# The Review - Synthesis of Tetracycline With Anti-Bacterial Activity

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***Abstract-*** *For more than 50 years, tetracycline antibiotics have been widely used in human and veterinary medicine. Because of their broad-spectrum antibacterial activity and structural complexity, enormous efforts have been made to develop a laboratory synthetic route for their preparation. The emergence of microbial drug resistance has narrowed the treatment options for infectious diseases. Tetracycline were discovered in the 1940 s and exhibited activity against a wide range of micro organisms including gram-positive and gram negative bacteria, chlamydiae, mycoplasm, rickettsiae ,and protozoan parasites. They are inexpensive antibiotics, which have been used extensively in the prophylaxis and therapy of human and animals infection and also at sub-therapeutic levels in animals feed as a growth promoters . The first tetracycline resistance bacterium , shigella dysentaria, was islolated in 1953. Tetracycline resistance often due to the acquisition of new genes, which codes for energy dependent efflux of tetracycline or for a protein that protects bacterial ribosome from the action of tetracycline Doxycyclin is a structural isomer of the tetracycline family that is semi-synthetic. It has good intracellular penetration and bacteriostatic activity against a wide range of bacteria. There are various types of bacterial resistance. The mechanism of acquired resistance is either ribosomal or plasmidic. Propionibacterium acnes resistance is caused by an ARNr mutation. Doxycycline has anti-inflammatory properties through a variety of mechanisms.*

***Keywords***- Tetracyclines, Antibacterial Agent, Resistance ,Ribosomes, Antibiotics.

## I. INTRODUCTION

Antibiotics such as tetracyclines (TCs), which were formerly highly-effective against both Gram-positive and Gram-negative pathogens, are now ineffective owing to widespread antibiotic resistance.[1] TCs are bacteriostatic; the first major class of therapeutics to be termed broadspectrum antibiotic.[2] Clinically important TCs, such as doxycycline, minocycline, and glycylcyclines (a new class of TCs), are termed typical TCs. Their mode of action involves binding to the ribosome during polypeptide elongation to inhibit translation.[6] Chelocardin (CHD,) which is produced by Amycolatopsis sulphurea, [3] is regarded as a structurally atypical TC and shows bactericidal activity.[4] Initial data on the mode of action of CHD exist, but the exact mechanism of action has yet to be elucidated.[5] CHD is effective against many multidrug-resistant pathogens, including some difficult-to-treat Gram-negative bacteria. Importantly, it is also effective against TC-resistant strains, except for Pseudomonas aeruginosa

Aside from its pharmacological significance, tetracycline (Tc) has a very interesting structure with many potential metal-binding sites: oxygens at the C10-C12 phenolic b-diketone system, enolic oxygen at C3, and nitrogens at C4 and the carboxamide group. Metal coordination influences Tc pharmacokinetics and bioavailability. The drug is transported as calcium complexes in blood plasma [6]. Magnesium complexes appear to be more important in the intracellular medium, where they most likely play a role in ribosome binding [7]. The presence of multiple metal coordination sites associated with different conformational states complicates the assignment of bonding sites.Other antibiotics in the Tc family have the same 4-ring carbocyclic structure and substitutent variations at carbon .

Chlortetracycline, the first member of the TC family, was isolated from Streptomycis aureofaciens. Following that, oxytetracycline was isolated from Streptomyces rimosus, followed by the family's main compound, tetracycline. Many semi-synthetic tetracyclines, such as doxycycline (Dox) and minocycline, were developed to improve Tc activity [8]. The 6-deoxy-6-demethyltetracycline backbone is required for antibacterial activity, i.e. the minimum pharmacophore .Tc's primary mode of action is the inhibition of protein synthesis. Tetracycline's strong binding to the bacterial 30S ribosomal subunit inhibits protein synthesis by disrupting the codon-anticodon interactions between tRNA and mRNA and, as a result, the bond between the aminoacyl-tRNA and the ribosomal acceptor site [9]. Magnesium appears to play an important role in ribosome binding because magnesium deficiency significantly reduces binding. Tetracycline resistance has limited their use in the treatment of bacterial infections in humans ..Many research groups have worked to understand the mechanisms of tetracycline resistance.

