FERROCENE-MODIFIED PORPHYRINS AS SONOSENSITIZERS FOR SONODYNAMIC THERAPY

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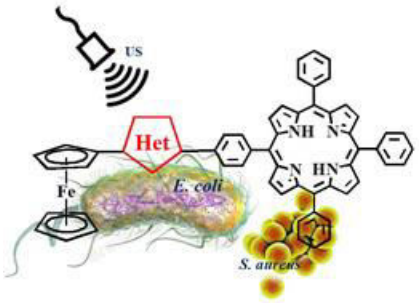
Abstract

This review is devoted to the synthesis of ferrocene-containing porphyrins for sonodynamic therapy which represents a modern method for the treatment of cancer and inflammatory diseases. Although these compounds are not yet used in clinical practice, the results of the preliminary evaluation of their sonodynamic activity show the great potential of further research in this field. The review summarizes mainly the authors' own results, including the synthesis of ferrocenyl-substituted heterocycles and target ferrocene–porphyrin hybrids, as well as the results of sonodynamic experiments with some of the compounds obtained against *Staphylococcus aureus* and *Escherichia coli*.



Key words: ferrocene, porphyrin, sonodynamic therapy, pyrazole, 1,2,3-triazole, heterocycle, ultrasound.

1. Introduction

Cancer is a well-known scourge of modern society, being one of the main medical and social problems worldwide due to high morbidity and mortality. The creation of new selective drugs for cancer treatment is one of the most pressing challenges of chemistry, biochemistry, and medicine. Recently, several non-invasive and safe methods have been developed for the treatment of cancer, including photothermal therapy (PTT), photodynamic therapy (PDT), and sonodynamic therapy (SDT) [1–4]. The mechanism of SDT is similar to that of PDT. Like the light of a certain wavelength in PDT, ultrasound in SDT causes the generation of reactive oxygen species which, then, destroy cancer cells [5]. However, SDT has mechanical effects that PDT does not exhibit. In addition, it can overcome the depth limits of PDT and affect the tumors located deep in organs and tissues. Therefore, sonodynamic therapy holds great promise for clinical use. It is important to note that this method can be very effective in treating socially significant diseases such as a diabetic foot (until recently, only PDT has been used for this purpose) [6]. SDT became famous in 1989 when the sonodynamic effect of hematoporphyrin was revealed [7]. The first *in vivo* tests were carried out in 1990 [8], and in 1992 this method received its name [9]. But only after 17 years, in 2009, SDT combined with PDT was used in clinical practice for the treatment of breast cancer [10, 11].

Despite the undeniable success of SDT, its mechanism has not been established in full detail. Furthermore, a search for new efficient sonosensitizers, the potential therapeutic agents that can be activated under the action of ultrasound, is continuing. Most of them were initially tested as photosensitizers for PDT. These mainly include porphyrins and their derivatives. The modification of porphyrins with ferrocene-containing compounds affords the systems with unique properties [12]. It is important to note that the first decade and a half of the 21st century have witnessed increased interest of biochemists and biologists in ferrocene compounds. This is evidenced by the appearance of a range of comprehensive reviews [13–19] and monographs [20, 21]. Attention to the biochemistry of ferrocene was provoked by several useful properties. The modification with ferrocene can be manifested in various aspects, including the following: the improvement of transport properties owing to the lipophilicity of a ferrocene core, a dramatic reduction in the toxicity of compounds upon introduction of a ferrocene moiety [22], antianemic and antineoplastic (antitumor) effects, tuberculostatic activity, and plant growth regulator properties. From the structural point of view, these changes include the conformational rigidity and bulkiness as well as the appearance of additional elements of chirality (planar and central). The introduction of ferrocene moieties can also enable different chemical transformations, redox activity, and reversible single-electron transition between ferrocene and ferricinium derivatives. Moreover, ferrocene compounds are stable in air and aqueous media. A variety of ferrocene-containing compounds are commercially available (for example, the Aldrich catalog for 2020 offers almost five dozens of such derivatives).

The derivatives of ferrocene that contain heterocyclic moieties in their structures were found to be effective against fungal and bacterial infections, malaria [23–26], and also exhibit antitumor activity [27–29]. Another important aspect is that the ferrocene-modified compounds display reduced toxicity while maintaining the target therapeutic effects.

Taking this into account, we initiated the project devoted to the creation of ferrocene-modified porphyrins using pyrazole and 1,2,3-triazole linkers. It should be noted that the syntheses of these heterocycles usually proceed in high yields, and a combination of certain substituents in the starting reagents often ensures high regioselectivity of the reactions.

The derivatives of pyrazole are known to interact with enzymes and receptors such as epidermal growth factor receptor (EGFR), Aurora kinases, cyclin-dependent kinases, and cyclooxygenases and can exhibit anticancer activity [30, 31]. The conjugation of ferrocene with a pyrazole pharmacophore represents a promising strategy for the development of novel anticancer drugs. The activity of these derivatives against MCF-7 and MDA-MB-231 breast cancer cell lines has already been shown [32]. The ferrocene–pyrazole hybrids can suppress cell viability and trigger either apoptosis or necrosis in human breast cancer cells, exhibiting low cytotoxicity to healthy breast epithelial cells. The ferrocene–pyrazole hybrids derived from the trifluoromethyl-substituted heterocycle displayed potential activity against A549, HepG2, and MDA-MB-45 cancer cell lines [33]. Interestingly, the efficiency of some ferrocene–pyrazole hybrids bearing (*R*)-chiral centers towards A549 and H322 cancer cell lines appeared to be higher than that of their (*S*)-chiral analogs [34].

Ferrocenylpyrazole-based amines demonstrated nonselective and strong activity against some of the most resistant pathogenic bacteria *B. subtilis*, *Enterococcus sp.*, and *P. aeruginosa*, whereas Amikacin, used as a reference, was either less efficient or comparable in action [35]. This shows the potential of the application of these derivatives against antibiotic-resistant strains of microorganisms. The biological studies revealed the involvement of ferrocene-containing amino acid esters featuring pyrazole linkers in the synaptic plasticity of the CA1 hippocampal brain area [36, 37].

A triazole unit can improve the pharmacological, pharmacokinetic, and physicochemical profiles of molecules [38]. Many triazole-containing compounds, including Cefatrizine and Carboxyamidotriazole, display high anticancer activities. The ferrocene–1,2,3-triazole hybrids were found to be moderately active against MCF-7 and HT-29 cancer cell lines [39]. Therefore, the modification of ferrocene with a triazole moiety can provide valuable therapeutic intervention for the treatment of cancer.

Our research interests focus on the synthesis of ferrocene-containing porphyrins in which a ferrocene core is bound with a porphyrin moiety through a heterocyclic unit. The convenient synthetic routes to the target compounds consist in the preparation of the ferrocene and porphyrin components followed by the conjugation of two functional fragments *via* a heterocyclic linker (Scheme 1). This approach ensures the synthesis of ferrocene-modified porphyrins with the required characteristics. The reactions leading to the formation of ferrocene–heterocycle–porphyrin triads included reductive amination and [3+2]-dipolar cycloaddition. 5,10,15,20-Tetraphenylporphyrin and its amino and azido derivatives were chosen as the porphyrin components.

