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BIOLOGICAL ACTIVITY OF THE NICKEL(II) COMPLEX OF 4-AMINOBENZOYLSULFANAMIDE

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Abstract. Sulfanilamides play an important role in medicinal chemistry due to their broad pharmacological properties. Complexes based on transition metal complexes, in particular nickel(II) with sulfanilamide ligands, allow to improve pharmacokinetic properties.

Keywords: nickel(II) complex, sulfonamide, synthesis, SCXRD, coordination geometry, antimicrobial activity, molecular docking, hydrogen bonding.

Аннотация. Сульфаниламиды играют важную роль в медицинской химии благодаря своим широким фармакологическим свойствам. Комплексы на основе комплексов переходных металлов, в частности никеля(II) с сульфаниламидными лигандами, позволяют улучшить фармакокинетические свойства.

Ключевые слова: комплекс никеля(II), сульфонамид, синтез, SCXRD, координационная геометрия, антимикробная активность, молекулярный докинг, водородные связи.

Annotatsiya. Sulfanilamidlar keng farmakologik xususiyatlari tufayli dorivor kimyoda muhim rol o'ynaydi. O'tish metall komplekslariga asoslangan komplekslar, xususan, sulfanilamid ligandlari bilan nikel(II), farmakokinetik xususiyatlarni yaxshilash imkonini beradi.

Kalit so‘zlar: nikel(II) kompleksi, sulfanamid, sintez, SCXRD, koordinatsiya geometriyasi, mikroblarga qarshi faollik, molekulyar doklash, vodorod bog'lanishi.

Introduction. Sulfonamides were identified in the early 20th century [1] and are indispensable in modern medical chemistry due to their wide spectrum of pharmacological activities, including antimicrobial, antitumor, anti-inflammatory, antidiabetic, and enzyme-inhibiting effects [2,3]. Over time, these compounds became universal bases for multifunctional therapeutic design [4,5]. It has been shown that their incorporation into hybrid molecules such as coumarin-based sulfonamides increases bioactivity, drug affinity, and target selectivity [6,7].

Transition metal complexes of sulfonamides, especially those derived from biologically important metal ions such as zinc, copper, nickel, cobalt, and platinum, are gaining increasing attention due to their pharmacokinetic properties and synergistic biological activity [8,9]. Metal coordination often increases antimicrobial, antitumor, and enzyme-inhibiting properties through the positive interaction of the metal center with important biomolecular targets [10,11]. In this regard, metal complexes continue to be of great interest as potential antimicrobial agents, since the addition of metal ions can modulate oxidation-reduction properties, coordination geometry, and the kinetics of ligand exchange, which increases biological effectiveness in relation to free ligands [12,13]. It has been shown that compounds based on 3d metals (e.g., Cu (II), Zn (II), Mn (II), Ni (II), etc.) disrupt microbial membranes, form active oxygen species, inhibit important enzymes, or bind to intracellular biomolecules, making them promising candidates against increased antibiotic resistance. [14,15]. Therefore, assessing the antimicrobial effectiveness of newly synthesized complexes across a wide bacterial spectrum provides an important understanding of potential applications in the field of medical and bio-inorganic chemistry [16,17].

Experimental methods: Synthesis. For the synthesis of bis[4-aminobenzene sulfonamide] bis (dimethylformamide) diaquanickel (II) nitrate, a 0.1 M solution of 4-aminobenzene sulfonamide was prepared by dissolving the corresponding amount in 50 ml of ethanol. This solution was slowly added to a pre-prepared 0.1 M nickel (II) nitrate

solution (25 ml) with constant stirring. The mixture was mixed using a magnetic stirrer to ensure uniformity. To fill the Ni (II) coordination region, 154 µl of dimethylformamide (DMF) was added to the reaction mixture and thoroughly mixed. The resulting solution was placed in a thermostat at a constant temperature of 25°C under slow evaporation conditions for crystallization and stored for 12 days. At the end of this period, green crystals corresponding to the analysis were formed. The reaction yield was 78%.

