



Cite this: *RSC Adv.*, 2021, 11, 16236

# Preparation of 3,5-diarylsubstituted 5-hydroxy-1,5-dihydro-2H-pyrrol-2-ones *via* base-assisted cyclization of 3-cyanoketones†

Nicolai A. Aksenov,<sup>id</sup>\*<sup>a</sup> Dmitrii A. Aksenov,<sup>id</sup><sup>a</sup> Igor A. Kurenkov,<sup>id</sup><sup>a</sup>  
Alexander V. Aksenov,<sup>id</sup><sup>a</sup> Anton A. Skomorokhov,<sup>a</sup> Lidiya A. Prityko,<sup>id</sup><sup>a</sup>  
and Michael Rubin<sup>id</sup>\*<sup>ab</sup>

Received 22nd March 2021

Accepted 13th April 2021

DOI: 10.1039/d1ra02279b

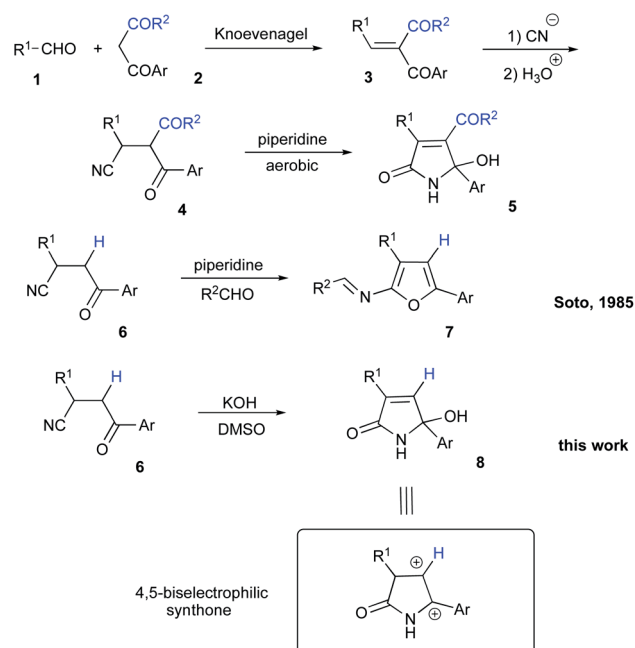
rsc.li/rsc-advances

A convenient preparative method is developed allowing for expeditious assembly of 3,5-diarylsubstituted 5-hydroxy-1,5-dihydro-2H-pyrrol-2-ones from routinely available inexpensive synthetic precursors. These compounds could not be prepared *via* the previously known protocols, as 2-aminofuran derivatives were produced instead.

## Introduction

Isomers of tetramic acid heterocyclic core of 3,5-disubstituted 5-hydroxy-1,5-dihydro-2H-pyrrol-2-one are highly attractive for modern medicinal chemistry. Compounds possessing this structural unit are found in nature and often demonstrate a wide array of important biological activities. For example, an array of alkaloids ianthellidones A–F, isolated from Australian marine sponges of *Ianthella* genus showed promising anti-cancer activity.<sup>1,2</sup> Antimicrobial agents myceliothermophins A–D, isolated from fungus *Myceliophthora thermophila*<sup>3</sup> were targets for synthetic exercises<sup>4</sup> and subject for mechanistic investigations.<sup>5</sup> Recently, a new wave of interest in these compounds was raised stimulated by their newly discovered cytotoxic activity (Fig. 1).<sup>6</sup> Tryptophan–polyketide hybrid, codinaeopsin, isolated from endophytic fungus *Codinaeopsis gonytrichoides* demonstrated potent anti-malarial properties<sup>7</sup> and was also a target for total synthesis.<sup>8</sup> Rolipyrrole, a representative of propentdyopents typical for animals, but highly unusual for plants, was isolated from magnolia *Rollinia mucosa* (Fig. 1).<sup>9</sup> Alkaloid cannabisin L originally isolated from seeds of black henbane (*Hyoscamus niger*)<sup>10</sup> was also recently discovered in devil's trumpet plants (*Datura metel*).<sup>11,12</sup> Finally, Penicillenol D, an alkaloid with an ample anti-tumor effect was isolated from marine-derived fungus *Trichoderma citrinoviride* (Fig. 1).<sup>13</sup> A typical synthetic approach to these nitrogen-based heterocycles involves the reaction of five-membered lactone precursors with

ammonia<sup>14–17</sup> or amines,<sup>18,19</sup> reductive cyclization of nitroolefins with 1,3-diketones,<sup>20</sup> or various aldol-type cyclocondensations.<sup>21–24</sup> In application to the synthesis of 3,5-diarylsubstituted 5-hydroxy-1,5-dihydro-2H-pyrrol-2-one, just a handful of synthetic approaches provided decent results,<sup>23,25</sup> while most of the described protocols rely on the utilization of precursors that are quite exotic. Herein, we report a novel synthesis of 3,5-diarylsubstituted 5-hydroxy-1,5-dihydro-2H-pyrrol-2-ones *via* unusual base-assisted cyclization of readily available 3-cyanoketones (Scheme 1).



Scheme 1 Alternative pathways for the cyclization of 3-cyanoketones.

<sup>a</sup>Department of Chemistry, North Caucasus Federal University, 1a Pushkin St., Stavropol 355009, Russian Federation. E-mail: aaksenov@ncfu.ru

<sup>b</sup>Department of Chemistry, University of Kansas, 1567 Irving Hill Rd, Lawrence, KS 66045-7582, USA. E-mail: mrubin@ku.edu; Tel: +1-785-864-5071

† Electronic supplementary information (ESI) available. CCDC 2069203 and 2069260. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra02279b



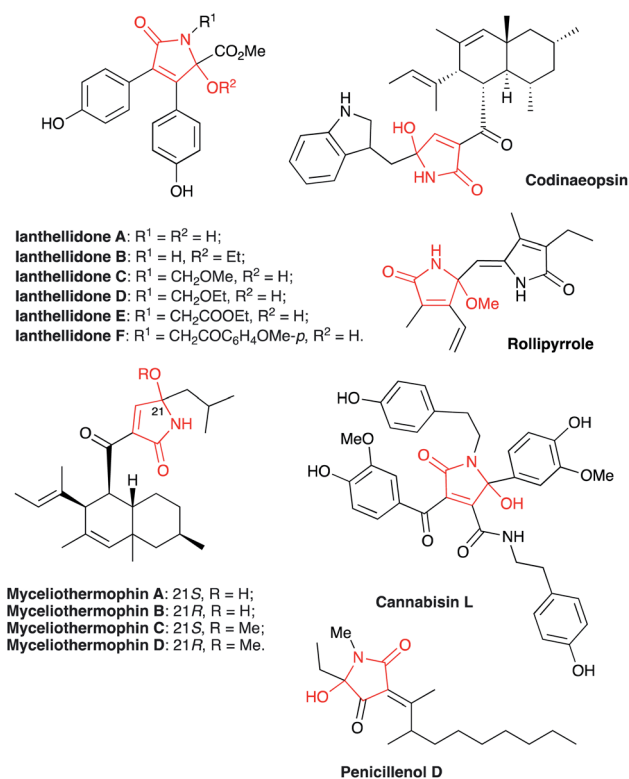
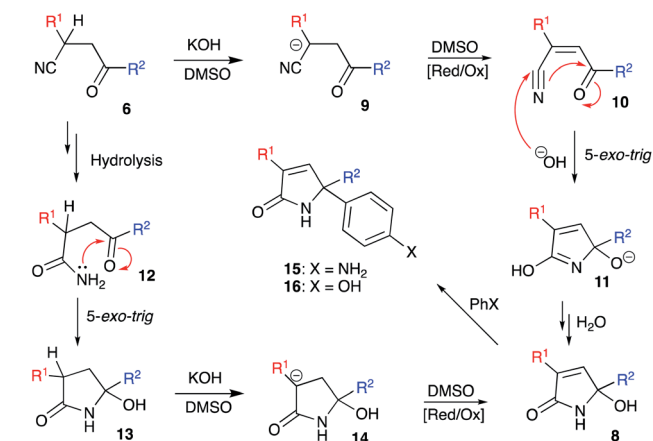


Fig. 1 Naturally occurring biologically active 5-hydroxy-1,5-dihydro-2H-pyrrol-2-ones.

