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Digest paper

The natural and synthetic indole weaponry against bacteria

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ABSTRACT

The emergence of drug resistant bacterial infections leading to high mortality rates has posed a formidable challenge to organic synthesis and medicinal chemists to deliver potent and novel antibacterial drug candidates. In particular, antibacterial agents based on novel chemotypes and first-in-class drug candidates with novel mode of actions are highly desired. Indole scaffold has found a consistent presence in the bioactive molecules of synthetic and natural origin. The potential of indole based small molecules as antibacterial agents has not been as much explored as in other areas of medicine, like cancer therapy. In this review, we present a brief account of indole based antibacterial small molecules which have been either synthesized in the laboratory or isolated from natural sources and provide intriguing potential leads in the antibiotic drug discovery research.

Contents

Introduction

Nature has been a tremendous source of small molecules endowed with varying structural complexities and a wide range of biological activities. The discovery and development of antibiotics against a variety of microbial infections is amongst the greatest triumphs of modern scientific research. The development of antibacterial drugs had been led primarily by the discovery of antibiotic natural products or their derivatives. The golden era of antibiotics indeed had gifted humanity a longer and healthier life. However, the emergence of drug-resistant microbial infections leading to increase in the mortality rate along with a scarce of new antimicrobial chemotypes is so worryingly alarming [1]. The decision of many pharmaceutical companies to abandon their antibiotic research has further augmented the threat of emerging drug-resistant infections to human life. More than 13 million deaths worldwide each year are caused by the fungal and bacterial infections [2]. Over the years, microbes, in particular the bacteria have evolved their genetic and biochemical permutations to evade the effects of antibacterial drugs. Infact, development of drug resistance in microbes is an evolutionary inevitability that calls for a constant development of new clinical drug candidates. The lack of specificity and narrow spectrum are major obstacles in current microbial therapy. Hence the development of more efficacious, safe and target specific new antimicrobial agents is an issue of current medicinal importance. Despite the known targets for antibiotic drugs, translation of target based discovery into drug candidates is highly challenging and many drugs fail to either enter the cell membranes of bacteria or do not keep their promising activities

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in rather complex cellular environment of bacteria. These issues have encouraged the older whole-cell screening strategies. However, it seems that compound collections lack the structural diversity required to discover novel and potent antibacterial small molecules.

While it is true that natural products had been a driving force in the discovery of antibiotics, the low-hanging fruits had already been harvested and often the known natural products are rediscovered during the search for new antibiotics of natural origin. Synthetic biology has to play a leading role in this area of discovery research and in providing practical access to novel natural product analogues. The consistent presence of some of the molecular frameworks as interacting partners of biological macromolecules offers them a privileged status and these molecular scaffolds have been well exploited for a diverse range of biological modulation and therapeutical applications. Indole framework is one of the privileged scaffolds that often decorate biologically active small molecules of natural or synthetic origin. In particular, isolation of natural products remains a witness to a regular presence of indole polycyclic molecules of varying structural complexities. Moreover, in contrast to the three-dimensional complexity that is often associated with biological activities [3], many structurally simpler and flat indoles have been reported to display intriguing antibacterial activities. In this article, we present small molecules based on indole polycyclic frameworks that are either isolated from nature or synthesized chemically and display antibacterial activities and thus offer intriguing bioactive structural space for drug discovery.

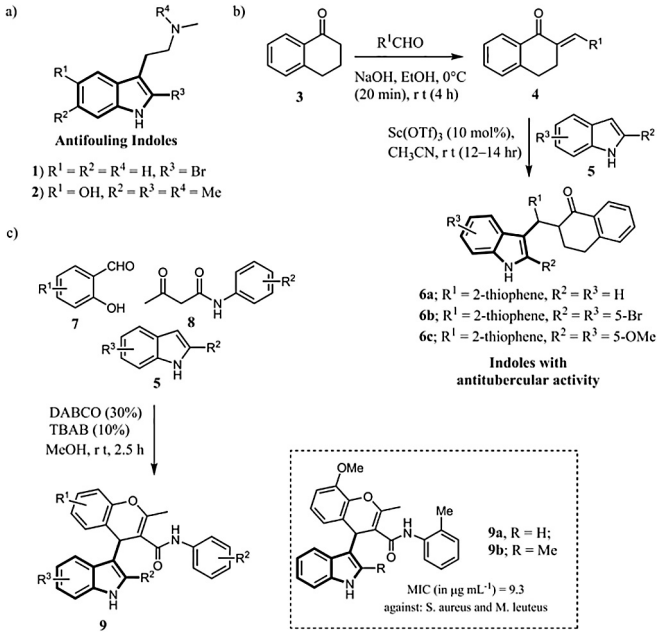
Antibacterial small molecules based on a simple indole scaffold

Indoles are natural organic compounds with an aromatic heterocyclic structure and structurally different indole based small molecules have been extensively explored in medicinal chemistry and drug discovery. A number of indole derivatives possess potent activities against viruses, fungi, Leishmania parasites and bacteria [4]. Their proven potential to influence wide-spectrum biological functions makes them suitable candidates for the development of drug candidates to overcome the current global problem of multidrug bacterial resistance [5].

