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# Synthesis, antimicrobial and antioxidant activity evaluation, DFT-calculation, and docking studies of 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles

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**A B S T R A C T**

A number of 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles were synthesized by cyclocondensation of imidazolidine-2-thione with phenacyl bromides, and their antimicrobial and antioxidant activity was evaluated. Bioscreening confirmed the moderate antibacterial activity against the reference strains of bacteria *Staphylococcus aureus*, *Escherichia coli* and *Proteus vulgaris* and excellent antifungal activity against *Candida albicans*. It was found that 3-(4-chlorophenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole **4h** (MIC = 15.625 μg/ml) has twice the antifungal effect compared to the control drug Furacilin. The study of the antioxidant activity of the synthesized compounds proved their ability to inhibit 60–97% of DPPH radicals. The best antiradical effect was found for 4-(5,6-dihydroimidazo[2,1-*b*]thiazol-3-yl)phenol **4e** (*I* = 97%). A probable mechanism of its action was proposed involving the formation of a radical cation by the SET process. For the most active antioxidants **4e-g**, reactivity and electrostatic surface potential were evaluated using the DFT method, and molecular docking was studied on the human peroxiredoxin 5 protein model.



## 1. Introduction

An important space among condensed nitrogen-containing compounds is occupied by the derivatives of the imidazo[2,1-*b*]thiazole system, which are privileged in medical chemistry due to a powerful spectrum of biological action.[1-4] Specifically, the imidazothiazole core is a key structural subunit of the anthelmintic and immunomodulating drug Levimazole **I**[5] and a potential anticancer agent Quizartinib **II**, which has demonstrated good activity in acute myeloid leukemia.[6] The imidazothiazole motif is also part of the anxiolytic agent WAY-181187 (SAX-187) **III**,[7] the antineoplastic agent pifithrin-β **IV**,[8] the sirtuin modulator SRT2140 **V**,[9] the inhibitor of the enzyme 15-lipoxygenase (15-LOX) **VI**[10], and the recombinant enzyme IDO1 (rhIDO1) **VII**11 (see **Fig. 1**), as well as compounds with pronounced antimicrobial,[12] antiviral[13] and neuroprotective[14] activity. It is worth noting that functionalized imidazothiazoles were tested as selective organocatalysts[15,16] and potential electroluminescent materials for OLED devices and LED chips.[17]

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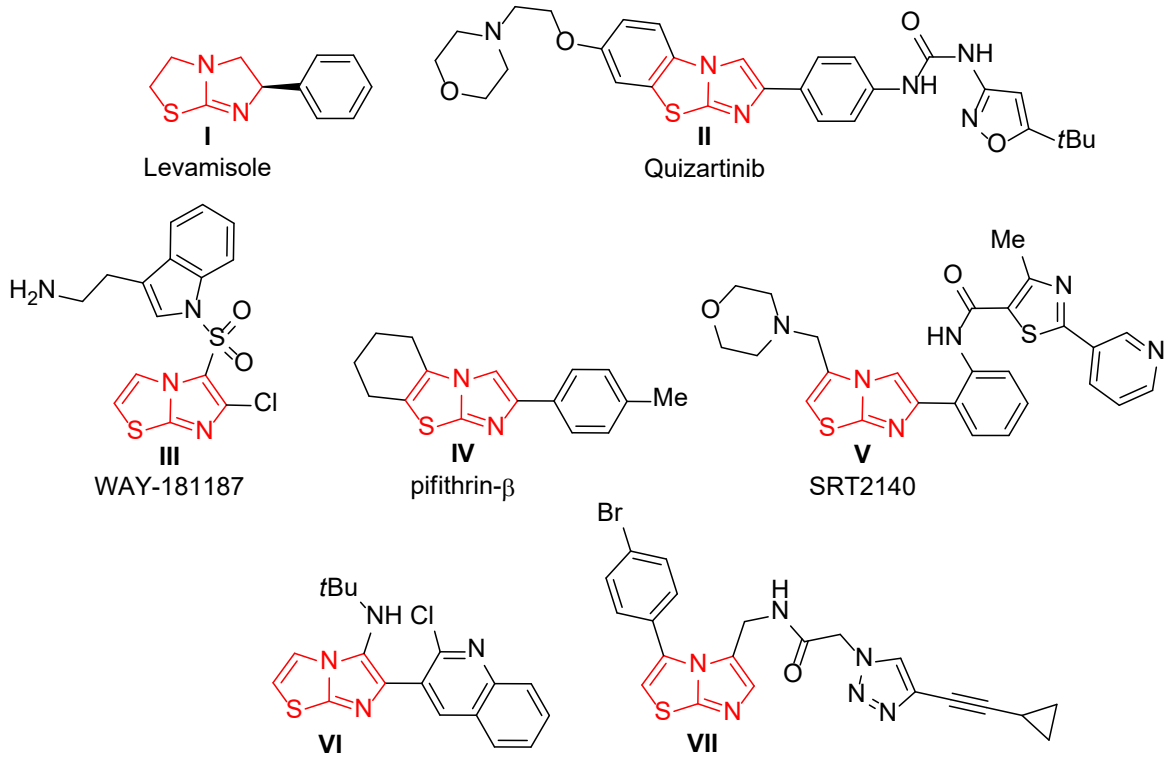



**Fig. 1**. Structure of some bioactive imidazo[2,1-*b*]thiazoles.

The last two decades oversaw a considerable interest in hydrogenated analogues of imidazothiazoles, particularly 5,6-dihydroimidazo[2,1-*b*]thiazoles, among which antimicrobial agents,[18] alkaline phosphatase inhibitors,[19] iodide efflux inhibitors in thyrocytes,[20] agonists of 5- HT1A and norepinephrine reuptake inhibitors,[21] potential probes for imaging of Huntington protein[22] were found. Taking into account the importance of the imidazothiazole core as a powerful medical and biological scaffold, the subject of this publication is the synthesis, evaluation of the antimicrobial and antioxidant potential of 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles, as well as DFT calculations and docking studies of their most promising representatives.

