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Small Organometallic Compounds as Antibacterial Agents

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ABSTRACT.

The emergence of bacterial resistance to commercial antibiotics is an issue of global importance. During the last two decades, the number of antibacterial agents that have been discovered and introduced into the market has steadily declined and failed to meet the challenges posed by rapidly increasing resistance of the pathogens against common antibacterial drugs. The development of new classes of compounds to control the virulence of the pathogens is therefore urgently required. This perspective describes the historical development in brief and recent advances on the preparation of small organometallic compounds as new classes of antibacterial agents with potential for clinical development.

Introduction.

The modern age of antimicrobial research is believed to have begun in 1928 with the accidental discovery of penicillin by *Alexander Fleming*.[1] However, first Penicillin-resistant *S. aureus* strains were already reported soon after the use of penicillin in the 1940s.[2] This was a warning to the community that misuse of antibiotics could lead to resistance development in bacteria. Methicillin, a β-lactamase resistant penicillin class of antibiotic, was introduced in 1959, but *S. aureus* rapidly acquired resistance, leading to the emergence of Methicillin-resistant *S. aureus* (MRSA).[3, 4] MRSAs posed further difficulties by developing resistance against other classes of antibiotics such as gentamycin, erythromycin and neomycin as well. The Gentamycin-resistant MRSA (GR-MRSA) was isolated in Australia, USA and Europe in the early 1980's. In the 1990's, resistance to ciprofloxacin, a fluoroquinolone antibiotic used for the treatment of MRSA infection, was also reported.[5] Vancomycin, a glycopeptide antimicrobial was used for the last two decades to control the virulence of such multi-resistant MRSAs. Due to the selective pressure of Vancomycin, reduced susceptibility of *S. aureus* towards this antibiotic emerged during this time. In 2002, Vancomycin-resistant *S. aureus* (VRSA) was first isolated in Michigan and Pennsylvania.[6, 7] It is evident that the development of antibiotic resistance to conventional and purely organic antibiotics is a routine process. Bacteria can develop resistance amazingly fast and, in some cases, resistance was already noticed even before the compound was commercially available for human use![8] This is probably the reason why quite a number of pharmaceutical companies are currently reluctant to invest money into the development of new antibiotics.

Antimicrobial resistance is a serious issue not only in patient care facilities such as hospitals where antibiotics are heavily used but also in surrounding communities because of rapid sharing of resistant genes between bacteria.[9] As a result, difficult-to-treat forms of infectious diseases caused by pathogenic superbugs are emerging. Most feared are those strains which are no longer treatable by any

available antibiotics. As shown in Figure 1, commercialization of antibiotics has decreased steadily after the 1980s. On the other hand, the significant occurrence of MRSA has begun mainly after 1995. During the last two decades, the number of antibacterial agents that have been discovered and introduced into the market has steadily declined and failed to meet the challenges posed by multidrug resistant pathogens.[10-12] Therefore, there is an urge to search for new classes of antimicrobial compounds with completely new modes of action to control the virulence of multidrug-resistant pathogens.

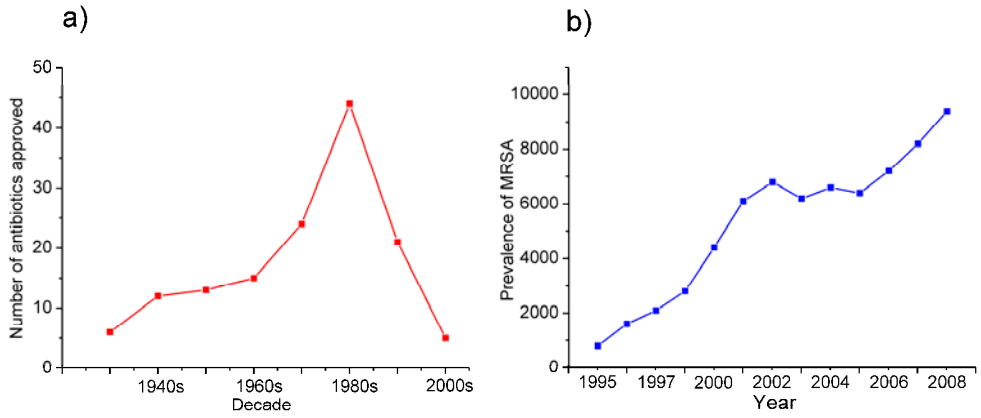

Figure 1. a) Decade wise approval of new antibiotics and b) prevalence of MRSA.[13]

Organometallic derivatization of an existing drug is an attractive approach to overcome the resistance issue. This strategy could indeed offer a metal-specific mode of action which is not available for the purely organic parent drug molecule. In this sense, one of the leading examples in medicinal organometallic chemistry is the antimalarial candidate ferroquine.[14-16] This ferrocenyl derivative of chloroquine reveals activity similar to that of the parent compound against a chloroquine-sensitive *P. falciparum* strain (HB3 5CQS), while comparison of activity of ferroquine and chloroquine against chloroquine-resistant *P. falciparum* (Dd2) showed that the former is ten times more active than the latter.[14, 15] In some cases, it was believed that the activity of a metal-derivatized-drug could be the sum

of the original activity and the inherent toxicity of the abiotic metal. For example, in the case of the arsenic-containing drug Salvarsan (see below), the general toxicity of As contributes to the overall antibacterial activity of the compound.[13] It is difficult for microorganisms to develop resistance against drugs with multiple targets, particularly, if resistance is associated with the target modification. Indeed, it has already been shown that the ability of bacteria to develop resistance against silver-based antimicrobials is limited, therefore enabling such antibiotics to survive long on the market.[17, 18]

