Current Chemistry Letters 13 (2024) 695–706

Contents lists available at GrowingScience

Current Chemistry Letters

homepage: www.GrowingScience.com

Functionalized 1,3-thiazoles by combined halogen dance

Vitalii O. Sinenko[a], Oleksandr V. Los[a], Lyudmyla M. Potikha[a,b] and Volodymyr S. Brovarets[a*]

[a]*V. P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Sciences of Ukraine, Academician Kukhar str. 1, 02094 Kyiv, Ukraine*
[b]*Taras Shevchenko National University of Kyiv, Volodymyrska str. 64, 010333, Kyiv, Ukraine*

C H R O N I C L E

Article history:
Received January 2, 2024
Received in revised form
March 25, 2024
Accepted May 7, 2024
Available online
May 7, 2024

Keywords:
1,3-thiazole, 2-bromo-5-(1,3-dioxolan-2-yl)-1,3-thiazole
Halogen dance
Lithiation
Lithium diisopropylamide

A B S T R A C T

It has been reported that the halogen dance reaction can be used to synthesize polyfunctionalized 1,3-thiazoles. The transformation into target products was carried out by lithiation of 2-bromo-5-(1,3-dioxolan-2-yl)-1,3-thiazole with lithium diisopropylamide (LDA) followed by treatment with various electrophiles. The obtained compounds were then successfully applied to prepare novel 4,5-difunctional thiazole derivatives.

1. Introduction

1,3-Thiazoles are a prominent class of heterocycles with a wide range of biological properties.[1-3] They, in particular, are characterized by high activity as selective enzyme inhibitors,[4,5] sigma receptors,[6] adenosine receptors antagonists,[7] and new T-type calcium channel blockers.[8] The thiazole framework is present in more than 18 FDA-approved drugs.[3] The interest in substituted thiazoles with reactive functionalities also resides in their synthetic potential as building blocks for natural product synthesis and/or as masked aldehydes.[1,9]

Substituted thiazoles can be prepared using two methods: directly via cyclization reactions[9] or by decorating simple thiazole building blocks. The latter approach is usually the more convenient one, especially for creating compound libraries. In this sense, Halogen Dance (HD) reactions are useful synthetic tools today, often allowing the efficient functionalization of positions that are otherwise difficult to address.[10] Moreover, an HD process allows the introduction of an external electrophile at the former position of the halogen by simultaneously creating a new reactive center at the new position of the halogen.

Some examples of the displacement of substituents in 1,3-thiazole under the action of metallating reagents were reported, including the HD process in the presence of LDA.[11-13] First, Sammakia described the bromine migration from positions 2 or 5 into 4 in combination with the introduction of electrophiles.[11] The object of the present study is the metalation of 2-bromo-5-(1,3-dioxolan-2-yl)-1,3-thiazole (**2**, **Fig. 1**) as a potential precursor for the synthesis of thiazole-5-carbaldehyde derivatives suitable for further modification to synthesize the libraries of thiazole derivatives for screening and searching for pharmacologically promising compounds.

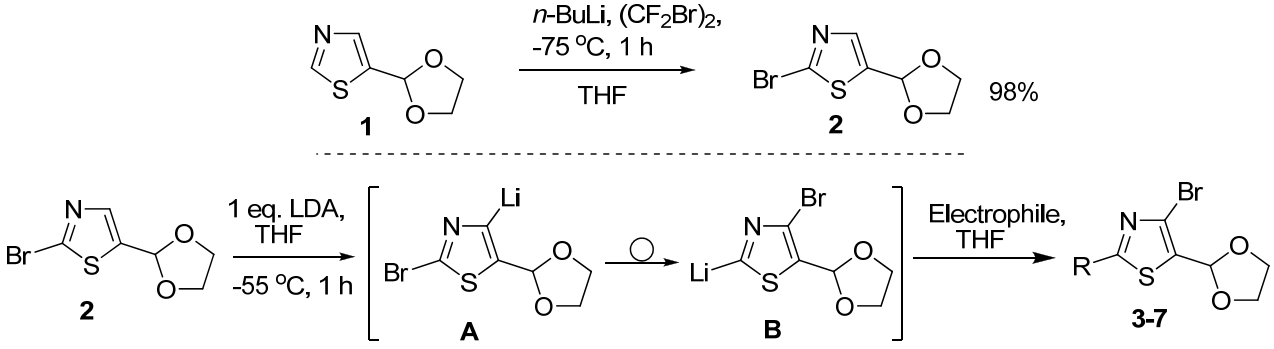
* Corresponding author
E-mail address brovarets@bpci.kiev.ua (V. S. Brovarets)

doi: 10.5267/j.ccl.2024.5.001

Only one approach to the construction of structure **2** is known,[14-16] which consists of the dioxolanylation of the aldehyde group of 2-bromo-1,3-thiazole-5-carbaldehyde. Compound **2** was an intermediate and was further used for metalation with *n*-butyllithium or the Turbo Grignard reagent. The subsequent interaction of the metalated thiazole with electrophiles led to 2-functionalized thiazoles and did not contain substituents in the 4-position.[14-16]

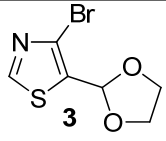
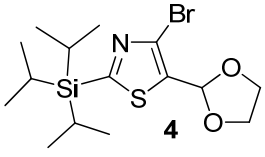
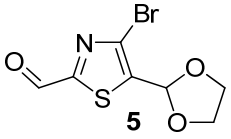
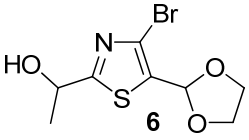
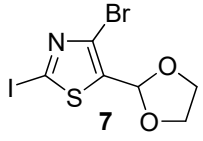
2. Results and Discussion

The key starting compound **2** was obtained by bromination of readily available 5-(1,3-dioxolan-2-yl)-1,3-thiazole (**1**).[17] The interaction of $(CF_2Br)_2$ with lithiated thiazole **1**, formed by the action of *n*-butyllithium at -75 °C, leads to the target product **2** in high yield (**Scheme 1**).



Scheme 1. Synthesis of 5-(1,3-dioxolan-2-yl)-1,3-thiazole derivatives **2-7** by lithiation reaction.

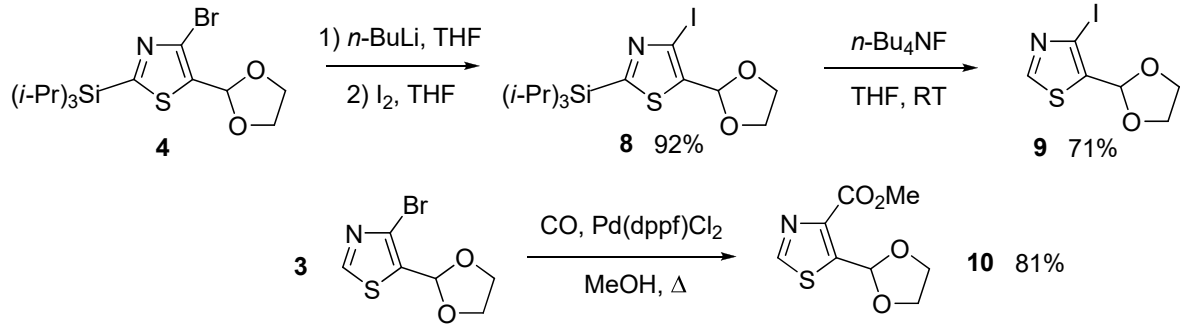
Table. 1. Lithiation of 2-bromo-5-(1,3-dioxolan-2-yl)-1,3-thiazole **2** with LDA.

Entry	Electrophile	Products	Yield (%)
1	H_2O	 **3**	96
2	$(i\text{-Pr})_3SiCl$	 **4**	74
3	DMF	 **5**	85
4	CH_3CHO	 **6**	87
5	I_2	 **7**	76

To introduce the functional groups into the thiazole structure, we performed lithiation of 1,3-thiazole **2** with LDA in tetrahydrofuran at -55 °C by treatment with various electrophiles. As a result, a series of 4-bromo-5-(1,3-dioxolan-2-yl)-2-R-1,3-thiazoles (**3-7**) was obtained with high yields (**Scheme 2, Table 1**). 2-Unsubstituted thiazole **3** was obtained using water as an electrophile. When DMF or acetaldehyde was added to a solution of lithiated thiazole **2**, it led to 1,3-thiazole-2-carbaldehyde **5** or 1-(1,3-thiazol-2-yl)ethanol **6**, respectively (**Table 1, Entry 3, 4**). Substitution products with iodine **7** and TIPS group **4** in position 2 were obtained using I_2 and Si(*i*-Pr)$_3$Cl, respectively (**Table 1, Entry 2, 5**). Compounds **3-7** are low-melting crystalline substances, and carbinol **6** is oil at room temperature. Mass spectrometry (LC/MS, GC/MS), IR, and NMR spectra have proven the structure of the reaction products, and the obtained data fully correspond to expectations. In particular, the signals of the CH fragment of the thiazole ring in the NMR spectra of 4-bromothiazole **3**, which is an isomeric for parent 2-bromothiazole **2**, are present in a weaker field (δ(H-4) 7.57 ppm and δ(C-4) 141.4 ppm for **2**, δ(H-2) 8.75 ppm and δ(C-2) 154.3 ppm for **3**).

The formation of products **3-7** occurs through a sequence of transformations that are classified as Halogen Dance Reactions. First, 2-bromo-4-lithiothiazole **A** (**Scheme 1**) is formed. Subsequent halogen migration into the 4-position leads to another 2-lithiothiazole intermediate **B**, which is more stable and was further captured by reactive electrophiles to form compounds **3-7**.