## 2. Results and Discussion

### *2.1. Chemistry*

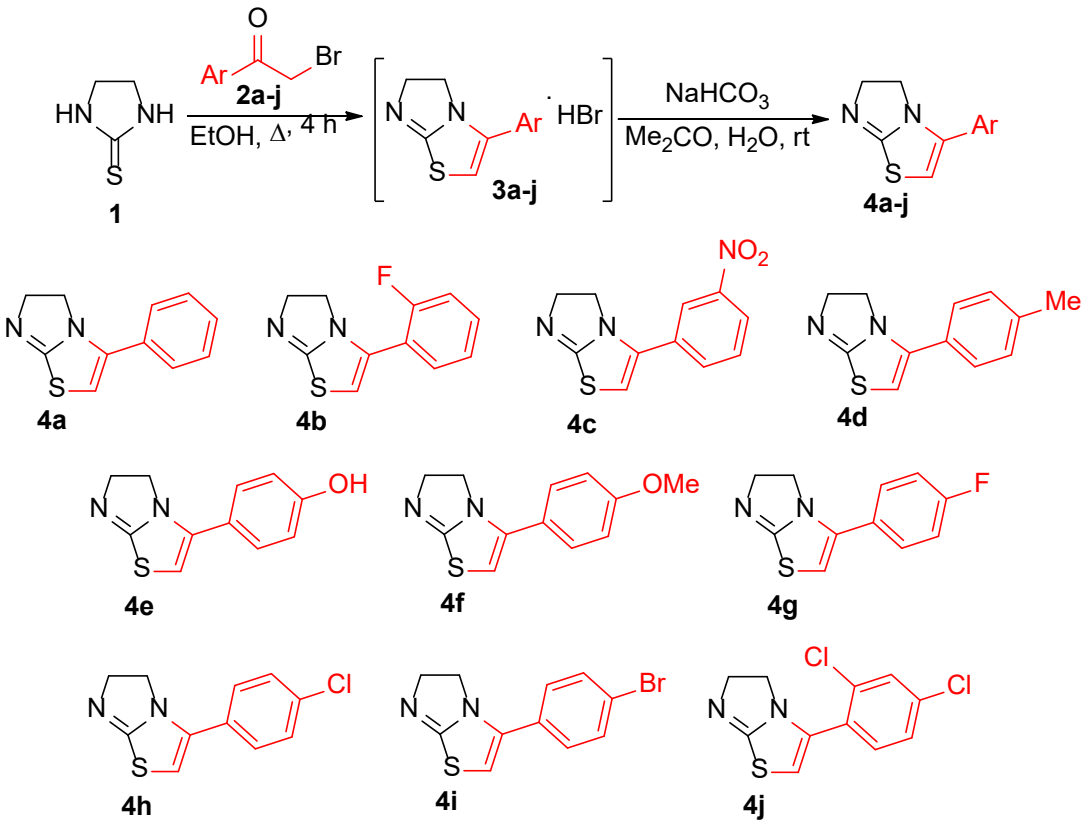
The traditional way of constructing imidazo[2,1-*b*]thiazoles and their condensed derivatives is the cyclocondensation of 2-aminothiazole and alkyl- or (het)aryl bromoketones,[23,24] and halogen-containing oxoacids and their esters are usually used for the synthesis of functionalized imidazothiazoles.[25-32] Whereas, partially hydrogenated imidazo[2,1-*b*]thiazoles are obtained by cyclocondensation of imidazolidine-2-thiones with α-bromoacetophenones.[16,18-20,22,33] To create a focused library of 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles **4a-j** for further biomedical research, the methods of obtaining their previously described representatives **4a,d,f,g,h,i** were optimized and improved, [16,34,35] and new compounds **4b,c,e,j** were synthesized. It was shown that the reaction of commercially available imidazolidin-2-thione **1** with α-bromoacetophenones **2a-j** is effective for this purpose. Heating the reagents in ethanol solution for 4 hours results in the annelation of the thiazole nucleus and the formation of the corresponding hydrobromides of imidazothiazoles **3a-j**. Further treatment of obtained salts in acetone solution with aqueous solution of $NaHCO_3$ at room temperature leads to the target products **4a-j** with yields of 69-86% (**Scheme 1**).

The composition and structure of products **4a-j** was proven by elemental analysis and the spectral research. Specifically, reliable confirmation of the annelation of the thiazole ring is the presence in the $^1$H NMR spectra of the thiazole ring proton singlet at 6.03-6.46 ppm and the signal of the corresponding carbon atom in the $^{13}$C NMR spectra in the range of 97.8-106.3 ppm.

### *2.2. Antimicrobial activity*

The results of the antimicrobial activity screening of 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles **4a-j** proved their moderate antibacterial activity against the reference strains of bacteria *S. aureus*, *E. coli* and *P. vulgaris* with values of the minimum inhibitory concentration of 31.25-125 μg/ml (**Table 1**). All synthesized derivatives demonstrated excellent antifungal activity against *C. albicans* which is the causative agent of opportunistic human infections. For instance, the

minimum inhibitory concentrations of compounds **4a-f,i,j** are 31.25 μg/ml and are at the level used for the control study of the antimicrobial drug Furacilin. 3-(4-Chlorophenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole **4h** is characterized by a higher antifungal effect (MIC = 15.625 μg/ml) than Furacilin (MIC = 31.25 μg/ml).




