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Synthesis and anticancer activity of novel thiopyrano[2,3-*d*]thiazole-based compounds containing norbornane moiety

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The series of 9,14-disubstituted 3,7-dithia-5,14-diazapentacyclo[9.5.1.$0^{2,10}$.$0^{4,8}$.$0^{12,16}$]heptadecen-4(8)-triones-6, 13, 15 were synthesized using *hetero*-Diels-Alder reactions starting from 4-thioxo-2-thiazolidinones and 5-norbornene-2,3-dicarboxylic acid imido-derivatives. Screening of anticancer activity *in vitro* yielded the most active compounds **5c, 5d,** and **7b** in micromolar concentrations at the GI_{50} level ($LogGI_{50}$ is −6.40 to −4.02 for different cell lines, $LogGI_{50}$ mean graph midpoint varies from −4.67 to −4.05); moreover, compounds **5c** and **5d** have a distinctive selectivity against leukemia. The highest sensitivity to compound **5d** showed leukemia cell lines CCRF-CEM ($LogGI_{50} = -6.40$) and SR ($LogGI_{50} = -6.06$).

Keywords: 4-thioxo-2-thiazolidones; thiopyrano[2,3-*d*]thiazole derivatives; hetero-Diels-Alder reaction; anticancer activity in-vitro; 5-norbornene-2,3-dicarboxylic acid imides

1. Introduction

Thiazolidine scaffold is a powerful biophore fragment used in the rational design of 'drug-like' compounds as innovative drugs prototypes. Current research in the area of pharmacological potential of 4-thiazolidinone derivatives, a well-known group of biologically active compounds, allowed us to identify the anticancer activity of some 4-thiazolidinone derivatives that possessed low acute toxicity and cytotoxicity (*1–5*). Data have been published that prove the affinity of such derivatives to biological targets involved in the biochemical processes of tumor cell growth (antiapoptic proteins complex Bcl-X_L-BH3, PPARγ receptors, TNFα-TNFRc-1 complex etc) (*6–8*).

Biological studies of thiopyrano[2,3-*d*]thiazole derivatives, which mimic some biophore fragments of 5-ylidene-4-thiazolidinones, allowed us to confirm our previous hypothesis about development of pharmacological activity of the mentioned heterocyclic systems, and this served as a basis for the synthesis of compounds rows with high biological potential (*4, 9, 10*) (Scheme 1).

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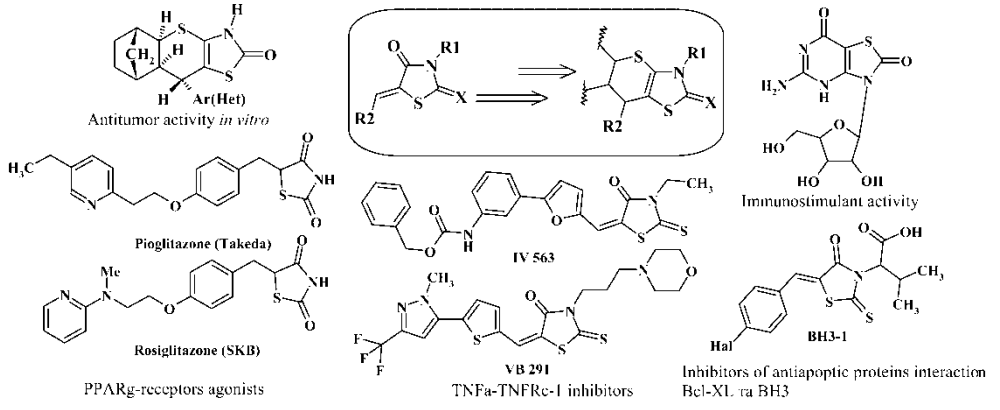


Scheme 1. Biologically active thiazolidinone derivatives.

Our previous research of antioxidant activity for these heterocyclic compounds identified thiopyrano[2,3-*d*]thiazole-2-one as a prospective scaffold in the search for novel antioxidants; moreover, a few hit-compounds were identified that had significant antioxidant activity, comparable with and higher than that of tocopherol (*11*).

Antioxidant systems play a huge role in different pathological processes. Earlier it was found that the administration of a mixture of well-known antioxidants, vitamin E and α-lipoic acid, to children living in the area of the Chernobyl nuclear accident significantly and synergistically suppressed leukocyte oxygen radical overproduction (*12*). Several contemporary studies seem to suggest the inhibitory effects of vitamin E on human prostate cancer and on the growth of some other tumors. Supplementation of various antioxidants (including ascorbic acid, α-lipoic acid, N-acetylcysteine (NAC) reduced glutathione, and vitamin E) causes a decrease in reactive oxygen species production in cancer patients (*13*). All these facts show a deep correlation between anticancer and antioxidant properties of molecules (*14*) and could motivate an investigation into the potential anticancer effect of compound rows that possess significant antioxidant activity.

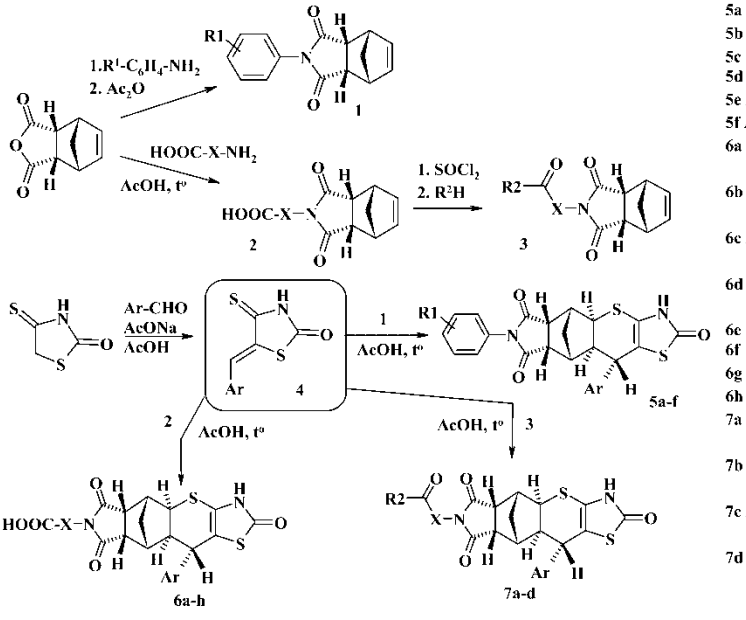
2. Results and discussion

Our synthetic investigation included studies of *hetero*-Diels-Alder reaction using the rows of 5-norbornene-2,3-dicarboxylic acid imides as dienophiles and aryl(hetaryl)idene-4-thioxo-2-thiazolidinones as heterodienes.

