ELECTRONIC STRUCTURE AND VIBRATIONAL ANALYSIS OF CLOZAPINE

8-CHLORO-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine

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ABSTRACT

A tricyclic dibenzodiazepine, classified as an atypical antipsychotic agent. It binds several types of central nervous system receptors, and displays a unique pharmacological profile. Clozapine is a serotonin antagonist, with strong binding to 5-HT 2A/2C receptor subtype. It also displays strong affinity to several dopaminergic receptors, but shows only weak antagonism at the dopamine D2 receptor, a receptor commonly thought to modulate neuroleptic activity. Agranulocytosis is a major adverse effect associated with administration of this agent. The optimized geometry and their properties such as equilibrium energy, frontier orbital energy, dipole moment and vibrational frequencies have been used to understand the activity of Clozapine . The calculated highest occupied molecule orbital or HOMO and the lowest un-occupied molecular orbital or LUMO energies shows that charge transfer within the molecule. The vibrational spectra of IR and Raman have been interpreted with the help of B3LYP level of theory with the 6-31G basis set from the Density function theory.

Key Words: *Vibrational spectra, DFT, HOMO, LUMO, Antipsychotic*

INTRODUCTION

Clozapine, sold under the brand name **Clozaril** among others, is an atypical antipsychotic medication.Clozapine was first made in 1956, and sold commercially in 1972. It was the first atypical antipsychotic. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system. It is available as a generic medication. Clozapine primarily used in people who are unresponsive to or intolerant to other antipsychotics. This means that they have failed to respond satisfactorily to at least two different antipsychotics. It has been shown to be more effective in reducing symptoms of schizophrenia than typical antipsychotics, with more pronounced effects in those who have responded poorly to other medication. It may also be used for the treatment of psychosis secondary to Parkinson's disease.

Clozapine is usually given by mouth in tablet or liquid form, however an unlicensed short-acting intramuscular injectable formulation is

available. It is not a depot injection, and instead has a similar duration of action as clozapine by mouth. The injectable formulation may be used in highly agitated people with schizophrenia who consistently refuse clozapine by mouth, but are predicted to respond well to clozapine therapy, with the injection being administered with the intention of transitioning the person to oral clozapine. The injectable form is reportedly difficult to use due to painful administration, higher doses requiring injection into multiple sites simultaneously, and even more stringent monitoring than oral clozapine (with the additional difficulty of withdrawing blood samples for testing from agitated individuals). Clozapine is associated with a relatively high risk of low white blood cells (agranulocytosis), a condition of suppressed immunity which may result in death. To decrease this risk, it is recommended that the white blood cell count be regularly monitored. Other serious risks include seizures, inflammation of the heart, high blood sugar levels, constipation, and in older people with psychosis as a result of dementia, an increased risk of death. Common side effects include drowsiness, increased saliva production, low blood pressure, blurred vision, and dizziness. The potentially permanent movement disorder tardive dyskinesia occurs in about 5% of people. Its mechanism of action is not entirely clear.

