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SYNTHESIS AND STRUCTURE INVESTIGATION OF 1,5-DIBENZIMIDAZOLYL FORMAZANS AND THEIR METAL COMPLEXES

M. Argirova[1], K. Anichina[2], D. Yancheva[1], S. Stoyanov[1], A. Mavrova[2]

[1]*Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria,*
[2]*University of Chemical Technology and Metallurgy, Department of Organic Synthesis, 8 Kliment Ohridski Blvd., 1756 Sofia, Bulgaria, e-mail: maargirova@abv.bg*

Formazans attract the attention of chemists, biologists, technologists and other specialists due to their application as dyes for different purposes, bio-chemical markers for redox processes, analytical reagents as well as a variety of biological activities such as antimicrobial, antioxidant, analgesic, anticancer [1].

2-Hydrazinobenzimidazoles, which undergo autoxidation readily, can undergo autoxidative coupling to formazans in pyridine-water solutions with a wide variety of hydrazones, including aromatic hydrazones [2]. The symmetric 1,5-dibenzimidazolylformazns are polydentate ligands with donor atoms so they are excellent complexing agents with many metals [3].

To the present contribution we report the synthesis of a series of 1,5-dibenzimidazolyl formazans and their conversion in Cu and Co complexes.

The molecular geometry and electron structure of 1,5-dibenzimidazolyl formazans and their metal complexes were theoretically evaluated using density functional theory (DFT) methods. The formazan molecules may exhibit in three configuration combinations – EZZ, EEZ and EEE, the EZZ configuration being the most stable. Elemental analysis, IR and NMR spectra indicated that the complexes are formed by coordination of two formazan molecules to three metal atoms via N1, N3 from the formazan fragments and the benzimidazolyl nitrogen atoms.

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EXPLORING THE ELECTROCHEMICAL REDUCTION OF NITROFURANTOIN THOUGH MODEL COMPOUNDS: A COMBINED IR AND COMPUTATIONAL STUDY

S. Stoyanov[1], D. Yancheva[1], A. Popova[1], K. Anichina[2]

[1]*Institute of Organic Chemistry with Centre of Phytochemistry BAS, Sofia 1113, Bulgaria,*
[2]*University of Chemical Technology and Metallurgy, Department of Organic Synthesis, 8 Kliment Ohridski Blvd., 1756 Sofia, Bulgaria,*
e-mail: s_stoyanov@orgchm.bas.bg (S. Stoyanov)

The study on nitroaromatic drugs reduction provides important insights on the mechanisms underlying their hepatotoxicity associated with bioreduction to radical anion and other hazardous intermediates *in vivo* [1-3].

In the present contribution the electrochemical reduction of anti-inflammatory drug nitrofurantoin, N-(5-Nitro-2-furfurylidene)-1-aminohydantoin, an antibacterial agent used to treat acute urinary tract infections, was studied by IR spectroscopy in an electrochemical IR liquid cell. It was shown that it leads to considerable decrease of the N-O and C=O stretching frequencies and increase of the C-NO_2 stretching frequency. In the same time the band for δ(N-H) disappeared. The observed IR spectral changes differ significantly from those expected on the bases of one-electron reduction to nitro radical anion, and comply better with the generation of dianion radical of nitrofurantoin. Comparison with theoretically predicted spectra of possible reduction products supports the dianion radical formation.

In order to clarify the observed IR spectral changes and assign them unambiguously a particular product, a series of IR measurements on nitrofurantoin derivatives was carried out. Nitrofurantoin was converted into anion by treatment with excess of dry CD_3ONa and the corresponding spectral and structural changes, accompanying the conversion were described by IR spectra in DMSO-d_6. N-methyl and oxadiazole derivative of nitrofurantoin along with a N,N-dimethyl hydrazine derivative of nitrofuran, were synthesized and their electrochemical reduction was monitored by IR spectroscopy. The structural and spectral changes arising from the conversion were assisted by DFT computations.

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STUDY OF THE SECONDARY STRUCTURE OF TWO FOLIC ACID-MODIFIED HEMOCYANINS IN COMPARISON TO THE NATIVE PROTEINS

D. Yancheva[1], M. Guncheva[1], Y. Raynova[1], K. Idakieva[1]

[1]*Institute of Organic Chemistry with Centre of Phytochemistry BAS, Sofia 1113, Bulgaria, e-mail: deni@orgchm.bas.bg (D. Yancheva)*

S2P33

Targeting the folate receptors (FR) is a strategy for imaging and selective delivery of drugs to several types of cancer cells, which are characterized by the overexpression of FR [1]. On the other hand, it has been reported that folate modified immunoglobulin G activates the natural killer (NK) cells to target FR-positive melanoma cells for lysis [2]. Hemocyanins (Hcs) are large copper-glycoproteins with an oxygen-transporting function that are found in some invertebrates (mollusks and arthropods) [3]. They exhibit diverse biological properties including immunostimulatory, antiviral and antibacterial activities, they can be used as protein-carriers or adjuvants [3]. In addition, conjugated with various organic molecules, carbohydrates or peptides Hcs are successfully applied in cancer immunotherapy.