4-Thioxo-2-thiazolidinone (isorhodanine) has a convenient combination of active 4-thioxo- and 5-methylene-groups for building up fused heterocycles. Starting 5-ylidene-4-thioxo-2-thiazolidinones **(4)** were synthesized using isorhodanine according to Knoevenagel (medium – glacial acetic acid, catalyst – fused sodium acetate). Combination of highly reactive sulfur atom at the 4-position and methylidene group in position 5 in 5-ylideneisorhodanines allows them to be used as highly active heterodiene components in *hetero*-Diels-Alder reactions (*15–19*).

5-Norbornene-2,3-dicarboxylic acid derivatives **1** and **2**, which were used for the first time in the Diels–Alder reaction with the above-mentioned heterodienes, have been obtained starting from 5-norbornene-2,3-dicarboxylic acid anhydride (endic anhydride) and appropriate amine component, namely the row of aromatic amines and different amino acids (*20*). The esters and amides **3** of amino acids **2** have been obtained via consequent treatment of an appropriate alcohol or amine with $SOCl_2$ in the presence of triethylamine according to standard procedure.

We established that the optimal conditions for the *hetero*-Diels-Alder reaction were a medium of glacial acetic acid and a catalytic amount of hydroquinone, as a side polymerization reaction inhibitor. Such an approach allowed us to obtain the series of pentacyclic fused heterosystem derivatives **5a–f, 6a–h,** and **7a–d** with high yields, which contain thiopyrano[2,3-*d*]thiazol-2-one fragment – 3,7-dithia-5,14-diazapentacyclo[9.5.1.$0^{2,10}$.$0^{4,8}$.$0^{12,16}$]heptadecene (Scheme 2).



5a Ar = 3,4-$(OMe)_2$-C_6H_3, R^1 = 4-Cl;
5b Ar = 4-Cl-C_6H_4, R^1 = 4-COOEt;
5c Ar = 3-Pyr, R^1 = 4-Cl;
5d Ar 4-OH-C_6H_4, R^1 3-CF_3;
5e Ar = 3-Pyr, R^1 = 3-CF_3;
5f Ar 4-F-C_6H_4, R^1 4-F;
6a A r=3,4-$(OMe)_2$-C_6H_3,
X = *i*-$PrCH_2CH$;
6b Ar = 3-OMe-4-OH-C_6H_3,
X = *i*-$PrCH_2CH$;
6c Ar = 3,4-$(OMe)_2$-C_6H_3,
X = $(CH_2)_3$;
6d Ar = 3-OMe-4-OH-C_6H_3,
X = $(CH_2)_5$;
6e Ar = 3-Pyridynyl, X = *i*-PrCH;
6f Ar 3-Pyridynyl, X CH_2;
6g Ar = 2-Thiophenyl, X = $(CH_2)_3$;
6h Ar – 4-Cl-C_6H_4, X –$(CH_2)_5$;
7a Ar = 3,4-$(OMe)_2$-C_6H_3,
X = CH_2, R^2 = OMe;
7b Ar = 3,4-$(OMe)_2$-C_6H_3,
X = CH_2, R^2 = OEt;
7c Ar 3,4-$(OMe)_2$-C_6H_3,
X – CH_2, R^2 – NHPh;
7d Ar = 3-Pyr, X = CH_2,
R^2 Morpholinyl

Scheme 2. Synthesis of 3,7-dithia-5,14-diazapentacyclo[9.5.1.$0^{2,10}$.$0^{4,8}$.$0^{12,16}$]heptadecenes.

The structures of all newly synthesized compounds were confirmed by elemental analyses, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectra showed that only one stereoisomer was present for all products, indicating that the reaction was stereoselective. The ^{1}H NMR spectra showed multiplets of the norbornane fragment in the 1.10–1.30 ppm region, signal from the CH group connected with the aromatic ring shows up as a doublet in the 3.36–3.98 region, which often overlays signals from the norbornane fragment. The absence of signal doubling in ^{1}H NMR spectra could confirm the only one stereoisomer in compounds. Taking into account a previously studied stereochemical configuration of analogue derivatives (9-substituted-3,7-dithia-5-azatetracyclo[9.2.1.$0^{2,10}$.$0^{4,8}$]tetradecene-4(8)-ones-6 (4) and starting dienophiles – N-substituted bicyclo[2.2.1]hept-5-ene-2,3-dicarboximides (*20*)), to our knowledge obtained substances exist as sole stereoisomers that are depicted in Scheme 2.

3. Evaluation of anticancer activity *in vitro*

Some new thiopyrano[2,3-*d*]thiazol-2-one fused derivatives **(5a,b, 6b, 7a–c)** were submitted and evaluated against the three human tumor cell lines panel, consisting of NCI-H460 (non-small cell lung cancer), MCF7 (breast cancer), and SF-268 (CNS cancer) cell lines. Primary anticancer assays were performed according to the US NCI protocol, and described elsewhere (*21–23*). The compounds were added at a single concentration and the cell culture was incubated for 48 h. End point determinations were made with a protein binding dye, sulforhodamine B. The results for

Table 1. Anticancer screening data at three cancer cell lines assay.

Compd.	NSC (NCI code)	Three cell lines assay[a] A	B	C	Active (selected for five-dose 60 cell lines assay)
5a	728381	97	123	103	N
5b	731880	36	85	67	N
6b	731913	130	111	131	N
7a	731900	128	106	117	N
7b	733599	8	22	30	Y
7c	731884	53	73	65	N

[a]Cancer cell lines: A-NCI-H460 (lung cancer); B-SF-268 (CNS Cancer); C-MCF7 (breast cancer).

each compound are reported as the percent growth of treated cells when compared with untreated control cells. The substance **7b,** which reduced the growth of the cell lines to 32% or less was passed on for evaluation in the full panel of 60 human tumor cell lines. The results for each compound are reported (Table 1) as the percent growth of treated cells when compared with untreated control cells accordingly for the following human tumor cell lines: (A) NCI-H460 (lung cancer), (B) SF-268 (CNS cancer), and (C) MCF7 (breast cancer).

