

IN VITRO ODREĐIVANJE ANTIOKSIDATIVNE AKTIVNOSTI HALKONA NA BAZI FEROCENA

IN VITRO ANTIOXIDANT ACTIVITY EVALUATION OF FERROCENYL CHALCONES

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Derivati ferocena su poznati antioksidansi, antiparazitici, antitumorni, antivirusni, antibakterijski i antifungalni agensi. Pored primene u medicinskoj hemiji, derivati ferocena su od izuzetnog značaja u sintetičkoj organskoj hemiji, naročito u katalizovanim asimetričnim sintezama. Primenuju se i u elektrohemiji i hemiji polimera, kao aditivi u gorivima, kao hemosenzori u agrohemiji i biosenzori glukoze i aktivnih komponenata u molekularnoj elektronici. U cilju dizajniranja novih antioksidativnih agenasa, u ovom radu, sintetisano je pet ferocenilchalkona koji su u potpunosti strukturno okarakterisani određivanjem temperature topljenja, FT-IR, ¹H i ¹³C NMR spektroskopskim metodama. Sintetisani halkoni međusobno se razlikuju prema vrsti i položaju supstituenta na fenil-grupi u položaju 1 linearnog nezasićenog karbonilnog sistema. Potencijalna antioksidativna aktivnost ovih jedinjenja procenjena je primenom ABTS (2,2'-azinobis-(3-etilbenzotiazolin-6-sulfonska kiselina) metode i određivanjem IC₅₀ vrednosti najefikasnijih jedinjenja.

Ključne reči: Halkoni; Farmakološka aktivnost; ABTS metoda.

Ferrocene derivatives are known as antioxidants, antiparasitic, antitumor, antiviral, antibacterial and antifungal agents. In addition to applications in medicinal chemistry and drug design, ferrocene derivatives are of exceptional importance in synthetic organic chemistry, especially in catalytic asymmetric transformations. They are also used in electrochemistry and polymer chemistry, as additives in fuels, as chemosensors in agrochemistry and biosensors of glucose and active components in molecular electronics. To design new antioxidant agents, five ferrocenyl chalcones were synthesized, and fully characterized by melting points, FT-IR, ¹H and ¹³C NMR spectroscopic methods. The synthesized chalcones differ in the nature and the position of the substituent attached to the phenyl group in position 1 of the linear unsaturated carbonyl system. The potential antioxidant activity of the synthesized compounds was evaluated using the ABTS (2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) method and IC₅₀ values of the most effective compounds were further determined.

Key words: Chalcones; Pharmacological activity; ABTS method.

1 Introduction

Ferrocene and its derivatives represent the leading compounds for the global chemical enterprise due to its multiple applications that range from biomedical to materials science [1]. In addition, chalcones represent naturally occurring derivatives of the parent compound 1,3-diphenyl-2-propen-1-one, pertaining to the flavonoid family of organic compounds. According to the literature, chalcones and their corresponding heterocyclic analogs possess wide spectrum of pharmacological activities due to occurrence of highly reactive unsaturated carbonyl moiety in skeleton [2]. Among them, our focus has been placed on ferrocenyl chalcones as a framework for further derivatization, especially for obtaining drugs with higher efficiency toward devastating diseases (bacteria, malaria, cancer, neurobiological diseases and free radicals). In agreement with literature review, classes of

