Procesing '21

ZBORNIK RADOVA

34. Međunarodni kongres o procesnoj industriji

3. i 4. jun 2021
Novi Sad

ZBORNIK RADOVA

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PROCESING ′21

Fakultet tehničkih nauka Univerziteta u Novom Sadu, Novi Sad

Izdavač
Savez mašinskih i elektrotehničkih
inženjera i tehničara Srbije (SMEITS)
Društvo za procesnu tehniku
Kneza Miloša 7a/II,
11000 Beograd

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PREDGOVOR

U ovom zborniku su kompletni radovi koje je Naučno-stručni odbor 34. Međunarodnog kongresa o procesnoj industriji Procesing '21. posle obavljenih recenzija prihvatio za izlaganje.

Zbornik radova će biti objavljen elektronski i na sajtu www.izdanja.smeits.rs.

Međunarodni karakter Procesinga '21 i ove godine ostvaren je inostranim učesnicima sa radovim, kao i članovima naučnog odbora. Zvanični jezici za izlaganje radova na kongresu su srpski i engleski.

Osnovni ciljevi kongresa su inoviranje i proširivanje znanja inženjera u procesnoj industriji, energetici, rudarstvu, komunalnom sektoru (vodovodima, toplanama) i podrška istraživačima u predstavljanju ostvarenih rezultata istraživačkih projekata.

Tematika Procesinga '21 obuhvata osnovne procesne operacije – mehaničke, hidromehaničke, toplotne, difuzione, hemijske i biohemijske, kao i procesna postrojenja i opremu (aparate i mašine).

Program Procesinga '21 obuhvata oblasti: projektovanja i razvoja u procesnoj industriji; konstruisanja mašina, aparata i uređaja; pripreme i vođenja izgradnje i montaže industrijskih postrojenja; industrijskih i laboratorijskih merenja; ispitivanja i atestiranja materijala, proizvoda, mašina i aparata; istraživanja i razvoja nove opreme i industrijskih sistema.

U program Procesinga '21 po tradiciji, pored prezentacije radova uključena su tri Okrugla stola iz aktuelnih tema u oblasti procesne tehnike:

- *Cirkularna ekonomija – alat za održivost industrije,*
- *Tretman voda u industriji – iskustva i buduće potrebe,*
- *Gasovi u industriji – primeri dobre prakse.*

Procesing '21 organizuje Društvo za procesnu tehniku pri SMEITS-u, a u Naučnom i Organizacionom odboru prisutni su predstavnici svih Mašinskih fakulteta u Srbiji kao i Tehnoloških i drugih fakulteta u okviru kojih je oblast procesne tehnike zastupljena u nastavi.

Pomoć u organizovanju Procesinga '21 dali su članovi Katedre za procesnu tehniku Mašinskog fakulteta Univerziteta u Beogradu i Departmana za energetiku i procesnu tehniku Fakulteta tehniničkih nauka iz Novog Sada.

Sa Tehnološko-metalurškog fakulteta u Beogradu, pored drugih vidova saradnje kroz Društvo za procesnu tehniku prijavljen je i značajan broja radova za ovogodišnji Procesing.

U Beogradu
juli 2021.

SADRŽAJ

Inženjerstvo životne sredine i održivi razvoj u procesnoj industriji

Procesi i postrojenja u pripremi i prečišćavanju vode u procesnoj industriji

Procesne tehnologije

Gasna tehnika

Osnovne i pomoćne operacije, aparati i mašine u procesnoj industriji

Energetska efikasnost u procesnoj industriji

Menadžment kvaliteta i standardizacija u organizacijama

Radovi koji će biti objavljeni u časopisu „Procesna tehnika“ u 2021. godini

SINTEZA I BIOLOŠKA SVOJSTVA NEKIH AZO BOJA NA BAZI 3-CIJANO-6-HIDROKSI-4-METIL-1-PROPIL-2-PIRIDONA

SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME AZO DYES BASED ON 3-CYANO-6-HYDROXY-4-METHYL-1-PROPYL-2-PYRIDONE