To study the possibility of further functionalizing the obtained 4-bromo-1,3-thiazoles, we carried out lithiation of compound **3** with *t*-BuLi and I_2 as an electrophile in THF at -90 - -75 °C. Note that data on the metalation of 4-halogen substituted 1,3-thiazole derivatives, which do not have a substituent in position 2, are currently unavailable in the literature. However, in our case, adding an electrophilic reagent to a solution of lithiated 4-bromo-1,3-thiazole **3** resulted in a complex mixture of products that could not be identified due to double lithiation at the 2 and 4 positions. In the case of the 2-substituted derivative **4**, the bromine substitution procedure carried out under similar conditions (1 eq. *n*-BuLi, THF, I_2, -75 °C) was successful. It led to the formation of 5-(1,3-dioxolan-2-yl)-4-iodo-2-(tripropan-2-ylsilyl)-1,3-thiazole (**8**) in high yield (**Scheme 2**). Next, the triisopropylsilyl group was selectively removed from sufficiently labile position two under the action of tetra-*n*-butylammonium fluoride in THF and 5-(1,3-dioxolan-2-yl)-4-iodo-1,3-thiazole (**9**) was obtained.



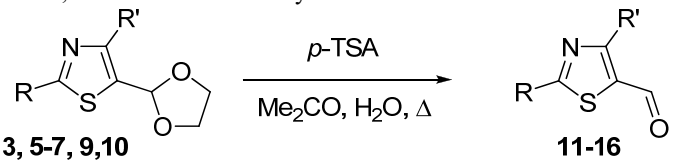
Scheme 2. Scheme of 4-functionalization of 4-bromo-1,3-thiazole derivatives **3, 4**.

For the introduction of the alkoxy carbonyl group in positions 4 of 4-bromo-1,3-thiazole **3**, we carried out its carbonylation in a CO atmosphere with the presence of triethylamine and Pd(dppf)Cl_2 in methanol. The transformation in methyl 5-(1,3-dioxolan-2-yl)-1,3-thiazole-4-carboxylate (**10**) takes place at 125 °C for 16 hours (**Scheme 2**).

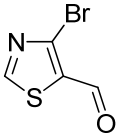
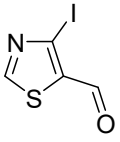
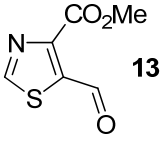
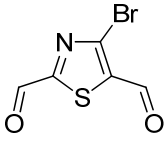
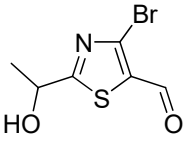
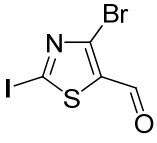
After removing the dioxolane protection, compounds **3**, **5-7**, **9**, and **10** were converted to the corresponding aldehydes **11-16** (**Table 2**), which are low molecular weight synthons for the synthesis of new 1,3-thiazole derivatives for the selection of various bioregulators among them. Among the obtained aldehydes, only 4-bromo-1,3-thiazole-5-carbaldehyde **11** is mentioned in literature[18] as an intermediate for synthesizing potent and selective antagonists of the CXCR3 chemokine receptor. The synthesis scheme of compound **11** in these cases included oxidation of the corresponding (4-bromo-1,3-thiazol-5-yl)methanol with Dess-Martin periodinane reagent with a yield of 82%.

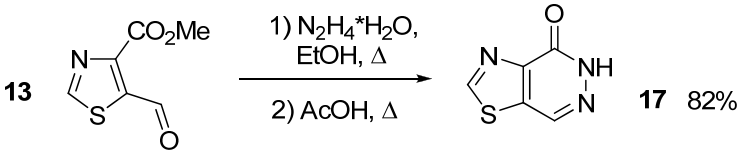
The previously unknown methyl 5-formyl-1,3-thiazole-4-carboxylate **13** is a promising 1,4-dielectrophilic reagent in organic synthesis, especially for constructing condensed heterocyclic systems with a thiazole nucleus. In this sense, we demonstrated the reactivity of compound **13** using the example of the synthesis of [1,3]thiazolo[4,5-*d*]pyridazin-4(5*H*)-one (**17**) (**Scheme 3**), which is easily formed by heating the starting compound **13** with hydrazine hydrate in ethanol. Compound **17** is the previously unknown simplest representative of this series. Previously used, a similar scheme of the pyridazinone ring addition to thiazole was to synthesize only 2,7-disubstituted derivatives based on 5-acyl-2-R-1,3-thiazole-4-carboxylic acid derivatives.[19-22] The structure of the **17** has been proven by mass spectrometry (LC/MS) and NMR spectra. Thus, the closure of the pyridazinone cycle causes a weak-field shift of the H-2 in the ^{1}H NMR (by 0.5 ppm) and C-2 signals in the ^{13}C NMR (by 2 ppm) spectra. The H-7 proton signal is present at 8.78 ppm. C-4 and C-7 carbon atoms of the condensed product **17** naturally resonate in a stronger field (158.0 and 133.6 ppm, respectively) compared to the atoms of the ester (161.6 ppm) and aldehyde (184.7 ppm) groups of the original compound **13**.

Table. 2. Synthesis of 2-R-4-R'-1,3-thiazole-5-carbaldehydes **11-16**.



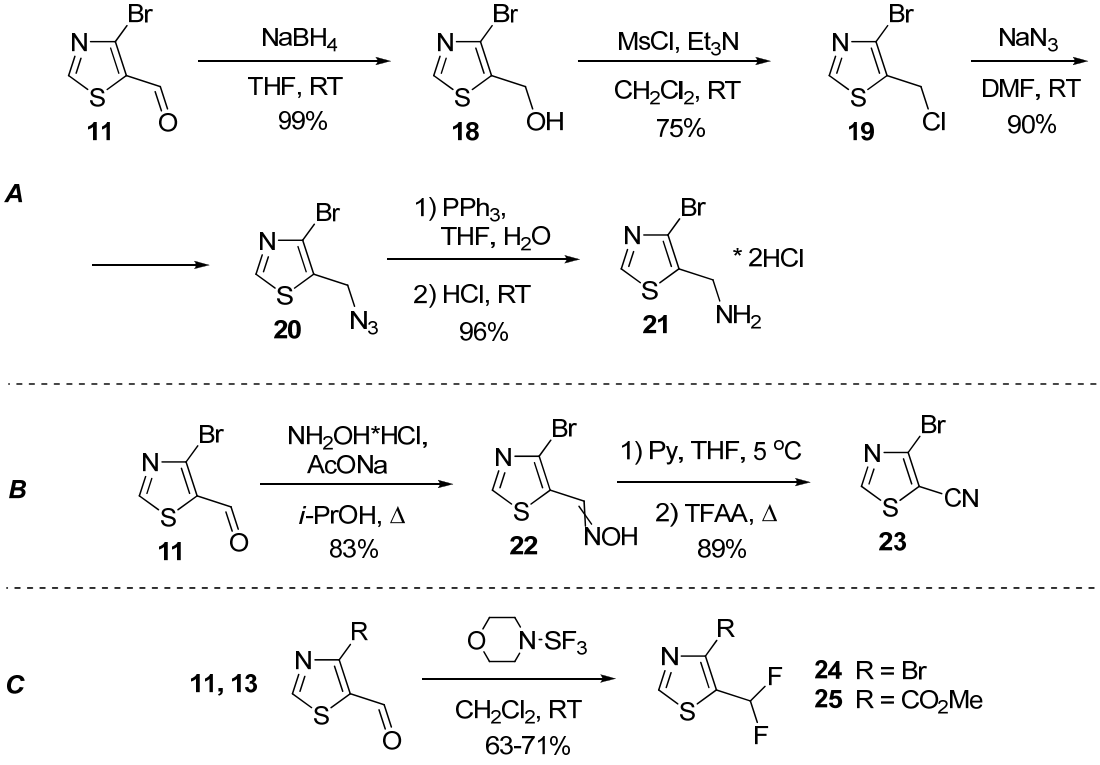
3, 5-7, 9,10 **11-16**

Entry	Reagents	Products	Yield (%)
1	**3**	 **11**	88
2	**5**	 **12**	84
3	**6**	 **13**	84
4	**7**	 **14**	68
5	**9**	 **15**	92
6	**10**	 **16**	85



Scheme 3. Scheme of the synthesis of [1,3]thiazolo[4,5-*d*]pyridazin-4(5*H*)-one **17**.

4-R-1,3-thiazole-5-carbaldehydes **11-16** are convenient precursors for obtaining a variety of 5-functionalized thiazoles. Using the examples of compounds **11** and **13**, we proposed effective conditions for carrying out a series of such transformations, the results of which are presented in **Scheme 4**. Thus, carbaldehyde **11** was quantitatively reduced with sodium borohydride in (4-bromo-1,3-thiazol-5-yl)methanol (**18**) (**Scheme 4 (*A*)**). Compound **18** is known and was previously[23] obtained by catalytic hydrogenation of (2,4-dibromo-1,3-thiazol-5-yl)methanol. At room temperature, mesyl chloride in the presence of Et_3N in dichloromethane was used to replace the hydroxyl group with chlorine. The obtained 4-bromo-5-(chloromethyl)-1,3-thiazole (**19**) was further transformed into 5-(azidomethyl)-4-bromo-1,3-thiazole (**20**) by the action of NaN_3 in DMF, and further reduced in 1-(4-bromo-1,3-thiazol-5-yl)methanamine (**21**) upon interaction with PPh_3 in THF. Amine **21** was isolated in an individual state as dihydrochloride **21*2HCl** with a yield of 96%. Note that (bromothiazolyl)methanamine hydrochloride **21*HCl** was previously obtained[24] as an intermediate by reducing the condensation product of aldehyde **11** with *t*-butylsulfinamide.

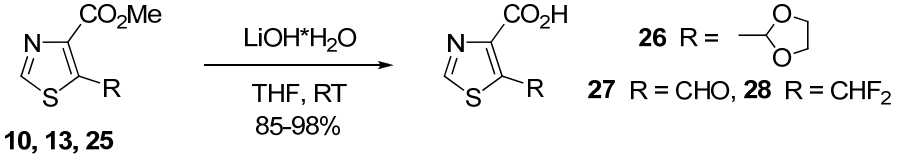


Scheme 4. Scheme of synthesis of 5-functionalized thiazoles **18-25.**

The structure of the reaction products **19-21** has been proven by mass spectrometry (LC/MS, GC/MS), IR, and NMR spectra and fully meets expectations. In particular, the formation of the dihydrochloride of amine **21*2HCl** is indicated by both the elemental analysis data and the IR spectrum. Protonation of the primary amino group is reflected in the 2870-3083 cm^{-1} region of several intense broadened bands of NH valence vibrations characteristic of $-N^{+}H_3$. In the region of 1800-2200 cm^{-1}, there are also several bands of medium intensity, indicating protonated sp^2-N.

