Synthesis and antitumor properties of some new N-(5-R-benzyl-1,3-thiazol-2-yl)-4,5-dihydro-1H-imidazole-2-carboxamides

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ABSTRACT

New N-(5-R-benzyl-1,3-thiazol-2-yl)-2-morpholin-4-yl-2-oxoacetamides have been prepared in good yields via the reaction of N-(5-R-benzyl-1,3-thiazol-2-yl)-2-chloroacetamides with sulfur and morpholine. These compounds react with ethylenediamine to form series of novel N-(5-R-benzyl-1,3-thiazol-2-yl)-4,5-dihydro-1H-imidazole-2-carboxamides with excellent yields. Anticancer activity screening of synthesized compounds was carried out within the framework of Developmental Therapeutic Program of the National Cancer Institute’s (DTP, NCI, Bethesda, Maryland, USA). It was showed that compounds are promising for new anticancer agents search. Keywords: organic synthesis, thiazole, imidazole, anticancer activity.

INTRODUCTION

2-Aminothiazole and their derivatives are of great importance in the organic and medicinal chemistry field (Nevagi, 2014; Chhabria et al., 2016; Aejazet et al., 2015). 2-Aminothiazole core is privileged structure for the compounds with a broad spectrum of activities, such as antibacterial (Vukovic et al., 2008), antifungal (Edwardset al., 2013), antitubercular (Al-Balas et al., 2009), anti-HIV (Venkatachalam et al., 2001), antioxidant (Chaban et al., 2019), pesticidal (Wilkes et al., 1991), anti-inflammatory (Holla et al., 2003) etc. Among 2-aminothiazole-based compounds 5-benzyl derivatives are of special interest over the last decades. Significant antimicrobial (Khalillet al., 2015) and anticancer activities of these compounds (Krasavin et al., 2009; Pokhodiol et al., 2014; Choi et al., 2011; Schiedel et al., 2016; Finiuk et al., 2017; Ostapiuk et al., 2018) have been reported. Aminothiazole derivatives have been also used as sensitive analytical reagents (Lozynska et al., 2015; Tymoshuk et al., 2019).

In this work we described the synthesis and anticancer activity of N-[5-R-benzyl]-1,3-thiazol-2-yl)-4,5-dihydro-1H-imidazole-2-carboxamides. The latter are the new class of organic compounds and their biological activity is not investigated. However, the synthesis and biological properties of compound with similar structure (1) were described. The antimicrobial (Sueleyman et al., 2005; Chaudhary et al., 2011) and anticancer (Beauchard et al., 2009) activity of such compounds were reported. They are also ligands of ad rencer a2 receptor (Saczzewski et al., 2006), inhibitors of cyclooxygenase (Tanaka et al., 1994), and glycogen synthase kinase-3 (Saczzewski et al., 2006), which can be considered as prominent anticancer targets (Satish and Woodgett, 2008).

MATERIALS AND METHODS

Chemicals and reagents

All chemicals were of analytical grade and commercially available. All reagents and solvents were used without further purification and drying.

Chemistry

All the melting points were determined in an open capillary and are uncorrected. 1H- spectra were recorded on a Varian Mercury 400 (400MHz for 1H). Mass spectra were run using Agilent 1100 series LC/MSD. Agilent Technologies Inc. with an API–ES/APCI ionization mode. The elemental analysis of experimental data on contents of Carbon, Hydrogen and Nitrogen were within ±0.3 % of the theoretical values.

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The general procedure for 2-morpholin-4-yl-N-aryl-2-thioxoacetamides (2a-e) preparation.

A suspension of 0.01 mol of powdered sulfur in 10 mL of morpholine was added for 5 min. The prepared solutions the chloroacetamides (0.05 mol) was added, and stirred for 60 min room temperature. The reaction mixture was poured into 200 mL water and left for 24 h. The solid precipitated was filtered off, washed with water (20 mL), dried and crystallized from ethanol.

