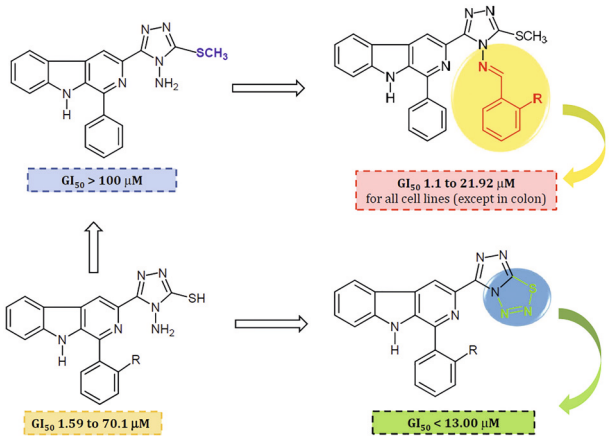
Synthesis G. Brand et al. Paper

# Synthesis and Antitumor Activity of Novel 1-Substituted 3-(4,5-Substituted 1,2,4-Triazol-3-yl)-β-carboline Derivatives

**George Brand**[a]
**Carla M. B. Gomes**[a]
**Willian F. Costa**[a]
**Mary A. Foglio**[b]
**Ana L. T. G. Ruiz**[c]
**Maria H. Sarragiotto***[a]

[a] Departamento de Química, Universidade Estadual de Maringá, Av. Colombo 5790, Maringá - PR, 87020-900, Brazil
mhsarragiotto@uem.br
[b] Faculdade de Ciências Farmacêuticas, Universidade Estadual de Campinas, Campinas - SP, 13083-859, Brazil
[c] Centro Pluridisciplinar de Pesquisas Químicas, Biológicas e Agrícolas (CPQBA), Universidade Estadual de Campinas, Campinas - SP, 13083-970, Brazil




Received: 04.07.2018
Accepted after revision: 30.08.2018
Published online: 26.09.2018
DOI: 10.1055/s-0037-1610291; Art ID: ss-2018-m0455-op

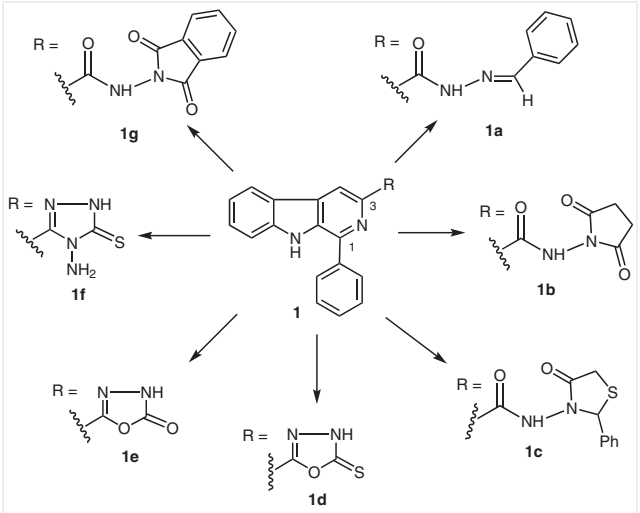
**Abstract** Schiff bases, 1,2,4-triazolo[4,3-*d*][1,2,3,4]thiatriazoles, and 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles carrying the β-carboline nucleus were synthesized from 3-(4-amino-5-mercapto-1,2,4-triazol-3-yl)-β-carbolines. The compounds were evaluated for their *in vitro* antitumor activity against eight human cancer cell lines. The 1,2,4-triazolo[4,3-*d*][1,2,3,4]thiatriazole derivatives showed a broad spectrum of antitumor activity, with $GI_{50}$ values lower than 13 μM for all cell lines tested. In general, all tested compounds showed potent activity against the breast (MCF-7) cancer cell line, with $GI_{50}$ values in the range of 2.07 to 4.58 μM.

