Chemical Sciences Journal
ISSN: 2150-3494
Suresh et al., Chem Sci J 2016, 7:1
http://dx.doi.org/10.4172/2150-3494.1000122
Research Article
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Schiff Base N-(5-Chlorosalicylidene) Aniline, a Novel Antifungal Agent: Insights from Crystallographic Analysis, Semi Empirical and Molinspirations Calculations

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Abstract

The single crystals of a Schiff base, N-(5-chlorosalicylidene) aniline suitable for X-ray diffraction were grown by slow evaporation from its ethanol solution. The geometrical, supramolecular features, energetics and biological activity of the title compound were analysed through a combined experimental and theoretical approach. The compound crystallizes in orthorhombic system with the space group $Pca2_1$. The unit cell parameters area=12.391 (6) Å, b=4.5223 (18) Å, c=19.514 (8) Å, α=β=γ=90.00°. V=1093.5 (8) Å^3, Z=4, Dx=Mg m^{-3} and μ=0.32 mm^{-1}. The crystal packing is mainly stabilized by dispersion forces from short H…H contacts. Also an intramolecular N-H…O hydrogen bonding is observed. For the optimised geometry, the HOMO-LUMO energy gap (7.071 eV) reflects the chemical activity. The compound is expected to have moderate hydrophilicity and hydrophobicity. Hence, have moderate permeability across cell membrane. Bioactivity scores suggest weakly bioactive nature of the compound.

Keywords: Schiff base; Non-covalent interactions; MOPAC; Semi-empirical calculations; Milogp calculations

Introduction

Schiff bases are the compounds carrying imine or azomethine (–C=N–) functional group. These are the condensation products of primary amines with carbonyl compounds. Schiff base ligands contain a variety of substituents with different electron-donating or electron-withdrawing groups, and therefore may have interesting chemical properties. They have attracted particular interest due to their biological activities such as radiopharmaceuticals for cancer targeting. They have also been used as model systems for biological macromolecules. Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory, analgesic, antimicrobial, anticonvulsant, anti-tubercular, anticancer, antioxidant, antihelmintic, and so forth. The nitrogen atom of azomethine may be involved in the formation of a hydrogen bond with the active centres of cell constituents and interferes in normal cell processes. Concisely, Schiff bases are among the molecules which have therapeutic potential for the treatment of various human diseases. These properties are greatly influenced by the topochemistry of the Schiff base molecules which in turn is highly affected by the crystal structure. Therefore, the study of crystal packing and the intermolecular interactions in the crystal structures of various Schiff bases can lead to valuable data for the design and synthesis of new materials [1].

In view of this importance, the crystal structure analysis of title compound (I) and semi-empirical quantum chemical calculations were performed to investigate the role of intermolecular interactions in controlling the crystal packing and thereby influencing the biological activity.

Materials and Methods

X-ray structure analysis

The IUPAC name of the compound (I), N-(5-chlorosalicylidene) aniline is 4-chloro-2-[(E)-(phenylimino) methyl] phenol and is shown in the Figure 1. Single crystals of the compound (I), $C_{13}H_{10}ClNO$ were grown by slow evaporation method using ethanol as solvent at room temperature. A suitable crystal was selected and mounted on a Bruker Smart [2] CCD Area Detector System using Mo-Kα (0.71073 Å) radiation for the crystal. The crystal was kept at 296(2) K during data collection. Intensity data were collected up to a θ_{max} of 25.0° for the compound in the ω–ϕ scan mode. A total of 3489 reflections were collected, resulting in 1561 independent reflections of which the number of reflections satisfying $I > 2\sigma(I)$ criteria were 1500, and these were treated as observed Corrections for Lorentz and polarisation effects were applied. Using Olex2 [3], the structure was solved with the olex2.solve [4] structure solution program using Charge Flipping and refined with the olex2.refine [5,6] refinement package using Gauss-Newton minimisation. The final R factor is 0.034. The details of crystal data, data collection and the refinement are given in Table 1.

