Synthesis, characterization, and antimicrobial activity of novel 2-ferrocenyl-1,3-thiazolidin-4-thiones

Todosijević Anka[1*], Jančić Minić Aleksandra[2], Mihailović Vladimir[3], Srećković Nikola[3]

1- University of Niš, Faculty of Agriculture, Kosančićeva 4, 37000 Kruševac, Serbia

2- University of Priština, Faculty of Technical Sciences, Knjaza Miloša 7, 38220 Kosovska Mitrovica, Serbia

3- University of Kragujevac, Faculty of Science Department of Chemistry, Radoja Domanovića 12, 34000 Kragujevac, Serbia

ABSTRACT

Synthesis of five novel 2-ferrocenyl-1,3-thiazolidin-4-thiones has been achieved in good to excellent yields through the treatment of 2-ferrocenyl-1,3-thiazolidin-4-ones with Lawesson's reagent. The reaction was performed by refluxing the reactants mixture in toluene overnight. All prepared compounds were characterized by the IR and NMR spectral data. Further, the obtained products were evaluated for their antibacterial and antifungal activity.

Keywords: Ferrocene, 2-Ferrocenyl-1,3-thiazolidin-4-thiones, 2-Ferrocenyl-1,3-thiazolidin-4-ones, Characterization, Antimicrobial activity.

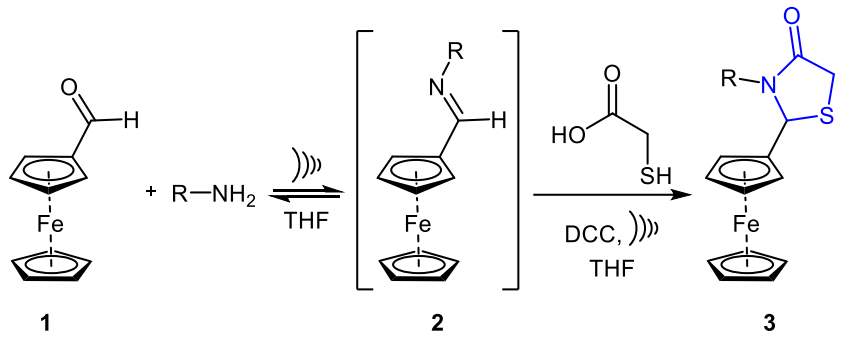
Todosijević Anka*: anka.pejovic@gmail.com
Minić Aleksandra: aleksandra.minic.989@gmail.com and aleksandra.minic@pr.ac.rs
Mihailović Vladimir: vladimir.mihailovic@pmf.kg.ac.rs
Srećković Nikola: nikola.sreckovic@pmf.kg.ac.rs

Introduction

Since the middle of the last century, antimicrobial agents have been efficiently used in health care. However, recent success in the application of antibiotics in infections treatment has been eroded by the increased resistance of bacteria. Therefore, there is a permanent interest in the development of novel compounds that exhibit antimicrobial activity (Hawkey, 2008; Cantón, 2009). Ferrocene derivatives have been demonstrated to possess a broad spectrum of biological activity, including antibacterial (Damljanović et al., 2009; Li et al., 2013), antifungal (Rubbiani, 2016), anti-inflammatory (Shinde et al., 2018), antitumor (Staveren and Metzler-Nolte, 2004; Fouda, 2007; Hillard, 2010; Biot, 2000) and anti-HIV (Kondapi et al., 2006) activity. In addition, due to the favorable electronic properties of ferrocene and its easy functionalization, these substances have been found many applications in materials science, including sensors (Labande and Astruc, 2000; Labande et al., 2002; Daniel et. al., 2003, Astruc et. al., 2004, Armada et al., 2006; Ornelas, 2007; Astruc, 2008; Ornelas et al., 2009; Djeda, 2010), catalysts (Astruc, 2008; Wei et al. 2002, Zhang et al., 2002; Ornelas et al., 2007; Diallo et al., 2007; Ornelas et al., 2008), electroactive materials (Daniel et al., 2006, Astruc et al., 2008; Ornelas et al., 2008; Wang et al., 2009; Astruc et al., 2009; Megiatto et al., 2010) and aerospace materials (Ansari et al., 2018; Neuenfeldt et al., 2011).

On the other hand, the chemistry of thiazolidinone ring is of substantial interest as it represents is a core structure in numerous synthetic medicaments displaying a wide variety of biological activities (Makwana and Malani, 2017). The thiazolidinone scaffold is also found in various natural products, especially thiamines, molecules possessing cardiac and glycemic benefits such as troglitazone (Ghazzi et al., 1997) and many metabolic products of fungi and primitive marine animals, including 2-(aminoalkyl)-4-carboxylic acids (Scmidt et al., 1987). A number of thiazolidinone derivatives have displayed various biological activities such are antidiabetic (Verma and Thareja, 2016), anticancer (Szychowski et al., 2017), anticonvulsant (Mishchenko et al., 2020), antimicrobial (Viswajanani et al., 2005), anti-HIV (Rawal et al., 2005), PAF antagonist (Tanabe et al., 1991), COX inhibitory (Ottana et al., 2002), tumor necrosis factor-α antagonist (Voss et al., 2003) and antioxidant (Shih and Ke, 2004). Besides, thiazolidinone derivatives are of interest in a wide range of pharmaceutical, agrochemical,

coordination, medicinal, and organic chemistry applications (Chaves et al., 2014; Corrêa et al., 2016; Deng et al., 2011).



Scheme 1. Synthesis of *N*-substituted 2-ferrocenyl-1,3-thiazolidin-4-ones **3** (Pejović et al., 2014).

Several years ago, our team reported an easy and efficient method for the synthesis of the novel thiazolidinone derivatives - 2-ferrocenyl-1,3-thiazolidin-4-ones **3** (Scheme 1) (Pejović et al., 2014). These heterocycles that showed strong anxiolytic activity also demonstrated great initial results in the synthesis of another ferrocene containing thiazolidinones (Pejović et al., 2018). Bearing all previously mentioned in mind, we planned to synthesize 2-ferrocenyl-1,3-thiazolidin-4-thiones using 2-ferrocenyl-1,3-thiazolidin-4-ones **3** as starting material. Thus, in this research, we put emphasis on the synthesis, assignment of ^{1}H and ^{13}C NMR spectral data of novel 2-ferrocenyl-1,3-thiazolidin-4-thiones as well as examination of their antimicrobial activity.