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Azo boje su najznačajnija grupa organskih sintetskih boja. Visoki molarni ekstencioni koeficijenti, koji karakterišu azo jedinjena, doprinose njihovoj širokoj upotrebi kako u tradicionalnom bojenju materijala, tako i sve većoj primeni u novijim tehnologijama kao što su optički materijali i solarne ćelije. Mnoga istraživanja pokazuju da azo boje dobijene iz heterocikličnih molekula imaju biološku aktivnost. Arilazo piridonske boje pripadaju klasi disperznih boja koje ispoljavaju antibakterijsku, antifungalnu, antikancerogenu i antioksidativnu aktivnost. U ovom radu sintetisane su tri azo boje polazeći iz 2-, 3- i 4-aminofenola i 3-cijano-6-hidroksi-4-metil-1-propil-2-piridona. Struktura jedinjenja potvrđena je ATR-FTIR, NMR i UV-Vis podacima. Antioksidsativna aktivnost jedinjenja ispitana je ABTS metodom. Fizičko-hemijski deskriptori i ADME parametari određeni su in silico pomoću SwissADME programa.

Ključne reči: *hidrazon; ADME; antioksidativna svojstva*

Azo dyes are the most important group of organic synthetic dyes. High molar extinction coefficients, which characterize azo compounds, contribute to their wide use in traditional dyeing of various materials, as well as the increasing application in new technologies such as optical devices and solar cells. Numerous studies show that azo dyes based on heterocyclic molecules possess biological activity. Arylazo pyridone dyes belong to the class of disperse dyes, which exhibit antibacterial, antifungal, anticancer and antioxidant properties. In this work, three azo dyes were synthesized starting from 2-, 3- and 4-aminophenol and 3-cyano-6-hydroxy-4-methyl-1-propyl-2-pyridone. The structure of dyes was confirmed by ATR-FTIR, NMR and UV-Vis spectroscopy. The antioxidant activity of compounds was examined by the ABTS method. Physico-chemical descriptors and ADME parameters were determined in silico using SwissADME program.

Key words: *hydrazone; ADME; antioxidant properties*

1 Introduction

The heterocyclic azo dyes are receiving constant attention over the years, due to its excellent coloration properties and broad spectrum of application in different fields, such as textile dyeing, photovoltaics and pharmaceuticals [1]. In comparison to simple arylazo dyes, heterocyclic azo compounds are more stable, brighter and ecologically acceptable [2]. Moreover, numerous studies have reviled that azo compounds derived from heterocyclic moieties exhibit prominent antibacterial, antifungal, antioxidant and anticancer activity [3].

Azo dyes based on 2-pyridone scaffolds are significant group of disperse dyes which display remarkable dyeing and biological properties. Recent studies have shown that 2-pyridone based azo compounds manifest cytotoxic action against several tumor cells and inhibit bacterial growth [4, 5]. Moreover, arylazo pyridone dyes may be strong antioxidants, especially if they have –OH or –NH groups in the structure. Antioxidants prevent biomolecules from undergoing oxidative damage

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through free radical mediated reactions, so they can be effective therapy for atherosclerosis, coronary heart disease, tumors, and aging itself [6].

In this work, three azo dyes have been synthesized starting from 2-, 3- and 4-aminophenol as diazo-component and 3-cyano-6-hydroxy-4-methyl-2-pyridone as coupling-component. The structure of dyes has been confirmed by melting points, ATR-FTIR, NMR and UV-Vis spectra. Antioxidant activity of the investigated dyes has been evaluated by ABTS method. The physico-chemical parameters and ADME (absorption, distribution, metabolism, and excretion) properties have been calculated using SwissADME, and druglikness was estimated.

