Research Article

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Synthesis, and Biological Investigation of Bis [N-(4-Pyridyl) Sulfonamide] Dichloride Palladium: MEP, and Molecular Docking as an Antibacterial and an Anticancer Agents

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ABSTRACT

In the present work, the compound (N-(4-pyridyl-p-toluene sulfonamide) as a ligand was prepared from the reaction of 4-aminopyridine and p-toluene sulfonyl chloride in presence of one molar potassium hydroxide solution as a base and tetrahydrofuran as a solvent. Palladium dichloride was used for the synthesis of [bis (N-(4-pyridyl-p-toluene sulfonamide)] complex. The structure of the synthesized compounds was confirmed by FTIR. Elemental analysis of palladium by Inductively Coupled Plasma (ICP) and hot loading filtration test. MEP (Molecular Electrostatic Potential) of ligand and molecular docking ligand and pd complex was performed. This research indicated ligand of sulfonamide was Biocompatible and has an antibacterial property and its pd complex is an anticancer agent.

Keywords: Bis (N-(4-pyridyl-para-toluenesulfonamide)) Dichloride Palladium Complex; Molecular Docking; HSA; DNA; 2JVU; MEP

Abbreviations: ICP: Inductively Coupled Plasma; MEP: Molecular Electrostatic Potential; PTS: P-Toluene Sulfonamide; HAS: Human Serum Albumin; PDB: Protein Data Bank; LGA: Lamarckian Genetic Algorithm; DFT: Density Functional Theory

Introduction

Sulfonamides are the category of drugs with interesting biological properties [1-4] including antimicrobial [5,6], antibacterial [7], and anticancer activities [8,9]. In addition, some activities for sulfonamides and sulfonyl derivatives as anticancer agents have been observed [10]. Sulfonamides are important agents in medicinal chemistry with anti-tumoral, anti-bacterial, and anti-inflammatory properties [11]. In this order, some sulfonamide derivatives have been employed as pharmacological agents in diabetes treatment [12,13] and antithyroid drugs [14,15]. Therefore, the clinical and medicinal importance of sulfonamides is well known [16]. In other words, the palladium complex has anticancer properties [17,18]. It has been accepted that changing the structural parts of the sulfonamide, and synthesis pd complex as the new drug has been designed in recent investigations [19-22]. These results prompted us to synthesize and evaluate a new series of sulfonamide derivatives for medicinal and pharmaceutical chemistry. Our previous report was related to the spectral and theoretical investigation of new drug-based materials [23]. For this purpose, we have selected pyridine as a part of the sulfonamide structure due to coordination with palladium and the preparation of new sulfonamide drugs. This sulfonamide derives as a ligand and its pd complex has medicinal properties. It can be attached to the target macromolecule of HSA, Escherichia coli, and DNA using molecular docking methods to evaluate it as a biocompatible material with antibacterial and anticancer properties.

Experimental

Physical Measurements and Materials

All compounds were purchased from Merck and Aldrich. Fourier transform infrared spectra of prepared compounds were obtained in the 400–4000 cm^{-1} region using KBr pellets on Shimadzu FT-IR 8400 spectrometer. 1H-NMR spectrum was recorded on a Bruker Ultrashield 400 MHz spectrometer using DMSO-d6 as solvent and tetramethyl silane as internal standard.

Preparation of N-(4-pyridyl) P- Toluene Sulfonamide (PTS): The synthetic method for preparation of the N-(4-pyridyl) p-toluene sulfonamide as a free ligand (PTS with chemical formula as $C_{12}H_{12}N_2O_2S$) is as follows. 3.81 g tosyl chloride (20 mmol), 1.88 g 4-amino pyridine (20 mmol), potassium hydroxide solution 1M (20 mL, used as a base) and THF (50 mL, used as solvent) were placed in a 100 mL round-bottomed flask, which in equipped with magnetic stirrer. The reaction mixture was stirred for 4 h at room temperature. The white precipitate appeared. The product was filtered and washed with THF (3×10mL) and used without further purification. The obtained product was analyzed without further purification.

Preparation of Complex Bis [N-(4-pyridyl) Sulfonamide] Di Chloro Palladium (PdL_2Cl_2): The synthetic method for preparation of compound 1 is as follows. 0.09 g PdC_{l2} (0.5 mmol) and CH_3CN (50 mL) were placed in a 100 mL round-bottomed flask which is equipped with a reflux condenser and a magnetic stirrer. The mixture was stirred and warmed to 70°C to give a light orange solution. Then, 0.25 g ligand (1 mmol) and sodium hydroxide 0.5M (2 mL) were added. The reaction mixture refluxed for 12 h. the yellow solid appeared. The yellow solution was filtered and washed with CH_3CN (3×10mL).