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ferrocenyl chalcones are primarily of two types: type 1, where the carbonyl group is at the α -position adjacent to the ferrocenyl ring, and type 2, where the carbonyl group is at the α -position adjacent to the phenyl ring. Henry demonstrated that novel functionalized type 2 ferrocenyl chalcones were effective against three kinds of clinically isolated drug resistant *S. aureus*, and against other non-resistant clinically isolated and laboratory-adapted Gram-positive bacteria [3]. Wu demonstrated that 1-(3-pyridyl)-3-ferrocenyl-2-propen-1-one and 1-ferrocenyl-3-(4-nitrophenyl)-2-propen-1-one with IC₅₀ of 4.5 and 5.1 mM, respectively, were the most active against a chloroquine resistant strain of *P. falciparum* [4]. The results of QSAR studies, performed to find quantitative relationship between fungicidal/nematicidal activity and chemical structure of synthesized ferrocenyl chalcones, demonstrated that the position of substituent on the phenyl ring in the molecule plays an important role in pharmacological activity of these compounds. Namely, (2*E*)-1-(5-chloro-2-hydroxyphenyl)-3-ferrocenyl-prop-2-en-1-one was found to be most active against *S. rolfsii*, while (2*E*)-1-(4-bromophenyl)-3-ferrocenyl-prop-2-en-1-one showed highest activity against *A. solani*. Concerning nematicidal activity, (2*E*)-1-(3-bromophenyl)-3-ferrocenyl-prop-2-en-1-one was the most potent [2]. Results of *in vitro* antiproliferative activity and SAR study of various ferrocenyl chalcones showed that the aldehyde unit of ferrocenyl chalcones containing halogens or dimethyl substituents was the most effective structural moiety against MDA-MB-231 cells [5]. Smit and coworkers demonstrated that aminoferrocenyl-chalcone amide containing a piperazinyl linker, possessed increased activity against three cancer cell lines: TK-10 (human kidney renal cell adenocarcinoma, UACC-62 (melanotic melanoma), and MCF-7 (breast cancer), compared to the reference drug, parthenolide [6]. Oxidative stress in biological systems could be defined as a complex process characterized by a disproportion between the production of free radicals and the ability of the body to eliminate these reactive species through the use of endogenous and exogenous antioxidants. During the metabolic processes, a wide diversity of reactions take place, where the promoters are the reactive oxygen species, such as hydrogen peroxide and the superoxide radical anion, among others. A biological system in the presence of an excess of reactive oxygen species could perform pathologies, from cardiovascular diseases to the promotion of cancer [7]. Meng et al. demonstrated that ferrocenyl-containing curcumin analogues can protect DNA against Cu²⁺/GSH induced oxidation, and scavenge free radicals in protecting DNA against AAPH induced oxidation. These analogues, which within their chemical structure contain powerful antioxidative group such as ferrocenyl group, provide a higher antioxidant activity than the traditional hydroxyl involved curcumin analogues [8]. Singh et al. demonstrated that ferrocene appended chalcone linked triazole allied organosilatrane possess high radical scavenging efficacy [9]. Moreover, other potential applications of investigated derivatives include molecular materials, redox-sensors, and polymers [1]. Our goal in this paper is to highlight the synthesis and antioxidant activity of ferrocenyl chalcones (Scheme 1) with particular prominence to the most active derivatives which represent an interesting starting point for the synthesis of some new pharmacologically active compounds.

