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A New Pyrazolone Schiff Base: Synthesis, Characterization and Molecular Docking and Antioxidant Studies

Ramasamy Uthayamalar,[a,b] Narayanasamy Nivetha[c] and Ganesan Ayyannan*[a]

[a]*Post-Graduate and Research Department of Chemistry, Sri Ramakrishna Mission Vidyalaya College of Arts and Science, Coimbatore – 641 020, Tamil Nadu, India.*

[b]*Department of Science and Humanities, Sri Krishna College of Technology, Coimbatore-641042, Tamil Nadu, India.*

[c]*Department of Chemistry, Karpagam Academy of Higher Education, Coimbatore 641021, Tamil Nadu, India*

***Corresponding author E-mail address**: ayyannang@gmail.com (G. Ayyannan)

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Abstract: A novel hetero atom containing Schiff base (NCQ) is synthesized by reacting 4-amino antipyrine with 2-Chloro-benzo[h]quinoline-3-carbaldehyde and the ligand was characterized using elemental analysis ultraviolet–visible spectroscopy (UV-vis), Fourier-transform infrared spectroscopy (FT-IR), 1H and 13C nuclear magnetic resonance spectroscopy (NMR). The molecular structure of the ligand was confirmed by single crystal X-ray diffraction studies. The synthesized compound has adopted a monoclinic crystal system with P21/n space group. Molecular docking studies were carried out for the synthesized compound (NCQ) in order to analyze its binding affinity towards cancer proteins 1DTO and 1JNX. The NCQ compound showed excellent interactions with cancer proteins 1DTO and 1JNX.

Keywords: Quinoline; Pyrazoline; Schiff base; Crystal structure; Docking studies

1. Introduction

Quinoline compounds have been widely studied in medicinal applications due to their versatile biological activities. The application of quinoline compounds in industry, analytical sensitivity and biological importance is also highly significant. Compounds containing a quinoline framework are often found applications in pharmaceuticals and often used as general synthetic building blocks for organic molecules synthesis. The heterocyclic N-atom present in the quinoline structural skeleton plays a key role in enabling the qiunoline compounds biologically very importance. Recently, development of heterocyclic compounds has gained huge attention, particularly, the design and development of the compounds that are biologically active molecules. Heterocyclic compounds play an important role in designing new classes of medicinally important structural entities. Particularly, the quinoline derivatives continuously gain attention due to its structural features.[1,2] Quinoline is an important class of heterocyclic compounds found in many synthetic and natural products with a wide range of pharmacological activities such as anti-inflammatory,[3] antimalarial,[4] antimicrobial,[5] anticancer,[6] antidiabetic[7] and antitumor[8] and platelet derived growth factor receptor tyrosine kinase inhibiting agents which can be well illustrated by the large number of drugs in the market. Genin et al.,[5] studied antibacterial activity of N−C-linked (azolylphenyl)oxazolidinones against the gram-negative organisms. Penov-Gasi et al.,[8] reported a convenient “click” synthesis for D-homo fused steroidal tetrazoles and the resultant compounds were evaluated as potential anti-proliferative agents against a panel of human cancer cell lines. Among the quinoline compounds studied, pyrazoline containing N-atom heterocyclic has exhibited remarkable biological activities. Alike pyrazoline, nitrogen heterocycles have also exhibited remarkable biological activities particularly in pharmaceuticals.[9-13]