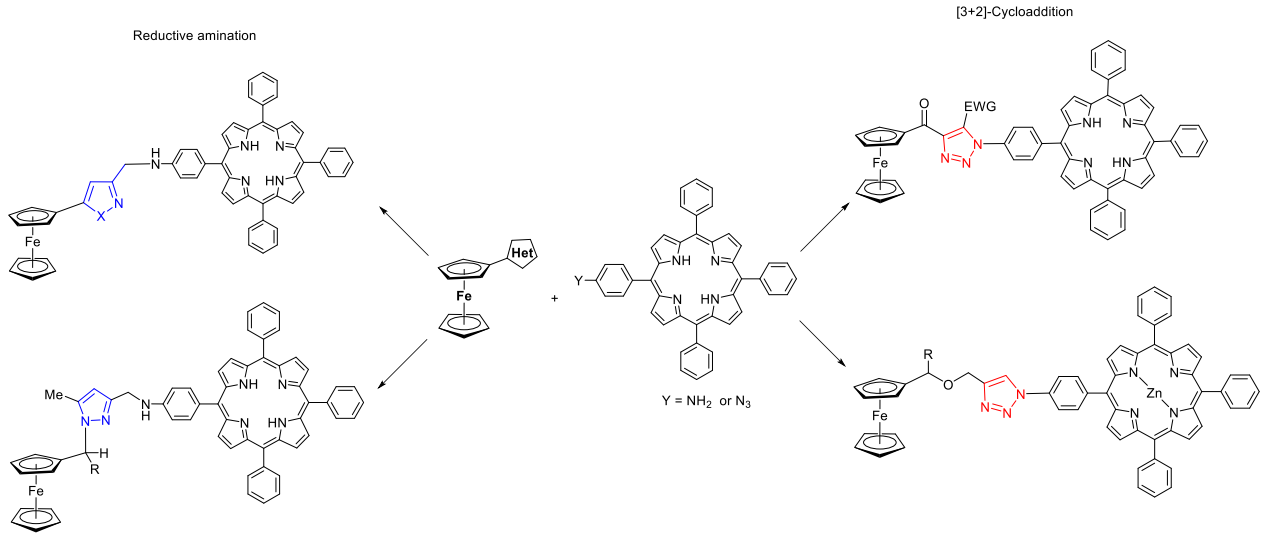
In turn, two types of compounds were used as ferrocenylheterocyclic components, namely, those bearing C–C and C–N bonds between the ferrocene and heterocyclic moieties. This choice was dictated by further medical studies which are beyond the scope of the current review. However, it should be noted that the C–N bond is more labile than the C–C bond and can be readily cleaved in the biological media. Some of the resulting ferrocenylheterocyclic porphyrins were tested *in vitro* for the sonodynamic antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* cells. These cells were used as the main research objects because their morphology is similar to that of cancer cells, and, at the same time, they have stronger cell walls than cancer ones. This implies that if their growth can be inhibited by our compounds and ultrasound, then cancer cells can be susceptive to their action too. Hence, the preliminary results on the efficiency of the ferrocene–heterocycle–porphyrin triads render further studies in this field very promising.

2. Synthesis of the ferrocene-modified porphyrins

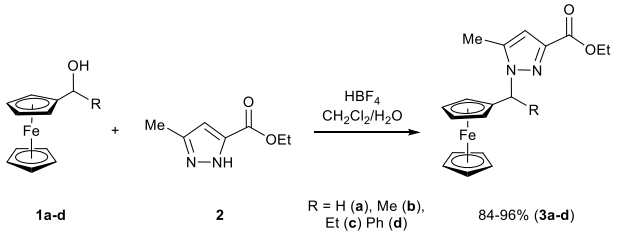
Synthesis of the compounds bearing the C–N bonds between the ferrocenyl and heterocyclic units

The development of efficient synthetic approaches to the ferrocene-containing heterocycles for the design of new biologically active compounds is still an important problem of modern organic synthesis. The introduction of a ferrocenylalkyl moiety into different structures can be accomplished by the ferrocenylalkylation. The reactions of α-hydroxyalkylferrocenes with different nucleophilic compounds proceed most efficiently in two-phase systems such as liquid–liquid mixtures. The reactions of equimolar amounts of α-ferrocenylcarbinols and heterocycles are carried out under vigorous stirring at room temperature. The two-phase system consists of an organic solvent (CH_2Cl_2) and an aqueous solution of tetrafluoroboric acid (45%). Under these conditions, the reactions proceed predominantly at an organic–inorganic interface. Dichloromethane contains the hydrophobic ferrocene compounds (initial compounds and/or reaction products), while the aqueous phase contains the acid. The polar hydroxy group of the organometallic carbinol contacts with the aqueous phase and, thus, is available for the protonation, resulting under mild conditions in a thermodynamically stable ferrocenyl carbocation. At the same time, the other part of the ferrocene compound remains in the organic phase and is not subjected to the protonation and oxidation. This enables efficient interaction of the ferrocenyl carbocation with the corresponding nucleophilic reagent and almost excludes other reactions (rearrangement, dimerization, polymerization, formation of ethers, *etc.*). However, the regioselectivity of ferrocenylalkylation is still poorly explored.

We studied the ferrocenylalkylation of pyrazoles [40, 41], including asymmetrically substituted derivatives [42–44] (Scheme 2). In addition, the regioselectivity of alkylation of other asymmetrically substituted heterocycles [44, 45] and *N*,*S*-bidentate heterocyclic nucleophiles [46–48] was also elucidated (Fig. 1). It was shown that the regioselective ferrocenylalkylation is possible only in the case of the asymmetrically substituted heterocycles in which the substituents significantly differ in the electronic properties and the electron- withdrawing group is located close to one of the



Scheme 1



Scheme2

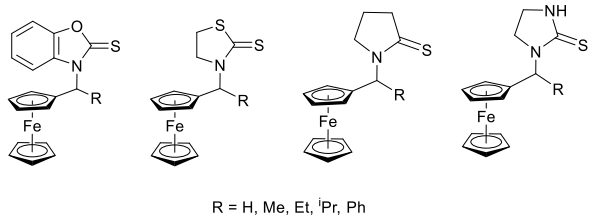


Figure 1

reaction centers. For example, the alkylation of 5(6)-nitrobenzimidazole in which the electron-withdrawing group is far from the reaction centers affords a mixture of regioisomers. In this case, the nitrogen atom the most distant from the electron-withdrawing group is alkylated. For the compounds bearing bulky substituents [42] (for example, ferrocenyl units), steric factors come into play. The alkylation of *N*,*S*-bidentate heterocyclic nucleophiles under phase-transfer catalysis results in the reaction of an intermediate with the hard nucleophilic center and gives rise to only *N*-isomers, which contradicts the results obtained in the previous work [49]. On the other hand, the reactions with ferrocenylalkyl esters of carbonic acid furnish only *N*-isomers even if this is accompanied by the loss of aromaticity in the heterocyclic moiety [50].

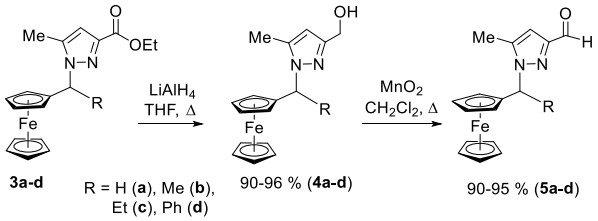
Esters **3a**–**d** were converted to the corresponding alcohols under the action of lithium aluminum hydride (Scheme 3). Resulting alcohols **4a**–**g** were oxidized with manganese(IV) oxide to aldehydes **5a**–**g**. The reactions were carried out under vigorous stirring in boiling dichloromethane.

All the compounds obtained were characterized by the standard spectral methods; their structures were determined by X-ray diffraction (Fig. 2).

Thus, a number of ferrocenylpyrazolecarbaldehydes were synthesized that can be subjected to reductive amination with tetraphenylporphyrinamine (*vide infra*).

Synthesis of the ferrocenylheterocycles bearing the C–C bonds between the ferrocenyl and heterocyclic units

Another approach to ferrocenylpyrazoles was based on the synthesis of the compounds bearing substituents in a pyrazole unit located at different positions relative to each other. For a further stage of reductive amination with porphyrinamines, we aimed, first of all, at producing ferrocenylpyrazolecarbaldehydes (Scheme 4).



