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Research Article

Synthesis and anticancer properties of 5-(1*H*-benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-ylcarboxilic acids

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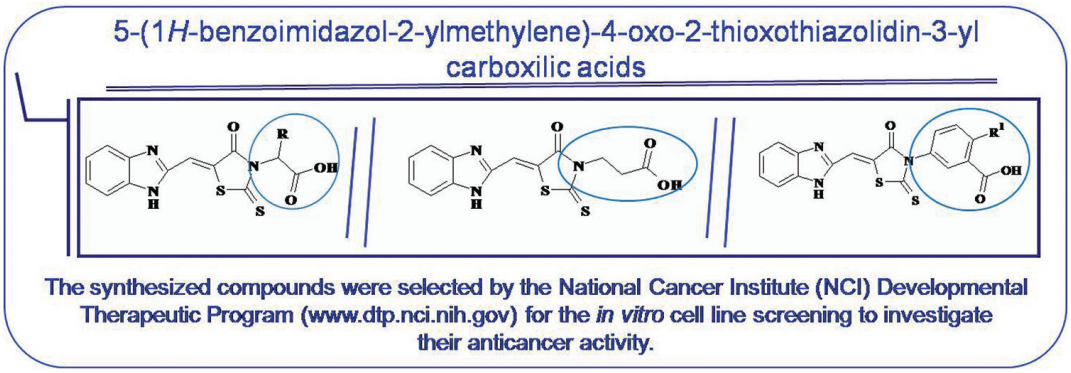
Abstract

The reaction of 1*H*-benzoimidazole-2-carbaldehyde with 4-oxo-2-thioxothiazolidin-3-ylcarboxilic acids was studied and the combinatorial library of 5-(1*H*-benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-ylcarboxilic acids has been prepared. The structures of target compounds **8a-f**, **9** and **10a, b** were confirmed by using ^{1}H NMR spectroscopy and elemental analysis. The synthesized compounds were selected by the National Cancer Institute (NCI) Developmental Therapeutic Program for the *in vitro* cell line screening to investigate their anticancer activity. The tested compounds displayed a weak to medium anticancer activity. The most sensitive cell lines turned out to be SNB-75 of CNS Cancer (GP = 74.84–85.73%) and UO-31, Renal cancer (GP = 71.53–82.16%) and to compound **10a** K-562 Leukemia cell lines (GP = 57.14).

Graphical abstract



Keywords

organic synthesis, 5-(1*H*-benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-ylcarboxilic acids, anticancer properties

Introduction

Benzimidazoles and its derivatives are an important group of heterocyclic compounds that show a wide range of pharmacological properties such as antitumor, antimicrobial, antihypertensive, antiviral, antiulcer, anticonvulsant, antiinflammatory activities. Their widespread use as scaffolds in medicinal chemistry establishes this moiety as a member of the class of privileged structures (Kaur et al. 2014; Arulmurugan et al. 2015; Salahuddin et al. 2017).

On the other hand a detailed study of rhodanine (2-thioxo-4-thiazolidone) derivatives has made it possible to identify a lot of highly active agents with a wide range of biological activity. Among the 5-arylidenerhodanines, a lot of lead- compounds that possess various activities, including antimicrobial, antituberculous, antiviral, antidiabetic, anti-inflammatory, antitumor, anticonvulsant activities have been also found. At the present stage of development of medical chemistry, the rhodanine motif is considered to be also privileged (Tomasić and Masic 2009; Kaminskyy et al. 2009, 2017a; Kaminskyy et al. 2017b).

These diverse biological applications of benzimidazole and rhodanine compounds have motivated new efforts in search for novel their hybrids derivatives with improved biological activity and diverse applications in pharmaceutical industry.

Experimental part

Materials and methods

All chemicals were of analytical grade and commercially available. All reagents and solvents were used without further purification and drying. All the melting points were determined in an open capillary and are uncorrected.^{1}H-spectra were recorded on a Varian Mercury 400 (400 MHz for ^{1}H) instrument with TMS or deuterated solvent as an internal reference. Satisfactory elemental analyses were determined on a Elementar Vario L cube instrument (C±0.17, H±0.21, N±0.19).