Computational studies

MOPAC calculations: Despite the interesting properties of N-salicylideneaniline derivatives, have been scarcely studied from a computational point of view [7]. Our goal was to compute quantum chemical derived properties that would be useful as starting points for understanding the properties of this type of ring system. Moreover, the other main task of conformational analyses of isolated molecule (I) was to examine the stable conformation and a global energy minimum for the studied molecule. If there was considerable energy difference

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Received March 07, 2016; **Accepted** March 08, 2016; **Published** March 16, 2016

Citation: Suresh S, Girija CR, Sathish CD, Venkatesha TV (2016) Schiff Base N-(5-Chlorosalicylidene) Aniline, a Novel Antifungal Agent: Insights from Crystallographic Analysis, Semi Empirical and Molinspirations Calculations. Chem Sci J 7: 122. doi:10.4172/2150-3494.1000122

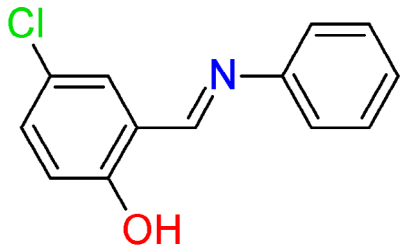

Figure 1: Schematic diagram of the title compound(I), ($C_{13}H_{10}ClNO$).

between the lowest energy types of conformer, then we concluded that theoretical calculations predicted one type of geometric molecule. Since, the size and the variety of heteroatoms in the N-(5-chlorosalicylidene) aniline are considerable, a full semi-empirical geometrical optimization is computationally very demanding. This work is simplified, if we use a realistic structure as starting geometry for the MM conformational search and quantum-chemical calculation. Therefore, the structure obtained by X-ray diffraction analysis is suitable to this end. The X-ray structure of the compound (I) is used as input to MOPAC which was optimized using molecular mechanics (MM) incorporated in Gabedit (GUI) software [8] using Newton Raphson method. Semi-empirical Quantum Chemical Calculations were performed on the refined parameters using MOPAC 2012 program [9] to optimize the structure with Parametrization Model 7 (PM7) approximation. The minimizations were terminated at r.m.s. gradient of less than 0.01 kJ-mol^{-1} Å^{-1}. Electronic structure calculations provide useful estimates of the energetic properties of chemical systems, including molecular structures, spectroscopic features and probable reaction pathways. The PM7 Hamiltonian in MOPAC package was used to calculate the bond lengths, bond angles, heats of formations, core-core repulsion energies, ionization potentials etc.

Molinspiration calculations

Quantitative Structure Activity Relationship (QSAR) studies were applied to find correlation between different calculated molecular descriptors of the compound (I) and biological activity. Structure of the title compound (I) was drawn in the online molinspiration software version 2014.06 (www.molinspiration.com) [10] for calculation of molecular properties and prediction of bioactivity score for drug targets.

Results and Discussion

X-ray crystal structure analysis

Geometrical features: The structure of 4-chloro-2[(E)-(phenylimino) methyl] phenol, $C_{13}H_{10}ClNO$, has orthorhombic *Pca*2_1 symmetry. The compound (I), $C_{13}H_{10}ClNO$, is planar with a dihedral angle of 9.49º between the planes of the two benzene rings. The compound exists in a trans-configuration about the central C=N bond [C7-N1=1.278 (3)Å] with a torsion angle C5–N1–C7–C8=-178.9(2)°. All other selected bond distances [11], bond angles and torsional angles are given in Tables 2-4, respectively have the normal values. The ORTEP [12] plot of the compound (I) is as shown in the Figure 2.

Supramolecular features: Intramolecular hydrogen bonding is observed between the oxygen atom of keto group and the H-atom of imine group, resulting in a keto-imine tautomeric form. A strong intramolecular N1—H1···O6 hydrogen bond generates an S(6) ring motif [13] as shown in the Figure 3a and 3b. A short H4···H7 contact [2.0984(5) Å] is also observed. The hydrogen bond geometry is listed in Table 5.

