INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Research Article……!!!

Received; accepted

SYNTHESIS AND ANTITUMOR ACTIVITY OF NOVEL 2-THIOXO 4-THIAZOLIDINONES WITH BENZOTHIAZOLE MOIETIES

Pritesh Patel*, Hardik Patel, Nilesh Darji, Bhagirath Patel

Sat Kaival College of Pharmacy, Sarsa, Anand, Gujarat-India

Keywords:

2-thioxo-4-thiazolidinones, benzothiazole, Knoevenagel condensation, antitumor activity, structure - activity relationship

For Correspondence:

Pritesh Patel*

Sat Kaival College of Pharmacy, Sarsa, Anand, Gujarat-India

E-mail:

prit.pharma@gmail.com

ABSTRACT

Following the reaction of benzothiazol-2-yl-hydrazine or (2-oxo-benzothiazol-3- yl)-acetic acid hydrazide with thiocarbonyl-bis-thioglycolic acid, 3-(benzothiazol-2-ylamino)-2-thioxothiazolidin-4-one (1) and 2-(2-oxobenzo thiazol-3-yl)-N-(4-oxo-2- thioxothiazolidin-3-yl)-acetamide (2) were synthesized, as starting compounds for obtaining New 5-arylidenederivatives (3-6)in Knoevenagel Condensation with aromatic aldehydes and isatines. The synthesized compounds showed antitumor activity on renal cancer, non-small cell lung cancer and ovarian cancer cell lines. The most efficient anticancer agent, 2-{2-[3-(benzothiazol-2-ylamino) -4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl]-4-chloro-phenoxy} -N-(4-methoxyphenyl)-acetamide 3d was found to be active with average values of -5.38 and -4.45 for $logGI_{50}$ and logTGI, respectively.

Introduction:

Thiazolidine derivatives, especially 4-thiazolidinones are peroxisome proliferator - activated receptors (PPAR-receptors) Agonists showing hypoglycemic, anti-inflammatory and antineoplastic activities [10]. Antitumor properties Of 4-thiazolidinones and related heterocycles are most probably related to their affinity to anticancer biotargets, such as JNK- stimulating phosphatase-1 (JSP-1) [4], tumor necrosis factor TNFα [3], anti- apoptotic biocomplex Bcl-X_L-BH3 [5], integrin $\alpha_V\beta_3$ receptor [6], etc. Combination of thiazolidine template with benzothiazole moiety is a perspective approach for drug-like molecules build-up, considering that benzothiazole derivatives have a wide spectrum of pharmacological activities [13]. Among mentioned Bicyclic Systems compound MKT 077 [8] has been reported as a registered antitumor agent. That is why the aim of Our research became the synthesis of novel 5-arylidene-2-thioxo-4-thiazolidinones (rhodanine derivatives) with benzothiazole and 2-oxobenzothiazole fragments for the pharmacological screening of antitumor activity.

Materials and methods:

All starting materials were purchased from Merck and used without purification. Melting points were measured in open capillary tubes on a BŰCHI B-545 melting point apparatus and are uncorrected. The elemental analyses (C, H, N) were performed using the Perkin-Elmer 2400 CHN analyzer and were within ±0.4% of the theoretical values. The ^{1}H-NMR spectra were recorded on Varian Gemini spectrometer at 300 MHz using a mixture of DMSO-*d6*+CCl4 as a solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts values are reported in ppm units with use of δ scale. Primary

anticancer assays were performed according to the US National Cancer Institute (NCI) protocol, and described elsewhere [1,2,7]. 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 (SRB). The results for each compound are reported as the percent growth of treated cells when compared to untreated control cells. The catatonic and/or growth inhibitory effects of the reported compounds were tested *in vitro* against the full panel of 60 human tumor cell lines derived from nine neoplastic diseases at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8} M. A 48-h continuous drug exposure protocol was followed and SRB protein assay was used to estimate cell viability or growth. For each compound, the 50% growth inhibition (GI_{50}) and total growth inhibition (TGI) were obtained for all the cell lines. Values were calculated for each of these parameters if the level of activity was reached; if the effect was not reached or was exceeded, the value is expressed as greater or less than the maximum or minimum concentration tested. The logGI_{50} and logTGI were then determined, defined as the log's of the individual GI_{50} and TGI values. The lowest values are obtained with the most sensitive cell lines. Compounds having values <-4.00 were declared to be active. Furthermore, a mean graph midpoints (MG_MID) were calculated for each of the parameters, giving an averaged activity parameter over all cell lines for each compound. For the calculation of the MG_MID, insensitive cell lines are included with the highest concentration tested.