Computational Details

The structure of Escherichia Coli (2jvu), Human Serum Albumin (HSA), and DNA were obtained from Protein Data Bank, respectively, (PDB ID: 2jvu, 1AO6, 432D). PASS (Prediction of Activity Spectra) [24] was used as an online server to predict the activity of the ligand. These molecular docking computations were performed on Auto Dock software. The most popular algorithm, the Lamarckian Genetic Algorithm (LGA), in Auto Dock for this docking was employed [25]. Calculations of the PTS and pd complex were performed using Gaussian 09 software [26]. These calculations include geometry optimization were performed using Density Functional Theory (DFT) [27,28]. The optimizations of ligand and its complex were carried out using 6-311G(p, d) and lanl2dz. Molecular docking has recently been used as a tool to get an insight into ligand – receptor interaction and screen molecules for the binding affinities against a special receptor. The output of geometry optimization for ligand and complex were used as the input for docking processes.

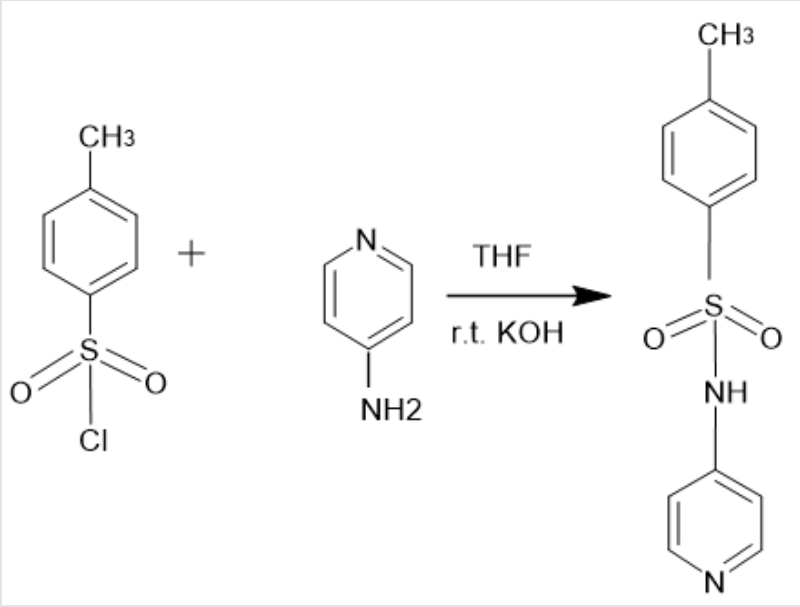
Results and Discussion

Synthesis and Characterization

The synthetic route of PTS and PdL2Cl2 which was previously reported in experimental are shown in Scheme 1 and Scheme 2.

Molecular Structural

The optimized geometry (opt-freq) using B3LYP method 6-311G (d,p) of ligand and LANL2DZ using palladium was calculated The structure ligand and pd complex are shown in Figure 1.



Scheme 1: Synthesis of N-(4-pyridyl) p-toluene sulfonamide as free ligand.

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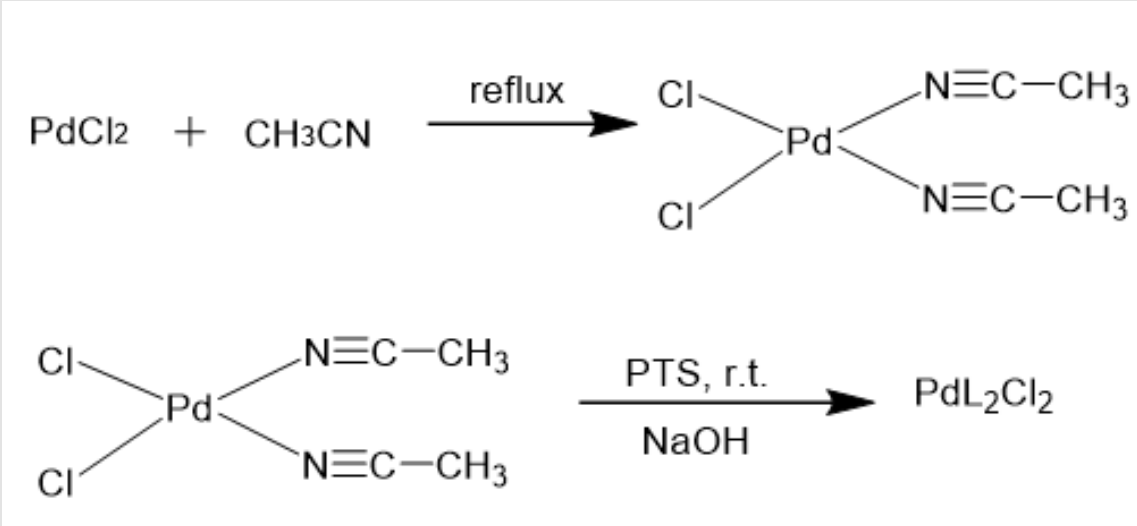

Scheme 2: Synthesis of Bis [N-(4-pyridyl) sulfonamide] di chloro palladium (PdL_2Cl_2).

