ФАРМАЦЕВТИЧЕСКАЯ ХИМИЯ

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ANTIMICROBIAL ACTIVITY AND THEORETICAL CALCULATIONS OF 2-(4-METHOXYPHENYL)-4,5-DIPHENYL-1-(4-(PHENYLDIAZENYL) PHENYL)-1H-IMIDAZOLE

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In this work 2-(4-methoxyphenyl)-4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazole was synthesized using a single-step method under microwave conditions with the presence and absence of a catalyst. The structure of the synthesized compound was analyzed and confirmed using ^{1}H, ^{13}C NMR and IR spectroscopy methods. Ionic liquid catalysts (1,4 dimethylpiperazine dihydrosulfate, N-methylpyrrolidone perchlorate, 1-butyl-3-methylimidazolehydrosulfate) were used in the process of synthesis, comparison of their effect on the reaction was made. The structure of the synthesized compound has been analyzed using ^{1}H, ^{13}C NMR and IR spectroscopy methods. Theoretical calculations of compounds have been made using the density functional theory (DFT/B3LYP) method with the basis set 6-31G(d,p). The geometry of the structure was optimized, bond lengths and angle degrees were set, important quantum-chemical parameters such as HOMO, LUMO orbitals, reactivity, stability, electrophilicity, electronegativity, chemical softness and chemical hardness were calculated. It was determined that the compound has high stability (ΔE = 2.662 eV) and high biological activity (ω = 5.670 eV). The sample effect regarding Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Bacillus anthracoides bacteria and Candida albicans fungus was studied.

Keywords: Imidazole, synthesis, microwave, ionic liquid catalysts, antimicrobial activity, theoretical calculations, stability.

INTRODUCTION

Imidazoles are considered to be very rich substances chemically because they have a unique nucleus. These compounds act as catalysts in enzymatic processes in living organisms. The imidazole ring is included in many synthetic bioactive molecules as well as many natural compounds. Thus, histidine, histamine, purine, biotin, vit-B12 and other compounds contain an imidazole ring. The most common of these compounds is histidine. It is an important part of hemoglobin, proteins and enzymes composition [1].

Due to their high biological activity, imidazole derivatives readily bind to a wide range of enzymes and receptors through weak interactions. This property increases its biological and pharmacological effect. The imidazole ring is present in several pharmacologically important drug molecules such as metronidazole, pretomanid, ketoconazole, tipifarnib, megazol, mafimidone, losartan, etc., which are considered the most important and famous drugs in pharmacology. Many imidazoles are widely used in medicine due to their pharmacophore properties with improved potency, efficacy and less toxicity [2]. Biologically active imidazoles are widely used in pharmacology due to its antibacterial, antioxidant, antidiabetic, anti-inflammatory, antiparasitic, anti-tuberculosis, anti-fungal, anti-depressant, anti-malarial, anti-cancer, anti-tumor, anti-Alzheimer, anti-thyroid properties [3–9].

Imidazoles are used as kinase inhibitors [10], plant growth regulators [11], flame retardants [12]. Imidazoles are also known to be used as luminophores in LED industry and defectoscopy [13, 14], as ionic liquids in green chemistry and organometallic catalysis [15], and as ligands in coordination chemistry [16]. One of the broadest fields of imidazoles use is their application as a corrosion inhibitor in industry [17–19].

Such a wide range of applications increases the interest in imidazole synthesis. Researchers have developed effective, simple and"green reactions" in this field [20–22]. One of the most modern approaches in the synthesis of imidazole is the use of ionic liquid catalysts. The advantage of this method is that the reaction occurs in one step and in a short period of time, the yield is high, the catalysts can be reused and they can be easily separated from the reaction products by dissolving in water [23–25].

Synthesis of imidazoles under microwave conditions is of particular importance due to its environmental friendliness. 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 compared to the yield of catalytic reactions. Recently, the "microwave and catalyst" synergism has been effectively used to boost the synthesis of chemical compounds' economic and environmental efficiency [26].