There are significant advances in the development of organometallic-containing, and more generally, metal-containing anticancer and anti-malarial compounds.[19-24] In contrast, very little attention has been paid to the development of organometallic antibacterial drugs. Hence, explorations of metal-based antibacterial compounds are desirable, since the metal-specific mode of action of the metallo-drug may provide opportunities to overcome the development of antibiotic resistance. In this perspective, we present recent advances on the development of such compounds. We will focus our attention only on organometallic compounds, i.e. ones that possess at least one direct metal-carbon bond (consequently, classical coordination compounds are not considered herein). Furthermore, due to space restriction, we have decided to review only small organometallic compounds, thereby excluding antibacterial organometallic-containing peptide conjugates[21, 25, 26] or nanoparticles.[27-30] An excellent perspective article describing the synthesis and antimicrobial activity of nanoparticle-encapsulated silver-carbene complexes has been recently published by Youngs *et al*.[17]

Organoarsenical Complexes as Antimicrobial Agents.

As surprising as it can be, arsenic compounds are still currently being employed in medicinal chemistry, as evidenced by the relatively recent approval (in 2003) by the FDA of As_2O_3 (sold under the trade name Trisenox®) for the treatment of patients with relapsed acute myeloid leukemia.[31, 32] But, in the field of medicinal organometallic chemistry, Atoxyl (Trypoxyl®, Figure 2) was the first compound to be clinically used, first against trypanosomiasis (often called sleeping sickness), and then

syphilis at the beginning of the 20th century, and this despite very serious side-effects.[32] A review article describes the structure, reactivity and biological activity of arsenic compounds was published by Sadler *et al.* few years ago.[33] An excellent book chapter on organoarsenical drugs has recently been published by Gibaud and Jaouen.[32] Readers of this perspective are encouraged to refer to the review and the book chapter for further information on this subject. Nonetheless, the golden age of organoarsenical complexes as antimicrobial agents and, more generally in the field of medicinal organometallic chemistry, has been the discovery by the Nobel laureate Paul Ehrlich[34] of Salvarsan® (1910) and later of the more soluble but slightly less effective Neosalvarsan® (1912) for the treatment of syphilis (Figure 2). Until the advent of these drugs in the early 1900s, syphilis was a major, and often deadly, infection which was treated with mercury and potassium iodide.[32] And despite their severe side-effects, these compounds were only supplanted by penicillin in the 1940s. Interestingly, while it was clear that the formulation of Salvarsan with an As=As double bond was only a formal one, the "real" structure of Salvarsan® as a mixture of three- and five-membered cyclic compounds was only discovered in 2005 by mass spectrometry (Figure 2).[35] It is also interesting to note that an arseno-bismuth compound Bimarsen® (Figure 2) was also used for the treatment of syphilis due its low toxicity, tonic effect and ease of administration as well as its ability to be relapsed more frequently in the central nervous system than other arsenic compounds.[32] This allows neurosyphilis to be treated.[32] In more recent times, other infections caused by *Entamoeba histolytica* (Amebiasis) or *Trichomonas Vaginalis* as well as Vincent's Angina were treated with organoarsenical complexes such as those presented in Figure 2.[32] A few of these compounds were withdrawn from the market only in the 1990s.