Scheme 3

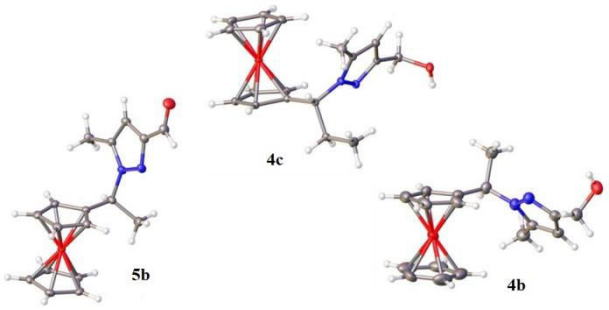
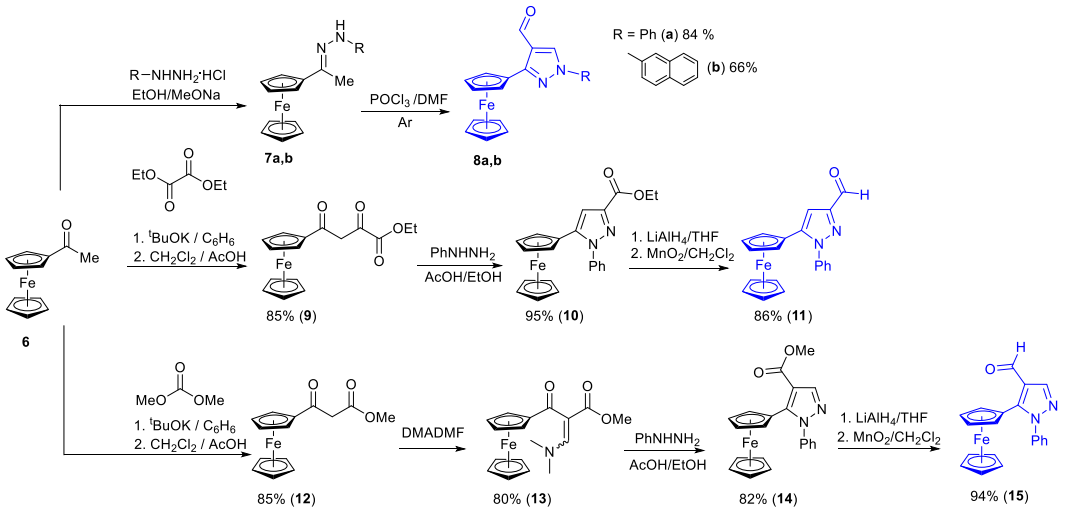


Figure 2



Scheme 4

1-Aryl-3-ferrocenyl-4-formylpyrazoles **8a,b** were obtained in two steps. The reaction of acetylferrocene **6** with arylhydrazines yielded arylhydrazones of acetylferrocene **7a,b**, which were, then, reacted with the Vilsmeier complex [51, 52]. It should be noted that hydrazones **7a,b** formed at the intermediate stage are unstable compounds, and, therefore, they were immediately introduced into cyclization without isolation. The structure of 1-(*β*-naphthyl)-3-ferrocenylpyrazole-4-carbaldehyde **8b** was elucidated by X-ray diffraction (Fig. 3).

Figure 3

Target isomeric aldehydes **11** and **15** [53] were obtained from pyrazolecarboxylic acid esters **10** and **14** (Scheme 4). Ferrocenoylpyruvic acid ester **9** was synthesized by the condensation of acetylferrocene **6** with diethyl oxalate using potassium *tert*-butoxide as a base. The reaction was performed in benzene since the potassium salt of ferrocenoylpyruvic acid is insoluble in it and, thus, facilitates the product isolation. The reactions of asymmetrically substituted 1,3-dicarbonyl compounds with phenylhydrazine can afford two products. The preferential formation of a particular regioisomer may be caused by the fact that the amino group attacks the carbonyl group with the greatest positive charge, *i.e.*, the carbon atom next to the electron-withdrawing group. Ferrocenoylacetic acid ester **12** was prepared using an analogous procedure. Its formylation with DMF dimethyl acetal afforded corresponding ester **13** in 80% yield. The reaction of the latter with phenylhydrazine in ethanol catalyzed by acetic acid led to ester **14** [53]. It should be noted that the cyclization with hydrazine also furnished a single product (owing to a difference in the reactivities of the formyl and keto groups). Finally, ferrocenylpyrazolecarbaldehydes **11** and **15** were synthesized from ferrocenylpyrazolecarboxylic acid esters **10** and **14** in two steps *via* the reduction with $LiAlH_4$ to the corresponding alcohols followed by the oxidation with MnO_2 [53].

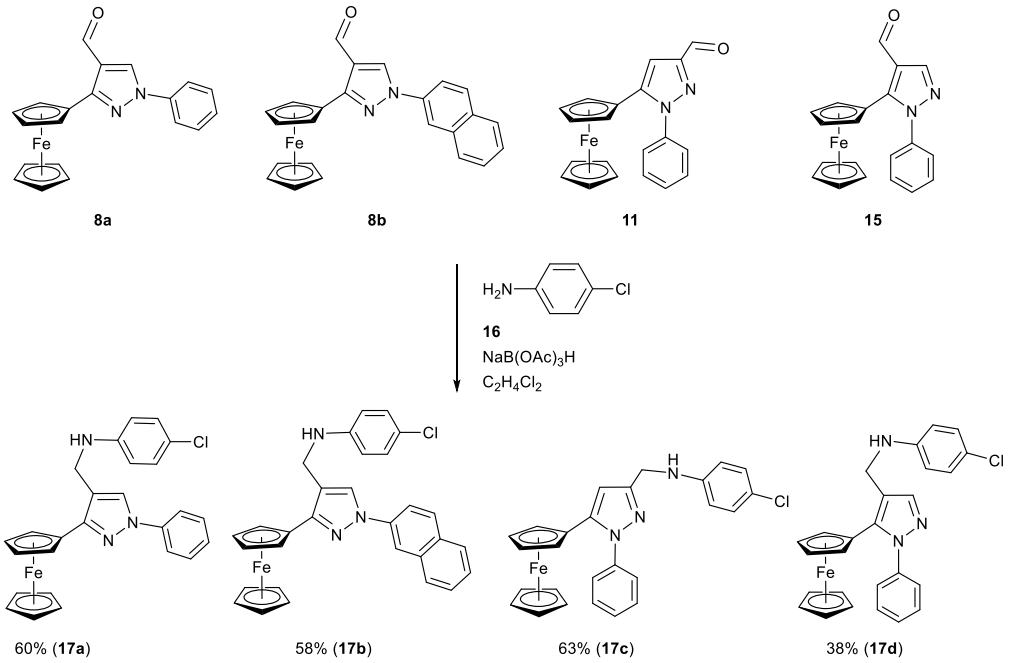
Hence, ferrocenylphenylpyrazoles **8a,b**, **11**, **15** were obtained, in which the ferrocene core is bound to the pyrazole unit *via* the C–C bonds. The resulting compounds represent isomers differing in the arrangement of the formyl group and the aryl substituent relative to the ferrocene core.

