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Review

Ferrocene derivatives as anti-infective agents

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ABSTRACT

Infectious diseases like malaria, tuberculosis or HIV are among the leading causes of death worldwide according to WHO estimations. Nevertheless, the fight against infectious diseases is aggravated through growing development of resistance towards current drugs and due to their severe adverse effects. The introduction of the lipophilic organometallic moiety ferrocene, a compound with a sandwich-like structure, in an existing bioactive molecule is a promising tool for the development of new more efficient drugs with innovative mechanisms of action. Thus, this review summarizes recent developments in the field of ferrocene conjugation to bioactive molecules like natural products, synthetically derived drugs, peptides as well as heterobimetallic complexes. Hereby, we will provide the reader with a summary of the most potent ferrocene derivatives reported for a plethora of infectious diseases by tabulating and critically assessing the corresponding IC_{50} values and the minimal inhibitory concentrations (MIC). Owing to the diverse field of infectious diseases the reported ferrocene derivatives were classified according to their targets into four main groups: antiparasitic (with antimalarial agents as biggest group), antibacterial, antifungal and antiviral agents.

Contents

Abbreviations: 7-ADCA, 7-aminodesacetoksycephalosporanic acid; AIDS, acquired immunodeficiency syndrome; 6-APA, 6-aminopenicillanic acid; Arg, arginine; Asn, asparagine; BM, bioactive molecule; CD4, cluster of differentiation-4; CQ, chloroquine; CTX-M, otaxime hydrolyzing capabilities; DAAs, directly acting antiviral agents; DHFR, dihydrofolate reductase; FabF, β-ketoacyl-(acyl-carrier-protein) synthase II; Fc, ferrocene; Fc+, ferrocenium radical cation; FQ, ferroquine; GSH, glutathione; Hb, hemoglobin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; Hz, hemozoin; IC_{50}, half maximal inhibitory concentration; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MTP1, metal transporter protein 1; MurG, undecaprenyl-diphospho-*N*-acetylmuramoyl-pentapeptide-β-*N*-acetylglucosaminyl transferase; NADP/NADPH, nicotinamide adenine dinucleotide phosphate; NS3/4A, nonstructural protein 3/4A; NS5A, nonstructural protein 5A; NS5B, nonstructural protein 5B; NTD, neglected tropical disease; OH-TAM, hydroxytamoxifen; OM-AMP, antimicrobial peptides with organometallic fragment; PBP, penicillin binding proteins; PFOR, pyruvate: ferredoxin oxidoreductase; Ph, phenyl group; PNP, purine nucleoside phosphorylase; Rc, ruthenocene; ROS, reactive oxygen species; Ser, serine; SOD, superoxide dismutase; sp., species; spp., species pluralis; TAM, tamoxifen; Thr, threonine; TRX, thioredoxin; TrxR, thioredoxin reductase; WHO, World Health Organization.

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1. Introduction

10,000 years ago, early humans changed from hunters and gatherers to farmers and cattle breeders (Neolithic Revolution) [1]. Although there was a rapid population growth associated to that change, entire populations were periodically decimated, especially by infectious diseases and epidemic plagues [2,3]. Pathogenic bacteria or viruses were the main infectious agents, but also protozoa, fungi and worms were among the causative agents of infection (Table 1) [2–5].

An infection is a process in which a microorganism matures or propagates in or on a host [5,6]. After a certain incubation time, in most of the cases, the host develops signs of illness, such as fever or nausea [6,13,20]. The infected human or animal can subsequently contaminate the environment (objects, air, water, etc.) with germs through secreted body fluids, e.g. urine, saliva, etc. [4,6,21]. According to the different transmission routes of pathogens nine different pathways can be distinguished (Table 1). Infectious diseases of humans and animals played an important role in history. Indeed, bacteria and viruses repeatedly wiped out entire areas, triggered the migration of people or decided wars [22]. For example, during the 14th century the Black Death epidemic decimated between a third and a half of the European population [2]. With the development of bacteriology at the end of the 19th century and the serendipitous discovery of penicillin by A. Fleming in 1928 the therapeutically applicable principle of antibiosis became prominent [23,24]. By means of antibiotics pathogenic bacteria could now be combated in a relatively simple way [23]. Infectious diseases lost their character as existential threat to entire societies, becoming a manageable problem. Nonetheless, at that time still referred to as "*miracle drugs*" [25], the excessive use of antibiotics nowadays, especially the prophylactic antibiotic therapy, poses a high potential danger: bacteria are very adaptable and develop quite rapidly resistances [25]. Without effective drugs for the prevention and treatment of infections, the human ability to combat common infectious diseases is threatened, resulting in prolonged illness, disability and death [25,26]. According to the World Health Organization 558,000 people developed multi-drug resistant tuberculosis globally in 2017, and drug resistance is starting to complicate the fight against malaria and HIV, as well [26–28]. The emergence and reemergence of infectious diseases of humans, animals and plants is dependent on a plethora of factors, comprising social, economic and ecological conditions and the access to healthcare [29]. Modern factory farming creates ideal conditions for the appearance of novel or multi-drug resistant pathogens and the globalized way of life ensures their rapid and efficient dissemination [30,31].

Additionally, many vector organisms, infectious agents, non-human reservoir species and pathogen replication rates are inextricably tied to climatic changes [29,32–37]. According to *Baylis et al.* continuing global warming will lead to complex changes in the prevalence, proliferation rates, transmission seasons and spatial distribution to higher latitudes or altitudes of pathogenic viruses, parasites, bacteria and fungi [38]. An increased spread of malaria [39–41], Ross river virus [42], leishmaniasis [43], yellow, dengue and chikungunya fever [44,45] and West Nile Virus [46], all transmitted by vectors like mosquitoes or sand flies, to more northern or southern regions from the equator is predicted [47,48]. Fungi, such as the wheat yellow rust plant pathogen *Puccinia striiformis f.* sp. *Tritici* [49,50] or the bacterial spirochete *Borrelia burgdorferi* [51], the causative agent of Lyme borreliosis, are some of the profiteers of global warming [52,53]. In view of this, a continuous development of new drugs to combat existing infectious diseases and new pathogens as well as to overcome resistance barriers are big concerns of the 21st century. Especially the search for active substances made by microorganisms, so called secondary metabolites, seems to be very promising [54–56]. For example, *Brady* and coworkers have recently isolated malacidins, new calcium-dependent antibiotics, with activity against multidrug-resistant *Staphylococcus aureus* (*S. aureus*) strains [57].

Table 1
Transmission pathways of infectious diseases [6].

Transmission pathway	Comments	Examples	Ref.
Foodborne	pathogens that adhere on or live in food	*Escherichia coli, Listeria*	[4,6–8]
through water			[4,6]
i) waterborne	i) pathogens transmitted through feces and by ingestion	i) *Salmonella*, *Vibrio cholerae*	
ii) water-washed	ii) caused by poor personal hygiene	ii) *Clamydia trachomatis*, *Toxocara canis*	
iii) water-based	iii) by aquatic invertebrate organisms transmitted	iii) blood flukes, *Legionella*	
iv) water-related	iv) by insects, that depend on water, transmitted	iv) *Plasmodium falciparum*	
Airborne	pathogens get during sneezing, coughing or speaking through tiny saliva droplets in the air, where they are inhaled by other potential hosts	*Mycobacterium tuberculosis, Aspergillus* sp.	[4,6,9–12]
vector-borne	pathogens transmitted through vectors	*Plasmodium falciparum, Flavivirus, Alphavirus, Japanese encephalitis virus, yellow fever virus, dengue virus, chikungunya virus*	[4,6,13–17]
Zoonoses	diseases transmitted by animals	*Rabiesvirus*, *Brucella*	[4,18]
Bloodborne	pathogens transmitted through contact with infected blood	*Hepatitis B virus*, *Hepatitis C*, HIV	[4,19]
sexually transmitted diseases	pathogens transmitted through sexual intercourse	HIV, *Treponema pallidum* ssp. *Pallidum*	[4,19]
Soilborne	by dormant (spores) or non-dormant pathogens in soil	*Bacillus anthracis, Clostridium tetani*	[4]
smear infections	pathogens transmitted through direct contact with host organism or contaminated objects (fecal-oral way)	*Adenovirus, Herpesviridae*	[4,6]

In parallel to these studies, secondary metabolites, but also approved drugs or peptides have been derivatized with organometallic moieties resulting in a plethora of new molecules with interesting biological effects [58–61]. Bioorganometallic chemistry investigates the link between classical organometallic chemistry, compounds that are characterized by at least one carbon-metal atom bond, to biology and medicine [58–61]. To date, one of the best studied organometallic compounds is ferrocene **1** (Fc = $(\eta^5\text{-}C_5H_5)_2Fe$; Fig. 1. A) with numerous applications in different fields of chemistry and medicine [58,62–67].

First reported in 1951, the metallocene contains an iron center, which is located between two cyclopentadienyl ligands [71–73]. The lipophilic sandwich-like molecule and most of its derivatives are air, water and thermally stable [73,74]. The conjugation/incorporation of ferrocene into a bioactive or an existing drug molecule (Fig. 1, ferroquine) or the replacement of a phenyl ring, a functional analogue of the ferrocenyl group (Fig. 1, ferrocifens), by ferrocene has become a widely used strategy in the enhancement of therapeutic activity [75]. Due to the lipophilic character of ferrocene, ferrocene derivatives trespass easier cell membranes. Remarkably, the ferrocenyl group undergoes a reversible one-electron oxidation under emission of an electron via a Fenton-like reaction under physiological conditions, which leads to the corresponding ferrocenium radical cation Fc^{+} **2** (Fig. 2) and ROS, offering interesting application possibilities in the field of medicinal chemistry. In general, low levels of ROS can act as cellular signaling messengers through modification of protein structure in healthy cells [76,77]. High levels of ROS instead lead to a disruption of normal cellular processes through a nonspecific attack of proteins, lipids and DNA (Fig. 2). In case of macromolecule oxidation possible nucleophilic targets are thiol groups of proteins or low molecular weight metabolites like glutathione, one of the most important antioxidant in human body [78–80]. Most of the newly prepared ferrocene derivatives were investigated towards their anticancer potential [81,82]. Ferrocifen type anticancer agents developed by *Jaouen et al.* as analogues of the anti-breast cancer drug tamoxifen are prominent examples (Fig. 1. A) [69].

In contrast to healthy cells, cancer cells produce ROS because of an increased metabolic rate, dysfunction of mitochondria, expression of oncogenes, increased peroxisome activities and elevated cell signaling [76,77]. By reprogramming glycolysis to assure an adequate supply of nicotinamide adenine dinucleotide phosphate (NADP/NADPH) cancer cells can more efficiently adapt to higher concentrations of ROS than non-cancerous cells [76,77]. Nevertheless, too high concentration of ROS leads to cytotoxicity within the cancer cell [77]. DNA oxidative damage can be observed because of highly increased ROS concentrations. Due to DNA oxidative damage from Fenton reactions and ROS, the cell cycle will be arrested in G2 phase. Lymphocyte activation and redox-active signaling occur due to the ferrocenyl group as well [75]. The Anticancer type

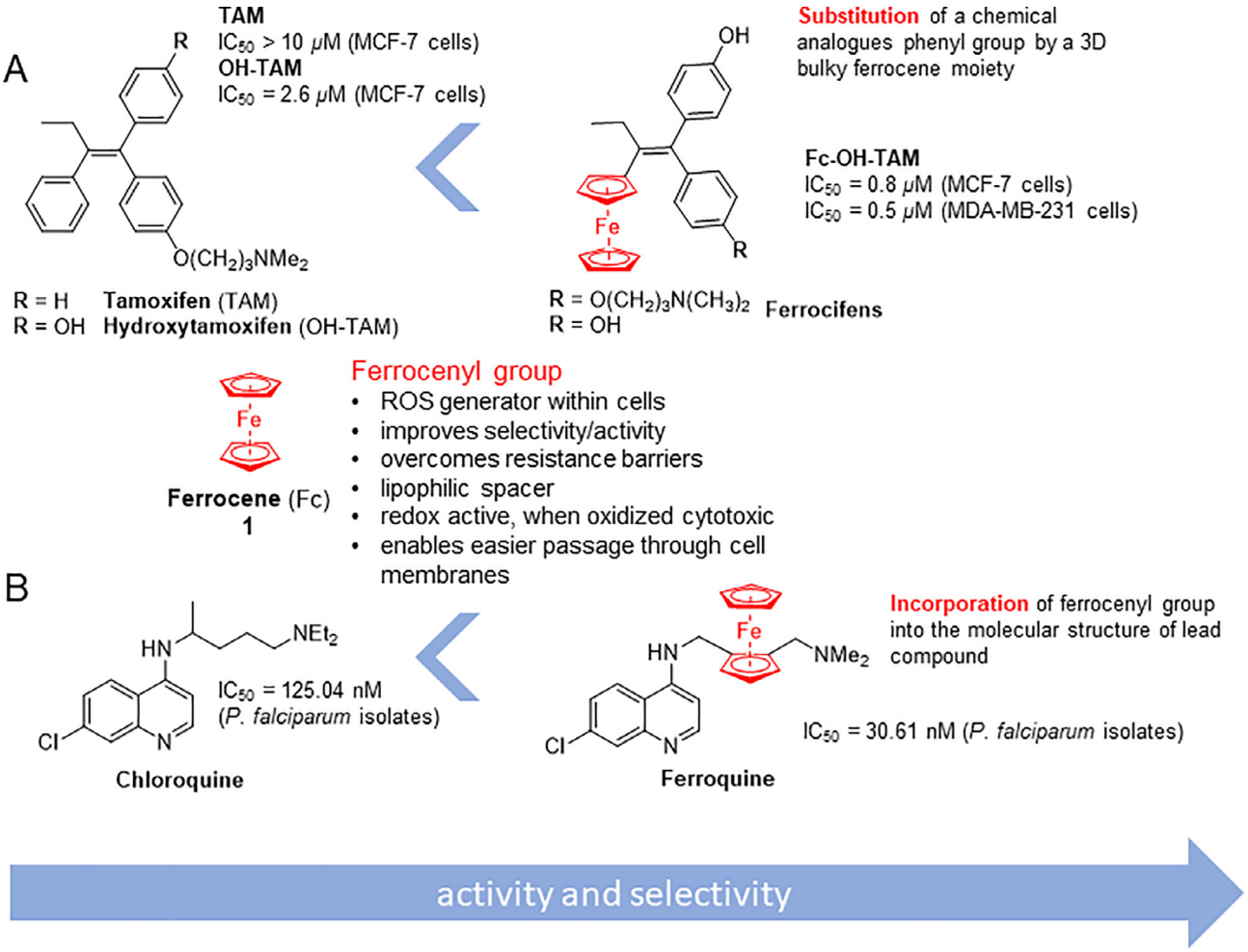


Fig. 1. Ferrocene conjugates of tamoxifen and chloroquine. A. Modification of hydroxytamoxifen [68] to ferrocifens [69] by substitution of a phenyl ring in the tamoxifen molecule leads to lower IC_{50} values in various cancer cell lines as the breast cancer cell lines MCF-7 and MDA-MB-231. B. Ferroquine, derived from the antimalarial drug chloroquine, shows high activity against several *Plasmodium falciparum* (*P. falciparum*) strains [70]. Here, the ferrocene is incorporated into the molecular structure.

