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Synthesis and antioxidant activity evaluation of some new 4-thiomethyl functionalised 1,3-thiazoles

Ivanna Danyliuk[a*], Nataliia Kovalenko[b], Valentyna Tolmachova[b], Olena Kovtun[b], Lesya Saliyeva[c], Nataliia Slyvka[c], Serhii Holota[c], Gennady Kutrov [d], Magdalina Tsapko[d] and Mykhailo Vovk[a]

[a]*Department of Functional Heterocyclic Systems, Institute of Organic Chemistry of National Academy of Sciences of Ukraine, Academika Kuharya St. 5, Kyiv 02660, Ukraine*
[b]*Department of Chemistry, Dragomanov Ukrainian State University, Pirogova St. 9, Kyiv 01601, Ukraine*
[c]*Department of Organic Chemistry and Pharmacy, Lesya Ukrainka Volyn National University, Voli Avenue 13, Lutsk 43025, Ukraine*
[d]*Department of Organic Chemistry, Taras Shevchenko Kyiv National University, Volodymyrska St. 64, Kyiv 01601, Ukraine*

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A B S T R A C T

The 4-bromomethyl-substituted thiazolium salts and corresponding thiazoles obtained through the condensation of 1,3-dibromoacetone with thioamide derivatives were utilised as efficient alkylating reagents for a series of thiophenols and heterylthiols. As a result, a small library of 4-thiomethyl-functionalised 1,3-thiazoles was synthesised in high yields, and their structures were characterised by ^{1}H, ^{13}C NMR, LC-MS and IR spectra. Antioxidant activity of obtained compounds was studied *in vitro* using the DPPH test. The synthesised compounds showed high absorption level of DPPH radicals in the 70-98% range. For the most active derivatives **7e,m,p,t** IC_{50} values were determined, which were in the range 191-417 μM (for ascorbic acid (reference) IC_{50} value was 29 μM). Obtained radical scavenging activity screening data suggest in-depth study of the antioxidant potential for these types of heterocyclic compounds.

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1. Introduction

Heterocyclic compounds occupy a key role in modern organic chemistry and are especially important in the context of the search for new biologically active compounds, natural products, medicines, agrochemicals and advanced organic materials.[1-4] These systems have long been a subject of great interest to researchers and considerable efforts are being made both to develop their synthetic strategies and to study their practical, primarily pharmacological properties.[5-8] A good reason for this is more that 85% of the most common drugs contain at least heterocyclic nuclei as an element of their molecular structure.[2]

Among mononuclear heterocyclic systems, 1,3-thiazoles occupy a special role as basic objects for biomedical research. Compounds that contain a thiazole fragment are characterised by a wide range of practically useful properties. In particular, the thiazole nucleus is a key element in the structure of such important naturally occurring compounds as vitamin B_1 and penicillin (**Fig. 1**).[9] Many synthetic medicinal products have also been developed based on thiazole derivatives, including the antiviral medication cobicistat,[10] the antiparasitic and antiprotozoal medication nitazoxanide,[11] the anticancer medications alpelisib[12] and dabrafenib,[13] antibiotics from the group of modified cephalosporins cefixime,[14] cefovecin,[15] overactive bladder treatment mirabegron,[16] hypnotic-sedative medication clomethiazole,[17] third-generation H_2-histamine receptor blocker famotidine[18] (**Fig. 1**).

* Corresponding author.
E-mail address ivannayu@ukr.net (I. Danyliuk)