Reductive amination of pyrazolyl-formylferrocenes

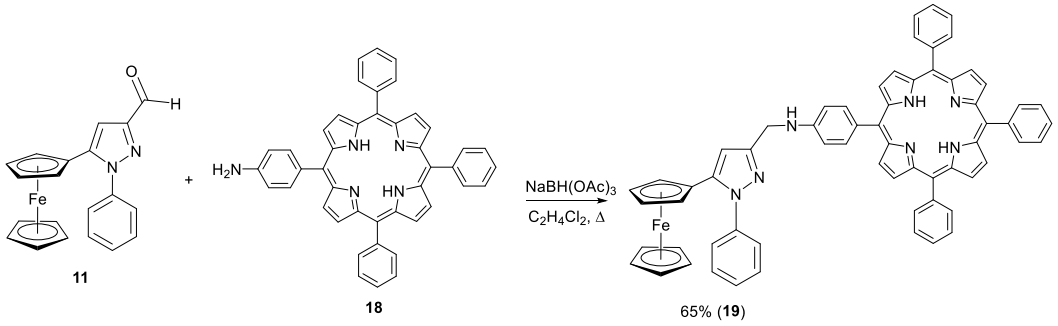
For the synthesis of the desired ferrocenylheterocyclic porphyrins, the reductive amination of aminotetraphenylporphyrin with the corresponding formyl-substituted heterocyclic derivatives of ferrocene was studied. The reaction conditions were optimized using a model reaction of ferrocenylformylpyrazoles **8a,b**, **11**, **15** with *p*-chloroaniline (Scheme 5) [54]. As can be seen, the best yields were achieved upon refluxing the reaction mixture in 1,2-dichloroethane using sodium triacetoxyborohydride as a reducing agent. The ferrocene derivatives of *p*-chloroaniline (compounds **17a–d**) were obtained in the yields up to 63% (Scheme 5). It is noteworthy that the reactions with aliphatic primary and secondary amines proceed in the higher yields up to the quantitative ones [54].

However, when aminotetraphenylporphyrin **18** was used as the amino component, the product of reductive amination was obtained only in the case of 1-phenyl-5-ferrocenyl-3-pyrazolecarbaldehyde **11** (compound **19**, Scheme 6) [55, 56]. In the case of the other aldehydes (compounds **8a,b**, **15**), the desired products were not obtained even upon variation of the reaction conditions. Apparently, this is connected with the steric hindrances caused not only by the amino component but also by the close proximity of the ferrocene unit to the carbonyl group.

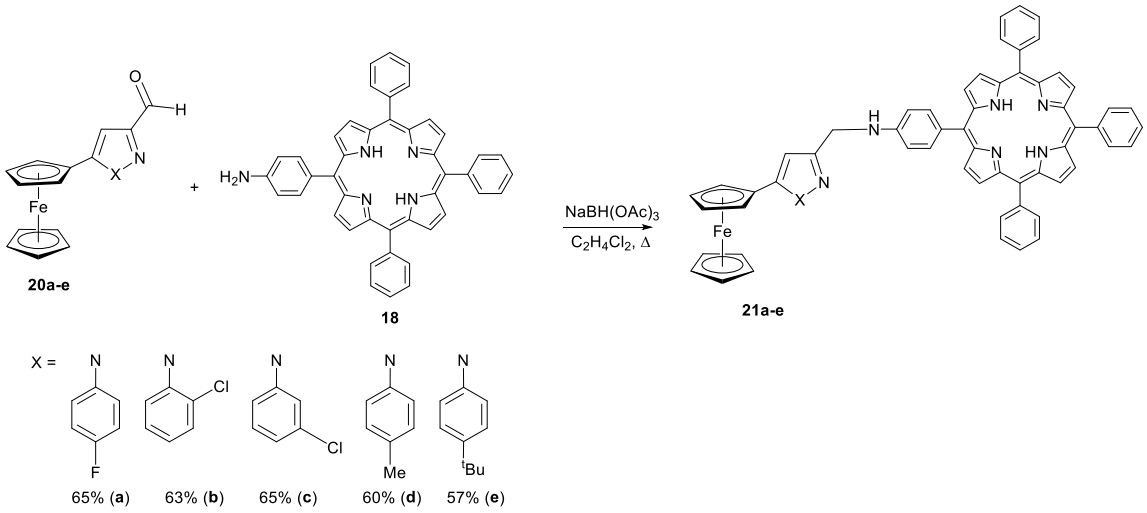
Indeed, the reactions with a range of ferrocenylazole aldehydes **20a–e** featuring the greatest distance between the ferrocene unit and the formyl group readily afforded the products of reductive amination in the yields up to 65% (compounds **21a–e**, Scheme 7) [56].



Scheme5



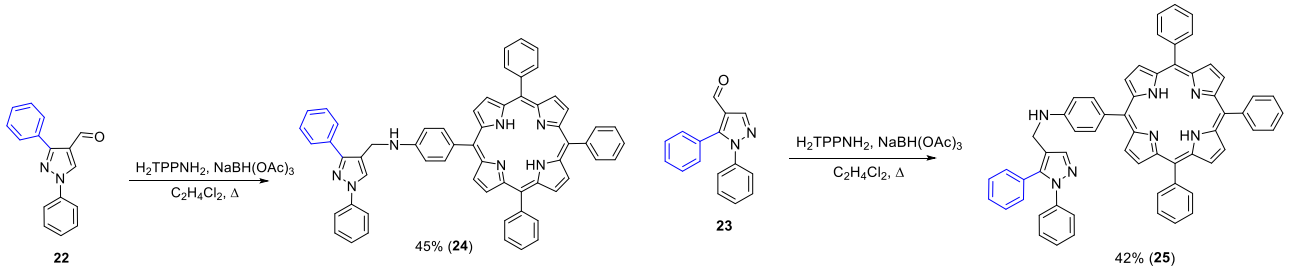
Scheme 6



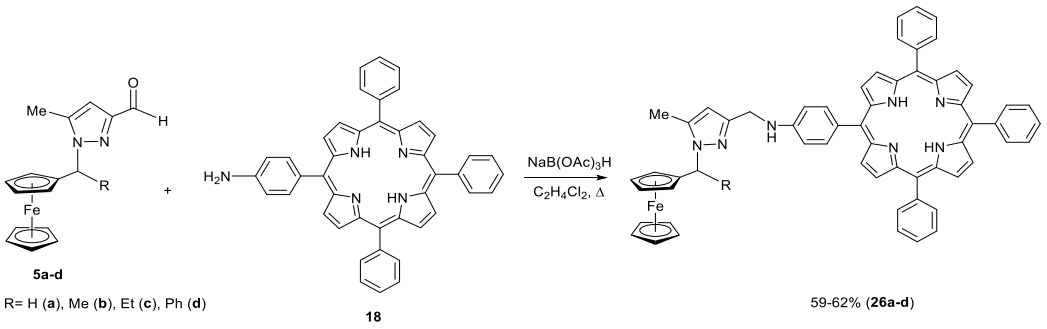
Scheme 7

To confirm the assumption about a key role of the steric factor in the case of the ferrocene derivatives, we synthesized diphenylformylpyrazoles **22** and **23** which were introduced into the reductive amination with H_2TPPNH_2 **18** and smoothly afforded products **24** and **25** (Scheme 8) [56].

The reductive amination of ferrocenylformylpyrazoles **5a**–**d** bearing the C–N bonds between the ferrocenyl and heterocyclic units afforded ferrocenylpyrazolylporphyrins **26a**–**d** (Scheme 9) [57].



Scheme 8



Scheme 9

[3+2]-Dipolar cycloaddition

The porphyrin–heterocycle–ferrocene triads were also prepared by the [3+2]-cycloaddition of azidotetraphenylporphyrin [58]. A possibility of application of diketones as dipolarophiles can be explained by their predominant existence in the enol form due to the keto-enol tautomerism of these derivatives. The regioselectivity of the dipolar addition to such substrates depends mainly on the relative stability of the resulting enol forms (Scheme 10).

The preferential formation of keto-enol **II** is possible only in the presence of a strong electron-withdrawing group; in other cases, the formations of both enol forms are equally probable. In our work, ferrocenoylpyruvic acid ester **9** (EWG = COOEt) and ferrocenoyltrifluoroacetone **27** (EWG = CF_3) were used as the ferrocene-containing dipolarophiles (Scheme 11). Compounds **9** and **27** were obtained by the Claisen condensation between acetylferrocene and diethyl oxalate or ethyl trifluoroacetate, respectively [53]. The NMR spectroscopic analysis confirmed the formation of only one enol form **II** in solution at room temperature.

