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Synthesis, Characterization, Investigation of Biological Activity, Docking Studies and Spectroscopic Properties of Hydrazone Compounds Containing Different Substituents

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Abstract

To assess electronic absorption spectra, molecular docking and the antibacterial activity, new twelve hidrazone compounds having different substituents and in different positions were synthesized and characterized. HOMO-LUMO energies and theoretical electronic spectra of synthesized compounds were computed via Gaussian 09 software. Global reactivity descriptors were computed from HOMO-LUMO energies. 1JXA protein was used molecular docking studies structure. It was selected *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATTC 29212 (as negative bacteria), *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 (as gram positive).

The compound 3 was observed to be the most effective against propagations of *E.Coli*. Similarly, compounds 7 and 9 were found to be the most effective against the reproduction of *P.aeruginosa*. The most powerful compound against the growth of *E.faecalis* was ascertained to be 7.

Keywords: Electronic absorption spectra, hydrazone, antibacterial activity, Docking Studies

Introduction

Hydrazone derivative compounds are widely used in chemistry. These compounds have both biological activity and light emission diode (LED) [1-4], and chemosensor properties [5-10]. It is quite popular in theoretical and X-ray studies of this class of compound [11-13]. To understand behaviour of a compound in solution is important to know how to act in a chemical reaction. Action in solvent of a dissolved compound is due to solute-solvent interactions. There are lots of article regarding this issue [14-16].

This compound class is also effective on enzymes. It has studied the monoamine oxidase enzyme of hydrazone derivatives. It has been shown that hydrazone derivatives interact with monoamine oxidase, and this interaction was confirmed with docking programs [17-21]. Also the activity of some hydrazone derives on cyclooxygenase 1 and on cyclooxygenase 2 have been investigated. These enzymes are responsible for inflammation [22-26].

Besides the properties mentioned above, the antibacterial activity of hydrazone derivatives has also been studied extensively. Several literatures on antibacterial activity are given below.

Souza et al. [27] investigated antibacterial and cytotoxic activity of biflorin based hydrazine. Anacona et al.[28] studied activity of diacetylpyridine bis(hydrazone)derivative. Aslan et al. [29] examined efficient of sulfonamides and sulfonyl hydrazones on bacteria. Soayed et al. [30] investigated antibacterial effect of barbturic-hydrazone complex. Bacteria have developed resistance very quickly against antibiotics. There are a lot of article about this topic [31-33]

New trend in drug development studies is to analyse of the chemical substance synthesized in the processing computer environment. Presently available in the relevant articles on this subject [34, 35]

Therefore, in our study, antibacterial activity of the title compounds has been studied. It is used software to identify the possible regions where ligands can bind to proteins. Such software allows predicting the binding site. For the detection of the regions affected by the compounds, theoretical calculation has been done in this study.

This study was synthesized and characterized twelve hydrazone derivatives. These compounds were synthesized for the first time by us. It was investigated different substituents' effect in DMSO with UV-Vis device of these compounds. Finally, it was observed antibacterial activity and Docking properties of the title compounds. For the title compounds are synthesized for the first time by us, this work is original.

Experimental Details

Benzaldehydes (3-F, 4-F, 2-Cl, 4-Cl, 4-CH₃, 4-NO₂) and thiosemicarbazide were from Merck. 3-Cl, 2-CH₃, 3-CH₃, and 2-NO₂ benzaldehydes were from Aldrich, and 2-F benzaldehyde was purchased from Sigma-Aldrich. 3-NO₂ benzaldehyde was obtained from Fluka Chemica. Genta (Ibrahim Ulagay), Mueller Hinton Agar and Mueller Hinton Broth (Oxoid) were used as test compound and to produce bacteria. Melting points were determined on a Gallenkamp melting point apparatus. IR spectra was recorded on a Mattson 1000 Fourier transform-infrared (FT-IR) Spectrometer using KBr pellets in the range from 4000 to 400

cm^{-1} . A Varian-Gemini 400 MHz spectrometer and a Perkin Elmer lambda 35 device were used to take NMR spectra and UV–Visible spectra respectively.

General Synthesis Scheme

The procedures for the synthesis of compounds are the same as described in our previous study [36]. Synthesis scheme and chemical structure of title compounds are given in Fig.1.