Because of ongoing changes in screening strategy and policy, a part of the compounds was tested primarily at single concentration of 10^{-5} M against the full panel of 57 cancer cell lines. However, none of these compounds possessed considerable activity and none of them was selected for an advanced assay against a full panel (approximately 60 cell lines) at five concentrations. The results of this screening are presented in Table 2.

Finally, the previously selected compound **7b**, as well as compounds **5c,d, 6c–e,i, 7d** without the preliminary pre-screening stage were tested *in vitro* against a full panel of about 60 tumor cell lines. The human tumor cell lines were derived from nine different cancer types: Leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers and used at 10-fold dilutions of five concentrations (100, 10, 1, 0.1 and 0.01 μM) (*21–23*). Based on the cytotoxicity assays, three antitumor activity dose-response parameters were calculated for each experimental agent against each cell line: GI_{50}, molar concentration of the compound that inhibits 50% net cell growth; TGI, molar concentration of the compound leading to total inhibition; and LC_{50}, molar concentration of the compound leading to 50% net cell death. Values were calculated for each of these parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the value was expressed as greater or less than the maximum or minimum concentration tested. Furthermore mean graph midpoints (MG_MID) were calculated for each of the parameters, giving an average activity parameter over all cell lines for each compound. For

Table 2. Anticancer screening data at 60 cancer cell lines assay in concentration 10^{-5}M.

Compd.	NSC (NCI code)	57 cell lines assay at one concentration 10^{-5}M: Mean Growth %	The most sensitive cell line	growth % of the most sensitive cell line	Active (selected for five-dose 60 cell lines assay)
5e	741027	97.55	UACC-62 (Melanoma)	57.66	N
5f	740930	92.60	HS 578T (Breast Cancer)	−9.29	N
6a	741022	102.94	NCI-H522 (NSC Lung Cancer)	79.81	N
6f	741059	98.46	CAKI-1 (Renal Cancer)	49.87	N
6h	741011	94.00	HS-578T (Breast Cancer)	−10.92	N

Table 3. Summary of anticancer screening data at 60 cancer cell lines dose-dependent assay.

Compd.	NSC (NCI code)	N[a]	Log GI_{50}			Log TGI			Log LC_{50}		
			N1[b]	Range	MG_MID	N2[b]	Range	MG_MID	N3[b]	Range	MG_MID
5c	**740757**	**57**	**12**	**−4.58 to −4.00**	**−4.05**	**0**	**–**	**−4.0**	**0**	**–**	**−4.0**
5d	**740763**	**59**	**59**	**−6.40 to −4.22**	**−4.67**	**51**	**−5.41 to −4.10**	**−4.28**	**22**	**−4.25** to **−4.02**	**−4.03**
6c	735692	56	0	–	−4.0	0	–	−4.0	0	–	−4.0
6d	735690	56	0	–	−4.0	0	–	−4.0	0	–	−4.0
6e	740758	57	2	−4.66 to −4.03	−4.01	0	–	−4.0	0	–	−4.0
6i	735691	56	1	−4.36	−4.01	0	–	−4.0	0	–	−4.0
7b	**733599**	**55**	**49**	**−4.75 to −4.02**	**−4.43**	**29**	**−4.44 to −4.01**	**−4.15**	**10**	**−4.15 to −4.01**	**−4.01**
7d	740755	59	0	–	−4.0	0	–	−4.0	0	–	−4.0

[a]N – Number of human tumor cell lines tested at the second stage assay.
[b]N1, N2, N3 – number of sensitive cell lines, against which the compound possessed considerable growth inhibition according to mentioned parameter (Parameter Log < -4.00).
[c]The most active substances are marked in bold.

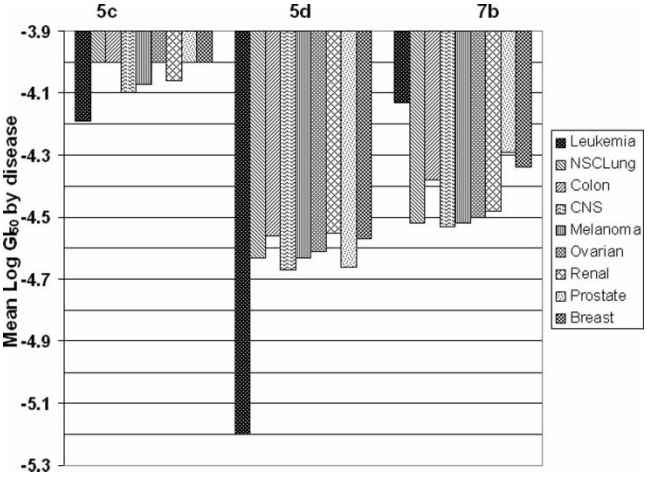


Figure 1. Anticancer selectivity pattern of the most active compounds **5c**, **5d** and **7b**.

the calculation of the MG_MID, insensitive cell lines are included with the highest concentration tested. The results of full panel screening at five concentrations are summarized in Table 3.

Compounds **5d** and **7b** showed the highest cytotoxicity against human tumor cell lines. Selectivity pattern analysis of cell lines by disease origin can definitely affirm selective action of compounds **5c** and **5d** on leukemia cell lines. One should note that the highest sensitivity to compound **5d** showed leukemia cell lines CCRF-CEM (Log $GI_{50} = -6.40$) and SR (Log $GI_{50} = -6.06$). Compound **7b** possessed considerable activity level; however, there was no observed clear-cut selectivity pattern for it. Selectivity to cell lines of certain disease types presented as mean values of parameter $LogGI_{50}$ by disease as depicted in Figure 1.

4. Conclusions

Preparative method of synthesis of novel 3,7-dithia-5,14-diazapenta-cyclo[9.5.1.$0^{2,10}$.$0^{4,8}$.$0^{12,16}$] heptadecene derivatives have been worked out. Anticancer activity studies of synthesized substances revealed that the highest antitumor activity is possessed by compounds **5d** and **7b**. Compound **5d** showed a distinctive pattern of selective action against leukemia cell lines.

5. Experimental

All starting materials were purchased from Merck, Sigma-Aldrich or Lancaster and used without purification. Melting points are uncorrected and were measured in open capillary tubes on Buchi B-545 melting point apparatus. The ^{1}H-NMR spectra were recorded on Varian Gemini 300 MHz and ^{13}C NMR spectra on Varian Gemini 100 Hz in DMSO-d_6 or DMSO-d_6+CCl_4 mixture using tetramethylsilane as an internal standard (chemical shift values are reported in ppm units, coupling constants (J) are in Hz). Abbreviations are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad. The elemental analyzes (C, H, N) performed at the Perkin-Elmer 2400 CHN analyzer and were within ±0.4% of the theoretical values. Mass spectra were obtained on Varian1200L instrument.

