ISSN 1814-9758. Ukr. Bioorg. Acta, 2022, Vol. 17, N 2
UDC 547.789.1 + 615.281.8 + 615.277.3
DOI: hpps://doi.org/10.15407/bioorganica2022.02.014

Ukrainica Bioorganica Acta
www.bioorganica.org.ua

RESEARCH ARTICLE

The *N*-(2,4-diarylthiazol-5-yl)benzamidines library creation and the effect of these compounds on cancer growth

Oleksandr O. Severin[1], Maryna V. Kachaeva[1], Stepan G. Pilyo[1], Olga V. Shablykina[1,2], Viktoriia S. Moskvina[1,2]*, Volodymyr S. Brovarets[1]

[1] *V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of the NAS of Ukraine, Kyiv, Ukraine*
[2] *Taras Shevchenko National University of Kyiv, Kyiv, Ukraine*

Abstract: A versatile and efficient protocol for the synthesis of library of *N*-(2,4-diarylthiazol-5-yl)benzamidines is described. We obtained a library of 25 diversity with different substituents in four positions in key framework. The synthesized amidine derivatives were evaluated for their *in vitro* anticancer activity. Analysis of anticancer activity on 60 cancer cell lines showed decreased proliferation of Colon Cancer and Leukemia cell lines by more than half and allowed to establish the structure-activity relationship.

Keywords: *N*-(2,4-diarylthiazol-5-yl)benzamidines; combinatorial library; anticancer activity.

Introduction

Among the most successful heterocycles in medical chemistry [1], 1,3-thiazole derivatives occupy an important place. They are convenient and perspective objects for researchers not only due to the pharmacophore nature of the basic heterocycle, but also due to the ease of synthesis and wide possibilities of variation of substituents in positions 2, 4, 5 [2], since the nature of the substituents in thiazole rarely changes with the type of biological activity of the molecule [3, 4]. All of the above fully contains thiazoles with an amino group in position 5. On the one hand, among 5-aminothiazoles, a substance with anticancer (Figure 1, structure **1** [5]), antimicrobial (Figure 1, structure **2** [6]), antioxidant properties activity were found (Figure 1, structure **3** [7]), as well as substances that can be useful in the treatment of prion diseases (Figure 1, structure **4** [8]).

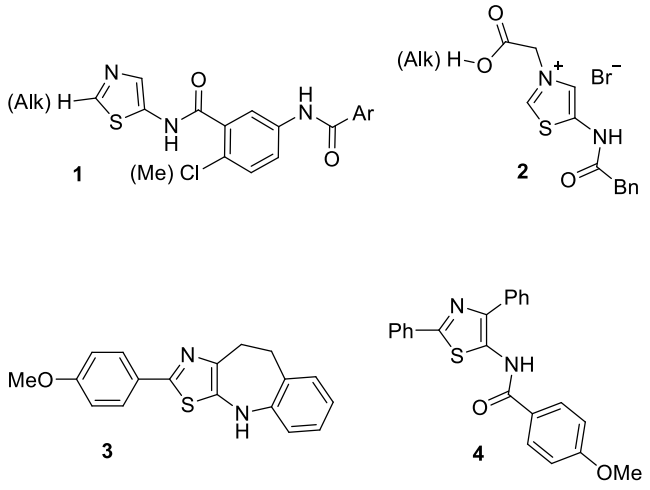


Figure 1. Examples of bioactive 5-aminothiazoles.

On the other hand, the synthetic methods of 5-aminothiazoles allow to vary the substituents in the heterocycle within quite wide limits, and the thiazole cycle is stable enough to allow for a number of modifications of the amino group. Among the variety of possibilities, we were interested in the synthesis of thiazoles with an amidine fragment in position 5.

Received: 14.09.2022
Revised: 28.09.2022
Accepted: 31.10.2022
Published online: 30.12.2022

* Corresponding author. Tel.: +380-44-239-3342;
e-mail: v.moskvina@gmail.com (V.S. Moskvina)
ORCID: 0000-0001-5556-9147

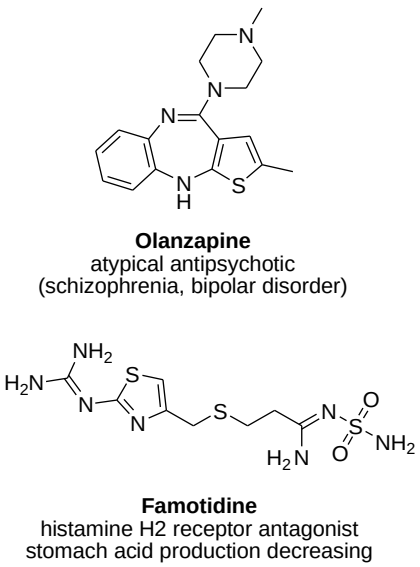


Figure 2. Examples of bioactive amidines.

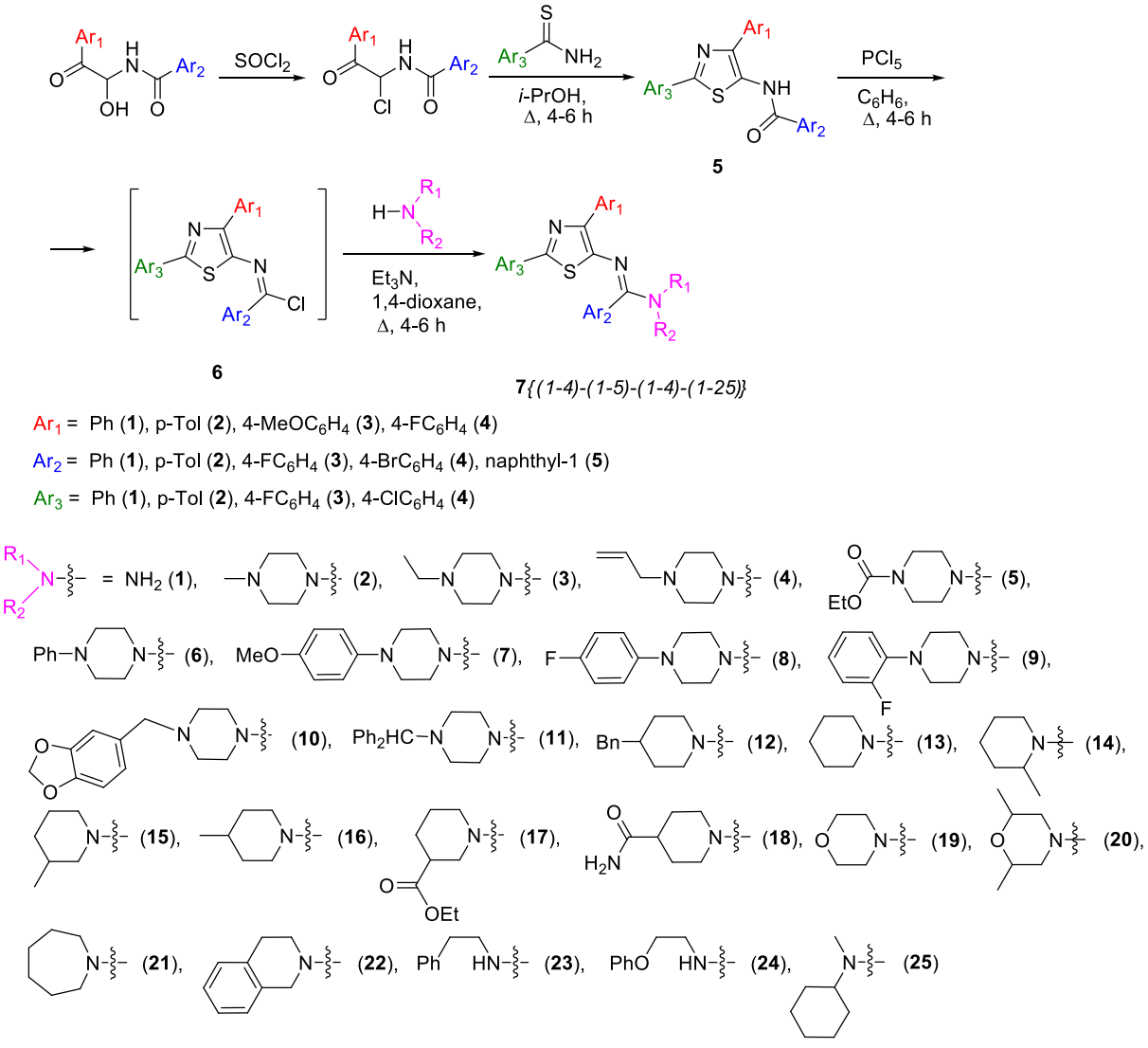
The amidine fragment is found in the structure of well-known drugs such as Olanzapine [9] and Famotidine [10] (Figure 2). One of the reasons for the biological activity of amidines may be their effect on L-Arginine metabolism [11]; there are data on the biological activity of platinum amidine complexes [12], as well as on the inflammatory activity of heterocyclic amidine derivatives [13].

