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COORDINATION BEHAVIOR OF TRANSITION METAL CATIONS WITH SUBSTITUTED SALICYLIC ACIDS AND COMPUTATIONAL STUDIES OF BIOLOGICAL POTENTIAL

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Abstract

The complexation behavior of several salicylic acid derivatives with Fe^{3+}, Co^{2+}, Cu^{2+}, and Zn^{2+} ions was examined using spectrophotometric titration. Under optimized conditions, the resulting metal complexes were isolated and their spectral characteristics were analyzed. Spectroscopic evidence indicates that these complexes form through bidentate coordination, involving the ionized hydroxyl group and the carboxylic oxygen atom. These observations align with FTIR data and previously reported X-ray crystallographic findings for related metal complexes of α-hydroxy carboxylic acids.In silico analyses were also conducted to assess the potential biological activities of the synthesized complexes compared to their free ligands. The computational results suggest that the most likely biological effects involve inhibition of the multiprotein complex within the respiratory electron transport chain and potential antitumor properties, both of which show slight modifications upon complexation. Furthermore, predictive modeling indicates that 2,3-dihydroxybenzoic acid, 3-methoxysalicylic acid, and their divalent metal complexes are likely to be absorbed through the gastrointestinal tract, whereas 3,5-dinitrosalicylic acid (3,5-DNSA) and Fe^{3+} complexes exhibit poor bioavailability.

INTRODUCTION

Hydroxy derivatives of aromatic carboxylic acids exhibit a wide range of pharmaceutical properties and usually are active as anti-inflammatory and antibacterial drugs [1-5]. Complexes of transition metals such as cobalt, manganese, nickel, copper, and zinc play an essential role in the life processes of living organisms, being components of enzymes, proteins, and vitamins [6,7]. Due to their low molecular weight, they are orally active drugs whose bioavailability is significantly enhanced in the solution phase, making it attractive to study their behavior in solutions.

The complexation process affects the change in the distribution of electronic density in the organic species that leads to the change in the physicochemical and biological properties of the chemical compound [8–11]. Studies have shown that transition metals influence the stability of the electron system of complexes with aromatic acids [12-15]. This impact depends not only on the properties of metal but also on the way the ligand–metal coordination is done.

Previously, we published synthesis and transformations of complexes of transition metals with several aliphatic and aromatic polyhydroxy acids [16-20]; however, the regularities of complexation processes in solutions were not investigated. Simultaneously, the optimization of metal complexes extraction processes includes a detailed study of the interaction between organic molecules and metal cations in solutions under synthesis conditions. However, despite the considerable work on the isolation and analysis of the structure, properties, and application of aromatic and heteroaromatic hydroxycarboxylic acids coordination compounds, the information on the composition and stability of metal complexes with these ligands in solution is quite limited.

The present study is devoted to the investigation of complexation processes of Fe^{3+}, Co^{2+}, Cu^{2+} and Zn^{2+} cations with the derivatives of salicylic acid, i.e. 3-hydroxy salicylic acid (namely, 2,3-dihydroxy benzoic acid, **2,3-DHBA**), 3-methoxy salicylic acid (**3-OMeSA**) and 3,5-dinitro salicylic acid (**3,5-DNSA**) in aqueous-ethanol solutions via electron spectroscopy and potentiometry methods and utilization of the obtained data to optimize the methodology for the metal complex precipitation and studies of their structure and potential biological activity.

MATERIALS AND METHODS

Chemicals

The substituted salicylic acids (Fig. 1) and inorganic salts: $CuCl_2·2H_2O$, $CoCl_2·6H_2O$, $Zn(NO_3)_2·6H_2O$, $FeCl_3·6H_2O$ were purchased from Merck and Sigma-Aldrich. All reagents of 99% purity are used without further purification.

