Concise strategy for diastereoselective annulation to afford fused [5:7] oxazepanone γ-lactams

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Abstract

A series of novel potentially biologically active fused [5:7] oxazepanone γ-lactams were synthesized and described. A series of functional group transformations, namely amination, syn-hydrogenation and intramolecular annulation reactions were used to obtain the [5:7] oxazepanone γ-lactams in reasonable yields. In the diastereoselective fused-annulation for the formation of the secondary ring, steric constrain and cis-geometrical configuration of C-3 and C-4 substituents were observed as the predetermined factors. These ring annulations were purposely constructed to suit the physicochemical enhancement of the biological activity of the title compounds via SAR study of γ-lactams.

Keywords: Oxazepanone, γ-lactam, pyrrolidinone, bicyclic γ-lactam, anti-MRSA

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) refers to a group of Gram-positive bacteria that has displayed multidrug-resistance (MDR) properties towards multiple structurally unrelated antibiotics and antimicrobial agents.\(^1,2\) MRSA is also one of the major causes of nosocomial infections, resulting in severe morbidity and mortality in many hospitals each year.\(^3-5\) Currently, only a handful of antibiotics can inhibit these dangerous pathogens, which includes clindamycin, doxycycline, trimethoprim-sulfamethoxazole, vancomycin and linezolid (See Figure. 1).\(^6-9\) Unfortunately, some MRSA strains lately have begun to display new-resistance to these available drugs.\(^10-13\) Therefore, quests for new sources and classes of antibiotics are in dire need to tackle this resistance problem.

![Figure 1. Examples of commercially-available anti-MRSA drugs.](image)

Pyrrolidinones on the other hand, represent a class of five-membered lactams with a four carbon heterocyclic ring.\(^14,15\) Pyrrolidinone derivatives can be found in natural and unnatural bioactive compounds such as lactacystin, clausenamide, piracetam, doxapram and cotinine (See Figure 2).\(^16,17\) Comprehensive literatures have reported that pyrrolidinone and its derivatives display a broad range of biological activities, such as HIV-1 integrase inhibitors, antimicrobial, anti-inflammatory and anticancer properties.\(^18-23\) Our interest in these types of molecules continues from when we discovered that a synthesized pyrrolidinone derivative exhibited good inhibitory activity against MRSA with MIC values between 7.8 and 31.3 \(\mu\)g/ml.\(^1,2\) This bioactivity value is very much comparable in terms of its biological activity with the commercialized antibiotic
drug, linezolid. This derivative also showed no toxicity effect on treated mice at an estimated median acute lethal dose (LD<sub>50</sub>) value of more than 300 mg/kg and less than 2000 mg/kg.<sup>1,2</sup>

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**Figure 2.** Examples of biologically active pyrrolidinones and oxazepanones.

In addition, oxazepanone is a seven-membered heterocyclic compound with a nitrogen and oxygen atom, with some compounds containing this structural motif displaying potent biological activities including antibacterial, antifungal and anticonvulsant properties.<sup>24</sup> Oxazepanone and its derivatives can be seen in important natural compound such as the neurotoxin batrachotoxin (See Figure 2).<sup>25,26</sup> Upon successfully accessed certain derivatives of pyrrolidinone as highly potential lead compounds for the treatment of MRSA,<sup>1,2</sup> a different structure activity relationship (SAR) enhancement program was initiated. It involved designing a variety of bicyclic compounds such as β-lactam-γ-lactam, β-lactone-γ-lactam and γ-lactam-γ-lactam ring templates as depicted in Scheme 1.<sup>27,28</sup> It was anticipated that by fusing two different heterocyclic rings on the same scaffold could lead to hybrid molecules with more potent biological activities as compared to the individual molecules.<sup>29</sup> This particular concept is further extended in this manuscript.