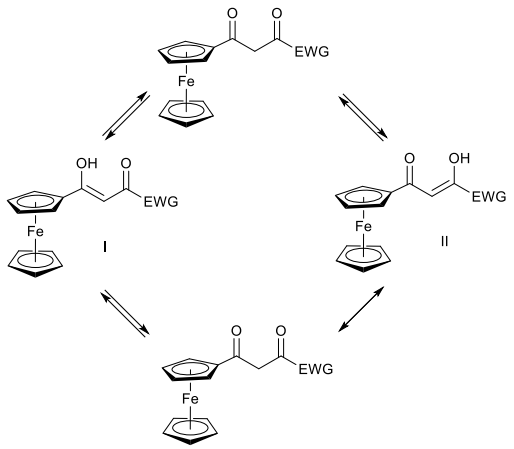
The reactions of tetraphenylporphyrinylazide **28** with ferrocenyl-containing dicarbonyl compounds **9** and **27** led to the formation of desired products **29a,b**. It should be noted that the nature of a base plays a significant role in these interactions. Thus, using different bases (potassium carbonate, sodium methoxide, triethylamine in toluene, pure triethylamine, and diisopropylethylamine (DIPEA) in toluene), we showed that the highest yields of porphyrins **29a,b** can be achieved with DIPEA in toluene. In this case, the regioselectivity did not depend on the nature of a base. Noteworthy, the reaction proceeded in the absence of toxic copper salts and the target porphyrins remained metal-free, which simplified their purification. Recently, we have reported the [3+2]-cycloaddition between ferrocene derivatives **30a,b** and porphyrinazide **28** (Scheme 12) [59, 60]. The products were isolated in high yields. In order to avoid the incorporation of copper into the porphyrin unit, the starting azidoporphyrin was metallated with zinc acetate. The catalytic amounts of copper acetate did not enable the activation of the terminal triple bond, whereas the reaction with an equivalent of copper acetate yielded the product with the copper ions coordinated with the porphyrin moiety.

Hence, we developed efficient synthetic routes to the ferrocene-modified porphyrins featuring the pyrazole and 1,2,3-triazole linkers.

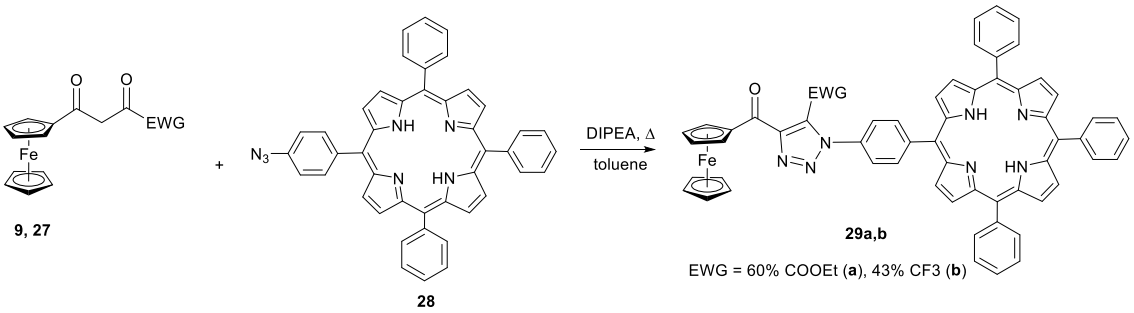
3. Sonosensitizers for sonodynamic therapy

Porphyrins and other derivatives

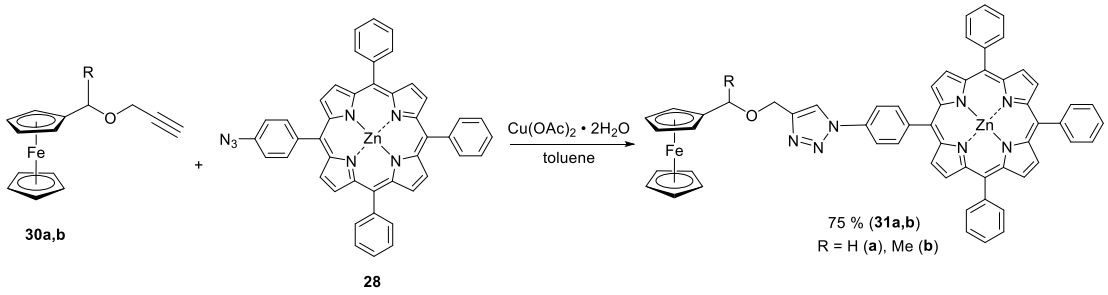
The most popular sensitizers for sonodynamic therapy are porphyrin derivatives (Fig. 4) [61–63] which are currently used as efficient agents in photodynamic therapy (PDT) [64–69]. However, these sonosensitizers are usually poorly soluble in water and can be easily removed from the bloodstream, resulting in low concentrations.



Scheme 10



Scheme 11



Scheme 12

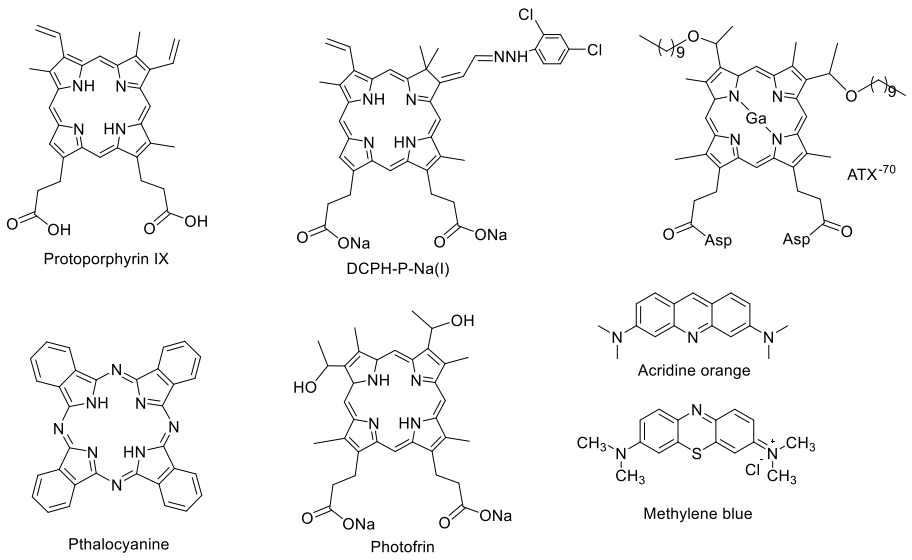


Figure 4

Acridine orange and methylene blue represent non-porphyrin sensitizers (Fig. 4). The former is a well-known photosensitizer that has been recently studied for sonodynamic properties [70]. Owing to its low molecular weight, acridine orange easily penetrates the cells and rapidly binds with DNA and lysosomes of living cells. Methylene blue is an inexpensive phenothiazine dye which features low toxicity and, thus, was approved for clinical use. Due to the similarity of the structure of methylene blue to that of acridine orange, it is assumed that the former can also exhibit a sonodynamic effect [71]. Both compounds were tested for the activity on sarcoma 180 cells upon exposure to ultrasound.

It should be noted that nanosonosensitizers can improve the hydrophobic properties and increase blood circulation for targeted accumulation [72, 73].

