Bulgarian Chemical Communications, Volume 55, Issue 3 (pp. 308-312) 2023 DOI: 10.34049/bcc.55.3.NCNTC13

2-(((3-Chlorophenyl) imino) methyl)-4-nitrophenol: synthesis, molecular and medicinal studies

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Accepted: August 07, 2023

In this study, an organic compound with Schiff base structure, 2-(((3-chlorophenyl) imino) methyl)-4-nitrophenol (ClSB) was synthesized, and its structure elucidation was performed by X-ray analysis. The molecular properties were investigated both structurally and electronically. The physicochemical properties and ADME parameters were investigated using a web server to evaluate the medicinal efficacy. The potential targets of the title compound were determined using the LigTMap server based on ligand similarity and binding similarity scores. We found potential targets in these enzyme classes: hydrolase, kinase, and transferase. Based on these results, the seven most potential targets were selected based on the docking scores obtained ($\Delta G \geq -7$ kcal mol^{-1}). Among all targets, thankyrase 2 was determined to be the most effective target for our compound with docking scores of -9.266 and -8.621 kcal mol^{-1}. Gastrointestinal absorption and blood-brain barrier permeability of the title compound were also determined.

Keywords: Chlorine compound, Schiff base, FMOs, ADME, docking.

INTRODUCTION

Schiff base compounds, also called imines or azomethines, are represented by the molecular formula > C=N- and attract attention due to their applications in biological and medical fields [1]. These compounds gain importance due to the presence of CH = N- bond and unpaired electrons on the nitrogen atom in their molecular structure [2]. Both Schiff base ligands and their complexes are functional materials in many fields including agro/bio-chemistry, health and pharmaceutical applications, catalytic and therapeutic activity [3]. Chlorinated compounds are valuable chemicals in medicinal chemistry, and there are more than 250 FDA-approved drugs containing a chlorine atom [4]. Frontier molecular orbitals (FMOs) are commonly used to determine the chemical reactivity, electronic properties, and NLO functions of the materials under study [5].

In the current study, we synthesized a Schiff base molecule by a classical condensation method between an active carbonyl and amine compound. The molecular structure of the synthesized molecule was verified by X-ray analysis. The compound was studied both chemically and medically using software and *in silico* web tools.

EXPERIMENTAL

Chlorinated Schiff base (ClSB) was synthesized by refluxing the mixture of aromatic amine (0.039 mmol, 5.1 mg) and aldehyde (0.039 mmol, 6.6 mg) in an ethanol solution for 24 hours. A schematic representation of the synthesis is shown in Fig. 1. The obtained solution was slowly cooled to room temperature and remained for one week without further purification methods. The crystals formed were taken for X-ray analysis. $C_{13}H_9ClN_2O_3$, yield: 68%.

SMILES: OC1=CC=C(C=C1\C=N\C1=CC(Cl)=CC=C1)[N+]([O-])=O

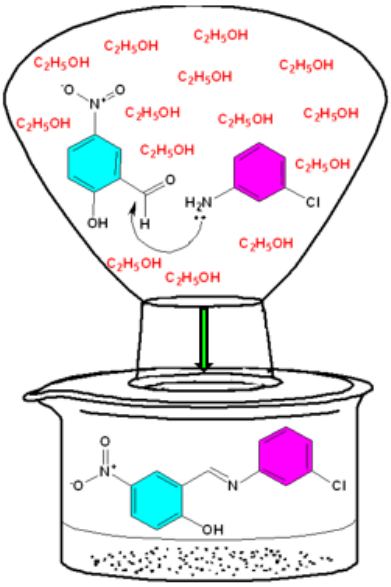

Fig. 1. Synthesis reaction of ClSB.

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MATERIALS AND METHODS

Chemicals: 2-hydroxy-5-nitrobenzaldehyde, 3-chloroaniline, and ethanol were purchased from commercial suppliers.

X-ray diffraction: A STOE IPDS 2 instrument was used for X-ray data collection. SHELXTL [6] was used to solve and refine the structure. Mercury was used to create molecular graphics. PublCIF was used to prepare the CIF file of the ClSB.

*ADME and target identification***:** in silico ADME studies were performed using the free web tool SwissADME [7]. LigTMap was used for target identification.

Docking studies: Docking experiments were performed using LigTMap [8].

