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In vitro DNA protective potential of selected ferrocenyl *N*-acyl pyrazolines

Chaired by Dr. Alfredo Berzal-Herranz and Prof. Dr. Maria Emília Sousa

pharmaceuticals MDPI

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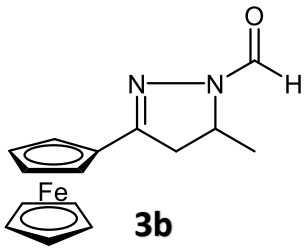
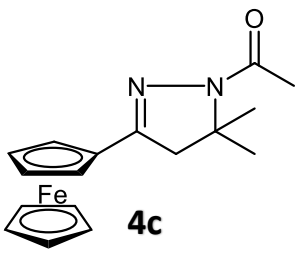
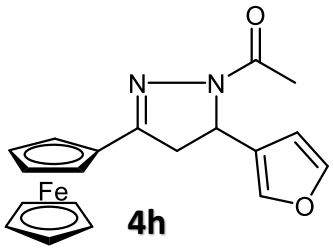
Graphical Abstract



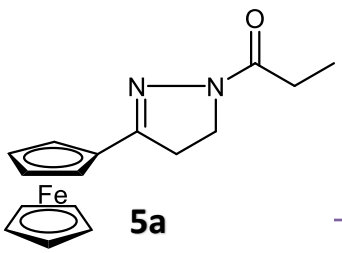
3b



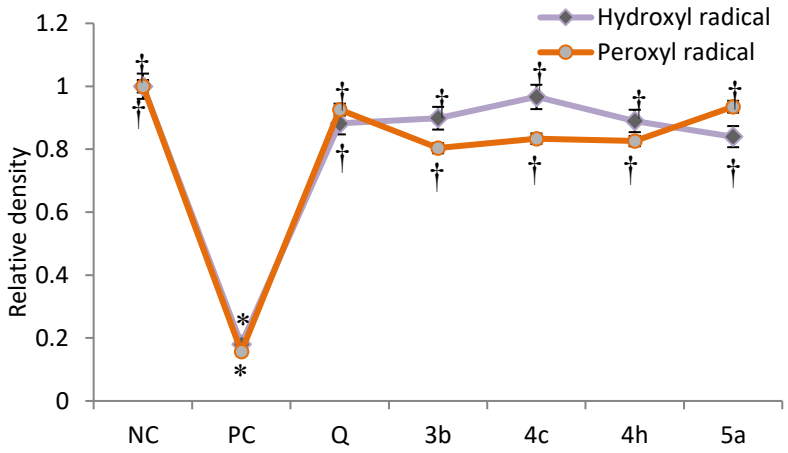
4c

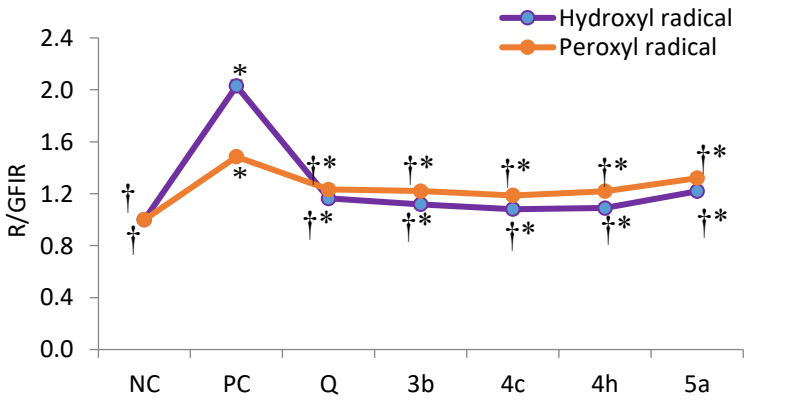


4h



5a





Abstract: Pyrazolines have played a crucial role in the development of various biologically active compounds. At the same time, the ferrocene moiety represents a significant part of the structure of these types of molecules. For this reason, we presumed that the incorporation of different pharmacophores in the same structure could lead to interesting changes, and we decided to synthesize some new ferrocenyl *N*-acyl pyrazolines. The DNA protective effect of four selected ferrocenyl *N*-acyl pyrazolines namely 5-methyl-3-ferrocenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (**3b**), 1-(5,5-dimethyl-3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**4c**), 1-(5-(furan-2-yl)-3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**4h**), and 1-(3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl)propan-1-one (**5a**) in concentration of 100 µg/mL against hydroxyl and peroxyl radicals-induced DNA damage was assessed using salmon sperm DNA sodium salt as a model system. The acridine orange assay was performed to analyze the DNA integrity of the selected compounds at the same concentrations. The tested compounds in the selected dose had a statistically significant potency to protect DNA from damage caused by hydroxyl and peroxyl radicals. According to the acridine orange assay selected compounds significantly reduced hydroxy and peroxyl radicals induced denaturation and damage to DNA. The results showed that the tested compounds revealed strong protective activity against hydroxy and peroxyl radicals-induced DNA damage.

Keywords: acridine orange assay; antigenotoxic activity; ferrocene; pyrazoline.