A sequence of transformations used to introduce a cyano group in position 5 of thiazole, including the synthesis of 1-(4-bromo-1,3-thiazol-5-yl)-*N*-hydroxymethanimine (**22**) (**Scheme 4 (*B*)**). Heating aldehyde **11** with hydroxylamine hydrochloride in the presence of sodium acetate leads to oxime **22**, which readily loses water on heating with trifluoroacetic anhydride to form the target 4-bromo-1,3-thiazole-5-carbonitrile (**23**) in high yield. Oxime **22** was obtained as a mixture of *E*- and *Z*-isomers in a ratio of 4:1 according to the data of ^{1}H NMR spectra. The aldehyde group in compounds **11** and **13** was also successfully transformed into difluoromethyl by the action of 4-(trifluoromethyl)morpholine under mild conditions, and the corresponding 5-(difluoromethyl)-1,3-thiazoles **24**, **25** were obtained (**Scheme 4 (*C*)**).

Considering the high biological and synthetic potential of 1,3-thiazole-4-carboxylic acid derivatives, [25, 26] the obtained esters **10**, **13**, **25** were hydrolyzed into the corresponding acids **26-28** under the action of lithium hydroxide (**Scheme 5**).



Scheme 5. Scheme of the synthesis of 1,3-thiazole-4-carboxylic acids **26-28.**

Acid **26** is also efficiently converted to compound **27** under the same dioxolane deprotection conditions used to obtain aldehydes **11-16** (*p*-TSA, acetone, H_2O, reflux). Acids **26-28** are solid substances that are moderately soluble in water and well in polar organic solvents. According to the data of the IR spectra, they exist in the solid state in the form of dimers. This is indicated by low-frequency shifts of the bands of valence vibrations of the CO_2H group ($\nu_{C=O}$ at 1688-1700 cm^{-1}). In particular, ν_{OH} is observed as a widened band of average intensity in the region of 2500-3000 cm^{-1}, which overlaps with bands of C-H bond vibrations. This position of the characteristic vibration band of the OH group is typical for dimers of acids. The intense band of deformation vibrations of δ_{OH} in the spectra of compounds **26-28** is present in the region of 1253-1274 cm^{-1}, which is also characteristic of acid dimers.

3. Conclusions

In conclusion, we found that the HD reaction combined with the subsequent treatment of the reaction mixture with electrophiles can be used as an efficient method for the synthesis of 2-functionalized 1,3-thiazole derivatives. HD reactions were performed on 2-bromo-5-(1,3-dioxolan-2-yl)-1,3-thiazole **2**, which, in turn, was synthesized from commercially available 1,3-thiazole-5-carbaldehyde in two steps with a total yield of 87%, significantly improving the previous routes. Good or excellent yields (74–97%) were obtained depending on the electrophile's nature. Found methods of further 4-functionalization of 1,3-thiazoles based on catalytic carbonylation of 4-bromo-1,3-thiazole-5-carbaldehyde **11** or metalation of 4-bromo-5-(1,3-dioxolan-2-yl)-2-(tripropan-2-ylsilyl)-1,3-thiazole **4** followed by reaction with an electrophile (I_2). Proposed conditions for carrying out a sequence of transformations based on 4-bromo-1,3-thiazole-5-carbaldehyde **11** and methyl 5-formyl-1,3-thiazole-4-carboxylate **13**. A series of 5-functionalized derivatives of 4-bromo-1,3-thiazole and 1,3-thiazole-4-carboxylate was obtained.

Acknowledgments

The authors are grateful to Enamine company for financial support of this work.

4. Experimental

All reagents and solvents were purchased from Enamine Ltd. (www.enamine.net). TLC characterization was performed with pre-coated silica gel GF254 (0.2 mm). NMR spectra of the obtained products were recorded on a Varian Unity Plus 400 spectrometer (400 MHz for ^{1}H, 376 MHz for ^{19}F), a Bruker 170 spectrometer (126 MHz for ^{13}C); ^{1}H NMR chemical shifts were calibrated using residual undeuterated DMSO (δ = 2.50 ppm), $CDCl_3$ (δ = 7.26 ppm) signals and $CFCl_3$ (δ = 0.0 ppm) as an external standard. ^{13}C NMR chemical shifts for ^{13}C NMR are reported relative to the central DMSO (δ = 40.45 ppm) signal and $CDCl_3$ (δ = 77.36 ppm) signal. LC/MS spectra were recorded on an Agilent 1100 Series high-performance liquid chromatograph HPLC system equipped with a diode matrix with an Agilent LC/MS mass selective detector. Parameters of LC/MS analysis: column Zorbax SBC18 1.8 μm, 4.6×15 mm (PN 821975-932); solvent: acetonitrile–water (95:5), 0.1% trifluoroacetic acid; eluent flow rate 3 mL min^{-1}, injection volume 1 μL, UV detecting at 215, 254, 265 nm, chemical ionization at atmospheric pressure, scan range *m/z* 80–1000. GC/MS spectra were obtained on an Agilent 5975C VL MSD instrument (electron impact ionization at 70 eV). IR spectra of the compounds were recorded on a Bruker Vertex 70 instrument (ATR technique for oils and liquids; from KBr pellets for solids), and vibration frequencies were given in cm^{-1}. Melting points were measured on a MPA100 OptiMelt automated melting point system. Elemental analyses were performed at the Analytical Laboratory of the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of NAS of Ukraine.

5-(1,3-Dioxolan-2-yl)thiazole **1** was prepared as described in the literature.[17]

2-Bromo-5-(1,3-dioxolan-2-yl)thiazole (2). A solution of 5-(1,3-dioxolan-2-yl)thiazole **1** (100.0 g, 0.636 mol) in dry THF (1000 mL) was cooled to -85 ºC. A solution of *n*-butyllithium (293 mL, 2.5 M solution in hexane, 0.732 mol) was added dropwise. The reaction mixture was stirred for 1 hour at -75 ºC, then was cooled to -90 ºC, and a solution of $(CF_2Br)_2$ (223.14 g, 0.859 mol) in dry THF (300 mL) was added dropwise, maintaining the temperature below -75 ºC. Then, the reaction mixture was stirred at room temperature for 10 hours and treated with water (400 mL). The resulting solution was extracted with MTBE, washed with brine, and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (MTBE), giving **2** (147.19 g, 98%) as a brown liquid.
ATR-IR (cm^{-1}): 2889, 1675, 1406, 1069 (C-O), 1005 (C-O), 935, 860, 593. ^{1}H NMR ($CDCl_3$), δ: 3.96–4.03 (2H, m, $O(CH_A\underline{H}_B)_2O$), 4.03–4.10 (2H, m, $O(C\underline{H}_AH_B)_2O$), 6.05 (1H, s, O-CH-O), 7.57 (1H, s, H-4). ^{13}C NMR ($CDCl_3$), δ: 65.59 (2C, CH_2), 98.42 (CH), 137.53 (C-2), 141.17 (C-5), 141.41 (C-4). GC/MS (I, %): 73 (36), 156 (100), 235 (19) $[M]^+$, 236 (10), 237 (19) $[M+2]^+$, 238 (10). Anal. calcd for $C_6H_6BrNO_2S$: C, 30.52; H, 2.56; Br, 33.85; N, 5.93; S, 13.58. Found: C, 30.57; H, 2.60; Br, 33.84; N, 5.94; S, 13.57.

General procedure. Lithiation of 2-bromo-5-(1,3-dioxolan-2-yl)thiazole with lithium diisopropylamide (LDA).
A solution of LDA was prepared as follows: to diisopropylamine (4.80 g; 47.4 mmol) in anhydrous THF (50 mL) at -30 ºC was added 16.2 mL of *n*-BuLi (2.5 M solution in hexane, 40.6 mmol) under Ar. After stirring at -10 ºC for 10 min, the reaction mixture was cooled at -80 ºC. To the LDA solution was added a solution of 2-bromo-5-(1,3-dioxolan-2-yl)thiazole **2** (8.00 g, 33.8 mmol) in anhydrous THF (50 mL) dropwise, and the mixture was stirred at -55 ºC for 1 h gave a mixture **A**.

4-Bromo-5-(1,3-dioxolan-2-yl)-1,3-thiazole (3). A solution of H_2O (1.83 g, 101.4 mmol) in THF (18 mL) was added dropwise to mixture **A** at -90°C. The reaction mixture was stirred until it warmed to 0 ºC, treated with water (50 mL) and brine (50 mL). The organic layer was separated, and the aqueous layer was extracted with MTBE. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (MTBE/hexane, 1:1), giving **3** (7.68 g, 96%) as a light brown solid, mp 39-40 °C.

IR (KBr, cm^{-1}): 3085, 2876, 1513, 1277, 1207, 1159 (C-O), 1074 (C-O), 960, 905, 805. ^{1}H NMR ($CDCl_3$), δ: 4.01–4.08 (2H, m, $O(CH_A\underline{H}_B)_2O$), 4.11–4.18 (2H, m, $O(C\underline{H}_AH_B)_2O$), 6.11 (1H, s, O-CH-O), 8.75 (1H, s, H-2). ^{13}C NMR ($CDCl_3$), δ:

65.82 (2C, CH_2), 98.98 (CH), 126.54 (C-4), 131.90 (C-5), 154.29 (C-2). GC/MS (I, %): 45 (35.5), 73 (47), 112 (100), 156 (43), 235 (28) $[M]^+$, 236 (15), 237 (29) $[M+2]^+$, 238 (15). Anal. calcd for $C_6H_6BrNO_2S$: C, 30.52; H, 2.56; Br, 33.85; N, 5.93; S, 13.58. Found: C, 30.58; H, 2.59; Br, 33.83; N, 5.91; S, 13.59.

