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# Synthesis and Biological Activity of Pyrazolo[1,5-*c*][1,3]benzoxazines Containing a Thiazolidin-4-one Fragment

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**Abstract**—5-[4-(2-Aryl-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl)benzylidene]-1,3-thiazolidin-4-ones were synthesized by reactions of 4-[(3-R-2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzaldehydes with 2-(3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)phenols and evaluated for antitumor and anti-inflammatory activities.

**Keywords:** pyrazolo[1,5-*c*][1,3]oxazines, 1,3-benzoxazines, thiazolidine-2,4-diones, rhodanine, antitumor activity, anti-inflammatory activity

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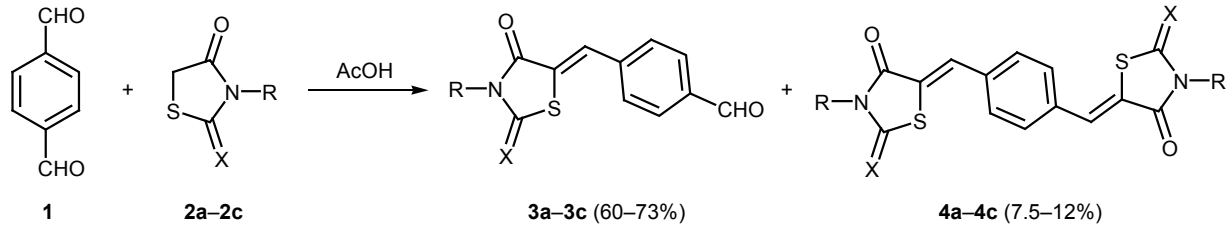
Fused aza heterocycles possess a combination of practically useful properties and therefore constantly attract researchers' attention. They exhibit various biological activities and are used as pharmaceuticals [1]. Many natural compounds, e.g., alkaloids, also contain fused aza heterocycles as structural fragments [2, 3]. In continuation of our studies [4–9] of the synthesis and biological properties of fused nitrogen heterocycles, we have developed a synthetic approach to 1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazines with a pharmacophoric 4-oxothiazolidine moiety, and the synthesized compounds have been evaluated for antitumor and anti-exudative activities. It should be noted that 1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazines constitute a poorly explored heterocyclic system. The reaction of 2-(3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)phenols with carbonyl compounds is virtually the only acceptable preparative method of synthesis of these heterocycles. Reactions of pyrazolylphenols with aromatic aldehydes and ketones [10–12] and cyclic ketones [12–14] have been reported. Biological activity of 1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazines also remains poorly studied. In particular, there are published data on their antimicrobial [14] and molluscicidal properties [15], and some derivatives have been found to act as 5-HT2B serotonin receptor antagonists [13].

The present study was aimed at synthesizing thiazolidin-4-one–pyrazolo[1,5-*c*][1,3]benzoxazine conjugates and evaluating them for antitumor and anti-inflammatory activities. In contrast to pyrazolo[1,5-*c*][1,3]benzoxazine derivatives, biological activity of compounds containing a 4-oxothiazolidine moiety has been well documented. These compounds exhibit a broad spectrum of biological activity, and some derivatives are used as medicines; therefore, 4-oxothiazolidine fragment is considered a privileged structure in medicinal chemistry [16–18]. It should also be emphasized that both antitumor and anti-inflammatory agents have been found among 5-arylmethylidene derivatives of thiazolidin-4-ones [16–18]. A combination of the privileged 4-oxothiazolidine fragment with pyrazolo[1,5-*c*][1,3]benzoxazine system could give rise to novel pharmacologically active compounds with important properties.

In the first stage of our study we developed a procedure for the synthesis of 4-[(4-oxo-1,3-thiazolidin-5-ylidene)methyl]benzaldehydes **3a**–**3c**. For this purpose, terephthalaldehyde (**1**) was reacted with 1,3-thiazolidine-2,4-dione (**2a**), 3-methyl-2-sulfanylidene-1,3-thia-

