# Molecular structure and Biological evaluation of of 3-allyl-1-(2-chloroacetyl)-2,6-diphenylpiperidin-4-one: DFT and Molecular docking studies

**V. Manjula**[a,d]

Department of Chemistry, Periyar University, Salem – 636 011, Tamil Nadu, India.

**R. Venkateswara moorthi**

Department of Chemistry, PGP College of Arts and Science, Namakkal – 637 207, Tamil Nadu, India.

**J. Dharmaraja**

Department of Chemistry, Arignar Anna Government Arts College, Vadachennimalai, Attur – 636 121, Tamil Nadu, India.

**S. Parvathy**

Department of Chemistry, Government Arts College (Autonomous), Salem – 636 007, Tamil Nadu,

**S. Bharanidharan**

Department of Physics, Panimalar Engineering College, Chennai – 600 123, Tamil Nadu, India.

**Abstract**

The 3-allyl-1-(2-chloroacetyl)-2,6-diphenylpiperidin-4-one (**ACDP**) was synthesized and characterized using FT-IR, $^{1}H$ NMR, and $^{13}C$ NMR spectral techniques. Furthermore the antibacterial and antifungal studies have been carried out for target compound against selected bacterial and fungal strains. The antimicrobial studies show very good activity for target compound **ACDP** against *S. aureus* for bacterial and against *C. galberta* for fungal organisms.To study the intra-molecular charge transfer within the molecule, the Lewis (bonding) and Non-Lewis (anti-bonding) structural calculation was performed. The HOMO-LUMO energy gap explains the eventual charge transfer that occurs within the molecule. MEP gives the visual representation of the chemically active sites and comparative reactivity of atoms. To establish information about the molecular interactions between protein and this novel compound theoretically, docking studies were carried out in detail.

**Keywords:** Piperidin-4-one, Spectral, Biological, DFT, Molecular docking

## 1. Introduction

An essential component of the search for new leads in a drug designing program is the synthesis of molecules, which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features. Certain small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules [1-3]. Various strategies are currently being employed to develop novel antibiotics and to improve the effectiveness of established antimicrobial compounds. Heterocyclic compounds having very good biological activity, specifically piperidine skeletons are attractive targets of organic synthesis owing to their pharmacological activity and wide occurrence in nature [4,5].

Heterocyclic ring systems having piperidin-4-one nucleus have aroused great interest in the past and recent years due to their wide variety of biological properties such as antiviral [6], antitumor [7], anti inflammatory [6], central nervous system [8], local anesthetic[9], anticancer

[10], and antimicrobial activity [11] and their derivative piperidines are also biologically important and act as neurokinin receptor antagonists [12], analgesic and antihypertensive agents [13]. The extensive studies undertaken in the past on 4-piperidones have their relation to the synthesis of drugs[14]. The utility of substituent at second, third and sixth positions, particularly aromatic substituent at second and/or sixth positions with regard to is biological activity [15]. Consequently, the establishment of general methods for the synthesis of piperidine derivatives has been the topic of considerable synthetic effort [16].

Similarly, N-acetyl derivatives are well known for their therapeutic values [17], anticonvulsant agent [18], antiepileptic [19], antispasmodic [20], antitumor, anti-MDR [21], antimicrobial [22], herbicidal [23], mild stimulant and depressant activities [24]. Recently, synthesized the various types of N-substituted piperidine-4-ones and briefly discussed their structural, crystal and biological properties. All reported biological activity considerably changed while substituting various groups in 2,6 and 3$^{rd}$ position of piperidine moiety. So we are introduced allyl group in the 3$^{rd}$ position and synthesized N-substituted piperidine-4-one and characterized by FT-IR and Proton Nuclear magnetic spectroscopy and Carbon Nucleus magnetic spectroscopy. Target compound was studied by using Density Functional Theory method and their HOMO–LUMO, MEP and NBO are discussed in detail. The structural information and the data for the target were collected from the "Protein Data Bank" (PDB). The PDB ID: 1EVE was used as the template for our studies.