4-Bromo-5-(1,3-dioxolan-2-yl)-2-(tripropan-2-ylsilyl)-1,3-thiazole (4). A solution of Si(*i*-Pr)$_3$Cl (9.12 g, 47.3 mmol) in THF (10 mL) was added dropwise to a mixture **A** at -90°C. The reaction mixture was stirred at room temperature overnight, treated with water (100 mL), and extracted with MTBE. The organic layer was separated, washed with brine, and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (MTBE/hexane, 1:15), giving **4** (9.82 g, 74%) as a colorless solid, mp 48-49 °C.
IR (KBr, cm^{-1}): 2958, 2942, 2864, 1516, 1464, 1354, 1228 (Si-C), 1199, 1071 (C-O), 1016 (C-O), 880, 651, 517. ^{1}H NMR ($CDCl_3$), *δ*: 1.14 (18H, d, *J* 7.6 Hz, SiCH(C$\underline{H}_3$)$_2$), 1.38–1.49 (1H, m, SiC$\underline{H}$(CH$_3$)$_2$), 4.07–4.10 (2H, m, O(CH$_A\underline{H}_B$)$_2$O), 4.13–4.21 (2H, m, O(C$\underline{H}_A$H$_B$)$_2$O), 6.14 (1H, s, O-CH-O). ^{13}C NMR ($CDCl_3$), *δ*: 11.83 (3C, SiCH), 18.73 (6C, CH_3), 65.86 (2C, CH_2), 99.48 (CH), 128.45 (C-4), 133.21 (C-5), 172.76 (C-2). GC/MS (I, %): 73 (93), 348 (86), 349 (65), 350 (100), 351 (67), 391 (13) $[M]^+$, 393 (14) $[M+2]^+$. Anal. calcd for $C_{15}H_{26}BrNO_2SSi$: C, 45.91; H, 6.68; Br, 20.36; N, 3.57; S, 8.17. Found: C, 45.95; H, 6.70; Br, 20.34; N, 3.58; S, 8.15.

4-Bromo-5-(1,3-dioxolan-2-yl)-1,3-thiazole-2-carbaldehyde (5). The reaction mixture **A** was cooled to -90 °C and DMF (4.20 g, 57.5 mmol) was added dropwise. The reaction mixture was stirred until it warmed to +10 °C, poured into a solution of acetic acid (12 mL) in water (90 mL), treated with brine (50 mL). The organic layer was separated, and the aqueous layer was extracted using MTBE. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel ($CHCl_3$), which gave **5** (7.60 g, 85%) as a yellow solid, mp 97-99 °C.
IR (KBr, cm^{-1}): 2905, 1691 (C=O), 1504, 1359, 1252, 1225, 1176, 1069 (C-O), 938, 873, 643. ^{1}H NMR ($CDCl_3$), *δ*: 4.04–4.12 (2H, m, O(CH$_A\underline{H}_B$)$_2$O), 4.12–4.20 (2H, m, O(C$\underline{H}_A$H$_B$)$_2$O), 6.13 (1H, s, O-CH-O), 9.89 (1H, s, 2-CHO). ^{13}C NMR ($CDCl_3$), *δ*: 66.10 (2C, CH_2), 98.71 (CH), 127.73 (C-4), 140.71 (C-5), 165.00 (C-2), 183.21 (C=O). GC/MS (I, %): 45 (59), 73 (100), 234 (81), 236 (82), 263 (17) $[M]^+$, 265 (18) $[M+2]^+$. Anal. calcd for $C_7H_6BrNO_3S$: C, 31.83; H, 2.29; Br, 30.26; N, 5.30; S, 12.14. Found: C, 31.80; H, 2.31; Br, 30.28; N, 5.29; S, 12.12.

1-[4-Bromo-5-(1,3-dioxolan-2-yl)-1,3-thiazol-2-yl]ethanol (6). A solution of acetaldehyde (3.72 g, 84.5 mmol) in THF (25 mL) was added dropwise to mixture **A** at -90°C. The reaction mixture was stirred until it warmed to 0°C, poured into water (50 mL), and treated with brine (50 mL). The organic layer was separated, and the aqueous layer was extracted using MTBE. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (CH_2Cl_2 – MTBE/CH_2Cl_2, 1:6), giving **6** (8.26 g, 87%) as a yellow oil.
ATR-IR (cm^{-1}): 3364 (OH), 2978, 2891, 1526, 1225, 1201, 1068 (C-O), 937, 856. ^{1}H NMR ($CDCl_3$), *δ*: 1.54 (3H, d, *J* 5.2 Hz, CH_3), 3.75 (1H, br.s, OH), 3.95–4.01 (2H, m, O(CH$_A\underline{H}_B$)$_2$O), 4.06–4.12 (2H, m, O(C$\underline{H}_A$H$_B$)$_2$O), 5.02 (1H, q, *J* 5.2 Hz, C$\underline{H}$CH$_3$), 6.00 (1H, s, O-CH-O). ^{13}C NMR ($CDCl_3$), *δ*: 23.97 (CH_3), 65.75 (2C, CH_2), 68.34 (CH), 99.09 (CH), 124.37 (C-4), 131.37 (C-5), 178.21 (C-2). LC/MS (I, %): 280 (85) $[M+H]^+$, 282 (100) $[M+H+2]^+$. Anal. calcd for $C_8H_{10}BrNO_3S$: C, 34.30; H, 3.60; Br, 28.52; N, 5.00; S, 11.45. Found: C, 34.37; H, 3.57; Br, 28.46; N, 4.94; S, 11.41.

4-Bromo-5-(1,3-dioxolan-2-yl)-2-iodo-1,3-thiazole (7). A solution of I_2 (12.01 g, 47.3 mmol) in THF (70 mL) was added dropwise to mixture **A** at -90°C. The reaction mixture was stirred until it warmed to 0°C, poured into a solution of sodium hydrosulfite (12 g) in water (110 mL), and extracted with MTBE. The organic layer was separated, washed with brine, and dried over sodium sulfate. The residue was dissolved in dichloromethane, filtered through silica gel, and washed with MTBE. The solvent was removed under reduced pressure; the residue was washed with hexane, filtered, and given **7** (9.32 g, 76%) as a colorless solid, mp 80-81 °C.
IR (KBr, cm^{-1}): 2890, 2821, 1522, 1373, 1219, 1079 (C-O), 992, 956, 927, 838. ^{1}H NMR ($CDCl_3$), *δ*: 3.98–4.06 (2H, m, O(CH$_A\underline{H}_B$)$_2$O), 4.07–4.15 (2H, m, O(C$\underline{H}_A$H$_B$)$_2$O), 6.05 (1H, s, O-CH-O). ^{13}C NMR ($CDCl_3$), *δ*: 65.88 (2C, CH_2), 98.61 (CH), 101.57 (C-2), 124.93 (C-4), 138.26 (C-5). LC/MS (I, %): 101 (35), 157 (100), 362 (70) $[M+H]^+$, 364 (75) $[M+H+2]^+$. Anal. calcd for $C_6H_5BrINO_2S$: C, 19.91; H, 1.39; Br, 22.07; N, 3.87; S, 8.86. Found: C, 19.87; H, 1.42; Br, 22.06; N, 3.88; S, 8.84.

5-(1,3-Dioxolan-2-yl)-4-iodo-2-(tripropan-2-ylsilyl)-1,3-thiazole (8). A solution of 4-bromo-5-(1,3-dioxolan-2-yl)-2-(tripropan-2-ylsilyl)-1,3-thiazole **4** (8 g, 20.4 mmol) in dry THF (80 mL) was cooled to -90°C, and a solution of *n*-butyllithium (9.8 mL, 2.5 M solution in hexane, 24.5 mmol) was added dropwise. The mixture was stirred for 1 hour at -75°C, cooled to -90°C, and a solution of iodine (7.24 g, 28.5 mmol) in dry THF (60 mL) was added dropwise, maintaining a temperature not higher than -80 °C. The reaction mixture was stirred at room temperature for 1 hour, treated with a solution of sodium hydrosulfite (7.00 g, 67.3 mmol) in water (70 mL), and extracted with MTBE. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (MTBE/hexane, 1:10), giving **8** (8.25 g, 92%) as a colorless solid, mp 45-46 °C.
IR (KBr, cm^{-1}): 2941, 2863, 1503, 1461, 1351, 1219 (Si-C), 1161, 1071 (C-O), 1017, 880, 688, 653, 517. ^{1}H NMR ($CDCl_3$), *δ*: 1.13 (18H, d, *J* 7.6 Hz, SiCH(C$\underline{H}_3$)$_2$), 1.38–1.49 (3H, m, SiC$\underline{H}$(CH$_3$)$_2$), 4.04–4.10 (2H, m, O(CH$_A\underline{H}_B$)$_2$O), 4.14–4.22 (2H, m, O(C$\underline{H}_A$H$_B$)$_2$O), 6.08 (1H, s, O-CH-O). ^{13}C NMR ($CDCl_3$), *δ*: 11.88 (3C, SiCH), 18.75 (6C, CH_3), 65.88 (2C, CH_2), 100.37 (C-4), 101.23 (CH), 137.37 (C-5), 174.27 (C-2). GC/MS (I, %): 73 (34), 282 (28), 312 (44), 396 (100), 397 (71),

439 (23) $[M]^+$. Anal. calcd for $C_{15}H_{26}INO_2SSi$: C, 41.00; H, 5.96; N, 3.19; S, 7.30. Found: C, 41.04; H, 5.94; N, 3.20; S, 7.28.