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**Results and Discussion**

Initially, synthesis of 1 was carried out by employing our previously reported one-pot reaction protocol.<sup>30,31</sup> Compound 1 could easily be transformed into its desired hydroxyethylamino derivative 2 via a typical 1,2-nucleophilic addition reaction (See Scheme 1). It was confirmed that compound 2 predominantly existed in its enamine - rather than its imine - tautomer due to better resonance stabilization of the enamine via hydrogen bonding. Similar observation of this pyrrolidone imine-enamine tautomerism was also reported for pyrrolyl hydrazine 3.<sup>27,32</sup> Different attempts on direct intramolecular annulation of compound 2 using different bases were carried out yet in vain (See Scheme 1). This failure could be due to the conjugation effect from the lone
pair of the enamine functionality which deactivates the electrophilicity of the carbonyl ester and thus disfavours the ring annihilation reaction. In a different study on the ring strain effect, more rigid cyclization for β-lactone-γ-lactam and β-lactam-γ-lactam employing 4 and 5, respectively were also attempted. Unfortunately, neither the lactonization, nor the lactamization reactions were successful; this indicating that the strain effect is indeed one of the most predetermined factors for the cyclization process. Thus, both synthetic strategies for lactonization and lactamization of β-(lactone/lactam)-γ-lactam type fused ring system were abandoned.

Scheme 1. i) NH$_2$(CH$_2$)$_2$OH, AcOH, EtOH, reflux, 12 hr; ii) NaH, THF, reflux; iii) t-BuOK, THF, reflux; iv) EtOH, stir, rt; v) NH$_2$NH$_2$.H$_2$O, EtOH, reflux; vi) Pd/C, H$_2$, AcOH, stir, rt; vii) BOP-Cl, Et$_3$N, DCM, stir, rt; viii) DCC, DMAP, Et$_3$N, DCM, stir, rt; ix) PhSO$_2$Cl, Pyridine, stir, 0-5°C; x) MsCl, Pyridine, stir, 0-4°C; xi) NH$_4$HCO$_2$, EtOH, reflux; xii) NaH, THF, reflux.

In further development towards the intended annulation reaction, ene-reduction of enamine 2 was conducted prior to hinder the resonance effects. This reduction was performed via catalytic hydrogenation employing different Pd-catalyst systems as depicted in Scheme 2 and Table 1. The used of Pd/C and Adam’s catalyst (PtO$_2$) led to a low yield of the reduced product. However, the Pearlman’s catalyst (Pd(OH)$_2$/C) was found to be a superior reagent for the reduction of enamine 2, leading to the all-cis isomer 6 as the sole reduced compound. This was in contradiction to enamine 3 where it was found that the Pd/C catalyst gave good to moderate yields of hydrazine γ-lactam 7 with cis-trans isomers as the major diastereomers. It is thus proposed that both Pd-assisted hydrogenation for 2 and 3 underwent different reduction mechanisms. We postulate that the terminal hydroxyl group of 2 controls the stereochemistry of the diastereomers by chelating with the metal catalyst, giving rise to the observed selectivity. In addition, the presence of a bulky substituent on C-5 significantly reduced the product yields; this is probably due to the poor complexation of the Pd and the enamine sites. Similar patterns on the product yield of the ene-reduction of 3 with Pd/C catalyst signifies similar steric impact towards successful complexation during the reaction.
Scheme 2. Mechanistic explanation of the ene-reduction of compound 2 and 3.
Table 1. Reduction of compound 2 to yield pyrrolidine 6

<table>
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<tr>
<th>Entry</th>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>Yield</th>
<th>J values (Hz)</th>
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<tr>
<td>1</td>
<td>6a</td>
<td>CH₃</td>
<td>H</td>
<td>83ᵇ</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>6b</td>
<td>CH₃</td>
<td>CH₃</td>
<td>25ᵇ</td>
<td>9.4, 8.5 (dd)</td>
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<tr>
<td>3</td>
<td>6c</td>
<td>CH₃</td>
<td>CH₂CH₃</td>
<td>23ᵇ</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>6d</td>
<td>CH₃</td>
<td>4-OCH₃Ph</td>
<td>34ᵇ</td>
<td>7.3</td>
</tr>
<tr>
<td>5</td>
<td>6e</td>
<td>CH₃</td>
<td>4-CH₃Ph</td>
<td>33ᵇ</td>
<td>7.3</td>
</tr>
</tbody>
</table>

ᵃ H₂, Pd/C, AcOH, 1 atm.ᵇ H₂, Pd(OH)₂/C, AcOH, EtOH, 1 atm.ᶜ H₂, PtO₂, AcOH, MeOH, 1 atm. * H-4 and H-5 give rise to a multiplet pattern.