Sonodynamic activity of ferrocene-modified porphyrins

Firstly, we evaluated *in vitro* sonodynamic activity of the resulting ferrocene-containing porphyrins against available bacterial cells *Staphylococcus aureus* and *Escherichia coli.* As it was already mentioned, the morphology of bacterial cells is similar to that of cancer ones. The compounds explored showed remarkable intrinsic antibacterial effects ant their bright amplification under the action of ultrasound.

Ultrasound experiments. The test culture (*Staphylococcus aureus* or *Escherichia coli*) was grown at 37 °C on Standard Methods Agar. A suspension of bacterial cells in a sterile isotonic solution was prepared by washing them off from the gel substrate. A 5-mL portion of a bacterial cell suspension

containing the test compound was placed into a vessel with a sound-transmitting bottom. The vessel was placed into a water bath maintained at 37 °C over an ultrasonic source (0.88 MHz), and the suspension was subjected to ultrasonic irradiation for 5 min at the intensity of 1.5 W/cm^2. A 1-mL sample was then taken and transferred onto a Petri dish charged with a nutrient medium. The Petri dish was placed into an air thermostat (37 °C), and the growth of bacteria was estimated after 24 h by counting colony-forming units in the test and control samples. Each experiment was performed in duplicate. The results were presented as the control/test percentage.

The performed experiments revealed the intrinsic antibacterial activity of compounds **19** and **26c** (Fig. 5) against *Staphylococcus aureus* (Table 1). When exposed to ultrasound, the enhancement of the effects was noted. The effects were studied in the concentrations of 20 μM and 40 μM. The cytotoxic activity of **26c** at 40 μM was so pronounced that even without ultrasound there were no survived cells after the experiment (Table 1). The results for compound **19** were comparable to those observed for tetrasodium salt of zinc phthalocyanine octacarbonyl ZnPc [11].

Recently the antibacterial sonodynamic effects of ferrocene-modified porphyrins **19**, **29a**, and **31a** against *Escherichia coli* were compared to those of 5,10,15,20-tetraphenylporphyrin (H_2TPP) and ferrocenecarboxylic acid ($FcCO_2H$) (Table 2) [58, 59]. The amounts of dead cells are presented as their percentages. The most active compounds appeared to be ferrocene-porphyrins **29a** and **31a** bearing the 1,2,3-triazole linkers. Compound **19** containing the pyrazole linker showed lower activity. It is noteworthy that tetraphenylporphyrin H_2TPP exhibited the same level of efficiency as the ferrocene-containing porphyrins.

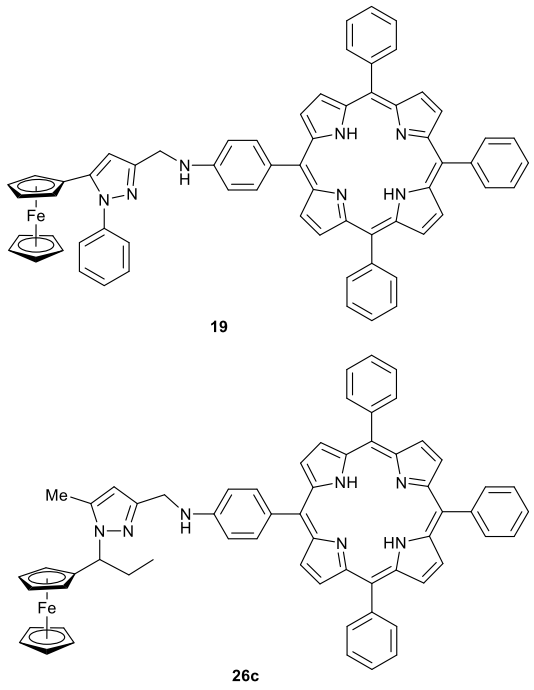


Figure 5

Table 1. Cytotoxicity of the ferrocenylporphyrins obtained in the ultrasound experiments against *Staphylococcus aureus*

Compound	Survived cell fraction %			
	Concentration 20 μM		Concentration 40 μM	
	Without ultrasound	Ultrasonic treatment	Without ultrasound	Ultrasonic treatment
19	79	**59**	38	**20**
26c	66	**30**	0	**0**
ZnPc	68	**50**		

Table 2. Cytotoxicity of the ferrocenylporphyrins obtained in the ultrasound experiments against *Escherichia coli*

Compound	DMSO μL/10 mL	US control, % dead cells	US+sample, % dead cells	Effect	Standard deviation
$FcCO_2H$	300	20	28	8	0.41
H_2TPP	300	20	38	18	0.72
19	300	20	29	9	0.47
29a	300	20	41	21	0.84
31a	300	20	36	16	0.71

4. Conclusions

To summarize the results presented, we developed efficient synthetic strategies to the ferrocenyl-substituted heterocycles and ferrocene–porphyrin hybrids on their base. The sonodynamic experiments with some of the compounds revealed their remarkable cytotoxic effects on *Staphylococcus aureus* and *Escherichia coli*. The resulting compounds exhibited intrinsic antibacterial activity which increased under the action of ultrasound. It should be noted that the sonodynamic activity of the ferrocene-modified porphyrins was studied for the first time. The next step will be the investigation of the sonodynamic activity of these compounds against tumor cells. The results of the preliminary tests demonstrated a principal possibility of the application of ferrocene-containing porphyrins as sonosensitizers for the creation of efficient SDT agents for the treatment of cancer and inflammatory diseases.

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References

1. K. Hachimine, H. Shibaguchi, M. Kuroki, H. Yamada, T. Kinugasa, Y. Nakae, R. Asano, I. Sakata, Y. Yamashita, T. Shirakusa, M. Kuroki, *Cancer Sci.*, **2007**, *98*, 916–920. DOI: 10.1111/j.1349-7006.2007.00468.x

