A Novel Catalyst-Free Tandem Reaction for the Synthesis of 5-Hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones in Water Medium

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Abstract: A novel catalyst-free, water-medium, tandem reaction for the synthesis of 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones was developed through a one-pot strategy from nitroethylenes and 1,3-dicarbonyl compounds. A series of 1-aryl-2-nitroethenes and 1-nitroalk-1-enes were surveyed to determine the scope of this tandem reaction with moderate to good yield.

Key words: 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones, catalyst-free, water medium, tandem reaction

Introduction

5-Hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones are important N-heterocyclic compounds in organic and medicinal chemistry, that show interesting pharmacological properties[1] and neuritogenic activity.[2] It has been reported that half of the small molecule drugs that received FDA approval in 2005–2006 contain at least one azole or azine ring.[3] A wide variety of biologically active natural products containing the 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one or 3,4-epoxy-5-hydroxypyrrolidin-2-one moiety have been isolated, such as oteromycin (Figure 1), which is an endothelin receptor antagonist,[2a] and epolactaene, which is effective in promoting neural outgrowth and arresting the cell cycle at the G0/G1 phase in a human neuroblastoma cell line, SH-SY5Y[2b] etc.

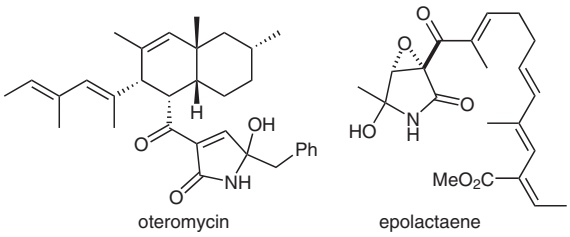

Figure 1 The structures of oteromycin and epolactaene

Furthermore, 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones are useful intermediates in organic synthesis.[4] Some approaches to the synthesis of the 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one skeleton have been reported including: the reaction of α,β-unsaturated ketones with isocyanides,[5] the reaction of α,β-diketones with acetamides,[2b,6] nucleophilic addition of organometallic reagents,[5] selective oxidation or reduction of pyrrolinones and maleimide derivatives,[4,7] and transition-metal-catalyzed coupling, oxidative or tandem process.[8] Strong nucleophilic reagents, oxidants, reductants, or organometallic reagents were generally used to promote the reaction. In many cases, the yields or selectivities are far from satisfactory due to the stepwise approach or several side reactions. Therefore, finding a novel and efficient approach to build the 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one framework has attracted a great deal of attention from researchers.

In recent years, water as reaction medium has exhibited great advantages and potential in modern organic synthesis.[9] These include that it is green, inexpensive, nontoxic, and safe; thus many organic reactions have been developed in a water medium.[10] This includes asymmetric catalytic carbon–carbon bond-formation reactions, radical reactions, and multicomponent processes. It is particularly important to develop more reactions in water as a medium for research. In the present work, we surprisingly found a novel catalyst-free tandem reaction for the synthesis of 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones in a water medium.

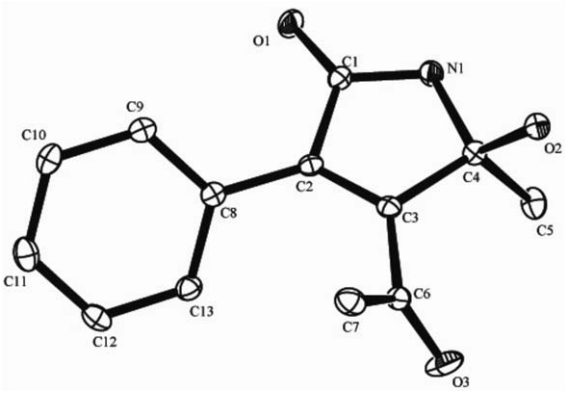

Figure 2 The single crystal structure of **5a**

In our previous research into the reaction of 1,3-dicarbonyl compounds with nitroethylenes, the Michael adduct **3a** and the hydroxyimino-substituted dihydrofuran derivative **4a** were obtained (Scheme 1). Further studies on constructing 3,4-dihydro-1,3-oxazin-2-one **6a** were carried out as one-pot tandem reactions. Surprisingly, the 5-hy-

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droxy-1,5-dihydro-2*H*-pyrrol-2-one **5a** rather than **6a** was found (Scheme 1). The structure of **5a** was confirmed by X-ray diffraction (Figure 2).[11] Comparing the ^{1}H NMR spectrum of **5a** with it after adding deuterium oxide led to the disappearance of the signals at $\delta = 6.27$ and 9.01, providing additional evidence for the assignment of the structure of **5a**.

Biographical Sketches

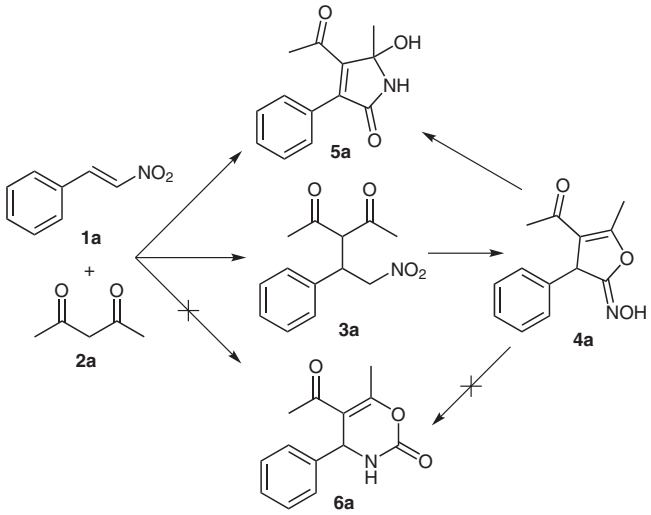
Ming-Yu Wu was born in Jiangxi province of China. He entered Sichuan University in 2006 in the college of chemistry, and in 2008 he began his Students Innovation Training under the supervision of Prof. Xiao-Qi Yu. After obtaining a B.S. degree in 2010, he began his Ph.D. in the Yu group. His current research interests focus on green synthesis methodology.

