One-Step Synthesis of 3,4-Diphenyl-2-pyrrolinones by Solvent-Free and Bi_2O_3-Catalyzed Approaches and Cytotoxicity Screening Against Glioma Cells

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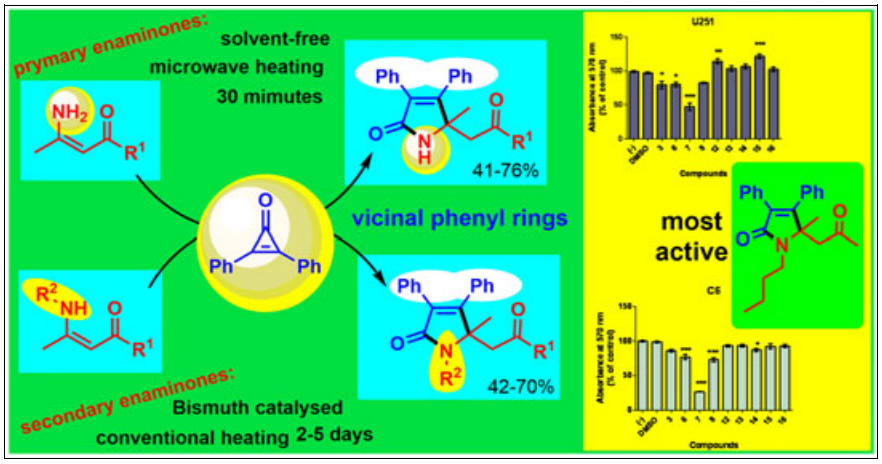


Multifunctionalized 2-pyrrolinones were synthesized from the formal aza-[3 + 2] cycloaddition reaction of acyclic enaminones and diphenylcyclopropenone. For primary enaminones, solventless reaction under microwave heating was developed. On the other hand, catalysis by Bi_2O_3 under conventional heating was the more suitable strategy when secondary enaminones were employed. These conditions allowed the synthesis of a set of 2-pyrrolinones with two vicinal phenyl substituents, which were evaluated for cytotoxicity against U251 and C6 glioblastoma cells. In general, all tested 2-pyrrolinones with two vicinal phenyl rings were more active than those without this structural moiety, and 1-butyl-5-methyl-5-(2-oxopropyl)-3,4-diphenyl-1,5-dihydro-2*H*-pyrrol-2-one was the most cytotoxic and appears to be a new possibility as an antitumor scaffold to this aggressive brain tumor.

INTRODUCTION

The 2-pyrrolinone core is present in several compounds that possess interesting biological activities [1–7]. Because of this aspect, the synthesis of densely substituted 2-pyrrolinone is a theme of ongoing interest, and the development of practical synthetic routes to access this heterocycle demands continuous improvements [8–13]. In a subclass of this δ-lactam, the occurrence of two vicinal phenyl substituents is a relevant structural scaffold because it increases the biological effect [1].

Acyclic enaminones are attractive as building blocks to the synthesis of polysubstituted heterocycles, because they can be easily prepared from 1,3-dicarbonyl compounds, among other precursors [14–24]. In this scenario, the formal aza-[3 + 2] cycloaddition of enaminones emerges as a versatile strategy to the preparation of five-membered *N*-heterocycles because two sigma bonds are formed in a single step, and catalysis by metal salts and metal-free annulations have already been reported [25–32] (Fig. 1).

Some characteristic features emerge from Figure 1: the adequate selection of the reaction conditions and electrophile affords the synthesis of pyrrole or pyrrolinone with regiochemical control of the substituents, and the heterocycles are formed by incorporating two carbons of the applied electrophile and two carbons and the nitrogen of the **─N─C═C─** moiety

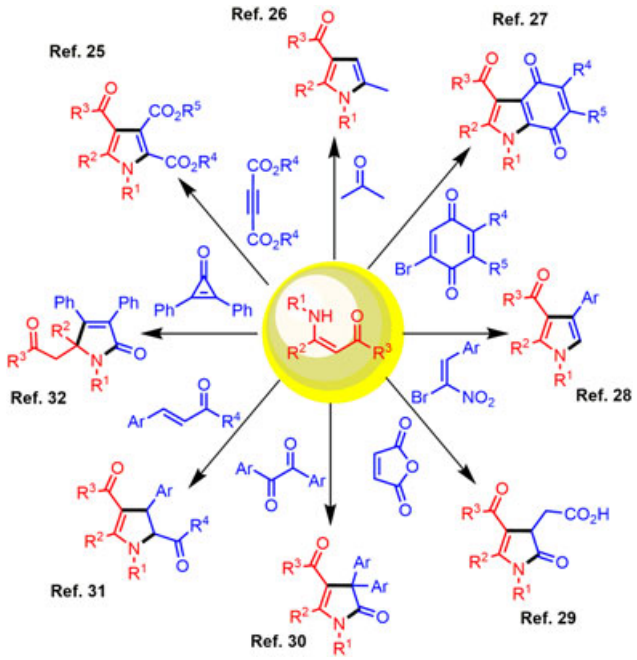


Figure 1. Examples of the formal aza-[3 + 2] cycloaddition of enaminones with newly formed sigma bonds in black. [Color figure can be viewed at wileyonlinelibrary.com]

of the enaminone [25–31], forming two new sigma bonds.

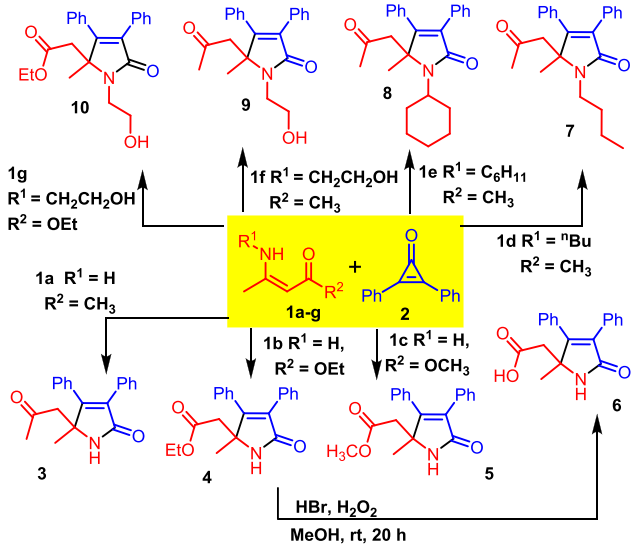
Despite the diversity of approaches that employ the formal aza-[3 + 2] cycloaddition of enaminones **1** as a direct route to 2-pyrrolinone [18–20,22,24–32], the one-step synthesis of such δ-lactam with two vicinal phenyl substituents is still scarce. On the other hand, the use of diphenylcyclopropenone **2** is strategic when two adjacent phenyl rings are required in planned targets [33–36]. Recently, we described the synthesis of 1-azabicyclic alkaloid-like compounds, which were obtained by the reaction of cyclic enaminones with diphenylcyclopropenone [37], which represents an improved synthesis of 1-azabicyclo[3.3.0]octanes as compared to that synthesized by the reaction of acyclic enaminones and diphenylcyclopropenone [38,39]. Particularly noteworthy is the heterocycle formed by incorporating three carbons of the cyclopropenone ring and two continuous atoms (─N─C─) of the enaminone instead of **─N─C═C─** moiety (Fig. 1), being a rare example of such reaction patterns to the formal [3 + 2] aza-annulations of this class of compounds [21,38–40], and in contrast with the other examples shown in Figure 1 [25–31].