2. I. Rosenthal, J. Z. Sostaric, P. Riesz, *Ultrason. Sonochem.*, **2004**, *11*, 349–363. DOI: 10.1016/j.ultsonch.2004.03.004
3. A. L. Nikolaev, A. V. Gopin, V. E. Bozhevolnov, S. E. Mazina, A. V. Severin, V. N. Rudin, N. V. Andronova, H. M. Treschalina, O. L. Kaliya, L. I. Solovyeva, E. A. Lukyanets, *Russ. Chem. Bull.*, **2014**, *63*, 1036–1047. DOI: 10.1007/s11172-014-0546-2
4. X. Pan, H. Wang, S. Wang, X. Sun, L. Wang, W. Wang, H. Shen, H. Liu, *Sci. China: Life Sci.*, **2018**, *61*, 415–426. DOI: 10.1007/s11427-017-9262-x
5. M. Trendowski, *Cancer Metastasis Rev.*, **2014**, *33*, 143–160. DOI: 10.1007/s10555-013-9461-5
6. S. Morley, J. Griffiths, G. Philips, H. Moseley, C. O'Grady, K. Mellish, C. L. Lankester, B. Faris, R. J. Young, S. B. Brown, L. E. Rhodes, *Brit. J. Dermatol.*, **2013**, *168*, 617–624. DOI: 10.1111/bjd.12098
7. N. Yumita, R. Nishigaki, K. Umemura, S.-i. Umemura, *Cancer Sci*., **1989**, *80*, 219–222. DOI: 10.1111/j.1349-7006.1989.tb02295.x
8. N. Yumita, R. Nishigaki, K. Umemura, S.-i. Umemura, *Cancer Sci.*, **1990**, *81*, 304–308. DOI: 10.1111/j.1349-7006.1990.tb02565.x
9. S. Umemura, K. Kawabata, N. Yumita, R. Nishigaki, K. Umemura, *IEEE Ultrasonics Symp. Proc.*, Tucson, USA, **1992**, vol. 2, pp. 1231–1240. DOI: 10.1109/ULTSYM.1992.275856
10. Z. Huang. H. Moseley, S. Bown, *Integr. Cancer Ther.*, **2010**, *9*, 317–319. DOI: 10.1177/1534735410376634
11. T. Inui, K. Makita, H. Miura, A. Matsuda, D. Kuchiike, K. Kubo, M. Mette, Y. Uto, T. Nishikata, H. Hori, N. Sakamoto, *Anticancer Res.*, **2014**, *34*, 4589–4593.
12. C. Bucher, C. H. Devillers, J.-C.Moutet, G. Royal, E. Saint-Aman, *Coord. Chem. Rev.*, **2009**, *253*, 21–36. DOI: 10.1016/j.ccr.2007.11.025
13. T. S. Zatsepin, S. Yu. Andreev, T. Hianik, T. S. Oretskaya, *Russ. Chem. Rev.*, **2003**, *72*, 537–554. DOI: 10.1070/RC2003v072n06ABEH000807
14. D. R. van Staveren, N. Metzler-Nolte, *Chem. Rev*., **2004**, *104*, 5931–5986. DOI: 10.1021/cr0101510
15. E. W. Neuse, *J. Inorg. Organomet. Polym. Mater.*, **2005**, *15*, 3–31. DOI: 10.1007/s10904-004-2371-9
16. H.-B. Kraatz, *J. Inorg. Organomet. Polym. Mater.*, **2005**, *15*, 83–106. DOI: 10.1007/s10904-004-2380-8
17. A. Singh, I. Lumb, V. Mehrac, V. Kumar, *Dalton Trans.*, **2019**, *48*, 2840–2860. DOI: 10.1039/C8DT03440K
18. C. Ornelas, *New J. Chem*., **2011**, *35*, 1973–1985. DOI: 10.1039/C1NJ20172G
19. G. Gasser, I. Ott, N. Metzler-Nolte, *J. Med. Chem*., **2011**, *54*, 3–25. DOI: 10.1021/jm100020w
20. X. Wu, M. L. Go, *Metallotherapeutic in Drugs and Metal-Based Diagnostic Agents: The Use of Metals in Medicine*, M. Gielen, E. R. T. Tiekink (Eds.), John Wiley & Sons, Ltd, **2005**. DOI: 10.1002/0470864052.ch10
21. *Bioorganometallics: Biomolecules*, *Labeling*, *Medicine*, G. Jaouen (Ed.), Wiley, Weinheim, **2006**.
22. L. V. Snegur, V. N. Babin, A. A. Simenel, Yu. S. Nekrasov, L. A. Ostrovskaya, N. S. Sergeeva, *Russ. Chem. Bull.*, **2010**, *59*, 2167–2178. DOI: 10.1007/s11172-010-0377-8
23. D. Dive, C. Biot, *ChemMedChem*, **2008**, *3*, 383–391. DOI: 10.1002/cmdc.200700127
24. Y.-S. Xie, X.-H. Pan, B.-X. Zhao, J.-T. Liu, D.-S. Shin, J.-H. Zhang, L.-W. Zheng, J. Zhao, J.-Y. Miao, *J. Organomet. Chem*., **2008**, *693*, 1367–1374. DOI: 10.1016/j.jorganchem.2008.01.043
25. M. D. Joksović, V. Marković, Z. D. Juranić, T. Stanojković, L. S. Jovanović, I. S. Damljanović, K. M. Szécsényi, N. Todorović, S. Trifunović, R. D. Vukićević, *J. Organomet. Chem*., **2009**, *694*, 3935–3942. DOI: 10.1016/j.jorganchem.2009.08.013
26. M. El Arbi, P. Pigeon, S. Top, A. Rhouma, S. Aifa, A. Rebai, A. Vessières, M.-A. Plamont, G. Jaouen, *J. Organomet. Chem*., **2011**, *696*, 1038–1048. DOI: 10.1016/j.jorganchem.2010.09.015
27. R. Wang, H. Chen, W. Yan, M. Zheng, T. Zhang, Y. Zhang, *Eur. J. Med. Chem*., **2020**, *190*, 112109. DOI: 10.1016/j.ejmech.2020.112109
28. L. V. Snegur, A. A. Simenel, A. N. Rodionov, V. I. Boev, *Russ. Chem. Bull.*, **2014**, *63*, 26–36. DOI: 10.1007/s11172-014-0390-4
29. V. N. Babin, Yu. A. Belousov, V. I. Borisov, V. V. Gumenyuk, Yu. S. Nekrasov, L. A. Ostrovskaya, I. K. Sviridova, N. S. Sergeeva, A. A. Simenel, L. V. Snegur, *Russ. Chem. Bull.*, **2014**, *63*, 2405–2422. DOI: 10.1007/s11172-014-0756-7
30. S. Ganguly, S. K. Jacob, *Mini-Rev. Med. Chem.*, **2017**, *17*, 959–983. DOI: 10.2174/1389557516666151120115302
31. S. Chauhan, S. Paliwal, R. Chauhan, *Synth. Commun*., **2014**, *44*, 1333–1374. DOI: 10.1080/00397911.2013.837186
32. H. Atmaca, A. N. Özkan, M. Zora, *Chem.-Biol. Interact*., **2017**, *263*, 28–35. DOI: 10.1016/j.cbi.2016.12.010
33. X.-F. Huang, L.-Z. Wang, L. Tang, Y.-X. Lu, F. Wang, G.-Q. Song, B.-F. Ruan, *J. Organomet. Chem*., **2014**, *749*, 157–162. DOI: 10.1016/j.jorganchem.2013.08.043
34. S.-L. Shen, J.-H. Shao, J.-Z. Luo, J.-T. Liu, J.-Y. Miao, B.-X. Zhao, *Eur. J. Med. Chem*., **2013**, *63*, 256–268. DOI: 10.1016/j.ejmech.2013.02.016
35. I. Damljanović, M. Vukićević, N. Radulović, R. Palić, E. Ellmerer, Z. Ratković, M. D. Joksović, R. D. Vukićević, *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 1093–1096. DOI: 10.1016/j.bmcl.2009.01.006
36. A. N. Rodionov, L. V. Snegur, Y. V. Dobryakova, M. M. Ilyin Jr, V. A. Markevich, A. A. Simenel, *Appl. Organomet. Chem*., **2020**, *34*, e5276. DOI: 10.1002/aoc.5276
37. A. N. Rodionov, L. V. Snegur, A. A. Simenel, Yu. V. Dobryakova, V. A. Markevich, *Russ. Chem. Bull*., **2017**, *66*, 136–142. DOI: 10.1007/s11172-017-1711-1
38. D. Dheer, V. Singh, R. Shankar, *Bioorg. Chem*., **2017**, *71*, 30–54. DOI: 10.1016/j.bioorg.2017.01.010
39. M. Maschke, M. Lieb, N. Metzler-Nolte, *Eur. J. Inorg. Chem*., **2012**, 5953–5959. DOI: 10.1002/ejic.201200798
40. A. A. Simenel, Y. V. Kuzmenko, E. A. Morozova, M. M. Ilyin, I. F. Gun'ko, L. V. Snegur, *J. Organomet. Chem.*, **2003**, *688,* 138–143. DOI: 10.1016/j.jorganchem.2003.08.039
41. L. V. Snegur, Yu. A. Borisov, Yu. V. Kuzmenko, V. A. Davankov, M. M. Ilyin, M. M. Ilyin Jr, D. E. Arhipov, A. A. Korlyukov, S. S. Kiselev, A. A. Simenel, *Molecules*, **2017**, *22*, 1410. DOI: 10.3390/molecules22091410
42. A. N. Rodionov, M. D. Gerasimova, E. Yu. Osipova, A. A. Korlyukov, A. S. Peregudov, A. A. Simenel, *Monatsh. Chem.*, **2017**, *148*, 925–932. DOI: 10.1007/s00706-016-1895-3
43. E. Yu. Osipova, A. N. Rodionov, D. E. Arkhipov, M. M. Il'in, A. A. Simenel, *Russ. Chem. Bull.*, **2014**, *63* 2285–2289. DOI: 10.1007/s11172-014-0736-y
44. E. Yu. Osipova, A. A. Simenel, A. N. Rodionov, V. V. Kachala, *Zh. Org. Khim.*, **2012**, *48*, 1449–1454.
45. L. V. Snegur, M. V. Lyapunova, D. D. Verina, V. V. Kachala, A. A. Korlyukov, M. M. Ilyin Jr, V. A. Davankov, L. A. Ostrovskaya, N. V. Bluchterova, M. M. Fomina, V. S. Malkov, K. V. Nevskaya, A. G. Pershina, A. A. Simenel, *J. Organomet. Chem.*, **2018**, *871*, 10–20. DOI: 10.1016/j.jorganchem.2018.06.019
46. E. Yu. Osipova, A. S. Ivanova, A. N. Rodionov, A. A. Korlyukov, D. E. Arkhipov, A. A. Simenel, *Russ. Chem. Bull.*, **2016**, *65*, 2868–2872. DOI: 10.1007/s11172-016-1670-y
47. E. Yu. Rogatkina (Osipova), A. S. Ivanova, A. N. Rodionov, A. S. Peregudov, A. A. Korlyukov, A. D. Volodin, Yu. A. Belousov, A. A. Simenel, *ARKIVOC*, **2018**, *5*, 272–282. DOI: 10.24820/ark.5550190.p010.413
48. A. N. Rodionov, K. Ya. Zherebker, L. V. Snegur, A. A. Korlyukov, D. E. Arhipov, A. S. Peregudov, M. M. Ilyin, M. M. Ilyin Jr, O. M. Nikitin, N. B. Morozova, A. A. Simenel, *J. Organomet. Chem.*, **2015**, *783*, 83–91. DOI: 10.1016/j.jorganchem.2015.01.031
49. V. I. Boev, P. M. Betankoirt, L. V. Popova, V. N. Babin, *Zh. Obshch. Khim*., **1991**, *61*, 1651–1655.

