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Development of a platform for the discovery and practical synthesis of new tetracycline antibiotics

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Tetracyclines have proven to be safe and effective antibiotics over decades but to date all approved members of the class have been discovered and manufactured by chemical modification of fermentation products, which greatly limits the number of new structures that can be explored as future medicines. This review summarizes research leading to the development of a platform synthetic technology that enabled the discovery of the clinical candidate eravacycline, as well as other promising new tetracycline antibiotics, and provides the basis for a practical route for their manufacture. The approach argues for a reassessment of other antibiotic classes based on natural products for which practical, fully synthetic routes have not yet been developed, suggesting that these may represent underdeveloped resources with great potential to offer safer and more effective anti-infective agents.

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Introduction

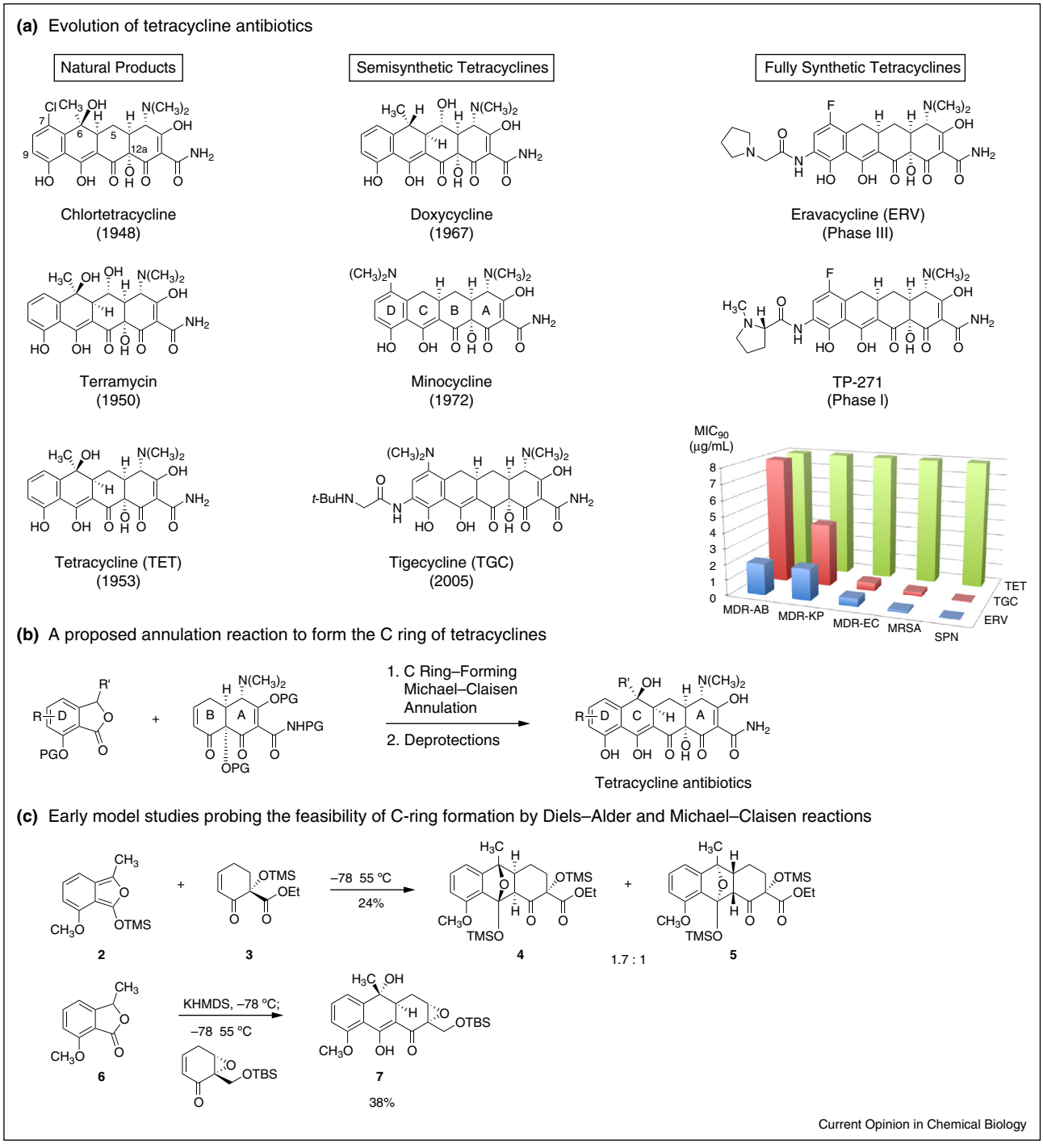
Tetracycline antibiotics have been in continuous clinical use for more than six decades and are generally regarded to be safe and effective medicines [1]. The class was discovered in 1948 when Benjamin Duggar isolated the natural product aureomycin, or 6-chlorotetracycline (chlortetracycline), from a bacterial culture (Figure 1a) [2]. Chlortetracycline was approved for human use in 1950, followed two years later with the launch of terramycin, or 5-oxytetracycline, a natural product isolated by Pfizer scientists [3]. Both natural products are unstable at the extremes of pH, but especially consequential in terms of use in humans is their propensity to undergo acid-catalyzed dehydration to form reportedly toxic anhydro-tetracycline derivatives (nephrotoxicity in particular is evidenced) [4].