In this work, we present a simple route to generate a library of 2,4-diarylthiazoles with an amidine (benzimidamide) moiety in the 5-position of the heterocycle and a preliminary evaluation of their prospects as anticancer agents.

Results and Discussion

Synthesis

Based on the previous developments of our scientific group in the field of bioactive thiazole derivatives as anticancer agent [14-16], we chose the following path for the synthesis of target structures. Thiazoles **5** containing an amide group in 5-position of the thiazole ring were synthesized by the reaction between *α*-chloroalkylamides and aromatic thioamides (Scheme 1). They can be obtained from acetophenone and the corresponding amides of carboxylic acids, some of which have been synthesized previously [17, 18].



Scheme 1. Synthesis of target thiazoles **7** with amidine group and scope of substituents.

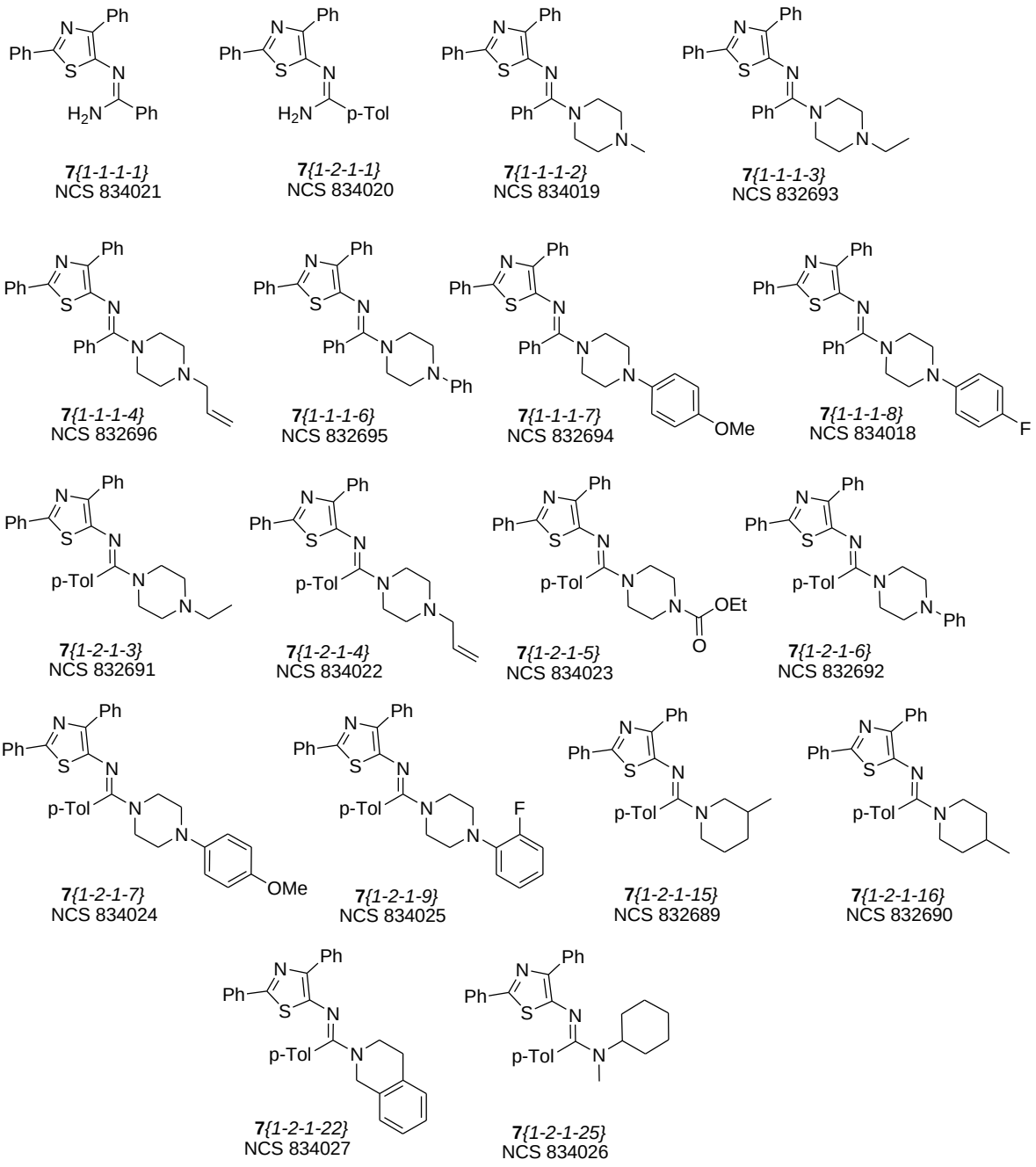


Figure 3. Scope of the 20 products **7** selected for anticancer activity research, and their NCS code (*E*-isomers, as the most possible configuration).

To form an amidine fragment, the amide group of compounds **5** was converted to a chloroamidine by reaction with PCl_5 (substances **6** in Scheme 1). By reacting compounds **6** with ammonia or secondary aliphatic amines, thiazoles **7** containing amides and a new fragment were obtained. An important advantage of this method of synthesizing amidines, among other approaches [19], is the possibility of varying the substituents in the amidine fragment.

Intermediate compounds **6**, in their individual state, were not isolated, because they hydrolyze quite quickly when in contact with the moisture of the environment, therefore, for example, the registration of their spectra should be carried out under special conditions, since when using the usual procedure, the sample will always contain an admixture of the corresponding amide **5**. Transformation **5** → **6** → **7** was carried out in anhydrous solvents, without isolating compounds **6** in an individual state (see Experimental section). The final products – thiazoles with an amidine fragment – are numbered in the format **7**{*A*-*B*-*C*-*D*}, where *A* – is the sequence number of the Ar_1 substituent, *B* – is the sequence number of the Ar_2 substituent, *C* – is the sequence number of the Ar_3 substituent, and *D* – is the sequence number of the NR_1R_2 group (Scheme 1).

Using substrates that allowed for 4 variations of the Ar_1 substituent, 5 variations of Ar_2, and 4 variations of Ar_3, as well as a set of 25 amines of the general formula HNR_1R_2. From the obtained library of compounds, 18 substances

were tested for anticancer activity; their structures are shown in Figure 3; ^{1}H- and ^{13}C-NMR and IR spectral data are given for this representative set of compounds in the experimental part.