**Scheme 1.**



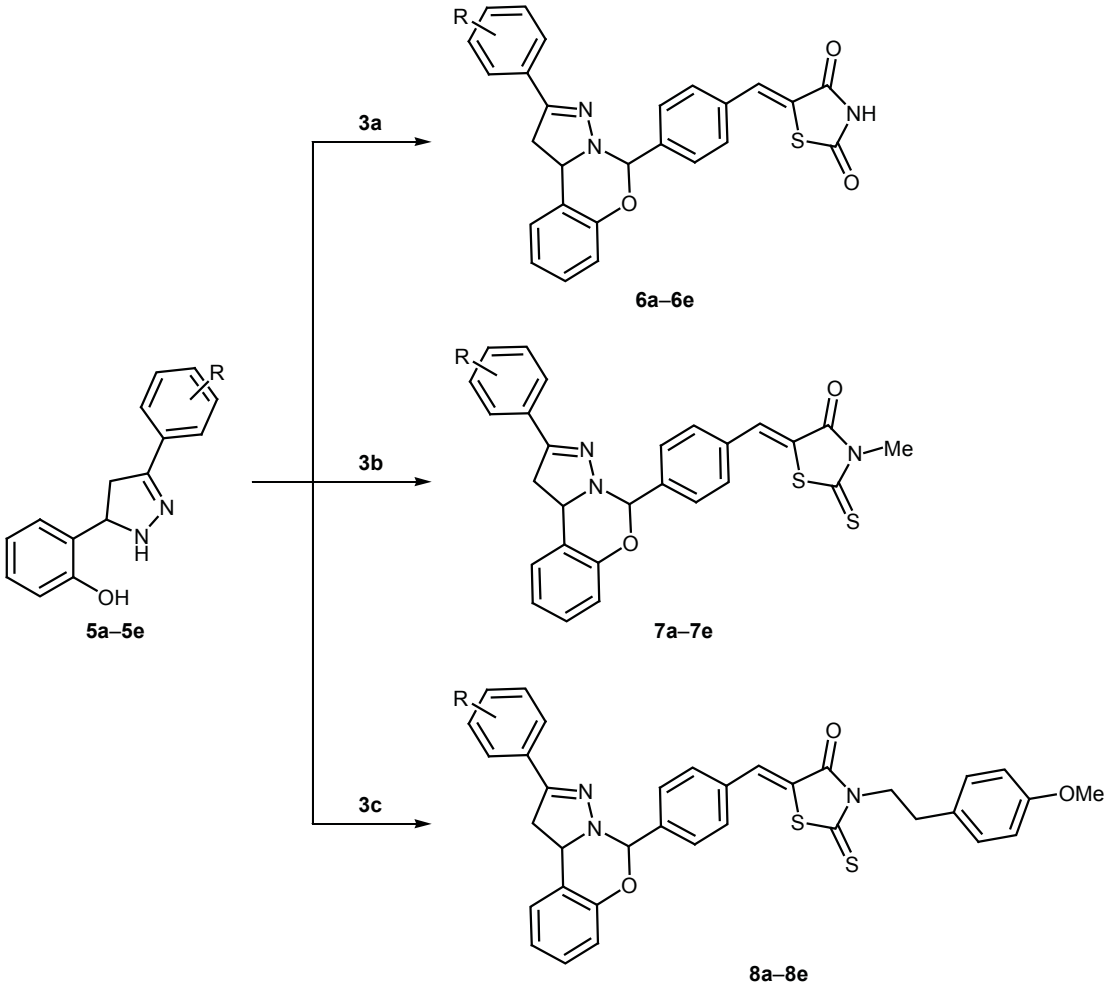

**1** **2a–2c** **3a–3c** (60–73%) **4a–4c** (7.5–12%)

**2**–**4**, R = H, X = O (**a**), R = Me, X = S (**b**), R = 4-MeOC$_6$H$_4$CH$_2$CH$_2$, X = S (**c**).

zolidin-4-one (**2b**), and 3-[2-(4-methoxyphenyl)ethyl]-2-sulfanylidene-1,3-thiazolidin-4-one (**2c**). The reactions were carried out in acetic acid using a slight excess of dialdehyde **1**. Apart from the target aldehydes **3a**–**3c**, minor 1 : 2 condensation products **4a**–**4c** were formed (Scheme 1). Compounds **3** and **4** were separated by crystallization from acetic acid due to significant difference in their solubilities.

We then studied reactions of aldehydes **3a**–**3c** with 2-(3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)phenols **5a**–**5e** which were prepared from salicylaldehyde and substituted acetophenones [14]. By heating equimolar amounts of **3a**–**3c** and **5a**–**5e** in boiling ethanol (or ethanol–DMF, 1 : 1) for 0.5–1 h we obtained 5-[4-(2-aryl-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl)benzylidene]-1,3-thiazolidin-4-ones **6**–**8**

**Scheme 2.**




**5**–**8**, R = H (**a**), 4-Me (**b**), 3-MeO (**c**), 4-MeO (**d**), 4-Cl (**e**).

(Scheme 2). The products were isolated as high-melting white (**6**) or light yellow (**7**, **8**) solids readily soluble on heating in DMF and DMSO and sparingly soluble in acetic acid.

Molecules **6**–**8** possess two chiral centers, and they could be formed as different diastereoisomers or their mixtures. In fact, some compounds were individual isomers, while the others were mixtures of diastereoisomers at different ratios. No distinct relations in the stereochemical results were found. This suggests possible interconversion of the isomers, which could be favored by the presence of traces of acids [10]. The diastereoisomer ratios were determined from the intensities of the 10b-H and 5-H signals whose positions were significantly different for the different isomers. One isomer was characterized by a doublet at δ 4.76–4.82 (10b-H) and a singlet at δ 6.7–6.9 ppm (5-H), and the other displayed a doublet at δ 5.39–5.46 (10b-H) and a singlet at δ 6.30– 6.35 ppm (5-H).

Compounds **6**–**8** were subjected to highly efficient antitumor screening according to the Developmental Therapeutic Program of the US National Institutes of Health (National Cancer Institute, Bethesda, Maryland, USA) [19–21]. The antitumor activity was assayed in vitro in 60 cancer cell lines covering almost all human malignancies at a single dose concentration of $10^{-5}$ M. The antitumor activity was evaluated as cancer cell growth percentage (GP, %) relative to control (Table 1) [19–21]. The most active were rhodanine derivatives **7a** and **8a** against CCRF-CEM leukemia with GP values of 37.38, and 36.63%, respectively. Substitution in the benzene ring led to loss of cytostatic effect on that cancer cell line. Renal cancer cell line UO-31 turned out to be one of the most sensitive to all tested compounds (GP 62.51–84.00%).