Electronic absorption spectra of 50% water-ethanol solutions containing organic ligands at various pH values and their titration spectra with aqueous solutions of metal salts were recorded on a Cary-50 spectrophotometer at 22 ± 1°C without background electrolyte to establish accurate ionic strength values in the wavelength range 200-450 nm in 1 cm wide cuvettes. The concentration of the solutions was selected individually for each titration and were values on the order of 10^{-4} mol/L. The amounts of inorganic salts added to 20 mL of the solutions of the ligands did not exceed 0.2 mL, so the change in intensities of the absorption bands in the UV spectra at spectrophotometric titration cannot be explained by dilution.

FTIR spectra of the samples were recorded using an AVATAR 370 spectrometer (Thermo Nicolet, USA) at a temperature of 22°C in the range of 4000–400 cm^{-1} with a resolution of 4 cm^{-1} in KBr pellets.

The canonical SMILES formats of ligands and their complexes were submitted to the SwissADME server (https://www.swissadme.ch/; [21–23], AdmetSar (https://lmmd.ecust.edu.cn/admetsar2; [24,25], and ADMETlab 2. [26] to compute all predictable physicochemical and medicinal chemistry attributes and target prediction. The Toxtree v2.5.1 software platforms (https://toxtree.sourceforge.net/) have also been employed to predict the class of toxicity.

The ligands and their metal complexes were screened for potential drug targets using computer-aided Prediction of Biological Activity Spectra (PASS) web resources [27]. PharmMapper [28] and SwissTargetPrediction [29] were also employed to search probable targets of ligands of interest.

Synthesis of complex compounds of Fe^{3+}, Co^{2+}, Cu^{2+}, and Zn^{2+} with 2,3-DHBA, 3-OMeSA, and 3,5-DNSA were isolated according to the following procedure. 10 mL of ethanol solutions containing 1 mmol of 2,3-DHBA, 3-OMeSA, or 3,5-DNSA were slowly added to 5 mL of aqueous solutions containing 0.5 mmol of corresponding metal chloride. The formed solutions were stirred continuously for 1 h and then kept in the air. After partial evaporation, powdered metal complexes were precipitated from the solution, filtered off, washed with a small amount of cooled ethanol, and dried in an oven at 100°C until the constant mass. Yields 60-70%.

Elemental analysis found/calculated % and some characteristics of the isolated complexes.

$Co(2,3\text{-}DHBA)_2$ ($C_{14}H_{10}CoO_8$), M 365.16: Co 16.44/16.14; C 46.58/46.05; H 3.21/2.76; yield 72%; FTIR: 3500, 3400 (νOH); 3145 (νCH); 1643 (νCO); UV-VIS: 317 nm, log Ɛ 2.654.

$Cu(2,3\text{-}DHBA)_2$ ($C_{14}H_{10}CuO_8$), M 369.77: Cu 17.43/17.19; C 45.64/45.47; H 3.12/2.73; yield 68%; FTIR: 3515, 3415 (νOH); 3158 (νCH); 1645 (νCO); UV-VIS: 319 nm, log Ɛ 3.140.

$Zn(2,3\text{-}DHBA)_2$ ($C_{14}H_{10}O_8Zn$), M 371.61: Zn 17.87/17.59; C 44.64/45.25; H 2.90/2.71; yield 70%; FTIR: 3515, 3410 (νOH); 3155 (νCH); 1650 (νCO); UV-VIS: 318 nm, log Ɛ 3.617.

$Co(3\text{-}OMeSA)_2$ ($C_{16}H_{14}CoO_8$), M 393.22: Co 15.23/14.99; C 48.34/48.87; H 3.44/3.59; yield 69%; FTIR: 3430 (νOH); 3130, 2915 (νCH); 1610 (νCO); UV-VIS: 317 nm, log Ɛ 2.654.

$Cu(3\text{-}OMeSA)_2$ ($C_{16}H_{14}CuO_8$), M 397.83: Cu 15.98/15.97; C 48.55/48.31; H 3.87/3.55; yield 72%; FTIR: 3410 (νOH); 3145, 2990 (νCH); 1595 (νCO); UV-VIS: 317 nm, log Ɛ 2.654.