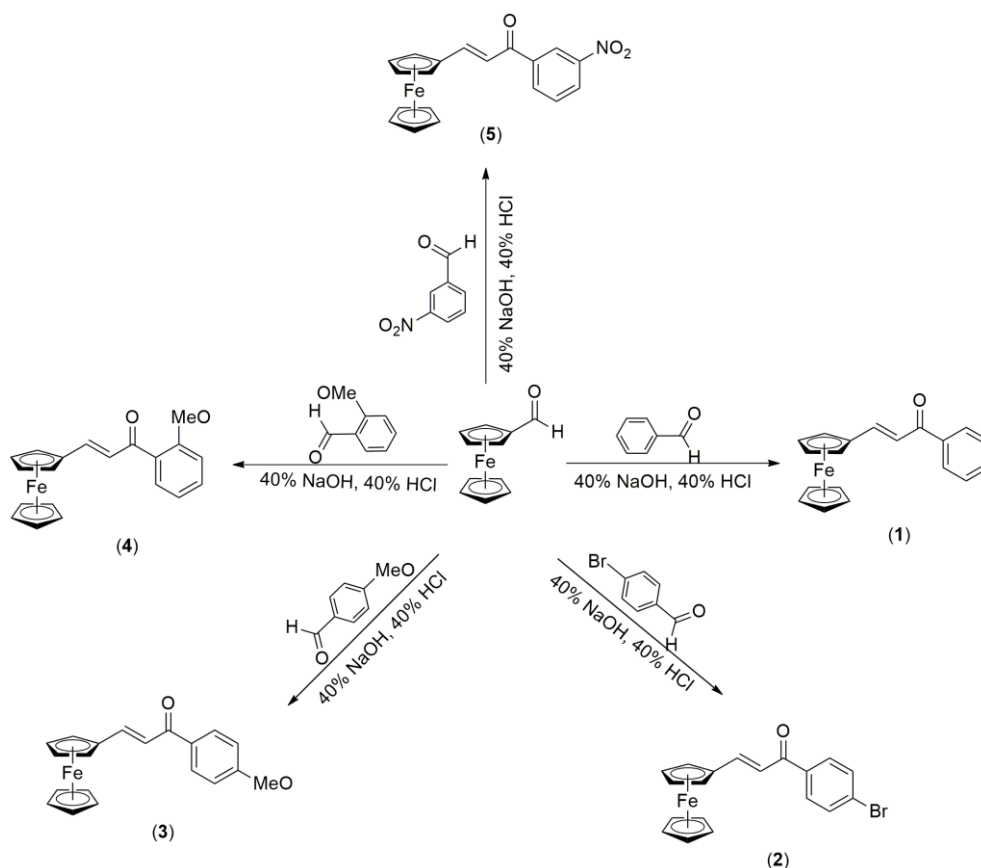
2 Experimental section

In order to study the influence of the chemical structure on the antioxidant activity of substituted ferrocenyl-chalcones, five compounds were synthesized. Ferrocenyl chalcones (**1–5**) were prepared according to modified literature procedure [10]. Synthetic pathway is illustrated on Scheme 1 and full structural characterization as melting points, FT-IR/ATR, ¹H and ¹³C NMR spectra are given. In addition, their antioxidant activity was determined using the ABTS method.

2.1 General procedure for the synthesis of substituted ferrocenyl chalcones

An equimolar amounts of ferrocene-carbaldehyde and the corresponding acetophenone (unsubstituted acetophenone, *p*-bromoacetophenone, *p*-methoxyacetophenone, *o*-methoxyacetophenone and *m*-nitroacetophenone) were dissolved in dry ethanol and the reaction mixture was stirred for 30 min at room temperature (Scheme 1). To the obtained reaction mixture an aqueous solution of sodium hydroxide (40% w/w) was added dropwise during which the reaction mixture turned violet–red. The solution was stirred for 6 h and kept in a freezer overnight. The mixture was

poured onto crushed ice and neutralized with diluted HCl (40%). The obtained precipitate was filtered and washed six times with water and recrystallized from methanol [10].



Scheme 1. Synthesis of the substituted ferrocenyl-chalcones.

2.2 Methods for the characterization of the synthesized compounds

The FT-IR/ATR spectra of all synthesized compounds were recorded in the wavelength range 400–4000 cm^{-1} using a Thermo Scientific Nicolet iS10 apparatus. ^1H and ^{13}C NMR spectra of compounds **1–3** were recorded on a Bruker Ascend 400 apparatus at room temperature in deuterated chloroform (CDCl_3), while spectra of compounds **4** and **5** were recorded in deuterated dimethyl sulfoxide ($\text{DMSO}-d_6$). All melting points were determined on Electrothermal apparatus. Elemental analysis of all studied compounds was performed using a microanalyzer of the element Elemental Vario EL III.

1-(Phenyl)-3-ferrocenylprop-2-en-1-one (1): Red-brown solid. Yield: 76%; m.p. 125–127°C, FT-IR/ATR (ν/cm^{-1}): 3068, 1660, 1600, 1589, 1577, 1469, 1449, 1410, 1393, 1376, 1356, 1301, 1290, 1248, 1220, 1190, 1177, 1103, 1061, 1043, 1036, 1028, 1012, 979, 970, 937, 848, 820, 647, 620, 607, 530, 492, 471; ^1H NMR (400 MHz, CDCl_3 , δ/ppm): 7.98 (d, 2H, $J = 7.6$ Hz, Ar-H), 7.76 (d, 1H, $J = 15.6$ Hz), 7.58–7.47 (m, 3H, Ar-H), 7.13 (d, 1H, $J = 15.2$ Hz), 4.60 (s, 2H, ferrocenyl), 4.49 (s, 2H, ferrocenyl), 4.18 (s, 5H, ferrocenyl); ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 189.9 (C=O), 146.8, 138.6–128.3 (aromatic C-atoms), 119.2, 79.1, 77.3, 77.0, 76.7, 71.3, 69.8, 69.0, 29.7.

