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The synthesis, antimicrobial activity and theoretical calculations of 4-(4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazol-2-yl)-N,N-dimethylaniline

Aim. To synthesize 4-(4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazol-2-yl)-N,N-dimethylaniline, as well as make theoretical calculations of its structure and study its antimicrobial properties.

Materials and methods. The synthesis procedures were performed in the presence of ionic liquid catalysts and under microwave conditions. The catalysts included 1-butyl-3-methylimidazolehydrosulfate, N-methylpyrrolidone perchlorate, and 1,4-dimethylpiperazinedihydrosulfate ionic liquids. Benzyl, ammonium acetate, p-aminoazobenzene and 4-(dimethylamino)benzaldehyde were taken as reagents. Ethanol was used as a solvent.

Results. The results of the conditions were compared and it was determined that the 1,4-dimethylpiperazinedihydrosulfate catalyst reacted under microwave conditions in a shorter time (19 min) with a higher yield (78.1 %). The structure of the compound synthesized was analyzed by ^{1}H, ^{13}C NMR and IR spectroscopy. The theoretical calculations of the compound were determined using the density functional theory (DFT/B3LYP) method with a basic set of 6-31G(d,p). The geometry of the structure was optimized, bond lengths, angle degrees were given, and important quantum chemical parameters, such as HOMO, LUMO orbitals, reactivity, stability, electrophilicity, electronegativity, chemical softness, chemical hardness were calculated. It was found that the compound had a high stability (ΔE = 2.359 eV) and a high biological activity (ω = 5.754 eV). The antimicrobial activity of the sample against bacteria of *S. aureus, E. coli, P. aeruginosa, K. pneumoniae, B. anthracoides* and *C. albicans* fungus was studied.

Conclusions. In this work, 4-(4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazol-2-yl)-N,N-dimethylaniline has been synthesized from benzyl, ammonium acetate, p-aminoazobenzene and 4-(dimethylamino)benzaldehyde in the presence of microwave and ionic liquid catalysts. It has been determined that 1,4-dimethylpiperazinedihydrosulfate catalyst reacts under microwave conditions in a shorter time (19 min) with a higher yield (78.1 %). The compound has been tested as an antimicrobial agent against bacteria of *S. aureus, E. coli, P. aeruginosa, K. pneumoniae, B. anthracoides* and *C. albicans* fungus, showing moderate and higher activity.

Keywords: *imidazole; synthesis; microwave; ionic liquid catalysts; antimicrobial activity; theoretical calculations; stability*

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Синтез, антимікробна дія та теоретичні розрахунки 4-(4,5-дифеніл-1-(4-(фенілдіазеніл)феніл)-1H-імідазол-2-іл)-N,N-диметиланіліну

Мета роботи – дослідити синтез і антимікробні властивості 4-(4,5-дифеніл-1-(4-(фенілдіазеніл)феніл)-1H-імідазол-2-іл)-N,N-диметиланіліну, а також виконати теоретичні розрахунки будови цієї сполуки.

Матеріали та методи. Процедури синтезу здійснювали в присутності іонних рідких каталізаторів в умовах мікрохвиль. Каталізатори містили іонні рідини 1-бутил-3-метилімідазолгідросульфат, перхлорат N-метилпіролідону та 1,4-диметилпіперазиндигідросульфат. Як реагенти використовували бензил, ацетат амонію, п-аміноазобензол і 4-(диметиламіно)бензальдегід, як розчинник – етанол.