Figure 1

Quantum chemical calculations were made using Gaussian 09 software [37]. Autodock Vina [38] and Discover Studio Visualizer 4.5 programs [39] were used for docking studies.

Antibacterial activity

Antibacterial activities of the compounds were tested against Gram-positive bacteria (*Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212) and Gram-negative bacteria (*Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853) by using the microdilution broth method. The test solution and reference compounds in the test medium furnished the required concentration ranging from $512 \mu\text{g mL}^{-1}$ to $1 \mu\text{g mL}^{-1}$. The microtiter plates were incubated at 35°C and read visually after 24 h. The minimum inhibitor concentration (MIC) values were recorded as the lowest concentrations of the substances that had no visible turbidity. DMSO was used as negative control. Gentamicin was used as the reference compound for antibacterial activity.

Results and discussion

A list of synthesized compounds in this study are given in and Table 1. The FT-IR spectra of used aromatic aldehydes showed absorption bands at $1686\text{--}1710\text{ cm}^{-1}$ for their $\text{C}=\text{O}$ groups. If this band is invisible in the reaction medium, it confirms the conversion of the $-\text{CHO}/>\text{C}=\text{O}$ group to the $-\text{CH}=\text{N}-$ group. Secondly, the absence of the $3490\text{--}3234\text{ cm}^{-1}$ band of NH_2 in thiosemicarbazone and the formation of the $1546\text{--}1623\text{ cm}^{-1}$ band $\text{C}=\text{N}$ in the thiazole ring indicate the end of the reaction.

Moreover, the ^1H -NMR spectra for thiazole derivatives showed bands approximately at $1.46\text{--}1.53\text{ ppm}$ ($-\text{CH}_3$), $2.30\text{--}2.66\text{ ppm}$ (cyclobutane ring), $6.22\text{--}6.78\text{ ppm}$ ($=\text{CH}-\text{S}$ in thiazole ring), $7.00\text{--}8.17\text{ ppm}$ (aromatics) and $7.75\text{--}8.17\text{ ppm}$ (azomethine). In the last step of the reaction, where thiazole derivatives converted their 2-chloroacetyl chloride derivative, the visibility of 1721 cm^{-1} band implies the completion of the reaction. The ^1H -NMR spectra for hydrazone derivatives occurring in the end of this reaction showed approximately 1.58 ppm ($-\text{CH}_3$), $2.48\text{--}2.71\text{ ppm}$ (cyclobutane ring), $4.83\text{--}4.86\text{ ppm}$ ($-\text{CH}_2\text{--Cl}$), $6.81\text{--}6.98\text{ ppm}$ ($=\text{CH}-\text{S}$ in thiazole ring), $7.01\text{--}8.44\text{ ppm}$ (aromatics), and $8.89\text{--}9.04\text{ ppm}$ (azomethine). Detailed spectral data for each compound are given below. As a representative NMR Spectra, ^1H NMR and ^{13}C NMR spectrums for compound **1** are given **Fig. 2(a)**, and **Fig. 2(b)**, respectively.

Table 1

2-chloro-N'-(2-fluorobenzylidene)-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)acetohydrazide (1)

Orange crystal. Yield % 50. M.p.: $180\text{ }^\circ\text{C}$, IR (KBr, ν , cm^{-1}): $2970\text{--}2853$ (aliphatics), 1722 ($\text{C}=\text{O}$), 1540 ($-\text{C}=\text{N}$ -thiazole ring), 734 ($-\text{CH}_2\text{--Cl}$). ^1H -NMR (CDCl_3 , TMS, δ ppm): 1.58

(s, 3H, -CH₃), 2.53-2.66 (m, 4H, -CH₂- cyclobutane ring), 3.77-3.86 (quint, $j=8.4$ Hz, 1H, >CH-), 4.84 (s, 2H -CH₂-Cl), 6.940-6.94 (d, 1H, $j=0.7$ Hz, =CH-S, far allylic effect), 7.06-7.85 (m, 9H, aromatics), 9.09 (s, 1H, azomethine). ¹³C NMR (CDCl₃, TMS, δ ppm): 167.85, 163.34, 157.46, 143.73, 132.82, 132.73, 128.41, 127.33, 125.55, 124.93, 124.76, 124.73, 116.43, 116.23, 43.76, 40.96, 39.12, 31.08, 30.19.