The most important known resistance mechanisms involve proteins that either I protect the ribosome from effective binding to Tc or (ii) pump Tc out of the bacterial cell [10]. The efflux mechanism, which is common in Gram-negative bacteria, restricts Tc access to the ribosome by lowering the intracellular antibiotic concentration below the level required for activity [11]. This mechanism, long known for tetracycline, is now common to several drugs and bacteria, with plasmid-coded bacteria being the most common. TetA, a transmembrane protein found in the cytoplasmic membranes of drug-resistant bacteria, is responsible for active drug efflux. It functions as an anti porter by coupling the efflux of a tetracycline monocationic magnesium complex to the influx of one proton. The transport rate is determined by the metal complex's stability constant [12].

## II. DERIVATIVES

There are three naturally occurring tetracycline ( oxytetracyclines , chlortetracycline , demethylchlortetracyclines ) and several that are derived semisynthetically (tetracycline , methacycllines, minocyclines , doxycyclines )etc.,

- **PENTACYCLINES :**

Pentacyclic analogs with promising antibacterial activity against both Grampositive and Gramnegativeorganisms.Theseanalogswerebasedona“pentacyc line” scaffold [13]which has anadditional benzene ring (E-ring) fused in a linear fashion to theC8 and C9 carbons on the tetracycline D-ring. The added E-ringnot only produces a unique tetracycline scaffold but also presentsseveral additional derivatization sites believed to have minimumeffect on ribosomal binding as expected from the binding modeof tetracycline with the 30S ribosome.

- **OMIDACYCLINES:**

Omadacycline is a third-generation aminomethylcycline (AMC) used to treat acute bacterial skin and skin structure infections (ABSSI) and community-acquired bacterial pneumonia (CABP). 1 On January 3, 2013, the FDA designated omadacycline as a Qualified Infectious Disease Product (QIDP) for the treatment of these infections. Omadacycline No. 2 (Nuzyra, Paratek Pharmaceuticals, Inc) When compared to older-generation tetracyclines (minocycline and doxycycline), omadacycline has higher activity against aerobic gram-positive and gram-negative bacteria.

In addition to a broad spectrum of activity, omadacycline has a half-life that allows for once-daily administration and provides comparable blood levels when administered intravenously (IV) or orally. [14]

- **MINOCYCLINES:**

Minocyclines is a tetracycline antibiotic that kills bacteria in the body. It is used to treat a variety of bacterial infections including urinary infections, respiratory infections, skin infections, and tick fever. It is generally preferred over tetracyclines and doxycyclines. Although minocyclines have a broader spectrum of activity than other members of the group, including activity against Neisseria meningitidis, they react acidic in aqueous solution.

- **CHLORTETRACYCLINES :**

Chlortetracyclines is the first tetracycline antibiotic to be discovered. Acenocoumarol's anticoagulant activity may be enhanced by chlortetracycline. When chlortetracycline is combined with acitretin, adapalene, or alitretinoin, the risk or severity of adverse effects increases. Aluminum phosphate and aluminium hydroxide can reduce chlortetracycline absorption, resulting in lower serum concentrations and potentially lower efficacy. When combined with chlortetracycline, the therapeutic efficacy of mecillinam (amdinocillin), amoxicillin, and ampicillin can be reduced. Chlortetracycline may enhance atracurium besilate's neuromuscular blocking properties. Chlortetracycline is a tetracycline isolated from Streptomyces aureofaciens with the formula C22H23ClN2O8. It functions as an antiprotozoal, fluorescent probe, calcium ionophore, and antibacterial agent. It belongs to the monochlorobenzene family, is a tertiary amino compound, a tertiary alcohol, a monocarboxylic acid amide, a tertiary alpha-hydroxy ketone, and is a tetracycline. It is a chlortetracycline conjugate acid .[15]

