ORIGINAL ARTICLE

A C G publications

Org. Commun. xx:x (xxxx) xxx-xxx

organic communications

Molecular docking and antioxidant activity studies of imidodithiocarbonate derivatives containing pyrimidine

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(Received December 17,2022; Revised January 22, 2023; Accepted February 07, 2023)

Abstract: Imidodithiocarbonate derivatives containing pyrimidine ring, potentially functional molecules were synthesized and characterized. FTIR, ^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis methods were used for characterization. The obtained compounds were screened for their antioxidant capacity using DPPH (1,1-diphenyl-2-picrylhydraziyl) free radical-scaving and ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonicacid) assays. The possible interactions between the molecular docking calculations of the synthesized imidodithiocarbonate derivatives and their binding potentials to the active sites of target enzymes.

Keywords: Pyrimidine; imidodithiocarbonate; molecular docking; antioxidant activity.

1. Introduction

Heterocyclic compounds are defined as ring compounds containing at least one heteroatom in their structure. The ring system can start from three members and include more members. The six-membered aromatic derivatives containing two nitrogen atoms have three isomers: pyridazine (1,2-diazine), pyrimidine (1,3-diazine), pyrazine (1,4-diazine). The pyrimidine skeleton is one of the most common heterocyclic ring system found in nature. Vitamin B1 (thiamine), Vitamin B2 (riboflavin) and folic acid, which are known for their strong antioxidant properties have possess a pyrimidine moiety. Uracil, thymine and cytosine, which are found in the nucleic acids that form the essence of life, are pyrimidine derivatives. The imidazole condensed pyrimidines are known as purines. Adenine and guanine, found in the nucleic acids that make up the essence of life, are purine derivatives. Caffeine, which is the active compound of coffee and tea, and theophylline and theobromine found in tea are also purine derivatives [1]. In addition to their biological importance, pyrimidine derivatives are popular compounds due to their pharmaceutical properties such as antioxidant, anti-inflammatory, anti-microbial, anti-HIV, antidiabetic, antiviral, and anticancer activities [2-4].

Oxidative processes are one of the basic metabolic processes necessary for the survival of all living organisms. This undesirable situation causes damage to some biomolecules and tissues containing proteins, DNA, lipids and reduces their antioxidant protection. These cellular damages play an important role in the development of many diseases such as cancer, asthma, respiratory diseases,

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The article was published by ACG Publications
http://www.acgpubs.org/journal/organic-communications © Month-Month 202X EISSN:1307-6175
DOI: http://doi.org/10.25135/acg.oc.143.2212.2658
Available online: February 28, 2023

cardiovascular dysfunctions and diabetes [5,6]. Antioxidants are free radical scavengers that play an important role in the prevention and spread of diseases caused by excessive oxidative stress [7,8]. However, there are many protective compounds present or produced in the cell to prevent these reactions, such as superoxide dismutase, catalase, glutathione peroxidase, tocopherol, ascorbic acid, glutathione and uric acid. These antioxidants neutralize and neutralize active free radicals by donating an electron. Thus, they transform it into a less active and less dangerous form to prevent irreversible negative effects and reduce its damaging capacity. Studies on the production and research of natural and synthetic antioxidants, which play such an important role in the prevention and treatment of many damages in the body, are becoming increasingly important [9-12].

In this study, three new imidodithiocarbonate compounds containing pyrimidine ring were synthesized and their antioxidant properties were determined by *in vitro* measurements. Then, MEP analysis was performed using the optimized structures of the three synthesized compounds revealed by theoretical studies and nucleophilic and electrophilic attack sites were identified and evaluated. The possible interactions between the molecular docking calculations of the synthesized **3a-c** molecules and their binding potentials to the active sites of the target enzymes, their binding patterns and antioxidant activities were investigated.

2. Experimental

Compounds **1** and **2** were prepared according to the literature [13-17]. Reagents and solvents were purchased from Merck, Fluka and Sigma, used without further purification. For purity tests, TLC: Merck precoated silica gel plates 60 F 254. M.p.: Electrothermal 9200 apparatus; uncorrected. IR Spectra: Shimadzu 8400 FT-IR spectrometer; in cm^{-1}. ^{1}H- and ^{13}C NMR Spectra: Bruker Avance III Ultrashield spectrometer operating at 400.13 MHz (^{1}H) and 100.61 MHz (^{13}C) in $CDCl_3$. The following abbreviations are used: singlet (s), multiplet (m), broad signal (br). Elemental analyses (C, H, N, S): LECO-932 CHNS-O analyzer.