N-[5-benzyl-1,3-thiazol-2-yl]-2-morpholin-4-yl-2-thioxoacetamide (2a)

Yield 86%, mp 188-190°C. 1H NMR (400 MHz, DMSO): δ = 12.61 (s, 1H, NH), 7.50-7.16 (m, 6H, C6H5 thioazole), 4.10 (s, 2H, PhCH2), 4.08 (d, J = 4.1 Hz, 2H, CH3), 3.73 (d, J = 4.0 Hz, 2H, CH3), 3.64 (s, 2H, CH2), 3.58 (s, 2H, CH2). Anal. calcld for C21H18N2O2S2: C, 55.31; H, 4.90; N, 12.15.

N-[5-(4-chlorobenzyl)-1,3-thiazol-2-yl]-2-morpholin-4-yl-2-thioxoacetamide (2b)

Yield 93%, mp 238-240°C. 1H NMR (400 MHz, DMSO): δ = 12.65 (s, 1H, NH), 7.36 (d, J = 8.2 Hz, 2H, C6H4), 7.34-7.26 (m, 3H, thiolele, C6H4), 4.10 (s, 2H, ArCH2), 4.07 (s, 2H, CH2), 3.73 (s, 2H, CH2), 3.64 (s, 2H, CH2), 3.58 (s, 2H, CH2). Anal. calcld for C17H14ClN2O2S2: C, 50.32; H, 4.22; N, 11.00. Found: C, 50.49; H, 4.30; N, 10.75.

N-[5-(2-chlorobenzyl)-1,3-thiazol-2-yl]-2-morpholin-4-yl-2-thioxoacetamide (2c)

Yield 99%, mp 191-193°C. 1H NMR (400 MHz, DMSO): δ = 12.67 (s, 1H, NH), 7.59-7.39 (m, 2H, C6H4), 7.37-7.17 (m, 3H, C6H5 thiolele), 4.21 (s, 2H, ArCH2), 4.14-3.93 (m, 2H, CH2), 3.72 (s, 2H, CH2), 3.63 (d, J = 4.1 Hz, 2H, CH3), 3.57 (s, 2H, CH2). Anal. calcld for C17H18ClN2O2S2: C, 50.32; H, 4.22; N, 11.00. Found: C, 50.17; H, 4.11; N, 11.15.

2-Morpholin-4-yl-2-thioxo-N-[5-[3-(trifluoromethyl)benzyl]-1,3-thiazol-2-yl]acetamide (2d)

Yield 81%, mp 187-189°C. 1H NMR (400 MHz, DMSO): δ = 12.73-12.64 (br.s, 1H, NH), 7.67 (s, 1H, C6H4), 7.63-7.54 (br.s, 3H, C6H4), 7.58 (s, 1H, thiolele), 4.23 (s, 2H, ArCH2), 4.11-4.03 (m, 2H, CH2), 3.72 (s, 2H, CH3), 3.64 (s, 2H, CH2), 3.61-3.53 (m, 2H, CH2). Anal. calcld for C17H18F3N2O2S2: C, 49.15; H, 3.88; N, 10.11. Found: C, 48.97; H, 3.72; N, 9.99.

N-[5-[2-chloro-5-(trifluoromethyl)benzyl]-1,3-thiazol-2-yl]-2-morpholin-4-yl-2-thioxoacetamide (2e)

Yield 71%, mp 207-209°C. 1H NMR (400 MHz, DMSO): δ = 12.67 (s, 1H, NH), 7.89 (s, 1H, C6H4), 7.71 (d, J = 7.3 Hz, 1H, C6H4), 7.66 (d, J = 7.0 Hz, 1H, C6H4), 7.36 (s, 1H, thiolele), 4.32 (s, 2H, ArCH2), 4.08 (s, 2H, CH2), 3.73 (d, J = 2.5 Hz, 2H, CH3), 3.64 (s, 2H, CH2), 3.59 (s, 2H, CH3). Anal. calcld for C23H19ClF3N2O2S2: C, 54.29; H, 3.36; N, 9.34. Found: C, 45.15; H, 3.23; N, 9.25.