Spectroscopically, the configuration of diastereomers 6 were confirmed by ¹H NMR and 2D NMR spectroscopy experiments. The correlation pattern of the NOESY spectra for all-cis 6 and all-cis 7 were similar.²⁷,³³ Of note was that the NOESY spectrum of the all-cis 6d showed no correlation between the proton signal at C-4 (3.95 ppm) and the aryl proton (7.14 ppm). It can be assumed that this proton is located on the opposite side of the aryl ring and this compound was therefore assigned as all-cis 6d structure. Besides, the low chemical shift values for the signals of the ester functionality of the all-cis 6d also confirmed that the ester functionality was located at the same side as the phenyl ring (Figure 3).

![Figure 3](image-url)

**Figure 3.** Diastereoisomeric configurations of 6d and 7.

Eventually, with compounds 6 in hand, the intramolecular annihilations to the corresponding title compounds were attempted using different methods either under basic or acidic conditions.³⁴,³⁵ By utilizing potassium tert-butoxide as the base in THF at 0°C, compounds 6 successfully gave the anticipated [5:7] oxazepanone γ-lactams (8) in 70-83% yields (Scheme 3). Earlier attempts at the lactonization of 6 with the aid of acid catalyst, p-toluenesulfonic acid in tetrahydrofuran or 1,4-dioxane, only led to the recovery of the starting material.
All synthesized title compounds are currently undergoing thorough MIC, toxicity and mice infection-protection MRSA studies in our laboratory and it is hoped that they will display superior activity compared to their parent compound 1.

Conclusions

In conclusion, we have disclosed a simple route for the synthesis of the title compounds via a series of reactions namely enamine reaction, syn-hydrogenation and finally intramolecular annulation to give products 8 in moderate to good yields. During the ene-hydrogenation reaction, high diastereoselectivity was observed, as only all-cis isomers 6 were obtained. Furthermore, biological studies involving the MRSA inhibition of the new heterocyclic compounds 8 are currently in progress in our laboratory.

Experimental Section

General. All the reagents were supplied by Merck Chemical Co., Sigma-Aldrich Co. and Acros Organics Co. Melting points were recorded using an automatic FP62 melting point apparatus from Mettler Toled and are uncorrected. Infrared spectra (4000-400 cm⁻¹) were recorded on Varian 3100 Excalibur Series FT/IR spectrometer. Microanalyses were performed on Flash Elemental Analyzer 110 series. ¹H and ¹³C NMR spectra were recorded on JEOL-400 (¹H 400 MHz, ¹³C 100 MHz) spectrometer. Molecular weights were determined using Agilent 1100 Liquid Chromatograph/Mass Selective Detector (LC/MSD). The progress of the reactions was monitored by thin layer chromatography (TLC) on silica gel 60 F254 and the spots were visualized with UV lamp (254 and 365 nm).

General procedure. Ethyl 4-(2-hydroxyethylamino)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylates 2a-e. Ethanolamine (6.02 mmol) was added to the solution of compound 2,3-dioxo-4-carboxy-5-(substituted)pyrrolidine (1) (5.02 mmol) and formic acid (8.03 mmol) in ethanol (25 mL) and allowed to reflux for 12 hours. After completion of the reaction, the solution was evaporated under reduced pressure, extracted with ethyl acetate, washed with water and dried over MgSO₄. The crude product was purified by column chromatography on silica gel (EtOAc/Hexane 1:1) to give the product 2.