Here, we report the synthesis of folate-modified Hcs isolated from garden snails *Helix lucorum* (HLH) and marine snails *Rapana thomasiana* (RtH). Hcs with different degree of modification were prepared, isolated and purified on a Sephadex G-25 resin. FTIR spectra of all samples were collected by direct deposition on attenuated total reflectance (ATR) element. Differences in the Amide I region (1600 – 1700 cm^{-1}) in ATR-FTIR spectra were used to monitor the changes in the secondary structure for each folate-conjugated Hcs in comparison to its native counterpart. At first, the second derivatives were obtained using the Savitzky – Golay algorithm in order to be determined all local maxima, the bands were assigned according to the literature, then the relative area of each structural component was assessed by curve fitting procedure of Opus software [4]. For the two Hcs, a correlation between the degree of the chemical modification and the conformational changes is done.

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SYNTHESIS, IR AND DFT STUDY ON THE ANION PRODUCTS OF N-(4-HYDROXY-3-METHOXYBENZYL)ACETAMIDE, A CAPSAICIN DERIVATIVE

D. Yancheva[1], S. Stoyanov[1], K. Anichina[2], S. Stamboliyska[1], E. Velcheva[1]

[1]*Institute of Organic Chemistry with Centre of Phytochemistry BAS, Sofia 1113, Bulgaria,*
[2]*University of Chemical Technology and Metallurgy, Department of Organic Synthesis, 8 Kliment Ohridski Blvd., 1756 Sofia, Bulgaria,*
e-mail: deni@orgchm.bas.bg (D. Yancheva)

The antioxidant activity of capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide, the pungent principle of hot red peppers, has been subject of several studies up to date [1,2]. In the same time, the exact mechanism of antioxidant action has been debated: donation of hydrogen atom from its C7-benzylic group or C4-phenolic group, radical adduct formation and/or sequential proton loss electron transfer [3,4]. In this context, further characterization of the anionic intermediates of capsaicin might help to understand fully the reactivity of capsaicin toward free radicals.

The spectral and structural variations, caused by the conversion of organic molecules into anions can be conveniently followed by IR spectroscopy measurement combined with DFT computations.

In the present study, a synthetic analogue of capsaicin – N-(4-hydroxy-3-methoxybenzyl)acetamide, was prepared by condensation of vanillylamine and acetyl chloride in a biphase water/chloroform system. Deprotonation of the capsaicin derivative was carried out in DMSO solution and the changes in the force field, steric and electronic structure were described in detail on the basis of both IEFPCM-B3LYP/6-311++G** computations and spectroscopic experiments. Molecular and electronic properties influencing the reactivity of capsaicin according to the different mechanisms were discussed in the light of available experimental data from antioxidant assays and compared with those of its simpler counterpart vanillin.

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SYNTHESIS OF N,N'-DISUBSTITUTED DERIVATIVES OF 5-NITROBENZIMIDAZOLE-2-THIONE AND IR STUDY ON THE ELECTROCHEMICAL GENERATION OF THEIR NITRO RADICAL ANIONS

N. Anastassova[1], D. Yancheva[1], S. Stoyanov[1], A. Mavrova[2]

[1]*Institute of Organic Chemistry with Centre of Phytochemistry-BAS, Sofia, Bulgaria,*
[2]*University of Chemical Technology and Metallurgy, Department of Organic Synthesis, Sofia, Bulgaria,*
e-mail: neda.anastassova@gmail.com (N. Anastassova)

S2P35

Previously we have synthesized N,N'-disubstituted benzimidazole-2-thione derivatives and their toxicological and antioxidant potential was tested on isolated rat hepatocytes [1, 2]. The study showed that the 5-nitrobenzimidazole-2-thione derivatives are associated with higher hepatotoxicity compared to the other derivatives with methyl, benzoyl group, or no substituent at 5-position.

It is known that cytotoxicity of nitroaromatic compounds could be due to the emerging reactive intermediates in the process of bioreduction, such as nitroanion radicals, which are capable of binding covalently to nucleophilic centres of proteins and nucleic acids.