METHOD, MATERIAL AND THEORY

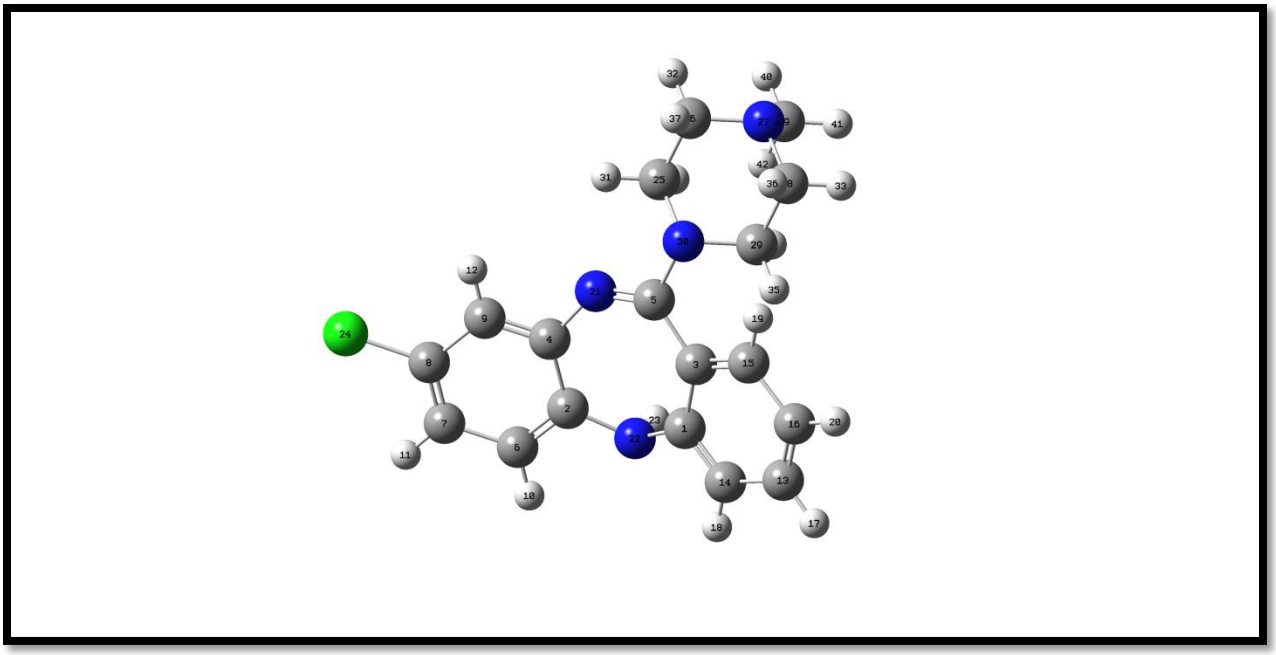
Density functional theory (DFT) has become very popular in recent years. This is justified based on the pragmatic observation that it is less computationally intensive than other methods with similar accuracy. The premise behind DFT is that the energy of a molecule can be determined from the electron density instead of a wave function.

DFT is a computational quantum mechanical modeling method used in physics, chemistry and material sciences. In the present contribution, the properties that can be calculated with DFT, such as geometries, energies, spectroscopic properties. Density functional theory (DFT) calculations have been performed to predict the IR and Raman spectra for the molecule. Fourier transform infrared (FTIR) and Raman spectra of the compound have been obtained experimentally. All FTIR and Raman bands of the compound obtained experimentally were assigned based on the modeling results obtained at the B3LYP/6-31G level.

In general, ab initio calculations give very good qualitative results and can yield increasingly accurate quantitative results as the molecules in question become smaller. The advantage of ab initio methods is that they eventually converge to the exact solution once all the approximations are made sufficiently small in magnitude.

DFT was applied using the B3LYP which is the keyword for the hybrid functional, which is a linear combination of the gradient functional proposed by Becke and Lee, Yang and Parr, together with the Hartree Fock local exchange function. Calculations were performed using the Gaussian 09. Gaussan is a general purpose computational chemistry software package. A basis set in theoretical and computational chemistry is a set of functions (called basis functions) that is used to represent the electronic wave function in the density-functional theory The DFT methods with 6-31G basis set calculations were made first to optimize the structures. The vibrational frequencies and non-linear optical properties were calculated by means of DFT methods at the corresponding optimized geometries. All the calculations converged to an optimized geometry which corresponds to a true energy minimum as revealed by the lack of imaginary values in the calculate vibration frequencies. Vibration frequencies are calculated using B3LYP/6-31G.

Optimized geometrical structure of Clozapine is shown in figure1.



IR AND RAMAN SPECTROSCOPY

Infrared spectroscopy (IR spectroscopy or vibrational spectroscopy) involves the interaction of infrared radiation with matter. It covers a range of techniques, mostly based on absorption spectroscopy. An IR spectrum can be visualized in a graph of infrared light absorbance (or transmittance) on the vertical axis vs. frequency or wavelength on the horizontal axis. Optimized geometric structure of IR Spectra of Clozapine is shown in figure-2.