Because of the synthetic potential of the formal cycloadditions of enaminones [40–45] as well as alkaloids and alkaloid-like compounds as privileged cytotoxic scaffolds in glial cells [46,47], we investigated herein the combination of solvent-free condition, microwave (MW)-assisted organic synthesis and the use of green bismuth catalysis [48,49] in the formal aza-[3 + 2] cycloaddition of acyclic enaminones with diphenylcyclopropenone, in search of a practical synthesis of polysubstituted 2-pyrrolinones with two vicinal phenyl substituents. In addition, the cytotoxicity against glioma cells was evaluated, and some 2-pyrrolinones without vicinal phenyl rings were synthesized to compare biological activity. New candidate molecules to treat glioma are a theme of huge importance because this is the most aggressive brain tumor in adults [50].

RESULTS AND DISCUSSION

The formal aza-[3 + 2] cycloaddition of enaminones with diphenylcyclopropenone was first described by Kascheres and coworkers [32]. This elegant route to 2-pyrrolinone was further applied to the synthesis of more elaborated polysubstituted derivatives [38,39]. Despite this achievement, reaction time is long when primary enaminones were employed (3 days), and the method is also very limited in scope and slower with secondary enaminones in toluene under reflux (6 days). To be useful in the medicinal chemistry arena, it needs be improved. Thus, to circumvent this and obtain a small set of 2-pyrrolinones in a quick way, the synthesis of known 2-pyrrolinones **3** and **4** was reinvestigated as model reactions, with the goal of the development of a greener practical reaction conditions (Scheme 1).

Scheme 1. Synthetic route to vicinal 3,4-diphenyl-2-pyrrolinones. [Color figure can be viewed at wileyonlinelibrary.com]



Although primary enaminones **1a**–**1c** are liquid compounds or solids of low melting points, a solvent-free reaction of these enaminones and solid diphenylcyclopropenone **2** was investigated aimed at obtaining the 2-pyrrolinones with a relatively short reaction time in relation to the described route [32] to such compound (3 days for **3** and **4**) (Scheme 1). To this end, the effect of MW heating and the use of bismuth salts catalysts were evaluated, with results summarized in Table 1.

Table 1

Conditions to the synthesis of 3,4-diphenyl-2-pyrrolinones by formal aza-[3 + 2] cycloaddition of enaminones with diphenylcyclopropenone.

Entry	Product	Solvent	Catalyst (10 mol%)	MW heating[a]		Conventional heating[b]	
				Time (min)	Yield (%)	Time (day)	Yield (%)
1	**3**	—	—	10	25	—	—
2	**3**	—	—	30	41[c]	—	—
3	**4**	—	—	10	64	—[d]	76
4	**4**	—	—	30	76[c]	—	—
5	**5**	—	—	10	57	—	—
6	**5**	—	—	30	60[c]	—	—
7	**7**	—	—	30	23	—	—
8	**7**	Toluene	—	—	—	7	CM
9	**7**	Toluene	$Bi(NO_3)_3$[e]	90	16	5	36
10	**7**	Toluene	Bi_2O_3	90	36	4	42
11	**8**	—	—	10	25	—	—
12	**8**	Toluene	—	—	—	7	CM
13	**8**	Toluene	$Bi(NO_3)_3$	30	18	4	26
14	**8**	Toluene	Bi_2O_3	90	26	2	70
15	**9**	—	—	30	CM	—	—
16	**9**	Toluene	—	—	—	7	CM
17	**9**	Toluene	$Bi(NO_3)_3$	90	CM	5	CM
18	**9**	Toluene	Bi_2O_3	90	CM	5	75
19	**10**	—	—	90	CM	—	—
20	**10**	Toluene	—	—	—	7	18
21	**10**	Toluene	$Bi(NO_3)_3$	90	CM	2	38
22	**10**	Toluene	Bi_2O_3	90	20	5	70

CM, complex mixture.
[a]Microwave heating, 150 °C.
[b]Conventional oil bath heating, under reflux (with solvent) or at 120 °C (solvent free).
[c]With two equivalents of enaminone.
[d]Time: 90 min.
[e]$Bi(NO_3)_3 \cdot 5H_2O$.

Equimolar amounts of **1a** and **2** were reacted under MW heating condition, and **3** could be isolated, however in a poor yield (Table 1, entry 1). The same transformation was also performed by employing twice the amount of enaminone, and compound **3** was formed in a better yield (entry 2). These reaction conditions were extended to primary enaminones **1b** and **1c**, and pyrrolinones **4** and **5** were formed. In general, obtained yields with primary enaminones were somewhat increased when an excess of the enaminone (**1a**–**1c**) was used (entries 3–6), and very short reaction times were observed when compared to the condition previously described to the thermal-induced formal aza-[3 + 2] cycloaddition reaction (reflux in toluene, 3 days) [32]. A tentative bromination [51] of the phenyl rings of **4** resulted only in the acid **6** through ester hydrolysis (Scheme 1).

A three-component reaction to the synthesis of 2-pyrrolinones **3**–**5** was also studied, using the corresponding 1,3-dicarbonyl compound, diphenylcyclopropenone, and ammonium acetate as an NH_3 source to form enaminone *in situ*, but only complex mixtures were formed under conventional and MW heating.

To test the influence of MW heating in the solvent-free method, a control reaction was undertaken, wherein equimolar amounts of enaminone **1b** and **2** were reacted under conventional heating. In this condition, pyrrolinone **5** was isolated in yield identical to the best MW heating condition, however with threefold reaction time (compare entries 3 and 4, Table 1). Therefore, the association of MW and solvent-free condition is beneficial to N–H 2-pyrrolinones synthesis from primary enaminones.

With the analysis of the ^{13}C-NMR spectra of obtained compounds, the amide-type regiochemistry [32,37] for heterocycles **3**–**5** is deduced from the chemical shifts of the endocyclic carbonyl (169 ppm) and beta vinyl carbon (159 ppm) of the **N─(C═O)─C(Ph)═C(Ph)─C** moiety of **3**–**5**.

Besides, the regiochemical assignment of compound **3** was investigated by ^{1}H, ^{13}C long-range correlation experiment, which showed a correlation (^{3}J) involving the hydrogen of CH_3 at position **5** of the 2-pyrrolinone nucleus and the beta vinyl carbon of the **C═C─C═O** moiety. This kind of correlation would not be observed for the opposite regiochemistry.