## 2. Experimental

### 2.1. Material and methods

All the chemicals utilized in this study were purchased from Merck chemical company without further purification. Infrared spectra were recorded on a Jasco FT-IR-4700 spectrophotometer. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on a bruker Advance III HD Nanobay 400MHz FT-NMR spectrometer in $CDCl_3$ at 400MHz in Gandhigram rural institute, Dindigul. All the NMR measurements were made in 5mm NMR tubes using solutions made by dissolving about 20mg of the substance in 1ml of $CDCl_3$. Silica gel was used for all the chromatographic purifications were performed with 100-200 mesh for column chromatography whereas TLC was performed on 60-120 mesh.

### 2.2. Synthesis of 3-allyl-1-(2-chloroacetyl)-2,6-diphenylpiperidin-4-one(ACDP)

A mixture of solution of 3-allyl-2,6-diphenylpieridin-4-one(I)(0.005mol)and triethylamine(0.005mol)in 20ml benzene was stirred well and chloroacetyl chloride(0.005mol)in 10ml of benzene was added drop wise for about 30 mins. Stirring continued with mild heat conditions. After completion of the reaction, it was poured into a crushed ice and extracted with diethyl ether. The collected diethyl ether extracts were then washed well with 3% sodium bicarbonate solution and dried over anhydrous sodium sulphate.The crude product **(ACDP)** was recrystalized by ethanol.

Brown colour, Solid, **Yield**: 85%; **m.p**. 95-97(°C); **M.F**: $C_{22}H_{22}ClO2$(367.1); **Elemental analysis Calcd.**(%): C, 71.83; H, 6.03; Cl, 9.64; N, 3.81; O, 8.70; **IR** (KBr, $cm^{-1}$): 1712(CO), 1649(N-CO), 910(C=H bending), 3066-2848(CH streching) ; **$^{1}$H NMR** ($CDCl_3$, 400MHz): δ 5.83(m, 1H, H-

8), 2.43(m, 2H, H-7), 2.55(m,1H,H-5a), 3.46(s, 1H, H-5e), 6.50(d, 1H, H-2), 5.32(d, 1H, H-3), 7.19(d, 1H, H-6), 4.12(s,2H, H-11),; **$^{13}$C NMR**($CDCl_3$, 400MHz): δ 35.1(C-7), 42.7(C-11), 53.5(C-3, C-5),54.2(C-2, C-6), 203.4(C=O), 118.4(C-9), 134.1(C-8), 165.9(N-C=O), 126.1-144.4(Aromatic carbons).

### 2.3. Antimicrobial studies

#### 2.3.1. Antibacterial activity by well diffusion method

The plates were incubated with freshly prepared, sterilized, and incubated overnight. About 0.2ml of working stock culture was transferred into Agar plated and spread thoroughly using a cotton swab to ensure the spread of the tested microbes on the surface of the plates completely. The 6mm diameter of the well was made with borer on the Agar plates. 10 mg of the synthesized compounds were filled into the well. The commercially available drug (*Ciprofloxacin*, 5 µl/mg) was used as the reference. Negative control (Chloroform, 100 µl/) was added to another well. They incubated the agar plates at 37±1ºC for about 18-24 h. Antibacterial activity was evaluated by measuring the zone of inhibition against tested organisms.

#### 2.3.2. Antifungal activity by well diffusion method

SDA medium was used for the growth of fungi testing was done in SDB (Sabouraud's dextrose broth) medium. For the antifungal studies, the same procedure is used for the antibacterial studies except for the temperature, which should be maintained at 28±1ºC for about 72h. *Ketaconazole* was used as a standard for antifungal studies.

### 2.4. Computational details

The entire calculations were performed at DFT/B3LYP/6-311++G(d,p) level of the basis set using Gaussian 09W [25] program package, invoking gradient geometry optimization [25, 26]. In this study, the density functional three parameter hybrid model DFT method with B3LYP/6-311++G(d,p) basis set was used to calculate various properties of the title molecule. The NBO calculations were performed using the NBO 3.1 program as implemented in the Gaussian 09W package. In addition FMO and MEP surfaces were calculated and analyzed at the same level of theory. Docking calculations were carried out on **Acetylcholinesterase (Aricept)** enzyme protein model [27]. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools [28].