**Key words** β-carbolines, 4,5-substituted 1,2,4-triazoles, Schiff bases, 1,2,4-triazolo[4,3-*d*][1,2,3,4]thiatriazoles, antitumor activity

The β-carboline nucleus is present in many synthetic and naturally occurring compounds displaying a large spectrum of important pharmacological and biological properties such as antitrypanosomal and antileishmanial,[1–3] herbicidal and fungicidal,[4,5] antiviral,[6–8] antiplatelet aggregation and antithrombotic,[9,10] anti-Parkinson[11] and Dyrk1A inhibition.[12,13]

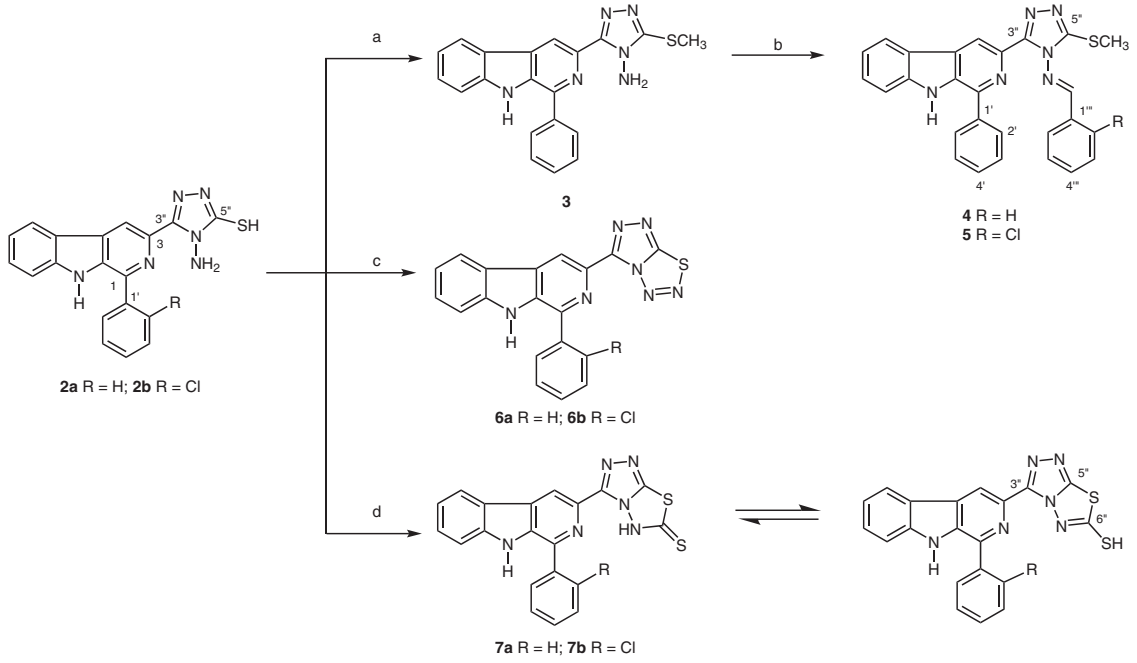
Among the reported properties, it is worth mentioning the potential of β-carboline derivatives as anticancer agents, which has stimulated studies on their synthesis and structure–activity relationship (SAR).[14–23] These studies revealed that the introduction of appropriate substituents at the 1-, 3- and 9-positions of the β-carboline ring can result in more potent drugs with reduced toxicity and neurotoxic effects.

In our previous work[24–27] we demonstrated that derivatives bearing an appropriately substituted phenyl group at position 1 and various substituents at position 3 of the β-carboline nucleus showed potent antitumor activity. The incorporation of a 4-amino-5-mercapto-1,2,4-triazole moiety at C-3 resulted in 1-(substituted phenyl)-3-(4-amino-5-mercapto-1,2,4-triazol-3-yl)-β-carbolines **1f** (Scheme 1) with significant antitumor activity.[24]




**Scheme 1** General structures of β-carboline derivatives synthesized in previous work

The presence of the amino and mercapto nucleophilic centers in the 4-amino-5-mercapto-1,2,4-triazole side chain at position 3 of β-carbolines makes it a useful site for




**Scheme 2** *Reagents and conditions*: a) MeI, KOH, EtOH, r.t., 48 h; b) PhCHO or 2-$ClC_6H_4CHO$, DMF, reflux, 48 h; c) $NaNO_2$, HCl, 0–5 °C, 12 h; d) $CS_2$, KOH, MeOH, 0–5 °C, then reflux, 48 h.

the synthesis of triazole-fused derivatives. Besides, Schiff bases can be obtained from the 4-amino group of this heterocyclic nucleus.