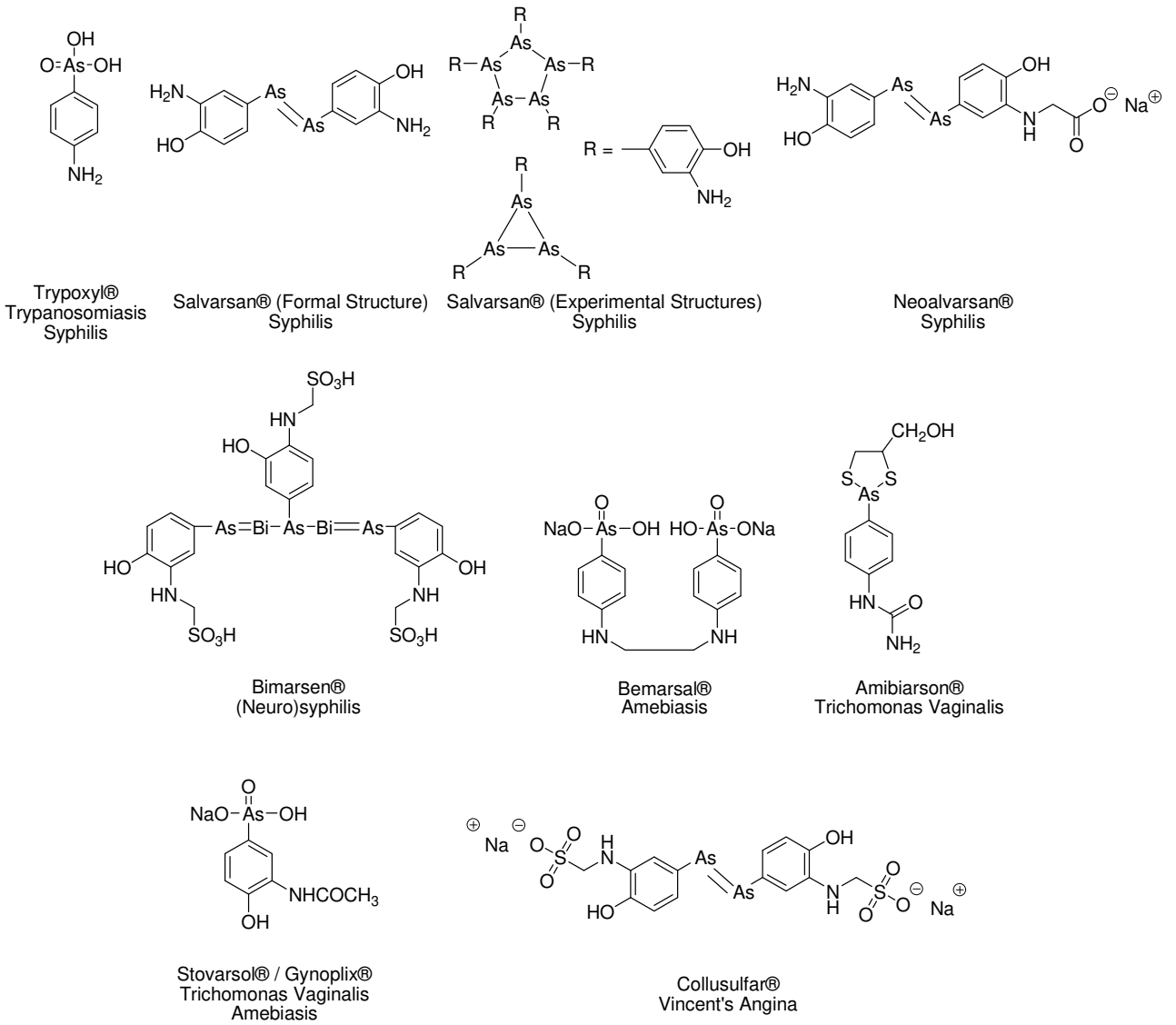

Figure 2. Structures of some relevant arsenic-based drugs (non-exhaustive list!). See the text for a discussion of formal structures of Salvarsan and its derivatives (with As=As bonds) vs. experimental ones.

Organometallic Derivatives of Penicilin and Quinolone Antibacterials.

In a more rational drug design approach, Epton, Marr and coworkers published a series of papers in the 1970s describing the synthesis of ferrocene analogues of well-established antibacterial drugs such as penicillins and cephalosporins.[36-39]

In their work, benzene rings in prominent positions were replaced by ferrocene. In particular, antibacterial drugs that inhibit the cell wall biosynthesis from the penicillin and cephalosphorin families were chosen. Figure 3 shows selected examples from their work. For compound **2** with R^1 = R^2 = H, the antibacterial activity was tested and found to be comparable with the parent benzyl-penicillin. Activity in this series decreased with increasing number of R = Me. None of the ferrocenyl derivatives of penicillin reached the potency of the organic analogues. However, no MIC values or more detailed information was given, and it was never investigated whether the metallocene analogues do actually follow the same mechanism of action as the parent compounds. It hence remains unclear whether they could help to overcome resistance against penicillin-resistant microbes in a manner similar to the anti-malarial compound ferroquine (vide infra).

More recently, two papers report on organometallic derivatives of quinolone antibiotics. Quinolones are exerting their bacteriocidal activity by inhibiting the topoisomerase II enzyme, which unwinds DNA, and thus interfere with DNA replication. Norfloxacin (nor) reacts with $W(CO)_6$ in 1M NaOH in a Pyrex tube, yielding a 1:1 complex with the formula (nor)$W(CO)_3(H_2O)$, of which a single crystal X-ray structure could be obtained.[40] Analogously, a suitable Ru precursor reacts with ofloxacin (oflo) and NaOH in methanol to give the complex (η^6-*p*-cymene)RuCl(oflo).[41] In both compounds, the quinolone is bidentately coordinated to the metal through the ring carbonyl and one of the carboxylic oxygen atoms (Figure 4). Both compounds exhibit good antibacterial activity and in addition, a direct interaction of the Ru complex with double-stranded DNA was proven.

Finally, a cyanoferrate(II) complex of isoniazid (ison), $[Fe(CN)_5(ison)]^{3-}$, inhibits both the wild-type and an isoniazid-resistant I21V mutant of enoyl reductase enzymes from *Mycobacterium tuberculosis*.[42] *In vitro*, this complex has about the same activity as isoniazid itself against wild type *M. tuberculosis*, the bacterium that causes tuberculosis.

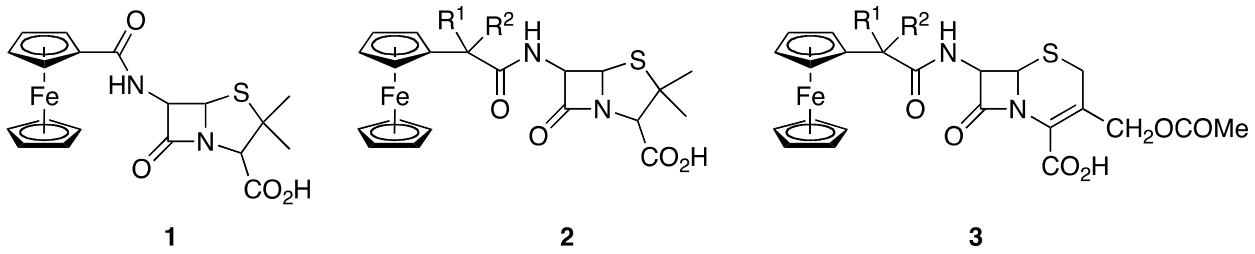

Figure 3. Structures of a ferrocenoyl-penicillin (**1**) and ferrocenyl-penicillin **2**, and a ferrocenyl-cephalosporin **3**.