5-(1,3-Dioxolan-2-yl)-4-iodo-1,3-thiazole (9). A solution of 5-(1,3-dioxolan-2-yl)-4-iodo-2-(tripropan-2-ylsilyl)-1,3-thiazole **8** (5.00 g, 11.4 mmol) in dry THF (50 mL) was cooled to +5 ºC, and the solution of tetrabutylammonium fluoride (22.8 mL, 1M solution in THF, 22.8 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 hour, treated with brine (60 mL), saturated sodium bicarbonate solution (60 mL), and extracted with MTBE. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (MTBE/hexane, 2:1), giving **9** (2.29 g, 71%) as a colorless solid, mp 66-67 °C.
IR (KBr, cm^{-1}): 3087, 2873, 1501, 1397, 1365, 1214, 1145, 1069 (C-O), 955, 897, 805. ^{1}H NMR ($CDCl_3$), δ: 4.033–4.10 (2H, m, $O(CH_A\underline{H_B})_2O$), 4.13–4.21 (2H, m, $O(C\underline{H_A}H_B)_2O$), 6.05 (1H, s, O-CH-O), 8.78 (1H, s, H-2). ^{13}C NMR ($CDCl_3$), δ: 65.92 (2C, CH_2), 97.68 (C-4), 100.80 (CH), 136.21 (C-5), 155.86 (C-2). LC/MS (I, %): 284 (100) $[M+H]^+$. Anal. calcd for $C_6H_6INO_2S$: C, 25.46; H, 2.14; N, 4.95; S, 11.33. Found: C, 25.50; H, 2.13; N, 4.94; S, 11.34.

Methyl 5-(1,3-dioxolan-2-yl)-1,3-thiazole-4-carboxylate (10). Triethylamine (25.74 g, 254.4 mmol) and $Pd(dppf)Cl_2$ (4.64 g, 6.4 mmol) were added to a solution of 4-bromo-5-(1,3-dioxolan-2-yl)thiazole **3** (50.00 g, 212.0 mmol) in methanol (700 mL). The reaction mixture was placed in an autoclave and stirred at 125 ºC for 16 hours in a CO atmosphere (20 bar). The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (MTBE), which gave **10** (36.92 g, 81%) as a yellow solid, mp 59-60 °C.
IR (KBr, cm^{-1}): 3087, 2957, 2882, 1730 (C=O), 1443, 1273 (C-O), 1209, 1175 (C-O), 1092 (C-O), 938, 852, 789, 660, 624. ^{1}H NMR ($CDCl_3$), δ: 3.95 (3H, s, CH_3), 4.01–4.06 (2H, m, $O(CH_A\underline{H_B})_2O$), 4.08–4.15 (2H, m, $O(C\underline{H_A}H_B)_2O$), 6.72 (1H, s, O-CH-O), 8.73 (1H, s, H-2). ^{13}C NMR ($CDCl_3$), δ: 52.82 (CH_3), 65.93 (2C, CH_2), 97.94 (CH), 143.70 (C-5), 146.94 (C-4), 152.72 (C-2), 162.19 (C=O). LC/MS (I, %): 184 (53), 216 (100) $[M+H]^+$. Anal. calcd for $C_8H_9NO_4S$: C, 44.64; H, 4.21; N, 6.51; S, 14.90. Found: C, 44.67; H, 4.20; N, 6.52; S, 14.88.

4-Bromo-1,3-thiazole-5-carbaldehyde (11). To a solution of 4-bromo-5-(1,3-dioxolan-2-yl)thiazole **3** (10.00 g, 42.4 mmol) in acetone (60 mL) was added water (30 mL) and *p*-TSA (0.73 g, 4.24 mmol). The reaction mixture was boiled for 9 hours, and then acetone was removed under reduced pressure. A saturated solution of sodium hydrogen carbonate (30 mL) was added to the residue and extracted with dichloromethane. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure to a volume of 50 mL and purified by chromatography on silica gel (MTBE/hexane, 1:2), giving **11** (7.16 g, 88%) as a colorless solid, mp 96-98 °C.
IR (KBr, cm^{-1}): 3089, 1663 (C=O), 1476, 1275, 920, 675. ^{1}H NMR ($CDCl_3$), δ: 9.00 (1H, s, H-2), 10.02 (1H, s, CHO). ^{13}C NMR ($CDCl_3$), δ: 133.06 (C-4), 135.61 (C-5), 160.39 (C-2), 183.35 (C=O). GC/MS (I, %): 57 (61), 190 (96), 191 (88) $[M]^+$, 192 (100), 193 (89) $[M+2]^+$. Anal. calcd for C_4H_2BrNOS: C, 25.02; H, 1.05; Br, 41.61; N, 7.29; S, 16.70. Found: C, 25.00; H, 1.04; Br, 41.63; N, 7.30; S, 16.72.

4-Iodo-1,3-thiazole-5-carbaldehyde (12). Water (6 mL) and *p*-TSA (0.12 g, 0.7 mmol) were added to a solution of 5-(1,3-dioxolan-2-yl)-4-iodothiazole **9** (2.00 g, 7.1 mmol) in acetone (12 mL). The reaction mixture was boiled for 7 hours. The solvent was removed under reduced pressure, and the residue was treated with a saturated solution of sodium bicarbonate (6 mL). The resulting solution was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (dichloromethane), giving **12** (1.42 g, 84%) as a colorless solid, mp 116-117 °C.
IR (KBr, cm^{-1}): 3080, 1658 (C=O), 1460, 1262, 1222, 908, 838, 669. ^{1}H NMR ($CDCl_3$), δ: 9.05 (1H, s, H-2), 9.92 (1H, s, 5-CHO). ^{13}C NMR ($CDCl_3$), δ: 107.54 (C-4), 136.01 (C-5), 161.35 (C-2), 185.14 (C=O). GC/MS (I, %): 45 (21), 127 (22), 239 (100) $[M]^+$. Anal. calcd for C_4H_2INOS: C, 20.10; H, 0.84; N, 5.86; S, 13.41. Found: C, 20.12; H, 0.83; N, 5.85; S, 13.43.

Methyl 5-formyl-1,3-thiazole-4-carboxylate (13). Water (65 mL) and *p*-TSA (1.60 g, 9.29 mmol) were added to a solution of 5-(1,3-dioxolan-2-yl)thiazole-4-carboxylate **10** (20.00 g, 92.9 mmol) in acetone (130 mL). The reaction mixture was boiled for 12 hours; the solvent was removed under reduced pressure. A saturated solution of sodium bicarbonate (60 mL) was added to the residue; the resulting solution was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (MTBE/hexane, 4:1), giving **13** (13.36 g, 84%) as a colorless solid, mp 82-84 °C.
IR (KBr, cm^{-1}): 3044, 1717 (C=O), 1668 (C=O), 1511, 1396, 1328, 1267 (^{as}C-O), 1003 (^{s}C-O), 912, 696. ^{1}H NMR ($CDCl_3$), δ: 4.06 (3H, s, CH_3), 9.02 (1H, s, H-2), 10.70 (1H, s, 5-CHO). ^{13}C NMR ($CDCl_3$), δ: 53.51 (CH_3), 144.69 (C-5), 140.08 (C-4), 158.08 (C-2), 161.57 (4-C=O), 184.66 (5-C=O). LC/MS (I, %): 140 (40), 172 $[M+H]^+$. Anal. calcd for $C_6H_5NO_3S$: C, 42.10; H, 2.94; N, 8.18; S, 18.73. Found: C, 42.14; H, 2.93; N, 8.19; S, 18.70.

4-Bromo-1,3-thiazole-2,5-dicarbaldehyde (14).
Water (6 mL) and *p*-TSA (0.13 g, 0.76 mmol) were added to a solution of 4-bromo-5-(1,3-dioxolan-2-yl)-1,3-thiazole-2-carbaldehyde **5** (2.00 g, 7.57 mmol) in acetone (12 mL). The reaction mixture was boiled for 12 hours, and then acetone was removed under reduced pressure. A saturated solution of sodium hydrogen carbonate (6 mL) was added to the residue and extracted with mixture MTBE/THF (1 : 1). The combined organic extracts were washed with brine and dried over

sodium sulfate. The solvent was removed under reduced pressure, and purified by chromatography on silica gel (CH_2Cl_2) gave **14** (1.20 g, 72%) as a colorless solid, mp 92-93 °C.

IR (KBr, cm^{-1}): 2895, 1694 (C=O), 1668 (C=O), 1459, 1259, 1221, 1185, 887, 722, 687. ^1H NMR ($CDCl_3$), δ: 9.96 (1H, s, 2-CHO), 10.09 (1H, s, 5-CHO). ^{13}C NMR ($CDCl_3$), δ: 135.28 (C-2), 137.81 (C-5), 169.16 (C-4), 182.92 (2-C=O), 183.24 (5-C=O). GC/MS (I, %): 57.0 (100), 81.9 (61), 134.8 (53), 217.9 (41), 218.9 (98) $[M]^+$, 219.9 (46), 220.9 (99) $[M+2]^+$. Anal. calcd for $C_5H_2BrNO_2S$: C, 27.29; H, 0.92; Br, 36.31; N, 6.37; S, 14.57. Found: C, 27.31; H, 0.95; Br, 36.30; N, 6.39; S, 14.55.

4-Bromo-2-(1-hydroxyethyl)-1,3-thiazole-5-carbaldehyde (15).

Water (10 mL) and *p*-TSA (0.12 g, 0.71 mmol) were added to a solution of 1-[4-bromo-5-(1,3-dioxolan-2-yl)-1,3-thiazol-2-yl]ethanol **6** (2.00 g, 7.14 mmol) in acetone (20 mL). The reaction mixture was boiled for 12 hours, and then acetone was removed under reduced pressure. A saturated solution of sodium hydrogen carbonate (6 mL) was added to the residue and extracted with mixture MTBE/THF (1 : 1). The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and purified by chromatography on silica gel (MTBE/CH_2Cl_2, 1:8) gave **15** (1.60 g, 95%) as a yellow oil.