50. E. V. Shevaldina, K. A. Opredelennova, O. A. Chichvarina, Yu. Ya. Spiridonov, A. F. Smol'yakov, P. V. Dorovatovskii, S. K. Moiseev, *Appl. Organomet. Chem.*, **2019**, *33*, e5228. DOI: 10.1002/aoc.5228
51. M. Joksović, Z. Ratković, M. Vukićević, R. D. Vukićević, *Synlett*, **2006**, *16*, 2581–2584. DOI: 10.1055/s-2006-950436
52. E. Yu. Osipova, A. A. Simenel, A. N. Rodionov, V. V. Kachala, K. Ya. Zherebker, *Vestnik MITKHT*, **2009**, *4*, 100–105.
53. A. N. Rodionov, A. A. Simenel, A. A. Korlyukov, V. V. Kachala, S. M. Peregudova, K. Ya. Zherebker, E. Yu. Osipova, *J. Organomet. Chem.*, **2011**, *696*, 2108–2115. DOI: 10.1016/j.jorganchem.2010.11.018
54. A. N. Rodionov, A. A. Simenel, Yu. S. Nekrasov, V. V. Kachala, E. Yu. Osipova, K. Ya. Zherebker, *Russ. Chem. Bull*., **2010**, *59*, 405–410. DOI: 10.1007/s11172-010-0093-4
55. E. Yu. Osipova, A. N. Rodionov, A. A Simenel, N. V. Konovalova, V. V. Kachala, *Macroheterocycles*, **2011**, *4*, 124–126. DOI: 10.6060/mhc2011.2.11
56. E. Yu. Osipova, A. N. Rodionov, A. A. Simenel, Yu. A. Belousov, O. M. Nikitin, V. V. Kachala, *J. Porphyrins Phthalocyanines*, **2012**, *16*, 1225–1232. DOI: 10.1142/S1088424612501246
57. E. Yu. Osipova, A. N. Rodionov, Yu. A. Belousov, M. M. Il'in, A. L. Nikolaev, A. V. Gopin, S. E. Mazina, A. A. Simenel, *Russ. J. Org. Chem.*, **2016**, *52*, 127–130. DOI: 10.1134/S1070428016010243
58. E. Yu. Osipova, A. N. Rodionov, E. F. Kudryashova, N. V. Konovalova, A. A. Simenel, *Macroheterocycles*, **2017**, *10*, 317–319. DOI: 10.6060/mhc170398o
59. E. Yu. Rogatkina, A. N. Rodionov, S. E. Mazina, A. A. Simenel, *J. Porphyrins Phthalocyanines*, **2020**, *in press*. DOI: 10.1142/S1088424620500431
60. E. Yu. Rogatkina, A. N. Rodionov, S. E. Mazina, Yu. A. Belousov, A. A. Simenel, *Macroheterocycles*, **2020**, *in press*.
61. Z.-J. Dai, S. Li, J. Gao, X.-N. Xu, W.-F. Lu, S. Lin, X.-J. Wang, *Med. Hypotheses*, **2013**, *80*, 300–302. DOI: 10.1016/j.mehy.2012.12.009
62. I. Rosenthal, J. Z. Sostaric, P. Riesz, *Ultrason. Sonochem.*, **2004**, *11*, 349–363. DOI: 10.1016/j.ultsonch.2004.03.004
63. M. Kuroki, K. Hachimine, H. Abe, H. Shibaguchi, M. Kuroki, S.-I. Maekawa, J. Yanagisawa, T. Kinugasa, T. Tanaka, Y. Yamashita, *Anticanser Res*., **2007**, *27*, 3673–3677.
64. K. Kalka, H. Merk, H. Mukhtar, *J. Am. Acad. Dermatol*., **2000**, *42*, 389–413. DOI: 10.1016/S0190-9622(00)90209-3
65. *The Porphyrin Handbook*, K. M. Kadish, K. M. Smith, R. Guilard (Eds.), Acad. Press, Amsterdam, **2003**.
66. E. V. Filonenko, V. V. Sokolov, V. I. Chissov, E. A. Lukyanets, G. N. Vorozhtsov, *Photodiagn. Photodyn. Ther*., **2008**, *5*, 187–190. DOI: 10.1016/j.pdpdt.2008.06.001
67. L. G. Arnaut, *Adv. Inorg. Chem.*, **2011**, *63*, 187–233. DOI: 10.1016/B978-0-12-385904-4.00006-8
68. H. Tsuru, H. Shibaguchi, M. Kuroki, Yu. Yamashita, M. Kuroki, *Free Radical Biol. Med.*, **2012**, *53*, 464–472. DOI: 10.1016/j.freeradbiomed.2012.04.025
69. H. Chen, X. Zhou, Y. Gao, B. Zheng, F. Tang, J. Huang, *Drug Discovery Today*, **2014**, *19*, 502–509. DOI: 10.1016/j.drudis.2014.01.010
70. N. Suzuki, K. Okada, S. Chida, C. Komori, Y. Shimada, T. Suzuki, *Anticancer Res*., **2007**, *27*, 4179–4184.
71. C. Komori, K. Okada, K. Kawamura, S. Chida, T. Suzuki, *Anticancer Res.*, **2009**, *29*, 2411–2415.
72. N. Bertrand, J. Wu, X. Xu, N. Kamaly, O. C. Farokhzad, *Adv. Drug Delivery Rev.*, **2014**, *66*, 2–25. DOI: 10.1016/j.addr.2013.11.009
73. T. Sun, Y. S. Zhang, B. Pang, D. C. Hyun, M. Yang, Y. Xia, *Angew. Chem., Int. Ed*., **2014**, *53*, 12320–12364. DOI: 10.1002/anie.201403036