Synthesis and anticancer properties of \( N-(5-R\text{-}benzyl\text{-}1,3\text{-}thiazol-2-yl})\text{-}2,5\text{-}dimethyl\text{-}3\text{-}furamides

Y. E. Matiichuk\(^1\), YV. Ostapiuk\(^2\), TI. Chaban\(^1\), VV. Ogurtsov\(^1\), VS. Matiychuk\(^2\)

\(^1\) Danylo Halytsky Lviv National Medical University
69, Pekarska Str., Lviv, Ukraine, 79010

\(^2\) Ivan Franko National University of Lviv
4, Hrushevskoho Str., Lviv, Ukraine, 79005
matichyk@mail.lviv.ua

**Aim.** Study of the synthesis and anticancer activity of a series of \( N-(5-R\text{-}benzyl\text{-}1,3\text{-}thiazol-2-yl})\text{-}2,5\text{-}dimethyl\text{-}3\text{-}furamides.**

**Methods.** Organic synthesis, analytical and spectral methods, pharmacological screening. **Results.** \( N-(5-R\text{-}benzyl\text{-}1,3\text{-}thiazol-2-yl})\text{-}2,5\text{-}dimethyl\text{-}3\text{-}furamides 7a-g have been prepared in good yields by the reaction of 2-amino-5-(R-benzyl)thiazoles with 2,5-dimethyl-3-furoylchloride. Their structure was confirmed by \(^1\)H NMR spectroscopy and microanalyses. The synthesized compounds have been evaluated for their anticancer activity against 60 cancer lines in the concentration of 10 \( \mu M \). The human tumour cell lines were derived from nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. It was found that compounds 7d,e,g exhibit a high activity with GP = 29.05–35.02 % whereas 7a-c,f – moderate activity with GP = 60.31–67.36 %. The most active compound 7g showed a high inhibition activity (GI\(_{50}<10 \mu M\)) against 54 of 58 human tumor cell lines with average GI\(_{50}\) values of 4.22 \( \mu M \) and the colon cancer subpanel demonstrated the highest sensitivity with [a] mean GI\(_{50}\) value of 2.53 \( \mu M \). The most sensitive line was T-47D (BreastCancer, GI\(_{50} = 0.088 \mu M\)). [The] MG-MID values for the most active compound 7g are less compared with those for 5-fluorouracil, curcumin and cisplatin when testing in the same manner. **Conclusions.** A series of new \( N-(5-R\text{-}benzyl\text{-}1,3\text{-}thiazol-2-yl})\text{-}2,5\text{-}dimethyl\text{-}3\text{-}furamides were prepared. The compounds with high anticancer activity have been identified.

**Keywords:** organic synthesis, arylation, acylation, 2-amino-5-arylmethylothiazole, anticancer activity.

**Introduction**

The diazonim salts are very important as starting materials in organic synthesis. In our previous works we have developed [the] methods of synthesis of furane [1,2], thiophene [3],...
pyrazole [4], thiazole[5-7], triazole [8] derivatives based on using diazonium salt as starting reagents. The condensed compounds were also prepared [9-11]. The advantage of the proposed method is that the synthesis of arene-diazonium salts from low-cost aromatic amines abundantly available in the market is very simple. It means that the variety of different substitutes in organic molecules can be introduced, which is very important for the purposes of medical chemistry. One of the heterocyclic core prepared by this strategy was 2-aminothiazole [5-7, 12], a privileged structure in medical chemistry[13-16].

The present work is devoted to the synthesis and evaluation of anticancer activity [of] 5-(5-R-benzyl-1,3-thiazol-2-yl)-2,5-dimethyl-3-furamides using diazonium salts as a starting material. Noteworthy, 5-1,3-thiazol-2-yl furamides display biological activity of different kind such as antivarial [17] and antibacterial [18], they are effective against both replicative and latent mycobacterium tuberculosis [19, 20], malaria parasites [21], as well as the ligands of adenosine receptors [22], allosteric glucokinase activators [23] and the inhibitors of the Src family kinase p56Lck [24]. The anticancer properties of N-1,3-thiazol-2-yl furamides were also reported [25-28]. Considering the above, the synthesis of N-(1,3-thiazol-2-yl)-2,5-dimethyl-3-furamides and the investigation of their biological properties are an actual task.