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, electrophilicity index, electronegativity, electron affinity, etc. In addition, bond lengths, bond angle degrees, bond twist degrees, atomic charges, etc., can be calculated in the optimized structure of matter using computer programs [27, 28].

Imidazoles with antimicrobial properties are widely used in pharmacology. In the presented study, the antimicrobial activity of the compound against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Bacillus anthracoides bacteria and Candida albicans fungus was studied.

MATERIALS AND METHODS

Reagents and solvents were purchased from Aldrich. 1H-, 13C-, NMR spectra of the synthesized compound were recorded on a BRUKER-Fourier (300 MHs) spectrometer at 20 °C, 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 the spectrometer "LUMOS FT-IR Microscope" (BRUKER Company of Germany). Elemental analysis was studied on the "TRUSPEC MICRO" device manufactured by the "LECO" company. The melting temperature was measured on a DSK-Q-20 device.

RESULTS AND DISCUSIONS

The presented imidazole compound was synthesized under 4 different conditions – under microwave conditions in the absence of a catalyst and in the presence of 3 different ionic liquid catalysts. 4 mmol each of benzyl, 4-methoxy benzaldehyde, p-aminoazobenzene, ammonium acetate, and 30 ml of ethanol are taken as reagents and are used as a solvent. The reaction mixture was irradiated in a 300W microwave oven at the boiling temperature of ethanol (figure 1). The reaction proceeds according to the following scheme**.**

To compare the conditions, the solvent and reagents were taken in the same amount. The progress of the reaction is monitored using TLC. After the reaction is finished, the mixture is poured into ice water. Catalysts are dissolved and separated. The obtained mass is recrystallized in ethanol. Table 1 shows the duration and yield of the reaction under different conditions.

As can be seen from the table 1, 1,4-DMPDHS catalyst is more effective than other ionic liquid catalysts. This can be explained by higher acid number of the 1,4-DMPDHS catalyst containing two HSO_4^- ions.

Spectral and analytical data

Empirical formula of substance: $C_{34}H_{26}N_4O$, Mr=506.44, Melting point: 137 °C.

^{1}H-NMR (acetone-d_6, δ, ppm): 3.92 (s., 3H, OCH_3), 7.12 (d., 2H, J=8.82 Hz), 7.41 (d., 2H, J=8.82 Hz), 7.53 -7.64 (m., 4H), 7.65 (d., 3H, J=7.89 Hz), 7.75-7.83(m., 2H), 7.91-8.02 (m., 10H). ^{13}C NMR: 55.23 (OCH_3), 113.82, 117.31, 122.17, 122.65, 122.97, 123.38, 124.34, 125.65, 129.54, 129.64, 129.84,