$Zn(3\text{-}OMeSA)_2$ ($C_{16}H_{14}O_8Zn$), M 399.66: Zn 16.76/16.36; C 48.64/48.08; H 3.63/3.53; yield 75%; FTIR: 3444 (νOH); 3115, 2970 (νCH); 1612 (νCO); UV-VIS: 317 nm, log Ɛ 2.654.

$Fe(3,5\text{-}DNSA)_3$ ($C_{21}H_9FeN_6O_{21}$), M 737.18:

Fe 7.98/7.58; C 34.58/34.22; N 12.01/11.40; H 2.33/1.23; yield 55%; FTIR: 3200 (OH); 3100 (CH); 1608 (CO); 1524, 1334 (NO_2); UV-VIS: 316 nm, log Ɛ 3.012.

$Co(3,5\text{-}DNSA)_2$ ($C_{14}H_6CoN_4O_{14}$), M 513.15: Co 11.84/11.48; C 33.01/32.77; N 11.11/10.92; H 2.52/1.18; yield 70%; FTIR: 3330 (OH); 3127 (CH); 1625 (CO); 1525, 1330 (NO_2); UV-VIS: 342 nm, log Ɛ 3.612.

$Cu(3,5\text{-}DNSA)_2$ ($C_{14}H_6CuN_4O_{14}$), M 517.77: Cu 12.23/12.27; C 32.54/32.48; N 10.55/10.82; H 2.48/1.17; yield 68%; FTIR: 3227 (OH); 3072 (CH); 1615 (CO); 1522, 1332 (NO_2); UV-VIS: 342 nm, log Ɛ 3.412.

$Zn(3,5\text{-}DNSA)_2$ ($C_{14}H_6N_4O_{14}Zn$), M 519.60: Zn 12.78/12.58; C 32.64/32.36; N 10.46/10.78; H 2.30/1.16; yield 70%; FTIR: 3230 (OH); 3100 (CH); 1625 (CO); 1525, 1335 (NO_2); UV-VIS: 341 nm, log Ɛ 4.423.

RESULTS AND DISCUSSIONS

The organic molecules studied here are aromatic systems containing electron-donating substituents that redistribute electron density and charges on the coordination centers. In addition, they have acidic properties and two mobile protons in their composition. This influences the processes of metal complexation with the above ligands. The electronic absorption spectra obtained from ethanol solutions of hydroxy aromatic acids are characterized by long-wave absorption bands in the region of 320 (logε 3.529) for 2,3-DHBA, 314 (logε 3.643) for 3-OMeSA and 340 (logε 4.141) for 3,5- DNSA, respectively.

At stepwise addition of aqueous solutions of 3d-metal salts to ethanol solutions of 2,3-DHBA, 3-OMeSA, and 3,5-DNSA, a slight hypsochromic shift of the bands with a change in their intensity is observed (Fig. 2). The isobestic points indicate equilibrium processes in solutions dealing with the complex formation. The saturation curves indicate the formation of the ML_2 complexes for divalent metals (Co, Cu, and Zn) and ML_3 complexes in the case of Fe^{3+}. It should be noted that the amounts of inorganic salts added to 20 mL did not exceed 0.2 mL. Thus, we can state that the changes in the spectra of the organic species deal only with the complexation processes. No precipitation was observed during the experiment, and no side reactions were observed.