2-chloro-N'-(3-fluorobenzylidene)-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)acetohydrazide (2)

White crystals. Yield: % 59. M.p.: 152 °C. IR (KBr, ν , cm⁻¹): 2980-2863 (aliphatics), 1718 (C=O), 1540 (-C=N-, thiazole ring), 730 (-CH₂-Cl). ¹H-NMR (CDCl₃, TMS, δ ppm): 1.59 (s, 3H, -CH₃), 2.54-2.60 (m, 2H, -CH₂-, cyclobutane ring), 2.63-2.68 (m, 2H, -CH₂-, cyclobutane ring) 3.77-3.86 (quint, $j=8.8$, 1H, >CH-), 4.85 (s, 2H, -CH₂-Cl), 6.91-6.92 (d, $j=0.7$ Hz, 1H, =CH-S, far allylic effect), 7.01-7.36 (m, 9H, aromatics), 9.073-9.074 (d, $j=0.7$ Hz, 1H, azomethine). ¹³C NMR (CDCl₃, TMS, δ ppm): 167.88, 164.46, 156.93, 152.46, 149.04, 136.09, 136.02, 130.73, 130.64, 128.54, 125.69, 124.90, 118.07, 113.72, 112.30, 43.83, 41.20, 39.05, 30.98, 30.40.

2-chloro-N'-(4-fluorobenzylidene)-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)acetohydrazide (3)

Yellow crystals. Yield: % 72. M.p.: 140 °C. IR (KBr, ν , cm⁻¹): 2980-2870 (aliphatic), 1722 (C=O), 1538 (-C=N-, thiazole ring), 737 (-CH₂-Cl). ¹H-NMR (CDCl₃, TMS, δ ppm): 1.58 (s, 3H, -CH₃), 2.53-2.58 (m, 2H, -CH₂- cyclobutane ring), 2.63-2.68 (m, 2H, -CH₂-

cyclobutane ring) 3.75-3.84 (quint, $j=8.8$ Hz, 1H, $>CH-$), 4.83 (s, 2H, $-CH_2-Cl$), 6.88 (s, 1H $=CH-S$, far allylic effect), 7.04-7.46 (m, 9H, aromatics), 9.14 (s, 1H, azomethine). ^{13}C NMR ($CDCl_3$, TMS, δ ppm): 167.72, 165.88, 163.37, 156.65, 155.43, 152.56, 150.16, 130.09, 130.00, 128.52, 125.60, 124.94, 116.40, 116.18, 111.93, 41.25, 30.96, 30.41.

2-chloro-N'-(2-chlorobenzylidene)-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)acetohydrazide (4)

Yellow crystals. Yield: % 55. M.p.: 187 °C. IR (KBr, ν , cm^{-1}): 2962-2859 (aliphatics), 1722 (C=O), 1601 ($-C=N-$, thiazole ring), 766 ($-CH_2-Cl$) 1H -NMR ($CDCl_3$, TMS, δ ppm): 1.57 (s, 3H, $-CH_3$), 2.52-2.57 (m, 2H, $-CH_2-$ cyclobutane ring), 2.63-2.68 (m, 2H, $-CH_2-$ cyclobutane ring) 3.77-3.86 (quint, $j=8.8$ Hz, 1H, $>CH-$), 4.85 (s, 2H, $-CH_2-Cl$), 6.88 (s, 1H, $=CH-S$, far allylic effect), 7.13-7.96 (m, 9H, aromatics), 9.38 (s, 1H, azomethine). ^{13}C NMR ($CDCl_3$, TMS, δ ppm): 167.89, 157.24, 154.82, 152.20, 146.72, 135.69, 132.01, 131.39, 130.31, 128.46, 127.44, 127.32, 125.57, 124.90, 112.73, 43.78, 40.84, 39.24, 31.24, 30.24.