1-(4-Bromophenyl)-3-ferrocenylprop-2-en-1-one (2): Red-brown solid. Yield: 84%; m.p. 155–158°C, FT-IR/ATR (ν/cm^{-1}): 3083, 1654, 1588, 1581, 1559, 1481, 1398, 1376, 1357, 1321, 1300, 1288, 1249, 1219, 1179, 1105, 1067, 1048, 1028, 1005, 980, 970, 937, 862, 808, 743, 727, 680, 658, 618, 537, 490, 475, 457; ^1H NMR (400 MHz, CDCl_3 , δ/ppm): 7.85 (d, 2H, $J = 8.0$ Hz, Ar-H), 7.77 (d, 1H, $J = 15.2$ Hz), 7.63 (d, 2H, $J = 7.6$ Hz), 7.07 (d, 1H, $J = 15.2$ Hz), 4.60 (s, 2H, ferrocenyl), 4.51 (s, 2H, ferrocenyl), 4.19 (s, 5H, ferrocenyl); ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 189.7 (C=O), 147.6, 137.5–129.8 (aromatic C-atoms), 118.4, 79.0, 77.3, 77.0, 76.7, 71.6, 69.9, 69.1, 29.7.

1-(4-Methoxyphenyl)-3-ferrocenylprop-2-en-1-one (3): Red-brown solid. Yield: 78%; m.p. 140–143°C, FT-IR/ATR (ν/cm^{-1}): 3082, 3010, 2936, 2837, 1648, 1566, 1511, 1461, 1438, 1422, 1393, 1357, 1328, 1301, 1288, 1259; ^1H NMR (400 MHz, CDCl_3 , δ/ppm): 8.01 (d, 2H, $J = 8.0$ Hz, Ar-H), 7.74 (d, 1H, $J = 8.0$ Hz), 7.15 (d, 1H, $J = 15.2$ Hz), 6.98 (d, 2H, $J = 8.0$ Hz, Ar-H), 4.59 (s, 2H, ferrocenyl), 4.48 (s, 2H, ferrocenyl), 4.18 (s, 5H, ferrocenyl), 3.89 (s, 3H, $-\text{OCH}_3-\text{C}_6\text{H}_4$); ^{13}C NMR (100 MHz, CDCl_3 , δ/ppm): 188.1 (C=O), 163.1, 145, 8, 136.5–128.8 (aromatic C-atoms), 118.9, 113.7, 77.3, 77.0, 76.7, 71.2, 69.7, 68.9, 55, 529.7.

1-(2-Methoxyphenyl)-3-ferrocenylprop-2-en-1-one (4): Black solid. Yield: 66%; m.p. 98–100°C, FT-IR/ATR (ν/cm^{-1}): 3378, 1656, 1596, 1485, 1464, 1435, 1358, 1289, 1243, 1179, 1163, 1016, 805, 754, 594, 487; ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ/ppm): 12.17 (s, 4H), 7.6–7.49 (m, 6H), 7.14 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.00 (d, 2H, $J = 7.2$ Hz, Ar-H), 4.69 (s, 1H), 4.48 (s, 1H), 4.16 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, δ/ppm): 199.3, 172.6, 170.2, 161.7, 158.8, 157.7, 137.1, 134.3, 130.1, 128.3, 120.7, 112.9, 71.9, 70.2, 69.5, 56.4, 32.2, 21.6.

1-(3-Nitrophenyl)-3-ferrocenylprop-2-en-1-one (5): Black solid. Yield: 74%; m.p. > 300 °C, 3370, FT-IR/ATR (ν/cm^{-1}): 3091, 1657, 1593, 1574, 1477, 1435, 1409, 1348, 1293, 1245, 1216, 1104, 1093, 1041, 1029, 1001, 969, 934, 815, 738, 707, 675, 639, 616, 479; ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ/ppm): 8.74 (s, 2H), 8.51 (d, 2H, $J = 7.2$ Hz, Ar-H), 8.47 (d, 2H, $J = 8$ Hz, Ar-H), 7.85 (t, 2H, $J = 7.6$ Hz), 7.78 (s, 1H), 7.75 (s, 1H), 7.5 (s, 1H), 7.47 (s, 1H), 4.91 (s, 5H), 4.6 (s, 5H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, δ/ppm): 186.9, 148.9, 148.8, 139.4, 134.9, 130.9, 127.6, 123.1, 118.6, 79.2, 72.2, 70.2, 70.1, 40.6, 39.4.