*2.1. General Procedure for Preparation of Compounds **3a-c***

1 mmol of the appropriate *N*-amino pyrimidine compound **2a-c** was dissolved in approximately 20 mL DMF. A solution of 0.06 g (1 mmol) KOH in 10 mL water was added. After shaking for five minutes, 0.18 mL (3 mmol) of CS_2 was added dropwise. The reaction flask was placed in the reflux and slightly heated, and stirred for approximately 20 min. Then, the heating process was stopped and cooled to room temperature. Then, 4 mmol of the propargyl bromide was added dropwise to the reaction flask. It was placed in a reflux cooler and boiled for 4-6 hours. At the end of the time, the reaction vessel was cooled to room temperature and approximately 50 mL of ice-water was added to it and stirred for 2-3 hours. Diethyl ether was added, and the extraction was carried out. Petroleum ether was added to the separated organic phase, and the was precipitated and filtered. The formed crude product was recrystallized from a suitable solvent.

*Dipropargyl (5-benzoyl-4-phenyl-2-oxo-1(2H)-pyrimidinyl) Dithiocarbonoimidate (**3a**)*: Color: White crystalline solid, yield 0.290 g, 66%, mp 148 ºC, FT-IR (ATR, cm^{-1}): υ_{max} 3302 (sp C-H), 3180-3043 (arom. C-H), 2914 (aliph. C-H), 2124 (–C≡CH), 1678, 1641 (C=O), 1576-1473 (C=C, C=N), 1234 (C-S-C). ^{1}H-NMR (400 MHz; $CDCl_3$, ppm): δ 8.04 (s,1H, C_6-H), 7.69-7.24 (m, 8H, Ar-H), 4.06, 3.86 (2s, 4H, 2xCH_2), 2.39, 2.32 (2s, 2xH, C≡C-H). ^{13}C-NMR (100 MHz; $CDCl_3$, ppm): δ 191.75 (C=O), 176.08 (N=C-S_2), 171.76 (C_2=O), 150.02, 147.95, 136.71, 136.49, 133.33, 131.16, 129.63, 129.35, 128.47, 128.21,116.30 (aromatic C=C and C=N), 74.07, 72.82 (–C≡CH), 21.96, 21.78 (-CH_2-). Anal. Calcd. for $C_{24}H_{17}N_3O_2S_2$ (443.54 g/mol): C, 64.99; H, 3.86; N, 9.47; S, 14.46. Found: C, 64.89; H, 3.81; N, 9.20; S, 14.04.

*Dipropargyl[5-(4-methylbenzoyl)-4-(4-methylphenyl)-2-oxo-1(2H)-pyrimidinyl]Dithiocarbonoimidate (**3b**)*: Color: White crystalline solid, yield 0.271 g, 61%, mp 175 ºC, FT-IR (ATR, cm^{-1}): υ_{max} 3229 (sp C-H), 3036 (arom. C-H), 2957 (aliph. C-H), 2123 (–C≡CH), 1680, 1641 (C=O), 1597, 1497, 1466 (C=C, C=N), 1269 (C-S-C). ^{1}H-NMR (400 MHz; $CDCl_3$, ppm): δ 7.92 (s,1H, C_6-H), 7.63 (2H, AA'BB'system, part AA'), 7.52(2H, AA'BB'system, part AA'), 7.15(2H, AA'BB'system, part BB'),

7.05(2H, AA'BB'system, part BB'), 4.04, 3.84 (2s, 4H, 2x -CH_2-), 2.36, 2.29 (2s, 6H, 2x-CH_3), 2.18 (2s, 2H, C≡C-H). ^{13}C-NMR (100 MHz; $CDCl_3$, ppm): δ 191.53 (C=O), 175.74 (N=C-S_2), 171.49 (C_2=O), 147.32, 144.48, 141.80, 134.12, 133.62, 129.91, 129.44, 128.97, 116.44 (aromatic C=C and C=N), 74.00, 72.78 (–C≡CH), 21.91, 21.74 (2 x CH_2), 21.65, 21.42 (2 x CH_3). Anal. Calcd. for $C_{26}H_{21}N_3O_2S_2$ (471.59 g/mol): C, 66.22; H, 4.49; N, 8.91; S, 13.60. Found: C, 66.36; H, 4.59; N, 8.66; S, 13.07.