Chemistry

*2-Dichloromethyl-1H-benzoimidazole hydrochloride (**3**).* 0.2 Mol benzene-1,2-diamine, 0.26 mol dichloroacetic acid in 180 ml 20% hydrochloric acid were refluxed for 20 hours. Cooled to 0 °C, the precipitated of -dichloromethyl-1*H*-benzoimidazole hydrochloride was filtered off and washed with cold 20% hydrochloric acid and water. Yield 35g (74%). The obtained dichloromethyl-1*H*-benzoimidazole hydrochloride was used without further purification.

*1H-Benzoimidazole-2-carbaldehyde (**4**).* 0,14 Mol of dichloromethyl-1*H*-benzoimidazole hydrochloride та 0,7 mole sodium acetate water 300 ml water stirred for 2 hours at 90–95 °C. Cooled to room temperature. The precipitated of 1*H*-benzoimidazole-2-carbaldehyde was filtered off and washed with water, methanol and diethyl ether, dried and recrystallize from DMF. Yield 18,1r (89%), m. p. 235°C.

*General procedure of the synthesis 5-(1H-benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-ylcarboxilic acids **8-10**.* The solution of 3 mmol 4-oxo-2-thioxothiazolidin-3-ylcarboxilic acids, 3.6 mmol 1*H*-benzoimidazole-2-carbaldehyde and 3 mmol anhydrous sodium acetate in 7 ml acetic acid was refluxed for 1 hours. Cooled to room temperature. The precipitated was filtered off and washed with acetic acids and water, dried and recrystallize from acetic acid or acetic acid-DMF.

*[5-(1H-Benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]acetic acid **(8a)**.* Yield 77%; m.p. = 272 °C decomp. ^{1}H NMR (400 MHz, DMSO-d_6) d 13.49 (s, 1H, COOH), 13.16 (s, 1H, NH), 7.80 (d, *J* = 7.8 Hz, 1H, benzoimidazole), 7.68 (s, 1H, CH=), 7.65 (d, *J* = 7.7 Hz, 1H, benzoimidazole), 7.33 (dt, *J* = 15.3, 6.7 Hz, 2H, benzoimidazole), 4.70 (s, 2H, CH_2). Anal. Calculated for $C_{13}H_9N_3O_3S_2$ %: C, 48.89; H, 2.84; N, 13.16. Found %: C, 48.70; H, 2.78; N, 13.21.

*2-[5-(1H-Benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]-3-methylbutyric acid **(8b).*** Yield 94%; m.p. = 260 °C decomp. ^{1}H NMR (400 MHz, d DMSO-d_6) d 13.26 (s, 1H, COOH), 13.20 (s, 1H, NH), 7.80 (d, *J* = 7.8 Hz, 1H, benzoimidazole), 7.67 (s, 1H, CH=), 7.65 (d, *J* = 7.6 Hz, 1H, benzoimidazole), 7.38–7.27 (m, 2H, benzoimidazole), 5.19 (d, *J* = 8.6 Hz, 1H, CH), 2.72 (dt, *J* = 20.8, 10.4 Hz, 1H, CH), 1.20 (d, *J* = 6.5 Hz, 3H, CH_3), 0.76 (d, *J* = 6.9 Hz, 3H, CH_3). Anal. Calculated for $C_{16}H_{15}N_3O_3S_2$ %: C, 53.17; H, 4.18; N, 11.63. Found %: C, 53.18; H, 4.25; N, 11.55.

*2-[5-(1H-Benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]-4-methylpentanoic acid **(8c).*** Yield 99%; m.p. = 244 °C decomp. ^{1}H NMR (400 MHz, DMSO-d_6) d 13.36 (s, 1H, COOH), 13.18 (s, 1H, NH), 7.80 (d, *J* = 7.4 Hz, 1H, benzoimidazole), 7.64 (s, 2H benzoimidazole + CH=), 7.38–7.27 (m, 2H, benzoimidazole), 5.59 (s, 1H, CH), 2.18 (d, *J* = 9.6 Hz, 1H, CH), 2.02 (ddd, *J* = 13.0, 8.5, 4.3 Hz, 1H, CH), 1.50 (s, 1H, CH), 0.92 (d, *J* = 6.5 Hz, 3H, CH_3), 0.87 (d, *J* = 6.6 Hz, 3H, CH_3). Anal. Calculated for $C_{17}H_{17}N_3O_3S_2$ %: C, 54.38; H, 4.56; N, 11.19. Found %: C, 54.66; H, 4.62; N, 11.29.