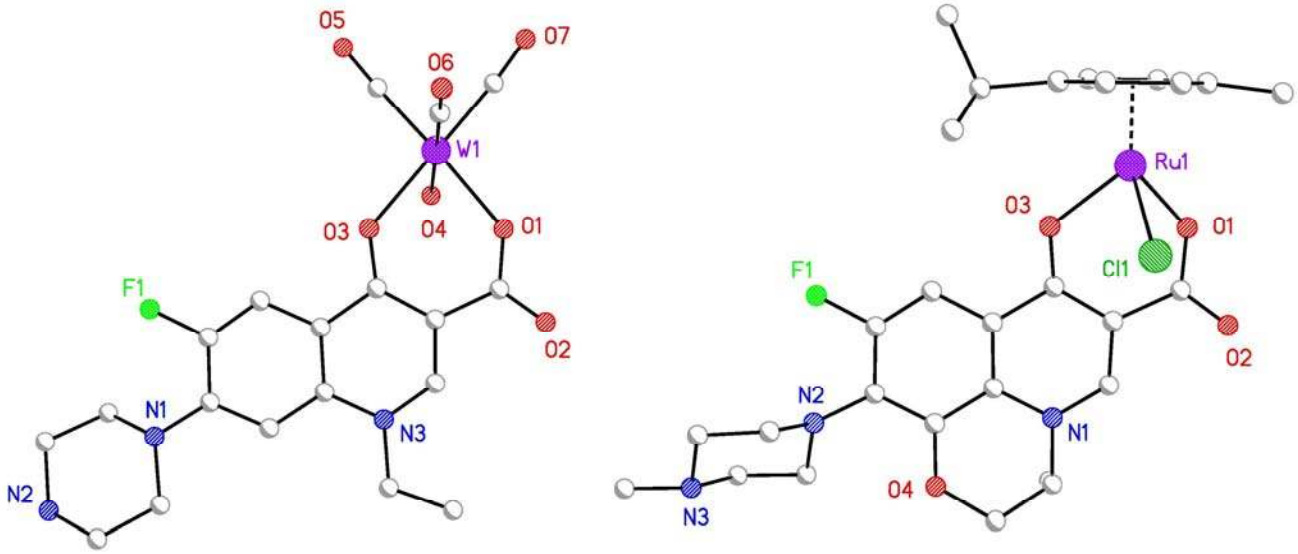

Figure 4. Single crystal structures of two organometallic derivatives of quinolone antibiotics (left: norfloxacin, right: ofloxacin).

***N*-Heterocyclic Carbene Complexes as antimicrobial agents.**

Silver and its salts have been used as antimicrobial agents since the 17th century.[43, 44] Not elemental silver itself but the cationic form (Ag^+) is the species responsible for the antibacterial activity of such compounds.[44] Despite evidence showing that Ag^+ has multiple targets (e.g. cell wall, enzyme and DNA/RNA), the mechanism of action of Ag^+ is still not fully understood.[17] The successive discovery of penicillin and other antibiotics after the 1940s has slowly suppressed their uses particularly for internal

use. However, there has been a renewed interest in the field of silver-based antimicrobials after 1965 when resistant organisms such as *P. aeruginisa* and *P. mirabilis* have emerged.[45]

The Youngs research group was the first to introduce *N*-heterocyclic carbenes (NHCs) as carrier ligands for Ag^+ in 2004 for antibacterial application purposes.[46] One representative example of such a class of compound is Silvamist (**4**, Figure 5), a caffeine derived Ag-NHC which exhibits excellent antibacterial activity against drug resistant pathogenic bacteria at low micromolar concentration.[17, 47-49] Ag-NHCs were also shown to exhibit activity against pathogens causing cystic fibrosis in *vitro* as well as in *vivo*.[32, 48-50] Worthy of note, recent publications by Roland, Tacke *et al.* described the antibacterial and cytotoxicity activities of several symmetrical and unsymmetrical new Ag-NHC complexes.[51-53] Although most of them have a promising antibacterial activity profile against Gram-positive as well as Gram-negative pathogens, they however suffer from the fact that they are also cytotoxic against mammalian cells. Since the advances in research on antimicrobial Ag-NHC complexes have been reviewed recently, we direct the readers to these articles for more details on this topic.[17, 44, 50, 54, 55]

Compared to silver, much less attention has been paid to the development of other metal-NHC complexes as antibacterial agents. [50, 55] In 2004, Cetinkaya *et al.* studied the antibacterial activity of six cationic gold-NHC complexes.[56] Different *N*-substituted imidazoles were used as carbene precursors to prepare the Au-NHC complexes. Among all, compounds **6**, **7** and **8** (Figure 5) were found to have good antibacterial activity *in vitro* against a series of bacterial strains at minimum inhibitory concentrations (MIC) of 3.1 - 6.3 µg/mL. Shortly after, Ghosh and co-workers reported [1-benzyl-3-tert-butylimidazol-2-ylidene]AuCl (**10**, Figure 5) which inhibits the growth of Gram-positive *B. subtilis* at a MIC of 15 ± 2.3 µM.[57] Interestingly, **10** is ca. two times more potent than its Ag analogue **9** (Figure 5). Very recently, the antibacterial activity of a few other Au-NHC complexes with different *N*-substituents on the benzimidazole and bis(iminoacenaphthene) (BIAN) scaffold was reported.[58, 59] However, all of them exhibited poor antibacterial activity. For more information on the subject, we invite the readers to consult the review article by Youngs and co-workers.[50]

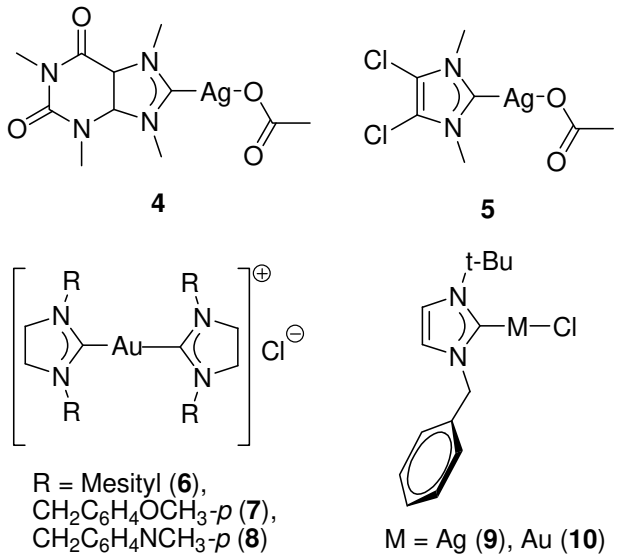

Figure 5. Structures of several potent antimicrobial Ag- and Au-NHC complexes.