Results and discussion:

3-Substituted rhodanines were obtained by reaction of benzothiazol-2-ylhydrazine or

(2-oxobenzothiazol-3-yl)-acetic acid hydrazide with thiocarbonyl-bis-thioglycolic acid in ethanol medium [11]. Synthesized compounds **1** and **2** are methylene active heterocycles. On the other hand, it was established previously [9], that in most cases the presence and nature of moiety in position 5 of thiazolidinones play the key role in the realization and direction of pharmacological effects. Mentioned thesis was rationale for synthesis of new 5-ylidenederivatives **3-6**, using standard Knoevenagel reaction procedure (medium– acetic acid, catalyst – fused sodium acetate) [9].

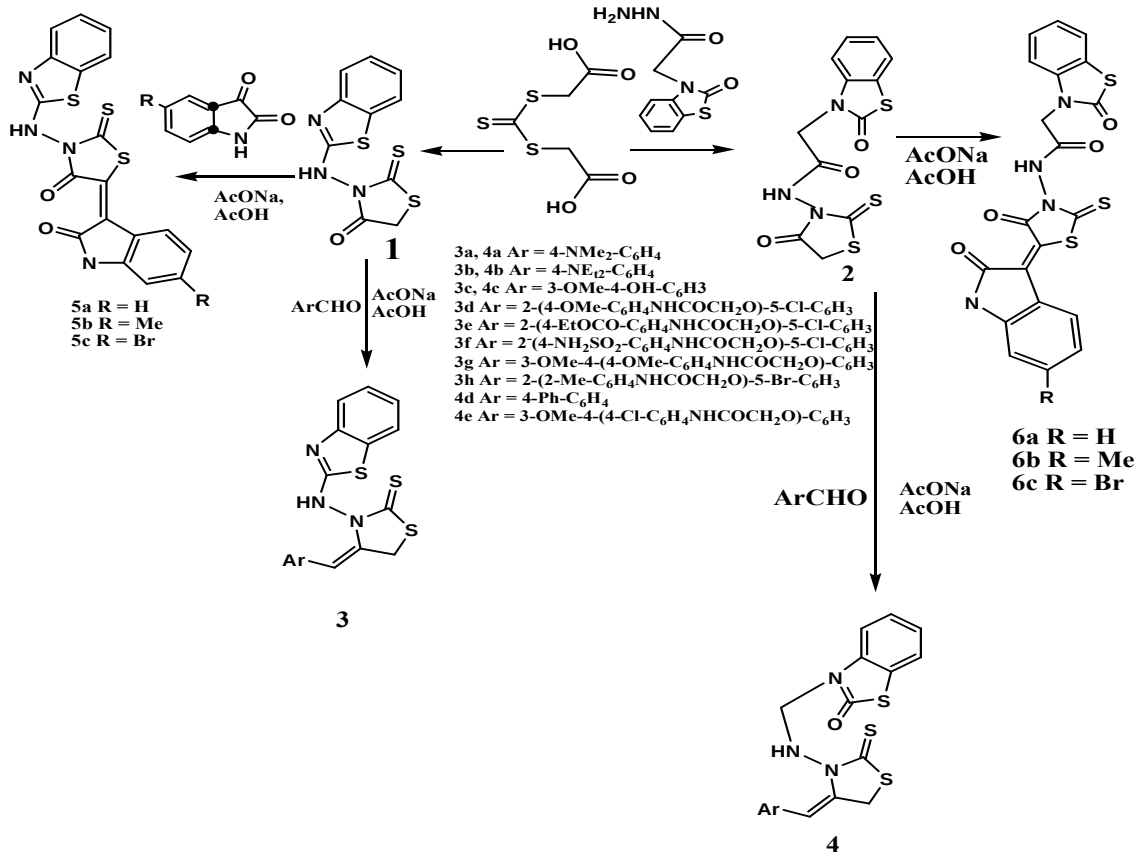

Figure: 1

The structures of synthesized rhodanine derivatives were confirmed by the NMR spectra. In the ^{1}H NMR spectra of synthesized compounds the protons of the benzothiazole moiety show the characteristic multiplets at δ =~7.05-7.55 ppm. The chemical shift for

