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# Synthesis, Characterization and Theoretical Calculations of Schiff Base Derived From 3-Amino-1,2,4-Triazole-5-Thiol as Potent Antimicrobial Agent

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## Abstract

Schiff bases are important chemical compounds in various fields such as inorganic, analytical and medicinal chemistry due to their versatilities. Schiff bases are formed by the condensation of aldehydes or ketones with primer amines. Their active group called azomethine (CH=N) or imine (C=N) makes them ideal candidates for developing new drugs. They can form numerous stable complexes when they are coordinated with different transition metal ions. Thus, metal complexes of Schiff bases have been studied extensively due to their various applications and chemical activities. And also, the compounds containing triazole derivatives possess chemotherapeutic effects including antibacterial activities against drug-sensitive as well as drug-resistant pathogens. 1,2,4-triazoles are a very important class of compounds that have attracted the attention of many scientists in medical and pharmaceutical fields due to their various biological activities such as anticancer, antimicrobial, anticonvulsant.

In this study, we synthesized Schiff base derived from 3-amino-1,2,4-triazole-5-thiol (ATT) and 5-chlorosalicylaldehyde (5ClSA), and characterized using spectroscopic method. In theoretical studies, the molecular structure of Schiff base was optimized using the density functional theory (DFT) with B3LYP/6-31+G (d,p) level of theory. In addition, the frontier molecular orbitals (FMOs: HOMO and LUMO) and the molecular electrostatic potential (MEP) map were performed by the same basis set using Gaussian 09 software. The global reactivity descriptors such as electronegativity ($\chi$), hardness ($\eta$), softness (S), chemical potential ($\mu$) and electrophilicity ($\omega$) were also calculated by using HOMO and LUMO energies

**Keywords:** Schiff bases, triazoles, DFT calculations, HOMO and LUMO energies.

## Introduction

Schiff bases are important chemical compounds in various fields such as inorganic, analytical and medicinal chemistry due to their versatilities [1,2]. Schiff bases are formed by the condensation of aldehydes or ketones with primer amines. Schiff bases formed from aromatic aldehydes are more stable than those of aliphatic aldehydes. Their active group called azomethine (CH=N) or imine (C=N) makes them ideal candidates for developing new drugs [3]. They can form numerous stable complexes when they are coordinated with different transition metal ions. Thus, metal complexes of Schiff bases have been studied extensively due to their various applications and chemical activities. And also, the compounds containing triazole derivatives possess chemotherapeutic effects including antibacterial activities against drug-sensitive as well as drug-resistant pathogens [4].

1,2,4-triazoles are a very important class of compounds that have attracted the attention of many scientists. 1,2,4-triazole and its derivatives have wide spread of uses in environmental, industrial and agricultural areas as well as biological properties. There are many triazole containg antifungals that play a leading role in the treatment of agricultural fungi infections such as; tebuconazole, triadimefon, cyproconazole and epoxiconazol [5].

Nitrogen-containing heterocyclic molecules are a part of many natural products and drugs that are vital for improving the quality of life [6,7].

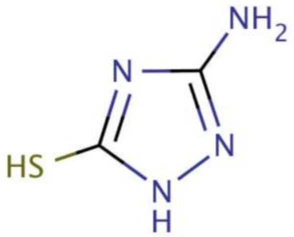


**Figure 1**. 3-amino-1,2,4-triazole-5-thiol(ATT)

1,2,4-Triazoles have wide importance in medicinal chemistry because of their stronger biological activities such as antibacterial, antifungal, anticancer, antitubercular , antioxidant, anticonvulsant, antiviral, antitubulin and inflammatory [8-10]. Due to the development of resistance and side effects to actively used antibiotics, it is necessary to the synthesis of new 1,2,4-triazole derivatives as potent antibacterial agents. Schiff bases derived from 1,2,4-triazoles have been also found to have extensive biological properties and a variety of applications [11]. Density functional theory (DFT) are used to determine the electronic structural properties which has a major contribution for predicting the biological activity [12]. According to Frontier Molecular Orbital (FMO) theory, the HOMO-LUMO energy levels and band gap affect the stability, chemical reactivity, hardness and many other electronic parameters. The small band gap causes low stability and high reactivity which means strong biological efficiency [13].

In this work, Schiff base derived from 3-amino-1,2,4-triazole-5-thiol (ATT) and 5-chlorosalicylaldehyde (5ClSA) was synthesized and characterized by spectroscopic methods. In the theoretical studies, the molecular structure of the Schiff base was optimized using density functional theory (DFT) at the B3LYP/6-31+G (d,p) level of theory. The geometrical parameters such as bond lenghts, bond angles and torsion angles were calculated by this set. In addition, Gaussian 09 software was used for frontier molecular orbitals (FMOs: HOMOs and LUMOs) and molecular electrostatic potential (MEP) surface map. The Global reactivity descriptors were also determined by using FMOs energy levels.