**Scheme 1**. Synthesis of the compounds **4a-j**.

**Table 1.** Antimicrobial activity of 3-aryl-5,6-dihydroimidazo[2,1-*b*]thiazoles **4a-j**.

| Compounds | *S. aureus* | *E. coli* | *P. vulgaris* | *C. albicans* |
|---|---|---|---|---|
| | MIC | MIC | MIC | MIC |
| **4a** | 62.5 | 62.5 | 62.5 | 31.25 |
| **4b** | 62.5 | 62.5 | 62.5 | 31.25 |
| **4c** | 62.5 | 62.5 | 62.5 | 31.25 |
| **4d** | 62.5 | 62.5 | 62.5 | 31.25 |
| **4e** | 62.5 | 62.5 | 62.5 | 31.25 |
| **4f** | 125 | 62.5 | 62.5 | 31.25 |
| **4g** | 62.5 | 62.5 | 62.5 | 31.25 |
| **4h** | 62.5 | 62.5 | 62.5 | **15.625** |
| **4i** | 31.25 | 62.5 | 62.5 | 31.25 |
| **4j** | 31.25 | 62.5 | 62.5 | 31.25 |
| **DMSO** | + | + | + | + |
| **Furacilin** | 3.91 | 7.81 | 7.81 | 31.25 |

*2.3. Antioxidant activity*

The antioxidant activity of the synthesized compounds was assessed by inhibition of 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals. It was experimentally established that 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles **4a-j** are able to absorb 60–97% of the formed radicals. The best antioxidant effect was observed for 4-(5,6-dihydroimidazo[2,1-*b*]thiazol-3-yl)phenol **4e** (*I* = 97%), which is consistent with literature data for compounds with a phenol fragment.[36] 3-(4-Methoxyphenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole **4f** and 3-(4-fluorophenyl)-5,6-dihydroimidazo[2,1-*b*] thiazole **4g** have somewhat lower DPPH radical inhibition values (92% and 89%, respectively) (**Fig. 2**).

Analysis of the "structure-activity" dependence proved the positive effect of substituents in the position 4 of the aromatic nucleus, including 2,4-dichloro derivative, on the antioxidant activity of the studied compounds. For instance, compounds **4d-j** absorb 74-97% of DPPH radicals, while 3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole **4a**, 2-fluoro- and 3-nitro-substituted derivatives **4b,c** inhibit only 60-70% radicals (**Fig. 3**).

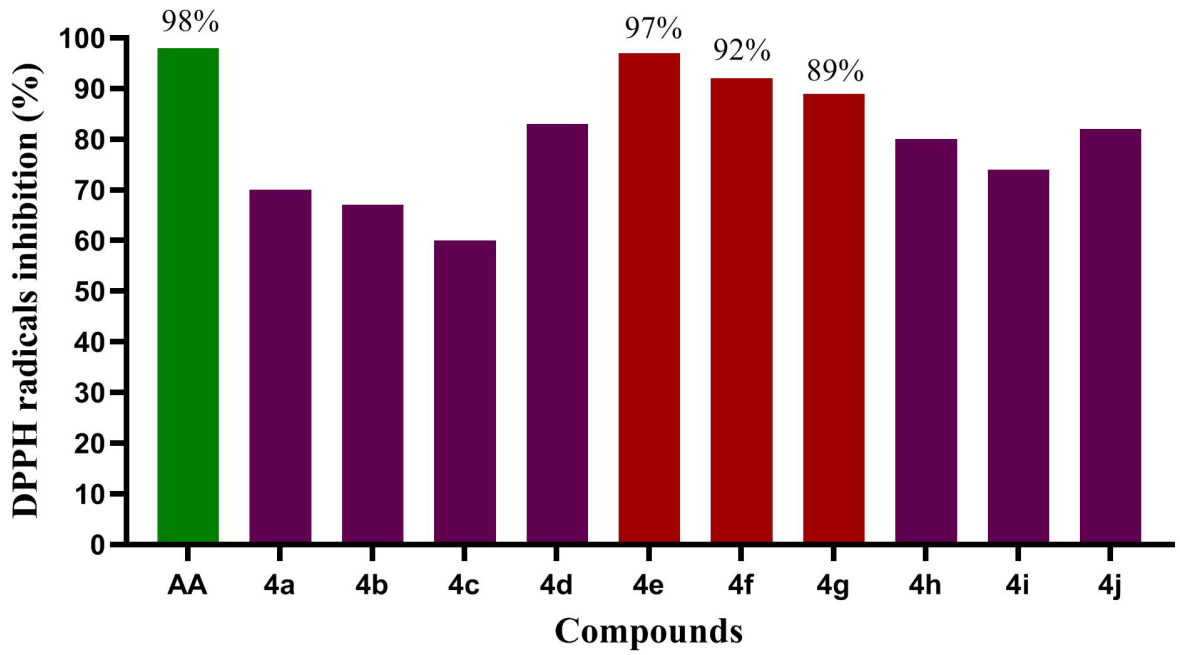



**Fig. 2.** The inhibition of DPPH radicals by the derivatives **4a-j** at 5 mM concentration. Ascorbic acid (AA) was employed as a positive control (green). The highest activity was observed for compounds **4e-g** (red).