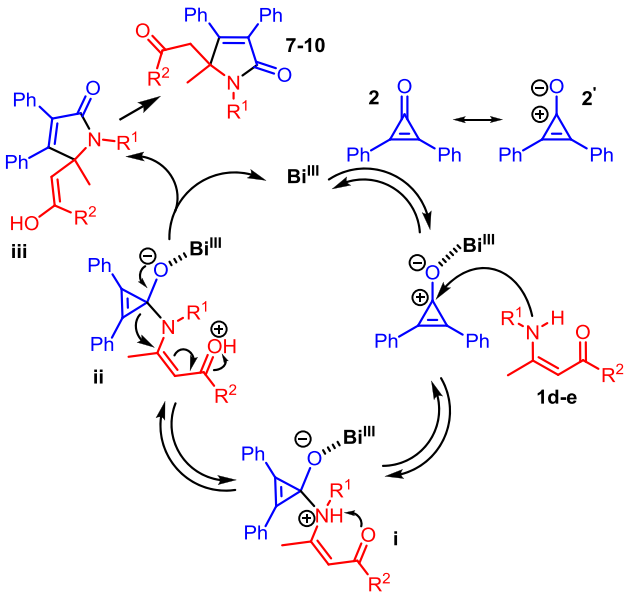
With a practical reaction condition developed to primary enaminones in hand, the synthesis of new *N*-substituted 2-pyrrolinones **7**–**10** was investigated (Scheme 1). However, the solvent-free reaction under the MW heating methodology was disappointing for the reaction involving secondary enaminones, affording low yields of **7** and **8** (23–25%, Table 1, entries 7 and 11) or complex mixtures of **9** and **10** (entries 15 and 19). Worse results were observed when conventional heating in toluene was applied (entries 8, 12, 16, and 20) because of long reactions time and complex mixture formation. To circumvent these serious limitations in the synthesis of *N*-substituted 2-pyrrolinones from secondary enaminones, other experimental conditions were investigated.

We recently discovered that $Bi(NO_3)_3{\cdot}5H_2O$ was efficient as a catalyst in the formal aza-[3 + 3] cycloaddition of enaminones [40,41]. Thus, we extended the bismuth salt catalysis (10 mol%) to the formal aza-[3 + 2] cycloaddition of enaminones with diphenylcyclopropenone, en route to the synthesis of *N*-substituted 2-pyrrolinones (Table 1).

To amplify the scope of the bismuth compound as a catalyst in the aza-cycloaddition of enaminones, we tested $Bi(NO_3)_3{\cdot}5H_2O$ and Bi_2O_3, the cheapest Bi(III) compounds available. Although the two heating conditions allowed isolation of desirable heterocycles **7**–**10**, the association of MW heating and bismuth catalysis was deleterious to the isolated yields as compared to conventional heating, being the catalysis by Bi_2O_3 more efficient than $Bi(NO_3)_3{\cdot}5H_2O$ (compare entries 9 and 10, 13 and 14, 17 and 18, and 21 and 22; Table 1 and Scheme 1).

Under Bi(III) catalysis condition, the mechanism for the formation of 2-pyrrolinones by formal aza-[3 + 2] cycloaddition can be tentatively rationalized as an ionic stepwise process (Scheme 2). Thus, coordination of Bi(III) catalyst with the oxygen atom of the diphenylcyclopropenone should increase its dipolar contribution **2′**, and then a sequence of transformations is initiated [32] by attachment of the nitrogen of the secondary enaminones **1d** and **1e** to the carbonyl carbon

Scheme 2. Mechanistic proposal for the Bi(III) catalysis in the formal aza-[3 + 2] cycloaddition. [Color figure can be viewed at wileyonlinelibrary.com]



of **2** via a hard–hard interaction. Adduct **i** is thus formed, which in sequence gives **ii** after proton shift. This late suffers a concomitant ring expansion and Michael reaction forming enol **iii**, which affords the 2-pyrrolinones **7**–**10**.

To amplify the set of dihydro-2-pyrrolinones to the cytotoxicity screening against glioblastoma cells, but now without two vicinal phenyl substituents, and thus compare the influence of this structural characteristic in the biological activity, some other derivatives were prepared. Toward this, we envisioned the known synthesis of dihydro-2-pyrrolinones via formal aza-[3 + 2] cycloaddition of enaminones with maleic anhydride **11a** and *N*-arylmaleimides **11b**–**11d** (Scheme 3) [29,45,52].

Derivatives **12** and **13** were easily obtained, but formation of analogous 2-pyrrolinone **14** from reaction of *N*-(4-nitrophehyl)-maleimide **11b** with primary enaminone **1a** was reluctant. Reaction in acetonitrile, benzene, or toluene under reflux afforded succinimide–enaminone **15** exclusively, and similar results were observed to *N*-arylmaleimides **11c** and **11d** yielding **16** and **17**. Formation of **14** through the formal aza-[3 + 2] cycloaddition was achieved by catalysis of AcOH in acetonitrile, and alternatively, by conversion of **15** under similar reaction conditions (Scheme 3).

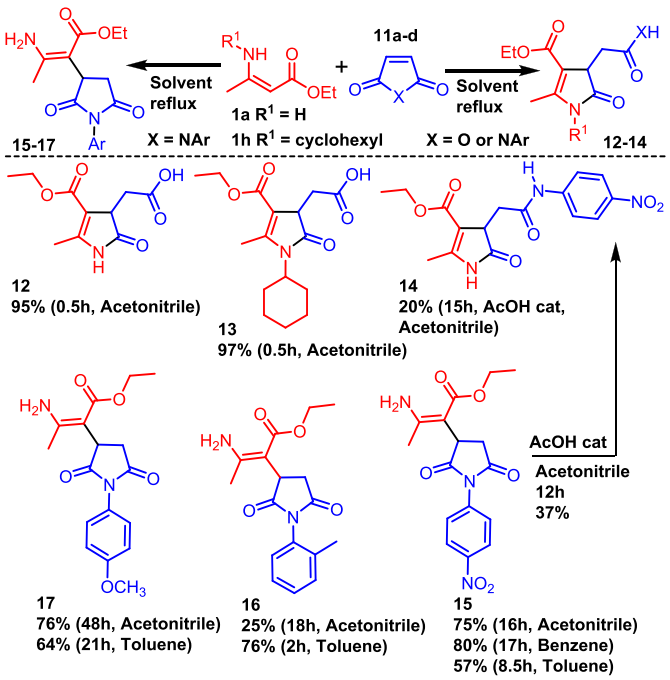
Cytotoxicity screening. Cytotoxicity studies of δ-lactam in glioblastoma cells are scarce, and the unique example that caused a decrease in human glioblastoma cell survival was rolipram, 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone [50]. Thus, with a set of dihydro-2-pyrrolinones with (**3**–**10**) and without (**12**–**14**) two vicinal phenyl substituents prepared, the *in vitro* cytotoxicity against U251 and C6 glioma cells was investigated, in search of new potential antitumor activity of synthesized molecules. For comparative purposes, succinimide–enaminones **15** and **16** were evaluated as well. Under the biological test conditions, esters **4** and **5** were partially converted into acid **6** and, together with compounds **9** and **10**, did not show reproducible results. Considering these facts, the cytotoxic evaluation of nine compounds was investigated, as indicated in Figure 2.