## Results and discussion

During our research involving nitrogen-based heterocyclic compounds<sup>26–28</sup> we got very enthusiastic about the possibility of employing synthetic equivalents of bis-electrophilic 3,4-dihydro-2H-pyrrol-1-ium-4-ylum synthon for expeditious assembly of bicyclic and tricyclic heterocyclic scaffolds. Although the structure of 5-hydroxy-1,5-dihydro-2H-pyrrol-2-ones **8** seems to be a suitable synthetic equivalent, lengthy and laborious synthetic approaches to these molecules rendered this idea cost-prohibitive and much less exciting. In 1985, Soto and co-workers reported on a very appealing strategy allowing for the preparation of very similar cyclic compound **5** from readily available and very inexpensive precursors.<sup>29</sup> Their method involved Knoevenagel condensation between aldehyde **1** and 1,3-dicarbonyl compound **2** to obtain conjugate olefin **3**, which was then subjected to hydrocyanation to provide nitrile **4**. Next, piperidine-assisted oxidative cyclization was carried out to furnish **5** (Scheme 2).<sup>29</sup> It should be pointed out, that this method is specific for the cyclization of dicarbonyl compounds **4** and can provide only heterocyclic products **5** with requisite acyl substituent at C-4 (Scheme 2). This substitution pattern is not suitable for our purposes, since this electron-withdrawing group would potentially revert the polarization of the C=C double bond. So, we opted for the preparation of the lactam **8**, non-substituted at this position. However, an attempt to involve mono-carbonyl precursor **6** into the reaction with piperidine did not provide any reactivity at room temperature (Table 1, entry 1).



Scheme 2 Mechanistic rationales for the featured transformation.

Upon heating, a different cyclization was triggered resulting in the formation of unstable 2-aminofuran, which could be isolated in a form of imine **7** (Scheme 2 and Table 1, entry 2).<sup>29</sup> It should be pointed out, that the same result can be achieved under acidic conditions in the presence of polyphosphoric acid, which was demonstrated in our recent report.<sup>30</sup>

To gain access to the desired lactam **8** we decided to search for alternative conditions for the cyclization of **6**. To this end, we tested KOH as a base in aqueous DMF for the reaction medium. When performed at room temperature in air, this reaction proceeded very sluggishly and provided the desired product in low yield, and was isolated along with unreacted starting material (entry 3). It should be stressed that the presence of the oxidant is crucial for this cyclization, which does not proceed at

Table 1 Optimization of the reaction conditions

#	Base	Oxidant/solvent	Time, h (temp., °C)	Yield <sup>a</sup> , %
1	Pyridine	Air/EtOH	48 (20)	NR
2	Pyridine	Air/EtOH	48 (100)	Decomposition <sup>b</sup>
3	KOH	Air/DMF–water	72 (20)	32% + 64% of <b>6a</b>
4	KOH	DMF–water <sup>c</sup>	4 (20)	NR
5	KOH	H <sub>2</sub> O <sub>2</sub> –urea/DMF	1.5 (20)	29
6	KOH	H <sub>2</sub> O <sub>2</sub> –urea/MeOH	1.5 (20)	40
7	KOH (2 equiv.)	DMSO (0.2 mL) <sup>d,e</sup>	0.5 (20)	48
8	KOH (4 equiv.)	DMSO (0.5 mL) <sup>d,e</sup>	1.0 (20)	71
9	KOH (4 equiv.)	DMSO (1 mL) <sup>d</sup>	0.67 (20)	85
10	KOH (4 equiv.)	DMSO (2 mL) <sup>d</sup>	2 (20)	72
11	KOH (4 equiv.)	DMSO (3 mL) <sup>d</sup>	4.5 (20)	41

<sup>a</sup> All test reactions were performed on 0.5 mmol scales. NMR yields are provided unless specified otherwise. <sup>b</sup> Forms **7a** ( $R^1 = R^2 = Ar = Ph$ ) in the presence of benzaldehyde. <sup>c</sup> Reaction was carried out under argon atmosphere. <sup>d</sup> 300  $\mu$ L of water was added to improve the solubility of the base. <sup>e</sup> Organic materials were poorly soluble in this mixture.

Table 2 Oxidative cyclization of 3-cyanoketones

	6, 8	R <sup>1</sup>	R <sup>2</sup>	Yield <sup>a</sup> , %
1	6a, 8a	Ph	Ph	72
2	6b, 8b	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Ph	71
3	6c, 8c	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub>	Ph	65
4	6d, 8d	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Ph	88
5	6e, 8e	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>	Ph	70
6	6f, 8f	<i>p</i> -Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Ph	68
7	6g, 8g	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	Ph	71
8	6h, 8h	<i>o</i> -FC <sub>6</sub> H <sub>4</sub>	Ph	66
9	6i, 8i	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Ph	68
10	6j, 8j	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	Ph	76
11	6k, 8k	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	Ph	59
12	6l, 8l	Ph	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	77
13	6m, 8m	Ph	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	59
14	6n, 8n	Ph	2-Naphthyl	77
15	6o, 8o	Ph	2,3-Dihydrobenzo[ <i>b</i> ][1,4]dioxin-6-yl	61
16	6p, 8p	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	64

<sup>a</sup> Isolated yields of purified materials are provided.

all under an inert atmosphere (entry 4). In an attempt to facilitate the oxidation step, we tested reactions in the presence of hydrogen peroxide/urea complex taking DMF or methanol as solvents. In both cases reaction proceeded much faster, going to completion within 1.5 h and affording 29 and 40% of lactam **8a**, respectively (entries 5 and 6).

Next, we tried to employ DMSO as an oxidant. This reaction was carried out in the presence of water as a co-solvent to improve the solubility of the base in the reaction mixture. The initial attempt involved 2 equiv. of KOH and 0.2 mL of DMSO to trigger a rather quick reaction, which provided, however, only marginal yield (entry 7). To facilitate the reaction, amounts of both base and DMSO were increased, and the yield was greatly improved (entry 8). However, organic materials were still quite poorly soluble in this combination of solvents, so we decided to increase the concentration of DMSO. In a mixture of water/DMSO 0.3 : 1, the observed rate of the reaction hits the maximum. The reaction was complete in 40 min at room temperature, affording 85% NMR yield, which translated into a 72% isolated yield of purified material (entry 9). Further increase in concentration of DMSO proved detrimental. The rate of the reaction slowed down, and the yields dropped quite noticeably (entries 10 and 11).

With optimized conditions in hand, we proceeded to perform the reaction on a 1 mmol scale to isolate the product **8a** in 72% yield (Table 2, entry 1). The reaction proved very general, and a series of 3,5-diarylsubstituted 5-hydroxy-1,5-dihydro-2H-pyrrol-2-ones were easily obtained in good to high isolated yields under the same conditions (Table 2). It was demonstrated, that phenyl groups with different alkyl, alkoxy, and halide substituents as well as 2-naphthyl and 2,3-dihydrobenzo

[*b*][1,4]dioxin-6-yl moieties are very well tolerated in the featured transformation.

The formation of the 1,5-dihydro-2H-pyrrol-2-one ring in the reaction of ketonitrile **6e** (entry 5) was unambiguously confirmed by single-crystal X-ray analysis of the product **8e** (Fig. 2).

We envision the described transformation to proceed *via* the following mechanistic pathway. Initial base-assisted cleavage of acidic  $\alpha$ -CH-bond of nitrile would lead to the formation of anionic moiety **9**, which should be susceptible to oxidation in the presence of DMSO. The resulting acrylonitrile **10** would then experience a nucleophilic attack with hydroxide species triggering subsequent 5-*exo-trig* cyclization to afford 5-hydroxy-2H-

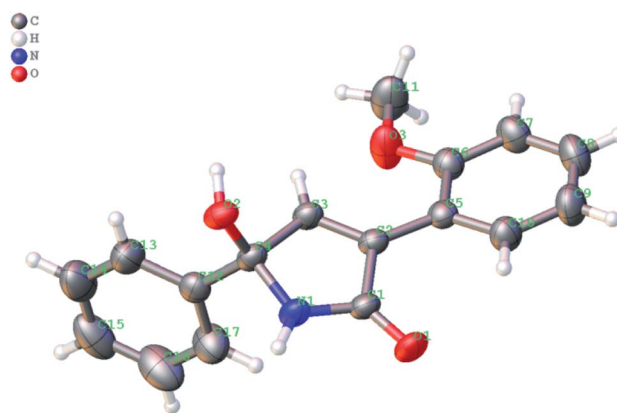
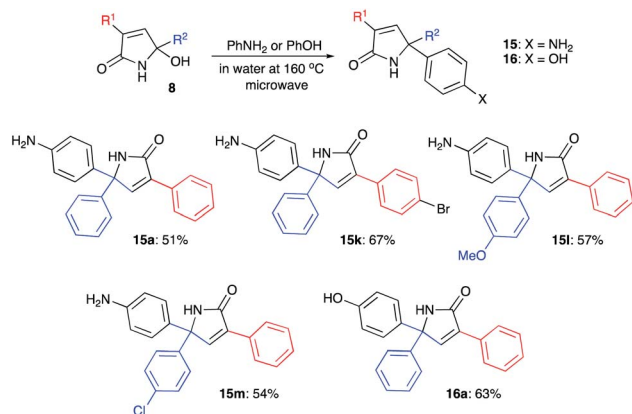


Fig. 2 X-ray structure of 5-hydroxy-3-(2-methoxyphenyl)-5-phenyl-1,5-dihydro-2H-pyrrol-2-one **8e** (the thermal ellipsoids are shown at 50% probability) (CCDC #2069260).





