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Synthesis, characterization, computational studies, antimicrobial activities and carbonic anhydrase inhibitor effects of 2-hydroxy acetophenone-*N*-methyl *p*-toluenesulfonylhydrazone and its Co(II), Pd(II), Pt(II) complexes

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ABSTRACT

2-Hydroxyacetophenone-*N*-methyl *p*-toluenesulfonylhydrazone (*afptsmh)* derived from *p*-toluenesulfonicacid-1-methylhydrazide *(ptsmh)* and its Co(II), Pd(II), Pt(II) complexes were synthesized for the first time. Synthesized compounds were characterized by spectroscopic methods (FT-IR, $^{1}H-^{13}C$ NMR, LC-MS, UV–vis), magnetic susceptibility and conductivity measurements. ^{1}H and ^{13}C shielding tensors for crystal structure of ligand were calculated with GIAO/DFT/B3LYP/6-311++G(d,p) methods in $CDCl_3$. The vibrational band assignments were performed at B3LYP/6-311++G(d,p) theory level combined with scaled quantum mechanics force field (SQMFF) methodology. The antibacterial activities of synthesized compounds were studied against some Gram positive and Gram negative bacteria by using microdilution and disc diffusion methods. In vitro enzyme inhibitory effects of the compounds were measured by UV–vis spectrophotometer. The enzyme activities against human carbonic anhydrase II (hCA II) were evaluated as IC_{50} (the half maximal inhibitory concentration) values. It was found that *afptsmh* and its metal complexes have inhibitory effects on hCA II isoenzyme. General esterase activities were determined using alpha and beta naphtyl acetate substrates (α- and β-NAs) of *Drosophila melanogaster (D. melanogaster).* Activity results show that afptsmh does not strongly affect the bacteria strains and also shows poor inhibitory activity against hCAII isoenzyme whereas all complexes posses higher biological activities.

1. Introduction

Sulfonamides have been intensively investigated as the first effective antibacterial [1,2] and chemotherapeutic agents employed systematically for the prevention and the cure of bacterial infections in humans and other animal systems [3,4]. Sulfamethoxazole with trimethoprim (SMX/TMP) is a drug combination with broad-spectrum of antibacterial activities against both Gram positive and Gram negative organisms. SMX/TMP is currently the most effective therapeutic agent against *P.J. pneumonia* in patients with AIDS [5]. Later on, many thousands of molecules containing sulfanilamide group have been created yielding formulations with greater effectiveness and less toxicity. Sulfa drugs are still widely used for conditions such as acne and urinary tract infections and they have great interest for the treatment of infections having bacterial resistant to other antibiotics. Also, the other activities include endotelin antagonism, anti-inflammatory activity, tubular transport inhibition, insulin release, carbonic anhydrase and saluretic actions [6]. Some metal sulfonamides have been attracted much attention due to higher activities than free ligands and the corresponding metallic salts. In particular, Ag-sulfadiazine has been proved to be an effective topical antimicrobial agent having

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significance in burn therapy with better activities than free ligand or $AgNO_3$ [7]. Moreover, several Cu(II), Ce(III), Bi(III), Cd(II) and Hg(II) sulfonamide complexes were evaluated for their antibacterial activities [8–10]. One of the most important activity of the sulfonamides is the enzyme inhibition effect to zinc containing metalloenzyme named as carbonic anhydrase (CA). Many sulfonamide CA inhibitors have been used as antiglaucoma, diuretic, antiobesity and antitumor agents and various neurological disorders [11–13].

In our previous studies, aliphatic/aromatic bis sulfonamides were synthesized and tested for antimicrobial activities [14–17]. Also, we have reported conformational analysis and vibrational spectroscopic investigation of the methanesulfonic acid hydrazide [18], methanesulfonic acid 1-methylhydrazide [19] and some methanesulfonylhydrazone derivatives [20,21]. In this work, 2-hydroxyacetophenone-*N*-methyl *p*-toluenesulfonylhydrazone (*afptsmh*) derived from *p*-toluenesulfonicacid-1-methylhydrazide *(ptsmh)* and its Co(II), Pd(II), Pt(II) complexes were synthesized and characterized by using elemental analyses, spectrometric methods (FT-IR, $^{1}H-^{13}C$ NMR, LC–MS, UV–vis), magnetic susceptibility and conductivity measurements. ^{1}H and ^{13}C shielding tensors for crystal structure of ligand were calculated with GIAO/DFT/B3LYP/6-311++G(d,p) methods in $CDCl_3$. The vibrational band assignments were performed at B3LYP/6-311++G(d,p) theory level combined with scaled quantum mechanics force field (SQMFF) methodology. The antibacterial activities of compounds were studied against Gram positive species; *B. subtilis* ATCC 6633, *B. cereus* NRRL-B-3711, *S. aureus* ATCC 6538, *E. faecalis* ATCC 29212, *S. agalactiae* ATCC 13813 and Gram negative species; *E. coli* ATCC 11230, *P. aeruginosa* ATCC 15442, *K. pneumonia* ATCC 70063 by using microdilution (as MICs) and disc diffusion (as mm zone) methods. The inhibition degrees of the compounds on carbonic anhydrase II (hCA II) have been evaluated as IC_{50} (the half maximal inhibitory concentration) and we also report the α esterase activities and the β-esterase activities from the model of insect *D. melanogaster*.