Результати та їх обговорення. У цій роботі 4-(4,5-дифеніл-1-(4-(фенілдіазеніл)феніл)-1H-імідазол-2-іл)-N,N-диметиланілін синтезовано з бензилу, ацетату амонію, п-аміноазобензолу та 4-(диметиламіно)бензальдегіду в присутності мікрохвильового та іонного рідкого каталізаторів. Визначено, що каталізатор 1,4-диметилпіперазиндигідросульфат проводить реакцію в мікрохвильових умовах за коротший час (19 хвилин) з вищим виходом (78,1 %). Структуру синтезованої сполуки досліджено методами ЯМР ^{1}H, ^{13}C та ІЧ-спектроскопії. Теоретичні розрахунки сполуки виконано за допомогою методу теорії функціоналу густини (DFT/B3LYP) з базисним набором 6-31G(d,p). Оптимізовано геометрію структури, задано довжини зв'язків, градусні кути, розраховано такі важливі квантово-хімічні параметри, як орбіталі HOMO, LUMO, реакційна здатність, стабільність, електрофільність,

електронегативність, хімічна м'якість, хімічна твердість. Виявлено, що сполука має високу стабільність (ΔE = 2,359 еВ) і високу біологічну активність (ω = 5,754 еВ). Вивчено антимікробну активність зразка щодо бактерій *S. aureus*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *B. anthracoides* та грибка *C. albicans*.

Висновки. Каталізатор 1,4-диметилпіперазиндигідросульфат проводить реакцію в умовах мікрохвильового випромінювання за коротший час з вищим виходом. Результати тестування синтезованої сполуки як антимікробного засобу засвідчили помірну та високу її активність проти бактерій *S. aureus, E. coli, P. aeruginosa, K. pneumoniae, B. anthracoides* та грибка *C. albicans.*

Ключові слова: *імідазол; синтез; мікрохвилі; іонні рідкі каталізатори; антимікробна активність; теоретичні розрахунки; стабільність*

Introduction. Imidazoles play a special role in the chemistry of heterocyclic compounds. Many natural compounds, including important compounds, such as purine, histamine, histidine, nucleic acids, have the imidazole ring. Currently, some medicinal substances contain, for example, etonitazene with the analgesic effect, omeprazole used against ulcers, pantoprazole, metronidazole used against bacteria, nitroso-imidazole, azathioprine used in the treatment of rheumatism, dacarbazine for Hodgkin's disease, and other drugs have the imidazole ring [1]. Since imidazoles have a high biological activity, imidazole-based medicinal chemistry is developing day by day. Imidazoles are part of drugs used in the treatment of cancer, diabetes, AIDS, malaria, etc. [2-7].

Imidazoles are used as ionic liquids in green chemistry and organometallic catalysis [8], as ligands in coordination chemistry [9], and as luminescent substances in the field of LED industry and defectoscopy [10-12].

Imidazoles are also widely used in the oil industry. Currently, imidazole compounds are used to solve corrosion problems in the world. As is well known, sulfate-reducing bacteria that infect pipes during oil extraction cause microbiological corrosion in pipes. This leads to destruction of tons of metals, pollution of seas and oceans, destruction of flora and fauna. Here, the application of inhibitory bactericides can contribute to environmental protection, as well as increasing economic efficiency [13-15].

The presence of such a wide range of applications increases the interest in the imidazole synthesis. Due to harsh reaction conditions, low yield and long reaction time, the efficient synthesis of imidazoles has always been of interest, and the search for more convenient synthesis routes is still relevant [16-18].

Nowadays, one of the methods successfully applied in the synthesis of imidazoles is synthesis reactions in the presence of ionic-liquid catalysts. A short reaction time, low temperature, one-stage reaction, high productivity, easy separation of catalysts from reaction products as a solution in water, and the possibility of reuse of catalysts can be mentioned as the causes for the efficiency of the reactions taking place with the participation of ionic liquid catalysts [19-21].

Microwave conditions are noted for their extreme environmental cleanliness. On the other hand, although the reaction time under microwave conditions is shorter than that of catalytic reactions, the yield of reaction products is less than that of catalytic reactions. Recently, "microwave and catalyst" synergism has been successfully applied in order to increase economic and environmental efficiency in the synthesis of chemical substances [21].

Quantum-chemical calculations, which are relevant in modern times, allow predicting a number of properties of chemical substances in advance without carrying out practical experiments. These properties include the spatial structure of matter, stability, electrophile index, electronegativity, electron lattice, etc. In addition, using calculation programs, it is possible to calculate bond lengths, bond angle degrees, bond twist rates, atomic charges, etc., in the optimized structure of the substance [22-24].