Table 2. The effect of compounds on the growth of cancer cells, determined by single-dose assay (C = 10^{-5} M); GP – Growth Percent, %; N_{75} – number of lines with 0 < GP ≤ 75%; N_{50} – number of lines with 0 < GP ≤ 50%

Compd (NCS code)	GP, Mean	GP, Range	N_{75}	N_{50}	The most significant inhibition, GP
7{*1-1-1-1*} (834021)	85.7	60.0	10	–	53.8 HT29 (Colon Cancer) 54.2 KM12 (Colon Cancer) 56.1 HCT-15 (Colon Cancer)
7{*1-2-1-1*} (834020)	77.5	74.3	17	4	26.7 CCRF-CEM (Leukemia) 28.5 K-562 (Leukemia) 41.4 KM12 (Colon Cancer)
7{*1-1-1-2*} (834019)	75.1	111.7	18	9	9.9 HT29 (Colon Cancer) 16.7 HCT-15 (Colon Cancer) 17.8 K-562 (Leukemia) 21.1 SR (Leukemia) 24.5 KM12 (Colon Cancer)
7{*1-1-1-3*} (832693)	76.6	81.5	23	4	31.8 OVCAR-4 (Ovarian Cancer) 32.6 HT29 (Colon Cancer) 32.8 K-562 (Leukemia)
7{*1-1-1-4*} (832696)	95.0	49.1	2	–	72.4 NCI-H226 (Non-Small Cell Lung Cancer)
7{*1-1-1-6*} (832695)	102.6	40.5	–	–	84.9 UACC-62 (Melanoma)
7{*1-1-1-7*} (832694)	100.3	42.7	–	–	79.6 NCI-H226 (Non-Small Cell Lung Cancer)
7{*1-1-1-8*} (834018)	98.9	39.4	–	–	80.1 NCI-H522 (Non-Small Cell Lung Cancer)
7{*1-2-1-15*} (832689)	106.4	24.8	–	–	–
7{*1-2-1-16*} (832690)	107.7	24.6	–	–	–
7{*1-2-1-3*} (832691)	100.2	69.7	1	–	53.3 HL-60(TB) (Leukemia) 78.1 KM12 (Colon Cancer) 79.0 NCI-H460 (Non-Small Cell Lung Cancer)
7{*1-2-1-4*} (834022)	89.4	84.7	11	–	57.2 HCT-116 (Colon Cancer) 64.3 K-562 (Leukemia) 64.9 PC-3 (Prostate Cancer)
7{*1-2-1-5*} (834023)	82.9	78.1	17	–	53.1 CAKI-1 (Renal Cancer) 53.7 ACHN (Renal Cancer) 57.5 HS 578T (Breast Cancer)
7{*1-2-1-6*} (832692)	104.9	19.9	–	–	–
7{*1-2-1-7*} (834024)	95.5	46.6	1	–	70.4 UACC-62 (Melanoma)
7{*1-2-1-9*} (834025)	99.2	53.3	1	–	74.2 UACC-62 (Melanoma)
7{*1-2-1-22*} (834027)	100.1	39.0	–	–	78.9 UO-31 (Renal Cancer)
7{*1-2-1-25*} (834026)	101.2	43.6	–	–	83.0 CAKI-1 (Renal Cancer)

Biological assay

The anticancer activity of synthesized compounds was tested according to the Developmental Therapeutic Program (DTP) of the National Cancer Institute (NCI, Bethesda, Maryland, USA) on 60 cancer cell lines [20]; a description of the technique is also given in [21].

The most significant data, expressed as a percentage of inhibition of the growth of cancer cells, are systematized in Table 2.

No derivatives with high cytotoxicity were found among the investigated substances. The most active of them (NCS 834019, 832693, 834020) were able to slow down the growth of a small number of cancer cell lines (4-9 out of 60) by more than half. Three more substances with low anticancer activity (NCS 834021, 834022, 834023) can be distinguished from the array by analyzing the number of lines whose growth was 75% or less of the initial one; the inhibitory ability of all other substances can be considered insignificant.

The *N*-methylpiperazine derivative (NCS 834019) shows the highest activity, the corresponding *N*-ethylpiperazine derivative (NCS 832693) is slightly inferior to it. When an aromatic substituent is introduced in the 4th position of the piperazine residue, the molecule completely loses its ability to slow down the growth of cancer cells; derivatives of 1,2,3,4-tetrahydroisoquinoline and methylcyclohexylamine also did not show a noticeable anticancer effect.

No derivatives with high cytotoxicity were found among the investigated substances. The most active of them (NCS 834019, 832693, 834020) were able to slow down the growth of a small number of cancer cell lines (4-9 out of 60) by more than half. Three more substances with low anticancer activity (NCS 834021, 834022, 834023) can be distinguished from the array by analyzing the number of lines whose growth was 75% or less of the initial one; the inhibitory ability of all other substances can be considered insignificant.

The *N*-methylpiperazine derivative NCS 834019 shows the highest activity, the corresponding *N*-ethylpiperazine derivative (NCS 832693) is slightly inferior to it. When an aromatic substituent is introduced in the 4th position of the piperazine residue, the molecule completely loses its ability to slow down the growth of cancer cells; derivatives of 1,2,3,4-tetrahydroisoquinoline and methylcyclohexylamine also did not show a noticeable anticancer effect.

Replacing the phenol group in the amidine fragment with a tolyl group in the case of NH_2-derivatives (compare NCS 834021 and 834020) gives a small positive effect, and in the case of piperazine derivatives - negative (for example, NCS 832693 and 832691).

It is worth noting for the most active NCS derivatives 834019, 832693, 834020 the tendency of inhibition mainly of Colon Cancer and Leukemia lines.

Thus, further modifications of the basic structure should be carried out in the direction of creating a greater variety of

N-methylpiperazine derivatives and amidines with the NH_2 group due to variations of the Ar^1–Ar^3 substituents (in the created library, the variations of these positions were inferior to the number of variations of the amine fragment); study of the influence of the latter on bioactivity; as well as determination of other types of biological action of such derivatives, in particular, antimicrobial.

Conclusions

In conclusion, we have developed an efficient protocol for the rapid synthesis of *N*-(2,4-diarylthiazol-5-yl)benzamidines, which provides easy variation of substituents in four positions. *In vitro* studies of the anticancer activity of 18 substances revealed only a moderate anticancer effect of 3 of them and a weak effect of another 3 derivatives. But the variety of possible compounds of this class provides grounds for further research in the direction of identifying substances with more powerful activity.

Notes

Acknowledgments and finances. We would like to thank US Public Health Service and National Cancer Institute, USA, for *in vitro* evaluation of anticancer activity (providing the NCI-60 cell testing) within the framework of Developmental Therapeutic Program (http://dtp.cancer.gov), and *Enamine* Ltd for the material and technical support for the synthetic part of this work.

Disclaimer. This material should not be interpreted as representing the viewpoint of the U.S. National Institutes of Health, or the National Cancer Institute.

Author contributions. O. O. S.: synthesis of compounds, Investigation, writing of abstract, writing experimental section, editing. **M. V. K.**: synthesis of compounds, analysis of bioactivity, formal analysis. **S. G. P.**: synthesis of compounds, investigation, formal analysis, editing. **O. V. S.**: formal analysis, writing experimental section, editing. **V. S. M.**: investigation, formal analysis, manuscript writing, editing. **V. S. B.**: conceptualization, supervision, writing, review & editing.