ATR-IR (cm^{-1}): 3379 (OH), 2982, 1658 (C=O), 1483, 1237 (C-O), 1107, 1008 868, 671. ^1H NMR ($CDCl_3$), δ: 1.65 (3H, d, *J* 6.2 Hz, CH_3), 3.66 (1H, br.s, OH), 5.15 (1H, q, *J* 6.2 Hz, C<u>H</u>CH_3), 9.93 (1H, s, CHO). ^{13}C NMR ($CDCl_3$), δ: 24.06 (CH_3), 68.99 (CH), 132.78 (C-4), 134.62 (C-5), 183. 55 (C=O), 185.54 (C-2). LC/MS (I, %): 157 (100), 236 (10) $[M+H]^+$, 238 (10) $[M+H+2]^+$. Anal. calcd for $C_6H_6BrNO_2S$: C, 30.52; H, 2.56; Br, 33.85; N, 5.93; S, 13.58. Found: C, 30.55; H, 2.54; Br, 33.86; N, 5.91; S, 13.60.

4-Bromo-2-iodo-1,3-thiazole-5-carbaldehyde (16).

Water (6 mL) and *p*-TSA (0.095 g, 0.55 mmol) were added to a solution of 4-bromo-5-(1,3-dioxolan-2-yl)-2-iodo-1,3-thiazole **7** (2.00 g, 5.53 mmol) in acetone (12 mL). The reaction mixture was boiled for 8 hours. The precipitate that fell after cooling to room temperature was filtered, washed with a mixture of acetone/H_2O (2:1), dried under reduced pressure and gave **16** (1.55 g, 88%) as a colorless solid, mp 133-134 °C.

IR (KBr, cm^{-1}): 1649 (C=O), 1466, 1377, 1330, 1241, 989, 891, 685. ^1H NMR ($CDCl_3$), δ: 9.89 (1H, s, CHO). ^{13}C NMR ($CDCl_3$), δ: 111.07 (C-2), 133.63 (C-4), 138.80 (C-5), 181.58 (C=O). GC/MS (I, %): 127 (34), 316 (58), 317 (100) $[M]^+$, 318 (66), 319 (95) $[M+2]^+$. Anal. calcd for $C_4HBrINOS$: C, 15.11; H, 0.32; Br, 25.13; N, 4.41; S, 10.09. Found: C, 15.14; H, 0.30; Br, 25.15; N, 4.40; S, 10.10.

[1,3]Thiazolo[4,5-d]pyridazin-4(5H)-one (17). Hydrazine hydrate (1.32 g, 26.3 mmol) was added to a solution of methyl 5-formylthiazole-4-carboxylate **13** (3.00 g, 17.5 mmol) in ethanol (40 mL), and boiled for 1 hour. Acetic acid (3.16 g, 52.6 mmol) was added to the reaction mixture, and boiled for 5 hours. The formed precipitate was filtered, washed with ethanol gave **17** (2.20 g, 82%) as a colorless solid, mp > 250°C.

IR (KBr, cm^{-1}): 3161 (NH), 3062, 2983, 1675 (C=O), 1652, 1608, 1185, 995, 899, 810, 692, 575. ^1H NMR (DMSO-d_6), δ: 8.71 (1H, s, H-7), 9.52 (1H, s, H-2), 13.12 (1H, br.s, NH). ^{13}C NMR (DMSO-d_6), δ: 133.57 (C-7), 137.57 (C-7a), 149.68 (C-3a), 158.00 (C=O), 160.94 (C-2). LC/MS (I, %): 154 (100) $[M+H]^+$. Anal. calcd for $C_5H_3N_3OS$: C, 39.21; H, 1.97; N, 27.44; S, 20.94. Found: C, 39.21; H, 1.97; N, 27.44; S, 20.94.

(4-Bromo-1,3-thiazol-5-yl)methanol (18). A solution of 4-bromothiazole-5-carbaldehyde **11** (8.00 g, 41.7 mmol) in a mixture of THF (40 mL) and methanol (20 mL) was cooled to +5°C, and then $NaBH_4$ (0.79 g, 20.9 mmol) was added in portions. The reaction mixture was stirred overnight; the solvent was removed under reduced pressure. A solution of H_2SO_4 (1.5 mL) in water (25 mL) was added to the residue, and the mixture was stirred overnight. The resulting solution was neutralized with potassium carbonate and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and given **18** (8.00 g, 99%) as a colorless solid, mp 66-68 °C. (Lit.: 63-64 °C).[23]

The data of the ^1H NMR and ^{13}C NMR spectra of **18** are fully consistent with the literature data.[23] IR (KBr, cm^{-1}): 3306 (OH), 3155, 3058, 1509, 1392, 1297, 1176, 1028 (C-O), 886. The data of ^1H and ^{13}C NMR spectra in $CDCl_3$ are considered to be given in the literature.[23]

4-Bromo-5-(chloromethyl)-1,3-thiazole (19). A solution of (4-bromothiazol-5-yl)methanol **18** (5.00 g, 25.8 mmol) and Et_3N (4.68 mL, 33.5 mmol) in dichloromethane (80 mL) was cooled to -30 °C, then MsCl (3.54 g, 30.9 mmol) was added dropwise. The reaction mixture was stirred overnight and treated with a saturated solution of sodium bicarbonate (60 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (MTBE/hexane, 1:1), giving **19** (4.08 g, 75%) as a light brown liquid.

ATR-IR (cm^{-1}): 1499, 1392, 1280, 1155, 942, 872, 802, 705 (C-Cl), 601. ^1H NMR ($CDCl_3$), δ: 4.72 (2H, s, CH_2), 8.72 (1H, s, H-2). ^{13}C NMR ($CDCl_3$), δ: 37.39 (CH_2), 127.85 (C-4), 130.70 (C-5), 154.22 (C-2). GC/MS (I, %): 70 (16), 176 (99), 178 (100), 211 (17) $[M]^+$, 213 (23) $[M+2]^+$, 215 (7) $[M+4]^+$. Anal. calcd for $C_4H_3BrClNS$: C, 22.61; H, 1.42; Br, 37.60; Cl, 16.68; N, 6.59; S, 15.09. Found: C, 22.65; H, 1.43; Br, 37.58; Cl, 16.67; N, 6.60; S, 15.11.

5-(Azidomethyl)-4-bromo-1,3-thiazole (20). A solution of 4-bromo-5-(chloromethyl)thiazole **19** (4.00 g, 18.8 mmol) in DMF (25 mL) was cooled to +5 °C, then NaN_3 (1.84 g, 28.2 mmol) was added. The reaction mixture was stirred for three days at room temperature, treated with water (160 mL), and extracted with ethyl acetate. The organic layer was separated,

washed with brine, and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (MTBE/hexane, 1:1), giving **20** (3.70 g, 90%) as a light brown liquid.
ATR-IR (cm^{-1}): 3085, 2094 ($^{as}N_3$), 1499, 1395, 1264 ($^{s}N_3$), 1220, 1168, 878, 799. ^{1}H NMR ($CDCl_3$), δ: 4.56 (2H, s, CH_2), 8.75 (1H, s, H-2). ^{13}C NMR ($CDCl_3$), δ: 47.02 (CH_2), 127.31 (C-4), 128.49 (C-5), 153.92 (C-2). GC/MS (I, %): 176 (98), 178 (100), 190 (56), 192 (55), 218 (23) $[M]^+$, 220 (24) $[M+2]^+$. Anal. calcd for $C_4H_3BrN_4S$: C, 21.93; H, 1.38; Br, 36.48; N, 25.58; S, 14.64. Found: C, 21.90; H, 1.36; Br, 36.50; N, 25.60; S, 14.63.

1-(4-Bromo-1,3-thiazol-5-yl)methanamine dihydrochloride (21). Water (8 mL) was added to a solution of 5-(azidomethyl)-4-bromothiazole **20** (3.50 g, 16.0 mmol) in THF (40 mL), cooled to +5 ºC, then PPh_3 (4.41 g, 16.8 mmol) was added in portions. The reaction mixture was stirred overnight; the solvent was removed under reduced pressure. 1M HCl solution (58 mL) was added to the residue; the resulting solution was stirred overnight at room temperature and filtered. The solvent was removed from the filtrate under reduced pressure. MeCN was added to the residue, and the colorless solid was filtered and gave **21** (4.08 g, 96%), mp 209-211 °C.
IR (KBr, cm^{-1}): 3083 (N^+H), 2972 (N^+H), 2870 (N^+H), 2177 (N^+H), 1930 (N^+H), 1825 (N^+H), 1595, 1573, 1554, 1486, 1448, 1223, 1201, 871, 789. ^{1}H NMR (DMSO-d_6), δ: 4.16 (2H, q, J 5.0 Hz, CH_2), 8.93 (3H, br.s, N^+H_3), 9.20 (1H, s, H-2) 12.40 (1H, br.s, H^+). ^{13}C NMR (DMSO-d_6), δ: 36.07 (CH_2), 127.48 (C-4), 129.15 (C-5), 158.33 (C-2). LC/MS (I, %): 193 (100) $[M+H]^+$, 195 (95) $[M+H+2]^+$. Anal. calcd for $C_4H_5BrN_2S$*2HCl: C, 18.06; H, 2.65; Br, 30.04; Cl, 26.66; N, 10.53; S, 12.06. Found: C, 18.04; H, 2.67; Br, 30.03; Cl, 26.68; N, 10.52; S, 12.07.