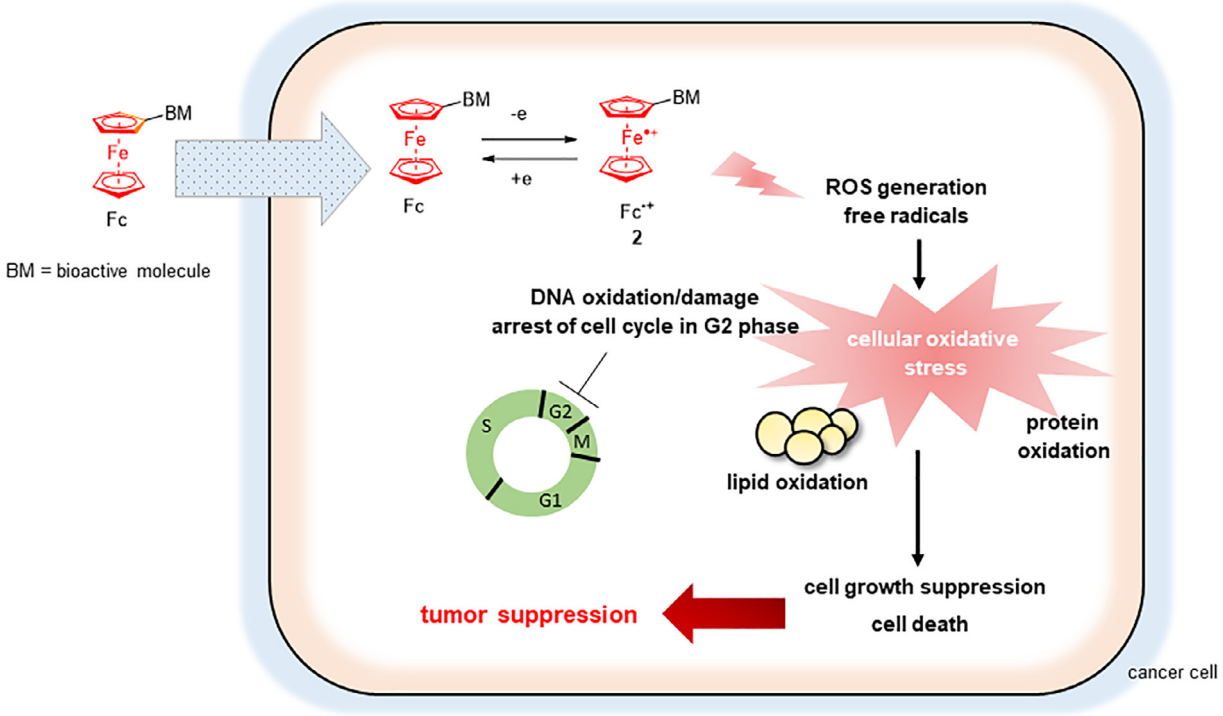


Fig. 2. The effects of oxidative stress on a cancer cell. After entering the cell, the ferrocenyl group of a ferrocene conjugate is oxidized to a ferrocenium radical cation ($Fc^{•+}$, **2**). Hereby free radicals as well as ROS are generated, which lead to cellular oxidative stress, DNA damage, lipid and protein oxidation. The consequences are cell death and tumor growth suppression.

ferrocene conjugates will not be treated here in depth; the reader is directed toward excellent reviews that have been recently published [60,83–85]. Besides their anticancer activity, some ferrocene conjugates show antifungal, antiparasitic and antibacterial properties. Ferroquine (FQ, Fig. 1. B), derived from the antimalaria drug chloroquine (CQ) and currently in phase II clinical trials, is an example of a promising antimalaria agent, particularly in respect of increasing resistance developments of some malaria strains [86]. Interestingly, very little attention has been paid to the investigation of the mode of action of ferrocene conjugated to natural products, peptides or other bioactive compounds regarding their antiparasitic, antifungal, antibacterial or antiviral activity, which is of key importance for the design of new drugs to combat infectious diseases. The present review article focuses on recent developments of such ferrocene conjugates, that show antiparasitic, antibacterial, antifungal or antiviral features. Newly designed compounds with the reported biological activity, published until the end of 2018, will be discussed. Also, a deeper insight into the mode of action of these "unusual" ferrocene conjugates will be presented.

2. Antiparasitic ferrocene conjugates

The coexistence of organisms can occur in multiple forms [87–90]. A mutualism is a close and long-term interaction between different organisms in which the organisms benefit from the presence of each other (e.g. nourishment, protection, crypsis etc.) [87–90]. Human intestinal bacteria, for example, act as digestive aids and thus undergo a mutualism with men [91]. They produce enzymes to break down non-usable food components (e.g. fibres) into components that our body can absorb [91]. If the benefits of the coexistence of two organisms are only on one side, but neither advantages nor disadvantages prevail for the other organism, then this relationship is called commensalism (e.g. the colonization of human skin by staphylococci, which subsist on components of the skin surface without harming the host) [88,89,92,93]. Parasitism, in contrast, exists, if an organism exploits another host organism of a different species, for example by depriving it of nutrients or utilizing it for reproduction purposes [6,89]. Thus, the benefit of this relationship lies one-sided on the parasite [89]. Parasites do not live in a mutualism or commensalism with their host, but rather harm and take advantage of their host: they injure the skin, destroy tissue or eliminate toxic metabolic products, with the result that frequently diseases are triggered [5,89]. Parasites are organisms that depend on one or more hosts during their life cycle [5,94–102]. Usually, the life cycles take place in different hosts (accidental host, intermediate host, final host) [5,6,100–103]. Based on their morphology and on their behavior, human and veterinary medicinal relevant parasites can be divided into three main eukaryotic groups: protozoa (unicellular), helminths (multicellular, parasitic worms) and arthropods (multicellular) [5,6,94–102].

Moreover, parasites can be roughly subdivided into ectoparasites, if they live on the host organism (e.g. fleas, ticks etc.), and endoparasites, if they live in the host organism, as cestodes [5]. Besides foodborne, waterborne and environmentally transmitted infections especially arthropod vectors play a crucial role in the spread of the most prominent parasitic diseases (as for the mosquito-borne diseases malaria [16], yellow fever [15] or dengue fever [17]) [4–6]. In a broader sense pathogenic bacteria and fungi can be also considered as parasites since the general definition of a parasite applies to them as well [5,104–106]. Some authors also include viruses in the definition, albeit biologically they are not living organisms [107,108]. For this chapter – according to the classical definition – the parasites will be grouped into the two categories protozoa and helminths. Ferrocene conjugates with activities against these parasitic groups will be discussed.

2.1. Antiprotozoal ferrocene conjugates

Parasitic protozoa, which are among the known parasites, are classified according to their movement organs such as flagella, pseudopodia or cilia [5,6]. They occur free-living or parasitic in nature [5,109]. Because of their ability to multiply in humans, a single organism can be enough to produce a serious infection [5,109].

2.1.1. Entamoeba histolytica

The most common subgroup of pathogenic *Sarcodina* are parasitic amoeba, which use pseudopods for their movement [5,6]. According to WHO estimations, around 50 million people are affected and 100,000 die each year because of amoebiasis with developing countries and tropical regions especially affected [110]. The causative agent of amoebiasis is the anaerobic microaerophilic pathogen *Entamoeba histolytica* (*E. histolytica*) [111]. Infections lead to mucus and/or blood containing severe diarrhea, abdominal pain and peritonitis [112,113]. *E. histolytica* occurs in two development stages, the cyst (resistant permanent form) stage and the vegetative (trophozoite) stage [112]. In a first step, after ingestion of cysts through food or by drinking water containing feces, the gastric acid-resistant cysts start to convert to trophozoites in the small intestine by excystment [111,112]. Subsequently, the trophozoites colonize and parasitize the upper colon by binding to intestinal absorptive cells (Fig. 3) [111]. In the upper colon, they can either multiply or, by encystment over three steps, develop again cysts [111,112].

Both stages are discarded by the feces. The cysts survive in the external environment for weeks and can infect again other humans, while the excreted ephemeral trophozoites are not contagious [111]. In case of an intestinal disease (Fig. 3, pathway B), the trophozoites located within the lumen of the intestine start an invasion of the intestinal mucosa (which leads to ulcers in the colon) [111–113]. After entering the blood stream, the liver, brain and the lungs can be attacked (extra-intestinal disease leading to amoebic abscesses, pathway A) [112,113]. By producing virulence factors, the pathogen is capable of adhering to human cells and nibbling at them (cell necrosis) [111–113]. Nitroimidazoles like metronidazole (IC_{50} = 1.81 μM [114] for HM1:IMSS strain of *E. histolytica*) are the drugs of choice to treat *E. histolytica* infections (Fig. 4. A) [111,115]. The drug combats effectively anaerobic bacteria and unicellular parasites [115]. The reduction of the nitro-group of metronidazole by thioredoxin reductase (TrxR) generates highly reactive intermediates (e.g. nitroradical anion, nitrosoimidazole) [115,116]. Subsequently, the nitroradical anion forms ROS upon reaction with oxygen, which leads to cell death [115]. Additionally, the radical anion reacts with DNA, especially thymine and adenine rich sequences, or proteins, so that irreparable cell damages are caused [117]. By accepting a further electron, the nitroradical anion gives nitrosoimidazole, a destructive agent for non-protein thiols and several enzymes such as for TrxR [115,116].

However, a long-term treatment with metronidazole is not indicated due to the potential carcinogenic effects and increasing risk of resistance development [118,119]. Several ferrocene deriva-

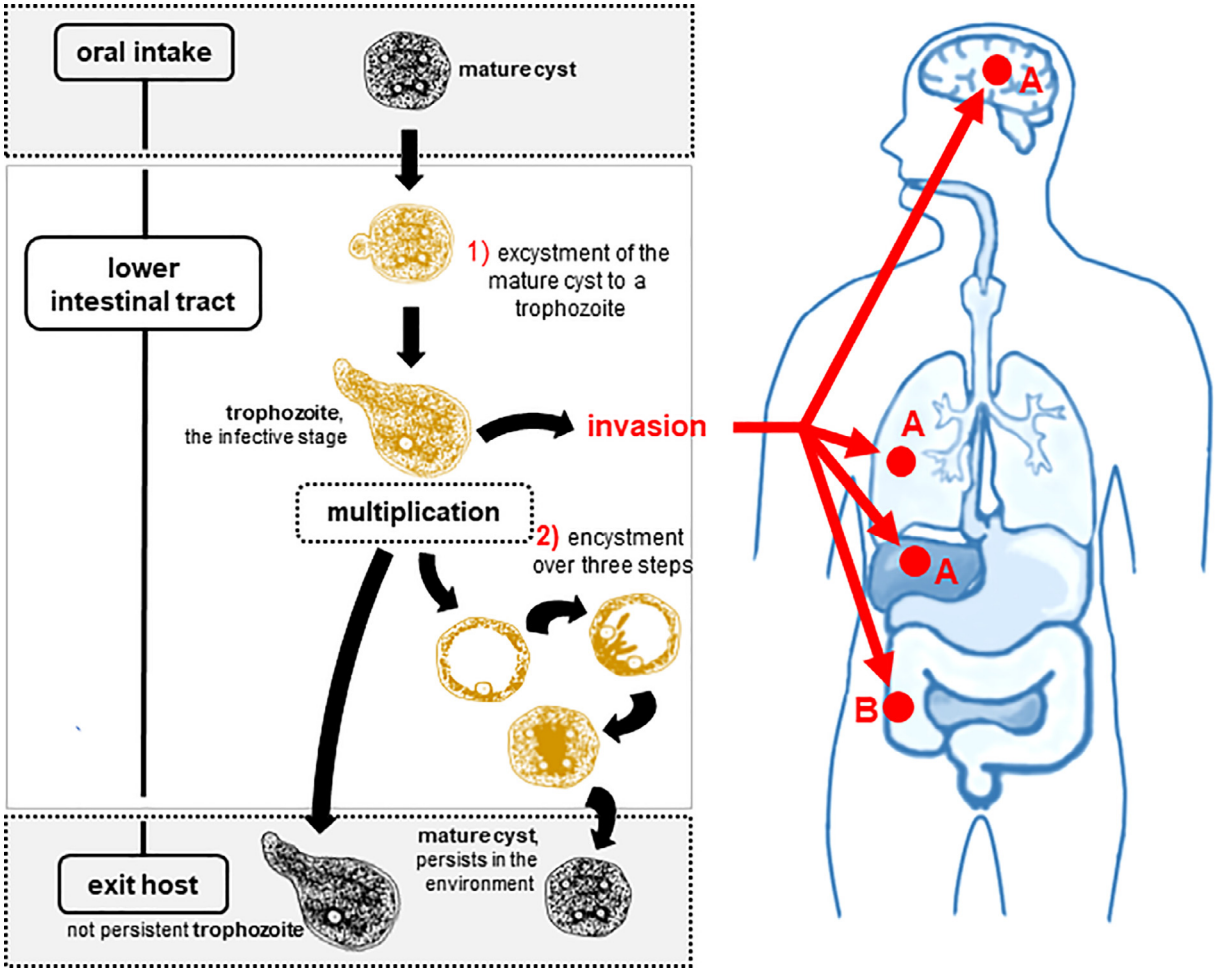


Fig. 3. The life cycle of *E. histolytica*. After entering the human body, the trophozoites can either be excreted, encysted or they invade other organs (extraintestinal disease, pathway A) or the intestinal mucosa (intestinal disease, pathway B).

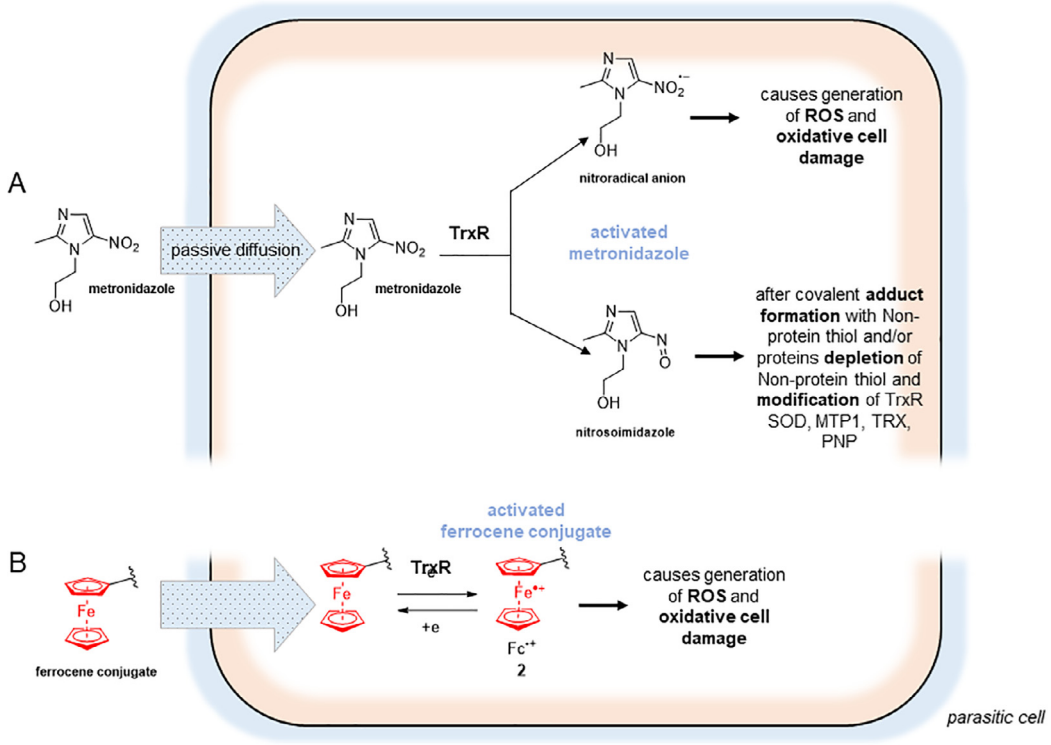


Fig. 4. General mode of action of metronidazole and ferrocene conjugates in a parasitic cell. A. After passive diffusion into the parasite, TrxR starts to activate metronidazole leading to nitroradical anions and nitrosoimidazole. Nitrosoimidazole modifies diverse enzymes and proteins as TrxR, superoxide dismutase (SOD), metal transporter protein 1 (MTP1), thioredoxin (TRX) and purine nucleoside phosphorylase (PNP). B. Proposed effect of ferrocene conjugates.