2-chloro-N'-(3-chlorobenzylidene)-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)acetohydrazide (5)

Yellow crystals. Yield: % 42. M.p.: 166 °C. IR (KBr, ν , cm^{-1}): 2980-2863 (aliphatic), 1718 (C=O), 1535 ($-C=N-$, thiazole ring), 735 ($-CH_2-Cl$) 1H -NMR ($CDCl_3$, TMS, δ ppm): 1.58 (s, 3H, $-CH_3$), 2.53-2.55 (m, 2H, $-CH_2-$ cyclobutane ring), 2.56-2.64 (m, 2H, $-CH_2-$ cyclobutane ring), 3.77-3.86 (quint, $j=8.8$ Hz, 1H, $>CH-$), 4.85 (s, 2H, $-CH_2-Cl$), 6.921-6.923 (d, 1H, $=CH-S$, far allylic effect $j=0.7$ Hz), 7.18-7.59 (m, 9H, aromatics), 8.85 (s, 1H,

azomethine). ^{13}C NMR (CDCl_3 , TMS, δ ppm): 167.87, 157.06, 152.40, 148.68, 135.61, 135.22, 131.14, 130.35, 128.54, 127.29, 126.67, 125.69, 124.88, 112.43, 43.82, 41.18, 39.06, 30.99, 30.35.

2-chloro-N'-(4-chlorobenzylidene)-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)acetohydrazide (6)

Brown crystals. Yield: % 44. M.p.: 156 °C. IR (KBr, ν , cm^{-1}): 2980-2848 (aliphatic), 1722 (C=O), 1488 (C=N-, thiazole ring), 767 (CH₂-Cl). ^1H -NMR (CDCl_3 , TMS, δ ppm): 1.58 (s, 3H, -CH₃), 2.54-2.57 (m, 2H, -CH₂- cyclobutane ring), 2.58-2.68 (m, 2H, -CH₂- cyclobutane ring), 3.76-3.84 (quint, $j=8.8$ Hz, 1H, >CH-), 4.85 (s, 2H, -CH₂-Cl), 6.890-6.892 (d, 1H, =CH-S far allylic effect $j=0.7$ Hz), 7.18-7.38 (m, 9H, aromatics), 9.15 (s, 1H, azomethine). ^{13}C -NMR (CDCl_3 , TMS, δ ppm): 167.80, 156.71, 155.34, 152.57, 149.63, 137.19, 132.30, 129.39, 129.22, 128.54, 125.62, 124.93, 112.04, 43.83, 41.25, 39.02, 30.96, 30.44.

2-chloro-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)-N'-(2-nitrobenzylidene)-acetohydrazide (7)

Yellow crystals, Yield: 11%, M.p: 189 °C. IR (KBr, ν , cm^{-1}): 2973-2866 (aliphatics), 1722 (C=O), 1591 (C=N-, thiazole ring), 733(-CH₂-Cl). ^1H -NMR (CDCl_3 , TMS, δ ppm): 1.57 (s, 3H, -CH₃), 2.54-2.65 (m, 4H, -CH₂- cyclobutane ring), 3.78-3.86 (quint, $j=8.8$ Hz, 1H, >CH-), 4.79 (s, 2H, -CH₂-Cl), 6.979-6.981 (d, $j=0.7$ Hz, 1H, =CH-S, far allylic effect), 7.01-8.05 (m, 9H, aromatics), 9.25 (s, 1H, azomethine). ^{13}C -NMR (CDCl_3 , TMS, δ ppm): 167.92,

157.99, 152.29, 144.92, 133.69, 131.15, 129.22, 128.79, 128.40, 125.49, 125.06, 124.93, 113.46, 43.42, 40.86, 39.15, 31.04, 30.36.

2-chloro-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)-N'-(3-nitrobenzylidene)-acetohydrazide (8)

Yellow crystals, Yield: 75 % M.p: 193 °C. IR (KBr, ν , cm^{-1}): 2977-2859 (aliphatics), 1715 (C=O), 1533 (-C=N-, thiazole ring), 747 (-CH₂-Cl). ¹H-NMR (CDCl₃, TMS, δ ppm): 1.59 (s, 3H, -CH₃), 2.56-2.67 (m, 4H, -CH₂- cyclobutane ring), 3.784-3.873 (quint, $j=8.8$ Hz, 1H, >CH-), 4.86 (s, 2H, CH₂-Cl), 6.95 (s, 1H, =CH-S), 7.16-8.44 (m, 9H, aromatics), 9.14 (s, 1H, azomethine). ¹³C-NMR (CDCl₃, TMS, δ ppm): 167.91, 157.19, 152.46, 148.94, 147.11, 135.67, 133.69, 130.19, 128.54, 125.62, 125.37, 124.87, 122.25, 112.69, 43.59, 41.18, 39.10, 30.98, 30.45.