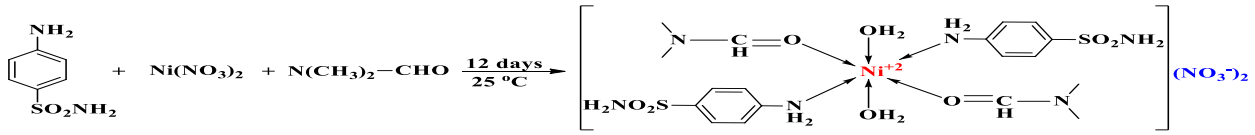

Figure 1. *Synthesis reaction of the bis[4-aminobenzene sulfanilamide] bis (dimethylformamide) diaquanickel (II) nitrate complex.*

X-ray structural analysis. The bis[4-aminobenzene sulfanilamide] bis (dimethylformamide) diaqua-nickel (II) nitrate compound crystallizes in an orthorhombic crystal system and has a centrally symmetric Pbca spatial group, which indicates a highly ordered molecular arrangement.

The asymmetric unit consists of one Ni (II) cation, two coordinated water molecules, two dimethylformamide (DMF) ligands, and two 4-aminobenzene sulfanilamide ligands, with the nitrate anion present as a counter ion outside the coordination sphere. The Ni^{2+} ion is in a hexacoordinated state with an octahedral geometry, and the coordination medium is formed with the participation of a nitrogen atom from two sulfanilamide groups (amine N), a carbonyl oxygen atom from two DMF molecules, and an oxygen atom from two water molecules (Fig.1). The crystal packaging diagram (Fig.1) reveals a three-dimensional supramolecular structure inside the orthorhombic crystal lattice. The structure is stabilized by a wide network of hydrogen bonds of the N-H···O, O-H···O, and C-H···O types, which are shown by pink lines on the diagram. Coordinated water molecules and sulfanilamide groups act as donors and acceptors of the main hydrogen bond, uniting adjacent asymmetric units into a strong three-dimensional framework.

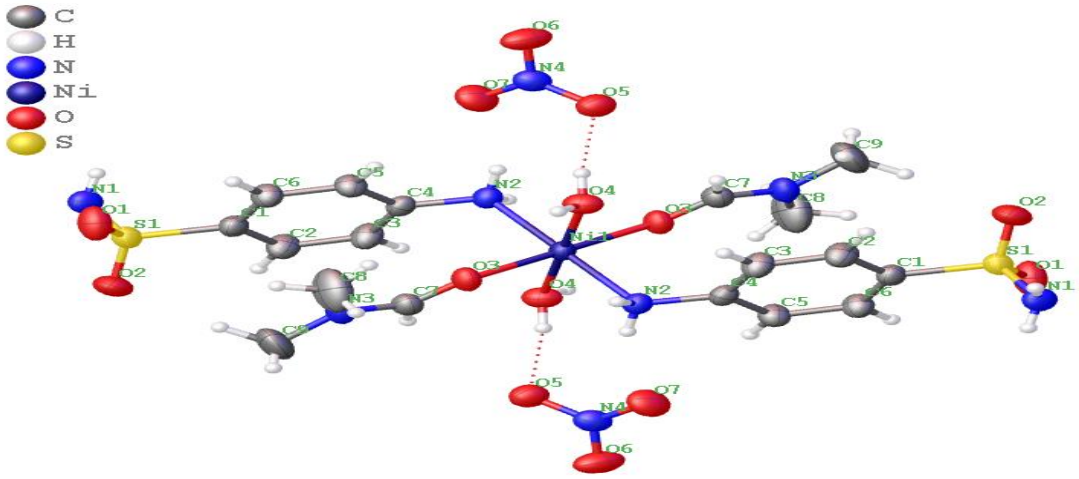

Figure 1. *(a) Atom numbering scheme and ORTEP image showing shift ellipsoids drawn with a probability of 35%. (b) Crystal packaging diagram of bis[4-aminobenzene sulfanilamide] bis (dimethylformamide) diaqua-nickel (II) nitrate.*

In particular, primary amine groups participate in strong hydrogen bonds, for example, the donor-acceptor distances of the N (1) -H (1A)···O (1) and N (1) -H (1B)···O (2) bonds are 3.012 (2) Å and 2.914 (2) Å, respectively, and the angles are linear, about 161° and 169°. Additional strong bonds are N (2) -H (2B)···O (5) and N (2) -H (2A)···O (7), with D···A distances of 3.010 (2) Å and 3.106 (2) Å, which make a significant contribution to the strength of the structure. Coordinated water molecules also form effective hydrogen bonds through O (4) -H (4A)···O (5) and O (4) -H (4B)···O (6), these bonds have short distances and linear angles of about 169° and 175°. Weaker secondary interactions, including C-H···O and C-H···N bonds (for example, C (8) -H (8A)···O (6), C (5) -H (5)···O (7), C (8) -H (8B)···N (1) and C (6) -H (6)···N (1)), contribute to the fusion of the crystal lattice (Fig.1).