*Dipropargyl [5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-2-oxo-1(2H)-pyrimidinyl] Dithiocarbo-oimidate (**3c**)*: Color: White crystalline solid, yield 0.381 g, 76%, mp 154 ºC, FT-IR (ATR, cm^{-1}): υ_{max} 3298 (sp C-H), 3174-3053 (arom. C-H), 2922, 2895 (aliph. C-H), 2114 (–C≡CH), 1676, 1651 (C=O), 1597, 1497, 1466 (C=C, C=N), 1256 (C-S-C). ^{1}H-NMR (400 MHz; $CDCl_3$, ppm): δ 7.89 (s,1H, C_6-H), 7.71 (2H, AA'BB'system, part AA'), 7.61(2H, AA'BB'system, part AA'), 6.82(2H, AA'BB'system, part BB'), 6.76(2H, AA'BB'system, part BB'), 4.04, 3.83 (2s, 4H, 2x CH_2, 3.77, 3.75 (2s, 6H, 2xOCH_3), 2.38, 2.30 (2s, 2xH, C≡C-H). ^{13}C-NMR (100 MHz; $CDCl_3$, ppm): δ 190.63 (C=O), 175.50 (N=C-S_2), 170.33 (C_2=O), 163.83, 162.26 (C-OCH_3), 150.20, 146.99, 132.17, 131.46, 129.46, 128.76, 116.35, 113.86, 113.71(C=C and C=N), 73.97, 72.75 (2 x C≡CH), 55.51, 55.31 (2x OCH_3), 21.91, 21.71 (CH_2). Anal. Calcd. for $C_{26}H_{21}N_3O_4S_2$ (503.59 g/mol): C, 62.01; H, 4.20; N, 8.34; S, 12.73. Found: C, 62.85; H, 4.08; N, 8.00; S, 12.39.

2.2. Biological Assay

2.2.1. Antioxidant Activities

The radical scavenging activities of compounds 3a-c were determined in vitro using ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) and DPPH (1,1-diphenyl-2-picrylhydrazyl) methods.

2.2.1.1. DPPH$^{\bullet}$ Free Radical Scavenging Assay

DPPH is one of the widely used techniques in model system to investigate the scavenging activities of synthesized and natural compounds. 0.15 mL of the synthesized compounds of different concentrations was mixed with 0.15 mL of freshly prepared DPPH (0.1 mM) and incubated for 50 min in the dark [18]. Results were given as SC_{50} values defined as the concentration of synthesized compounds required to scavenge 50% of DPPH free radicals (mg sample/ mL). The radical scavenging activities of the synthesized compounds were calculated by comparison with DPPH.

2.2.1.2. ABTS$^{\bullet+}$ Radical Scavenging Assay

The ABTS$^{\bullet+}$ free radical cation scavenging ability assay of the synthesized compounds was performed using the actual method in the literature [19]. The ABTS$^{\bullet+}$ scavenging capacities of the synthesized compounds were compared with the Trolox (Sigma Chemical Co, USA). Results were expressed as SC_{50} values defined as the concentration of the samples that causes 50% scavenging of ABTS radicals (mg sample/ mL).

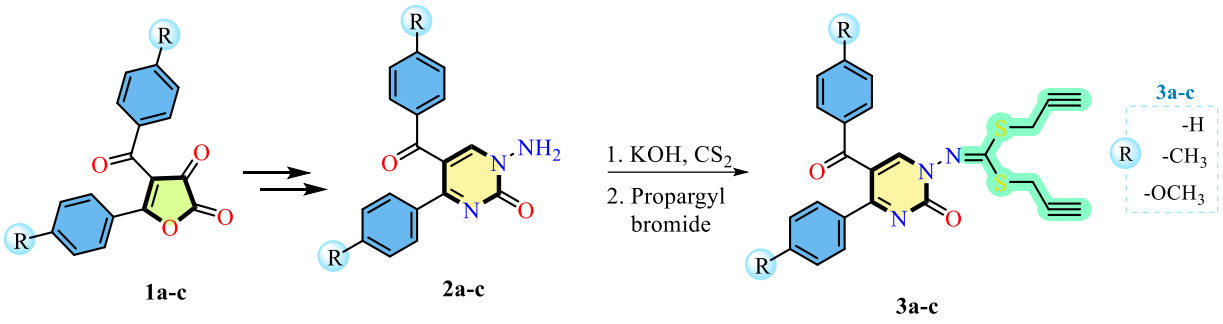
2.3. Molecular Docking Analysis Procedure

Utilizing the DFT/B3LYP theory/functional and 6-311++G(d,p) basis set with the Gaussian 09W package [20] and Gauss View 5.0 interface [21] programs, the optimized structures of the **3a**, **3b**, and **3c** molecules were determined in the gas phase. Using AutoDock Vina [22], the ensuing in silico molecular docking calculations were carried out.