Organometallic Derivatives of Platensimycin.

The recent discovery of the naturally occurring bacterial fatty acid biosynthesis inhibitor, namely, platensimycin (**11**, Figure 6) is a breakthrough in antibiotic research.[60] **11** displays potent antibacterial activity against the Gram-positive pathogens such as Methicillin-resistant *S. aureus* (MRSA) or Vancomycin resistant *E. faecalis* at minimum inhibitory concentration (MIC) 0.5-2 μg/mL. It selectively inhibits one of the important enzymes, namely FabF in bacterial fatty acid biosynthesis. Indeed, **11** was co-crystallized with its target enzyme (a and b, Figure 8, from PDB code 2gfx).[60] The polar benzoic acid unit is buried deep in the malonyl binding pocket while the lipophilic tetracyclic cage is placed into the mouth of the enzyme pocket (b, Figure 8). Following the identification of this lead structure, chemical synthesis efforts were undertaken to provide numerous chemically modified derivatives for structure activity relationship (SAR) studies.[61-64] Concurrently with the emergence of purely organic derivatives of **11**, our group embarked on a project to investigate the possibility of

replacing parts of this complicated organic molecule by organometallic groups (see Figure 6 for the design). Our hypothesis was to provide organometallic derivatives of **11**, which would be synthetically easily accessible and, at the same time, would exhibit potent antibacterial activity. Moreover, a metal specific mode of action was expected from the organometallic derivatives. Various structurally diverse and stable metallocenes were employed for this purpose to provide four different types of achiral and chiral bioorganometallics (see Figure 7 for the structures).

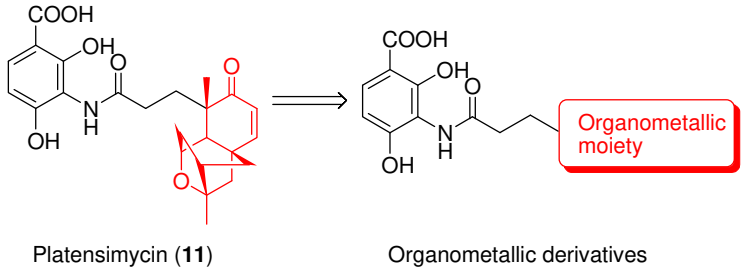

Figure 6. Design of organometallic derivatives of platensimycin (**11**).