Scheme 3 Further modification of 1,5-dihydro-2H-pyrrol-2-ones via electrophilic aromatic substitution.

pyrrol-2-olate **11**. Re-protonation of this species, followed by tautomerization of the imidic acid entity into lactam function would finally provide product **8** (Scheme 2). An alternative pathway would include initial hydrolysis of nitrile function in **6** to afford primary amide **12**, which could undergo a subsequent 5-*exo-trig* cyclization providing lactam **13**. Deprotonation of  $\alpha$ -CH-bond would lead to the formation of anionic intermediate **14**, which would be further oxidized into 1,5-dihydro-2H-pyrrol-2-one **8** with DMSO. The latter rationale, however, seems less likely, as in the absence of DMSO as an oxidizing agent we failed to detect the formation of intermediate **12** or **13**. The hydrolysis step did not proceed and nitrile function remained unchanged. This suggests that the oxidation process should proceed prior to cyclization.

Next, we evaluated the possibility of further increasing the molecular complexity of the synthesized scaffolds by targeting the introduction of a third aryl substituent to obtain products **15**, **16** (Scheme 2). To this end, we tested the  $S_EAr$  reaction between 1,5-dihydro-2H-pyrrol-2-ones and electron-rich aromatic compounds, such as aniline and phenol. The

reactions were carried out in a sealed tube upon heating at 160 °C with microwave irradiation (Scheme 3). Gratifyingly, all the tested reactions proceeded smoothly affording compounds **15a**, **k–m** and **16a** in moderate to good yields (Scheme 3). Successful installation of the new aniline moiety at C-5 was unambiguously confirmed by the single-crystal X-ray diffraction analysis of compound **15k** re-crystallized from benzene (Fig. 3).

As suggested by the reviewer of this paper, we also evaluated the possibility of lowering the reaction temperature employing Brønsted acid catalysis. To this end, reactions of phenol with lactam **8a** were carried out in the presence of 20 mol% of  $\text{HClO}_4$  (70% aqueous, the 0.60 M reaction mixture was heated in nitromethane at 70 °C for 1 h)<sup>31,32</sup> or  $\text{MeSO}_3\text{H}$ <sup>33</sup> (0.60 M reaction mixture was heated in toluene at 70 °C for 1 h). Upsettingly, these reactions afforded only marginal yields of the corresponding product **16a**, 46% and 48%, respectively. The reaction of **8a** with aniline carried out in the presence of  $\text{MeSO}_3\text{H}$  under the same reaction conditions was accompanied by significant decomposition and allowed for the isolation of **15a** in very low yield (12%).

## Conclusion

In conclusion, a novel synthetic method allowing for highly efficient preparation of formerly poorly-accessible 3,5-diaryl-substituted 5-hydroxy-1,5-dihydro-2H-pyrrol-2-ones was developed. The method relies on the employment of routinely available and very inexpensive precursors and provides good yields of the target products. Following the modification of the prepared structures *via* thermally-induced  $S_EAr$  reaction with aniline or phenol allowed for the introduction of the third aryl substituent at this heterocyclic scaffold, which seems attractive for building diverse libraries for drug discovery. Evaluation of biological activities of the synthesized compounds and further exploration of their reactivity as bis-electrophiles is currently underway in our laboratories.

## Experimental part

### General information

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance-III spectrometer (400 or 100 MHz, respectively) equipped with a BBO probe in  $\text{CDCl}_3$  or  $\text{DMSO}-d_6$ , using TMS as an internal standard. High-resolution mass spectra were obtained using a Bruker Maxis spectrometer (electrospray ionization, MeCN solution, using  $\text{HCO}_2\text{Na}-\text{HCO}_2\text{H}$  for calibration). Melting points were measured with a Stuart SMP30 apparatus. All reactions were performed in oven-dried flasks equipped with reflux condensers and magnetic stir bars. All reactions were followed by thin-layer chromatography (TLC) using ALUGRAM Xtra SIL G UV254 plates, which were visualized under UV light (254 nm), with hexane/EtOAc mixtures as eluent. Nitriles **6c**,<sup>34</sup> **6h**, **6n**,<sup>34</sup> **6o**, **6p**<sup>35</sup> were synthesized according to the protocols provided below from the corresponding chalcones. All other nitriles were prepared according to known procedures and their physical and spectral properties were identical to those described in the literature.<sup>36</sup> Reagents and solvents were

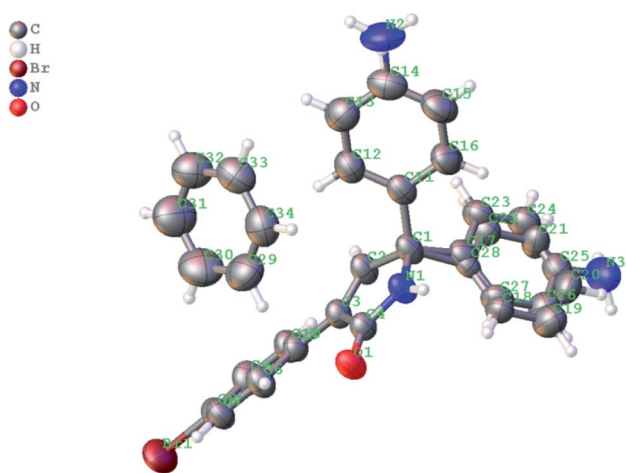


Fig. 3 X-ray structure of 5-(4-aminophenyl)-3-(4-bromophenyl)-5-phenyl-1,5-dihydro-2H-pyrrol-2-one **15k** as solvate with benzene. Two enantiomers of **15k** are disordered in the crystalline lattice and their overlay is shown (the thermal ellipsoids are shown at 50% probability) (CCDC #2069203).





purchased from commercial vendors and used as received. Abbreviation "PE" is used for light petroleum ether employed as an eluent for preparative chromatography.

### 2-(4-Ethylphenyl)-4-oxo-4-phenylbutanenitrile (6c)<sup>34</sup>

Use of well-ventilated fume hood is necessary as the release of hydrogen cyanide occurs during the reaction. In a 25 mL round bottom flask equipped with magnetic stir bar (*E*)-3-(4-ethylphenyl)-1-phenylprop-2-en-1-one<sup>37</sup> (472 mg, 2.00 mmol), KCN (195 mg, 3 mmol), EtOH (5 mL), H<sub>2</sub>O (0.3 mL) AcOH (114  $\mu$ L, 120 mg, 2.00 mmol) were placed, closed with reflux condenser and allowed to stir under reflux for 2 h (TLC control). After the consumption of the starting material, the reaction mixture was cooled to room temperature and the precipitated product was collected by vacuum filtration, washed twice with H<sub>2</sub>O. Colorless solid, mp 114.3–115.4 °C (EtOH); yield 420 mg (1.6 mmol, 80%). *R*<sub>f</sub> = 0.49, EtOAc/hexane (1 : 4, v/v). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.00–7.85 (m, 2H), 7.63–7.56 (m, 1H), 7.52–7.42 (m, 2H), 7.38–7.30 (m, 2H), 7.26–7.19 (m, 2H), 4.54 (dd, *J* = 7.9, 6.0 Hz, 1H), 3.72 (dd, *J* = 17.9, 8.0 Hz, 1H), 3.50 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  194.9, 144.7, 135.9, 134.0, 132.6, 120.0 (2C), 128.9 (2C), 128.2 (2C), 127.6 (2C), 120.9, 44.7, 31.7, 28.6, 15.6. FTIR (ZnSe)  $\nu$  (cm<sup>-1</sup>): 2969, 2241, 1769, 1675, 1595, 1511, 1443, 1352, 1246, 1053, 998; HRMS (ES TOF, *m/z*) calcd for C<sub>18</sub>H<sub>17</sub>NNaO<sup>+</sup> ([M + Na]<sup>+</sup>): 286.1202, found 286.1200 (0.9 ppm).