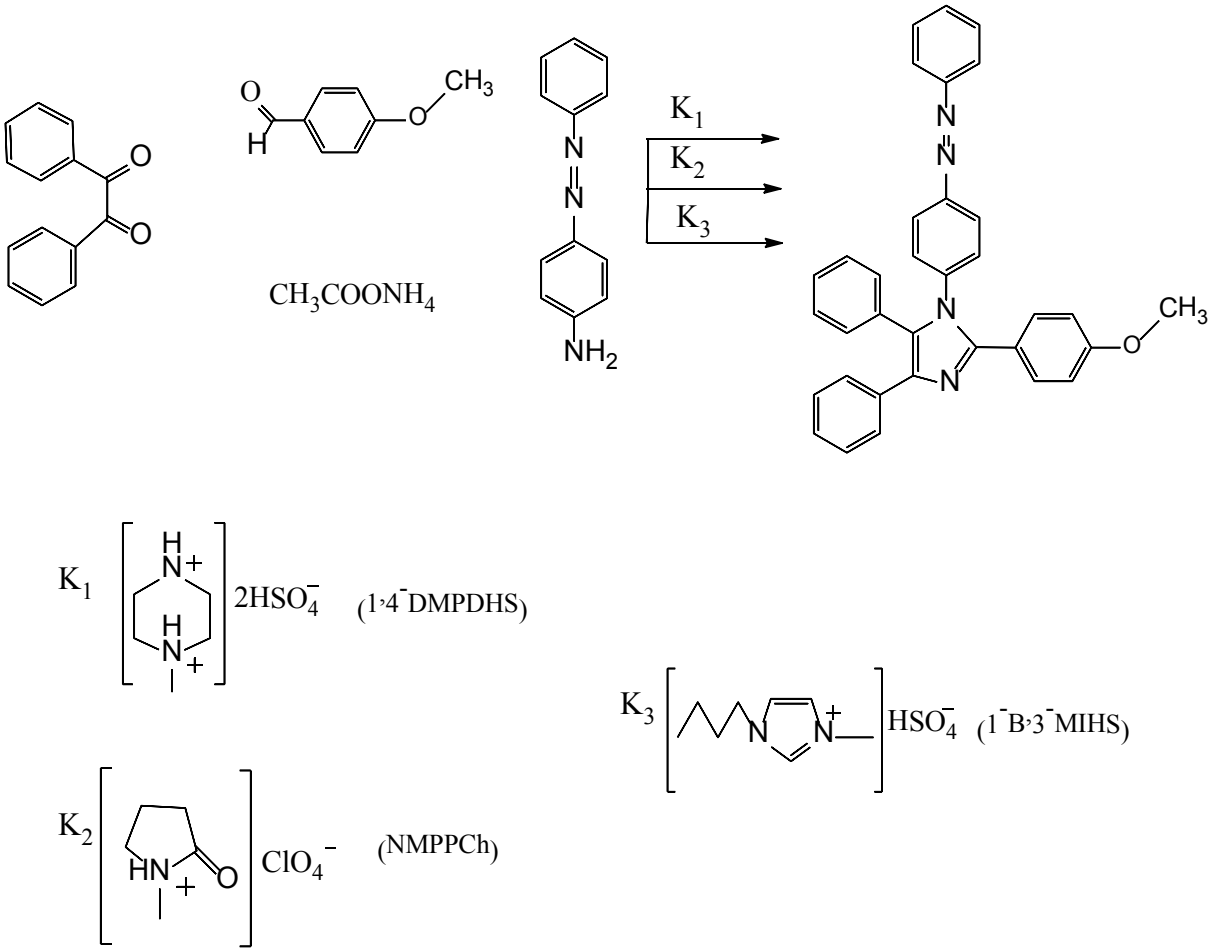

Figure 1. – Synthesis of 2-(4-methoxyphenyl)-4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazole

Table 1. – Comparison of catalytic and microwave synthesis in terms of yield and reaction time

Conditions	Reaction time, min	yield
Microwave	27	66.8
1,4-DMPDHS & microwave	17	81.3
NMPPCI & microwave	22	74.5
1-B,3-MİHS & microwave	20	78.6

129.95, 131.05 1.66, 133.15, 135.28 (C-Ar), 143.24, 150.53, 152.91 . 153.33 (C-N), 161.36 (C-O).IR (cm^{-1}): ν-1654 (C=N), δ-683, 717, 765, 846 (C-H, aromatics), ν-1596(C-C), ν-1566(N=N), ν-1307 (C-N), ν-1026, 1245 (C-O), ν-2839, 2958 (C-H), δ-1372, 1459(C-H, (–CH3)).

Antimicrobial activity

The antimicrobial activity of the synthesized sample was studied using disc-diffusion method. Staphylococcus aureus (gold staphylococci), Gram-negative bacteria Escherichia coli (intestinal bacilli) and Pseudomonas aeruginosa (blue-green pus bacilli) and Klebsiella pneumoniae (capsular bacilli) kept in the Department of Medical Microbiology and Immunology as test cultures.), Bacillus anthracoides (spored), Candida albicans laboratory strains, considered one of the causative agents of opportunistic mycosis, were used.