2-chloro-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)-N'-(4-nitrobenzylidene)-acetohydrazide (9)

Orange crystals Yield: 49%, M.p: 175 °C. IR (KBr, δ , cm^{-1}): 2980-2859 (aliphatics), 1729 (C=O), 1536 (-C=N-, thiazole ring), 636 (-CH₂-Cl). ¹H-NMR (CDCl₃, TMS, δ ppm): 1.59 (s, 3H, -CH₃), 2.55-2.61 (m, 2H, -CH₂- cyclobutane ring), 2.65-2.71 (m, 2H, -CH₂- cyclobutane ring), 3.77-3.86 (quint, $j=8.4$ Hz, 1H, >CH-), 4.86 (s, 2H, -CH₂-Cl), 6.93 (s, 1H, =CH-S), 7.20-8.22 (m, 9H, aromatics), 9.38 (s, 1H, azomethine). ¹³C-NMR (CDCl₃, TMS, δ ppm): 168.02, 156.78, 155.10, 152.67, 149.16, 147.27, 139.80, 128.59, 125.67, 124.93, 124.30, 112.28, 43.57, 41.29, 39.04, 30.91, 30.57.

2-chloro-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)-N'-(2-methylbenzylidene)acetohydrazide (10)

Brown crystals, Yield: % 65, M.p: 141 °C. IR (KBr, ν , cm^{-1}): 2966-2863 (aliphatics), 1722 (C=O), 1578 (-C=N-, thiazole ring), 732 (-CH₂-Cl). ¹H-NMR (CDCl₃, TMS, δ ppm): 1.58 (s, 3H, -CH₃), 2.25 (s, 3H, -CH₃), 2.51-2.57 (m, 2H, -CH₂- cyclobutane ring), 2.61-2.66 (m, 2H, -CH₂- cyclobutane ring), 3.76-3.83 (quint, $j=8.8$ Hz, 1H, >CH-), 4.85 (s, 2H, -CH₂-Cl), 6.90-6.91 (d, $j=0.7$ Hz, 1H, =CH-S, far allylic effect), 7.14-7.78 (m, 9H, aromatics), 9.35 (s, 1H, azomethine). ¹³C-NMR (CDCl₃, TMS, δ ppm): 167.78, 156.62, 152.24, 150.67, 138.45, 131.79, 131.26, 131.05, 128.49, 127.09, 126.57, 125.63, 124.87, 112.14, 44.05, 40.93, 39.20, 31.26, 30.22, 19.65.

2-chloro-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)-N'-(3-methylbenzylidene)acetohydrazide: (11)

Red crystals, Yield: % 68, M.p: 120 °C. IR (KBr, ν , cm^{-1}): 2977-2859 (aliphatics), 1722 (C=O), 1535 (-C=N-, thiazole ring), 743 (-CH₂-Cl). ¹H-NMR (CDCl₃, TMS, δ ppm): 1.59 (s, 3H, -CH₃), 2.39 (s, 3H, -CH₃), 2.53-2.59 (m, 2H, -CH₂- cyclobutane ring), 2.62-2.67 (m, 2H, -CH₂- cyclobutane ring), 3.71-3.86 (quint, $j=8.4$ Hz, 1H, >CH-), 4.87 (s, 2H, -CH₂-Cl), 6.915-6.917 (d, $j=0.7$ Hz, 1H, =CH-S, far allylic effect), 7.16-7.41 (m, 9H, aromatics), 8.89 (s, 1H, azomethine). ¹³C-NMR (CDCl₃, TMS, δ ppm): 167.75, 157.09, 155.33, 152.34, 151.23,

138.81, 133.63, 132.18, 128.99, 128.49, 128.34, 125.63, 124.92, 112.35, 43.96, 41.17, 39.05, 31.06, 30.20, 21.59.