Experimental

Reagents and chemicals

All chemicals were commercially available and used as received, except the solvents, which were purified by distillation. Chromatographic separations were carried out using silica gel 60 (Merck, 230–400 mesh ASTM), whereas silica gel 60 on Al plates, layer thickness 0.2 mm (Merck) was used for TLC. Melting points (uncorrected) were determined on a Mel-Temp capillary melting points apparatus, model 1001. The ^{1}H and ^{13}C NMR spectra of the samples in $CDCl_3$ were recorded on a Varian Gemini (200 MHz) (^{1}H at 200 MHz, ^{13}C at 50 MHz) NMR

spectrometer. Chemical shifts are expressed in δ (ppm), relative to residual solvent protons as the internal standard ($CDCl_3$: 7.26 ppm for ^1H and 77 ppm for ^{13}C). IR measurements were carried out with a Perkin–Elmer FTIR 31725-X spectrophotometer.

2-Ferrocenyl-1,3-thiazolidin-4-ones (3a-e)

2-Ferrocenyl-1,3-thiazolidin-4-ones (**3a-e**) were synthesized according to the previously described procedure (Pejović et al., 2014).

General procedure for the synthesis of 2-ferrocenyl-1,3-thiazolidin-4-thiones (5a-e)

A toluene solution of the suitable 2-ferrocenyl-1,3-thiazolidin-4-one (1 mmol), obtained according to a previously reported procedure (Pejović et al., 2014), was heated under stirring with Lawesson's reagent (1 mmol) overnight. The solvent was then evaporated, and the residue extracted with dichloromethane (three 20 mL portions). After drying overnight (anhydrous Na_2SO_4), the solvent was evaporated and the crude product purified by column chromatography (SiO_2, hexane/ethyl acetate = 8: 2).

3-Butyl-2-ferrocenyl-1,3-thiazolidin-4-thione (**5a**). Orange solid. Yield 88%; m.p. = 119 ºC; IR (neat): ν_{max} = 2952, 1181 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, ppm): δ 5.88 (br t, 1H), 4.50 – 4.44 (m, 1H), 4.37 – 4.17 (m, 5H), 4.25 (s, 5H), 3.94 – 3.74 (m, 1H), 3.35 – 3.13 (m, 1H), 1.68 – 1.12 (m, 4H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 195.3, 83.6, 71.5, 70.1, 70.0, 69.3, 68.9, 68.1, 47.5, 45.2, 27.7, 20.1, 13.7.

2-Ferrocenyl-3-hexyl-1,3-thiazolidin-4-thione (**5b**). Orange solid. Yield 90%; m.p. = 92 ºC; IR (neat): ν_{max} = 2928, 1176 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, ppm): δ 5.88 (br t, 1H), 4.51 – 4.41 (m, 1H), 4.36 – 4.05 (m, 6H), 4.24 (s, 5H), 3.90 – 3.70 (m, 1H), 3.35 – 3.15 (m, 1H), 1.65 – 1.07 (m, 8H), 0.84 (t, *J* = 6.5 Hz, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 195.1, 83.5, 71.4, 70.1, 70.0, 69.2, 68.8, 68.0, 47.7, 45.2, 31.1, 26.4, 25.5, 22.4, 13.9.

2-Ferrocenyl-3-octyl-1,3-thiazolidin-4-thione (**5c**). Orange solid. Yield 88%; m.p. = 78 ºC; (neat): ν_{max} = 2920, 1203 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, ppm): δ 5.87 (br t, 1H), 4.49 – 4.31 (m, 1H), 4.35 – 4.14 (m, 6H), 4.25 (s, 5H), 3.92 – 3.66 (m, 1H), 3.37 – 3.13 (m, 1H), 1.74 – 1.04

(m, 12H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 195.3, 83.6, 71.5, 70.1, 70.0, 69.3, 68.8, 68.1, 47.8, 45.2, 31.7, 29.0, 26.8, 25.6, 22.6, 14.1.

2-Ferrocenyl-3-(*m*-tolyl)-1,3-thiazolidin-4-thione (**5d**). Orange solid. Yield 65%; m.p. = 78 ^{o}C; IR (neat): ν_{max} = 2956, 1165 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 7.35 – 7.29 (m, 2H), 6.93 – 6.83 (m, 2H), 6.16 (br s, 1H), 4.36 – 4.07 (m, 4H), 4.25 (s, 5H), 3.86 (d, *J* = 10.3 Hz, 1H), 3.45 (d, *J* = 10.3 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 198.4, 139.6, 129.2, 128.6, 127.9, 83.3, 74.5, 70.7, 69.7, 69.1, 68.7, 67.5, 45.7.

2-Ferrocenyl-3-(*p*-tolyl)-1,3-thiazolidin-4-thione (**5e**). Yield 60%, brown oil; IR (neat): ν_{max} = 2917, 1168 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 7.09 – 6.93 (m, 2H), 6.90 – 6.68 (m, 2H), 6.10 (br s, 1H), 4.55 – 4.36 (m, 4H), 4.23 (s, 5H), 3.84 (d, *J* = 10.3 Hz, 1H), 3.55 (d, *J* = 10.3 Hz, 1H), 2.77 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 195.24, 158.18, 130.07, 129.59, 113.86, 83.38, 71.96, 70.23, 70.19, 69.25, 68.91, 68.11, 49.70, 30.9.

Antimicrobial activity determination

The antimicrobial activity of newly synthesized compounds was tested on four bacterial (*Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, and *Salmonella enteritidis* ATCC 13076) and four fungal strains (*Candida albicans* ATCC 10231, *Fusarium oxysporum* FSB 91, *Aspergillus brasiliensis* ATCC 16404, and *Penicillium canescens* FSB 24). The microorganisms were obtained from the Institute of Public Health, Kragujevac, Serbia. For the determination of the antimicrobial activity of synthesized compounds, bacterial strains were grown on nutrient agar 24 h before the experiment, *C. albicans* was grown on sabouraud dextrose agar for 48 h, while molds were grown on potato glucose agar for 3–7 days before testing.