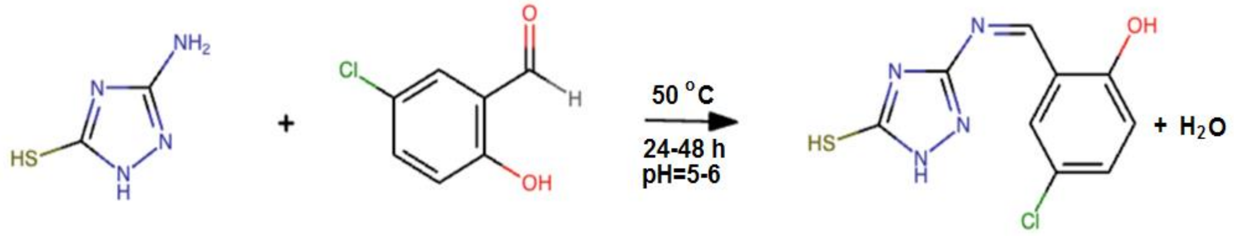
## 1. Experimental

### 1.1. Physical Measurements and Chemicals

Melting points were measured on a Gallenkamp apparatus using a capillary tube, Infrared spectra (4000–400 cm$^{-1}$) was recorded using a Thermo Nicolet 6700 FT-IR spectrometer on ATR in Chemistry Deparment of Gazi University. $^1$H-NMR spectra was also recorded using Bruker NMR 500 MHz in $d_6$-DMSO in MERLAB of Gazi University.

### 1.2. The synthesis of 5-chloro-2-((5-mercapto-1H-1,2,4-triazole-3-ylimino)methyl)phenol

The synthesis method of the Schiff base was depicted schematically in Scheme1. To 3-amino-1,2,4-triazole-5-thiol (0.160 g, 1 mmol) in 10 mL ethanol, 5-chlorosalicylaldehyde (0.216 g, 1 mmol) in 5 mL ethanol was added and stirred at 50 oC for 24-48 hours by reflux. Yellow precipitate appeared was filtered, washed with ethanol. The product was dried and recrystallized from ethanol. $C_9H_7N_4OSCl$ ( Mw: 254,696 g/mol), Mp: > 200 °C)



**Scheme1.** Synthesis of 5-chloro-2-((5-mercapto-1H-1,2,4-triazole-3-ylimino)methyl)phenol

### 1.3. Computational methods

Computational studies were performed by density functional theory (DFT) by Becke's three-parameter hybrid functional combined with the Lee–Yang–Parr correlation functional (B3LYP) [14-15]. The optimized geometries, geometrical parameters (bond lenghts. bond angles and torsion angles), Frontier Molecular Orbitals (FMOs:HOMOs and LUMOs), Global reactivity descriptors and Molecular Electrostatic Potential (MEP) map were performed by the same basis set using Gaussian 09 software. The global reactivity descriptors were calculated by following equations: Ionization potential (I)= -EHOMO, electron affinity (A)= -ELUMO, electronegativity (χ) = (I+A) /2, hardness (η)=(I-A)/2, softness (S) = 1/2η, chemical potential (μ)= - χ and electrophilicity (ω) = μ2 /2η.

## 2. Results and discussion

This study, we prepared Schiff base by the reaction of 3-amino-1,2,4-triazole-5-thiol with 5-chlorosalicylaldehyde.

### 2.1. FTIR spectra

By the formation of Schiff base; the strong vibration band at 1636 cm-1 was observed due to azomethine (HC=N) bond streching in FT-IR spectra.

**Table 1**. FT-IR spectra

| | Wave numbers (cm$^{-1}$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Compound** | **υ(O-H)** | **υ(NH$_2$)** | **υ(HC-H)$_{ar}$** | **υ(S-H)** | **υ(HC=N)$_{as}$** | **υ(C=N)** | **υ(C=C)$_{sym}$** | **υ(C-C)** | **υ(C-Cl)** |
| **ATT** | - | 3213 | 2875 | 2615 | - | 1622 | - | - | - |
| **Schiff base** | 3374 | - | 2875 | 2615 | 1679 | 1637 | 1568 | 1273 | 830 |

### 2.2. NMR spectra

1H NMR spectra of Schiff base was obtained in DMSO-d6 at room temperature using TMS as an internal Standard. Phenolic OH proton (1H, s), imine (CH=N) proton (1H, s), aromatic protons (3H, m) were observed around 9,6- 6,5 ppm range in weak field. DMSO-d6 peaks were obsered at 3,4 ppm and 2,5 ppm as expected.