RESULTS AND DISCUSSION

X-ray analysis and structural properties

A yellow stick-shaped crystal with the dimensions 0.52×0.23×0.05 mm^3 was selected for X-ray data acquisition. A STOE IPDS 2 diffractometer was used for measurements. The measurements were performed at room temperature without using an extra cooling apparatus. The unit cell parameters were determined to be 14.77, 3.79, and 21.57 Å (a, b, and c, respectively) lengths and 90.00°, 90.00°, and 91.73° (α, γ, and β, respectively) angles. The crystal system and space group of ClSB were determined monoclinic and $P2_1/n$ in the above-mentioned order. A unit cell deposits four monomeric units in a volume of 1209.54 $Å^3$ (Z=4). The calculated density of ClSB is 1.519 Mgm^{-3}. The structure was refined by the method F^2 with 176 parameters. All atoms except hydrogen atoms were refined anisotropically. The solution was completed with the scores $wR(F^2)$ 0.281 and GooF 1.09. The other crystallographic parameters are listed in Table 1. Three hydrogen bonds were detected in the molecule, in which two of them (H6…O3/2.53 Å and H13…O3/2.65 Å) are intermolecular hydrogen bonds, and one of them intramolecular hydrogen (H1…N1/1.55 Å) bond (Table 2). The atom numbering style indicated in these interactions is shown in Fig. 2.

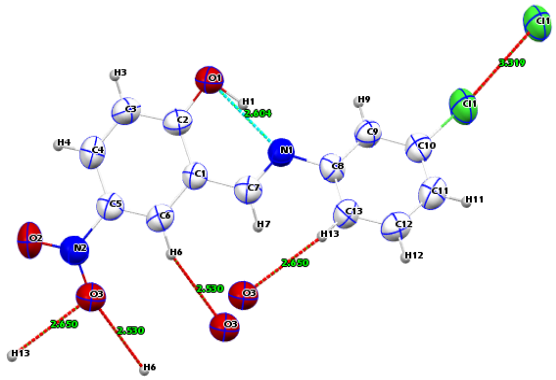


Fig. 2. Molecular representation of ClSB with the numbered scheme.

Table 1. Crystallographic data obtained by the CIF file of ClSB.

Crystal Data		Data Collection	
CCDC deposition number	2211897	Diffracto-meter	STOE IPDS 2
Chemical formula	$C_{13}H_9ClN_2O_3$	θ min-max for data collection (°)	1.7; 25.1
Formula weight	276.67	Index ranges; h, k, l	-17/15; -4/4; -25/25
Temperature (K)	293	Measurement method	Rotation method
Wavelength (Å)	0.71073	Measured reflections	6531
Crystal system	Monoclinic	Independent reflections	2153
Space group	$P2_1/n$	Reflections with I> 2σ(I)	1296
a ≠ b ≠c (Å)	14.77; 3.79; 21.57	Absorption correction	X-RED32 [9]
α = γ ≠ β (°)	90; 90; 91.73	$T_{min-max}$	0.913; 0.932
Crystal size (mm)	0.52; 0.23; 0.05	R_{int}	0.119
Z	4	Refinement method	
Volume, V ($Å^3$)	1209.54	Refinement method	F^2
μ (mm^{-1})	0.32	No of parameters	176
F (000)	568	R [F^2 > 2σ(F^2)]	0.095
θ (°)	1.4-39.1	$wR(F^2)$	0.281
Calculated density (Mgm^{-3})	1.519	GooF=S	1.09
Color and shape	Yellow; stick	$\Delta\rho_{min-max}$ (e $Å^{-3}$)	-0.28; 0.27

Table 2. Hydrogen bond geometry list for ClSB (Å)

D—H···A	D—H	H···A	D···A	D—H···A
C6—H6···O^{3i}	0.93	**2.53**	3.380 (8)	152
C13—H13···O^{3ii}	0.93	**2.65**	3.569 (8)	170
O1—H1···N1	1.08 (9)	**1.55 (9)**	2.602 (7)	163 (8)

Symmetry codes: (i)−x, −y−2, −z−1; (ii) −x, −y−1, −z−1.