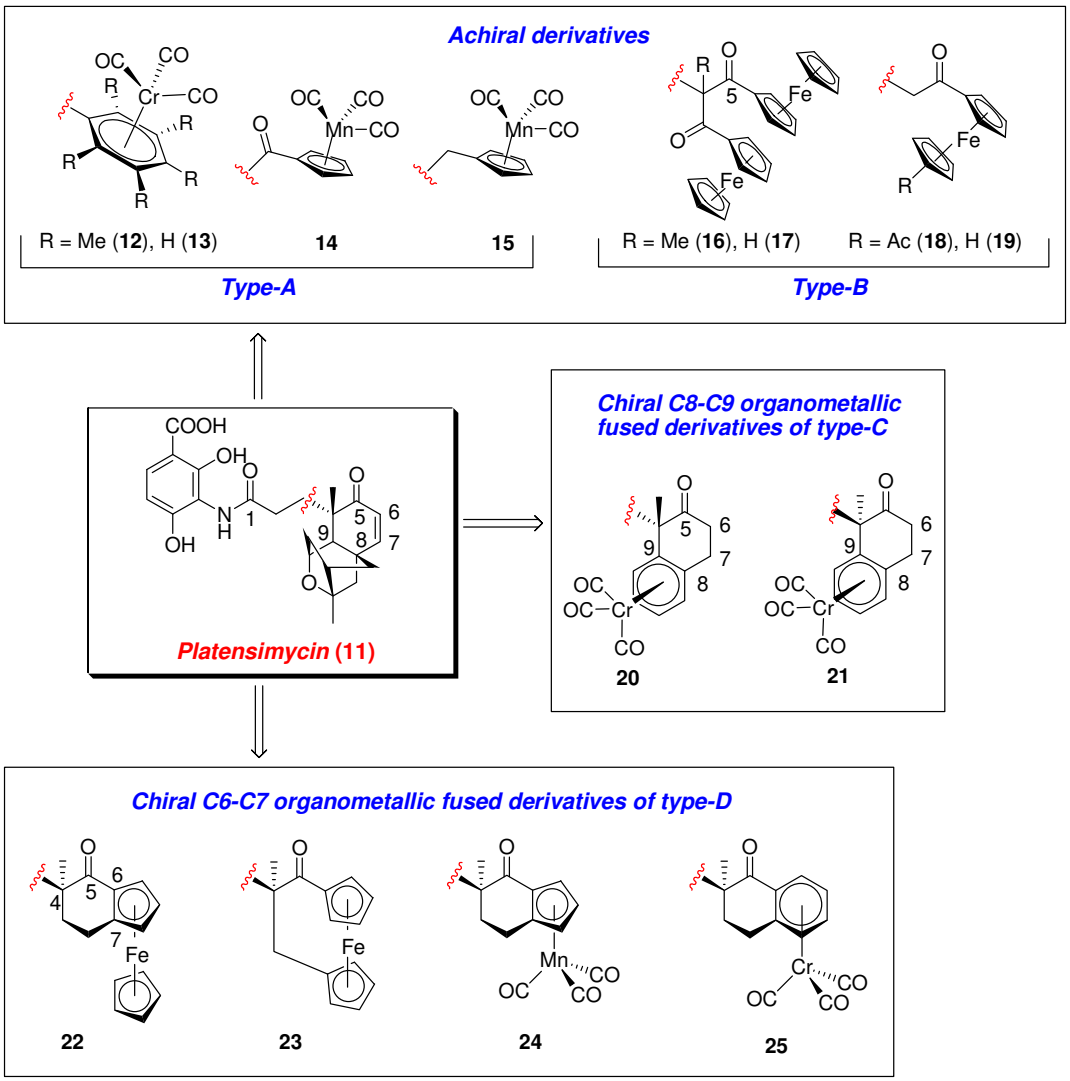

Figure 7. Structural overview of various organometallic derivatives of **11**.

Achiral organometallic derivatives of type **A** were obtained by replacing the tetracyclic cage with ($\eta^{5/6}$-arene)M(CO)$_3$ (arene = C_6Me_5, C_6H_5, C_5H_4 and M = Cr, Mn) metal half sandwich moieties.[65, 66] As shown in Figure 8 (c), docking experiment with **12** showed that the organometallic moiety fits nicely into the active site of the FabF enzyme. Among all type **A** derivatives, only the (η^6-C_6Me_5)Cr(CO)$_3$ containing derivative **12** inhibited the Gram-positive *B. subtilis* growth at a MIC of 80 µg/mL. The activity is moderate compared to its parent compound platensimycin (MIC = 0.2 µg/mL against *B. subtilis*). Interestingly, the analogous (η^6-C_6H_5)Cr(CO)$_3$ containing derivative **13** did not exhibit any

antibacterial activity. This finding was correlated to the poor cellular uptake of **13** compared to **12** as confirmed by measuring the Cr-content inside the bacteria by ASS after treatment of *B. subtilis* cells with these compounds. In order to investigate whether **12** inhibits the bacterial fatty acid biosynthesis or has another mechanism of action, Bandow and co-workers studied the proteomic signature of *B. subtilis* after treatment with compound **12**.[67] As shown in Figure 9, the proteomic responses to **11** and **12** were compared as the former induced exclusively the proteins belonging to the fatty acid biosynthesis inhibition signature. Neither the six signature markers nor any of the compound-specific marker proteins was induced by **12**, indicating that it does not inhibit fatty acid biosynthesis. However, at least seventeen proteins were significantly upregulated upon treatment with **12**. The comparison of the proteomic response to **12** with the proteomic profiles in the reference compendium[68] did not yield a close match, although some of the marker proteins are also induced by membrane-active antibiotics. Furthermore, in contrast to **11** which is only bacteriostatic, compound **12** was found to be bacteriolytic at higher doses. This means that compound **12** not only inhibits bacterial growth, but destroys the bacteria by lysis. In summary, in this case, organometallic derivatization has changed the mechanism of action completely; the compound no longer inhibits the FabF enzyme but exhibits a multi-causal death effect. This unexpected new mode of action is important as the medicinal usefulness of fatty acid biosynthesis inhibitors has been questioned.[69]

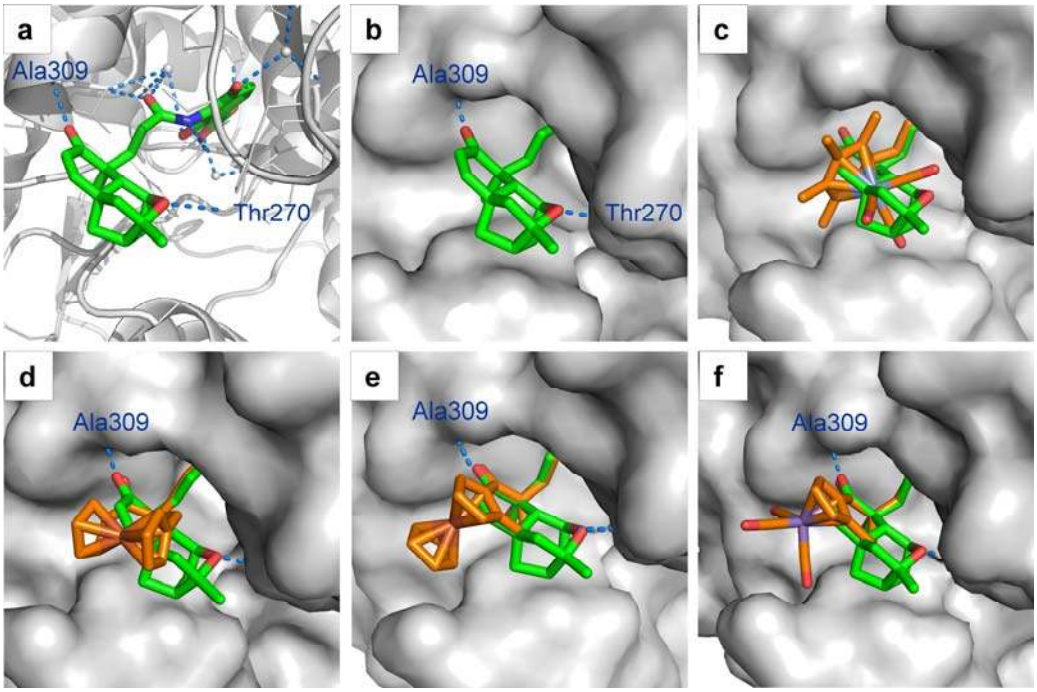

Figure 8: Binding of platensimycin with FabF enzyme (a; cartoon and b; surface, PDB code 2gfx) and surface models of the manual docking of bioorganometallics **12** (c), **23** (d), **22** (e) and **24** (f) into the FabF enzyme pocket.[65, 66, 70] Bioorganometallics and platensimycin are presented in orange and green, respectively.