The anti-inflammatory activity of compounds **6a**–**6e** was evaluated using the rat paw edema assay [22]. Outbred white rats with a weight of 180–250 g were injected under aseptic conditions with 0.1 mL of a 2% carrageenan solution under the hind paw aponeurosis (subplantar injection), and the paw volume was measured by the oncometric method before the injection and 4 h after the injection. Test compounds were administered intraperitoneally 1 h before carrageenan injection. The percent inhibition of edema was calculated by the formula

$$(\Delta V_{contr} - \Delta V_{test})/\Delta V_{contr} \times 100\%,$$

where $\Delta V_{contr}$ and $\Delta V_{test}$ are the average differences in the paw volumes before and after the injection of carrageenan in the control group and test sample-treated group, respectively. For comparison, the anti-exudative effect of standard anti-inflammatory drugs (diclofenac, ketorolac, indomethacin, and phenylbutazone) was evaluated under similar conditions. The results are summarized in Table 2. The anti-exudative effect of compounds **6a** and **6d** was comparable with those of indomethacin and ketorolac but slightly weaker than the effect of diclofenac and phenylbutazone.

## EXPERIMENTAL

The $^1$H NMR spectra were recorded on a Varian Mercury spectrometer at 400 MHz using DMSO-$d_6$ as solvent and tetramethylsilane as internal standard. The elemental analyses were obtained with a Carlo Erba 1106 analyzer. The melting points were measured on a Boetius melting point apparatus.

Commercially available reagents (Merck, Acros Organics) with a purity of no less than 97% were used.

**4-[(2,4-Dioxo-1,3-thiazolidin-5-ylidene)methyl]-benzaldehyde (3a).** Thiazolidine-2,4-dione (**2a**), 9.4 g (80 mmol), terephthalaldehyde (**1**), 13.4 g (0.1 mol), and fused sodium acetate, 6.6 g (80 mmol), were dissolved in 100 mL of hot acetic acid with stirring. The mixture was slowly cooled to 45–50°C and kept for 10 days at that temperature. The mixture was cooled, and the precipitate was filtered off, washed with acetic acid and ethanol, and dried. The product was heated in 600 mL of boiling acetic acid and filtered while hot to separate undissolved compound **4a**. The filtrate was cooled, and the precipitate of aldehyde **3a** was filtered off and recrystallized from propan-2-ol. Yield of **3a** 13.4 g (71%), mp 249–251°C. $^1$H NMR spectrum, δ, ppm: 7.80 d (2H, $C_6H_4$, $J$ = 8.4 Hz), 7.85 s (1H, CH=), 8.02 d (2H, $C_6H_4$, $J$ = 8.4 Hz), 10.04 s (1H, CHO), 12.77 br.s (1H, NH). Found, %: C 56.38; H 2.87; N 6.13. $C_{11}H_7NO_3S$. Calculated, %: C 56.64; H 3.03; N 6.01.

**(5*Z*,5′*Z*)-5,5′-[1,4-Phenylenedimethylidene]di-(1,3-thiazolidine-2,4-dione) (4a)** was recrystallized from DMF–AcOH. Yield 1.0 g (7.5%), mp > 270°C. $^1$H NMR spectrum, δ, ppm: 7.71 s (4H, $C_6H_4$), 7.79 s (2H, CH=), 12.70 br.s (2H, NH). Found, %: 50.70; H 2.58; N 8.32. $C_{14}H_8N_2O_4S_2$. Calculated, %: C 50.59; H 2.43; N 8.43.

**4-[(3-Methyl-4-oxo-2-sulfanylidene-1,3-thiazolidin-5-ylidene)methyl]benzaldehyde (3b)** was synthesized as described above for **3a**; the mixture was heated at 45–50°C for 48 h. Yield 15.36 g (73%), mp 192–

**Table 1.** Cytotoxicity of compounds **6a**–**6e**, **7a**–**7e**, and **8a**–**8e** at a single-dose concentration of $10^{-5}$ M against most sensitive cancer cell lines

| Compound no. | Mitotic activity | |
|---|---|---|
| | GP range, % | Most sensitive cancer cell lines; GP, % |
| **6a** | 67.87–112.01 | LOX IMVI (melanoma); 67.87<br>UO-31 (renal cancer); 74.75 |
| **6b** | 68.55–114.17 | CHB-75 (CNS cancer); 86.96<br>LOX IMVI (melanoma); 69.02<br>UO-31 (renal cancer); 68.55<br>T-47D (breast cancer); 81.49 |
| **6c** | 70.48–118.50 | EKVX (non-small-cell lung cancer); 85.43<br>LOX IMVI (melanoma); 70.48<br>UO-31 (renal cancer); 73.17 |
| **6d** | 67.40–112.15 | LOX IMVI (melanoma); 67.40<br>UO-31 (renal cancer); 71.63 |
| **6e** | 62.51–121.22 | EKVX (non-small-cell lung cancer); 77.55<br>LOX IMVI (melanoma); 68.61<br>IGROV1 (ovarian cancer); 76.70<br>UO-31 (renal cancer); 62.51 |
| **7a** | 37.38–137.62 | **CCRF-CEM (leukemia); 37.38**<br>CHB-75 (CNS cancer); 78.49<br>CAKI-1 (renal cancer); 77.24<br>UO-31 (renal cancer); 69.39 |
| **7b** | 66.30–113.67 | CHB-75 (CNS cancer); 76.22<br>CAKI-1 (renal cancer); 73.60<br>UO-31 (renal cancer); 66.30 |
| **7c** | 77.59–123.58 | MOLT-4 (leukemia); 81.81<br>CHB-75 (CNS cancer); 81.26<br>UO-31 (renal cancer); 77.59 |
| **7d** | 71.88–118.48 | CAKI-1 (renal cancer); 71.88<br>UO-31 (renal cancer); 72.23 |
| **7e** | 71.76–119.33 | NCI-H522 (non-small-cell lung cancer); 83.96<br>CAKI-1 (renal cancer); 83.84<br>UO-31 (renal cancer); 71.76 |
| **8a** | 36.63–117.37 | **CCRF-CEM (leukemia); 36.63**<br>UO-31 (renal cancer); 80.71 |
| **8b** | 78.59–116.61 | CHB-75 (CNS cancer); 81.93<br>CAKI-1 (renal cancer); 83.76<br>UO-31 (renal cancer); 78.59 |
| **8c** | 82.05–107.32 | UO-31 (renal cancer); 82.05 |
| **8d** | 84.00–113.65 | EKVX (non-small-cell lung cancer); 88.77<br>UO-31 (renal cancer); 84.00 |
| **8e** | 68.13–118.06 | EKVX (non-small-cell lung cancer); 81.45<br>CHB-75 (CNS cancer); 77.16<br>UO-31 (renal cancer); 68.13 |