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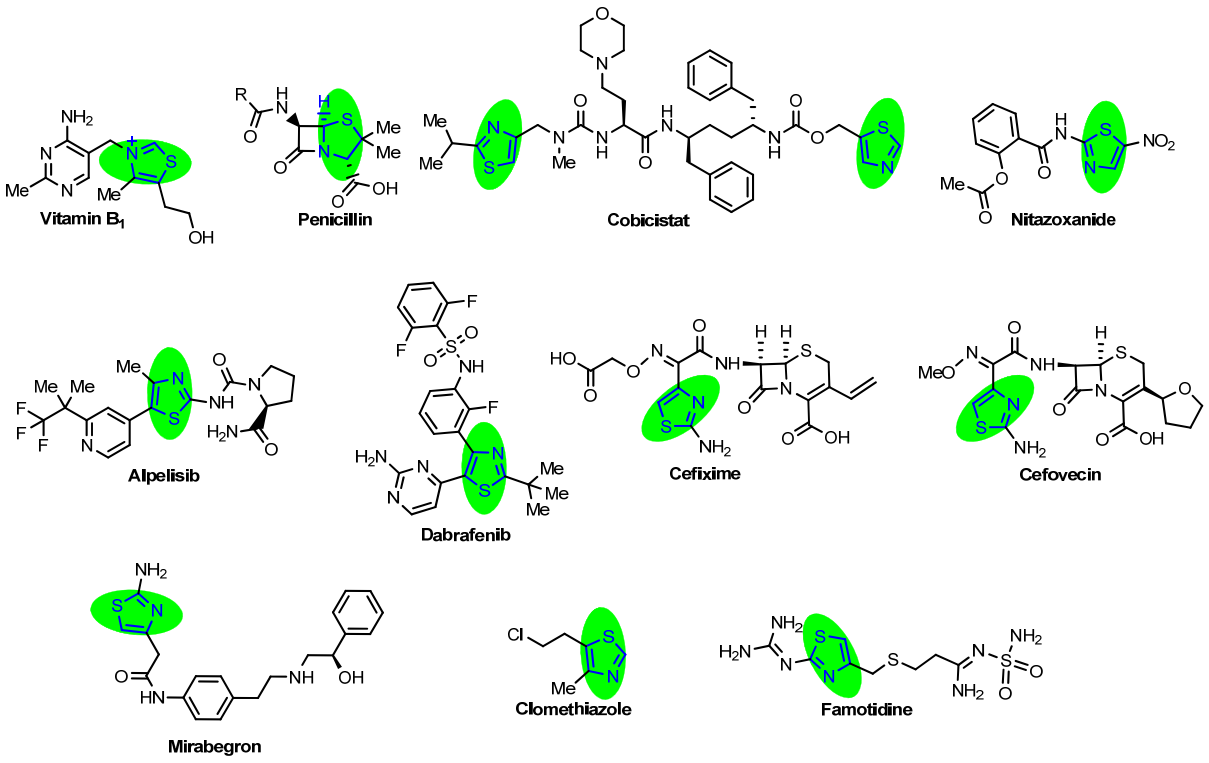


Fig. 1. Pharmaceutical preparations based on the 1,3-thiazole.

The above-mentioned series of compounds emphasises the importance of thiazole scaffolds in the search for new broad-spectrum bioregulators. Among them, our attention was drawn to the medication famotidine,[18] which is a polyfunctional thioether with an incorporated thiazole nucleus. It should be noted that several thiazole-containing thioether derivatives have been found to exhibit anticancer,[19] antituberculosis,[20] antibacterial,[21-26] antiviral,[27] antiulcer,[28] antioxidant,[29] and antiparasitic[30] activity. In addition, they are useful synthesis blocks for the design of more complex bioprospective molecular structures, such as deoxycytidine kinase (dCK),[31-34] galectin-3,[35] myeloid cell leukemia-1 (MCL-1) inhibitors,[36] DNA methyltransferase l (DNMTl),[37] NLR family pyrin domain containing 3 (NLRP3),[38] cyclin-dependent kinase 2 (CDK2),[39] and anti-HIV[40], and can also be used as antagonists of $P2X_7$[41], apelin[42], adenosine A_{2B},[43] A_1,[44-46] histamine H_1, H_2, gastrin,[47,48] chemokine 2 (CXCR2)[49,50] receptors and adenosine receptor ligands.[51] Moreover, representatives of these types of compounds are effective in the treatment of Alzheimer's disease[52] and gastric ulcer disease[53] and are also useful as pesticides.[54,55]