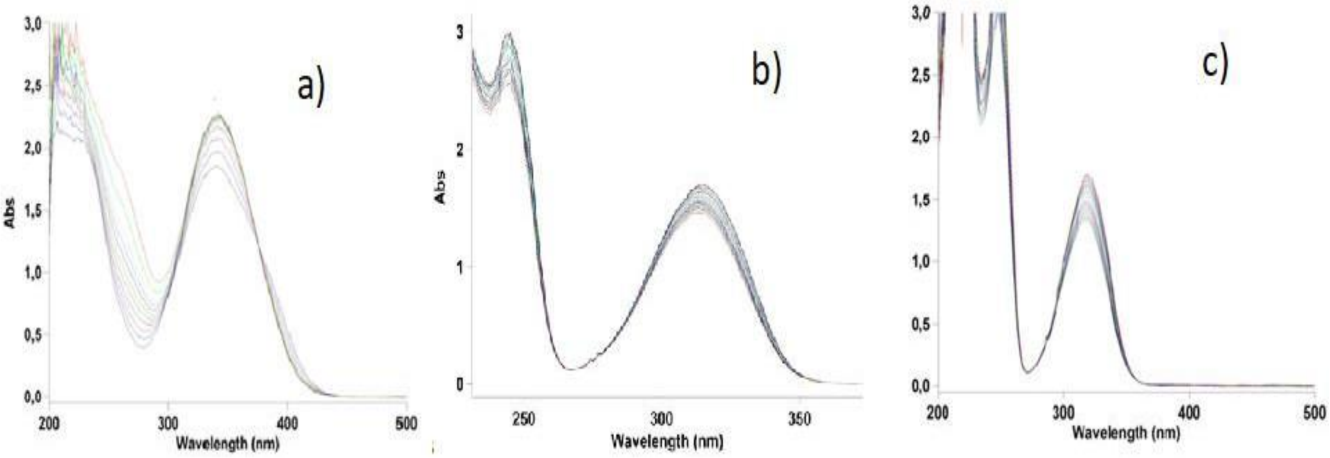

Figure 1. Changes in the electronic absorption spectra of 2,3-DHBA (a), 3-OMeSA (b), and 3,5-DNSA (c) at gradual addition of $CuCl_2$ solution.

The IR spectra of non-coordinated organic species are characterized by absorption bands at 1685-1690 cm^{-1} assigned to C=O stretching of carboxylic groups. At coordination, their position shifts to lower frequencies, indicating their involvement in coordination (Fig. 3).

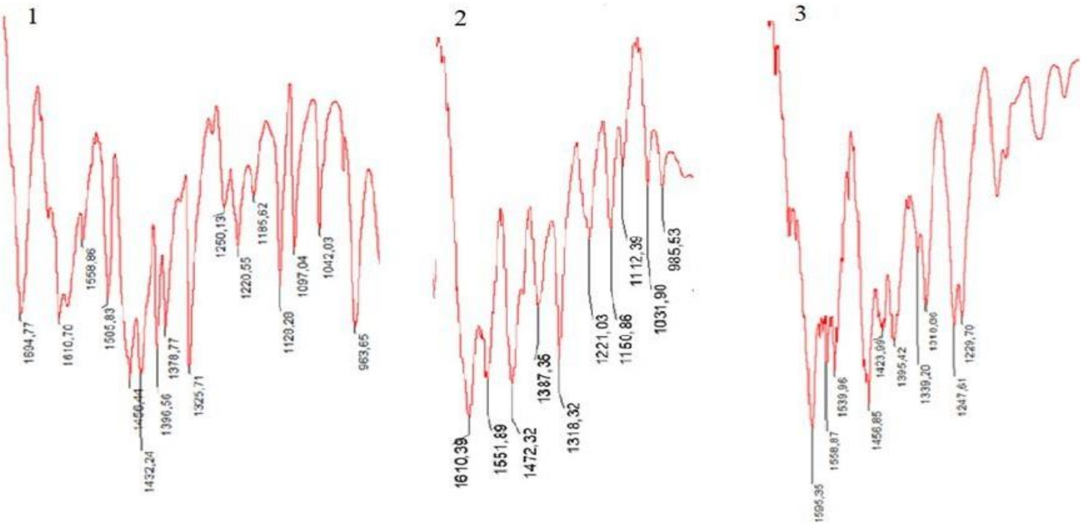

Figure 2. FT IR spectra (KBr pellets) of 3-OMeSA (1), Co(3-OMeSA)$_2$ (2), and Cu(3-OMeSA)$_2$ (3).