**Table 2.** Anti-exudative activity of compounds **6a**–**6e** and some reference drugs

| Compound no. | Dose, mg/kg | Paw volume increase after 4 h, % | Inflammation inhibition, % |
|---|---|---|---|
| **6a** | 50 | 82.0 | 37.7 |
| **6b** | 50 | 120.7 | 8.4 |
| **6c** | 50 | 96.2 | 27.0 |
| **6d** | 50 | 82.7 | 37.2 |
| **6e** | 50 | 90.2 | 31.6 |
| Control | – | 131.7 | – |
| Diclofenac | 8 | 74.3 | 43.6 |
| Ketorolac | 10 | 80.9 | 38.6 |
| Indomethacin | 10 | 84.4 | 35.9 |
| Phenylbutazone | 50 | 72.4 | 45.0 |

193°C (from AcOH). $^1$H NMR spectrum, δ, ppm: 3.42 s (3H, $CH_3$), 7.85 d (2H, $C_6H_4$, $J$ = 8.0 Hz), 7.88 s (1H, CH=), 8.04 d (2H, $C_6H_4$, $J$ = 8.0 Hz), 10.06 s (1H, CHO). Found, %: C 54.58; H 3.31; N 5.47. $C_{12}H_9NO_2S_2$. Calculated, %: C 54.73; H 3.44; N 5.32.

**(5*Z*,5′*Z*)-5,5′-[1,4-Phenylenedimethylidene]di-(3-methyl-2-sulfanylidene-1,3-thiazolidine-2,4-dione) (4b)** was isolated as described above for **4a**. Yield 1.7 g (11%), mp > 270°C (from DMF). $^1$H NMR spectrum, δ, ppm: 3.44 s (6H, $CH_3$), 7.75 s (4H, $C_6H_4$), 7.91 s (2H, CH=). Found, %: 49.15; H 3.18; N 6.95. $C_{16}H_{12}N_2O_2S_4$. Calculated, %: C 48.96; H 3.08; N 7.14.

**4-({3-[2-(4-Methoxyphenyl)ethyl]-4-oxo-2-sulfanylidene-1,3-thiazolidin-5-ylidene}methyl)benzaldehyde (3c)** was synthesized as described above for **3b**. Yield 18.4 g (60%), mp 165–166°C (from *i*-PrOH). $^1$H NMR spectrum, δ, ppm: 2.89 t (2H, $CH_2$, $J$ = 7.6 Hz), 3.71 s (3H, $CH_3O$), 4.20 t (2H, $CH_2N$, $J$ = 7.6 Hz), 6.85 d (2H, $C_6H_4$, $J$ = 8.4 Hz), 7.13 d (2H, $C_6H_4$, $J$ = 8.4 Hz), 7.84 d (2H, $C_6H_4$, $J$ = 8.4 Hz), 7.85 s (1H, CH=), 8.04 d (2H, $C_6H_4$, $J$ = 8.4 Hz), 10.06 s (1H, CHO). Found, %: C 62.53; H 4.35; N 3.72. $C_{20}H_{17}NO_3S_2$. Calculated, %: C 62.64; H 4.47; N 3.65.

**(5*Z*,5′*Z*)-5,5′-[1,4-Phenylenedimethylidene]bis-{3-[2-(4-methoxyphenyl)ethyl]-2-sulfanylidene-1,3-thiazolidine-2,4-dione} (4c)** was isolated as described above for **4a**. Yield 3.0 g (12%), mp 263–264°C (from DMF). $^1$H NMR spectrum, δ, ppm: 2.92 t (4H, $CH_2$, $J$ = 7.2 Hz), 3.73 s (6H, $CH_3O$), 4.25 t (4H, $CH_2N$, $J$ = 7.2 Hz), 6.86 d (4H, $C_6H_4$, $J$ = 8.4 Hz), 7.14 d (4H, $C_6H_4$, $J$ = 8.4 Hz), 7.75–7.77 m (6H, $C_6H_4$, CH=). Found, %: C 60.85; H 4.51; N 4.29. $C_{32}H_{28}N_2O_4S_4$. Calculated, %: C 60.73; H 4.46; N 4.43.