Molecular docking experiments

We searched potential druggable targets of ClSB *via* LigTMap and listed the docking parameters in Table 5 for top candidates. The search was performed in 17 target classes. Among them, hydrolase, kinase and transferases were determined as most potential candidates for our compound. We selected and listed them, if the docking score was equal to or lower than -7.00 kcal/mol. In this sense, cAMP and cAMP-inhibited cGMP 3',5'-cyclic phosphodiesterase 10A, serine/threonine-protein kinase pim-1, cell division protein kinase 2, cell division protein kinase 5, sulfotransferase 1A1, and thankyrase-2 were determined as potential biological targets. We listed in Table 5 the docking results and other parameters calculated. Top ranked target was found thankyrase 2 with the docking scores of -9.266 and -8.621 kcal/mol. Thankyrase 2 (TNKS 2) plays a role in fundamental cellular processes [10] and is connected with diseases such as cancer [11].

Frontier molecular orbitals (FMOs)

The FMOs obtained with the DFT/B3LYP 6-311 G ++ (d, p) basis set are shown in Fig. 3 for ClSB. We calculated HOMO and LUMO orbitals to predict electronic transitions in the molecule and to study its chemical reactivity parameters. The energy levels of HOMO and LUMO, which are the most important orbitals for chemical reactions, and the band gap were calculated to be -7.11 eV, -2.84 eV, and 4.27 eV, respectively. We also calculated reactivity descriptors including the chemical and ionization potentials, softness and hardness, electron affinity and electronegativity, electrophilicity and charge transfer index using the energy values of the HOMO and LUMO orbitals. These parameters, their formulas and calculated values are listed in Table 3**.**

BOILED-Egg model

Prediction of gastrointestinal absorption and BBB penetration was performed using a free web tool developed by Daine and Zoate [12].

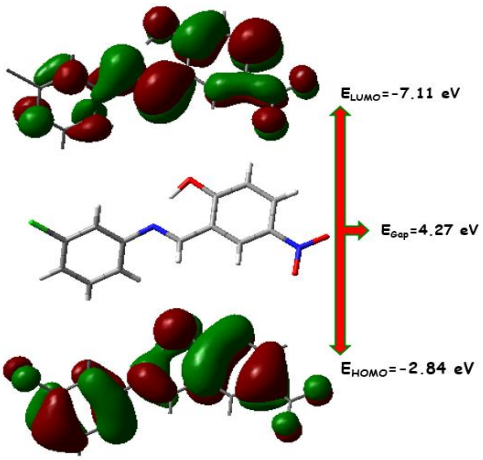


Fig. 3. HOMO and LUMO orbitals of ClSB

Table 3. Chemical reactivity descriptors of THSB

Parameters	Value (eV)
E_{HOMO}	-7.11
E_{LUMO}	-2.84
Energy band gap ($\Delta E = E_{LUMO}$-E_{HOMO})	4.27
Ionization potential ($I = -E_{HOMO}$)	7.11
Electron affinity ($A = -E_{LUMO}$)	2.84
Chemical hardness ($\eta = (I-A)/2$)	2.13
Chemical softness ($S = 1/2\eta$)	0.23
Electronegativity ($\chi = (I+A)/2$)	4.97
Chemical potential ($\mu = -(I+A)/2$)	-4.97
Electrophilicity index ($\omega = \mu^2/2\eta$)	5.79

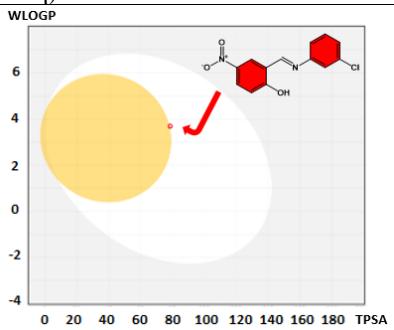
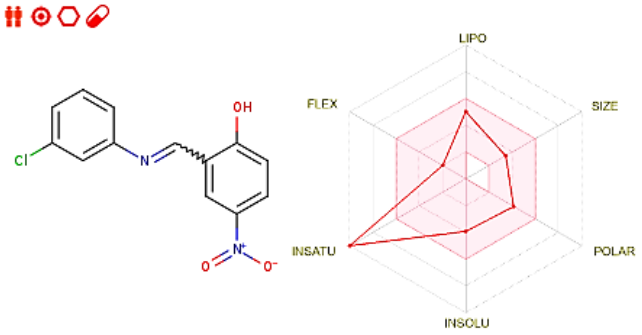


Fig. 4. BOILED-Egg model of the title compound for BBB permeation and GI absorption.