Kun Li was born in Shandong province of China in 1980. He obtained his B.S. degree from Yantai University in 2003. In the same year, he entered Sichuan University for his M.Sc. degree and won a chance to study for a doctoral degree (under the supervision of Prof. Xiao-Qi Yu) in 2005. After obtaining his Ph.D. in 2008, he joined the Yu group as a lecturer. He continued his postdoctoral studies at Hong Kong University with Dr. Patrick-Henry Toy from 2010. His research interests focus on biocatalysis and green synthesis methodology.

Na Wang received her B.S. from Guizhou University in 1998. She obtained her Ph.D. in 2006 from Zhejiang University under the supervision of Prof. Xian-Fu Lin. Later she joined Prof. Xiao-Qi Yu's group as a lecturer at Sichuan University. Her research focuses on enzymatic synthesis methodology and enzyme engineering.

Ting He was born in Shaanxi province of China in 1987. She received her B.Sc. in chemistry from Sichuan University in 2009. She is currently a Ph.D. student under the supervision of Prof. Xiao-Qi Yu working on the design and synthesis of low-molecular-weight gelators and seeking to exploit their catalytic properties.

Xiao-Qi Yu received his M.S. and Ph.D. from Sichuan University in 1987 and 1993. Subsequently, he was a lecturer and associate professor from 1993 to 1999, and then full professor at Sichuan University; between 1998 and 2001, he was a research associate at Hong Kong University with Prof. Chi-Ming Che. After that, he was acting deputy director in the key laboratory of Green and Technology (Sichuan University), Ministry of Education. His research focuses on gene transfection, biocatalysis, and green synthesis methodology.



Scheme 1 A novel process for the synthesis of 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones

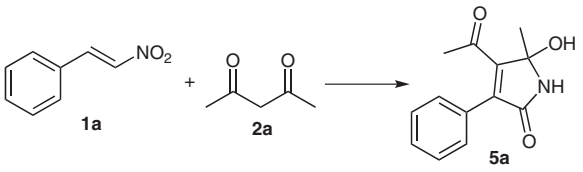
Results and Discussion

With the aim of identifying a novel and efficient process to synthesize of **5a**, the model reaction of pentane-2,4-dione (**2a**) with β-nitrostyrene (**1a**) was investigated in detail. We first examined the influence of solvent on the reaction. Several commonly used solvents or mixtures were screened, the results are shown in Table 1. Generally, the reaction did not proceed favorably in all of the organic solvents examined, but did so successfully in mixtures of water and organic solvents. It is notable that this reaction could be carried out in pure water (entry 1), though a poor yield was obtained due to the low solubility of the substrates. Among all of the mixtures of water with organic solvents examined, aprotic polar solvents such as dimethyl sulfoxide, *N*,*N*-dimethylformamide, and acetonitrile were observed as much better than protic solvents and aprotic nonpolar solvent such as butyl alcohol, toluene, tetrahydrofuran, and 1,4-dioxane. Dimethyl sulfoxide–water mixtures gave the best result. In all of the mixture solvents with water, only toluene had a poor miscibility with water at 80 °C. This led us to examine phase-transfer agents; however, low yields were obtained in these reactions (entries 9 and 10). Thus the dimethyl sulfoxide–water mixture was chosen as the solvent in the following study.

Encouraged by these results, we then examined the influence of the amount of water in the mixture on the yield of this catalyst-free reaction. The relationship between water content and yield is a bell-shaped curve, and at 50% water the highest yields were observed (Figure 3). Thus, at the outset as the content of water increased, the yield of **5a** is seen to improve, however, once the water content surpasses 50%, the yield decreased due to the poor solubility.

To extend the scope of substrates in this novel catalyst-free, water-medium process, a wide range of nitroethylenes **1** and 1,3-dicarbonyl compounds **2** were investigated (Table 2). All these substrates could undergo the desired reaction to afford corresponding products **5** efficiently. Among them, 1-aryl-2-nitroethenes **1a–k** were more reactive than 1-nitroalk-1-ene **1l**, and 1-aryl-2-nitroethenes with *ortho*-substituted aryl groups **1h**,**i** were significantly better. Pentane-2,4-dione (**2a**) was much more reactive than heptane-3,5-dione (**2b**) in the reaction, while ethyl acetoacetate and diethyl malonate did not work smoothly, and only trace product was obtained with cyclohexane-1,3-dione.

Table 1 Influence of Solvent on the Reaction[a]



Entry	Solvent	Yield[b] (%)
1	H_2O	21
2	DMSO–H_2O	84
3	DMF–H_2O	48
4	MeCN–H_2O	30
5	1,4-dioxane–H_2O	20
6	THF–H_2O	25
7	BuOH–H_2O	12
8	toluene–H_2O	7
9	toluene–H_2O[c]	13
10	toluene–H_2O[d]	24

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (2 equiv), solvent–H_2O (1:1, 1 mL), 80 °C, 12 h.
[b] Yield was determined by HPLC.
[c] Et_4NCl (10 mg) was added.
[d] Et_4NI (10 mg) was added.