The entire complex of these interactions forms a clearly defined three-dimensional hydrogen-bound supramolecular network, as shown in the packaging diagram. The Ni-O bond length varies within the range of 2.0468 (12) -2.0474 (10) Å, and the Ni-N bond length is slightly longer - 2.1567 (13) Å. The average bond length in the coordination sphere is 2.0837 Å. The coordination polyhedron is moderately distorted, the bond length has a distortion index of 0.02337, and the angular variance is 11.4858 deg2. The effective number of coordinates is 5.8704, and the volume of the polyhedron is 11.9959 Å3, and this set of parameters is characteristic of compact pseudo-octahedral geometry.

Antimicrobial activity evaluation

The antimicrobial activity of sulfanilamide, nickel nitrate, and the synthesized nickel(II) coordination complex was evaluated against representative Gram-positive bacteria (Bacillus subtilis and Staphylococcus aureus) and Gram-negative bacteria (E. coli and Pseudomonas aeruginosa) (Fig. 2). These organisms were selected because they are

clinically relevant opportunistic pathogens and are widely used as standard indicator strains for assessing the antimicrobial potential of metal complexes. Evaluating both Gram-positive and Gram-negative bacteria is important due to their distinct cell-wall structures, which significantly influence drug permeability and susceptibility, an aspect well documented in the antibacterial behaviour of coordination compounds. All samples were prepared in DMSO (20 mg/mL), and antimicrobial activity was determined using the agar well diffusion method. Bacterial cultures (≥107 CFU/mL) were uniformly spread on meat-peptone agar plates, and 50 µL of each test solution was applied. Plates were incubated at 30°C for 48 h. Inhibition zones (mm) were measured in triplicate, and mean values are summarized in Table 1. DMSO and $Ni(NO_3)_2$ exhibited no activity against any strain, confirming their biological inactivity under these conditions.