## 2.3. Computational studies

The ground state geometry of Schiff base was obtained by DFT using B3LYP method. In the calculations, 6-31G+(d,p) basis set was used. The calculations have been performed using Gaussian 09 package program. The optimized geometry with the lowest energy and the highest stability was obtained by using this basis set (Figure 2). The geometrical parameters (bond lenght, bond angles and torsion angles) of stable conform was calculated by this set and presenten in Table 2. The dipole moment of molecule was calculated as 3,4842 Debye and the point group of molecule was found as C1.

The frontier molecular orbitals (FMOs:HOMO-LUMO) and molecular electrostatic potential (MEP) map and contour lines of the compound were obtained by density functional theory calculations. The electrophilic and nucleophilic sites are theoretically evaluated by molecular electrostatic potential [16].

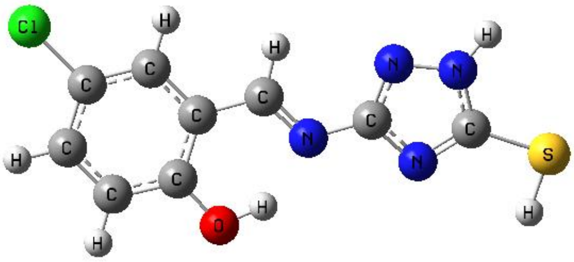


**Figure 2.** Optimized structure of Schiff base.

### 2.3.1. *Gerometrical Parameters*

The molecular structure of Schiff base with the atom numbering scheme is shown in Figure 3.

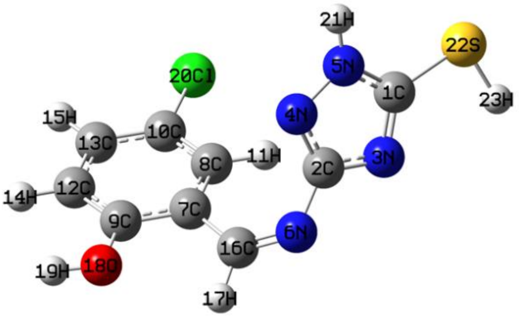


**Figure 3.** Atomic numbered 3D structure of Schiff base

The optimized structure of Schiff base is shown in Figur 3 with numbering of the atoms. The bond lenght, bond angles and torsion angles were compute by using DFT method with B3LYP/3-1+G basis set at Gaussian 09 software. These geometrical parameters are given in Table 2 and Table 3.

**Table 2.** Calculated bond lenghts and bond angles of Schiff base

| bond lengths (Å) | | | | | |
|---|---|---|---|---|---|
| **Assigned** | **Calculated*** | **Assigned** | **Calculated*** | **Assigned** | **Calculated*** |
| C10—Cl20 | 1.7590 | C7—C9 | 1.4096 | C2—N4 | 1.3291 |
| C10—C13 | 1.3962 | C7—C16 | 1.4821 | N4—N5 | 1.3691 |
| C12—C13 | 1.3932 | C16—N6 | 1.2797 | N5—C1 | 1.3517 |
| C9—C12 | 1.3983 | N6—C2 | 1.3919 | C1—N3 | 1.3226 |
| C9—O18 | 1.3677 | C2—N3 | 1.3722 | C1—S22 | 1.7645 |

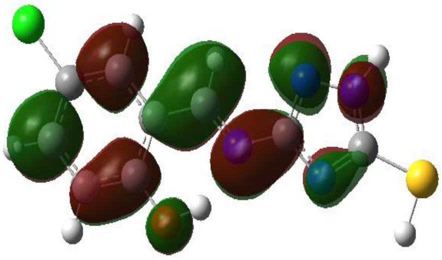
**Table 3.** Calculated bond and torsion angles of Schiff base