Most probably, a chelating coordination involving the C=O group and a neighboring deprotonated OH group occurs. This is in accordance with the X-ray structure determination of metal complexes with similar ligands containing neighboring OH and COOH groups [30-33]. Authors indicate that ionization occurs for hydroxy groups, and the ligands exist in the form of mono anions. The proton of carboxylic groups is involved in intra- and intermolecular H-bonds. The same conclusion was made in our previous study of complex compounds of metals with **2,4,6-trihydroxy benzoic acid [34] by DFT modeling. The optimizing of structures of complexes indicates that the preferable coordination is one of monoanionic ligands with bidentate chelate coordination through a deprotonated OH group and a C=O group of a carboxylic fragment of the organic species. *In silico studies* of the probable biological activity indicate that the most probable activity is the inhibition of the multiprotein complex of the respiratory electron transport chain and antitumor activity which slightly changes at complexation (Fig. 3).**

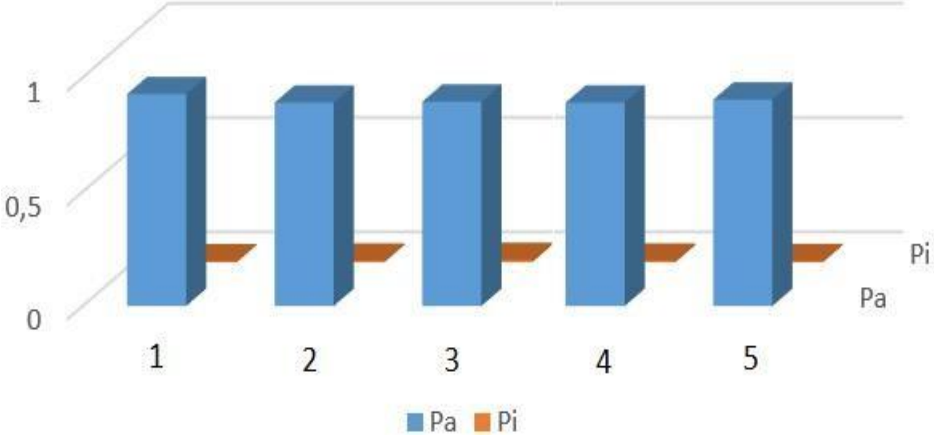

Figure 3. Probability of inhibition of multiprotein complex of the respiratory electron transport chain by 3,5-DNSA (1), Co(3,5-DNSA)2 (2), Cu(3,5-DNSA)2 (3), Zn(3,5-DNSA)2 (4), and Fe(3,5-DNSA)3 (5).

The physicochemical property, medicinal chemistry, and the absorption, distribution, metabolism, excretion, and toxicity (ADMET) computations are considered as an initial phase in the pipeline of drug design/discovery. Figure (4) provides information on critical ADME-related properties of the ligands and their complexes with respect to Lipinski's rule of five (molecular weight ≤ 500; MLOGP ≤ 4.15; number of (N + O) ≤ 10; number of (NH + OH) ≤ 5).