Docking of small molecules into the active site of the receptor, and evaluating the binding affinity of the complex is more significant for the structure based drug designing process. Docking studies estimate the favourable conformations and binding strength of a ligand molecule which bound to a protein pocket. Docking applications are wide array which include protein function prediction,[14] drug level optimization,[15] drug repositioning,[16] polypharmacology prediction,[17] and binding pocket prediction.[18] Furthermore, the anti-cancer activities of the compound toward cervical cancer (1DTO) and breast cancer (1JNX) were also evaluated. Anti-oxidant activities of the synthesized compounds were identified by DPPH and OH assays. Owing to the highly promising biological activities of quinoline and pyrazoline, we synthesized quinoline and pyrazolinee fused analog. In the present work, we report the synthesis and characterization of quinoline based pyrazolone compound. Anti-cancer potential of the 4-((2-chlorobenzo[h]quinolin-3-yl)methyleneamino)-1,5-dimethyl-2phenyl-1,2-dihydropyrazol-3-one were also screened through molecular docking studies. The prepared compound was characterized using elemental analysis UV-visible, FT-IR, ^{1}H and ^{13}C NMR spectroscopy. The molecular structure of the ligand was confirmed by single crystal

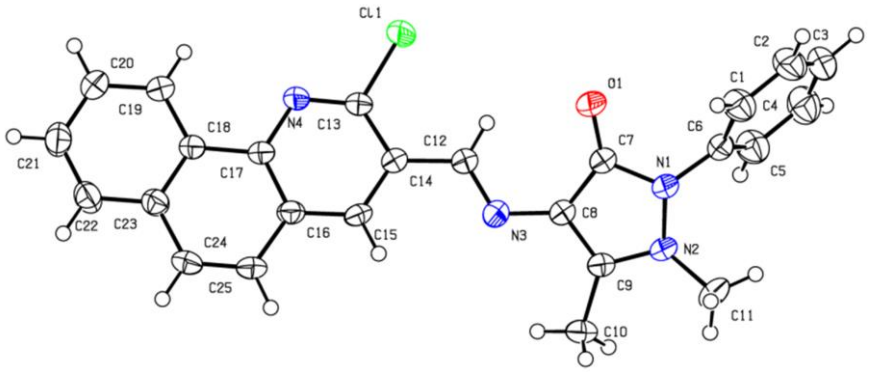


Fig. 1. ORTEP diagram of **NCQ** with thermal ellipsoid at 50% probability.

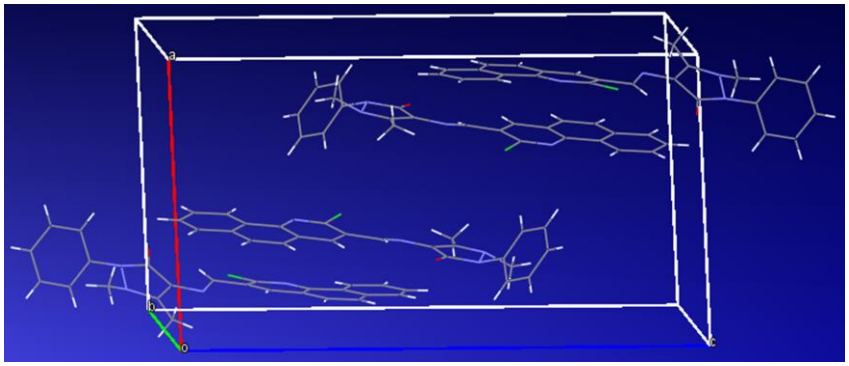


Fig. 2. Crystal packing diagram of **NCQ.**

X-ray diffraction studies. In addition, molecular docking studies were carried out for the synthesized compound in order to analyze its binding affinity towards cancer proteins 1DTO and 1JNX.