| Bond and Torsion Angles (°) | | | | | |
|---|---|---|---|---|---|
| H19—O18—C9 | 110.3009 | C12—C9—C7 | 120.5699 | N3—C1—S | 126.7077 |
| O18—C9—C7 | 117.3248 | C12—C9—O18 | 122.0993 | N3—C1—N5 | 110.1792 |
| C9—C7—C8 | 118.4956 | C8—C7—C16 | 122.5430 | C1—N5—N4 | 110.1462 |
| C7—C8—C10 | 120.4508 | C7—C16—N6 | 130.0574 | N5—N4—C2 | 101.7665 |
| C8—C10—C13 | 120.8881 | C16—N6—C2 | 123.1892 | N4—C2—N3 | 115.1269 |
| C10—C13—C12 | 119.2726 | N6—C2—N3 | 121.4043 | N4—C2—N6 | 123.1568 |
| C13—C12—C9 | 120.3123 | C2—N3—C1 | 102.7789 | C2—N3—C1—N5 | 0.4925 |
| H19—O18—C9—C12 | 2.8365 | Cl20—C10—C8—C7 | 179.6572 | N6—C2—N3—C1 | 174.2104 |
| O18—C9—C12—C13 | 179.8579 | C10—C8—C7—C16 | 176.2085 | C2—N3—C1—S22 | 179.2517 |
| C9—C12—C13—C10 | 0.0673 | C8—C7—C16—N6 | 32.9163 | N13—C1—S22—H23 | 8.1211 |
| C12—C13—C10—Cl20 | 179.1589 | C7—C16—N6—C2 | 9.2407 | N3—C1—N5—N4 | 0.4214 |
| C13—C10—C8—C7 | 0.0861 | C16—N6—C2—N3 | 124.0406 | C1—N5—N4—C2 | 0.1373 |
| N5—N4—C2—N6 | 173.8429 | N4—C2—N6—C16 | 62.6898 | N4—C2—N3—C1 | 0.4317 |

* by DFT/ B3LYP/6–311+G(2d,p) quantum set

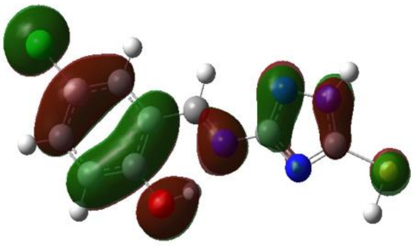
### *2.3.2. Frontier Molecular Orbitals (HOMOs and LUMOs)*

HOMO is highest occupied molecular orbital and LUMO is least unoccupied molecular orbital. The HOMO is the highest energy molecular orbital that consists of electrons while the LUMO is the next highest energy orbital that is empty [10]. In the FMOs shapes of Schiff base, HOMO and LUMO was localized on the whole molecule except butyl and sulfo groups. The energy gap between HOMO energy (-6,2844 eV) and LUMO energy (-2,4506 eV) levels (ΔE=ELUMO-EHOMO) was calculated as 3,8338 eV. The values of FMOs are relating with chemical stability and reactivity.

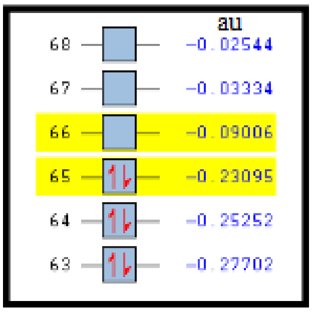


(66) $E_{LUMO} =$ -2,4506 eV

$\Delta E = E_{LUMO} - E_{HOMO}$



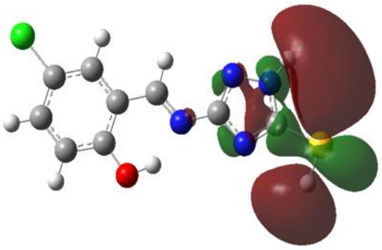
(65) $E_{HOMO} =$ -6,2844 eV



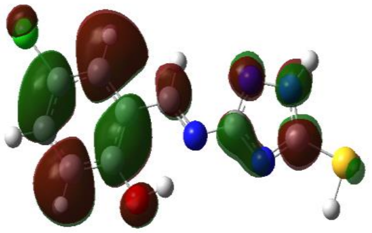
|  |  | au |
|---|---|---|
| 68 | ☐ | −0.02544 |
| 67 | ☐ | −0.03334 |
| 66 | ☐ | −0.09006 |
| 65 | ↑↓ | −0.23095 |
| 64 | ↑↓ | −0.25252 |
| 63 | ↑↓ | −0.27702 |

FMOs energy levels

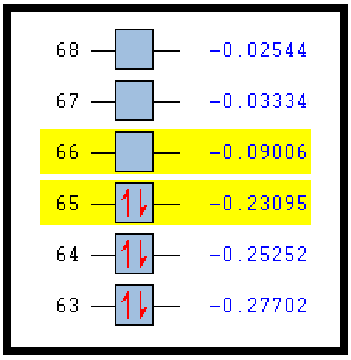
**Figure 4.** Frontier molecular orbitals (HOMO and LUMO)