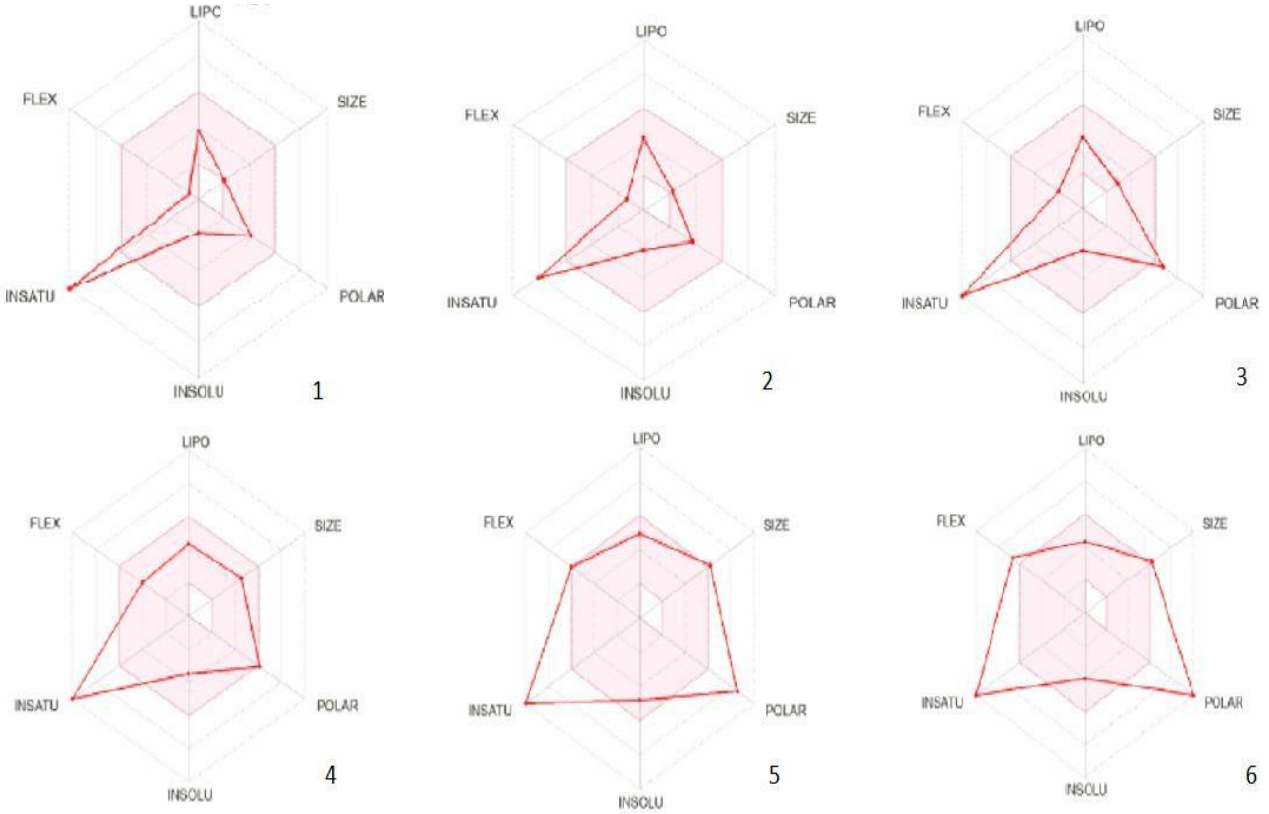

Figure 4. **Bio-availability radars construction enable a first glance at the drug-likeness of synthetic ligands. The pink area represents the optimal range for physicochemical properties (lipophilicity: XLOGP3 between −0.7 and +5.0, size: MW (molecular weight) between 150 and 500 g/mol, polarity: TPSA (topological polar surface area) between 20 and 130 Å^2, solubility: log S not higher than 6, saturation: fraction of carbons in the Csp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds: 1– 2,3-DHBA; 2 – 3-OMeSA; 3 – 3,5-DNSA; 4 – Zn(2,3-DHBA)2; 5 – Fe(2,3-DHBA)3; 6 – Zn(3,5-DNSA)2.**

Among the suitable physicochemical properties of the organic ligands for oral bioavailability that are shown in radars, only saturation (fraction Csp3) was lesser than the minimum value of 0.22. In the case of complexes of Fe^{3+} and all the complexes, at least two or three parameters do not follow Lipinski's rule. The most probable way of absorption of 2,3- DHBA, 3-OMeSA, and their complexes with divalent metals is predicted to be through the gastrointestinal tract (Fig. 5) as well as 3,5-DNSA and Fe^{3+} complexes cannot be absorbed by organisms.