**5-[4-(2-Aryl-1,10b-dihydropyrazolo[1,5-*c*]-[1,3]benzoxazin-5-yl)benzylidene]-1,3-thiazolidin-4-ones 6–8 (***general procedure***).** Aldehyde **3**, 1 mmol, was dissolved in 30 mL of boiling ethanol (**3a**) or DMF–ethanol (1:1, **3b**, **3c**), and 1 mmol of 2-(3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)phenol **5a**–**5e** was added with stirring to the hot solution. The mixture was refluxed for 0.5–1 h, and the precipitate was filtered off from the hot mixture, washed with ethanol, dried, and recrystallized from DMF–ethanol.

**5-[4-(2-Phenyl-1,10b-dihydropyrazolo[1,5-*c*]-[1,3]benzoxazin-5-yl)benzylidene]-1,3-thiazolidine-2,4-dione (6a).** Yield 0.38 g (84%), mp 220–221°C. $^1$H NMR spectrum, δ, ppm: 3.31–3.35 m (1H, $CH_2$), 3.50–3.61 m (1H, $CH_2$), 4.80 d (0.4H, 10b-H, $J$ = 9.4 Hz), 5.44 d (0.6H, 10b-H, $J$ = 9.1 Hz), 6.33 s (0.4H, 5-H), 6.83–6.95 m (1.6H, $H_{arom}$, 5-H), 7.01–7.06 m (1H, $H_{arom}$), 7.12–7.19 m (1H, $H_{arom}$), 7.25–7.56 m (6H, H, $H_{arom}$), 7.61 d (0.6H, $H_{arom}$, $J$ = 8.5 Hz), 7.65–7.79 m (3H, $H_{arom}$), 7.86–7.87 m (1.4H, $H_{arom}$, CH=), 12.68 br.s (1H, NH). Found, %: C 68.75; H 4.17; N 9.20. $C_{26}H_{19}N_3O_3S$. Calculated, %: C 68.86; H 4.22; N 9.27.

**5-{4-[2-(4-Methylphenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-1,3-thiazolidine-2,4-dione (6b).** Yield 0.38 g (81%), mp 218–219°C. $^1$H NMR spectrum, δ, ppm: 2.26 s (1H, $CH_3$), 2.31 s (2H, $CH_3$), 3.26–3.34 m (1H, $CH_2$), 3.47–3.58 m (1H, $CH_2$), 4.78 d (0.67H, 10b-H, $J$ = 9.4 Hz), 5.41 d (0.33H, 10b-H, $J$ = 9.4 Hz), 6.31 s (0.33H, 5-H), 6.85–6.94 m (2.33H, $H_{arom}$, 5-H), 6.99–7.08 m (1H, $H_{arom}$), 7.10–7.29 m (3.33H, $H_{arom}$), 7.40 d (0.67H, $H_{arom}$, $J$ = 8.1 Hz), 7.56–7.62 m (2.67H, $H_{arom}$), 7.65–7.73 m (2H, $H_{arom}$), 7.76 s (0.67H, CH=), 7.82–

7.89 m (1H, $H_{arom}$, CH=), 12.67 br.s (1H, NH). Found, %: C 69.19; H 4.50; N 8.81. $C_{27}H_{21}N_3O_3S$. Calculated, %: C 69.36; H 4.53; N 8.99.

**5-{4-[2-(3-Methoxyphenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-1,3-thiazolidine-2,4-dione (6c).** Yield 0.42 g (87%), mp 222–223°C. $^1$H NMR spectrum, δ, ppm: 3.31–3.35 m (1H, $CH_2$), 3.52–3.55 m (1H, $CH_2$), 3.71 s (1.38H, $OCH_3$), 3.78 s (1.62H, $OCH_3$), 4.80 d (0.54H, 10b-H, *J* = 9.5 Hz), 5.43 d (0.46H, 10b-H, *J* = 9.0 Hz), 6.32 s (0.46H, 5-H), 6.82–7.36 m (8.54H, $H_{arom}$, 5-H), 7.61 d (1H, $H_{arom}$, *J* = 8.4 Hz), 7.68 d (1H, $H_{arom}$, *J* = 8.4 Hz), 7.71 d (1H, $H_{arom}$, *J* = 8.4 Hz), 7.76 s (0.54H, CH=), 7.85–7.87 m (1.46H, $H_{arom}$, CH=), 12.67 br.s (1H, NH). Found, %: C 67.15; H 4.47; N 8.48. $C_{27}H_{21}N_3O_4S$. Calculated, %: C 67.07; H 4.38; N 8.69.

**5-{4-[2-(4-Methoxyphenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-1,3-thiazolidine-2,4-dione (6d).** Yield 0.40 g (83%), mp 216–217°C. $^1$H NMR spectrum, δ, ppm: 3.31–3.34 m (1H, $CH_2$), 3.43–3.57 m (1H, $CH_2$), 3.72 s (1.2H, $OCH_3$), 3.77 s (1.8H, $OCH_3$), 4.76 d (0.6H, 10b-H, *J* = 9.2 Hz), 5.39 d (0.4H, 10b-H, *J* = 9.1 Hz), 6.30 s (0.4H, 5-H), 6.83–6.98 m (4H, $H_{arom}$, 5-H), 6.99–7.06 m (1H, $H_{arom}$), 7.11–7.19 m (1H, $H_{arom}$), 7.26 d (0.6H, $H_{arom}$, *J* = 7.4 Hz), 7.45 d (1H, $H_{arom}$, *J* = 8.9 Hz), 7.58–7.73 m (4H, $H_{arom}$), 7.76 s (0.6H, CH=), 7.83–7.88 m (1.4H, $H_{arom}$, CH=), 12.67 br.s (1H, NH). Found, %: C 66.92; H 4.24; N 8.67. $C_{27}H_{21}N_3O_4S$. Calculated, %: C 67.07; H 4.38; N 8.69.