3. Results and Discussion

3.1. Chemistry

We report here the synthesis and characterization of dipropargyl substituted pyrimidines from the *N*-amino pyrimidines (**2a-c**). Compounds **2a-c** was prepared from 2,3-furandiones derivatives by a two-step synthesis process [13-17]. The target compounds were obtained from the reaction of **2a-**c with carbon disulfide and propargyl bromide via one pot synthesis as shown in the Scheme 1.



Scheme 1. Synthesis of imidodithiocarbonates compounds **3a-c**

The structures of the obtained imidodithiocarbonates **3a-c** were confirmed by the ^{1}H, ^{13}C NMR, IR spectra, and elemental analysis data. In particular, the signals of protons of the dipropargyl substituent in compounds **3a-c**, are observed methylene (-CH_2-) at around 4.04-3.84 ppm and acetylenic (≡CH) at about 2.18-2.39 ppm in the ^{1}H NMR spectra. The formation of imidodithiocarbonates **3a-c** was also verified by the signals of the carbon atom of N=C-S groups at 176.08, 175.74, 175.50 ppm, respectively, in ^{13}C NMR spectra. The absorption bands of imidodithiocarbonate (C-S-C) fragment at 1234 cm^{-1} (**3a**), 1269 cm^{-1} (**3b**), 1256 cm^{-1} (**3c**) are observed in the IR spectra of compounds **3a-c**.

3.2. Antioxidant Activity

To verify the theoretical work, all the synthesized compounds were assayed for their $ABTS^{\bullet+}$ and $DPPH^{\bullet}$ scavenging activities. $ABTS^{\bullet+}$ and $DPPH^{\bullet}$ scavenging activities of the compounds were compared with representative standard of Trolox (Table 1). All compounds exhibited good to moderate antioxidant activity. **3c** compound has the highest DPPH and ABTS radical scavenging abilities with SC_{50} values ranging from 0.014±0.008 mg/mL to 0.173±0.018 mg/mL, respectively.

Table 1. DPPH and ABTS radical scavenging activities of compounds

Compounds and standard	DPPH[a] (SC_{50}, mg/mL)	ABTS[a] (SC_{50}, mg/mL)
3a	0.027±0.007	0.345±0.025
3b	0.030±0.001	0.347±0.015
3c	0.014±0.008	0.173±0.018
Trolox	0.002±0.000	0.021±0.007

[a]: Mean ± standard deviation.

3.3. Computational Analyses

3.3.1. Mep Analysis

The relative reactivity sites in a species for nucleophilic and electrophilic attack are predicted by the molecular electrostatic potential (MEP) [23, 24]. By employing the optimized structures with the B3LYP/6-311G++(d,p) basis set, the DFT calculation was used to calculate the MEP surface analysis

of the molecules. Figure 1 shows the mapped electrostatic potential surfaces of the chemicals under study. The compounds' color codes for **3a**, **3b**, and **3c** range from -6.889e-2 to 6.889e-2, -7.126e-2 to 7.126 eV and -7.085e-2 to 7.085e-2, respectively. The MEP structure's red and blue colors denote regions that are more electron-rich and electron-poor, respectively. The chemicals exhibit definite polarization effects. In the MEP, the electronegative atoms (oxygen, nitrogen, and sulfur) are localized over the negative potential regions, whereas the electro-positive atoms (hydrogen) are localized over the positive potential regions.

