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Investigation of anticancer and anti-parasitic activity of thiopyrano[2,3-*d*]thiazoles bearing norbornane moiety

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Aim. To study anticancer activity of a series of new thiopyrano[2,3-*d*]thiazoles with a norbornane fragment in the molecules. The search for trypanocidal properties of target compounds. **Methods.** Organic synthesis, analytical and spectral methods, pharmacological screening, COMPARE and SAR analysis. **Results.** Fused thiopyrano[2,3-*d*]thiazoles bearing the norbornane moiety were synthesized and modified at the C9 and N5 positions of the main core in order to obtain the compounds with a satisfactory pharmacological profile. A number of compounds with significant level of cancer cells growth inhibition were identified; they include a hit-compound N1-(4-chlorophenyl)-2-{2-[6-oxo-5,9-dithia-7-azatetracyclo [9.2.1.02,10.04,8]tetradec-4(8)-en-3-yl]phenoxy}acetamide IId that selectively inhibited Leukemia cell lines at submicromolar concentrations. Moreover, a series of thiopyrano[2,3-*d*]thiazoles showed a moderate antitrypanosomal activity. **Conclusions.** New thiopyrano[2,3-*d*]thiazoles with the norbornane fragment as well as their analogues with different substituents at the N5 and C9 position were designed and synthesized. The compounds showed significant levels of anticancer activity towards the selected cancer cell lines and may be used for further optimization. The compounds with a high antitumor activity inhibited the growth of *Trypanosoma brucei brucei* in *in vitro* tests. The combined anticancer and antitrypanosomal effect of compounds is the basis for further modification and search for a possible mode of action of the target compounds.

Keywords: Thiopyrano[2,3-*d*]thiazoles, norbornane, synthesis, anticancer activity, anti-trypanosomal activity, SAR.

Introduction

Thiopyranothiazole core is a good scaffold for design of new pharmacologically interesting

molecules [1–6]. The most efficient method for their synthesis is based on *hetero*-Diels-Alder reaction of 5-ene-4-thioxo-2-thiazolidinones (5-eneisorhodanines). Thus, thiopyrano-

thiazoles are the derivatives of widely investigated 4-thiazolidinones. There are a number of drug candidates and approved drugs based on 4-thiazolidinone core, such as hypoglycemic glytazones – PPAR γ agonists – Rosiglitazone, Pioglitazone (2,4-thiazolidinone derivatives) [7] and aldose reductase inhibitor – Epalrestat (rhodanine derivative) [8]; anti-inflammatory dual inhibitor of COX-2/5-LOX – Darbufelon (2-aminothiazolidinone derivative) [9]; diuretic Etozoline (2-ylidene-4-thiazolidinone derivative) [10]; anticonvulsant Ralitolone (2-ylidene-4-thiazolidinone derivative) *etc.* [11]. Despite this, modern medicinal chemistry is still interested in the 4-thiazolidinone derivatives as a source of new drugs and a lot of research have been done in this area [12, 13]. Though, there are also comments of some scientists claiming the 4-thiazolidinones, namely 5-ene-4-thiazolidinones (one of the most powerful subtypes of mentioned heterocycles), as pan assay interference compounds (PAINS) due to their possible Michael acceptor functionality, wide spectrum of biological activities and low selectivity [14, 15]. The issues of PAINS remain controversial [12, 13]. Thiopyranothiazoles are hypothesized as biomimetics of the pharmacologically active 5-ene-4-thiazolidinones (synthetic precursors of thiopyranothiazoles) without mentioned Michael acceptor functionality [1, 2, 6]. Taking into account the results of biological activities study of thiopyranothiazoles one can conclude that these compounds might have good pharmacological profile but reveal different chemical and physical properties. The pharmacological activities associated with thiopyranothiazole core are antitumor [1, 2, 5, 6, 16, 17], antitrypanosomal [18–20], antioxi-

dant and anti-inflammatory [21] *etc.* Moreover, our previous findings showed that introduction of norbornane fragment in thiopyranothiazole molecules contributed to their antitumor activity with selectivity towards lung, renal, breast, leukemia and melanoma cancer types [1, 2]. A search for new anticancer agents among thiopyranothiazoles seems to be promising, and the target compounds of this work are shown in Fig. 1.

A number of hypotheses has been put forward in order to explain possible modes of antitumor action of the thiazolidinone derivatives and speculatively thiopyranothiazoles. For example, a mitochondria-depended proapoptotic mode of action related with G₀/G₁ arrest and an activation of ROS production; the caspase-depended and Bcl-depended pathways are the most discussed [13, 22].

The present work is an extension of our ongoing efforts towards a search for new thiazolidinone-based anticancer agents. Another objective of the study was to discover whether there is any correlation between anticancer and antitrypanosomal activity as the latter was shown for a series of related thiopyranothiazoles [20]. A repurposing approach is one of the currently used methods to discover new active antitrypanosomal agents [18, 23]. For example, anticancer drug Bortezomid showed excellent results in *in vitro* test against *Trypanosome brucei* inhibiting the parasites growth at nanomolar concentrations [24]. The DNA topoisomerase inhibitors (aclerubicin, doxorubicin and mitoxantrone) were also tested against bloodstream forms of *Trypanosoma brucei* and their trypanocidal activities were comparable with those of commercial antitrypanosomal drugs [25].

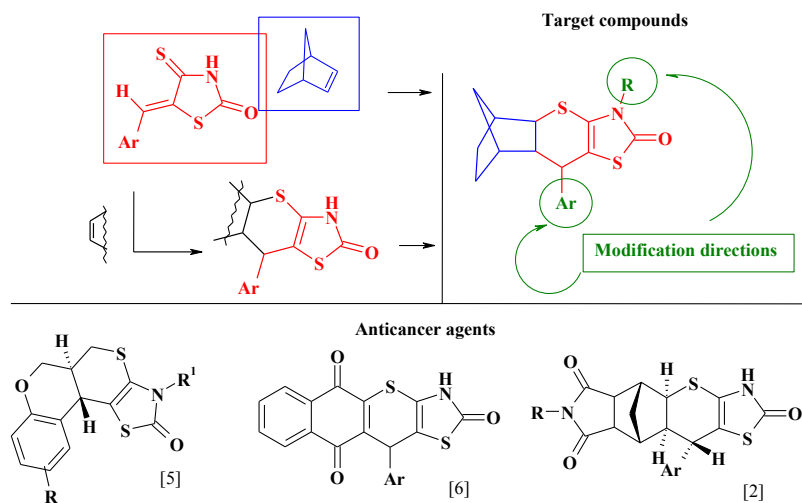


Fig. 1. Structure of active thiopyrano[2,3-*d*]thiazoles and target compounds

Here we addressed the screening of anticancer and antitrypanosomal effects *in vitro* of new thiopyrano[2,3-*d*]thiazoles with norbornane core and their N-3 derivatives.

Materials and Methods

Chemistry

All chemicals were of the analytical grade and commercially available. All reagents and solvents were used without further purification and drying. The starting 5-eneisorhodanines (**I**) [1] and 2,4-thiazolidinedione-5-acetic acid [26] were synthesized as described previously. NMR spectra were determined with Varian Mercury 400 (400 MHz) spectrometer, in DMSO-*d*₆ using tetramethylsilane as an internal standard. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 2400 CHN analyzer and were within $\pm 0.4\%$ from the theoretical values. Mass spectra were obtained using electrospray ionization (ESI) techniques on an Agilent 1100 Series LCMS. The purity of the compounds was checked by thin-layer

chromatography performed with Merck Silica Gel 60 F254 aluminum sheets.

General procedure for the synthesis of 9-aryl(heteryl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradecan-4(8)-ones-6 (II). A mixture of 5-ene-4-thioxo-2-thiazolidinone **I** (5 mmol), 2-norbornene (6 mmol), catalytic amounts of hydroquinone and acetic acid (15 mL) was heated under reflux during 1 hour and then cooled. Obtained solid products were filtered off, dried and recrystallized from the mixture of DMF/EtOH (1:2) or acetic acid.

9-(2-Pyridyl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-4(8)-en-6-one (IIa). Yield 68 %, mp 226–228 °C. ¹H NMR (DMSO-*d*₆) δ : 1.14 m, 1.23 (d, *J* = 9.8 Hz), 1.35 m, 1.45 m, 1.62 m, 1.95 m, 2.10 m, 2.24 m (9H, norbornane fragment), 3.42–3.48 (m, 2H, ArCH, SCH), 7.67 (m, 1H, arom.), 7.86 (d, 1H, *J* = 6.8 Hz, arom.), 8.57 (s, 1H, arom.), 8.75 (d, 1H, *J* = 5.0 Hz, arom.), 11.05 (s, 1H, NH). LCMS (ESI) *m/z* 317 (97 %, (M+H⁺)). Calcd. for C₁₆H₁₆N₂OS₂: C,

60.73; H, 5.10; N, 8.85; Found: C, 60.00; H, 8.90; N, 9.00.

9-(4-Methyloxycarboxyphenyl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-4(8)-en-6-one (IIb). Yield 70 %, mp 243–245 °C. ¹H NMR (DMSO-*d*₆) δ: 1.05 m, 1.18 (d, *J* = 10.2 Hz), 1.32 m, 1.38 m, 1.58 m, 1.89 m, 2.11(d, *J* = 10.1 Hz), 2.24 m (9H, norbornane fragment), 3.44 (d, 1H, *J* = 7.6 Hz, ArCH), 3.56 (d, 1H, *J* = 10.2 Hz, SCH), 3.85 (s, 3H, CH₃), 7.54 (d, 2H, *J* = 8.0 Hz, arom.), 7.974 (d, 2H, *J* = 8.0 Hz, arom.), 11.53 (s, 1H, NH). LCMS (ESI) *m/z* 374 (98 %, (M+H⁺)). Calcd. for C₁₉H₁₉NO₃S₂: C, 61.10; H, 5.13; N, 3.75; Found: C, 61.00; H, 5.00; N, 4.00

9-(3,5-Dimethoxy-4-hydroxyphenyl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-4(8)-en-6-one (IIc). Yield 75 %, mp >250 °C. ¹H NMR (DMSO-*d*₆) δ: 1.11 m, 1.22 (d, *J* = 10.0 Hz), 1.33 m, 1.44 m, 1.64 m, 1.98 m, 2.16 m, 2.23 m (9H, norbornane fragment), 3.30 (d, 1H, *J* = 7.9 Hz, ArCH), 3.37 (d, 1H, *J* = 10.1 Hz, SCH), 3.84 (s, 6H, 2*CH₃), 7.32 (brs, 2H, arom), 9.08 (s, 1H, OH), 11.26 (s, 1H, NH). Calcd. for C₁₉H₂₁NO₄S₂: C, 58.29; H, 5.41; N, 3.58; Found: C, 58.40; H, 5.60; N, 3.40.