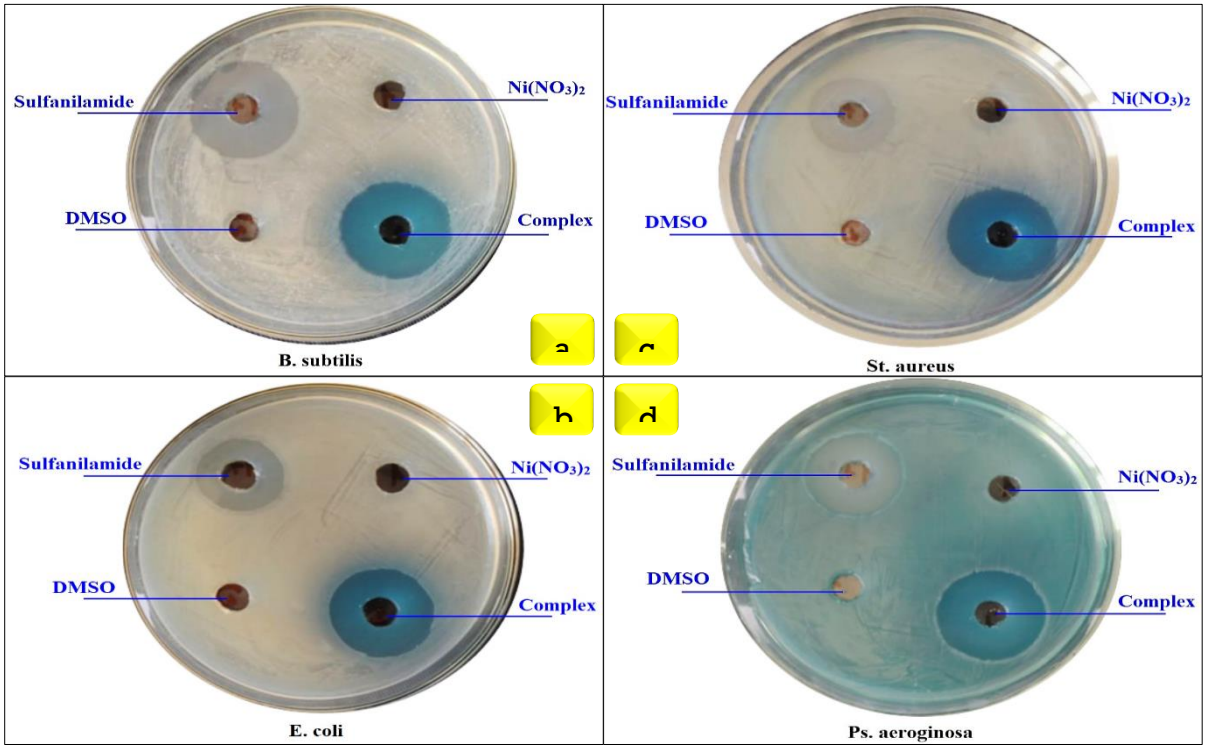

Fig.2 *Zone of inhibition exhibited by DMSO (solvent control), $Ni(NO_3)_2$, sulfanilamide (standard drug), and the synthesized Ni(II) complex against (a, b) Gram-positive bacteria (Bacillus subtilis, Staphylococcus aureus) and (c, d) Gram-negative bacteria*

In contrast, sulfanilamide exhibited moderate antimicrobial activity against all tested organisms, with inhibition zones ranging from 14 to 18 mm. The synthesized nickel(II) complex showed significantly enhanced antibacterial efficacy, producing the largest inhibition zones against B. subtilis and P. aeruginosa (22 mm each), followed by S. aureus and E. coli (20 mm each). These findings suggest that coordination of sulfanilamide to Ni(II) improves its antimicrobial performance, likely through increased lipophilicity, metal-assisted ligand activation, and stronger interactions with bacterial cell membranes. To further elucidate the molecular basis of this enhanced activity, molecular docking

simulations were performed to investigate interactions between the complex and bacterial protein targets.

Compounds	***B. subtilis***	***St. aureus***	***E. coli***	***Ps. aeroginosa***
DMSO	0	0	0	0
Ni(NO3)2	0	0	0	0
Sulfanilamide	18 mm ± 0.4	16 mm ± 0.4	14 mm ± 0.1	16 mm ± 0.1
Complex	22 mm ± 0.1	20 mm ± 0.1	20 mm ± 0.1	22 mm ± 0.1

Table 1. Antibacterial activity of the synthesized nickel(II) complex compared to sulfanilamide, $Ni(NO_3)_2$, and DMSO against Gram-positive (*B. subtilis* and *St. aureus*) and Gram-negative (*E. coli* and *Ps. aeruginosa*) bacterial strains (Concentration of conditional pathogens not less than 107 CFU/ml).

Molecular docking

Molecular docking simulations were performed using AutoDock Vina (v1.2.3) to investigate interactions between the nickel(II) complex, bis [4-aminobenzenesulfonamide]bis(dimethylformamide)diaqua-nickel (II), and four bacterial protein targets. It should be noted that the nitrate ion, which is uncoordinated in the crystal structure and acts as a counterion, was not included in the docking studies. Therefore, the docking results reflect interactions of the coordinated Ni(II)-ligand framework only, and not molecular caging involving the nitrate group. The simulations revealed that the complex exhibited favourable binding affinities toward all four bacterial protein targets, with calculated binding energies ranging from − 8.6 to − 10.3 kcal/mol (Fig. 3). Among these, the E. coli protein (PDB ID: 7AB3) showed the strongest binding affinity (− 10.3 kcal/mol), followed by Bacillus subtilis (8I2F, − 9.8 kcal/mol), Pseudomonas aeruginosa (9G59, − 9.4 kcal/mol), and Staphylococcus aureus (5ISP, − 8.6 kcal/mol).

Detailed 2D interaction analysis indicated that the complex was stabilized through a combination of conventional hydrogen bonds, π-π stacking, π-sulfur interactions, and van der Waals contacts. Some unfavourable donor-donor interactions were observed in specific complexes but did not significantly destabilize binding. Docking pose analysis revealed that the high binding affinity for the E. coli complex arises from multiple strong hydrogen bonds with polar residues such as ASP259, GLY194, and ASP65, while hydrophobic residues LEU296 and ILE198 contribute van der Waals stabilization, and π-interactions with ILE61 enhance binding specificity (Fig. 3(a)).

