4-((4-HYDROXY-3-METHOXY-5-NITROBENZYLIDENE)AMINO)PYRIMIDIN-2(1H)-ONE: SYNTHESIS, CHARACTERIZATION, BACTERIAL ASSAY, GEOMETRICAL ANALYSIS AND MOLECULAR DOCKING

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Abstract: ***4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one was obtained by the condensation of cytosine with 5-nitrovanillin and characterized by spectroscopic studies viz., Fourier-transform infrared and proton Nuclear Magnetic Resonance. The synthesised compound has been tested against Klebsiella aerogenes and Escherichia coli have significant antibacterial activity. 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one also subjected computational studies to were found to the geometrical, structural relative properties and molecular docking against Escherichia coli (PDB ID:3D3B).***

Keywords: Molecular Docking, 5-nitrovanillin, cytosine, Klebsiella aerogenes and Escherichia coli

I. INTRODUCTION

Schiff bases are condensation products of primary amines and carbonyl compounds and they were discovered by a German chemist, Nobel Prize winner, Hugo Schiff in 1864 [1]. The classical synthesis reported by Schiff involves the condensation of a carbonyl compound with an amine under azeotropic distillation. Schiff bases are characterized by an imine group –N=CH-, which helps to clarify the mechanism of transamination and racemization reaction in biological system [1]. It exhibits antibacterial and antifungal effect biological properties [2, 3]. Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base.

Schiff bases are used in optical and electrochemical sensors, as well as in various chromatographic methods to enable detection of enhanced selectivity and sensitivity [4-6]. Among the organic reagents actually used, Schiff bases possess excellent characteristics, structural similarities with natural biological substances, relatively simple preparation procedures and the synthetic flexibility that enables design of suitable structural properties [7]. Another important role of Schiff base structure is transamination [8]. Transamination reactions are catalysed by a class of enzymes called transaminases. They have attracted particular interest due to their biological activities [9] eg., acting as radio pharmaceuticals for cancer targeting [10]. Besides the biological activity, solid-state thermochromism and photochromism are an another characteristic of these compounds leading to their application in various areas of materials science such as control and measurement of radiation intensity, display systems and optical memory devices [11].

Quantum chemistry methods are of particular importance to understand stability and reactivity of target molecules [12]. In this sense, quantum chemical descriptors take advantage of structure and properties relationship to estimate and determine the reactivity. Global reactivity indexes have been widely used to study molecules and reactions [12-16] and have been effectively handled by the conceptual density functional theory (DFT)[16,17].

They are important compound due to their wide range of biological activities and industrial application. The objectives of the present investigations are (i) To synthesis of new Schiff bases. (ii) To characterization by FTIR and ^{1}H NMR. (iii) To study the antibacterial activity. (iv) To study geometry by computational method and (v) To study molecular docking to receptor-protein.

II. EXPERIMENTAL PROCEDURE

2.1 Materials

Cytosine and 5-nitrovanillin were purchased from Merck specialities Ltd., Mumbai, India. The solvents used were of Analar Reagent grade and purity was verifying by standard procedure.

2.2 Preparation of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one

25 ml of ethanolic solution of cytosine (1.11g, 0.01 mol) was added to 25 ml of ethanolic solution of 5-nitrovanillin (1.97 g, 0.01 mol). Then three drops of acetic acid was added to the reaction mixture. The reaction mixture was heated and refluxed for about 5 hours at 90°C. The resulting solution was further concentrated by water bath. The product 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one obtained was precipitated, cooled and collected after filtration. The precipitate was purified by washing with distilled water and then with ethanol. The 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one was again recrystallized in ethanol and then dried over vacuum desiccator.

2.3 Antibacterial Assay

The anti-microbial activity for the given sample was carried out by Disc Diffusion Technique (Indian Pharmacopoeia, Vol II A-105). The microorganisms of *Klebsiella aerogenes* and *Escherichia coli* were obtained from National Chemical Laboratory (NCL) Pune and maintained by periodical sub culturing on Nutrient agar medium for bacteria. The effect produced by the sample was compared with the effect produced by the positive control (Reference standard Ciprofloxacin 5µg/disc for bacteria). This work was carried out at Periyar College of Pharmaceutical Sciences Trichy-21.

2.4 Computational Aids

The geometries of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one was quantum chemical calculations were performed at B3LYP/6-31G (from "Becke, 3-parameter, Lee-Yang-Parr") level using Gaussian05W software package and GaussView05 visualization programs[18]. These optimized structures of the complexes were further considered for molecular docking analysis using HEX 6.3 i.e. an interactive protein docking and molecular superposition program and is usually used for feasible docking of protein–protein, ligands with proteins, enzymes, and DNA[19]. The docking parameters were set to include ligand–DNA interactions and various non-covalent interactions as implemented in the program. The crystal structure of B-DNA (the duplex DNA d(CGCGAATTCGCG)2 dodecamer (PDB ID: 3D3B)) was taken from Protein Data Bank (PDB) and used for docking studies.

III. RESULTS AND DISCUSSION

3.1 FTIR Spectra

The vibrational Spectra of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one shows valuable information on the subject of the nature of functional groups in **Fig 1**. 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one having a broad with weak band appeared at 3280 cm^{-1} & a sharp peak at 796 cm^{-1} showed amide functional group, a broad peak at 3262 cm^{-1} & a sharp peak at 751 cm^{-1} refers to hydroxyl group in benzylidine ring, a sharp peak at 1741 cm^{-1} designates ketone group, a strong sharp peak presented at 1642 cm^{-1} confirms the azomethine, a sharp peak at 1633 cm^{-1} indicates secondary ketimine, a medium sharp peak at 1570 cm^{-1} designates aromatic nitro group in benzylidine ring, a sharp eak at 1309 cm^{-1} showed aromatic methoxy group in benzylidine ring and a sharp peak at 1246 cm^{-1} refers to methoxy oxygen-carbon group.