### 2-(2-Fluorophenyl)-4-oxo-4-phenylbutanenitrile (6h)

Product **6h** was obtained *via* the method described for **6c** employing (*E*)-3-(2-fluorophenyl)-1-phenylprop-2-en-1-one<sup>38</sup> (452 mg, 2.00 mmol), and purified by recrystallization from ethanol. Colorless solid, mp 125.3–126.4 °C (EtOH); yield 385 mg (1.52 mmol, 76%). *R*<sub>f</sub> = 0.51, EtOAc/hexane (1 : 4, v/v). <sup>1</sup>H NMR (400 MHz, chloroform-*d*)  $\delta$  7.99–7.91 (m, 2H), 7.65–7.52 (m, 2H), 7.52–7.43 (m, 2H), 7.42–7.30 (m, 1H), 7.21 (td, *J* = 7.6, 1.2 Hz, 1H), 7.12 (ddd, *J* = 10.3, 8.2, 1.2 Hz, 1H), 4.75 (dd, *J* = 8.5, 5.4 Hz, 1H), 3.74 (dd, *J* = 18.0, 8.5 Hz, 1H), 3.55 (dd, *J* = 18.0, 5.3 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  194.6, 160.1 (d, *J* = 248.2 Hz), 135.7, 134.1, 130.6 (d, *J* = 8.4 Hz), 129.8 (d, *J* = 3.2 Hz), 129.0 (2C), 128.2 (2C), 125.1 (d, *J* = 3.7 Hz), 122.4 (d, *J* = 13.6 Hz), 119.6, 116.3 (d, *J* = 21.0 Hz), 42.6 (d, *J* = 1.6 Hz), 26.8 (d, *J* = 3.1 Hz). FTIR (ZnSe)  $\nu$  (cm<sup>-1</sup>): 2242, 1677, 1595, 1496, 1451, 1410, 1357, 1304, 1246, 1212, 1000; HRMS (ES TOF) calcd for C<sub>16</sub>H<sub>12</sub>FNNaO<sup>+</sup> ([M + Na]<sup>+</sup>): 276.0795, found 276.0795 (0.0 ppm).

### 4-(Naphthalen-2-yl)-4-oxo-2-phenylbutanenitrile (6n)

Product **6n** was obtained *via* the method described for **6c**, employing (*E*)-1-(naphthalen-2-yl)-3-phenylprop-2-en-1-one<sup>39</sup> (516 mg, 2.00 mmol), and purified by recrystallization from ethanol. Colorless solid, mp 109.6–110.4 °C (EtOH), lit<sup>40</sup> mp 128 °C (EtOH); yield 496 mg (1.74 mmol, 87%). *R*<sub>f</sub> = 0.54, EtOAc/hexane (1 : 4, v/v). <sup>1</sup>H NMR (400 MHz, chloroform-*d*)  $\delta$  8.42 (s, 1H), 8.00 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.91–7.85 (m, 2H), 7.62 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 7.51–7.45 (m, 2H), 7.44–7.38 (m, 2H), 7.38–

7.32 (m, 1H), 4.63 (dd, *J* = 8.0, 5.9 Hz, 1H), 3.87 (dd, *J* = 17.8, 8.0 Hz, 1H), 3.65 (dd, *J* = 17.8, 6.0 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  194.7, 136.0, 135.5, 133.1, 132.5, 130.2, 129.7, 129.4 (2C), 129.1, 128.9, 128.5, 128.0, 127.7 (2C), 127.2, 123.6, 120.8, 44.7, 32.2. FTIR (ZnSe)  $\nu$  (cm<sup>-1</sup>): 2241, 1680, 1624, 1595, 1455, 1405, 1366, 1258, 1173, 1128, 1017; HRMS (ES TOF, *m/z*) calcd for C<sub>20</sub>H<sub>15</sub>NNaO<sup>+</sup> ([M + Na]<sup>+</sup>): 308.1046, found 308.1042 (1.1 ppm).

### 4-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-4-oxo-2-phenylbutanenitrile (6o)

Product **6o** was obtained *via* the method described in literature employing (*E*)-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-phenylprop-2-en-1-one<sup>40</sup> (532 mg, 2.00 mmol), and purified by recrystallization from ethanol. White solid, mp 108.9–109.4 °C (EtOH); yield 410 mg (1.4 mmol, 70%). *R*<sub>f</sub> = 0.27, EtOAc/hexane (1 : 4, v/v). <sup>1</sup>H NMR (400 MHz, chloroform-*d*)  $\delta$  7.53–7.29 (m, 7H), 6.90 (d, *J* = 8.2 Hz, 1H), 4.55 (dd, *J* = 7.9, 6.0 Hz, 1H), 4.36–4.23 (m, 4H), 3.64 (dd, *J* = 17.7, 7.9 Hz, 1H), 3.42 (dd, *J* = 17.7, 6.1 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  193.1, 148.8, 143.6, 135.5, 129.7, 129.4 (2C), 128.5, 127.6 (2C), 122.4, 120.9, 117.8, 117.6, 64.8, 64.2, 44.3, 32.1. FTIR (ZnSe)  $\nu$  (cm<sup>-1</sup>): 2241, 1665, 1602, 1501, 1431, 1345, 1284, 1260, 1166, 1135, 1063; HRMS (ES TOF, *m/z*) calcd for C<sub>18</sub>H<sub>15</sub>NNaO<sub>3</sub><sup>+</sup> ([M + Na]<sup>+</sup>): 316.0944, found 316.0948 (−1.1 ppm).

### 2,4-Bis(4-methoxyphenyl)-4-oxobutanenitrile (6p)<sup>35</sup>

Product **6p** was obtained *via* the method described for **6c** employing (*E*)-1,3-bis(4-methoxyphenyl)prop-2-en-1-one<sup>41</sup> (536 mg, 2.00 mmol), and purified by recrystallization from ethanol. White crystals, mp 112.6–113.3 °C (EtOH); yield 0.354 mg (1.20 mmol, 60%). *R*<sub>f</sub> = 0.21, EtOAc/hexane (1 : 1, v/v). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.94–7.85 (m, 2H), 7.39–7.30 (m, 2H), 6.97–6.86 (m, 4H), 4.52 (dd, *J* = 7.7, 6.3 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.63 (dd, *J* = 17.6, 7.6 Hz, 1H), 3.43 (dd, *J* = 17.6, 6.4 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  193.3, 164.2, 159.6, 130.6 (2C), 129.0 (2C), 128.8, 127.5, 121.2, 114.7 (2C), 114.1 (2C), 55.7, 55.5, 44.3, 31.3. FTIR (ZnSe)  $\nu$  (cm<sup>-1</sup>): 2246, 1675, 1598, 1516, 1361, 1306, 1248, 1219, 1164, 1022; HRMS (ES TOF, *m/z*) calcd for C<sub>18</sub>H<sub>17</sub>NNaO<sub>3</sub><sup>+</sup> ([M + Na]<sup>+</sup>): 318.1101, found 318.1104 (−1.0 ppm).

### 5-Hydroxy-3,5-diphenyl-1,5-dihydro-2H-pyrrol-2-one (8a)

In a 5 mL vial equipped with a magnetic stirring bar, KOH (224 mg, 4 mmol) was dissolved in H<sub>2</sub>O (0.6 mL), followed by the addition of 4-oxo-2,4-diphenylbutanenitrile<sup>36</sup> (235 mg, 1 mmol) and DMSO (2 mL). The reaction mixture was allowed to stir at r.t. for approximately 1 hour. After the consumption of all the starting compound, the reaction mixture was diluted with water (15 mL), extracted with ethyl acetate (4  $\times$  15 mL), washed with water (2  $\times$  15 mL) and purified by column chromatography (gradient: EtOAc/PE 1 : 3–1 : 1). The fractions were concentrated on a rotary evaporator. Compounds can also be purified by recrystallization from a suitable solvent. White solid, mp 234.1–236.1 °C (EtOAc); yield 181 mg (0.72 mmol, 72%). *R*<sub>f</sub> = 0.31, EtOAc/hexane (1 : 2, v/v), *R*<sub>f</sub> = 0.42, EtOAc/hexane (1 : 1, v/v). <sup>1</sup>H



NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.17–9.05 (m, 1H), 8.05–7.90 (m, 2H), 7.59–7.47 (m, 2H), 7.46–7.24 (m, 7H), 6.63 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  170.8, 145.8, 140.8, 131.8, 131.15, 128.5, 128.3 (2C), 128.3 (2C), 127.9, 127.2 (2C), 125.7 (2C), 86.1. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3242, 2960, 1767, 1617, 1605, 1501, 1463, 1447, 1433, 1363, 1234, 1204; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{13}\text{NNaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 274.0838, found 274.0839 (−0.2 ppm).