*2-[5-(1H-Benzoimidazol-2-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-3-methylpentanoic acid **(8d).*** Yield 66%; m.p. = 259 °C decomp. ^{1}H NMR (400 MHz DMSO-d_6) d 13.25 (s, 1H, COOH), 13.20 (s, 1H, NH), 7.80 (d, *J* = 7.9 Hz, 1H, benzoimidazole), 7.66 (s, 1H, benzoimidazole), 7.64 (s, 1H, CH=), 7.33 (dt, *J* = 15.0, 6.9 Hz, 2H. benzoimidazole), 5.24 (d, *J* = 9.0 Hz, 1H, CH), 1.25 (s, 1H, CH), 1.16 (d, *J* = 6.4 Hz, 3H, CH_3), 0.96 (s, 1H, CH), 0.80 (t, *J* = 7.3 Hz, 3H, CH_3). Anal. Calculated for $C_{17}H_{17}N_3O_3S_2$ %: C, 54.38; H, 4.56; N, 11.19. Found %: C, 54.57; H, 4.44; N, 11.33.

*2-[5-(1H-Benzoimidazol-2-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-3-phenylpropionic acid **(8e).*** Yield 83%; m.p. = 258 °C decomp. ^{1}H NMR (400 MHz, DMSO-d_6) d 13.49 (s, 1H, COOH), 13.15 (s, 1H, NH), 7.76 (d, *J* = 7.9 Hz, 1H, benzoimidazole), 7.64 (d, *J* = 7.9 Hz, 1H, benzoimidazole), 7.60 (s, 1H, CH=), 7.32 (dt, *J* = 15.2, 6.8 Hz, 2H, benzoimidazole), 7.24–7.12 (m, 5H, Ph), 5.88 (s,

1H, CH), 3.51 (d, *J* = 5.6 Hz, 2H, CH_2). Anal. Calculated for $C_{20}H_{15}N_3O_3S_2$ %: C, 58.66; H, 3.69; N, 10.26. Found %: C, 58.74; H, 3.55; N, 10.25.

2-[5-(1H-Benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]-3-(4-hydroxy-phenyl)propionic acid ***(8f).*** Yield 99%; m.p. = 278 °C decomp. ^{1}H NMR (400 MHz, DMSO-d_6) d 13.18 (s, 1H, NH), 9.20 (s, 1H, OH), 7.77 (d, *J* = 7.9 Hz, 1H, benzoimidazole), 7.64 (d, *J* = 7.7 Hz, 1H, benzoimidazole), 7.60 (s, 1H, CH=), 7.32 (dt, *J* = 15.2, 7.0 Hz, 2H, benzoimidazole), 6.93 (d, *J* = 8.3 Hz, 2H, C_6H_4OH), 6.57 (d, *J* = 8.4 Hz, 2H, C_6H_4OH), 5.78 (s, 1H, CH), 3.36 (s, 2H, CH_2). Anal. Calculated for $C_{20}H_{15}N_3O_3S_2$ %: C, 56.46; H, 3.55; N, 9.88. Found %: C, 56.14; H, 3.41; N, 9.61.

3-[5-(1H-Benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]propionic acid ***(9)***. Yield 95%; m.p. = 262 °C decomp. ^{1}H NMR (400 MHz, DMSO-d_6) d 13.08 (s, 1H, NH), 12.44 (s, 1H, COOH), 7.78 (d, J = 7.8 Hz, 1H, benzoimidazole), 7.64 (s, 1H, CH=), 7.61 (s, 1H, benzoimidazole), 7.37–7.26 (m, 2H, benzoimidazole), 4.24 (t, J = 7.7 Hz, 2H, CH_2), 2.65 (t, J = 7.7 Hz, 2H, CH_2). Anal. Calculated for $C_{14}H_{11}N_3O_3S_2$ %: C, 50.44; H, 3.33; N, 12.60. Found %: C, 50.16; H, 3.29; N, 12.48.