Prompted by these observations, and to provide additional data for SAR studies, we decided to explore the potential of β-carbolines **2** as precursors for new 3-(4,5-substituted 1,2,4-triazol-3-yl)-β-carboline derivatives. Thus, in this work we synthesized Schiff bases **4** and **5**, 1,2,4-triazolo[4,3-*d*][1,2,3,4]thiatriazoles **6a**,**b**, and 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **7a**,**b**, all carrying the β-carboline nucleus. The new compounds **4**, **5**, **6a** and **6b** were assayed for their *in vitro* activity against eight human cancer cell lines, and against human normal keratinocytes (HaCaT, noncancer cell line).

The synthesis of Schiff bases **4** and **5**, of 1,2,4-triazolo[4,3-*d*][1,2,3,4]thiatriazoles **6a**,**b**, and of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **7a**,**b**, all carrying the β-carboline nucleus, is outlined in Scheme 2. The 3-(4-amino-5-mercapto-1,2,4-triazol-3-yl)-β-carbolines **2a**,**b** were obtained via Pictet–Spengler condensation of L-tryptophan methyl ester with benzaldehyde or 2-chlorobenzaldehyde, according to our previously reported procedure.[24]

Firstly, attempts towards the synthesis of Schiff bases were made from 3-(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)-1-phenyl-9*H*-β-carboline (**2a**), which was subjected to condensation with benzaldehyde or 2-chlorobenzaldehyde under various conditions, such as $H_2SO_4$ catalysis, using ethanol/water as solvent,[28,29] and *p*-TsOH catalysis, in DMF as solvent.[30] However, in contrast to the reported 4-amino-5-mercapto-1,2,4-triazole derivatives having other substituents at the 3-position, Schiff base formation was not observed. The $^1$H NMR spectra obtained for the crude products indicated a complex mixture, showing no signals for the benzylideneamino group.

To avoid undesired reactions of the 5-mercapto group, β-carboline **2a** was S-methylated with methyl iodide, under basic conditions,[24] affording product **3**. Refluxing of a DMF solution of S-alkylated **3**, in the presence of benzaldehyde or 2-chlorobenzaldehyde, furnished the corresponding Schiff bases **4** and **5**, after purification by column chromatography. The NMR spectra of Schiff bases **4** and **5** showed signals at $\delta_H$ 8.98–9.00 and $\delta_C$ 162.4–169.1, corresponding to the imine hydrogen and carbon of the benzylideneamino groups, together with signals at $\delta_H$ 2.71–2.73 and $\delta_H$ 11.7 assigned to the $SCH_3$ and NH groups, respectively, of the triazole and β-carboline moieties.

Preparation of the 1,2,4-triazolo[4,3-*d*][1,2,3,4]thiatriazole derivatives **6a**,**b** was carried out by treatment of **2a**,**b** with sodium nitrite in hydrochloric acid, according to the report by El Shehry and co-workers.[31] The absence of SH and $NH_2$ signals in the $^1$H NMR spectra, together with changes observed for the C-3″ and C-5″ chemical shifts of **6a**,**b** in the $^{13}$C NMR spectra, in relation to their precursors **2a**,**b**, provided evidence for the formation of the triazolothiatriazole nucleus. For example, in **6a** the peaks for C-3″ and C-5″ appear at $\delta_C$ 157.4 and 158.3, while in **2a** these carbons resonate at $\delta_C$ 147.3 (C-3″) and 163.8 (C-5″).

**Table 1** $GI_{50}$ Values (μM) for Previously Reported β-Carbolines **2a**, **2b** and **3**, and for New Synthesized Compounds **4**, **5**, **6a** and **6b**[a]

| Compound | R | Cell lines | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Lung NCI-H460 | Colon HT-29 | Prostate PC-3 | Breast MCF-7 | Renal 786-0 | Glioma U-251 | Ovarian Resistant NCI/ADR-res | Ovarian OVCAR-3 | HaCaT |
| **2a** | H | 1.59 | 15.0 | 10.9 | 15.0 | 10.9 | NT | NT | 12.0 | NT |
| **2b** | Cl | 15.4 | 33.0 | 24.7 | 70.1 | 39.5 | NT | NT | 6.80 | NT |
| **3** | – | >100 | >100 | >100 | >100 | >100 | NT | NT | >100 | NT |
| **4** | H | 3.19 | 17.77 | 3.02 | 3.73 | 6.87 | 1.53 | 1.11 | 6.43 | 1.91 |
| **5** | Cl | 7.84 | >100 | 4.21 | 2.07 | 8.52 | 13.75 | 5.06 | 21.92 | 0.09 |
| **6a** | H | 1.16 | 1.98 | 2.70 | 2.76 | 2.88 | 3.45 | 3.47 | 12.63 | 0.08 |
| **6b** | Cl | 2.97 | 12.28 | 7.98 | 4.58 | 9.16 | 5.74 | 3.99 | 12.35 | 1.16 |
| Doxorubicin[b] | | 0.014 | 0.32 | 0.058 | 0.045 | 0.034 | 0.015 | 0.11 | 0.17 | 0.018 |

[a] NT = not tested.
[b] Doxorubicin = positive control.