Ethyl 4-(2-hydroxyethylamino)-1-methyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (2a). White yellowish solid; Yield: 92%; mp 72-74°C; IR (KBr) ν/cm⁻¹ 3346, 1662, 1623, 1215, 1096; ¹H NMR (400 MHz, CDCl₃) δ 4.15 (q, 2H, J 7.2 Hz, OCH₂), 3.94-3.90 (m, 4H, CH-5 & CH₂), 3.70 (t, 2H, J 5.3 Hz, CH₂), 3.00 (s, 3H, NCH₃), 1.24 (t, 3H,
Ethyl 4-(2-hydroxyethylamino)-1,2-dimethyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (2b). Dark brown oil; Yield: 62%; IR (KBr) ν/cm⁻¹ 3201, 1670, 1622, 1217, 1051; ¹H NMR (400 MHz, CDCl₃) δ 4.23-4.09 (m, 2H, OCH₂), 3.99 (q, 1H, J 6.4 Hz, CH-5), 3.95-3.83 (m, 2H, CH₂), 3.68 (t, 2H, J 5.3 Hz, CH₂), 2.90 (s, 3H, NCH₃), 1.30 (d, 3H, J 6.4 Hz, CH₃), 1.24 (t, 3H, J 7.1 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 165.83, 165.31, 147.71, 103.84, 63.16, 59.63, 55.39, 44.45, 27.26, 18.01, 14.53; LCMS (ESI): calculated for C₁₁H₁₈N₂O₄ 265.1 [M+Na]⁺, found 265.1.

Ethyl 2-ethyl-(2-hydroxyethylamino)-1-methyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (2c). Yellow oil; Yield: 67%; IR (KBr) ν/cm⁻¹ 3204, 1673, 1629, 1031; ¹H NMR (400 MHz, CDCl₃) δ 4.22-4.10 (m, 3H, OCH₂ & CH-5), 4.04-3.97 (m, 1H, CH₂), 3.89-3.82 (m, 1H, CH₂), 3.75-3.66 (m, 2H, CH₂), 2.88 (s, 3H, NCH₃), 2.11-2.04 (m, 1H, CH₂CH₃), 1.79 (m, 1H, CH₂CH₃), 1.25 (t, 3H, J 7.1 Hz, CH₃), 0.48 (t, 3H, J 7.5 Hz, CH₃CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 166.03, 165.73, 148.57, 100.57, 63.07, 59.58, 59.27, 44.49, 27.30, 21.64, 14.50, 5.52; LCMS (ESI): calculated for C₁₂H₂₁N₂O₄ 279.1 [M+Na]⁺, found 279.1.

Ethyl 4-(2-hydroxyethylamino)-2-(4-methoxyphenyl)-1-methyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (2d). Dark yellow solid; Yield: 60%; mp 89-90°C; IR (KBr) ν/cm⁻¹ 3478, 1692, 1621, 1242, 1031; ¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, 2H, J 8.7 Hz, CHAr), 6.80 (d, 2H, J 8.7 Hz, CHAr), 4.87 (s, 1H, CH-5), 4.10-3.90 (m, 4H, OCH₂ & CH₂), 3.76-3.74 (m, 5H, OCH₃ & CH₂), 2.70 (s, 3H, NCH₃), 1.01 (t, 3H, J 7.1 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 165.94, 165.51, 159.46, 147.67, 129.02, 128.83, 113.87, 103.68, 63.40, 63.23, 59.53, 55.33, 44.60, 27.63, 14.19; CHN: Found C, 59.64; H, 6.54; N, 7.74 requires C, 61.07; H, 6.63; N, 8.38%; LCMS (ESI): calculated for C₁₇H₂₃N₂O₄ 357.1 [M+Na]⁺, found 357.1.

Ethyl 4-(2-hydroxyethylamino)-1-methyl-5-oxo-2-p-tolyl-2,5-dihydro-1H-pyrrole-3-carboxylate (2e). White solid; Yield: 62%; mp 123-125°C; IR (KBr) ν/cm⁻¹ 3362, 1668, 1617, 1203, 1087; ¹H NMR (400 MHz, CDCl₃) δ 7.06 (d, 2H, J 8.2 Hz, CHAr), 6.98 (d, 2H, J 7.8 Hz, CHAr), 4.87 (s, 1H, CH-5), 4.07-3.89 (m, 4H, OCH₂ & CH₂), 3.74 (t, 2H, J 5.3 Hz, CH₂), 2.69 (s, 3H, NCH₃), 2.28 (s, 3H, CH₃), 1.00 (t, 3H, J 7.1 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 165.97, 165.45, 147.56, 137.88, 134.10, 129.18, 127.59, 103.46, 63.72, 63.03, 59.53, 44.67, 27.67, 21.20, 14.13; CHN: Found C, 63.07; H, 6.79; N, 7.94 requires C, 64.13; H, 6.97; N, 8.80%; LCMS (ESI): calculated for C₁₇H₂₂N₂O₄ 341.1 [M+Na]⁺, found 341.1.