N¹-(4-Chlorophenyl)-2-{2-[6-oxo-5,9-dithia-7-azatetracyclo [9.2.1.0^{2,10}.0^{4,8}]tetradec-4(8)-en-3-yl]phenoxy}acetamide (IIId). Yield 78 %, mp 194–196°C. ¹H NMR (DMSO-*d*₆) δ: 1.16 m, 1.31 m, 1.44 m, 1.63 m, 1.92 brs, 2.10 m, 2.21 m, 2.31 m (9H, norbornane fragment), 3.39 (d, 1H, *J* = 7.8 Hz, ArCH), 4.00 (d, 1H, *J* = 10.2 Hz, SCH), 4.68 (s, 2H, OCH₂), 6.99 (m, 2H, arom.), 7.26–7.40 (m, 4H, arom.), 7.59 (d, 2H, *J* = 8.0 Hz, arom.), 10.02 (s, 1H, NH), 11.30 (s, 1H, NH). LCMS (ESI) *m/z* 499/501 (96 %, (M+H⁺)). Calcd. for

C₂₅H₂₃ClN₂O₃S₂: C, 60.17; H, 4.65; N, 5.61; Found: C, 60.00; H, 4.60; N, 5.80.

9-(4-N-Dimethylaminophenyl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-4(8)-en-6-one (IIe). Yield 72 %, mp 246–248 °C. ¹H NMR (DMSO-*d*₆) δ: 1.13 (m, 1H, norbornane fragment), 1.16 (t, 6H, *J* = 6.9 Hz, 2*CH₃), 1.20 m, 1.31 m, 1.47 m, 1.64 m, 2.11 m, 2.12 (d, *J* = 10.0 Hz), 2.21 (d, *J* = 3.9 Hz) (8H, norbornane fragment), 3.17 (d, 1H, *J* = 7.8 Hz, ArCH), 3.34 (m, 4H, 2*CH₂), 3.37 (m, 1H, SCH), 6.56 (d, 2H, *J* = 8.2 Hz, arom.), 7.01 (d, 2H, *J* = 8.2 Hz, arom.), 11.10 (s, 1H, NH). LCMS (ESI) *m/z* 387 (95.6 %, (M+H⁺)). Calcd. for C₂₁H₂₆N₂O₂S₂: C, 65.25; H, 6.78; N, 7.25; Found: C, 65.35; H, 6.85; N, 7.10.

9-(Thiophen-2-yl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-4(8)-one-6 (IIIf). Analytical and spectral data are described [1].

9-(4-Chlorophenyl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-4(8)-one-6 (IIg). Analytical and spectral data are described [1].

9-(4-(3,5-Diphenyl-4,5-dihydro-pyrazol-1-yl)-phenyl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-4(8)-one-6 (IIh). Yield 76 %, mp 133–135 °C. ¹H NMR (DMSO-*d*₆) δ: 1.14 m, 1.28 m, 1.39 m, 1.62 m, 1.86 m, 2.10 m, 2.23 m, 2.32 m (9H, norbornane fragment), 3.39 (d, 1H, *J* = 7.8 Hz, ArCH), 3.48 (m, 1H, CH₂CH), 3.85 (m, 1H, CH₂CH), 3.94 (d, 1H, *J* = 10.2 Hz, SCH), 5.76 (m, 1H, CH₂CH), 6.84–6.92 (m, 2H, arom.), 7.21–7.28 (m, 4H, arom.), 7.56–7.62 (m, 4H, arom.), 7.69–7.73 (brs, 4H, arom), 11.02 (s, 1H, NH). LCMS (ESI) *m/z* 536 (96.2 %, (M+H⁺)). Calcd. for C₃₂H₂₉N₃OS₂: C, 71.74; H, 5.46; N, 7.84; Found: C, 72.00; H, 5.70; N, 7.60.

9-(4-Metoxyphenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6 (III). Analytical and spectral data are described [1].

9-(4-Hydroxyphenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6 (IIj). Analytical and spectral data are described [1].

9-(5-Nitro-2-(2-chlorobenzyloxyphenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6 (IIk). Yield 63 %, mp 232–233 °C. ¹H NMR (DMSO-*d*₆) δ: 1.07 m, 1.21 (d, *J* = 9.6 Hz), 1.28 m, 1.39 m, 1.58 m, 1.92 m, 2.20 m, 2.38 m, (9H, norbornane fragment), 3.42 (m, 1H, ArCH), 3.99 (d, 1H, *J* = 9.7 Hz, SCH), 5.28 (s, 2H, OCH₂), 7.22–7.24 (m, 2H, arom.), 7.30–7.40 (m, 2H, arom.), 7.90 (m, 2H, arom.), 8.22 (s, 1H, arom.), 11.54 (s, 1H, NH). LCMS (ESI) *m/z* 501/503 (95.6 %, (M+H⁺)). Calcd. for C₂₄H₂₁ClN₂O₄S₂: C, 57.54; H, 4.22; N, 5.59; Found: C, 57.80; H, 4.30; N, 5.40.

9-(2-Hydroxy-3-methoxyphenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6 (III). Yield 75 %, mp 215–216 °C. ¹H NMR (DMSO-*d*₆) δ: 1.05 m, 1.20 (d, *J* = 9.2 Hz), 1.31 m, 1.42 m, 1.60 m, 1.92 brs, 2.08 (d, *J* = 7.8 Hz), 2.20 brs, 2.27 m, (9H, norbornane fragment), 3.41 (d, 1H, *J* = 7.8 Hz, ArCH), 3.47 (d, 1H, *J* = 10.1 Hz, SCH), 3.82 (s, 3H, CH₃), 6.80–6.84 (m, 1H, arom.), 6.86–6.93 (m, 2H, arom.), 8.78 (s, 1H, OH), 11.40 (s, 1H, NH). LCMS (ESI) *m/z* 362 (97.8 %, (M+H⁺)). Calcd. for C₁₈H₁₉NO₃S₂: C, 59.81; H, 5.30; N, 3.87; Found: C, 60.00; H, 5.50; N, 3.70.

9-(2-Nitrophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6 (IIl). Yield 75 %, mp 236–238 °C. ¹H NMR (DMSO-*d*₆) δ: 1.12m, 1.20 (d, *J* =

10.1 Hz), 1.32 m, 1.47 m, 1.65 m, 2.06 m, 2.12 m, 2.22 m (9H, norbornane fragment), 3.22 (d, 1H, *J* = 7.6 Hz, ArCH), 3.35 (d, 1H, *J* = 10.4 Hz, SCH), 7.22–7.28 (m, 3H, arom.), 7.92 (brs, 1H, arom.), 11.12 (s, 1H, NH). LCMS (ESI) *m/z* 361 (96 %, (M+H⁺)). Calcd. for C₁₇H₁₆N₂O₃S₂: C, 56.65; H, 4.47; N, 7.77; Found: C, 56.85; H, 4.65; N, 7.50.

9-(3,4-Dimethoxyphenyl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6 (IIl). Yield 69 %, mp 242–243 °C. ¹H NMR (DMSO-*d*₆) δ: 1.08m, 1.17 (d, *J* = 10.2 Hz), 1.35 m, 1.44 m, 1.60 m, 1.97 brs, 2.06 m, 2.22 m (9H, norbornane fragment), 3.40 (d, 1H, *J* = 7.9 Hz, ArCH), 3.47 (d, 1H, *J* = 10.1 Hz, SCH), 3.76 (s, 3H, CH₃), 3.78 (s, 3H, CH₃), 6.94 (d, 1H, *J* = 8.2 Hz, arom.), 6.96 (d, 1H, *J* = 8.3 Hz, arom.), 6.98 (s, 1H, arom.), 11.45 (s, 1H, NH). LCMS (ESI) *m/z* 376 (97 %, (M+H⁺)). Calcd. for C₁₉H₂₁NO₃S₂: C, 60.77; H, 5.64; N, 3.73; Found: C, 60.50; H, 5.50; N, 5.80.

9-(3-Methoxy-4-hydroxyphenyl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-one-6 (IIo). Analytical and spectral data are described [1].

General procedure for the synthesis of 2-(9-aryl(heteryl)-3,7-dythia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6-yl-5) acetic acid amides and ester (III).

The mixture of appropriate compound II (3 mmol), potassium hydroxide (3 mmol), appropriate *N*-substituted chloroacetamide or ethylchloroacetate (3.3 mmol) and catalytic amounts of KI in the medium of methanol / DMF (2:1) was heated under reflux for 3 hours and cooled. Formed precipitate was filtered and recrystallized from buthanol, acetic acid or mixture of DMF/methanol (1:1).

2-(9-(4'-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]/tetradecen-4(8)-one-6-yl-5)-N-phenyl-acetamide (IIIa). Yield 71 %, mp 105–107 °C. ¹H NMR (DMSO-*d*₆) δ: 1.11 m, 1.16 (d, *J* = 10.0 Hz), 1.32 m, 1.41 m, 1.62 m, 2.07 m, 2.21 m, (9H, norbornane fragment), 3.38 (d, 1H, *J* = 7.8 Hz, ArCH), 3.52 (d, 1H, *J* = 10.1 Hz, SCH), 4.58 (brs, 2H, CH₂CO), 6.72–6.78 (m, 4H, arom.), 6.94–7.05 (m, 3H, arom.), 7.12–7.15 (m, 2H, arom.), 10.98 (s, 1H, NH). LCMS (ESI) *m/z* 483/485 (95.6 %, (M+H⁺)). Calcd. for C₂₅H₂₃ClN₂O₂S₂: C, 62.16; H, 4.80; N, 5.80; Found: C, 62.40; H, 5.00; N, 4.60.