MOPAC calculations

Geometry optimization: The significant difference in C-N, C-O bond distances of atoms involved in intramolecular hydrogen bond interactions are observed between refined X-ray data and optimized geometrical data. The comparison of these results along with bond distances, angles and torsion angles are given in Table 6 and that of hydrogen bond geometries are given in Table 5. The change in torsion angles indicates how the crystal packing effect significantly influences these interactions.

HOMO-LUMO studies: The heat of formation is equal to -12.66715 kcal mol^{-1} for the molecule in the asymmetric unit. The ionization potential, dipole moment and self-consistency field (SCF) factor are calculated as 8.516512 eV, 4.945 Debye and 40 respectively. The geometry optimization using MOPAC2012 results in HOMO-LUMO energies as -8.517 and -1.446 eV respectively. LUMO as an electron

Crystal Data	
Molecular formula, Mol. mass	$C_{13}H_{10}ClNO$,231.67
Unit Cell Parameters	a=12.391 (6)Å, b=4.5223 (18) Å, c=19.514 (8) Å, α=b=γ=90.00°,
	V=1093.5 (8) Å^3, Z=4, D_x=Mg m^{-3} and m=0.32 mm^{-1}
Crystal System, space group	Orthorhombic, *Pca*2_1
Data collection	
Diffractometer	Bruker SMART CCD area detector
Data collection method	ω /φ, mode
Absorption correction	multi-scan (SADABS)
No. of measured reflections	3489
No. of independent reflections	1561
No. of observed reflections	1500
Criterion for observed reflections	I>2σ (I)
R_{int}	0.034
θ_{max} (°)	4.2, 25.0°
Range of h, k, 1	*h*=-12→ 14
	k=-5→ 5
	l=-19→ 23
Refinement	
Refinement on	F^2
R[F^2>2 σ(F^2)]	0.033
wR	0.089
S	1.05
No. of reflections used in refinement	1561
No. of parameters used	149
No.of restraints applied	1
Weighting scheme W=l/[o2(Fzo)-+(0.0894P)2+2.0000PI Where *P=(F2+2F,f)/3*	
$\Delta\rho_{max}$ (e A^{-3})	0.25 e Å-3
$\Delta\rho_{min}$ (e A^{-3})	−0.30 e Å^{-3}
Friedel pairs	480
Absolute structure parameter [Flack parameter] [6]	−0.01 (8)

Table 1: Crystal data, data collection and refinement details of compound(I).

O -C12 1.355(3)	N1 -C5 1.409(3)
N1 -C7 1.278(3)	
Short Contacts (Å) H4-H7 2.1000	

Table 2: Selected Bond Distances (Å).

C5-N1-C7	122.75(19)	**N1-C5-C6**	116.97(19)
N1-C5 -C4	24.0(2)	**N1-C7-C8**	121.6(2)
C10-C11-C12	120.9(2)	**O6-C12-C11**	119.14(19)
O6-C12 -C8	121.2(2)		

Table 3: Selected Bond Angles (°).

C7-N1-C5 -C6	-177.0(2)	**C5-N1-C7 -C8**	-178.9(2)
C7-N1-C5 -C4	2.7(3)	**C3-C4-C5 -N1**	-179.4(2)
N1-C5-C6 -C1	179.5(2)	**N1-C7-C8 -C9**	177.1(2)
N1-C7-C8 -C12	-3.9(4)	**C7-C8-C12 -O6**	1.0(4)
C7-C8-C12 -C11	-180.0(2)	**C8-C9-C13 -Cl1**	78.41(18)
C10-C11-C12 -O6	179.2(2)		

Table 4: Selected Torsion Angles (°).