N-Butyl derivative **7** was the most active in the two glioma cell lines evaluated. As a general trend, all tested 2-pyrrolinones with two vicinal phenyl rings (**3** and **6**–**8**) were more active than those without this structural moiety (**12**–**14**). Apparently, the presence of a 2-pyrrolinone core is not sufficient to be cytotoxic against tested cells, because the activity levels of **12**–**14** were comparable to those of **15** and **16** (Fig. 2).

To examine the biological effect of the most active *N*-butyl dihydro-2-pyrrolinone **7**, C6 tumor cells were treated with it at different concentrations (1, 10, 50, and 100 μ*M*) during 24 and 72 h (Fig. 3). A dose-dependent effect was observed, and cytotoxicity at 10, 50, and 100 μ*M* was observed only after 72 h of exposure of C6 tumor cells (Fig. 3A).

The morphology patterns of C6 cells in control conditions and in those treated with vehicle DMSO

Scheme 3. Synthetic route to pyrrolinones and succinimides from enaminones. [Color figure can be viewed at wileyonlinelibrary.com]



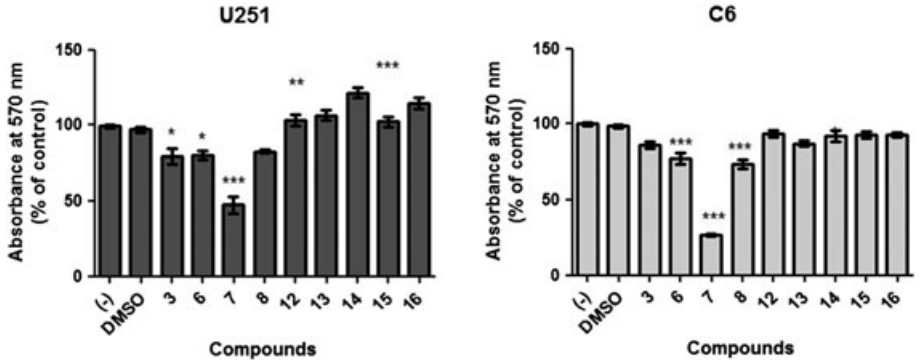


Figure 2. Cytotoxicity screening of selected 2-pyrrolinones **3**, **6**–**8**, and **12**–**14** and succinimides **15** and **16** with viability percentage on U251 and C6 glioma cells by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells were treated for 72 h with 100 μ*M* of each compound. (-): Control (cells cultured without vehicle or any compound). DMSO: vehicle control (cells cultured with 0.1% DMSO). Three experiments with $R^2 \geq 0.9$ were considered ($n = 8$). The viability was expressed as mean values and standard error medium from three different experiments. One-way analysis of variance followed by Bonferroni test for multiple comparisons was used. $^{**}P < 0.01$ and $^{***}P < 0.001$.

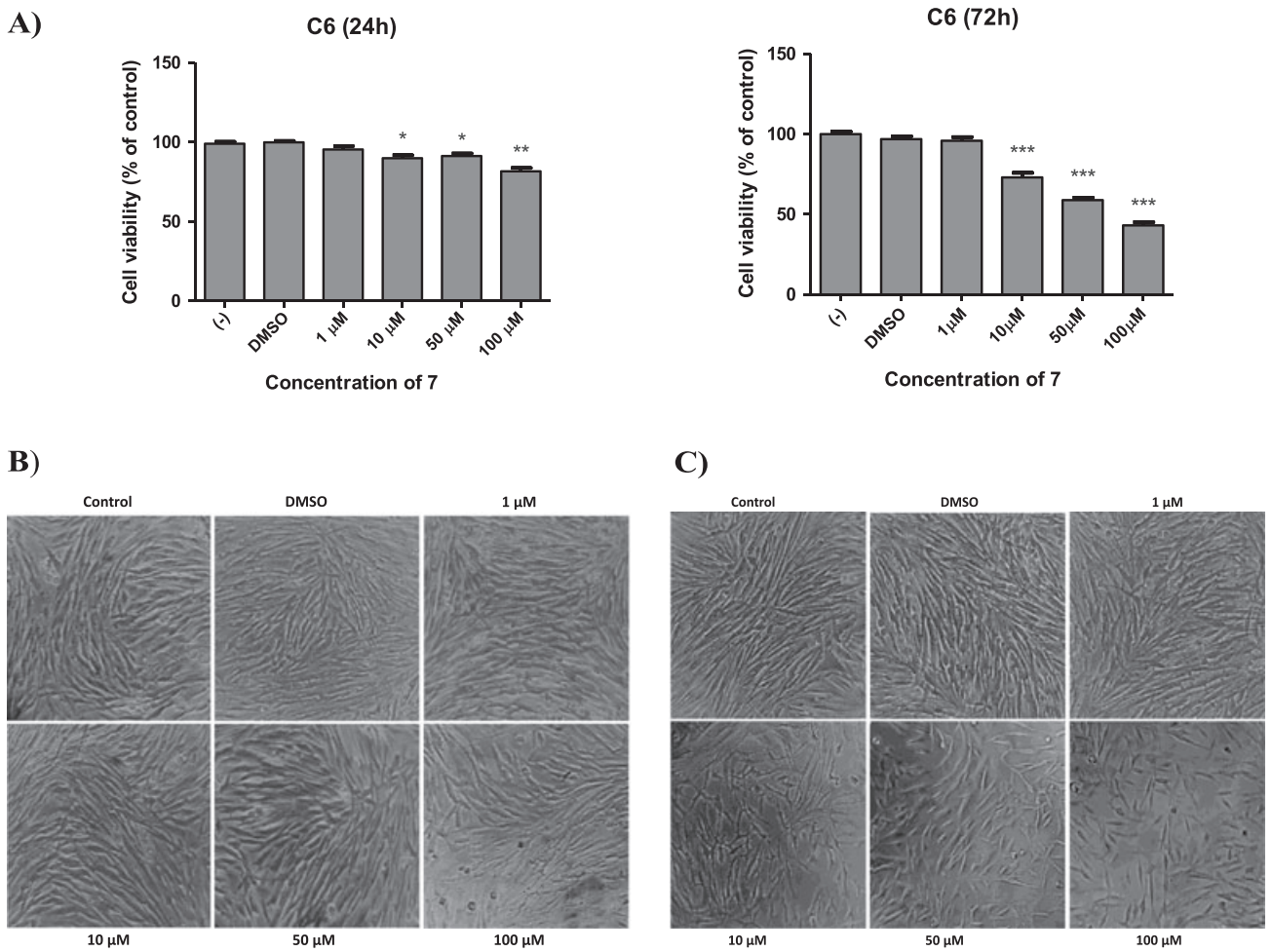


Figure 3. Cytotoxic study of compound **7**. (A) Dose-dependent effect and cytotoxicity at 1, 10, 50, and 100 μ*M* after 24 and 72 h of exposure to tumor C6 cells. (B) Photomicrography of C6 cells after treatment with 1, 10, 50, and 100 μ*M* during 24 h. (C) Photomicrography of C6 cells after treatment with 1, 10, 50, and 100 μ*M* during 72 h, showing time and dependent effects. Objective 10 × 0.20.