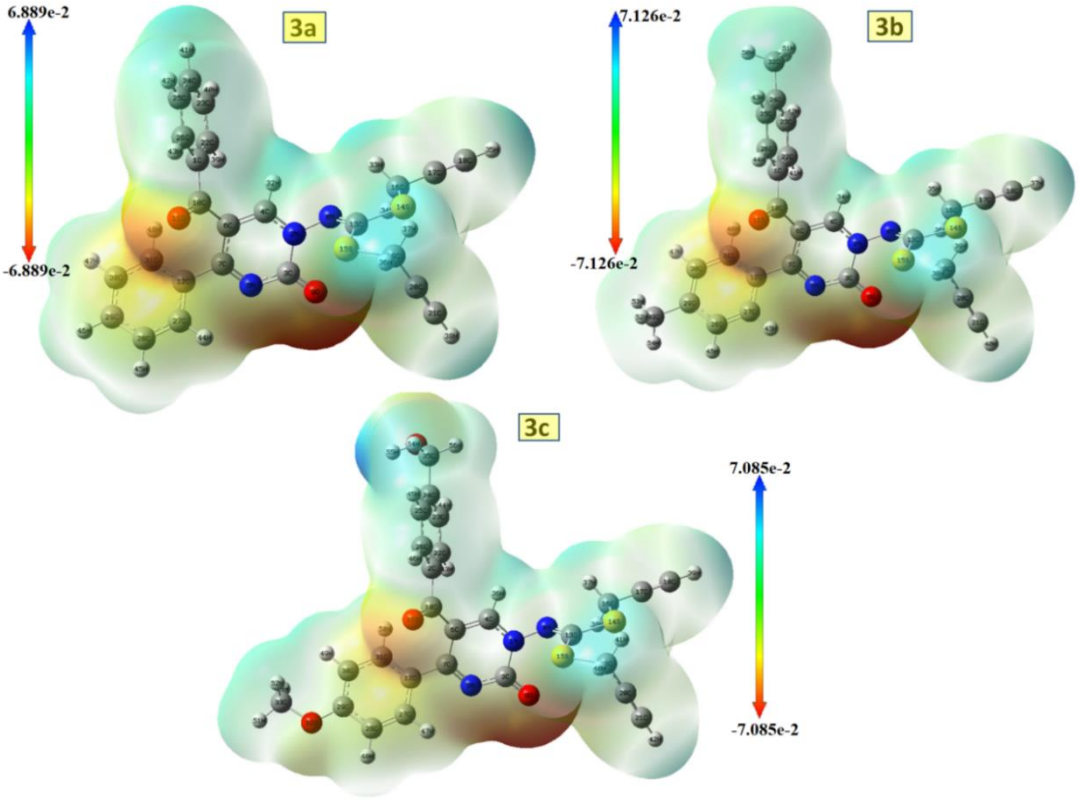


Figure 2. The MEP surfaces of **3a-c** molecules

3.3.2. Frontier Molecular Orbital Analysis

The value of HOMO and LUMO energy can be used to determine a molecule's capacity for both electron donation and reception. These molecular orbitals are essential for understanding biological mechanisms, luminescence, photochemical reactions, quantum chemistry, and electrical and optical characteristics [25-28].

Table 2. The HOMO-LUMO energies and related parameters of **3a**, **3b** and **3c** molecules

Parameters (eV)	**3a**	**3b**	**3c**
E_{LUMO} (eV)	-2.204	-2.096	-2.177
E_{HOMO} (eV)	-6.619	-6.487	-6.199
Energy bandgap $\lvert E_{HOMO}- E_{LUMO}\rvert$	4.415	4.391	4.021
Ionization potential ($I = -E_{HOMO}$)	6.619	6.487	6.199
Electron affinity ($A = -E_{LUMO}$)	2.204	2.096	2.177
Chemical hardness ($\eta = (I-A)/2$)	2.208	2.195	2.011
Chemical softness ($\zeta = 1/2\eta$)	0.226	0.228	0.249
Electronegativity ($\chi = (I+A)/2$)	4.412	4.292	4.188
Chemical potential ($\mu = -(I+A)/2$)	-4.412	-4.292	-4.188
Electrophilicity index ($\omega = \mu^2/2\eta$)	4.408	4.194	4.362
Max. Charge transfer index (ΔNmax.)	1.998	1.955	2.083

The energy gap of the frontier molecular orbital supports the idea that the structure is stable. FMOs also provide information regarding a molecule's chemical reactivity and kinetic stability. The FMOs also aid in anticipating an examined molecule's most reactive location. HOMO and LUMO orbitals have predicted energies of -6.619 and -2.204 eV for **3a**, -6.487 and -2.096 eV for **3b** and -6.199 and -2.177 eV for **3c**, respectively. The energy gap between E_{HOMO} and E_{LUMO} of the aforementioned organic compounds were discovered to be 4.415, 4.391 and 4.021 eV for **3a**, **3b** and **3c**, respectively. The HOMO-LUMO distributions of the compounds were depicted in Figure 2.