The synthesis of β-carbolines **7a**,**b** bearing the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole group was achieved by treating the 1,2,4-triazoles **2a**,**b** with carbon disulfide and potassium hydroxide.[32] The NMR data for **7a** revealed a tautomeric thiol–thione equilibrium, as evidenced by the presence of a singlet at $\delta_H$ 13.9 (6″-SH) and signals at $\delta_C$ 143.2 (C-6″–SH) and $\delta_C$ 155.5 (C-6″=S).

The new compounds **4**, **5**, **6a** and **6b** were evaluated *in vitro* against a panel of eight human cancer cell lines consisting of lung (NCI-H460), colon (HT-29), prostate (PC-3), breast (MCF-7), renal (786-0), glioma (U-251), ovarian resistant (NCI/ADR-res) and ovarian (OVCAR-3), and against a normal cell line (HaCaT, immortalized human skin keratinocytes). The $GI_{50}$ values obtained for the new β-carboline derivatives, and those previously reported for the 3-(4-amino-5-mercapto-1,2,4-triazol-3-yl)-β-carbolines **2a**,**b** and for the S-methylated derivative **3**,[24] are summarized in Table 1. The assay results demonstrated that the triazolothiatriazoles **6a** and **6b** and the new Schiff base **4** show a broad spectrum of antitumor activity, with $GI_{50}$ values lower than 18 μM for all cell lines assayed.

The data for compounds **4**, **5**, **6a** and **6b** show a highest growth inhibitory activity towards ovarian resistant (NCI/ADR-res) and breast cancer (MCF-7) cell lines for these compounds, with $GI_{50}$ values in the range of 1.11 to 5.06 μM.

Comparison of the $GI_{50}$ values for the newly synthesized compounds with those for **2a** and **2b**[24] (Table 1) revealed that compounds **6a** and **6b** display a better antitumor activity, indicating that formation of the fused triazolothiatriazole system leads to an enhancement of antitumor activity, providing evidence that a free thiol and amino is a key structural feature of this class of inhibitors.

The assay results for compounds **7a** and **7b** were not conclusive due to the lack of solubility of these compounds in the assay medium, and these results are not included. On the other hand, comparison of the average activity (mean $GI_{50}$) against the normal cell line (HaCaT) revealed that the compounds are more toxic to normal cells than to other cell lines, as well as for doxorubicin.

To summarize, Schiff's bases and triazolo-thiatriazole derivatives carrying the β-carboline nucleus were easily prepared in one step from the readily available 3-(4-amino-5-mercapto-1,2,4-triazol-3-yl)-β-carbolines **2a**,**b**. The potent anticancer activity presented for synthesized compounds, together with their easiness of synthesis, makes these compounds promising anticancer agents. These investigations corroborated the previous reports that the antitumor activity of β-carboline derivatives is dependent of the substituents at the positions 1 and 3 of the β-carboline ring.

All reagents were purchased from commercial suppliers. Reactions were monitored by thin-layer chromatography conducted on Merck TLC plates (silica gel 60 $F_{254}$). NMR spectra were recorded on a Varian Mercury plus BB spectrometer at 300 MHz (for $^1H$) and 75 MHz (for $^{13}C$), with TMS as internal standard and deuterated solvents, DMSO-$d_6$ and $CDCl_3$. Mass spectra (ESI-MS) were recorded on a Thermo Electron Corporation Focus DSQ II spectrometer. Melting points were determined on a Microquímica MQAPF-301 apparatus and are uncorrected.

