Bioorganometallic compounds in medicine: The search for new antibacterial agents

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ABSTRACT

Bioorganometallic Chemistry is an inter-disciplinary area of research that midwife researches in organometallic Chemistry, Biology and Medicine. It is a relatively new research area. We recall that the biological application of organometallic compounds date back to the use of Paul Erlich's Salversan and its analogues in the treatment of syphilis during the world wars. Development in the screening of these compounds for medicinal purposes was however hampered by the issue of toxicity due mainly to their high reactivity. Recent discoveries that certain organometallics are stable in air and water coupled with their ability to alter the structure of well-known organic drugs including their redox chemisties have renewed interest in the screening and testing of these compounds as drug candidates. Here we review the current trends and potentials of this interdisciplinary area of research in the search for novel antibacterial agent. We describe the role of organometallic enzymes/biomolecules as an impetus to the natural biocompatibility of organometallic compounds. The discovery of certain antimicrobial agents that will help restore the activity of some drugs as well as overcome resistance. These worthwhile findings may help in exposing the potentials of this class of compounds so as to encourage researchers, especially in Africa to diversify our research for drug molecules capable of addressing peculiar problems ravaging the continent such as the scourge of malaria, EVD and HIV/AIDS.


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1. INTRODUCTION

The term bioorganometallic chemistry was first used in 1985 by Gerard Jaouen [1], to describe the biological chemistry of organometallic species. He defined bioorganometallic chemistry as the study of biomolecules or biologically active molecules that contain at least one carbon directly bonded to a metal or metalloid [2]. Organometallics were thought to have no role in modern medicine because of issues of toxicity due to high reactivities. The search for metallopharmaceuticals and metal active species in drug design have been bedeviled by the sheer generalization that ‘metal based drugs will inevitably interact with cellular DNA as their target. While the initial success of certain metallomedicines such as cisplatin and carboplatin have prompted the screening of inorganic coordination complexes for drug design, their organometallic counterpart have continue to suffer setback until the present time. The development of bioorganometallic drugs have for long time been hampered not only by their perceived interaction with DNA, but also by the paradigm that ‘bioorganometallics are toxic and unstable in air and water’ [2,3] and hence thought to be incompatible with biological systems.

Recent research findings have shown that certain bioorganometallic compounds are stable in air and water and in some cases metals as well as their particular complexes exhibit a diversity of chemical properties and hence because of issues of speciation ‘the notion that they should all come down to one and the same cellular target- DNA seems ridiculously unlikely [3]. These paradigms therefore seem untrue. Preceding the period of these teaching paradigms, organometallics have played vital roles in biology. Some organometallic
compounds existed naturally as biomolecules, these include the cobalamines such as vitamin B$_{12}$ and its derivatives, the hydrogenase family which catalyzes the useful process of the reversible conversion of dihydrogen into protons and electrons in biological system. Carbon monoxide dehydrogenase, another naturally occurring organometallic species are major components in the global carbon cycle, they catalyse the conversion of CO to CO$_2$ [4]. Few other organometallics were used as drugs long time ago. Organoarsenicals are good examples, the most popular being Paul Ehrlich’s Salversan (1) and its analogues (2). They were the only remedy for syphilis at a time when syphilis ravaged like AIDS did at the present time [5-7].

For a very long time melasoprol, (3) another organometallic drug remained the first-line treatment for patients with trypanosome brucel gambiense trypanosomiasis and is still used in African countries even though it is toxic and treatment result in the development of an extremely severe reactive arsenic encephalopathy (RAE). The reality is; in the face of this unacceptable toxicity melasoprol will be in use as it is unlikely that any new drug will replace it anytime soon [7].

Exploits in bioorganometallic chemistry in the past three decades have renewed hope in the design of drugs that will combat ailments, restore potency by overcoming drug resistance which have bedeviled well-known organic drugs, and of course, tackling the issue of toxicity. This short review will x-ray the trend in the search for organometallic antibacterial agents and the hope of this interdisciplinary research area in medicine.