Materials and Methods
All starting materials were purchased from Merck and used without purification. NMR spectra were determined with Varian Mercury 400 (400 MHz) spectrometer, in DMSO-d6. Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by thin-layer chromatography performed with Merck Silica Gel 60 F254 aluminum sheets.

5-R-benzylthiazol-2-ylamines 5a-g were prepared according to the procedure described in [12].

N-(5-R-benzyl-1,3-thiazol-2-yl)-2,5-dimethylfuran-3-carboxamides(7a-g)

General procedure. To a solution of 0.01 mol of 2-aminothiazole 5a-g and 1 ml of triethylamine in 30 ml of anhydrous dioxane we added under stirring 1.59g (0.01 mol) of 2,5-dimethyl-3-furoyl chloride 6. The mixture was left for 0.5 h and diluted with water, and the precipitate was filtered off, washed with water, and recrystallized from mixture alcohol – DMF.

N-(5-benzyl-1,3-thiazol-2-yl)-2,5-dimethylfuran-3-carboxamide (7a) Yield 80 %, m.p. 157-158 °C. 1HNMR (400 MHz, [D6]DMSO): δ = 11.90 (s, 1H, NH), 7.38–7.25 (m, 5H, C6H4, thiazole), 7.22 (t, J = 7.0 Hz, 1H, C6H4), 6.81 (s, 1H, furane), 4.08 (s, 2H, CH2), 2.49 (s, 3H, CH3), 2.22 (s, 3H, CH3). Anal. Calcd. for C17H16N2O2S: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.22; H, 5.09; N, 8.88.

2,5-Dimethyl-N-[5-(3-methylbenzyl)-1,3-thiazol-2-yl]furan-3-carboxamide (7b) Yield 76 %, m.p. 116-117 °C. 1HNMR (400 MHz, [D6]DMSO): δ = 11.90 (s, 1H, NH), 7.27 (t, J = 7.4 Hz, 1H, C6H4), 7.19 (s, 1H, thiazole), 7.12–6.99 (m, 3H, C6H4), 6.81 (s, 1H, furane), 4.03 (s, 2H, CH2), 2.49 (s, 3H, CH3), 2.27 (s, 3H, CH3), 2.22 (s, 3H, CH3). Anal. Calcd. for C18H18N2O2S: C, 66.23; H, 5.16; N, 8.97. Found: C, 65.22; H, 5.09; N, 8.88.
5.56; N, 8.58. Found: C, 66.06; H, 5.49; N, 8.41.

2,5-Dimethyl-N-[5-(4-methylbenzyl)-1,3-thiazol-2-y1]furan-3-carboxamide (7c). Yield 84 %, m.p. 155-156 °C. 1H NMR (400 MHz, [D$_6$]DMSO): δ = 11.89 (s, 1H, NH), 7.25 (s, 1H, thiazole), 7.15 (d, J = 7.9 Hz, 2H, C$_6$H$_4$), 7.11 (d, J = 7.9 Hz, 2H, C$_6$H$_4$), 6.80 (s, 1H, furane), 4.02 (s, 2H, CH$_2$), 2.49 (s, 3H, CH$_3$), 2.26 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$). Anal. Calcd for C$_{18}$H$_{18}$N$_2$O$_2$S: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.11; H, 5.48; N, 8.47.

N-[5-(4-Ethylbenzyl)-1,3-thiazol-2-y1]-2,5-dimethylfuran-3-carboxamide (7d). Yield 74 %, m.p. 123-124 °C. 1H NMR (400 MHz, [D$_6$]DMSO): δ = 11.89 (s, 1H, NH), 7.26 (s, 1H, thiazole), 7.17 (d, J = 8.1 Hz, 2H, C$_6$H$_4$), 7.14 (d, J = 8.2 Hz, 2H, C$_6$H$_4$), 6.81 (s, 1H, furane), 4.03 (s, 2H, CH$_2$), 2.56 (q, J = 7.6 Hz, 2H, CH$_2$), 2.49 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 1.15 (t, J = 7.6 Hz, 3H, CH$_3$) Anal. Calcd for C$_{19}$H$_{20}$N$_2$O$_2$S: C, 67.03; H, 5.92; N, 8.23. Found: C, 66.88; H, 5.80; N, 8.11.