## 3. Result and Discussion

### 3.1. Synthesis

The functionalized piperidone molecule has been synthesized by the addition of chloroacetyl chloride to the mixture of 3-allyl-2,6-diphenylpiperidin-4-one and triethylamine in benzene. Schematic representation of 3-allyl-1-(2-chloroacetyl)-2,6-diphenylpiperidin-4-one (**ACDP**)is furnished in Scheme 1.

### 3.2. IR spectral analysis of 3-allyl-1-(2-chloroacetyl)-2,6-diphenylpiperidin-4-one (ACDP)

The irrational frequencies provide important structural information about a compound and these peaks tell about the presence of some particular functional groups present in the target compounds. The FT-IR spectrum of compound **(ACDP)** shown in Fig. 1. The aromatic C-H stretching vibrations are observed at 3066 $cm^{-1}$ and 3022 $cm^{-1}$. The stretching vibration band appearing at 2848 $cm^{-1}$ and 2918 $cm^{-1}$ has been assigned to –CH asymmetric and symmetric stretching vibration bands of the target compounds.

The strong and sharp band appeared at 1712 $cm^{-1}$ is assigned to the ring carbonyl stretching vibration of the piperidine moiety. Tertiary amide will exhibit a carbonyl stretching frequency from 1680-1630 $cm^{-1}$. The medium intense band appeared at 1649 $cm^{-1}$ is assigned for amide carbonyl stretching frequency. Generally =CH bending vibration bands appeared at the range of 1000-650 $cm^{-1}$. In the synthesized compounds =CH bending vibration band appeared at 910 $cm^{-1}$ and 981 $cm^{-1}$.

### 3.3. NMR spectral analysis

#### 3.3.1. $^{1}$HNMR spectral analysis of 3-allyl-1-(2-chloroacetyl)-2,6-diphenylpiperidin-4-one (ACDP)

The $^{1}$H NMR spectrum of **(ACDP)** is shown on Fig. 2.In $^{1}$H NMR spectrum of compound **(ACDP)** the signals appeared in the range of 7.24-7.39ppm corresponding to ten protons integral which are assigned to the aromatic protons of the two phenyl rings are attached to the C-2 and C-6 positions of the piperidine ring. There is a multiplet appearing in the up field region with three protons integral value at 2.43ppm and 2.55ppm assigned to H-7 and H-5a protons respectively. A doublet appeared at 3.46ppm with one proton integral value corresponding to the H-5e proton. Methylene proton (H-11) signal appeared as a singlet with one proton integral value appeared at 4.12ppm. A triplet appearing at 5.13ppm with two protons integral value is assigned to H-9 protons of the allylic chain. In the down field region two doublets appeared at 5.32pp and 6.50ppm. In these two signals, the up field signal at 5.32ppm with one proton integral value is H-3 proton. Similarly the down field signal at 6.50ppm with one proton integral value is H-2 proton. H-8 proton signal appeared as a multiplet with one proton integral value at 5.83pp. Likewise H-6 proton signals appeared as a doublet with one proton integral value at 7.19ppm.

**3.3.2. $^{13}$C NMR spectral analysis of 3-allyl-1-(2-chloroacetyl)-2,6-diphenylpiperidin-4-one (ACDP)** The $^{13}$C NMR spectrum of **(ACDP)** is shown on Fig. 3. Aromatic carbons and quaternary carbons appear in the down field region range from 126.1-144.4ppm. The signals are observed in the up field region at 35.1ppm and 42.7ppm. In these two signals a higher frequency signal is assigned for C-11 carbon and a low frequency signal is assigned for C-7 carbon. The higher frequency region signals at 53.4ppm and 54.2ppm appear with medium intensities. In this higher frequency signal at 54.2ppm is assigned to Benzylic carbons(C-2 and C-6) and lower frequency signal at 53.4ppm is assigned to methylene carbons (C-3 and C-5) respectively. There are two signals observed at higher frequency regions at 118.4ppm and 134.0ppm is assigned to C-9 and C-8 carbon signals respectively. The amide carbonyl carbon signals appeared in the downfield region at 165.9ppm. Likewise ring carbonyl carbon signals appeared in the most downfield region at 203.3ppm with low intensity.