(0.1%) as well as those treated with dihydro-2-pyrrolinone **7** in studied concentrations were observed under phase contrast microscopy and are presented in the photomicrographs indicated in Figure 3B, C. It can be inferred that the observed dose-dependent effect is corroborated, because after 24 h of exposure of C6 cells to compound **7**, a significant reduction in the number of viable cells was observed only with a concentration of 100 μ*M*. However, after 72 h of treatment with dihydro-2-pyrrolinone **7** in concentrations of 10, 50, and 100 μ*M*, as indicated in the photomicrographs presented in Figure 3B, C, progressive morphological features in relation to tested concentrations, like cell shrinkage, cell wall deformation and mainly reduced number of viable cells were observed, whereas these morphological features were absent in the control cell conditions and in cells treated with vehicle DMSO (0.1%).

CONCLUSION

This study represents a green one-step approach to dihydro-2-pyrrolinones with vicinal phenyl rings via formal aza-[3 + 2] cycloaddition of enaminones with diphenylcyclopropenone. For primary enaminones, solventless reactions under MW heating are adequate, while for secondary enaminones, catalysis by Bi_2O_3 constitutes a practical synthetic route. In this way, these newly developed conditions afford practical access to multifunctionalized dihydro-2-pyrrolinones with two vicinal phenyl substituents in a simple way and are adequate for the purpose of synthesizing a small set of such δ-lactam in a quick way for biological screening. In this case, among tested heterocycles, compound **7** was the most cytotoxic against U251 and C6 glioma cells and appears to be a new possibility as an antitumor scaffold [53], paving the way for diaryl-dihydro-2-pyrrolinones to be further investigated in this aggressive brain tumor [50].

EXPERIMENTAL

Chemistry. Melting points were determined on a Microquímica MQAPF 301 hot plate apparatus and are uncorrected. Infrared spectra were recorded as KBr disks on a SHIMADZU IR Affinity-1 instrument. NMR spectra were recorded using a Varian Gemini 300 spectrometer, a Bruker 250 MHz, or a Bruker Advance III 500 spectrometer, and the field strengths are indicated in each compound. Chemical shifts are reported in parts per million downfield from reference (internal TMS). MW heating reactions were performed in a CEM Discover SP using a 10-mL Pyrex pressure vial for closed-vessel reactions, under the indicated power that automatically reaches and maintains the set temperature, specified in each case, with IR temperature control and medium stirring speed using cylindrical stir bars (10 × 3 mm) and a default ramp time of 10 min. Enaminones **1a**–**1h** [32,38], diphenylcyclopropenone **2** [54], and maleimides **11b**–**11d** [55] were prepared according to known procedures.

General synthetic procedure for solvent-free synthesis of 3, 4, and 5. To a 10-mL Pyrex pressure vial for closed vessel for MW heating reaction was added 97 mg (1 mmol) of enaminone **1a** and 103 mg (0.5 mmol) of diphenylcyclopropenone **2**. The mixture was subjected to MW heating at 150 °C (200 W) for 10 min. The heating cycle was repeated twice, affording a total reaction time of 30 min. After this time, the crude residue was recrystallized from diisopropyl ether/hexane, affording 63 mg (41% yield) of **3**.

5-Methyl-5-(2-oxopropyl)-3,4-diphenyl-1H-pyrrol-2(5H)-one (3). For **3**: white solid, m.p. 172.0–172.6 °C (Lit. [32] 171–172 °C). IR (cm^{-1}) 3419, 1720, 1693, 1359, 1217, 1184, 1145, 759, 696. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.36–7.42 (m, 5H), 7.17–7.20 (m, 5H), 2.89 (d, *J* 18 Hz, 1H), 2.62 (d, *J* 18 Hz, 1H), 2.15 (s, 3H), 1.55 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 206.5, 171.1, 159.8, 133.4, 132.1, 130.7, 129.3, 128.8, 128.6, 128.5, 127.8, 127.7, 61.9, 49.8, 31.8, 22.5.

Ethyl 2-(2-methyl-5-oxo-3,4-diphenyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (4). For **4**: 129 mg (1 mmol) of enaminone **1b** and 103 mg (0.5 mmol) of diphenylcyclopropenone **2** afforded 117 mg (76% yield) of **4**, white solid, m.p. 118.5–119.3 °C (Lit. [32] 120–125 °C). IR (cm^{-1}) 3070, 1724, 1689, 1363, 1317, 1300, 1271, 1222, 1028, 802, 754, 698. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.34–7.38 (m, 5H), 7.18–7.20 (m, 5H), 7.00 (br, 1H), 4.19 (ddt, *J* 7 and 14 Hz, 2H), 2.72 (d, *J* 16 Hz, 1H), 2.60 (d, *J* 16 Hz, 1H), 1.55 (s, 3H), 1.26 (t, *J* 7 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 171.0 (2 C), 159.4, 133.7, 132.7, 131.1, 129.8, 129.3, 129.1, 129.0, 128.3 (2 CH), 61.5, 61.2, 42.6, 23.5, 14.6.

Methyl 2-(2-methyl-5-oxo-3,4-diphenyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5). For **5**: 117 mg (1 mmol) of enaminone **1c** and 113 mg (0.6 mmol) of diphenylcyclopropenone **2** afforded 192 mg (60% yield) of **5** as a brown oil, which solidified upon standing, m.p. 118.5–119.8 °C, yellow solid, m.p. 119.5–120.2 °C. IR (cm^{-1}) 3414, 2935, 1666, 1446, 1419, 1465, 1365, 712, 698. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.32–7.38 (m, 5H), 7.16–7.20 (m, 5H), 7.06 (s, 1H), 3.71 (s, 3H), 2.74 (d, 1H, *J* 15 Hz), 2.59 (d, 1H, *J* 15 Hz), 1.54 (s, 3H). ^{13}C-NMR ($CDCl_3$, 62.5 MHz) δ 171.0, 170.6, 159.0, 133.2, 132.3, 130.6, 129.4, 128.8, 128.7, 128.6, 127.9 (2 CH), 60.8, 52.0, 42.0, 23.1. *Anal*. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75%; H, 5.96%; N, 4.36%. Found: C, 74.32%; H, 6.21%; N, 4.13%.