- **TIGECYCLINES :**

Tigecycline, also known as Tygacil, is a tetracycline antibiotic used to treat a variety of bacterial infections. It is glycylcycline given intravenously. It was created in response to the increasing prevalence of antibiotic-resistant bacteria like Staphylococcus aureus, Acinetobacter baumannii, and E. coli. [16] Its structural modifications as a tetracycline derivative antibiotic have expanded its therapeutic activity to include Gram-positive and Gram-negative organisms, including those with multi-drug resistance.

- **DOXYCYCLINES :**

Doxycycline is a broad-spectrum tetracycline antibiotic that is used to treat bacterial and parasitic infections. It is used to

treat bacterial pneumonia, acne, chlamydia infections, Lyme disease, cholera, typhus, and syphilis, among other conditions. [17] When combined with quinine, it is also used to prevent malaria. [17]

Doxycycline can be administered orally or intravenously. [17] Diarrhea, nausea, vomiting, abdominal pain, and an increased risk of sunburn are all common side effects. [17] It is not advised to use this product while pregnant. [17] It, like other tetracycline-class agents, either slows or kills bacteria by inhibiting protein production. [17] 18] It kills malaria by targeting the apicoplast, a plastid organelle.

- **OXYTETRCYCLINES:**

Oxytetracycline is the second broad-spectrum tetracycline antibiotic to be discovered. Oxytetracycline works by interfering with bacteria's ability to produce essential proteins. Bacteria cannot grow, multiply, or multiply in number unless these proteins are present.

As a result, oxytetracycline prevents the spread of the infection, and the remaining bacteria are either killed by the immune system or die.Oxytetracycline is an antibiotic with a broad spectrum of activity against a wide range of bacteria.

However, some bacteria strains have developed resistance to this antibiotic, reducing its effectiveness in treating certain types of infections.Oxytetracycline is used to treat Chlamydia infections (such as psittacosis of the chest, trachoma of the eyes, and urethritis of the genital tract) as well as Mycoplasma infections (e.g. pneumonia)

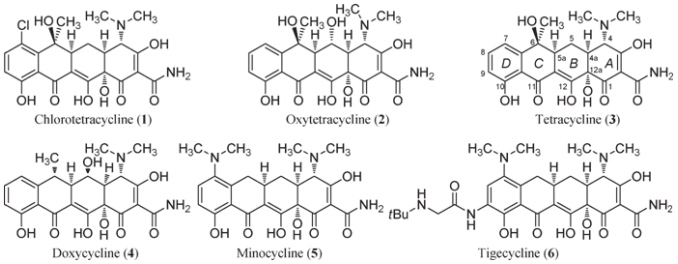



**Figure 1. STRUCTURE KNOWN OF TETRACYCLINES**

## III.CHEMISTRY AND PHARMACOLOGY

Tetracycline is named after its naphthacene core structure and the combination of four aromatic ring structures. depicts the chemical structure ofminocycline, with its four aromatic ring core, and omadacycline, a third-generation tetracycline.[19] All tetracyclines, including omadacycline, bind to the 30S subunit of the bacterial ribosome and inhibit the binding of aminoacyl-tRNA to prevent protein synthesis. [20] Tetracycline antibiotics were discovered in the late 1940s, with the first product being chlortetracycline, followed by 5-oxytetracycline in the early 1950s. 13 Both of these products were isolated naturally from bacterial fermentation. [21] Unfortunately, these tetracyclines were unstable at pH extremes and when administered to animals .humans.[22] Additional chemical modifications resulted in the development of tetracycline, doxycycline, and minocycline in the 1950s and 1960s. These semisynthetic enhancements resulted in compounds that were more stable and had stronger antibacterial activity. [23] Over the last 15 years, researchers have worked to improve the structure of minocycline in order to increase its activity against resistant bacteria. Tigecycline and eravacycline were discovered as a result of these additional structural changes. [24] Minocycline was converted to tigecycline via C7 (dimethylamino) and C9 modifications (N-tertiary-butyl-glycylamido). [25] Eravacycline was created by combining a fluorine at position C7 with a pyrrolidinoacetamido group at position C9. 13 As shown in Figure 1, omadacycline, an AMC, has a dimethylamino group at the C7 position of the D ring and an aminomethyl group at the C9 position. [26,27] When compared to tigecycline, the C7 functional group and C9 modifications provide stability against efflux and ribosomal protection proteins, increased bioavailability, and decreased nausea and vomiting. [28,29,30]\sMicrobiology