Figure 1: Optimized geometry of PTS and pd complex.

FT-IR Spectra of PTS and Pd Complex

The FT-IR spectra of the PTS as ligand and its complex in Figures 2 & 3 are shown. The 3220 ν(N-H) vibrational band at cm^{-1} is assigned to the ligand. This band disappears for the complex because the nitrogen atom in the ligand is deprotonated and attached to palladium, due to the formation of the Pd-N bond. The vibrational frequency range of cm^{-1} 3055-2821 is related to aliphatic C-H (methyl group) and aromatic C-H (phenyl ring). The frequencies of 1629 cm^{-1} and 1531 cm^{-1} correspond to ν(C=N) and ν(C=C) vibrations, respectively. C=C stretching vibration appeared in the range of 1430-1650 cm^{-1} and C-H bending bands appeared in the regions of 1000-1275 cm^{-1} (C-H in-plane) and 690-900 cm^{-1} (out-of-plane C-H). The νas(S=O) FT-IR spectrum attributed to the SO_2 group in the ligand and complex shifts from 1350 cm^{-1} to 1317 cm^{-1}. But the group νs (S = O) is almost unchanged. The absence of ν(N-H) vibrational band in the spectrum of the complex was due to deprotonation and coordination of anions to palladium and the formation of Pd-N bonds.

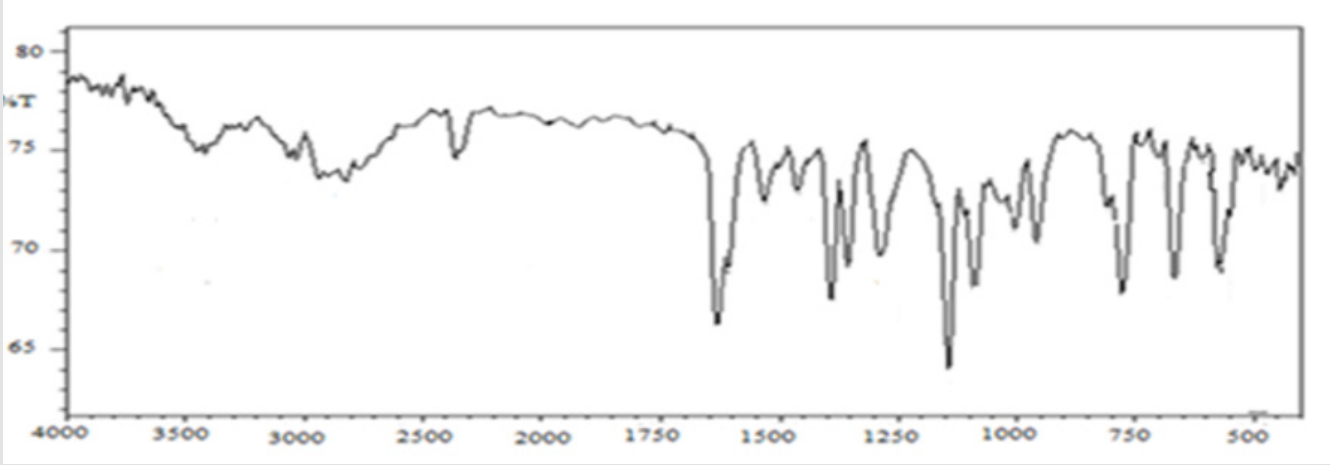

Figure 2: FT-IR spectrum of PTS.