### 5-Hydroxy-5-phenyl-3-(*p*-tolyl)-1,5-dihydro-2H-pyrrol-2-one (8b)

Product **8b** was obtained *via* the method described for compound **8a** employing 4-oxo-4-phenyl-2-(*p*-tolyl)butanenitrile<sup>36</sup> (249 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 2–2 : 1) or recrystallization from ethanol. Reaction time: 1 hour. Yellow solid, mp 161.6–163.8 °C (EtOH); yield 188 mg (0.71 mmol, 71%).  $R_f$  = 0.45, EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.09 (s, 1H), 7.86 (dd,  $J$  = 8.3, 2.2 Hz, 2H), 7.56–7.49 (m, 2H), 7.40–7.29 (m, 4H), 7.20 (d,  $J$  = 7.9 Hz, 2H), 6.60 (d,  $J$  = 2.3 Hz, 1H), 2.31 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  171.0, 144.8, 141.0, 138.0, 131.6, 128.9 (2C), 128.3, 128.2 (2C), 127.8, 127.1 (2C), 125.7 (2C), 86.0, 20.9. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3268, 2362, 1672, 1508, 1489, 1426, 1207, 1087, 1058, 976; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{17}\text{H}_{15}\text{NNaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 288.0995, found 288.0989 (1.9 ppm).

### 3-(4-Ethylphenyl)-5-hydroxy-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (8c)

Product **8c** was obtained *via* the method described for compound **8a**, employing 2-(4-ethylphenyl)-4-oxo-4-phenylbutanenitrile (263 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 2–2 : 1) or recrystallization from ethanol. White solid, mp 164.4–165.2 °C (EtOH); yield 181 mg (0.65 mmol, 65%).  $R_f$  = 0.23, EtOAc/hexane (1 : 2, v/v),  $R_f$  = 0.58, EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.09 (s, 1H), 7.90–7.83 (m, 2H), 7.56–7.48 (m, 2H), 7.41–7.26 (m, 4H), 7.22 (d,  $J$  = 8.1 Hz, 2H), 6.60 (s, 1H), 2.61 (q,  $J$  = 7.6 Hz, 2H), 1.17 (t,  $J$  = 7.6 Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  171.0, 144.9, 144.3, 141.0, 131.8, 128.6, 128.2 (2C), 127.8, 127.7 (2C), 127.2 (2C), 125.7 (2C), 86.1, 28.0, 15.5. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3258, 1672, 1511, 1489, 1414, 1231, 1202, 1087, 1058, 976; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{18}\text{H}_{17}\text{NNaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 302.1151, found 302.1149 (0.9 ppm).

### 5-Hydroxy-3-(4-methoxyphenyl)-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (8d)

Product **8d** was obtained *via* the method described for compound **8a**, employing 2-(4-methoxyphenyl)-4-oxo-4-phenylbutanenitrile<sup>36</sup> (265 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 2–2 : 1) or recrystallization from ethanol. White solid, mp 163.4–164.1 °C (EtOH); yield 247 mg (0.88 mmol, 88%).  $R_f$  = 0.15, EtOAc/hexane (1 : 2, v/v),  $R_f$  = 0.5, EtOAc/hexane (2 : 1, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.07 (d,  $J$  = 1.8 Hz, 1H), 7.97–7.90 (m, 2H), 7.55–7.48 (m, 2H), 7.40–7.34 (m, 2H), 7.33–7.28 (m, 1H), 7.27 (d,  $J$  = 1.7 Hz, 1H), 6.98–6.90 (m, 2H), 6.56 (s, 1H), 3.77 (s, 3H).  $^{13}\text{C}$

NMR (101 MHz, DMSO- $d_6$ )  $\delta$  171.1, 159.5, 143.6, 141.1, 131.2, 128.6 (2C), 128.2 (2C), 127.8, 125.7 (2C), 123.6, 113.8 (2C), 86.0, 55.1. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3297, 1699, 1667, 1446, 1255, 1048, 966; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{17}\text{H}_{15}\text{NNaO}_3^+$  ( $[\text{M} + \text{Na}]^+$ ): 304.0944, found 304.0944 (−0.3 ppm).

### 5-Hydroxy-3-(2-methoxyphenyl)-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (8e)

Product **8e** was obtained *via* the method described for compound **8a**, employing 2-(2-methoxyphenyl)-4-oxo-4-phenylbutanenitrile<sup>36</sup> (265 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 2–2 : 1) or recrystallization from ethanol. Reaction time: 1 h. Colorless crystals, mp 193.9–195.4 °C (EtOH); yield 0.196 g (0.7 mmol, 70%).  $R_f$  = 0.61, EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.05 (s, 1H), 8.22 (dt,  $J$  = 7.7, 1.6 Hz, 1H), 7.51 (d,  $J$  = 8.3 Hz, 2H), 7.42–7.27 (m, 5H), 7.07 (dd,  $J$  = 8.5, 1.1 Hz, 1H), 6.98 (td,  $J$  = 7.5, 1.1 Hz, 1H), 6.59 (s, 1H), 3.80 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  171.4, 157.9, 148.7, 141.2, 129.6, 129.6, 128.3 (2C), 127.8, 127.8, 125.7 (2C), 119.9, 119.6, 111.2, 86.1, 55.5. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3268, 3195, 1670, 1614, 1489, 1407, 1243, 1216, 1045; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{17}\text{H}_{15}\text{NNaO}_3^+$  ( $[\text{M} + \text{Na}]^+$ ): 304.0944, found 304.0951 (2.2 ppm).

### 3-(4-(Dimethylamino)phenyl)-5-hydroxy-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (8f)

Product **8f** was obtained *via* the method described for compound **8a** 2-(4-(dimethylamino)phenyl)-4-oxo-4-phenylbutanenitrile<sup>36</sup> (278 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 2–2 : 1) or recrystallization from ethanol. Reaction time: 1.5 h. Colorless solid, mp 270.9–273.3 °C (EtOH); yield 200 mg (0.68 mmol, 68%).  $R_f$  = 0.55, EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.97 (s, 1H), 7.83 (d,  $J$  = 8.3 Hz, 2H), 7.50 (d,  $J$  = 8.1 Hz, 2H), 7.39–7.24 (m, 3H), 7.10 (s, 1H), 6.69 (d,  $J$  = 8.5 Hz, 2H), 6.49 (d,  $J$  = 1.2 Hz, 1H), 2.92 (s, 6H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  172.0, 150.7, 142.0, 141.5, 132.1, 128.6 (2C), 128.5 (2C), 128.1, 126.2 (2C), 119.2, 112.1 (2C), 86.5, 40.3 (2C). FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3268, 2762, 2540, 2366, 1663, 1612, 1525, 1424, 1359, 1198, 1051; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_2\text{NaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 317.1260, found 317.1252 (2.7 ppm).

### 3-(4-Fluorophenyl)-5-hydroxy-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (8g)

Product **8g** was obtained *via* the method described for compound **8a** employing 2-(4-fluorophenyl)-4-oxo-4-phenylbutanenitrile<sup>36</sup> (253 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 2–2 : 1) or recrystallization from ethanol. White solid, mp 186.1–187.1 °C (EtOH); yield 191 mg (0.71 mmol, 71%).  $R_f$  = 0.26, EtOAc/hexane (1 : 2, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.16 (s, 1H), 8.08–7.98 (m, 2H), 7.54–7.50 (m, 2H), 7.43 (d,  $J$  = 1.7 Hz, 1H), 7.41–7.34 (m, 2H), 7.34–7.29 (m, 1H), 7.26–7.14 (m, 2H), 6.64 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  170.8, 162.2 (d,  $J$  = 246.1 Hz), 145.6 (d,  $J$  = 1.9 Hz), 140.8, 130.7, 129.4 (2C, d,  $J$  = 8.1 Hz), 128.3 (2C), 127.9, 127.7 (d,  $J$  = 3.2 Hz), 125.7 (2C), 115.3 (2C, d,  $J$  = 21.3 Hz),

86.1. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3253, 1771, 1704, 1672, 1499, 1414, 1229, 1159, 1051; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{12}\text{FNNaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 292.0744, found 292.038 (2.1 ppm).

### 3-(2-Fluorophenyl)-5-hydroxy-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (8h)

Product **8h** was obtained *via* the method described for compound **8a** employing 2-(2-fluorophenyl)-4-oxo-4-phenylbutanenitrile (253 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 2–2 : 1) or recrystallization from ethanol. White solid, mp 183.0–184.0 °C (EtOH); yield 177 mg (0.66 mmol, 66%).  $R_f$  = 0.25, EtOAc/hexane (1 : 2, v/v). 0.62 (EtOAc/hexane, 2 : 1).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.23 (s, 1H), 8.13 (td,  $J$  = 7.7, 1.9 Hz, 1H), 7.53 (dd,  $J$  = 7.5, 1.8 Hz, 2H), 7.48–7.22 (m, 7H), 6.73 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  170.3, 160.3 (d,  $J$  = 249.7 Hz), 149.5 (d,  $J$  = 9.2 Hz), 140.6, 130.4 (d,  $J$  = 8.6 Hz), 130.2 (d,  $J$  = 2.9 Hz), 128.3 (2C), 128.0, 126.5 (d,  $J$  = 1.6 Hz), 125.7 (2C), 124.2 (d,  $J$  = 3.4 Hz), 118.9 (d,  $J$  = 12.3 Hz), 115.7 (d,  $J$  = 21.9 Hz), 86.5. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3253, 1672, 1489, 1446, 1224, 1053, 971; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{12}\text{FNNaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 292.0744, found 292.0744 (0.2 ppm).