Chlortetracycline was observed to undergo smooth hydrodechlorination with palladium and hydrogen, and the resulting semisynthetic molecule, tetracycline, was found to have superior stability, a better safety profile with respect to gastrointestinal toxicity, and a similar spectrum of activity relative to terramycin and aureomycin [5,6]. It was later found that tetracycline is also naturally occurring [7]. But a paradigm had been established with the chemical semisynthesis of tetracycline: that safer, more effective, and proprietary medicines can be obtained by chemical modification of naturally occurring antibiotics. This approach soon dominated discovery efforts and subsequently all approved tetracycline antibiotics were prepared by chemical modification of fermented tetracyclines. However, the chemical instabilities of tetracyclines and the dense array of polar functional groups that encircle their scaffold of four linearly fused six-membered rings make efficient and specific chemical transformations very challenging and rare. This is likely a primary reason that there have been fewer than 10 approved tetracycline antibiotics in 60 years, whereas >40 quinolone and >50 beta-lactam antibiotics (which are much more easily synthesized and modified) have been launched within the same period of time [8•].

The chemical advances leading to new semisynthetic tetracyclines are few and easily categorized. In the late 1950s scientists at Pfizer established efficient 3–4-step chemical protocols to reductively remove the labile 6-hydroxy substituents of terramycin, tetracycline, and 6-demethyltetracycline [9–11]. The resulting des-oxy products were far more stable compounds and retained good antibiotic activities [12]. In 1967, Pfizer launched the important medicine doxycycline, which they prepared in 4 steps from terramycin [13,14]. This antibiotic remains one of the most prescribed generic antibiotics in use today.

The greater acid stability of 6-deoxytetracyclines permitted for the first time limited electrophilic aromatic substitution reactions at position C7, leading to the discovery of minocycline (Lederle laboratories), which was launched in 1972 [15–17]. Like doxycycline, minocycline remains one of the most prescribed generic antibiotics, but it should be noted that resistance to both drugs, as well as all older tetracyclines, is now very widespread among both Gram-positive and Gram-negative pathogens [18]. In spite of growing resistance to doxycycline and minocycline, they remain drugs of choice for the treatment of atypical pneumonia caused by *Legionella* [19] and

Figure 1



(a) The evolutionary pathway of human development of tetracycline antibiotics, from fermentation products to semisynthetic derivatives, to fully synthetic tetracyclines. Inset, lower right: a comparison of MIC_{90} values (minimum inhibitory concentration to inhibit the growth of 90% of organisms) for natural (TET), semisynthetic (TGC), and fully synthetic (ERV) tetracyclines in multidrug-resistant (MDR) isolates of *Acinetobacter baumannii* (AB), *Klebsiella pneumonia* (KP), *Escherichia coli* (EC), methicillin-resistant *Staphylococcus aureus* (MRSA), and *Streptococcus pneumonia* (SPN) [33••]. **(b)** A proposed late-stage annulation reaction to form the C ring in fully synthetic tetracyclines, as originally conceived. PG = protective group. **(c)** Early model experiments to examine the viability of the proposed annulation reactions to construct the C ring of tetracyclines. Stereochemical assignments are tentative.