3-[5-(1H-Benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]benzoic acid ***(10a).*** Yield 77%; m.p. = >280 °C. ^{1}H NMR (400 MHz, DMSO-d_6) d 13.12 (s, 1H, NH), 8.08 (dd, *J* = 5.8, 2.7 Hz, 1H, Ar), 8.04 (s, 1H, Ar), 7.83 (d, *J* = 7.6 Hz, 1H, benzoimidazole), 7.73–7.69 (m, 2H, Ar), 7.67 (d, *J* = 6.4 Hz, 1H, benzoimidazole), 7.65 (s, 1H, CH=), 7.38–7.28 (m, 2H, benzoimidazole). Anal. Calculated for $C_{18}H_{11}N_3O_3S_2$ %: C, 56.68; H, 2.91; N, 11.02. Found %: C, 56.44; H, 3.12; N, 11.25.

5-[5-(1H-Benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]-2-hydroxybenzoic acid ***(10b).*** Yield 90%; m.p. = 279 °C decomp. ^{1}H NMR (400 MHz, DMSO-d_6) d 13.10 (s, 1H), 7.88 (s, 1H, benzoimidazole), 7.64 (s, 1H, CH=), 7.61 (s, 1H, benzoimidazole) 7.56 (d, *J* = 8.9 Hz, 1H, Ar), 7.34 (s, 2H, benzoimidazole), 7.12 (d, *J* = 8.8 Hz, 1H, Ar). Anal. Calculated for $C_{18}H_{11}N_3O_4S_2$ %: C, 54.40; H, 2.79; N, 10.57. Found %: C, 54.02; H, 2.84; N, 10.66.

Pharmacology

Primary anticancer assay was performed at approximately-sixty human tumor cell lines panel derived from nine neoplasticdiseases, in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda (Monks et al. 1991; Boyd et al. 1995; Shoemaker 2006). Tested compounds were added to the culture at a single concentration (10^{-5}M) and the cultures were incubated for 48 h. End pointdeterminations were made with a protein binding dye, sulforhodamine B (SRB). Results for each tested compound were reported as the percent of growth of the treated cells when compared to the untreated control cells. The percentage growth was evaluated spectrophotometrically versus controls not treated with test agents.

Using the absorbance measurements [time zero, (*Tz*); control growth in the absence of drug, (*C*); and test growth in the presence of drug at the mentioned concentration (*Ti*)], the percentage growth inhibition was as:

$$[(Ti - Tz) / (C - Tz)] \times 100 \text{ when } Ti \geq Tz,$$

$$[(Ti - Tz) / Tz] \times 100 \text{ when } Ti < Tz.$$

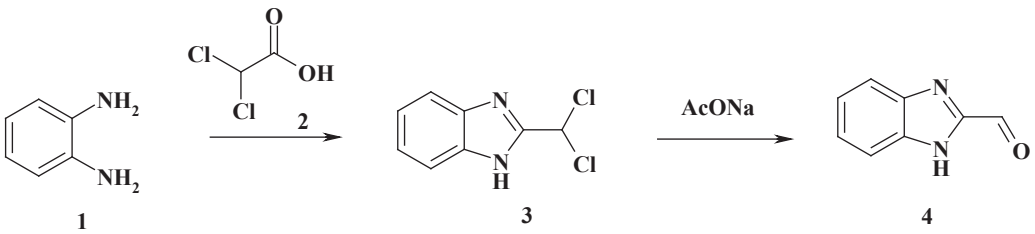
spectrophotometrically versus controls not treated with the test agents.

