ROS-activated prodrugs based on ferrocenyliminoboronates: Redox dependent stability and cytotoxicity

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Elevated levels of reactive oxygen species (ROS) have been detected in almost all types of cancers. ROS play an interesting dualistic role in tumour proliferation, promoting its growth at certain levels and causing cell death through oxidative stress at higher levels.[1] Ferrocene derivates were observed to induce cell death through a Fenton-like mechanism, where hydrogen peroxide reacts with iron to form hydroxyl radicals and other reactive species that react with organic material.[2]

We have tested four commercially available ferrocene derivates and found the one with the lowest redox potential (aminoferrocene) to be the most cytotoxic. Thus, four novel derivatives (**Figure 1**) consisting of aminoferrocene and phenylboronic acid have been synthesized with the intent to use them as ROS-activated prodrugs. We have employed a labile imine bond between these two components as it has shown accelerated hydrolysis under oxidative conditions, and as such, it should release the cytotoxic agent in the area of elevated ROS levels. The novel derivatives were characterized regarding their time-dependent stability in aqueous environments. Then, we performed electrochemical measurements at oxidative conditions to confirm the ROS-responsivity of the synthesized molecules. Finally, the cytotoxicity of the synthesized molecules was tested using cancer MG-63 cells and noncancerous NIH-3T3 cells. Out of the derivatives prepared, *para*-isomers showed improved stability and cytotoxicity over *ortho*-isomers.

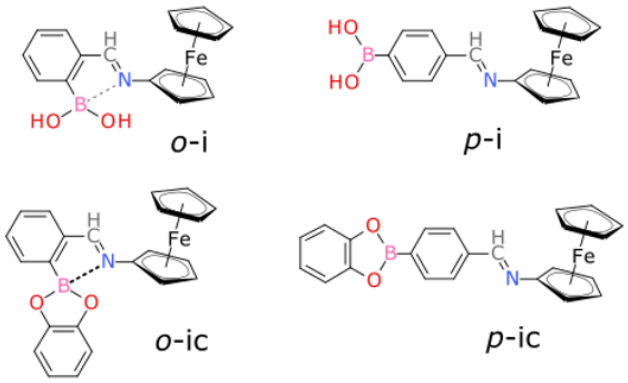

Figure 1: The four prepared and studied *(ferrocenylimino)methyl)phenylboronic acids*

References

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Acknowledgements

This research has been financially supported by the Ministry of Education, Youth and Sports of the Czech Republic under the project CEITEC 2020 (LQ1601), by Masaryk University under the project (MUNI/A/1424/2019), and by the Czech Science Foundation, grant nr.19-16273Y. We also acknowledge CF Nanobiotechnology supported by MEYS CR (LM2015043) and CEITEC Nano+ project CZ.02.1.01/0.0/0.0/16_013/0001728.