The Brain Or IntestinaL EstimateD permeation method (BOILED-Egg) places the studied molecules in an Egg model according to their octanol/water partition coefficient (WLOGP) and topological polar surface area (TPSA). It can be operated by uploading the simplified molecular-input line-entry system (SMILES) of the compounds under investigation. After the calculations, an output scheme was obtained as in Fig. 5 (for ClSB**).** In this figure, the yolk-colored and white regions represent

good brain access and gastrointestinal absorption, respectively. A molecule in the Egg-yolk area has access to the brain and can be absorbed by the gastrointestinal tract; in the other condition, the molecule is taken up only in the gastrointestinal tract. The grey area shows negative results in terms of both GI absorption and BBB penetration. The small red circle in Fig. 5 shows the location of ClSB. According to the above explanations, ClSB has no BBB permeation but it can be absorbed by the gastrointestinal tract.

Table 4. Physicochemical and pharmacokinetics properties of the title compound.



SMILES Clc1cccc(c1)/N=C/c1cc(ccc1O)[N+](=O)[O-]

Physicochemical Properties	
Formula	C13H9ClN2O3
Molecular weight	276.68 g/mol
Num. heavy atoms	19
Num. arom. heavy atoms	12
Fraction Csp3	0.00
Num. rotatable bonds	3
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	75.99
TPSA	78.41 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.89
Log $P_{o/w}$ (XLOGP3)	3.32
Log $P_{o/w}$ (WLOGP)	3.70
Log $P_{o/w}$ (MLOGP)	2.05
Log $P_{o/w}$ (SILICOS-IT)	1.81
Consensus Log $P_{o/w}$	2.55

Water Solubility	
Log *S* (ESOL)	-3.92
Solubility	3.35e-02 mg/ml ; 1.21e-04 mol/l
Class	Soluble
Log *S* (Ali)	-4.64
Solubility	6.30e-03 mg/ml ; 2.28e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-4.43
Solubility	1.04e-02 mg/ml ; 3.74e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-5.63 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	3 alerts: imine_1, nitro_group, oxygen-nitrogen_single_bond
Leadlikeness	Yes
Synthetic accessibility	2.51

Table 5. Docking parameters of ClSB with the targets predicted.

	Target Name	PDB ID	Target class	Ligand name	Ligand similarity score	Binding similarity score	LigT Map score	Predicted affinity (-logM)	Docking score (PSOVina2, kcal/mol)
1	cAMP and cAMP-inhibited cGMP 3',5'-cyclic phosphodiesterase 10A	4LM0	Hydrolase	5NI	0.41	0.4	0.407	5.14	-7.003
2	Serine/threonine-protein kinase pim-1	4ENX	Kinase	Z20	0.487	0.5	0.491	6.163	-7.435
3	Cell division protein kinase 2	3LE6	Kinase	2BZ	0.426	0.333	0.398	6.163	-7.292
4	Cell division protein kinase 5	3O0G	Kinase	3O0	0.44	0.182	0.363	6.163	-8.519
5	Sulfotransferase 1A1	3QVU	Transferase	NPO	0.544	0.2	0.441	6.29	-7.245
6	Thankyrase-2	410T	Transferase	1V0	0.425	0.25	0.373	6.29	-9.266
7	Thankyrase-2	4TKI	Transferase	33E	0.402	0.222	0.348	6.29	-8.621

CONCLUSION

In summary, a Schiff base molecule was synthesized and characterized. Its molecular structure was analyzed to determine its crystalline nature and secondary interactions. HOMO and LUMO orbitals were studied, and chemical reactivity descriptors were calculated. For medicinal chemistry evaluation, physicochemical properties, ADME descriptors, and drug-like properties were determined using SwissADME. Potential targets were screened in 17 enzyme classes and the top three classes (hydrolase, transferase, kinase) were selected for further docking evaluation. Seven enzymes within three enzyme classes achieved high docking scores (in this study, we reported the enzymes with docking scores equal to or lower than -7 kcal mol^{-1}). The best efficiency (docking scores of -9.266 and 8.621 kcal mol^{-1}) of the title compound was found against thankyrase 2, which belongs to the enzyme class of transferases. The title compound showed good absorption in the intestine, but unfavorable permeation through the BBB.

Acknowledgement: *This current study was not supported by any institution.*

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