Results and discussion

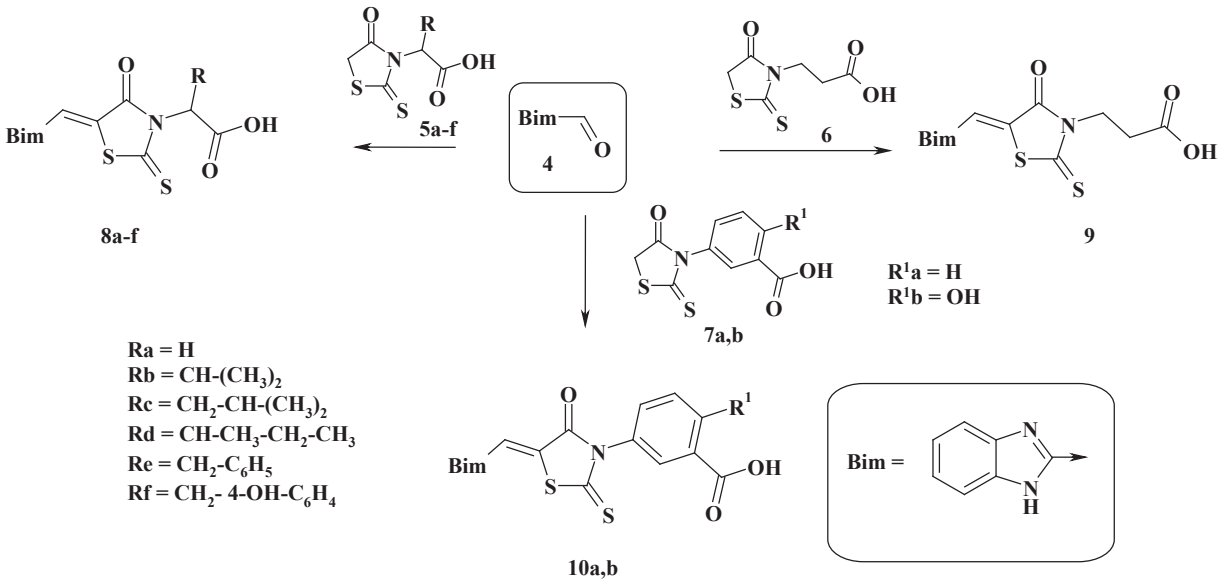
Chemistry

Continuing our works (Zimenkovskii et al. 2006; Matiichuk et al. 2008; Obushak et al. 2009; Pokhodylo et al. 2009a, b; Zubkov et al. 2010; Klenina et al. 2013, 2017; Chaban et al. 2014, 2016, 2017a, b, 2018a, b, 2019a, b; Lozynska et al. 2015; Zelisko et al. 2015; Tymoshuk et al. 2019), on the synthesis and study of biological activity of azole derivatives we prepare combinatorial libraries of [5-(1*H*-benzoimidazol-2-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl-carboxilc and investigated their anticancer activities. We have been developed the method of the synthesis of 1*H*-benzoimidazole-2-carbaldehyde (**4**). At first stage orthophenylenediamine (**1**) we condensed with dichloroacetic acid (**2**). As result 2-dichloromethyl-1*H*-benzoimidazole (**3**) was prepared. 2-dichloromethyl group under go hydrolysis by aqueous solution sodium acetate to form target 1*H*-benzoimidazole-2-carbaldehyde (**4**) (Scheme 1).

We investigated the reaction of 1*H*-benzoimidazole-2-carbaldehyde with 4-oxo-2-thioxothiazolidin-3-ylcarboxilic acids. We found that the optimal condition for the condensation is boiling acetic acid in presence of sodium acetate as a catalyst. As the result a series of novel derivatives [5-(1*H*-benzoimidazol-2-ylmethylene)-4-oxo-2-thioxo-thiazolidine-3-ylcarboxilc acid **8-10** were prepared (Scheme 2). The yields of the reaction products were 66–



Scheme 1. Synthesis of 1*H*-benzoimidazole-2-carbaldehyde.



Scheme 2. Synthesis of 5-(1*H*-benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin -3-ylcarboxilic acids.

99%. The resulting 5-(benzimidazolidine-2)rhodanine-3-carboxylic acids **8-10** are powders of yellow-orange, orange or orange-red color, well soluble in DMF, DMSO, boiling acetic acids, insoluble in alcohol, benzene, ethers and water.