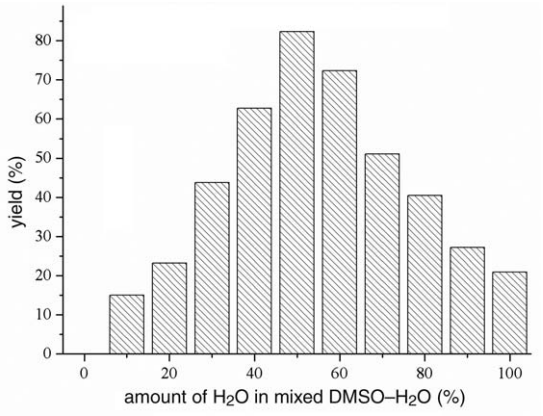
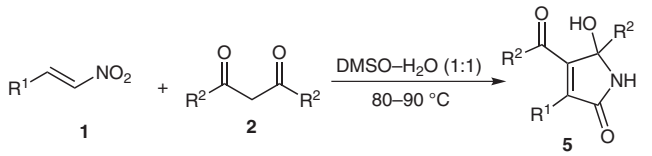


Figure 3 The influence of different water contents on the reaction of **1a** with **2a**

Table 2 Synthesis of 5-Hydroxy-1,5-dihydro-2*H*-pyrrol-2-one Derivatives **5** with Different Nitroethylenes **1** and Pentane-2,4-dione (**2a**) or Heptane-3,5-dione (**2b**)[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	Ph	Me	**5a**	65
2	4-MeC_6H_4	Me	**5b**	61
3	4-$MeOC_6H_4$	Me	**5c**	56
4	4-FC_6H_4	Me	**5d**	50
5	4-ClC_6H_4	Me	**5e**	60
6	4-BrC_6H_4	Me	**5f**	70
7	4-$F_3CC_6H_4$	Me	**5g**	61
8	2-ClC_6H_4	Me	**5h**	92
9	2-BrC_6H_4	Me	**5i**	71
10	3-ClC_6H_4	Me	**5j**	65
11	furan-2-yl	Me	**5k**	53
12	Pr	Me	**5l**	25
13	Ph	Et	**5m**	50
14	4-MeC_6H_4	Et	**5n**	48
15	4-$MeOC_6H_4$	Et	**5o**	55
16	4-FC_6H_4	Et	**5p**	50
17	4-ClC_6H_4	Et	**5q**	50
18	4-BrC_6H_4	Et	**5r**	52
19	4-$F_3CC_6H_4$	Et	**5s**	50
20	2-ClC_6H_4	Et	**5t**	75
21	2-BrC_6H_4	Et	**5u**	64
22	3-ClC_6H_4	Et	**5v**	55
23	Pr	Et	**5w**	trace

[a] The reaction was conducted with nitroethylenes **1** (2 mmol), pentane-2,4-dione (**2a**) or heptane-3,5-dione (**2b**) (4 mmol) DMSO–H_2O (1:1, 20 mL), entries 1–12: 80 °C, 12 h; entries 13–24: 90 °C, 48 h.
[b] Isolated yield.

To understand this water-promoted tandem reaction clearly, we utilized ^{13}C NMR to monitor the progress of the reaction. The NMR spectra at different times (2, 6, and 12 h, Figure 4) were collected; the chemical shifts of **3a** (a, b, c, and d), **4a** (e, f, g, and h), as well as **5a** (i, j, k and l) were compared to determine their existence in the reaction medium. Compounds **3a** and **4a** could be detected and isolated. From NMR spectroscopy of the reaction system at different times, only the Michael product **3a** was found during the first two hours, **3a** decreased gradually and transformed to **4a** and **5a** within 2–6 hours, but **4a** was the major product. After six hours, **4a** and residual **3a** had almost completely converted into **5a**. From the above data, we could conclude that **3a** and **4a** were the intermediates in this tandem reaction.

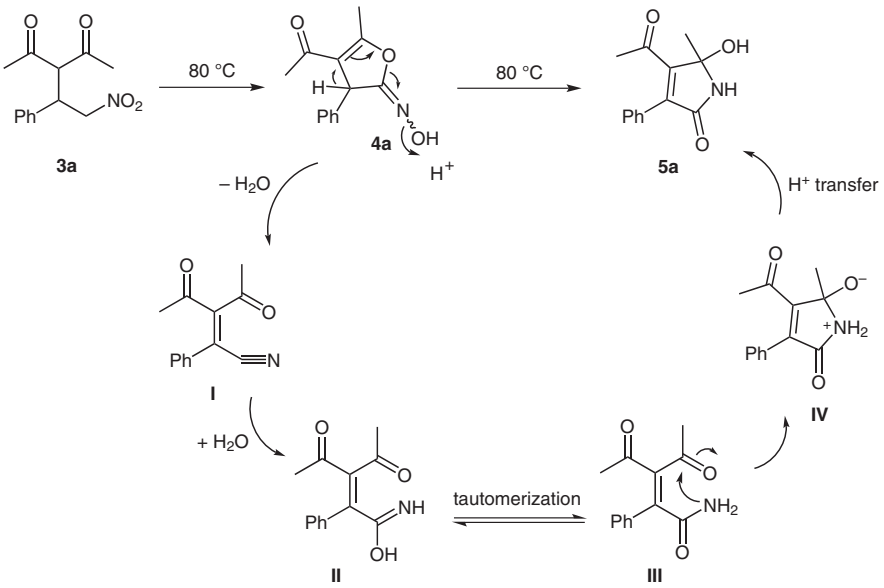
Nicolaou[12] and Quai[5a] proposed a mechanism for the synthesis of 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones going through a intermediate (iminolactone) which is very similar to **4a**. However, our reaction proceeds smoothly when conducted under argon, while the mechanism reported by Nicolaou required an oxidant, namely oxygen. When **4a** was dissolved in dimethyl sulfoxide–water at 80 °C, formation of **5a** was very slow. However, when a drop of acetic acid was added, **5a** was formed very quickly. On the other hand, when **3a** was used as the starting material, both **4a** and **5a** were formed, and **4a** could be completely converted into **5a** after several hours. Thus, perhaps a proton generated from the conversion of **3a** into **4a** promoted the transformation of **4a** to **5a**.