### 3-(4-Chlorophenyl)-5-hydroxy-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (8i)

Product **8i** was obtained *via* the method described for compound **8a** employing 2-(4-chlorophenyl)-4-oxo-4-phenylbutanenitrile<sup>36</sup> (269 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc : PE 1 : 2–2 : 1) or recrystallization from ethanol. Reaction time: 1 h. Colorless solid, mp 148.1–148.7 °C (EtOH); yield 194 mg (0.68 mmol, 68%).  $R_f$  = 0.40, EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.18 (d,  $J$  = 1.8 Hz, 1H), 8.07–7.97 (m, 2H), 7.51 (dd,  $J$  = 8.1, 1.6 Hz, 3H), 7.49–7.43 (m, 2H), 7.42–7.26 (m, 3H), 6.66 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  170.6, 146.4, 140.6, 133.2, 130.5, 130.0, 128.9 (2C), 128.4 (2C), 128.3 (2C), 128.0, 125.8 (2C), 86.1. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3292, 1708, 1670, 1487, 1455, 1417, 1200, 1089, 1051; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{12}\text{ClNNaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 308.0449, found 308.0446 (0.8 ppm).

### 3-(2-Chlorophenyl)-5-hydroxy-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (8j)

Product **8j** was obtained *via* the method described for compound **8a**, employing 2-(2-chlorophenyl)-4-oxo-4-phenylbutanenitrile<sup>36</sup> (269 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 2–2 : 1). This product is unstable upon heating above 60 °C. Yellowish amorphous solid; yield 217 mg (0.76 mmol, 76%).  $R_f$  = 0.15, EtOAc/hexane (1 : 2, v/v),  $R_f$  = 0.53, EtOAc/hexane (2 : 1, v/v).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.15 (s, 1H), 7.63–7.48 (m, 4H), 7.44–7.36 (m, 4H), 7.37–7.29 (m, 1H), 7.22 (d,  $J$  = 1.6 Hz, 1H), 6.75 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  170.0, 149.7, 140.7, 132.6, 132.1, 131.4, 130.2, 129.9, 129.7, 128.3 (2C), 128.0, 126.9, 125.7 (2C), 86.8. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3330, 1696, 1663, 1448, 1255, 1058, 1036, 756; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{12}\text{ClNNaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 308.0449, found 308.0449 (–0.2 ppm).

### 3-(4-Bromophenyl)-5-hydroxy-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (8k)

Product **8k** was obtained *via* the method described for compound **8a**, employing 2-(4-bromophenyl)-4-oxo-4-phenylbutanenitrile<sup>36</sup> (313 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 2–2 : 1) or recrystallization from benzene. Reaction time: 2 hours. Colorless solid, mp 152.6–155.2 °C (benzene); yield 194 mg (0.59 mmol, 59%).  $R_f$  = 0.54, EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.19 (s, 1H), 7.95 (d,  $J$  = 8.2 Hz, 2H), 7.59 (d,  $J$  = 8.3 Hz, 2H), 7.55–7.46 (m, 3H), 7.37–7.27 (m, 3H), 6.66 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  170.5, 146.5, 140.6, 131.3 (2C), 130.6, 130.4, 129.2 (2C), 128.3 (2C), 128.0, 125.8 (2C), 121.9, 86.1. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3248, 1663, 1612, 1487, 1451, 1424, 1210, 1055, 1010, 970; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{12}\text{BrNNaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 351.9944, found 351.9952 (–2.5 ppm).

### 5-Hydroxy-5-(4-methoxyphenyl)-3-phenyl-1,5-dihydro-2H-pyrrol-2-one (8l)

Product **8l** was obtained *via* the method described for compound **8a**, employing 4-(4-methoxyphenyl)-4-oxo-2-phenylbutanenitrile<sup>35</sup> (265 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 2–2 : 1) or recrystallization from ethanol. Colorless solid, mp 176.8–179.0 °C (ethanol); yield 216 mg (0.77 mmol, 77%).  $R_f$  = 0.22, EtOAc/hexane (1 : 2, v/v),  $R_f$  = 0.7, EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.07 (s, 1H), 7.94 (d,  $J$  = 7.6 Hz, 2H), 7.57–7.27 (m, 6H), 6.93 (d,  $J$  = 8.3 Hz, 2H), 6.53 (s, 1H), 3.75 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  170.8, 159.0, 146.0, 132.7, 131.4, 131.2, 128.5, 128.3 (2C), 127.2 (2C), 127.0 (2C), 113.6 (2C), 85.9, 55.2. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3354, 3258, 1703, 1662, 1515, 1419, 1243, 1183, 1062; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{17}\text{H}_{15}\text{NNaO}_3^+$  ( $[\text{M} + \text{Na}]^+$ ): 304.0944, found 304.0941 (1.1 ppm).

### 5-(4-Chlorophenyl)-5-hydroxy-3-phenyl-1,5-dihydro-2H-pyrrol-2-one (8m)

Product **8m** was obtained *via* the method described for compound **8a**, employing 4-(4-chlorophenyl)-4-oxo-2-phenylbutanenitrile<sup>36</sup> (269 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 3–1 : 1) or recrystallization from benzene. White solid, mp 157.9–159.6 °C (benzene); yield 168 mg (0.59 mmol, 59%).  $R_f$  = 0.33, EtOAc/hexane (1 : 2, v/v).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.17 (d,  $J$  = 1.8 Hz, 1H), 8.01–7.91 (m, 2H), 7.56–7.50 (m, 2H), 7.48–7.32 (m, 6H), 6.75 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  170.8, 145.4, 140.0, 132.6, 132.1, 131.0, 128.6, 128.3 (2C), 128.3 (2C), 127.8 (2C), 127.3 (2C), 85.7. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3354, 3258, 1768, 1698, 1667, 1414, 1243, 1062; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{12}\text{ClNNaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 308.0449, found 308.0440 (3.0 ppm).

### 5-Hydroxy-5-(naphthalen-2-yl)-3-phenyl-1,5-dihydro-2H-pyrrol-2-one (8n)

Product **8n** was obtained *via* the method described for compound **8a**, employing 4-(naphthalen-2-yl)-4-oxo-2-phenylbutanenitrile<sup>34</sup> (285 mg, 1.00 mmol), and purified by column





chromatography (gradient: EtOAc/PE 1 : 3–1 : 1) or recrystallization from ethanol. White solid, mp 175.9–177.9 °C (ethanol); yield 232 g (0.77 mmol, 77%).  $R_f$  = 0.33, EtOAc/hexane (1 : 2, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.27 (s, 1H), 8.14 (s, 1H), 8.09–7.80 (m, 5H), 7.59 (d,  $J$  = 8.7 Hz, 1H), 7.56–7.48 (m, 3H), 7.46–7.26 (m, 3H), 6.82 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  170.9, 145.7, 138.3, 132.7, 132.6, 132.2, 131.2, 128.6, 128.4 (2C), 128.1, 127.9, 127.5, 127.3 (2C), 126.3, 126.3, 124.3, 124.2, 86.2. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3258, 1768, 1665, 1624, 1424, 1231, 1043; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{20}\text{H}_{15}\text{NNaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 324.0995, found 324.1003 (–2.4 ppm).

#### 5-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-hydroxy-3-phenyl-1,5-dihydro-2H-pyrrol-2-one (8o)

Product **8o** was obtained *via* the method described for compound **8a**, employing 4-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-4-oxo-2-phenylbutanenitrile (293 mg, 1.00 mmol), and purified by column chromatography (gradient/EtOAc : PE 1 : 3–1 : 1) or recrystallization from ethanol. Reaction time: 1 h. White solid, mp 161.8–164.6 °C (EtOH); yield 0.189 g (0.61 mmol, 61%).  $R_f$  = 0.58, EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.04 (s, 1H), 7.93 (d,  $J$  = 7.2 Hz, 2H), 7.43–7.30 (m, 4H), 6.99 (d,  $J$  = 2.1 Hz, 1H), 6.94 (dd,  $J$  = 8.4, 2.2 Hz, 1H), 6.84 (d,  $J$  = 8.4 Hz, 1H), 6.53 (s, 1H), 4.22 (s, 4H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  170.8, 145.8, 143.1, 143.0, 133.9, 131.5, 131.2, 128.5, 128.3 (2C), 127.2 (2C), 118.6, 116.8, 114.7, 85.7, 64.1, 64.1. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3248, 1667, 1498, 1431, 1313, 1277, 1253, 1060, 1000; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{18}\text{H}_{15}\text{NNaO}_4^+$  ( $[\text{M} + \text{Na}]^+$ ): 332.0893, found 332.0895 (–0.4 ppm).