Synthetic procedure for additional solvent-free synthesis of 3, 4, and 5 (Table 1). To a 10-mL Pyrex pressure vial for closed vessel for MW heating reaction was added 59 mg (0.5 mmol) of enaminone **1a** and 59 mg (0.6 mmol) of diphenylcyclopropenone **2**. The mixture was subjected to MW heating at 150°C (200 W) for 10 min. After this time, the crude residue was recrystallized from diisopropyl ether/hexane, affording 40 mg of **3**, 25% yield, m.p. 170.0–171.2 °C (Lit. [32] 171–172 °C).

For **4**: A mixture of 30 mg (0.2 mmol) of enaminone **1b** and 42 mg (0.2 mmol) of diphenylcyclopropenone **2** was MW heated at 150 °C (200 W) for 10 min. After this time, the crude residue was recrystallized from diisopropyl ether/hexane, affording 43 mg of **4**, 64% yield, m.p. 121.4–122.4 °C (Lit. [32] 120–120.5 °C). Alternatively, a mixture of 25 mg (0.2 mmol) of enaminone **1b** and 44 mg (0.2 mmol) of diphenylcyclopropenone **2** was heated at 110 °C in an oil bath for 90 min. After this time, the crude residue was recrystallized from diisopropyl ether/hexane, affording 51 mg of **4**, 76% yield, m.p. 121.4–122.4 °C (Lit. [32] 120–120.5 °C).

For **5**: 31 mg (0.3 mmol) of enaminone **1c** and 43 mg (0.2 mmol) of diphenylcyclopropenone **2** afforded 38 mg of **5**, 57% yield, m.p. 118.5–119.8 °C.

2-(2-Methyl-5-oxo-3,4-diphenyl-2,5-dihydro-1H-pyrrol-2-yl) acetic acid (6). To a solution of 68 mg (0.2 mmol) of **4** in 5 mL of methanol maintained under magnetic stirring and ice bath was added 70 μL of 48% hydrobromic acid (2.1 mmol) and 50 μL of hydrogen peroxide drop by drop. After 20 h, the reaction mixture was poured into ice, and a white solid was precipitated. After filtration, the solid was air dried, leading to 50 mg (80%) of **6**. IR (cm^{-1}) 3426, 2981, 1728, 1683, 1519, 1345, 1199, 1029, 744, 696. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.75 (br, 1H), 7.33–7.40 (m, 5H), 7.19–7.23 (m, 5H), 3.71 (3H, s), 2.68 (d, 1H, *J* 15 Hz), 2.82 (d, 1H, *J* 15 Hz), 1.68 (3H, s). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 174.3, 172.8, 160.7, 133.2, 132.0, 130.5, 129.6, 129.1, 128.9, 128.7, 128.23, 128.17, 62.3, 41.7, 22.8. *Anal*. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25%; H, 5.58%; N, 4.56%. Found: C, 74.11%; H, 5.67%; N, 4.12%.

General synthetic procedure for 7, 8, 9, and 10. A mixture of 47 (0.3 mmol) of enaminone **1d**, 53 mg (0.3 mmol) of diphenylcyclopropenone **2**, and 12 mg (0.03 mmol) of Bi_2O_3 in 5-mL toluene was heated at 110 °C in an oil bath for 4 days. After this time, the product was purified by column chromatography in hexane/ethyl acetate 1:1, affording 36 mg (49% yield) of **7**.

1-Butyl-5-methyl-5-(2-oxopropyl)-3,4-diphenyl-1,5-dihydro-2H-pyrrol-2-one (7). Yellow oil, IR (cm^{-1}) 3456, 3055, 2958, 1716, 1678, 1404, 1265, 698. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.32–7.38 (m, 5H), 7.16–7.21 (m, 5H), 3.56 (ddd, 1H, *J* 14.0, 10.5 and 5.0 Hz), 3.27 (ddd, 1H, *J* 14.0, 10.5 and 5.0 Hz), 2.91 (d, 1H, *J* 16.0 Hz), 2.71 (d, 1H, *J* 16.0 Hz), 2.04 (s, 3H), 1.59–1.80 (m, 2H), 1.46 (s, 3H), 1.38–1.44 (m, 2H), 0.97 (t, *J* 7.5 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 204.2, 169.8, 156.2, 134.0, 133.4, 131.8, 131.4, 129.7, 129.3, 128.8, 128.5, 127.9, 127.8, 65.8, 47.2, 40.6, 31.5, 24.2, 20.9, 14.0. *Anal*. Calcd. for $C_{24}H_{27}NO_2$: C, 79.74%; H, 7.53%; N, 3.87%. Found: C, 80.02%; H, 7.21%; N, 3.41%.

1-Cyclohexyl-5-methyl-5-(2-oxopropyl)-3,4-diphenyl-1,5-dihydro-2H-pyrrol-2-one (8). For **8**: 44 mg (0.2 mmol) of enaminone **1e**, 42 mg (0.2 mmol) of diphenylcyclopropenone **2**, and 10 mg (0.02 mmol) of Bi_2O_3 afforded 60 mg (77% yield) of **8**, brown oil, IR (cm^{-1}) 1713, 1667, 1366, 698. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.36–7.38 (m, 5H), 7.14–7.19 (m, 5H), 3.11 (tt, 1H, *J* 12.0 and 3.5 Hz), 2.87 (d, 1H, *J* 17 Hz), 2,65 (d, 1H, *J* 17 Hz), 2.49–2.60 (m, 2H), 2.04 (s, 3H), 1.83–1.89 (m, 2H), 1.53–1.61 (m, 3H), 1.49 (s, 3H), 1.27–128 (m, 3H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 203.8, 169.2, 155.0, 134.0, 133.9, 131.3, 129.6, 129.9, 128.6, 128.3, 127.6, 127.4, 65.7, 53.7, 46.5, 31.3, 30.02, 29.6, 26.6, 26.5 25.3, 23.7. *Anal*. Calcd. for $C_{26}H_{29}NO_2$: C, 80.59%; H, 7.54%; N, 3.61%. Found: C, 80.05%; H, 8.00%; N, 3.33%.

1-(2-Hydroxyethyl)-5-methyl-5-(2-oxopropyl)-3,4-diphenyl-1,5-dihydro-2H-pyrrol-2-one (9). For **9**: 31 mg (0.2 mmol) of enaminone **1f**, 41 mg (0.2 mmol) of diphenylcyclopropenone **2**, and 26 mg (0.05 mmol) of Bi_2O_3, 7 days, afforded 29 mg (42% yield) of **9**, yellow oil, IR (cm^{-1}) 3361, 2954, 1740, 1643, 1367, 692. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.33–7.37 (m, 5H), 7.14–7.21 (m, 5H), 3.78–3.98 (m, 2H), 3.56–3.60 (m, 2H), 2.88 (d, 1H, *J* 17 Hz), 2.71 (d, 1H, *J* 17 Hz) 2.03 (s, 3H), 1.48 (s, 3H). ^{13}C-NMR ($CDCl_3$, 62.5 MHz) δ 204.5, 172.0, 157.1, 133.7, 133.2, 131.1, 129.7, 129.1, 129.1, 128.9, 128.1, 66.1, 62.7, 46.5, 44.4, 31.6, 23.8. *Anal.* Calcd. for $C_{22}H_{23}NO_3$: C, 75.62%; H, 6.63%; N, 4.01%. Found: C, 75.41%; H, 6.88%; N, 4.73%.