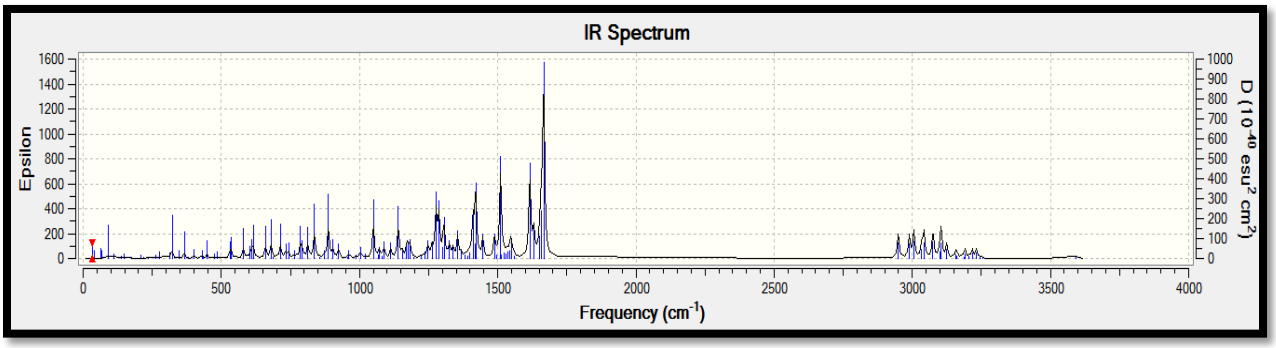


Fig 2

A RAMAN spectrum is a plot of the intensity of RAMAN scattered radiation as a function of its frequency difference from the incident radiation (usually in units of wavenumbers, cm^{-1}). This difference is called the *RAMAN shift*, because it is a difference value, the Raman shift is independent of the frequency of the incident radiation. Optimized geometric structure of Raman Spectra of Clozapine is shown in figure3.

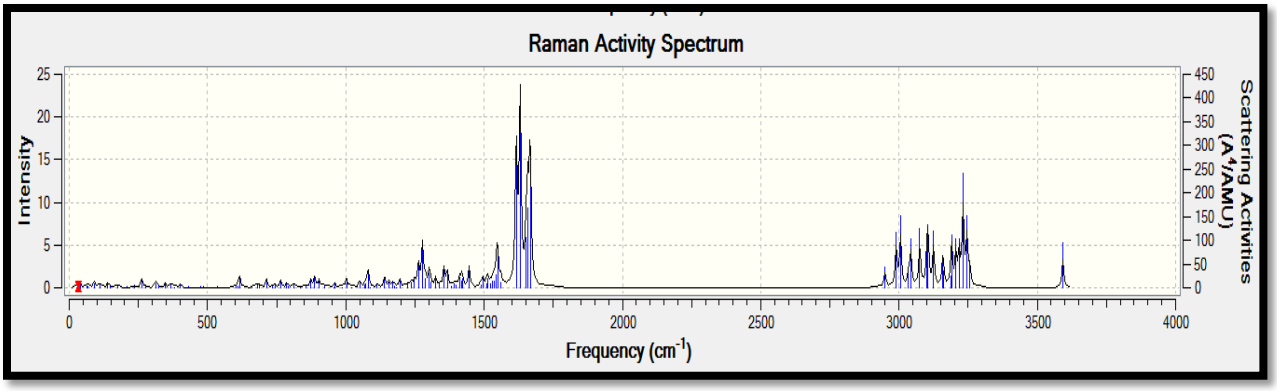


Fig 3

DEPOLARIZATION SPECTRA-

The depolarization ratio is the intensity ratio between the perpendicular component and the parallel component of the Raman scattered light. Two polarizations occur i.e. p- polarization and u-polarization. The optimized spectra of p-depolarization and u-depolarization are shown in the fig-4 and fig-5.