#### 5-Hydroxy-3,5-bis(4-methoxyphenyl)-1,5-dihydro-2H-pyrrol-2-one (8p)

Product **8p** was obtained *via* the method described for compound **8a**, employing 2,4-bis(4-methoxyphenyl)-4-oxobutanenitrile<sup>35</sup> (295 mg, 1.00 mmol), and purified by column chromatography (gradient: EtOAc/PE 1 : 2–2 : 1) or recrystallization from ethanol. Reaction time: 40 min. Yellow solid, mp 141.2–143.1 °C (EtOH); yield 199 mg (0.64 mmol, 64%).  $R_f$  = 0.50, EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.00 (d,  $J$  = 1.8 Hz, 1H), 7.98–7.90 (m, 2H), 7.47–7.38 (m, 2H), 7.24 (d,  $J$  = 1.7 Hz, 1H), 7.01–6.86 (m, 4H), 6.46 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  171.1, 159.4, 158.9, 143.7, 133.0, 130.8, 128.5 (2C), 127.0 (2C), 123.7, 113.7 (2C), 113.5 (2C), 85.8, 55.1, 55.1. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3335, 3244, 1704, 1602, 1506, 1417, 1304, 1251, 1183, 1067; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{18}\text{H}_{17}\text{NNaO}_4^+$  ( $[\text{M} + \text{Na}]^+$ ): 334.1050, found 334.1048 (0.4 ppm).

#### 5-(4-Aminophenyl)-3,5-diphenyl-1,5-dihydro-2H-pyrrol-2-one (15a)

5-Hydroxy-3,5-diphenyl-1,5-dihydro-2H-pyrrol-2-one (251 mg, 1.00 mmol) and aniline (186 mg, 2.00 mmol) were placed in a glass vial G10 Anton PAAR, equipped with a magnetic stirring bar heated in a boiling water bath for 1 min to homogenize the reaction mass. Then the vial was placed in an Anton PAAR

microwave oven and heated to 160 °C for 40 min (temperature control using an infrared sensor). Next, the mixture was transferred from the reactor to chromatography column (gradient: EtOAc/PE 1 : 3–2 : 1) for anilines and (gradient: EtOAc/PE 1 : 4–1 : 2) for phenols. The fractions were concentrated on a rotary evaporator.

Anilines can also be purified by dissolving in 20% HCl, rinsing with EtOAc, neutralizing with  $\text{NaHCO}_3$  and subsequent extraction with  $\text{CH}_2\text{Cl}_2$  ( $4 \times 15$  mL) followed by evaporation on a rotary evaporator.

Yellowish transparent solid, mp 119.5–122.1 °C; yield 143 mg (0.44 mmol, 44%).  $R_f$  = 0.36, EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.59 (d,  $J$  = 2.0 Hz, 1H), 8.20 (d,  $J$  = 1.9 Hz, 1H), 8.04–7.99 (m, 2H), 7.45–7.21 (m, 8H), 7.06–6.92 (m, 2H), 6.58–6.46 (m, 2H), 5.10 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  170.6, 147.9, 147.8, 143.0, 131.6, 131.5, 128.9, 128.3 (5C), 127.5 (2C), 127.1, 126.9 (2C), 126.7 (2C), 113.5 (2C), 68.0. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3380, 3253, 2998, 1771, 1679, 1516, 1369, 1241, 1048; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{NaO}^+$  ( $[\text{M} + \text{Na}]^+$ ): 349.1311, found 349.1307 (1.2 ppm).

#### 5-(4-Aminophenyl)-3-(4-bromophenyl)-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (15k)

Product **15k** was obtained *via* the method described for compound **15a**, employing 3-(4-bromophenyl)-5-hydroxy-5-phenyl-1,5-dihydro-2H-pyrrol-2-one (329 mg, 1.00 mmol) and aniline (186 mg, 2.00 mmol). Additional purification can be achieved by recrystallization from ethanol. Colorless solid, mp 247.0–249.5 °C (ethanol); yield 271 mg (0.67 mmol, 67%).  $R_f$  = 0.36, EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.65 (d,  $J$  = 1.9 Hz, 1H), 8.29 (d,  $J$  = 1.9 Hz, 1H), 8.10–7.86 (m, 2H), 7.66–7.53 (m, 2H), 7.42–7.21 (m, 5H), 7.04–6.93 (m, 2H), 6.59–6.41 (m, 2H), 5.10 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  170.4, 148.5, 148.0, 142.8, 131.3 (2C), 130.8, 130.3, 129.0 (2C), 128.7, 128.3 (2C), 127.5 (2C), 127.2, 126.7 (2C), 121.7, 113.6 (2C), 68.2. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3431, 3349, 1679, 1619, 1513, 1489, 1294, 1178, 1074; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{22}\text{H}_{17}\text{BrN}_2\text{NaO}^+$  ( $[\text{M} + \text{Na}]^+$ ): 427.0416, found 427.0407 (2.3 ppm).

#### 5-(4-Aminophenyl)-5-(4-methoxyphenyl)-3-phenyl-1,5-dihydro-2H-pyrrol-2-one (15l)

Product **15l** was obtained *via* the method described for compound **15a**, employing 5-hydroxy-5-(4-methoxyphenyl)-3-phenyl-1,5-dihydro-2H-pyrrol-2-one (281 mg, 1.00 mmol) and aniline (186 mg, 2.00 mmol). Additional purification can be achieved by recrystallization from ethanol. Colorless solid, mp 256.3–258.6 °C; yield 1.015 g (3.44 mmol, 86%).  $R_f$  = 0.25, EtOAc/hexane (1 : 2, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.50 (d,  $J$  = 2.0 Hz, 1H), 8.14 (d,  $J$  = 1.9 Hz, 1H), 8.03–7.95 (m, 2H), 7.43–7.23 (m, 5H), 6.97 (d,  $J$  = 8.2 Hz, 2H), 6.89 (d,  $J$  = 8.7 Hz, 2H), 6.50 (d,  $J$  = 8.2 Hz, 2H), 5.07 (s, 2H), 3.73 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  170.6, 158.2, 148.1, 147.8, 134.8, 131.7, 131.1, 129.1, 128.3 (2C), 128.2, 127.9 (2C), 127.4 (2C), 126.9 (2C), 113.6 (2C), 113.5 (2C), 67.5, 55.1. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3370, 1773, 1674, 1592, 1513, 1445, 1356, 1248, 1211; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_2^+$  ( $[\text{M} + \text{H}]^+$ ): 357.1598, found 357.1588 (2.8 ppm).





### 5-(4-Aminophenyl)-5-(4-chlorophenyl)-3-phenyl-1,5-dihydro-2H-pyrrol-2-one (15m)

Product **15m** was obtained *via* the method described for compound **15a**, employing 5-(4-chlorophenyl)-5-hydroxy-3-phenyl-1,5-dihydro-2H-pyrrol-2-one (285 mg, 1.00 mmol) and aniline (186 mg, 2.00 mmol). Colorless solid, mp 209.0–211.9 °C; yield 166 mg (0.46 mmol, 46%).  $R_f = 0.36$ , EtOAc/hexane (1 : 1, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.61 (s, 1H), 8.19 (d,  $J = 1.8$  Hz, 1H), 8.07–7.95 (m, 2H), 7.48–7.21 (m, 7H), 6.99 (d,  $J = 8.4$  Hz, 2H), 6.52 (d,  $J = 8.4$  Hz, 2H), 5.13 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  170.6, 148.1, 147.4, 142.0, 131.8, 131.7, 131.5, 128.6 (2C), 128.4, 128.4, 128.3 (2C), 128.3 (2C), 127.4 (2C), 127.0 (2C), 113.6 (2C), 67.6. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3161, 2997, 1766, 1681, 1513, 1489, 1241, 1091; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{22}\text{H}_{17}\text{ClN}_2\text{NaO}^+$  ( $[\text{M} + \text{Na}]^+$ ): 383.0922, found 383.0911 (2.8 ppm).