The starting compounds of 2,4-thiazolidinedione, 4-thioxo-2-thiazolidinone were obtained according to the methods described previously (*15*). 5-ylidene-4-thioxo-2-thiazolidinones (**4**) were prepared by treating 4-thioxo-2-thiazolidinone with appropriate aldehyde R^1-CHO in glacial acetic acid in the presence of a catalytic amount of fused sodium acetate in a water bath (100 °C) for 20 minutes, as described (*15*).

5.1. *General procedure for the preparation of 9-R-3,7-dithia-5-azatetracyclo[9.2.1.$0^{2,10}$.$0^{4,8}$] tetradecen-4(8)-ones-6 (5a–f, 6a–h, and 7a–d)*

A mixture of appropriate 5-R-methylidene-4-thioxo-2-thiazolidinone (10 mmol) and 5-norbornene-2,3-dicarboxylic acid derivative (11 mmol) was refluxed for 1 h with a catalytic amount of hydroquinone (2–3 mg) to prevent polymerization processes in 10 ml of glacial acetic acid, and then left overnight at room temperature. The precipitated crystals were filtered off, washed with methanol (5–10 ml), and recrystallized from butanol (10–15 ml).

Substances **5a–f, 6a–h,** and **7a–d** were isolated as white or yellowish powders.

5.2. *14-(4-Chlorophenyl)-9-(3,4-dimethoxyphenyl)-3,7-dithia-5,14-diazapentacyclo [9.5.1.$0^{2,10}$.$0^{4,8}$.$0^{12,16}$]heptadec-4(8)-ene-6,13,15-trione (5a)*

Yield 86%, mp >250°C. ^{1}H NMR (DMSO-d_6)δ: 11.47 (s, 1H, NH), 7.54d (d, 2H, J = 8.6 Hz, arom.), 7.37 (d, 2H, J = 8.6 Hz, arom.), 6.90 (m, 3H, arom.), 3.74 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.50 (m, 3H), 3.26 (m, 1H), 2.71 (d, 1H, J = 4.9 Hz), 2.52 (m, 1H), 2.41 (d, 1H, J = 5.3 Hz), 2.30 (t, 1H, J = 8.6 Hz), 1.70 (d, 1H, J = 10.0 Hz) - norbornane fragment, CHAr. ^{13}C NMR (DMSO-d_6)δ: 176.74, 176.67, 171.70, 149.42, 148.85, 133.68, 133.34, 131.64, 130.05, 129.62, 121.42, 120.69, 115.65, 112.79, 112.21, 56.03, 55.94, 52.57, 48.96, 47.60, 45.80, 45.46, 44.88, 39.42, 38.87. EI-MS (m/z): 554 (M^+). Anal. Calcd. for $C_{27}H_{23}ClN_2O_5S_2$ (555.08): C, 58.42; H, 4.18; N, 5.05. Found: C, 58.59; H, 4.32; N, 4.95.

5.3. *Ethyl 4-[9-(4-Chlorophenyl)-6,13,15-trioxo-3,7-dithia-5,14-diazapentacyclo-[9.5.1.0^{2,10}.0^{4,8}.0^{12,16}]heptadec-4(8)-en-14-yl]benzoate (5b)*

Yield 80%, mp >240°C. ^{1}H NMR (DMSO-d_6)δ: 11.56 (s, 1H, NH), 8.05 (d, 2H, J = 8.4 Hz, arom.), 7.48 (d, 2H, J = 8.4 Hz, arom.), 7.41 (m, 4H, arom.), 4.33 (q, 2H, J = 7.0 Hz, O$\underline{CH_2}$CH$_3$), 3.64 (d, 1H, J = 10.1 Hz), 3.36 (m, 1H), 3.50 (m, 2H), 2.52 (m, 1H), 2.72 (d, 1H, J = 6.0 Hz), 2.38 (d, 1H, J = 5.2 Hz), 2.32 (t, 1H, J = 8.7 Hz), 1.71 (d, 1H, J = 9.8 Hz), 1.32 (t, 3H, J = 7.2 Hz, CH$_3$) – norbornane fragment, $\underline{CH}$Ar. ^{13}C NMR (DMSO-d_6)δ: 176.55, 176.48, 171.41, 165.93, 140.16, 136.85, 133.14, 131.33, 130.38, 130.31, 129.51, 128.33, 121.26, 114.22, 61.61, 52.81, 48.98, 48.91, 47.41, 45.90, 45.23, 44.78, 38.86. EI-MS (m/z): 566 (M$^+$). Anal. Calcd. for $C_{28}H_{23}ClN_2O_5S_2$(567.09): C, 59.31; H, 4.09; N, 4.94. Found: C, 59.36; H, 4.14; N, 4.83.

5.4. *14-(4-Chlorophenyl)-9-(3-pyridyl)-3,7-dithia-5,14-diazapentacyclo-[9.5.1.0^{2,10}.0^{4,8}.0^{12,16}]heptadec-4(8)-ene-6,13,15-trione (5c)*

Yield 75%, mp >250°C. ^{1}H NMR (DMSO-d_6)δ: 1.74 (d, 1H, J = 10.2 Hz), 2.32 (t, 1H, J = 9.4 Hz), 2.42 (d, 1H), 2.53d (d, 1H, J = 10.2 Hz), 2.73 (d, 1H, J = 5.3 Hz), 3.32 (m, 1H), 3.50 (m, 2H), 3.65 (d, 1H, J = 10.0 Hz) – norbornane fragment, $\underline{CH}$Ar; 7.38 (d, 2H, J = 7.2 Hz, arom.), 7.42 (m, 1H, Py), 7.50d (d, 2H, J = 7.2 Hz, arom.), 7.76 (d, 1H, J = 8.0 Hz, Py), 8.56 (m, 2H, Py), 11.53 (s, 1H, NH). ^{13}C NMR (DMSO-d_6)δ: 39.12, 43.42, 44.80, 45.94, 47.23, 48.64, 49.13, 52.48, 114.11, 115.30, 121.50, 130.58, 132.15, 133.07, 133.45, 136.77, 141.74, 148.04, 148.26, 171.50, 176.40, 176.62. EI-MS (m/z): 495 (M$^+$). Anal. Calcd. for $C_{24}H_{18}ClN_3O_3S_2$ (496.01): C, 58.12; H, 3.66; N, 8.43. Found: C, 58.27; H, 3.70; N, 8.25.