The **aim** of our work is to synthesize 4-(4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazol-2-yl)-N,N-dimethylaniline, as well as make theoretical calculations of its structure and study its antimicrobial properties.

Materials and methods. Reagents and solvents were purchased from Aldrich. ^{1}H-, ^{13}C-, NMR spectra of the compound synthesized were recorded on a BRUKER-Fourier (300 MHs) spectrometer at 200 ºC, tetramethylsilane (TMS) was used as an internal standard, and DMSO was used as a solvent. The IR spectrum was taken in the wavelength range of 600-4000 cm^{-1} on a "LUMOS FT-IR Microscope" spectrometer (BRUKER Company of Germany). The elemental analysis was performed on a "TRUSPEC MICRO" device manufactured by the "LECO" company. The melting point was measured on a DSK-Q-20 apparatus.

Results and discussion. The imidazole compound was synthesized under 4 different conditions – under microwave conditions without the presence of a catalyst and in the presence of 3 different ionic liquid catalysts. 3 mmol of benzyl, 3 mmol of 4-(dimethylamino) benzaldehyde, 3 mmol of p-aminoazobenzene, 3 mmol of ammonium acetate, 20 ml of ethanol were taken as reagents. The reaction mixture was irradiated in a 300W microwave oven at the boiling temperature of ethanol (Figure 1). The reaction proceeds according to the scheme shown below.

The synthesis reactions were carried out according to the optimization in the amount of 10 % (mol) of catalysts and at the boiling temperature of ethanol (78 °C). The progress of the reaction was monitored by means of thin layer chromatography (TLC). After the reaction was completed, the mixture was poured into ice water, the solid mass was separated by filtration, and recrystallized in ethanol.

As can be seen from Table 1, the 1,4-DMPDHS catalyst is more effective than other ionic liquid catalysts.

The empirical formula of the substance synthesized is $C_{35}H_{29}N_5$, Mr = 519.09. Concerning the melting point, no melting is observed up to 300 °C (evaporation, volatilization may occur). ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.10 (s., 6H, CH3), 6.84 (d.d., 4H, J = 6.9, 1.5 Hs), 7.39

