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New aminocoumarin antibiotics as gyrase inhibitors

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ABSTRACT

The aminocoumarins novobiocin, clorobiocin and coumermycin A_1 are structurally related antibiotics produced by different *Streptomyces* strains. They are potent inhibitors of bacterial gyrase. Their binding sites and their mode of action differ from those of fluoroquinolones such as ciprofloxacin. Novobiocin has been introduced into clinical use against *Staphylococcus aureus* infections, and *S. aureus* gyrase is particularly sensitive to inhibition by aminocoumarins, while topoisomerase IV is much less sensitive. Modern genetic techniques have allowed the engineering of the producer strains, resulting in a diverse range of new aminocoumarins, including compounds which are more active than the natural antibiotics as well as a compound which is actively imported across the cell envelope of Gram-negative bacteria. A further group of aminocoumarins are the simocyclinones which bind simultaneously to two different sites of gyrase and show a completely new mode of inhibition. Both the simocyclinones and the "classical" aminocoumarins strongly inhibit the fluoroquinolone-induced activation of RecA and thereby the SOS response in *S. aureus*. Therefore, a combination of aminocoumarins and fluoroquinolones strongly reduced the risk of resistance development and may offer new prospects in anti-infective therapy.

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Introduction

DNA gyrase belongs to the best-validated targets in antibacterial drug therapy (Chopra et al., 2012; Collin et al., 2011; Pommier et al., 2010; Sanyal and Doig, 2012). Gyrase was discovered in *E. coli* in 1976 (Gellert et al., 1976), but the two most important classes of gyrase inhibitors were already discovered before that date. The quinolone nalidixic acid was found accidentally as a side product of the synthesis of the antimalarial chloroquine (Lesher et al., 1962). Based on nalidixic acid, the fluoroquinolones were developed and became one of the principal clinical weapons in the fight against bacterial infections. However, their usefulness is now endangered by the rapid emergence of resistance.

The only other class of gyrase inhibitors which has been introduced into clinical use are the aminocoumarins. Novobiocin (Fig. 1) was discovered in the 1950s in screening programs for antibiotics produced by microorganisms. It was introduced into human anti-infective therapy in 1964 under the name Albamycin® by the Upjohn company and used for the treatment of *Staphylococcus aureus* infections, including multiresistant MRSA strains. Novobiocin is also active against *Borrelia burgdorferi*, the causative agent of Lyme disease (Samuels and Garon, 1993).

Shortly after novobiocin, the even more potent compounds clorobiocin and coumermycin A_1 were discovered. These three "classical" aminocoumarins show structural similarity (Fig. 1). An aminocoumarin moiety is linked via an amide bond to an aromatic acid, and via a glycosidic bond to the unusual deoxysugar L-noviose, which carries an acyl moiety attached to its 3-hydroxy group. This acyl moiety, the deoxysugar and the aminocoumarin moiety form the principal site of interaction with gyrase.

Beyond these three "classical" compounds (and close analogs thereof), only two other natural aminocoumarins have been discovered: rubradirin which lacks the deoxysugar moiety at the 7-OH group of the aminocoumarin and which therefore is not a gyrase inhibitor (Kim et al., 2008), and the simocyclinones which will be discussed below. All these compounds are produced by soil bacteria of the genus *Streptomyces*. Coumermycin has also been found in strains of the genus *Actinoallomurus*, distantly related to *Streptomyces* (Pozzi et al., 2011). Further, a new isolate of a *Streptomyces* strain producing novobiocin and analogs thereof has been described (Cheenpracha et al., 2010).

In biochemical assays, aminocoumarins inhibit DNA gyrase with IC_{50} values which are lower than that of modern fluoroquinolones (Alt et al., 2011b). However, the advantage of a higher target affinity is offset by a more attractive mechanism of action exerted by the fluoroquinolones. While the aminocoumarins act as competitive inhibitors of gyrase, the fluoroquinolones act as "poisons" of this enzyme. They stabilize the covalent gyrase-DNA complex, thereby leading to protein-stabilized breaks of DNA and ultimately to cell death, even at a relatively low occupancy of the inhibitor (Collin et al., 2011). Therefore, minimal inhibitory concentrations