N-[5-(4-Methoxybenzyl)-1,3-thiazol-2-y1]-2,5-dimethylfuran-3-carboxamide (7e): Yield 88 %, m.p. 155-156 °C. 1H NMR (400 MHz, [D$_6$]DMSO): δ = 11.88 (s, 1H, NH), 7.24 (s, 1H, thiazole), 7.18 (d, J = 8.5 Hz, 2H, C$_6$H$_4$), 6.87 (d, J = 8.6 Hz, 2H, C$_6$H$_4$), 6.80 (s, 1H, furane), 4.00 (s, 2H, CH$_2$), 3.72 (s, 3H, OCH$_3$), 2.49 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$). Anal. Calcd for C$_{18}$H$_{18}$N$_2$O$_3$S: C, 63.14; H, 5.30; N, 8.18. Found: C, 63.01; H, 5.22; N, 8.19.

N-[5-(4-Fluorobenzyl)-1,3-thiazol-2-y1]-2,5-dimethylfuran-3-carboxamide (7f). Yield 91 %, m.p. 146-147 °C. 1H NMR (400 MHz, [D$_6$]DMSO): δ = 11.91 (s, 1H, NH), 7.31 (dd, J$_{HH}$ = 8.1, J$_{HF}$ = 5.7 Hz, 2H, C$_6$H$_4$), 7.27 (s, 1H, thiazole), 7.13 (t, J = 8.8 Hz, 2H, C$_6$H$_4$), 6.81 (s, 1H, furane), 4.08 (s, 2H, CH$_2$), 2.49 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$). Anal. Calcd for C$_{17}$H$_{15}$FN$_2$O$_2$S: C, 61.80; H, 4.57; N, 8.35. Found: C, 61.60; H, 4.53; N, 8.35.

N-[5-(4-Chlorobenzyl)-1,3-thiazol-2-y1]-2,5-dimethylfuran-3-carboxamide (7g). Yield 93 %, m.p. 140-141 °C. 1H NMR (400 MHz, [D$_6$]DMSO): δ = 11.90 (s, 1H, NH) 7.35 (2H, J = 8.3 Hz, ClC$_6$H$_4$), 7.30-7.25 (3H, ClC$_6$H$_4$ + thiazole), 6.81 (s, 1H, furane) 4.94 (s, 2H, CH$_2$), 2.49 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$). Anal. Calcd for C$_{17}$H$_{15}$FN$_2$O$_2$S: C, 61.73; H, 4.57; N, 8.47. Found: C, 61.60; H, 4.53; N, 8.35.

 Results and Discussion

A series of new N-(5-R-benzyl-1,3-thiazol-2-y1)-2,5-dimethyl-3-furamides were prepared according to the scheme. The diazonium salts were used as starting material. They react with acroleine under the Meerwein reaction condition [29] to form 3-aryl-2-chloropropanales [12]. These aldehydes were converted into 5-R-benzyl-thiazol-2-ylamines with high yields according to the previously reported synthetic protocols [12]. The acylation of 5-(R-benzyl)-1,3-thiazole-2-amines was carried out by the classical method using 2,5-dimethyl-3-furol chloride. The obtained amides 7a-g are high-melted substances of white or grey colour, poorly soluble in non-polar solvents, good in DMSO and DMF.

The structure of synthesized compounds was confirmed by 1H NMR and microanalyses. In [the] 1H NMR spectra, the signals for the protons of all the structural units were observed in their characteristic ranges. The protons of thiazole and furan rings were recorded...
as singlet at δ 7.24–7.27 ppm and 6.80–6.81 ppm respectively. H–N amide protons appeared as a singlet at δ 11.88–11.91 ppm and methylene groups at 4.00–4.08 ppm. Two other singlets at δ 2.49 and 2.22 ppm indicated methyl groups of furan rings.

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. The primary anticancer assay was performed at approximately sixty human tumor cell lines panel derived from nine neoplastic diseases, in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda [30-33]. The tested compounds were added to the culture at a single concentration (10⁻⁵M) and the cultures were incubated for 48 h. Determination of the endpoint was 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.