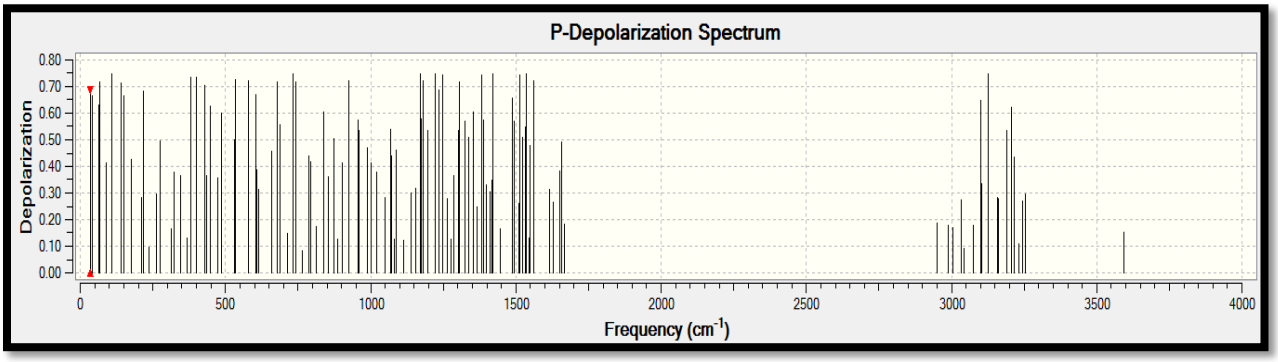


Fig 4

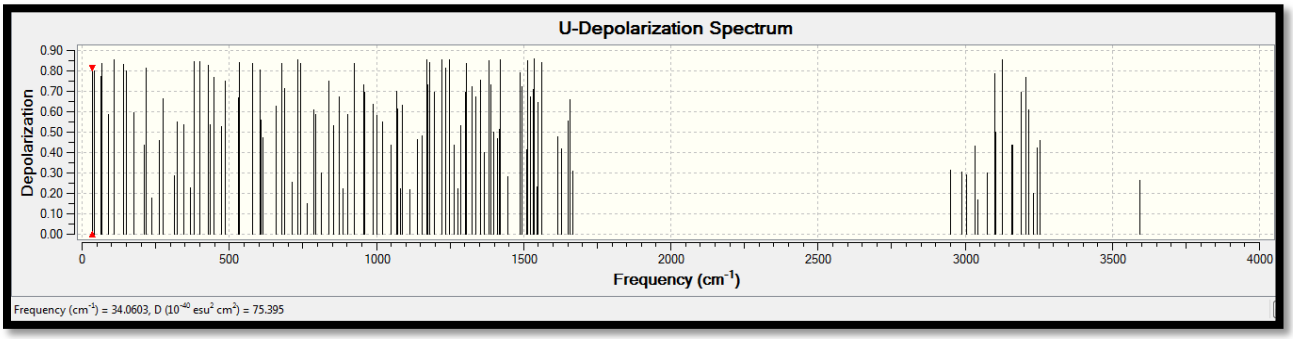


Fig 5

Theoretically computed ground state optimized parameters

Parameters	Clozapine (B3LYP/6-31G)
Energy (in a.u.)	-1376.27385978
Dipole moment (in Debye)	5.5409

1 Debye = $3.34*10^{-30}$ cm.

1 *a.u.* of *energy* = 1hartree = 4.360×10^{-18} J. = 27.211*eV* = 2625kJ/mol = 627.5kcal/mol.