2-(9-(4-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]/tetradecen-4(8)-one-6-yl-5)-N-3-methylphenyl-acetamide (IIIb). Yield 71 %, mp 164–166 °C. ¹H NMR (DMSO-*d*₆) δ: 1.20 m, 1.31 m, 1.51 m, 1.62 m, 2.12 m, 2.24 m, (9H, norbornane fragment), 2.33 (s, 3H, CH₃), 3.39 (d, 1H, *J* = 7.8 Hz, ArCH), 3.70 (d, 1H, *J* = 10.2 Hz, SCH), 4.58 (m, 2H, CH₂CO), 7.35 (d, 2H, *J* = 8.2 Hz, arom.), 7.42 (d, 2H, *J* = 8.2 Hz, arom.), 7.50–7.56 (m, 3H, arom), 7.68 (brs, 1H, arom.), 10.52 (s, 1H, NH). LCMS (ESI) *m/z* 497/498 (95.6 %, (M+H⁺)). Calcd. for C₂₆H₂₅ClN₂O₂S₂: C, 62.82; H, 5.07; N, 5.64; Found: C, 63.00; H, 5.20; N, 5.50.

2-(9-(4-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]/tetradecen-4(8)-one-6-yl-5)-N-3-trifluoromethylphenyl-acetamide (IIIc). Yield 65 %, mp 176–178 °C. ¹H NMR (DMSO-*d*₆) δ: 1.17 (t, *J* = 10.2 Hz), 1.23 (d, *J* = 9.8 Hz), 1.33 (t, *J* = 10.2 Hz), 1.49 (t, *J* = 10.0 Hz), 1.64 m, 2.06 m, 2.24 m, (9H, norbornane fragment), 3.32 (d, 1H, *J* = 7.8 Hz, ArCH), 3.55 (d, 1H, *J* = 10.1 Hz, SCH), 4.47 (d, 1H, *J* = 16.0 Hz, CH₂CO), 4.60 (d, 1H, *J* =

16.0 Hz, CH₂CO), 7.23 (d, 2H, *J* = 8.1 Hz, arom.), 7.61 (d, 2H, *J* = 8.1 Hz, arom.), 7.34–7.37 (m, 3H, arom.), 10.16 (s, 1H, NH). LCMS (ESI) *m/z* 551/553 (97.2 %, (M+H⁺)). Calcd. for C₂₆H₂₂ClF₃N₂O₂S₂: C, 56.67; H, 4.02; N, 5.08; Found: C, 56.50; H, 3.90; N, 5.30.

2-(9-(4-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]/tetradecen-4(8)-one-6-yl-5)-N-4-chlorophenyl-acetamide (IIIId). Yield 68 %, mp 138–140 °C. ¹H NMR (DMSO-*d*₆) δ: 1.16 m, 1.22 m, 1.36 m, 1.52 m, 2.01 m, 2.14 m, 2.23 m (9H, norbornane fragment), 3.37–3.43 (m, 2H, ArCH, SCH), 4.94 (d, 1H, *J* = 16.0 Hz, CH₂CO), 5.02 (d, 1H, *J* = 16.0 Hz, CH₂CO), 7.30 (d, 2H, *J* = 8.6 Hz, arom.), 7.34 (d, 2H, *J* = 8.6 Hz, arom.), 7.52 (d, 2H, *J* = 8.6 Hz, arom.), 7.62 (d, 2H, *J* = 8.6 Hz, arom.), 10.67 (s, 1H, NH). LCMS (ESI) *m/z* 517/518/519 (95.6 %, (M+H⁺)). Calcd. for C₂₅H₂₂Cl₂N₂O₂S₂: C, 58.02; H, 4.29; N, 5.41; Found: C, 58.20; H, 4.50; N, 5.30.

2-(9-(4-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]/tetradecen-4(8)-one-6-yl-5)-N-4-methylphenyl-acetamide (IIIe). Yield 76 %, mp 189–191 °C. ¹H NMR (DMSO-*d*₆) δ: 1.21 m, 1.27 m, 1.38 m, 1.52 m, 2.14 m, 2.23 m (9H, norbornane fragment), 2.31 (s, 3H, CH₃), 3.34 (m, 1H, ArCH) 3.92 (d, 1H, *J* = 10.2 Hz, SCH), 4.92 (d, 1H, *J* = 16.2 Hz, CH₂CO), 4.96 (d, 1H, *J* = 16.2 Hz, CH₂CO), 7.28 (d, 2H, *J* = 8.2 Hz, arom.), 7.32 (d, 2H, *J* = 8.0 Hz, arom.), 7.38 (d, 2H, *J* = 8.2 Hz, arom.), 7.54 (d, 2H, *J* = 8.0 Hz, arom.), 10.57 (s, 1H, NH). LCMS (ESI) *m/z* 497/498 (97.0 %, (M+H⁺)). Calcd. for C₂₆H₂₅ClN₂O₂S₂: C, 62.82; H, 5.07; N, 5.64; Found: C, 63.00; H, 5.20; N, 5.40.

2-(9-(4-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]/tetradecen-4(8)-

one-6-yl-5)-N-2-methylphenyl-acetamide (III_f). Yield 74 %, mp 215–217 °C. ¹H NMR (DMSO-*d*₆) δ: 1.22 m, 1.28 m, 1.34 m, 1.51 m, 2.14 m, 2.23 m (9H, norbornane fragment), 2.33 (s, 3H, CH₃), 3.32 (d, 1H, *J* = 7.8 Hz, ArCH), 3.91 (d, 1H, *J* = 10.4 Hz, SCH), 4.87 (d, 1H, *J* = 16.0 Hz, CH₂CO), 4.96 (d, 1H, *J* = 16.0 Hz, CH₂CO), 7.32 (d, 2H, *J* = 8.4 Hz, arom.), 7.36 (d, 2H, *J* = 8.3 Hz, arom.), 7.42 (d, 1H, *J* = 8.3 Hz, arom.), 7.52–7.56 (m, 3H, arom.), 10.60 (s, 1H, NH). LCMS (ESI) *m/z* 497/499 (97.0 %, (M+H⁺)). Calcd. for C₂₆H₂₅ClN₂O₂S₂: C, 62.82; H, 5.07; N, 5.64; Found: C, 62.70; H, 5.00; N, 5.60.

2-(9-(4-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-one-6-yl-5)-N-4-methoxyphenyl-acetamide (III_g). Yield 78 %, mp 132–134 °C. ¹H NMR (DMSO-*d*₆) δ: 1.18 m, 1.22 m, 1.33 m, 1.51 m, 2.12 m, 2.31 m (9H, norbornane fragment), 3.30 (d, 1H, *J* = 7.6 Hz, ArCH), 3.81 (s, 3H, CH₃), 3.87 (d, 1H, *J* = 10.2 Hz, SCH), 4.52 (d, 1H, *J* = 16.0 Hz, CH₂CO), 4.62 (d, 1H, *J* = 16.0 Hz, CH₂CO), 7.30 (d, 2H, *J* = 8.4 Hz, arom.), 7.34 (d, 2H, *J* = 8.3 Hz, arom.), 7.52 (d, 2H, *J* = 8.3 Hz, arom.), 7.56 (d, 2H, *J* = 8.3 Hz, arom.), 10.57 (s, 1H, NH). LCMS (ESI) *m/z* 513/515 (97.0 %, (M+H⁺)). Calcd. for C₂₆H₂₅ClN₂O₃S₂: C, 60.87; H, 4.91; N, 5.46; Found: C, 61.00; H, 5.10; N, 4.70.

2-(9-(Thiophen-2-yl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-one-6-yl-5)-N-4-methylphenyl-acetamide (III_h). Yield 73 %, mp 230–232 °C. ¹H NMR (DMSO-*d*₆) δ: 1.24 m, 1.30 (t, *J* = 9.2 Hz), 1.53 m, 1.64 m, 2.13m, 2.23 m (9H, norbornane fragment), 2.27 (s, 3H, CH₃), 3.33 (d, 1H, *J* = 7.6 Hz, ArCH), 3.91 (d, 1H, *J* = 10.6 Hz, SCH), 4.46 (d, 1H, *J* = 16.0 Hz, CH₂CO), 4.51

(d, 1H, *J* = 16.0 Hz, CH₂CO), 7.10 (m, 4H, arom.), 7.41 (d, 2H, *J* = 8.2 Hz, arom.), 7.45 (d, 1H, *J* = 6.8 Hz, arom.), 10.16 (s, 1H, NH). LCMS (ESI) *m/z* 469 (97 %, (M+H⁺)). Calcd. for C₂₄H₂₄N₂O₂S₃: C, 61.51; H, 5.16; N, 5.98; Found: C, 61.70; H, 5.30; N, 6.10.

2-(9-(Thiophen-2-yl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-one-6-yl-5)-N-2-trifluorophenyl-acetamide (III_i). Yield 69 %, mp 153–155 °C. ¹H NMR (DMSO-*d*₆) δ: 1.24 m, 1.32 m, 1.54 m, 1.63 m, 2.18 m, 2.23 m (9H, norbornane fragment), 3.34 (d, 1H, *J* = 7.6 Hz, ArCH), 3.71 (d, 1H, *J* = 7.8 Hz, SCH), 4.52 (d, 1H, *J* = 16.0 Hz, CH₂CO), 4.54 (d, 1H, *J* = 16.0 Hz, CH₂CO), 7.05–7.10 (m, 2H, arom.), 7.25–7.30 (m, 2H, arom.), 7.36 (m, 2H, arom.), 7.40 (d, 1H, *J* = 7.5 Hz, arom.), 9.81 (s, 1H, NH). LCMS (ESI) *m/z* 523 (98.2 %, (M+H⁺)). Calcd. for C₂₄H₂₁F₃N₂O₂S₃: C, 55.16; H, 4.05; N, 5.36; Found: C, 55.30; H, 4.30; N, 5.50.