The screening results are shown in Table 1. The synthesized compounds display different levels of activity in the in vitro screening on the tested cell lines. Compounds 7d,e,g showed [a] high activity with GP = 29.05–35.02 % whereas 7a-c,f – [a] moderate [activity] with GP = 60.31–67.36 %. Compounds 7d,e were very sensitive to the cell lines MDA-MB-435 (Melanoma), HL-60(TB) (Leukemia), SNB-75 (CNS Cancer) and compounds 7g – to MDA-MB-435 (Melanoma), UACC-62 (Melanoma). In all mentioned cases the cytotoxic effect was observed. Noteworthy also, compounds 7a-c stimulate the activity of COLO 205 (Colon Cancer) cell line with GP = 113.99–115.05 %.

\[
\begin{align*}
1, 3, 5, 7 & \ R = H(a), 3-CH_3(b), 4-CH_3(c), 4-C_2H_5(d), 4-CH_3O(e), 4-F(f), 4-Cl(g) \\
\text{Scheme. Synthesis of } & \text{N-(5-R-benzyl-1,3-thiazol-2-yl)-2,5-dimethyl-3-furamides 7a-g.}
\end{align*}
\]
Finally, compound 7g was selected for an advanced assay against a panel of approximately sixty tumor cell lines at 10-fold dilutions of five concentrations (100 µM, 10 µM, 1.0 µM, 0.1 µM and 0.01 µM) (Table 2). The percentage growth was evaluated spectrophotometrically versus controls not treated with the test agents after 48-h exposure using the SRB protein assay to estimate the cell viability or growth. The dose–response parameters were calculated for each cell line: GI50 – molar concentration of the compound leading to
the 50% inhibition of net cell growth; TGI – molar concentration of the compound leading to the total inhibition; and LC$_{50}$ – molar concentration of the compounds leading to [the] 50% net cell death. Furthermore, the mean graph midpoints (MG_MID) were calculated for GI$_{50}$, giving an average activity parameter over all cell lines for the tested compound. For the calculation of MG_MID, the insensitive cell lines were included with the highest concentration tested.

The most active compound 7g showed [a] high inhibition activity (GI$_{50}$<10 µM) against 54 of 58 human tumor cell lines with [the] average GI$_{50}$ values of 4.22 µM and the colon cancer subpanel demonstrated the highest sensitivity with [the] mean GI$_{50}$ value of 2.53 µM (Table 2). The most sensitive line was T-47D.