The minimal inhibitory concentrations (MICs) of tested compounds, standard antibiotic chloramphenicol, and antimycotic nystatin against selected bacterial and fungal strains were determined by the microdilution method in the sterile 96-well microtiter plates (A. Pejović et al., 2017). The different concentrations of compounds for antimicrobial testing were made in the sterile 96-well microtiter plates using Mueller–Hinton broth for bacterial strains and sabouraud dextrose broth for fungal growth. The evaluation of antibacterial and antifungal activities was

performed according to the CLSI recommendations (Clinical and Laboratory Standards Institute, 2012; Clinical and Laboratory Standards Institute, 2008a; Clinical and Laboratory Standards Institute, 2008b). Indicator resazurin was used for the detection of bacterial growth in microtiter plates, while the growth of fungi was monitored visually. The lowest concentration (in mg per mL) of tested compounds that inhibit visible bacterial or fungal growth was considered as minimal inhibitory concentration (MIC) value.

Results and Discussion

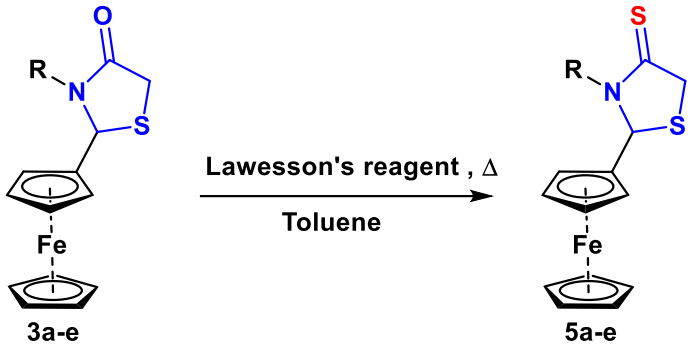
General synthesis of 2-ferrocenyl-1,3-thiazolidin-4-thiones 5a-e

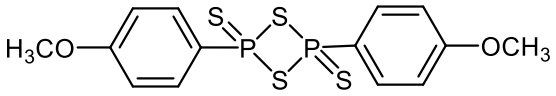
The obtaining of target compounds was conceived as the functionalization of the 2-ferrocenyl-1,3-thiazolidin-4-ones (Table 1, **3a-e**). It should comprise their thionation to afford the series of appropriate 2-ferrocenyl-1,3-thiazolidin-4-thiones. The thionation reaction of the thiazolidinone derivatives is commonly carried out in one of two reagents, phosphorus pentasulfide (P_4S_{10}) or Lawesson's reagent (LR) (Ozturk et al., 2008). In the last few years, scientists are claimed that Lawesson's reagent has advantages over P_4S_{10} in terms of requirements for excess P_4S_{10}, longer reaction time and higher temperature (Ozturk et al., 2008). Therefore, we considered synthesizing a series of novel ferrocene-containing thiazolidinthiones using Lawesson's reagent, and all in order to evaluate antimicrobial potential of the desired products.

The realization of this synthetic plan began with the preparation of the ferrocene-containing thiazolidinones, 2-ferrocenyl-1,3-thiazolidin-4-ones (Table 1, **3a-e**). A few years ago, we designed and optimized reaction conditions for their synthesis in high yields. The protocol involved a 25 min ultrasonic irradiation of the reaction mixture consisting of an amine, ferrocenecarboxaldehyde and thioglycolic acid in the ratio of 1/1/2. Thus, we synthesized the starting material by using this protocol. After the preparation of starting material, in the test experiment, the reaction between **3a** and Lawesson's reagent **4** was investigated. This reaction mixture was refluxed in the toluene during the night. After usual workup and column chromatography (SiO_2/hexane = 8:2, v/v), the desired thiazolidinthione **5a** was obtained in great

yield (88%, Table 1, entry 1). These results did not require additional screenings, so we accepted them as the optimal ones.

Table 1. The substrate scope of synthesis of 2-ferrocenyl-1,3-thiazolidin-4-thiones **5a-e**





Lawesson's reagent

4

Entry	R	Product	Yields* (%)
1	n-Butyl	**5a**	88
2	n-Hexyl	**5b**	90
3	n-Octyl	**5c**	88
4	*m*-Tolyl	**5d**	65
5	*p*-Tolyl	**5e**	60

*Isolated yield after column chromatography.

The scope of the reaction was investigated on five known ferrocene-containing thiazolidinones. The desired products **5a-e** have been obtained in moderate to excellent yields (up to 90%) after the purification by means of column chromatography. Structural characterization has been confirmed by spectroscopic methods (NMR, IR) for all prepared compounds.

We have observed that electronic properties, as well as steric hindrance of the substituents on the *N*-atom, have an influence on reaction outcomes (See Table 1). Regarding that, the products with the aliphatic group bonded to the *N*-atom were obtained in excellent yields (up to 90%). The hexyl derivatives were isolated in the highest yield (90%, Table 1, entry

2), while the butyl derivative was obtained in a slightly low yield (88%, Table 1, entry 1). These results can be explained by electron-donating effect of these groups. The octyl derivative deviates a little bit from this rule (88%, entry 3, Table 1). We believe that the volume of the octyl group influenced the reaction outcome. In addition, the electronic properties also have an influence on the reaction outcome since the thiazolidinones with a methyl group on the phenyl ring leads to moderate yields (60 and 65%, Table 1, entries 5 nad 4).