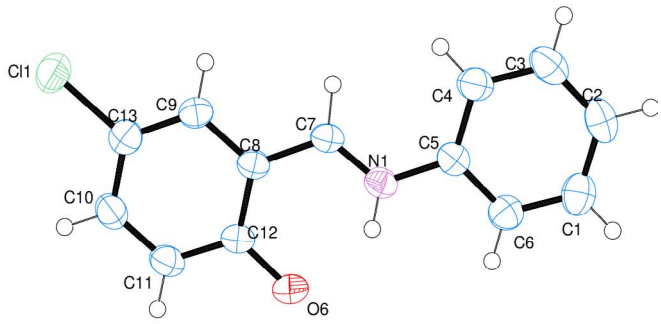

Figure 2: View of the molecular structure of the compound(I) with displacement ellipsoids drawn at the 50% probability level.

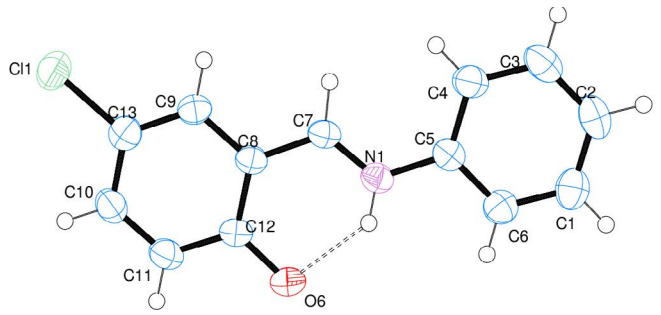

Figure 3a: View of the molecular structure of the compound(I) showing intramolecular N1-H1…O6 hydrogen bond forming a S(6) loop.

acceptor (electrophilic) represents the ability to obtain an electron; HOMO represents the ability to donate an electron (nucleophilic). The HOMO-LUMO energy gap of 7.071 eV reflects the chemical activity of molecule, resulting in charge transfer interaction from π-bonding MO of a phenyl ring from the salicylidine moiety in HOMO to a π*-anti-bonding MO of the aniline moiety extended to imine group in LUMO (Figure 4). According to the Pearson`s maximum hardness principle (PMHP) the molecules arrange themselves with maximum hardness [14-17]. The conformation has the maximum hardness value, which is the minimum energy conformation. In the finite different approximation, the ionization energy and electron affinity can be replaced by the HOMO and LUMO energy, respectively, using Koopmans'theorem, [15] within a Hartree–Fock and/or density functional theory schemes, with

$I=-\varepsilon_{HOMO}$ and $A=-\varepsilon_{LUMO}$, yielding

$\mu=-1/2(\varepsilon_{HOMO}+\varepsilon_{LUMO})$ and $\eta=1/2(\varepsilon_{HOMO}-\varepsilon_{LUMO})$

The calculated chemical hardness η is found to be 3.535 eV and chemical potential μ 4.9815 eV. The energy values and dipole moments resulting from Semi-empirical Quantum Chemical Calculations are given in Table 7. A larger value of the energy gap indicates low reactivity to a chemical species because the energy gap is related to the softness or hardness of a molecule. A soft molecule is more reactive than a hard molecule because a hard molecule has a larger energy gap. Dipole moment (μ) is the measure of polarity in a bond and is related to the distribution of electrons in a molecule. Schiff bases are an important class of organic compounds which, has a high dipole moment and is capable of hydrogen bonding, which could be favourable in the binding of biomolecular targets.

Packing coefficient

70.2% as calculated using the program PLUTON [18]. The crystallographic symmetry elements present in the compound are 2-fold screw axis and glide plane. The crystal structure is thermodynamically favoured as the packing efficiency is relatively high.