Table 2. Influence of compound 7g on the growth of tumor cell lines

| Disease            | Cell line   | GI$_{50}$, µM | Disease            | Cell line   | GI$_{50}$, µM |
|--------------------|-------------|---------------|--------------------|-------------|---------------|
| Leukemia           | CCRF-CEM    | 5.84          | Melanoma           | LOX IMVI    | 3.31          |
|                    | HL-60(TB)   | 3.03          |                    | MALME-3M   | 6.12          |
|                    | K-562       | 1.31          |                    | M14         | 2.83          |
|                    | MOLT-4      | 3.18          |                    | MDA-MB-435 | 1.58          |
|                    | RPMI-8226   | 4.97          |                    | SK-MEL-2   | 1.70          |
|                    | SR          | 0.657         |                    | SK-MEL-28  | 6.77          |
| Non-Small Cell     | A549/ATCC   | 1.22          | Ovarian Cancer     | IGROV1      | 7.82          |
| Lung Cancer        | EKVX        | 4.15          |                    | OVCAR-3     | 3.76          |
|                    | HOP-62      | 4.63          |                    | OVCAR-4     | 1.02          |
|                    | HOP-92      | 4.83          |                    | OVCAR-5     | -             |
|                    | NCI-H226    | 21.8          |                    | OVCAR-8     | 5.75          |
|                    | NCI-H23     | 3.87          |                    | NCI/ADR-RES | 2.21          |
|                    | NCI-H322M   | 11.9          |                    | SK-OV-3     | 12.1          |
|                    | NCI-H460    | 0.432         | Renal Cancer       | 786-0       | 2.42          |
|                    | NCI-H522    | 2.64          |                    | A498        | 2.96          |
|                    | COLO 205    | 4.90          |                    | ACHN        | -             |
| Colon Cancer       | HCC-2998    | 0.740         |                    | CAKI-1      | 0.798         |
|                    | HCT-116     | 3.54          |                    | RXF 393     | 4.88          |
|                    | HCT-15      | 0.728         |                    | SN12C       | 5.07          |
|                    | HT29        | 3.64          |                    | TK-10       | 9.80          |
|                    | KM12        | 0.893         |                    | UO-31       | 1.93          |
| CNS Cancer         | SF-268      | 3.73          | Breast Cancer      | MCF7        | 0.659         |
|                    | SF-295      | 0.589         |                    | MDA-MB-231/ATCC | 1.51        |
|                    | SF-539      | 3.85          |                    | HS 578T     | 12.8          |
|                    | SNB-19      | 9.37          |                    | BT-549      | 3.70          |
|                    | SNB-75      | 12.6          |                    | T-47D       | 0.088         |
|                    | U251        | 3.58          |                    | MDA-MB-468  | 1.70          |
| Prostate Cancer    | PC-3        | 5.92          |                    |             |               |
|                    | DU-145      | 3.21          |                    |             |               |
Synthesis and anticancer properties of N-(5-R-benzyl-1,3-thiazol-2-yl)-2,5-dimethyl-3-furamides (Breast Cancer, GI$_{50}$ = 0.088 µM). [The] Values of TGI and LC$_{50}$ were above the 100 µM except [the] data of TGI for Non-Small Cell Lung Cancer cell lines HOP-92 (TGI = 62.5 µM), CNS Cancer cell lines SF-295 (TGI = 40.0 µM) and SNB-75 (TGI = 90.1 µM), Melanoma cell lines MDA-MB-435 (TGI = 5.10 µM), SK-MEL-5 (TGI = 31.3 µM) and UACC-62 (TGI = 90.1 µM), Renal Cancer cell line MDA-MB-468 (TGI = 56.8 µM), RXF 393 (TGI = 63.7 µM) and Breast Cancer cell line MDA-MB-468 (TGI = 8.29 µM).

The selectivity index (SI) obtained by dividing the full panel MG-MID (µM) of the compound 7g by its individual subpanel MG-MID (µM) was considered as a measure of compound’s selectivity. The value between 3 and 6 refers to moderate selectivity. The index SI greater than 6 indicates a high selectivity toward the corresponding cell line, whereas the compounds meeting neither of the criteria are rated as non-selective [34]. In this context, the active compound 7g does not demonstrate any selectivity toward all tested cell lines (Table 3).

Table 3. Anticancer selectivity pattern of the most active compound 7g at the GI$_{50}$ (C, µM) levels

| Cpd | Parameters | Cpd | Subpanel tumor cell lines | L | NSCLC | ColC | CNSC | M | OV | RC | PC | BC |
|-----|------------|-----|---------------------------|---|-------|------|------|---|-----|----|----|----|
| 7g  | GI$_{50}$  |     |                           | 3.17 | 6.16 | 2.53 | 5.62 | 3.13 | 5.44 | 3.98 | 4.57 | 3.41 |
|     | SI         |     |                           | 1.33 | 0.69 | 1.67 | 0.75 | 1.35 | 0.78 | 1.06 | 0.92 | 1.24 |
L – leukemia, NSCLC – non-small cell lung cancer, ColC – colon cancer, CNSC – CNS cancer, M – melanoma, OV – ovarian cancer, RC – renal cancer, PC – prostate cancer, BC – breast cancer.