2. ORGANOMETALLIC ANTIBACTERIAL AGENTS

Issues associated with drug resistant pathogens remain the biggest challenge facing the antibacterial market, during the last two decades, this factor have caused a decline in the number of antibiotics in the market [8]. The alternative therefore is to turn to new compounds with new modes of actions capable of overcoming the resistant strains. The current promising approaches to doing this is the organometallic derivatisation of previously known drugs or completely new organometallic drugs [9-13]. The organometallic derivatisation of old drugs approach have been used extensively by the research groups of Gerard Jaouen and Nils Metzler-Nolte in the synthesis and activation of new tamoxifen [14-16], platensimycin [17-20], and et cetera.

The earliest attempt at conjugating organometallic fragment to a known antibacterial drug was in the mid-1970s when, Roger Epton [21], George mar and co-workers [22-24] reported a series of research where they introduced the ferrocenyl moieties into penicillin and cephalosporin. They introduced the side chain substituent into 6-amino penicillic acid and 7-aminocephalosporanic acid by either condensation with appropriate acid chloride in the presence of tertiary amine or with acid anhydride or by direct coupling of an acid in the presence of NN'-dicyclohexylcarbodiimide. The ferrocenyl-penicillin 4 ferrocenyl-penicillin 5, and the ferrocenyl-cephalosporin 6 have been synthesized.
**In vitro** antibiotic test for these compounds showed good antibacterial activity for some of the ferrocenyl-penicillin tested. A particular ferrocenyl-penicillin exhibited high antibiotic activity, comparable to that of benzyl-penicillin. The ferrocenyl-cephalosporin also showed antibacterial activities but they were less active than the cephalothin control, but interestingly they were found to behave as β-lactamase inhibitor, indicating the possibility of overcoming resistance arising from β-lactamases which degrade antibacterial drugs.

Similarly, Kaushik et al [25] derivatised the first organometallic penicillin conjugate where the penicillin moiety is directly bound to a metal ion. Spectroscopic investigation of the cyclopentadienyl and indenyl complex derivatives 7, confirmed direct coordination of the penicillin moiety to the metal ions in a bidentate coordination mode while in vivo testing shows the compounds were biologically active against various strains of drug resistant bacteria.

Several other well-known biologically active compounds have been attached to the ferrocene molecule and their compounds as well as their complexes with metal ions have been screened for antibacterial activities. Zahid et al, published a series of papers that investigated antibacterial, antifungal and cytotoxic properties of some sulfonamides [28], mono and diethanolamine [27] and 1,1-dicarbohydrazone [28] derivatized ferrocene complexes. In vitro antibacterial screening against pathogenic bacterial strain for these compounds and their complexes shows good antibacterial and antifungal activities. These activities were found to increase on coordination with metal ion.

Similarly, The quinolone antibiotic norfloxacin was coordinated to tungsten carbonyl [29], this involves the hydrothermal reaction of norfloxacin with W(CO)₆ and 1M NaOH in a sealed Pyrex tube giving the complexes; [W(H₂O)(CO)₆(nor)], where the quinolone is bidentately coordinated to the tungsten metal via two oxygen atoms from one of quinolone ring and another through the carboxylate group of the norfloxacin. In vitro susceptibility testing of norfloxacin and this tungsten carbonyl complex with a concentration of 10µ/disk respectively showed higher activities for the norfloxacin complex for both gram negative and gram positive bacterial tested.

