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Theoretical and experimental investigations into structural, electronic, molecular and biological properties of 4-(3-chlorophenyl)-1-(3-chloropropyl) piperazin-1-ium chloride

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ABSTRACT

A convenient and facile synthesis of 4-(3-chlorophenyl)-1-(3-chloropropyl)piperazin-1-ium chloride is accomplished by stirring 1-(3-Chlorophenyl)piperazine hydrochloride with 3-chloropropanal by reductive amination in ethanol. The resulting compound was characterized using spectral data analysis augmented by X-ray. Single crystal analysis depicted that the synthesized compound crystallizes in monoclinic crystal system with ***P 21/c*** point group. The structural and electronic properties of the title compound have been calculated at DFT/B3LYP/6-311G (d,p) level of theory. Theoretically obtained parameters were well compared to the experimentally obtained results, showing excellent agreement. Molecular electrostatic potential surface, frontier orbital analysis and vibrational analysis were also carried out. HOMO-LUMO energy gap was calculated which allowed the calculation of relative properties like chemical hardness, chemical inertness, chemical potential, nucleophilicity and electrophilicity index of the synthesized products. Pass prediction was carried out which revealed that the target compound can be active against Prostate specific membrane protein, bearing *Pa* value of 0.411. Based on Pass, molecular docking studies of compound was carried out against Prostate specific membrane protein. The title compound depicted a binding free energy of −6.3 kcal/mol and is seen to be involved in key bonding interactions which include both alkyl and mixed pi-alkyl hydrophobic interactions: Alkyl hydrophobic interactions: (LEU 259; 4.64 Å, LEU 261; 3.79 Å), mixed Pi/alkyl hydrophobic interactions: (HIS 552; 4.96 Å, HIS 553; 4.64, 5.31 Å LEU; 3.45 Å) respectively with Prostate specific membrane protein. Target compound was screened for their cytotoxic potential with various cancer cell lines being most effective against prostate. In short, this study reveals the synthesis of a 4-(3-Chlorophenyl)-1-(3-chloropropyl) piperazin-1-ium chloride and exposes its structural, electronic and biological properties, paving way for further research in the field of drug development.

1. Introduction

N,N′-disubstituted piperazines have found application as ligands in metal complexes and form the basis of various natural products that exhibit favorable pharmacological properties. Piperazine is conveniently substituted at the N and N′ positions via reductive amination and nucleophilic substitution reactions. Synthetic piperazines are important in biomedical applications as ion channel and anticancer agents [1,2]. The substitutional flexibility of piperazines also makes them tunable ligands. The behavior of piperazine ligands in metal complexes is also of interest because they can act either as chelating or bridging ligands. Although the cyclohexane-type ring is relatively flexible, the chelate bite of the nitrogen atoms requires adoption of a boat conformation leading to significant ring strain. Therefore, the piperazine is at least as likely to engage in bridging behavior between metal centers despite the well known thermodynamic preference for chelation [3–11]. Many, but not all, chelated piperazine complexes feature ancillary

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coordination from pendant groups. A variety of bridging piperazine complexes has been reported, including metal dimers and tetramers, polymeric chains, and 2-D and 3-D frameworks [3,12–22].

Based on the above mentioned versatile properties and our previous work on the development of pharmacologically potent scaffolds [23–28], we explored the structural, molecular, electronic and vibrational properties of the synthesized compound both experimentally and theoretically which depicted a notable agreement to each other. Furthermore to explore the predicted biological properties of this compound, molecular docking studies with prostate specific membrane protein was carried out.

2. Experimental

2.1. Materials and methods

3-chloropananal, 1-(3-chlorophenyl) piperazine hydrochloride, sodium triacetoxy borohydride ($NaBH(OAc)_3$), deuterated chloroform were procured from Sigma–Aldrich (USA) and used as received. FT-IR spectra of the compound was recorded on Agilent FT-IR spectrometer in KBr discs (4000–400 cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin DPX-400 NMR spectrometer at 400.13 and 100.47 respectively using TMS as an internal standard. The diffraction data on single crystals of title compound was collected on a Bruker AXS SMART Apex CCD diffractometer using Mo–Kα (0.71073 Å) radiations at 100 K. The software SADABS [29] was used for absorption correction and SHELXTL for space group, structure determination and refinements [30,31]. All non-hydrogen atoms were refined anisotropically. All the computations are carried out using GAUSSIAN 09 software [32]. The DFT modeling method, using the hybrid B3LYP [33] functional was used to calculate theoretical parameters for title compound with the basis set combination 6–311 G (d,p) [34]. Geometry optimization was carried out until global minima were achieved. The SRB cytotoxic assay was used to screen the compounds for cell cytotoxicity [35,36]. Various human cancer cell lines, human leukemia (THP-1, at a density of 7×10^3), human lung carcinoma cell line (A-549, at a density of 8×10^3 cells per mL per 100 μL per well), human prostate cancer cell line (PC-3, at a density of 8×10^3 cells per mL per 100 μL per well) and human colon cancer cell line (HCT-116, at a density of 1×10^4 cells per mL per 100 μL per well) used in this study were purchased from European collection of cell culture (ECACC) USA) and seeded in flat-bottomed 96-well plates.