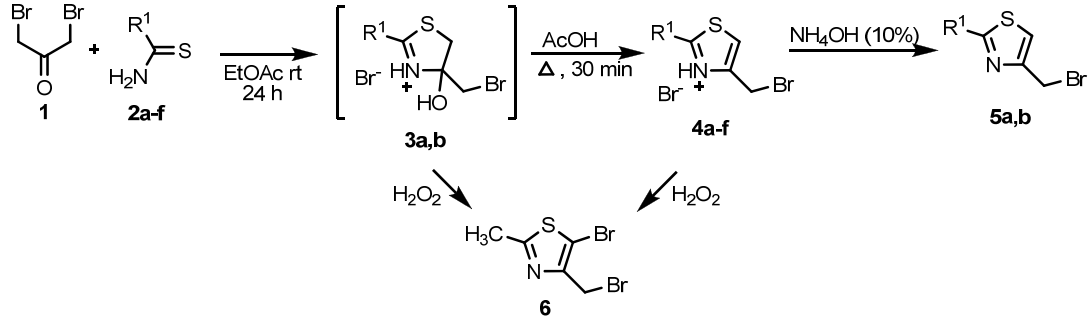
One of the priority areas of modern medicinal and pharmaceutical chemistry is the search for substances with antioxidant properties, as they reduce the risk of developing cancer, as well as neurological and cardiovascular pathologies. In addition, synthetic antioxidants are successfully used in food, pharmaceuticals, and cosmetics due to their high efficiency, low cost, and stability.[56,57] The prevalence of the thiazole cycle in medicines is a good reason for the targeted search, screening, development, and implementation of medications with antioxidant effects based on it.[58] Therefore, in this study, we focused on the design, synthesis, and evaluation of the antioxidant properties of new 1,3-thiazole derivatives, *exo*-functionalised with aryl and hetarylthio substituents.

2. Results and Discussion

2.1 Chemistry

One of the most convenient methods for the synthesis of thiazole derivatives is the interaction of thioamides with *a*-halogen ketones, known as the classical Hantzsch reaction.[59] The variation of these two components allows to determine the limits of this reaction, however, it usually leads to derivatives with substituents at position 4 of the thiazole nucleus, which are inactive before further transformations. This problem can be partially solved by using αα'-dihaloketones, for example, 1,3-dichloro- or 1,3-dibromoacetone, as 1,2-bioelectrophilic components. That is why the basic substrates for the preparation of new 1,3-thiazole thioethers were obtained by the interaction of 1,3-dibromoacetone **1** with thioacetamide **2a,** thiobenzamide **2b,** thiourea **2c,** α-cyanoethanethioamide **2d** and its derivatives **2e,f** (**Scheme 1**). This, in turn, contributed to the expansion of the scope of the Hantzsch reaction, both due to the appearance of a highly reactive bromomethyl group at position 4 of the thiazole nucleus and the use of alkylidene derivatives of α-cyanoethanethioamide.

We have shown that thioamides **2a,b** react with 1,3-dibromoacetone **1** in ethyl acetate to form thiazolidine salts **3a,b,** which undergo dehydration when heated in glacial acetic acid and are converted to thiazolium bromides **4a,b** in yields above 90%. The treatment of compounds **4a,b** with 10% ammonia solution gives 4-bromomethylthiazoles **5a,b** that were previously described in the literature.[60,61] Instead, the interaction of dibromoacetone **1** with thiourea **2c,** α-cyanoethanethioamide **2d,** and their derivatives **2e,f** leads to the formation of salts **4c-f,** whose bases are unstable. However, the stable 5-bromo-4-(bromomethyl)-2-methyl thiazole **6** can be obtained from the corresponding salts **3a,4a** under the action of hydrogen peroxide (**Scheme 1**). The physicochemical characteristics of compounds **3a,b, 4a-f, 5a,b,** and **6** are given in the supplementary materials.