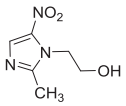
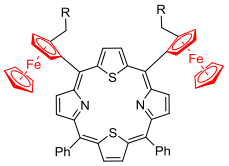
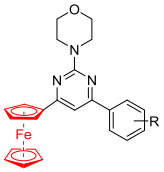
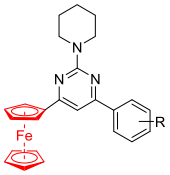
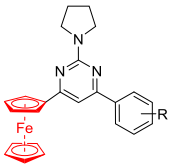
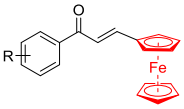
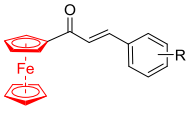
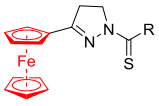
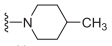
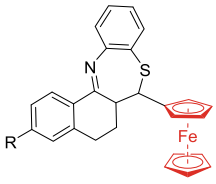
tives of porphyrins [120], pyrimidines [121,122], pyrazolines [114,123], thiazepines [124] and chalcones [125] have been synthesized, and tested as antiamoebic agents against *E. histolytica*. These conjugates seem to be promising alternatives as ferrocene compounds generate ROS (Fig. 4. B). Table 2 summarizes the most representative ferrocene conjugates with antiamoebic activity.

Azam and co-workers synthesized a series of bis-ferrocenyl-substituted, core-modified porphyrins, by introducing two lipophilic, amino-substituted ferrocenyl groups in the *meso* position under acidic conditions (**3** and **4**) [120]. The amino-substituents bear simple alkanes, phenyl substituents or saturated cyclic alkanes. Antiamoebic activity against the strain HM1:IMSS of *E. histolytica* was up to 3 times higher for compound **3** than the standard clinical used drug metronidazole (IC_{50} = 1.81) [120]. In further studies ferrocenyl moieties were also conjugated to pyrimidines [121,122], chalcones [125] and pyrazolines [114,123], and tested for antiamoebic activity against HM1:IMSS strain. The ferrocene-linked pyrimidines have either a morpholine (**5**–**9**), a piperidine (**10**–**14**) or a pyrrolidine (**15**–**18**) group in 2-position of the pyrimidine ring, whereas the ferrocene moiety and a substituted phenyl ring can be found in positions 4 and 6 [121,122]. Compounds bearing hydroxy, methoxy or chloro substituents showed high antiamoebic activity with IC_{50} values below 0.6 μM [122], which are significantly lower than the IC_{50} value found for metronidazole (1.8 μM) in the same assay [122]. Especially the morpholine-containing compound **6** (IC_{50} = 0.055 μM) can be deemed to be a very promising antiamoebic agent [121]. Chalcones **19**–**28** show low IC_{50} values, especially in case of trimethoxy-, chloro- or nitro-substitution of the phenyl ring (IC_{50} value below 0.6 μM) [125]. In case of pyrazoline derivatives **29**–**33**, especially the cyclic amines- or aliphatic amines-substituted compounds **29**, **30** and **33** exhibit IC_{50} values between 0.05 and 0.5 μM [114,123]. The cytotoxicity of nearly all derivatives towards human kidney epithelial cells or embryonic kidney-293 (HEK-293) cells has been tested as well. All compounds possess IC_{50} values higher than 90 μM, demonstrating a non-toxic behavior toward the examined cell lines. Ferrocene-linked thiazepines **34** and **35**, presented by *Klimova* and co-workers, show moderate antiamoebic activities, with IC_{50} values higher than the reference drug metronidazole (6.8 μM in the same assay) [124].

2.1.2. Trychomonas vaginalis

Trychomonas vaginalis (*T. vaginalis*) is a human urogenital mucosal membrane pathogen that belongs to the flagellates [126]. It is the causative agent for the venereal disease trichomoniasis, one of the most common protozoan infections in industrialized countries [126,127]. Trichomoniasis can be only transmitted through direct host to host contact, most notably by sexual intercourse [126]. *T. vaginalis* appears only in form of a trophozoite, thus it cannot persist in the environment for a long time [128]. The anaerobic parasitic pathogen nests in the urogenital system as well as the intestinal tract of humans and subsists particularly on bacteria [126]. The reproduction proceeds through binary fission of the trophozoites [126]. The chemotherapeutic option for trichomoniasis is, as for most of anaerobic parasites, metronidazole [126]. Like the mode of action in *E. histolytica*, the nitro-group of metronidazole is first reduced (Fig. 4. A). In contrast to *E. histolytica* (where it is especially done by TrxR) the enzyme pyruvate:ferredoxin oxidoreductase (PFOR) in the hydrogenosomes of the parasite is the main actor for this process [129–131]. Hydrogenosomes occur as a replacement for mitochondria in some ciliates and trichomonads. They allow survival under anaerobic conditions. The reduction of metronidazole leads to DNA-damage as well as ROS generation [129,132]. DNA-damage occurs especially in thymine and adenine residue-rich regions and therefore the selectivity of metronidazole for the pathogen can be explained by the fact that *T. vaginalis*

Table 2
Overview of important ferrocene derivatives with activity against *E. histolytica*.[a]

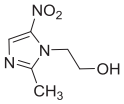
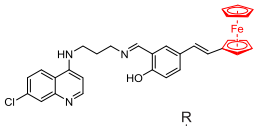
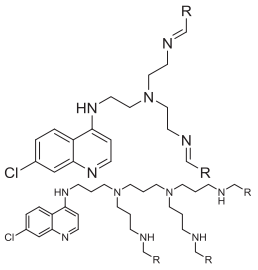
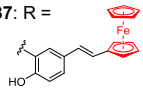
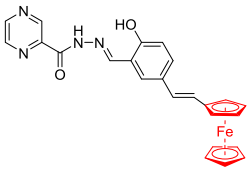
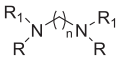
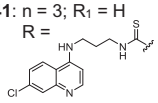
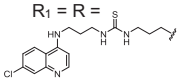
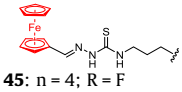
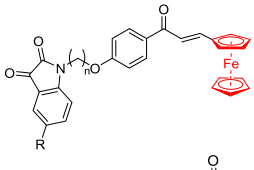
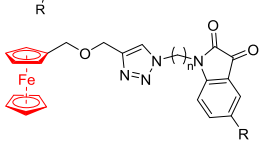
Classification	Structure		IC_{50} [μM]	Comments	Ref.
nitroimidazole		metronidazole	**1.81**	**reference drug**	[114,121,122]
core-modified porphyrins		**3**: R = 	0.59	bis-ferrocenyl derivative	[120]
		4: R = 	0.72		
pyrimidine derivatives		**5**: R = 4-OH	0.142	conjugates with a morpholine group	[121]
		6: R = 4-OCH_3	0.055		
		7: R = 2,5-$(OCH_3)_2$	0.251		
		8: R = H	0.815		
		9: R = 3,4-$(CH_3)_2$	0.697		
		**10**: R = 2,5-$(OCH_3)_2$	0.48	conjugates with a piperidine group	[122]
		11: R = 4-OCH_3	0.53		
		12: R = 4-Cl	0.41		
		13: R = 3,4,5-$(OCH_3)_3$	1.58		
		14: R = 4-SCH_3	1.13		
		**15**: R = 4-OCH_3	0.62	conjugates with a pyrrolidine group	[122]
		16: R = 2,5-$(OCH_3)_2$	0.91		
		17: R = 3,4,5-$(OCH_3)_3$	0.71		
		18: R = 4-SCH_3	1.21		
chalcone derivatives		**19**: R = H	0.89	ferrocene conjugated via an alkene bridge to the ketone	[125]
		20: R = 4-OCH_3	1.09		
		21: R = 4-Cl	0.51		
		22: R = 4-NO_2	0.67		
		**23**: R = H	0.62	ferrocene conjugated directly to the ketone	[125]
		24: R = 2,5-$(OCH_3)_2$	1.16		
		25: R = 4-OCH_3	0.92		
		26: R = 3,4,5-$(OCH_3)_3$	0.58		
		27: R = 4-Cl	0.47		
		28: R = 4-NO_2	0.42		
pyrazoline derivatives		**29**: R = NH-$CH(CH_3)_2$	0.050	1-N-substituted thiocarbomoyl-3-ferrocenyl-2-pyrazoline derivatives	[123]
		30: R = 	0.128		
		31: R = N-$C_4H_9(CH_3)$	1.360		
		32: R = 	1.130		
		33: R = 	0.504		
thiazepine derivatives		**34**: R = H	12.6[b]	within this study all derivatives showed lower activity than metronidazole	[124]
		35: R = OCH_3	7.50[b]		

[a] tested on HM1:IMSS strain of *Entamoeba histolytica*.
[b] IC_{50} value of metronidazole in the same assay: 6.8 μM.

exhibits around 71% adenine and thymine sequences in its genome [126,133]. For ferrocene containing compounds conversion into ferrocenium cations in the hydrogenosomes has been also proposed, with consequent production of ROS and oxidative stress which leads finally to cell death (Fig. 4. B). *Smith et al.* synthesized a series of ferrocene compounds bearing quinoline-based polyamine (**36**–**39**) [134] and pyrazinyl (**40**) [135] groups as well as thioureas conjugated to polyamine scaffolds (**41**–**44**) (Table 3) [136].

The resulting molecules were tested for their antitrichomonad activity against *T. vaginalis*. They all revealed moderate activity with 10–20 times higher IC_{50} values than the reference drug metronidazole (IC_{50} value in the same assay: 0.72 μM [134–136]). The compounds were tested as antimalarial compounds as well

Table 3
Overview of important ferrocene derivatives with activity against *T. vaginalis*.

Classification	Structure		IC_{50} [μM] or growth inhibition [%]	Comments	Ref.
nitroimidazole		**metronidazole**	**0.720** **100%**	**reference drug**	[134] [136]
quinoline-based polyamines		**36**	24.53	mono-, bis- and tris-ferrocenyl derivatives	[134]
		**37**: R = 	22.21		[134]
		38: R = 	18.84		[134]
		39	41.24		[134]
pyrazinyl derivative		**40**	10.41	derived from pyrazinoic acid hydrazide	[135]
thiourea derivatives		**41**: n = 3; R_1 = H R = 	55.9%	Percentage parasite growth inhibition (%); metronidazole showed 100% inhibition	[136]
		42: n = 4; R_1 = R = 	58.7%		
		43: n = 2; R_1 = H R = 	59.6%		
		44: n = 4; R_1 = R = 	61.5%		
isatin derivatives		**45**: n = 4; R = F **46**: n = 6; R = Cl	9.01 7.13	isatin-ferrocenyl chalcone conjugates	[137]
		**47**: n = 4; R = H **48**: n = 5; R = CH_3 **49**: n = 5; R = F	5.53 2.26 2.96	1H-1,2,3-triazole-tethered isatin – ferrocene conjugates	[137]

but with moderate success. Among the isatin derivatives compounds **47**–**49** display IC_{50} values in the low micromolar range (3–6 μM), being **49** the most active conjugate (IC_{50} = 2.96 μM). Nevertheless, much effort still needs to be undertaken to find real alternatives to metronidazole.

2.1.3. *Leishmania spp.*

The vector-borne disease leishmaniasis is especially found in tropical and subtropical regions [138]. In humans, this neglected tropical disease (NTD) can be caused by more than 20 species of the intracellular flagellate *Leishmania* (*L.* spp.) [139]. *L.* spp. are transmitted by phlebotomine female sand flies and attack viscera, the skin as well as the mucosa [140]. Typical symptoms are skin damages in case of cutaneous leishmaniasis to sepsis, destruction of the nasal septum (skin and mucosal leishmaniasis) and infestation throughout all organ systems (visceral leishmaniasis) [140]. The propagation of *L.* spp. takes place in two different hosts: the sand fly and a vertebrate (dog, cat, human as accidental host) (Fig. 5) [140]. After the bite of an infected sand fly the infective stage, the promastigotes, are transmitted through the proboscis of the insect to the animal/human body [140]. In the next step, the flagellated promastigotes are incorporated by dermal macrophages

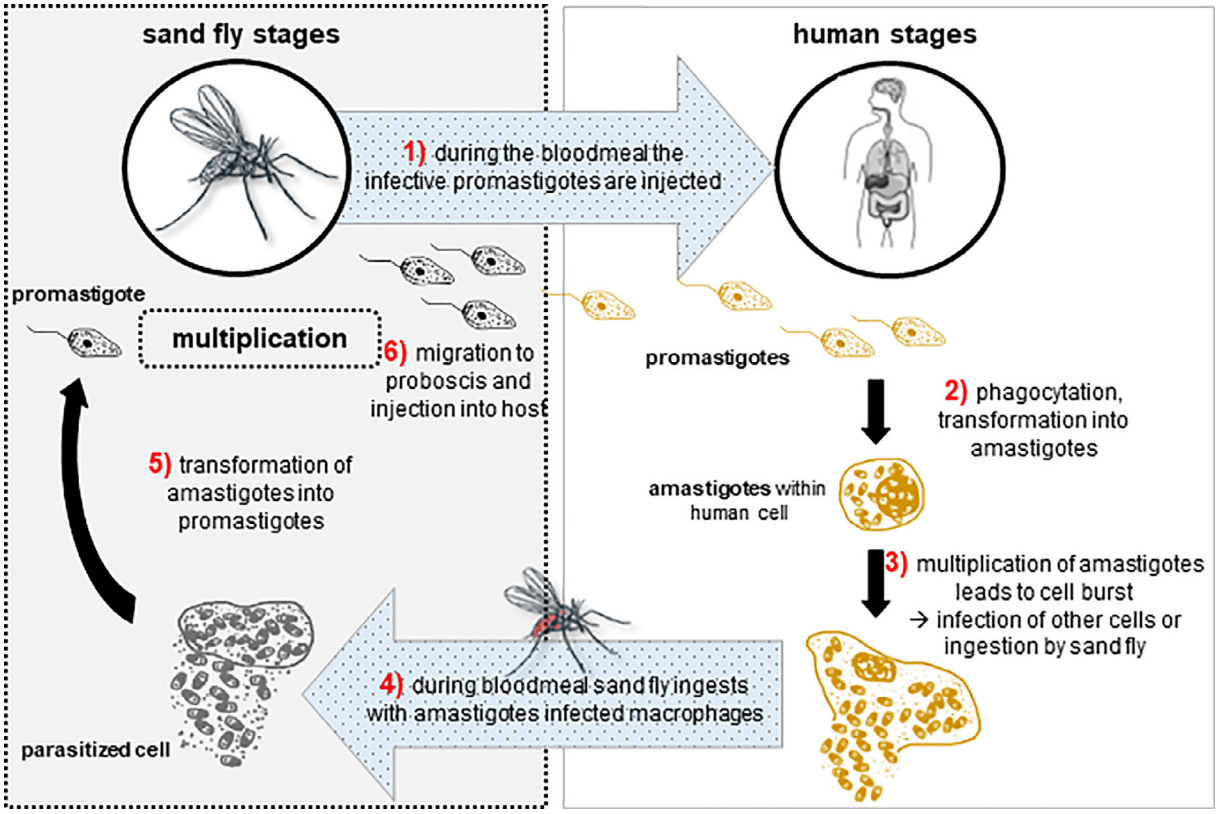


Fig. 5. The life cycle of leishmaniasis. After the bite of an infected sand fly the incorporated promastigotes are phagocytized by macrophages or other types of mononuclear phagocytic cells. After transformation of promastigotes into amastigotes, these start to multiply till they are released due to cell burst. The amastigotes can subsequently infect other human cells or are ingested by another sand fly. There the amastigotes transform over several steps to promastigotes. These migrate to the proboscis of the sand fly.

and other mononuclear phagocytic cell types, where they transform into the amastigote form (intracellular life form) [140].