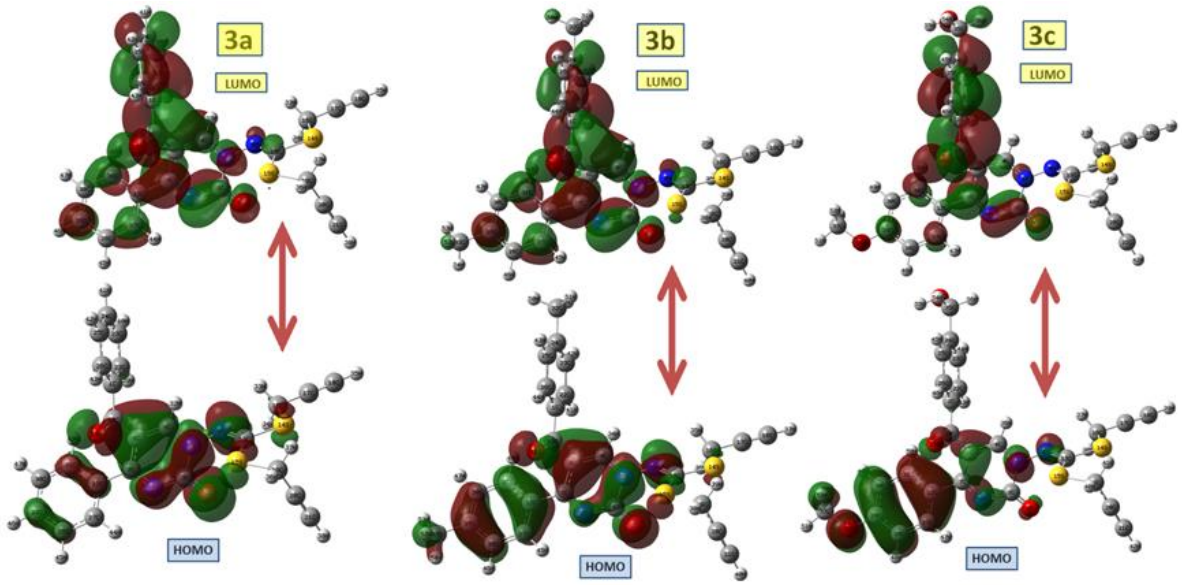


Figure 2. The HOMO and LOMO distributions of **3a, 3b** and **3c** molecules

Additionally, the compounds' chemical reactivity properties such as ionization potential, electron affinity, chemical hardness and softness, electronegativity, chemical potential, electrophilicity index and maximum charge transfer index parameters were calculated with the help of energy of HOMO and LUMO orbitals and tabulated as in Table 2.

3.3.3. Molecular Docking Analysis

In this section, the ability of **3a**, **3b** and **3c** molecules to inhibit the antioxidant receptor PDB: 1HD2 protein was investigated by molecular docking method. For molecular docking, Dr. AutoDock Vina [22], a free program developed by Oleg Trott and his team, was used. The processes and results can be briefly examined as follows:

- The 3D structure of the PDB: 1HD2 protein [29] was obtained from the RCSB (Protein Data Bank) [30], and the necessary preparations were made with the Discover Studio Visualizer 4.0 (DSV 4.0) software [31], such as cleaning the water atoms in the protein and deleting the other cofactor structure.
- Human peroxiredoxin 5 (PRDX5) is a thioredoxin reductase that lowers peroxynitrite, alkyl hydroperoxides, and H2O2 (PDB code: 1HD2). A unique kind of mammalian thioredoxin peroxidase called PRDX5 is found cellularly in the cytosol, peroxisomes, and mitochondria. In terms of functionality, PRDX5 has been connected to cellular signal transduction as well as antioxidant protection mechanisms [32,33].
- The optimizations of **3a**, **3b**, and **3c** molecules were performed with quantum mechanical computation (DFT/B3LYP/6-311++G(d,p)) in the Gaussian 09W package program [20] and recorded in PDB and PDBQT formats.
- The active sites of 1HD2 protein were determined as LEU149, THR147, GLN133, ARG127, SER118, SER115, ASP113, LYS93, GLU91, ALA90, GLN68, GLY66, ALA64, LYS63,

CYS47, GLY46, PRO45, THR44, and PRO40. Accordingly, the grid parameters of the protein were taken as follows: x_dim=22, y_dim=32, z_dim=28, space=0.375 Å, x_cent=9.612, y_cent=41.444, z_cent=34.948. Therefore molecular docking computations were performed.