## IV. RESISTANCE

Tetracycline resistance can be caused by at least four mechanisms: efflux, ribosomal protection, degradation, and rRNA mutations.The most common are efflux pump and ribosomal protection.13 Omadacycline was created to prevent these resistance mechanisms.[31] On omadacycline, the C7 dimethylamino functional group prevents efflux pump resistance, and the C9 aminomethyl group prevents ribosomal protection resistance.[32] Group 1, which includes Tet, is the largest group of efflux pumps (A). [33] Tet(A) is a gram-negative bacteria enzyme that works by exchanging tetracycline with a proton (H+) against a gradient. [34]Omadacycline was developed to target Tet(A) and other Tet efflux genes and has been shown to have lower minimum inhibitory concentration (MIC) values for Escherichia coli with the Tet(A) efflux gene than tetracycline.[35] In vitro activity of omadacycline against Staphylococcus aureus with Tet(K) efflux genes, Enterococcus faecalis withTet(L) efflux genes and Tet(B) efflux genes in Enterobacteriaceae.[36]Tetracycline resistance is stimulated by 12 different classes of ribosomal protection proteins, the most common of which are Tet(O) and Tet(M). [37] In vitro, omadacycline was found to be active against gram positive

bacteria (Staphylococcus aureus, Enterococcus faecalis, and Streptococcus pneumoniae) with Tet (M). [38] Bacterial exposure to omadacycline sub-MIC concentrations did not promote resistance formation in single or multistep studies. [39]

## V. PHARMACODYNAMIC

Tetracyclines have been demonstrated to have time-dependent activity. [40] The pharmacokinetic/pharmacodynamic target that supports the area under the curve/MIC (AUC/MIC)
Tetracycline efficacy.28 The AUC/MIC ratios were calculated using neutropenic murine-thigh (Staphylococcus aureus and Streptococcus pneumoniae) and lung (Streptococcus pneumoniae) infection models, as well as an in vitro epithelial lining fluid (ELF) model (H influenzae)

## VI. MECHANISM OF ACTION

- **Binding of aminoacylt-RNA to ribosomes:**

It has been proposed that the 70S ribosomehas two binding sites for aminoacyl-tRNA [41]. Tetracyclines were found to inhibit the binding of aminoacyl-tRNA to ribosomes by no more than 50% led to the hypothesis that these antibiotics blocked one of the two proposed aminoacyl-tRNA binding sites [42]. Many researchers have attempted to pinpoint the nature and location of the tetracycline-sensitive binding site on the ribosome.

- **Protein biosynthesis:**

Tetracycline inhibited the GTP-dependent release of deacylated transfer RNA [43]. Tetracycline's mechanism of inhibition of this specific reaction is unknown.be explained as a result of an inhibition of aminoacyl-tRNA binding at the A site of the ribosome.After the synthesis of a given polypeptide chain has been completed, a mechanism for the release of peptides free of transfer RNA is required for messenger RNA translation.