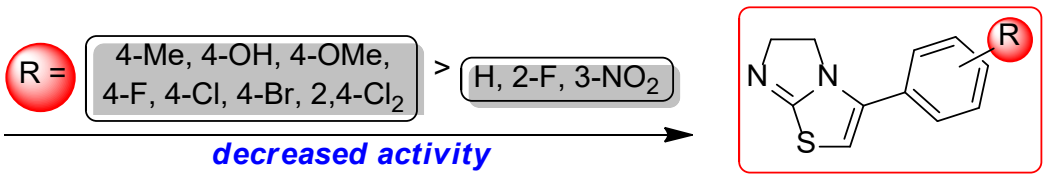
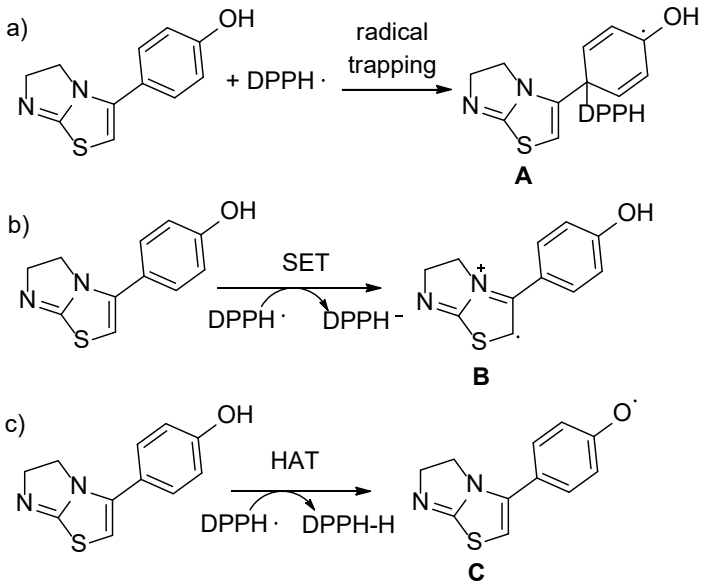



**Fig. 3.** Structure-anti-radical activity relationships of 3-arylimidazo[2,1-*b*]thiazoles **4a-j**.

Considering the recent study[37] which allows for the possibility of several directions of antioxidant action of organic compounds, we studied possible options for inhibiting DPPH free radicals for the most active imidazothiazole **4e** (**Scheme 2**). They include the mechanism of spin capture, which results in the formation of spin adduct **A** with DPPH (pathway a); sequential electron transfer (SET) (pathway b) and/or hydrogen atom transfer (HAT) (pathway c).




**Scheme 2**. Probable pathways of DPPH inhibition by compound **4e**.

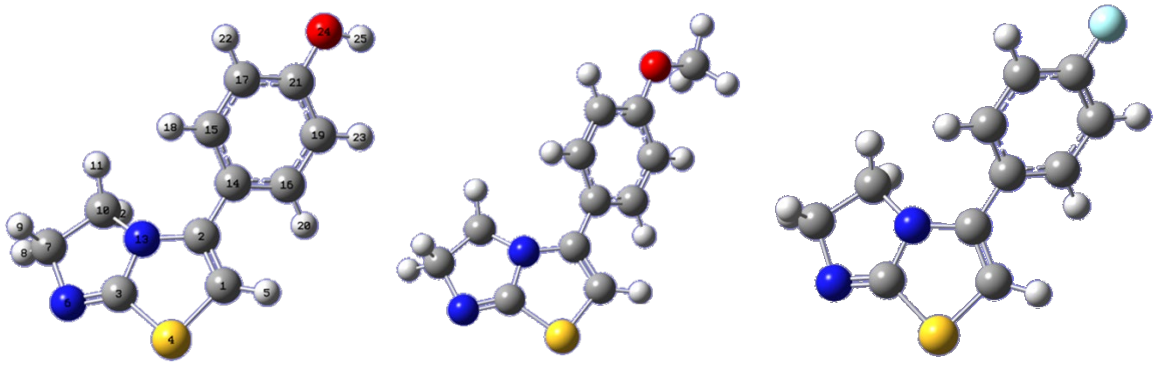
*2.4. Structure and reactivity analysis by the method of DFT-calculation*

The structures of compounds with the highest antioxidant activity **4e-g** were optimized using Gaussian 09 software,[38] and the results were visualized using GaussView 5.0.8. The geometry of all studied structures was optimized using the Density Functional Theory in the B3LYP approach with the standard set of basic functions 6-311++G(d,p).

The reactivity parameters of the **4e-g** molecules, such as ionization potential (IP), electron affinity (EA), chemical hardness (η), global electrophilicity power (ω)[39-41] and nucleophilic (N) power in scale that referred to tetracyanoethylene (TCE) taken as a reference because it presents the lowest HOMO energy in a large series of molecules already considered.[42]

$IP = -E_{HOMO}$
$EA = -E_{LUMO}$
$\eta = IP - EA$
$\mu = -0{,}5(IP + EA)$
$\omega = \mu^2/2\eta$
$N = IP(TCE) - IP(Nu)$

According to the B3LYP/6-311++G(d,p)-based DFT-simulation of molecular structures **4e-g** in vacuum (**Fig. 4**), the angle between the aryl substituent and the thiazole fragment is about 40°, and the angle N13–C2–C14–C15 is 39.7° (**4e**); 40.1° (**4f**) and 39.3° (**4g**), correspondingly.



**4e** **4f** **4g**

**Fig. 4.** DFT-optimized structure of the compounds **4e-g**.

The energy of the frontier MOs depends on the electron donating power of the substituent in the phenyl nucleus. Thus, the highest energy of the frontier MOs is found in compound **4g** with a fluorine atom, and the lowest in the compound **4f** with a methoxy group. The calculated values of HOMO, LUMO, and other electronic parameters are shown in Table 2. The calculated HOMO energy show that they increase in the order **4g** > **4e** > **4f**, and compound **4f** is the best electron donor. This is also proved by the lowest value of the nucleophilic (N) powers.