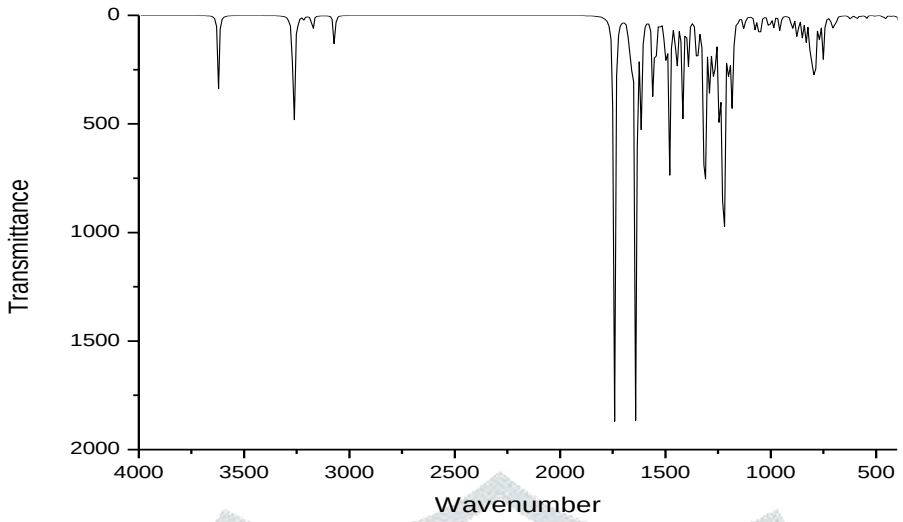


Fig 1. FTIR Spectra Evidence of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one

3.2 ^{1}HNMR Spectra

The ^{1}NMR spectra results given in the **Fig 2** confirm the presence of compound 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one. 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one having a weak & with broad singlet band at 14.15 ppm showed hydroxyl proton in benzylidine ring, a strong singlet peak at 10.99 ppm denotes amide proton in pyrimidine ring, a stronger with sharp singlet peak at 8.30 ppm confirms azomethine proton, a medium sharp singlet peak at 8.30 ppm indicates single proton in benzylidine ring, a singlet peak with sharp medium at 7.76 ppm mentions a single proton in benzylidine ring, a medium sharp doublet peak at 7.38 ppm (J=8.4) refers to single proton in pyrimidine ring, a medium sharp doublet peak at 5.35 ppm (J=7.9) specifies single proton in pyrimidine ring and a strong sharp singlet peak at 3.83 ppm refers to three methoxy proton in benzylidine ring.

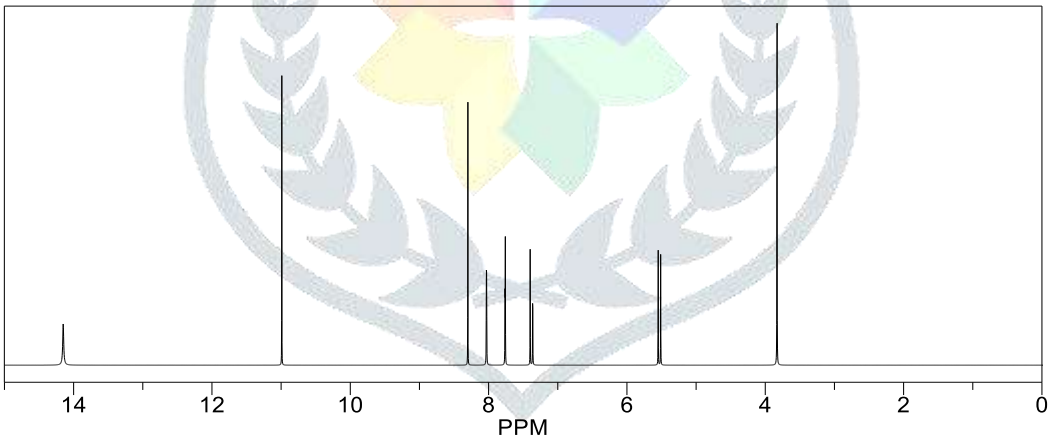


Fig 2. ^{1}HNMR Spectral Evidence of 4-((4-hydroxy-3-methoxybenzylidene)amino)pyrimidin-2(1H)-one

3.3 Antibacterial Study

Pyrimidine derived compound 4-((4-hydroxy-3-methoxybenzylidene)amino)pyrimidin-2(1H)-one were tested against two gram negative microorganisms (*Klebsiella aerogenes* and *Escherichia coli*) by Disc Diffusion Method results given in **Table 1 & 2**. From the observation report values given in diameter of growth of bacteria inhibited or killed by the pyrimidine derived compound 4-((4-hydroxy-3-methoxybenzylidene)amino)pyrimidin-2(1H)-one having strong electron donating hydroxyl group. 4-((4-hydroxy-3-methoxybenzylidene)amino)pyrimidin-2(1H)-one against *Klebsiella aerogenes* in 23 mm & *Escherichia coli* in 31 mm and Standard was 30 mm & 38 respectively i.e., pyrimidine derivative compound highly active.