2-(9-(Thiophen-2-yl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-one-6-yl-5)-N-4-chlorophenyl-acetamide (III_j). Yield 74 %, mp 232–234 °C. ¹H NMR (DMSO-*d*₆) δ: 1.23 m, 1.28 m, 1.58 m, 1.64 m, 2.21 m, 2.24 m (9H, norbornane fragment), 3.34 (d, 1H, *J* = 7.2 Hz, ArCH), 3.93 (d, 1H, *J* = 8.8 Hz, SCH), 4.42 (d, 1H, *J* = 16.0 Hz, CH₂CO), 4.46 (d, 1H, *J* = 16.0 Hz, CH₂CO), 7.05 (brs, 1H, arom.), 7.12 (brs, 1H, arom.), 7.39 (d, 2H, *J* = 8.0 Hz, arom.), 7.60 (d, 1H, *J* = 4.0 Hz, arom.), 7.96 (d, 2H, *J* = 7.4 Hz, arom.), 10.35 (s, 1H, NH). LCMS (ESI) *m/z* 489/491 (97.0 %, (M+H⁺)). Calcd. for C₂₃H₂₁ClN₂O₂S₃: C, 56.48; H, 4.33; N, 5.73; Found: C, 56.70; H, 4.50; N, 5.50.

2-(9-(Thiophen-2-yl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-

one-6-yl-5)-N-4-metoxyphenyl-acetamide (IIIk). Yield 75 %, mp 264–266 °C. ¹H NMR (DMSO-*d*₆) δ: 1.26 (d, *J* = 9.5 Hz) 1.35 m, 1.55 (t, *J* = 8.9 Hz), 1.68 m, 2.21 m, 2.38 m (9H, norbornane fragment), 3.10 (s, 3H, CH₃), 3.37 (d, 1H, *J* = 7.7 Hz, ArCH), 3.92 (d, 1H, *J* = 10.7 Hz, SCH), 4.55 (d, 1H, *J* = 16.0 Hz, CH₂CO), 4.57 (d, 1H, *J* = 16.0 Hz, CH₂CO), 7.06 (t, 1H, *J* = 4.2 Hz, arom.), 7.13 (brs, 1H, arom.), 7.42 (d, 1H, *J* = 4.8 Hz, arom.), 7.73 (d, 2H, *J* = 8.2 Hz, arom.), 7.93 (d, 2H, *J* = 8.3 Hz, arom), 10.35 (s, 1H, NH). LCMS (ESI) *m/z* 485 (98.0 %, (M+H⁺)). Calcd. for C₂₄H₂₄N₂O₃S₃: C, 59.48; H, 4.99; N, 5.78; Found: C, 59.70; H, 5.10; N, 5.50.

2-(9-(Thiophen-2-yl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6-yl-5)-N-3-trifluorophenyl-acetamide (IIIl). Yield 68 %, mp 182–184 °C. ¹H NMR (DMSO-*d*₆) δ: 1.26 m, 1.36 m, 1.56 m, 1.68 m, 2.21 m, 2.28 (9H, norbornane fragment), 3.38 (d, 1H, *J* = 7.7 Hz, ArCH), 3.92 (d, 1H, *J* = 10.6 Hz, SCH), 4.54 (d, 1H, *J* = 16.0 Hz, CH₂CO), 4.57 (d, 1H, *J* = 16.0 Hz, CH₂CO), 7.06 (m, 1H, arom.), 7.13 (brs, 1H, arom.), 7.35 (t, 1H, *J* = 8.3 Hz, arom.), 7.40 (d, 1H, *J* = 4.8 Hz, arom.), 7.51 (t, 1H, *J* = 7.9 Hz, arom), 7.76 (d, 1H, *J* = 7.9 Hz, arom.), 8.07 (s, 1H, arom), 10.57 (s, 1H, NH). LCMS (ESI) *m/z* 523 (97.0 %, (M+H⁺)). Calcd. for C₂₄H₂₁F₃N₂O₃S₃: C, 55.16; H, 4.05; N, 5.36; Found: C, 55.00; H, 3.90; N, 5.50.

2-(9-(Thiophen-2-yl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6-yl-5)-N-3,4-dichlorophenyl-acetamide (IIIm). Yield 72 %, mp 219–221 °C. ¹H NMR (DMSO-*d*₆) δ: 1.26 (d, *J* = 9.7 Hz), 1.38 (t, *J* = 9.3 Hz), 1.56 (t, *J* = 9.8 Hz), 1.68 m, 2.18 m, 2.28 (9H, norbornane fragment), 3.36 (d, 1H,

J = 7.3 Hz, ArCH), 3.90 (d, 1H, *J* = 10.4 Hz, SCH), 4.52 (d, 1H, *J* = 16.7 Hz, CH₂CO), 4.56 (d, 1H, *J* = 16.0 Hz, CH₂CO), 7.06 (d, 1H, *J* = 4.7 Hz, arom.), 7.11 (brs, 1H, arom.), 7.40 (d, 1H, *J* = 4.73 Hz, arom.), 7.42 (m, 2H, arom.), 7.96 (s, 1H, arom), 10.51 (s, 1H, NH). LCMS (ESI) *m/z* 523/524/525 (96.0 %, (M+H⁺)). Calcd. for C₂₃H₂₀Cl₂N₂O₃S₃: C, 52.77; H, 3.85; N, 5.35; Found: C, 52.90; H, 4.00; N, 5.20.

2-(9-(4'-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6-yl-5)-acetic acid ethyl ester (IIIo). Yield 78 %, mp 178–180 °C. ¹H NMR (DMSO-*d*₆) δ: 1.16 m, 1.26 (d, *J* = 9.2 Hz), 1.32 m, 1.30 (t, 3H, *J* = 7.2 Hz, CH₃), 1.50 (t, *J* = 8.2 Hz), 1.67 (t, *J* = 9.0 Hz), 2.07 m, 2.21 m (9H, norbornane fragment), 3.31 (d, 1H, *J* = 17.6 Hz, SCH), 3.50 (d, 1H, *J* = 10.2 Hz, ArCH), 4.21 (q, 2H, *J* = 7.2 Hz, CH₂CH₃), 4.37 (s, 2H, CH₂CO), 7.33–7.36 (m, 4H, arom.). LCMS (ESI) *m/z* 436/438 (96 %, (M+H⁺)). Calcd. for C₂₁H₂₂ClNO₃S₂: C, 57.85; H, 5.09; N, 3.21; Found: C, 58.00; H, 5.20; N, 4.90.

2-(9-(4'-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6-yl-5)-acetic acid hydrazide (IIIo). A mixture of IIIo (3 mmol) and hydrazine hydrate (4 mmol) in ethanol (20 mL) was heated under reflux for 5 h. The precipitate was filtered off and recrystallized from acetic acid. Yield 60 %, mp 219–221 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.14 m, 1.23 (d, *J* = 10.3 Hz), 1.31 (t, *J* = 10.7 Hz), 1.48 m, 1.66 m, 2.02 m, 2.20 m, 2.26 m (9H, norbornane fragment), 3.32 (d, 1H, *J* = 7.9 Hz, ArCH), 3.52 (d, 1H, *J* = 9.7 Hz, SCH), 4.31 (d, 1H, *J* = 16.3 Hz, CH₂CO), 4.41 (d, 1H, *J* = 16.0 Hz, CH₂CO), 7.37 (m, 4H, arom.), 8.10 (brs, 1H,

NH), 9.60 (brs, 2H, NH₂). LCMS (ESI) m/z 422/424 (98%, (M+H⁺)). Calcd for C₁₉H₂₀ClN₃O₂S₂: C, 54.08; N, 9.96; S, 15.20. Found: C, 54.10; N, 9.98; S, 15.25.

4-[9-(4'-Chlorophenyl)-6-oxo-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradec-4(8)-ene-5-yl]-acetyl-1-phenyl-thiosemicarbazide (III_t) The mixture of **III_o** (3 mmol), phenylisothiocyanate (4 mmol) in ethanol (20 mL) was heated under reflux during 1 h and then cooled. Solid product was filtered off, washed with ethanol, diethyl ether and recrystallized from ethanol. Yield, 64 %, mp 188–190 °C. ¹H NMR (400 MHz, DMSO-*d*₆): 1.18 m, 1.23 m, 1.37 m, 1.52 m, 2.12 m, 2.22 m, (9H, norbornane fragment), 3.31 (d, 1H, *J* = 7.8 Hz, ArCH), 3.62 (d, 1H, *J* = 10.7 Hz, SCH), 4.32 (d, 1H, *J* = 16.3 Hz, CH₂CO), 4.36 (d, 1H, *J* = 16.3 Hz, CH₂CO), 7.32 (d, 2H, *J* = 8.2 Hz, arom.), 7.38 (d, 2H, *J* = 8.2 Hz, arom.), 7.48–7.52 (m, 5H, arom.), 8.11 (brs, 1H, NH), 9.62 (brs, 2H, NH₂). LCMS (ESI) m/z 558/560 (96 %, (M+H⁺)). Calcd for C₂₆H₂₅ClN₄O₂S₃: C, 56.05; N, 10.06; S, 17.26. Found: C, 56.15; N, 10.10; S, 17.20.

Dihydrazide of 2-(9-(4'-chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-one-6-yl-5)-acetic acid and 2,4-thiazolidinedione-5-acetic acid (III_p) The solution of 2,4-thiazolidinedione-5-acetic acid chloride (3 mmol) in dioxane (3 mL) was added to the solution of **III_o** (3 mmol) and triethylamine (3 mmol) in dioxane (12 mL). The mixture was heated at 80 °C during 15 min and cooled. The product of the reaction was precipitated with water. Solid precipitate was filtered off and recrystallized from ethanol. Yield 81 %, mp. 192–194 °C (dec.). ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.09 m, 1.21 m,

1.31 m, 1.45 m, 1.64 m, 1.97 m, 2.18 m, 2.25 m (9H, norbornane fragment), 3.33 (d, 1H, *J* = 7.7 Hz, ArCH), 3.54 (d, 1H, *J* = 10.5 Hz, SCH), 2.85 (dd, 1H, *J* = 16.5, 8.7 Hz, CH₂CH), 3.06 (dd, 1H, *J* = 8.7, 4.0 Hz, CH₂CH), 4.36 (m, 2H, CH₂CO), 4.58 (dd, 1H, *J* = 3.6, 9.0 Hz, CHCH₂), 7.38–7.43 (m, 4H, arom.), 10.26 (s, 1H, NH), 10.37 (s, 1H, NH). LCMS (ESI) m/z 580/582 (95 %, (M+H⁺)). Calcd for C₂₄H₂₃ClN₄O₅S₃: C, 49.78; N, 9.67; S, 16.61. Found: C, 49.85; N, 9.70; S, 16.60.