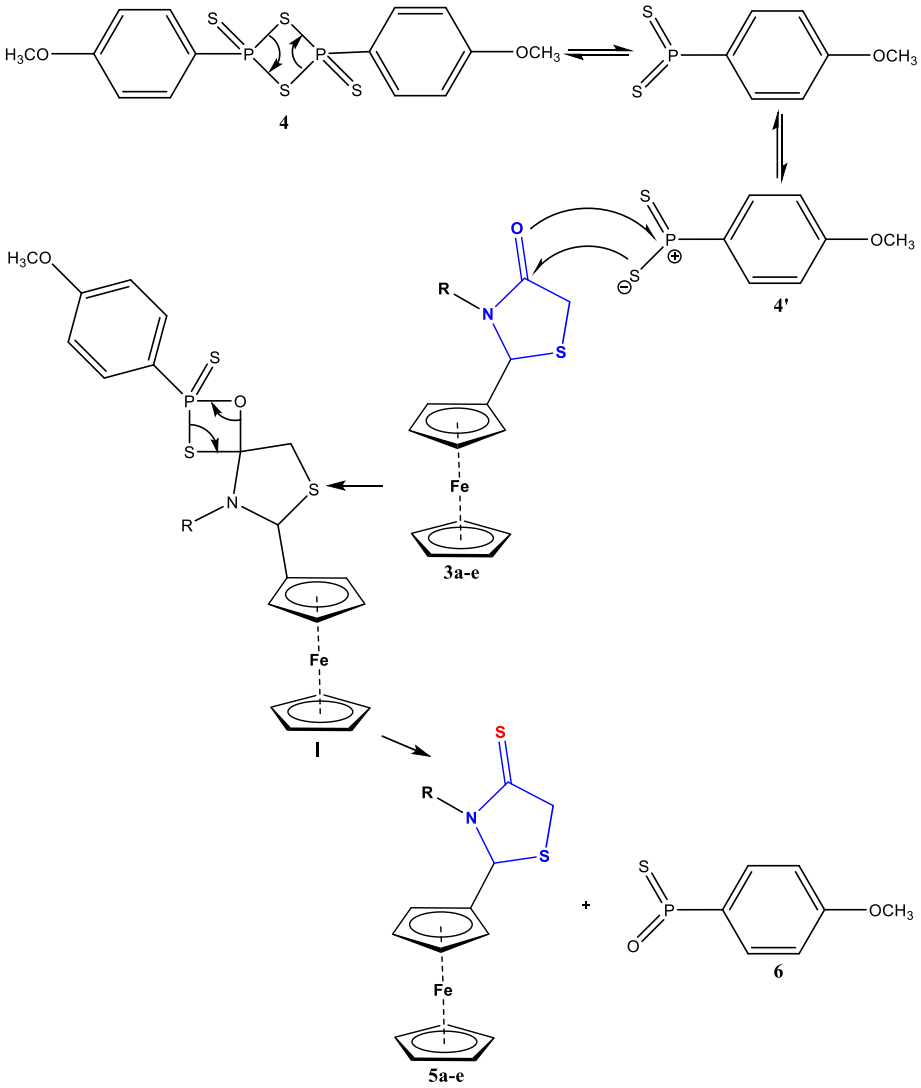
Several research groups investigated a mechanism of the thionation reaction of carbonyl compounds with Lawesson's reagent (Ozturk et al., 2008). Thus, a plausible reaction mechanism of thionation of ferrocene-containing thiazolidinone **3a** with Lawesson's reagent **4** is illustrated in Scheme 2. The first step of the mechanism of the reaction involves dissociation of Lawesson's reagent **4**. After dissociation, the reaction takes place through a two-step mechanism involving (i) a concerted cycloaddition between dithiophosphine ylide **4'** and the thiazolidinone compound **3a** to form a four-membered intermediate thiaoxaphosphetane **I** and (ii) a cycloreversion leading to the thiocarbonyl derivative **5a** and phenyl(thioxo)phosphine oxide **6**.

Spectral characterization

All synthesized ferrocene-containing thiazolidin-4-thiones **5a-e** were characterized by standard spectroscopic techniques (IR, ^{1}H-, and ^{13}C NMR). The collected data were in complete agreement with the proposed structures.

The main common feature of the IR spectra of five new thiazolidin-4-thiones **5a-e** is a strong band in range 1203-1165 cm^{-1}, which is attributed to the C=S stretching vibrations. NMR spectra utterly confirm the structures of synthesized compounds. Thus, in the ^{1}H NMR spectra of all thiazolidin-4-thiones **5a-e** signals of the cyclopentadienyl rings, protons appear at similar positions in the spectra (4.25-4.23 ppm for the unsubstituted, and 4.55 - 4.05 ppm for the substituted rings). The ^{1}H NMR spectra of **5a-e** also contain characteristic signals for aliphatic and aromatic protons. They are located in the expected regions of ^{1}H NMR spectra. In addition, in ^{1}H NMR spectra of **5a-e**, one signal appears at about 6.16-5.87 ppm, which corresponds to the methine protons of thiazolidinthione moiety. On the other hand, their ^{13}C NMR spectra lack the carbonyl carbon from the thiazolidinone ring resonances, thus distinguishing themselves from

the corresponding precursors **3a-e**. The ^{1}H-, and ^{13}C NMR spectra of **5a** are presented in Figure 1 and Figure 2.



Scheme 2. The plausible schematic mechanism for the synthesis of titled compounds **5**