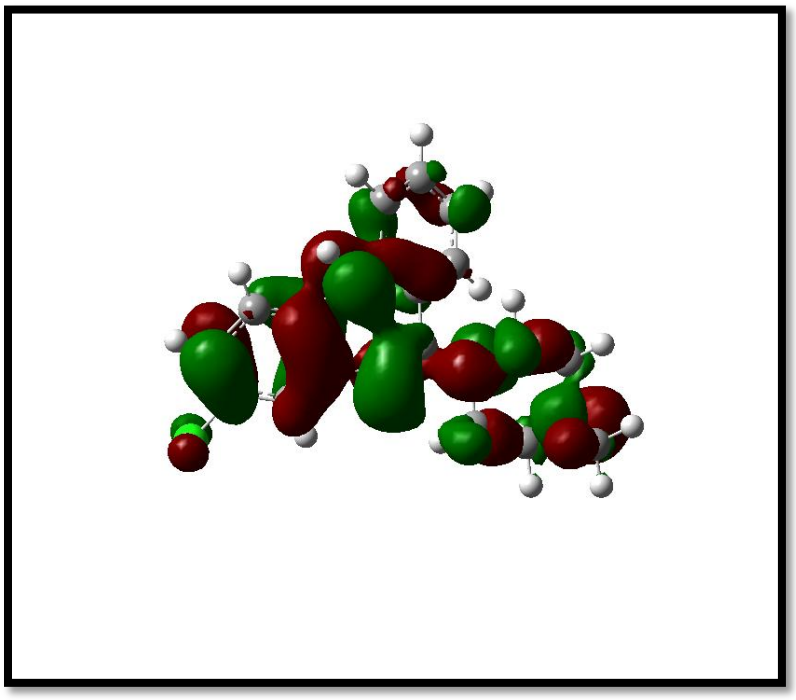
MOLECULAR ORBITAL ENERGIES

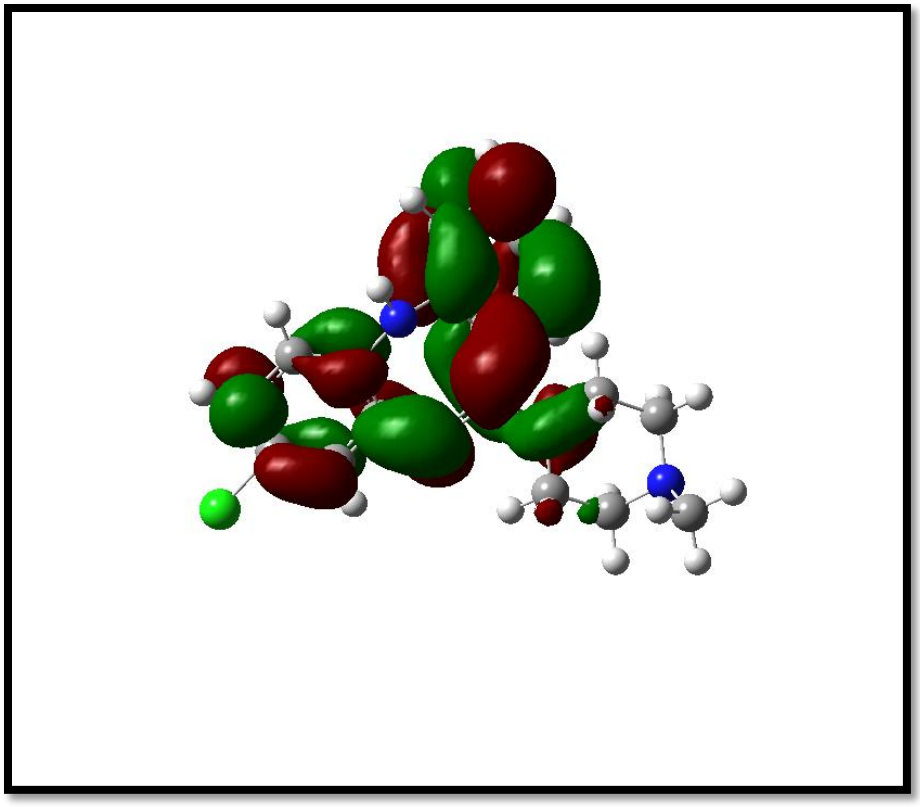
The most important orbitals in a molecule are the frontier molecular orbitals, called highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO).These orbitals determine the way the molecule interacts with other species. The frontier orbital gap helps characterize the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier orbital gap is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule.

The density plot of the HOMO and LUMO of Clozapine is calculated at B3LYP/6-31G level of theory and are shown in Figure 6and 7.