- As a result of the docking, the **3a** molecule binds to the protein with -7.9 kcal/mol binding energy, 1.61904 μM inhibition constant and 1 hydrogen bond, the **3b** molecule binds to the protein with -8.4 kcal/mol binding energy, 0.696234 μM inhibition constant and 2 hydrogen bonds. Finally, it was observed that the **3c** molecule binds to the protein with a binding energy of -7.4 kcal/mol, an inhibition constant of 3.76496 μM, and 2 hydrogen bonds. Here, the inhibition values of the interactions were calculated similar to the studies in the literature [34-36], depending on the binding values.
- According to the obtained results, it was determined that the **3b** molecule has the potential to better inhibit the antioxidant receptor PDB: 1HD2 than **3a** and **3c** molecules. For this interaction 3D (a) and 2D (b) forms were displayed in Figure 3. Additionally in Figure 3 (b), the bond lenghts were shown. In addition, the placement of the **3b** molecule in the active site of the 1HD2 protein was shown in Figure 4 (a). The optimization structure of **3b** molecule was depicted in Figure 4 (b).
- For **3a**+PDB:1HD2 and **3c**+PDB:1HD2 interactions, the obtained 3D forms were depicted in Figure 5.

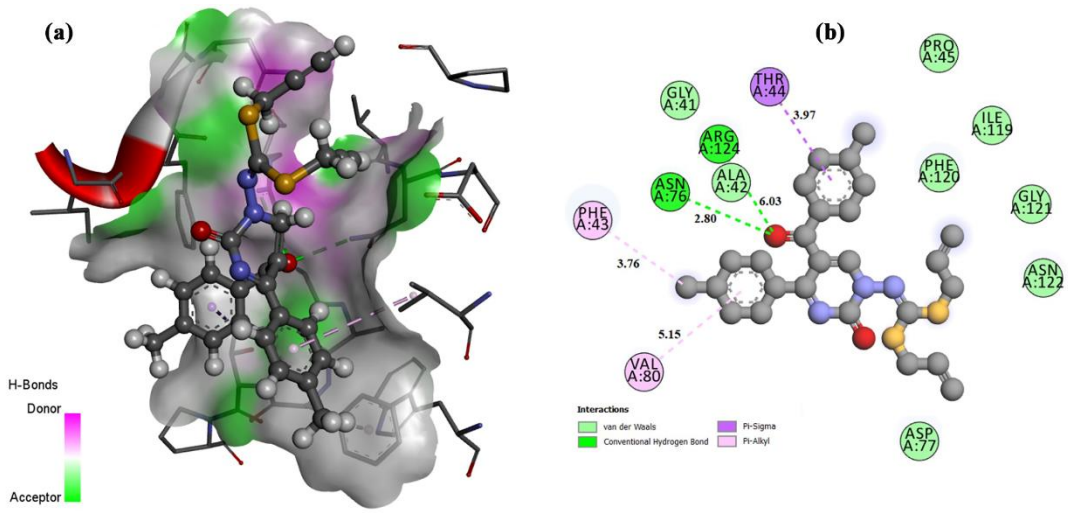


Figure 3. The 3D and 2D forms of **3b**+PDB:1HD2 interaction

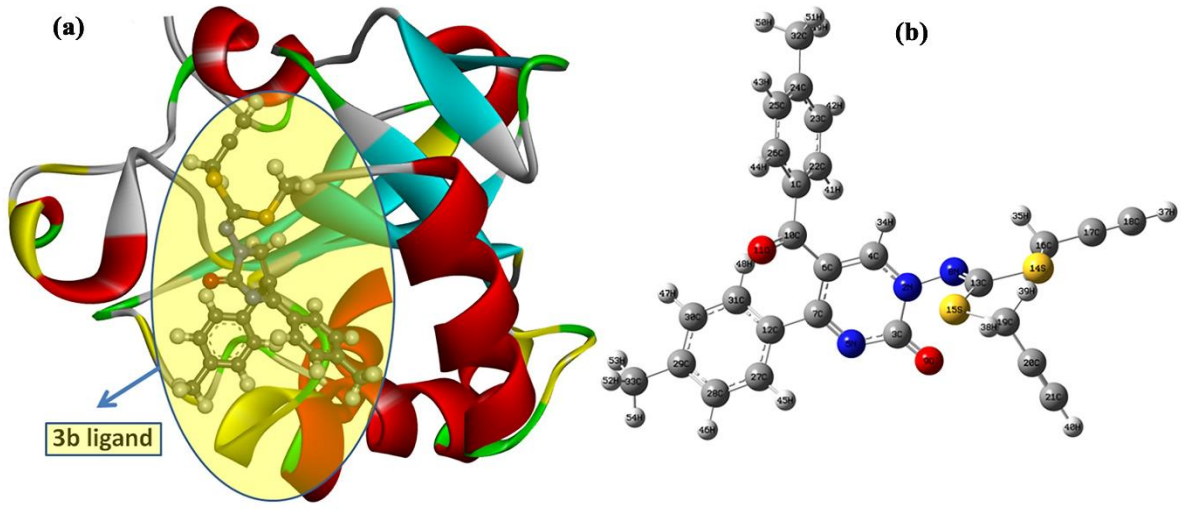


Figure 4. The placement of **3b** molecule in the active site of the protein (a) and the optimization of **3b**