2.3 Determination of antioxidant activity

The antioxidant activity of the investigated compounds **1–5** was determined using ABTS radical-scavenging assay. A stock solution of the $\text{ABTS}^{\bullet+}$ 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 the recorded absorbance at 734 nm was 0.700 ± 0.02 . Subsequently, 20 μL of the methanolic solutions of the investigated compounds (5 mM) were mixed with 2 mL of the ABTS radical solution, shaken and stored in the dark for 10 min. Afterward the absorbance was measured at 734 nm. Each test was done in triplicate. The inhibition percentage of $\text{ABTS}^{\bullet+}$ was calculated using the formula:

$$\text{Inhibition} = ((\text{Ac}-\text{As})/\text{Ac}) 100 \quad (1)$$

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 ability of the most promising derivatives **2** and **3** was further evaluated by determination of the IC_{50} values. The methanolic solutions of the corresponding compound and ascorbic acid was prepared in the concentration range 5–0.5 mM. IC_{50} values were calculated and presented with standard deviation ($\pm\text{SD}$) [11].

3 Results and discussion

In the last decades, the integration of an organometallic moiety with bioactive organic frameworks is becoming an attractive approach to investigate the potential pharmacological activity of newly compounds for the treatment of various diseases. Besides the complexes of transition metals such as Pt, Ru, Os, and Ir known for anti-cancer activity, bis(cyclopentadienyl)iron(Fc, ferrocene) is a widely used structure in biomedical chemistry. According to literature review, ferrocene derivatives represent a useful structural feature in antioxidants. Zhao et al. demonstrated that aianthoidol ferrocene possess good radical scavenging activity for AAPH^{\bullet} (2,2'-azobis(2-amidinopropane)-dihydrochloride) and $\text{ABTS}^{\bullet+}$ radicals, while Štimac et al. demonstrated that the adamantly ferrocene possess antioxidant activity toward DPPH \bullet the (1,1-diphenyl-2-picrylhydrazine) radical. Tabrizi et al. demonstrated that derivatives obtained by a condensation reaction between the amino ferrocene and hydroxycinnamic acids, that is, caffeic acid (CA) and ferulic acid (FA) possess good

free radical scavenging activity toward the numbers of free radicals [12]. Inspired by all these results, we determined the potential antioxidant activity of the ferrocenyl chalcones using the ABTS method. The obtained results were compared with the values for ascorbic acid, which was used as a standard. Based on the obtained results, it can be concluded that the nature and position of the substituent on the phenyl nucleus significantly influence the value of the antioxidant activity (Figure 1). Among the analyzed ferrocene derivatives (**1–5**), only compounds **2** and **3**, which have a strong electron-donor (methoxy group) or electron-acceptor substituent (bromine atom) in the *p*-position of the phenyl nucleus, have significant activity (51.8 and 74.8%, respectively). Compounds **1** (with an unsubstituted phenyl nucleus) and **5** (with a nitro group in the *m*-position of the phenyl nucleus) show moderate activity (22.5 and 33.1%, respectively), while compound **4** with a methoxy group in the *o*-position has weak antioxidant activity (5.1%).

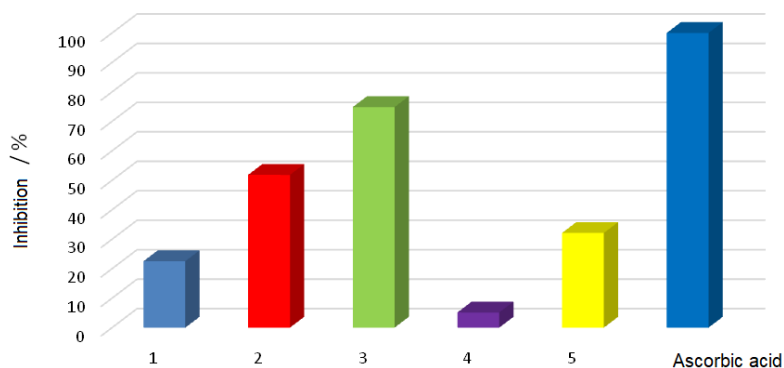


Figure 1. Antioxidant activity of the ferrocenyl chalcones (**1–5**) using the ABTS method.