the methylidene group of 5-arylidenederivatives **3** and **4** is insignificantly displaced in weak magnetic field**,** δ 7.76-7.89 ppm, and clearly indicated that only *Z*-isomers were obtained [12]. Aromatic protons of mentioned compounds show characteristic patterns at δ 6.82-8.32 ppm. The chemical shifts of the protons of the methylene group (compounds **2**, **4**, **6**) were determined to δ = 4.91–4.95 ppm with coupling constants J = 17.1–17.3 Hz. For the NH protons of compounds 1**, 3, 5** three broad singlets at δ = 8.07-8.12 ppm (hydrazine form), δ ~11.60 ppm and δ ~12.45 ppm (*Z*-and *E*-hydrazone Forms) are observed. This can be explained by the presence of hydrazine-hydrazono tautomerism of these derivatives.

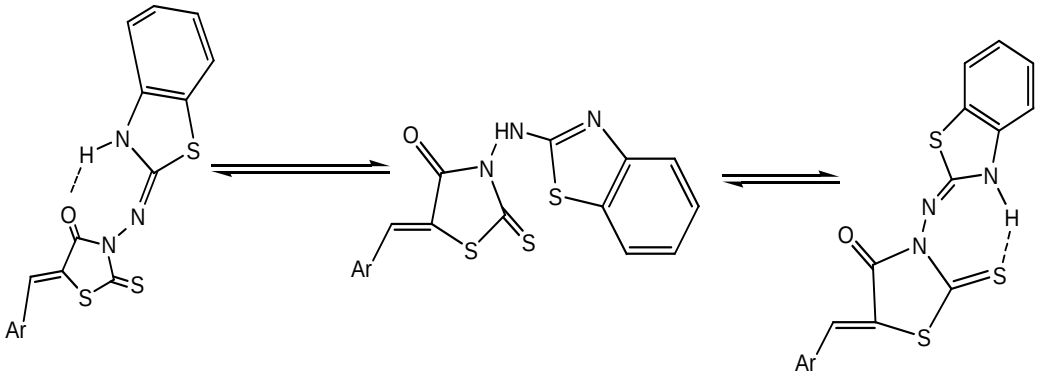

Figure: 2

Anticancer assays of the compounds **2-6** were performed according to the US NCI protocol, as described elsewhere [1, 2, and 7]. The activity of some of the new thiazolidinones at a single concentration of 10^{-5} M against 57 cancer cell lines was evaluated. The synthesized 5-ylidene-2-thioxo-4- thiazolidinones (**3-6**) displayed moderate activity in the *in vitro* screening on the tested cell lines. It is noteworthy that there was observed

selective influence of compounds on some cancer cell lines (Table I). Compounds **2** and **3c** were highly active on Renal Cancer RXF 393 cell line (-3.57% and -0.71%), compound **3h** was highly active on Non-Small Cell Lung Cancer HOP-92 cell line (0.74%) and **5c** – on Ovarian Cancer IGROV1 cell line (4.59%). Compound **3d** showed the highest cytotoxicity and was active against all tested human tumor cell lines and was selected in advanced assay against a panel of approximately sixty tumour cell lines at 10-fold dilutions of five concentrations (100, 10, 1, 0.1 and 0.01 mM). The tested compound showed a broad spectrum of growth inhibition activity against all human tumor cells with average $lgGI_{50}$ and lgTGI values -5.38 and -4.45 respectively (Table II). One should note that mentioned compound showed no toxicity in Nontumored Animal Toxicity Assays. Compound **3d** was selected as "matrix" for further drug design of 4-thiazolidones as possible anticancer agents.