Combining the results from the ^{13}C NMR analysis of the reaction process and the experiments described above, we proposed a mechanism for the conversion of **4a** into **5a** (Scheme 2); we note that a similar reaction for an analogue of **4a** has been reported.[13] It is well known that oximes undergo Beckman rearrangement to produce amides under acidic or thermal reaction conditions. However, we observed formation of **5a**, a five-membered-ring-containing product, rather than six-membered-ring product **6a**. Thus, based on the above results we propose that once **4a** is formed from **3a**, loss of the benzylic proton and water leads to the formation of highly conjugated intermediate **I**. Hydration of **I** then leads to **II**, which can tautomerize to form **III**. Subsequently, nucleophilic attack by the amide nitrogen on the ketone carbon leads to **IV**. Finally, proton transfer accounts for the formation of **5a**.

Conclusion

We have developed a novel, catalyst-free, water-medium, tandem process for the synthesis of 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones from nitroethylenes and 1,3-dicarbonyl compounds and this approach have a good universality. The initial materials are inexpensive or can be prepared via cost-effective synthesis. In addition, it is easy to operation and environmentally friendly as a catalyst-free and tandem process in water medium. We believe that these results could afford a novel access to functionalize 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones and their derivatives.

^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument using $CDCl_3$ and DMSO-d_6 as the solvent with TMS as an internal standard at r.t. HPLC was carried out using a Shimadzu organizer consisting of a LC-2010A HT Integrator, a UV/VIS Detector. C18 column was used in the HPLC experiments with MeCN–



Scheme 2 The proposed mechanism of the reaction from **4a** to **5a**

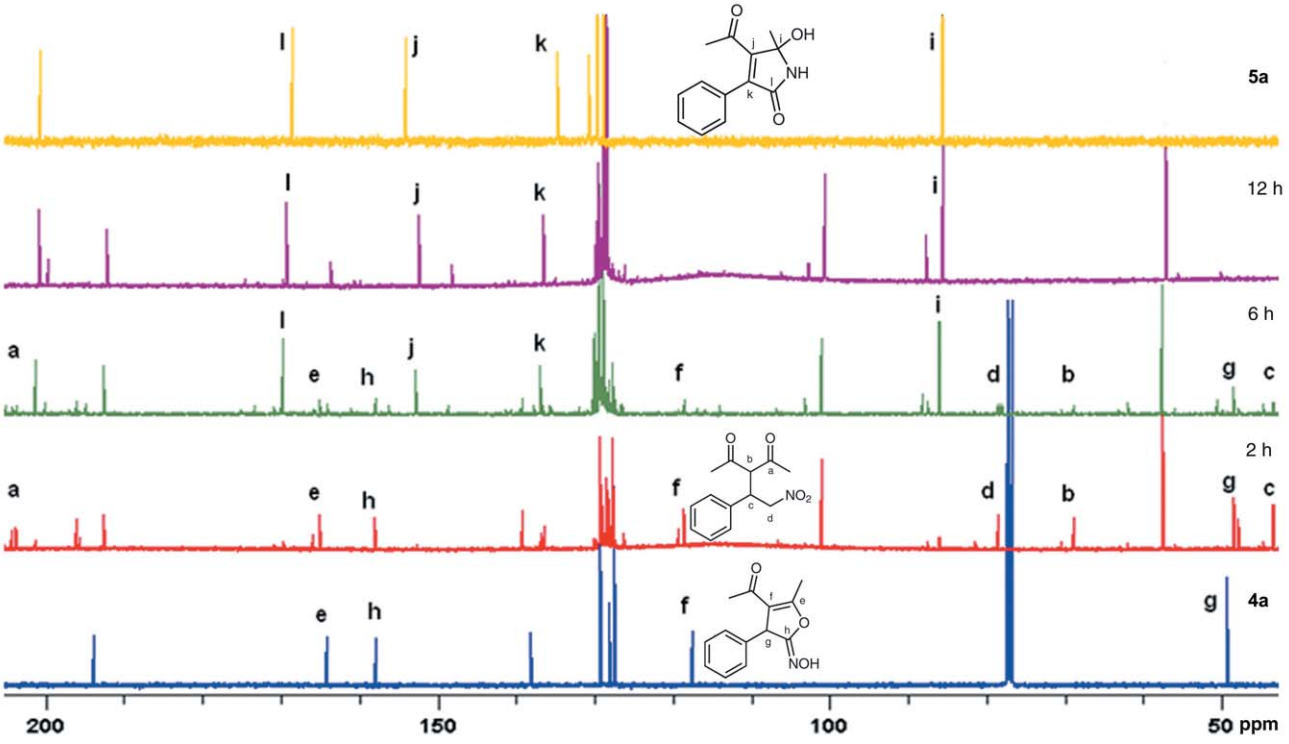


Figure 4 The NMR spectra at different times

H_2O (50:50), 0.8 mL/min and UV = 254 nm. HRMS were performed on Bruker Daltonics Bio TOF mass spectrometer. Melting points were determined on a microscopic apparatus and are uncorrected. In some cases (**5n**,**s**), low melting points were observed, presumably owing to the presence of water within the solid products. Attempts to remove the water (by vacuum drying, heating, etc.) were unsuccessful.