These are highly specialized for a survival in the phagolysosome of the cell [140]. Through division the pathogen starts to replicate within the host phagocytic cells until they burst [140]. The subsequently released amastigotes are either phagocytized again by other mononuclear phagocytic cells or resorbed by a vector sand fly during its blood meal [140]. The life cycle of the pathogen is completed when the incorporated amastigotes are transformed to promastigotes within the gut of the sand fly [140]. Finally, the foregut as well as the proboscis of the insect are filled with promastigotes to infect a vertebrate again. The therapeutic approach depends on the type of leishmaniasis, being antimony compounds (Sb(IV)) or miltefosine widely used [141]. Miltefosine, an alkyl phospholipid, acts as an inhibitor of glycosomal enzymes that are involved in the synthesis of GPI-anchored (GPI = glycophosphatidylinositol) glycoproteins and glycolipids occurring on the cell surface of some kinds of *L.* spp. [142,143]. Thus, the normal function and the structure of the cell membrane is disrupted, leading to cell bursting (Fig. 6. A) [143]. Additionally, the normal function of the oxidoreductase cytochrome *c* oxidase is disrupted as well as the DNA is fragmented [142].

The addition of a ferrocene moiety to a chloroquinoline-containing molecule by copper-catalyzed azide alkyne cycloaddition leads to a promising inhibitor (**50**) of intracellular amastigotes and promastigotes (IC_{50} = 15.3 μM; miltefosine: IC_{50} = 21 μM) of *L. donovani* AG83 [144]. Interestingly, **50** presents no cytotoxicity towards host splenocytes (Table 4). Several biological analyses revealed a decrease in reduced glutathione (GSH) due to high amounts of ROS generated by the ferrocene moiety [144]. Consequently, apoptosis occurs because of subsequent mitochondrial cell membrane potential loss, lipid peroxidation and DNA fragmentation (Fig. 6) [144]. In addition, an increase in nitric oxide (NO) levels in infected macrophages can be observed as well [144]. *Hernandéz-Luiz et al.* showed that the quinazoline-based ferrocene conjugate **51** successfully inhibited *L. mexicana* promastigotes and intracellular amastigotes [145]. The group demonstrated the importance of both the ferrocene and the quinazoline moiety by electrochemical and docking experiments [145].

They have further shown that the ferrocene compound acts as a ROS generator in the pathogenic cell [145]. Other studies demonstrated that ferrocene derivatives of primaquine (**52** and **53**, tested against *L. infantum*) [146] and of *N*-heterocyclic compounds (**54**–**56**, tested against *L. mexicana*) [139] present moderate antipromastigote activity [139].

2.1.4. Trypanosoma spp.

The flagellate *Trypanosoma brucei* (*T. brucei*), transmitted by the tsetse fly, is the causative agent of African trypanosomiasis, also called sleeping sickness, while *T. cruzi*, transmitted by kissing bugs, causes American trypanosomiasis (“Chagas-disease”) [147]. In the case of sleeping sickness, after the prick of an infected tsetse fly, metacyclic trypomastigotes enter the bloodstream (transformation to bloodstream trypomastigotes) and later the central nervous system [148]. Limb pain to coma and death are classical symptoms if the disease remains untreated [148]. The remaining life cycle of *T. brucei* proceeds within the tsetse fly (Fig. 7. A).

After ingestion of infected blood from a vertebrate host, the trypomastigotes transform over several steps to epimastigotes in the flýs midgut [149]. These accumulate in the salivary glands of the fly where they differentiate to trypomastigotes again [149]. In the case of *T. cruzi*, the pathogen is transmitted by the feces of

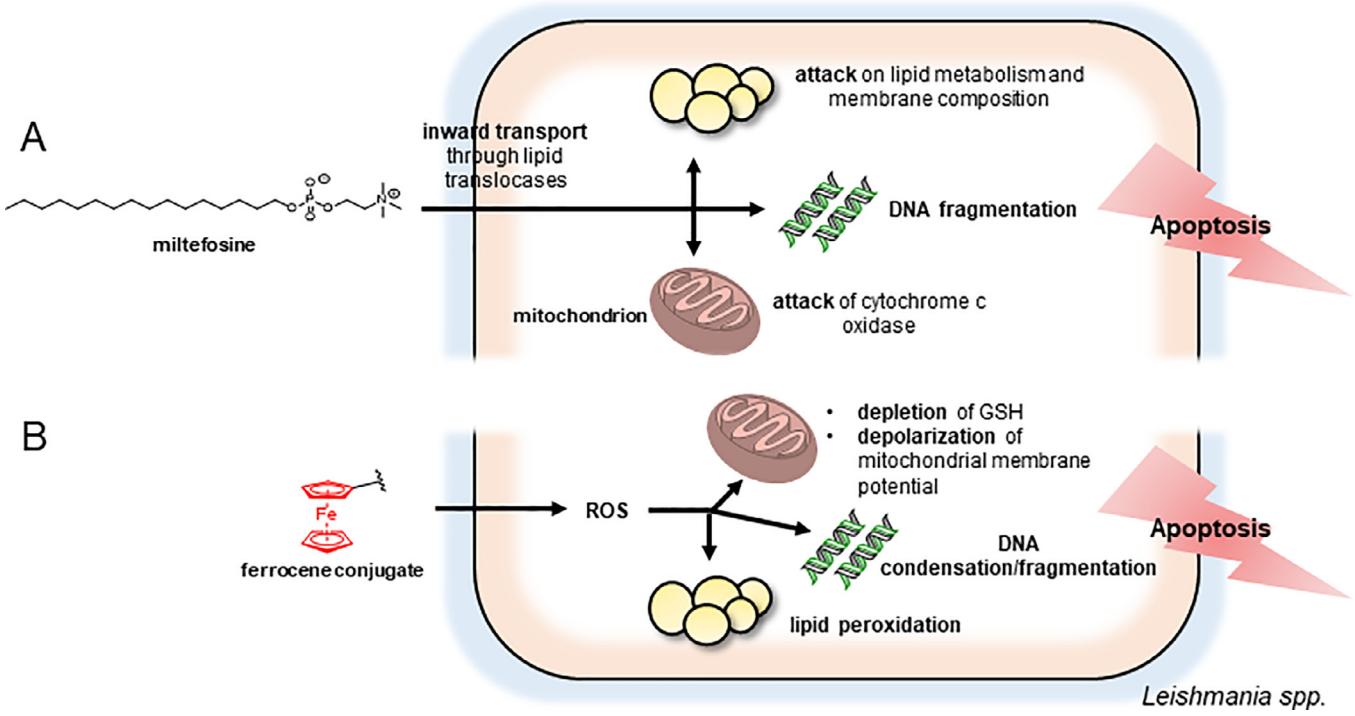
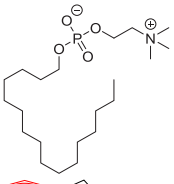
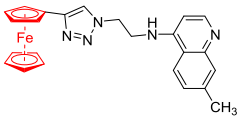
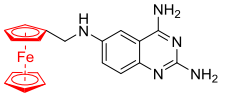
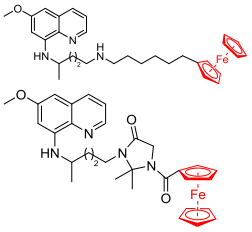
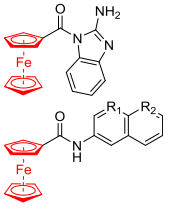


Fig. 6. The effect of miltefosine and ferrocene conjugates. A. Miltefosine leads to an attack on the membrane of the parasite as well as on the mitochondrion. B. Ferrocene conjugates generate ROS. These lead to a depletion of reduced glutathione as well as DNA fragmentation and lipid peroxidation.

Table 4
Overview of important ferrocene derivatives with activity against *L.* spp.

Classification	Structure		IC_{50} [μM]	Comments	Ref.
alkylphospho-choline		**Miltefosine**	**21.00**[a] **14.40**[b] **17.0**[c]	**reference drug**	[144,146]
quinoline derivative		**50**	15.26[a]	no cytotoxicity towards host splenocytes	[144]
quinazoline derivative		**51**	0.93[c]	glucantime as reference drug with an IC_{50} value of 182.7 μM	[145]
primaquine derivatives		**52** **53**	4.9[b] 11.5[b]	miltefosine reference: IC_{50} = 14.40 μM miltefosine reference: IC_{50} = 14.40 μM	[146] [146]
N-heterocyclic compounds		**54** **55**: R_1 = CH; R_2 = N **56**: R_1 = N; R_2 = CH	91.0[c] 92.0[c] 64.0[c]	miltefosine reference: IC_{50} = 17.0 μM	[139] [139]

[a] tested on Leishmania donovani AG83.
[b] tested on *Leishmania infantum* promastigotes.
[c] tested on *Leishmania mexicana* promastigotes.

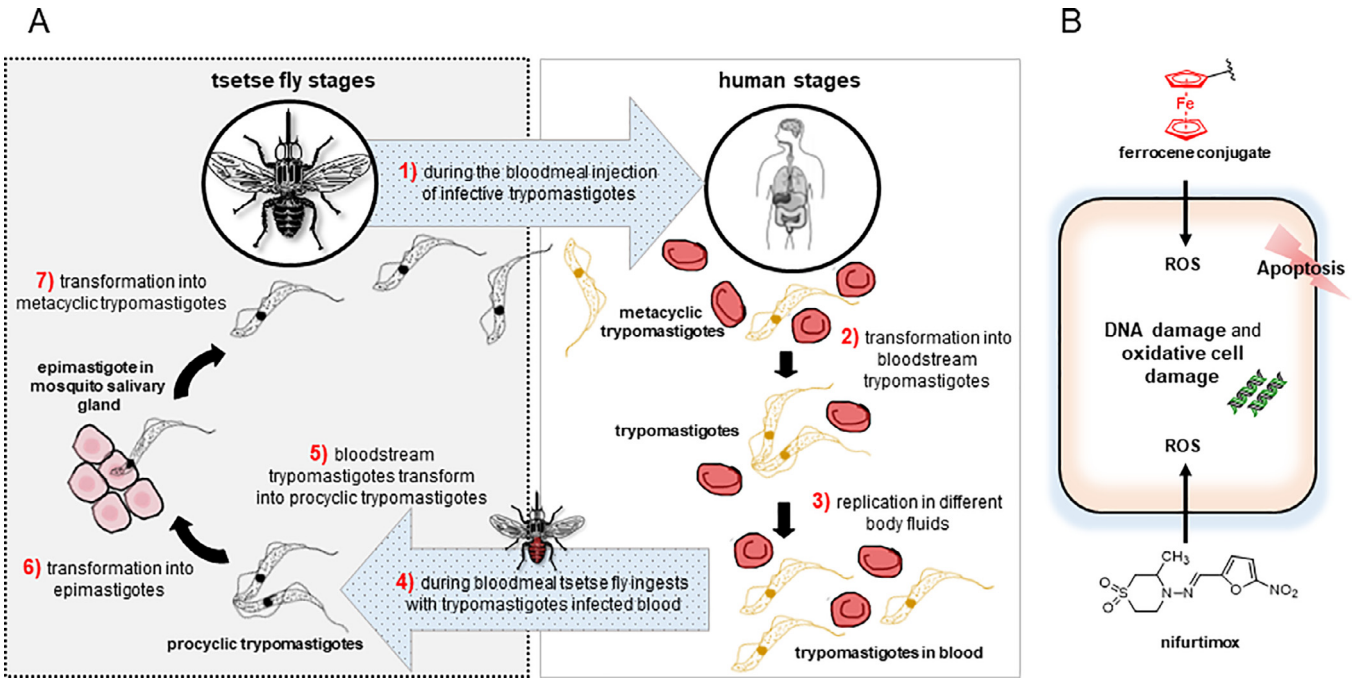


Fig. 7. Life cycle of *T. spp* and effect of ferrocene conjugates and nifurtimox on the parasite. A. After injection of infective metacyclic trypomastigotes, these multiply within different body fluids. Hereby they can reach different parts of the human body. The bloodstream trypomastigotes are ingested during bloodmeal by another tsetse fly, where they transform over several steps again into metacyclic trypomastigotes. B. After production of ROS by ferrocene derivatives or nifurtimox, DNA damage and apoptosis can occur.

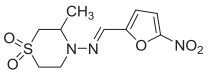
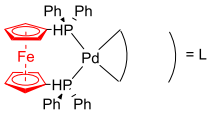
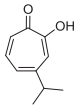
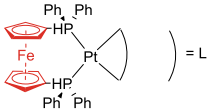
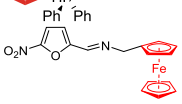
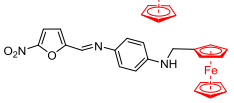
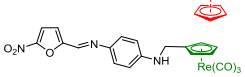
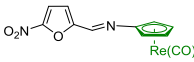
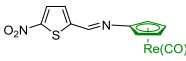
kissing bugs [150]. After penetrating the host skin, the trypomastigotes enter different cell types and transform finally to intracellular amastigotes [150]. Particularly human smooth muscle cells, the reticuloendothelial system and neuroglia cells are affected by the amastigotes [151,152]. The exact mechanism of the standard drug nifurtimox is not known yet [153]. It is argued that reduced nifurtimox leads to free radicals that kills the pathogen [154]. The development of resistance in several strains of *Trypanosoma* highlight the need for the discovery of new drug candidates [153]. Antitrypanosomal ferrocene containing compounds for both the sleeping sickness and the Chagas-disease have been synthesized by several groups (Table 5) [78,147,155–159].

Among them, the heterobimetallic derivatives of ferrocene and palladium or platinum (Table 5, **57**–**60**) showed lower IC_{50} values (range: 1.3–4.5 μM) than the reference drug nifurtimox (IC_{50} = 15 - μM) for *T. brucei* [78]. The high antiproliferative activity of the compounds was assigned to ROS generation by the ferrocenium group (Fig. 7. B) [78]. Furthermore, a DNA binding mode of action was assumed [78]. This could be demonstrated by fluorescent studies through a competitive binding between ethidium bromide and the complexes **57**–**60** [78]. While the intercalating agent ethidium bromide leads to a fluorescent DNA probe a non-fluorescence emission results from the interaction of **57**–**60** with the DNA [78]. Accordingly, upon increasing concentrations of the complexes **57**–**60** a quenching in the emission of the DNA-ethidium bromide probe was observed, leading to the suggestion that the complexes intercalate into the DNA or induce conformational changes of the DNA [78]. **57**–**60** were also tested against *L. infantum* and *Mycobacterium tuberculosis* (*M. tuberculosis*) (strain H37Tv), but only for *T. brucei* high selectivity was measured [78]. Antichagasic activity of ferrocenyl- or cyrhetrenyl-containing 5-nitrofuranes or 5-nitrothiophenes (**61**–**65**) was analyzed for *T. cruzi* [155,158]. Compounds **62** and **63** with an electronic communication (1,4-phenyldimine bridge) between the iron or rhenium moiety displayed the highest activities [155]. In this case, the nitro-group could be more easily reduced to a nitroradical anion due to the electron-withdrawing effect of especially the cyrhetrenyl group [155]. Thus, the ferrocene conjugates presented lower activities than the corresponding rhenium compounds.