**5-{4-[2-(4-Chlorophenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-1,3-thiazolidine-2,4-dione (6e).** Yield 0.44 g (90%), mp 223–224°C. $^1$H NMR spectrum, δ, ppm: 3.31–3.36 m (1H, $CH_2$), 3.50–3.61 m (1H, $CH_2$), 4.82 d (0.6H, 10b-H, *J* = 9.4 Hz), 5.46 d (0.4H, 10b-H, *J* = 9.2 Hz), 6.34 s (0.4H, 5-H), 6.85–6.97 m (2.4H, $H_{arom}$, 5-H), 7.01–7.05 m (1H, $H_{arom}$), 7.12–7.20 m (1H, $H_{arom}$), 7.27 d (0.4H, $H_{arom}$, *J* = 7.6 Hz), 7.39 d (0.8H, $H_{arom}$, *J* = 8.5 Hz), 7.47 d (1.2H, $H_{arom}$, *J* = 8.5 Hz), 7.52 d (0.8H, $H_{arom}$, *J* = 8.6 Hz), 7.61 d (1.2H, $H_{arom}$, *J* = 8.3 Hz), 7.65–7.74 m (3H, $H_{arom}$), 7.76 s (0.6H, CH=), 7.83–7.88 m (1.2H, $H_{arom}$, CH=), 12.66 br.s (1H, NH). Found, %: C 64.13; H 3.59; N 8.46. $C_{26}H_{18}ClN_3O_3S$. Calculated, %: C 64.00; H 3.72; N 8.61.

**3-Methyl-5-[4-(2-phenyl-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl)benzylidene]-2-sulfanylidene-1,3-thiazolidin-4-one (7a).** Yield 0.46 g (95%), mp 222–224°C. $^1$H NMR spectrum, δ, ppm: 3.34–3.36 m (1H, $CH_2$), 3.43 s (3H, $CH_3$), 3.54 d.d (1H, $CH_2$, *J* = 16.4, 9.5 Hz), 5.44 d (1H, 10b-H, *J* = 9.1 Hz), 6.34 s (1H, 5-H), 6.87 d (1H, $H_{arom}$, *J* = 8.1 Hz), 7.03 t (1H, $H_{arom}$, *J* = 7.4 Hz), 7.17 t (1H, $H_{arom}$, *J* = 7.8 Hz), 7.28 d (1H, $H_{arom}$, *J* = 7.5 Hz), 7.30–7.36 m (3H, $H_{arom}$), 7.50–7.54 m (2H, $H_{arom}$), 7.76 d (2H, $H_{arom}$, *J* = 8.2 Hz), 7.87–7.91 m (3H, $H_{arom}$, CH=). Found, %: C 67.14; H 4.30; N 8.81. $C_{27}H_{21}N_3O_2S_2$. Calculated, %: C 67.06; H 4.38; N 8.69.

**3-Methyl-5-{4-[2-(4-methylphenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-2-sulfanylidene-1,3-thiazolidin-4-one (7b).** Yield 0.48 g (96%), mp 232–234°C. $^1$H NMR spectrum, δ, ppm: 2.25 s (3H, $CH_3$), 3.31 d (1H, $CH_2$, *J* = 16.7 Hz), 3.42 s (3H, $NCH_3$), 3.50 d.d (1H, $CH_2$, *J* = 16.7, 9.2 Hz), 5.41 d (1H, 10b-H, *J* = 9.2 Hz), 6.33 s (1H, 5-H), 6.87 d (1H, $H_{arom}$, *J* = 8.2 Hz), 7.02 t (1H, $H_{arom}$, *J* = 7.8 Hz), 7.10–7.20 m (3H, $H_{arom}$), 7.27 d (1H, $H_{arom}$, *J* = 7.6 Hz), 7.40 d (2H, $H_{arom}$, *J* = 8.1 Hz), 7.76 d (2H, $H_{arom}$, *J* = 8.4 Hz), 7.84–7.92 m (3H, $H_{arom}$, CH=). Found, %: C 67.38; H 4.61; N 8.32. $C_{28}H_{23}N_3O_2S_2$. Calculated, %: C 67.58; H 4.66; N 8.44.