### 3.4. DFT Studies of 3-allyl-1-(2-chloroacetyl)-2,6-diphenylpiperidin-4-one (ACDP)

#### 3.4.1. HOMO-LUMO Analysis

Based on molecular orbital theory the Highest occupied molecular orbitals (HOMOs) are electron-rich (nucleophilic or Lewis basic) and interact strongly with lowest unoccupied molecular orbitals (LUMOs) which are electron deficient (electrophilic or Lewis acid). HOMO and LUMO are the very important parameters for quantum chemistry. The energy values of HOMO (π-donor) and LUMO (π-acceptor) and their energy gap reflects the chemical activity of the molecule. The HOMO and LUMO energy was calculated by the B3LYP/6-311++G(d,p) basis set. The optimized molecular structure of **ACDP**as shown in Fig. 4 with atom numbering scheme. The atomic compositions of frontier molecular orbitals are shown in Fig. 5. The HOMO is located over thepiperidone ring and LUMO is located atAllyl chain substituted at C-3.The HOMO and LUMO energies are predicted as -7.04113 eV and -2.64101 eV, respectively. The calculated HOMO-LUMO energy gap is 4.40012 eV, which explains the eventual charge transfer taking place within the molecule. In addition, the physic-chemical properties of **ACDP** were listed in Table 1.

#### 3.4.2. MEP Analysis

Molecular electrostatics used extensively for interpreting potentials have been predicting the reactive behavior of a wide variety of chemical systems in both electrophilic and nucleophilic reactions, the study of biological recognition processes and hydrogen bonding interactions [29]. An electrostatic potential map, also known as electrostatic potential energy maps or MEP surfaces, illustrates the charge distributions of molecules three dimensionally. These maps allow us to visualize variably charged regions of a molecule. Knowledge of the charge distributions can be used to determine how molecules interact with one another. Electrostatic potential maps are very useful three-dimensional diagrams of molecules. They enable us to visualize the charge distributions of molecules and charge related properties of molecules. They also allow us to visualize the size and shape of molecules. In organic chemistry, electrostatic potential maps are invaluable in predicting the behavior of the complex molecules.

The molecular electrostatic potential (MEP) is widely used as a reactivity map displaying most probable regions for the electrophilic attack of charged parts on organic molecules. MEP plot provides a simple way of predicting the interaction of different geometries. In order to predict the reactive sites for electrophilic and nucleophilic attacks of the title molecule, MEP was calculated with B3LYP/6-311++G(d,p) basis set. The negative (red color) and positive (blue color) regions of MEP are related to electrophilic and nucleophilic reactivity respectively as shown in Fig. 6. The negative region is located over the C=O group and the positive region is located over Hydrogen atoms in the **(ACDP)** molecule.

#### 3.4.3. NBO Analysis

The NBO analysis provides an efficient method for studying intra- and inter-molecular bonding and interaction among bonds, and also provides a convenient basis for investigating charge transfer or conjugative interaction in molecular systems [30]. In this present study, the NBO analysis has been carried out with the DFT method at B3LYP/6-311++G(d,p) level of the basis set and which deals with the intra-molecular charge transfer within the molecule. In any

molecule, the π character of the bond plays an important role when compared with σ bond character. In such a way that this molecule delivers maximum delocalization energy during the transition between π and π* bond whereas the ED of the donor (Lewis) bond decreases with increasing ED of acceptor (Non-Lewis) bonds. In our case, the conjugative π bonds in the phenyl ring shows maximum delocalization during the interaction with π* acceptor bonds. It is evident from our title compound that the energy transfer from πC7-C9 to π*C2-C4 and πC16-C20 to π*C13-C14 reveals the hyperconjugative energy about 89.75 and 85.81 KJ/mol, respectively. Similarly, the lone pair atoms such as oxygen and nitrogen also transfer more energy to donor and acceptor bonds. The LP(2)O28 to C24-N48 and LP(1)N48 to C24-O28 bonds transfer the energy about 108.37 and 123.64 KJ/mol, respectively and are listed in Table 2. The maximum hyperconjugative $E^{(2)}$ energy of lone pair atoms during the intramolecular interaction leads the molecule towards medicinal and biological applications.