Introduction

Pyrazolines are well-known class of heterocyclic compounds with remarkable biological activities and numerous structural possibilities. Ferrocene is one of the most promising organometallic compound with important biological properties such as antimicrobial, antitumour, and anti-inflammatory (Sharma and Kumar, 2021).

Till date, there are only one report on the antigenotoxic activity of *N*-acetyl and *N*-formyl pyrazoline derivatives from vanillin (Muškinja et al., 2019).

B. Sharma, V. Kumar, Has ferrocene really delivered its role in accentuating the bioactivity of organic scaffolds?, Journal of Medicinal Chemistry 2021, 64 (23), 16865-16921.

J. Muškinja, S. Matić, S. Stanić, Z. Ratković, *S*ynthesis of N-acetyl and N-formyl pyrazoline derivatives from vanillin and their antigenotoxic activity, in Proceedings of the 5th International Electronic Conference on Medicinal Chemistry (ECMC-5), 1–30 November 2019, MDPI: Basel, Switzerland, doi:10.3390/ECMC2019-06358.

Introduction

Thus, in this study, four novel ferrocenyl *N*-acyl pyrazolines (**Figure 1**) namely 5-methyl-3-ferrocenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (**3b**), 1-(5,5-dimethyl-3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**4c**), 1-(5-(furan-2-yl)-3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**4h**), and 1-(3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl)propan-1-one (**5a**) were evaluated for the ability to prevent DNA damage caused by Fe^{2+}, H_2O_2, and AAPH (2,2'-azobis(2-amidinopropane) dihydrochloride).

Introduction

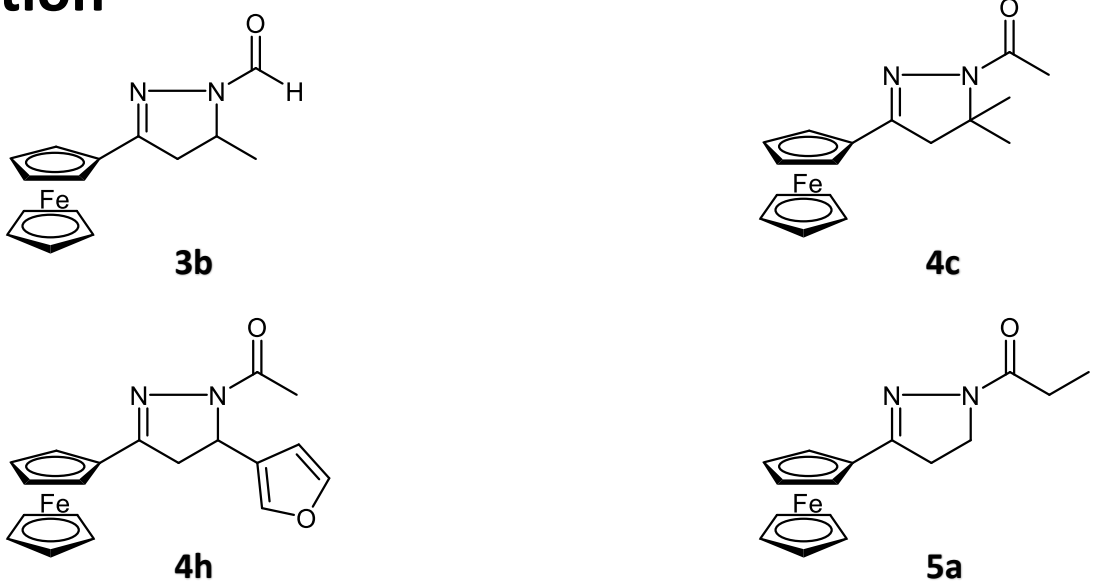


Figure 1. Chemical structures of four novel ferrocenyl *N*-acyl pyrazolines 5-methyl-3-ferrocenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (**3b**), 1-(5,5-dimethyl-3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**4c**), 1-(5-(furan-2-yl)-3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**4h**), and 1-(3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl)propan-1-one (**5a**)

Results and discussion

The results indicated that all tested compounds exhibited significant DNA protective effect (**Figure 2**).