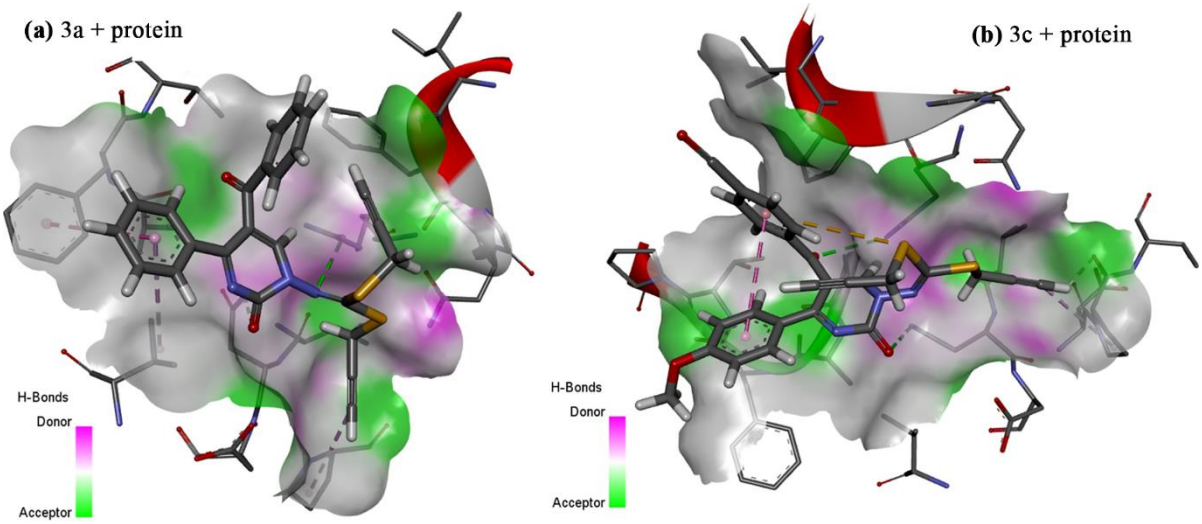


Figure 5. The 3D forms of **3a**+HD2 and **3c**+HD2 interactions

4. Conclusion

A suitable route has been proposed to obtain new imidodithiocarbonate derivatives containing pyrimidine ring from the reaction of potassium dithioimidocarbonate, which is formed as an intermediate from the interaction of *N*-amino pyrimidine with CS_2 in the presence of KOH, with propargyl bromide in DMF. In antioxidant activity studies using ABTS and DPPH methods, it was observed that 3c exhibited a better antioxidant capacity than other compounds. As shown in Scheme 1, when the other substituents of the pyrimidine ring were the same, the trend in the antioxidant activity of the three different imidodithiocarbonates was as follows: -Ph-OCH_3 >-Ph >-Ph-CH_3. These results may be related to the electron-donating ability and inductive effect of -OCH_3 groups. The molecular docking mechanism between the antioxidant target-PDB: 1HD2 and the **3a**, **3b**, and **3c** ligands was examined in this paper using Autodock Vina. According to the results, the **3b** molecule has a better inhibition than the **3a** and **3c** molecules because it is better docked to the target receptor.

Acknowledgements

The authors are very thankful to KAYÜ BAP (FHD-2022-1095) for providing financial support and Prof. Dr. Fatih Ucun for his helpful contribution for Gaussian calculations.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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