(67) ELUMO+1= - 0,9061 eV

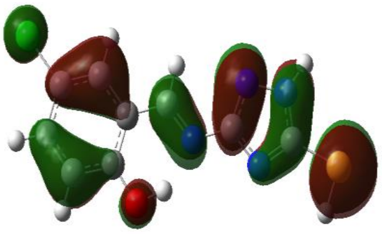


(68) ELUMO+2= - 0.6922 eV

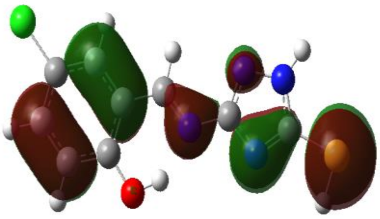


au

|  |  |  |
|---|---|---|
| 68 | ☐ | −0.02544 |
| 67 | ☐ | −0.03334 |
| 66 | ☐ | −0.09006 |
| 65 | ↑↓ | −0.23095 |
| 64 | ↑↓ | −0.25252 |
| 63 | ↑↓ | −0.27702 |



(64) EHOMO-1= - 6.8708 eV



(63) EHOMO-2= - 7,5380 eV

**Figure 5.** HOMOs and LUMOs shapes with energy levels

### *2.3.3 Global Reactivity Descriptors*

The global reactivity descriptors can be calculated by frontier molecular orbital (HOMO and LUMO) energy values. Global reactivity descriptors are used in the analysis of the chemical stability and reactivity of the molecule. A small energy gap with lower hardness gives high chemical reactivity and also lower electrophilicty implies more reactivity.

**Table 4.** The global chemical reactivity descriptors*

| $E_{HOMO}$ | $E_{LUMO}$ | $\Delta E= E_{LUMO}-E_{HOMO}$. | $I= -E_{HOMO}$ | $A= -E_{LUMO}$ |
|---|---|---|---|---|
| -6,2844 eV | -2,4506 eV | 3,8338 eV | 6,2844 eV | 2,4506 eV |
| χ= (I+A) /2 | μ = - χ | η =(I-A)/2 | S= 1/2η | ω = μ2 /2η |
| 4,3675 eV | - 4,3675 eV | 1.9169 eV | 0,2608 eV-1 | 4,9755 eV |

*HOMO and LUMO energies, energy band gap (ΔE), Ionization potential (I), electron affinity (A), electronegativity (χ), chemical potential (μ), global hardness (η), global softness (S) and global electrophilicity index (ω) [17]

### *2.3.4. Molecular Electrostatic Potential (MEP) Map*

MEP analysis is an important tool in describing the reactivity of molecules. It gives information on shape, size, charge density, polarity, and site of chemical reactivity of molecules.

In the MEP map, the regions of negative potential (red colour) are expected to be sites of protonation or nucleophilic attack, whereas the regions of positive potential (blue colour) are submitted to electrophilic attack [18].

Also, in the MEP contour lines , the denser area represent the stronger electrostatic field than the region with less contour lines. MEPs and contour lines show that negative potential sites (electrophilic regions) are located over electronegative donors such as phenolic-OH, imine-N, triazole ring-N and substitue-Cl.

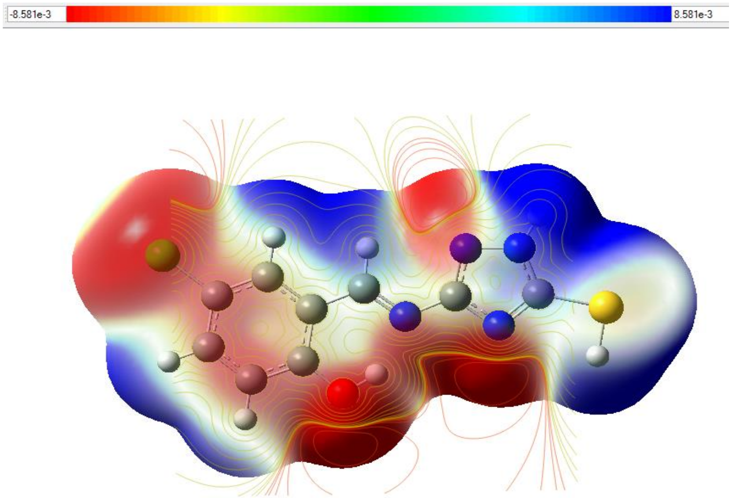


**Figure 6.** Molecular Electrostatic Potential (MEP) map and contour lines.

## Author Contribution

The synthesis of compound and experimental studies were conducted by Musa Alkan, while planning of the study and theoretical calculations were carried out by Ayla Balaban Gündüzalp.

## Conflict of Interests

The authors declare no conflict of interest.

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