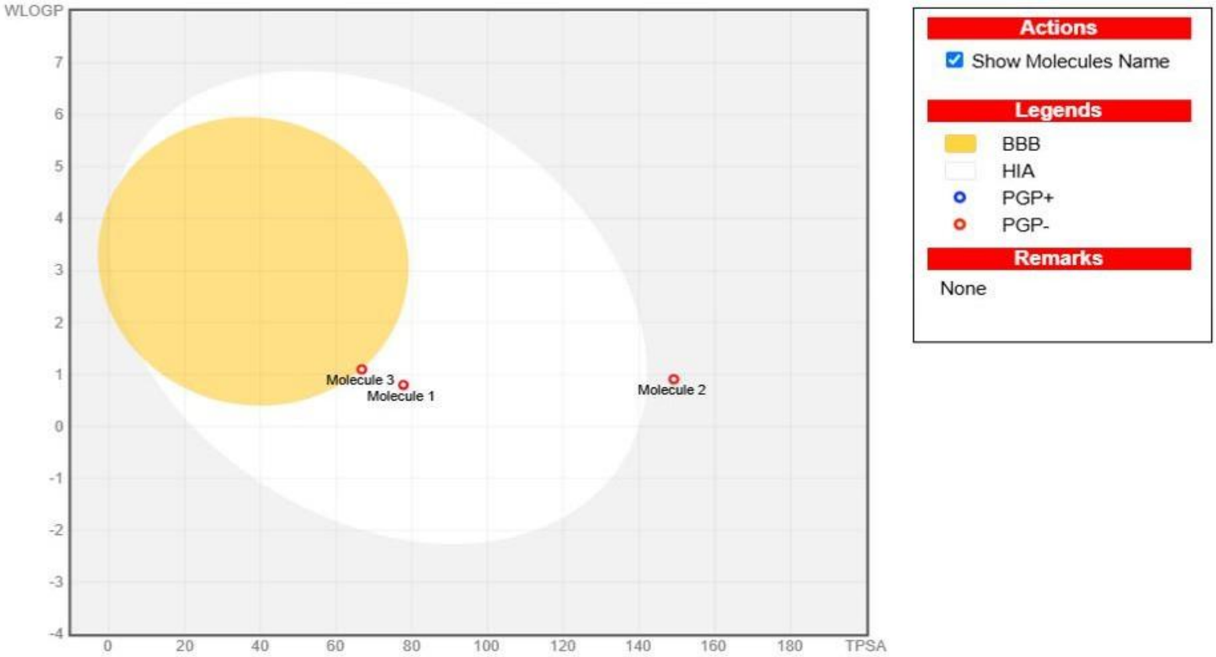

Figure 5. Probable ways of absorption of 2,3-DHBA (1), 3,5-DNSA (2) and 3-OMeSA (3) by the organism. The white region is the physicochemical space of molecules with highest probability of being absorbed by the gastrointestinal tract, and the yellow region (yolk) is the physicochemical space of molecules with highest probability to permeate to the brain.

It should be noted that the complexes are water soluble and isolated from the solutions only at partial evaporation. The spectrophotometric titration and calculation of their stability constants (*log*7.30-19.82) indicate that they are quite stable in aqueous solutions. Unfortunately, solubilities in physiological liquids were not studied. Still, we could suppose their solubility and stability will not change a lot, and the complexes of divalent metals with 2,3-DHBA and 3-OMeSA could be proposed as potential biologically active substances.

CONCLUSION

The complexation processes of 2,3-DHBA, 3-OMeSA, and 3,5-DNSA with Fe^{3+}, Co^{2+}, Cu^{2+}, and Zn^{2+} were studied by spectrophotometric titration. The complex compounds were isolated in the crystalline state, and their composition, spectral characteristics, and ways of coordination were proposed. *In silico* studies of the biological activity showed that 2,3-DHBA, 3-OMeSA, and their complexes with divalent metals agree with Lipinski's rule. The most probable way of absorption by organisms is through the gastrointestinal tract.

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