### 3. CO-RMS ANTIBACTERIAL AGENTS

Transition metal carbonyls have been recognized as the most promising among the so called carbon monoxide-releasing molecules (CO-RMs) [30]. CO like NO is a signaling molecule with vast role in biological system. Endogenous production of CO by humans was first reported by Torgny Sjostrand in 1966. The catabolism of heme by heme-oxygenase enzyme produces equimolar amounts of CO, Fe⁰ and billiverdin. The billiverdin is further acted upon by billiverdin reductase leading to the formation of bilirubin. Bilirubin is a major scavenger of reactive oxygen species in the biological system, these activities have been adequately reviewed [31-33]. The labile Fe⁰ induces the expression of the ferritin H chain which combines with the ferritin L chain to form a monomeric (24-subunit) complex with high Fe storing capacity (4500 Fe atoms per ferritin). The heteropolymer oxidizes F⁰ to Fe⁰ [34]. The major target of CO in the biological system is the activation of the soluble guanylyl cyclase, which upregulate cGMP level by the conversion of GTP to GMP, this activation process have been reported to induce vasorelaxation by lowering intracellular calcium concentrations and/or decreasing the sensitivity of the contractile system to free Ca²⁺. These
discovery has opened up research into the role of CO in cardiovascular diseases. Some CO-RMs are already been patented [35,36] in this regard. This review does not include the role of transition metal carbonyls in cardiovascular diseases, rather it focuses on a review of these organometallic molecules as antibacterial agents based on their ability to release and deliver CO to tissues and cells which can bind to heme and cytochromes, impair bacteria respiration and eventual death [34,37].

Saraiva et al. in a series of publications reported the antibacterial action of CO-RMs. They reveal that CO released by CORMs exert bactericidal effects, this have been reviewed elsewhere [38], and that these bactericidal CORMs alter the transcription of several genes involved in oxidative stress responses, leading to the conclusion that CORMs elicit the production of reactive oxygen species (ROS) with bactericidal actions [39]. The group further investigated the mediating role of CO-RM generated ROS in bactericidal killing [40] and recently they reported the bactericidal activity of CORMs against Helicobacter pylori, the major pathogenic cause of gastric and duodenal ulcer. The good response of CORM-2 was compared against known drugs [41]. The outcomes were inspiring.

Fig 4: Structure of CORM-1, CORM-2, and CORM-3

Concern for the level of ROS generated endogenously in cells treated with CORM-2 and ALF062 were further examined in another work [42], and gave data revealing significant increase in ROS content. The ROS formed were confirmed to have been generated by CO; cells exposed to CORM-2 were shown to be under oxidative stress by testing the activity of compounds treated with CORM-2 against the activity of glutamate dehydrogenase, whose activity is known to decrease under oxidative stress.

In a different study the possible action of CO on bacterial growth rate was investigated [43]. The study compared the action of the direct delivery of CO gas and CO-RMs 1 and 2 on Escherichia coli and Staphylococcus aureus in both aerobic and anaerobic conditions. They were found to reduce the viability of the bacteria since after about 30 minutes of the exposure of CORM-2 to the bacteria, the percentage of surviving cells diminished to less than 30%. CORM-3 gave similar results, however Staphylococcus aureus showed some resistance to CORM-3. The bactericidal effects of these CO-RMs were confirmed to be due to CO release by CO-RM by carrying out cell growth experiments with CO-RM in the presence of the CO scavenger hemoglobin. CO-RMs have better bactericidal actions than CO gas.

Haven established the ability of CORMs to deliver CO to bacterial cells thereby significantly inhibiting their viability, researchers proceeded to study the analysis of the global transcriptome of bacteria treated with CO-RMs [44-46].

Analysis of of transcriptomes can be used to understand the molecular mechanism and signaling pathways which is useful in assessing the safety of drugs. Saraiva and coworkers [40,41] studied the analysis of the global transcriptome of Escherichia coli treated with CORM-2. A microarray expression analysis of Escherichia coli treated with CORM-2 allowed for the comparison of the transcriptomal response of a bacterium when treated with the subject CO-RM in both aerobic and anaerobic environments. CORM-2 showed a broad effect on gene expression levels dependent on CO release. The expression level of key transcriptional regulators together with the phenotypic analysis of the mutant strains reveal that CORM-2 triggers a network of responses.

4. CONCLUSION

Bioorganometallic compounds offers hope in the fight against the scourge of deadly diseases such as MALARIA, HIV/AIDS & EVD that have continued to ravage humankind. These compounds are able to overcome issues of drug resistance and restore potency to some previously known drugs. There are expected challenges in this area of collaborative research as organometallic compounds are ideally synthesized under inert atmosphere in the absence of oxygen and water. These challenges are not too difficult to surmount, we therefore implore researchers to key into this relatively new multi-disciplinary research area in the search for novel and potent antibacterial and other drug candidates.
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