General procedure. Ethyl 4-(2-hydroxyethylamino)-5-oxopyrrolidine-3-carboxylate 6a-e. A solution 2-oxo-4-carboethoxy-5-substituted-3-ethanolaminepyrrolines 2a-e (2.19 mmol) in ethanol (15 mL), and glacial acetic acid (4.38 mmol) was hydrogenated in the presence of 20% wt Pd(OH)₂/C (0.59 mmol) under pressure 1 atm at room temperature for 12 hours. The catalyst was removed by filtration over Celite and rinsed with methanol. The filtrate was dried under reduced pressure and the crude product was purified by column chromatography on silica gel (EtOAc/Hexane 4:1) to give a racemic mixture 6.

Ethyl 4-(2-hydroxyethylamino)-1-methyl-5-oxopyrrolidine-3-carboxylate (6a). Light yellow oil; Yield: 83%; IR (KBr) ν/cm⁻¹ 3377, 1646, 1558, 1222, 1069; ¹H NMR (400 MHz, CDCl₃) δ 4.93 (brs, 1H, OH), 4.20 (qd, 2H, J 7.2, 1.5 Hz, OCH₂), 3.75 (s, 1H, NH), 3.73 (d, 1H, J 10.1 Hz, CH-3), 3.67-3.55 (m, 2H, CH₂OH), 3.52-3.43 (m, 2H, CH₂), 3.09-3.00 (m, 1H, CH-4), 2.89-2.86 (m, 5H, NHCH₂ & NCH₃), 1.28 (t, 3H, J 7.1 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 173.29, 172.24, 61.78, 61.69, 61.31, 50.05, 48.35, 45.76, 30.12, 14.25; LCMS (ESI): calculated for C₁₀H₁₈N₂O₃ 253.1 [M+Na]⁺, found 253.1.

Ethyl 4-(2-hydroxyethylamino)-1,2-dimethyl-5-oxopyrrolidine-3-carboxylate (6b). Light yellow oil; Yield: 25%; ¹H NMR (400 MHz, CDCl₃) δ 4.22 (q, 2H, J 7.2 Hz, OCH₂), 3.77 (s, 1H, NH), 3.75 (d, 1H, J 9.6 Hz, CH-3), 3.66-3.54 (m, 3H, CH₂OH & CH-5), 2.88-2.83 (m, 2H, CH₂NH), 2.81 (s, 3H, NCH₃), 2.52 (dd, 1H, J 9.4, 8.5 Hz, CH-4), 1.35 (d,
Yield: 70%; \(^1\)H NMR (400 MHz, CD\(_2\)OD) \(\delta\) 3.85-3.91 (m, 4H, CH(OH)), 3.27 (m, 4H, CH(OH)), 2.70 (s, 3H, NCH\(_3\)), 2.03 (s, 3H, NCH\(_3\)), 1.57 (s, 3H, NCH\(_3\)), 0.73 (t, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CD\(_2\)OD) \(\delta\) 178.29, 173.47, 61.88, 62.56, 49.32, 47.36, 44.89, 29.12 ppm; LCMS (ESI): calculated for C\(_{17}\)H_{24}N\(_2\)O\(_5\) 359.1 [M+Na]+, found 359.1.