2. Experimental Section

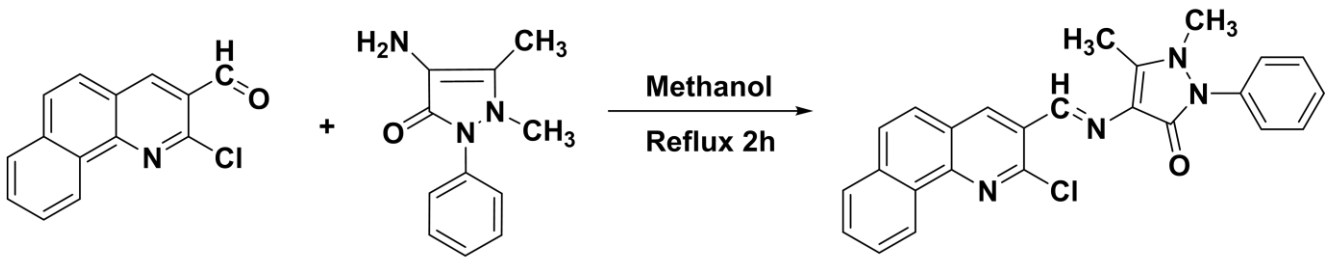
2.1. Materials and Methods

All the reagents used were of analytical or chemically pure grade. Solvents were purified and dried according to standard procedures.[19] Microanalyses (C, H and N) were performed on a Vario EL III CHNS analyser. IR spectra were recorded as KBr pellets in the 400-4000 cm^{-1} region using a Perkin Elmer FT-IR 8000 spectrophotometer. Electronic spectra were recorded in DMSO solution with a Systronics double beam UV-vis spectrophotometer 2202 in the range 200-800 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV III 500 MHZ instrument using TMS as an internal standard. Melting points were recorded with Veego VMP-DS heating table.

2.2. Synthesis of Pyrazolone Schiff base (NCQ)

In the typical synthesis, 4-Amino antipyrine (911 mg, 0.01 mol) dissolved in warm methanol (50 ml) was added to a methanol solution (50 ml) containing 2-Chloro-benzo[h]quinoline-3-carbaldehyde (1.73 g, 0.01 mol). The mixture was refluxed for 1 h and yellow precipitate was obtained. The reaction mixture was then cooled to room temperature and the solid was filtered out. It was then washed with methanol and dried under vacuum. Yellow colored single crystals suitable for X-ray diffraction studies were obtained from slow evaporation of a solution of NCQ in a DMF/methanol mixture.

4-[(2-Chloro-benzo[h]quinolin-3-ylmethylene)-amino] -1, 5 dimethyl - 2 - phenyl-1, 2-dihydro-pyrazol-3-one (NCQ): Yield: 91%; M.P: 176°C. Anal. calcd. for $C_{25}H_{19}ClN_4O$ (%): C, 70.34; H, 4.49; N, 13.12, Found (%): C, 69.32; H, 3.87; N, 13.91. IR (KBr, cm^{-1}): 1658 ν(C=O); 1598 ν(C=N); 768 ν(C-Cl); UV–vis (DMSO), λ_{max} (nm): 295, 360 (π → π*, n→ π*). ^{1}H NMR (DMSO-d_6): δ 8.47 (CH=N), δ 7.2-7.6



Scheme 1. Synthesis of heterocyclic Schiff base (**NCQ**).