An antibacterial small molecule needs to penetrate the bacterial cell envelope to display its bactericidal or bacteriostatic effects. Millions of years of evolution has fine-tuned the molecular properties of structurally complex natural products to modulate biological functions and that is why they remain a major source of drug candidates. However, structurally simple indole molecules of both natural and synthetic origin also possess interesting molecular and pharmacological properties and display potent and intriguing antibacterial activities. For instance, the investigation of the Mediterranean gorgonian *Paramuricea clavata* led to the isolation of derivatives of 2-bromo-*N*-methyltryptamine (Scheme 1a). These are the very first of the bromoindoles isolated from a natural source. Compounds **1** and **2** possess putative antifouling properties and their low toxicity also grant them good potential as environmentally friendly antifoulants [6].

A similar collection with 2,3-substituted indole ring having an appended dihydronaphthalenone hybrid analogs (**6**) delivered molecules with antitubercular activity. The indoles (**6**) were synthesized *via* Lewis acid catalyzed Michael addition of indoles (**5**) to the arylidene/hetero arylidene ketones (**4**, Scheme 1b). Indoles **6b** and **6c** displayed the minimum inhibition concentration (MIC) of 6.25 μg/ml in antitubercular activity that was comparable to the antibacterial drugs Pyrazinamide and Streptomycin (each with MIC 5 μg/ml) [7].

Another privileged chromene ring was appended to 2-indole *via* a multicomponent one-pot reaction between salicylaldehydes, substituted acetoacetanilides, and indoles in methanol. The



Scheme 1. Natural and synthetic antibacterial agents with a 2,3-substituted indole framework.

reaction was catalyzed by 1,4-diazabicyclo[2,2,2]octane (DABCO) (30 mol%) at room temperature. The series delivered potent antibacterial compounds. In particular, **9a–b** exhibited good activity against *Staphylococcus aureus* and *Micrococcus luteus* [8].

The alarming increase in the spread of drug resistant bacterial mutants is a grave threat to human race. In particular, the methicillin resistant *Staphylococcus. aureus* (MRSA) is a major community-acquired pathogen that causes skin and soft tissue infections, respiratory disease, pneumonia, endocarditis, and sepsis [9]. Bacteria induce either the drug target modification or drug inactivation to develop the bacterial resistance. In addition to that, bacteria use efflux pump to get rid of an antibacterial agent from the cells. Efflux pumps are transport proteins that help removal of toxic substrates, including antibiotics from within cells into the external environment [10]. For instance, the antibiotic resistance in *S. aureus* antibiotic stems from the use of NorA efflux pump, which removes the selected antibacterial drugs and biocides from the membrane, and thereby lowers their effective concentrations. Inhibition of NorA therefore, presents a promising strategy that would allow recycling of substrate antimicrobial agents. Interestingly, indole scaffold based small molecules have been particularly effective among various NorA inhibitors (Scheme 2).

An indole compound collection with three sites of diversity points around indole core was synthesized. Substituted 5-hydroxyindole (**12**, Scheme 2) was the key precursor of the target indoles, and was synthesized in two steps from benzyl amine (**10**). The compounds were evaluated for the ability to inhibit the efflux of ethidium bromide. In addition to IC_{50} determinations, compounds inducing at least 80% efflux inhibition were evaluated for their intrinsic antimicrobial activity. Among many acylations and alkylations on the hydroxyl-indole moiety, the reaction with *N*,*N*-dimethyl-chloroethane provided the potent efflux pump inhibitor **13** [11]. Further medicinal chemistry based structural optimization of the active scaffold, in particular appropriate substitution of the indole C5 position, and the presence of a propoxyl chain carrying terminal cyclic amino group resulted in a potent efflux pump inhibitor (**14**–**16**, Scheme 2) [12].

Bacteria employ various chemical signals such as *N*-acylated L-homoserine lactones (AHL) to regulate, monitor and coordinate