2.1.5. Toxoplasma gondii

The arc-shaped sporozoa *Toxoplasma gondii* (*T. gondii*) is an intracellular, worldwide occurring parasite with a low host and cell selectivity [160]. Sporozoa are organisms whose adult stage is not motile. *T. gondii* is related to the malaria causing parasite *P. falciparum* [161]. In humans, *T. gondii* infects cells of nearly all organs and of the central nervous system [160,162]. Nevertheless, for healthy humans the infection toxoplasmosis will proceed with mild symptoms such as chorioretinitis or influenza-like symptoms [160]. Humans represent intermediate hosts, whereas cats are defined as final hosts (Fig. 8. A) [160]. Generally, the ingestion of *T. gondii* occurs through food, water and environmental objects contaminated with cat excrements or by eating raw or improperly cooked meat of animals contaminated with cysts [163]. After stomach passage, the incorporated oocysts transform into tachyzoites and spread to especially neural and muscle tissue (unlike many apicomplexans *T. gondii* passes the blood–brain barrier) [162,163]. There, the tachyzoites transform into tissue cyst bradyzoites (persistent infection, cause for chronic toxoplasmosis) [163]. Owing to the severe side effects ranging from intolerance, allergic reactions to hepatic necrosis of the approved antiparasitic drugs pyrimethamine in combination with sulfadiazine or atovaquone for toxoplasmosis, an intensive research for new drug candidates has been pursued during the last years (Fig. 8. B) [160–169]. The diaminopyrimidine pyrimethamine acts as dihydrofolate reductase (DHFR) inhibitor. As a result, parasites as *T. gondii*, bacteria and rapidly dividing cells like cancerous cells that need DHFR for their multiplication are suppressed in their normal growth [170]. Sulfadiazine acts synergistically with pyrimethamine (first-line therapy) as inhibitor of folic acid metabolism in some protozoa and bacteria [171]. The antirespiratory drug atovaquone, a hydroxynaphthoquinone and structural analogue of protozoan ubiquinone,

Table 5
Overview of important ferrocene derivatives with activity against *T.* spp.

Classification	Structure		IC_{50} [μM]	Comments	Ref.
nitrofuran		**nifurtimox**	**15.4**[a] **10.4**[b]	**reference drug**	[78,155]
heterobimetallic derivatives		**57**: L = (HTrop) 	1.3[a]	ferrocene-palladium heterobimetallic conjugates	[78]
		58: L = (HHino) 	1.2[a]		
		**59**: L = HTrop **60**: L = HHino	2.1[a] 4.5[a]	ferrocene-platinum heterobimetallic conjugates	[78]
imine derivatives		**61**	76.4[b]	5-nitrofurane imine conjugates of ferrocene	[155]
		**62**	45.5[b]		[155]
		**63**	43.6[b]	cyrhetrenyl derivatives of 5-nitrofurane	[155]
		**64**	47.3[b]		[155]
		**65**	15.9[b]	5-nitrothiophene conjugate with rhenium	[158]

[a] tested on *Trypanosoma brucei*.
[b] tested on *Trypanosoma cruzi*.

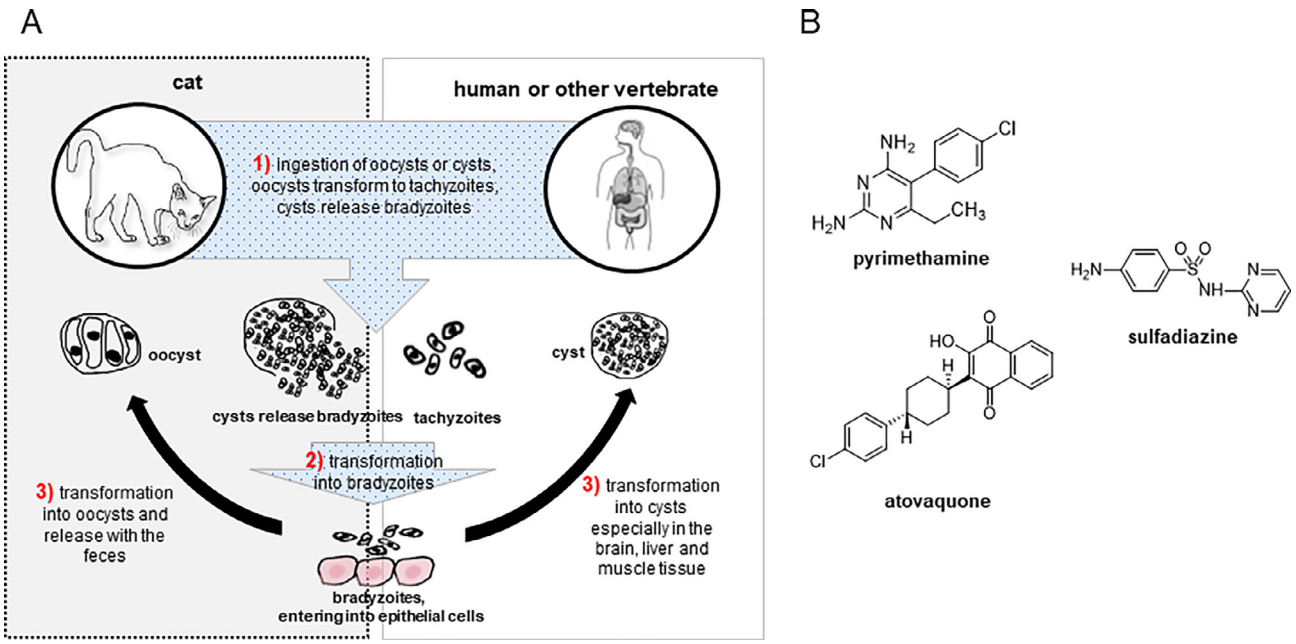


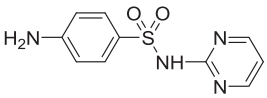
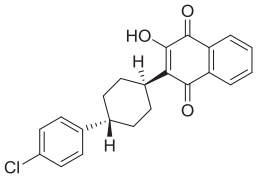
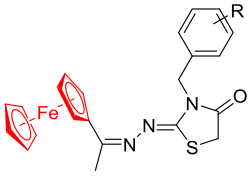
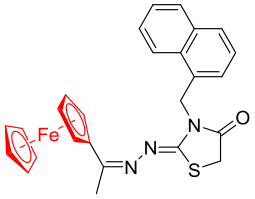
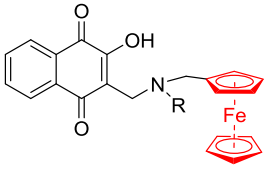
Fig. 8. Life cycle of *T. gondii* and structure of widely used drugs against it. A. After ingestion of parasitic cysts the transformation intro bradyzoites starts within the human body. These can either transform into cysts and remain in the body or are excreted via oocysts. B. Structures of pyrimethamine, atovaquone and sulfadiazine.

is in general used in combination with pyrimethamine when first-line therapy is contraindicated [162,172]. In *in vitro* cell culture atovaquone showed high activity against tachyzoites [162,173].

Thiazolidinone derivatives bearing pendant ferrocene or organic groups have been introduced by *Secci* and co-workers (Table 6) [164]. The ferrocenyl compounds **66**–**74** appeared as the most active, with high tachyzoite inhibition (IC_{50} < 10 μM; sulfadiazine: IC_{50} = 43 μM) [164].

Pelinski and co-workers synthesized ferrocenyl derivatives **75**–**77** of atovaquone, an aminohydroxynaphthoquinone, which were tested *in vitro* against the PLK and ATO strains of *T. gondii* as well as against 3D7 and Dd2 strain of *P. falciparum* [161]. It

Table 6
Overview of important ferrocene derivatives with activity against *T. gondii*.

Classification	Structure		IC_{50} [μM]	Comments	Ref.
sulfonamide		**sulfadiazine**	**43.0**[a]	**reference drug**	[164]
hydroxy-napthochinone-derivative		**atovaquone**	**15.0**[b]	**reference drug**	[161]
thiazolidinone derivatives		**66**: R = 2-NO_2	15.0[a]	thiazolidinone conjugates show high activity against *T. gondii*	[164]
		67: R = 3-NO_2	24.0[a]		
		68: R = 2-F	17.0[a]		
		69: R = 3-F	8.00[a]		
		70: R = 4-F	6.00[a]		
		71: R = 2-Cl	9.00[a]		
		72: R = 3-Cl	8.00[a]		
		73: R = 4-Cl	10.0[a]		
		**74**	5.00[a]		[164]
aminohydroxy-naphthoquinone derivatives		**75**: R = $(CH2)_5$-CH_3	1.40[b]	naphthoquinone conjugates show high activity against *T. gondii*	[161]
		76: R = $(CH2)_6$-CH_3	1.20[b]		
		77: R = $(CH2)_7$-CH_3	1.10[b]		

[a] tested on tachyzoites of *Toxoplasma gondii.*
[b] tested on ATO strain of *Toxoplasma gondii*

was concluded that the activity against the *T. gondii* strains was higher than the *P. falciparum* inhibition [161]. Particularly in the ATO strain, the IC_{50} values were 10 to 15 times lower than the reference drug atovaquone (IC_{50} = 15 μM) [161].

2.1.6. Plasmodium spp.

Most of the ferrocene derivatives introduced in the last decade aimed at the treatment of malaria. Thus, several reviews and an enormous number of publications deal with the analysis of ferrocene conjugates towards their antimalarial activity especially against strains of the sporozoa *P. falciparum* [83,86,174–194]. The symptoms of malaria infected patients, depending on the stage, may include fever, nausea, hemolytic anemia, unconsciousness, jaundice, hepatosplenomegaly to acute renal failure due to hemoglobinuria, lung edema and coma [195]. According to the periodicity of fever attacks five subspecies of plasmodia are distinguished: *P. falciparum* (pathogen of the malaria tropica), *P. vivax* and *P. ovale* (malaria tertiana), *P. malariae* (malaria quartana) and *P. knowlesi* (malaria quotidiana) [196,197]. The best method to avoid a *Plasmodium* infection is an adequate protection against the malaria transmitting vector, the female *Anopheles* mosquito, such as mosquito nets or the use of repellents. The *Anopheles* mosquito occurs in tropical as well as subtropical regions of Asia, Africa, South and Central America [176,197]. Typical for *P.* spp. is the change between an asexual and a sexual reproduction, simultaneously linked with a host change (human/monkey-mosquito) [198]. In humans, an asexual proliferation can be observed, so-called schizogony (Fig. 9) [100]. After the bite of an *Anopheles* mosquito the sporozoites, the infectious form of the germ, are incorporated from the mosquitós saliva and transform within liver cells to extracellular merozoites that pass into the blood [100,198].

During the now starting erythrocytic schizogony, the merozoites infect the erythrocytes, evolve to mature intracellular trophozoites and either remain in the human body affecting new red blood cells or transform into gametocytes that are ingested by a female *Anopheles* mosquito again [196]. In the case of retention in the human body, the in the red blood cells located trophozoites develop to new, infective merozoites [100,196,198]. Generally, within an acidic compartment (pH = 5.2–5.6), the digestive vacuole, the trophozoites digest 60–80% of red blood cell hemoglobin (Hb, Fe^{II}) to receive essential amino acids for their energy metabolism [196,199,200]. The parasite can transform the thereby occurring harmful hematin (Fe^{III}) into the non-harmful, insoluble, microcrystalline hemozoin (Hz), the so-called malaria pigment (“*detoxification mechanism*”) [196]. Thus, *P.* spp. evaded the cell destructive properties of free heme [201]. In the last 20 years hundreds of ferrocene derivatives were synthesized and tested against drug-resistant (especially CQ-resistant) and non-drug-resistant strains of *Plasmodium* [86,176,183,185,186,188-190,193,194,202–211]. Those molecules can be subdivided into synthetically derived ferrocene conjugates and ferrocenes based on natural products. Here, either organic compounds with known antimalarial activity were chosen as conjugates to ferrocene – the majority – or substances with completely unknown activity towards *P.* spp. were derivatized.

Synthetic ferrocene conjugates: The most important synthetic antimalarial organometallic conjugate is FQ, a conjugate of the widely used antimalarial chemotherapeutic substance CQ and

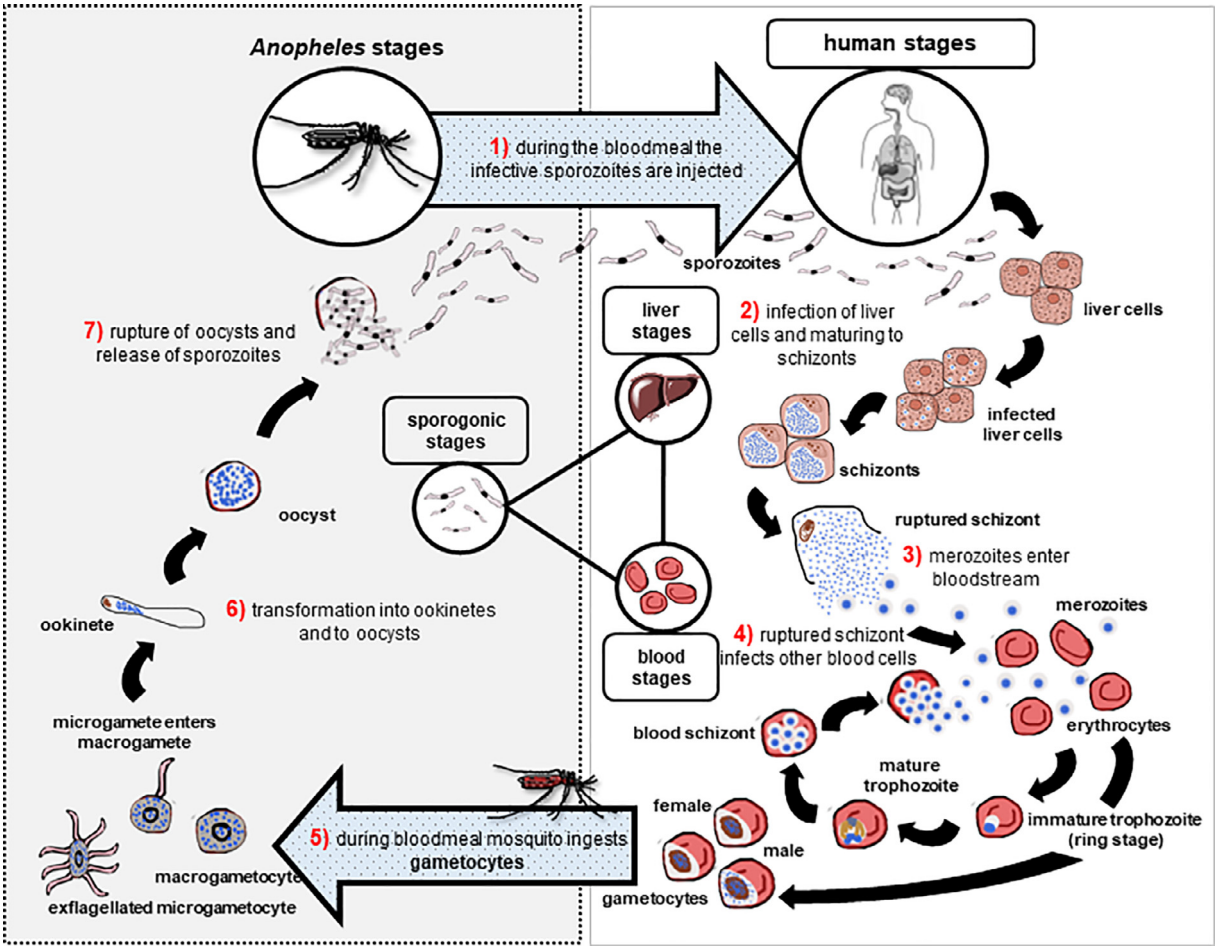


Fig. 9. Life cycle of *P.* spp. The life cycle consists of three different steps: liver cycle (exo-erythrocytic cycle), blood cycle (erythrocytic cycle) and sporogonic cycle (within the mosquito).

ferrocene, which was introduced by *Biot* and co-workers (Table 7) [86,176]. The antimalarial drug CQ is active against the digestive vacuole of the parasite [212,213]. CQ leads to heme accumulation and parasitical harm through interference with the parasitic enzyme heme polymerase that converts deleterious heme into hemozoin [212,213]. Nevertheless, the mode of hemozoin inhibition by CQ is not well understood yet [212,213]. A 22-fold higher activity against *P. berghei* in *in vivo* tests, significant lower IC_{50} values in *in vitro* tests against *P. falciparum* in comparison to CQ as well as low cytotoxicities against diverse mammalian cell lines paved the way for FQ as new antimalarial drug with high potential against resistant strains of *Plasmodium* [86,176]. Consequently, FQ has entered phase II clinical trials, leading to the subsequent synthesis of several FQ analogues with high to moderate activity against *P. falciparum* [214].