The general procedure for 4,5-dihydro-1H-imidazole-2-carboxamides (3a-e) preparation

Method A. 0.0015 mol of the corresponding morpholin-4-yl-2-thioxoacetamide 2a-e and 4 mL of ethylenediamine was stirred at 50°C for 30 min. The mixture was cooled and poured into the 30 mL of water. The precipitate was filtered, washed with water, dried and recrystallized from an alcohol.

Method B. 1 g of sulfur was dissolved in ethylenediamine (10 mL), and stirred for 30 min. To the formed solution, 0.006 mol of the corresponding chloroacetamide was added with constant stirring for 10 min. The mixture was continued stirred for 30 min, then cooled and poured into the 100 mL of water and left for 1 day. The precipitate was filtered, washed with water, dried and recrystallized from an alcohol.

N-[5-benzyl-1,3-thiazol-2-yl]-4,5-dihydro-1H-imidazole-2-carboxamide (3a)

Yield 85%, mp 235°C. 1H NMR (400 MHz, DMSO): δ = 7.31-7.17 (m, 5H, C6H4), 7.14 (s, 1H, thiolele), 4.01 (s, 2H, ArCH2), 3.83 (s, 4H, 2CH2). ESI-MS: m/z 287 [M+H]+; Anal. calcld for C16H11N2O: C, 58.72; H, 4.93; N, 19.57. Found: C, 58.45; H, 4.82; N, 19.43.

N-[5-(4-chlorobenzyl)-1,3-thiazol-2-yl]-4,5-dihydro-1H-imidazole-2-carboxamide (3b)

Yield 97%, mp 230°C (decomp.). 1H NMR (400 MHz, DMSO): δ = 7.33 (d, J = 8.3 Hz, 2H, C6H4), 7.24 (d, J = 8.3 Hz, 2H, C6H4), 7.13 (s, 1H, thiolele), 4.00 (s, 2H, ArCH2), 3.81 (s, 4H, 2CH2). Anal. calcld for C16H12ClN2O: C, 52.42; H, 4.08; N, 17.46. Found: C, 52.15; H, 4.10; N, 17.67.

N-[5-(2-chlorobenzyl)-1,3-thiazol-2-yl]-4,5-dihydro-1H-imidazole-2-carboxamide (3c)

Yield 95%, mp 230°C (decomp.). 1H NMR (400 MHz, DMSO): δ = 7.42 (d, J = 7.4 Hz, 1H, C6H4), 7.35 (d, J = 7.3 Hz, 1H, C6H4), 7.31-7.21 (m, 2H, C6H4), 7.12 (s, 1H, thiolele), 4.12 (s, 2H, ArCH2),
N-[5-[3-(trifluoromethyl)benzyl]-1,3-thiazol-2-yl]-4,5-dihydro-1H-imidazole-2-carboxamide (3d)

Yield 79%, mp 253-255°C. 1H NMR (400 MHz, DMSO): δ = 7.57 (s, 1H, C6H4), 7.54-7.50 (m, 3H, C6H4), 7.17 (s, 1H, thiazole), 4.13 (s, 2H, ArCH2), 3.83 (s, 4H, CH2). Anal. calcd. for C25H18ClF3N4OS: C, 52.42; H, 3.57; N, 15.58. Found: C, 52.17; H, 3.97; N, 15.58.

Pharmacology
Cytotoxic activity against malignant human tumor cells

The tested compounds were added to the culture at a single concentration (10-5M) and the cultures were incubated for 48 h. Endpoint determinations were made with a protein binding dye, sulforhodamine B (SRB). Results for each tested compound were reported as the percent growth of the treated cells when compared to the untreated control cells. The percent growth was evaluated spectrophotometrically versus not treated controls. The percent growth inhibitory effects of the most active compounds were tested in vitro against the full panel of about 60 human tumor cell lines at 5-fold dilutions of five concentrations ranging from 10-11 to 10-8 M. The 48-h continuous drug exposure protocol was followed and an SRB protein assay was used to estimate cell viability or growth.