Nitroalkenes 1; General Procedure

Aldehyde (0.05 mol), $MeNO_2$ (0.05 mol), and MeOH (10–20 mL) were added to a round-bottom flask and then stirred vigorously. NaOH soln (10 mL of 10.5 M) was added dropwise in an ice bath, a larger amount of a white or yellow solid precipitated, stirring continued for 15 min. Distilled H_2O was added until the soln became clear, then the soln was added dropwise to concd HCl (30 mL) and a yellow solid precipitated. The yellow solid was filtered and washed with H_2O, then evaporated in a vacuum drying oven. After recrystallization (EtOH), yellow needle-like crystalloids were obtained.

5-Hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones; General Procedure

Nitroethylene **1** (2 mmol), 1,3-dicarbonyl compound **2** (4 mmol), DMSO (10 mL), and H_2O (10 mL) were added to a 50-mL round-bottom flask. The mixture was stirred at 80–90 °C for 12–48 h, then

brine (20 mL) was added and the soln was extracted with EtOAc (3 × 30 mL). The organic phase was combined and washed with brine (30 mL), then dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, 300–400 mesh) to give the product.

4-Acetyl-5-hydroxy-5-methyl-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (5a)

Yield: 300.1 mg (65%); white solid; mp 135–137 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.01 (s, 1 H, NH), 7.47–7.38 (m, 5 H, H_{Ph}), 6.27 (s, 1 H, OH), 2.12 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 200.6, 168.6, 154.1, 134.7, 130.7, 129.6, 129.5, 128.8, 85.6, 31.5, 25.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{13}NO_3Na$: 254.0788; found: 254.0784.

4-Acetyl-5-hydroxy-5-methyl-3-(4-tolyl)-1,5-dihydro-2*H*-pyrrol-2-one (5b)

Yield: 300.3 mg (61%); white solid; mp 120–121 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.94 (s, 1 H, NH), 7.30 (d, *J* = 8 Hz, 2 H, H_{Ph}), 7.25 (d, *J* = 8.0 Hz, 2 H, H_{Ph}), 6.20 (s, 1 H, OH), 2.34 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 200.8, 168.7, 153.5, 139.3, 134.5, 129.5, 129.4, 127.8, 85.6, 31.5, 25.7, 21.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{15}NO_3Na$: 268.0944; found: 268.0945.

4-Acetyl-5-hydroxy-3-(4-methoxyphenyl)-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one (5c)

Yield: 291.5 mg (56%); white solid; mp 112–115 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.93 (s, 1 H, NH), 7.37 (d, *J* = 8.8 Hz, 2 H, H_{Ph}), 7.01 (*J* = 8.8 Hz, 2 H, H_{Ph}), 6.17 (s, 1 H, OH), 3.79 (s, 3 H, OCH_3), 2.13 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 200.8, 168.9, 160.5, 152.5, 134.2, 131.1, 122.8, 114.3, 85.5, 55.6, 31.4, 25.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{15}NO_4Na$: 284.0893; found: 284.0898.

4-Acetyl-3-(4-fluorophenyl)-5-hydroxy-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one (5d)

Yield: 248.7 mg (50%); white solid; mp 140–142 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.00 (s, 1 H, NH), 7.46–7.43 (m, 2 H, H_{Ph}), 7.29 (t, *J* = 9.0 Hz, 2 H, H_{Ph}), 6.25 (s, 1 H, OH), 2.15 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 205.2, 173.2, 167.8 (d, J_{F-C} = 252 Hz), 158.8, 138.3, 136.5 (d, J_{F-C} = 9 Hz), 131.8, 120.6 (d, J_{F-C} = 21 Hz), 90.4, 36.3, 30.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{12}FNO_3Na$: 272.0693; found: 272.0702.

4-Acetyl-3-(4-chlorophenyl)-5-hydroxy-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one (5e)

Yield: 320 mg (60%); white solid; mp 139–140 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.03 (s, 1 H, NH), 7.52 (d, *J* = 8.4 Hz, 2 H, H_{Ph}), 7.42 (*J* = 8.8 Hz, 2 H, H_{Ph}), 6.28 (s, 1 H, OH), 2.16 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 200.4, 168.3, 154.5, 134.5, 133.4, 131.3, 129.5, 128.9, 85.7, 31.6, 25.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}ClNO_3$: 266.0578; found: 266.0577.

4-Acetyl-3-(4-bromophenyl)-5-hydroxy-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one (5f)

Yield: 431.8 mg (70%); white solid; mp 141–143 °C.

^{1}H NMR (400 MHz, TMS, DMSO-d_6): δ = 9.03 (s, 1 H, NH), 7.65 (d, *J* = 8.4 Hz, 2 H, H_{Ph}), 7.35 (*J* = 8.4 Hz, 2 H, H_{Ph}), 6.29 (s, 1 H, OH), 2.17 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 200.4, 168.2, 154.5, 133.5, 131.8, 131.6, 129.8, 123.2, 85.7, 31.6, 25.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}BrNO_3$: 310.0073; found: 310.0077.