5-(1-Phenyl-2-mercapto-1,3,4-triazolylmethylene)-9-(4'-chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-one-6 (III_u) The mixture of **III_t** (2.5 mmol) and 10 mL of 2 % sodium hydroxide solution was heated under reflux during 2 h. After cooling the reaction mixture was acidified with the HCl, pH=5 and then the solid product was filtered off. The precipitate was recrystallized from the DMF : EtOH (1:2) mixture. Yield 72 %, mp > 250 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.11 m, 1.20 (d, *J* = 9.0 Hz), 1.30 m, 1.44 m, 1.63 m, 1.95 m, 2.15 m, 2.23 m, (9H, norbornane fragment), 3.25 (d, 1H, *J* = 7.6 Hz, ArCH), 3.49 (d, 1H, *J* = 10.5 Hz, SCH), 4.74 (d, 1H, *J* = 16.9 Hz, CH₂CO), 4.78 (d, 1H, *J* = 16.9 Hz, CH₂CO), 7.40–7.5 (m, 5H, arom), 7.56–7.60 (m, 4H, arom), 13.90 (s 1H, SH). LCMS (ESI) m/z 539/541 (96 %, (M+H⁺)). Calcd for C₂₆H₂₃ClN₄O₅S₃: C, 57.92; N, 10.39; S, 17.84. Found: C, 58.03; N, 10.41; S, 17.80.

General procedure for the synthesis of 2-(9-aryl-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-one-6-yl-5)-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazides (III_{q-s}) A mixture of hydrazide **III_o** (3 mmol), appropriate isatin

(3 mmol) in ethanol (20 mL) in the presence of acetic acid (2 mL) was heated under reflux during 5 h and then cooled. Obtained solid products were filtered off, dried and recrystallized from the mixture of DMF/EtOH (1:2) or acetic acid.

2-(9-(4'-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-one-6-yl-5)-acetic acid (2-oxo-1,2-dihydroindol-3-ylidene)-hydrazide (IIIq). Yield 76 %, mp. 272–274 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.15 m, 1.23 (d, *J* = 9.7 Hz), 1.33 m, 1.47 m, 1.68 m, 2.02 m, 2.18 m, 2.25 m (9H, norbornane fragment), 3.34 (d, 1H, *J* = 6,7 Hz, ArCH), 3.56 (d, 1H, *J* = 9.9 Hz, SCH), 4.92 (d, 1H, *J* = 17.6 Hz, CH₂CO), 5.02 (d, 1H, *J* = 17.6 Hz, CH₂CO), 6.94 (d, 1H, *J* = 7.2 Hz, arom.), 7.06 (t, 1H, *J* = 7.7 Hz, arom.), 7.34 (t, 1H, *J* = 7.7 Hz, arom.), 7.41 (brs, 4H, arom.), 7.57 (d, 1H, *J* = 6.7 Hz, arom.), 11.26 (s, 1H, NH), 12.76 (s, 1H, NH). LCMS (ESI) *m/z* 552/554 (96 %, (M+H⁺)). Calcd for C₂₇H₂₃ClN₄O₃S₂: C, 58.85; H, 4.21; N, 10.17; Found: C, 59.00; H, 4.40; N, 10.00.

2-(9-(4'-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-one-6-yl-5)-acetic acid (2-oxo-1,2-dihydro-5-bromoindol-3-ylidene)-hydrazide (IIIr). Yield 78 %, mp. > 250 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.16 m, 1.24 m, 1.34 m, 1.48 m, 1.66 m, 2.03 m, 2.19 m, 2.23 m (9H, norbornane fragment), 3.34 (d, 1H, *J* = 7,1 Hz, ArCH), 3.54 (d, 1H, *J* = 10.3 Hz, SCH), 4.94 (d, 1H, *J* = 16.6 Hz, CH₂CO), 5.02 (d, 1H, *J* = 16.9 Hz, CH₂CO), 6.91 (d, 1H, *J* = 6.9 Hz, arom.), 7.41 (brs, 4H, arom.), 7.47 (d, 1H, *J* = 7.8 Hz, arom.), 7.72 (s, 1H, arom.), 11.47 (s, 1H, NH), 12.69 (s, 1H, NH). LCMS (ESI) *m/z* 629/631/632/633 (98 %, (M+H⁺)). Calcd for

C₂₇H₂₂BrClN₄O₃S₂: C, 51.48; H, 3.52; N, 8.89; Found: C, 51.60; H, 3.70; N, 8.70.

2-(9-(4'-Chlorophenyl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-one-6-yl-5)-acetic acid (2-oxo-1,2-dihydro-5-chloroindol-3-ylidene)-hydrazide (IIIs). Yield 72 %, mp. > 250 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.16 m, 1.24 (d, *J* = 9.7 Hz), 1.34 m, 1.48 m, 1.62 m, 2.03 m, 2.19 (d, *J* = 9.6 Hz), 2.25 m (9H, norbornane fragment), 3.33 (d, 1H, *J* = 7,3 Hz, ArCH), 3.56 (d, 1H, *J* = 10.3 Hz, SCH), 4.98 (m, 2H, CH₂CO), 6.94 (d, 1H, *J* = 8.0 Hz, arom.), 7.33 (d, 1H, *J* = 7.6 Hz, arom.), 7.41 (brs, 4H, arom.), 7.58 (s, 1H, arom.), 11.38 (s, 1H, NH), 12.67 (s, 1H, NH). LCMS (ESI) *m/z* 586/588 (95%, (M+H⁺)). Calcd for C₂₇H₂₂Cl₂N₄O₃S₂: C, 55.39; H, 3.79; N, 9.57; Found: C, 55.60; H, 4.00; N, 9.40.

Pharmacology

Anticancer activity screening. *In vitro* cell line screening of anticancer activity of the synthesized compounds was carried out at the National Cancer Institute within Developmental Therapeutic Program (www.dtp.nci.nih.gov). Anticancer assays were performed according to the US NCI protocol, which was described elsewhere [27–29].

Antitrypanosomal activity screening. Bloodstream forms of *Trypanosoma brucei* (*Tbb*) strain 90-13 were cultured in HMI9 medium supplemented with 10 % FCS at 37 °C in an atmosphere of 5 % CO₂ [30]. In all experiments, log-phase cell cultures were harvested by centrifugation at 3000×g and immediately used. Drug assays were based on the conversion of a redox-sensitive dye (resazurin) to a fluorescent product by viable cells [31]. Drug stock solutions were prepared

in DMSO. *Tbb* bloodstream forms (10^5 cells/mL) were cultured in 96-well plates either in the absence or in the presence of different concentrations of inhibitors in a final volume of 200 μ l. After the 72 h incubation, resazurin solution was added in each well at the final concentration of 45 μ M and fluorescence was measured at 530 nm and 590 nm absorbance after further 4 h incubation. The percentage of inhibition of parasite growth rate was calculated by comparing the fluorescence of parasites maintained in the presence of drug to that in the absence of drug. DMSO was used as a control. Concentration inhibiting 50% of parasite growth (IC_{50}) value was given as the mean \pm the standard deviation of three independent experiments.

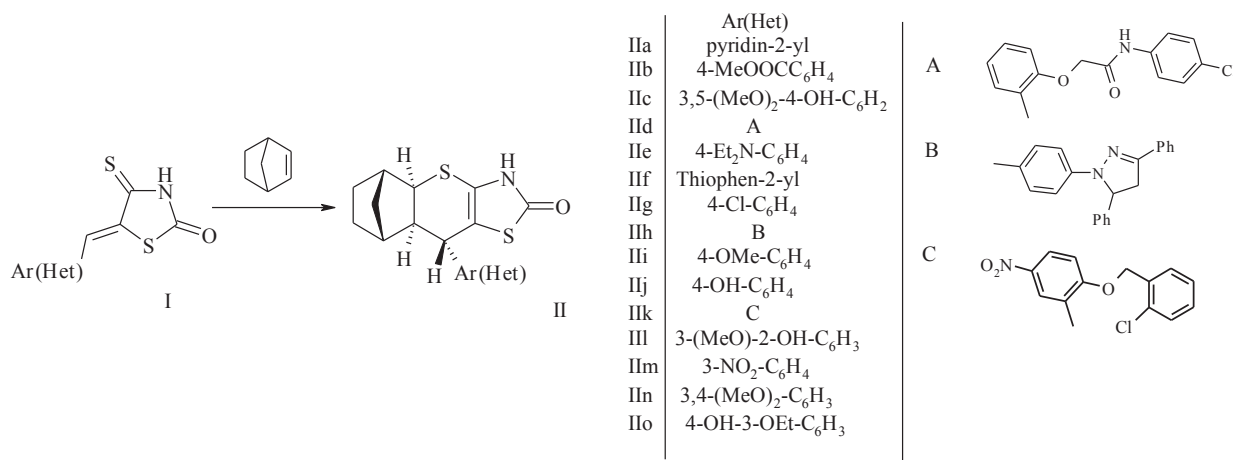
Results and Discussion

Chemistry

An approach to the target compounds synthesis was based on the developed protocol utilizing

5-eneisorhodanines as heterodienes and norbornene as dienophile in the *hetero*-Diels-Alder reaction following our previous findings [1, 2]. This approach was proved to be an efficient regio- and stereoselective tool for the functionalized thiazolothioapyrane core formation [4, 32]. One of the promising directions of thiazolothioapyrane optimization is modification of the C5-fragment of the starting 5-eneisorhodanines [5]. For this purpose different 5-eneisorhodanines with bulky benzylidene fragment and heterocyclic fragments at C5 position, including substances bearing substituted phenolic OH group [33, 34] (Scheme 1), have been used. *Hetero*-Diels-Alder reaction of starting 5-ene-4-thioxothiazolidin-2-ones (**I**) and norbornene led to the target 9-aryl(heteryl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-ones-6 (**II**) with high yields.