5.5. *9-(4-Hydroxyphenyl)-14-(3-trifluoromethylphenyl)-3,7-dithia-5,14-diazapentacyclo-[9.5.1.0^{2,10}.0^{4,8}.0^{12,16}]heptadec-4(8)-ene-6,13,15-trione (5d)*

Yield 84%, mp >250°C. ^{1}H NMR (DMSO-d_6)δ: 11.46 (s, 1H, NH), 9.43 (s, 1H, OH), 7.68–7.84 (m, 4H, arom.), 7.10 (d, 2H, J = 8.4 Hz, arom.), 6.72 (d, 2H, J = 8.4 Hz, arom.), 3.56 (d, 1H, J = 7.8 Hz), 3.44 (m, 2H), 3.35 (m, 1H), 2.73 (d, 1H, J = 5.2 Hz), 2.51 (m, 1H), 2.42 (d, 1H, J = 4.9 Hz), 2.27 (t, 1H, J = 9.2 Hz), 1.70 (d, 1H, J = 10.3 Hz) – norbornane fragment, $\underline{CH}$Ar. ^{13}C NMR (DMSO-d_6)δ: 176.68, 176.46, 172.35, 156.60, 151.28 (d, 1C, J = 85 Hz, CF$_3$), 139.69, 135.90, 133.52, 133.40, 130.30, 129.40, 127.88, 124.57, 121.20, 114.36, 52.33, 48.93, 47.24, 45.90, 45.15, 44.80, 43.44, 38.95. EI-MS (m/z): 544 (M$^+$). Anal. Calcd. for $C_{26}H_{19}F_3N_2O_4S_2$ (544.58): C, 57.35; H, 3.52; N, 5.14. Found: C, 57.43; H, 3.62; N, 5.06.

5.6. *9-(3-Pyridyl)-14-(3-trifluoromethylphenyl)-3,7-dithia-5,14-diazapentacyclo-[9.5.1.0^{2,10}.0^{4,8}.0^{12,16}]heptadec-4(8)-ene-6,13,15-trione (5e)*

Yield 70%, mp >250°C. ^{1}H NMR (DMSO-d_6)δ: 11.43 (s, 1H, NH), 8.54 (m, 2H, arom.), 7.70 (m, 5H, arom.), 7.38 (m, 1H, arom.), 3.58 (m, 2H), 3.48 (m, 1H), 3.32 (m, 1H), 2.76 (d, 1H, J = 5.1 Hz), 2.58 (d, 1H), 2.52 (m, 1H), 2.40 (t, 1H), 1.81 (d, 1H, J = 10.5 Hz) – norbornane fragment, $\underline{CH}$Ar. ^{13}C NMR (DMSO-d_6)δ: 176.60, 176.57, 171.29, 150.81 (d, 1C, J = 81 Hz, CF$_3$), 149.90, 136.89, 136.81, 133.49, 132.60, 130.80, 130.29, 129.97, 125.88, 124.87, 124.57, 121.45, 113.84, 52.33, 49.01, 48.98, 47.38, 45.83, 44.72, 43.30, 39.05. EI-MS (m/z): 529 (M$^+$). Anal. Calcd. for $C_{25}H_{18}F_3N_3O_3S_2$ (529.56): C, 56.70; H, 3.43; N, 7.93. Found: C, 56.82; H, 3.50; N, 7.85.

5.7. *9,14-Di-(4-fluorophenyl)-3,7-dithia-5,14-diazapentacyclo[9.5.1.0^{2,10} .0^{4,8}.0^{12,16}] heptadec-4(8)-ene-6,13,15-trione (5f)*

Yield 85%, mp >200°C. ^{1}H NMR (DMSO-d_6+CCl_4)δ: 11.32 (s, 1H, NH), 7.34 (m, 4H, arom.), 7.21 (t, 2H, arom.), 7.12 (t, 2H, arom.), 3.42-3.56 (m, 3Í), 3.32 (m, 1H), 2.74 (m, 1H), 2.52 (m, 2H), 2.27 (t, 1H), 1.74 (d, 1H, J = 10.0 Hz) – norbornane fragment, ArCH. ^{13}C NMR (DMSO-d_6)δ: 176.86, 176.76, 171.48, 163.56 (d, J = 242 Hz, C–F), 163.12 (d, J = 200 Hz, C–F), 137.37, 131.44, 131.36, 130.53, 130.44, 129.02, 121.08, 116.57, 116.34, 116.14, 114.69, 52.80, 48.86, 48.80, 47.42, 45.85, 45.13, 44.72, 38.83. EI-MS (m/z): 496 (M^+). Anal. Calcd. for $C_{25}H_{18}F_2N_2O_3S_2$ (496.56): C, 60.47; H, 3.65; N, 5.64. Found: C, 60.36; H, 3.71; N, 5.42.

5.8. *2-[9-(3,4-Dimethoxyphenyl)-6,13,15-trioxo-3,7-dithia-5,14-diazapentacyclo-[9.5.1.0^{2,10} .0^{4,8}.0^{12,16}]heptadec-4(8)-en-14-yl]-4-methylpentanoic acid (6a)*

Yield 64%, mp >250°C. ^{1}H NMR (DMSO-d_6)δ: 11.49 (s, 1H, NH), 6.94 (m, 1H, arom.), 6.82 (d, 1H, arom.), 6.77 (d, 1H, arom.), 4.57 (m, 1H, CH_2<u>CH</u>COOH), 3.77s (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.42–3.53 (m, 3H), 3.25–3.33 (m, 2H), 2.70 (m, 1H), 2.41(m, 1H), 2.32 (m, 1H), 2.02 (m, 1H), 1.73 (m, 1H), 1.64 (d, 1H) – norbornane frament, CH<u>CH$_2$</u>CH, <u>CH</u>Ar, 1.36 (m, 1H, $(CH_3)_2$<u>CH</u>), 0.83 (s, 6H, 2×CH_3). ^{13}C NMR (DMSO-d_6)δ: 177.77, 177.55, 171.63, 171.49, 149.50, 148.86, 132.98, 121.18, 120.59, 116.77, 116.37, 112.32, 112.10, 55.96, 52.14, 51.52, 50.90, 48.66, 48.09, 45.40, 44.70, 38.60, 36.52, 24.99, 23.55, 21.47, 21.37. EI-MS (m/z): 558 (M^+). Anal. Calcd. for $C_{27}H_{30}N_2O_7S_2$(558.68): C, 58.05; H, 5.41; N, 5.01. Found: C, 58.14; H, 5.67; N, 4.88.