1-(4-Bromo-1,3-thiazol-5-yl)-N-hydroxymethanimine (22). Hydroxylamine hydrochloride (3.19 g, 45.6 mmol) and sodium acetate trihydrate (8.51 g, 62.6 mmol) were added to a solution of 4-bromothiazole-5-carbaldehyde **11** (8.00 g, 41.7 mmol) in *i*-PrOH (100 mL). The mixture was boiled for 4 hours; the solvent was removed under reduced pressure. Water (30 mL) was added to the residue, and the precipitate was filtered, washed with a mixture of MTBE (20 mL) and hexane (20 mL), and dried under vacuum gave **22** (7.2 g, 83%) as a colorless solid, mp 220-221 °C.
IR (KBr, cm^{-1}): 3148 (OH), 3072, 3012, 2822, 1432, 1278, 942 (N-O), 911, 764. ^{1}H NMR (DMSO-d_6), δ: 7.83 (1H, s, 5-CH (*E*-)), 8.17 (0.26H, s, 5-CH (*Z*-)), 9.11 (0.26H, s, H-2 (*Z*-)), 9.24 (1H, s, H-2 (*E*-)), 12.60 (1.3H, br.s, OH (*E*- + *Z*-). ^{13}C NMR (DMSO-d_6), δ: 120.80 (C-5 (*E*-)), 127.36 (C-4 (*Z*-)), 128.05 (C-5 (*Z*-)), 130.52 (C-4 (*E*-)), 137.69 (5-CH (*E*-)), 141.31 (5-CH (*Z*-)), 157.00 (C-2 (*Z*-)), 159.35 (C-2 (*E*-)). LC/MS (I, %): 157 (100), 207 (90) $[M+H]^+$, 209 (95) $[M+H+2]^+$. Anal. calcd for $C_4H_3BrN_2OS$: C, 23.20; H, 1.46; Br, 38.59; N, 13.53; S, 15.49. Found: C, 23.24; H, 1.45; Br, 38.61; N, 13.51; S, 15.50.

4-Bromo-1,3-thiazole-5-carbonitrile (23). A solution of 1-(4-bromo-1,3-thiazol-5-yl)-N-hydroxymethanimine **22** (7.00 g, 33.8 mmol) in THF (110 mL) was cooled to +5 ºC, and then pyridine (9.36 g, 118.4 mmol) was added. Trifluoroacetic anhydride (10.65 g, 50.7 mmol) was added dropwise under stirring. The reaction mixture was stirred for 20 min under ice cooling, then boiled for 5 hours and cooled to +5 ºC. Ice (50 g) was added to the mixture in portions, neutralized with sodium bicarbonate, and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (dichloromethane), giving **23** (5.69 g, 89%) as a colorless solid, mp 82-84 °C.
IR (KBr, cm^{-1}): 3095, 2228 (CN), 1461, 1374, 1281, 904, 814, 650 (C-Br). ^{1}H NMR ($CDCl_3$), δ: 8.94 (1H, s, H-2). ^{13}C NMR ($CDCl_3$), δ: 105.91 (CN), 111.21 (C-5), 137.72 (C-4), 158.31 (C-2). GC/MS (I, %): 82 (73), 161 (44), 163 (45), 188 (96) $[M]^+$, 190 (100) $[M+2]^+$. Anal. calcd for C_4HBrN_2S: C, 25.42; H, 0.53; Br, 42.27; N, 14.82; S, 16.96. Found: C, 25.46; H, 0.51; Br, 42.30; N, 14.81; S, 16.95.

4-Bromo-5-(difluoromethyl)-1,3-thiazole (24). A solution of 4-bromothiazole-5-carbaldehyde **11** (8.00g, 41.7 mmol) in dichloromethane (120 mL) was cooled to -40 ºC, and morpholino sulfur trifluoride (14.61 g, 83.4 mmol) was added in portions. The reaction mixture was stirred overnight, and then it was added in portions to a mixture of ice (70 g), water (80 mL), and sodium bicarbonate (40 g). The mixture was stirred for 20 min., the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The organic layer was separated, washed with brine, and dried over sodium sulfate. The solvent was removed under reduced pressure and distilled with column (15 cm) in a vacuum (10 mm Hg, 87 °C), giving **24** (5.07 g, 71%) as a colorless liquid.
ATR-IR (cm^{-1}): 1510, 1280 ($^{as}CF_2$), 1221, 1161, 1074 ($^{s}CF_2$), 1023, 906, 811, 711, 567. ^{1}H NMR ($CDCl_3$), δ: 6.94 (1H, t, J_{HF} 54.0 Hz, CHF_2), 8.90 (1H, s, H-2). ^{13}C NMR ($CDCl_3$), δ: 110.96 (t, J_{CF} 236.5 Hz, CHF_2), 127.11 (t, J_{CF} 27.1 Hz, C-5), 128.37 (t, J_{CF} 7.8 Hz, C-4), 155.79 (C-2). ^{19}F NMR ($CDCl_3$), δ: -99.73. GC/MS (I, %): 45 (40), 107 (45), 213 (98) $[M]^+$, 215 (100) $[M+2]^+$. Anal. calcd for $C_4H_2BrF_2NS$: C, 22.45; H, 0.94; Br, 37.33; N, 6.54; S, 14.98. Found: C, 22.43; H, 0.97; Br, 37.30; N, 6.55; S, 14.98.

Methyl 5-(difluoromethyl)-1,3-thiazole-4-carboxylate (25). A solution of methyl 5-formylthiazole-4-carboxylate **13** (10.00g, 58.4 mmol) in dichloromethane (240 mL) was cooled to -45 ºC and morpholinosulfur trifluoride (27.64 g, 157.7 mmol) was added in portions. The reaction mixture was stirred for 3 hours at room temperature, and then it was added in portions to a mixture of ice (120 g), water (180 mL), and sodium bicarbonate (70 g). The resulting mixture was stirred for 20 min, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure, and the

residue was purified by distillation with a column (15 cm) in a vacuum (0.7 mm Hg, 64 °C) gave **25** (7.11 g, 63%) as a colorless solid, mp 30-31 °C.

IR (KBr, cm^{-1}): 3081, 2968, 1736 (C=O), 1527, 1442, 1337, 1275 (^{as}C-O, $^{as}CF_2$), 1212, 1164, 1081 ($^{s}CF_2$), 1031 (^{s}C-O), 841, 721, 632. ^{1}H NMR ($CDCl_3$), δ: 3.01 (3H, s, CH_3), 7.62 (1H, t, J_{HF} 55.2 Hz, CHF_2), 8.90 (1H, s, H-2). ^{13}C NMR ($CDCl_3$), δ: 53.25 (CH_3), 109.75 (t, J_{CF} 237.6 Hz, CHF_2), 140.17 (t, J_{CF} 26.2 Hz, C-5), 145.30 (t, J_{CF} 7.1 Hz, C-4), 154.23 (C-2), 161.64 (C=O). ^{19}F NMR ($CDCl_3$), δ: -98.80. GC/MS (I, %): 134 (39), 135 (36), 161 (82), 162 (100), 193 (23) $[M]^+$. Anal. calcd for $C_6H_5F_2NO_2S$: C, 37.31; H, 2.61; N, 7.25; S, 16.60. Found: C, 37.34; H, 2.60; N, 7.27; S, 16.58.

5-(1,3-Dioxolan-2-yl)-1,3-thiazole-4-carboxylic acid (26). A solution of methyl 5-(1,3-dioxolan-2-yl)thiazole-4-carboxylate **10** (8.00 g, 37.2 mmol) in THF (80 mL) was cooled to +5 °C, and then a solution of LiOH*H_2O (1.56 g, 37.2 mmol) in water (80 mL) was added. The reaction mixture was stirred for two days at room temperature. The solvent was removed under reduced pressure, and the residue was treated with brine (25 mL). The resulting solution was extracted with MTBE, and the organic layer was separated. The aqueous phase was treated with 3M HCl solution (12.39 mL) and extracted with a mixture of MTBE/THF (1:1). The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and gave **26** (6.81 g, 91%) as a colorless solid, mp 173-175 °C.

IR (KBr, cm^{-1}): 3075, 2973, 2898, 1688 (C=O), 1536, 1432, 1274 (δOH), 1072 (C-O), 957, 929, 845, 744. ^{1}H NMR (DMSO-d_6), δ: 3.93–4.01 (2H, m, $O(CH_A\underline{H}_B)_2O$), 4.02–4.10 (2H, m, $O(C\underline{H}_AH_B)_2O$), 6.61 (1H, s, O-CH-O), 9.08 (1H, s, H-2), 13.24 (1H, br.s, OH). ^{13}C NMR (DMSO-d_6), δ: 66.14 (2C, CH_2), 97.91 (CH), 145.53 (C-4), 146.19 (C-5), 155.07 (C-2), 163.50 (C=O). LC/MS (I, %): 202 (100) $[M+H]^+$. Anal. calcd for $C_7H_7NO_4S$: C, 41.79; H, 3.51; N, 6.96; S, 15.94. Found: C, 41.80; H, 3.50; N, 6.98; S, 15.96.

5-Formyl-1,3-thiazole-4-carboxylic acid (27).

Method A: A solution of methyl 5-formylthiazole-4-carboxylate **13** (4.00 g, 23.4 mmol) in THF (40 mL) was cooled to +5 °C, a solution of LiOH*H_2O (1.18 g, 28.0 mmol) in water (40 mL) was added. The reaction mixture was stirred for two days at room temperature. The solvent was removed under reduced pressure, and the residue was treated with brine (25 mL). The resulting solution was extracted with MTBE, and the organic layer was separated. The aqueous phase was treated with 3M HCl solution (10.28 mL) and extracted with a mixture of MTBE/THF (1:2). The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and gave **27** (3.13 g, 85%) as a colorless solid, mp 159-161 °C.

Method B: To a solution of 5-(1,3-dioxolan-2-yl)thiazole-4-carboxylic acid **26** (4.00 g, 19.9 mmol) in acetone (30 mL) was added water (15 mL) and *p*-TSA (0.17 g, 1.0 mmol). The reaction mixture was boiled for 12 hours; then, acetone was removed under reduced pressure. The residue was treated with brine, and the resulting solution was extracted with THF. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and purified by recrystallization (H_2O), given **27** (2.31 g, 74%).

IR (KBr, cm^{-1}): 3112, 2871, 2799, 2500, 1727 (C=O), 1701 (C=O), 1669, 1515, 1435, 1318, 1261 (δOH), 1209, 974, 867, 713. ^{1}H NMR (DMSO-d_6), δ: 9.40 (1H, s, H-2), 10.50 (1H, s, 5-CHO), 13.94 (br.s, OH). ^{13}C NMR (DMSO-d_6), δ: 143.97 (C-5), 151.51 (C-4), 160.74 (4-C=O), 162.99 (C-2), 186.38 (5-C=O). LC/MS (I, %): 157 (100) $[M]^+$, 158 (12) $[M+H]^+$. Anal. calcd for $C_5H_3NO_3S$: C, 38.21; H, 1.92; N, 8.91; S, 20.40. Found: C, 38.25; H, 1.93; N, 8.89; S, 20.38.