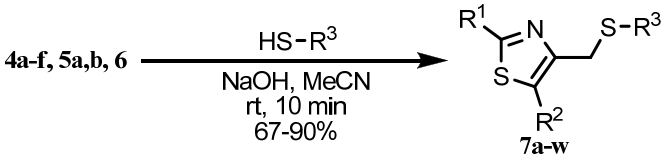


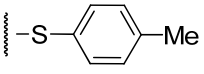
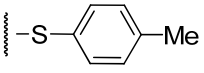
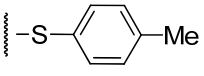
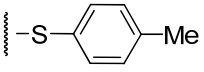
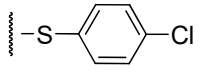
R^1 = Me (**a**), Ph (**b**), NH_2 (**c**), CH_2CN (**d**), C(CN)=CHPh (**e**), $C(CN)=CHC_6H_3$-3-OMe-4-OH (**f**)

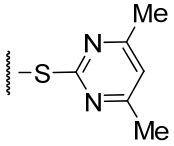
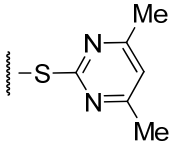
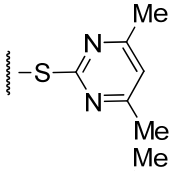
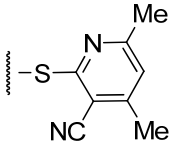
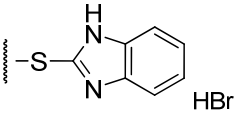
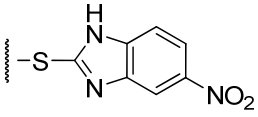
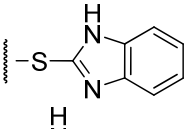
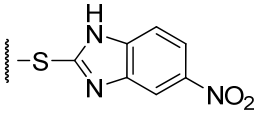
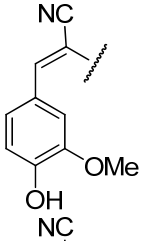
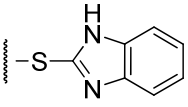
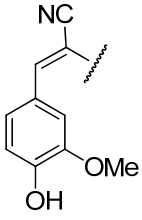
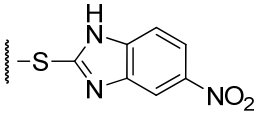
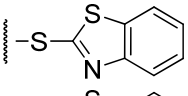
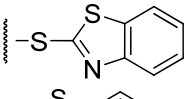
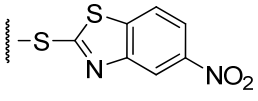
Scheme 1. Synthesis of the compounds **3-6**

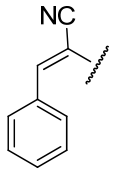
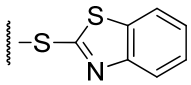
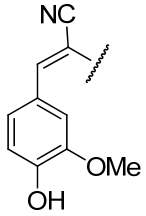
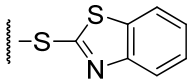
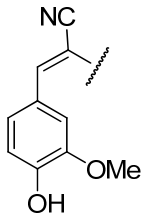
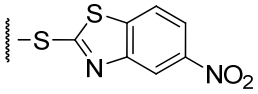
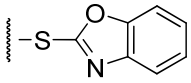
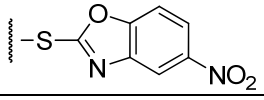
The synthesised bromomethyl-substituted thiazole salts **4a-f** and thiazoles **5a,b, 6** are effective molecular platforms for further structural modification of the thiazole nucleus by biophoric aryl and heteroaryl thiols groups. It was discovered that their interaction with the corresponding thiols (benzenethiols, pyrimidine-2-thiols, pyridine-2-thiols, 1*H*-benzimidazole-2-thiols, 1,3-benzothiazole-2-thiols and 1,3-benzoxazole-2-thiol) proceeds smoothly according to the S-alkylation scheme in the presence of twofold excess of NaOH as a base at room temperature or upon heating in MeCN. This reaction results in the formation of new biologically appealing thioethers **7a-w**, withyields ranging from 70-90% (**Table 1**). The structure of these thioethers was confirmed through their ^{1}H-NMR, ^{13}C-NMR, and Mass spectra. In particular, their ^{1}H and ^{13}C NMR spectra, in addition to the signals of substituents R^1, $R,^2$ and R^3, contain characteristic CH_2S singlets in the range of 3.94-4.85 ppm in ^{1}H NMR spectroscopy and 28.9-34.2 ppm in ^{13}C NMR spectra.

