Eleventh International Conference on Radiation, Natural Sciences, Medicine, Engineering, Technology and Ecology
June 19 - 23, 2023 | Hunguest Hotel Sun Resort | Herceg Novi | Montenegro

Anthranilic acid amide and its complex with Cu(II) ions

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INTRODUCTION

The anthranilic acid and its analogues form an important constituent in several bioactive compounds and commercialized drugs, while their derivatives present a wide range of biological activities in the management of several diseases and in regulating the disease-causing pathways (Elshaarawy & Janiak, 2016; Jayanthi & Rajakumar, 2017; Merk et al., 2015; Patrone et al., 2016). The presence of functional head groups, such as –COOH, $–NH_2$, $–CONH_2$, $–COOCH_3$, and $–NHCOCH_3$ on the anthranilic acid and its analogues enable their conjugation and derivatization for developing rationally designed molecules deliberated for interacting with their biological targets (Kwon et al., 2017; Schrey et al., 2019; Teponno et al., 2017). These functional groups act as sites for tailoring of molecules and for studying the structure activity relationship (SAR) analysis of anthranilic acid-based libraries for identifying suitable pharmacophores.

Based on the impressive biological profile provided by anthranilic acid and its analogues, this nucleus has been extensively investigated for developing pharmaceuticals aimed at modulating the biochemical and metabolic pathways contributing to the onset of various diseases' pathogenesis.

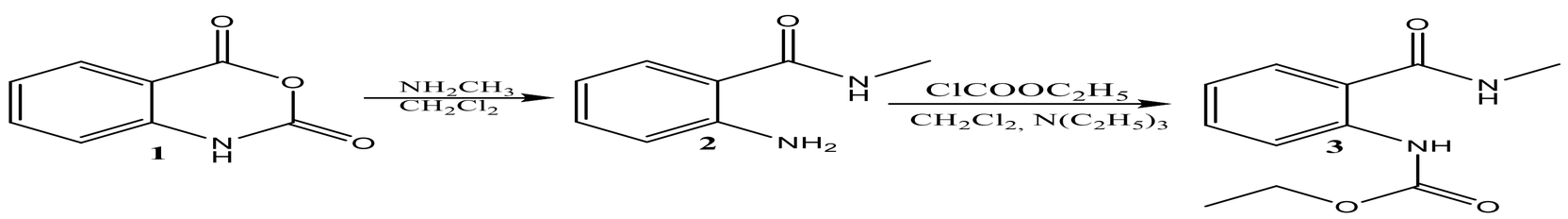
The anthranilic acid derivatives also have intriguing antibacterial, antiviral, and insecticidal capabilities, while those based on the structure of anthranilic diamide have potential uses as P-glycoprotein inhibitors for controlling drug resistance in cancer cells. Nevertheless, the transition metal complexes of anthranilic acid derivatives offer therapeutic applications in diabetes mellitus, and obesity by regulating the activity of a-glucosidase.

AIM

Based on the pharmacological activities of anthranilic acid derivatives and their metal complexes, we considered the synthesis of (2-(methylcarbamoyl)phenyl)carbamate and its metal complexes. The functional groups for the ethyl (2-(methylcarbamoyl)phenyl)carbamate were chosen due to the presence of both diamide and ester bonds.

Experimental

To synthesize the anthranilic acid diamide we used a known proc edure, namely, ring opening of isatoic anhydride **1** with methylamine to form the amine **2**, which upon the acylation affords the anthranildiamide, **3 (L)**.



The resultant compound is characterized by its melting point, IR, ^1H, and ^{13}C-NMR spectra. Spectral data confirmed the structure of the resultant diamide **3**.

SYNTHESIS OF CU(II) COMPLEX OF ETHYL (2-(METHYLCARBAMOYL)PHENYL)CARBAMATE (L)

Synthesis of Cu(II) complex of (L) M:L:OH^- =1:2:2

0,0269 g (0,0002 mol) Cu(II)Cl_2 in 5 mL H_2O;
0,0889 g (0,0004 mol) of L in 5 mL DMSO;
0,016 g (0,0004 mol) NaOH in 5 mL H_2O.

5 mL of NaOH was added slowly to the L solution while stirring at pH = 9. The solution of the metal salt was added dropwise from a burette during stirring with an electromagnetic stirrer. The precipitation of the formed complexes started after 2 h. The complex was formed as a blue-green precipitate. The precipitate was filtered and washed with 10-20 cm^3 H_2O and dried over $CaCl_2$ for 2 weeks.

We found that the reaction of ethyl (2-(methylcarbamoyl)phenyl)carbamate with the transition metal ion afforded a 37% yield of a stable solid compound. The obtained complex has a green colour and is soluble in DMSO and insoluble in water, THF, C_2H_5OH, EtOAc, and C_6H_{12}.

ACKNOWLEDGEMENTS: This work is support by the Scientific research fund at the PU "Paisii Hilendarski", contract **SP23-HF-006**.

The IR band at 3345 cm^{-1} and 3258 cm^{-1} of L that was observed may refer to the stretching vibrations of the N-H groups of the diamide. One of the same bands in the spectrum of the copper(II) complex is missed. This showed that the NH group of the ligand is participated in the coordination with Cu(II). In the IR spectrum of ethyl (2-(methylcarbamoyl)phenyl)carbamate the bands at 1739 cm^{-1} and 1633 cm^{-1} can be attributed to stretching vibrations of C=O groups from the diamide. The same bands in the spectrum of the copper(II) complex was observed at 1717 cm^{-1} and 1645 cm^{-1} and that one of them is seen to be shifted to lower frequencies by 22 cm^{-1} and the another one was shifted by 12 cm^{-1} to higher frequencies. This showed that the C=O groups of the ligand is participated in the coordination with Cu(II). In the IR spectrum of the Cu(II)L complex a broad band is observed at 3600-3500 cm^{-1}, confirming the presence of hydroxyl group from a water molecule.