2 Experimental

2.1 Matetials and methods

All chemicals were obtained from Merck, Fluka and Acros and were used without further purification. Fourier transform infrared spectroscopy (FT-IR) spectra of the dyes were recorded using a Nicolet™ iS™ 10 FT-IR Spectrometer (Thermo Fisher SCIENTIFIC) spectrometer, with Smart iTR™ Attenuated Total Reflectance (ATR) sampling accessories. The ATR-FTIR spectra were recorded in the 500–4000 cm^{-1} range with 20 scans per spectrum. The melting points were determined on the melting point apparatus Electrothermal. The ^1H NMR spectra were taken on a Bruker Ascend 400 apparatus (400 Hz) in deuterated dimethylsulfoxide (DMSO-d_6) with tetramethylsilane (TMS) as an internal standard. The ultraviolet–visible (UV–Vis) absorption spectra were recorded on a Schimadzu 1700 spectrophotometer, at concentration of the solutions $4 \cdot 10^{-5}$ mol/L. All spectroscopic measurements were carried out at room temperature (25 °C).

2.2 Synthesis of azo dyes 1-3

The azo dyes **1**-**3** (Figure 1) were synthesized *via* classical diazo-coupling reaction, starting from 2-, 3- and 4-aminophenol as diazo-component, and 3-cyano-6-hydroxy-4-methyl-1-propyl-2-pyridone as coupling-component. Target 2-pyridone was prepared according to previously reported method [7]. The corresponding aminophenol (10 mmol) was dissolved in concentrated hydrochloric acid (2.5 mL) and cooled to 0 °C. Sodium nitrate (11 mmol) was dissolved in cold water (4 mL) and added dropwise to the aminophenol solution. The mixture was stirred for an hour to give related diazonium salt. The obtained 2-pyridone (10 mmol) was dissolved in an aqueous potassium hydroxide solution and cooled to 0 °C. Then corresponding diazonium salt was added dropwise to the solution of 2-pyridone. The mixture was stirred for 3 hours at temperature 0–5 °C, and then left in the refrigerator overnight. The crude dyes were filtrated, washed with water and air dried. The azo dyes **1**–**3** were recrystallized from ethanol. The overall synthesis is presented in Figure 1.

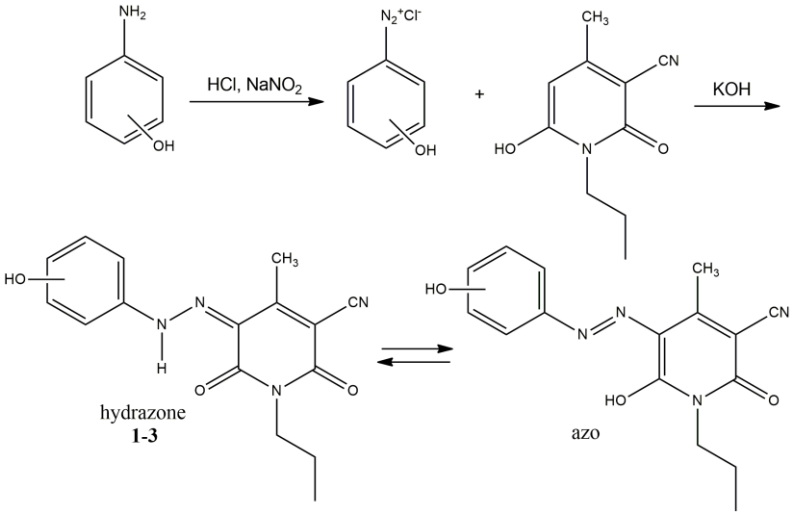

*Figure 1. The synthesis of arylazo pyridone dyes **1**–**3** (**1**: 2-OH, **2**: 3-OH, **3**: 4-OH).*

*5-(2-Hydroxyphenylazo)-3-cyano-6-hydroxy-4-methyl-1-propyl-2-piridone (**1**)*: Dark red powder; yield 70%; m.p. 252-253 °C; ATR-FTIR (ν/cm^{-1}): 3213 (NH), 2224 (CN), 1659 (CO), 1625

(CO), 1509 (NH); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 0.87 (3H, t, J = 7.4 Hz, C$\underline{H}_3$), 1.51-1.60 (2H, m, CH_2), 2.52 (3H, s, CH_3), 3.80 (2H, t, J = 7.4 Hz, C$\underline{H}_2$), 6.94–7.01 (2H, m, Ar–H), 7.16 (1H, t, J = 7.8 Hz, Ar–H), 7.70 (1H, d, J = 8.0 Hz, Ar–H), 10.86 (1H, s, OH), 14.98 (1H, s, NH hydrazone). UV-Vis (EtOH) (λ_{max}/nm (log ε/mol^{-1}dm^{3}cm^{-1})): 459.5 (4.40).