Using the seven absorbance measurements (time zero, Tz), control growth in the absence of drug, (C), and test growth in the presence of drug at the five concentration levels (Ti), the percent growth was calculated at each of the drug concentrations levels. Percent growth inhibition was calculated as:

\[
\frac{(Ti - Tz)}{(C - Tz)} \times 100 \text{ for concentrations for which } Ti < Tz
\]

\[
\frac{(Ti - Tz)}{Tz} \times 100 \text{ for concentrations for which } Ti \geq Tz
\]

Three dose-response parameters were calculated for each compound. Growth inhibition of 50% (GI50) was calculated from [(Ti – Tz)/(C – Tz)] × 100-50, which is the drug concentration resulting in a 50% lower net protein increase in the treated cells (measured by SRB staining) as compared to the net protein increase seen in the control cells. The drug concentration resulting in total growth inhibition (TGI) was calculated from Ti = Tz. The LC50 (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment was calculated from [(Ti – Tz)/Tz] × 100 = -50. Values were calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the value for that parameter was expressed as more or less than the maximum or minimum concentration was tested.

RESULTS AND DISCUSSION

Chemistry

Diazonium salts are important reagents in organic synthesis, which are easily obtained from readily available aromatic amines. The utilization of diazonium salts in the design and synthesis of combinatorial libraries of furane (Obushak et al., 2009; Gorak et al., 2009; Obushak et al., 2008), pyrazole (Matiuchuk et al., 2008), and 1,2,3-triazole (Obushak et al., 2009) derivatives, as well as some fused heterocycles (Chaban et al., 2019; Zelisko et al., 2015; Chaban et al., 2017; Zubkov et al., 2010; Klenina et al., 2017; Chaban et al., 2018) has been shown in our previous works. In this work we developed the new method of the synthesis of N-[5-R-benzyl]-1,3-thiazol-2-yl]-4,5-dihydro-1H-imidazole-2-carboxamide 3a-e based on diazonium salt as a started reagents. At the first stage 2-chloro-N-[5-(R-benzyl)-thiazol-2-yl]-acetamides were prepared via described protocol (Scheme 1) (Obushak et al., 2004; Ostapiuk et al., 2012).

It well known that chloroacetanilides react with sulfur and morfoline to form corresponding monothiooxamides (Yarovenko et al., 1999). But chloracetamide derivatives of heterocyclic amines were not investigated in this reaction. So, we study the reaction of chloracetamides 1a-e, sulfur and morfoline. The optimal conditions for the synthesis of target monothiooxamides were the next: firstly, sulfur was stirred with morfoline for 30min. (this time is needed to obtain a sufficient amount of polysulfides in the reaction mixture);
after, the corresponding chloroacetyl derivative was added and mixture and stirred for 1 hour. This protocol affords compounds 2a–e in a very high purity and in excellent yields (Scheme 2).

Synthesized N-[5-R-benzyl-1,3-thiazol-2-yl]-2-morpholin-4-yl-2-oxoacetamides 2a–ewere investigated in the reaction with ethylenediamine. It was found that the heating of reagents for 30 min at 50°C led to the closure of the imidazoline ring to form N-[5-R-benzyl]-1,3-thiazol-2-yl]-4,5-dihydro-1H-imidazole-2-carboxamides 3a–e(Scheme 2).

We examined the possibility of the synthesis of 4,5-dihydroimidazole-2-carboxamides 3a–e in one-pot reaction of 1, sulfur, and ethylenediamine (Scheme 2). The reaction was carried out by heating in DMF within 5–6 hours, but yields of the final products were lower and required additional crystallizations.
The structures of the obtained compounds were confirmed by $^1$H NMR, mass spectroscopy and elemental analysis. Spectroscopic data of all compounds were in accordance to the proposed structures. In $^1$H NMR spectra, signals of methylene group protons of N-[5-R-benzyl]-1,3-thiazol-2-yl]-4,5-dihydro-1H-imidazole-2-carboxamides appear as a singlets at 3.81-3.84 ppm. Such a character of the spectrum is due to a rapid tautomeric transformation (Scheme 3).