Introduction of a variety of substituents at the N3 position of the thiazole ring is another efficient approach to the thiazolothioapyrane core modification in order to obtain new bio-

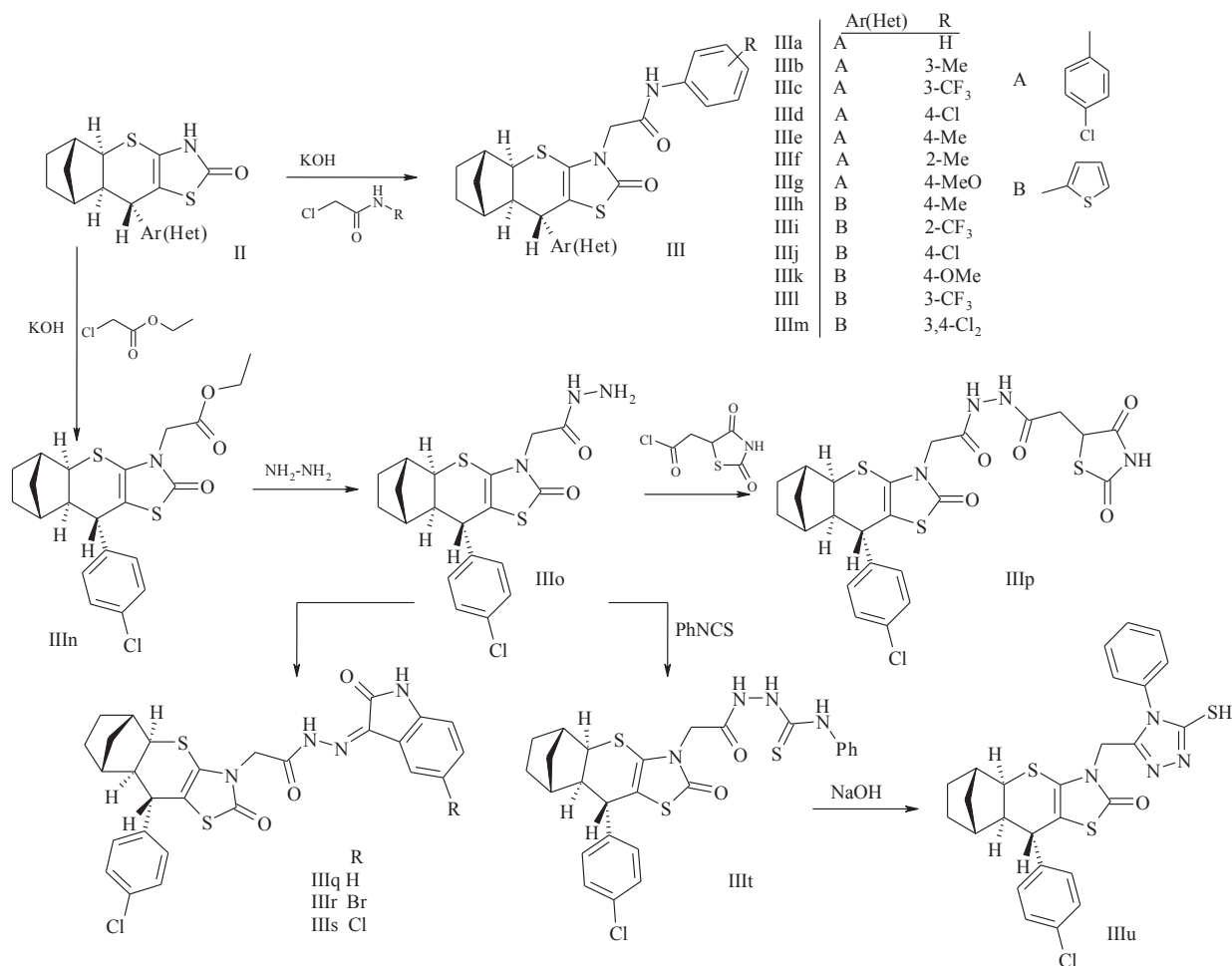


Scheme 1. General scheme of the target 9-aryl(heteryl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-ones-6 (**II**) synthesis

logically active analogues [26, 35]. One more argument in favor of this approach is a decreased toxicity of the *N*-substituted structurally related 4-thiazolidinones [36]. This goal was achieved *via* the alkylation reaction and further modification of the exocyclic functional groups. Synthetic protocol included *in situ* 9-aryl(heteryl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-ones-6 *N*-potassium salts formation. A series of

N-substituted chloroacetamides were used as alkylating agents.

Modification of carboxylic group at N3 of thiazolidinone fragment yielded compounds **IIIo**, **IIIp** and **IIIu**. *N*-(4-Chlorophenyl)-2-(9-(4-chlorophenyl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-one-6-yl-5) acetic acid hydrazide **IIIo** was synthesized in the reaction of appropriate ester **IIIn** with hydrazine hydrate in the ethanol medium. **IIIp**



Scheme 2. General scheme of the *N*-substituted 9-aryl(heteryl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-ones-6 synthesis

was synthesized in acylation reaction of hydrazide **IIIo** by 2,4-thiazolidinedione-5-acetic acid chloride. Compound **IIIu** was obtained based on hydrazide **IIIo** in the reaction with phenylisothiocyanate yielding 4-[9-(4'-chlorophenyl)-6-oxo-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-ene-5-yl]-acetyl-1-phenyl-thiosemicarbazide via known approach. Phenylthiosemicarbazide fragment in the basic medium was cyclized giving compound **IIIu** with 1,3,4-triazole fragment at N5 position of the thiopyranothiazole core. Compounds **IIIq-IIIs** were synthesized in the reaction of hydrazide **IIIo** with isatins in ethanol medium.

The purity and structure of synthesized compounds were confirmed by the analytical and spectral data. ¹H NMR spectra of the synthesized compounds showed classic system of doublets, triplets and multiplets at δ 1.10–3.30 ppm characteristic for norbornane fragment. A signal of the CH-group's proton linked to the aromatic ring shows doublet at δ 3.36–3.98 ppm and is often overlapped with the norbornane proton signals. In the most cases, signal of the N-CH₂-CO group corresponds to two doublets of the diastereotopic methylene protons with the spin-spin coupling constant ~16.0 Hz that is caused by the diastereotopicity of the protons of methylene group. The AMX-system in the form of 3 doublets of doublets is characteristic for CH₂-CH group (compounds **IIIp** and **IIIi**).

Anticancer activity

Compounds **IIb**, **IIIh**, **IIIh** were selected for primary screening on three tumor cell lines: *NCI-H460* (Lung cancer), *MCF7* (Breast cancer), *SF-268* (CNS cancer) at 10⁻⁴M concentra-

tion. These compounds did not show significant growth inhibition of mentioned cancer cell lines. Moreover, the derivative with thiophene ring in the molecule even increased tumor cell growth (data not shown).

The compounds **IIc**, **IIe**, **IIIn** and **IIIu** were evaluated at one dose assay towards approximately 60 cell lines (concentration 10⁻⁵ M). The human tumor cell lines represent all forms of cancer (such as, non-small cell lung cancer, colon cancer, breast cancer, ovarian cancer, leukemia, renal cancer, melanoma, prostate cancer). In the screening protocol, each cell line was inoculated and pre-incubated for 24–48 h on a microtiter plate. Test agents were then added at a single concentration and the culture was incubated for further 48 h. The end point determinations were made with a protein binding dye, sulforhodamine B. The results for each test agent were reported as the percent growth (GP) of the treated cells compared to the untreated control cells. The screening results are shown in Table 1.

All the tested compounds showed rather good growth inhibition levels against Leukemia cell lines. The best growth inhibition results against Leukemia panel were observed for **IIe**: cell lines *CCRF-CEM* (GI = 8.12 %) and *HL-60(TB)* (GI = -44.16 %) and for **IIc** cell lines *CCRF-CEM* (GI = 7.01 %). These data cohere with our previously findings about leukemia selective action of the related thiazolidinones [13]. The latter compound also inhibited Non-small cell lung cancer line *NCI-H522* (GI = 8.12 %). Compound **IIIn** inhibited growth of Leukemia cell lines and showed cytostatic effect on *HCT-15* line of Colon cancer (GI = -100 %). Complication of the basic core with triazole cycle did not influence the

Table 1. Anticancer screening data (one dose assay, 10 μ M).

Comp.	Mean growth. %	Range of growth %	The most sensitive cell lines	GP% of the most sensitive cell lines	Positive cytostatic effect ^a
IIc	82.30	7.01 to 112.94	<i>CCRF-CEM</i> /L <i>HL-60(TB)</i> /L <i>NCI-H522</i> /NscLC <i>HOP-92</i> /NscLC <i>HS 578T</i> /BC <i>HL-60(TB)</i> /L	7.01 53.79 -5.03 40.77 53.61 -44.16	3/56
IIe	89.71	-44.16 to 136.08	<i>CCRF-CEM</i> /L <i>SR</i> /L <i>K-562</i> /L <i>CCRF-CEM</i> /L <i>K-562</i> /L <i>HCT-116</i> /CC <i>HCT-15</i> /CC <i>HT-29</i> /CC <i>SK-MEL-5</i> /M <i>CAKI-1</i> /Rc <i>UO-31</i> /Rc <i>PC-3</i> /PC <i>T-47D</i> /BC <i>SF-295</i> /CNSC <i>IGROV1</i> /OC <i>UO-31</i> /Rc <i>MCF7</i> /BC	8.12 37.85 52.77 13.40 29.06 38.78 -100.00 50.49 41.34 22.75 50.33 42.85 38.85 33.33 50.21 29.35 46.73	3/57
IIIa	63.53	-100.00 to 92.68			8/59
IIIu	77.84	29.35 to 116.31			3/59

^a Ratio between number of cell lines with percent growth from 0 to 50 and total number of cell lines.

L – Leukemia; NscLC- Non-Small Cell Lung Cancer; BC – Breast cancer; CC – Colon Cancer; OC – Ovarian Cancer; RC – Renal Cancer; M – Melanoma; CNSC – CNS Cancer

activity level, so **IIIu** showed only moderate anti-tumor activity with the best GI against renal cancer cell line *UO-31* (GI = 29.35 %).