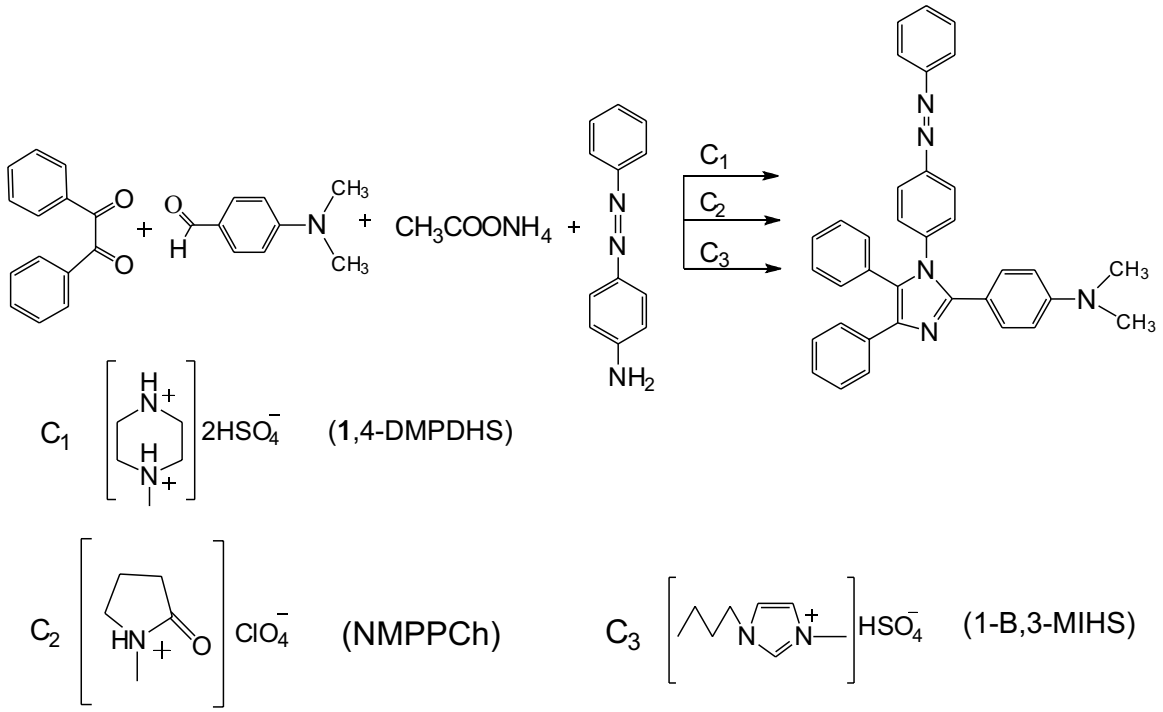

Fig. 1. The synthesis of 2-(4-chlorophenyl)-4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazole

Table 1

The comparison of catalysts and the microwave synthesis in terms of yield and reaction time

Conditions	Reaction time, min	Yield (%)
Microwave	28	56.8
1,4-DMPDHS & Microwave	19	78.1
NMPPCh & Microwave	23	70.7
1-B,3-MIHS & Microwave	22	73.5

(d.d., 4H, J = 6.6, 2.1 Hs), 7.57-7.60 (m., 3H), 7.86 (d.d., 4H, J = 6.9, 2.1 Hs), 7.93 (d.d., 4H, J = 6.6, 1.8 Hs), 7.97 (d.d., 4H, J = 6.9, 2.1 Hs). ^{13}C NMR: 42.16 (CH3), 118.05, 118.69, 120.07, 122.06, 122.68, 124.01, 124.54, 125.34, 126.12, 128.14, 129.29, 129.65, 131.22 1.98, 132.64, 133.61 (C-Ar), 136.02, 151.09, 151.67, 152.84 (C-N). IR (cm^{-1}): ν-1662 (C=N), δ-636, 685, 717, 766, 795, 844, 874 (C-H), ν-1597(C-C), ν-1571(N=N), ν-1313 (C-N).

The antimicrobial activity of the sample synthesized was studied by the disk diffusion method. *Staphylococcus aureus* (gold staphylococci), gram-negative bacteria *Escherichia coli* (intestinal bacilli), *Pseudomonas aeruginosa* (blue-green pus bacillus) with a high natural resistance to antibiotics, *Klebsiella pneumoniae* (capsulated), *Bacillus anthracoides* (spored), *Candida albicans* laboratory strains considering one of the causative agents of opportunistic mycosis were used. These bacteria were cultured on the meat-peptone agar, and candida were cultured on the Sabouraud's medium. The study used one-day test cultures, 500 million suspensions of microbial cells in 1 ml of saline solution. Each suspension of microorganisms prepared by this method was evenly distributed over the surface of the corresponding nutrient medium using buffers. After that, the sample (as well as its 1, 2, and 4-fold dilutions) was soaked on sterile paper discs with a diameter of 6 mm and placed on the nutrient media inoculated with microbes. After incubating for one day at 37 °C, the results were recorded for the development of microorganisms around the disks impregnated with the substance. The diameter of the sterile zones indicated the degree of sensitivity of the microorganism to the substance.

As can be seen from Table 2, the sample showed a moderate and high antimicrobial activity against bacteria and fungi. According to the results obtained, the test sample inhibited fungi more effectively than bacteria. The sample showed a relatively weak activity (21.4 mm in 50 μg/ml) against *P. aeruginosa*. As a result, the test sample sufficiently inhibited (32.3 mm in 100 μg/ml) the culture of *C. albicans*.