Ethyl 2-(1-(2-hydroxyethyl)-2-methyl-5-oxo-3,4-diphenyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (10). For **10**: 45 mg (0.3 mmol) of enaminone **1g**, 45 mg (0.2 mmol) of diphenylcyclopropenone **2**, and 20 mg (0.04 mmol) of Bi_2O_3, 5 days, afforded 59 mg (78% yield) of **10**, yellow oil, IR (cm^{-1}) 3417, 1666, 1419, 1265, 744. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.31–7.37 (m, 7H), 7.18–7.19 (m, 3H), 4.10 (q, 2H, *J* 7.0 Hz), 3.92 (m, 2H), 3.71 (m, 1H), 3.54 (m, 1H), 2.82 (d, 1H, *J* 15 Hz), 2.76 (d, 1H, *J* 15 Hz), 1.43 (s, 3H), 1.21 (t, 3H, *J* 7.0 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 171.8, 168.7, 157.2, 133.4, 133.0, 130.8, 129.5, 129.3, 128.9, 128.7, 128.1, 128.0, 66.4, 62.8, 61.2, 44.8, 40.1, 23.4, 14.3. *Anal*. Calcd. for $C_{23}H_{25}NO_4$: C, 72.80%; H, 6.64%; N, 3.69%. Found: C, 72.76%; H, 6.36%; N, 4.17%.

2-(4-(Ethoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl)acetic acid (12). A mixture of 129 mg (1 mmol) of enaminone **1a** and 98 mg of maleic anhydride **11a** (1 mmol) in acetonitrile (5 mL) was magnetically stirred at room temperature for 0.5 h. After this time, the reaction mixture was concentrated under reduced pressure, and the residue was washed with cold acetone, affording 215 mg (95% yield) of **12**. ^{13}C-NMR (acetone-D_6, 75 MHz) δ 179.8, 172.5, 164.6, 154.2, 106.7, 69.8, 45.9, 44.4, 39.2, 14.6, 14.2.

2-(1-Cyclohexyl-4-(ethoxycarbonyl)-5-methyl-2-oxo-2,3-dihydro-1H-pyrrol-3-yl)acetic acid (13). A mixture of 130 mg (1 mmol) enaminone of **1h** and 99 mg (1 mmol) of anhydride maleic **11a** in 5 mL of acetonitrile was reacted for 30 min under magnetic stirring at room temperature. After this time, the reaction mixture was concentrated under reduced pressure, and the residue was purified by washing with acetone at −5 °C, affording 300 mg (97% yield) of **13** as a yellow oil. ^{1}H-NMR (acetone-D_6, 300 MHz) δ 4.15 (dd, *J* 7.0 and 13.7 Hz, 2H), 4.13 (m, 1H), 3.70 (tt, *J* 3.6 and 12 Hz, 1H), 3,32 (m, 1H), 2.86 (dd, *J* 4.8 and 16.5 Hz, 2H), 2.49 (s, 1H), 2.21 (m, 2H), 1.72 (m, 4H), 1.27 (m, 3H), 1.26 (t, J 7.0 Hz, 3H). ^{13}C-NMR (acetone-D_6, 75 MHz) δ 178.4, 171.8, 164.0, 156.3, 105.9, 59.3, 53.9, 43.3, 33.7, 29.8, 29.4, 26.2, 26.1, 25.4, 14.1, 12.3. *Anal*. Calcd. for $C_{16}H_{23}NO_5$: C, 62.12%; H, 7.49%; N, 4.53%. Found: C, 62.32%; H, 7.21%; N, 4.44%.

Ethyl-2-methyl-4-(2-((4-nitrophenyl)amino)-2-oxoethyl)-5-oxo-4,5-dihydro-1H-pyrrole-3-carboxylate (14). A mixture of 131 mg (1 mmol) of enaminone **1a** and 220 mg (1 mmol) of *N*-(*p*-nitrophenyl)maleimide **11b** in 5 mL of acetonitrile was added one drop of acetic acid. The mixture was heated under reflux for 15 h and, after this time, was allowed to cool to room temperature and concentrated. The crude residue was recrystallized with cold ethanol, yielding 72 mg (20%) of **14**, as an off-white solid, m.p. 180–182 °C. IR (cm^{-1}) 3294, 1662, 1620, 1508, 1340, 1166. ^{1}H-NMR (DMSO-D_6, 300 MHz) δ 10.55 (sl, 1H), 8.17 (d, *J* 9.0 Hz, 2H), 7.77 (d, *J* 9.0 Hz, 2H), 4.02 (m, 2H), 2.99 (dd, *J* 15.6 and 5.1 Hz, 1H), 2.87 (dd, *J* 15.6 and 5.1 Hz, 1H), 2.50 (sl, 1H), 2.25 (s,3H), 1.12 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (DMSO-D_6, 75 MHz) δ 179.2, 169.6, 163.6, 153.9, 145.2, 142.1, 124.9, 118.7, 105.3, 58.9, 43.4, 36.0, 14.2, 13.5. *Anal*. Calcd. for $C_{16}H_{17}N_3O_6$: C, 55.33%; H, 4.93%; N, 12.10%. Found: C, 55.58%; H, 5.20%; N, 11.74%.

Alternatively, **14** can be prepared from **15**: to a solution of 35 mg (0.1 mmol) of **15** in 5 mL of acetonitrile was added one drop of acetic acid, and this mixture was heated under reflux for 12 h. After this time, the reaction mixture was allowed to cool to room temperature and concentrated. The crude residue was triturated with cold ethanol, affording 13 mg (37%) of **15**, as a white solid.