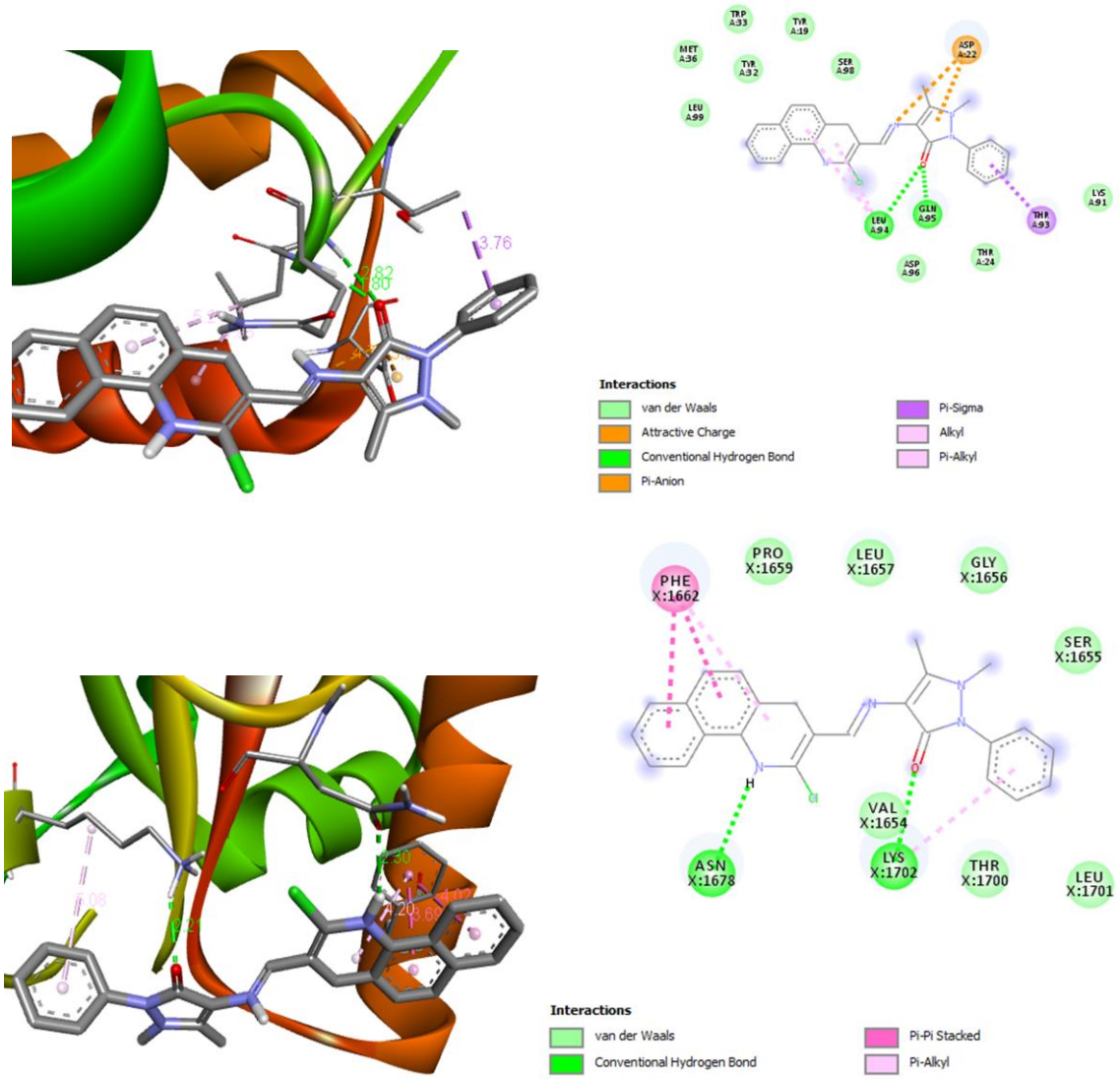


Fig. 3. Three-dimensional (3D) and two-dimensional (2D) binding interaction of compound **NCQ** with 1DTO and 1JNX proteins.

(m, H aromatic), δ 3.17 (N-CH_3), δ 3.45 (C-CH_3). ^{13}C NMR: δ 166 (C=O), δ 160 (C=N), δ 154 (C-Cl), δ 125-129 (m, C, aromatic), δ 64 (CH_3), δ 14 (N-CH_3).

2.3. Crystal Structure Determination

Single crystal X-ray diffraction data of NCQ were collected at room temperature on a Bruker AXS KAPPA APEX2 CCD diffractometer equipped with a fine focused sealed tube. The unit cell parameters were determined and the data collections of compound were performed using a graphite-mono chromate Mo Kα radiation (k = 0.71073 Å) by u and x scans. The data collected were reduced by SAINT program and the empirical absorption corrections were carried out using the SADABS program.[20,21] The structure of the NCQ was solved by direct methods[22] using SHELXS-97, which revealed the position of all non-hydrogen atoms, and was refined by full-matrix least squares on F^2 (SHELXL-97).[23] All non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were placed in calculated positions and refined as riding atoms.