Experimental section

The solvents were purified according to the standard procedures. All materials were purchased from commercial sources and used without further purification. The success rate was calculated as the number of successful experiments divided by the total number of experiments. ^{1}H NMR spectra were recorded on a Varian VXR-400 spectrometer (400 MHz) and ^{13}C NMR spectra were recorded at Bruker 170 spectrometer (126 MHz) spectra in DMSO-d_6 or CF_3CO_2D, or $CDCl_3$ solution. Chemical shifts are reported in ppm downfield from TMS as internal standards. Mass spectra were recorded on an LC-MS instrument with chemical ionization (CI). LC-MS data were acquired on an Agilent 1200 HPLC system equipped with DAD/ELSD/LCMS-6120 diode matrix and mass-selective detector. Melting points were measured on a MPA100 OptiMelt automated melting point system. Combustion elemental analysis was performed by hand in the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry analytical laboratory. The carbon and hydrogen contents were determined using the Pregl gravimetric method, nitrogen – using the Duma's gasometrical micromethod, sulfur – by the Scheininger titrimetric method.

*A representative procedure for the synthesis of N'-(2,4-diphenylthiazol-5-yl)benzimidamide (**7**{1-1-1-1}).*

20.8 g (0.1 mol) of PCl_5 was added to a solution of 35.6 g (0.1 mol) of *N*-(2,4-diphenylthiazol-5-yl)benzamide (**5**) in 300 ml of benzene, and the solution was boiled with stirring for 5 h and left for 10-12 hours at 20-25 ºC. An excess of sulfur dioxide (SO_2) gas was blown through the solution for 20-25 minutes, then the reaction mixture was left for 1 hour. The solvent was evaporated *in vacuo* and formed solid residue was treated with hexane, filtered and dried *in vacuo*. The obtained *N*-(2,4-diphenylthiazol-5-yl)benzimidoyl chloride (**6**) was used for further syntheses.

To a solution of 0.01 mol of imidoyl chloride in 50 ml of anhydrous 1,4-dioxane, an excess of a saturated solution of ammonia (NH_3) in dioxane (5 ml) was added, and the reaction mixture was left for 10-12 hours at 20-25 ºC. The solvent was evaporated *in vacuo*, the formed solid residue was treated with water, filtered, dried and purified by crystallization from acetonitrile.

A solution of 0.01 mol of imidoyl chloride, 0.011 mol of the corresponding secondary aliphatic amine and 0.011 mol (1.55 ml) of Et_3N was boiled with stirring for 5 hours, then left for 12 hours at 20-25 °C. The solvent was evaporated in vacuo, the formed solid residue was treated with water, filtered, dried and purified by crystallization from acetonitrile with the addition of a small amount of dimethylformamide. Yield: 2.70 g, 76%. Colorless solid, mp 163-165 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, *J* 7.7 Hz, 2H), 8.07 (br s, 2H), 7.94 (br d, *J* 7.0 Hz, 2H), 7.58-7.43 (m, 8H), 7.39 (t, *J* 7.7 Hz, 2H), 7.24 (t, *J* 7.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.8, 156.1, 144.5, 140.3, 135.4, 134.6, 134.0, 130.9, 129.3, 129.1 × 2, 128.4 × 2, 128.1 × 2, 127.4 × 2, 126.9 × 2, 126.4, 125.4 × 2. IR (KBr) ν 3432, 3328, 3061, 3024, 1621 (vs), 1596 (s), 1563 (vs), 1504, 1478, 1443, 1377, 1340, 1311, 1207, 1071, 1046, 1025, 966, 917, 853, 774, 758, 692 (vs), 597, 558. HPLC (CI) m/z $(M+H)^+$ 354. Found, %: C, 74,62; H, 4,96; N, 11,78; S, 9,00. $C_{22}H_{17}N_3S$. Calculated, %: C, 74.34; H, 4.82; N, 11.82; S, 9.02.

*N'-(2,4-Diphenylthiazol-5-yl)-4-methylbenzimidamide (**7**{1-2-1-1}).*

Yield: 3.00 g, 81.3%. Colorless solid, mp 149-151 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, *J* 7.6 Hz, 2H), 8.02-7.86 (m, 4H), 7.57-7.41 (m, 5H), 7.39 (t, *J* 7.5 Hz, 2H), 7.32 (d, *J* 8.0 Hz, 2H), 7.24 (t, *J* 7.5 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.8, 144.5, 141.1, 135.2, 134.5, 133.9, 131.4, 129.4, 129.1 × 2, 129.0 × 2,

128.1 × 2, 127.9 × 2, 127.5, 126.9, 126.5 × 2, 125.4 × 2, 21.00. IR (KBr) ν 3362, 3297, 3158, 3054, 1634 (s), 1581, 1556 (vs), 1510 (s), 1477, 1436, 1396, 1335, 1305, 1285, 1203, 1177, 1062, 1025, 975, 914, 893, 862, 828, 758 (s), 722, 692 (s), 672, 621, 534. HPLC (CI) m/z $(M+H)^+$ 370. Found, %: C, 74.92; H, 5.39; N, 11.39; S, 8.69. $C_{23}H_{19}N_3S$. Calculated, %: C, 74.77; H, 5.18; N, 11.37; S, 8.68.

*N-(2,4-Diphenylthiazol-5-yl)-1-(4-methylpiperazin-1-yl)-1-phenylmethanimine (**7**{1-1-1-2}).*

Yield: 3.47 g, 79%. Colorless solid, mp 161-163 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, *J* 7.8 Hz, 2H), 7.60 (d, *J* 7.2 Hz, 2H), 7.56-7.47 (m, 3H), 7.47-7.30 (m, 5H), 7.30-7.22 (m, 3H), 4.04-3.78 (br s, 4H with other signals), 3.28-3.01 (br s, 4H, with other signals), 2.22 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.8, 156.1, 144.5, 140.3, 141.1, 135.4, 134.6, 134.0, 129.4, 291.0 × 2, 129.0 × 2, 128.4 × 2, 128.4, 128.1 × 2, 126.9 × 2, 126.4 × 2, 124.9, 52.1, 49.7, 11.9. IR (KBr) ν 3052, 2939, 2883, 2841, 2803, 1603, 1575 (vs), 1498, 1445, 1418 (s), 1362, 1341, 1292, 1279, 1254, 1134, 1104, 1073, 999, 979, 928, 890, 841, 781, 755, 687 (s), 654, 598. HPLC (CI) m/z $(M+H)^+$ 439. Found, %: C, 74.21; H, 6.13; N, 12,71; S, 7.29. $C_{27}H_{26}N_4S$. Calculated, %: C, 73.94; H, 5.98; N, 12.77; S, 7.31.

*N-(2,4-Diphenylthiazol-5-yl)-1-(4-ethylpiperazin-1-yl)-1-phenylmethanimine (**7**{1-1-1-3}).*

Yield: 3.44 g, 80%. Colorless solid, mp 161-163 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, *J* 7.7 Hz, 2H), 7.60 (d, *J* 7.4 Hz, 2H), 7.54-7.46 (m, 3H), 7.43 (t, *J* 7.6 Hz, 2H), 7.36 (p, *J* 6.3 Hz, 3H), 7.25 (d, *J* 8.1 Hz, 3H), 3.91 (s, 1H), 3.33-3.15 (br s, 4H with other signals), 2.37 (br s, 4H with other signals), 1.03 (q, *J* 8.5, 7.2 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.8, 156.1, 144.5, 140.3, 135.4, 134.6, 134.0, 130.3, 129.4, 129.0 × 2, 128.5 × 2, 128.0 × 2, 127.4 × 2, 126.9 × 2, 126.3, 125.4 × 2, 52.1 × 2, 51.5 × 2, 48.7, 11.9. IR (KBr) ν 3047, 2973, 2887, 2850, 2808, 1569 (vs), 1497, 1443, 1420 (s), 1366, 1342, 1311, 1259 (s), 1152, 1123, 1015, 979, 940, 887, 840, 763, 687 (s), 650, 600, 546. HPLC (CI) m/z $(M+H)^+$ 453.2. Found, %: C, 74.42; H, 6.36; N, 12.35; S, 7.06. $C_{28}H_{28}N_4S$. Calculated, %: C, 74.30; H, 6.24; N, 12.38; S, 7.08.