Several factors are proposed to determine the antiplasmodial activity of FQ [176,196]. Hz is undoubtfully the target as FQ accumulates at the lipid-water interface. Thus, FQ inhibits the formation of Hz, while hematin remains in the soluble state and cannot form hemozoin crystals anymore (Fig. 10) [79,80,196,221].

Furthermore, *Biot et al.* demonstrated the presence of noncovalent interactions between FQ and Hz by docking experiments [80]. When the drug is unbound to water, the intramolecular H-bond of FQ leads to a folded, neutral conformation (Table 7). FQ then switches to an open, diprotonated conformation while building up intermolecular contacts with the growing Hz crystal faces and thus inhibits formation of hemozoin [80]. In the folded conformation the lipophilic ferrocene moiety (FQ is 100-fold more lipophilic than CQ) builds up easier *van der Waals* interactions with lipid structures positioning FQ in the same catalytic site as hematin [79]. Thereby, FQ can be addressed a better inhibition of hemozoin production in comparison to CQ [79]. On top of that, this flip/flop H-bond mechanism helps FQ passing easier through the hydrophobic membranes of the parasite and thus the accumulation rates are higher than for CQ [79]. The nitrogen atoms of FQ play an important role during vacuolar accumulation through pH-trapping [79]. In conclusion, having a look at the structure–activity relationship for FQ, the activity of FQ against *P.* spp. can be explained due to more than one route. The lipophilic ferrocene core does not only target the site of lipid heme crystallization and enables easier passage through hydrophobic membranes, but also produce ROS within the digestive vacuole leading to membrane damage [79,196,222]. Because of the specific acidic and oxidative digestive vacuole conditions and the special redox behavior of ferrocene ROS can easily be generated [79,196,222]. The created lethal hydroxyl radicals from H_2O_2 due to ferrocene attack unsaturated fatty acids within membrane phospholipids [79,223]. Similar to CQ, the 4-aminoquinoline cycle is required for stacking interaction with hematin, while the chlorido group acts as charge distributor and inhibitor of hemozoin formation [79].

However, not only CQ analogues (Table 7, **78**–**81**) [86,194,203,206,207,210,211,215,222], but also other antimalarials served as conjugation platform for ferrocene. Derivatives of mefloquine (**82**, **83**) [193,207], primaquine (**84**, **85**) [202,216], atovaquone (**86**–**88**) [161] and quinine (**89**) [193] have been also tested but nearly all resulting conjugates were less active than

Table 7
Overview of important ferrocene derivatives with activity against *P.* spp.

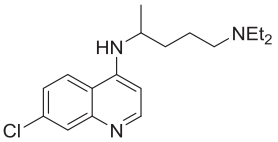
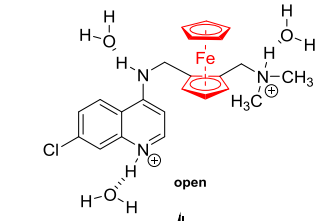
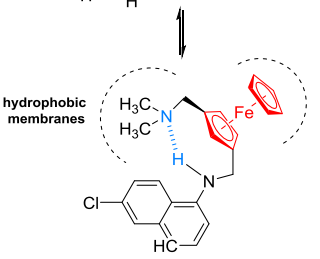
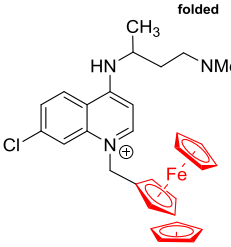
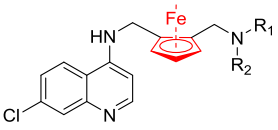
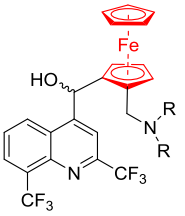
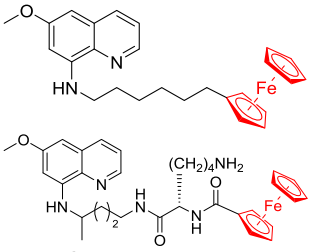
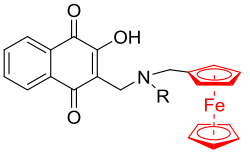
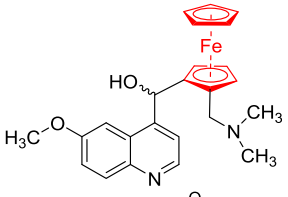
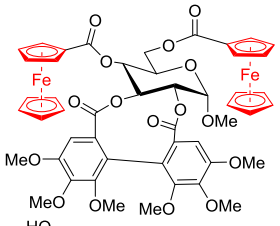
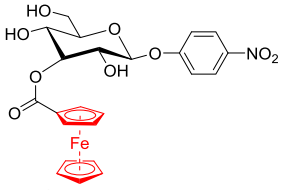
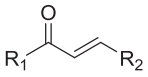
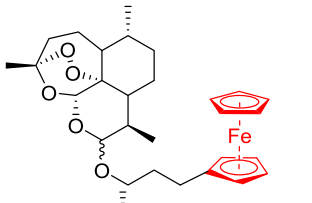
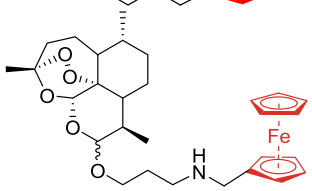
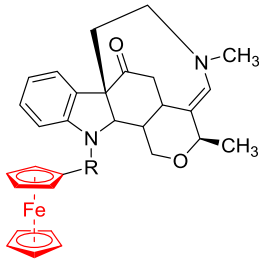
Classification	Structure		IC_{50} [μM]	Comments	Ref.
4-amino-quinoline		**Chloroquine**	12[a] 22[b] 62[c] 352[d]	**reference drug**	[176]
chloroquine derivatives		Ferroquine	7[a] 20[b] 19[c] 14[d]	ferroquine switches between an open, diprotonated and a folded, neutral conformation (intramolecular H-bridges, blue, are formed); this flip/flop H-bond may enable transport through membranes	[79,176]
					
		**78**	n.r.	the charged molecule **78** was not able to cross cell membranes	[176]
		**79**: $R_1 = R_2 = C_2H_5$ **80**: $R_1 = CH_3$; $R_2 = H$ **81**: $R_1 = FcCH_2$; $R_2 = H$	12.4[b] 17.7[c] 29.6[b] 23.2[c] 155.5[b] 169.5[c]	Bis- and tris-ferrocenyl-derivatives lead to lower activity	[176,215]
mefloquine derivatives		**82**: R = (CH_2)-CH_3 **83**: R = CH_3	0.20[b] 0.10[b]	R = alkyl chains	[193,207]
primaquine derivatives		**84** **85**	>10[e] 0.17[f] 3.48[e] 6.46[f]	only primacenes with a basic aliphatic amine group conserve activities of parent drug primaquine for liver stage *P. berghei*	[202,216] [191,208]
atovaquone derivatives		**86**: R = $(CH2)_5$-CH_3 **87**: R = $(CH2)_6$-CH_3 **88**: R = $(CH2)_7$-CH_3	2.50[c] 5.00[c] 6.00[c]		[161]

Table 7 (*continued*)

Classification	Structure		IC$_{50}$ [μM]	Comments	Ref.
quinine derivative		**89**	1.10[b]		[193]
sugar derivative		**90**	0.6[g]	ferrocene sugars as hexose transporter inhibitors	[217]
		**91**	30[g]		[217]
chalcone derivative		**92**: R_1 = Fc; R_2 = Ph **93**: R_1 = Fc; R_2 = 4-nitroPh **94**: R_1 = Fc; R_2 = 4-quinoline	19[d] 5.1[d] 14[d]		[177,218]
artemisinin derivatives		**95-*S*/95-*R***	86[c] 36[b] 86[c] 36[b]		[219]
		**96-*S*/96-*R***	14[c] 12[b]		[219]
strychnobra-siline derivatives		**97**: R = CH_2 **98**: R = C = O	n.r. 4.83	failed in *in vivo* tests	[220]

[a] tested in 3D7 strain of *Plasmodium falciparum.*
[b] tested in HB3 strain of *Plasmodium falciparum.*
[c] tested in Dd2 strain of *Plasmodium falciparum.*
[d] tested in K1 strain of *Plasmodium falciparum.*
[e] tested in W2 strain of *Plasmodium falciparum.*
[f] tested in liver stage *Plasmodium berghei.*
[g] tested in FCR-3 strain of *Plasmodium falciparum.*

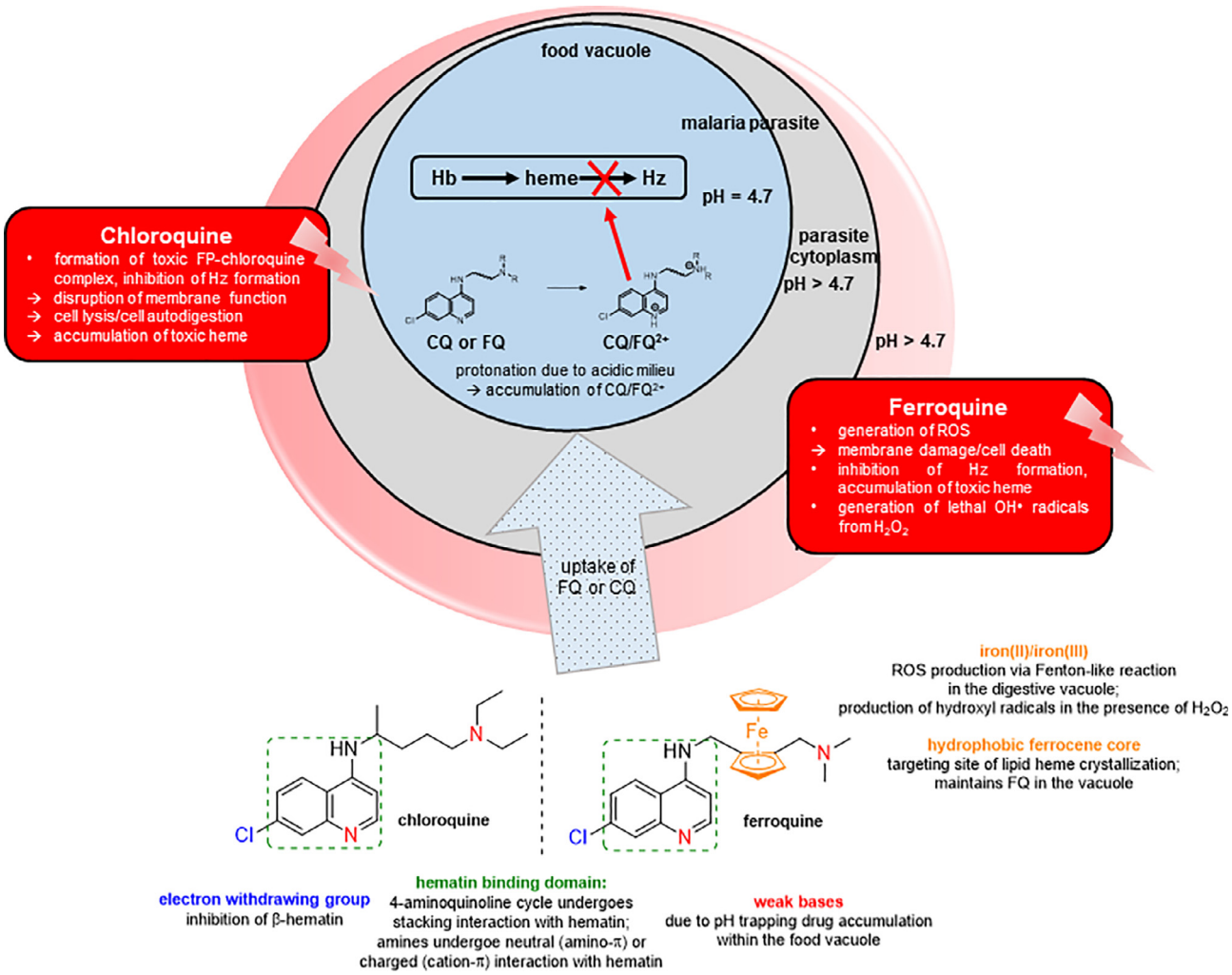


Fig. 10. Mode of action of CQ and FQ and proposed structure–activity relationship. CQ inhibits Hz formation from Hb by formation of ferriprotoporphyrin IX-chloroquine complexes (FP-CQ). These are highly toxic, thus leading to cell death. FQ inhibits Hz formation as well. Additionally, FQ creates ROS and hydroxyl radicals leading to a higher cytotoxicity for the parasite. Healthy cells are not attacked by FQ.

the parent organic antimalarials. The ferrocene sugars **90** and **91** have been also proposed aiming to inhibit the hexose transporter (expressed in xenopus oocyte) [217]. Other effectively ROS generating ferrocene conjugates (**92**–**94**) were prepared upon coupling ferrocene to chalcones [177,218]. Moreover, derivatives of indole [208], triazacyclonane quinoline [224], naphtoquinone [186], pyrimidine [191], isatin [185] – to name only a few – have been described, but in comparison to FQ they showed lower activity against different *P. falciparum* strains [176].

Natural product ferrocene conjugates: Among the natural product conjugates, artemisinin derivatives seem to be the most prominent molecules with IC_{50} values in the low micromolar range (Table 7, **95**, **96**) [189,190,209,219,225]. On the contrary, ferrocene-strychnobrasiline conjugates **97**, **98** failed during *in vivo* tests [220]. Moreover, egonol [183,204], thymoquinone [204], novobiocin [205] and ciprofloxacin [175] derivatives have been tested for their antimalarial properties. However, none of the synthesized compounds was as effective as FQ.