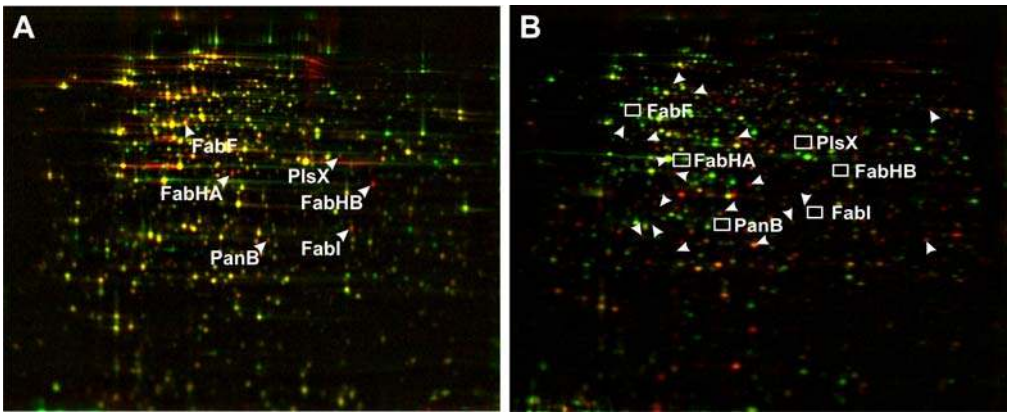

Figure 9: The protein expression profiles of *B. subtilis* to treatment with 5 μg/mL platensimycin (A) and 25 μg/mL **12** (B) do not share marker proteins. Marker proteins are indicated by arrowheads. Boxes in (B) indicate the locations of fatty acid biosynthesis marker proteins. Pulse-labeled cytosolic proteins were separated by 2D-PAGE. Red false-color images representing protein biosynthesis after antibiotic treatment were warped onto green false-color images showing protein synthesis under control conditions. Antibiotic induced proteins appear red, repressed proteins green, and proteins synthesized at equal rates under both conditions appear yellow.[67] Reproduced with permission of the publisher from reference.[67]

As mentioned in the introduction, there has been a resurgence of interest in the derivatization of existing drugs with ferrocene, mainly in anticancer and antimalarial research.[15, 21, 71-73] With this in mind, we designed achiral derivatives of type **B**, where ferrocene was employed as surrogate for the tetracyclic cage of **11** (see Figure 7).[74] Moreover, we incorporated an acyclic keto group in the C5 position that is absent in type **A** derivatives. The C5 keto group was assumed to serve a similar purpose as the cyclic keto group in the tetracyclic cage of **11** that forms a strong H-bond with the Ala309 residue while bound to FabF enzyme (a and b, Figure 8).[60, 74] Among the compounds **16-19**, only **17** containing a 1,3-di keto functionality showed weak antibacterial activity (MIC of 128 μg/mL) against Gram-positive *S. aureus* Mu50 (VISA).

Chirality often plays an important role in the biological activity of drugs. After getting two moderately active compounds (**12** and **17**) in the preliminary stage of this project, we extended our concept one step further by introducing chirality into the design of the next generation of bioorganometallic platensimycin analogues. Various metallocene-fused cyclohexanone moieties were employed as a surrogate for the tetracyclic cage of **11** (see Figure 7). These chiral derivatives are structurally even more similar to **11** compared to the achiral analogues. Both diastereomers of a C8-C9 (η^6-benzene)$Cr(CO)_3$ fused derivative (**20** and **21**, Figure 7) of **11**, abbreviated as type **C**, were synthesized.[75] Unfortunately, both compounds **20** and **21** failed to exhibit any antibacterial activity. However, during the synthesis of these compounds, we had the opportunity of exploring various reactivity aspects associated with (η^6-2-tetralone)$Cr(CO)_3$ moiety. Analysis of the surface model of the crystal structure of **11** bound FabF enzyme showed the existence of a pocket for the C6-C7 fused cage.[60] This observation led us to design C6-C7 organometallic fused derivatives of **11**.[66, 70] All these type **D** analogues are chiral molecules like type **C** and contain various metallocene moieties, however, not fused in the C8-C9 position (like **20** and **21**, Figure 3), but fused in the C6-C7 position of the cyclohexanone ring. All previously reported bioactive purely organic analogues of **11** mainly focused on the modification of the C8-C9 fused tetracyclic cage. In contrast, type **D** derivatives represent a completely new class of analogues of **11** with C6-C7 substitution pattern. The rationale behind this design concept was verified by manual computer docking experiments of both metallocene-fused analogues **22** and **24**, respectively (e and f, Figure 8). The metallocene moieties fit nicely in the active site when superimposed manually on **11** bound to its target enzyme FabF.[60] The C6-C7 fused ferrocene/cymantrene occupies a pocket similarly to the C8-C9 fused tetracyclic cage of **11** and the keto carbonyl oxygen is capable of forming an H-bond with Ala309. The [3]-ferrocenophane-1-one based derivative **23** also showed similar result (d, Figure 8). We therefore expected that this new substitution pattern would provide crucial information on the effect of steric bulk fused at C6-C7 position instead of C8-C9 position on the biological activity of **11**. The organometallic compounds

employed were (η^6-benzene)$Cr(CO)_3$, ferrocene and cymantrene for the type **D** analogues. The size of the organometallic moieties increases in the order ferrocene < cymantrene < (η^6-benzene)$Cr(CO)_3$. Despite both **22** and **23** containing ferrocene, they still possess significant structural differences. While **22** consists of a homo-annular ferrocene moiety, the [3]-ferrocenophane-1-one based derivative **23** contains a hetero-annular C_3 bridged ferrocene moiety which is slightly strained. Although the manual docking showed the newly designed organometallic analogues fit into the active site of FabF, the compounds did not exhibit any antibacterial activity against either Gram-positive or Gram-negative bacterial strains. The lack of activity is perhaps due to insufficient cell permeability of the bioorganometallic compounds as recently demonstrated for several other synthetic and natural purely organic congeners of **11** having a modified tetracyclic cage.[63, 64]

Conclusions.