HOMO=-0.18684

LUMO=-0.04698

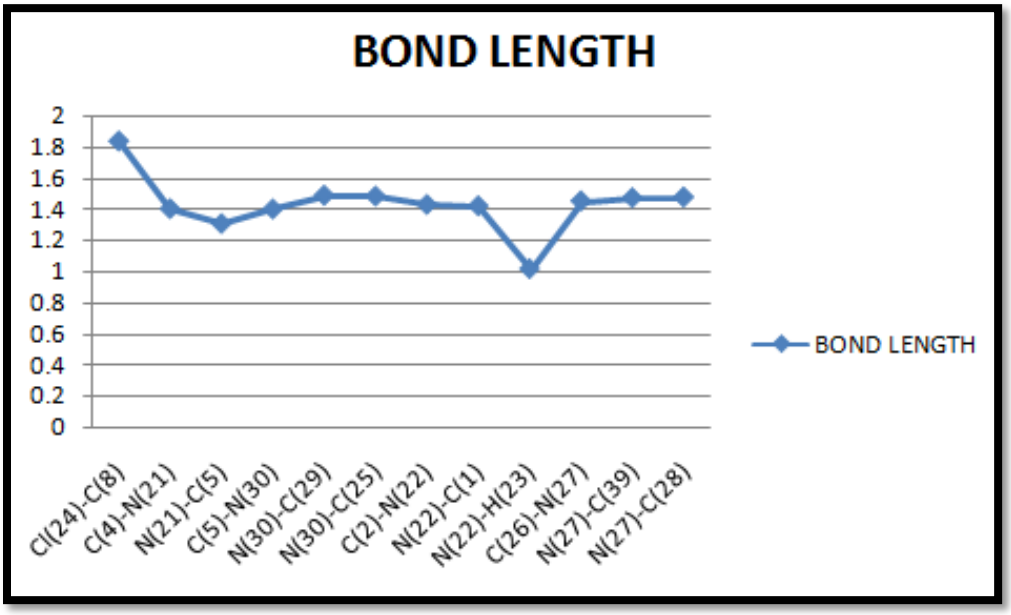




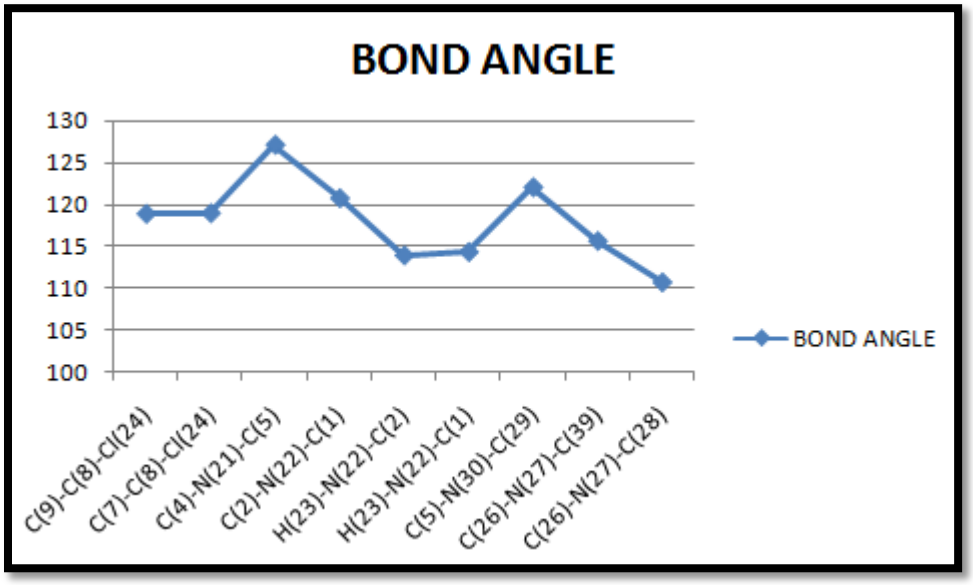
BOND LENGTH AND BOND ANGLE

In molecular geometry, bond length or bond distance is the average distance between nuclei of two bonded atoms in a molecule. It is a transferable property of a bond between atoms of fixed types, relatively independent of the rest of the molecule. Molecular geometries can be specified in terms of bond lengths and bond angles. The bond length is defined to be the average distance between the nuclei of two atoms bonded together in any given molecule. A bond angle is the angle formed between three atoms across at least two bonds. Such as bond lengths and bond angle are the optimized structural parameters, so these parameters were determined at B3LYP level theory with 6-31G basis set and they are presented in a table. Bond length table and graph of Clozapine is given below.

ATOM	BOND LENGTH
Cl(24)-C(8)	1.83255
C(4)-N(21)	1.39767
N(21)-C(5)	1.30222
C(5)-N(30)	1.39584
N(30)-C(29)	1.48314
N(30)-C(25)	1.47849
C(2)-N(22)	1.42454
N(22)-C(1)	1.41593
N(22)-H(23)	1.01183
C(26)-N(27)	1.4479
N(27)-C(39)	1.46832
N(27)-C(28)	1.47238



ATOM	BOND ANGLE
C(9)-C(8)-Cl(24)	118.941
C(7)-C(8)-Cl(24)	119.016
C(4)-N(21)-C(5)	127.126
C(2)-N(22)-C(1)	120.794
H(23)-N(22)-C(2)	114.007
H(23)-N(22)-C(1)	114.417
C(5)-N(30)-C(29)	122.092
C(26)-N(27)-C(39)	115.714
C(26)-N(27)-C(28)	110.807



CONCLUSION

Simulation work of Clozapine is in the process. Simulation report of Clozapine we will reported very soon.

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