Comp	60 cell lines assay in 1 dose 10^{-5} M conc				Active (selected for 5- dose 60 cell lines assay)
	Mean growth %	Range of growth %	The most sensitive cell line	growth % of the most sensitive cell line	
2	108.47	-3.57 to 210.28	RXF 393 (Renal Cancer)	-3.57	N
3b	98.52	77.27 to 121.76	UO-31 (Renal Cancer)	77.27	N
3c	97.65	-0.71 to 129.24	RXF 393 (Renal Cancer)	-0.71	N
3d	50.36	-71.48 to 117.53	SR (Leukemia)	-71.48	A
3e	74.74	20.02 to 115.14	RPMI-8226 (Leukemia)	20.02	N
3f	107.21	63.83 to 156.53	SR (Leukemia)	63.83	N
3g	107.49	78.63 to 131.69	UO-31 (Renal Cancer)	78.63	N
3h	100.36	0.74 to 192.37	HOP-92 (Non-Small Cell Lung Cancer)	0.74	N
4c	105.28	85.48 to 150.15	UO-31 (Renal Cancer)	85.48	N
4d	103.22	78.99 to 129.85	MALME-3M (Melanoma)	78.99	N

4e	105.93	74.53 to 318.51	T-47D (Breast Cancer)	74.53	N
5a	96.88	58.38 to 139.01	CAKI-1 (Renal Cancer)	58.38	N
5b	102.60	79.10 to 146.65	IGROV1 (Ovarian Cancer)	79.10	N
5c	96.42	4.59 to 131.77	IGROV1 (Ovarian Cancer)	4.59	N
6b	106.91	91.91 to 125.63	ACHN (Renal Cancer)	91.91	N

Table I. Anticancer Screening Data of 60 Cancer Cell Lines Assay at 10^{-5} M Concentration

Panel/cell line	1			2 evaluation		
	logGI50	logTGI	logLC50	logGI50	logTGI	logLC50
Leukemia						
CCRF-CEM	-5.61	>-4.00	>-4.00	-5.50	>-4.00	>-4.00
HL-60 (TB)	-5.64	-5.16	>-4.00	-5.58	-5.06	>-4.00
K-	-5.50	>-4.00	>-4.00	-5.56	>-4.00	>-4.00
MOLT-4	-5.57	>-4.00	>-4.00	-5.57	>-4.00	>-4.00
RPMI-8226	-5.75		>-4.00	-5.27	-4.89	>-4.00
SR				-5.81	>-4.00	>-4.00
Non-Small Cell						
A549/ATCC	-4.78	-4.06	>-4.00	-4.49	>-4.00	>-4.00
EKVX	-5.30	>-4.00	>-4.00	-5.27	>-4.00	>-4.00
HOP-62	-4.72	-4.27	>-4.00	-4.88	-4.23	>-4.00
HOP-92	-5.55	-4.04	>-4.00	-5.34	>-4.00	>-4.00
NCI-H226	-5.53	-5.16	>-4.00	-5.52	>-4.00	>-4.00
NCI-H23	-4.70	-4.12	>-4.00	-5.12	-4.17	>-4.00
NCI-H322M	-4.87	>-4.00	>-4.00	-5.01	>-4.00	>-4.00
NCI-H460	-4.81	>-4.00	>-4.00	-.509	>-4.00	>-4.00
NCI-H522	-4.69	>-4.00	>-4.00	-5.30	>-4.00	>-4.00
Colon cancer						
COLO 205	-5.02	-4.60	-4.18	-5.40	-4.69	>-4.00
HCC-2998	-4.90	-4.58	-40.25	-5.51	-5.05	-4.27
HCT-116	-5.45	-4.81	-4.12	-5.57	-4.73	>-4.00
HCT-15	-5.41	-4.81	-4.29	-5.50	-4.60	>-4.00
HT29	-5.42	>-4.00	>-4.00	-5.38	>-4.00	>-4.00
KM12	-5.65	-5.31	-4.84	-5.36	-4.27	>-4.00
SW-620	-5.61	-5.20	>-4.00	-5.52	>-4.00	>-4.00
CNS Cancer						
SF-268	-5.48	-4.82	>-4.00	-5.31	>-4.00	>-4.00
SF-295	-5.64	-4.65	>-4.00	-5.19	-4.44	>-4.00
SF-539	-5.51	-4.88	>-4.00	-5.52	-4.55	>-4.00
SNB-19	-5.11	>-4.00	>-4.00	-4.77	>-4.00	>-4.00
SNB-75	-5.80	-5.02	>-4.00	-5.29	>-4.00	>-4.00
U251	-5.53	-5.03	-4.49	-5.27	>-4.00	>-4.00
Melanoma						
LOX IMVI	-5.78	-5.49	-5.20	-5.69	-5.34	-4.87
MALME-3M	-5.58	-5.02	-4.05	-5.71	-5.35	-4.91
M14	-5.35	-4.64	>-4.00	-5.55	-5.01	>-4.00
SK-MEL-28	-5.66	-5.35	-5.03	-5.77	-5.36	-4.67
SK-MEL-5	-5.49	-4.93	-4.40	-5.54	-4.89	-4.20
UACC-257	-5.21	-4.71	-4.33	-5.43	-4.83	>-4.00
UACC-62	-5.53	-5.06	-4.23	-5.87	-5.52	-5.17
Ovaria						
IGROV1	-5.38	-4.74	-4.20	-5.41	>-4.00	>-4.00
OVCAR-3	-5.70	-5.43	-5.16	-5.60	-5.23	>-4.00
OVCAR-4	-5.42	>-4.00	>-4.00	-5.14	>-4.00	>-4.00
OVCAR-5	-4.57	-4.16	>-4.00	-4.86	-4.10	>-4.00
OVCAR-8	-4.71	-4.08	>-4.00	-4.76	>-4.00	>-4.00
SK-OV-3	-5.08	-4.39	>-4.00	-4.95	-4.30	>-4.00
Renal Cancer						
786-0	-5.25	>-4.00	>-4.00	-5.13	>-4.00	>-4.00
A498	-5.59	-5.24	-4.48	-5.66	-5.25	-4.49
ACHN	-5.55	>-4.00	>-4.00	-5.28	>-4.00	>-4.00
CAKI-1	-5.47	-4.55	>-4.00	-5.44	-4.69	-4.05
RXF 393				-5.29	-4.34	>-4.00
SN12C	-5.29	>-4.00	>-4.00	-5.53	-4.63	>-4.00