### 5-(4-Hydroxyphenyl)-3,5-diphenyl-1,5-dihydro-2H-pyrrol-2-one (16a)

Product **16a** was obtained *via* the method described for compound **15a**, employing 5-hydroxy-3,5-diphenyl-1,5-dihydro-2H-pyrrol-2-one (251 mg, 1.00 mmol) and phenol (188 mg, 1.00 mmol). White solid, mp 138.1–140.6 °C; yield 206 mg (0.63 mmol, 63%).  $R_f = 0.64$ , EtOAc/hexane (1 : 2, v/v).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.69 (d,  $J = 1.7$  Hz, 1H), 9.49 (s, 1H), 8.26 (d,  $J = 1.9$  Hz, 1H), 8.07–7.89 (m, 2H), 7.47–7.23 (m, 8H), 7.21–7.12 (m, 2H), 6.78–6.69 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  170.6, 156.6, 147.6, 142.6, 132.5, 131.8, 131.5, 128.4 (3C), 128.3 (2C), 128.0 (2C), 127.2, 127.0 (2C), 126.7 (2C), 115.1 (2C), 67.9. FTIR (ZnSe)  $\nu$  ( $\text{cm}^{-1}$ ): 3344, 3176, 1679, 1513, 1492, 1359, 1241, 1173, 1096; HRMS (ES TOF,  $m/z$ ) calcd for  $\text{C}_{22}\text{H}_{17}\text{NNaO}_2^+$  ( $[\text{M} + \text{Na}]^+$ ): 350.1151, found 350.1139 (3.5 ppm).

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by the Russian Science Foundation (grant #19-73-00091).

## Notes and references

- X.-C. Huang, X. Xiao, Y.-K. Zhang, T. T. Talele, A. A. Salim, Z.-S. Chen and R. J. Capon, *Mar. Drugs*, 2014, **12**, 3818–3837.
- H. Zhang, M. M. Conte, X.-C. Huang, Z. Khalil and R. J. Capon, *Org. Biomol. Chem.*, 2012, **10**, 2656–2663.
- Y.-L. Yang, C.-P. Lu, M.-Y. Chen, K.-Y. Chen, Y.-C. Wu and S.-H. Wu, *Chem.-Eur. J.*, 2007, **13**, 6985–6991.
- N. Shionozaiki, T. Yamaguchi, H. Kitano, M. Tomizawa, K. Makino and H. Uchiro, *Tetrahedron Lett.*, 2012, **53**, 5167–5170.
- L. Li, P. Yu, M.-C. Tang, Y. Zou, S.-S. Gao, Y.-S. Hung, M. Zhao, K. Watanabe, K. N. Houk and Y. Tang, *J. Am. Chem. Soc.*, 2016, **138**, 15837–15840.
- Y.-L. Gao, M.-L. Zhang, X. Wang, H.-D. Zhang, J.-Z. Huang and L. Li, *Nat. Prod. Res.*, 2019, DOI: 10.1080/14786419.2019.1641810.
- R. Kontnik and J. Clardy, *Org. Lett.*, 2008, **10**, 4149–4151.
- M. Ramanathan, C.-J. Tan, W.-J. Chang, H.-H. G. Tsai and D.-R. Hou, *Org. Biomol. Chem.*, 2013, **11**, 3846–3854.
- R. Y. Kuo, F. R. Chang and Y. C. Wu, *Tetrahedron Lett.*, 2001, **42**, 7907–7909.
- W.-N. Zhang, J.-G. Luo and L.-Y. Kong, *J. Agric. Food Chem.*, 2012, **60**, 1682–1687.
- Y. S. Hui, L. Yan, W. Qi, S. Y. Ping, G. Wei, L. Yuan, Y. B. You and K. H. Xue, *Heterocycles*, 2020, **100**, 568–584.
- B.-y. Yang, Y. Liu, X. Wang, Y.-g. Xia, Q.-h. Wang and H.-x. Kuang, *Zhongcaoyao*, 2013, **44**, 1877–1880.
- X. Hu, M.-W. Gong, W.-W. Zhang, Q.-H. Zheng, Q.-Y. Liu, L. Chen and Q.-Q. Zhang, *Heterocycles*, 2014, **89**, 189–196.
- B. Almohaywi, T. T. Yu, G. Iskander, D. S. H. Chan, K. K. K. Ho, S. Rice, D. S. Black, R. Griffith and N. Kumar, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 1054–1059.
- S. Mykhaylychenko, D. Harakat, G. Dupas, Y. G. Shermolovich and J.-P. Bouillon, *J. Fluorine Chem.*, 2009, **130**, 418–427.
- S. Seo and M. C. Willis, *Org. Lett.*, 2017, **19**, 4556–4559.
- R. Shiraki, A. Sumino, K.-i. Tadano and S. Ogawa, *Tetrahedron Lett.*, 1995, **36**, 5551–5554.
- W.-K. Goh, C. R. Gardner, K. V. G. Chandra Sekhar, N. N. Biswas, S. Nizalapur, S. A. Rice, M. Willcox, D. S. Black and N. Kumar, *Bioorg. Med. Chem.*, 2015, **23**, 7366–7377.
- W. K. Goh, G. Iskander, D. S. Black and N. Kumar, *Tetrahedron Lett.*, 2007, **48**, 2287–2290.
- M.-Y. Wu, K. Li, N. Wang, T. He and X.-Q. Yu, *Synthesis*, 2011, 1831–1839.
- R. Adhikari, D. A. Jones, A. J. Liepa and R. H. Nearn, *Aust. J. Chem.*, 2005, **58**, 882–890.
- W. Birru, R. T. Fernley, L. D. Graham, J. Grusovin, R. J. Hill, A. Hofmann, L. Howell, P. J. James, K. E. Jarvis, W. M. Johnson, D. A. Jones, C. Leitner, A. J. Liepa, G. O. Lovrecz, L. Lu, R. H. Nearn, B. J. O'Driscoll, T. Phan, M. Pollard, K. A. Turner and D. A. Winkler, *Bioorg. Med. Chem.*, 2010, **18**, 5647–5660.
- C. Li, K. Jiang, Q. Ouyang, T.-Y. Liu and Y.-C. Chen, *Org. Lett.*, 2016, **18**, 2738–2741.
- H. Roeber and K. Hartke, *Chem. Ber.*, 1975, **108**, 3262–3270.
- F.-M. Liao, Z.-Y. Cao, J.-S. Yu and J. Zhou, *Angew. Chem., Int. Ed.*, 2017, **56**, 2459–2463.
- A. V. Aksenov, V. Khamraev, N. A. Aksenov, N. K. Kirilov, D. A. Domenyuk, V. A. Zelensky and M. Rubin, *RSC Adv.*, 2019, **9**, 6636–6642.
- A. V. Aksenov, D. A. Aksenov, N. A. Arutiunov, N. A. Aksenov, E. V. Aleksandrova, Z. Zhao, L. Du, A. Kornienko and M. Rubin, *J. Org. Chem.*, 2019, **84**, 7123–7137.
- A. V. Aksenov, D. A. Aksenov, G. D. Griaznov, N. A. Aksenov, L. G. Voskressensky and M. Rubin, *Org. Biomol. Chem.*, 2018, **16**, 4325–4332.
- J. A. Ciller, C. Seoane and J. L. Soto, *Liebigs Ann. Chem.*, 1985, 51–57.



- 30 N. A. Aksenov, D. A. Aksenov, A. A. Skomorokhov, L. A. Prityko, A. V. Aksenov, G. D. Griaznov and M. Rubin, *J. Org. Chem.*, 2020, **85**, 12128–12146.
- 31 L. Chen, F. Zhou, T.-D. Shi and J. Zhou, *J. Org. Chem.*, 2012, **77**, 4354–4362.
- 32 L. Chen and J. Zhou, *Chem.-Asian J.*, 2012, **7**, 2510–2515.
- 33 D. Glavac, N. Topolovcan and M. Gredicak, *J. Org. Chem.*, 2020, **85**, 14253–14261.
- 34 M. S. Hidayetulla, R. C. Shah and T. S. Wheeler, *J. Chem. Soc.*, 1941, 111–112, DOI: 10.1039/JR9410000111.
- 35 Z. Li and J. Yin, *Chin. J. Chem.*, 2017, **35**, 1179–1184.
- 36 S. Lin, Y. Wei and F. Liang, *Chem. Commun.*, 2012, **48**, 9879–9881.
- 37 A. Stroba, F. Schaeffer, V. Hindie, L. Lopez-Garcia, I. Adrian, W. Froehner, R. W. Hartmann, R. M. Biondi and M. Engel, *J. Med. Chem.*, 2009, **52**, 4683–4693.
- 38 G. Bist, N. T. Pun, T. B. T. Magar, A. Shrestha, H. J. Oh, A. Khakurel, P.-H. Park and E.-S. Lee, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 1205–1209.
- 39 P. Shaykhutdinova and M. Oestreich, *Org. Lett.*, 2018, **20**, 7029–7033.
- 40 Y.-S. Yang, B. Yang, Y. Zou, G. Li and H.-L. Zhu, *Bioorg. Med. Chem.*, 2016, **24**, 3052–3061.
- 41 R. Kumar, P. Sharma, A. Shard, D. K. Tewary, G. Nadda and A. K. Sinha, *Med. Chem. Res.*, 2012, **21**, 922–931.