Table 2

The study of the effect of chemical substances on microorganisms by the disk-diffusion method (The numbers are the diameter of the area where the microbe does not develop and are shown in mm)

Conc.	*S. aureus*	*E. coli*	*P. aeruginosa*	*B. anthracoides*	*K. pneumoniae*	*C. albicans*
50 μg/ml	27.1	28.6	21.4	22.3	26.3	31.5
100 μg/ml	29.6	30.5	23.2	23.3	28.2	32.3

Note: less than 15 mm is considered as a weak effect, 15-25 mm as a medium effect, over 25 mm as a high effect.

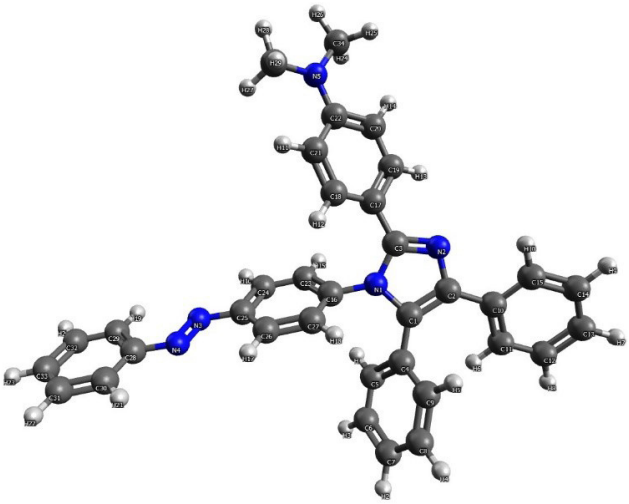

Fig. 2. The optimized structure of 4-(4,5-difenil-1-(4-(fenildiazenil)fenil)-1H-imidazol-2-il)-N,N-dimetilanilin

The theoretical calculations of the compound were performed using well-known DFT (Density functional theory) method, the geometry optimization was carried out on the basis of 6-31G(d,p) basic sets and the B3LYP level of theory. The ORCA-4.2.1 computational package was used for calculations [25]. Such important parameters as E_{HOMO}, E_{LUMO}, chemical hardness, chemical softness, electronegativity, chemical potential, electrophilicity index, ionization potential and electron affinity were calculated. The optimized structure is shown in Fig. 2.

The length of the C22-N5 bond in the optimized structure is 1.333 Å. C atoms (CH_3) are bonded to N5 atom with a bond angle of 119.7°, and the bond length is 1.445 Å. Phenyl rings bonded to the imidazole ring are not in the same plane. More rotation (C1-C2-C4-C9 - 56.7°) is observed in the phenyl ring bonded to C1.

The HOMO and LUMO orbitals of the molecule are given in Fig. 3.

As can be seen from Fig. 3, the LUMO orbitals are mainly delocalized on the phenyldiazenylphenyl fragment, including C3 and C1 carbons of the imidazole ring and look like C-H sp^2-s orbitals. The HOMO orbitals are delocalized over the imidazole ring, the aromatic rings are bonded to the imidazole ring, and CH_3 group. The HOMO orbitals appear mainly as C-C sp^2-sp^2 and C-H sp^3-s orbitals.

The quantum-chemical parameters of the molecule were calculated using the appropriate equations based on literature sources [21, 26, 27]. They are listed in Table 3. The energy gap is the difference between the HOMO and LUMO energies ($\Delta E = E_{LUMO} - E_{HOMO}$) and is the main quantity expressing the chemical stability of the molecule. Thus, a higher value of ΔE means that the molecule is more stable. It can be noted that the compound studied (ΔE = 2.359 eV) is quite stable chemically. The ionization potential and electron affinity are equal to the opposite value of E_{HOMO} and E_{LUMO} energies, respectively ($I = -E_{HOMO}$, $A = -E_{LUMO}$). The high value of the ionization potential (4.864 eV) is related to the stability of the molecule.