*1-(4-Allylpiperazin-1-yl)-N-(2,4-diphenylthiazol-5-yl)-1-phenylmethanimine (**7**{1-1-1-4}).*

Yield: 3.57 g, 77%. Colorless solid, mp 143-145 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, *J* 7.5 Hz, 2H), 7.60 (d, *J* 7.2 Hz, 2H), 7.43-7.11 (m, 11H), 3.13 (s, 2H), 2.38 (s, 3H), 1.88 (s, 2H), 1.63 (s, 4H), 1.45 (s, 1H), 0.97 (d, *J* 72.9 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.8, 155.0, 144.7, 140.5, 135.6, 135.1, 133.7, 131.3, 130.3, 129.4, 129.1, 129.0 × 2, 128.4 × 2, 128.0 × 2, 127.4 × 2, 126.3 × 2, 125.0 × 2, 118.0, 60.7, 53.4 × 2, 50.1 × 2. IR (KBr) ν 3059, 3041, 2978, 2932, 2914, 2886, 2844, 2811, 2762, 1573 (vs), 1495 (s), 1444 (s), 1418 (s), 1364, 1344 (s), 1306, 1259 (s), 1218, 1140, 1089, 999 (s), 977, 921, 891, 842, 813, 752 (s), 696 (s), 598, 545. HPLC (CI) m/z $(M+H)^+$ 465. Found, %: C, 75.13; H, 6.16; N, 12.03; S, 6.87. $C_{29}H_{28}N_4S$. Calculated, %: C 74.97; H 6.07; N 12.06; S 6.90.

*N-(2,4-Diphenylthiazol-5-yl)-1-phenyl-1-(4-phenylpiperazin-1-yl)methanimine (**7**{1-1-1-6}).*

Yield: 3.90 g, 78%. Colorless solid, mp 195-197 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, *J* 7.8 Hz, 2H), 7.61 (d, *J* 7.4 Hz, 2H), 7.54 (d, *J* 6.6 Hz, 3H), 7.46-7.31 (m, 7H), 7.25 (t, *J* 7.4 Hz, 3H), 6.99 (d, *J* 7.9 Hz, 2H), 6.82 (t, *J* 7.4 Hz, 1H), 4.06 (br s, 4H with other signals), 3.16-3.03 (br s, 4H, with other signals). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.8, 156.1, 144.5, 140.3, 135.4, 134.6, 134.0, 130.9, 129.5, 129.3, 129.0 × 2, 128.6 × 2, 128.1 × 2, 128.0, 127.5, 127.4 × 2, 126.9 × 2, 126.4, 126.2, 125.4, 125.0, 115.8 × 2, 56.4 × 2, 52.3 × 2. IR (KBr) ν 3060, 3019, 2895, 2814, 1579, 1551 (vs), 1497 (s), 1448, 1422 (s), 1376, 1337 (s), 1307, 1269, 1223 (s), 1141, 1101, 1070, 1011, 975, 930, 876, 847, 754 (s), 691 (s), 517. HPLC (CI) m/z $(M+H)^+$ 501.2. Found, %: C, 76.89; H, 5.73; N, 11.17; S, 6.39. $C_{32}H_{28}N_4S$. Calculated, %: C, 76.77; H, 5.64; N, 11.19; S, 6.40.

*N-(2,4-Diphenylthiazol-5-yl)-1-(4-(4-methoxyphenyl)-piperazin-1-yl)-1-phenylmethanimine (**7**{1-1-1-7}).*

Yield: 4.13 g, 78%. Colorless solid, mp 177-179 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, *J* 7.8 Hz, 2H), 7.61 (d, *J* 7.3 Hz, 2H), 7.53 (q, *J* 6.3 Hz, 3H), 7.43 (t, *J* 7.6 Hz, 2H), 7.40-7.25 (m, 6H), 6.94 (d, *J* 9.0 Hz, 2H), 6.84 (d, *J* 9.0 Hz, 2H), 4.06 (br s, 4H with other signals), 3.69 (s, 3H), 3.23-3.05 (br s, 4H with other signals). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.8, 156.1, 144.5, 140.3, 135.4, 134.6, 134.0, 130.9, 129.5, 129.3, 129.0 × 2, 128.6 × 2, 128.1 × 2, 128.0, 127.5, 127.4 × 2, 126.9 × 2, 126.4, 126.2, 125.4, 125.0, 115.8 × 2, 56.4 × 2, 52.3 × 2, 56.8. IR (KBr) ν 3058, 2986, 2901, 2811, 1556 (vs), 1507 (s), 1449, 1423 (s), 1379, 1337, 1306, 1266, 1243 (s), 1223, 1180, 1144, 1099, 1039, 1014, 971, 929, 825, 758 (s), 713, 692 (s), 631, 609, 532. HPLC (CI) m/z $(M+H)^+$ 533. Found, %: C, 74.82; H, 5.79; N, 10.54; S, 6.03. $C_{33}H_{30}N_4OS$. Calculated, %: C, 74.69; H, 5.70; N, 10.56; S, 6.04.

*N-(2,4-Diphenylthiazol-5-yl)-1-(4-(4-fluorophenyl)-piperazin-1-yl)-1-phenylmethanimine (**7**{1-1-1-8}).*

Yield: 4.20 g, 81%. Colorless solid, mp 213-215 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, *J* 7.8 Hz, 2H), 7.61 (d, *J* 7.4 Hz, 2H), 7.53 (q, *J* 6.6 Hz, 3H), 7.44 (t, *J* 7.6 Hz, 2H), 7.34 (ddt, *J* 22.0, 15.7, 7.2 Hz, 6H), 7.08 (t, *J* 8.7 Hz, 2H), 7.00 (dd, *J* 9.1, 4.6 Hz, 2H), 4.06 (br s, 4H with other signals), 3.09 (br s, 4H with other signals). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.7, 155.1, 147.6, 144.5, 140.8, 135.6, 133.7, 131.2, 130.4, 129.5, 129.0 × 2, 128.6 × 2, 128.1 × 2, 128.0, 127.5, 127.4 × 2, 126.9 × 2, 126.4, 125.0, 117.7, 115.5, 115.3 × 2, 56.4 × 2, 52.3 × 2. IR (KBr) υ 3047, 3017, 2906, 2822, 1550 (vs), 1503 (vs), 1448, 1423 (s), 1379, 1337, 1307, 1286, 1266, 1230 (s), 1156, 1141, 1099, 1070, 1013, 974, 931, 815, 755, 693 (s), 632, 600, 517. HPLC (CI) m/z $(M+H)^+$ 519.2. Found, %: C, 74.23; H, 5.29; N, 10.76; S, 6.15. $C_{32}H_{27}FN_4S$. Calculated, %: C, 74.11; H, 5.25; F, 3.66; N, 10.80; S, 6.18.