*5-(3-Hydroxyphenylazo)-3-cyano-6-hydroxy-4-methyl-1-propyl-2-piridone (**2**)*: Red powder; yield 75%; m.p. > 300 °C; ATR-FTIR (ν/cm^{-1}): 3367 (NH), 2220 (CN), 1667 (CO), 1621 (CO), 1501 (NH); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 0.87 (3H, t, J = 7.4 Hz, C$\underline{H}_3$), 1.53–1.59 (2H, m, CH_2), 2.52 (3H, s, CH_3), 3.80 (2H, t, J = 7.4 Hz, C$\underline{H}_2$), 6.70 (1H, d, J = 8.4 Hz, Ar–H), 7.12 (2H, d, J = 8.0 Hz, Ar–H), 7.24-7.28 (1H, m, Ar–H), 9.88 (1H, s, OH), 14.52 (1H, s, NH hydrazone). UV-Vis (EtOH) (λ_{max}/nm (log ε/mol^{-1}dm^{3}cm^{-1})): 440.0 (4.41).

*5-(4-Hydroxyphenylazo)-3-cyano-6-hydroxy-4-methyl-1-propyl-2-piridone (**3**)*: Dark orange powder; yield 70%; m.p. > 300 °C; ATR-FTIR (ν/cm^{-1}): 3367 (NH), 2222 (CN), 1662 (CO), 1624 (CO), 1505 (NH); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 0.87 (3H, t, J = 7.4 Hz, C$\underline{H}_3$), 1.52-1.58 (2H, m, CH_2), 2.51 (3H, s, CH_3), 3.80 (2H, t, J = 7.2 Hz, C$\underline{H}_2$), 6.87 (2H, d, J = 8.8 Hz, Ar–H), 7.59 (2H, d, J = 8.4 Hz, Ar–H), 9.94 (1H, s, OH), 14.88 (1H, s, NH hydrazone). UV-Vis (EtOH) (λ_{max}/nm (log ε/mol^{-1}dm^{3}cm^{-1})): 468.5 (4.44).

2.3 Antioxidant activity

The antioxidant activity of dyes **1**–**3** was determined by the ABTS radical-scavenging assay [8]. A stock solution of the ABTS$^{\bullet+}$ radical cation was prepared in the reaction of ABTS (4.912 mL, 7 mM in phosphate-buffered saline (PBS)) and potassium persulfate (0.088 mL, 140 mM in distilled water). After 16 h of incubation in the dark, the stock solution was diluted with methanol until absorbance recorded at 734 nm was 0.700 ± 0.02. Subsequently, 20 μL of the methanolic dye solutions (5 mM) were mixed with 2 mL of the ABTS radical solution, shaken and stored in the dark for 10 min. Afterwards the absorbance was measured at 734 nm. Each test was done in triplicate. The inhibition percentage of ABTS$^{\bullet+}$ was calculated using the formula:

Inhibition (%) = (Ac–As) / Ac × 100,

where Ac is the absorbance of the control solution (20 μL of methanol in 2 mL of ABTS solution) and As is the absorbance of the sample solution. Ascorbic acid was used as a standard antioxidant. The antioxidant activity was further evaluated by determination of the IC_{50} values. The methanolic solutions of dyes and ascorbic acid were prepared at concentrations 5, 2.5, 1.25 and 0.5 mM, and obtained IC_{50} were compared.

2.4 ADME evaluation

The molecular structures of hydrazones **1–3** were converted into SMILES database using ChemDraw Ultra 12.0. Then, these SMILES were inserted in SwissADME [9] website to calculate the physicochemical descriptors, ADME (absorption, distribution, metabolism, and excretion) and drug-like properties.