Table 4. Mean growth inhibitory concentration (GI$_{50}$, µM) of compound 7g in comparison with 5-FU, Cisplatin and Curcumin

| Cpd | Subpanel tumor cell lines | L | NSCLC | ColC | CNSC | M | OV | RC | PC | BC | MG-MID |
|-----|---------------------------|---|-------|------|------|---|-----|----|----|----|---------|
| 7g  |                           | 3.17 | 6.16 | 2.53 | 5.62 | 3.13 | 5.44 | 3.98 | 4.57 | 3.41 | 4.22    |
| 5-FU|                           | 15.1 | >100 | 8.4 | 72.1 | 70.6 | 61.4 | 45.6 | 22.7 | 76.4 | 52.5    |
| Cisplatin |                           | 6.3 | 9.4 | 21.0 | 4.7 | 8.5 | 6.3 | 10.2 | 5.6 | 13.3 | 9.48    |
| Curcumin |                           | 3.7 | 9.2 | 4.7 | 5.8 | 7.1 | 8.9 | 10.2 | 11.2 | 5.9 | 7.41    |

Conclusions
A series of novel N-(5-R-benzyl-1,3-thiazol-2-yl)-2,5-dimethylfuran-3-carboxamides were synthesized and their anticancer activity was investigated. The compounds with significant levels of anticancer activity towards the selected cancer cell lines have been found and may be used for the further optimization.

Acknowledgements
We are grateful to Dr. VL. Narayanan from Drug Synthesis and Chemistry Branch, National Cancer Institute, Bethesda, MD,
USA, for in vitro evaluation of [the] anticancer activity.

REFERENCES

1. Gorak YuI, Obushak ND, Matiichuk VS, Lytvyn RZ. Synthesis of heterocycles from arylation products of unsaturated compounds: XVIII. 5-Arylfuran-2-carboxylic acids and their application in the synthesis of 1,2,4-thiadiazole, 1,3,4-oxadiazole and [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives. Russ J Org Chem. 2009; 45(4):541–50.

2. Obushak ND, Gorak YuI, Matiichuk VS, Lytvyn RZ. Synthesis of heterocycles based on arylation products of unsaturated compounds: XVII. Arylation of 2-acetylfuran and synthesis of 3-R-6-(5-aryl-2-furyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines. Russ J Org Chem. 2008; 44(11):1689–94.

3. Pokhodylo NT, Matiychuk VS, Obushak MD. Synthesis of ethyl 4,5-disubstituted 2-azido-3-thiophencarboxylates and use in the synthesis of thieno[3,2-e][1,2,3]triazolo[1,5-a]pyrimidin-5(4H)-ones. Tetrahedron. 2009; 65(13):2678–83.

4. Matiichuk VS, Potopnyk MA, Obushak ND. Molecular design of pyrazolo[3,4-d]pyridazines. Russ J Org Chem. 2008; 44(9):1352–61.

5. Ostapiuk YV, Obushak ND, Matiichuk VS, Naskrent M, Gzella A. A convenient method for the synthesis of 2-

6. Zimenkovskii BS, Kutsky RV, Lesyk RB, Matiychuk VS, Obushak ND, Klyufinska TI. Synthesis and antimicrobial activity of 2,4-dioxothiazolidine-5-acetic acid amides. Pharm Chem J. 2006; 40(6):303–306.

7. Tsyalkovsky VM, Kutsky RV, Matiychuk VS, Obushak ND, Klyufinska TI. Synthesis and antimicrobial activity of 5-(R1-benzyl)-2-(R 2-benzylidenehydrazono)-3-(2-furimethy)thiazolidin-4-ones. Pharm Chem J. 2005; 39(5):245–7.

8. Pokhodylo NT, SavkaRD, Matiichuk VS, Obushak ND. Synthesis and selected transformations of 1-(5-methyl-1-aryl-1H-1,2,3 - triazol-4-yl)ethanones and 1-[4-(4-R-5-methyl-1H-1,2,3-triazol-1-yl)phenyl]ethanones. Russ J Gen Chem. 2009; 79(2):309–14.

9. Obushak MD, Matiychuk VS, Trytysya VV. A new approach to the synthesis of 3,4-dihydroisocoumarin derivatives. Tetrahedron Lett. 2009; 50(45):6112–5.

10. Zubkov FI, Ershova JD, Zaytsev VP, Obushak MD, Matiychuk VS, Sokolova EA, Khristalev VN, Varlamov AV. The first example of an intramolecular Diels-Alder furan (IMDAF) reaction of iminium salts and its application in a short and simple synthesis of the isoidolo[1, 2-a]isoquinoline core of the jamtine and hisrsutine alkaloids. Tetrahedron Lett. 2010; 51(52):6822–4.