**Table 2.** Calculated energy of the frontier MOs, electron affinity (EA), ionization potential (IP), chemical hardness (η), chemical potential (μ), global electrophilicity power (ω) and nucleophilic (N) powers.

| | **4e** | **4f** | **4g** |
|---|---|---|---|
| LUMO, eV | -1.10 | -1.03 | -1.39 |
| HOMO, eV | -5.31 | **-5.26** | -5.49 |
| EA, eV | 1.10 | 1.03 | 1.39 |
| IP, eV | 5.31 | 5.26 | 5.49 |
| η, eV | 4.20 | 4.23 | 4.10 |
| μ, eV | -3.21 | -3.15 | -3.44 |
| ω, eV | 1.22 | 1.17 | 1.44 |
| N, eV | 4.18 | **4.23** | 4.00 |

The molecular electrostatic surface potential (MESP) is an important factor for describing the active sites of ligands.[43,44] It was calculated for the molecules of compounds **4e-g** using optimized structures with the B3LYP/6-311++G(d,p) basis for studying nucleophilic and electrophilic surface spots. All compounds have a negatively charged spot (electrophilic center) located near the nitrogen atom at position 7 of the imidazo[2,1-*b*]thiazole cycle (**Fig. 5**). Comparison of the MESP gradient boundaries of compounds **4f** and **4g** shows that they are wider for compound **4f** due to higher negative potential on the nitrogen atom caused by the donor effect of the methoxyl substituent. Instead, compound **4e** has even wider MESP gradient boundaries due to the more positively charged spot (electrophilic center) on the phenolic hydrogen atom.

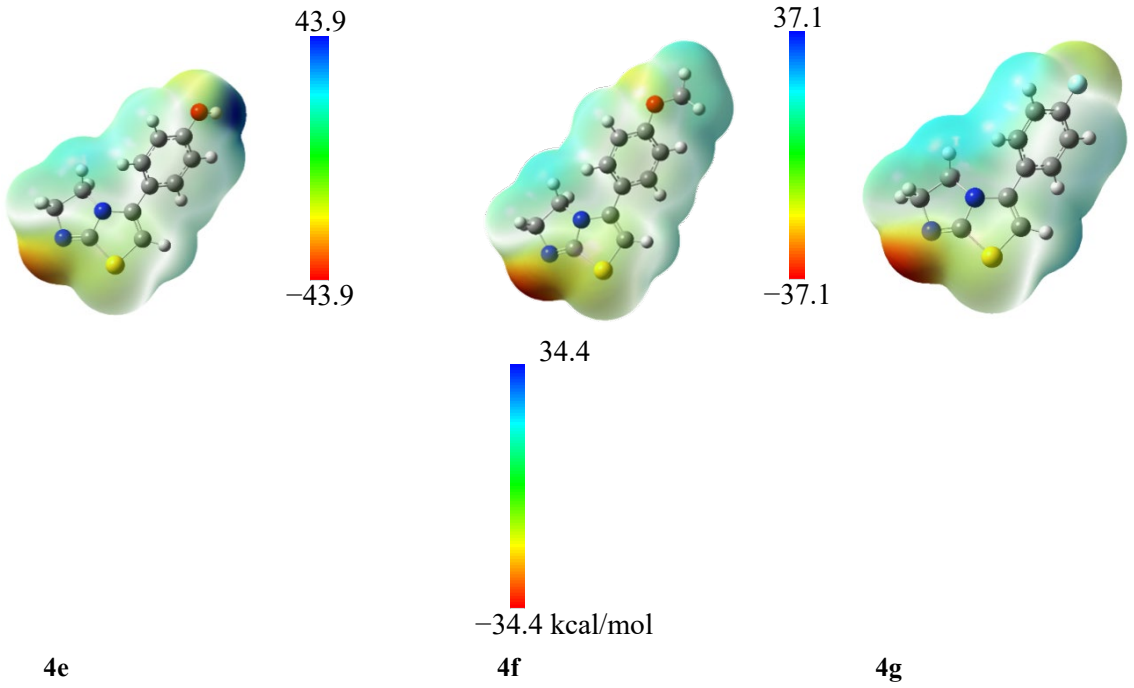



**Fig. 5.** Calculated MESP for the molecules of **4e-g**.

In our case DPPH is model radical, **Scheme 2** summarizes possible reaction mechanisms that could take place between DPPH and the compound **4e**. In a typical DPPH assay, conjugated compounds are therefore expected to quench DPPH free radicals via a spin trapping mechanism following pathway (a), giving rise to spin adduct **A**. But this process is unlikely due to significant steric interferences. That is why the formation of cationic radical B by the SET process seems more likely (Scheme 2, pathway b). The analysis of its spin density (*s*) shows that it is mainly focused on the carbon atom in the position 2 (*s*(C1) = 0.365) and on the nitrogen atom in the position 7 (*s*(N6) = 0.322) of the imidazo[2,1-*b*]thiazole cycle, and the total spin density from MESP (**Fig. 6b**) indicates the location of the unpaired electron above the carbon atom in the position 2. In addition, the electrostatic potential of cation-radical **B** (**Fig. 6a**) indicates the presence of a positively charged site near the nitrogen atom in position 4 which leads to the conclusion of its structure as shown in **Scheme 2**, pathway b.