**3-[4-Benzylideneamino-5-(methylthio)-4*H*-1,2,4-triazol-3-yl]-1-phenyl-9*H*-β-carbolines 4 and 5; General Procedure**

To a solution of 3-[4-amino-5-(methylthio)-4*H*-1,2,4-triazol-3-yl]-1-phenyl-9*H*-β-carboline (**3**; 186.0 mg, 0.5 mmol) in DMF (5 mL) was added benzaldehyde (63.7 mg, 0.6 mmol) or 2-chlorobenzaldehyde (84.3 mg, 0.6 mmol). The solution was refluxed for 48 h then poured onto crushed ice with stirring. The precipitate was collected by filtration and washed with water. The crude product was purified by column chromatography (silica gel; hexane/EtOAc, 40% to 100%) to afford the corresponding Schiff base **4** or **5**.

**3-{4-[(*E*)-Benzylideneamino]-5-(methylthio)-4*H*-1,2,4-triazol-3-yl}-1-phenyl-9*H*-β-carboline (4)**

White solid; yield: 73.6 mg (32%); mp 210.6–213.9 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 11.70 (s, 1 H, NH), 8.98 (s, 1 H), 8.89 (s, 1 H), 8.45 (d, *J* = 7.5 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 2 H), 7.77 (d, *J* = 8.0 Hz, 2 H), 7.69–7.52 (m, 5 H), 7.39–7.30 (m, 2 H), 7.22 (t, *J* = 7.5 Hz, 2 H), 2.71 (s, 3 H).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ = 169.1, 150.2, 149.8, 141.5, 141.4, 137.1, 135.4, 132.9, 132.8 (2 x C), 132.0, 130.1, 129.1 (3 x C) 129.0 (2 x C) , 128.7, 128.6, 128.3 (2 x C), 122.0, 120.9, 120.1, 114.0, 112.6, 14.0.

ESI-MS: *m*/*z* = 461.05 [M + H]$^+$.

**3-{4-[(*E*)-2-Chlorobenzylideneamino]-5-(methylthio)-4*H*-1,2,4-triazol-3-yl}-1-phenyl-9*H*-β-carboline (5)**

White solid; yield: 87.1 mg (35%); mp 149.5–150.4 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 11.70 (s, 1 H, NH), 9.00 (s, 1 H), 8.87 (s, 1 H), 8.44 (d, *J* = 7.5 Hz, 1 H), 8.15 (d, *J* = 9.0 Hz, 1 H,) 7.79 (d, *J* = 9.0 Hz, 2 H), 7.69 (d, *J* = 7.5 Hz, 1 H), 7.51 (m, *J* = 7.5 Hz, 2 H), 7.42–7.37 (m, 3 H), 7.37–7.25 (2m, 3 H), 2.73 (s, 3 H).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ = 162.4, 150.5, 150.1, 141.5, 141.4, 137.2, 135.3, 135.1, 134.2, 132.9, 130.2, 130.0, 129.2, 128.8, 128.7, 128.3, 128.2, 128.1, 127.9, 122.1, 120.9, 120.2, 114.4, 112.6, 14.0.

ESI-MS: *m*/*z* = 495.00 [M + H]$^+$.

**3-(1-Aryl-9*H*-β-carbolin-3-yl)-1,2,4-triazolo[4,3-*d*][1,2,3,4]thiatriazoles 6a and 6b; General Procedure**

A solution of **2a** (179.0 mg, 0.5 mmol) or **2b** (196.0 mg, 0.5 mmol) in 37% HCl (5 mL) was cooled to 0 °C and a cold solution of $NaNO_2$ (34.5 mg, 0.5 mmol) in water (0.5 mL) was gradually added. The reaction mixture was stirred at 0–5 °C for 2 h, kept for 10 h at 5 °C then diluted with water. The precipitate was collected by filtration and recrystallized from EtOH to give **6a** and **6b**, respectively.

**3-(1-Phenyl-9*H*-β-carbolin-3-yl)-1,2,4-triazolo[4,3-*d*][1,2,3,4]thiatriazole (6a)**

White solid; yield: 131.1 mg (70%); mp 251.6–252.8 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 11.86 (s, 1 H, NH), 8.88 (s, 1 H), 8.41 (d, *J* = 6.0 Hz, 1 H), 8.23 (d, *J* = 6.0 Hz, 2 H), 7.71–7.58 (m, 5 H), 7.28 (t, *J* = 6.0 Hz, 1 H).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ = 158.3, 157.4, 142.4, 142.1, 137.7, 135.6, 133.9, 130.5, 129.5, 129.4, 129.3 (C-3′/5′), 129.2 (2 x C), 122.6, 121.5, 120.6, 113.1, 112.9.