Ethylen-4-(2-hydroxyethylamino)-2-(4-methoxyphenyl)-1-methyl-5-oxopyrrolidine-3-carboxylate (6d). Light yellow oil; Yield: 33%; IR (KBr) \(\nu/cm^{-1}\) 3477, 1714, 1614, 1195, 1030; \(^1\)H NMR (400 MHz, CD\(_2\)OD) \(\delta\) 7.23 (d, 2H, J 8.7 Hz, CH\(_{Ar}\)), 6.96 (d, 2H, J 8.7 Hz, CH\(_{Ar}\)), 5.05 (d, 1H, J 7.3 Hz, CH-5), 4.59 (dd, 1H, J 7.3 Hz, CH-3), 3.90 (t, 1H, J 7.3 Hz, CH-4), 3.83-3.72 (m, 4H, OCH\(_2\), CH\(_2\)OH, NHCH\(_2\)), 3.53-3.45 (m, 2H, NHCH\(_2\)CH\(_2\)OH), 2.70 (s, 3H, NCH\(_3\)), 2.34 (s, 3H, CH\(_3\)), 0.73 (3H, J 7.1 Hz, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CD\(_2\)OD) \(\delta\) 169.74, 168.23, 139.62, 138.47, 130.14, 128.82, 128.21, 77.28, 68.89, 61.52, 57.89, 49.73, 46.05, 25.88, 20.02, 13.44; LCMS (ESI): calculated for C\(_{17}\)H_{24}N\(_2\)O\(_3\) 343.1 [M+Na]+, found 343.1.

General procedure. 6-Substituted-7-methyltetrahydro-1H-pyrrolo[3,4-e][1,4]oxazepine-5,8-diones 8a–e. 2-Oxo-4-carboethoxy-5-substituted-3-ethanoliminepyrrolidines 6 (0.43 mmol) was added to the mixture of potassium tert-butoxide (1.52 mmol) in dry tetrahydrofuran (5 mL) at 0°C and allowed to stir for 3 hours. The precipitate was filtered out and washed with ethyl acetate to give the product 8.

7-Methyltetrahydro-1H-pyrrolo[3,4-e][1,4]oxazepine-5,8-dione (8a). Orange solid; Yield: 86%; \(^1\)H NMR (400 MHz, CD\(_2\)OD) \(\delta\) 3.73 (d, 1H, J 8.4 Hz, CH-3), 3.67-3.54 (m, 3H, CH-5 & CH\(_2\)OH), 3.42 (dd, 1H, J 9.9, 8.4 Hz, CH-5), 2.91-2.84 (m, 3H, NHCH\(_2\) & CH-4), 2.84 (s, 3H, NCH\(_3\)) ppm; \(^{13}\)C NMR (100 MHz, CD\(_2\)OD) \(\delta\) 178.29, 173.47, 61.88, 62.56, 49.32, 47.36, 44.89, 29.12 ppm; LCMS (ESI): calculated for C\(_8\)H\(_{12}\)N\(_2\)O\(_3\) 207.1 [M+Na]+ found 207.1.

6,7-Dimethyltetrahydro-1H-pyrrolo[3,4-e][1,4]oxazepine-5,8-dione (8b). Orange solid; Yield: 61%; \(^1\)H NMR (400 MHz, CD\(_2\)OD) \(\delta\) 3.62 (d, 1H, J 9.1 Hz, CH-3), 3.68-3.55 (m, 3H, CH\(_2\)OH & CH-5), 2.81-2.79 (m, 2H, NHCH\(_2\)), 2.78 (s, 3H, NCH\(_3\)), 2.35 (t, J 9.7 Hz, 1H, CH-4), 1.34 (d, J 6.4 Hz, 3H, CH\(_3\)) ppm; \(^{13}\)C NMR (100 MHz, CD\(_2\)OD) \(\delta\) 178.35, 174.06, 62.57, 60.32, 57.00, 56.89, 48.71, 26.29, 18.33 ppm; LCMS (ESI): calculated for C\(_9\)H\(_{12}\)N\(_2\)O\(_3\) 221.1 [M+Na]+ found 221.1.