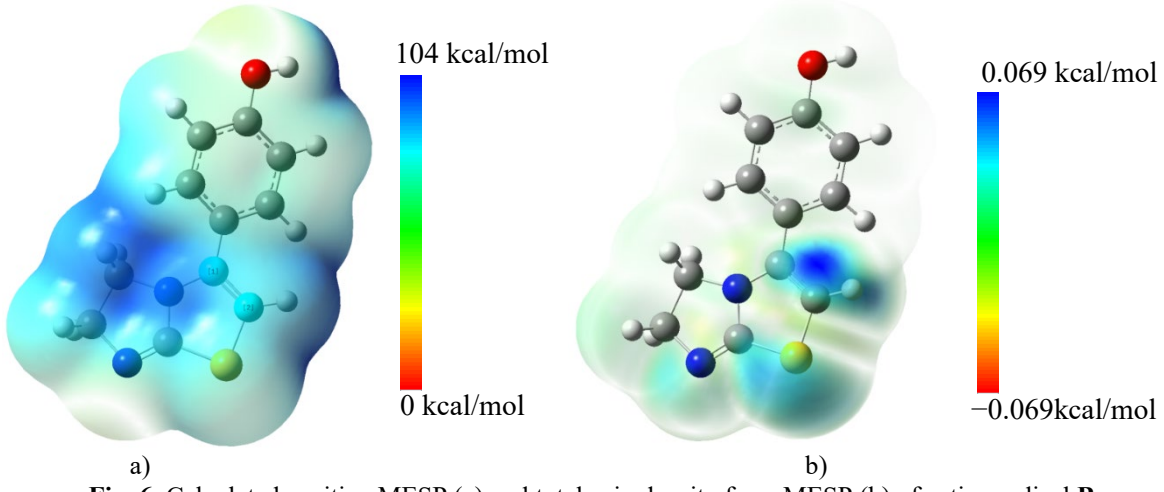



**Fig. 6.** Calculated positive MESP (a) and total spin density from MESP (b) of cation radical **B**.

*2.5. Docking studies*

The molecular docking study was performed by the Autodoc Vina software[45] using previously optimized structures. The crystal structure of human peroxiredoxin 5 (PRDX5) which is associated with antioxidant mechanisms[46,47] was downloaded from the Protein Data Bank (PDB 1HD2), water molecules were removed, polar hydrogen atoms were added, and the Gasteiger charge was added. A center of the ligand docking cavity (9.6; 41.4; 34.9) was determined using BIOVIA Discovery Studio Visualizer v21.1 and the cavity dimension was 22; 30; 28. Binding was visualized using BIOVIA Discovery Studio Visualizer v21.1.

According to the molecular docking simulation, 9 positions were found with the corresponding ligand-protein affinity for every ligand. They show that the studied compounds do not have a high affinity for human peroxiredoxin 5 (**Table 3**).

**Table 3**. Ligand-protein interaction of compounds **4e-g** with human peroxiredoxin 5 (1HD2).

| No | Parameter | **4e** | **4f** | **4g** |
|---|---|---|---|---|
| 1 | Best binding energy to protein, kcal/mol | –4.3 | –4.4 | –4.5 |
| 2 | Hydrogen bonds | – | Asn76 (2.68Å) | Pro45(Carbon Hydrogen Bond) |
| 3 | Hydrophobic interactions | – | Val80, Ile119 | Phe120, Trh44 |
| 4 | π-cationic interaction | Phe120 | – | Arg124 |
| 5 | π-sulfur interaction | Arg124 | – | – |

The ligand-protein interactions for compounds **4e-g** visualized in BIOVIA Discovery Studio Visualizer are shown in **Fig. 7**. Generally, all the compounds studied bind to peroxiredoxin 5 at the active site by nonpolar and π-interactions. Compound **4f** acts as a hydrogen bond donor to Asn76, and the fluorine atom of compound **4g** is a donor of an electron pair for the hydrogen atom in the α-position to the nitrogen atom of Pro45.