**5-{4-[2-(3-Methoxyphenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-3-methyl-2-sulfanylidene-1,3-thiazolidin-4-one (7c).** Yield 0.46 g (89%), mp 201–203°C. $^1$H NMR spectrum, δ, ppm: 3.32–3.35 m (1H, $CH_2$), 3.39 s (1H, $NCH_3$), 3.42 s (2H, $NCH_3$), 3.47–3.60 m (1H, $CH_2$), 3.71 s (2H, $OCH_3$), 3.78 s (1H, $OCH_3$), 4.79 d (0.33H, 10b-H, *J* = 9.2 Hz), 5.43 d (0.67H, 10b-H, *J* = 9.2 Hz), 6.34 s (0.67H, 5-H), 6.84–7.37 m (7.33H, $H_{arom}$, 5-H), 7.65–7.72 m (1H, $H_{arom}$), 7.75–7.81 m (2H, $H_{arom}$), 7.85–7.91 m (3H, $H_{arom}$, CH=). Found, %: C 65.27; H 4.41; N 8.09. $C_{28}H_{23}N_3O_3S_2$. Calculated, %: C 65.48; H 4.51; N 8.18.

**5-{4-[2-(4-Methoxyphenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-3-methyl-2-sulfanylidene-1,3-thiazolidin-4-one (7d).** Yield 0.48 g (94%), mp 225–227°C. $^1$H NMR spectrum, δ, ppm: 3.31–3.36 m (1H, $CH_2$), 3.40 s (1H, $NCH_3$), 3.42 s (2H, $NCH_3$), 3.46–3.58 m (1H, $CH_2$), 3.73 s (2H, $OCH_3$), 3.78 s (1H, $OCH_3$), 4.77 d (0.33H, 10b-H, *J* = 9.3 Hz), 5.40 d (0.67H, 10b-H, *J* = 9.1 Hz), 6.30 s (0.67H, 5-H), 6.84–6.98 m (3.67H, $H_{arom}$, 5-H), 7.01–7.07 m (1H, $H_{arom}$), 7.12–7.19 m (1H, $H_{arom}$), 7.27 d (0.67H, $H_{arom}$, *J* = 7.8 Hz), 7.43–7.48 m (1.33H, $H_{arom}$), 7.60–7.73 m (2H, $H_{arom}$), 7.75 d (1.33H, $H_{arom}$, *J* = 8.4 Hz), 7.79 s (0.33H, CH=), 7.89 m (2H, $H_{arom}$, CH=). Found, %: C 65.57; H 4.40; N 8.12. $C_{28}H_{23}N_3O_3S_2$. Calculated, %: C 65.48; H 4.51; N 8.18.

**5-{4-[2-(4-Chlorophenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-3-methyl-2-sulfanylidene-1,3-thiazolidin-4-one (7e).** Yield 0.50 g (97%), mp 246–248°C. $^1$H NMR spectrum, δ, ppm: 3.37 d (1H, $CH_2$, *J* = 16.4 Hz), 3.43 s (3H, $CH_3$), 3.54 d.d (1H, $CH_2$, *J* = 16.4, 9.7 Hz), 5.46 d (1H, 10b-H, *J* = 9.7 Hz), 6.35 s (1H, 5-H), 6.88 d (1H, $H_{arom}$, *J* = 8.1 Hz), 7.03 t (1H, $H_{arom}$, *J* = 7.5 Hz), 7.18 t (1H, $H_{arom}$, *J* = 7.9 Hz), 7.27 d (1H, $H_{arom}$, *J* = 8.0 Hz), 7.39 d (2H, $H_{arom}$, *J* = 8.6 Hz), 7.52 d (2H, $H_{arom}$, *J* = 8.5 Hz), 7.76 d (2H, $H_{arom}$, *J* = 8.3 Hz), 7.84–7.91 m (3H, $H_{arom}$, CH=). Found, %: C 62.41; H 3.77; N 7.98. $C_{27}H_{20}ClN_3O_2S_2$. Calculated, %: C 62.60; H 3.89; N 8.11.

**3-[2-(4-Methoxyphenyl)ethyl]-5-[4-(2-phenyl-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl)-benzylidene]-2-sulfanylidene-1,3-thiazolidin-4-one (8a).** Yield 0.57 g (94%), mp 204–206°C. $^1$H NMR spectrum, δ, ppm: 2.91 t (2H, $NCH_2C\mathbf{H}_2$, *J* = 7.7 Hz), 3.31–3.35 m (1H, $CH_2$), 3.54 d.d (1H, $CH_2$, *J* = 16.4, 9.4 Hz), 3.72 s (3H, $CH_3O$), 4.22 t (2H, $CH_2N$, *J* = 7.7 Hz), 4.81 d (0.1H, 10b-H, *J* = 9.3 Hz), 5.44 d (0.9H, 10b-H, *J* = 9.4 Hz), 6.34 s (0.9H, 5-H), 6.83–6.94 m (3.1H, $H_{arom}$), 7.03 t (1H, $H_{arom}$, *J* = 7.6 Hz), 7.11–7.19 m (3H, $H_{arom}$), 7.25–7.36 m (3H, $H_{arom}$), 7.47–7.54 m (2H, $H_{arom}$), 7.65–7.69 m (1H, $H_{arom}$), 7.76 d (2H, $H_{arom}$, *J* = 8.0 Hz), 7.85 s (1H, CH=), 7.89 d (2H, $H_{arom}$, *J* = 8.1 Hz). Found, %: C 69.50; H 4.65; N 6.91. $C_{35}H_{29}N_3O_3S_2$. Calculated, %: C 69.63; H 4.84; N 6.96.