Minić Jančić et al. demonstrated that some substituents in different positions of the phenyl nucleus may significantly reduce the antioxidant activity of the investigated derivatives [13]. The influence of these substituents on antioxidant activity could be complex and it further depends on their electron donating and accepting capabilities, as well as on the conformation of the molecule. A voluminous *o*-methoxy group makes it difficult for the molecule to bind the free radicals and thus disable electron exchange. Contrary, when methoxy group is in *para* position, steric interferences are reduced, hence free radical scavenging is increased. In addition, the positive resonant effect of the methoxy group results in the formation of a more stable radical form and higher antioxidant activity [13]. In order to determine IC_{50} values of the most active compounds **2** and **3**, i.e. concentrations required for inhibition of initial ABTS radical concentration by 50%, antioxidant activities are determined in the range of 5–0.5 mM (Figure 2). In general, high IC_{50} values indicate low antioxidant activity. The obtained IC_{50} values for compounds **2** and **3** are 2.44 and 2.11 mM, respectively, and are higher compared to the value for ascorbic acid (1.45 mM).

4 Conclusion

In order to create new pharmacologically active compounds, potential antioxidants, in this work, five ferrocenyl chalcones were synthesized and fully structurally characterized by melting points, FT-IR/ATR, 1H and ^{13}C NMR spectroscopic methods. The synthesized compounds differ from each other according to the nature and position of the substituent attached to the phenyl group in position 1 of the linear unsaturated carbonyl system. Results of the evaluation of antioxidant activity obtained using ABTS assay indicate that the nature and position of the substituent on the phenyl nucleus significantly influence the antioxidant activity. Among the analyzed ferrocenyl chalcones (**1–5**), only compounds **2** and **3**, bearing a strong electron-donor (methoxy group) or electron-acceptor substituent (bromine atom) in the *p*-position of the phenyl nucleus, possess moderate activity. The obtained IC_{50} values for compounds **2** and **3** are 2.44 and 2.11 mM, respectively. It has been shown that ferrocenyl chalcones exhibit less potent activity when compared to the ascorbic

acid, wherein compounds **2** and **3** could be considered as prominent antioxidant molecules. The general conclusion based on these evaluations is that the ferrocenyl chalcones represent an interesting starting point for the synthesis of some new pharmacologically active compounds.

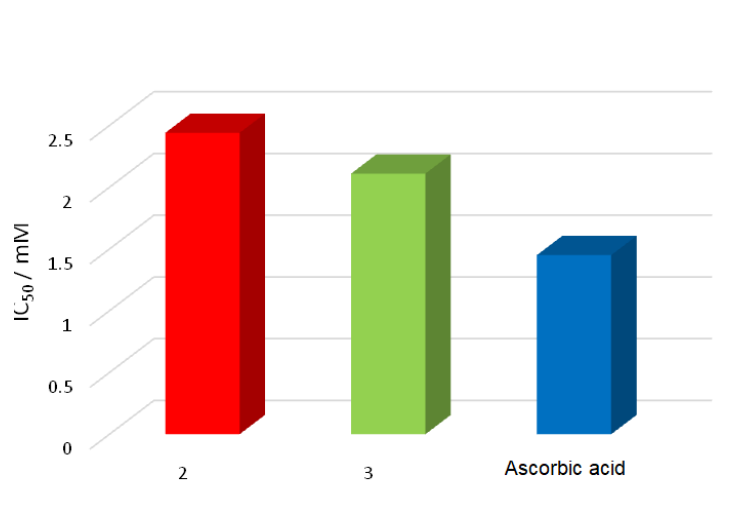


Figure 2. IC₅₀ value of compounds **2**, **3** and ascorbic acid.

4.1 Acknowledgement

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