For the same reason, the NH protons of the amide group of the 4,5-dihydro-1H-imidazole ring do not appear at all. Signals of protons of the methylene group of the benzyl radical are at 4.00 - 4.13 ppm. The 4-H proton signals of the thiazole moiety are at 7.12 - 7.17 ppm.

Table I. Overview of the preliminary anticancer assay at single dose concentration of 10μM.

| Test compounds | Average growth, % | Range of growth, % | Most sensitive cell line (cancer line/type) GP% | Positive cytostatic effecta |
|----------------|-------------------|--------------------|-----------------------------------------------|-----------------------------|
| 2a             | 100.84            | 78.99-115.40       | UO-31 (RenalCancer) 78.99;                     | 0/60                        |
| 2b             | 103.91            | 80.33-123.38       | UO-31 (Renal Cancer) 80.33;                    | 0/60                        |
| 2c             | 99.72             | 69.30-110.27       | CCRF-CEM (Leukemia) 69.30; UO-31 (RenalCancer) 72.21 | 1/60                        |
| 2d             | 100.00            | 74.53-118.71       | UACC-62 (Melanoma) 74.77; CAKI-1 (RenalCancer) 79.31; UO-31 (RenalCancer) 74.53 | 2/60                        |
| 2e             | 90.13             | 67.14-114.39       | UACC-62 (Melanoma) 72.57; CAKI-1 (RenalCancer) 67.14; UO-31 (RenalCancer) 69.52 | 4/60                        |
| 3a             | 90.59             | 57.10-120.12       | CCRF-CEM (Leukemia) 54.37; HL-60(TB) (Leukemia) 40.80; K-562 (Leukemia) 48.68; MOLT-4 (Leukemia) 69.14; RPMI-8226 (Leukemia) 58.04; EKVX (Non-Small Cell Lung Cancer) 64.09; NCI-H23 (Non-Small Cell Lung Cancer) 68.17; HCT-15 (Colon Cancer) 67.36; SK-MEL-5 (Melanoma) 62.84; UO-31 (Renal Cancer) 59.68 | 15/60                       |
| 3b             | 80.86             | 40.80-121.62       | CCRF-CEM (Leukemia) 13.34; HL-60(TB) (Leukemia) 8.60; K-562 (Leukemia) 10.33; MOLT-4 (Leukemia) 17.55; SR (Leukemia) 19.89; A549/ATCC (Non-Small Cell Lung Cancer) 23.55; NCI-H460 (Non-Small Cell Lung Cancer) 13.67; HCT-116 (Colon Cancer) 36.93; KM12 (Colon Cancer) 35.70; SF-295 (CNS Cancer) 4.89; SF-539 (CNS Cancer) 2.96; LOX IMVI (Melanoma) 53.09; M14 (Melanoma) 30.71; MDA-MB-435 (Melanoma) 30.36; UACC-62 (Melanoma) 38.95; OVCAR-4 (Ovarian Cancer) 31.04; OVCAR-8 (Ovarian Cancer) 34.53; NCI/ADR-RES (Ovarian Cancer) 36.71; 786-0 (Renal Cancer) 45.35; ACHN (Renal Cancer) 33.01; Caki-1 (Renal Cancer) -53.18; SN12C (Renal Cancer) 38.86; UO-31 (Renal Cancer) -17.10 | 50/60                       |
| 3c             | 41.92             | -53.18-95.07       |                                              |                             |

aRatio between number of cell lines with percent growth from 0 to 75 and total number of cell lines.
Table 2. In vitro anticancer activity at 60 human tumor cell lines for compound 3c.