2-chloro-N-(4-(3-methyl-3-phenylcyclobutyl)thiazol-2-yl)-N'-(4-methylbenzylidene)acetohydrazide (12)

Yellow crystals, Yield: % 80, M.p: 161 °C. IR (KBr, ν , cm^{-1}): 2984-2859 (aliphatics), 1714 (C=O), 1488 (-C=N-, thiazole ring), 733 (-CH₂-Cl). ¹H-NMR (CDCl₃, TMS, δ ppm): 1.58 (s, 3H, -CH₃), 2.40 (s, 3H, -CH₃), 2.52-2.58 (m, 2H, -CH₂-, cyclobutane ring), 2.62-2.67 (m, 2H, -CH₂- cyclobutane ring), 3.76-3.85 (quint, $j=8.8$ Hz, 1H, >CH-), 4.85 (s, 2H, -CH₂-Cl), 6.88-6.89 (d, $j=0.732$ Hz, 1H, =CH-S, far allylic effect), 7.17-7.40 (m, 9H, aromatics), 8.973 (s, 1H, azomethine). ¹³C-NMR (CDCl₃, TMS, δ ppm): 167.70, 156.87, 152.43, 151.55, 141.80, 130.98, 129.81, 128.50, 128.11, 125.58, 124.94, 112.05, 43.96, 41.19, 39.02, 31.01, 30.28, 21.80.

Figure 2a

Figure 2b

Electronic absorption spectra

Compounds in this study have the same molecular skeleton with different substituents located on the benzene ring and same substituents different located on the benzene ring. Electronic absorption spectra were investigated in DMSO. The spectra of the different substituents attached to the same position were plotted on the same graph to examine the spectra more conveniently. Bands at 280-360 and 450-550 nm are attributed to $n \rightarrow \pi^*$ and to π

$\rightarrow\pi^*$ transitions and these are the result of electronic transitions of azo-hydrazo tautomer forms [40]. In this study, the absorption peaks at 420-580 nm are probably related to N-N=CH group.

As can be seen in Fig. 3, Fig.4 and Fig.5, there are wide peaks at 440-580 nm regions for compounds **1**, **2**, and **3**. For the compounds containing F atom in *ortho* and in *para* position, it was observed their absorption wavelength maxima approximately at 513 nm. When F atom is connected in *meta* position on benzene ring, $\lambda_{\max}$ was observed at 471 nm. When Cl substituent is located in *ortho* position, peaks in 420-600 nm regions for compounds were not observed. This effect can be attributed to inductively electron-withdrawing properties of the chlorine atom. If Cl atom located in *meta* and in *para* position in the compounds, a 515 nm absorption peak was observed. We can say that the dominant mesomeric effect in *meta* and in *para* positions for compounds **5** and **6**, and in *meta* and in *para* positions. If methyl group is in *ortho*, *meta* and *para* positions, compounds display similar absorption spectra in 420-600 nm regions. As known, NO₂ group has electron withdrawing character. Compounds, nitro group connected to their benzene rings, absorption peaks shifted blue region and were observed at 350-450 nm for compounds **7**, **8**, and **9**.

Figure 3, Figure 4, figure 5

Electronic spectra were calculated in terms of time-dependend density functional theory (TD-SCF) and presented in Fig. 6.

The experimental and calculated electronic spectrum values of the compounds are given in Table 2. Because only one molecule is calculated in the theoretical calculations. In experimental electronic spectra the number of molecule is more than one. In theoretical

calculations the interaction of molecules does not participate in the calculation. So there are differences between the results

Table 2

Antibacterial activity

The compound **1** did not show any effect against *E. coli* as seen in Table 3. If fluorine atom is shifted down to *para* position, the MIC value of the compound was measured as 1 µg/mL. The compound **3** was observed to be the most effective against propagations of *E. Coli*. Similarly, compounds **7** and **9** were found to be the most effective against the reproduction of *P. aeruginosa*. The most powerful compound against the growth of *E. faecalis* was ascertained to be **7**. The MIC values of compounds are summarized in Table 3.

