

Some DFT calculations and ADME studies on (3-aminomethylpyridine)-5-chloro salicyldiene Schiff Base

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ABSTRACT

In this work, the optimized geometry and some geometric and electronic parameters of the (3-aminomethylpyridine)-5-chlorosalicyldiene were calculated. In the theoretical calculations, the stable structure geometry of the isolated molecule in gas phase was investigated under framework of density functional theory (DFT) with B3LYP/6-311++G(d,p) level of theory. Molecular electrostatic potential (MEP), frontier molecular orbital (FMO) analysis and nonlinear optical properties (NLO) of the title compound were obtained from computational process. In addition, the ADME properties of the (3-aminomethylpyridine)-5-chlorosalicyldiene were investigated and some drug similarity, physicochemical, lipophilicity and pharmacokinetic parameters of this molecule were determined.

Key words: DFT, Schiff Base, MEP, NLO, ADME

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INTRODUCTION

Schiff bases are compounds obtained from the condensation of aldehydes or ketones with primary amines. They are called “imine” or “azomethine” compounds because they contain C=N in their structures. Schiff bases are shown with the general formula $R_1R_2C=NR_3$. R_1R_2 and/or R_3 are alkyl or aryl substituents [1,2]. It is possible to obtain a wide variety of Schiff bases depending on the amount and structure of aldehydes and ketones.

The area of use of Schiff bases and metal complexes is quite wide. Schiff bases are important compounds in various branches such as pharmacy, medicine, biological systems, cosmetics, agriculture, production of dyes, plastic industry, aircraft industry, liquid crystal technology, electronics industry and analytical chemistry[3-7]. In addition to the properties of these compounds such as synthetic oxygen carrier, intermediate product generator in enzymatic reactions, antitumor effect, their use in analytical chemistry as spectrophotometric reagents by giving selective and specific reactions against some metal ions is also important. Schiff Bases are generally colored solids.

They can be used quite a lot in the paint industry by taking advantage of these properties. Apart from these, they can also be used as liquid crystals in electronic display systems and as polymer formation accelerators. Due to their definite melting points, they are used in the recognition of carbonyl compounds and in the determination of metal amounts because they have the ability to give coordination compounds with metals. In addition, some Schiff bases can be found in the composition of fungicide and insecticide drugs.

In this study, some geometric, electronic and nonlinear optical properties of (3-aminomethylpyridine)-5-chlorosalicyldiene compound were investigated by DFT method. Also, the potential of the compound to become a drug was also investigated.

MATERIALS AND METHODS

The stable structure of the molecule was obtained as a result of the geometry optimization calculation. In the theoretical calculations section, the Density Functional Theory was selected as the computational method using the Gaussian 09 package program[8]. In the DFT calculations, the B3LYP functional, which is a three-parameter hybrid exchange correlation functional that includes Becke's exchange and Lee, Yang and Parr's correlation terms, was used. 6-311++G(d,p), one of the most preferred basis sets, was selected as the basis set because it provides a good geometry and meaningful energy values. All theoretical calculations were performed at the same level of theory. The online Swiss ADME [9] program was recorded for drug similarity features.

RESULTS AND DISCUSSION

OPTIMIZED GEOMETRY

The molecular structure was optimized with the 6-311++G(d,p) basis set by the density functional theory (DFT) method (Figure 1). Since there are no crystal data for the compound, its structural parameters were compared with similar molecular structures in the literature. The experimental findings of Kuşbaşıoğlu measured the C–C bond lengths on the benzene ring as 1.393 Å, 1.409 Å and 1.385 Å, and these values closely agree with the theoretical calculations[10]. In our DFT-based computational study using the B3LYP/6-311G++(d,p) method, these structural parameters were investigated with higher precision and the C–C bond

lengths on the aromatic ring were calculated as approximately 1.394, 1398 Å and 1.401 Å. In the literature, all C-H bond lengths in the benzene ring have been measured as approximately 1.084 Å, and C-C bond lengths as 1.397 Å [11,12]. In this study, the aromatic C-H values were calculated as 1.083, 1.085 and 1.086 Å.