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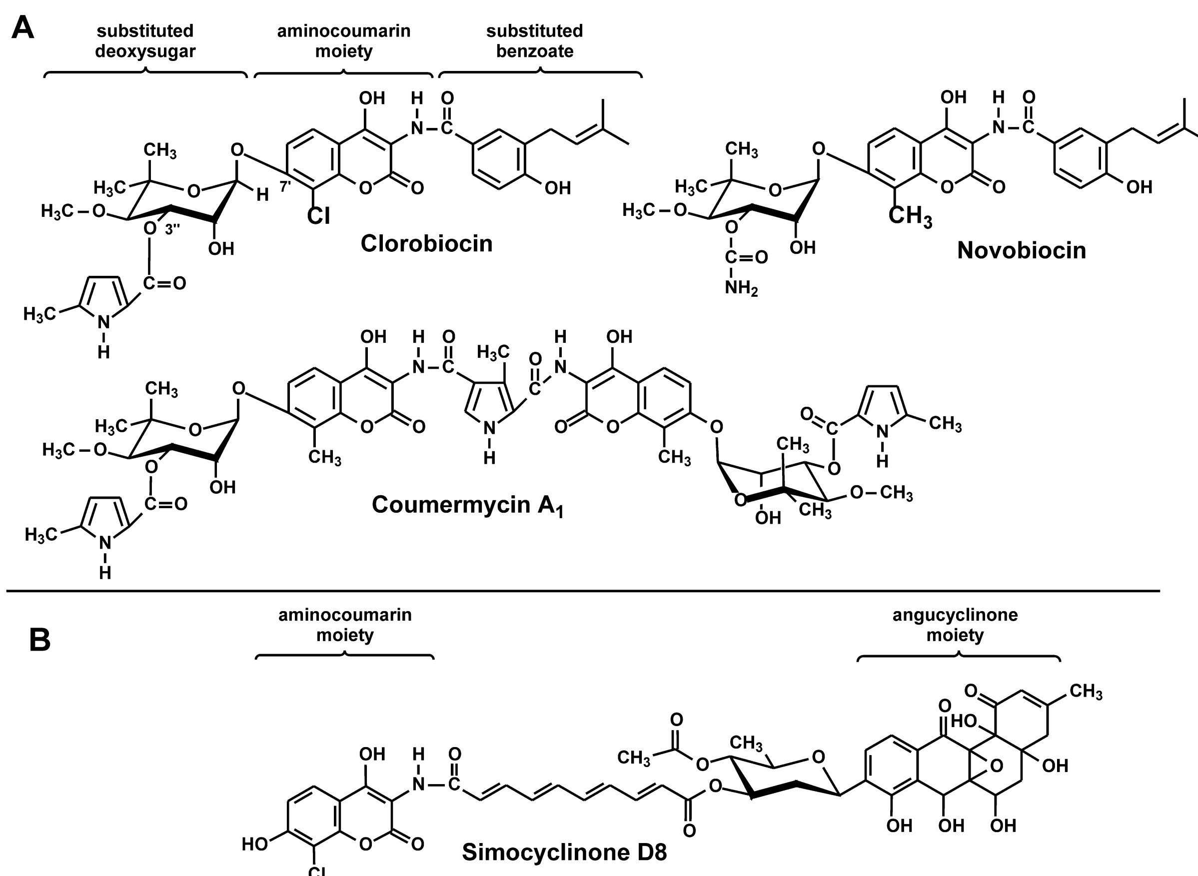

Fig. 1. (A) Structures of the three "classical" aminocoumarin antibiotics novobiocin, clorobiocin and coumermycin A_1. (B) Structure of simocyclinone D8.

(MICs) of the fluoroquinolones against pathogenic bacteria are in a similar range as those of aminocoumarin antibiotics (Schröder et al., 2012).

Despite the fact that fluoroquinolones are usually referred to a "gyrase inhibitors", their primary target in many pathogenic bacteria is in fact not gyrase but topoisomerase IV (= topo IV). Topo IV is a similar heterotetrameric enzyme as gyrase. *E. coli* gyrase consists of two GyrA and two GyrB subunits, and topo IV of two ParC and two Par E subunits. Gyrase and topo IV share 40% sequence identity. Both belong to the type II topoisomerases which catalyze changes in the topology of DNA involving the transient break of both strands of DNA. Both gyrase and topo IV can relax supercoiled DNA, but gyrase is unique by its capability to introduce negative supercoils. The energy for this reaction is derived from the hydrolysis of ATP, catalyzed by the GyrB subunit.

In Gram-negative bacteria, usually gyrase is the primary target of the fluoroquinolones, while in Gram-positive bacteria often topo IV is the primary target (Collin et al., 2011). Also aminocoumarins can interact both with gyrase and with topo IV, but gyrase is the primary target (see below).

Detailed structures of the ternary complexes of fluoroquinolones with gyrase and DNA have been published only recently (Laponogov et al., 2010; Wohlkonig et al., 2010). In contrast, the structural basis of the interaction of aminocoumarins with gyrase has been extremely well characterized from several high resolution crystal structures over the last 15 years (Collin et al., 2011; Lewis et al., 1996; Maxwell and Lawson, 2003). The binding site of the aminocoumarins (especially of their substituted deoxysugar moiety) overlaps with the binding site of ATP on the GyrB subunit, and this explains the competitive inhibition of gyrase-catalyzed ATP hydrolysis by aminocoumarins.

Gyrase belongs to the GHKL family of enzymes, named after its founding members gyrase, heat-shock protein 90 (Hsp90), certain protein kinases and the DNA mismatch repair protein MutL (Dutta and Inouye, 2000). Proteins of this family share a common type of ATP-binding fold, and therefore the aminocoumarins interact not only with bacterial gyrase but also with eukaryotic Hsp90 which is an emerging target in anticancer therapy (Hong et al., 2012). A number of novobiocin analogs have been synthesized and tested as Hsp90 inhibitors (Burlison et al., 2006; Donnelly and Blagg, 2008).

Following the discovery and the functional analysis of the biosynthetic gene clusters of the three classical aminocoumarins (Pojer et al., 2002; Steffensky et al., 2000; Wang et al., 2000), it has become possible to generate a multitude of new aminocoumarin analogs by modern genetic techniques, such as combinatorial biosynthesis, mutasynthesis and synthetic biology (Heide, 2009b). This, together with the ever-increasing problem of antibacterial drug resistance, has renewed the interest in aminocoumarins as antibacterial agents.

Measurement of gyrase and topoisomerase IV inhibition by aminocoumarin antibiotics

Determination of the inhibitory activity of aminocoumarins and fluoroquinolones on gyrase and topo IV by biochemical assays in vitro is not trivial, and the IC_{50} values reported in the literature vary considerably according to the methods used. Different assay types are available, e.g. supercoiling, relaxation, DNA cleavage and decatenation assays (Morgan-Linnell et al., 2007; Pan and Fisher, 1999). The supercoiling assay is considered most suitable for the assessment of the inhibition of gyrase by aminocoumarins, and the decatenation assay for the topo IV inhibition. The former

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