Table 1. 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one

Name of the Microorganisms	Zone of Inhibition (d in mm)		
	Schiff Base	Solvent control	Standard
Klebsiella aerogenes	23	-	30
Escherichia coli	31	-	38

Table 2. Observation Report

Inhibition Zone >15 mm	Highly Active
Inhibition Zone > 10 mm	Moderately Active
Inhibition Zone > 5 mm	Slightly Active
Inhibition Zone ≤ 5mm	Inactive

3.4 Molecular Geometry and Structure-Property Relationship

The term computational chemistry is usually used when a mathematical method is sufficiently well developed that it can be automated for implementation on a computer. Computational chemistry is the application of chemical, mathematical and computing skills to the solution of interesting chemical problems.

The B3LYP exchange-correlation functional (from "Becke, 3-parameter, Lee-Yang-Parr") is based on Density Functional Theory (DFT), so all the properties of a given system are calculated based on its electronic density. Theoretically, compared to methods such as Hartree-Fock (HF), for instance, the consideration of correlation effects increases its prediction capacity.

The molecular structure and numbering of the atoms of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one was shown in **Fig 3**. The optimized geometrical parameters of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one obtained by DFT/B3LYP and HF with 6-31+G(d) basic set are presented in Table 3.

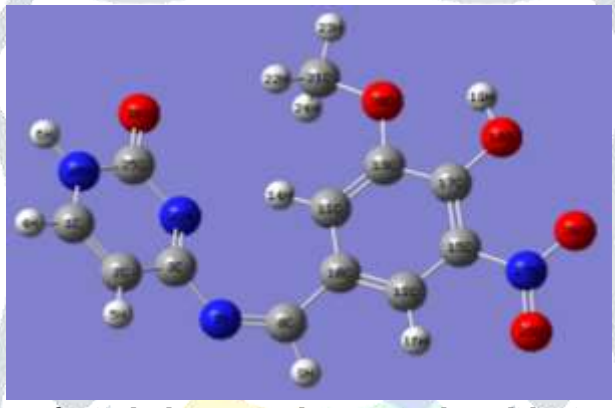


Fig 3. Optimised geometry of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one

In the present work, geometry optimization parameters for 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one have been employed without symmetry constrain. From **Table 3**, it is found that the bond lengths, bond angles and dihedral angles calculated by DFT/B3LYP and HF methods were consistent with experimental value.

Table 3. A comparison between the optimized geometrical parameters calculated at DFT/B3LYP and HF at 6-31+G(d) level of theory for 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one

Radius	Values in Angstroms		Angle	Values in Degrees		Dihedral Angle	Values in Degrees	
	DFT	HF		DFT	HF		DFT	HF
R(1C,2C)	1.364	1.4295	A(2C,1C,4H)	123.2772	116.2559	D(4H,1C,2C,3C)	179.1662	-179.7131
R(1C,7N)	1.0826	1.4024	A(2C,1C,30N)	119.8774	123.1405	D(4H,1C,2C,5H)	0.8096	0.1783
R(1C,28O)	1.37	1.298	A(4H,1C,30N)	116.8444	120.6028	D(30N,1C,2C,3C)	-0.4637	-0.0464
R(2C,3C)	1.4392	1.3461	A(1C,2C,3C)	117.3955	116.3667	D(30N,1C,2C,5H)	-178.8202	179.845
R(2C,4H)	1.0793	1.0662	A(1C,2C,5H)	122.3475	120.3722	D(2C,1C,30N,6H)	-178.9242	-172.0554
R(3C,5H)	1.3845	1.0699	A(3C,2C,5H)	120.2365	123.261	D(2C,1C,30N,25C)	-1.6771	8.7789
R(3C,29O)	1.3338	1.3601	A(2C,3C,7N)	115.8738	123.3573	D(4H,1C,30N,6H)	1.4226	4.9511
R(6H,29O)	1.0112	0.9939	A(2C,3C,31N)	122.2059	119.9966	D(4H,1C,30N,25C)	178.6698	-174.2146
R(7N,8C)	1.2942	1.2734	A(7N,3C,31N)	121.7831	116.6461	D(1C,2C,3C,7N)	-175.8504	0.1234
R(8C,9H)	1.0927	1.0782	A(7N,8C,9H)	113.7401	120.9471	D(1C,2C,3C,31N)	-0.0394	179.7762
R(8C,10C)	1.4702	1.4609	A(7N,8C,10C)	132.9728	121.52	D(5H,2C,3C,7N)	2.5425	179.9705
R(10C,11C)	1.4198	1.3987	A(9H,8C,10C)	113.2178	117.5327	D(5H,2C,3C,31N)	178.3535	0.0087
R(10C,12C)	1.4003	1.3807	A(8C,10C,11C)	124.0969	119.8773	D(2C,3C,8C,9H)	52.3052	0.0825
R(11C,13C)	1.3797	1.3744	A(8C,10C,12C)	116.898	121.1893	D(2C,3C,8C,10C)	-125.501	-179.8793
R(11C,14H)	1.0836	1.0723	A(11C,10C,12C)	118.9764	118.9333	D(31N,3C,8C,9H)	-141.2794	179.9475