Ethyl(Z)-3-amino-2-(1-(4-nitrophenyl)-2,5-dioxopyrrolidin-3-yl)but-2-enoate (15). A mixture of 65 mg (0.5 mmol) of enaminone **1a** and 111 mg (0.5 mmol) of **11b** was heated under reflux in 5 mL of acetonitrile for 16 h and, after this time, was allowed to cool to room temperature and concentrated. The crude residue was triturated with ethyl acetate (or cold ethanol), yielding 130 mg (75%) of **15**, as an off-white solid, m.p. 167–169 °C. IR (cm^{-1}) 3440, 3319, 2985, 1708, 1612, 1523, 1344, 1267, 1162, 1024, 950, 856, 773, 702. ^{1}H-NMR (DMSO-D_6, 300 MHz) δ 8.40 (d, J 9.0 Hz, 2H), 7.60 (d, J 9.0 Hz, 2H), 7.22 (sl, 1H), 4.0 (m, 2H), 3.15 (dd, *J* 18.0 and 9.6 Hz, 1H), 2,60 (dd, *J* 18.0 and 5.4 Hz, 1H), 2.43 (m, 1H), 2.05, (s, 3H), 1.05 (t, *J* 7.0 Hz, 3H). *Anal*. Calcd. for $C_{16}H_{17}N_3O_6$: C, 55.33%; H, 4.93%; N, 12.10%. Found: C, 55.07%; H, 5.51%; N, 12.47%.

Alternatively, a mixture of 65 mg (0.5 mmol) of enaminone **1a** and 111 mg (0.5 mmol) of **11b** was heated under reflux in 5 mL of toluene (or benzene) for 16 h and, after this time, was allowed to cool to room temperature and concentrated. The crude residue was triturated with cold ethanol, affording 100 mg (57%, or 80% in benzene) of **15**, as an off-white solid, m.p. 164–166 °C.

Ethyl(Z)-3-amino-2-(2,5-dioxo-1-(o-tolyl)pyrrolidin-3-yl)but-2-enoate (16). A mixture of 132 mg (1 mmol) of enaminone **1a** and 174 mg (1 mmol) of **11c** was heated under reflux in acetonitrile for 18 h and, after this time, was allowed to cool to room temperature and concentrated. The crude residue was triturated with cold ethyl acetate, yielding 74 mg (25%) of **16**, as an off-white solid, m.p. 139.6–140.1 °C. IR (cm^{-1}) 3477, 3317, 2985, 1703, 1618, 1517, 1380, 1265, 1186, 1101, 1027, 946, 759, 721. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.30 (4H, m), 7.10 (1H, dd) 4.20 (2H, m), 3.8 (1H, dd, *J* 9.6 and 5.7 Hz), 2.98 (2H, dd), 2.8 (1H, dd, *J* 18 and 5.7 Hz), 2.7 (3H, t, 21.3 Hz), 2.09 (3H, s), 1.24 (3H, t, *J* 7.2 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (to the major rotamer) 175.7, 168.3, 159.8, 135.5, 131.1, 129.2, 128.0, 127.7, 126.7, 59.4, 40.1, 36.4, 21.5, 17.8, 14.8. *Anal*. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.54%; H, 6.37%; N, 8.86%. Found: C, 64.87%; H, 6.69%; N, 8.50%.

Alternatively, a mixture of 190 mg (1 mmol) of enaminone **1a** and 13 mg (1 mmol) of **11c** was heated under reflux in toluene for 2 h and, after this time, was allowed to cool to room temperature and concentrated. The crude residue was recrystallized from ethyl acetate and hexane, yielding 131 mg (76%) of **16** as an off-white solid, m.p. 139.7–141.1 °C.

Ethyl(Z)-3-amino-2-(1-(4-methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)but-2-enoate (17). A mixture of 66 mg (0.5 mmol) of enaminone **1a** and 105 mg (0.5 mmol) of **11d** was heated under reflux in acetonitrile for 48 h and, after this time, was allowed to cool to room temperature and concentrated. The crude residue was recrystallized from

ethyl acetate and hexane, yielding 131 mg (76%) of **17**, as an off-yellow solid, m.p. 120.1–122.4 °C. IR (cm^{-1}) 3465, 3319, 1714, 1614, 1394, 1178, 1031, 769. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8,60 (1H, br), 7.25 (2H, d), 7.05 (2H, d), 4.15 (2H, m), 3.80 (3H, s), 3.70 (1H, dd, *J* 9.6 and 5.7 Hz), 3.01 (1H, dd, *J* 18 and 9.6 Hz), 2.75 (1H, dd, *J* 18 and 5.7 Hz), 2.10 (3H, s), 1.60 (1H, sl), 1.15 (3H, t). ^{13}C-NMR ($CDCl_6$, 62.5 MHz) δ 179.0, 176.0, 168.5, 159.5, 159.4, 127.5, 125.0, 114.5, 91.0, 59.5, 55.5, 40.0, 35.5, 21.5, 14.5. *Anal*. Calcd. for $C_{17}H_{20}N_2O_5$: C, 61.44%; H, 6.07%; N, 8.43%. Found: C, 61.70%; H, 6.22%; N, 8.11%.

Alternatively, a mixture of 41 mg (0.3 mmol) of enaminone **1a** and 65 mg (0.3 mmol) of **11d** was heated under reflux in toluene for 21 h and, after this time, was allowed to cool to room temperature and concentrated. The crude residue was recrystallized from a mixture of ethyl acetate and hexane, yielding 131 mg (76%) of **17**, as a pale yellow solid, m.p. 120.3–122.7 °C.

Biological study. The human U251 glioblastoma cell line [56] and murine C6 glioma cell line [57] were cultured as previously described [58]. Briefly, cells were grown until confluence in the cell culture dishes (TPP) in Dulbecco's modified Eagle's medium (Cultilab, Campinas, SP, Brazil) and were supplemented with 100 UI/mL penicillin G, 100 µg/mL streptomycin, 7 m*M* glucose, 2 m*M* L-glutamine, 0.011 g/L pyruvate, and 10% fetal calf serum (Gibco, Grand Island, NY) in a humidified atmosphere with 5% CO_2 at 37 °C. Compounds were dissolved in DMSO (Sigma, St. Louis, MO) at a concentration of 20 m*M* and stored in the dark at −20 °C. The compounds were then dissolved in medium at final concentrations of 1–100 µ*M* and incubated for 24–72 h. Control cells were treated with the same volume of DMSO, not exceeding 0.1%, and did not show any significant effect within the parameters analyzed compared to cultures not exposed to this solvent; therefore, these cells were adopted as the negative control.

The effect of compounds on U251 and C6 cell viability was tested using the MTT (Sigma) test after 24 and 72 h of exposure in 96-well plates (TPP, Trasadingen, Switzerland, 1 × 104 cells per well). The cell viability was quantified by the conversion of yellow MTT by mitochondrial dehydrogenases of living cells to purple MTT formazan [59]. Three hours before the end of exposure, the medium was removed and replaced with Dulbecco's modified Eagle's medium without supplementation containing MTT (1 mg/mL). Afterwards, 100 µL/well of a buffer containing 20% SDS and 50% DMF, pH 4.7, was added, and the plate was kept for 12 h at 37 °C for complete dissolution of the formazan crystals. The optic absorbency of each sample was measured at a wavelength of 565 nm using a spectrophotometer (Varioskan Flash Multimode Reader, Thermo Plate, Thermo Fisher Scientific, Vantaa, Finland). Eight replicate wells were used for each analysis in three independent experiments. The results were determined as the average and standard deviation and expressed as percentages of the control.

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