*N-(2,4-Diphenylthiazol-5-yl)-1-(3-methylpiperidin-1-yl)-1-(p-tolyl)methanimine (**7**{1-2-1-15}).*

Yield: 3.79 g, 84%. Colorless solid, mp 198-200 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 2H), 7.70-7.53

(m, 2H), 7.44-7.24 (m, 8H), 7.18-7.05 (m, 2H), 2.98 (d, *J* 13.4 Hz, 2H), 2.39 (s, 3H), 2.33 (d, *J* 13.8 Hz, 3H), 1.49 (d, *J* 169.2 Hz, 3H), 1.00-0.90 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.8, 144.5, 141.1, 135.2, 134.5, 133.9, 131.4, 129.4, 129.1 × 2, 129.0 × 2, 128.1 × 2, 127.9 × 2, 127.5, 126.9, 126.5 × 2, 125.4 × 2, 21.00, 53.1, 45.7, 31.2, 29.1, 23.4, 18.0. IR (KBr) ν 2939, 2919, 2844, 1556 (vs), 1501, 1423, 1368, 1345, 1258, 1118, 1084, 967, 903, 851, 829, 756, 685, 598, 550. HPLC (CI) m/z $(M+H)^+$ 452.2. Found, %: C, 77.25; H, 6.56; N, 9.26; S, 7.08. $C_{29}H_{29}N_3S$. Calculated, %: C, 77.12; H, 6.47; N, 9.30; S, 7.10.

*N-(2,4-Diphenylthiazol-5-yl)-1-(4-methylpiperidin-1-yl)-1-(p-tolyl)methanimine (**7**{1-2-1-16}).*

Yield: 3.62 g, 80%. Colorless solid, mp 165-167 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 2H), 7.70-7.53 (m, 2H), 7.44-7.24 (m, 8H), 7.18-7.05 (m, 2H), 2.98 (d, *J* 13.4 Hz, 2H), 2.39 (s, 3H), 2.33 (d, *J* 13.8 Hz, 3H), 1.49 (d, *J* 169.2 Hz, 3H), 1.20-1.05 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.8, 144.5, 141.1, 135.2, 134.5, 133.9, 131.4, 129.4, 129.1 × 2, 129.0 × 2, 128.1 × 2, 127.9 × 2, 127.5, 126.9, 126.5 × 2, 125.4 × 2, 21.00, 45.2 × 2, 34.7 × 2, 32.2, 20.6. IR (KBr) ν 3055, 3040, 2954, 2920, 2853, 1573 (vs), 1502, 1446, 1408 (s), 1372, 1344, 1310, 1252 (s), 1218, 1121, 1088, 965, 911, 883, 826, 803, 758 (s), 717, 690 (s), 650, 598, 542. HPLC (CI) m/z $(M+H)^+$ 452.2. Found, %: C, 77.22; H, 6.53; N, 9.28; S, 7.11. $C_{29}H_{29}N_3S$. Calculated, %: C, 77.12; H, 6.47; N, 9.30; S, 7.10.

*N-(2,4-Diphenylthiazol-5-yl)-1-(4-ethylpiperazin-1-yl)-1-(p-tolyl)methanimine (**7**{1-2-1-3}).*

Yield: 3.70 g, 79%. Colorless solid, mp 165-167 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, *J* 7.6 Hz, 2H), 7.62 (d, *J* 7.2 Hz, 2H), 7.47 7.32 (m, 5H), 7.32 7.23 (m, 3H), 7.13 (d, *J* 7.2 Hz, 2H), 4.04 3.76 (br. s, 2H, NCH_2), 3.25-3.03 (br s, 4H with other signals), 2.50 (br s, 4H with other signals), 2.37 (d, *J* 17.4 Hz, 5H), 1.02 (t, *J* 6.6 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.8, 144.5, 141.1, 135.2, 134.5, 133.9, 131.4, 129.4, 129.1 × 2, 129.0 × 2, 128.1 × 2, 127.9 × 2, 127.5, 126.9, 126.5 × 2, 125.4 × 2, 57.3 × 2, 50.2 × 2, 48.4, 21.00, 12.1. IR (KBr) ν 3049, 3032, 2972, 2923, 2883, 2848, 2812, 1567 (vs), 1503, 1442, 1421 (s), 1368, 1344, 1309, 1287, 1258, 1156, 1122, 1069, 1015, 977, 946, 891, 824, 776, 759, 688, 648, 598, 547. HPLC (CI) m/z $(M+H)^+$ 467. Found, %: C, 74.82; H, 6.54; N, 12.02; S, 6.85. $C_{29}H_{30}N_4S$. Calculated, %: C, 74.64; H, 6.48; N, 12.01; S, 6.87.

*1-(4-Allylpiperazin-1-yl)-N-(2,4-diphenylthiazol-5-yl)-1-(p-tolyl)methanimine (**7**{1-2-1-4}).*

Yield: 3.88 g, 81%. Colorless solid, mp 138-140 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, *J* 7.7 Hz, 2H), 7.60 (d, *J* 7.4 Hz, 2H), 7.54-7.47 (m, 3H), 7.43 (t, *J* 7.6 Hz, 2H), 7.36 (p, *J* 7.1, 6.5 Hz, 3H), 7.25 (d, *J* 8.1 Hz, 2H), 5.91 (s, 1H), 5.18 (s, 2H), 3.43 (br s, 2H with other signals), 3.15 (d, 2H), 2.37 (t, *J* 7.3 Hz, 4H), 1.02 (t, *J* 7.2 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.1, 154.9, 145.0, 140.2, 139.9, 135.6, 135.1, 133.8, 129.8 × 2, 129.0, 128.9 × 2, 128.3 × 2, 128.2, 127.9 × 2, 127.3 × 2, 126.2, 125.0 × 2, 117.8, 60.6, 52.9 × 2, 55.6 × 2, 21.0. IR (KBr) ν, 1643, 1558 (vs), 1503 (s), 1479, 1426 (s), 1367, 1339 (s), 1289, 1242, 1209, 1150, 1126, 1079, 1030, 1001 (s), 971, 931, 915, 858, 817, 757 (s), 692 (s), 663, 595, 550. HPLC (CI) m/z $(M+H)^+$ 479.2. Found, %: C, 75.36; H, 6.39; N, 11.70; S, 6.69. $C_{30}H_{30}N_4S$. Calculated, %: C, 75.28; H, 6.32; N, 11.71; S, 6.70.

*Ethyl 4-(((2,4-diphenylthiazol-5-yl)imino)(p-tolyl)-methyl)piperazine-1-carboxylate (**7**{1-2-1-5}).*

Yield: 4.24 g, 83%. Colorless solid, mp 156-158 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, *J* 7.6 Hz, 2H), 7.62 (d, *J* 7.0 Hz, 2H), 7.44 (t, *J* 7.6 Hz, 2H), 7.41-7.23 (m, 6H), 7.17 (d, *J* 7.8 Hz, 2H), 4.08 (q, *J* 7.0 Hz, 2H), 4.02-3.72 (br s, 2H), 3.71-3.36 (br s, 4H), 3.28-3.01 (br s, 2H), 2.35 (s, 3H), 1.20 (t, *J* 6.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.2, 155.2, 154.6, 144.6, 140.6, 140.1, 135.5, 133.7, 130.0 × 2, 129.1, 129.0 × 2, 128.5 × 2, 128.0 × 3, 127.4 × 2, 126.3, 125.0 × 2, 61.0, 47.1 × 2, 43.2 × 2, 21.0, 14.6. IR (KBr) ν 3049, 2987, 2917, 2854, 1706 (s), 1693 (s), 1567 (vs), 1506, 1467, 1422 (s), 1344, 1308, 1276, 1231 (s), 1168, 1141, 1102, 1069, 1005, 977, 893, 825, 761, 690, 596, 548. HPLC (CI) m/z $(M+H)^+$ 511. Found, %: C, 70.60; H, 5.98; N, 11.01; S, 6.26. $C_{30}H_{30}N_4O_2S$. Calculated, %: C, 70.56; H, 5.92; N, 10.97; S, 6.28.