## VII. SYNTHESIS

Our (-)-1 synthesis began with the tricyclic AB precursor 2, which we prepared from benzoic acid in 10 steps (11% yield, >95% ee). [44] We previously demonstrated that the enone 2 could be transformed into a wide range of structurally diverse 6-deoxytetracycline derivatives in just four steps. 4 We show that 2 can also be converted into (-)-tetracycline (1) in seven steps (10% yield, Scheme 1).To that end, we first introduced a phenylthio substituent in the enone 2's R-position, which served to activate the molecule toward Diels-Alder cycloaddition5 and, later, as a means to desaturate the C-ring and introduce oxygen at C6 (vide infra). This was accomplished by R-brominating 2 with pyridinium hydrobromideperbromide to form an intermediate vinyl bromide, followed by bromide displacement with thiophenol and 1,8-diazabicyclo[5.4.0]- undec-7-ene in N,N-dimethylformamide at 0 °C to yield the vinyl sulphide 3. (two steps).

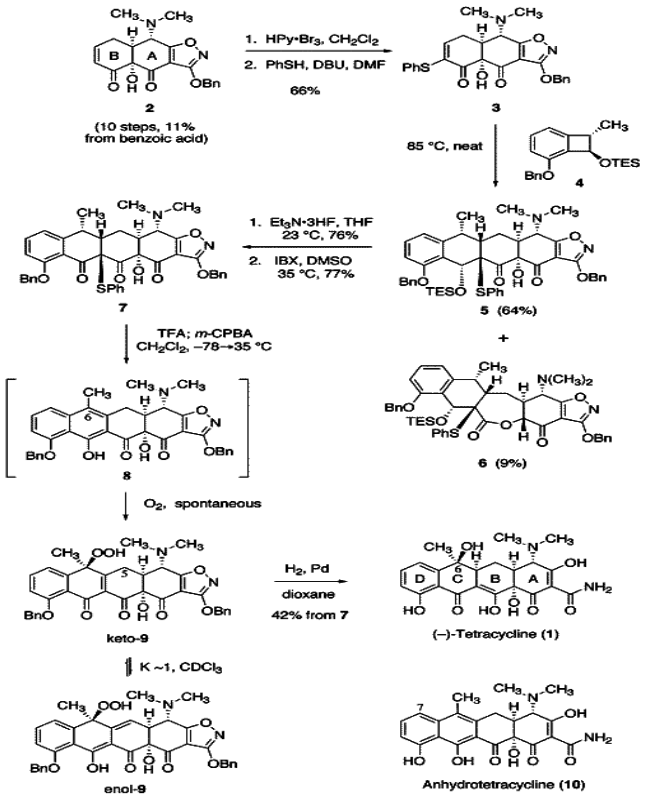
The Diels-Alder diene precursor, triethylsilyloxybenzocyclobutene derivative 4, was synthesised in five steps (49% yield) from 2-bromo-3-(benzyloxy)benzyl alcohol using methods described by Durst et al. (see Supporting Information). 6 The endo-Diels Alder cycloadduct 5 was produced in 64% yield by heating a neat mixture of 3 (1 equiv) and 4 (7.7 equiv) at 85 °C for 48 hours. Flash column chromatography was used to recover the excess diene precursor (4) in >95% yield while also removing a seven-membered ring lactone byproduct (6, 9% yield).
The cycloadduct 5 was crystallised from methanol; X-ray analysis of the crystals obtained confirmed the gross structure of 5 and all stereochemical assignments (see Supporting Information). In contrast to the success of the Diels-Alder reaction of 3 and 4, all attempts to produce detectable amounts of cycloadducts by cycloaddition of hydroxyl-protected variants of enone 3 (or 2) with the diene precursor 4 or with dienes such as isobenzofuran derivatives8 with or without Lewis acid additives failed. 9

Prior work from the Danishefsky laboratory established that trans-1,2-bis-(tert-butyldimethylsilyoxy)benzocyclobutene generates an o-quinodimethane intermediate with sufficient reactivity to undergo thermal cycloaddition with the unactivated dienophile cyclohexenone, and they provide additional experimental data that support this conclusion. The presence of the free R-hydroxyl group within enone 3 is thought to be an important feature of the successful Diels-Alder cyclization that we observe. [46]