Table 1. Synthesis and antioxidant activity of new 1,3-thiazoles derivatives



№	R^1	R^2	R^3	Yield (%)	DPPH radicals inhibition (%)
7a	Me	H		85	**87.8**
7b	Me	Br		80	**96.5**
7c	Ph	H		84	**92.9**
7d	NH_2	H		70	**79.1**
7e	$CNCH_2$	H		72	**97**

7f	Ph	H		90	**91.5**
7g	NH_2	H		84	**79.1**
7h	$CNCH_2$	H		80	**96**
7i	$CNCH_2$	H		85	**96.4**
7j	Me	Br		79	**89.4**
7k	Me	Br		88	**72.6**
7l	$CNCH_2$	H		83	**94.9**
7m	NH_2	H		71	**98.0**
7n		H		71	**87**
7o		H		74	**79.2**
7p	NH_2	H		88	**97**
7q	$CNCH_2$	H		87	**94.9**
7r	$CNCH_2$	H		87	**93.1**

7s		H		75	**70.9**
7t		H		83	**97.4**
7u		H		84	**71.8**
7v	NH_2	H		78	**94.8**
7w	$CNCH_2$	H		81	**95**

2.1 Antioxidant activity

Research on antioxidant activity. To evaluate the antioxidant activity of the synthesised compounds, the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical inhibition assay was used according to the described method[62]. 1 ml of DPPH solution (8 mg/100 ml) was added to methanolic solutions of the studied compounds and ascorbic acid as a standard and left at room temperature in a dark place for 1 h. The absorbance was determined at 517 nm relative to the control using a UV-1800 spectrophotometer (Shimadzu, Japan). Each sample was analysed in triplicate. The percentage of inhibition was calculated relative to the blank sample:

$$\mathrm{I\%} = \frac{(A_{\mathrm{blank}} - (A_{\mathrm{sample+DPPH}} - A_{\mathrm{sample}})}{A_{\mathrm{blank}}} \cdot 100\%$$

where A_{blank} is the absorbance of the control reaction (includes all reagents except the test compounds); $A_{sample+DPPH}$ is the absorbance of the test compounds after 60 min incubation with DPPH solution;
A_{sample} is the absorbance of the test compounds without DPPH solution.

Statistical analysis. All results were expressed as averages ± SEM (standard error of the mean), and the data were analysed using analysis of variance (ANOVA) followed by Student's t-distribution. The results were considered statistically significant if $P < 0.05$.

Results and discussion. Seven subtypes of aryl(heptaryl)thiomethyl-functionalised 1,3-thiazoles **7a-w**, whose structures are given in **Table 1**, were tested in vitro for their ability to inhibit DPPH radicals. The initial stage of experimental studies included the evaluation of DPPH radical scavenging activity of **7a-w** derivatives (methanolic solution, measurements after 60 min) at a concentration of 5 μM. This approach allows for the rapid identification of potential hit compounds, with savings in time and amounts of substances. Ascorbic acid was used as a standard compound. The results of the radical scavenging activity screening at a concentration of 5 μM of compounds **7a-w** are shown in **Fig. 2.** All tested compounds demonstrated a high level of DPPH radical inhibition in the range from 70.2 to 97.5%.