ESI-MS: *m*/*z* = 371.95 [M + 3 H]$^+$.

**3-[1-(2-Chlorophenyl)-9*H*-β-carbolin-3-yl]-1,2,4-triazolo[4,3-*d*]-[1,2,3,4]thiatriazole (6b)**

White solid; yield: 137.2 mg (70%); mp 170.4–172.0 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 11.60 (s, 1 H, NH), 8.97 (s, 1 H), 8.43 (d, *J* = 6.0 Hz, 1 H), 7.72 (d, *J* = 6.0 Hz, 2 H, H-3′ and H-6′), 7.63–7.58 (m, 4 H), 7.31–7.25 (m, 1 H).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ = 158.2, 157.4, 142.0, 141.7, 136.6, 135.3, 135.0, 133.2, 132.6, 131.2, 130.1, 129.6, 129.4, 127.9, 122.8, 121.3, 120.6, 113.7, 112.8.

ESI-MS: *m*/*z* = 377.84 [M – $N_2$ + 3 H]$^+$.

**3-(1-Aryl-9*H*-β-carbolin-3-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiols/thiones 7a and 7b; General Procedure**

To a solution of **2a** (143.2 mg, 0.4 mmol) or **2b** (156.8 mg, 0.4 mmol) in methanolic KOH (2 M, 10 mL), at 0–5 °C, was added $CS_2$ (0.027 mL, 0.45 mmol) dropwise with stirring. The reaction mixture was refluxed for 48 h, then cooled to r.t. and poured onto crushed ice. The solution was acidified with concentrated HCl, and the precipitate was collected by filtration, washed with water and recrystallized from EtOH to give **7a** and **7b**, respectively.

**3-(1-Phenyl-9*H*-β-carbolin-3-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiol (7a)**

Yellow solid; yield: 85.9 mg (54%); mp 234.9–235.5 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 13.90 (s, 1 H, SH), 12.10/11.90 (s, 1 H, NH), 9.18/8.82 (s, 1 H), 8.38 (d, *J* = 6.0 Hz, 1 H), 8.21/8.09 (d, *J* = 6.0 Hz, 2 H), 7.76–7.67 (m, 5 H), 7.40–7.30 (m, 1 H).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ = 163.9, 155.5/143.2, 147.4, 141.75/141.71, 141.6, 133.3, 129.2, 129.1, 129.2, 129.0, 128.9, 128.6 122.1/121.8, 120.9/120.8, 120.3, 114.3/114.0, 113.1/112.8, 134.2/133.8, 129.9/129.5, 137.8/136.8.

ESI-MS: *m*/*z* = 401.03 [M + H]$^+$.

**3-[1-(2-Chlorophenyl)-9*H*-β-carbolin-3-yl]-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-thiol (7b)**

Yellow solid; yield: 94.1 mg (54%); mp 261.4–263.5 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 13.90 (s, 1 H, SH), 11.70 (s, 1 H, NH), 8.93 (s, 1 H), 8.40 (d, *J* = 6.0 Hz, 1 H), 7.71–7.76 (m, 2 H), 7.60–7.64 (m, 4 H), 7.32–7.37 (m, 1 H).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ = 164.3, 147.7, 142.0 (2 x C), 141.0, 139.5, 136.5, 134.7, 134.3, 132.9, 132.4, 131.2, 130.4, 129.5, 128.1, 122.6, 121.1, 120.7, 115.2, 112.8.

ESI-MS: *m*/*z* = 435.01 [M + H]$^+$.