Finally, the compounds **IIIa** and **IIIu** were selected for an advanced assay against a panel of approximately sixty tumor cell lines at 10-fold dilutions of five concentrations (0.01–100 μ M). Additionally, compounds **IIa**, **IId**, **IIIc**, **IIIg**, were involved into the study without prescreening. The percentage of growth was evaluated spectrophotometrically versus

controls not treated with test agents after 48-h exposure and using SRB protein assay to estimate cell viability or growth. The dose-response parameters were calculated for each cell line: GI₅₀ – molar concentration of the compound that inhibits 50 % net cell growth; TGI – molar concentration of the compound leading to the total inhibition; and LC₅₀ – molar concentration of the compound leading to 50 % net cell death. Furthermore, a mean graph midpoints (MG_MID) were calculated

for GI_{50} , giving an average activity parameter over all cell lines for the tested compound. The meanings of the GI_{50} at the range of concentrations for the tested compounds are given in the table 2. Compound **IIa** with pyridine fragment at the C9 position and unsubstituted N5 position didn't show significant levels of $\log GI_{50}$ (from -4.00 to -4.48) and was the less active compound among tested. Better results were observed for the compounds bearing *p*-Cl-phenyl fragment at the C9. Compound **IIIg** selectively inhibited growth of Leukemia cell lines with the best $\log GI_{50}$ level of -5.36

against SR line. Derivatives **IIIId** and **IIIu** showed significant cytostatic effects towards all tested cell lines with the MID of -4.98 and -5.09 respectively. Though, the ester **IIIIn**, in general, did not inhibit the cancer cell lines' growth, except some Leukemia lines: HL-60(TB) ($\log GI_{50} = -5.06$) and RPMI-8226 ($\log GI_{50} = -4.81$). The highest cytostatic effect was observed for the compound **IIId**, which selectively inhibited Leukemia cell lines at submicromolar concentrations: $\log GI_{50} = -6.03$ (HL-60(TB) line), $\log GI_{50} = -7.37$ (SR line), $\log GI_{50} < -8.00$ (MOLT-4 line).

Table 2. Total values of the in-depth *in vitro* anticancer activity screening in 5 concentrations (10^{-4} – 10^{-8} M).

Cancer cell lines	Concentration of the compound that inhibits 50 % net cell growth, $\log GI_{50}$					
	IIa	IIId*	IIIg	IIIId	IIIu	IIIIn
Leukemia						
CCRF-CEM	ND	ND/-4.20	-4.03	-5.35	-5.48	-4.11
HL-60(TB)	-4.44	-6.03 /-4.60	-4.26	-5.23	-4.86	-5.06
K-562	-4.43	-4.57/-4.38	-4.50	-5.52	-5.32	>-4.00
MOLT-4	-4.48	<-8.00 /-4.55	-4.46	-5.23	-5.25	>-4.00
RPMI-8226	-4.19	-4.61/-4.24	-4.49	-5.50	-5.30	-4.81
SR	-4.30	-7.37 /-4.72	-5.36	-5.72	-5.48	>-4.00
NSC lung cancer						
A549/ATCC	-4.18	-4.16/-4.26	>-4.00	-4.67	-5.04	-4.08
EKVX	>-4.00	-4.51/-4.10	>-4.00	-4.75	-5.27	>-4.00
HOP-62	ND	ND>/-4.00	>-4.00	-4.91	-4.70	>-4.00
HOP-92	-4.21	-4.76/-4.59	-4.99	-5.36	-5.21	-4.42
NCI-H226	>-4.00	>-4.00/>-4.00	>-4.00	-4.71	-5.02	>-4.00
NCI-H23	>-4.00	>-4.00>-4.00	>-4.00	-5.35	-5.04	-4.20
NCI-H322M	>-4.00	>-4.00/-4.47	>-4.00	-5.45	-4.92	>-4.00
NCI-H522	>-4.00	-4.29/-4.44	>-4.00	-5.45	ND	-4.21
NCI-H460	-4.12	-4.18/-4.06	ND	-4.86	-5.28	-4.21
Colon cancer						
COLO 205	-4.08	>-4.00/-4.55	>-4.00	-5.22	-4.83	-4.03
HCC-2998	>-4.00	>-4.00/>-4.00	ND	ND	-5.17	ND
HCT-116	-4.24	-4.43/-4.39	-4.78	-5.67	-5.05	-4.42
HCT-15	-4.21	-4.21/-4.17	>-4.00	-4.83	-5.11	>-4.00
HT29	-4.34	-4.04/-4.07	-4.21	-5.58	-4.91	-4.32
KM12	>-4.00	-4.07/-4.37	>-4.00	-5.29	-5.09	-4.14
SW-620	>-4.00	>-4.00/>-4.00	>-4.00	-5.30	-4.86	>-4.00

CNS cancer						
<i>SF-268</i>	>-4.00	>-4.00/-4.26	>-4.00	-4.56	-4.99	>-4.00
<i>SF-295</i>	-4.08	>-4.00/-4.16	>-4.00	-5.19	-5.47	-4.08
<i>SF-539</i>	>-4.00	>-4.00/>-4.00	>-4.00	-5.33	-5.09	>-4.00
<i>SNB-19</i>	>-4.00	>-4.00/>-4.00	>-4.00	-4.99	-4.87	>-4.00
<i>SNB-75</i>	-4.44	-4.18/-4.53	-4.07	>-4.00	-5.33	-4.27
<i>U251</i>	-4.05	-4.25/-4.15	>-4.00	-4.84	-5.26	>-4.00
Melanoma						
<i>LOXIMVI</i>	-4.14	-4.04/>-4.00	>-4.00	-5.28	-4.98	-4.18
<i>MALME-3M</i>	>-4.00	>-4.00/-4.33	>-4.00	>-4.00	-4.74	-4.17
<i>M14</i>	ND	ND/-4.07	-4.36	-5.52	ND	>-4.00
<i>MDA-MB-435</i>	>-4.00	>-4.00/-4.17	>-4.00	-5.40	-5.24	>-4.00
<i>SK-MEL-2</i>	>-4.00	>-4.00/>-4.00	>-4.00	-4.34	-4.94	>-4.00
<i>SK-MEL-28</i>	-4.37	>-4.00/>-4.00	>-4.00	-4.89	-4.99	-4.77
<i>SK-MEL-5</i>	-4.47	-4.37/>-4.00	>-4.00	-4.98	-5.30	-4.47
<i>UACC-257</i>	>-4.00	>-4.00/>-4.00	>-4.00	-4.32	-4.92	-4.13
<i>UACC-62</i>	-4.28	-4.26/-4.27	>-4.00	-5.36	-5.65	>-4.00
Ovarian Cancer						
<i>IGROVI</i>	>-4.00	>-4.00/-4.69	>-4.00	-5.05	-4.95	>-4.00
<i>OVCAR-3</i>	-4.15	>-4.00/-4.35	>-4.00	-4.47	-4.92	>-4.00
<i>OVCAR-4</i>	-4.34	>-4.00/-4.26	-4.33	-4.37	-5.09	-4.40
<i>OVCAR-5</i>	>-4.00	>-4.00/>-4.00	-4.63	-5.91	-4.66	>-4.00
<i>OVCAR-8</i>	>-4.00	>-4.00/>-4.00	>-4.00	-4.52	-4.76	>-4.00
<i>NCI/ADR-RES</i>	>-4.00	>-4.00/>-4.00	-4.20	-4.99	-4.94	-4.20
<i>SK-OV-3</i>	>-4.00	>-4.00/>-4.00	>-4.00	>-4.00	-4.70	>-4.00
Renal Cancer						
<i>786-0</i>	>-4.00	>-4.00/>-4.00	>-4.00	-5.12	-5.19	>-4.00
<i>A498</i>	>-4.00	>-4.00/>-4.00	>-4.00	-4.01	-5.03	>-4.00
<i>ACHN</i>	-4.10	>-4.00/>-4.00	>-4.00	-4.88	-4.85	>-4.00
<i>CAKI-1</i>	-4.14	>-4.00/-4.32	>-4.00	-4.72	-5.42	>-4.00
<i>RXF 393</i>	ND	-4.34/-4.13	>-4.00	-4.43	-5.72	-4.09
<i>SN12C</i>	>-4.00	>-4.00/-4.12	>-4.00	-4.99	-5.32	>-4.00
<i>TK-10</i>	-4.12	>-4.00/-4.23	>-4.00	-5.57	-4.57	>-4.00
<i>UO-31</i>	-4.28	-4.00/-4.35	>-4.00	-4.63	-5.13	>-4.00
Breast Cancer						
<i>MCF7</i>	-4.08	-4.09/>-4.00	>-4.00	-4.93	-5.30	-4.13
<i>MDA-MB-231/ATCC</i>	-4.07	-4.49/-4.53	-4.69	-5.66	-4.92	>-4.00
<i>HS 578T</i>	-4.17	>-4.00/>-4.00	>-4.00	>-4.00	-4.96	-4.24
<i>BT-549</i>	-4.25	>-4.00/>-4.00	>-4.00	-4.72	-5.34	-4.10
	-4.15	-4.04/-5.10	>-4.00	-4.82	-5.16	-4.42
Prostate Cancer						
<i>PC-3</i>	-4.06	-4.55/-4.56	-4.71	-5.15	-5.43	ND
<i>DU-145</i>	-4.03	-4.64/>-4.00	ND	ND	-4.82	>-4.00
Quantity of the “sensitive lines”^a	33/56 (59%)	25/56/36/59 (45%)/(61%)	16/57 (28%)	53/57 (93%)	57/57 (100%)	26/57 (46%)

* data of two independent studies; ND – not investigated

^a s/t – ratio of sensitive lines ($\log GI_{50} < -4.00$) to the total number of tested lines.

COMPARE analysis

The obtained results of the tested compounds' antitumor activity led us to establishing a possible mode of their action. For this purpose COMPARE analysis was performed. NCI's COMPARE algorithm [37, 38] allows establishing possible biochemical mechanisms of action of the novel compounds on the basis of their *in vitro* activity profiles when comparing with those of standard agents. We performed COMPARE computations for the compounds **IIa**, **IIc**, **IId**, **IIE**, **IIId**, **IIIg**, **IIIn**, and **IIIU** against the NCI "Standard Agents" database at the GI₅₀ level (Table 3).