*N-(2,4-Diphenylthiazol-5-yl)-1-(4-phenylpiperazin-1-yl)-1-(p-tolyl)methanimine (**7**{1-2-1-6}.*

Yield: 4.33 g, 84%. Colorless solid, mp 202-204 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, *J* 8.0 Hz, 2H), 7.63 (d, *J* 6.9 Hz, 2H), 7.44-7.32 (m, 7H), 7.28-7.19 (m, 5H), 6.98 (d, *J* 8.1 Hz, 2H), 6.82 (t, *J* 7.2 Hz, 1H), 4.05 (s, 4H), 3.53 (br s, 4H, with other signals), 2.37 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.8, 144.5, 141.1, 135.2, 134.5, 133.9, 131.4, 129.9, 129.4, 129.1 × 2, 129.0 × 2, 128.5, 128.1 × 2, 128.0, 127.9 × 2, 127.4, 126.9, 126.5 × 2, 125.4 × 2, 125.0, 119.3, 115.8, 47.1 × 2, 43.2 × 2, 21.0. IR (KBr) ν 3044, 2909, 2884, 2812, 1552 (vs), 1499, 1448 (s), 1421 (s), 1373, 1338, 1308, 1264, 1229, 1141, 1095, 1013, 973, 929, 825, 758, 692, 524. HPLC (CI) m/z $(M+H)^+$ 515.2. Found, %: C, 77.24; H, 5.92; N, 10.84; S, 6.21. $C_{33}H_{30}N_4S$. Calculated, %: C, 77.01; H, 5.88; N, 10.89; S, 6.23.

*N-(2,4-Diphenylthiazol-5-yl)-1-(4-(4-methoxyphenyl)-piperazin-1-yl)-1-(p-tolyl)methanimine (**7**{1-2-1-7}).*

Yield: 4.47 g, 82%. Colorless solid, mp 187-189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, *J* 7.5 Hz, 2H), 7.63 (s, 2H), 7.47-7.29 (m, 8H), 7.20 (d, *J* 7.6 Hz, 2H), 6.90 (dd, *J* 35.5, 6.2 Hz, 4H), 4.07 (s, 2H), 3.70 (t, *J* 4.4 Hz, 4H), 3.02 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.8, 163.1, 161.1, 155.0, 153.3, 145.0, 144.8, 140.4, 140.0, 135.6 × 2, 133.7 × 2, 129.9 × 2, 129.0 × 2, 128.4, 128.1, 128.0 × 2, 127.4, 126.3, 125.0, 117.9 × 2, 114.3 × 2, 55.8, 55.1 × 2, 49.9 × 2, 21.0. IR (KBr) ν 3058, 2990, 2950, 2911, 2807, 1555 (vs), 1506 (vs), 1423 (s), 1378, 1339, 1308, 1288, 1268, 1245 (s), 1228, 1179, 1141, 1037, 1014, 973, 926, 825, 761, 693, 626, 597, 533. HPLC (CI) m/z $(M+H)^+$ 545. Found, %: C, 75.06; H, 6.03; N, 10.27; S, 5.88. $C_{34}H_{32}N_4OS$. Calculated, %: C, 74.97; H, 5.92; N, 10.29; S, 5.89.

*N-(2,4-Diphenylthiazol-5-yl)-1-(4-(2-fluorophenyl)-piperazin-1-yl)-1-(p-tolyl)methanimine (**7**{1-2-1-9}).*

Yield: 4.26 g, 80%. Colorless solid, mp 158-160 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J 7.8 Hz, 2H), 7.63 (d, J 6.8 Hz, 2H), 7.44 (t, J 7.6 Hz, 2H), 7.41-6.96 (m, 12H), 4.06 (br s, 4H with other signals), 3.01 (br s, 4H with other signals), 2.36 (d, J 2.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.8, 163.1, 161.1, 156.0, 155.1, 154.0, 144.8, 140.5, 140.0, 139.4, 135.5 × 2, 133.7, 129.9, 129.0, 128.4, 128.0 × 2, 127.4, 126.3, 125.0, 124.9, 124.8, 122.9, 122.8, 119.7, 119.6, 116.1, 115.9, 47.1 × 2, 43.2 × 2, 21.0. IR (KBr) ν 3048, 2999, 2972, 2916, 2888, 2847, 1576 (vs), 1500 (s), 1416 (s), 1368, 1342, 1310, 1269, 1235 (s), 1204, 1137, 1091, 1013, 977, 935, 884, 825, 747 (s), 720, 690 (s), 650, 596, 544. HPLC (CI) m/z (M+H)$^+$ 533.4. Found, %: C, 74.52; H, 5.58; N, 10.50; S, 6.02. $C_{33}H_{29}FN_4S$. Calculated, %: C, 74.41; H, 5.49; F, 3.57; N, 10.52; S, 6.02.

1-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(2,4-diphenyl-thiazol-5-yl)-1-(p-tolyl)methanimine (7{1-2-1-22}).

Yield: 3.94 g, 81%. Colorless solid, mp 165-167 °C. ^{1}H NMR (400 MHz, CF_3COOD) δ 8.32-7.35 (m, 18H), 5.72 (s, 1H), 5.05 (s, 1H), 4.71 (s, 1H), 4.23 (s, 1H), 3.78 (s, 1H), 3.44 (s, 1H) 2.89 (d, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.3, 164.2, 159.8, 150.9, 142.4, 139.8, 134.1, 133.4, 131.5 × 2, 130.6 × 2, 129.2 × 4, 129.1 × 2, 128.7 × 2, 128.6, 127.5 × 2, 125.5, 125.4, 118.7, 116.3, 115.6, 43.2, 41.5, 21.8, 16.4. IR (KBr) ν 3063, 3031, 2927, 2844, 1592, 1559 (vs), 1502 (s), 1477, 1443, 1417 (s), 1364, 1341, 1297, 1278, 1243, 1218, 1189, 1133, 1099, 1043, 977, 915, 847, 825, 744, 684, 595. HPLC (CI) m/z (M+H)$^+$ 486.2. Found, %: C, 79.26; H, 5.68; N, 8.63; S, 6.57. $C_{32}H_{27}N_3S$. Calculated, %: C, 79.14; H, 5.60; N, 8.65; S, 6.60.

(N-Cyclohexyl-N'-(2,4-diphenylthiazol-5-yl)-N,4-dimethylbenzimidamide (7{1-2-1-25}).

Yield: 3.73 g, 80%. Colorless solid, mp 181-183 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, J 7.5 Hz, 2H), 7.60 (d, J 7.2 Hz, 2H), 7.43-7.30 (m, 8H), 7.14 (d, J 7.2 Hz, 2H), 3.42 (s, 3H), 3.13 (s, 2H), 2.66 (s, 1H), 2.38 (s, 3H), 1.75 (d, J 101.9 Hz, 8H). ^{13}C NMR (126 MHz, DMSO-d_6, DMSO-d_6) δ 170.8, 163.1, 160.1, 147.8, 143.2, 139.9, 133.3, 130.9 × 2, 130.3 × 2, 129.6 × 2, 129.3 × 2, 129.0 × 2, 128.6 × 2, 127.5 × 2, 125.6, 63.4, 34.1, 30.0 × 2, 25.7, 25.1 × 2, 21.8. IR (KBr) ν 3057, 3044, 3019, 2919, 2852, 1596, 1546 (vs), 1502 (s), 1448, 1397 (s), 1340, 1214, 1133, 1072, 1024, 1003, 980, 909, 889, 831, 813, 777, 758, 687, 598. HPLC (CI) m/z (M+H)$^+$ 466.2. Found, %: C, 77.44; H, 6.76; N, 9.03; S, 6.87. $C_{30}H_{31}N_3S$. Calculated, %: C, 77.38; H, 6.71; N, 9.02; S, 6.88.

Biological assay

The antiviral activity of synthesized compounds was tested in the Department of Pediatrics, University of Alabama, Birmingham; description of the technique see in [11].