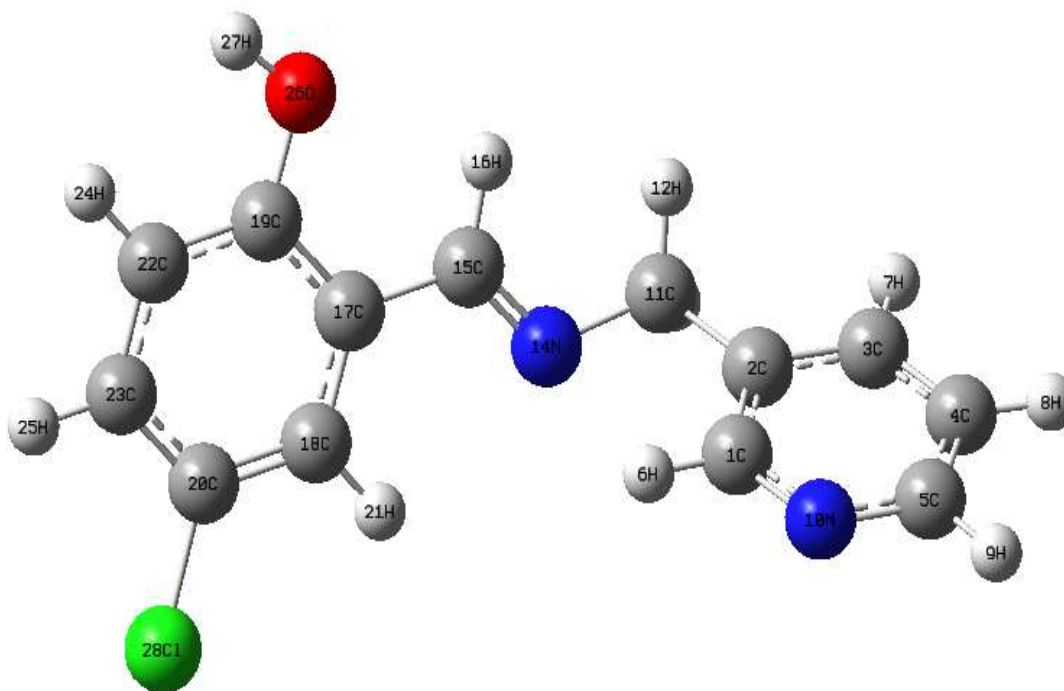


Fig. 1: Optimized molecular structure of the (3-aminomethylpyridine)-5-chlorosalicyldiene

In addition, one of the most important bonds in the studied molecules is the imine bond (C=N). The experimental values of the C=N bond lengths (1E,2E)-phenyl-[(1-phenylethyl) imino]-ethanal oxime were measured as 1,280 Å and 1,275 Å, respectively [13]. Theoretical values were calculated as 1,280 Å and 1,276 Å, respectively (Küçük 2019). In this study, the C=N imine bond for studied compound was calculated as 1.272 Å. The torsion angles such as H-C-C-C were calculated as 179.9°, indicating an almost planar molecular configuration.

FRONTIER MOLECULAR ORBITALS (FMOs)

Frontier orbitals are expressed by the highest occupied orbital (HOMO) and the lowest unoccupied regular orbital (LUMO). Frontier orbitals are used for stability of tissue structures, chemical activation, kinetic inertia, light absorption, optical and physical properties of movement. The HOMO and LUMO molecular orbital surfaces of the (3-aminomethylpyridine)-5-chlorosalicyldiene compound are given in Fig. 2. The calculated theoretical HOMO and LUMO energies of the compound are (-6.5843 eV) and (-1.9768 eV), respectively