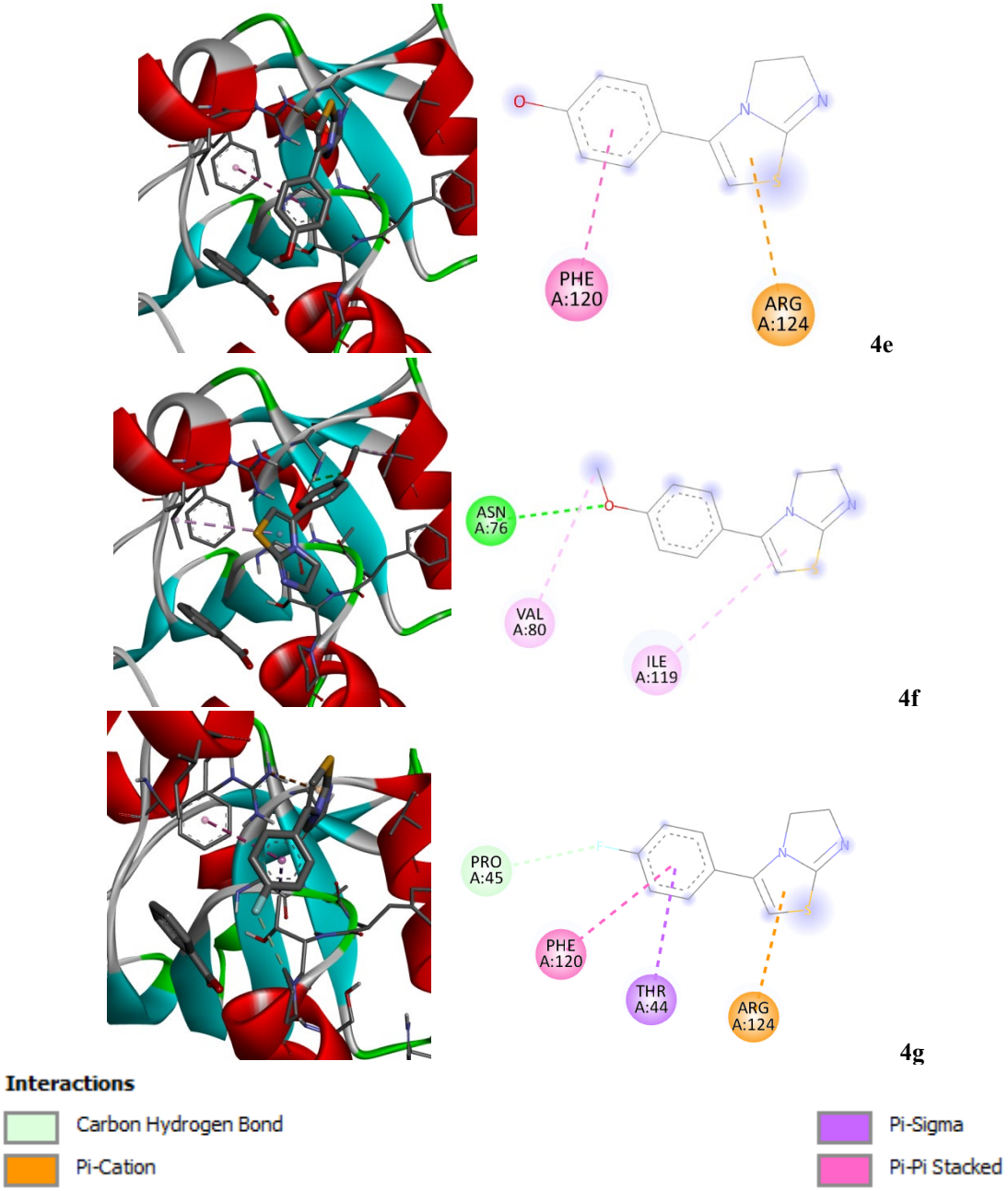



**Fig. 7**. 3D (left) and 2D (right) interactions of compounds **4e-g** inside the active site of the protein.

## 3. Conclusions

The interaction of imidazolidine-2-thione with phenacyl bromides resulted in a series of 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles which were tested for antimicrobial and antioxidant activity. According to the results of the bioscreening,

it was established that all derivatives are characterized by a moderate antibacterial effect (MIC = 31.25-125 μg/ml), and compound **4h** is characterized by a higher antifungal effect (MIC = 15.625 μg/ml) than the medical drug Furacilin (MIC = 31.25 μg/ml). The evaluation of the antioxidant activity of the synthesized derivatives proved that they are capable of inhibiting 60–97% of DRPH radicals. Derivatives **4e-g** (*I* = 97–89%) were found to be potential synthetic antioxidants and of interest for further pharmacological research. Their structure, reactivity, and electrostatic surface potential were analyzed by DFT calculations, and the affinity for human peroxiredoxin protein 5 was evaluated by molecular docking.

## 4. Experimental

### *4.1. Chemistry*

$^{1}$H and $^{13}$C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 126 MHz, respectively) in pulsed Fourier mode in DMSO-$d_6$ and in $CDCl_3$, with TMS as the internal standard. Mass spectra were recorded on an Agilent LC/MSD SL instrument, Zorbax SB-C18 column, 4.6×15 mm, 1.8 μm (PN 82(c)75-932), DMSO-$d_6$ as the solvent, electrospray ionization at atmospheric pressure. Elemental analysis was performed on a PerkinElmer CHN Analyzer 2400 series in the analytical laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. Melting points were determined according to a Kofler bench and are uncorrected. Reagents and solvents were purchased from UkrOrgSyntez Ltd.

*4.1.1 General procedure for the synthesis of 3-aryl-5,6-dihydroimidazo[2,1-b]thiazoles* **4a-j**. 4.9 mmol of respective phenacyl bromide **2a-j** was added to a suspension of 0.5 g (4.96 mmol) of imidazolidine-2-thione **1** in 20 mL of EtOH. The reaction mixture was boiled for 4 h, the solvent was evaporated, the solid residue of hydrobromide **3a-j** was dissolved in 30 mL of acetone, neutralized with an aqueous $NaHCO_3$ solution and extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were dried with $Na_2SO_4$ and evaporated.

*4.1.2. 3-Phenyl-5,6-dihydroimidazo[2,1-b][1,3]thiazole* (**4a**). Yellow solid, mp 111-112 °C (ethyl acetate); yield 86%.[16,34,35]

*4.1.3. 3-(2-Fluorophenyl)-5,6-dihydroimidazo[2,1-b][1,3]thiazole* (**4b**). Brown solid, mp 70-71 °C (ethyl acetate); yield 77 %. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 3.76 (t, $^{3}J$ = 9.0 Hz, 2H, $CH_2$), 4.07 (t, $^{3}J$ = 9.0 Hz, 2H, $CH_2$), 6.20 (s, 1H, SCH), 7.27-7.38 (m, 2H, Ar), 7.46-7.58 (m, 2H, Ar). $^{13}$C NMR (150 MHz, DMSO-$d_6$): δ = 47.8 ($C^5$), 59.9 ($C^6$), 101.7 (d, $^{5}J_{C,F}$ = 3.0 Hz, $C^2$), 116.7 (d, $^{2}J_{C,F}$ = 21.0 Hz, Ar), 118.5 (d, $^{3}J_{C,F}$ = 13.5 Hz, Ar), 125.4, 130.3, 131.0 (Ar), 131.7 (d, $^{4}J_{C,F}$ = 7.5 Hz, $C^3$), 159.4 (d, $^{1}J_{C,F}$ = 247.5 Hz, Ar), 168.3 ($C^{7a}$). MS: m/z 221 (M + H). Anal. Calcd. for $C_{11}H_9FN_2S$ (%): C, 59.98; H, 4.12; N, 12.72. Found: C, 60.19; H, 4.15; N, 12.59.