The anticancer activity of synthesized compounds was tested according to the International Program of the National Institutes of Health – DTP (Developmental Therapeutic Program) of the National Cancer Institute (NCI, Bethesda, Maryland, USA) on 60 cancer cell lines [14]; a description of the technique is also given in [15].

References

1. Zhang T.Y. The Evolving Landscape of Heterocycles in Drugs and Drug Candidates. *Advances in Heterocyclic Chemistry*. **2017**, *121*, 1-12.
2. Narasimhamurthy, K.H.; Sajith, A.M.; Joy, M.N.; Rangappa, K.S. An Overview of Recent Developments in the Synthesis of Substituted Thiazoles. *Chemistry Select.* **2020**, *5*, 5629-5656.
3. Zhang, Z.; Shu, B.; Zhang, Y.; Deora, G.S.; Li, Q.S. 2,4,5-Trisubstituted Thiazole: A Privileged Scaffold in Drug Design and Activity Improvement. *Curr Top Med Chem*. **2020**, *20*, 2535-2577.
4. Borcea, A.M.; Ionuț, I.; Crișan, O.; Oniga, O. An Overview of the Synthesis and Antimicrobial, Antiprotozoal, and Antitumor Activity of Thiazole and Bisthiazole Derivatives. *Molecules*. **2021**, *26*, 624.
5. Scott, D.A.; Aquila, B.M.; Bebernitz, G.A.; Cook, D.J.; Dakin, L.A.; Deegan, T.L.; Maureen, M.H.; Stephanos, I.; Paul, D.L.; Charles, A.O.; Minwei, Y.; Zheng, X. Pyridyl and thiazolyl bisamide CSF-1R inhibitors for the treatment of cancer. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4794-4797.
6. Vilain, A.C.; Pirotte, B.; Vergely, I.; Boggetto, N.; Masereel, B.; Schynts, M.; Jacques, D.; Reboud-Ravaux, M. Evaluation of the Inhibitory Activity on Serine and Aspartic Proteases of 4-Amino-4H-1,2,4-triazole and 5-Aminothiazole Derivatives Structurally Related to β-Lactam Antibiotics. *J. Pharm. Pharmacol.* **1993**, *45*, 466-472.
7. Uchikawa, O.; Fukatsu, K.; Suno, M.; Aono, T.; Doi, T. In vivo Biological Activity of Antioxidative Aminothiazole Derivatives. *Chem. Pharm. Bull*. **1996**, *44*, 2070-2077.
8. Heal, W.; Thompson, M.J.; Mutter, R.; Cope, H.; Louth, J.C.; Chen, B. Library Synthesis and Screening: 2,4-Diphenylthiazoles and 2,4-Diphenyloxazoles as Potential Novel Prion Disease Therapeutics. *J. Med. Chem.* **2007**, *50*, 1347-1353.
9. Mauri, M.C.; Volonteri, L.S.; Colasanti, A.; Fiorentini, A., De Gaspari, I.F.; Bareggi, S.R. Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. *Clin. Pharmacokinet*. **2007**, *46*, 359-388.
10. Berlin, R.G.; Clineschmidt, B.V.; Majka, J.A. Famotidine: An appraisal of its mode of action and safety. *Am. J. Med*. **1986**, *81*, 8-12.
11. Maccallini, C.; Fantacuzzi, M.; Amoroso, R. Amidine-Based Compounds Affecting L-Arginine Metabolism. In *L-Arginine in Clinical Nutrition. Nutrition and Health*; Patel, V., Preedy, V., Rajendram, R., Eds.; Springer International Publishing Imprint: Humana Press, Cham. 2017, pp 41-53.
12. Michelin, R.A.; Sgarbossa, P.; Mazzega, I.; Sbovata, S.; Gandin, V.; Marzano, C.; Bertani, R. Chemistry and Biological Activity of Platinum Amidine Complexes. *Chem. Med. Chem*. **2011**, *6*, 1172-1183.
13. Sondhi, S.M.; Rani, R.; Roy, P.; Agrawal, S.K.; Saxena, A.K. Conventional and microwave assisted synthesis of small molecule based biologically active heterocyclic amidine derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 902-908.
14. Severin, A.O.; Pilyo, S.G.; Potikha, L.M.; Brovarets, V.S. Synthesis and Antitumor Activity of 5-Phenyl-1,3-thiazole-4-sulfonamide Derivatives. *Rus. J. Gen. Chem.* **2022**, *92*, 174-184.
15. Turov, K.V.; Mitiukhin, O.P.; Chumachenko, S.A.; Zyabrev, V.S.; Brovarets, V.S. Anticancer evaluation of di- and trifunctional substituted 1,3-thiazoles. *Ukr. Bioorg. Acta*. **2020**, *15*, 2-11.
16. Pat. 109165 UA, IPC C07D277/32, C07D417/04, A61P35/00, 2,4-Disulfanyl-5-cycloamino substituted thiazoles and their using as anticancer drugs / Zyabrev, V.S; Babiy, S.B; Turov, K.V; Vasilenko, O.M; Vinogradova, T.K.; Brovarets, V.S.; Publ. 27.07.2015 (in Ukrainian).
17. Drach, B.S.; Dolgodushina, I.Yu.; Kirsanov, A.V. Interaction of ω-chloro-ω-acylamidoacetophenones with thioacetamide. *Russ. J. Org. Chem*. **1973**, *9*, 414-419.
18. Belyuga, A.G.; Brovarets, V.S.; Chernega, A.N.; Drach, B.S. Preparation of 6-aryl-5-acylaminoimidazo[2,1-b]thiazoles, as well as their 1,3,4-thiadiazole analogues based on amidophenacylating reagents. *J. Org. Pharm. Chem*. **2005**, *3*, 38-42.
19. Aly, A.A.; Brässe, S.; Gomaa, A.M. Amidines: their synthesis, reactivity, and applications in heterocyclic synthesis. *Arkivoc*, **2018**, *6*, 85-138.
20. NCI-60 Human Tumor Cell Lines Screen. DTP Developmental Therapeutics Program, NIH website [Internet]. Available from: https://dtp.cancer.gov/discovery_development/nci-60/default.htm (accessed on September 14, 2022).

21. Velihina, Ye.S.; Pil'o, S.G.; Zyabrev, V.S.; Moskvina, V.S.; Shablykina, O.V.; Brovarets, V.S. 2-(Dichloromethyl)pyrazolo[1,5-*a*][1,3,5]triazines: synthesis and anticancer activity. *Biopolym. Cell.* **2020**, *36*, 61-74.

Створення бібліотеки *N*-(2,4-діарилтіазол-5-іл)бензамідинів та вплив цих сполук на ріст ракових клітин

О.О. Северін[1], М.В. Качаєва[1], С.Г. Пільо[1], О.В. Шабликіна[1,2], В.С. Москвіна[1,2]*, В.С. Броварець[1]

[1] *Інститут біоорганічної хімії та нафтохімії ім. В.П. Кухаря НАН України, Київ, Україна*
[2] *Київський національний університет імені Тараса Шевченка, Київ, Україна*

Резюме: Досліджено ефективний метод отримання бібліотеки *N*-(2,4-диарилтіазол-5-іл)бензамідинів. Створено бібліотеку з 25 похідних з різними замісниками в чотирьох положеннях у ключовій структурі. Проаналізовано активність синтезованих похідних амідину "*in vitro*" на 60 лініях ракових клітин та встановлено залежність «структура-активність». Виявлено, що зниження проліферації клітинних ліній раку товстої кишки та лейкемії сполуками NCS 834019, 832693, 834020 більш ніж на половину.

Ключові слова: *N*-(2,4-діарилтіазол-5-іл)бензамідини; комбінаторна бібліотека; антиракова активність.