2.4. Docking Procedure

Docking studies were performed for the synthesized compound (NCQ) against the target proteins (PDB ID: 1DTO and 1JNX) using AutoDock Tool (ADT). The 2D structure of the synthesized compound (ligand) was drawn and prepared for docking by using Chem3D Ultra 8.0. Protein data bank was utilized to download target proteins (receptor). AutoDock 4.2 version was used for docking studies and Chimera 1.10 and Discovery studio 4.5 were employed for visualization. Docking results were evaluated for binding score and hydrogen bonds between the ligand and the target receptor. Certain steps should be done before docking which includes: 3D structure of ligand, running conformational analysis, choosing the least energetic conformer and applying the docking procedures for the ligand using the receptors.

2.5. Antioxidant Assays

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity of the synthesized compound (NCQ) was measured according to the

Table 1. Crystal and structure refinement data

Compound	NCQ
Empirical formula	$C_{25}H_{19}ClN_4O$
Formula weight	426.89
Temperature	296(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a (Å)	12.4997(7) A
b (Å)	7.4015(3)
c (Å)	22.4304(12)
α (˚)	90
β (˚)	94.519(2)
γ (˚)	90
Volume ($Å^3$)	2068.73(18)
Z	4
Density (calculated) Mg/m^3	1.371
Absorption coefficient mm^{-1}	0.210
F(000)	888
Crystal size/mm^3	0.40 x 0.35 x 0.30
Theta range for data collection (°)	1.81 to 28.33
Index ranges	-16<=*h*<=16, -5<=*k*<=9, -29<=*l*<=29
Reflections collected	18067
Independent reflections	5080 [*R*(int) = 0.0292]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5080 / 0 / 284
Goodness-of-fit on F^2	0.831
Final *R* indices [*I*>2*σ* (*I*)]	R_1 = 0.0506, wR_2 = 0.1684
R indices (all data)	R_1 = 0.0752, wR_2 = 0.2131
Largest diff. peak and hole e.$Å^{-3}$	0.377 and -0.317

Table 2. Selected bond lengths [Å] and angles [°] of compound (**NCQ**).

Bond lengths		Bond angles	
C(12)-N(3)	1.280(2)	C(5)-C(6)-N(1)	121.41(19)
C(8)-N(3)	1.389(2)	O(1)-C(7)-N(1)	122.74(18)
C(12)-C(14)	1.459(2)	O(1)-C(7)-C(8)	131.76(18)
C(12)-H(12)	0.9300	N(1)-C(7)-C(8)	105.50(15)
C(13)-C(14)	1.413(2)	C(9)-C(8)-N(3)	123.23(17)
C(13)-N(4)	1.302(2)	C(9)-C(8)-C(7)	107.55(16)
C(13)-Cl(1)	1.7460(18)	N(3)-C(8)-C(7)	129.21(17)
C(17)-N(4)	1.370(2)	N(2)-C(9)-C(8)	110.13(17)
C(7)-C(8)	1.433(3)	N(2)-C(9)-C(10)	121.73(17)
C(8)-C(9)	1.375(2)	C(7)-N(1)-N(2)	108.30(15)
C(7)-O(1)	1.234(2)	N(3)-C(12)-C(14)	120.67(17)
C(7)-N(1)	1.402(2)	N(3)-C(12)-H(12)	119.7
N(1)-N(2)	1.404(2)	C(14)-C(12)-H(12)	119.7
C(11)-N(2)	1.456(3)	N(4)-C(13)-C(14)	126.81(17)
C(9)-N(2)	1.350(2)	N(4)-C(13)-Cl(1)	115.04(14)
C(9)-C(10)	1.488(3)	N(4)-C(17)-C(16)	121.84(17)
C(6)-N(1)	1.427(2)	N(4)-C(17)-C(18)	117.76(15)
C(17)-N(4)	1.370(2)	C(7)-N(1)-N(2)	108.30(15)

Table 3. Antioxidant activity of the NCQ

Compound	IC_{50} values (µM)	
	$DPPH^{\cdot}$	$OH^{\cdot}$
NCQ	35.13	18.52
Ascorbic acid (Asc)	27.75	5.11

method of Blois.[24] The DPPH radical is a stable free radical having a λ_{max} at 517 nm. A fixed concentration of the experimental NCQ was added to a solution of DPPH in methanol (125 µM, 2 mL), and the final volume was made up to 4 mL with double distilled water. The solution was incubated at 37 ºC for 30 min in the dark. The decrease in absorbance of DPPH was measured at 517 nm.