| Disease    | Cell line | GI50, µM | TGI, µM | Disease    | Cell line | GI50, µM | TGI, µM |
|------------|-----------|----------|---------|------------|-----------|----------|---------|
| Leukemia   | CCRF-CEM  | 1.56     | >100    | Melanoma   | LOX IMVI  | 0.15     | 1.12    |
|            | HL-60(TB) | 2.80     | 11.5    |            | MALME-3M  | 65.9     | >100    |
|            | K-562     | 3.93     | >100    |            | M14       | 6.85     | >100    |
|            | MOLT-4    | 2.23     | >100    |            | MDA-MB-435| 7.65     | >100    |
|            | RPMI-8226 | 5.38     | >100    |            | SK-MEL-2  | 11.0     | 55.4    |
|            | SR        | 1.77     | >100    |            | SK-MEL-28 | 54.6     | >100    |
| Lung cancer| A549/ATCC | 2.23     | >100    | Ovarian Cancer | IGROV1 | 3.92     | >100    |
|            | EKVX      | 5.70     | >100    |            | UACC-257  | 5.99     | >100    |
|            | HOP-62    | 19.4     | 58.5    |            | UACC-62   | 11.6     | 79.0    |
|            | HOP-92    | 2.85     | 10.3    |            | IGROV1    | 3.92     | >100    |
|            | NCI-H226  | 2.57     | 80.9    |            | OV1CAR-3  | 4.99     | >100    |
|            | NCI-H23   | 6.98     | >100    |            | OV1CAR-4  | 12.3     | >100    |
|            | NCI-H322M | >100     | >100    |            | OV1CAR-5  | 12.2     | >100    |
|            | NCI-H460  | 3.20     | >100    |            | OV1CAR-B  | 4.60     | >100    |
|            | NCI-H522  | 1.97     | 58.1    |            | NCI/ADR-RES| 6.01     | >100    |
| Colon      | COLO 205  | 8.68     | >100    | Renal Cancer| 40.7     | >100    |
| Cancer     | HCC-2998  | 16.2     | >100    | Cancer      | 786-0     | 3.71     | 35.1    |
|            | HCT-116   | 7.27     | >100    |            | A498      | 41.3     | >100    |
|            | HCT-15    | 6.13     | >100    |            | ACHN      | 3.93     | 19.6    |
|            | HT29      | 5.81     | >100    |            | Caki-1    | 3.43     | 28.3    |
|            | KM12      | 2.89     | 23.1    |            | RXF 393   | 4.27     | 20.3    |
|            | SW-620    | 7.07     | >100    |            | SN12C     | 7.89     | 21.2    |
| CNS Cancer | SF-268    | 5.30     | >100    | Breast Cancer| 3.21     | 9.94    |
|            | SF-295    | 2.71     | 9.79    |            | UO-31     | 2.88     | 15.5    |
|            | SF-539    | 3.95     | >100    |            | MCF7      | 7.73     | >100    |
|            | SNB-19    | 2.99     | >100    |            | MDA-MB    | >100     | >100    |
|            | SNB-75    | 1.57     | 4.43    |            | 231/ATCC  | 4.81     | >100    |
|            | U251      | 7.83     | >100    |            | HS 578T   | 8.47     | 5.99    |
| Prostate   | PC-3      | 6.52     | >100    |            | BT-549    | 8.33     | >100    |
| Cancer     | DU-145    | 1.54     | >100    |            | T-47D     | 5.13     | >100    |

Pharmacology

Among newly synthesized compounds substances 2a-e and 3a-c were selected by the National Cancer Institute (NCI) Developmental Therapeutic Program for the in vitro cell line screening to investigate their anticancer activity. The human tumor cell lines were derived from nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. Primary anticancer assays were performed according to the DTP protocol (NCI USA), which was described elsewhere (Boyd et al., 1995; Boyd et al., 1997; Shoemaker et al., 2006). The results of primary screening are reported as the percent of cancer cell line growth (GP%) (Table I). The range of GP% shows the lowest and the highest values found for different cancer cell lines.