2. Experimental

2.1. Instrumentation

The elemental analyses (C, H, N and S) were performed on a LECO CHNS 9320 type elemental analyzer. The IR spectra (4000–400 cm^{-1}) were recorded on a Mattson 1000 FT-IR Spectrophotometer with samples prepared as KBr pellets. LC/MS-APCI was recorded on an AGILENT 1100 Spectrometer. The melting points were measured using an Opti Melt apparatus. TLC was conducted on 0.25 mm silica gel plates ($60F_{254}$, Merck). The molar magnetic susceptibilities were measured on powdered samples using Gouy method. The molar conductance measurements were carried out using a Siemens WPA CM 35 conductometer. All solvents were purchased from Merck and reagents were obtained from Aldrich Chem. Co. (ACS grade) and used as received. The microdilution broth method was used to determine antibacterial activities of the compounds against Gram positive species; *B. subtilis* ATCC 6633, *B. cereus* NRRL-B-3711, *S. aureus* ATCC 6538, *E. faecalis* ATCC 29212, *S. agalactiae* ATCC 13813 and Gram negative species; *E. coli* ATCC 11230, *P. aeruginosa* ATCC 15442, *K. pneumonia* ATCC 70063. The enzyme activity measurements were also performed by using microplate reader (Biotek spectrophotometer, Vermont, USA).

2.2. Synthesis

2.2.1. p-Toluenesulfonic acid 1-methylhydrazide(ptsmh)

p-Toluenesulfonyl chloride (0.04 mol, 7.626 g) in tetrahydrofuran (30 mL) was added dropwise to solution of methylhydrazine (0.05 mol, 1.60 mL) in ethanol/ethyl acetate (1:1) while the temperature was maintained between 268 and 273 K. The mixture was stirred for 24 h mean while the completion of the reaction was monitored by TLC and then, the solvent was evaporated. The colorless crude compound was purified in THF/n-hexane (1:1) by column chromatography and then the product was recrystallized from THF/n-hexane mixture (1:1) [22]. Yield 72%; mp: 115–117 °C. Elemental analysis results for $C_8H_{12}N_2O_2S$: (Calc.%) C, 47.98; H, 6.04; N, 13.99; S, 16.01. (Found%): C, 45.55; H, 6.20; N, 14.25; S, 17.10. LC-MS: *m/z* (abudance %) $[M+1]^+$:200.15 (54%), $[M-N(CH_3)-NH_2]^+$:155.85 (100%).

2.2.2. 2-Hydroxyacetophenone-N-methyl p-toluenesulfonylhydrazone (afptsmh)

p-Toluenesulfonic acid 1-methylhydrazide (1.5 g, 4.72 mmol) in ethanol/ethyl acetate (1:1) solution was added dropwise to solution of 2'-hydroxyacetophenone (0.52 g, 5.0 mmol) in ethanol/ethyl acetate (1:1) maintaining the temperature at about 323 K. Then, the mixture was stirred for 24 h at room temperature. The precipitated product was recrystallized from ethanol/n-hexane (2:1) mixture. The yellow crystalline solid was dried in vacuo to remove ethanol/n-hexane vapour. Yield 65%. Mp. 155–157 °C. Elemental analysis for $C_{16}H_{18}N_2O_3S$ (Calc.%) C 60.36, H 5.70, N 8.80, S 10.07. (Found%) C 59.80, H 5.74, N 9.20, S 10.22. LC-MS: *m/z* (abudance %) 319.8 $[M+2]^+$:319.8 (25.5%), $[M\text{-}AfOH]^+$: 198.6 (100%).

2.2.3. Synthesis of the complexes

All metal complexes were prepared by the following general method: To solution of *afptsmh* (2.0 mmol) in acetonitrile (2.0 mL), anhydrous 0.80 mmol MCl_2 (where M: Pt(II), Pd(II) and Co(II)) dissolved in methanol/acetonitrile (2:1, 30 mL) was added and then, NaOH in methanol (2 mL) was added to obtain alkaline media. The reaction mixture was heated at 60 °C for 1 h by stirring on magnetic stirrer. The metal complexes were precipitated at room temperature and filtered off, dried in a desiccator over $CaCl_2$.

2.2.4. Trans-bis(2-Hydroxyacetophenone-N-methyl p-toluenesulfonylhydrazonato)platinum(II) (Pt(afptsmh)$_2$)

Yield 85%. Mp. 317–319 °C. Elementel analysis for $C_{32}H_{34}N_4O_6S_2Pt$ (Calc.%) C 46.32, H 4.13, N 6.75, S 7.73, Pt 23.51. (Found%) C 48.10, H 3.80, N 6.95, S 7.24, Pt 23.48. APCL-MS: *m/z* (abudance %) $[M+1]^+$: 830.2 (14.8%).

2.2.5. Trans-bis(2-Hydroxyacetophenone-N-methyl p-toluenesulfonylhydrazonato)palladium(II) (Pd(afptsmh)$_2$)

Yield 70%. Mp. 287–289 °C. Elemental analysis for $C_{32}H_{34}N_4O_6S_2Pd$ (Calc.%) C 51.86, H 4.62, N 7.56, S 8.65, Pd 14.36 (Found%) C 50.16, H 4.45, N 7.14, S 8.85, Pd 14.28. APCL-MS *m/z* (abudance%) $[M+1]^+$: 741.8 (19.9%).

2.2.6. Trans-bis(2-Hydroxyacetophenone-N-methyl p-toluenesulfonylhydrazonato)cobalt(II)

(*Co(afptsmh)$_2$*) Yield 80%. Mp. 284–286 °C. μ_{eff}:3.89 BM. Elemental analysis for $C_{32}H_{34}N_4O_6S_2Co$ (Calc.%) C 55.40, H 4.94, N 8.08, S 9.24, Co 8.50. (Found%) C 55.31, H 4.55, N 8.22, S 8.95, Co 8.45. APCL-MS *m/z* (abudance%) $[M+1]^+$: 694.1(12.6%).