R(12C,15C)	1.4006	1.3885	A(10C,11C,13C)	119.4926	121.5864	D(31N,3C,8C,10C)	40.9144	-0.0495
R(12C,16H)	1.0824	1.0689	A(10C,11C,14H)	118.3703	120.8346	D(2C,3C,31N,25C)	2.7206	-0.0168
R(13C,17C)	1.4205	1.3995	A(13C,11C,14H)	122.1165	117.5758	D(7N,3C,31N,25C)	178.2862	179.9862
R(13C,18O)	1.3888	1.3692	A(10C,12C,15C)	121.0685	119.7711	D(7N,8C,10C,11C)	-28.5396	179.8527
R(15C,17C)	1.4056	1.403	A(10C,12C,16H)	121.3591	120.0484	D(7N,8C,10C,12C)	153.4349	-0.0331
R(15C,21C)	1.4602	1.4383	A(15C,12C,16H)	117.5665	120.1805	D(9H,8C,10C,11C)	154.7486	-0.0499
R(17C,19H)	1.36	1.3454	A(11C,13C,17C)	122.1828	120.1632	D(9H,8C,10C,12C)	-23.2769	-179.9357
R(18O,24H)	0.9864	1.4481	A(11C,13C,20O)	125.544	118.4663	D(8C,10C,11C,13C)	-179.6736	-179.9649
R(19H,20O)	1.4659	0.9571	A(17C,13C,20O)	112.2692	121.2504	D(8C,10C,11C,14H)	-1.2879	0.6986
R(20O,23H)	1.0926	1.8467	A(12C,15C,17C)	120.4307	121.6499	D(12C,10C,11C,13C)	-1.6864	-0.0766
R(21C,22H)	1.0884	1.2169	A(12C,15C,27N)	117.1871	117.5623	D(12C,10C,11C,14H)	176.6993	-179.413
R(21C,23H)	1.0939	1.2427	A(17C,15C,27N)	122.3795	120.7858	D(8C,10C,12C,15C)	-179.0337	-179.9095
R(24H,25C)	1.2477	1.0758	A(13C,17C,15C)	117.7918	117.8921	D(8C,10C,12C,16H)	0.0669	0.0237
R(24H,26O)	1.4193	1.0757	A(13C,17C,18O)	118.0925	116.623	D(11C,10C,12C,15C)	2.8353	0.2036
R(24H,27N)	1.388	1.0823	A(15C,17C,18O)	124.0932	125.4835	D(11C,10C,12C,16H)	-178.0641	-179.8632
R(28O,30N)	1.2598	1.378	A(17C,18O,19H)	108.0866	120.7577	D(10C,11C,13C,17C)	-0.3614	-0.4145
R(29O,30N)	1.2711	1.3957	A(13C,20O,21C)	118.7746	114.375	D(10C,11C,13C,20O)	178.8556	-176.4799
R(30N,31N)	1.4391	1.2213	A(20O,21C,22H)	111.3431	119.1168	D(14H,11C,13C,17C)	-178.6844	178.9428
			A(20O,21C,23H)	104.9164	118.5722	D(14H,11C,13C,20O)	0.5327	2.8773
			A(20O,21C,24H)	110.269	122.311	D(10C,12C,15C,17C)	-1.9271	0.1584
			A(22H,21C,23H)	110.4912	105.0545	D(10C,12C,15C,27N)	178.6604	179.66
			A(22H,21C,24H)	109.2827	110.3335	D(16H,12C,15C,17C)	178.9393	-179.7747
			A(23H,21C,24H)	110.4848	110.1467	D(16H,12C,15C,27N)	-0.4732	-0.2731
			A(26O,25C,30N)	119.9256	110.6119	D(11C,13C,17C,15C)	1.2758	0.7523
			A(26O,25C,31N)	123.9363	109.9859	D(11C,13C,17C,18O)	179.6229	-179.6675
			A(30N,25C,31N)	116.1075	110.577	D(20O,13C,17C,15C)	-178.0358	176.7063
			A(15C,27N,28O)	119.1933	121.6078	D(20O,13C,17C,18O)	0.3114	-3.7135
			A(15C,27N,29O)	117.2672	121.062	D(11C,13C,20O,21C)	-5.1595	-118.3909
			A(28O,27N,29O)	123.5378	123.4214	D(17C,13C,20O,21C)	174.1244	65.5882
			A(1C,30N,6H)	121.3726	115.5167	D(12C,15C,17C,13C)	-0.134	-0.6335
			A(1C,30N,25C)	122.981	115.4669	D(12C,15C,17C,18O)	-178.3732	179.8274
			A(6H,30N,25C)	115.594	124.6294	D(27N,15C,17C,13C)	179.2473	179.8809
			A(3C,31N,25C)	121.2804	119.9037	D(27N,15C,17C,18O)	1.0081	0.3417
			L(3C,7N,8C,10C,-1)	132.5441	183.0855	D(12C,15C,27N,28O)	-172.9385	1.2374
			L(3C,7N,8C,10C,-2)	182.9981	1.3345	D(12C,15C,27N,29O)	6.6021	-178.8162
						D(17C,15C,27N,28O)	7.6612	-179.2566
						D(17C,15C,27N,29O)	-172.7982	0.6899
						D(13C,17C,18O,19H)	-0.2495	178.0201
						D(15C,17C,18O,19H)	177.9848	-2.4355
						D(13C,20O,21C,22H)	61.0145	169.3156
						D(13C,20O,21C,23H)	-179.445	-71.4459
						D(13C,20O,21C,24H)	-60.4689	50.9119
						D(26O,25C,30N,1C)	-173.921	-0.1517
						D(26O,25C,30N,6H)	3.473	179.8519
						D(31N,25C,30N,1C)	4.146	0.117
						D(31N,25C,30N,6H)	-178.46	-179.8864
						D(26O,25C,31N,3C)	173.398	-179.8801
						D(30N,25C,31N,3C)	-4.5827	0.1165