Over the last years, research in medicinal organometallic chemistry has mainly focused on the preparation of organometallic compounds for anticancer and antimalarial purposes. Despite stunning results, it is surprising that organometallic compounds have not received more attention as antimicrobial agents, especially considering that the first, and probably the most prominent organometallic complex to date, namely Salvarsan®, was an anti-infective drug! Taking into account the urgent need for novel antibiotics, we strongly believe that more organometallic compounds deserve to be tested for antimicrobial purposes in the very near future, and their mechanism of action be investigated. Clearly, metal complexes have the potential for completely new, metal-specific modes of action that may make it difficult for bacteria to develop mechanisms of resistance.

Acknowledgements.

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Malay Patra obtained his M. Sc. in chemistry at the Indian Institute of Technology Bombay in 2007, Mumbai, India, working with Prof. Goutam Kumar Lahiri on photolabile ruthenium-nitrosyl complexes. He then pursued his PhD in the group of Prof. Nils Metzler-Nolte at the Ruhr-University Bochum (Germany) where he was involved in the development of novel organometallic-based antibacterial agents. He completed his doctoral study in July 2011 with distinction. Currently, he is carrying out a post-doc in the group of Prof. Gilles Gasser at the Institute of Inorganic Chemistry, University of Zurich (Switzerland) working on the synthesis of novel metal-based compounds for medicinal and biological applications.

Gilles Gasser obtained his M.Sc. in chemistry at the University of Neuchâtel (Switzerland) in 2000. He then worked for one year in the agro-pharmaceutical company Lonza in Visp (Switzerland) before returning to Neuchâtel to complete his PhD thesis in 2004 with Prof. Helen Stoeckli-Evans, in collaboration with Dr. James Tucker from the University of Exeter, UK (now at the University of

Birmingham). From 2004-2007, Gilles carried out a post-doc with Prof. Leone Spiccia (Monash University, Melbourne, Australia) before being awarded an Alexander von Humboldt research fellowship in 2007 that he undertook at the Ruhr-University Bochum (Germany) in the group of Prof. Nils Metzler-Nolte. In 2010, Gilles started his independent career at the Institute of Inorganic Chemistry of the University of Zurich (Switzerland) first as a Swiss National Science Foundation (SNSF) Ambizione research fellow and, then, since 2011, as a SNSF assistant professor. Gilles' group current interest focuses on the preparation and use of (organo)metallic complexes for medicinal and biological purposes.

Nils Metzler-Nolte studied chemistry at the Universities of Hamburg, Freiburg, and Munich where he obtained a PhD with Prof. H. Nöth. After a postdoc with Prof. M. L. H. Green in Oxford he started his independent research on Bioorganometallic Chemistry at the Max-Planck-Institut für Strahlenchemie (nowadays MPI for Bioinorganic Chemistry) in Mülheim in 1996. He was appointed professor for pharmaceutical and bioinorganic chemistry at the University of Heidelberg's Institute for Pharmacy and Molecular Biotechnology in 2000, and accepted an offer as full professor of Inorganic Chemistry at the Ruhr-University Bochum in 2006. Nils has received several fellowships and awards and has organized national and international meetings. He is currently serving as Speaker of the Ruhr University Research School and Vice-President of this University, and is also Speaker of the DFG-funded Research Unit "Biological Function of Organometallic Compounds" and a Council Member of the Society of Biological Inorganic Chemistry. He serves as member of the international advisory boards of several journals, among them the RSC journals *Dalton Transactions* and *Chemical Science*. With research

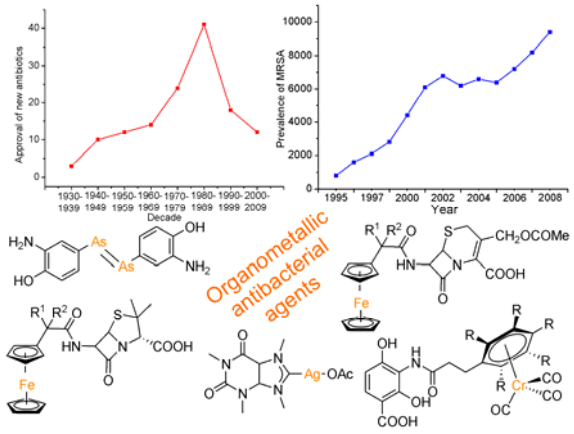
interests including model systems for bioorganometallic enzymes, medicinal organometallic chemistry, functional metal bioconjugates, and most recently biocompatible nanoparticles, the group is running the full program of inorganic and organic chemical synthesis and characterization through to cell culture and biochemical investigations.

TOC Entry

Small Organometallic Compounds as Antibacterial Agents

Malay Patra, Gilles Gasser and Nils Metzler-Nolte

This perspective article describes the historical development in brief and recent advances on the preparation of small organometallic compounds as new classes of antibacterial agents with potential for clinical development.



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