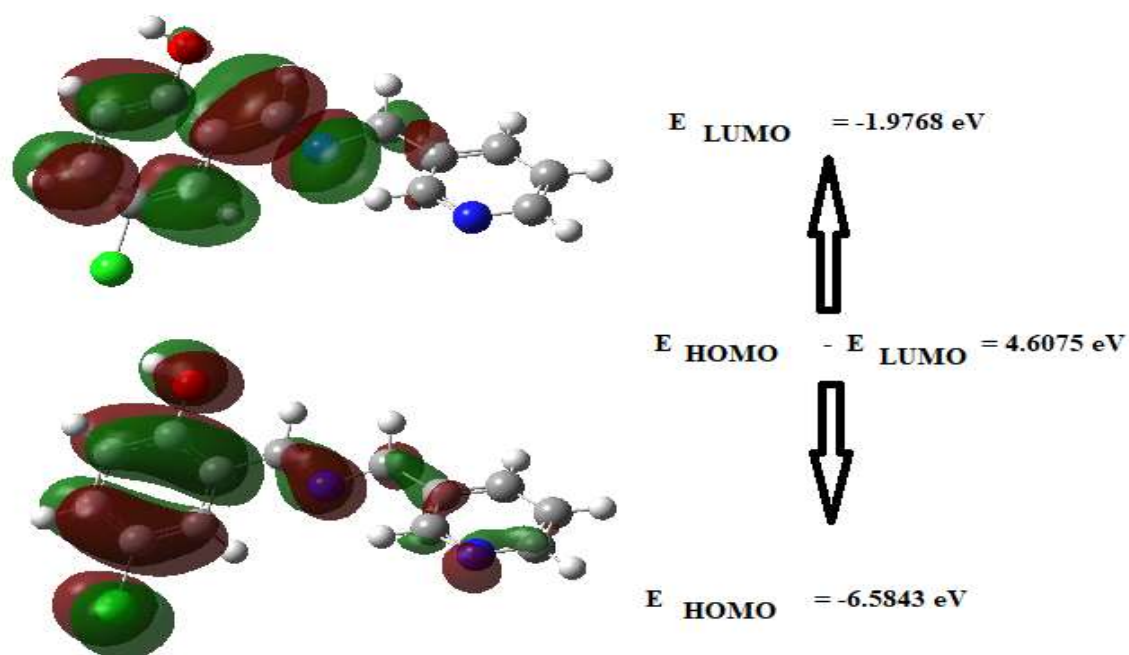


Fig. 2: The frontier molecular orbitals of the (3-aminomethylpyridine)-5-chlorosalicyldiene

The difference between the energies was obtained as $\Delta E = E_{\text{HOMO}} - E_{\text{LUMO}} = 6.621 \text{ eV}$, which indicates that the studied compound has a stable structure. HOMO and LUMO energies are used to determine descriptors such as electronegativity, hardness, softness, electrophilicity index, local reactivity. Koopmans theorem was used to calculate molecular parameters such as ionization potential (I), electron affinity (A), electronegativity (χ), chemical hardness (η) and softness (S)[14-18].

As a result of theoretical calculations, the chemical hardness value of (3-aminomethylpyridine)-5-chlorosalicyldiene compound was found to be 2.3037 eV and the chemical softness value was found to be $0.4341 (\text{eV})^{-1}$. In addition to the data mentioned above, it is useful to state the chemical activation data of the compound. According to these data, electronegativity was found to be 5.5959 eV , chemical potential -5.5959 eV and electrophilic index was found to be 6.7965 eV . According to the chemical activation parameters obtained theoretically, high hardness and low softness values may indicate that (3-aminomethylpyridine)-5-chlorosalicyldiene is a stable and hard compound with low chemical activation, high kinetic breakthrough.

MOLECULAR ELECTROSTATIC POTENTIAL (MEP) ANALYSIS

MEP map allows to investigate the relationship between structure and activity of the molecule electrostatically. MEP surface is a helpful tool in estimating the size, shape, proton affinity, dissolution process and electrostatic charges of molecules. It also allows to investigate the molecular structure with the relationships of physico-chemical properties. MEP surface shapes are shown as color gradation in positive, negative and neutral electrostatic potential regions. The MEP

surface of the (3-aminomethylpyridine)-5-chlorosalicyldiene molecule is shown in **Figure 3**. As can be seen from the figure, the electron densities are very low on the outer surface and near the hydrogen atoms (blue and light blue regions). Therefore, the electrostatic potentials near these regions are positive. The average electron density is higher in the green regions due to the presence of less electronegative carbon atoms. Therefore, the electrostatic potential is less negative near these regions. The electron densities are very high in the yellow and red regions. This is due to the presence of strongly electronegative atoms such as nitrogen and oxygen. The MEP map shows the negative potential regions on the nitrogen and oxygen atoms, while the positive potential regions are located around the hydrogen atoms.