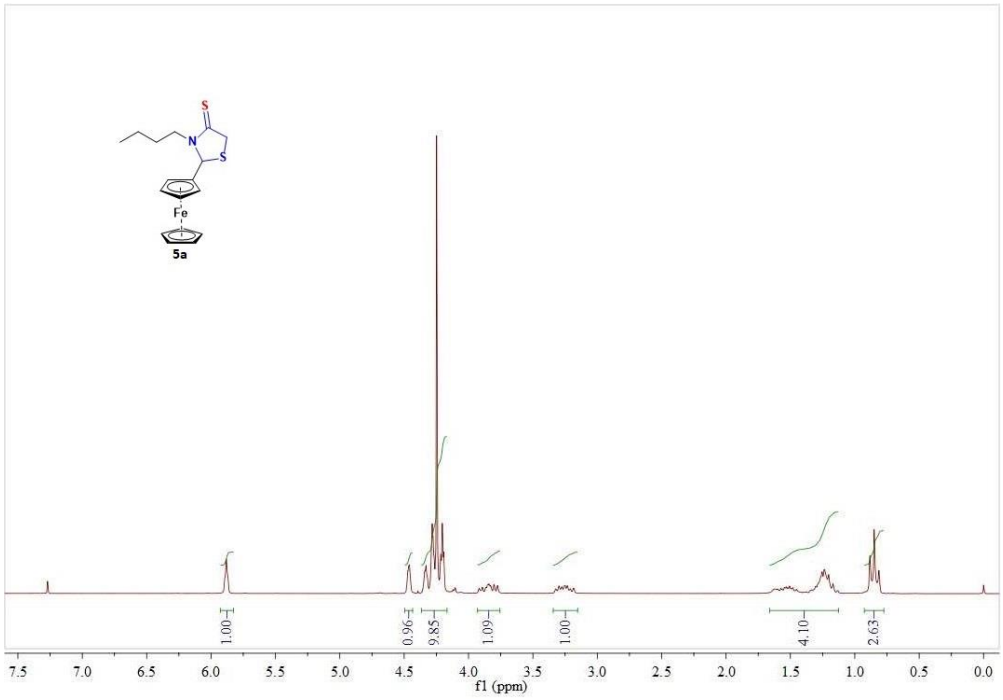


Figure 1. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of 5a

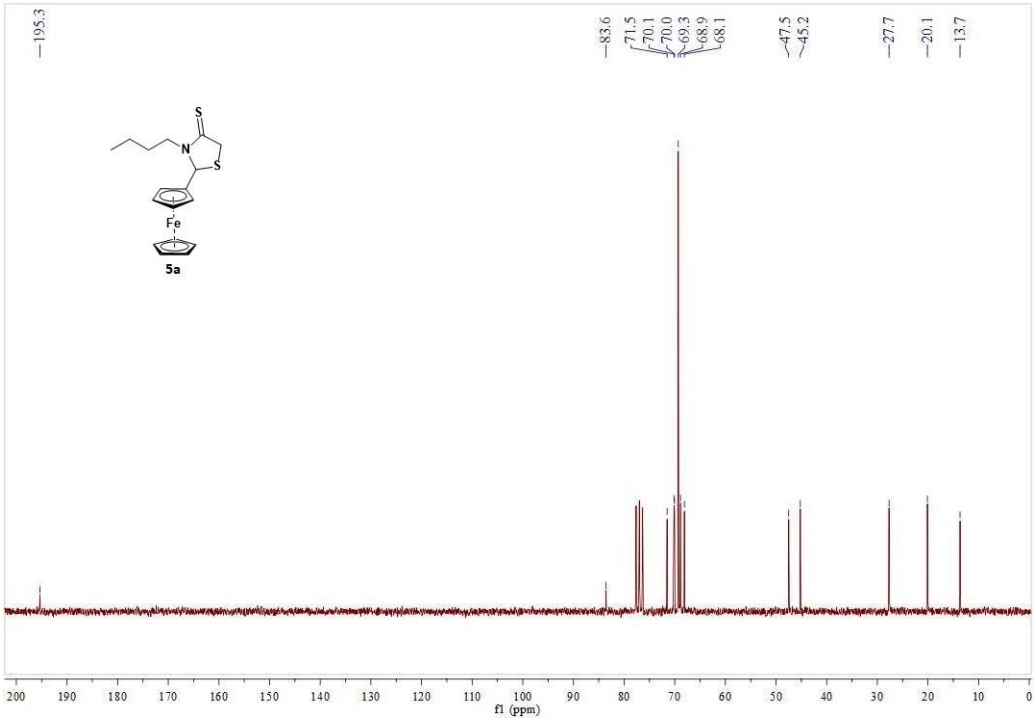


Figure 2. ^{13}C NMR (50 MHz, $CDCl_3$) spectrum of 5a

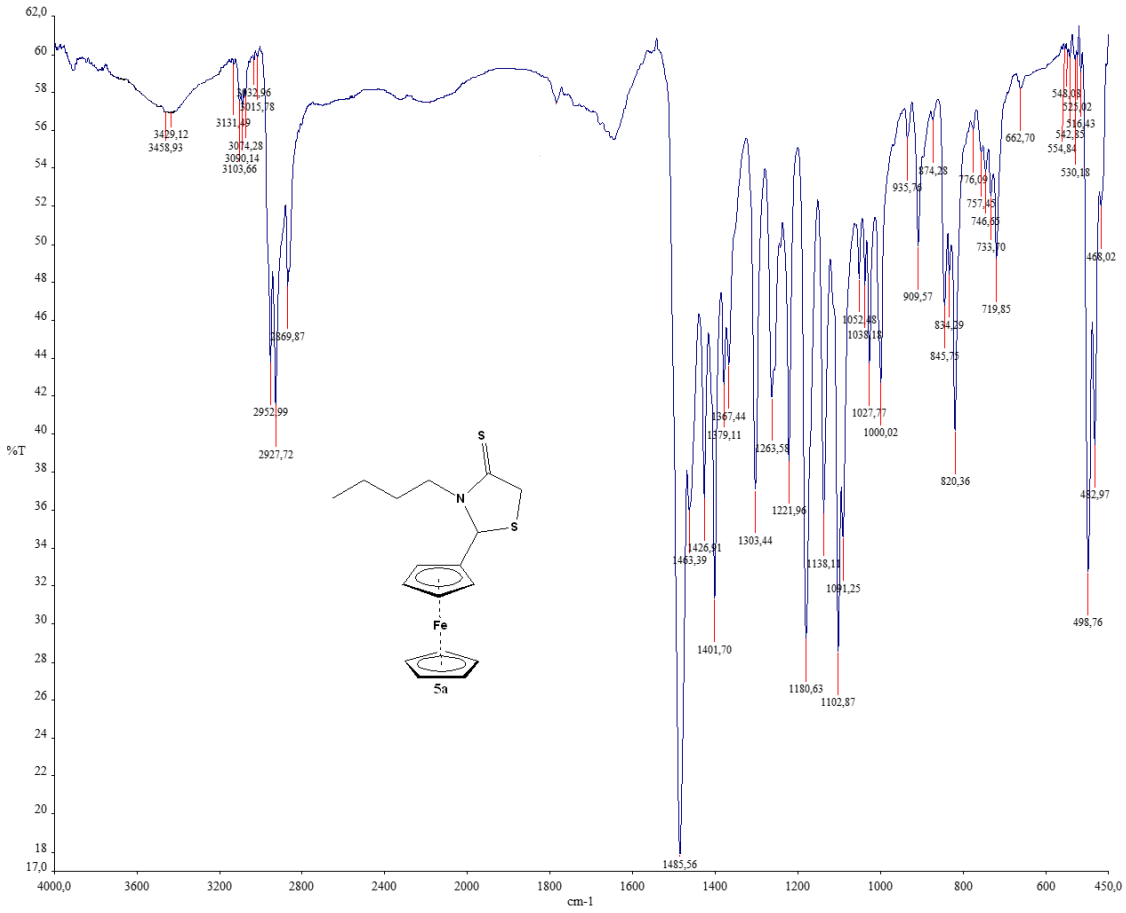


Figure 3. FTIR spectrum of 5a

Antimicrobial activity

All types of synthesized compounds showed a low to moderate antimicrobial activity against most of the tested bacterial and fungal species. The most active compounds against *E. faecalis* (0.5 mg/mL) were **5a** and **5d**, while the MIC values for other bacteria were ranged from 1 to 2 mg/mL for all tested compounds, as presented in **Table 2**. However, **5e** did not show antibacterial activity against *S. aureus* in applied concentration. The antifungal activity of synthesized compounds was slightly better than their antibacterial activity according to obtained MIC values in tests with bacteria and fungi. The most of synthesized compounds inhibited the growth of tested molds and *C. albicans* in a concentration of 1 mg/mL. The only exception was *A. brasiliensis*, as the most resistant fungi on tested compounds with MIC values of 2 mg/mL for all compounds. MIC values of synthesized compounds were compared with the well-known

antibiotic (chloramphenicol) and antimycotic (nystatin), whereby results indicated much higher antibacterial and antifungal activities than synthesized compounds.

Table 2. Antibacterial and antifungal activities of synthesized compounds

Bacteria		MIC[a] (mg/mL)					MIC (μg/mL)
		5a	**5b**	**5c**	**5d**	**5e**	Chloramphenicol
E. faecalis	ATCC 29212	0.5	1	2	0.5	2	0.625
E. coli	ATCC 25922	2	2	1	2	2	0.625
S. aureus	ATCC 25923	2	2	2	2	>2	5
S. enteritidis	ATCC 13076	2	2	2	2	2	2.5
Fungi							Nystatin
C. albicans	ATCC 10259	1	1	1	2	1	2.5
F. oxysporom	FSB 91	1	1	1	1	2	1.25
A. brasiliensis	ATCC 16404	2	2	2	2	2	1.25
P. canescens	FSB 24	1	2	1	1	1	2.5

[a]MIC- minimum inhibitory concentration.

Conclusion

Five novel 2-ferrocenyl-1,3-thiazolidin-4-thiones were prepared in moderate to excellent yields (up to 90%) using the standard synthetic protocol. The structures of all the obtained products were confirmed by the usage of standard spectroscopic methods.

The prepared heterocycles were tested against four bacterial (*Enterococcus faecalis*, *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella enteritidis*) and four fungal strains (*Candida albicans*, *Fusarium oxysporum*, *Aspergillus brasiliensis*, and *Penicillium canescens*) using the microdilution method. The results of the experiment indicated that synthesized heterocycles showed moderate to weak antibacterial activity against less number of examined microorganisms. Besides, it was found that *N*-butyl and *N*-*m*-tolyl derivatives are the most active compounds against *E. faecalis*. Furthermore, antifungal activity of the synthesized ferrocene