11. Pokhodylo NT, Matiychuk VS, Obushak ND. A convenient method for the synthesis of thiopyrano[4,3-c]quinoline, a new heterocyclic system. Chem Heterocycl Compd (N Y). 2009; 45(1):21–2.

12. Obushak ND, Matiichuk VS, Vasylshyn RYa, Ostapiuk YuV. Heterocyclic syntheses on the basis of arylation products of unsaturated compounds: X. 3-aryl-2-chloropropanals as reagents for the synthesis of 2-amino-1,3-thiazole derivatives. Russ J Org Chem. 2004; 40(3):383–9.

13. Nevagi RJ. Biological and medicinal significance of 2-aminotiazoles. Pharm Let. 2014; 6(5):134–50.

14. Das D, Sikdar P, Bairagi M. Recent developments of 2-aminotiazoles in medicinal chemistry. Eur J Med Chem. 2016; 109(15):89–98.

15. Girish Kumar Gupta, Vinod Kumar. Thiazole: A privileged scaffold in drug discovery. Chemical Drug Design. Walter de Gruyter GmbH & Co KG, 2016; 297p.

16. Chhabria MT, Patel S, Modi P, Brahmkshatriya PS. Thiazole: A Review on Chemistry, Synthesis and Therapeutic Importance of its Derivatives. Curr Top Med Chem. 2016; 16(26):2841–62.

17. Ohba M, Oka T, Ando T, Arahata S, Ikegaya A, Takagi H, Ogo N, Owada K, Kawamori F, Wang Q, Saif LJ, Asai A. Discovery and synthesis of heterocyclic carboxamide derivatives as potent antinorovirus agents. Chem Pharm Bull. 2016; 64(5):465–75.

18. Ran K, Gao C, Deng H, Lei Q, You X, Wang N, Shi Y, Liu Z, Wei W, Peng C, Xiong L, Xiao K, Yu L. Identification of novel 2-aminothiazole conjugated nitrofuran as antiutibacterial andantibacterial agents. Bioorg Med Chem Lett. 2016; 26(15):3669–74.

19. Jeankumar VU, Chandran M, Samala G, Alvala M, Koushik PV, Yogeeswari P, Salina EG, Sriram D.
Synthesis and anticancer properties of N-(5-R-benzyl-1,3-thiazol-2-yl)-2,5-dimethyl-3-furamides

18. Meissner A, Boshoff HI, Vasan M, Duckworth BP, Barry CE 3rd, Aldrich CC. Structure-activity relationships of 2-aminothiazoles effective against Mycobacterium tuberculosis. Bioorg Med Chem. 2013;21(24):7414–7. 20. Meissner A, Boshoff HI, Vasan M, Duckworth BP, Barry CE 3rd, Aldrich CC. Structure-activity relationships of 2-aminothiazoles effective against Mycobacterium tuberculosis. Bioorg Med Chem. 2013;21(24):7414–7.

22. Jung KY, Kim SK, Gao ZG, Gross AS, Melman N, Jacobson KA, Kim YC. Structure-activity relationships of thiazole and thiadiazole derivatives as potent and selective human adenosine A3 receptor antagonists. Bioorg Med Chem. 2011;20(18):5417–22.

24. Wityak J, Das J, Moquin RV, Shen Z, Lin J, Chen P, Doweyko AM, Pitt S, Pang S, Shen DR, Fang Q, de Fex HF, Schieven GL, Kanner SB, Barrish JC. Discovery and hit-to-lead optimization of novel allosteric glucokinase activators. Bioorg Med Chem Lett. 2011;21(18):5417–22.

26. Xie YM, Deng Y, Dai XY, Liu J, Ouyang L, Wei YQ, Zhao YL. Synthesis and biological evaluation of novel ace-naphthene derivatives as potential antitumor agents. Molecules. 2011;16(3):2519–26.

28. Hranjec M, Sović I, Ratkaj I, Pavlović G, Ilić N, Vajjal L, Pavelić K, Kraljević Pavelić S, Karinski-Zamola G. Antiproliferative potency of novel benzofuran - 2-carboxamides on tumor cell lines: cell death mechanisms and determination of crystal structure. Eur J Med Chem. 2013;59:111–9.