Molinspiration calculations

The molecular properties (miLog P, Total polar surface area, number of hydrogen bond donors and acceptors, molecular weight, number of atoms, number of rotatable bonds etc.) and the bioactivity scores for drug targets (GPCR ligands, kinase inhibitors KI, ion channel modulators ICM, enzymes inhibitor EI, Protease inhibitor PI and nuclear receptors NRL) of the title compound (I) are valued in Table 8. The miLogP value of the compound (I) is found to be 4.07 which clearly obeys Lipinski`s rule of five [19]. The compound (I) is expected to have moderate hydrophilicity and also moderately lipophilic. This indicates that the compound will have moderate permeability across cell membrane. The title compound (I) having low molecular mass (231.68) [drug molecules (<500)] is known to be easily transported, diffuse and absorbed as compared to heavy molecules. Total polar surface area (TPSA) is found to be 32.59 (<160 Å limit), closely related to the hydrogen bonding potential of a molecule and is a very good predictor of drug transport properties such as intestinal absorption, bioavailability, blood brain barrier penetration etc.

Number of rotatable bonds is a simple topological parameter that measures molecular flexibility and is considered to be a good descriptor of oral bioavailability of drugs. The screened compound (I) is flexible with (2 rotatable bonds). As a general rule, larger is the bioactivity score, higher is the probability that investigated compound will be active. Therefore, a molecule having bioactivity score more than 0.00 is most likely to possess considerable biological activities, while values -0.50 to 0.00 are expected to be moderately active and if score is less than -0.50 it is presumed to be inactive. The results of the present study demonstrated that the investigated compound is biologically inactive molecule. The bioactivity score for GPCR ligand is found to be -0.87, for ion channel modulator activity is -0.81. Similar results are obtained for kinase inhibition showed score -0.59, indicates the molecules were inactive towards this drug target. Bioactivity scores for nuclear receptor ligand, protease inhibitor and enzyme inhibition was found to be in the range of -0.82, -0.99 and -0.43 respectively, suggest weakly bioactive nature of molecules. The interaction between the HOMO drug with the LUMO receptor and vice-versa play important role in intermolecular interactions [20], the interactions stabilised inversely with energy gap between the interacting orbitals. Increasing HOMO energy and

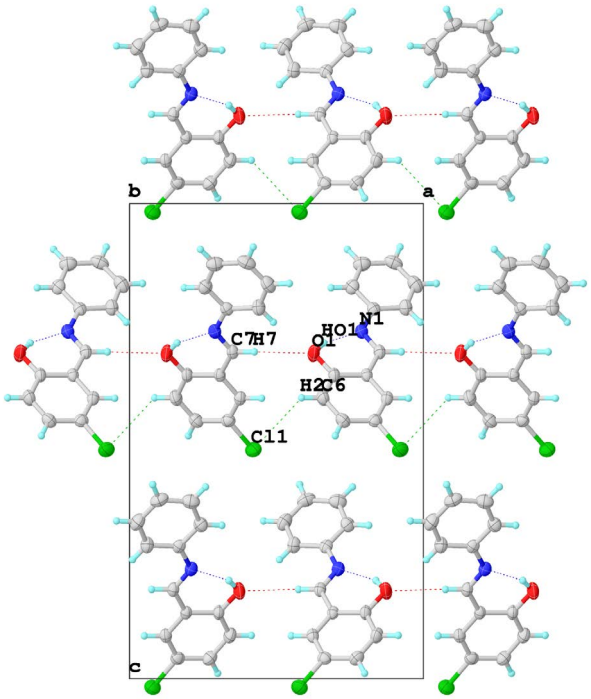

Figure 3b: Crystal packing diagram of the title compound(I) showing intermolecular interactions

D-H…A	D-H		H…A		D…A		D-H…A	
	XRD	MOPAC	XRD	MOPAC	XRD	MOPAC	XRD	MOPAC
N1- H1… O6	0.8600	1.061	1.9100	1.804	2.610(3)	2.607	137.00	129.11

Symmetry codes: (i) x, y, z

Table 5: Hydrogen Bond geometry (Å, °).