3.5 Global Reactivity descriptor

The interaction between two atomic or molecular orbital leads to the formation of two new orbitals, higher energy orbital (Anti-bonding orbital) and the lower energy orbital (Bonding orbital). When one of the initial is filled with a pair of electrons (Lewis base) and the other is empty (Lewis acid), we can place the two electrons in to bonding orbital. The 'filled- empty' interaction is therefore stabilizing i.e., frontier orbitals. The interacting molecular orbital, interact generally with the higher energy occupied molecular orbital (LUMO) of the molecule. These orbitals are the pair of orbitals in the molecule, which allow them to interact most strongly. These orbitals are also called 'frontier' orbitals, because they lie at the outermost boundaries of the electrons of the molecule. The HOMO-LUMO analysis for the titled molecule is carried out by using B3LYP/6-31+G(d) level.

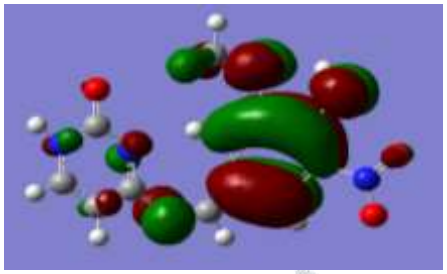


Fig 4. HOMO (DFT)

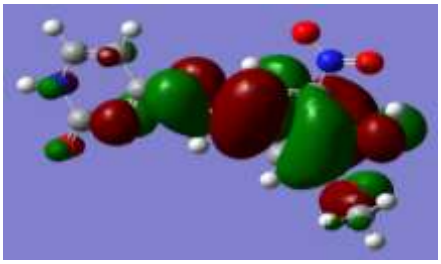


Fig 5. HOMO (HF)

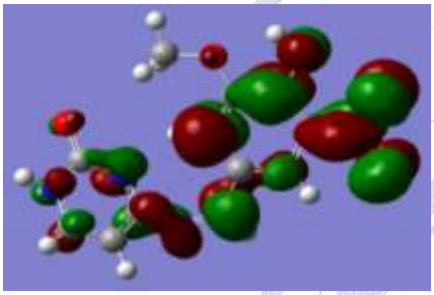


Fig 6. LUMO (DFT)

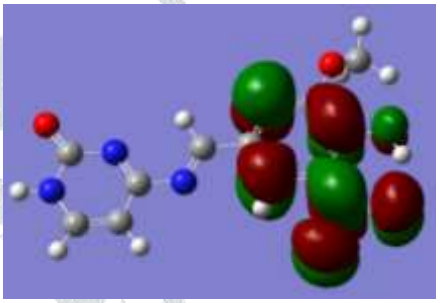


Fig 7. LUMO (HF)

Pyrimidine derivative 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one both DFT and HF level HOMO & LUMO images are shown in **Fig 4, 5, 6 & 7**. 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one having molecular orbital energy both DFT/B3LYP and HF with 6-31+G(d) level HOMO present at nitrogen in azomethine, at oxygen in hydroxyl group located in benzylidine ring and oxygen in methoxy group located in benzylidine ring. Similarly, at same level LUMO present at two oxygen atoms in nitro group located in benzylidine ring and whole benzylidine ring.

4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one band gap having both level shown in **Table 4**.

Table 4. A comparison between the Molecular Orbital Energy (eV) level calculated at DFT/B3LYP and HF at 6-31+G(d) level of theory for 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one

Method	HOMO-3 a.u.	HOMO-2 a.u.	HOMO-1 a.u.	HOMO a.u.	LUMO a.u.	LUMO+1 a.u.	LUMO+2 a.u.	LUMO+3 a.u.	Band Gap in eV
DFT	-0.275	-0.261	-0.253	-0.242	-0.097	-0.086	-0.048	-0.014	3.9455
HF	-0.424	-0.387	-0.348	-0.343	0.015	0.025	0.106	0.136	9.7414

3.6 Molecular Docking

The Schiff base of pyrimidine derived compound undergoes to molecular docking with *Escherichia coli* receptor-protein (PDB ID: 3D3B). 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one optimized geometries shown in **Fig 3**. and the selected bond parameters with the crystal structure data are given in **Table 3**.