The indicated bacteria were cultured on meat-peptone agar, and candida were cultured on Saburo's medium. In the study, suspensions of one-day test cultures with 500 million microbial cells in 1 ml of physiological solution were used. Each microorganism suspension prepared in this method is spread evenly on the surface of the respective nutrient media by means of 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 microbe-inoculated nutrient media. After incubation for one day at 37 °C, results were recorded for the growth of microorganisms around the impregnated discs. Areas around the disk where microbes do not develop – the diameter of the sterile zones is shown in mm. The diameter of the sterile zones indicates the degree of sensitivity of the microorganism to the substance.

The effect of *2-(4-methoxyphenyl)-4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazole* on various bacteria was studied and the results of the study are shown in table 2.

Table 2. – The study results 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, mm)

Concentration	S. aureus	E. coli	P. aeruginosa	B. anthracoides	K. pneumoniae	C. albicans
50 μg/ml	25.8	27.0	19.0	20.6	23.5	30.1
100 μg/ml	28.7	29.5	20.2	21.5	25.3	31.6

Note: less than 15 mm is considered as weak impact, 15–25 mm as medium impact, and above 25 mm as high impact

According to the obtained results, the effect of the studied sample on *Pseudomonas aeruginosa, Bacillus anthracoides* and *Klebsiella pneumoniae* bacteria is assessed as medium effect, and the effect on *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans fungi* is assessed as high effect. The highest effect is observed in yeast-like fungi. As can be seen from the table 2, the studied sample sufficiently inhibited the development of *Candida albicans* culture.

Theoretical calculations

ORCA-4.2.1 computational package was used for theoretical calculations [29]. Calculations were performed using the well-known DFT (Density functional theory) method, geometric optimization was performed based on 6-31G(d,p) basis sets and the B3LYP level of theory. Important parameters such as E_{HOMO}, E_{LUMO}, chemical hardness, chemical softness, electronegativity, chemical potential, electrophilicity index, ionization potential and electron affinity were studied. The optimized structure is shown in figure 2.

In the optimized structure (figure 2), the C3-N1 bond belonging to the imidazole ring (1.388 Å) is longer than the C3-N2 bond (1.316 Å). This is due to the double bond between C3-N2. One notable point is the

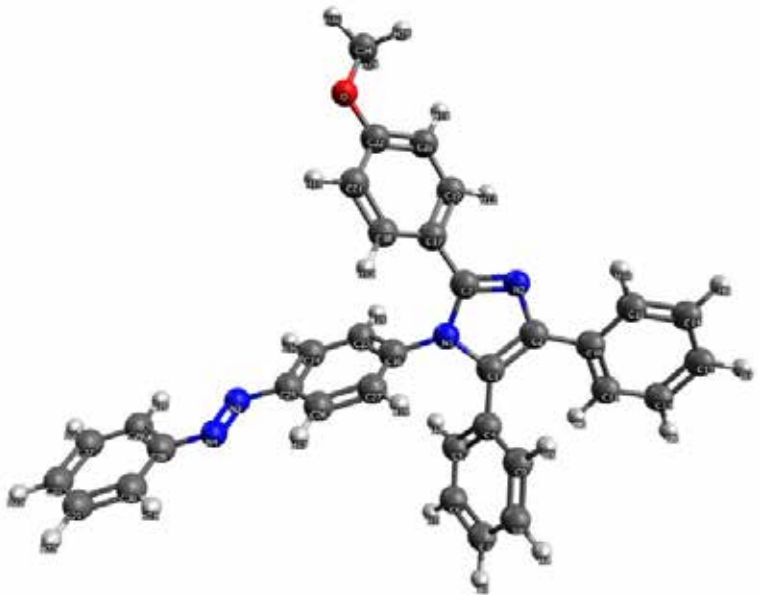

Figure 2. – The optimized structure of 2-(4-methoxyphenyl)-4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazole

difference in the lengths of the N1-C1 and N2-C2 single bonds. The fact that the N2-C2 bond (1.372 Å) is shorter than the N1-C1 bond (1.401 Å) can be explained by the fact that the double-bonded N2 atom attracts the C2 atom towards itself with a greater force. On the other hand, the partial charge value of C2 atom (0.098) is greater than the partial charge value of C1 atom (0.082). It is clear that in this case the C2 atom will be attracted by the electronegative atom (N) with a higher force. The C22-O bond is 1.356 Å long, and the O-CH_3 bond is 1.410 Å long. An angle degree of 119.4° is observed in the O-CH_3 fragment. The HOMO and LUMO orbitals in the molecule are given in figure 3.

Figure 3 shows that the HOMO orbitals are delocalized over the imidazole and phenyl fragments and also include the oxygen atom. LUMO orbitals are delocalized on the phenyldiazenephenyl fragment and extended to carbons (C1 and C3) belonging to the imidazole nucleus. LUMO orbitals are mostly sp-s and HOMO orbitals are sp-sp orbitals.

Important quantum-chemical parameters of the compound were calculated and listed in Table 3.

It can be seen from the table 3 that the compound has considerable chemical stability (ΔE = 2.662 eV). Thus, in compounds with high stability, the difference between the energies of the HOMO and LUMO orbitals is large. Low value of chemical softness (σ = 0.848 eV) and relatively high value of chemical hardness (1.331 eV) of the compound can be explained by its low reactivity. A low chemical potential value means the ability of the compound to receive electrons (electron

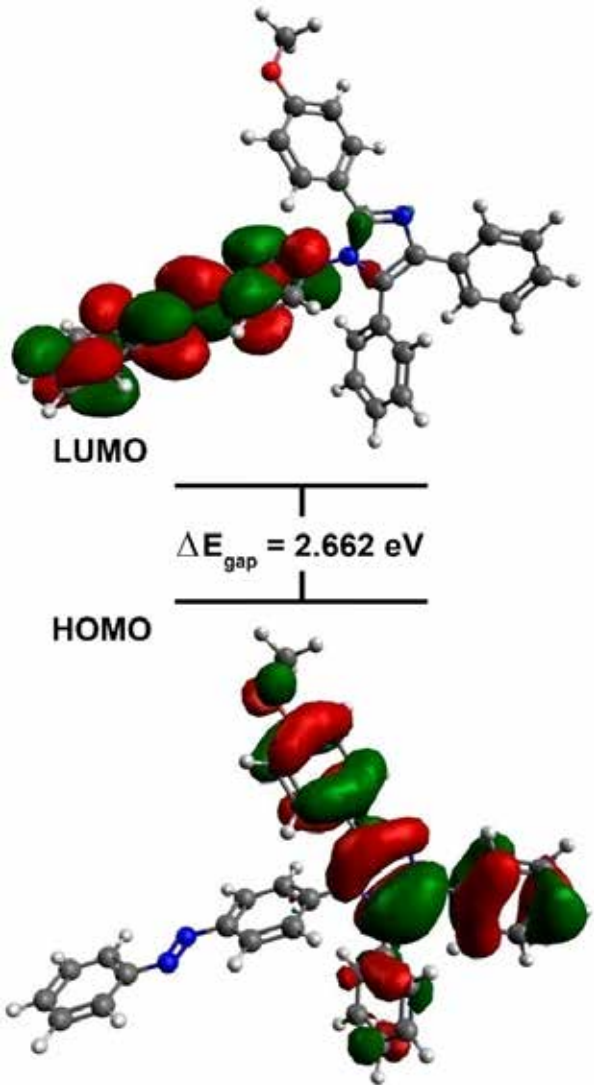

Figure 3. – HOMO and LUMO orbitals of 2-(4-methoxyphenyl)-4,5-diphenyl-1-(4-(phenyldiazenyl)phenyl)-1H-imidazole