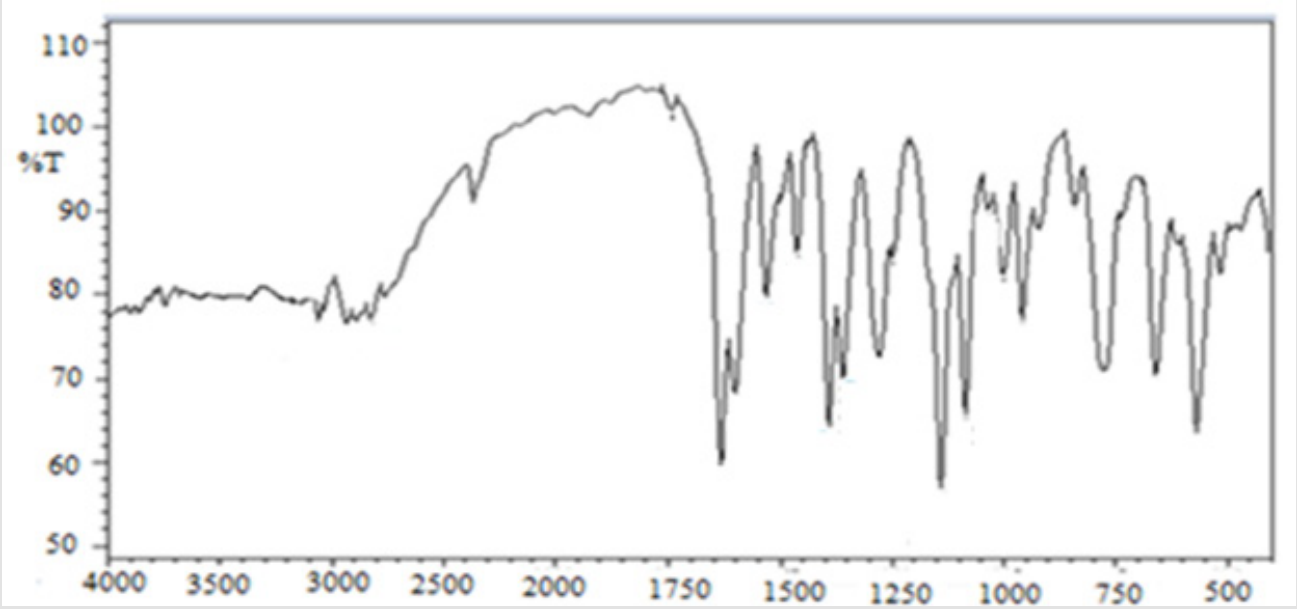

Figure 3: FT-IR spectrum of palladium complex.

Determination of Pd Content

Determination of Pd content was performed by ICP (Inductively Coupled Plasma–Atomic Emission Spectrometer) analysis. The Pd content of the Pd complex was 0.13 mmol/g.

Molecular Electrostatic Potential

MEP (Molecular Electrostatic Potential) is an important tool to predict electrophilic and nucleophile attacks for biological interactions. The MEP of the PTS optimized geometry using B3LYP method 6-311G (p, d) basis set. As can be seen in Figure 4. The different colors in this plot indicate different values of electrostatic potential. Red<orange< yellow<green<blue. The blue demonstrates the strongest attraction. The positive areas are located around vinyl and phenyl groups. These areas have positive potential. The negative area is related to nitrogen atoms and SO_2. In these areas having negative potential are over the electronegative atoms such as oxygen and nitrogen atoms. The red indicates the strongest repulsion. These regions of negative potential are associated with the lone pair of electronegative atoms. The residuals species are surrounded by zero potential.

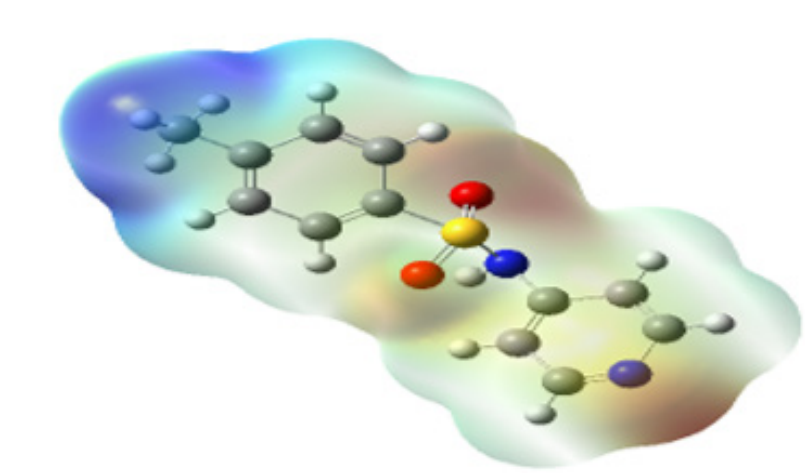

Figure 4: MEP (Molecular electrostatic potential) plot of PTS.