The hydroxyl (OH) radical scavenging activities of the compounds have been investigated using the Nash method.[25] In vitro hydroxyl radicals were generated by Fe^{3+} /ascorbic acid system. The detection of hydroxyl radicals was carried out by measuring the amount of formaldehyde formed from the oxidation reaction with DMSO. The formaldehyde produced was detected spectrophotometrically at 412 nm. A mixture of 1.0 mL of iron-EDTA solution (0.13% ferrous ammonium sulphate and 0.26% EDTA), 0.5 mL of EDTA solution (0.018%), and 1.0 mL of DMSO (0.85% DMSO (v/v) in 0.1 M phosphate buffer, pH 7.4) were sequentially added in the test tubes. The reaction was initiated by adding 0.5 mL of ascorbic acid (0.22%) and incubated at 80-90 ºC for 15 min on a water bath. After incubation, the reaction was terminated by the addition of 1.0 mL of ice-cold TCA (17.5% w/v). Subsequently, 3.0 mL of Nash reagent was added to each tube and left at room temperature for 15 min. The intensity of the colour formed was measured spectrophotometrically at 412 nm against a reagent blank.

3. Results and Discussions

3.1. Synthesis and Characterization

Pyrazolone Schiff base was synthesized by heating the methanolic mixture of 2-chloro-benzo[h]quinoline-3-carbaldehyde, 4-amino antipyrine and two drops of acetic acid at 90ºC for 10 min under microwave irradiation. It was confirmed that the obtained compounds are air stable and have good solubility in DMF, DMSO, methanol and 1% DMSO/50 mM Tris-HCl buffer solution. The structure of compound was elucidated by elemental analysis and various techniques, viz. FT-IR, UV-Vis, ^{1}H NMR and ^{13}C NMR spectroscopy. The crystal structure of compound was confirmed by the XRD study.

3.1.1. Elemental Analysis

The analytical data of the synthesized compound are in good agreement with the proposed molecular formulae of 1:1 amine to aldehyde stoichiometry (refer experimental part). Synthesized compound are quite stable in air and light and soluble in most of the organic solvents, such as methanol, ethanol, CH_2Cl_2, $CHCl_3$, DMF and DMSO.

3.1.2. Spectroscopic Studies

FT-IR spectroscopy is a preliminary tool to confirm the successful formation of target compound NCQ. The IR spectrum of the Schiff base compound showed characteristic absorption bands of the azomethine C=N stretching at 1598 cm^{-1} and strong band C=O at 1658 cm^{-1}. The electronic absorption spectrum of compound is recorded in the UV-Visible region using DMSO as a solvent. Electronic spectrum of the NCQ showed two strong absorption bands at 295 nm and 360 nm assigned to π-π* and n-π* transitions, respectively.[26]

NMR spectrum is recorded for as-synthesized NCQ and the structure is confirmed on the basis of observed chemical shifts. The 1H NMR spectrum of NCQ showed a sharp singlet at 8.47 ppm corresponding to azomethine proton. A compound overlap of signals as a multiplet at 7.2-7.6 ppm, corresponding to aromatic protons, was observed in the NMR spectrum of the Schiff base, NCQ. Further, the compound NCQ showed peaks at 3.17 and 3.45 ppm due to the $N\text{-}CH_3$ and $C\text{-}CH_3$ protons, respectively. The spectrum of the compound showed a single resonance at 142.12 ppm for the azomethine carbon which also confirms the structure of the Schiff base. The signal at 166.21 ppm due to C=O carbon of the compound, NCQ. The signals due to CH_3 and $N\text{-}CH_3$ carbon of NCQ compound appear at δ 64 and 14, respectively.[27,28]