29. Obushak ND, Lexyuk AI, Gorak YI, Matiichuk VS. Mechanism of Meerwein arylation of furan derivatives. Russ J Org Chem. 2009;45(9):1375–81.
Результати. У результаті взаємодії 2-аміно-5-(R-бензил) тіазолів з 2,5-диметил-3-фуроїлхлоридом було отримано відповідні N-5-R-бензил-1,3-тиазол-2-іл)-2,5-диметил-3-фураміди 7а-g з хорошими виходами. Структуру синтезованих сполук підтверджено ЯМР спектроскопією та мікроаналізом. Протипухлинну активність синтезованих сполук вивчали in vitro на 60 лініях ракових клітин у концентрації 10 мкМ. Лінії пухлинних клітин людини отримували з дев’яти різних типів раку: лейкемії, меланоми, легенів, товстої кишки, ЦНС, яєчників, нирки, простати та молочної залози. Встановлено, що сполуки 7d, e, г проявили високу активність з GP = 29,05 – 35,02 %, тоді як 7а-c, f – умерену при GP = 60,31–67,36 %. Найактивніша сполука 7g виявилася високо ингібуючою активністю (GI50 < 10 мкМ) проти 54 з 58 клітинних ліній пухлин людини із середнім значенням GI50= 4,22 мкМ, а субпанель раку товстої кишки продемонструвала найвищу активність із середнім значення GI50= 2,53 мкМ. Найбільш чутливою лінією була Т-47D (Рак молочної залози, GI50 = 0,088 мкМ). Значення MG-MID для найбільш активної сполуки 7g меншим, у порівнянні з 5-фторурацилом, куркуміном та цисплатином при тестуванні аналогічним чином. Висновки. Отримано ряд нових N-(5-R-бензил-1,3-тиазол-2-іл)-2,5-диметил-3-фурамідів. Виявлено сполуки з високою протираковою активністю.

Ключові слова: органічний синтез, арилировання, ацилировання, 2-амино-5-арилметилтіазоли, протипухлинна активність.

Синтез и противоопухолевые свойства N-(5-R-бензил-1,3-тиазол-2-ил)-2,5-диметил-3-фурамидов

Ю. Е. Матийчук, Ю. В. Остапюк, Т. И. Чабан, Огурцов В.В., Матийчук В.С.

Цель. Синтез и исследование противоопухолевой активности N-(5-R-бензил-1,3-тиазол-2-ил)-2,5-диметил-3-фурамидов. Методы. Органический синтез, аналитические и спектральные методы, фармакологический скрининг. Результаты. В результате взаимодействия 2-амино-5-(R-бензил)тиазолов с 2,5-диметил-3-фуроилхлоридом было получено соответствующие N-5-R-бензил-1,3-тиазол-2-ил)-2,5-диметил-3-фурамиды 7а-g с хорошими выходами. Структуру синтезированных соединений подтверждено методом спектроскопии ЯМР и микроанализом. Противоопухолевую активность синтезированных соединений изучали in vitro на 60 линиях раковых клеток в концентрации 10 мкм. Линии опухолевых клеток человека получали из девяти различных типов рака: лейкемии, меланомы, легких, толстой кишки, ЦНС, яичников, почек, простаты и молочной железы. Установлено, что соединения 7d, e, г показали высокую активность с GP = 29,05–35,02 %, тогда как 7а-c, f – умеренную при GP = 60,31–67,36 %. Найактивнейшее соединение 7g обнаружено высокую ингибирующееактивность против 54 из 58 клеточных линий из различных типов рака: лейкемии, меланомы, легких, толстой кишки, ЦНС, яичников, почек, простаты и молочной железы. Значение MG-MID для наиболее активного соединения 7g меньше, по сравнению с 5-фторурацилом, куркумом и цисплатином при тестировании аналогичным образом. Выводы. Получен ряд новых N-(5-R-бензил-1,3-тиазол-2-ил)-2,5-диметил-3-фурамидов. Обнаружено высокую активность против опухолевой активностью.

Ключевыe слова: органический синтез, арилирование, ацилирование, 2-амино-5-арилметилтіазоли, противоопухолевая активность.

Received 01.12.2019