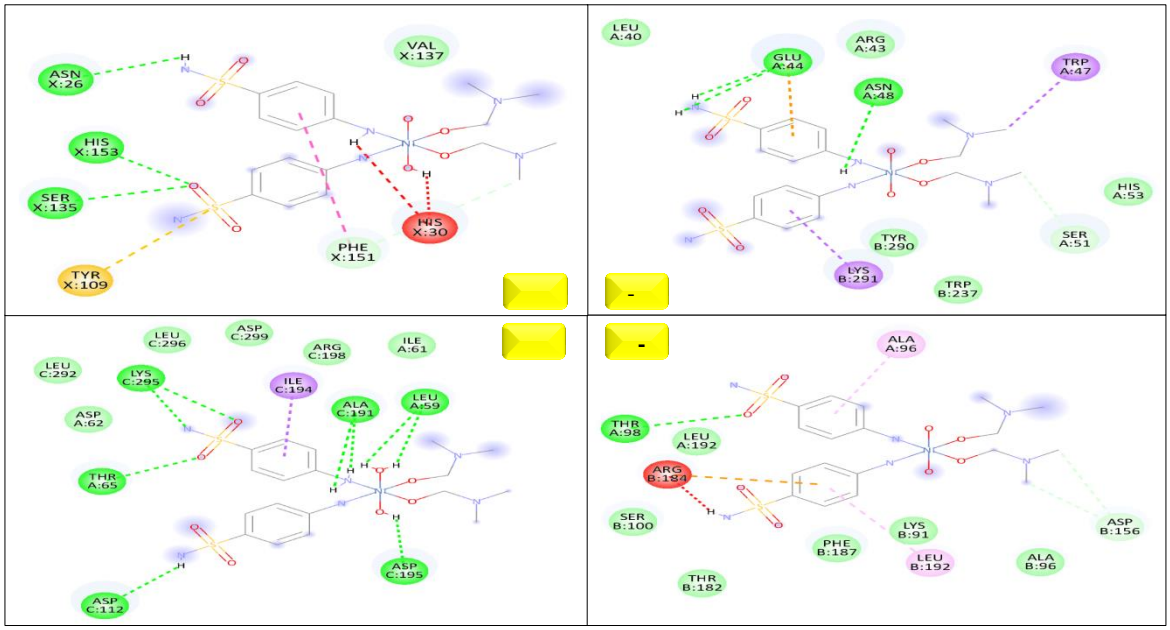

Fig.3 2D interaction diagrams of the test ligand docked with four bacterial protein targets: (**a**) *Staphylococcus aureus* (5ISP), (**b**) *Bacillus subtilis* (8I2F), (**c**) *Escherichia coli* (7AB3), and (**d**) *Pseudomonas aeruginosa* (9G59). Key interactions such as hydrogen bonds (green),

In the B. subtilis (8I2F) complex, the ligand engaged in π–π stacking with TRP237 and TYR290, and formed hydrogen bonds with ASN48 and ARG43. Despite an unfavourable donor–donor interaction with ARG43, the overall binding remained favourable. For P. aeruginosa (9G59), π-π stacking with PHE187, π-anion interaction with ARG100, and hydrogen bonds with ASP156 and SER100 stabilized the ligand, though minor steric hindrance from ARG100 was noted. The S. aureus (5ISP) complex exhibited weaker binding, likely due to limited hydrogen bonding capacity, but aromatic interactions with PHE151 and HIS30, along with hydrogen bonds to SER135 and ASN26, maintained a moderately stable conformation. These results are consistent with prior studies where strong binding affinities are associated with increased polar and aromatic residues in the active site. The analysis confirms that the enhanced antibacterial activity of the nickel(II) complex arises from interactions of the coordinated metal-ligand framework, rather than any effect of nitrate-mediated molecular caging.

Conclusion. In this work, a novel nickel(II) coordination complex based on the 4-aminobenzenesulfonamide ligand was synthesized and fully characterized by crystallographic methods. Single crystal X-ray diffraction results showed that the complex has a clear octahedral geometry stabilized by an extensive hydrogen bond system. Biological studies confirmed that the nickel(II) complex exhibits higher antimicrobial activity than the free ligand and the metal salt, revealing significant inhibitory effects against Gram-positive and Gram-negative bacteria. This increase in activity is explained by

increased lipophilicity, metal-mediated activation, and enhanced interactions with bacterial membranes. Molecular docking calculations supported the experimental results, indicating favorable binding energies, a large number of hydrogen bonds, and high binding affinity, especially for E. coli. In general, the obtained experimental and computational results show that coordination with metal significantly increases the biological potential of sulfonamide derivatives and confirm the importance of nickel(II) sulfonamide complexes as promising antimicrobial agents. This work creates a solid scientific basis for a deeper study of metal-sulfonamide systems, including MIC/MBC analyses, identification of mechanisms of action, and design of new biologically active complexes.

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