derivatives tested on the human pathogen yeasts *C. albicans*, *F. oxysporom*, and *P. canescens*, showed that the obtained compounds have more pronounced antifungal potential.

Acknowledgment

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Agreement No. 451-03-68/2020-14/200122).

Conflict-of-Interest Statement

None.

References

Ansari, M. F., Idrees, D., Hassan, Md. I., Ahmad, K., Avecilla, F., Azam, A. (2018). Design, synthesis and biological evaluation of novel pyridine-thiazolidinone derivatives as anticancer agents: Targeting human carbonic anhydrase IX. European Journal of Medicinal Chemistry, 144, 544–556.

Armada, M. P. G., Losada, J., Zamora, M., Alonso, B., Cuadrado, I.,. Casado, C. M. (2006). Electrocatalytical properties of polymethylferrocenyl dendrimers and their applications in biosensing. Bioelectrochemistry, 69, 65–73.

Astruc, D., Daniel, M. C., Ruiz, J. (2004). Dendrimers and gold nanoparticles as exo-receptors sensing biologically important anions. Chemical Communication, 2637–2649.

Astruc, D., Ornelas, C., Aranzaes, J. R. (2008). Ferrocenyl-terminated dendrimers: Design for applications in molecular electronics, molecular recognition and catalysis. Journal of Inorganic Organometallic Polymers and Materials, 18, 4–17.

Astruc, D., Ornelas, C., Ruiz, J. (2008). Metallocenyl dendrimers and their applications in molecular electronics, sensing, and catalysis. Accounts of Chemical Research, 41, 841–856.

Astruc, D., Ornelas, C., Ruiz, J. (2009). Dendritic molecular electrochromic batteries based on redox-robust metallocenes. Chemistry A European *J*ournal, 15, 8936–8944.

Biot, C., François, N., Maciejewski, L., Brocard, J., Poulain, D. (2000). Synthesis and antifungal activity of a ferrocene–fluconazole analogue. Bioorganic & Medicinal Chemistry Letters, 10, 839–841.

Cantón, R. (2009). Antibiotic resistance genes from the environment: a perspective through newly identified antibiotic resistance mechanisms in the clinical setting. Clinical Microbiology and Infecttion, 15, 20–25.

Chaves, J. D. S., Neumann, F. T., Francisco, T. M., Corrêa, C. C., Lopes, M. T. P., Silva, H., Fontes, A. P. S., Almeida, M. V. (2014). Synthesis and cytotoxic activity of gold(I) complexes containing phosphines and 3-benzyl-1,3-thiazolidine-2-thione or 5-phenyl-1,3,4-oxadiazole-2-thione as ligands. Inorganica Chimica Acta, 414, 85–90.

Clinical and Laboratory Standards Institute (2008a). Reference method for broth dilution antifungal susceptibility testing of yeasts (approved standard. document M27-A3). (3rd ed.).Wayne, PA.

Clinical and Laboratory Standards Institute (2008b). Reference method for broth dilution antifungal susceptibility testing of filamentous fungi (approved standard. document M38-A2.). (2nd ed.). Wayne, PA.

Clinical and Laboratory Standards Institute (2012). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically (approved standard. document M07-A9). (9th ed.). Wayne, PA.