5.9. *2-[9-(4-Hydroxy-3-methoxyphenyl)-6,13,15-trioxo-3,7-dithia-5,14-diazapentacyclo [9.5.1.0^{2,10} .0^{4,8}.0^{12,16}]heptadec-4(8)-en-14-yl]-4-methylpentanoic acid (6b)*

Yield 58%, mp >250°C. ^{1}H NMR (DMSO-d_6+CCl_4)δ: 13.26 (br.s, 1H, COOH), 11.44 (s, 1H, NH), 8.98 (s, 1H, OH), 6.65–6.78 (m, 3H, 3-OMe-4-OH-<u>C$_6$H$_3$</u>), 4.55 (m, 1H, <u>CH</u>COOH), 3.72 (s, 3H, OCH_3), 3.51 (d, 1H, J = 10.8 Hz), 3.42 (m, 2H), 3.22 (m, 2H), 2.67 (m, 1H), 2.37 (m, 2H), 1.96 (m, 1H), 1.71 (m, 1H), 1.63 (d, 1H, J = 10.2 Hz) – norbornane fragment, <u>CH$_2$</u>CH$(CH_3)_2$, <u>CH</u>Ar, 1.33 (m, 1H, <u>CH</u>$(CH_3)_2$), 0.81 (m, 6H, 2×CH_3). ^{13}C NMR (DMSO-d_6)δ:, 177.76, 177.45, 171.68, 171.52, 148.36, 146.64, 131.52, 121.91, 120.45, 117.09, 116.17, 115.95, 112.48, 56.03, 52.16, 51.57, 50.88, 48.55, 45.40, 44.69, 38.65, 36.56, 25.00, 23.56, 23.51, 21.47. EI-MS (m/z): 544 (M^+). Anal. Calcd. for $C_{26}H_{28}N_2O_7S_2$(544.65): C, 57.34; H, 5.18; N, 5.14. Found: C, 57.18; H, 5.24; N, 5.05.

5.10. *4-[9-(3,4-Dimethoxyphenyl)-6,13,15-trioxo-3,7-dithia-5,14-diazapentacyclo[9.5.1.0^{2,10} .0^{4,8}.0^{12,16}]heptadec-4(8)-en-14-yl]butanoic acid (6c)*

Yield 70%, mp 252-254°C. ^{1}H NMR (DMSO-d_6+CCl_4)δ: 12.09s (1H, COOH), 11.47s (1H, NH), 6.92 (d, 1H, J = 8.1 Hz, arom.), 6.83 (m, 2H, arom.), 3.76 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.44 (d, 1H, J = 10.3 Hz), 3.36 (m, 2H), 3.24 (t, 2H, J = 8.0 Hz), 3.14 (m, 1H), 2.63 (d, 1H, J = 5.1 Hz), 2.41 (d, 1H, J = 10.6 Hz), 2.32 (d, 1H, J = 5.3 Hz), 2.18 (t, 2H, J = 7.4 Hz), 2.08 (t, 1H, J = 8.9 Hz), 1.64 (m, 3H) – norbornane fragment, 3×CH_2, <u>CH</u>Ar.^{13}C NMR (DMSO-d_6)δ: 177.71, 177.66, 174.62, 171.58, 149.44, 148.84, 133.11, 121.49, 120.79, 115.87, 112.39, 112.18, 55.95, 52.37, 48.59, 47.74, 45.42, 45.38, 44.44, 38.66, 38.02, 31.55, 23.25. EI-MS (m/z): 530 (M^+). Anal. Calcd. for $C_{25}H_{26}N_2O_7S_2$(530.62): C, 56.59; H, 4.94; N, 5.28. Found: C, 56.68; H, 5.00; N, 5.23.

5.11. *6-[9-(4-Hydroxy-3-methoxyphenyl)-6,13,15-trioxo-3,7-dithia-5,14-diazapentacyclo [9.5.1.0^{2,10} .0^{4,8}.0^{12,16}]heptadec-4(8)-en-14-yl]hexanoic acid (6d)*

Yield 52%, mp 254-256°C. ^{1}H NMR (DMSO-d_6+CCl_4)δ: 11.85 (s, 1H, COOH), 11.35 (s, 1H, NH), 8.86 (s, 1H, OH), 6.73 (d, 1H, J = 8.0 Hz, arom.), 6.71 (s, 1H, arom.), 6.63 (d, 1H, J = 8.0 Hz, arom.), 3.78 (s, 3H, OCH_3), 3.37d (1H, J = 10.7 Hz), 3.26–3.38 (m, 3H), 3.15 (m, 2H), 2.63 (d, 1H, J = 5.2 Hz), 2.41 (m, 2H), 2.13 (t, 2H, CH_2), 2.04 (t, 1H, J = 8.9 Hz), 1.66 (d, 1H, J = 10.3 Hz), 1.50 (m, 4H, 2×CH_2), 1.26 (m, 2H, CH_2). ^{13}C NMR (DMSO-d_6)δ: 177.70, 177.68, 175.12, 171.54, 148.36, 146.65, 131.51, 121.70, 120.73, 116.28, 116.14, 112.68, 56.06, 52.42, 48.57, 47.91, 45.36, 44.41, 38.59, 38.42, 33.93, 27.46, 26.50, 24.50. EI-MS (m/z): 544 (M^+). Anal. Calcd. for $C_{26}H_{28}N_2O_7S_2$(544.65): C, 57.34; H, 5.18; N, 5.14. Found: C, 57.26; H, 5.30; N, 4.97.