Table 3

Analysis of frontier molecular orbitals and global reactivity descriptors

The energies of the HOMO and the LUMO energy are calculated using B3LYP/6-311 method and the energy gap of the LUMO-HOMO is by taking the energy difference. When the HOMO energy is on localized benzene and thiazole rings and CH₂-Cl group, the LUMO energy are localized benzene ring and CH₂-Cl group for **1** and **3**. For **2**, the HOMO energy is on localized thiazole ring and CH₂-Cl group. The LUMO energy is localized benzene ring and CH₂-Cl group. The HOMO and the LUMO energy diagrams for **1** are given in Fig.7.

Figure 7

Energies of frontier molecular orbitals (E_{HOMO} , E_{LUMO}), have been used to calculate global reactivity descriptors. Electronegativity, Chemical potential, Global hardness, Global softness,

electrophilicity index were calculated according to literature [41-44]. The global reactivity descriptors of all the compounds are given Table 4.

The highest compound of electronegativity value was calculated as compound and the lowest compound was compound 12 (Table 4). Electronegativity of **9** and **12** were calculated as 7.0783 and 4.1993.

Table 4

Molecular Docking Studies

Crystal structure of *Escherichia coli* organism ((pdb code: 1JKA) is downloaded the Protein Data Bank (<http://www.rcsb.org/pdb>) to use the docking study. Docking studies was made according literature[45]. Results of the docking studies are summarized in Table 5. After the docking process, representation of the compound **1** embedded in the active site of 1JXA receptor is also given in Figure 8. It was taken RMSD value smaller than 2Å [46].

Table 5

During Docking process, the RMSD value of 12 molecules resulting less than 2 Å has shown that 1JXA protein structure might be the right selection for the compounds. The smallest binding affinity has been found as -10.0 kcal/mol for compound **1**.

Figure 9a-figure 9b

As it could be seen in Table 5, it has been seen that ligand **1** with the best binding ligand affinity has binded to the receptor's substrate binding sites with weak non-covalent interactions yet more noticeable with hydrogen bond interactions. As shown in Figure 7b,

while a 1.79Å-long hydrogen bond occurred between PRO377 and the N atom of ligand's triazol ring, between the ligand and PRO377, ILE234, VAL376, TYR25, ARG26, PHE205 there are pi-sigma, pi-pi, pi-alkyl and alkyl bonds occurred. Compounds 4,5,6 and 11 for which no classic hydrogen bonds occurred, binded the receptor with pi-pi, pi-sigma, pi-alkyl and alkyl-alkyl type of other interactions.

It can be stated that all ligands, based on their binding affinities, may be considered as molecules which could constitute potential inhibitor compounds for the 1JXA target protein structure. As a result, these potential inhibitor compounds are promising hope for the future studies followed by next stage activity tests for conformity researches and design of a drug with high selectivity.

Conclusions

Twelve new hydrazone derivative compounds were synthesized and characterized in this study. These compounds were synthesized for the first time by us. Electronic absorption spectra of compounds were investigated in DMSO. The effectiveness of antibacterial activity title compounds against studied bacteria strains was investigated. It was found that the compound **3** was more active than other compounds against *E.coli*. It was observed that the compounds **7** and **8** were more efficient than the other compounds against *P.aeruginosa*. The compound **7** was the most active compound against *E.faecalis*. Finally, docking studies was made to determine the possible bonding site of title molecules to *E.coli*. Many contents, especially compounds, existing in this article are from the Engin YILMAZ's Ph thesis[47].

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Fig. 1. Synthesis scheme for the title compounds.

Fig. 2. (a) ^1H NMR spectrum of compound 1 Fig. 2. (b) ^{13}C NMR spectrum of compound 1

Fig.3. UV-Vis absorption spectra of compounds, 1,4,7,10

Fig.4. UV-Vis absorption spectra of compounds, 2,5,8,11 **Fig.5.** UV-Vis absorption spectra of compounds, 3,6,9,12 **Fig.6.** Electronic spectra of compounds, 1-12 calculated by TD-SCF

Fig. 7. HOMO and LUMO energy diagram for compound 1

Fig. 8. Pictorial representation of the compound 1 embedded in the active site of 1JXA receptor.