3 Results and discussion

3.1 ATR-FTIR and NMR results

The synthesized arylazo pyridone dyes **1-3**, contain hydroxy group in the pyridone moiety, in the *ortho*- position to the azo bond, which enables intramolecular proton transfer, and thus the existence of azo and hydrazone tautomeric forms (Figure 1) [10]. The ATR-FTIR and NMR spectra of dyes **1-3** suggest the existence of the hydrazone tautomeric form (Figure 1) in the solid state, as well as, in the DMSO-d_6 solution. The stretching vibrations of two carbonyl groups in pyridone ring, appear in the ATR-FTIR spectra in the region of 1667–1659 and 1625-1621 cm^{-1}. The N-H stretching vibrations of the hydrazone group appear in the region of 3367–3213 cm^{-1}. Additional confirmation of the presence of the hydrazone tautomer is intensive band appearing in the region of 1509–1501 cm^{-1} which is ascribed to mutual stretching of C=N and bending of N–H vibrations. The ^{1}H NMR spectra of all dyes, obtained in DMSO-d_6 solution, contain the signal of the hydrazone N-H group in the range of 14.98–14.52 ppm.

3.2 UV-Vis analysis

The UV-Vis absorption spectra of investigated dyes, in ethanol, are shown in Figure 2. The obtained spectra, also, suggest the existence of hydrazone tautomeric form in case of all dyes [11]. The absorption bands at 459.5 (**1**), 440.0 (**2**) and 465.8 (**3**) nm are ascribed to π-π* transitions between pyridone and phenyl moiety in hydrazone tautomer. Hydroxy group in phenyl moiety manifests positive resonance effect in *para*- and *ortho*- positions and causes a batochromic shift in comparison to *meta*- substituted dye where only negative inductive effect is involved. *Ortho*- substituted dye (**1**) have displayed a hypsochromic shift, comparing to *para*- substituted dye (**3**), due to the steric effect which prevents effective delocalization [10].

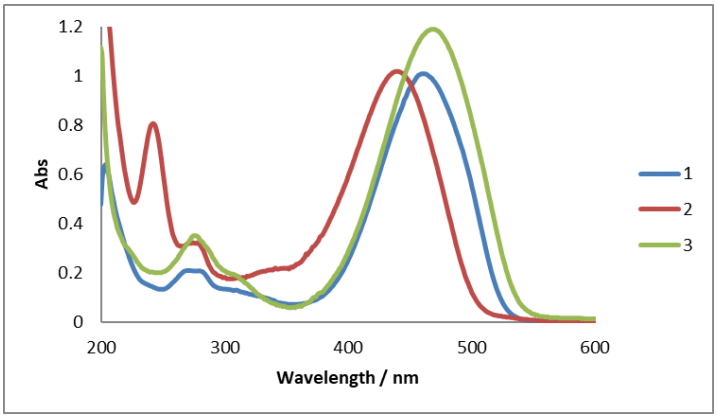

*Figure 2. UV-Vis spectra of dyes **1-3** in ethanol*

3.3 Antioxidant activity

Antioxidant properties of dyes **1-3** have been assayed using the ABTS method. The scavenging activity of azo dyes was compared to the activity of ascorbic acid (Figure 3). The results have shown remarkable activity of the compounds, indicating that –OH group in the phenyl ring affect the oxidant ability of investigated molecules. Namely, **1** (89.7%), **2** (94.3%) and **3** (95.0%) expressed excellent ability to scavenge the $ABTS^{\bullet+}$ radical cation, comparing to the inhibition of ascorbic acid (95.3%).