5.12. *3-Methyl-2-[6,13,15-trioxo-9-(3-pyridyl)-3,7-dithia-5,14-diazapentacyclo[9.5.1.0^{2,10} .0^{4,8}.0^{12,16}]heptadec-4(8)-en-14-yl]butanoic acid (6e)*

Yield 65%, mp >250°C. ^{1}H NMR (DMSO-d_6)δ: 13.16 (br.s, 1H, COOH), 11.49 (s, 1H, NH), 8.53 (m, 2H, arom.), 7.68 (d, 1H, J = 7.5 Hz, arom.), 7.41 (m, 1H, arom.), 4.19 (d, 1H, J = 8.0 Hz, CHCOOH), 3.46–3.61 (m, 2H), 3.32 (m, 2H), 2.69 (d, 1H, J = 5.1 Hz), 2.57 (m, 1H), 2.40 (m, 2H), 2.34 (d, 1H, J = 5.3 Hz), 1.68 (d, 1H, J = 10.4 Hz) – norbornane fragment, CH-Ar, $CH(CH_3)_2$; 1.05d (d, 3H, J = 8.0 Hz, CH_3), 0.75 (d, 3H, J = 8.0 Hz, CH_3). ^{13}C NMR (DMSO-d_6)δ: 177.48, 177.41, 171.19, 170.62, 150.73, 149.88, 136.81, 136.54, 124.49, 121.43, 114.53, 57.56, 51.30, 48.64, 47.64, 47.59, 45.63, 44.71, 43.21, 38.84, 27.90, 21.45, 19.77. EI-MS (m/z): 485 (M^+). Anal. Calcd. for $C_{23}H_{23}N_3O_5S_2$(485.58): C, 56.89; H, 4.77; N, 8.65. Found: C, 56.98; H, 4.90; N, 8.46.

5.13. *2-[6,13,15-Trioxo-9-(3-pyridyl)-3,7-dithia-5,14-diazapentacyclo-[9.5.1.0^{2,10} .0^{4,8}.0^{12,16}]heptadec-4(8)-en-14-yl]acetic acid (6f)*

Yield 75%, mp >250°C. ^{1}H NMR (DMSO-d_6)δ: 13.15 (br.s, 1H, COOH), 11.54 (s, 1H, NH), 8.53 (m, 2H, arom.), 7.61 (d, 1H, J = 8.0 Hz, arom.), 7.41 (d, 1H, J = 8.0 Hz, arom.), 4.03 (dd, 2H, CH_2, J_{AB} = 16.0 Hz), 3.66 (d, 1H, J = 9.3 Hz) 3.48 (d, 1H, J = 7.2 Hz), 3.42 (m, 1H), 3.23 (m, 1H), 2.70 (d, 1H, J = 5.1 Hz), 2.61 (t, 1H, J = 10.8 Hz), 2.47 (m, 1H), 2.34 (d, 1H, J = 5.2 Hz), 1.67 (d, 1H, J = 10.4 Hz) – norbornane fragment, CHAr. ^{13}C NMR (DMSO-d_6)δ: 177.18, 177.17, 171.18, 169.87, 150.68, 149.89, 136.63, 136.55, 124.52, 121.65, 114.71, 51.55, 48.66, 48.65, 47.90, 45.48, 44.56, 43.19, 39.40, 38.86. EI-MS (m/z): 443 (M^+). Anal. Calcd. for $C_{20}H_{17}N_3O_5S_2$(443.50): C, 54.16; H, 3.86; N, 9.47. Found: C, 54.33; H, 4.02; N, 9.40.

5.14. *4-[6,13,15-Trioxo-9-(2-thienyl)-3,7-dithia-5,14-diazapentacyclo[9.5.1.0^{2,10} .0^{4,8}.0^{12,16}]-heptadec-4(8)-en-14-yl]butanoic acid (6g)*

Yield 72%, mp 238–240°C. ^{1}H NMR (DMSO-d_6)δ: 12.02 (s, 1H, COOH), 11.46 (s, 1H, NH), 7.46 (d, 1H, J = 6.4 Hz, thiophene), 7.04 (m, 2H, thiophene), 3.87d (1H, J = 9.8 Hz), 3.38 (t, 2H, CH_2), 3.32 (m, 2H), 3.18 (m, 1H), 2.63 (d, 1H, J = 5.4 Hz), 2.44 (d, 1H, J = 5.4 Hz), 2.40 (d, 1H, J = 10.6 Hz), 2.17 (t, 2H), 2.05 (t, 1H), 1.69 (m, 3H). ^{13}C NMR (DMSO-d_6)δ:, 177.56, 177.47, 174.60, 171.37, 143.54, 127.76, 127.42, 126.52, 121.12, 115.03, 53.73, 48.55, 48.49, 47.58, 45.41, 44.73, 41.02, 38.64, 38.01, 31.54, 23.22. EI-MS (m/z): 476 (M^+). Anal. Calcd. for $C_{21}H_{20}N_2O_5S_3$(476.60): C, 52.92; H, 4.23; N, 5.88. Found: C, 53.11; H, 4.32; N, 5.76.

5.15. *6-[9-(4-Chlorophenyl)-6,13,15-trioxo-3,7-dithia-5,14-diazapentacyclo-[9.5.1.0^{2,10}.0^{4,8}.0^{12,16}]heptadec-4(8)-en-14-yl]hexanoic acid (6h)*

Yield 72%, mp 248–250°C. ^{1}H NMR (DMSO-d_6) δ: 11.97 (s, 1H, COOH), 11.57 (s, 1H, NH), 7.46 (d, 2H, $J = 8.5$ Hz, arom.), 7.32 (d, 2H, $J = 8.5$ Hz, arom.), 3.59 (d, 1H, $J = 10.2$ Hz), 3.27 (m, 2H), 3.13 (m, 1H), 2.64 (d, 1H, $J = 5.3$ Hz), 2.42 (d, 1H, $J = 10.5$ Hz), 2.27 (d, 1H, $J = 5.1$ Hz), 2.14 (m, 3H), 1.63 (d, 1H, $J = 10.2$ Hz) – norbornane fragment, CH_2, CHAr, 1.45 (m, 4H, 2×CH_2), 1.20 (m, 2H, CH_2). ^{13}C NMR (DMSO-d_6)δ: 176.61, 176.57, 171.42, 168.79, 149.83, 136.18, 133.03, 131.42, 130.40, 121.68, 114.46, 56.22, 52.65, 48.92, 45.93, 45.87, 44.76, 38.78, 38.40, 33.56, 27.60, 26.33, 24.89. EI-MS (m/z): 532 ($M^+ - 1$). Anal. Calcd. for $C_{25}H_{25}ClN_2O_5S_2$(533.07): C, 56.33; H, 4.73; N, 5.26. Found: C, 56.50; H, 4.81; N, 5.09.