Fig. 9(a)

Fig. 9(b)

Fig. 9. Representation of docking results of compound **1** in the active site of 1JXA protein, **a)**3D and **b)**2D

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Table 1. Chemical structures of synthesized compounds in this study.

Entry	R ₁	R ₂	R ₃
1	F	H	H
2	H	F	H
3	H	H	F
4	Cl	H	H
5	H	Cl	H
6	H	H	Cl
7	NO ₂	H	H
8	H	NO ₂	H
9	H	H	NO ₂
10	CH ₃	H	H
11	H	CH ₃	H
12	H	H	CH ₃

Table 2. Calculated and experimental electronic spectra values of compounds

Compound	Calculated (nm)	Experimental (nm)
1	297	313,366 shoulder peak, 526
2	292	311,359 shoulder peak, 492
3	292	306,369 shoulder peak, 526
4	298	317,392 shoulder peak
5	293	316,372 shoulder peak, 534
6	300	310,335 shoulder peak, 527
7	241,296	411
8	241,300	372 shoulder peak, 536
9	264	362
10	300	297 shoulder peak, 515
11	293	303 shoulder peak, 514
12	297	300 shoulder peak, 514

Table 3. The in vitro activities of the compounds and reference drugs (MIC values µg/mL)

Entry	<i>E.coli</i> ATTC 25922	<i>P.aeruginosa</i> ATTC 27853	<i>E.faecalis</i> ATTC 29212	<i>S.aureus</i> ATTC 29213
1	-	2	256	-
2	32	16	32	-

3	1	2	256	-
4	64	4	16	-
5	32	8	32	-
6	-	8	-	-
7	32	1	2	-
8	16	1	128	-
9	16	16	32	-
10	-	16	-	-
11	-	512	512	-
12	32	8	-	-
Gentamicin	2	4	4	2

Table 4. Global reactivity descriptors for the title compounds.

Entry	χ	μ	η	S	ω	HOMO-LUMO gap
1	4.3413	-4.3413	2.2882	0.2185	4.1183	4.5764
2	4.5339	-4.5339	2.2854	0.2188	4.4973	4.5707
3	4.3967	-4.3967	2.2954	0.2178	4.2108	4.5909
4	5.0989	-5.0989	4.1732	0.1198	3.1150	8.3463
5	4.5343	-4.5343	2.2752	0.2198	4.5183	4.5503
6	4.4541	-4.4541	2.2345	0.2238	4.4393	4.4690
7	6.9281	-6.9281	1.3157	0.3800	18.2408	2.6314
8	7.0369	-7.0369	1.2286	0.4070	20.1522	2.4572
9	7.0783	-7.0783	1.1772	0.4247	21.2807	2.3543
10	4.2971	-4.2971	2.2552	0.2217	4.0940	4.5103
11	4.2696	-4.2696	2.2894	0.2184	3.9813	4.5789
12	4.1993	-4.1993	2.2811	0.2192	3.8652	4.5623

Electronegativity (χ), chemical potential (μ), global hardness (η), global softness (S), electrophilicity index (ω)

Table 5. Affinity and minimum RMS values belonging to different molecule-protein conformations of the ligands used in this study

Ligands	Binding Affinity (kcal/mol)	RMSD(min)	Classic Hydrogen Bond	Distance Donor...Acceptor (Å)	Donor group(Å)	Acceptor group(Å)
1	-10.0	1.962	N(lig)...GLY378	1.7852	N(lig)	GLY378
2	-9.6	1.712	N(lig)...GLY378	2.0481	N(lig)	GLY378
3	-9.4	1.626	N(lig)...PRO377	2.3012	N(lig)	PRO377
4	-7.8	1.697	-	-	-	-
5	-8.8	1.340	-	-	-	-
6	-9.3	1.738	-	-	-	-
7	-9.5	1.864	GLN193...O(lig)	2.3848	GLN193	O(lig)
8	-9.4	1.578	-	-	-	-
9	-9.9	1.588	ASN237...O(lig)	2.3243	ASN237	O(lig)
10	-9.8	1.586	N(lig)...GLY378	2.4227	N(lig)	GLY378
11	-9.7	1.768	-	-	-	-
12	-9.8	1.591	N(lig)...PRO377	2.3765	N(lig)	PRO377