Among them, compound **4c** displayed the most DNA protective activity against hydroxyl radical, while compound **5a** showed the most significant DNA protective potential against peroxyl radical compared with quercetin as the well-known antioxidant.

Results and discussion

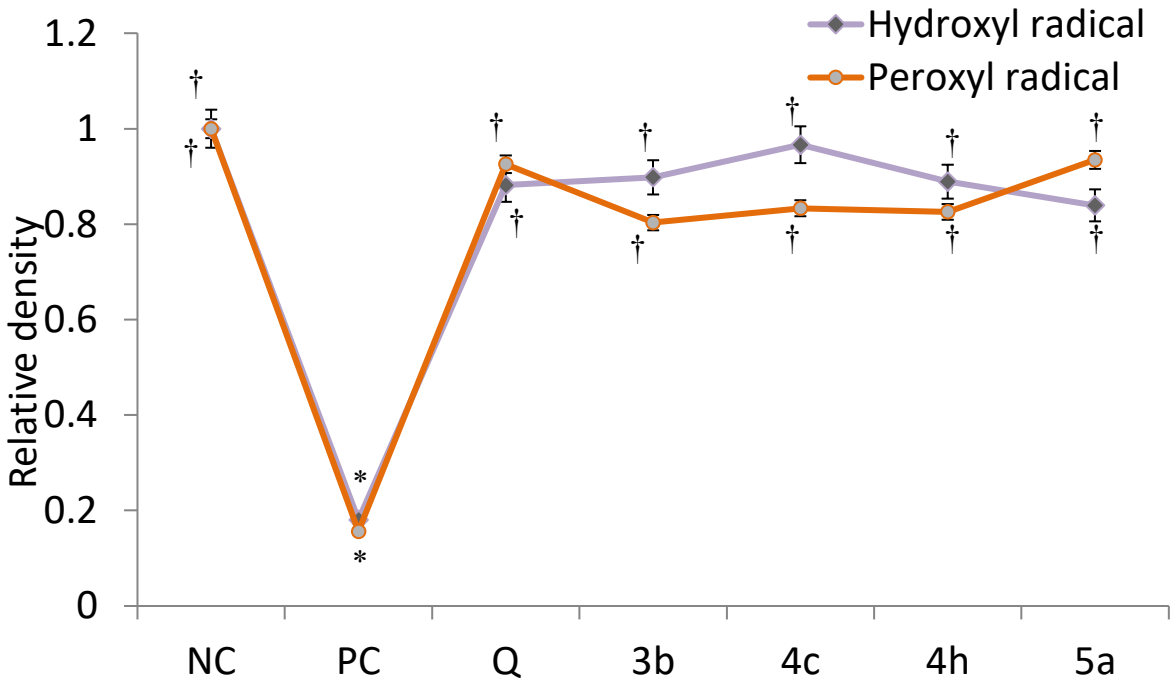


Figure 2. DNA protective effect of compounds **3b**, **4c**, **4h**, and **5a** against hydroxyl and peroxyl radicals-induced DNA damage.
DNA from salmon sperm (NC, negative control), DNA damage control (PC, positive control), quercetin (Q, 100 µg/mL, standard), selected compounds at the concentrations of 100 µg/mL (**3b**, **4c**, **4h**, and **5a**). *$p < 0.05$ when compared with the negative control group; $^{\dagger}p < 0.05$ when compared with the positive control group

Results and discussion

According to the acridine orange assay, Fe^{2+}, H_2O_2, and AAPH induced significant denaturation and damage to DNA (**Figure 3**).

The results showed that values for R/GFIR were statistically significant increased compared to negative control, where the highest damage of DNA integrity was observed in positive control. However, there are statistically significant decreasing of DNA damages in tested compounds compared to positive control.