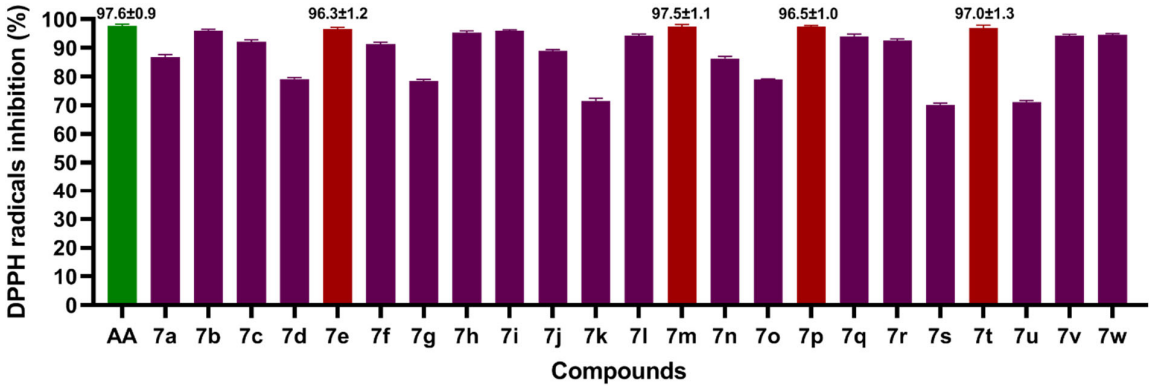


Fig. 2. The inhibition of DPPH radicals by the 1,3-thiazole derivatives **7a-w** at 5 mM concentration. Ascorbic acid (AA) was employed as a positive control (green). The highest activity was observed for compounds **7e**, **7m**, **7p** and **7t** (red).

The next stage of the research was the determination of the IC_{50} for the most active derivatives **7e, 7m, 7p,** and **7t,** which showed promising levels of inhibition at a concentration of 5 mM. The IC_{50} result corresponds to the concentration of the sample that can scavenge 50% of the free radicals present in the reaction mixture. Low IC_{50} results indicate a high antioxidant activity of the compound sample. Serial dilutions of the initial methanol solutions at five concentrations (0.31, 1.25, 5.0 mM, and 10, 40, 80 µM, measured after 60 min) were used for the research. A similar experiment was also performed to determine the IC_{50} of ascorbic acid. The results of DPPH radical inhibition at different concentrations and IC_{50} data are shown in **Fig. 3**.

The screening results demonstrate that the tested compounds exhibit a high level of DPPH radical inhibition, and the IC_{50} data were: 347 µM (**7e**), 191 µM (**7m**), 417 µM (**7p**), 193 µM (**7t**), while for ascorbic acid IC_{50} = 29 µM (**Fig. 3**). The analysis of the "structure-activity" relationship shows that the most effective antioxidants **7e,m,p** are characterised by the presence of a cyanomethyl or amino group at position 2 of the thiazole cycle, and aryl thiomethyl (compounds **7e,m**) and benzthiazolyl thiomethyl (compound **7p**) substituents at position 4. The antiradical properties of compound **7t** can be partially explained by the presence of a phenolic group which is a classical antioxidant pharmacophore.