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 synthesized imidazole

Parameters	Value
E_{HOMO}(eV)	-5,216
E_{LUMO}(eV)	-2,554
ΔE (eV)	2,662
Chemical hardness, (η), (eV)	1,331
Chemical softness (σ), (eV)	0,848
Electronegativity (λ), (eV)	3,885
Chemical potential (μ), (eV)	-3,885
Electrophilicity index (ω), (eV)	5,670
İonization potential (I), (eV)	5,216
Electron affinity (A), (eV)	2,554

acceptor). On the other hand, negative chemical potential value (μ = -3.885 eV) indicates that the molecule is not decomposed into elements. One of the main noteworthy parameters in the table is the electrophilicity index which is related to biological activity. Thus, highly electrophilic compounds have high antimicrobial properties. Compounds with an electrophilicity index value above 1.5 eV are considered highly electrophiles. The electophilicity index of the studied compound is 5.670 eV indicating high biological activity of this compound. High value of the ionization potential (5.216) futher confirms that the compound is chemically stable. In summary, it can be noted that the compound is chemically stable, weakly reactive and has high biological activity [23, 27, 30, 31].

CONCLUSIONS

In this work, **2-(4-methoxyphenyl)-4,5-diphenyl-1-(4-(phenyldiazenyl) phenyl)-1H-imidazole** was synthesized from benzyl, ammonium acetate, p-aminoazobenzene and 4-methoxy benzaldehyde in the presence of microwave and ionic liquid catalysts. It was determined that 1,4-dimethylpiperazinedihydrosulfate catalyst conducts the reaction under microwave conditions in a shorter time **(17 minutes)** with a high yield **(81.3%)**. The compound was tested as antimicrobial against the bacteria Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Bacillus anthracoides, Klebsiella pneumoniae and Candida albicans fungus, showing higher activity against Candida albicans fungus. Theoretical calculations of the molecule were performed, quantum chemical parameters were given. According to theoretical calculations, the compound has high chemical stability **(ΔE = 2.662 eV)** and high biological activity **(ω = 5.670 eV)**.

РЕЗЮМЕ

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АНТИМИКРОБНАЯ АКТИВНОСТЬ И ТЕОРЕТИЧЕСКИЕ РАСЧЕТЫ 2-(4-МЕТОКСИФЕНИЛ)-4,5-ДИФЕНИЛ-1-(4-(ФЕНИЛДИАЗЕНИЛ)ФЕНИЛ)-1Н-ИМИДАЗОЛА

В настоящей работе представлен одностадийный синтез 2-(4-метоксифенил)-4,5-дифенил-1-(4-(фенилдиазенил)фенил)-1Н-имидазола в микроволновых условиях в присутствии катализатора и без его присутствия. Структура синтезированного соединения проанализирована и подтверждена методами ^{1}H, ^{13}C ЯМР и ИК-спектроскопии. В процессе синтеза использовали ионно-жидкие катализаторы (1,4-диметилпиперазин дигидросульфат, N-метилпирролидон перхлорат, 1-бутил-3-метилимидазол гидросульфат), было проведено сравнение их влияния на реакцию. Строение синтезированного соединения проанализировано методами ^{1}H, ^{13}C ЯМР и ИК-спектроскопии. Теоретические расчеты соединений были выполнены с использованием метода теории функционала плотности (DFT/B3LYP) с базисным набором 6-31G(d,p). Оптимизирована геометрия структуры, заданы длины связей, угловые степени, рассчитаны важные квантово-химические параметры, такие

как ВЗМО, НСМО-орбитали, реакционная способность, стабильность, электрофильность, электроотрицательность, химическая мягкость, химическая жесткость. Установлено, что соединение обладает высокой стабильностью (ΔE = 2,662 эВ) и высокой биологической активностью (ω = 5,670 эВ). Изучали действие образца в отношении Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, бактерий Bacillus anthracoides и гриба Candida albicans.

Ключевые слова: имидазол, синтез, микроволны, ионно-жидкие катализаторы, антимикробная активность, теоретические расчеты, стабильность.

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