6-Ethyl-7-methyltetrahydro-1H-pyrrolo[3,4-e][1,4]oxazepine-5,8-dione (8c). Orange solid; Yield: 56%; \(^1\)H NMR (400 MHz, CD\(_2\)OD) \(\delta\) 3.68 (d, 1H, J 8.7 Hz, CH-3), 3.66-3.56 (m, 3H, CH\(_2\)OH & CH-5), 2.81 (t, J 5.3 Hz, 2H, NHCH\(_2\)), 2.78 (s, 3H, NCH\(_3\)), 2.50 (t, J 8.2 Hz, 1H, CH-4), 1.92 (m, 1H, CH\(_2\)CH\(_3\)), 1.57-1.67 (m, 1H, CH\(_2\)CH\(_3\)), 0.92 (t, J 7.5 Hz, 3H, CH\(_3\)) ppm; \(^{13}\)C NMR (100 MHz, CD\(_2\)OD) \(\delta\) 179.32, 174.14, 62.85, 61.73, 60.31, 53.52, 49.00, 26.75, 24.45, 6.64 ppm.

6-(4-Methoxyphenyl)-7-methyltetrahydro-1H-pyrrolo[3,4-e][1,4]oxazepine-5,8-dione (8d). Orange solid; Yield: 70%; \(^1\)H NMR (400 MHz, CD\(_2\)OD) \(\delta\) 7.21 (d, J 8.7 Hz, 2H, CH\(_{Ar}\)), 6.91 (d, J 8.7 Hz, 2H, CH\(_{Ar}\)), 4.55 (d, J 7.8 Hz, 1H, CH\(_{Ar}\)), 3.55 (m, 3H, CH\(_2\)OH), 2.91-2.84 (m, 3H, NHCH\(_2\) & CH-4), 2.84 (s, 3H, NCH\(_3\)), 2.35 (t, J 9.7 Hz, 1H, CH-4), 1.34 (d, J 6.4 Hz, 3H, CH\(_3\)) ppm; \(^{13}\)C NMR (100 MHz, CD\(_2\)OD) \(\delta\) 178.35, 174.06, 62.57, 60.32, 57.00, 56.89, 48.71, 26.29, 18.33 ppm; LCMS (ESI): calculated for C\(_9\)H\(_{12}\)N\(_2\)O\(_3\) 221.1 [M+Na]+ found 221.1.
Hz, 1H, CH-5), 3.80 (d, J 7.8 Hz, 1H, CH-3), 3.76 (s, 3H, OCH3), 3.68-3.58 (m, 2H, CH2OH), 2.85 (t, J 5.3 Hz, 2H, NHCH2), 2.74-2.67 (m, 1H, CH-4), 2.56 (s, 3H, NCH3) ppm; 13C NMR (100 MHz, CD3OD) δ 178.02, 174.35, 159.95, 131.06, 128.33, 114.17, 65.51, 62.91, 60.34, 58.78, 54.41, 48.72, 27.31 ppm.

7-Methyl-6-p-tolyltetrahydro-1H-pyrrolo[3,4-e][1,4]oxazepine-5,8-dione (8e). Orange solid; Yield: 68%; 1H NMR (400 MHz, CD3OD) δ 7.17 (s, 4H, CHAr), 4.58 (d, J 7.8 Hz, 1H, CH-5), 3.80 (d, J 9.1 Hz, 1H, CH-3), 3.70-3.58 (m, 2H, CH2OH), 2.87 (t, J 5.0 Hz, 2H, NHCH2), 2.71-2.76 (m, 1H, CH-4), 2.56 (s, 3H, NCH3), 2.30 (s, 3H, CH3) ppm; 13C NMR (100 MHz, CD3OD) δ 177.79, 174.43, 138.04, 136.30, 129.23, 127.31, 65.78, 62.89, 60.22, 58.60, 48.67, 27.35, 19.83 ppm.

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Supplementary Material

1H NMR and 13C NMR spectra of compounds 2a, 2b, 2c, 2d, 2e, 6a, 6b, 6c, 6d, 6e, 8b, 8c, 8d, and 8e are given in the Supplementary Material file associated with this paper.

References


31. Mohammat, M. F.; Shaameri, Z.; Hamzah, A. S. *Molecules* 2009, 14, 250. [http://dx.doi.org/10.3390/molecules14010250](http://dx.doi.org/10.3390/molecules14010250)


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