2.2. Anthelminthic ferrocene conjugates

Pathogenic helminths represent a group of multicellular parasites that are, according to their macroscopic appearance, subdivided into three main groups: cestodes (tapeworms), nematodes (roundworms) and trematodes (flukes) [226]. Cestodes as well as flukes are hermaphrodites, whereas nematodes exist as bisexual worms [226]. Generally, all helminths traverse three different stages during their development: egg, larval and adult (Fig. 11. A) [226].

The life cycles of all helminths are thus comparable, only the hosts they affect are different [226]. Generally the eggs are incorporated by an intermediate host, such as vertebrates or mollusks, or directly by the final host [226]. In the intermediate host, the larval stage is formed, most of the times in the musculature [226]. After ingestion of the intermediate host by the final host, the eaten larvae develop to adult worms that produce eggs [226]. In case of the tropical disease bilharziosis, also known as schistosomiasis, the trematode *Schistosoma* (*S.* spp.) enters a freshwater snail in form of a miracidium [226]. Within the snail, the miracidium matures to cercaria (Fig. 11. A) [226]. These are secreted into the fresh water, where they can invade a final host through the skin [226]. The liver, kidney or the lung are usually affected during a bilharziosis [226]. *Gasser* and co-workers synthesized ferrocenyl derivatives (**99**–**106**) of the anthelmintic drug praziquantel (Table 8), the most used drug against bilharziosis [227,228].

In a first step praziquantel promotes opening of a Ca^{2+} channel in the worms membrane, leading to paralysation due to the increased potassium transport into the cell [231,232]. Aiming to overcome rapid metabolization of praziquantel as well as to find therapeutic alternatives to that drug due to the increasing number

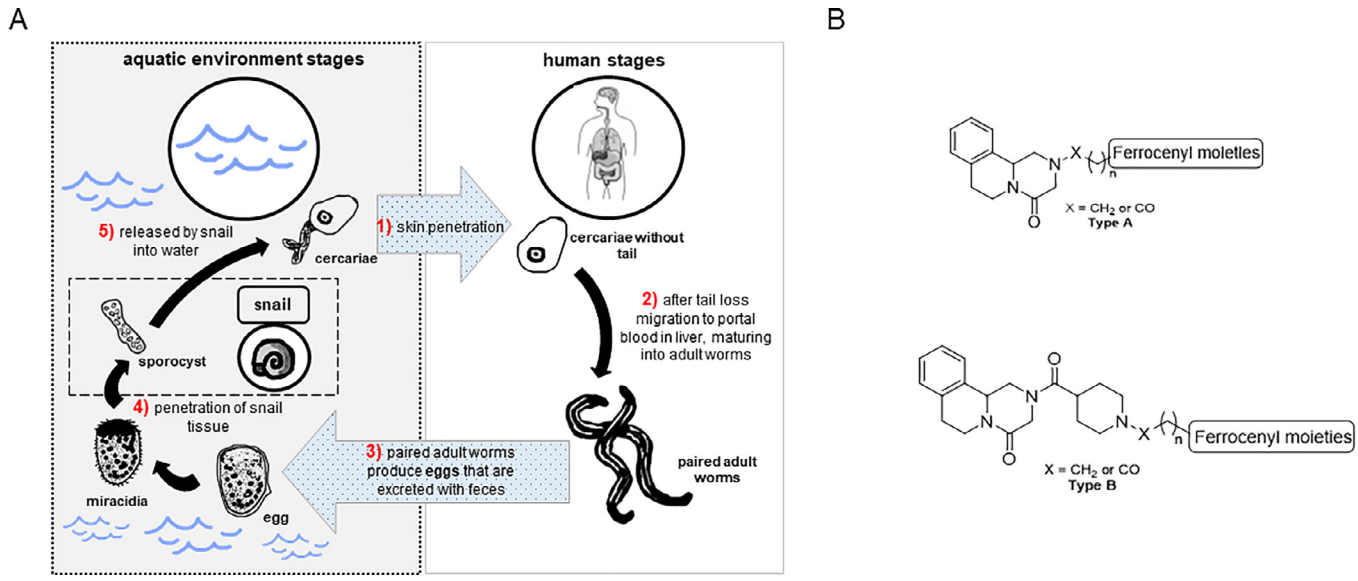


Fig. 11. The life cycle of helminths, exemplary shown for the parasite *Schistosoma* (*S.* spp.) and general structures of praziquantel-ferrocene conjugates. A. After entering the human body through the skin, the parasite matures to paired adult worms. The eggs, produced by the worms, are excreted and finally enter a freshwater snail. One stage of the parasitic life cycle happens thus in aquatic environment. B. The two types of possible ferrocene conjugation to a praziquantel molecule.

of resistant parasites, *Gasser et al.* investigated the impact of a ferrocene moiety in the structure of praziquantel [227,232]. Different conjugates were synthesized following two strategies. After replacement of the cyclohexane ring of praziquantel, ferrocene was on the one hand directly attached to praziquanamine via different linkers (type A, Fig. 11. B). On the other hand, an additional piperidine moiety between ferrocene and praziquanamine was introduced (type B, Fig. 11. B) [227]. *In vitro* testing against *S. mansoni* revealed moderate activities in the micromolar range [227]. More recently, *Gasser* and co-workers demonstrated that ferrocene conjugates of the antimalaria agent mefloquine (**107**, **108**) showed selective activity against *S. mansoni* ($IC_{50} < 4$ μM; mefloquine $IC_{50} = 3.5$ μM) as well [230]. In relation to FQ additional modes of action were assumed for the ferrocene derivatives by the authors but this has not been investigated so far [227,230,233]. Nonetheless, ROS production and subsequent oxidation of DNA, proteins and lipids can be assumed.

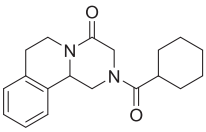
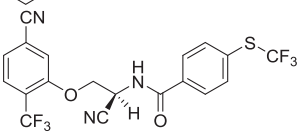
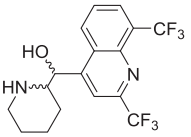
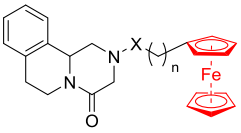
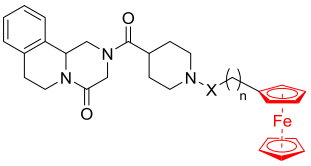
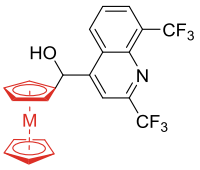
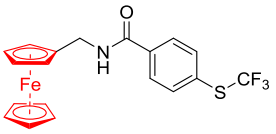
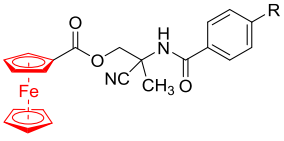
Conjugates of ferrocene with monepantel (Table 8, **109**–**113**), an approved molecule against nematode infections in sheep that activates ion channels, have been evaluated [229,234–238]. Those derivatives were tested against *Haemonchus contortus*, *Dirofilaria immitis* and *Trichostrongylus colubriformis*. Among this family, only **109** show high activity against all three pathogens, whereas the other derivatives display moderate activities [229]. It is assumed by the authors, that the generation of ROS inside the parasite is responsible for the activity [229]. This was proven by replacement of the ferrocene moiety of **110** by a ruthenocene molecule [229]. In contrast **110** the ruthenocene derivative is expected not to produce ROS and consequently the activity was lower [229]. The hydrophobic ferrocene should enhance the accumulation of the drug within the parasite as well [229].

3. Antibacterial ferrocenyl derivatives

Headlines like "*Too few antibiotics in pipeline to tackle global drug-resistance crisis, WHO warns*" [239], "*Ukraine's TB problem is ticking time bomb for Europe*" [240] or "*Infection Killed 19,000 in 2005, Study Says* [about methicillin-resistant *S. aureus* (MRSA) in the United States]" [241] reveal the increasingly obvious problem of multidrug-resistant bacteria worldwide. The search for new antibiotics emerging from plants or microorganisms [242–244] as well as the use of inhibition strategies like virulence inhibition [245–248] through attacking the virulence-regulating systems in bacteria represent possible ways to overcome the development of antibiotic resistance. In general, bacteria multiply very rapidly, resulting in a high probability of spontaneous genetic mutations. Some of these mutations can lead to the development resistance to antibiotics. Ferrocene as well as ruthenocene or cobaltocene derivatives of natural products or synthetically derived molecules gained much attention in the design of potential new antibiotics over the last decades [83,249]. Several groups synthesized diverse ferrocene conjugates with antimicrobial activities (Table 9) [250–259].

β-Lactam antibiotics as penicillin or cephalosporin interfere with the cell wall synthesis of dividing bacteria leading to cell death [242]. They bind covalently to the serine residue in the active center of penicillin binding proteins (PBP) due to their structural resemblance to the natural substrate D-alanyl-D-alanine. This leads to an irreversible inhibition of the activity of the transpeptidase. β-Lactamases instead are the natural weapon of bacteria in the survival fight against naturally occurring antibiotics. By cleaving the β-lactam ring, these enzymes inactivate the antibiotic and therefore, the bacteria become resistant to its action. Already in the 1970s penicillin and cephalosporin derivatives of ferrocene were synthesized and show moderate activity [266]. Within this context, *Xiang* and co-workers generated a series of ferrocene-penem conjugates (Table 9, **114**–**116**) [260]. The MIC values (MIC = minimal inhibitory concentration of a molecule which prevents visible bacterial growth) obtained for the derivatives show high activities especially against MRSA in comparison to the reference drug faropenem (Table 9) [260]. The antibacterial activity against gram-negative species of *Escherichia coli* (*E. coli*) and *Serratia marcescens* (*S. marcescens*) is in the same range as the activity of faropenem [260]. Other β-lactam antibiotics conjugates have been prepared upon conjugation of 6-aminopenicillanic acid (6-APA) as well as 7-amino desacetoxycephalosporanic acid (7-ADCA) to ferrocenyl and ruthenocyl keto acids (Table 9, **117**–**124**) [259,261,262]. The ruthenocyl conjugates, especially compound **118**, show high activity against *S. aureus* and *S. epidermidis* bacterial strains with MIC in

Table 8
Overview of important ferrocene derivatives with activity against trematodes and nematodes.

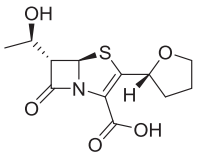
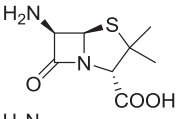
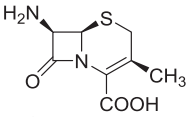
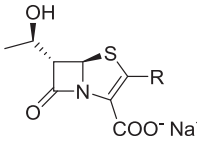
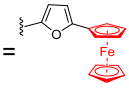
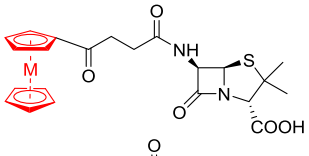
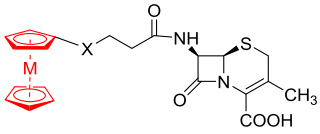
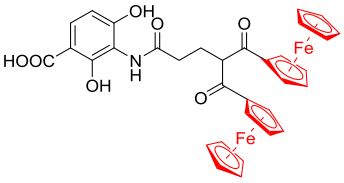
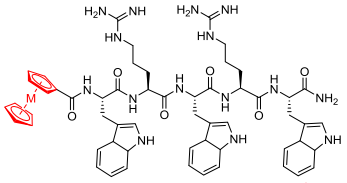
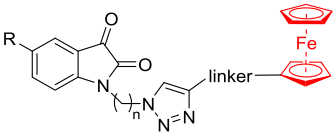
Classification	Structure		IC_{50} [μM]	Comments	Ref.
isoquinolin-pyrazine		**praziquantel**	**0.10**[a]	**reference drug; against trematodes**	[227]
amino-acetonitrile-derivative (AAD)		**monepantel**	**5.25**[b]	**reference drug; against nematodes**	[229]
quinoline-methanol derivative		**mefloquine**	**3.5**[a]	**reference drug; antimalaria agent**	[230]
praziquantel derivatives		**99**: n = 0; X = CH_2 **100**: n = 2; X = CO **101**: n = 3; X = CO **102**: n = 4; X = CO	68.0[a] 51.6[a] 25.6[a] 48.6[a]	type A derivatives	[227]
		**103**: n = 0; X = CH_2 **104**: n = 2; X = CO **105**: n = 3; X = CO **106**: n = 4; X = CO	>59[a] >54[a] >53[a] >52[a]	type B derivatives	[227]
mefloquine derivatives		**107**: M = Fe **108**: M = Ru	3.3[a] 4.0[a]	derivatization with an antimalaria agent	[230]
monepantel derivatives		**109**	5.25[b]		[229]
		**110**: R = S-CF_3 **111**: R = F **112**: R = Cl **113**: R = S-CH_3	>19.37[b] >23.03[b] >22.19[b] >18.45[b]		[229]

[a] tested against *Schistosoma mansoni*.
[b] tested against *Dirofilaria immitis*.

the low micromolar range (ca. 4.0 μg/mL) [259,262]. Further studies revealed a non-covalent binding of the organometallic compounds in the active site of the bacterial enzyme CTX-M β-lactamase (serine β-lactamase) [262]. An extensive hydrogen bond network between those compounds and the residues Asn104, Ser130, Asn132, Thr235, Ser237 and a water mediated bond with the residue Arg276 of the bacterial enzyme could be observed by X-ray crystallography. Additionally, the 7-ADCA-complexes of ferrocene **123** and especially ruthenocene **122** demonstrated high inhibitory effects on the tested bacterial strains [261]. In the case of 7-ADCA-conjugates, a covalent acyl-enzyme complex is formed in the active site of the enzyme CTX-M-14 E166A β-lactamase (determined by X-ray crystallography) [261]. Here, the cyclopentadienyl ring of the ruthenocyl moiety switches between two conformations: an open conformation, where a non-covalent bond is built up with the Thr171 residue of the enzyme and a stacked conformation, where the organometallic ring is located in the protein backbone [83].

Metzler-Nolte and co-workers generated several platensymicin [263,267], peptidic [264,268,269] and hetero-tri-organometallic [270] conjugates. Platensymicin, a natural product derived from *Streptomyces platensis*, shows high antibacterial activity against gram-positive bacteria as MRSA or *E. faecalis* (vancomycin-resistant) [83]. Platensymicin leads to bacterial death through lipid biosynthesis inhibition. Hereby, the drug targets the key enzyme FabF, a bacterial synthetase. The ferrocene-containing derivative **125** show moderate to no antibacterial activity against gram-positive as well as gram-negative bacteria [263]. Upon modification of "*antimicrobial peptides*" [264], so called AMPs, with an organometallic fragment (OM-AMPs) as ferrocene or ruthenocene, it has been possible to generate some of the most active synthetically derived AMPs, namely compounds **126** and **127** [264]. Cell wall enzymes as MurG (essential for cell wall biosynthesis) or the bacterial respiratory chain enzyme cytochrome *c* were displaced from the cell wall after integration of the OM-AMPs into the cell membrane [264]. Consequently, lipid II, a cell wall forming

Table 9
Overview of important ferrocene derivatives with antibacterial activity.