2.2. Synthesis of 4-(3-chlorophenyl)-1-(3-chloropropyl) piperazin-1-ium chloride

To a stirring solution of 1-(3-chlorophenyl)piperazine hydrochloride in dichloro methane, 3-chloropropanal in the same solvent was added drop wise under dry nitrogen and the resulting solution stirred for 0.25 h. Thereafter sodium triacetoxy borohydride ($NaBH(OAc)_3$) was added in pinches and the resulting solution was stirred overnight. Cream coloured solid precipitate obtained was further purified and recrystallized using ethanol. Cylindrical crystals were obtained after allowing the solvent to evaporate slowly at room temperature.

3. Results and discussion

The molecule crystallizes in monoclinic crystal systems with P 21/c point group (Fig. 1). The crystal refinement of the molecule is shown in Table 1. The piperazine ring adopts a chair conformation with the exocyclic N–C bonds in equatorial orientations. The dihedral angle between the piperazine ring (all atoms) and the benzene ring is 28.47 (5)°. The chloropropyl group has an extended conformation [N–C–C–C = −177.25 (8)° and C–C–C–Cl = 174.23 (7)°]. In the crystal, charge-assisted N–H···Cl hydrogen bonds link the cation and anion into ion pairs. Numerous weak C–H···Cl interactions link the ion pairs into a three-dimensional network. Short Cl···Cl contacts [3.2419 (4) Å] are also observed (see: Scheme 1)

Theoretical studies using Density Functional Theory (DFT) involving the well-known Becke three-parameter Lee-Yang-Parr function (B3LYP) and 6-311G (d, p) basis set for the synthesized compound was carried out Geometric optimization of the title compound was carried out. Theoretically determined bond lengths and bond angles were well compared with those determined experimentally (X-ray) and depicted an excellent agreement (Table 2). Theoretical calculations allowed the estimation of MEPS, FMO's, HUMO-LUMO energy gap and related parameters which depicted the potential kinetic stability and reactivity of the target compound.

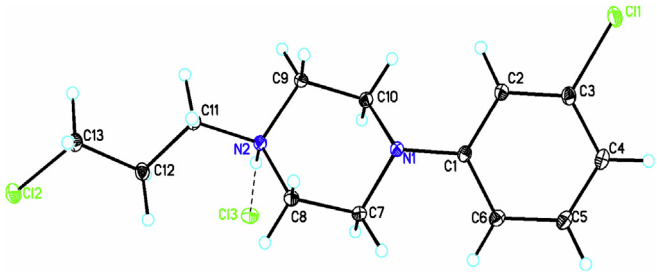

Fig. 1. Single crystal structure of 4-(3-chlorophenyl)-1-(3-chloropropyl)piperazin-1-ium chloride.

Table 1
Crystal data and structure refinement for the title compound.

Identification code	shelx	
Empirical formula	$C_{13}H_{19}Cl_3N_2$	
Formula weight	309.65	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 10.9608(9) Å	α = 90°
	b = 9.5199(8) Å	β = 95.3980(10)°
	c = 14.0262(11) Å	γ = 90°
Volume	1457.1(2) Å3	
Z	4	
Density (calculated)	1.412 Mg/m3	
Absorption coefficient	0.613 mm-1	
F(000)	648	
Crystal size	0.550 × 0.320 × 0.300 mm^3	
Theta range for data collection	2.589–32.106°.	
Index ranges	−16 ≤ h<=16, −14 ≤ k<=14, −20 ≤ l<=20	
Reflections collected	32810	
Independent reflections	4808 [R(int) = 0.0247]	
Completeness to theta = 25.500°	99.9%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F2	
Data/restraints/parameters	4808/0/167	
Goodness-of-fit on F2	1.075	
Final R indices [I > 2sigma(I)]	R1 = 0.0296, wR2 = 0.0811	
R indices (all data)	R1 = 0.0328, wR2 = 0.0833	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.688 and −0.326 e.Å-3	