5-(Difluoromethyl)-1,3-thiazole-4-carboxylic acid (28). A solution of methyl 5-(difluoromethyl)thiazole-4-carboxylate **25** (4.00 g, 20.7 mmol) in THF (40 mL) was cooled to +5 °C, and then a solution of LiOH*H_2O (0.96 g, 22.8 mmol) in water (40 mL) was added. The reaction mixture was stirred for two days at room temperature. The solvent was removed under reduced pressure, and the residue was treated with brine (25 mL). The resulting solution was extracted with MTBE, and the organic layer was separated. The aqueous phase was treated with 3M HCl solution (8.35 mL) and extracted with a mixture of MTBE/THF (1:1). The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and gave **28** (3.64 g, 98%) as a colorless solid, mp 152-154°C.

IR (KBr, cm^{-1}): 3089, 2890, 2821, 2471, 1700 (C=O), 1548, 1431, 1253 ($^{as}CF_2$, δOH), 1067 ($^{s}CF_2$), 962, 847, 725. ^{1}H NMR (DMSO-d_6), δ: 7.72 (1H, t, J_{HF} 54.0 Hz, CHF_2), 9.30 (1H, s, H-2), 13.85 (1H, br.s, OH). ^{13}C NMR (DMSO-d_6), δ: 111.42 (t, J_{CF} 236.0 Hz, CHF_2), 139.21 (t, J_{CF} 25.3 Hz, C-5), 147.42 (t, J_{CF} 6.2 Hz, C-4), 156.93 (C-2), 162.85 (C=O). ^{19}F NMR (DMSO-d_6), δ: -97.83. LC/MS (I, %): 162 (100), 180 (30) $[M+H]^+$. Anal. calcd for $C_5H_3F_2NO_2S$: C, 33.52; H, 1.69; N, 7.82; S, 17.90. Found: C, 33.55; H, 1.67; N, 7.82; S, 17.88.

References

1 Ramos-Inza S., Aydillo C., Sanmartín C., Plano D. (**2020**) Thiazole Moiety: An Interesting Scaffold for Developing New Antitumoral Compounds, in: Nandeshwarappa B. P. (Eds) *Heterocycles - Synthesis and Biological Activities.* IntechOpen.

2 Alizadeh S. R., Hashemi S. M. (**2021**) Development and therapeutic potential of 2-aminothiazole derivatives in anticancer drug discovery. *Med. Chem. Res*., 30 (4) 771-806.

3 Petrou A., Fesatidou M., Geronikaki A. (**2021**) Thiazole Ring—A Biologically Active Scaffold. *Molecules,* 26 (11) 3166-3241.

4 Giroud M., Ivkovic J., Martignoni M., Fleuti M., Trapp N., Haap W., Kuglstatter A., Benz J., Kuhn B., Schirmeister T., Diederich F. (**2017**) Inhibition of the Cysteine Protease Human Cathepsin L by Triazine Nitriles: Amide Heteroarene π-

Stacking Interactions and Chalcogen Bonding in the S3 Pocket. *Chem. Med. Chem.,* 12 (3) 257-270.
5 James D. I., Smith K. M., Jordan A. M., Fairweather E. E., Griffiths L. A., Hamilton N. S., Hitchin J. R., Hutton C. P., Jones S., Kelly P., McGonagle A. E., Small H., Stowell A. J., Tucker J., Waddell I. D., Waszkowycz B., Ogilvie D. J. (**2016**) First-in-class chemical probes against poly(ADPribose) glycohydrolase (PARG) inhibit DNA repair with differential pharmacology to olaparib. *ACS Chem. Biol.*, 11 (11) 3179-3214.
6 Wei Z., Kozikowski A. P. (**2003**) A Short and Efficient Synthesis of the Pharmacological Research Tool GW501516 for the Peroxisome Proliferator-Activated Receptor δ. *J. Org. Chem.*, 68 (23) 9116-9118.
7 Brunschweiger A., Koch P., Schlenk M., Rafehi M., Radjainia H., Küppers P., Hinz S., Pineda F., Wiese M., Hockemeyer J., Heer J., Denonne F., Müller C. E. (**2016**) 8-Substituted 1,3-dimethyltetrahydropyrazino[2,1-f]purinediones: Water-soluble adenosine receptor antagonists and monoamine oxidase B inhibitors. *Bioorg. Med. Chem.*, 24 (21) 5462-5481.
8 Siegrist R., Pozzi D., Jacob G., Torrisi C., Colas K., Braibant B., Mawet J., Pfeifer T., DeKanter R., Roch C., Kessler M., Corminboeuf O., Bezençon O. (**2016**) Structure-Activity Relationship, Drug Metabolism and Pharmacokinetics Properties Optimization, and in Vivo Studies of New Brain Penetrant Triple T-Type Calcium Channel Blockers. *J.Med. Chem.*, 59 (23) 10661-10675.
9 Kikelj D. and Urleb U. (**2002**) Product Class 17: Thiazoles, in: Schaumann E. (Eds) *Science of Synthesis, Volume 11: Category 2, Hetarenes and Related Ring Systems.* Georg Thieme Verlag, Stuttgart, 627-834.
10 Schnürch M., Spina M., Khan A. F., Mihovilovic M. D. and Stanetty P. (**2007**) Halogen dance reactions – A review. *Chem. Soc. Rev*., 36 (7) 1046-1057.
11 Stangeland E. L., Sammakia T. (**2004**) Use of Thiazoles in the Halogen Dance Reaction: Application to the Total Synthesis of WS75624B. *J. Org. Chem.*, 69 (7) 2381-2385.
12 Stanetty P., Schnürch M., Mereiter K., Mihovilovic M. D. (**2005**) Investigations of the Halogen Dance Reaction on N-Substituted 2-Thiazolamines. *J. Org. Chem.,* 70 (2) 567-574.
13 Schnürch M., Khan A. F., Mihovilovic M. D., and Stanetty P. (**2009**) Polyarylated Thiazoles via a Combined Halogen Dance – Cross-Coupling Strategy. *Eur. J. Org. Chem.*, 2009 (19) 3228-3236.
14 Pevarello P., Lohmer S., Liberati C., Seneci P., Pesenti C., Prandi A. (**2015**) Substituted thiazole or oxazole P2X7 receptor antagonists. **WO Patent 2015/118019**.
15 Bur D., Grisostomi C., Nayler O., Remen L., Vercauteren M., Welford R. (**2015**) Tricyclic piperidine compounds. **WO Patent 2015/75023**.
16 Nakano T., Imoto H., Naka K. (**2021**) Synthesis and Optical Properties of Thiazolo-Chlorin and Porphyrin Skeletons. *Org. Lett*., 23 (20) 7996-8000.
17 Sinenko V. O., Slivchuk S. R., Bal'on Ya. G., and Brovarets V. S. (**2015**) Synthesis of 2,5-Di(hydroxyalkyl)-1,3-thiazoles. *Russ. J. Gen. Chem*., 85 (8) 1855-1861.
18 Meyer E. A., Äänismaa P., Froidevaux S., Keller M., Piali L., Caroff E. (**2022**) Discovery and in Vivo Evaluation of ACT-660602: A Potent and Selective Antagonist of the Chemokine Receptor CXCR3 for Autoimmune Diseases. *J. Med. Chem*., 65 (17) 11513-11532.
19 House J. B., Pandya B., Kaplan A. P. (**2023**) Heterocyclic compounds as triggering receptor expressed on Myeloid cells 2 agonists. **WO Patent 2023/86799**.
20 Faidallah H. M., Rostom S. A. F., Basaif S. A., Makki M. S. T., Khan K. A. (**2013**) Synthesis and biological evaluation of some novel urea and thiourea derivatives of isoxazolo[4,5-d]pyridazine and structurally related thiazolo[4,5-d]pyridazine as antimicrobial agents. *Arch. Pharm. Res*., 36 (11) 1354-1368.
21 McCluskey A., Finn M., Bowman M., Smith R., Keller P. A. (**2000**) 2,7-Dimethylthiazolo[4,5-d]pyradazine-4-(5H)-thione: A Corticotrophin-Releasing Hormone Type 1 Receptor Agonist. *Aust. J. Chem*., 53 (11-12) 905-908.
22 Makki M. S. I., Faidallah H. M. (**1996**) Synthesis and Biological Evaluation of New Fused Thiazolo[4,5-d]Pyridazine Derivatives. *J. Chin. Chem. Soc*., 43 (5) 433-438.
23 Alluri S., Eisenberg S. M., Grisanti L. A.,Tanner M., Volkow N. D., Kim S. W., Kil K.-E. (**2022**) Preclinical evaluation of new C-11 labeled benzo-1,4-dioxane PET radiotracers for brain α2C adrenergic receptors. *Eur. J. Med. Chem*., 243 Art.No: 114764.
24 Reeves C., Romero F. A., Jones C. T., Fenaaux M. (**2023**) Benzimidazole carboxylic acids as GLP-1R agonists. **WO Patent 2023/49518**.
25 Enjuro H., Shunsuke M., Keisuke F., Etsu T., Daisuke U., Yasuhiro I. (**2022**) Bisprenyl naphthoquinone and chlorinated calcimycin congener bearing thiazole ring from an actinomycete of the genus Phytohabitans. *J. Antibiot. (Tokyo)*, 75 (10) 542-551.
26 Li F.-Y., Guo X.-F., Fan Z.-J., Zhang Y.-Q, Zong G.-N., Qian X.-L., Ma L.-Y., Chen L, Zhu Y.-J., Kalinina T., Morzherin Yu.Yu., Belskaya N. P. (**2015**) Synthesis and biological activities of novel 2-amino-1,3-thiazole-4-carboxylic acid derivatives. *Chin. Chem. Lett.*, 26 (10) 1315-1318.