The stretching vibration of C=O groups appears at 1730 cm^{-1} and 1641 cm^{-1} in the Raman spectrum of free ligand.

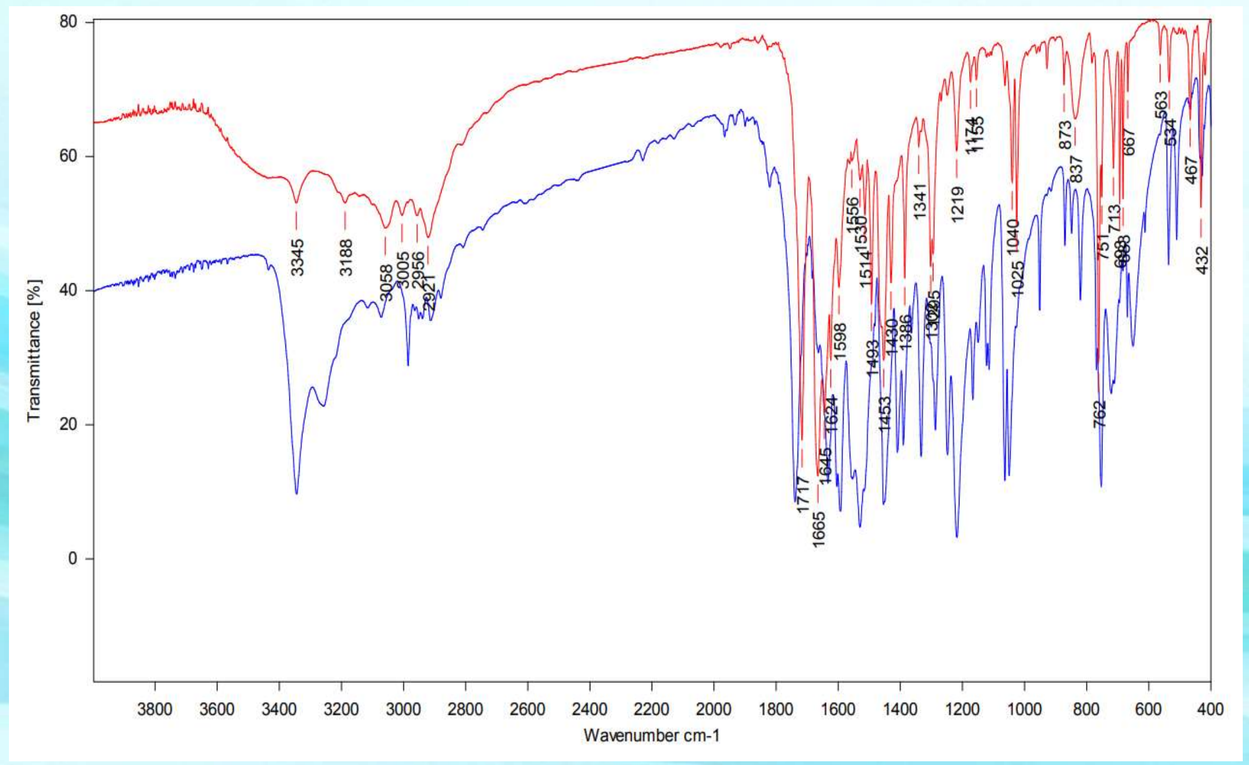


Figure 1. IR spectra of free ligand (in blue color) and its metal complexes with copper(II) (in red color)

IR (ν, cm^{-1}) L: 3345 (NH), 3258 (NH), 3116 (CH), 3072 (CH), 2985, 2951, 2913, 2880, 1739 (C=O), 1664, 1633 (C=O), 1605, 1593, 1554, 1530, 1454, 1409, 1390, 1364, 1333, 1287, 1248, 1218, 1167, 1149, 1122, 1114, 1063, 1049, 951, 870, 849, 820, 768, 753, 721, 669, 651, 536, 510

IR (ν, cm^{-1}) Cu(II)L: 3345 (NH), 3188 (CH), 3058 (CH), 3005, 2956, 2921, 1717 (C=O), 1665, 1645 (C=O), 1624, 1598, 1556, 1530, 1514, 1493, 1453, 1430, 1386, 1341, 1302, 1295, 1219, 1174, 1155, 1040, 1025, 873, 837, 762, 751, 713, 693, 683, 667, 563, 534, 467, 432

Raman (ν, cm^{-1}) L: 2939, 1730 (C=O), 1641 (C=O), 1604, 1592, 1555, 1463, 1454, 1392, 1366, 1334, 1305, 1288, 1249, 1219, 1169, 1151, 1123, 1052, 1012, 915, 849, 822, 613, 395, 364

Conclusion

Based on the obtained data, we can conclude that the diamide was easily prepared using isatoic acid anhydride. The further reaction of the diamide with Cu(II) and its spectral characteristics showed participation of C=O and NH groups in the complex formation with chelate structure. Our future goal is to investigate biological activities of the synthesized diamide and its Cu(II) complex.

ACKNOWLEDGEMENTS: This work is support by the Scientific research fund at the PU "Paisii Hilendarski", contract **SP23-HF-006**.