### 3.5. Antimicrobial studies of 3-allyl-1-(2-chloroacetyl)-2,6-diphenylpiperidin-4-one (ACDP)

#### 3.5.1. Antibacterial studies

The synthesized compound of **ACDP** was evaluated in vitro for their activity to inhibit the growth of bacterial strains viz., *staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *E faecalis.Ciprofloxacin* was used as standard drugs and zone of inhibition is summarized in Table 3.Among the tested pathogens, compound shows very good activity against *S.aureus*, better activity against *P. aeruginosa* and *E. faecalis*Fig. 7.Further the compound has no activity against *E. coli* and *K. pneumonia*.

#### 3.5.2. Antifungal studies

The target compound **ACDP** was carried out in vitro antifungal activity against *Aspergillusniger*, *Aspergillusflavus*, *Mucor. Sp.,* Candida*galberta* and *Rhizopus sp.*The *Ketocanazole*was used as standard drugs and the zone of inhibition is summarized in Table 4. The antifungal results shows that compound exhibits very good activity against *C. galberta*, better activity against *A. niger*, *A. flavus*, *Mucor sp*. and compound **ACDP** did not shown any inhibition against *Rhizopus sp*. Fig. 8.

The antimicrobial activities concluded that very good activity shows against *S. aureus* and*C. galberta* of bacterial and fungal strains, respectively.

### 3.6. Molecular docking studies of 3-allyl-1-(2-chloroacetyl)-2,6-diphenylpiperidin-4-one (ACDP)

The docked, glide energy and hydrogen bonding interactions of the title compound and co-crystallized ligand are given in Table 5. A view of the X-ray crystal structure of the title compound in the **Acetylcholinesterase (Aricept)** Receptor active site showing the key hydrogen contacts between inhibitor and enzyme is depicted in Fig. 9. The co-crystallized ligand in the Acetylcholinesterase (Aricept) Receptor active site showing the key hydrogen contacts between inhibitor and enzyme is depicted in Fig. 10. The surface diagram showing the title

compound docked at the active site of Acetylcholinesterase (Aricept) Receptor is depicted in Fig. 11.

X-ray crystal structures confirmed the expected binding mode, and consideration of binding orientation and electronic properties enabled optimization to piperidine as a more potent second-generation lead. The title compound is shown to be an effective inhibitor. The amide group in the VAL152 interacts with the oxygen atom of the carbonyl group at a distance of 3.4 Å. The co-crystallized ligand also docked well and it shows better interactions with residues ASN71 and GLY70, respectively. The results show that the title compound having better binding energy and the co-crystallized ligand have comparable interactions.

**Conclusion**

The synthesized compound **ACDP**wascharacterized by using FT-IR and NMR spectral techniques.The DFT approach was used for the first time to calculate the quantum chemical properties of the title molecule. The charge transfer within the molecule is reflected in the NBO result, and the π-π* transition has the most energy. The HOMO-LUMO band gap is estimated to be 4.40012 eV, making the title molecule less stable and more reactive. The reactive sites for electrophilic and nucleophilic assault are predicted by MEP surfaces. The antimicrobial activities suggest that the bacterial and fungal strains, respectively, have extremely strong activity against S. aureus and C. galberta.The hypothesized binding mode was confirmed by X-ray crystal structures, and analysis of binding orientation and electrical characteristics allowed piperidone to be optimized as a more effective second-generation lead.

**Conflict of interest**:

The authors declare that they've no conflicts of interest.

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