CH_3), 4.03 (q, *J*=7.5 Hz, 2H, OCH_2CH_3), 4.28 (s, 2H, NCH_2), 4.87 (s, 2H, OCH_2), 6.89–7.72 (m, 14H, PhH); δ for *E*-isomer (31%) 1.42 (t, *J*=7.5 Hz, 3H, OCH_2CH_3), 4.05 (q, *J*=7.5 Hz, 2H, OCH_2CH_3), 4.40 (s, 2H, NCH_2), 5.38 (s, 2H, OCH_2), 6.89–7.72 (m, 14H, PhH); IR: 3026, 2984, 1682, 1609, 1501, 1391, 1229, 1125, 949 cm^{-1}; MS (EI) m/z: 428 (M^+), 322, 120, 105, 77 (100), 65. Analysis: calculated for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 72.75; H, 5.47; N, 6.39.

(*Z,E*)-1-(2,6-Dimethylphenyl)-3-[α-(propoxyamino)benzylidene]pyrrolidine-2,4-dione (5p): White powder; yield 29%; mp 159.0–160.2°C; ^{1}H NMR: δ for *Z*-isomer (61%) 0.84 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.45–1.53 (m, 2H, CH_2CH_3), 2.17 (s, 6H, $2PhCH_3$), 3.74 (t, *J*=7.5 Hz, 2H, OCH_2), 3.89 (s, 2H, NCH_2), 7.05–7.53 (m, 8H, PhH); δ for *E*-isomer (39%) 1.04 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.60–1.69 (m, 2H, CH_2CH_3), 2.17 (s, 6H, $2PhCH_3$), 4.37 (t, *J*=7.5 Hz, 2H, OCH_2), 4.09 (s, 2H, NCH_2), 7.05–7.53 (m, 8H, PhH); IR: 3444, 3022, 2966, 1700, 1585, 1474, 1391, 1220, 1184, 961 cm^{-1}; MS (EI) m/z: 364 (M^+), 305, 174, 132 (100), 117, 104, 77, 57. Analysis: calculated for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.66; H, 6.52; N, 7.80.

(*Z,E*)-1-(2,6-Dimethylphenyl)-3-[α-(isopropoxyamino)benzylidene]pyrrolidine-2,4-dione (5q): White powder; yield 25%; mp 162.8–164.0°C; ^{1}H NMR: δ for *Z*-isomer (66%) 1.16 [d, *J*=6.0 Hz, 6H, $CH(CH_3)_2$], 2.24 (s, 6H, $2PhCH_3$), 3.99 (s, 2H, NCH_2), 4.70–4.80 (m, 1H, OCH), 7.10–7.78 (m, 8H, PhH); δ for *E*-isomer (34%): 1.45 [d, *J*=6.3 Hz, 6H, $CH(CH_3)_2$], 2.24 (s, 6H, $2PhCH_3$), 4.19 (s, 2H, NCH_2), 4.52–4.61 (m, 1H, OCH), 7.10–7.78 (m, 8H, PhH); IR: 3443, 3023, 2975, 1701, 1583, 1476, 1323, 1215, 1176, 978 cm^{-1}; MS (EI) m/z: 364 (M^+), 305, 174, 132 (100), 105, 77, 45. Analysis: calculated for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.58; H, 6.49; N, 7.67.

(*Z,E*)-3-[α-(Allyloxyamino)benzylidene]-1-(2,6-dimethylphenyl)pyrrolidine-2,4-dione (5r): White powder; yield 20%; mp 160.7–161.2°C; ^{1}H NMR: δ for *Z*-isomer (68%) 2.20 (s, 6H, $2PhCH_3$), 4.03 (s, 2H, NCH_2), 4.75 (d, *J*=6.0 Hz, 2H, OCH_2), 5.33–5.38 (m, 2H, $CH=CH_2$), 5.79–5.96 (m, 1H, $CH=CH_2$), 7.09–7.72 (m, 8H, PhH); δ for *E*-isomer (32%) 2.20 (s, 6H, $2PhCH_3$), 4.39 (s, 2H, NCH_2), 4.86 (d, *J*=6.9 Hz, 2H, OCH_2), 5.43–5.49 (m, 2H, $CH=CH_2$), 6.04–6.22 (m, 1H, $CH=CH_2$), 7.09–7.72 (m, 8H, PhH); IR (KBr) ν/cm^{-1}: 3024, 2972, 1677, 1585, 1477, 1414, 1211, 1178, 910 cm^{-1}; MS (EI) m/z: 362 (M^+), 306, 174, 144, 132 (100), 102, 77, 57. Analysis: calculated for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.79; H, 6.33; N, 7.70.

(*Z,E*)-3-[α-(Butoxyamino)benzylidene]-1-(2,6-dimethylphenyl)-pyrrolidine-2,4-dione (5s): White powder; yield 27%; mp 152.8–155.9°C; ^{1}H NMR: δ for *Z*-isomer (62%) 0.81 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.18–1.48 (m, 4H, OCH_2CH_2), 2.21 (s, 6H, $2PhCH_3$), 3.89 (t, *J*=6.6 Hz, 2H, OCH_2), 3.99 (s, 2H, NCH_2), 7.09–7.72 (m, 8H, PhH); δ for *E*-isomer (38%) 0.97 (t, *J*=6.9 Hz, 3H, CH_2CH_3), 1.49–1.86 (m, 4H, OCH_2CH_2), 2.28 (s, 6H, $2PhCH_3$), 4.23 (s, 2H, NCH_2), 4.37 (t, *J*=6.6 Hz, 2H, OCH_2), 7.09–7.72 (m, 8H, PhH); IR: 3450, 3068, 2955, 1682, 1610, 1501, 1390, 1229, 1182, 924 cm^{-1}; MS (EI) m/z: 378 (M^+), 306 (100), 132, 103, 77, 55. Analysis: calculated for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.66; H, 6.97; N, 7.68.

(*Z,E*)-3-[α-(Propoxyamino)benzylidene]-1-(p-tolyl)pyrrolidine-2,4-dione (5t): White powder; yield 33%; mp 158.8–159.8°C; ^{1}H NMR: δ for *Z*-isomer (64%) 0.79 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.54–1.61 (m, 2H, CH_2CH_3), 2.33 (s, 3H, $PhCH_3$), 3.85 (t, *J*=6.3 Hz, 2H, OCH_2), 4.19 (s, 2H, NCH_2), 7.14–7.71 (m, 9H, PhH); δ for *E*-isomer (36%) 1.04 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.83–1.90 (m, 2H, CH_2CH_3), 2.39 (s, 3H, $PhCH_3$), 4.35 (t, *J*=6.3 Hz, 2H, OCH_2), 4.40 (s, 2H, NCH_2), 7.14–7.71 (m, 9H, PhH); IR: 3025, 2966, 1699, 1581, 1515, 1442, 1379, 1226, 1175, 971 cm^{-1}; MS (EI) m/z: 350 (M^+), 290 (100), 119, 91, 77, 57, 45. Analysis: calculated for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.04; H, 6.25; N, 7.82.

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