**Antitumor Assays**

Compounds **4**, **5**, **6a** and **6b** were evaluated *in vitro* against a panel of eight human cancer cell lines consisting of lung (NCI-H460), colon (HT-29), prostate (PC-3), breast (MCF-7), renal (786-0), glioma (U-251), ovarian resistant (NCI/ADR-res), and ovarian (OVCAR-3), kindly provided by the National Cancer Institute (Frederick, MA, USA). In addition, a normal cell line (HaCaT, immortalized human skin keratinocytes) was used. Stock and experimental cultures were grown in medium containing 5 mL RPMI 1640 (GIBCO BRL) supplemented with 5% fetal bovine serum (GIBCO BRL). Penicillin/streptomycin mixture (1000 U·mL$^{-1}$:1000 µg·mL$^{-1}$, 1 mL·L$^{-1}$ RPMI) was added to the experimental cultures. Cells in 96-well plates (100 µL cells·well$^{-1}$) were exposed to sample concentrations in DMSO/RPMI (0.25, 2.5, 25, 250 µg·mL$^{-1}$) in triplicate at 37 °C, 5% $CO_2$ in air, for 48 h. The final DMSO concentration did not affect cell viability. Doxorubicin (0.025 to 25 µg·mL$^{-1}$) was used as a positive control. Before ($T_0$ plate) and after the sample addition ($T_1$ plates), cells were fixed with 50% trichloroacetic acid, and cell proliferation was determined by spectrophotometric quantification (540 nm) of cellular protein using the sulforhodamine B assay. All compounds were tested in triplicate for each concentration. Using the dose–response curve for each cell line, the concentration that inhibits cell growth by 50% ($GI_{50}$) was determined through nonlinear regression analysis using ORIGIN software version 8.0 (OriginLab Corporation).[33] Compounds with $GI_{50}$ values >100 µM were considered inactive.

## Funding Information

This work was supported by Fundação Araucária (Brazil, PR) and Fundação de Amparo à Pesquisa de São Paulo (FAPESP).

## Acknowledgment

We thank Fundação Araucária, CAPES and CNPq for fellowships (G.B., C.M.B.G.). The authors are thankful to Dr Eduardo J. Pilau and Dr Carla Porto for the ESI-MS spectra.