**3-[2-(4-Methoxyphenyl)ethyl]-5-{4-[2-(4-methylphenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-2-sulfanylidene-1,3-thiazolidin-4-one (8b).** Yield 0.51 g (83%), mp 204–206°C. NMR spectrum $^1$H, δ, ppm: 2.26 s (3H, $CH_3$), 2.85–2.96 m (2H, $NCH_2C\mathbf{H}_2$), 3.31–3.35 m (1H, $CH_2$), 3.51 d.d (1H, $CH_2$, *J* = 16.6, 9.2 Hz), 3.72 s (3H, $CH_3O$), 4.18–4.25 m (2H, $CH_2N$), 5.42 d (1H, 10b-H, *J* = 9.3 Hz), 6.31 s (1H, 5-H), 6.81–6.92 m (3H, $H_{arom}$), 7.02 t (1H, $H_{arom}$, *J* = 7.4 Hz), 7.12–7.23 m (5H, $H_{arom}$), 7.27 d (1H, $H_{arom}$, *J* = 7.6 Hz), 7.40 d (2H, $H_{arom}$, *J* = 7.8 Hz), 7.75 d (2H, $H_{arom}$, *J* = 7.8 Hz), 7.84 s (1H, CH=), 7.89 d (2H, $H_{arom}$, *J* = 8.0 Hz). Found, %: C 70.12; H 5.14; N 6.67. $C_{36}H_{31}N_3O_3S_2$. Calculated, %: C 69.99; H 5.06; N 6.80.

**5-{4-[2-(3-Methoxyphenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-3-[2-(4-methoxyphenyl)ethyl]-2-sulfanylidene-1,3-thiazolidin-4-one (8c).** Yield 0.52 g (82%), mp 207–209°C. $^1$H NMR spectrum, δ, ppm: δ 2.91 t (2H, $NCH_2C\mathbf{H}_2$, *J* = 7.2 Hz), 3.33–3.39 m (1H, $CH_2$), 3.53 d.d (1H, $CH_2$, *J* = 16.9, 9.6 Hz), 3.72 s (6H, $CH_3O$), 4.22 t (2H, $CH_2N$, *J* = 6.9 Hz,), 5.44 d (1H, 10b-H, *J* = 9.6 Hz), 6.33 s (1H, 5-H), 6.80–7.33 m (12H, $H_{arom}$), 7.75 d (2H, $H_{arom}$, *J* = 7.9 Hz), 7.84 s (1H, CH=), 7.89 d (2H, $H_{arom}$, *J* = 7.7 Hz). Found, %: C 68.08; H 4.84; N 6.47. $C_{36}H_{31}N_3O_4S_2$. Calculated, %: C 68.22; H 4.93; N 6.63.

**5-{4-[2-(4-Methoxyphenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-3-[2-(4-methoxyphenyl)ethyl]-2-sulfanylidene-1,3-thiazolidin-4-one (8d).** Yield 0.53 g (84%), mp 203–205°C. $^1$H NMR spectrum, δ, ppm: 2.82–2.94 m (2H, $NCH_2C\mathbf{H}_2$), 3.28–3.34 m (1H, $CH_2$), 3.43–3.58 m (1H, $CH_2$), 3.70 s (3H, $CH_3O$), 3.77 s (3H, $CH_3O$), 4.14–4.26 m (2H, $CH_2N$), 4.76 d (0.8H, 10b-H, *J* = 9.2 Hz), 5.40 d (0.2H, 10b-H, *J* = 9.4 Hz), 6.31 s (0.2H, 5-H), 6.21–7.76 m (11.2H, $H_{arom}$, 5-H), 7.27 d (0.2H, $H_{arom}$, *J* = 7.5 Hz), 7.45 d (0.4H, $H_{arom}$, *J* = 8.6 Hz), 7.58–7.91 m (6H, $H_{arom}$, CH=). Found, %: C 68.13; H 4.79; N 6.58. $C_{36}H_{31}N_3O_4S_2$. Calculated, %: C 68.22; H 4.93; N 6.63.

**5-{4-[2-(4-Chlorophenyl)-1,10b-dihydropyrazolo[1,5-*c*][1,3]benzoxazin-5-yl]benzylidene}-3-[2-(4-methoxyphenyl)ethyl]-2-sulfanylidene-1,3-thiazolidin-4-one (8e).** Yield 0.56 g (88%), mp 208–210°C. $^1$H NMR spectrum, δ, ppm: 2.91 t (2H, $NCH_2C\mathbf{H}_2$, *J* = 7.7 Hz), 3.31–3.34 m (1H, $CH_2$), 3.54 d.d (1H, $CH_2$, *J* = 17.5, 9.7 Hz), 3.71 s (3H, $CH_3O$), 4.22 t (2H, $CH_2N$, *J* = 7.7 Hz), 5.46 d (1H, 10b-H, *J* = 9.3 Hz), 6.35 s (1H, 5-H), 6.85–6.95 m (3H, $H_{arom}$), 7.03 t (1H, $H_{arom}$, *J* = 7.1 Hz), 7.11–7.20 m (3H, $H_{arom}$), 7.27 d (1H, $H_{arom}$, *J* = 7.8 Hz), 7.38 d (2H, $H_{arom}$, *J* = 8.4 Hz), 7.52 d (2H, $H_{arom}$, *J* = 8.2 Hz), 7.75 d (2H, $H_{arom}$, *J* = 8.2 Hz), 7.81–7.93 m (3H, $H_{arom}$, CH=). Found, %: C 66.04; H 4.48; N 6.51. $C_{35}H_{28}ClN_3O_3S_2$. Calculated, %: C 65.87; H 4.42; N 6.58.

## CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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