TK-10	-5.09	>-4.00	>-4.00	-5.43	-4.08	>-4.00
UO-31	-5.47	-4.85	-4.23	-5.43	>-4.00	>-4.00
Prostate Cancer						
PC-3	-5.41	>-4.00	>-4.00	-5.12	>-4.00	>-4.00
DU-145	-5.68	-5.40	-5.12	-5.30	-4.65	>-4.00
Breast Cancer						
MCF7	-5.46	>-4.00	>-4.00	-5.42	>-4.00	>-4.00
NCI/ADR-RES	-4.54	>-4.00	>-4.00	-5.14	>-4.00	>-4.00
MDA-MB-231/ATCC	-5.12	>-4.00	>-4.00	-5.68	-5.23	>-4.00
HS 578T				-5.55	-4.09	>-4.00
MDA-MB-435	-5.43	>-4.00	>-4.00	-5.71	-5.40	-5.09
BT-549	-5.52	-5.05	>-4.00	-5.72	-5.39	-5.06
T-47D	-5.30	>-4.00	>-4.00	-5.48	>-4.00	>-4.00
MDA-MB-468	-5.64	>-4.00	>-4.00	-5.60	-5.15	>-4.00

Table II. *In vitro* anticancer activity at 60 human tumor cell lines for compound 3d

Synthesis of 3-(benzothiazol-2-ylamino)-2-thioxothiazolidin-4- one (1) and 2-(2-oxobenzothiazol-3-yl)-N-(4-oxo-2-thioxothiazolidin-3-yl)-acetamide (2)

A mixture of 50 mmol 2-hydrazinobenzothiazole or (2- oxobenzothiazol-3-yl)-acetic acid hydrazide and 50 mmol thiocarbonyl-bis- thioglicolic acid was refluxed in 30 ml of ethanol for 5 hours. The product was obtained as a precipitate after cooling of the reaction mixture, filtering off and recrystallization with acetic acid.

Compound 1. Yellow crystals; yield 78%; m.p. 137 -140^{o}C

Compound 2. Yellow crystals; yield 75%; m.p. 226-228^{o}C; ^{1}H NMR, δ: 4.39 s (2H, CH_2), 4.87 dd (2H, CH_2, J = 18.2 Hz), 7.16 d, 7.19 t, 7.35 t, 7.66 d (4H, C_6H_4), 11.59 s (1H, NH).

Synthesis of 5-ylidene-2-thioxo-4-thiazolidinones (3-6)

The mixture of 5 mmol of compound **1** or **2**, 5 mmol of anhydrous sodium acetate, 6.25 mmol of appropriate aldehyde or isatin and 10 ml of glacial acetic acid where heated

under reflux for5 hours. The precipitate was filtered off and recrystallized with the solvents mixture DMF- AcOH (1:1).

