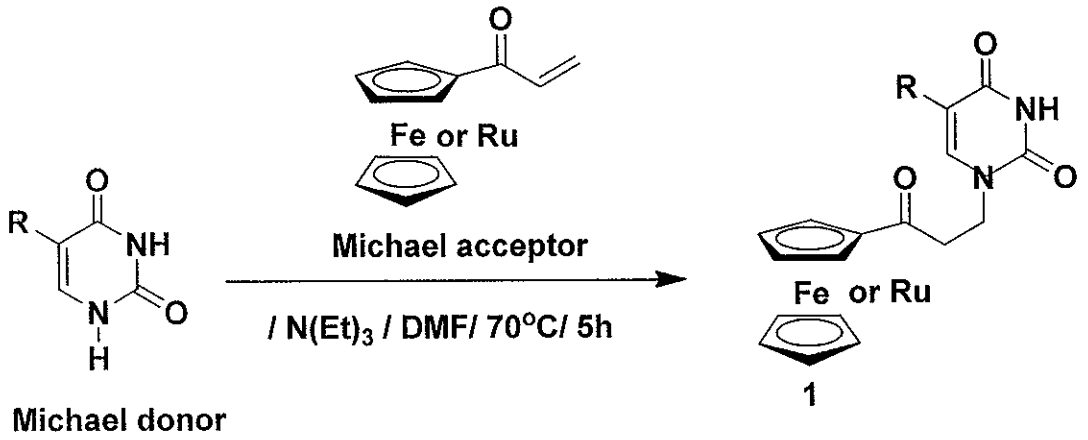
Joanna Skiba

Summary of the dissertation entitled

„Metalocenyl derivatives of nucleic bases and β-lactam antibiotics – as new class of biorganometallic conjugates with anticancer and antibacterial activity"

Nucleotides, nucleosides, and nucleobases have found therapeutic applications to treat virus infections and cancer diseases. Currently nucleoside analogs represents *ca.* fifty percent of all antiviral drugs in clinical use. Furthermore, fourteen nucleoside derivatives are approved for the treatment of cancer [1].

Metallocene-nucleobases are complexes bearing a metllocenyl (in most cases ferrocenyl) moiety attached to the nucleobase entity. This group of molecules was a first subject of my PhD thesis. Major aim of my work was to elaborate effective synthetic methods for the obtaining of novel metallocenyl (ferrocenyl and ruthenocenyl) nucleobase complexes [2]. To rich this goal a Michael addition reaction of *in situ* generated acryloylferrocenes with nucleobeses was developed and optimized (Scheme 1) [2-4].



Scheme 1. Formation of Michael adducts **1**

Complexes of class **1** were further transformed into corresponding alkohols **2** [2,3], olefins **3** [3], and derivatives bearing aliphatic Fc-nucleobase linkers **4** [4] (Fig. 1). Iodouracil derivatives were coupled to ethynylferrocene under the Sonogashira reaction conditions to afford dinuclear complexes **5** (Fig. 1) [4].

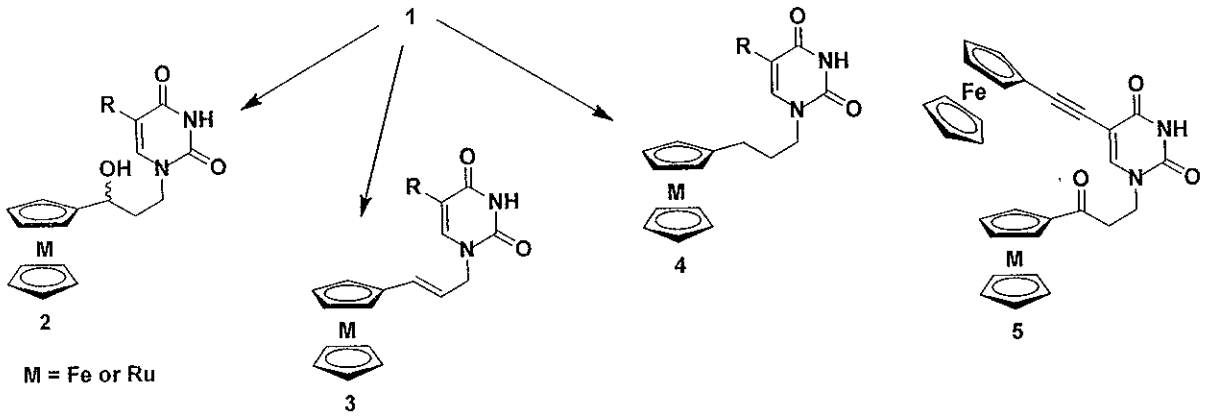


Fig. 1 Structure of metallocenyl nucleobases studied in my work

Compounds **1-5** represents new classes of organometallic-nucleobase complexes. They were fully characterized by means of spectroscopic and cyclic voltammetry methods and five X-ray crystal structures were solved for these complexes. Majority of newly obtained compounds **1-5** were antibacterial and anticancer tested. Some of them showed significant bactericidal and anticancer activity [2-4].

Second aim of my PhD thesis was to obtain ferrocenyl and ruthenocenyl derivatives of 6-aminopenicillanic (6-APA) and ampicillin. The synthetic approach for the preparation of these complexes involves reaction of either 6-APA or ampicillin with 4-oxo-4-(metallocenyl) butanoic and 5-oxo-5-(metallocenyl) pentanoic *N*-succinimidyl esters [5]. Lack of antibacterial activity was observed for ampicillin derivatives while 6-APA conjugates **6-8** (Fig. 2) showed significant bactericidal activity against *S. aureus* strains.

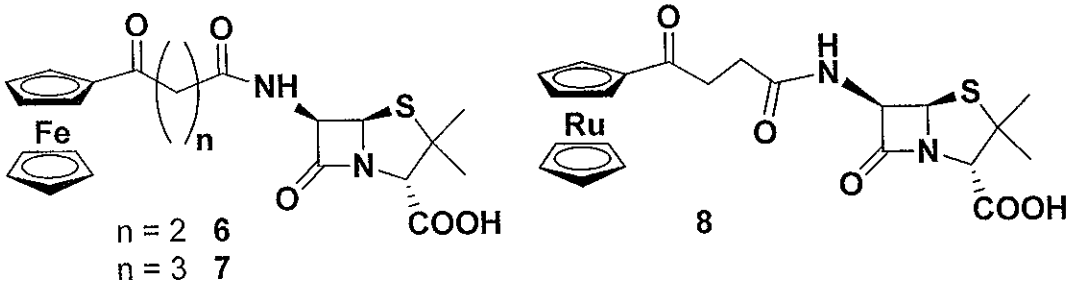


Fig. 2 Structures of bactericidal metallocenyl conjugates of 6-APA

An atomic resolution X-ray crystal structure of complex **8** bind to bacterial CTX-M β-lactamase was determined [6].

References

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