4-Acetyl-5-hydroxy-5-methyl-3-[4-(trifluoromethyl)phenyl]-1,5-dihydro-2*H*-pyrrol-2-one (5g)

Yield: 364.7 mg (61%); white solid; mp 135–137 °C.

^{1}H NMR (400 MHz, DMSO-d_6): 9.08 (s, 1 H, NH), 7.81 (d, *J* = 8.4 Hz, 2 H, H_{Ph}), 7.61 (*J* = 8.4 Hz, 2 H, H_{Ph}), 6.36 (s, 1 H, OH), 2.19 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 200.0, 168.0, 155.6, 134.9, 133.4, 130.3, 130.1, 129.8, 129.5 129.2, 128.6, 125.9, 125.6, 125.6, 125.5, 123.2, 85.8, 31.6, 25.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}F_3NO_3$: 300.0842; found: 300.0854.

4-Acetyl-3-(2-chlorophenyl)-5-hydroxy-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one (5h)

Yield: 485.3 mg (92%); white solid; mp 126–128 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.03 (s, 1 H, NH), 7.56 (d, *J* = 8.4 Hz, 1 H, H_{Ph}), 7.48–7.41 (m, 2 H, H_{Ph}), 7.30 (d, *J* = 8.8 Hz, 1 H, H_{Ph}), 6.28 (s, 1 H, OH), 2.02 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.9, 167.7, 153.8, 137.1, 132.8, 131.5, 131.0, 130.9, 129.8, 127.5, 86.2, 30.8, 26.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}ClNO_3$: 266.0578; found: 266.0577.

4-Acetyl-3-(2-bromophenyl)-5-hydroxy-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one (5i)

Yield: 436.9 mg (71%); white solid; mp 128–131 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.05 (s, 1 H, NH), 7.72 (d, *J* = 8.0 Hz, 1 H, H_{Ph}), 7.49–7.28 (m, 3 H, H_{Ph}), 6.23 (s, 1 H, OH), 1.99 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.9, 167.1, 152.5, 138.9, 132.6, 132.4, 130.6, 130.6, 127.6, 122.4, 85.7, 30.5, 25.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}BrNO_3$: 310.0073; found: 310.0077.

4-Acetyl-3-(3-chlorophenyl)-5-hydroxy-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one (5j)

Yield: 345 mg (65%); white solid; mp 137–139 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.05 (s, 1 H, NH), 7.52–7.45 (m, 3 H, H_{Ph}), 7.30 (d, *J* = 7.2 Hz, 1 H, H_{Ph}), 6.31 (s, 1 H, OH), 2.18 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 200.2, 168.1, 155.0, 133.4, 133.1, 132.7, 130.7, 129.4, 129.0, 128.2, 85.7, 31.6, 25.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}ClNO_3$: 266.0578; found: 266.0577.

4-Acetyl-3-(furan-2-yl)-5-hydroxy-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one (5k)

Yield: 232.5 mg (53%); white solid; mp 124–126 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.99 (s, 1 H, NH), 7.84 (s, 1 H, H_{Ar}), 7.16 (d, J = 3.2 Hz, 1 H, H_{Ar}), 6.63 (d, J = 1.6 Hz, 1 H, H_{Ar}), 6.31 (s, 1 H, OH), 2.04 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 201.5, 166.9, 150.3, 145.6, 145.5, 120.6, 113.2, 112.5, 86.0, 32.2, 25.4.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{11}H_{11}NO_4Na$: 244.0580; found: 244.0579.

4-Acetyl-5-hydroxy-5-methyl-3-propyl-1,5-dihydro-2*H*-pyrrol-2-one (5l)

Yield: 96 mg (25%); white solid; mp 90–93 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.71 (s, 1 H, NH), 7.06 (s, 1 H, OH), 3.38 (s, 3 H, CH_3), 3.36 (m, 2 H, CH_2), 2.50 (s, 3 H, CH_3), 2.46–2.37 (m, 2 H, CH_2), 1.85 (t, J = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 198.1, 169.5, 151.2, 141.6, 85.8, 31.4, 26.2, 25.9, 21.8, 14.4.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{10}H_{15}NO_3Na$: 220.0944; found: 220.0953.

5-Ethyl-5-hydroxy-3-phenyl-4-propionyl-1,5-dihydro-2*H*-pyrrol-2-one (5m)

Yield: 260.2 mg (50%); white solid; mp 110–112 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.83 (s, 1 H, NH), 7.46–7.42 (m, 3 H, H_{Ph}), 7.37–7.35 (m, 2 H, H_{Ph}), 6.28 (s, 1 H, OH), 2.47–2.41 (m, 1 H, CH_2), 2.37–2.30 (m, 1 H, CH_2), 1.99–1.86 (m, 2 H, CH_2), 0.87 (t, J = 7.2 Hz, 3 H, CH_3), 0.80 (t, J = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 230.8, 168.7, 153.0, 134.2, 13.1, 129.1, 128.8, 128.4, 88.3, 36.3, 29.8, 7.9, 7.2.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{17}NO_3Na$: 282.1101; found: 282.1102.

5-Ethyl-5-hydroxy-4-propionyl-3-(4-tolyl)-1,5-dihydro-2*H*-pyrrol-2-one (5n)

Yield: 262.2 mg (48%); white solid; mp 65–70 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.79 (s, 1 H, NH), 7.26 (d, J = 8.4 Hz, 2 H, H_{Ph}), 7.24 (d, J = 8.4 Hz, 2 H, H_{Ph}), 6.23 (s, 1 H, OH), 2.46–2.39 (m, 1 H, CH_2), 2.38–2.32 (m, 1 H, CH_2), 2.33 (s, 3 H, CH_3), 1.99–1.85 (m, 2 H, CH_2), 0.87 (t, J = 7.2 Hz, 3 H, CH_3), 0.78 t, J = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 204.5, 169.3, 152.8, 139.3, 134.5, 129.5, 129.2, 127.7, 88.7, 36.7, 30.3, 21.4, 8.4, 7.7.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{19}NO_3Na$: 296.1257; found: 296.1257.