*4.1.4. 3-(3-Nitrophenyl)-5,6-dihydroimidazo[2,1-b][1,3]thiazole* (**4c**). Orange solid, mp 174-175 °C (ethyl acetate); yield 83 %. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 3.90 (t, $^{3}J$ = 9.0 Hz, 2H, $CH_2$), 4.10 (t, $^{3}J$ = 9.0 Hz, 2H, $CH_2$), 6.46 (s, 1CH, SCH), 7.71-7.76 (m, 1H, Ar), 8.01 (d, $^{3}J$ = 6.0 Hz, 1H, Ar), 8.23 (d, $^{3}J$ = 9.0 Hz, 1H, Ar), 8.30 (s, 1H, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ = 47.9 ($C^5$), 60.3 ($C^6$), 100.8 ($C^2$), 120.6, 123.2, 130.5, 131.8, 132.2 (Ar), 134.8 ($C^3$), 148.1 (Ar), 167.9 ($C^{7a}$). MS: m/z 248 (M + H). Anal. Calcd. for $C_{11}H_9N_3O_2S$ (%): C, 53.43; H, 3.67; N, 16.99. Found: C, 53.25; H, 3.63; N, 17.12.

*4.1.5. 3-(p-Tolyl)-5,6-dihydroimidazo[2,1-b][1,3]thiazole* (**4d**). Brown gummy mass; yield 69 %.[34]

*4.1.6. 4-(5,6-Dihydroimidazo[2,1-b][1,3]thiazol-3-yl)phenol* (**4e**). White solid, mp > 210 °C (ethyl acetate); yield 84 %. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ the OH-group proton is exchanged with water molecules of deuterosolvent, 4.05-4.17 (m, 4H, $2CH_2$), 6.28 (s, 1H, SCH), 6.84 (d, $^{3}J$ = 6.0 Hz, 2H, Ar), 7.40 (d, $^{3}J$ = 9.0 Hz, 2H, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ = 47.7 ($C^5$), 56.8 ($C^6$), 98.4 ($C^2$), 115.7, 120.3, 128.1 (Ar), 137.1 ($C^3$), 158.4 (Ar), 169.3 ($C^{7a}$). MS: m/z 219 (M + H). Anal. Calcd. for $C_{11}H_{10}N_2OS$ (%): C, 60.53; H, 4.62; N, 12.83. Found: C, 66.74; H, 4.58; N, 12.99.

*4.1.7. 3-(4-Methoxyphenyl)-5,6-dihydroimidazo[2,1-b][1,3]thiazole* (**4f**). Brown solid, mp 87-88 °C (ethyl acetate); yield 70 %.[16,34]

*4.1.8. 3-(4-Fluorophenyl)-5,6-dihydroimidazo[2,1-b][1,3]thiazole* (**4g**). Orange solid, mp 91-92 °C (ethyl acetate); yield 82 %.[35]

*4.1.9. 3-(4-Chlorophenyl)-5,6-dihydroimidazo[2,1-b][1,3]thiazole* **4h**. Light brown solid, mp 111-112 °C (ethyl acetate); yield 80 %.[34,35]

*4.1.10. 3-(4-Bromophenyl)-5,6-dihydroimidazo[2,1-b][1,3]thiazole* (**4i**). Light yellow solid, mp 144-145 °C (ethyl acetate); yield 81 %.[35]

*4.1.11. 3-(2,4-Dichlorophenyl)-5,6-dihydroimidazo[2,1-b][1,3]thiazole* (**4j**). Light brown solid, mp 142-143 °C (ethyl acetate); yield 80 %. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 3.60 (t, $^{3}J$ = 9.0 Hz, 2H, $CH_2$), 4.05 (t, $^{3}J$ = 9.0 Hz, 2H, $CH_2$), 6.10

(s, 1H, SCH), 7.53 (s, 2H, Ar), 7.78 (s, 1H, Ar). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ = 46.7 ($C^5$), 60.0 ($C^6$), 100.8 ($C^2$), 127.8, 128.3, 129.6, 132.0, 132.4, 133.1 (Ar), 134.8 ($C^3$), 167.3 ($C^{7a}$). MS: m/z 272 (M + H). Anal. Calcd. for $C_{11}H_8Cl_2N_2S$ (%): C, 48.72; H, 2.97; N, 10.33. Found: C, 48.96; H, 2.99; N, 10.48.

*4.2. Antimicrobial activity*

Antimicrobial activity was studied by the micromethod of two-time serial dilutions in a liquid nutrient medium. The minimum inhibitory concentrations of 3-aryl-5,6-dihydroimidazo[2,1-*b*]thiazoles **4a-j** against reference strains of bacteria (*Staphylococcus aureus, Escherichia coli, Proteus vulgaris*) and fungi (*Candida albicans*) were determined. Solutions of the studied compounds were prepared for the micromethod of serial dilutions (at a concentration of 1000 μg/ml), using dimethyl sulfoxide (DMSO) as a solvent and the antimicrobial agent Furacilin produced by JSC Halychpharm as a control. To obtain reliable results, the experiments were performed three times with each concentration of the compound and the investigated culture of microorganisms.[48]

*4.3. Antioxidant activity (DPPH assay)*

Antioxidant activity of the synthesized compounds was assessed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical inhibition assay.[49] 1 ml of DPPH solution (8 mg/100 ml) was added to solutions of the tested compounds and ascorbic acid in methanol as a standard and left at room temperature in a dark place for 1 hour. The amount of absorption of radicals was determined at 517 nm relative to the standard on a UV-1800 spectrophotometer (Shimadzu, Japan). Each sample was analyzed in triplicate. The percentage of inhibition was calculated relative to the blank sample:

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

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

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