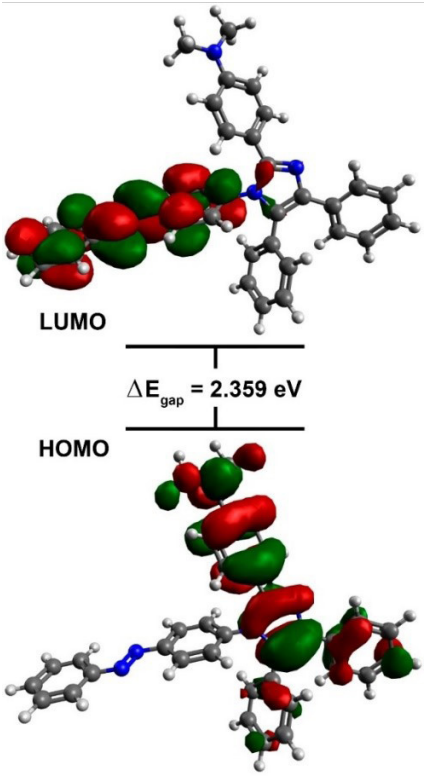

Fig. 3. The HOMO and LUMO orbitals of 4-(4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazol-2-yl)-N,N-dimethylaniline

Chemical hardness ($\eta = \frac{[I-A]}{2}$) is half of the difference between the values of the ionization potential and electron affinity. Chemical softness is inversely proportional to chemical hardness ($\sigma = \frac{1}{\eta}$). Low chemical hardness and high chemical softness are related to a high reactivity and binding efficiency of the molecule. Considering that these parameters are opposite in the compound studied (η = 1.180, σ = 0.848 eV), it can be noted that the compound has a weak reactivity. Electronegativity is half of the sum of the ionization potential and electron affinity values ($\lambda = \frac{[I+A]}{2}$) and indicates the ability of the molecule to attract electrons and its reactivity. Another

Table 3

The value of E_{HOMO}, E_{LUMO}, ΔE, chemical hardness (η), chemical softness (σ), electronegativity (λ), chemical potential (μ), electrophilicity index (ω), ionization potential (I) and electron affinity (A) of the imidazole synthesized

Parameters	Value
E_{HOMO}(eV)	-4.864
E_{LUMO}(eV)	-2.505
ΔE (eV)	2.359
Chemical hardness (η), (eV)	1.180
Chemical softness (σ), (eV)	0.848
Electronegativity (λ), (eV)	3.685
Chemical potential (μ), (eV)	-3.685
Electrophilicity index (ω), (eV)	5.754
Ionization potential (I), (eV)	4.864
Electron affinity (A), (eV)	2.505

important parameter is the electrophilicity index, which is calculated using the equation $\omega = \frac{\mu^2}{2\pi}$. The electrophilicity index is used to predict the biological activity of a molecule. Weak electrophiles have an electrophilic index less than 0.8 eV, medium electrophiles have an electrophilic index between 0.8 and 1.5 eV, while strong electrophiles have an electrophilic index more than 1.5 eV. Considering that the electrophilicity index of the molecule is 5.754 eV, it can be noted that it has a high biological activity. In a known source [21], quantum-chemical parameters of a similar imidazole were calculated, the electrophilicity index of 5.174 eV was recorded. It indicates that it has a slightly lower biological activity than the imidazole studied. Summarizing the theoretical calculations, it can be noted that the imidazole studied has a weak reactivity, high stability and high biological activity [28-30].

Conclusions and prospects for further research. In this work, 4-(4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazol-2-yl)-N,N-dimethylaniline has been synthesized from benzyl, ammonium acetate, p-aminoazobenzene and 4-(dimethylamino)benzaldehyde in the presence of microwave and ionic liquid catalysts. It has been determined that 1,4-dimethylpiperazinedihydrosulfate catalyst reacts under microwave conditions in a shorter time (19 min) with a higher yield (78.1 %). The compound has been tested as an antimicrobial agent against bacteria of *S. aureus, E. coli, P. aeruginosa, K. pneumoniae, B. anthracoides* and *C. albicans* fungus, showing moderate and higher activity. The theoretical calculations of the molecule have been performed; quantum chemical parameters are given. According to the theoretical calculations, the compound has a high chemical stability (ΔE = 2.359 eV) and a high biological activity (ω = 5.754 eV).

Conflict of interests: authors have no conflict of interests to declare.

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