Molecular Docking Studies

The study of molecular docking is a significant tool for the prediction of ligand-receptor interactions and was performed to indicate the HSA and 2JVU-binding sites for PTS. The crystal structures of HSA and Escherichia coli (PDB ID: 1AO6, 2JVU) were taken from the Protein Data Bank, respectively. These crystals were prepared for the docking system. Flexible ligand docking was carried out by Auto Dock 4.2.5.1 molecular docking program using the implemented empirical free energy function and the Lamarckian Genetic Algorithm. We decided to show this compound has antimicrobial properties in the human body. The Cu complex as a ligand was prepared for docking by using the B3LYP method 6-311G (d, p) basis set. In the first step, the docking of the ligand with 1AO6 and 2JVU, a blind docking with 126 lattice points along X, Y, and Z axes was performed to find the binding site of the complex on these crystals with a grid point spacing of 0.375 Å, to allow the complex to rotate freely. In the next step, the second docking was performed using a cubic box with 60×60×60 Å dimensions. Among the docked conformations, the best-scored conformation predicted by the AutoDock scoring function was visualized for ligand-HSA and ligand-2JVU interactions in AutoDock software.

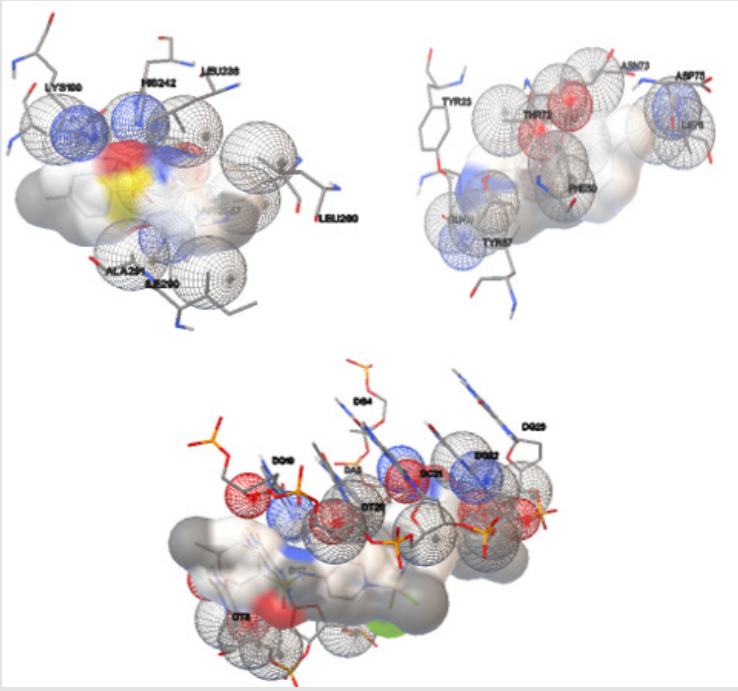

Figure 5: The interactions and hydrogen bonding across the binding interface of HSA - PTS in the left top, 2JVU - PTS in the right top, and, DNA–pd complex in the middle bottom.

The resulting docking for the obtained molecular docking in which the PTS binds into HSA and 2JVU, as a receptor is illustrated in Figure 5. The HSA creates three hydrogen bonds (LYS199, HIS242, and ARG257) with the PTS and 2JVU forming one hydrogen bond (TYR23). There are hydrophobic contacts between PTS as a ligand with HSA (LEU238, LEU260, ILE290, ALA291, GLN198, TYR150) and 2JVU (GLN18, TYR87, PHE50, THR72, GLY20, VAL21, ASN73, ILE76, ASP75, PHE50), respectively. The binding free energies (ΔG°) of -7.8 and -6.77 kcal mol-1 were predicted for HSA and 2JVU in the best conformation of the ligand. Now, in continuation, the study of molecular docking of pd complex as an anticancer was performed. The crystal structures of DNA (PDB ID: 423D) were taken from the Protein Data Bank. The DNA creates two hydrogen bonds (DG4, and DG7) with the Pd complex. There are hydrophobic contacts between pd complex with DNA (DG19, DG4, DA5, DG7, DT20, DC21, DG22, DG23, DT8). These results indicated that PTS as a ligand has antibacterial property and its pd complex has anticancer property.

Conclusion

We report the new compound of based-pyridyl sulfonamide. N-(4-pyridyl) p- toluene sulfonamide as a ligand and its pd complex was characterized using FT-IR spectroscopy. Molecular electrostatic potentials indicated nitrogen atom attached to palladium and pd complex was formed. This research led us to find that this compound has antibacterial and anticancer properties. These biological investigation results suggest that pd complex can be used for the design and synthesis of new based-drug materials.

Acknowledgment

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