3.1.3. X-ray crystallography

The molecular structure of the quinoline Schiff base compound NCQ was determined by single crystal XRD studies. The summary of data collected and the refinement parameters are given in Table 1. The selected bond lengths and bond angles are given in Table 2. An ORTEP representation and crystal packing diagram of the compound is shown in Figure 1 and 2, respectively. The single crystal XRD study of Schiff base showed that it has the empirical formula $C_{25}H_{19}ClN_{4O}$ with formula weight 426.89. The compound crystallizes in a triclinic space group P21/n and unit cell comprises of four molecules. The formation of Schiff base is confirmed by using azomethine C(8)-N(2) bond length, 1.278(2) Å is in conformity with a formed C=N double bond length, 1.28 Å. The bond distances for N(1)-N(2) at 1.404(2), C(13)-Cl(1) at1.7460(18) and for N(2)-C(8) at 1.389(2)Å are closer to N-N, C-Cl and N-C normal single bonds respectively.[29] The analysis of the bond lengths and angles of the synthesized compound gives further support to the formation of Schiff base in equivalent molar ratio.

3.2. Molecular Docking

Molecular docking studies were carried out for the compound NCQ against target proteins cervical cancer (PDB ID: 1DTO) and breast cancer (PDB ID: 1JNX) to know the binding affinity between the ligand and the receptor. To the active site of each protein, the ligand was docked using Autodock tools. The ligand showed excellent interaction with these proteins (Fig 3). The compound NCQ showed a docking score of -8.0 and -8.4 kcal/mol with 1DTO and 1JNX proteins. The compound NCQ docked against 1DTO protein forms a hydrogen bonding interaction with LEU A94 and GLN A95, alkyl and pi-alkyl

interaction with LEU A94 and pi-sigma interaction with THR A93. The compound NCQ against 1JNX protein forms hydrogen bonding interaction with ASN X1678 and LYS X1702 and pi-alkyl interaction with PHE X1662 and LYS X1702. The hydrogen bonding and hydrophobic forces were found to be the prominent interaction of quinoline peptides with protein.[1,30]

3.3. Antioxidative Activity

The antioxidant properties of Schiff base compound NCQ have attracted a lot of interests, mainly in the in vitro system. Hence, a systematic study was carried out on the antioxidant potential of the new compound NCQ along with standard, such as ascorbic acid (Aca), against DPPH and OH radicals with respect to different concentrations of the ligand and the results are shown in Table 3. The NCQ displayed almost comparable radical scavenging activity with respect to standard antioxidant ascorbic acid (Aca). From the above results, the scavenging effect of the present quinoline Schiff base compound is significantly good when compared to standard which is due to the hetero atom present in of the present NCQ compound.

4. Conclusions

In summary, a new hetero atom containing Schiff base (NCQ) was successfully synthesized and characterized by various spectral and analytical techniques. The molecular structure of the compound NCQ was confirmed by single crystal X-ray diffraction studies. The single crystal XRD results of synthesized compound confirmed the Schiff base formation and three dimensional crystal structure of the compound was elucidated and refined to good R factors. The molecular docking studies were performed for the compound NCQ against cancer proteins 1DTO and IJNX. The compound has good binding scores, and conventional H-bond, Alkyl and pi-alkyl interactions with the active sites of amino acids. Molecular docking studies exhibit that the NCQ could acts as good anti-cancer agent. This study gives an idea for the designing of more efficient anti-cancer agents. The quinoline Schiff base compound subjected to in vitro DPPH antioxidant assays and the results showed that the synthesized compound possess good antioxidant.

Conflicts of Interest

The authors declare no conflict of interest.

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