## References

(1) Tonin, L. T.; Panice, M. R.; Nakamura, C. V.; Rocha, K. J. P.; Dos Santos, A. O.; Ueda-Nakamura, T.; Da Costa, W. F.; Sarragiotto, M. H. *Biomed. Pharmacother.* **2010**, *64*, 386.
(2) Valdez, R. H.; Tonin, L. T.; Ueda-Nakamura, T.; Silva, S. O.; Dias Filho, B. P.; Kaneshima, E. N.; Yamada-Ogatta, S. F.; Yamauchi, L. M.; Sarragiotto, M. H.; Nakamura, C. V. *Antimicrob. Agents Chemother.* **2012**, *56*, 507.
(3) Gohil, M. V.; Brahmbhatt, K. G.; Loiseau, P. M.; Bhutani, K. K. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3905.
(4) Weng, Q. F.; Huang, J. F.; Zeng, Y.; Deng, Y. Y.; Hu, M. Y. *Molecules* **2012**, *17*, 3969.
(5) Song, H. J.; Liu, Y. X.; Liu, Y. X.; Wang, L. Z.; Wang, Q. M. *J. Agric. Food Chem.* **2014**, *62*, 1010.
(6) Formagio, A. S. N.; Santos, P. R.; Zanoli, K.; Ueda-Nakamura, T.; Tonin, L. T. D.; Nakamura, C. V.; Sarragiotto, M. H. *Eur. J. Med. Chem.* **2009**, *44*, 4695.
(7) Ashok, P.; Sharma, H.; Lathiya, H.; Chander, S.; Murugesan, S. *Med. Chem. Res.* **2015**, *24*, 513.
(8) Ashok, P.; Chander, S.; Ganguly, S.; Murugesan, S. *Med. Chem. Res.* **2014**, *23*, 3662.
(9) Liu, J. W.; Jiang, X. Y.; Zhao, M.; Zhang, X. Y.; Zheng, M. Q.; Peng, L.; Peng, S. Q. *J. Med. Chem.* **2010**, *53*, 3106.
(10) Yao, K.; Zhao, M.; Zhang, X. Y.; Wang, Y. J.; Li, L.; Zheng, M. Q.; Peng, S. Q. *Eur. J. Med. Chem.* **2011**, *46*, 3237.
(11) Polanski, W.; Reichmann, H.; Gille, G. *Expert Rev. Neurother.* **2011**, *11*, 845.
(12) Drung, B.; Scholz, C.; Barbosa, V. A.; Nazari, A.; Sarragiotto, M. H.; Schmidt, B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4854.
(13) Adayev, T.; Wegiel, J.; Hwang, Y. *Arch. Biochem. Biophys.* **2011**, *507*, 212.
(14) Chen, Z. Y.; Cao, R. H.; Yu, L. A.; Shi, B. X.; Sun, J.; Guo, L. A.; Ma, Q.; Yi, W.; Song, X. A.; Song, H. C. *Eur. J. Med. Chem.* **2010**, *45*, 4740.
(15) Cao, R. H.; Guan, X.; Shi, B. X.; Chen, Z.; Ren, Z. H.; Peng, W.; Song, H. C. *Eur. J. Med. Chem.* **2010**, *45*, 2503.
(16) Zhang, G. X.; Cao, R. H.; Guo, L.; Ma, Q.; Fan, W. X.; Chen, X. M.; Li, J. R.; Shao, G.; Qiu, L. Q.; Ren, Z. H. *Eur. J. Med. Chem.* **2013**, *65*, 21.
(17) Shi, B. X.; Cao, R. H.; Fan, W. X.; Guo, L.; Ma, Q.; Chen, X. M.; Zhang, G. X.; Qiu, L. Q.; Song, H. C. *Eur. J. Med. Chem.* **2013**, *60*, 10.
(18) Chen, H.; Gao, P. C.; Zhang, M.; Liao, W.; Zhang, J. W. *New J. Chem.* **2014**, *38*, 4155.
(19) Wu, Q. F.; Bai, Z. S.; Ma, Q.; Fan, W. X.; Guo, L.; Zhang, G. X.; Qiu, L. Q.; Yu, H. J.; Shao, G.; Cao, R. H. *MedChemComm* **2014**, *5*, 953.
(20) Ghasemi, J. B.; Davoudian, V. *J. Chem.* **2014**, *2014*, 1.
(21) Lin, Y.; Xia, X. P.; Yao, R. X.; Ni, L.; Hu, J.; Guo, W. J.; Zhu, B. L. *Chem. Pharm. Bull.* **2014**, *62*, 343.
(22) Kamal, A.; Srinivasulu, V.; Nayak, V. L.; Sathish, M.; Shankaraiah, N.; Bagul, C.; Reddy, N. V. S.; Rangaraj, N.; Nagesh, N. *ChemMedChem* **2014**, *9*, 2084.
(23) Kamal, A.; Sathish, M.; Nayak, V. L.; Srinivasulu, V.; Kavitha, B.; Tangella, Y.; Thummuri, D.; Bagul, C.; Shankaraiah, N.; Nagesh, N. *Bioorg. Med. Chem.* **2015**, *23*, 5511.
(24) Formagio, A. S. N.; Tonin, L. T. D.; Foglio, M. A.; Madjarof, C.; De Carvalho, J. E.; Da Costa, W. F.; Cardoso, F. P.; Sarragiotto, M. H. *Bioorg. Med. Chem.* **2008**, *16*, 9660.
(25) Savariz, F. C.; Formagio, A. S. N.; Barbosa, V. A.; Foglio, M. A.; De Carvalho, J. E.; Duarte, M. C. T.; Dias Filho, B. P.; Sarragiotto, M. H. *J. Braz. Chem. Soc.* **2010**, *21*, 288.
(26) Barbosa, V. A.; Formagio, A. S. N.; Savariz, F. C.; Foglio, M. A.; Spindola, H. M.; De Carvalho, J. E.; Meyer, E.; Sarragiotto, M. H. *Bioorg. Med. Chem.* **2011**, *19*, 6400.
(27) Savariz, F. C.; Foglio, M. A.; Ruiz, A. L.; Da Costa, W. F.; Silva, M. M.; Santos, J. C.; Figueiredo, I. M.; Meyer, E.; De Carvalho, J. E.; Sarragiotto, M. H. *Bioorg. Med. Chem.* **2014**, *22*, 6867.
(28) Kaplancıklı, Z. A.; Turan-Zitouni, G.; Özdemir, A.; Revial, G. *Eur. J. Med. Chem.* **2008**, *43*, 155.
(29) Suresh Kumar, G. V.; Rajendra Prasad, Y.; Mallikarjuna, B. P.; Chandrashekar, S. M. *Eur. J. Med. Chem.* **2010**, *45*, 5120.
(30) Chidananda, N.; Poojary, B.; Sumangala, V.; Kumari, N. S.; Shetty, P.; Arulmoli, T. *Eur. J. Med. Chem.* **2012**, *51*, 124.
(31) El Shehry, M. F.; Abu-Hashem, A. A.; El-Telbani, E. M. *Eur. J. Med. Chem.* **2010**, *45*, 1906.
(32) Ramaprasad, G. C.; Balakrishna, K.; Sunil Kumar, B. *Med. Chem. Res.* **2014**, *23*, 3644.
(33) Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, *83*, 757.