Corrêa, R. S., Silva, M. M., Graminha, A. E., Meira, C. S., Santos, J. A. F., Moreira, D. R. M., Soares, M. B. P., Poelhsitz, G. V., Castellano, E. E., Bloch, C., Cominetti, M. R., Batista, A. A. (2016). Ruthenium(II) complexes of 1,3-thiazolidine-2-thione: Cytotoxicity against tumor cells and anti-*Trypanosoma cruzi* activity enhanced upon combination with benznidazole. Journal of Inorganic Biochemistry, 156, 153–163.

Daniel, M. C., Ruiz, J., Astruc, D. (2003). Supramolecular H-bonded assemblies of redox-active metallodendrimers and positive and unusual dendritic effects on the recognition of $H_2PO_4^-$. Journal of the American Chemical Society, 125, 1150–1151.

Daniel, M. C., Sakamoto, A., Ruiz, J., Astruc, D., Nishihara, H. (2006). Photoisomerization-induced Change in the Size of Ferrocenylazobenzene-attached Dendrimers. Chemistry Letters, 35, 38–39.

Damljanović, I., Vukićević, M., Radulović, N., Palić, R., Ellmerer, E., Ratković, Z., Joksović, M. D., Vukićević, R. D. (2009). Synthesis and antimicrobial activity of some new pyrazole derivatives containing a ferrocene unit. Bioorganic & Medicinal Chemistry Letters, 19, 1093–1096.

Deng, X., Chen, N., Wang, Z., Li , X., Hu, H., Xu. J. (2011). A convenient synthesis of thiazolidin-2-ones from thiazolidine-2-thiones: Antibiotic activity and revisiting the mechanism. Phosphorus, Sulfur, Silicon Related Elements, 186, 1563–1571.

Diallo, A. K., Ornelas, C., Salmon, L., Aranzaes, J. R., Astruc, D. (2007). "Homeopathic" catalytic activity and atom-leaching mechanism in Miyaura–Suzuki reactions under ambient conditions with precise dendrimer-stabilized Pd nanoparticles. Angewandte Chemie International Edition, 46, 8644–8648.

Djeda, R., Rapakousiou, A., Liang, L., Guidolin, N., Ruiz, J., Astruc, D. (2010). Click syntheses of 1,2,3-triazolylbiferrocenyl dendrimers and the selective roles of the inner and outer ferrocenyl groups in the redox recognition of ATP^{2-} and Pd^{2+}. Angewandte Chemie Intenational Edition, 49, 8152–8156.

Fouda, M. F. R., Abd-Elzaher, M. M., Abdelsamaia, R. A., Labib, A. A. (2007). On the medicinal chemistry of ferrocene. Applied Organometallic Chemistry, 21, 613–625.

Hawkey, P. M. (2008). The growing burden of antimicrobial resistance. Journal of Antimicrobial Chemotherapy, 62, 1–9.

Hillard, E. A., Vessières A., Jaouen, G. (2010). Ferrocene functionalized endocrine modulators as anticancer agents. Topics in Organometallic Chemistry, 32, 81–117.

Kondapi, A. K., Satyanarayana, N., Saikrishna, A. D. (2006). A study of the topoisomerase II activity in HIV-1 replication using the ferrocene derivatives as probes. Archives of Biochemistry and Biophysics, 450, 123–132.

Labande, A., Astruc, D. (2000). Colloids as redox sensors: recognition of $H_2PO_4^-$ and HSO_4^- by amidoferrocenylalkylthiol–gold nanoparticles. Chemical Communications, 1007–1008.

Labande, A., Ruiz, J., Astruc, D. (2002). Supramolecular gold nanoparticles for the redox recognition of oxoanions: Syntheses, titrations, stereoelectronic effects, and selectivity. Journal of the American Chemical Society, 124, 1782–1789.

Li, S., Wang, Z., Wei, Y., Wu, C., Gao, S., Jiang, H., Zhao, X., Yan, H., Wang, X. (2013). Antimicrobial activity of a ferrocene-substituted carborane derivative targeting multidrug-resistant infection. Biomaterials, 34, 902–911.

Makwana, H. R., Malani, A. H. (2017). A brief review article: thiazolidines derivatives and their pharmacological activities Journal of Applied Chemistry, 10, 76–84.

Megiatto, J. D., Li, K., Schuster, D. I., Palkar, A., Herranz, M. A., Echegoyen, L., Abwandner, S., Miguel, G., Guldi, D. M. (2010). Convergent synthesis and photoinduced processes in multi-chromophoric rotaxanes. The Journal of Physical Chemistry B, 114, 14408–14419.

Mishchenko, M., Shtrygol, S., Kaminskyy, D., Lesyk, R. (2020). Thiazole-bearing 4-thiazolidinones as new anticonvulsant agents. Scientia Pharmceutica, 88, 16.

Neuenfeldt, P. D., Drawanz, B. B., Aguiar, A. C. C., Figueiredo, Jr. F., Krettli, A. U., Cunico, W. (2011). Multicomponent synthesis of new primaquine thiazolidinone derivatives. Synthesis, 23, 3866–3870.

Ornelas, C., Aranzaes, J. R., Cloutet, E., Alves, S., Astruc, D. (2007). Click assembly of 1,2,3-triazole-linked dendrimers, including ferrocenyl dendrimers, which sense both oxo anions and metal cations. Angewandte Chemie International Edition, 46, 872–877.

Ornelas, C., Aranzaes, J. R., Salmon, L., Astruc, D. (2008). "Click" dendrimers: Synthesis, redox sensing of $Pd(OAc)_2$, and remarkable catalytic hydrogenation activity of precise Pd nanoparticles stabilized by 1,2,3-triazole-containing dendrimers. Chemistry– A European Journal, 14, 50–64.

Ornelas, C., Ruiz, J., Astruc, D. (2009). Dendritic and ion-pairing effects in oxo-anion recognition by giant alkylferrocenyl dendrimers. Organometallics, 28, 4431–4437.

Ornelas, C., Ruiz, J., Belin, C., Astruc, D. (2009). Giant dendritic molecular electrochrome batteries with ferrocenyl and pentamethylferrocenyl termini. Journal of the American Chemical Society, 131, 590–601.

Ornelas, C., Salmon, L., Aranzaes, J. R., Astruc, D. (2007). Catalytically efficient palladium nanoparticles stabilized by "click" ferrocenyl dendrimers. Chemical Communications, 46, 4946–4948.