5-Ethyl-5-hydroxy-3-(4-methoxyphenyl)-4-propionyl-1,5-dihydro-2*H*-pyrrol-2-one (5o)

Yield: 317.3 mg (55%); white solid; mp 115–117 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.78 (s, 1 H, NH), 7.33 (d, J = 9.0 Hz, 2 H, H_{Ph}), 7.00 (d, J = 8.4 Hz, 2 H, H_{Ph}), 6.20 (s, 1 H, OH), 3.79 (s, 3 H, CH_3), 2.47–2.35 (m, 2 H, CH_2), 1.97–1.91 (m, 1 H, CH_2), 1.90–1.84 (m, 1 H, CH_2), 0.89 (t, J = 7.2 Hz, 3 H, CH_3), 0.77 (t, J = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 204.6, 169.4, 160.5, 151.8, 134.1, 130.8, 122.8, 114.4, 88.6, 55.7, 36.6, 30.4, 8.4, 7.8.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{19}NO_4Na$: 312.1206; found: 312.1206.

5-Ethyl-3-(4-fluorophenyl)-5-hydroxy-4-propionyl-1,5-dihydro-2*H*-pyrrol-2-one (5p)

Yield: 277.3 mg (50%); white solid; mp 84–86 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.86 (s, 1 H, NH), 7.42 (q, J_1 = 6.0 Hz, J_2 = 9.0 Hz, 2 H, H_{Ph}), 7.29 (t, J = 9.0 Hz, 2 H, H_{Ph}), 6.29 (s, 1 H, OH), 2.49–2.44 (m, 1 H, CH_2), 2.40–2.33 (m, 1 H, CH_2), 1.96–1.85 (m, 2 H, CH_2), 0.89 (t, J = 7.2 Hz, 3 H, CH_3), 0.79 (t, J = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 204.2, 169.0, 163.5, 162.9 (d, J_{F-C} = 244.5 Hz), 153.5, 133.5, 131.5 (d, J_{F-C} = 7.5 Hz), 127.0, 116.0 (d, J_{F-C} = 22.5 Hz), 88.8, 36.8, 30.3, 8.4, 7.7.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{16}FNO_3Na$: 300.1006; found: 300.1056.

3-(4-Chlorophenyl)-5-ethyl-5-hydroxy-4-propionyl-1,5-dihydro-2*H*-pyrrol-2-one (5q)

Yield: 292.4 mg (50%); white solid; mp 90–92 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.89 (s, 1 H, NH), 7.52 (d, J = 8.4 Hz, 2 H, H_{Ph}), 7.39 (d, J = 8.4 Hz, 2 H, H_{Ph}), 6.34 (s, 1 H, OH), 2.49–2.46 (m, 1 H, CH_2), 2.41–2.34 (m, 1 H, CH_2), 1.95–1.85 (m, 2 H, CH_2), 0.89 (t, J = 6.0 Hz, 3 H, CH_3), 0.79 (t, J = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 204.1, 168.8, 154.1, 134.4, 133.3, 131.0, 129.4, 129.0, 88.8, 36.9, 30.3, 8.3, 7.6.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{16}ClNO_3Na$: 316.0711; found: 316.0722.

3-(4-Bromophenyl)-5-ethyl-5-hydroxy-4-propionyl-1,5-dihydro-2*H*-pyrrol-2-one (5r)

Yield: 350.5 mg (52%); white solid; mp 91–93 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.87 (s, 1 H, NH), 7.63 (d, J = 8.4 Hz, 2 H, H_{Ph}), 7.30 (d, J = 8.4 Hz, 2 H, H_{Ph}), 6.36 (s, 1 H, OH), 2.48–2.44 (m, 1 H, CH_2), 2.40–2.33 (m, 1 H, CH_2), 1.93–1.86 (m, 2 H, CH_2), 0.88 (t, J = 7.2 Hz, 3 H, CH_3), 0.77 (t, J = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 208.9, 173.5, 158.8, 138.1, 136.7, 136.0, 134.5, 127.9, 93.6, 41.7, 35.0, 13.1, 12.4.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{16}BrNO_3Na$: 362.0206; found: 362.0180.

5-Ethyl-5-hydroxy-4-propionyl-3-(4-(trifluoromethyl)phenyl)-1,5-dihydro-2*H*-pyrrol-2-one (5s)

Yield: 326.8 mg (50%); white solid; mp 60–63 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.98 (s, 1 H, NH), 7.82 (d, J = 8.4 Hz, 2 H, H_{Ph}), 7.60 (d, J = 7.8 Hz, 2 H, H_{Ph}), 6.43 (s, 1 H, OH), 2.59–2.52 (m, 1 H, CH_2), 2.44–2.38 (m, 1 H, CH_2), 1.97–1.91 (m, 2 H, CH_2), 0.91 (t, J = 7.2 Hz, 3 H, CH_3), 0.83 (t, J = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 203.9, 168.6, 155.3, 134.7, 133.2, 130.1, 129.7, 129.5, 125.8, 125.7, 125.4, 123.6, 88.9, 37.0, 30.2, 8.3, 7.6.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{17}F_3NO_3$: 328.1155; found: 328.1146.