The feasibility of a nitro radical anion formation from the corresponding ester through electrochemical generation and IR measurements in DMSO solution was measured [3]. As a continuation of our previous work we are reporting the electrochemical reduction of 5-nitrobenzimidazole-2-thione hydrazones. The IR analysis provided detailed and useful spectral information which could be interpreted in terms of structural characteristics. Theoretically calculated molecular characteristics such as spin density distribution, energy differences between the lowest unoccupied and the highest occupied molecular orbital, and adiabatic electron affinities were analyzed in order to assess the propensity of the studied compounds to generate radical anions in biological systems.

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SYNTHESIS OF NEW N,N'-DISUBSTITUTED BENZIMIDAZOLE-2-THIONES CONTAINING VARIOUS ARYLHYDRAZONE MOIETIES AS MODULATORS OF OXIDATIVE STRESS

N. Anastassova,[a] D. Yancheva,[a] N. Hristova-Avakumova,[b] V. Hadjimitova[b]

[a] *Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria*
[b] *Department of Medical Physics and Biophysics, Faculty of Medicine, Medical University-Sofia, Bulgaria*

S2P36

For the evaluation of the anti-radical properties of the studied hydrazine derivatives of the benzimidazole have been used chemiluminescent model systems. With its low limits of detection and possibility to study the kinetics of the interaction during free radical processes luminol dependent chemiluminescence is a reliable method for the characterization of anti-oxidant properties of newly designed compounds. The potency of the hydrazones to influence the concentration of ROS responsible for the initial step of free radical generation cascade reactions and inflammatory processes will be determined by their capability to decrease the chemiluminescent lightening in systems containing the hypochlorite and the superoxide anion radical.

In the superoxide model systems the three compounds experienced different effect on the chemiluminescent lightening – decreased in the presence of vanillin residue containing compound and the one with syringaldehyde and increased when to samples has been added the veratral substituted compound. The best anti-radical activity against $O_2^{-\bullet}$ demonstrated the one with syringaldehyde. At the lowest tested concentration of 10 μmol/L the CL-SI index in the samples was around 25%.

All the tested hydrazones demonstrated capability to decrease the chemiluminescent scavenging index in the hypochlorite containing system in μmol/L concentration range. The calculated from the concentration dependence of the CL-SI index C-50 values denoted nessetity of similar concentration from HN_Ver and HN_Van to decrease the CL-SI value to 50% suggesting similar extent of antiradical properties of vertral and vanillin residues containing benzimidazoles. C-50 for the syringaldehyde containing benzimidazole was 0.173 μmol/L.

SYNTHESIS, ANTINEMATODAL ACTIVITY AND HEPATOTOXICITY OF SOME PIPERAZINE-CONTAINING BENZIMIDAZOLE DERIVATIVES

K. Anichina[1], A. Mavrova[1], D. Vutchev[2], M. Kondeva-Burdina[3], D. Yancheva[4], S. Stoyanov[4]

[1]*University of Chemical Technology and Metallurgy, 1756 Sofia, Bulgaria, e-mail: kameliya_anichina@uctm.edu; e-mail: anmav@abv.bg*
[2]*Departmant of Infectious diseases, Parasitology and Tropical medicine, Medical University, 4002 Plovdiv, Bulgaria, e-mail: d_vutchev@abv.bg; e-mail: galia_val@mail.bg*
[3]*Laboratory of Drug metabolism and Toxicity, Department of Pharmacology, Pharmacotherapy and Toxicology, Faculty of Pharmacy, Medical University of Sofia, 1000 Sofia, Bulgaria; e-mail: magdalenakondeva@gmail.com*
[4]*Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria; e-mail: deni@orgchm.bas.bg; e-mail: s_stoyanov@orgchm.bas.bg*

S2P37

Benzimidazole compounds are from special interest in studies on new antinematodal agents development because for the therapeutic management of parasitic infections the main class of anthelmintic agents available in clinical use are benzimidazole drugs such as albendazole, mebendzole, fenbendazole, ect. [1]. Here we report an extension of our previous works where we presented the synthesis and antitrichinellosis potential of some piperazine containing benzimidazole derivatives [2, 3]. Having in view these previous results novel benzimidazole – piperazine hybrid molecules were synthesized by using two methods and were screened *in vitro* against *Trichinella spiralis*. The data from the *in vitro* analysis showed that some of the compounds exhibit a higher activity than the reference drug albendazole in the 24 – hour incubation of samples at concentrations of 50 μg/ml. The results of the hepatotoxicity test showed that all exam compounds revealed cytotoxicity compared to the control (non-treated hepatocytes). Only two derivatives had lower cytotoxic effects on the parameters, characterizing functional-metabolic status of the hepatocytes.

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