The structure of compounds **8-10** was confirmed by ^{1}H NMR spectroscopy. In ^{1}H NMR spectra, signals for the protons of all the structural units were observed in their characteristic ranges. The chemical shift for the methylidene group is insignificantly displaced in a weak magnetic field, δ = 7,60–7,68 ppm and clearly indicated that only Z-isomers were obtained. NH proton of benzoimidazole ring shows the singlet at 13,08–13,20 ppm. Due to steric hindrances, the rotation around the N-C bond in the position 3 in compound **8b** is difficult and the methyl groups are not equivalent. The protons of methyl groups appear as two doublets at 0.76 and 1.20 ppm. Similar effects are observed in the case of compound **8c**.

Anticancer activity

The synthesized compounds were selected by the National Cancer Institute (NCI) Developmental Therapeutic Program (www.dtp.nci.nih.gov) for the *in vitro* cell line screening to investigate their anticancer activity. Anticancer assays were performed according to the NCI protocol, which is described elsewhere (Monks et al. 1991; Boyd et al. 1995; Boyd et al. 1997; Shoemaker et al. 2006). The human tumor cell lines were derived from nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers. Initially, a single high concentration was used (10 μM) in the full NCI 60-cell panel. In the screening protocol, each cell line was inoculated and preincubated for 24–48 h on a microtiter plate. Then test substances were added to the plate and the culture was incubated for further 48 h. End point determiations were made with a protein binding dye, sulforhodamine B. Results for each test agent were reported as the percent growth of the treated cells when compared to the untreated control cells and are shown in Table 1.

Table 1. Cytotoxic activity of the tested compounds in the concentration 10^{-5} M against 60 cancer cell lines.

Test compounds	Mitotic activity 60 cancer cell lines GP %		Most sensitive cell line (cancer line/type) GP, %
	Average growth, %	Range of growth, %	
8a	98.93	74.37–143.90	SNB-75 (CNS Cancer) 83.89
			MALME-3M (Melanoma) 81.63
			UO-31 (Renal Cancer) 74.37
8b	100.30	76.42–122.20	SNB-75 (CNS Cancer) 83.70
			UO-31 (Renal Cancer) 76.42
8c	100.49	78.88–127.16	SNB-75 (CNS Cancer) 78.88
			UO-31 (Renal Cancer) 80.50
8d	101.36	73.79–154.33	SNB-75 (CNS Cancer) 85.73
			UO-31 (Renal Cancer) 73.79
8e	101.23	81.40–136.54	SNB-75 (CNS Cancer) 81.40
			UO-31 (Renal Cancer) 82.16
8f	101.06	71.53–127.99	SNB-75 (CNS Cancer) 78.08
			CAKI-1 (Renal Cancer) 83.37
			UO-31 (Renal Cancer) 71.53
9	98.79	73.24–123.19	SNB-75 (CNS Cancer) 75.43
			UO-31 (CNS Cancer) 73.24
10a	99.38	57.14–111.51	K-562 (Leukemia) 57.14
			SNB-75 (CNS Cancer) 74.84
			UO-31 (Renal Cancer) 76.84
10b	101.36	73.79–154.33	SNB-75 (CNS Cancer) 85.73
			UO-31 (Renal Cancer) 73.79

The tested compounds displayed a weak to medium anticancer activity. The most sensitive cell lines turned out to be SNB-75 of CNS Cancer (GP = 74.84–85.73%) and UO-31, Renal cancer (GP = 71.53–82.16%) and to compound **10a** K-562 Leukemia cell lines (GP = 57.14). It should also be noticed that all compounds stimulate the growing of CCRF-CEM and SR Leukemia cell lines.

Conclusions

In our work, we presented an efficient synthesis and anticancer activity evaluation of some 5-(1*H*-benzoimidazol-2-ylmethylene)-4-oxo-2-thioxothiazolidin-3-ylcarboxilic acids. First, anticancer activity was detected among the compounds tested. Further optimization of the structure to improve their activities is currently in progress.

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