Tested compounds 2a-e showed a low antitumor activity in the in vitro screening assay. For the compounds 3a and 3b the average levels of cell growth (GPMean) were 90.59% and 80.86% respectively. It should be noted, that selective action of tested compounds was observed towards Leukemia cell lines (range of GP= 57.10-71.88% (compound 3a) and GP= 35.01-69.14% (3b). The most active compound 3c was found to be effective against 50 cell lines with the average cell growth.
percent (GPmean) of 41.92%. Moreover, this derivative demonstrated cytotoxic effect on Leukemia cell lines CCRF-CEM (GP=13.34%), MOLT-4 (GP=17.55%) and SR (GP=19.89%), Melanoma cell lines LOXIMVI (GP=53.09%), Renal Cancer cell lines CAKI-1 (GP=53.18%), UO-31 (GP=17.10%). Significant cytostatic effect was observed toward Leukemia cell lines HL-60(TB) (GP=8.60), CNS Cancer cell lines SF-295 (GP=4.89) and SF-539 (GP=2.96).

Finally, compound 3c was selected for an advanced assay against a panel of approximately sixty tumor cell lines at 10-fold dilutions of five concentrations (100µM, 10µM, 1.0µM, 0.1µM and 0.01µM) (Table II). The percentage of growth was evaluated spectrophotometrically versus controls not treated with test agents after 48h exposure and using SRB protein assay to estimate cell viability or growth. 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 GI50, giving an average activity parameter over all cell lines for the tested compound. For the MG_MID calculation, insensitive cell lines were included with the highest concentration tested.

The mentioned derivative demonstrated a high activity toward the SR Leukemia cell lines (GI50=1.77µM), NCI-H522NSC lung cancer cell lines (GI50=1.97µM), SNB-75 CNS Cancer cell lines (GI50=1.57µM), and DU-145 Prostate Cancer cell lines (GI50=1.97µM). For some cancer cell lines the cytotoxic effect was observed: HOP-92 Non-Small Cell Lung Cancer cell lines LC50=62.0 µM; LOX IMVI Melanoma cell lines LC50=4.48µM; and RXF Renal Cancer cell lines LC50=69.5µM.

The selectivity index (SI) obtained by dividing the full panel MG-MID (µM) of the compound 3c by its individual subpanel MG-MID (µM) was considered a measure of compound’s selectivity. Ratios between 3 and 6 refer to moderate selectivity, ratios greater than 6 indicate high selectivity toward the corresponding cell line, while compounds not meeting either of the criteria are rated non-selective (Rostom, 2006). In this context, the active compound 3c demonstrates moderate selectivity toward Leukemia cell lines at the GI50 levels (SI=3.08) and low selectivity toward Renal Cancer cell lines (SI=2.49) at the TGI levels (Table III).
The screening results revealed that compound 3c possesses potent in vitro antitumor activity, with MG-MID = 9.01 in comparison with standard anticancer agent 5-fluorouracil (5-FU). Cisplatin MG-MID = 22.60 and Curcumin MG-MID = 7.41 (Table IV).

CONCLUSIONS

Here, we have shown the development of new efficient protocol for N-[5-benzyl-1,3-thiazol-2-yl]-4,5-dihydro-1H-imidazole-2-carboxamides synthesis. The row of N-[5-R-benzyl-1,3-thiazol-2-yl]-4,5-dihydro-1H-imidazole-2-carboxamides was synthesized with high yields. Primary anticancer assay of synthesized compounds was performed at approximately sixty human tumor cell lines panel within DTP protocol (Drug Evaluation Branch, National Cancer Institute, Bethesda, USA). The compounds with significant levels of anticancer activities have been found, that can be used for further optimization. N-[5-(2-chlorobenzyl)-1,3-thiazol-2-yl]-4,5-dihydro-1H-imidazole-2-carboxamide (3c) could be treated as prospective antitumor agent. The results prove the necessity of further investigations to clarify the features underlying the antitumor effect of tested compounds.

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