Ottana, R., Mazzon, E., Dugo, L., Monforte, F., Maccari, R., Sautebin, L., De Luca, G., Vigorita, M. G., Alcaro, S., Ortuso, F., Caputi, A. P., Cuzzocrea, S. (2002). Modeling and biological evaluation of 3,3'-(1,2-ethanediyl)bis[2-(4-methoxyphenyl)-thiazolidin-4-one], a new synthetic cyclooxygenase-2 inhibitor. European Journal of Pharmacology, 448, 71–80.

Ozturk, T., Ertas, E., Mert, O. (2007). Use of Lawesson's reagent in organic syntheses. Chemical Reviews, 107, 5210–5278.

Pejović, A., Denić, M. S., Stevanović, D., Damljanović, I., Vukićević, M., Kostova, K., Tavlinova-Kirilova, M., Randjelović, P., Stojanović, N. M., Bogdanović, G. A., Blagojević, P., D'hooghe, M., Radulović, N. S., Vukićević, R. D. (2014). Discovery of anxiolytic 2-ferrocenyl-1,3-thiazolidin-4-ones exerting $GABA_A$ receptor interaction *via* the benzodiazepine-binding site. European Journal of Medicinal Chemistry, 83, 57–73.

Pejović, A., Damljanović, I., Stevanović, D., Minić, A., Jovanović, J., Mihailović, V., Katanić, J., Bogdanović, G. A. (2017). Synthesis, characterization and antimicrobial activity of novel ferrocene containing quinolines: 2-ferrocenyl-4-methoxyquinolines, 1-benzyl-2-ferrocenyl-2,3-dihydroquinolin-4(1*H*)-ones and 1-benzyl-2-ferrocenylquinolin-4(1*H*)-ones. Journal of Organometallic Chemistry, 846, 6–17.

Pejović, A., Minić, A., Jovanović, J., Pešić, M., Ilić Komatina, D., Damljanović, I., Stevanović, D., Mihailović, V., Katanić, J., Bogdanović, G. A. (2018). Synthesis, characterization, antioxidant and antimicrobial activity of novel 5-arylidene-2-ferrocenyl-1,3-thiazolidin-4-ones. Journal of Organometallic Chemistry, 869, 1–10.

Rawal, R. K., Prabhakar, Y. S., Katti, S. B., Clercq, E. D. (2005). 2-(Aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones as selective HIV-RT inhibitors. Bioorganic Medicinal Chemistry, 13, 6771–6776.

Rubbiani, R., Blacque, O., Gasser, G. (2016). Sedaxicenes: potential new antifungal ferrocene-based agents? Dalton Transactions, 45, 6619–6626.

Scmidt, U., Utz, R., Lieberknecht, A., Griesser, H., Potzolli, B., Bahr, J., Wagner, K., Fischer, P. (1987). Amino acids and peptides; Synthesis of biologically active cyclopeptides; Synthesis of 16 isomers of dolastatin 3; Synthesis of the 2-(1-aminoalkyl)-thiazole-4-carboxylic acids. Synthesis, 233–236.

Shih, M. H., Ke, F. Y. (2004). Syntheses and evaluation of antioxidant activity of sydnonyl substituted thiazolidinone and thiazoline derivatives. Bioorganic & Medicinal Chemistry, 12, 4633–4643.

Shinde, D. N., Trivedi, R., Krishna, N. V., Giribabu, L., Sridhar, B., Rathod, B. B., Prakasham, R. S. (2018). Facile synthesis, characterisation and anti-inflammatory activities of ferrocenyl ester derivatives of 4-arylidene-5-imidazolinones. Applied Organometallic Chemistry, 32, e4021.

Staveren, D. R., Metzler-Nolte, N. (2004). Bioorganometallic chemistry of ferrocene. Chemical Reviews, 104, 5931–5986.

Szychowski, K. A., Leja, M. L., Kaminskyy, D. V., Binduga, U. E., Pinyazhko, O. R., Lesyk, R. B., Gmiński, J. (2017). Study of novel anticancer 4-thiazolidinone derivatives. Chemico-Biological Interactions, 262, 46–56.

Tanabe, Y., Suzukamo, G., Komuro, Y., Imanishi, N., Morooka, S., Enomoto, M., Kojima, A., Sanemitsu, Y., Mizutani, M. (1991). Structure-activity relationship of optically active 2-(3-pyridyl)thiazolidin-4-ones as a PAF antagonists. Tetrahedron Letters, 32, 379–382.

Verma, S. K., Thareja, S. (2016). Molecular docking assisted 3D-QSAR study of benzylidene-2,4-thiazolidinedione derivatives as PTP-1B inhibitors for the management of type-2 diabetes mellitus. RSC Advances, 6, 33857–33867.

Viswajanani, J. S., Ajay, S., Smita, S., Seema, K., Manisha, P., Pragya, B., Tarun, M., Ashok, R., Mohan, K. J., Anitha, M. (2005). Synthesis and antimicrobial activity of novel thiazolidinones. ARKIVOC, 46–59.

Voss, M. E., Carter, P. H., Tebben, A. J., Scherle, P. A., Brown, G. D., Thampson, L. A., Xu, M., Lo, Y. C., Yang, G., Liu, R. Q., Strzemenski, P., Everlof, J. G., Trzaskos, J. M., Decicco, C. P. (2003). Both 5-arylidene-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-diones and 3-thioxo-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-ones are light-dependent tumor necrosis factor-α antagonists. Bioorganic & Medicinal Chemistry Letters, 13, 533–538.

Wang, A., Ornelas, C., Astruc, D., Hapiot, P. (2009). Electronic communication between immobilized ferrocenyl-terminated dendrimers. Journal of the American Chemical Society, 131, 6652–6653.

Wei, B., Vajtai, R., Choi, Y. Y., Ajayan, P. M., Zhu, H., Xu, C., Wu, D. (2002). Structural characterizations of long single-walled carbon nanotube strands. Nano Letters, 2, 1105–1107.

Zhang, X., Cao, A., Wei, B., Li, Y., Wei, J., Xu, C., Wu, D. (2002). Rapid growth of well-aligned carbon nanotube arrays. Chemical Physics Letters, 362, 285–290.