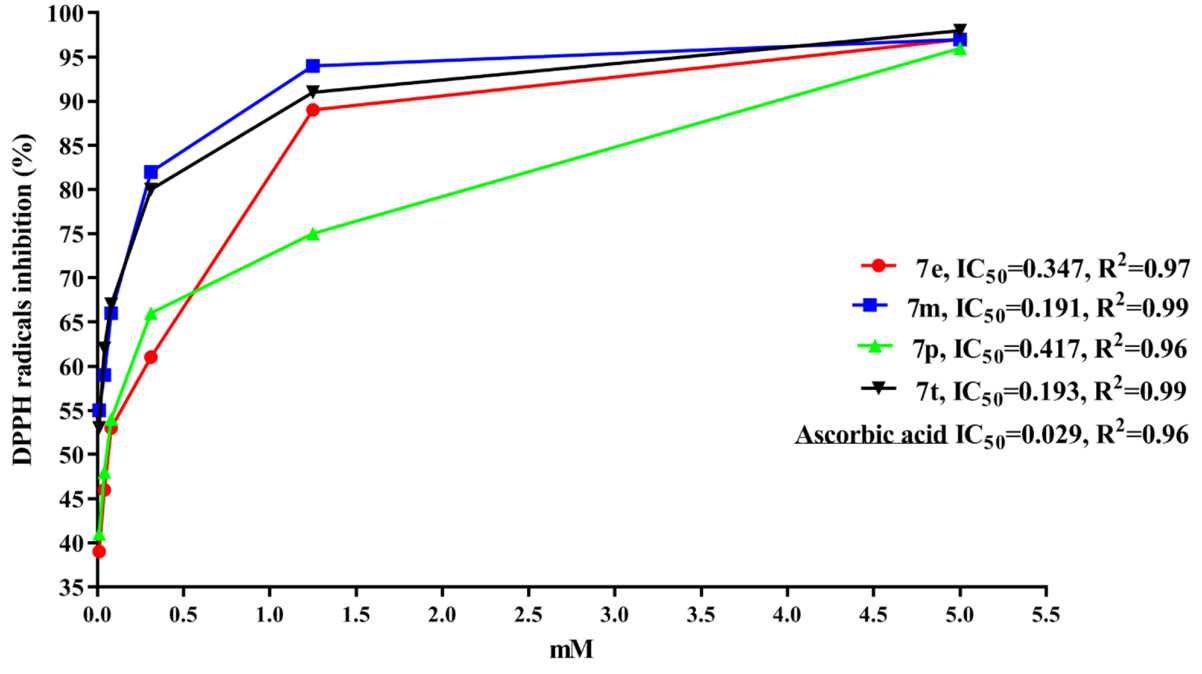


Fig.3. DPPH free radical inhibition at different concentrations and IC_{50} values of compounds **7e**, **7m**, **7p** and **7t**.

3. Conclusions

The experimental studies convincingly demonstrate that the Hantzsch reaction of 1,3-dibromoacetone **1** with thioacetamide **2a**, thiobenzamide **2b**, thiourea **2c**, α-cyanoethanethioamide **2d** and their derivatives **2e,f** is a convenient synthetic approach to the design of bromomethyl-substituted thiazolium salts **4a-f** and thiazoles **5a,b,6**. Their efficiency as alkylating reagents was demonstrated by the interaction with several thiophenols and heterarylthiols (pyrimidine-2-thiol, pyridine-2-thiol, 1*H*-benzimidazole-2-thiols, 1,3-benzothiazole-2-thiols and 1,3-benzoxazole-2-thiols), which allowed the synthesis of previously unknown thiazole-containing sulfides **7a-w.** All the synthesised compounds are characterised by high free radical scavenging activity under DPPH conditions (percentage of inhibition 70-97.5 %). Many hit compounds **7e,m,p,t** with antiradical activity were identified, which are of interest for in-depth pharmacological investigations and the design of potential synthetic antioxidants.

Conflict of interest

The authors declare no conflict of interest.

4. Experimental

4.1. Materials and Methods

Commercially available reagents and solvents were used without further purification. Melting points were measured on a Kofler melting point device and are uncorrected. IR spectra were recorded on Bruker Vertex 70 FT-IR spectrometer for samples in KBr pellets. The NMR spectra were recorded with Varian VXR-300 (400, 500, 600) instruments (400, MHz for ^{1}H, and 125, 150 MHz for ^{13}C) in DMSO.d_6 solution, with TMS as an internal standard. LC–MS spectra were recorded on an Agilent 1100 Series high performance liquid chromatograph equipped with a diode matrix with an Agilent LC\MSD SL mass selective detector. Mass spectrometric detection of samples were performed with an Infinity 1260 UHPLC system (Agilent Technologies, Waldbronn, Germany) coupled to a 6224 Accurate Mass TOF LC/MS system (Agilent Technologies, Singapore). Elemental analysis was performed on a PerkinElmer 2400 CHN Analyzer. The individuality of the obtained compounds was monitored by TLC on Silutol UV-254 plates (eluent MeOH-$CHCl_3$, 1:20).

4.2. General procedure for the synthesis of compounds (**7a-w**).

1 mmol of salt **4a-f** or base **5a,b, 6** was added to the corresponding thiol (1 mmol) and NaOH (2 mmol) in acetonitrile (25 mL) and stirred until completely dissolved (heated if necessary) and left until the reaction product is completely isolated. After cooling, the precipitate is filtered, washed with 1 mL of acetonitrile and 20 mL of water. The precipitate is extracted with (3×25 mL) benzene or (3×40 mL) chloroform. The organic phase is separated, left over a desiccant ($CaCl_2$) and passed through a thin layer of silica gel. The solvent is evaporated. The reaction products are converted to salts in dry ethanol with an appropriate amount of 40% HBr and crystallised.

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