Results and discussion

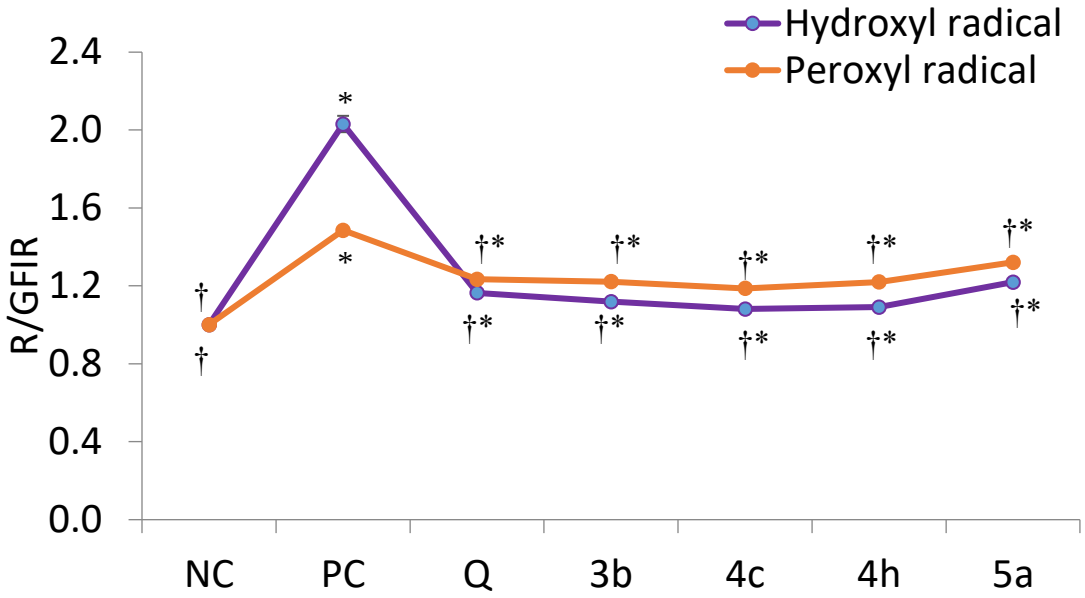


Figure 3. DNA protective effect of compounds **3b**, **4c**, **4h**, and **5a** against hydroxyl and peroxyl radicals-induced DNA damage.
DNA from salmon sperm (NC, negative control), DNA damage control (PC, positive control), quercetin (Q, 100 µg/mL, standard), selected compounds at the concentrations of 100 µg/mL (**3b**, **4c**, **4h**, and **5a**). The results are presented as red (single stranded DNA) to green (double stranded DNA) fluorescence intensity ratios (R/GFIR) of AO, measured as relative density from sample bands.
*$p < 0.05$ when compared with the negative control group; †$p < 0.05$ when compared with the positive control group

Results and discussion

To the best of our knowledge there is only one report for antigenotoxic potential of novel *N*-acetyl and *N*-formyl pyrazoline derivatives from vanillin (Muškinja et al., 2019). Burmudžija et al. (2016) reported a significant larger affinity of 1-[5-(3,4-dimethoxyphenyl)-3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl]ethanone and 3-(4-butoxy-3-methoxyphenyl)-5-ferrocenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde to substitute ethidium bromide from the DNA-ethidium bromide complex than 1-[5-(4-benzyloxy-3-methoxyphenyl)-3-ferrocenyl-4,5-dihydro-1*H*-pyrazol-1-yl]ethanone and 3-(3,4-dimethoxyphenyl)-5-ferrocenyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde.

A. Burmudžija, Z. Ratković, J. Muškinja, N. Z. Janković, B. Ranković, M. Kosanić, S. Đorđević, Ferrocenyl based pyrazolines derivatives with vanillic core: synthesis and investigation of its biological properties, RSC Advances 2016, 6, 91420-91430

Conclusion

The present work describes the DNA protective effect of four selected ferrocenyl *N*-acyl pyrazolines in concentration of 100 µg/mL against hydroxyl and peroxyl radicals-induced DNA damage using salmon sperm DNA sodium salt as a model system.

The results showed that four novel ferrocenyl *N*-acyl pyrazolines showed strong protective activity against hydroxyl and peroxyl radicals-induced DNA damage.

Acknowledgments

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