5.16. *Methyl 2-[9-(3,4-dimethoxyphenyl)-6,13,15-trioxo-3,7-dithia-5,14-diazapentacyclo-[9.5.1.0^{2,10}.0^{4,8}.0^{12,16}]heptadec-4(8)-en-14-yl]acetate (7a)*

Yield 65%, mp >230°C. ^{1}H NMR (DMSO-d_6)δ: 11.28 (s, 1H, NH), 6.85 (d, 1H, $J = 8.4$ Hz, arom.), 6.74 (m, 2H, arom.), 4.15 (dd, 2H, CH_2COO, $J_{AB} = 15.4$ Hz), 3.77 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.47 (d, 1H, $J = 10.4$ Hz), 3.38 (m, 2H), 3.20 (m, 1H), 2.66 (d, 1H, $J = 5.2$ Hz), 2.43 (m, 2H), 2.37 (d, 1H), 1.67 (d, 1H, $J = 10.0$ Hz) – norbornane fragment, CHAr. ^{13}C NMR (DMSO-d_6)δ: 177.03, 176.98, 171.51, 168.63, 149.41, 148.85, 133.12, 121.45, 120.88, 116.05, 112.18, 55.94, 55.81, 52.95, 51.83, 48.78, 48.72, 47.80, 45.52, 45.31, 44.72, 38.80. EI-MS (m/z): 516 (M^+). Anal. Calcd. for $C_{24}H_{24}N_2O_7S_2$(516.60): C, 55.80; H, 4.68; N, 5.42. Found: C, 55.67; H, 4.75; N, 5.34.

5.17. *Ethyl 2-[9-(3,4-dimethoxyphenyl)-6,13,15-trioxo-3,7-dithia-5,14-diazapentacyclo-[9.5.1.0^{2,10}.0^{4,8}.0^{12,16}]heptadec-4(8)-en-14-yl]acetate (7b)*

Yield 68%, mp >230°C. ^{1}H NMR (DMSO-d_6)δ: 11.34 (s, 1H, NH), 6.85 (d, 1H, $J = 8.4$ Hz, arom.), 6.74 (m, 2H, arom.), 4.04–4.17 (m, 4H, CH_2COO, CH_2CH_3), 3.76 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.50 (d, 1H), 3.40 (m, 3H), 3.22 (m, 1H), 2.65 (m, 1H), 2.42 (m, 2H), 1.67 (d, 1H, $J = 9.8$ Hz) – norbornane fragment, CHAr, 1.19 (t, 3H, CH_3CH_2). ^{13}C NMR (DMSO-d_6)δ: 177.01, 176.99, 171.50, 167.97, 149.41, 148.87, 133.07, 121.40, 120.87, 116.08, 112.28, 112.25, 62.06, 55.95, 55.82, 51.87, 48.77, 47.70, 45.54, 45.29, 44.68, 38.80, 14.28. EI-MS (m/z): 530 (M^+). Anal. Calcd. for $C_{25}H_{26}N_2O_7S_2$(530.62): C, 56.59; H, 4.94; N, 5.28. Found: C, 56.70; H, 5.02; N, 5.15.

5.18. *N1-Phenyl-2-[9-(3,4-dimethoxyphenyl)-6,13,15-trioxo-3,7-dithia-5,14-diazapentacyclo[9.5.1.0^{2,10}.0^{4,8}.0^{12,16}]heptadec-4(8)-en-14-yl]acetamide (7c)*

Yield 58%, mp >240°C. ^{1}H NMR (DMSO-d_6)δ: 11.52 (s, 1H, NH), 10.34 (s, 1H, CH_2CONH), 7.53 (d, 2H, $J = 7.9$ Hz, arom.), 7.32 (t, 2H, $J = 7.9$ Hz, arom.), 7.08 (t, 1H, $J = 7.3$ Hz, arom.), 6.84 (m, 3H, arom.), 4.22 (dd, 2H, CH_2CONH, $J_{AB} = 15.0$ Hz), 3.74 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.52 (d, 1H, arom.), 3.36–3.47 (m, 2H), 3.19 (m, 1H), 2.72 (m, 2H), 2.43 (d, 1H), 2.36 (d, 1H), 1.68 (d, 1H) – norbornane fragment, CHAr. ^{13}C NMR (DMSO-d_6)δ: 177.42, 177.32, 172.91, 171.65, 165.50, 149.38, 148.75, 139.24, 133.34, 129.60, 124.39, 121.70, 120.84, 119.71, 116.33, 111.97, 111.95, 55.88, 55.45, 51.64, 48.88, 48.73, 48.19, 45.53, 45.43, 44.76, 38.37. EI-MS (m/z): 577 (M^+). Anal. Calcd. for $C_{29}H_{27}N_3O_6S_2$(577.68): C, 60.30; H, 4.71; N, 7.27. Found: C, 60.40; H, 4.85; N, 7.14.

5.19. *14-(2-Morpholino-2-oxoethyl)-9-(3-pyridyl)-3,7-dithia-5,14-diazapentacyclo [9.5.1.0^{2,10}.0^{4,8}.0^{12,16}]heptadec-4(8)-ene-6,13,15-trione (7d)*

Yield 60%, mp >250°C. ^{1}H NMR (DMSO-d_6+CCl_4)δ: 11.42 (s, 1H, NH), 8.46 (m, 2H, arom.), 7.59 (d, 1H, J = 8.8 Hz, arom.), 7.34 (t, 1H, arom.), 4.20 (dd, 2H, CO-CH_2-N, J = 16.4 Hz), 3.40–3.67 (m, 10H), 3.25 (m, 2H), 2.73 (t, 1H, J = 10.2 Hz), 2.63 (d, 1H, J = 5.1 Hz), 2.52 (m, 1H), 2.35 (d, 1H, J = 5.2 Hz), 1.69 (d, 1H, J = 10.8 Hz) - morpholine and norbornane fragments, CHAr. ^{13}C NMR (DMSO-d_6)δ: 177.28, 177.24, 171.13, 164.97, 150.63, 149.78, 136.90, 136.71, 124.52, 121.64, 114.01, 66.52, 66.48, 51.22, 48.73, 48.69, 47.47, 45.63, 45.11, 44.65, 43.14, 42.47, 39.03. EI-MS (m/z): 512 (M^+). Anal. Calcd. for $C_{24}H_{24}N_4O_5S_2$(512.61): C, 56.24; H, 4.72; N, 10.93. Found: C, 56.37; H, 4.80; N, 10.77.

5.20. *In vitro anticancer screening*

In vitro anticancer screening assays were performed according to NCI procedures (*21–23*). The detailed method description is available as supplementary information.

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