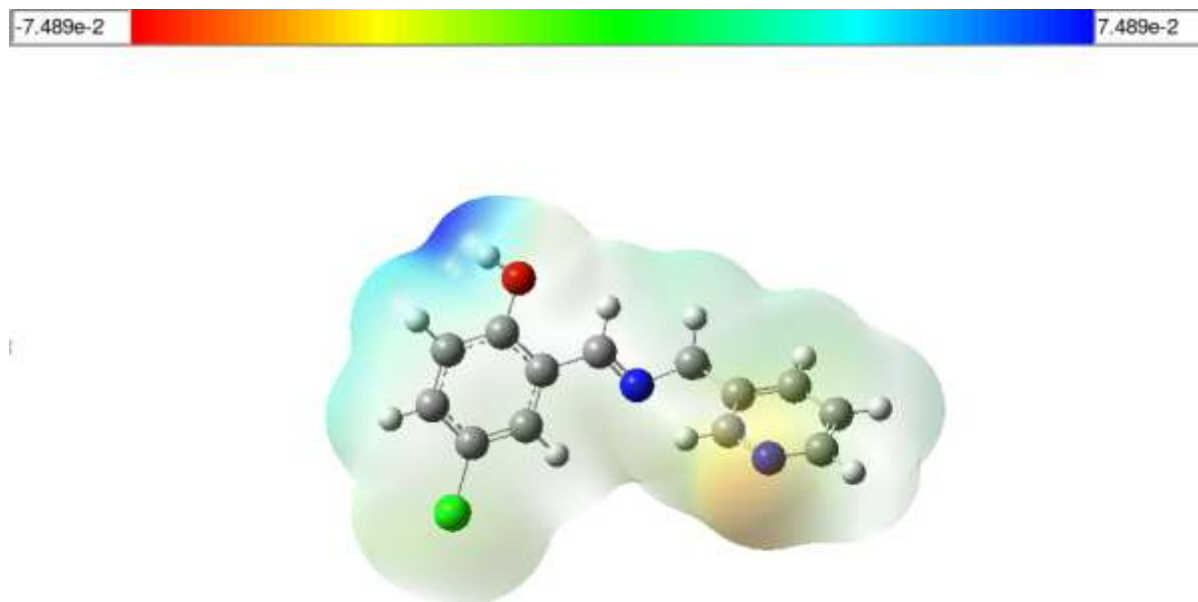


Fig. 3 MEP diagrams of (3-aminomethylpyridine)-5-chlorosalicyldiene compound

NONLINEAR OPTICAL (NLO) PROPERTIES

Polarizability (α) and hyperpolarizability (β) values are used to predict nonlinear optical properties (NLO) computationally[19]. Optical properties in organic-based materials are defined by polarizability. Hyperpolarizability is a quantity that affects the performance of the nonlinear optical properties of the material[20]. In order for a molecule to exhibit NLO properties, polarizability, hyperpolarizability and dipole moment should be high and the HOMO-LUMO energy difference should be small. When calculating nonlinear optical properties; for average linear polarizability,

$$\alpha = 1/3(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \quad (1)$$

and for the total static hyperpolarizability,

$$\beta_{\text{tot}} = [(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{xxy} + \beta_{yzz})^2 + (\beta_{zzz} + \beta_{xxz} + \beta_{yyz})^2]^{1/2} \quad (2)$$

equations were used. In Table 1, the polarizability (α) and hyperpolarizability (β) values calculated using the molecule in the gas phase are given.

Table1. Dipole moment (D), average polarizability (α_{ave}) and total first-order hyperpolarizability (β_{tot}) of the Schiff base ligand molecule

Parametre	Ligand	Parametre	Ligand
μ_x	-1.3860	β_{xxx}	111.9
μ_y	5.2936	β_{xxy}	135.8
μ_z	-0.4424	β_{xyy}	64.5
μ_{tot}	5.4899	β_{yyy}	73.9
α_{xx}	266.19	β_{xxz}	-50.0
α_{xy}	-0.06	β_{xyz}	-12.1
α_{yy}	182.94	β_{yyz}	4.8
α_{xz}	-16.92	β_{xzz}	26.2
α_{yz}	-4.40	β_{yzz}	-8.2
α_{zz}	126.08	β_{zzz}	-10.4
$\langle\alpha\rangle$ (a.u)	191.74	β_{tot} (a.u)	291.1
$\langle\alpha\rangle$ (esu)	24.42×10^{-24} esu	β_{tot} (esu)	2514.9×10^{-33} esu

α : 1a. u = 0.1482×10^{-24} esu; β : 1a. u = 8.6393×10^{-33} esu

The total dipole moment (μ) of the studied ligand molecule was found to be 5.49 D, and the average polarizability (α_{ave}) was found to be 24.42×10^{-24} esu. In addition, the first-order static hyperpolarizability of this compound was found to be 2514.9×10^{-33} esu. Based on these results, the nonlinear optical properties of the studied compound were understood to be an interesting molecular system for future studies.

DRUG SIMILARITY OF THE COMPOUND

Drug similarities of compounds, the examination of drug similarities is a useful application that increases the rate of drug conversion in the research of new drugs and the development of existing drugs. It basically directs research by taking into account the physicochemical parameter and structural similarities of the molecules under investigation with existing drugs. Today, drug similarity parameters, which are directly related to molecular structures and are recommended by many different drug research organizations, can be used through package programs and internet pages.