Classification	Structure		MIC[a] [μg/mL]	Comments	Ref.
β-Lactam derivatives		**faropenem**	**6.25**[b] **0.1**[c] **>100**[d]	**reference drug**	[260]
		**6-APA**	**1600**[b]	**reference compound**	[259]
		6-ADCA	**4661**[e]	**reference compound**	[261]
					
		**114**: R = Ph-4-Fc	7.7[b] 0.09[c] 42.9[d]	faropenem conjugates	[260]
		115: R = Ph-3-(OCH_3)-4-Fc	7.32[b] 0.082[c] 35.15[d]		
		116: R = 	6.78[b] 0.18[c] 28.8[d]		
		**117**: M = Fe **118**: M = Ru	160[b] 2.0[b]	ferrocene/ruthenocene conjugates of 6-APA	[259,262]
		**119**: M = Fe; X = CO **120**: M = Ru; X = CO **121**: M = Fe; X = CH_2CO **122**: M = Ru; X = CH_2CO **123**: M = Fe; X = CH_2 **124**: M = Ru; X = CH_2	142[e] 200[e] 126[e] 65[e] 82[e] 117[e]	ferrocene/ruthenocene conjugates of 6-ADCA	[261]
platensymicin derivative		**125**	128[f]		[263]
organometallic fragment conjugates		**126**: M = Fe **127**: M = Ru	28[d] 28–57[g] 5.8[d] 20.1[g]	peptidic derivatives	[264]
triazole derivative		**128**	137–140[h]	triazole has favorable properties for bacterial binding, the isatin moiety is responsible for anti-TB activity	[265]

[a] MIC = minimal inhibitory concentration of tested compound which impedes visible bacterial growth.
[b] tested against *Serratia marcescens IAM 1136.*
[c] tested against *Escherichia coli NIHJ JC-2.*
[d] tested against *Staphylococcus aureus* (MRSA).
[e] tested against *Bacillus cereus 569/H9.* IC_{50} value [μM].
[f] tested against *Staphylococcus aureus Mu50 VISA.*
[g] tested against *Escherichia coli.*
[h] tested against *Mycobacterium tuberculosis.* Standard drug in the same assay: 0.12–144 μM (MIC).

lipid, is disturbed in its normal function due to the absence of these essential enzymes [264]. Because of this "*missing-enzyme defect*" [264] the analyzed bacteria seem to be more vulnerable. As a result, they are not thus far prone to the buildup of resistance barriers as conventionally treated bacteria.

According to WHO, around 1.6 million people died because of tuberculosis (TB) in 2017 [28]. The causative agent is *M. tuberculosis,* and several ferrocene-containing compounds have been proposed as anti-TB agents [78,257,265,271–275]. *Feng* and co-workers generated triazole derivatives (Table 9, **128**), where the lipophilic ferrocene is linked to an isatin-like backbone [265]. By blocking the lipid biosynthesis of *M. tuberculosis*, these compounds show moderate activities against the bacterium.

4. Ferrocene conjugates with antifungal and antiviral activity

4.1. Antifungal ferrocene conjugates

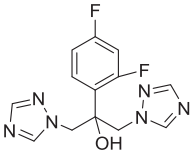
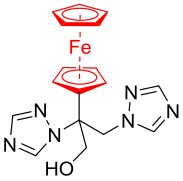
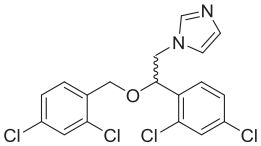
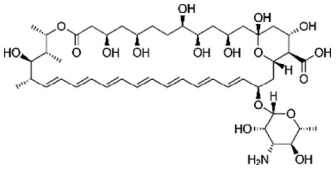
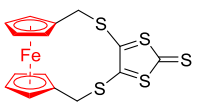
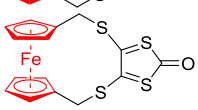
In humans, fungi can cause several diseases, ranging from skin – superficial – infections to systemic, organic mycoses [276–278]. When fungi enter the blood stream they can affect inner organs like the lungs (e.g. aspergillosis), the heart, brain, blood, eyes and bones (e.g. invasive candidiasis) or the central nervous system (e.g. *Cryptococcus gattii* cryptococcosis). Fluconazole (Table 10) is a widely used antimycotic drug indicated for the treatment of systemic mycoses, especially those caused by fungi of the genus *Candida* (*C.* spp.) [279].

Fluconazole is a triazole-containing molecule that inhibits the cytochrome P450 enzyme lanosterol-14α-demethylase, a key enzyme in the ergosterol biosynthesis pathway [281,282]. The fungal membrane sterol ergosterol is important for the membrane fluidity as well as for its function [281,283,284]. *Biot* and co-workers synthesized a ferrocene-containing fluconazole derivative (**129**) with moderate antifungal activity [279]. The substitution of a phenyl ring of fluconazole by a ferrocene moiety had nearly no effect on the antifungal properties. Starting with ferrocene-dimethanol, *Chohan* prepared dithiothione and dithioketone derivatives of ferrocene (**130** and **131**) [280]. These compounds are comparable to the drugs miconazole (diameter of growth inhibition in the same assay: *C. albicans*: 20 mm; *A. flavus:* 25 mm) and amphotericin B (diameter of growth inhibition in the same assay: *C. albicans*: 25 mm; *A. flavus:* 30 mm) in their activity against several fungal genera, among them are *C. albicans* and *Aspergillus flavus* (*A. flavus*) [280]. Miconazole interacts with the cytochrome P450 enzyme 14-α demethylase, an essential enzyme to produce ergosterol, a component of the fungal cell membrane [282,285]. An inhibition of ergosterol synthesis causes loss of membrane integrity and leakage of cellular components [282]. Amphotericin B binds to sterols as ergosterol having the same effect as miconazole [282]. The compounds **130** and **131** were tested against bacteria as well, where they showed moderate antibacterial activity [280].

4.2. Antiviral ferrocene conjugates

Since the family of human lymphotropic retroviruses, better known as human immunodeficiency viruses HIV, which lead to acquired immunodeficiency syndrome AIDS, were formally recognized and identified as a new health condition in the 1980s, there exists no vaccine nor a curative treatment for HIV or AIDS so far [286-288]. Subsequent studies provide strong evidence that HIV

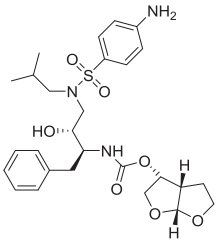
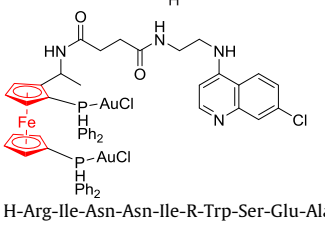
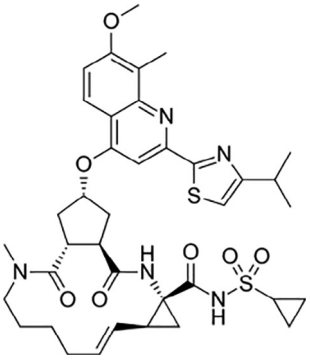
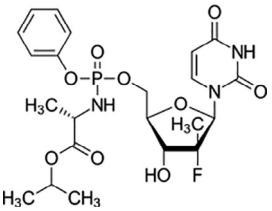
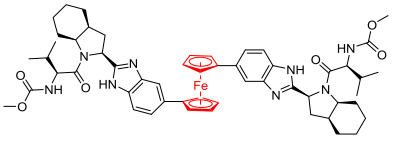
Table 10
Overview of important ferrocene derivatives with activity against fungi.

Classification	Structure		Comments	Ref.
isoquinolin-pyrazine		**fluconazole**	**reference drug** *C. albicans* strain: MIC < 1.5 μg/mL *C. paraspilosis* strain: MIC < 12 μg/mL	[279]
fluconazole derivative		**129**	*C. albicans* strain: MIC < 1.5 μg/mL *C. paraspilosis* strain: MIC < 12 μg/mL	[279]
imidazole		**miconazole**	**reference drug** Diameter of growth inhibition [mm]: *C. albicans*: 20 *A. flavus*: 25	[280]
polyene-macrolactone		**amphotericin B**	**reference drug** Diameter of growth inhibition [mm]: *C. albicans*: 25 *A. flavus*: 30	[280]
dithiothione derivative		**130**	Diameter of growth inhibition [mm]: *C. albicans*: 25 *A. flavus*: 28	[280]
dithioketone derivative		**131**	Diameter of growth inhibition [mm]: *C. albicans*: 28 *A. flavus*: 32	[280]

targets and destroys $CD4^+$ T helper cells (CD4 = cluster of differentiation 4), important infection fighting cells of the immune system [289,290]. It is supposed that the impaired cellular immune response by reason of reduced amount of $CD4^+$ T cells as well as a concomitant loss of $CD4^+$ T cell function is the main cause of immunodeficiency [290]. The entry of HIV (and thereby the target of the virus) is on the one hand dependent on expression of primary CD4 receptor on immunocompetent cells, on the other hand on expression of co-receptors (chemokine receptors) [290]. The administration of a cocktail of several drugs prevents the proliferation of the virus and further infection of immunocompetent cells in the blood and thus most of the affected people can live without suffering from AIDS several years. This so called combination therapy (HAART, highly active antiretroviral therapy) blocks the viral replication within two replication stages in the human blood [291]. The subsequent emergence of resistant HIV-1 (HIV-1 is the global most common type of HIV) leads to the discovery of HIV-1 protease inhibitors like darunavir (**132**, IC_{50} = 3 nM in HIV-1 infected human T-cell leukaemia MT-2 cells), which represents a big step in drug development of HIV/AIDS agents [292–296].

It has been shown that a bimetallic ferrocene-digold complex bearing a CQ unit (Table 11, **133**) stops HIV virus proliferation at

Table 11
Overview of important ferrocene derivatives with activity against viruses.

Classification	Structure		Comments	Ref.
darunavir		**132**	**approved drug against HIV**; acts as inhibitor of HIV-1 protease; IC_{50} = 3 nM (in HIV-1 infected human leukaemia MT-2 cells)	[296]
ferrocene-digold-complex		**133**	20 μg/mL: 100% virus inhibition of the HIV-1 enveloped pseudovirus ZM53	[297]
HNG-156	H-Arg-Ile-Asn-Asn-Ile-R-Trp-Ser-Glu-Ala-Met-Met-Co-NH_2	**134**	IC_{50} = 96 nM (in HIV-1 infected P4-CCR5 MAGI cells, a CD4 expressing HeLa-based cell line)	[298]
simeprevir		**135**	**DAAs against HCV**; acts as inhibitor of HCV NS3/4A protease; IC_{50} = 13−37 nM (for HCV genotypes 1a, 1b, 2, 4, 5, 6)	[299]
sofosbuvir		**136**	**DAAs against HCV**; acts as inhibitor of HCV polymerase NS5B; IC_{50} = 0.7−2.6 μM (for HCV genotypes 1a, 1b, 2, 4, 5, 6)	[300]
di-substituted ferrocene derivative		**137**	HCV genotype-1a: IC_{50} = 15 pM HCV genotype-1b: IC_{50} = 2 pM	[301,302]

non-toxic concentrations [297]. Moreover, the molecule offers cytostatic properties, arresting the human epithelial HeLa cell line TZM-bl in the S and G2/M phase during cell cycle [297]. *Chaiken* and co-workers synthesized a HIV entry inhibitor, a ferrocene peptide conjugate, HNG-156 (**134**), whose antiviral potency for HIV-1 envelope gp120 was tested [298]. The glycoprotein gp120 is exposed on the surface of HIV envelope and plays a crucial role in virus invasion as it attaches to specific cell surface receptors of the immune system like the CD4 receptor on immunocompetent cells [303]. The binding affinities of HNG-156 to different subtypes of gp120 are located in the nanomolar range [298]. Through surface plasmon resonance competition analysis the authors could measure with increasing concentrations of HNG-156 a binding inhibition of gp120 to soluble CD4 and to antibodies targeting the two binding sites of gp120 (CD4 binding site as well as CD4-induced and co-receptor binding sites) [298]. In this way, *Chaiken* and co-workers demonstrated that **134** acts as a dual receptor site antagonist of virus envelope gp120 [298]. Furthermore, HNG-156 showed a low IC_{50} value (96 nM) for the inhibition of P4-CCR5 MAGI (CD4 expressing HeLa-based cells) cell infection caused by HIV-1 whole virus [298].

Ferrocene conjugates were analyzed not only for their anti-HIV activity but also for their potential activity against other viruses as the hepatotropic RNA virus hepatitis C virus (HCV). HCV causes acute and chronic hepatic inflammation (hepatitis) which might finally lead to hepatocellular carcinoma [304–307]. The blood-borne virus enters via clathrin-mediated endocytosis host cells, where its 9.6 kb single stranded RNA genome is released and directly translated to a single polyprotein precursor that is cleaved by host and viral proteases into single proteins. These finally form a replication complex that generates multiple copies of HCV RNA which exit the host cell [308]. Therapies with directly acting antiviral agents (DAAs) that inhibit diverse proteins and enzymes involved in crucial steps of HCV life cycle became popular in the last years [307,308]. The combination of two or three DAAs with different targets, like viral protease (e.g. simeprevir **135**, inhibitor of NS3/4A protease, responsible for the cleavage of the polyprotein precursor at site NS3; IC_{50} = 13−37 nM [299]) or RNA-polymerase (e.g. sofosbuvir **136**, inhibitor of RNA-dependent RNA polymerase nonstructural protein 5B NS5B; IC_{50} = 0.7−2.6 μM [300]) can cure HCV in over 90% of the patients [307]. Due to the above-mentioned achievements in HCV treatment several groups tried to generate new DAAs [309,310]. *Wiles et al.* synthesized a metalorganic compound with a 1,1́-ferrocenediyl scaffold and a biplanar organic structure (**1 3 7**) [301,302]. This molecule targets and inhibits nonstructural protein 5A NS5A, a zinc-binding phosphoprotein that plays a key role in the viral RNA replication cycle and possesses quite low IC_{50} values for HCV genotypes 1a and 1b (15 pM; 2 pM) [301,311,312].

5. Conclusion

After the development of the antimalarial agent FQ and the anticancer drug ferrocifen (both in clinical trials), ferrocene derivatives experienced increasing interest in medicinal chemistry, leading to hundreds of compounds synthesized and evaluated biologically. Ferrocene conjugates due to their unique substitution possibilities at the cyclopentadienyl ring and mode of action (generation of ROS, DNA, protein and lipid oxidation, tumor growth suppression) can be considered promising drug candidates, especially in the fight against infectious diseases. Regarding non-anticancer conjugates, the antiparasitic, namely antimalarial molecules, encompass the most numerous groups of ferrocene conjugates. Derivatives with sugars or natural products as artemisinin have been extensively explored, but the properties of FQ remained unsurpassed. Conjugates directed at the treatment of other tropical diseases as leishmaniasis or trypanosomiasis, worm and amoebic infections as well as bacterial, veneral, food- and water-derived or viral illnesses have been investigated as well. Especially the antiamoebic ferrocene-linked pyrimidine **6**, introduced by *Azam* and co-workers, is a promising drug candidate for future clinical studies due to a 36 times lower IC_{50} value than the standard drug metronidazole, and nearly no toxicity against human cells. Also, bimetallic derivatives of ferrocene and palladium prepared against *T.* spp. or the bimetallic ferrocene-digold complex **133** – to name only a few promising antibacterial and antiviral conjugates – might become interesting for clinical studies as well. Despite some drawbacks of ferrocene conjugates against diseases like toxoplasmosis or trichomoniasis, ferrocene maintains its auspicious status, especially with respect to the continuously growing amount of publications regarding antiparasitic, -viral, -bacterial and -fungal ferrocene conjugates. Considering the amount of existing ferrocene conjugates against infectious diseases to date, the continuous search for bioactive ferrocene conjugates will certainly provide us with interesting compounds in the future.

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Declaration of Competing Interest

None.

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