3.6.1 Interactions of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with Receptor-protein

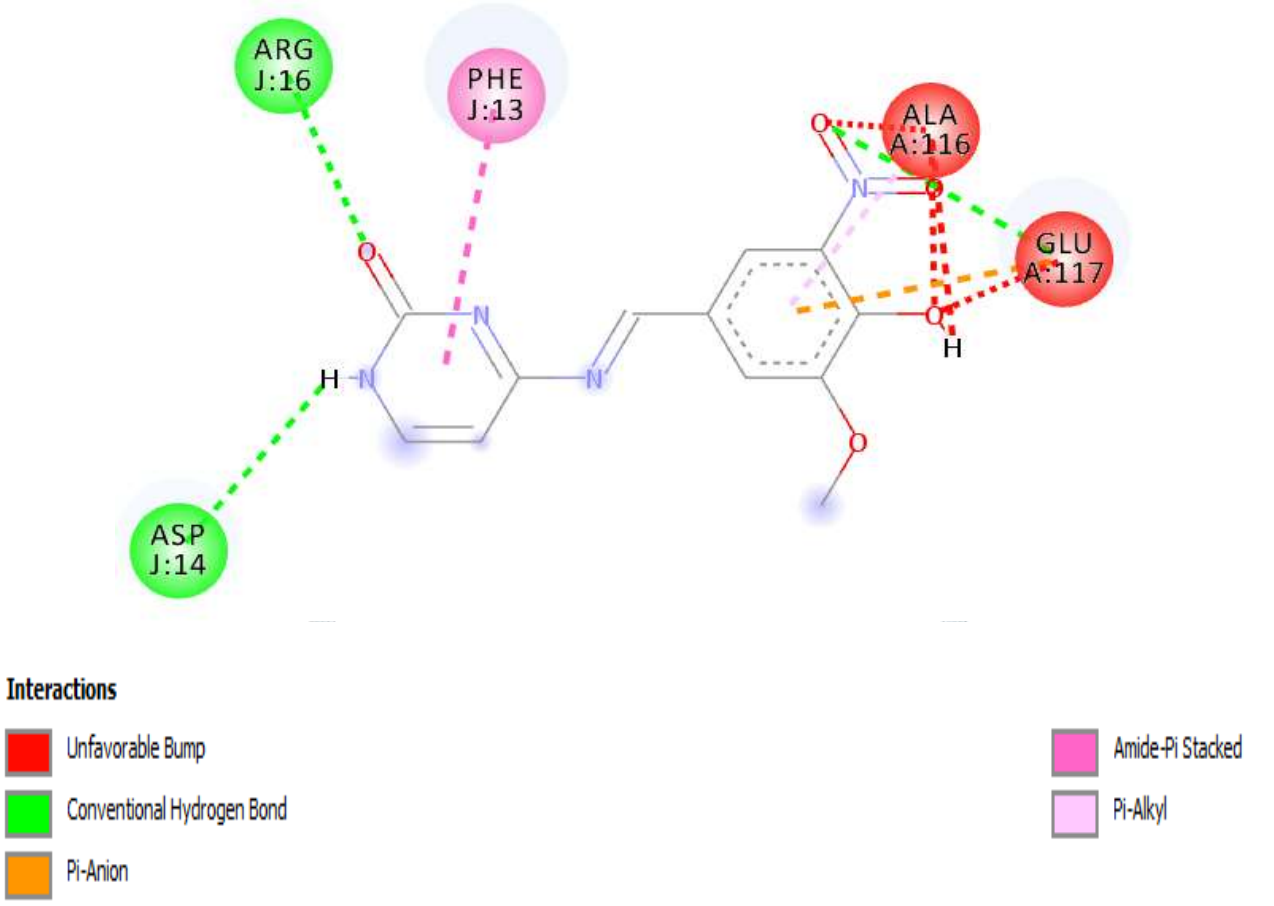


Fig 8. Interactions of receptor-protein with 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one

Conventional hydrogen bond between glutamic acid (GLU A:117) to hydroxyl oxygen in benzylidine ring (18O) with band distance 2.8699 Å. Glutamic acid (GLU A:117) to benzylidine ring having nitro group oxygen (28O) conventional bond having distance 2.5189 Å. Arginine (ARG J:16) to oxygen (26O) at ketonic group in pyrimidine ring having interatomic distance 2.3357 Å and Interatomic distance 7.7663 Å refers to the conventional hydrogen bond between pyrimidine ring hydrogen (6H) to aspartic acid (ASP J:14).

The carbon hydrogen bond 2.7858 Å indicates intra-hydrogen bond between methoxy hydrogen (22H) in benzylidine ring to ketonic oxygen (26O) in pyrimidine ring.

Amide-Pi Stacked and Pi-Alkyl bonds were hydrophobic type of bond. Amide-Pi Stacked bond showed from Phenylalanine (PHE J:13) to amide ring with interatomic distance 3.218 Å and from alanine (ALA A:116) alkyl to benzylidine ring Pi-Alkyl bond with 5.1556 Å.

The steric effect shown unfavourable bump between ligand and receptor-protein in **Fig 8**. From alanine (ALA A:116) carbon atom(s) having interatomic distance 2.1982 Å, 1.8643 Å, 1.4873 Å, 1.7525 Å and 0.9146 Å confirms to hydroxyl oxygen, nitro group oxygen, hydroxyl hydrogen (from another carbon), hydroxyl hydrogen and nitro group oxygen (from another carbon) in benzylidine ring respectively. The interatomic distance 2.0237 Å indicates unfavourable non-bonding bump from glutamic acid (GLU A:117) nitrogen atom to hydroxyl oxygen (18O) and the interatomic distance 1.1732 Å refers to hydroxyl oxygen from another nitrogen atom from glutamic acid (GLU A:117).