Unfortunately, the calculated Pearson correlation coefficients (PCC) did not indicate cytotoxicity mechanisms of the tested compounds with high probability. The highest correlation at the GI₅₀ level was observed for the compound **IId** (PCC = 0.661) with alkylating agent fluorodopan. Interestingly, other 4-azolidinone derivatives also have significant value of correlation coefficients to the above-mentioned substance [26, 39–40]. Pearson correlation coefficients exceeding 0.6 were

also calculated for the **IIId** (PCC = 0.631) with hydroquinone ansamycin antibiotic macbecin II, and for **IIE** (PCC = 0.603) with hydroxyurea which is the ribonucleotide reductase inhibitor and belongs to the class of antimetabolites. Probably, the PCC < 0.5 for the hit-compound **IIIU** indicates other molecular mechanisms underlying its anticancer effect.

Antitrypanosomal activity

Antitrypanosomal activity of a series of 9-aryl(hetaryl)-3,7-dithia-5-azatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradecen-4(8)-ones and N-substituted analogues was evaluated in the *in vitro* assay against *Trypanosoma brucei brucei*. All compounds were first tested at a range of concentrations. IC₅₀ values were further derived from the dose-response curves.

Most of the tested compounds showed moderate trypanocidal activity at micromolar range of concentrations. Though, some substituents in the 9th position of the main scaffold increased the activity, e.g. ether moiety with the nitrophenyl fragment in **IIk** (IC₅₀ =

Table 3. COMPARE analysis results

Comp.	PCC	Target	Mode of action ^a
IIa	0.482	thalicarpine	p-glycoprotein inhibitor, arrests cancer cells at the G2/M and G1 phase
IIc	0.584	fluorodopan	alkylating agent
IId	0.661	fluorodopan	alkylating agent
IIE	0.603	hydroxyurea	ribonucleotide reductase inhibitor
IIId	0.631	macbecin II	antitumor antibiotic
IIIg	0.538	CCNU	alkylating agent
IIIn	0.45	trimethyltrimethylolmelamin	-
IIIU	0.499	methyl-CCNU	alkylating agent

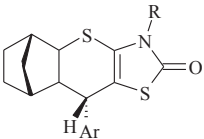
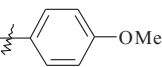
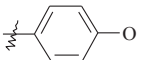
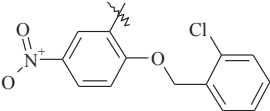
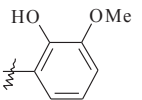
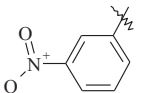
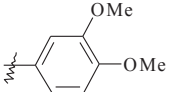
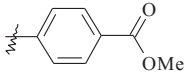
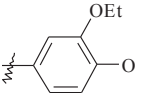
^a Putative mechanisms of action were identified with the use of literature sources; PCC – Pearson correlation coefficients

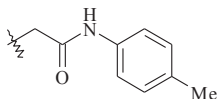
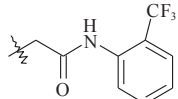

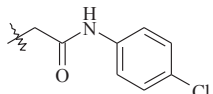
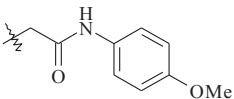
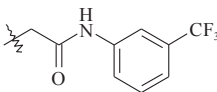
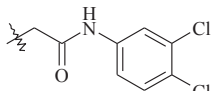
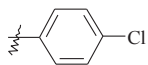
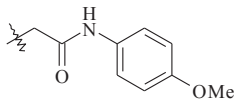
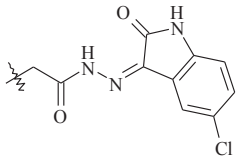
4.17 μM) or *p*-chlorophenyl substituent in **IIg** ($\text{IC}_{50} = 3.72 \mu\text{M}$). *p*-Oxomethyl- (**IIf**) and *p*-oxophenyl (**IIj**) substituents negatively influence trypanocidal properties.

Anticancer activity levels were also low for these compounds, but they were highly active towards selected cancer cell lines (**IIf**:

$\log \text{GI}_{50} = -7.01$ melanoma SK-MEL-2; **IIj**: $\log \text{GI}_{50} = <-8.00$ renal cancer RXF-393). An interesting situation was observed for the compounds **IIf** with thiophene fragment, introduction of which led to the significant antitrypanosomal activity decrease; whilst its N-substituted derivatives inhibited the para-

Table 4. IC_{50} values against *Trypanosoma brucei brucei*

Compound			$\text{IC}_{50}, \mu\text{M}$
	Ar	R	
IIi		H	21.99
IIj		H	20.52
IIk		H	4.17
III		H	22.68
IIIm		H	23.45
IIIn		H	20.24
IIb		H	14.46
IIo		H	17.84

IIf		H	53.81
IIIh			7.47
IIIi			6.31
IIIj			7.16
IIIk			4.13
IIIl			7.65
IIIm			7.64
IIg		H	3.72
IIIg			3.9
IIIs			13.32

site growth at the concentrations 10 times lower.

Comparing anticancer profile of the tested compounds, it is worth to mention that **IIg** selectively inhibited growth of the Leukemia cell lines ($\log GI_{50} = -5.16, -5.59$) as well as its *N*-substituted derivative **IIIg**; and both have shown trypanocidal effects.

Conclusions

A series of novel thiopyranthiazole derivatives were synthesized and their anticancer activity was investigated. Being moderately active towards approximately 60 tumor cell lines, all tested compounds showed rather good growth inhibition against Leukemia cell lines. Chemical structures of the identified hit-com-

pounds **II**d and **III**u indicate that the presence of the arylidene and heterocyclic fragments in the basic system enhances the antitumor effect of such compounds. To establish possible biochemical mechanisms of the action of novel compounds the COMPARE analysis was performed showing correlation at the GI₅₀ level for **II**d (PCC = 0.661) with alkylating agent fluorodopan. A number of 9-aryl(heteryl)-3,7-dithia-5-azatetracyclo-[9.2.1.0^{2,10}.0^{4,8}]-tetradecen-4(8)-ones were tested *in vitro* against *Trypanosoma brucei brucei*. Thiopyranothiazoles with different arylidene fragments in the N5 position showed higher inhibition level than their *N*-unsubstituted analogues. Interesting is dual antitumor and antitrypanosomal effect observed for some compounds that may be used for establishing molecular modes of action for this class of compounds.

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Вивчення протиракової та протипаразитарної активності тіопірано[2,3-*d*]тіазолів з норборнановим фрагментом

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Мета. Вивчення протипухлинної та трипаноцидної активності серії нових тіопірано[2,3-*d*]тіазолів з норборнановим фрагментом у молекулах. **Методи:** органічний синтез, аналітичні та спектральні методи, фар-

макологічний скринінг, COMPARE та SAR аналізи. **Результати.** З метою одержання сполук з відповідним фармакологічним профілем синтезовано нові конденсовані похідні тіопірано[2,3-*d*]тіазолу з норборнановим фрагментом у молекулах, які модифіковані за положеннями С9 та N5 базового гетероциклу. Ідентифіковано ряд сполук з суттєвим рівнем інгібування росту ракових клітин, серед яких сполука-хіт N^1 -(4-хлорофеніл)-2-{2-[6-оксо-5,9-дитіа-7-азатетрацикло[9.2.1.0^{2,10}.0^{4,8}]тетрадец-4(8)-ен-3-іл]фенокси}ацетамід **II**_d, що селективно інгібує лінії клітин лейкемії в субмікромольних концентраціях. Крім того, ряд тіопірано[2,3-*d*]тіазолів також проявляють перспективну протитрипаносомну активність. **Висновки.** Синтезовано нові тіопірано[2,3-*d*]тіазоли з норборнановим фрагментом у молекулах а також їх похідні з різноманітними субституентами в положеннях N5 та С9 базової гетероциклічної системи. Сполуки проявили суттєвий рівень протипухлинної активності і можуть бути використані для подальшої оптимізації структури як потенційні протиракові агенти. Окрім того, сполуки з високим рівнем протипухлинного ефекту *in vitro* інгібують ріст *Trypanosoma brucei brucei*. Поєднання протиракової та протитрипаносомної активності синтезованих сполук є основою для наступної структурної модифікації та пошуку імовірних механізмів реалізації їх біологічної активності.

Ключові слова: тіопірано[2,3-*d*]тіазоли, норборнан, синтез, протиракова активність, протитрипаносомна активність, SAR.

Изучение противораковой и протипаразитарной активности тиопирано[2,3-*d*]тиазолов из норборнановым фрагментом

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Цель. Изучение противоопухолевой и трипаноцидной активности серии новых тиопирано[2,3-*d*]тиазолов из норборнановым фрагментом в молекулах. **Методы:** органический синтез, аналитические и спектральные методы, фармакологический скрининг, COMPARE и SAR анализы. **Результаты.** С целью получения соединений с соответствующим фармакологическим профилем синтезированы новые производные тиопира-

но[2,3-*d*]тиазола из норборнановым фрагментом в молекулах, которые модифицированы по положениях С9 и N5 базового гетероцикла. Идентифицировано ряд соединений с существенным уровнем ингибирования роста раковых клеток, среди которых соединение-хит *N*¹-(4-хлорфенил)-2-{2-[6-оксо-5,9-дитиа-7-азатетрацикло[9.2.1.0^{2,10}.0^{4,8}]тетрадец-4(8)-ен-3-ил]фенокси}ацетамид **Пд**, который селективно ингибирует линии клеток лейкемии в субмикромольных концентрациях. Кроме того, некоторые тиопирано[2,3-*d*]тиазолы также проявляют перспективную протитрипаносомную активность. **Выводы.** Синтезированы новые тиопирано[2,3-*d*]тиазолы из норборнановым фрагментом у молекулах, а также их производные из различными заместителями в положениях N5 и С9 базовой гетероциклической системы. Соединения проявили

существенный уровень противоопухолевой активности и могут быть использованы для дальнейшей структурной оптимизации как потенциальные противораковые агенты. Кроме того, соединения с высоким уровнем противоопухолевого эффекта *in vitro* ингибируют рост *Trypanosoma brucei brucei*. Сочетание противораковой и противотрипаносомной активности синтезированных соединений может быть основой для дальнейшей оптимизации структуры и поиска возможных механизмов реализации их биологической активности.

Ключевые слова: тиопирано[2,3-*d*]тиазолы, норборнан, синтез, противораковая активность, противотрипаносомная активность, SAR.

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