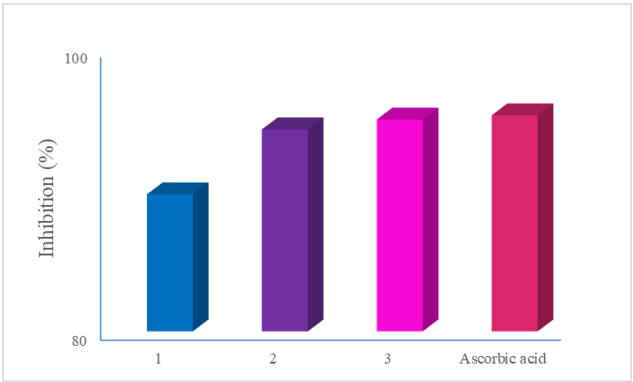

Figure 3. Antioxidant properties of investigated dyes

Thus, all investigated molecules have been further evaluated by determination of IC_{50} values, which corresponds to the concentration of sample able to scavenge 50% of ABTS radicals in the solution (Figure 4). It is known that low IC_{50} values suggest high antioxidant activity. The antioxidant activity based on IC_{50} values of studied dyes was found to be as follows: **3** (0.3 mM) > **2** (0.45 mM) > **1** (2.80 mM). Furthermore, the antioxidant capacity of dyes **2** and **3** was better than ascorbic acid (IC_{50} value 1.25 mM), indicating that related molecules are promising antioxidants.

The computational study of the synthesized dyes **1-3** was performed to evaluate physicochemically and ADME properties, using SwissADME [9]. With respects to the physicochemical properties (Table 1), all synthesized compounds have zero violations for Lipinski´s rule, for orally active drugs [12]. All topological polar surface areas (TPSA) are less than 112 $Å^2$ indicating good cell membrane permeability. In addition, absorption (%ABS) was calculated by the equation % ABS = 109 – (0.345

x TPSA) [13], and obtained value of 72.5% demonstrates that these dyes have good cell permeability and bioavailability. All compounds have 4 rotatable bonds, which indicate molecular flexibility to their bio-target. Regards to the pharmacokinetic and medicinal chemistry results evaluated by SwissADME, it was found that all azo molecules have high gastro-intestinal absorption and have no permeation to the blood brain barrier, which ensures no side effects to CNS.

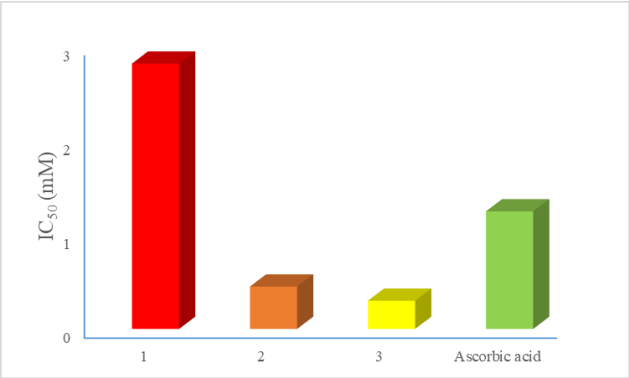

Figure 4. IC_{50} values of studied compounds

3.4 In silico evaluation of physicochemical and ADME properties

Table 1. The physicochemical properties of investigated dyes calculated using SwissADME

Dye	HBD[a]	HBA[b]	M log *P*[c]	MW[d]	Lipinski's violations[e]	TPSA [Å²][f]	%ABS[g]	Rot. Bond[h]
1-3	2	5	0.76	312.32	0	105.79	72.50	4

[a] The number of hydrogen bond donors; [b] The number of hydrogen bond acceptors;
[c] The octanol/water partition coefficient; [d] The molecular weight;
[e] The number of Lipinski's rule violation; [f] The topological polar surface area;
[g] The absorption; [h] The number of rotatable bonds.

4 Conclusion

In this work three hydroxy substituted 5-phenylazo-3-cyano-6-hydroxy-4-methyl-1-propyl-2-piridones were synthesized and their structures have been confirmed by ATR-FTIR, NMR and UV-Vis data. The ATR-FTIR and NMR spectra confirmed that synthetized dyes **1**–**3** exist in hydrazone tautomeric form, in solid state, as well as in DMSO-d_6 solution. The UV-Vis analysis in ethanol showed that all investigated dyes have one absorption maximum ascribed to the hydrazone tautomer. The antioxidant assay evinced that synthesized azo dyes **1-3** have excellent antioxidant properties comparing to antioxidant ability of ascorbic acid. Furthermore, IC_{50} values of dyes **2** and **3** were lower than IC_{50} value of ascorbic acid indicating remarkable antioxidant properties. The last, but not the least, ADME evaluation *in silico* has shown that all investigated compounds may be orally bioavailable with no permeation to the blood brain barrier.

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