3-(2-Chlorophenyl)-5-ethyl-5-hydroxy-4-propionyl-1,5-dihydro-2*H*-pyrrol-2-one (5t)

Yield: 440 mg (75%); white solid; mp 95–98 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.86 (s, 1 H, NH), 7.56–7.55 (m, 1 H, H_{Ph}), 7.47–7.42 (m, 2 H, H_{Ph}), 7.28 (d, J = 6.6 Hz, 1 H, H_{Ph}), 6.28 (s, 1 H, OH), 2.40–2.33 (m, 1 H, CH_2), 2.31–2.24 (m, 1 H, CH_2), 2.14–2.08 (m, 1 H, CH_2), 1.96–1.90 (m, 1 H, CH_2), 0.82 (t, J = 7.2 Hz, 3 H, CH_3), 0.80 (t, J = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 200.6, 168.4, 153.1, 136.7, 132.7, 131.6, 131.0, 130.8, 129.9, 127.6, 89.6, 36.1, 30.5, 8.5, 7.6.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{16}ClNO_3Na$: 316.0711; found: 316.0722.

3-(2-Bromophenyl)-5-ethyl-5-hydroxy-4-propionyl-1,5-dihydro-2*H*-pyrrol-2-one (5u)
Yield: 431.2 mg (64%); white solid; mp 101–103 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.89 (s, 1 H, NH), 7.72 (d, J = 8.4 Hz, 1 H, H_{Ph}), 7.50–7.16 (m, 3 H, H_{Ph}), 6.22 (s, 1 H, OH), 2.43–2.21 (m, 2 H, CH_2), 2.14–2.07 (m, 1 H, CH_2), 1.99–1.93 (m, 1 H, CH_2), 0.85–0.80 (m, 6 H, CH_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 200.1, 168.5, 152.3, 138.7, 133.1, 133.0, 131.4, 131.1, 128.1, 122.8, 89.7, 36.1, 3.4, 8.7, 7.7.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{16}BrNO_3Na$: 360.0206; found: 360.0180.

3-(3-Chlorophenyl)-5-ethyl-5-hydroxy-4-propionyl-1,5-dihydro-2*H*-pyrrol-2-one (5v)
Yield: 322 mg (55%); white solid; mp 94–97 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.75 (s, 1 H, NH), 7.30–7.26 (m, 3 H, H_{Ph}), 7.11 (d, J = 7.2 Hz, 1 H, H_{Ph}), 6.21 (s, 1 H, OH), 2.38–2.31 (m, 1 H, CH_2), 2.26–2.19 (m, 1 H, CH_2), 1.79–1.72 (m, 2 H, CH_2), 0.72 (t, J = 7.5 Hz, 3 H, CH_3), 0.63 (t, J = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 204.0, 168.7, 154.7, 133.5, 133.0, 132.6, 130.8, 129.4, 128.7, 127.9, 88.9, 27.0, 30.2, 8.3, 7.6.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{16}ClNO_3Na$: 316.0711; found: 316.0722.

5-Ethyl-5-hydroxy-4-propionyl-3-propyl-1,5-dihydro-2*H*-pyrrol-2-one (5w)
Yield: 17 mg (4%); white solid; isomeric mixture; mp 80–82 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.44 (8.41) (s, 1 H, NH), 6.20 (6.18) (s, 1 H, OH), 2.89–2.86 (m, 1 H, CH_2), 2.72–2.63 (m, 1 H, CH_2), 2.29–2.15 (m, 1 H, CH_2), 1.49–1.37 (m, 1 H, CH_2), 1.00–0.88 (m, 8 H, CH_2, CH_3, CH_3), 0.85 (q, J = 7.8 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 202.1 (201.7), 170.8 (170.6), 152.1 (150.8), 141.1 (139.7), 91.0 (90.6), 70.8 (69.1), 36.2 (36.0), 26.2 (26.0), 21.9 (21.9), 18.1 (17.9), 14.3 (14.2), 7.8 (7.6).

HRMS (ESI): m/z $[M + K]^+$ calcd for $C_{12}H_{19}NO_3K$: 264.0997; found: 264.1220.

3-(2-Nitro-1-phenylethyl)pentane-2,4-dione (3a)
White solid; mp 96–98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 3 H, H_{Ph}), 7.20–7.17 (m, 2 H, H_{Ph}), 4.63 (dd, J = 3.2, 5.2 Hz, 2 H, CH_2), 4.37 (d, J = 10.8 Hz, 1 H, CH), 4.27–4.21 (m, 1 H, CH), 2.30 (s, 3 H, CH_3), 1.94 (s, 3 H, CH_3).

^{13}C NMR (100, MHz, $CDCl_3$): δ = 201.8, 201.0, 136.0, 129.4, 128.6, 127.9, 78.2, 70.8, 42.8, 30.4, 29.5.

MS (ESI): m/z = 272.1 $[M + Na]^+$.

1-[5-(Hydroxyimino)-2-methyl-4-phenyl-4,5-dihydrofuran-3-yl]ethanone (4a)
White solid; mp 140–142 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (s, 1 H, OH), 7.36–7.27 (m, 3 H, H_{Ph}), 7.19–7.17 (m, 2 H, H_{Ph}), 4.90 (d, J = 2 Hz, 1 H, CH), 2.51 (d, J = 1.6 Hz, 3 H, CH_3), 1.97 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.9, 164.2, 157.9, 138.2, 129.3, 128.1, 127.5, 117.6, 49.3, 29.8, 14.3.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{14}NO_3$: 232.0968; found: 232.0974.

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