Parameters	XRD refined	MOPAC2012
Bond length (Å)		
C7-N1	1.278(2)	1.349
C12-O6	1.354(3)	1.229
Bond angle (°)		
C8-C12-C11	119.6(2)	118.21
N1-C7-C8	121.5(2)	121.80
Dihedral angle (°)		
C5-N1-C7-C8	-178.9(2)	-179.742
C4-C5-N1-C7	2.7(3)	0.046
N1-C7-C8-C9	177.1(2)	-179.92

Table 6: Optimized geometrical parameters for the compound(I).

Final heat of formation	-12.66715 kcal/mol=-52.99936 kJ/mol
Total energy (eV)	-2479.37797
Electronic energy (eV)	-14419.00509
Point group	Cs
Core-core repulsion (eV)	11939.62711
Ionization potential (eV)	8.516512
HOMO LUMO energies (eV)	-8.517 , -1.446
No. of filled levels	40
Dipole moment (in D)	4.945

Table 7: Energy values obtained from optimised geometry of the compound(I).

Molinspiration calculations							Drug-likeness					
Compound	MW (g/mol)	miLogP	TPSA	nOH-NH	nrotb	Volume	GPCRL	ICM	KI	NRL	PI	EI
(I)	231.68	4.07	32.59	1	2	200.27	-0.87	-0.81	-0.59	-0.82	-0.99	-0.43

Table 8: Molecular properties and bioactivity score of compound(I).

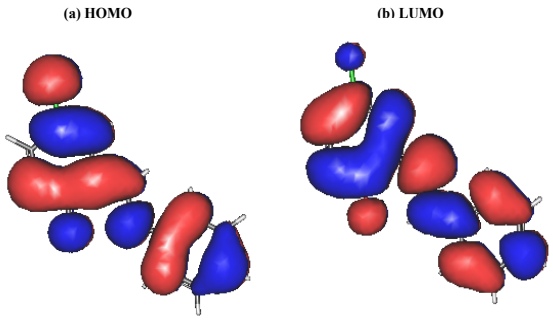

Figure 4: The salicylidine moiety in HOMO to a π*-anti-bonding MO of the aniline moiety extended to imine group in LUMO.

decreasing LUMO energy in the drug molecule lead to enhanced stabilising interactions and hence, binding with the receptor.

Conclusion

The title compound (I) is mainly stabilized by strong intra molecular N-H…O hydrogen bond and also dispersion forces from H…H contacts. The HOMO-LUMO energy gap of 7.071 eV reflects the chemical activity of molecule, resulting in charge transfer interaction from π-bonding MO of a phenyl ring from the salicylidine moiety in HOMO to a π*-anti-bonding MO of the aniline moiety extended to imine group in LUMO. The dipole moment of 4.945D indicates moderately polar nature. The compound (I) is expected to have moderate hydrophilicity and lipophilicity. Hence, have moderate permeability across cell membrane. The title compound (I) having low molecular mass (231.68) known to be easily transported, diffuse and absorbed as compared to heavy molecules. Total polar surface area (TPSA) is found to be 32.59, closely related to the hydrogen bonding potential of a molecule and is a very good predictor of drug transport properties such as intestinal absorption, bioavailability and blood brain barrier penetration. Bioactivity scores for nuclear receptor ligand, protease inhibitor and enzyme inhibition suggest weakly bioactive nature of the title compound (I).

Computational analysis suggests that the dipole moment and geometry of molecule may be good descriptors for the QSAR studies of novel N-salicylideneanilines as potent antibacterial agents.

Acknowledgements

The authors thank Solid State Chemistry Unit (SSCU), Indian Institute of Science (IISc), Bengaluru, Karnataka, India, for the X-ray intensity data collection. SS thank Rashtriya Sikshana Samsthe Trust (RSST) and the Principal, SSMRV Degree College, Bengaluru, for their constant support and encouragement for carrying out research work.

Competing Interest

Authors have declared that no competing interests exist.

Supplementary Data

The CIF file was deposited at the Cambridge Crystallographic Data Centre, The deposition number is CCDC- 1444547. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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