3.6.2 Basic group of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with Receptor-protein

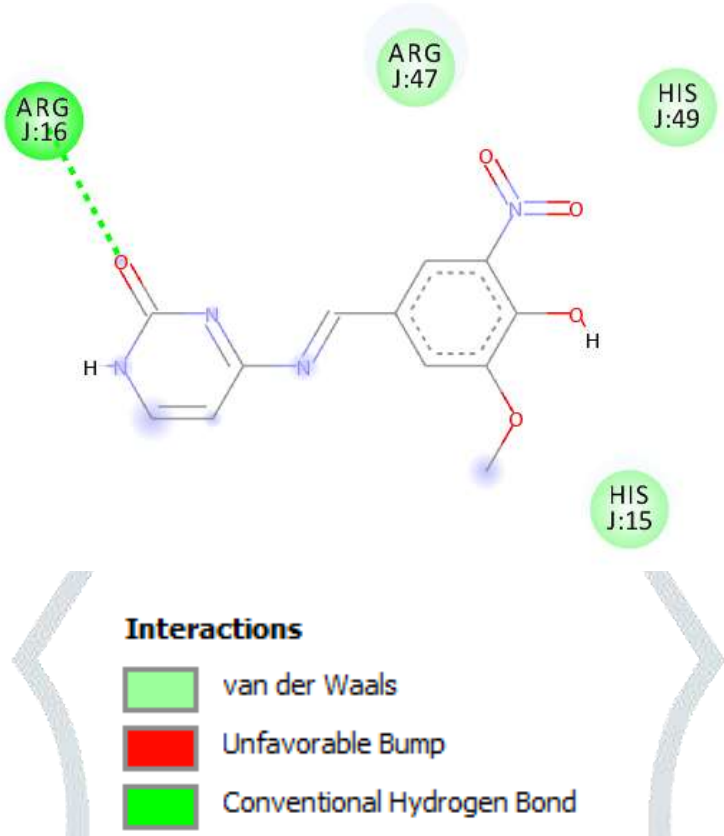


Fig 9. Basic group of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with Receptor-protein

In **Fig 9** shown 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one having van der Waals bond as a basic groups were as with Arginine (ARG J:16) having pKa=12, arginine (ARG J:47) consuming pKa=12, histidine (HIS J:15) with pKa=6 and histidine (HIS J:49) with pKa=6.

3.6.3 Neutral group of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with Receptor-protein

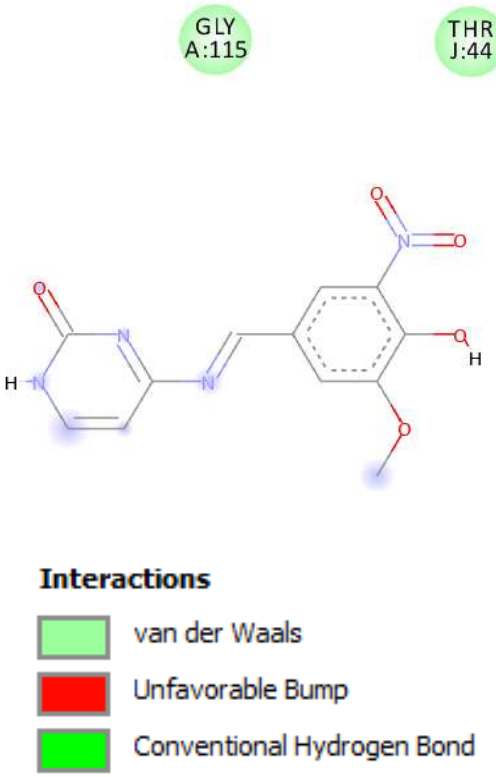


Fig 10. Neutral group of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with Receptor-protein

The neutral groups of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with glycine (GLY A:115) and threonine (THR J:44) without pKa values showed in **Fig 10**.

3.6.4 Acidic group of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with Receptor-protein

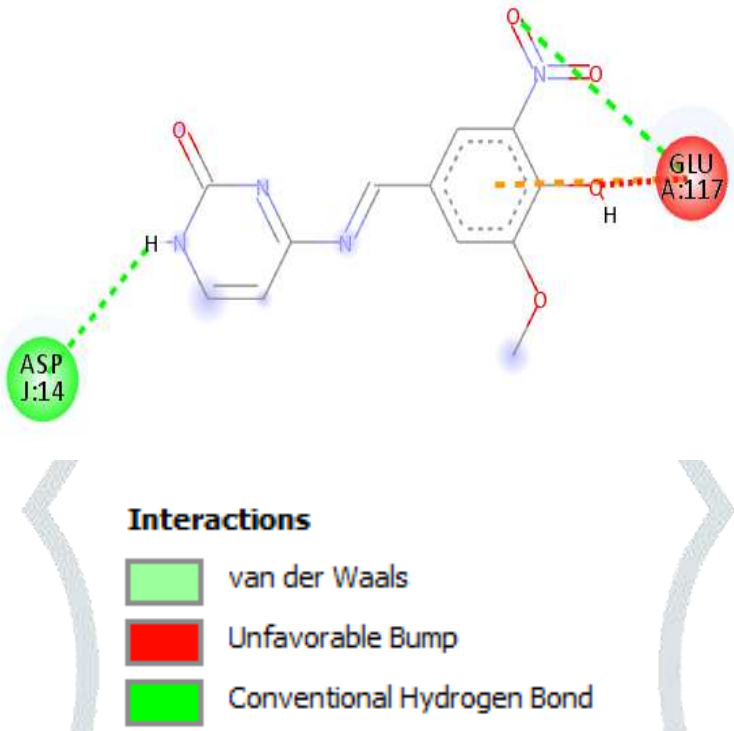
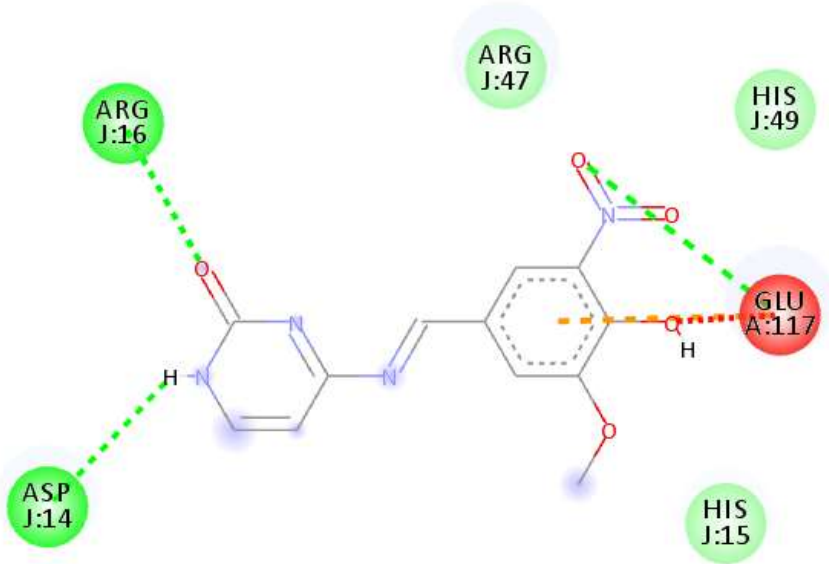