Compound 3a. Yellow crystals; yield 59%; m.p. >220°C; ^{1}H NMR, δ: 3.07 s (6H, $(CH_3)_2N$), 7.16 m, 7.34 m, 7.70 m (4H, C_6H_4), 6.88 d, 7.53 d (4H, 4- NMe_2-C_6H_4, J = 8.0 Hz), 7.78 br s (1H, =CH), 8.07 s (1H, NH)**.**

Compound 3b. Yellow crystals; yield 63%; m.p. >220°C.

Compound 3c. Yellow crystals; yield 78%; m.p. 208-210°C.

Compound 3d. Yellow crystals; yield 73%; m.p. 151-152^{o}C; ^{1}H NMR, δ:3.68 s (3H, OCH_3), 4.92 s (2H, CH_2), 6.86 d, 7.12 m, 7.30 br s, 7.46-7.58 m (11H, C_6H_4, 4-MeO-C_6H_4, C_6H_3), 8.05 br s (1H, =CH), 8.46 s, 10.00 s, 10.12 s, 11.84 br s (2H, 2*NH).

Compound 3e. Yellow crystals; yield 71%; m.p. >220°C; ^{1}H NMR, δ: 1.24 t (3H, CH_2CH_3), 4.24 q (2H, CH_2CH_3), 5.01 s (2H, CH_2), 7.12 d, 7.29 m,7.53 br s, (7H, C_6H_4, C_6H_3), 7.73 d, 7.89 d (4H, 4-EtOCO-C_6H_4, J = 8.7 Hz) 8.03 br s (1H, =CH), 10.58 s, 11.85 br s (2H, 2*NH).

Compound 3f. Yellow crystals; yield 59%; m.p. 228-229°C.

Compound 3g. Yellow crystals; yield 68%; m.p. >220°C; ^{1}H NMR, δ: 3.70 s (3H, OCH_3), 3.89 s (3H, OCH_3), 4.79 s (2H, OCH_2), 6.86 d, 7.12 m, 7.29 d, 7.48 d, 7.66 d (11H, C_6H_4, 4-MeO-C_6H_4, C_6H_3), 7.87 s (1H, =CH), 10.02 s (1H, NH), 11.84 br s (1H, N-NH).

Compound 3h. Yellow crystals; yield 81%; m.p. 212-214°C.

Compound 4a. Yellow crystals; yield 76%; m.p. >220°C; ^{1}H NMR, δ: 3.03 s (6H, 2*CH_3), 4.93 dd, (2H, CH_2**,** J = 17.1 Hz), 6.84 d, 7.22 br s, 7.37 t,7.51 d, 7.66 d (8H,

C_6H_4, C_6H_4), 7.75 s (1H, =CH), 11.86 br s (1H, NH).

Compound 4b. Yellow crystals; yield 73%; m.p. >220°C.

Compound 4c. Yellow crystals; yield 65%; m.p. >220°C; ^{1}H NMR, δ: 3.82 s (3H, OCH_3), 4.91dd, (2H, CH_2**,** J = 17.2 Hz), 6.96 t, 7.14 m, 7.38 t, 7.65 d (7H, C_6H_4, C_6H_3), 7.83 s (1H, =CH), 10.30 br s (1H, OH), 11.80 br s (1H, NH).

Compound 4d. Yellow crystals; yield 59%; m.p. >220°C; ^{1}H NMR, δ: 3.03 s (6H, 2*CH_3), 4.93 dd, (2H, CH_2**,** J = 17.1 Hz), 6.84 d, 7.22 br s, 7.37 t,7.51 d, 7.66 d (8H, C_6H_4, C_6H_4), 7.75 s (1H, =CH), 11.86 br s (1H, NH).

Compound 4e. Yellow crystals; yield 68%; m.p. >220°C; ^{1}H NMR, δ: 3.86 s (3H, OCH_3), 4.82 s (2H, OCH_2), 4.93 dd, (2H, CH_2, J = 17.3 Hz), 7.05 d, 7.23 m, 7.29 d, 7.65 d, 7.69 br s (11H, C_6H_4, 4-Cl-C_6H_4, C_6H_3), 7.87 s (1H, =CH), 10.33 s (1H, NH), 11.82 br s (1H, NH).