Table2. ADME prediction scores for the selected compounds

Properties	Compounds	
	Studied compound	Paracetamol
Physicochemical properties		
Mol. Wt. (g/mol)	246.69	151.16
Num. heavy atoms	17	11
Num. Arom. heavy atoms	12	6
Fraction Csp3	0.08	0.12
No. of rotatable bonds	3	2
No. of H-bond acceptors	3	2
No. of H-bond donors	1	2
Molar refractivity	69.22	42.78
TPSA (Å ²)	45.48	49.33
Lipophilicity		
Log Po/w (iLOGP)	2.17	1.21
Log Po/w (XLOGP3)	2.36	0.46
Log Po/w (WLOGP)	2.91	1.16
Log Po/w (MLOGP)	1.60	0.91
Log Po/w (SILICOS-IT)	3.81	0.89
Consensus Log Po/w	2.57	0.93
Water solubility		
Log S (ESOL)	-3.18	-1.34
Solubility(mol/L)	6.60x10 ⁻⁴	4.59x10 ⁻²
Class	Soluble	Very Soluble
Log S (Ali)	-2.96	-1.06
Solubility(mol/L)	1.11x10 ⁻³	8.62x10 ⁻²
Class	Soluble	Very Soluble
Log S (SILICOS-IT)	-5.09	-2.19
Solubility(mol/L)	8.18x10 ⁻⁶	6.43x10 ⁻³
Class	Moderately Soluble	Soluble
Pharmacokinetics		
GI absorption	High	High
BBB permeant	Yes	Yes
P-gp substrate	No	No
CYP1A2 inhibitor	Yes	No
CYP2C19 inhibitor	Yes	No
CYP2C9 inhibitor	No	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Skinpermeation, cm/s)	-6.13	-6.90
Drug-likeness		
Lipinski	Yes; 0 violation	Yes; 0 violation
Ghose	Yes	No; 1 violation: MW<160
Veber	Yes	Yes
Egan	Yes	Yes
Muegge	Yes	No; 1 violation: MW<200
Bioavailability score	0.55	0.55
Medicinal chemistry		
PAINS	0 alert	0 alert
Brenk	1 alert imine_1	1 alert hydroquinone
Lead-likeness	No;1 violations:MW>250,	No;1 violations:MW<250,
Synthetic accessibility	2.40	1.00

Lipinski(Pfizer) filter: $MW \leq 500$; $MLOGP \leq 4.15$; N or $O \leq 10$; NH or $OH \leq 5$
Ghose filter: $160 \leq MW \leq 480$; $-0.4 \leq WLOGP \leq 5.6$; $40 \leq MR \leq 130$; $20 \leq \text{atoms} \leq 70$
Veber (GSK) filter: Rotatable bonds ≤ 10 ; $TPSA \leq 140$
Egan (Pharmacia) filter: $WLOGP \leq 5.88$; $TPSA \leq 131.6$
Muegge (Bayer) filter: $200 \leq MW \leq 600$; $-0.2 \leq WLOGP \leq 5$; $TPSA \leq 150$; Num. Rings ≤ 7 ; Num. Carbon > 4 ; Num. Heteroatoms > 1 ; Num. Rotatable bonds ≤ 15 ; H-bond acc. ≤ 10 ; H-bond don. ≤ 5

There are different rules used in drug similarity. Some of the parameters investigated in this context are; topological polar surface area (TPSA) value, partition coefficient (LogP) and molecular weight (MW). XLogP3, WLogP and MLogP are the technique-specific parameters used in the calculation of the partition coefficient. Some important parameters used in drug similarity analyses for the studied Ligand compound are given in Table 2.

According to the table, the Ligand compound fully satisfies the Lipinski, Muegge, Ghose, Veber and Egan rules. It is important that the molecule under study satisfies all of these 74 rules defined by various drug research organizations and has different limits. As can be seen from the table, the widely used antipyretic and analgesic drug paracetamol satisfies the Lipinski, Veber and Egan rules but violates the Ghose and Muegge rules. The rules given here are defined only for the purpose of investigating the drug potential.

CONCLUSION

In this study, calculations were made for optimized molecular structural parameters, HOMO-LUMO energy gap, chemical reactivity parameters, total dipole moment, potential energy surface and nonlinear optical properties for the (3-aminomethylpyridine)-5-chlorosalicyldiene molecule. The geometrical parameters of the studied molecule obtained by the DFT-B3LYP method using the 6-311++G(d,p) basis set are in good agreement with the structural parameters of similar molecules in the literature. MEP and HOMO-LUMO analysis can be used to accurately predict the chemical reactivity, charge transfer and electrostatic properties of the studied compound.

Studies on Nlo have shown that the compound exhibits moderate nonlinear optical activity. In ADME study, the ligand compound fully satisfies the Lipinski, Muegge, Ghose, Veber and Egan rules. The widely used antipyretic and analgesic drug paracetamol satisfies the Lipinski, Veber and Egan rules but violates the Ghose and Muegge rules. According to these results, the studied ligand compound showed very good drug similarity property.

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