Fig 11. Acidic group of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with Receptor-protein

The van der Waals force make acidic groups in aspartic acid (ASP J:14) consuming pKa=3.9 and glutamic acid (GLU A:117) having pKa=4.3 with 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one in **Fig 11**.

3.6.5 Hydrophilic group of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with Receptor-protein



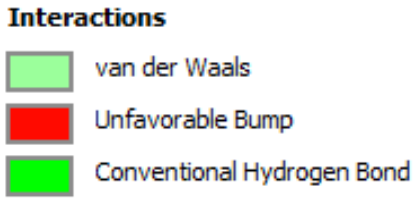


Fig 12. Hydrophilic group of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with Receptor-protein

In **Fig 12** shows 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one is hydrophilic in nature, since it attracts the water molecule from the receptor-protein. Arginine (ARG J:16) and arginine (ARG J:47) possess hydrophobicity -4.5 and pKa=12, glutamic acid (GLU A:117) having hydrophobicity -3.5 and pKa=4.3 and aspartic acid (ASP J:14) takes hydrophobic -3.5 and pKa=3.9, histidine (HIS J:15) and histidine (HIS J:49) having pKa=6 and hydrophobic value -3.2 with 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one

3.6.6 Hydrophobic group of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with Receptor-protein

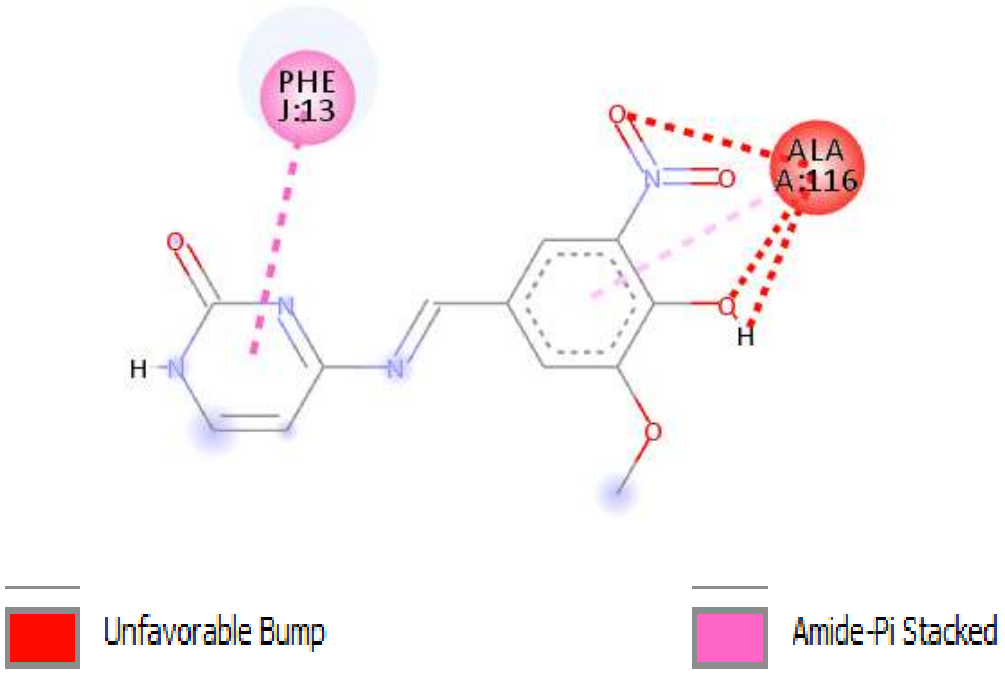


Fig 13. Hydrophobic group of 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one with Receptor-protein

4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one having water repellent nature i.e., hydrophobic groups with receptor-protein. Phennylalanine (PHE J:13) and alanine (ALA A:116) having positive hydrophobic values were +2.8 and +1.8 respectively without any pKa values showed in **Fig 13**.

IV. CONCLUSIONS

In the present research work, our efforts were to synthesis and characterise the 4-((4-hydroxy-3-methoxy-5-nitrobenzylidene)amino)pyrimidin-2(1H)-one by condensation method. This compound was characterized by various spectral analysis with literature evident pharmacological importance and applications. Significant advances continue to be made in the fields of molecular docking screens that are benefiting drug discovery. Molecular docking provides an extremely rapid way to evaluate likely binders from a large chemical library with minimal cost. Unfortunately, limitations in the accurate ranking of true binders by molecular docking programs require further experimental validation. The molecular modelling techniques has been shown to enable the rapid determination of reliable protein–ligand co-structures, the identification of new therapeutic targets, and the successful discovery of new drug leading.

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