Compound 5a. Red crystals; yield 82%; m.p. 257-258°C

Compound 5b. Red crystals; yield 77%; m.p. 262-264°C **Compound 5c.**

Red crystals; yield 69%; m.p. 268-269°C

Compound 6a. Red crystals; yield 89%; m.p. >240°C

Compound 6b. Red crystals; yield 75%; m.p. >220°C; ^{1}H NMR, δ: 2.26 s (3H, CH_3), 4.95 dd (2H, CH_2, J = 17.1 Hz), 6.82 d, 7.23 m, 7.42 m, 7.65 d,8.54 s (7H, C_6H_4, C_6H_3), 11.18 br s (1H, NH).

Compound 6c. Red crystals; yield 71%; m.p. >240°C

Conclusions:

In the present paper, twenty one new 2-thioxo-4-thiazolidinone derivatives were described, which were tested for *in vitro* anticancer activity in the National Cancer Institute. Synthesized compounds displayed antitumor activity on renal cancer, non-small cell lung cancer, ovarian cancer cell lines. The most efficient anticancer agent 2-{2-[3-(benzothiazol-2-ylamino)-4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl]-4-chloro-phenoxy}-N-(4-methoxyphenyl)-acetamide **3d** was found to be active with average $logGI_{50}$ and logTGI values: -5.38 and -4.45 respectively. Compound **3d** was selected as "matrix" for further drug design of 4- thiazolidones as possible anticancer agents.

References:

1. Alley M.C., Scudiero D.A., Monks P.A. et al. – Feasibility of Drug Screening with Panels of Human Tumor Cell Lines Using a Microculture Tetrazolium Assay, *Cancer Research*, 1988, 48, 589-601
2. Boyd M.R., Paull K.D. – Some Practical Considerations and Applications of the National Cancer Institute In Vitro Anticancer Discovery Screen, *Drug Development Research*, 1995, 34, 91-109
3. Carter P.H.; Scherle P.A.; Muckelbauer J.A. et al. – Photochemically enhanced binding of small molecules to the tumor necrosis factor receptor-1 inhibits the binding of TNF-α, *Proc. Natl. Acad. Sci. U.S.A.,* 2001, 98, 11879-11886
4. Cutshall N. S., O'Day C., Prerzhdo M. – Rhodanine derivatives as inhibitors of

JSP-1, *Bioorg. Med. Chem. Lett.,* 2005, 15, 3374-3379

5. Degterev A., Lugovskoy A., Cardone M. et al. – Identification of small-molecule inhibitors of interaction between the BH3 domain and Bcl-xl. *Nature Cell Biol.* 2001, 3 (2), 173-182

6. Dayam R., Aiello F., Deng J. et al. – Discovery of Small Molecule Integrin α v β 3 Antagonists as Novel Anticancer Agents, *J. Med.Chem.,* 2006, 49, 4526-4534

7. Grever M.R., Schepartz S.A., Grabner B.A. – The National Cancer Institute: Cancer Drug Discovery and Development Program, *Seminars in Oncology*, 1992, 19(6), 622-638

8. Masayuki Kawakami, Keizo Koya, Tochinao Ukai et al. – Structure – activity of novel rhodacyanine dyes as antitumor agents, *Journal of Medicinal Chemistry*, 2002, 37, 197–206

9. Lesyk R., Zimenkovsky B. – 4-Thiazolidones: Current Status and Perspectives for Modern Organic and Medicinal Chemistry, *Current Organic Chemistry*, 1998, 41(1), 130-142

10. Murphy G.J., Holder J.C. – PPAR-γ agonists: therapeutic role in diabetes, inflammation and cancer, *Trends in Pharmacological Sciences,* 2000, 21, 469–474

11. Roman O., Lesyk R. – Synthesis and anticancer activity in vitro of some 2- thioxo-4-thiazolidone derivatives, *Farmacia*, 2007, LV (6), 640-648

12. Popov-Pergal K., Cekovic Z., Pergal M. – Condensation of 2,4 dioxotetrahydro-1,3-thiazole with aromatic aldehydes, *J. Gen. Chem*. USSR. 1991, 61(1), 9, 1958-1962

13. Stanton Hon Lung Kok, Gambari R., Chung Hin Chui et al. – Synthesis and anti-cancer activity of benzothiazole containing phthalimide on human carcinoma cell lines, *Bioorganic & Medicinal Chemistry,* 2008, 16, 3626–3631.