To complete the synthesis of (-)-tetracycline, we first cleaved the triethylsilyl ether group of the Diels- Alder adduct 5 (triethylamine trihydrofluoride, 76% yield) and oxidised the hydroxyl group liberated in dimethyl sulfoxide11 (77% yield). The resulting 2-(phenylthio)-1,3-diketone [47] was then oxidised with m-chloroperoxybenzoic acid in the presence of trifluoroacetic acid to form an intermediate sulfoxide(s) that was observed to eliminate upon warming to 35 °C, yielding the anyhydrotetracycline derivative 8. The attempted isolation of 8 was complicated by the fact that it spontaneously underwent stereoselective autoxidation in the air at room

temperature, which was used to advantage preparatively. Thus, the hydroperoxide 9 was produced by dissolving crude naphthol 8 in chloroform and stirring the resulting solution in the air. The latter product, however, was not isolated.1st Scheme05/20/2005 8292 9 J. AM. CHEM. SOC. 2005, 127, 8292-8293 10.1021/ja052151d CCC: $30.25 2005 American Chemical Society, but was hydrogenated in the presence of palladium black, yielding (-)-tetracycline (1) in 42% yield (from 7) after preparative HPLC purification. In every way, the synthetic product was shown to be identical to an authentic sample of natural tetracycline.

**SCHEME 1.**




The transformation of naphthol 8 to hydroperoxide 9 is functionally equivalent to the photooxygenation-reduction transformation of 7-chloroanhydrotetracycline to 7-chlorotetracycline (aureomycin) first demonstrated by Scott and Bedford. 12 Later, using a dye-sensitized photooxygenation procedure, the same transformation was successfully applied to anhydrotetracycline(10). 13 Both transformations were found to be extremely stereoselective. In the case of photooxygenation of anhydrotetracycline (10), the observed stereoselectivity was attributed to the selective ene reaction of singlet oxygen with the (pseudoaxial) 5-â-hydrogen atom. [48]With regard to these precedents, two observations in the current work are noteworthy.in relation to these precedents. The first is that 1H NMR analysis of the oxygenation reaction (8 f 9, CDCl3) revealed that the keto form of 9 (keto-9) was the sole direct product of the reaction. After standing for several hours, keto-9 solutions in CDCl3 were observed to equilibrate with the enol form (enol-9, K 1). This observation rules out the possibility that enol-9 is a direct result of the oxygenation of 8, and thus dismisses the possibility of an ene mechanism involving C5.14. The second observation concerns the extraordinary ability of substrate 8 to oxygenate, which far outperforms that of anhydrotetracycline (10). The reaction of 8 to form 9 at 23 °C is visible within minutes of being exposed to air in daylight; only by rigorously excluding light is the oxidation prevented. These findings are similar to the autoxidation of 2-naphthols with bulky 1-alkyl groups reported several years ago, which also produced hydroperoxide products. Although a mechanism involving singlet oxygen in the transformation of 8 to 9 (via Diels-Alder reaction, then 1,4- endoperoxide hemiketal opening) cannot be ruled out, a simple photoinitiated freeradical autoxidation mechanism may be at work instead. So far, the data does not allow us to distinguish between these possibilities. In either case, stereoelectronic factors appear to be the most likely explanation for the stereochemistry of oxygen addition to 8 (creating a pseudoaxial hydroperoxy group).[49]

## VIII. CONCLUSION

In the above study we conclude that , Tetracyclines (TCs), which were once highly effective against both Gram-positive and Gram-negative pathogens, are now rendered ineffective due to widespread antibiotic resistance. There are three naturally occurring tetracyclines (oxytetracyclines, chlortetracyclines, and demethylchlortetracyclines) and several semisynthetically derived tetracyclines (tetracyclines, methacyclines, minocyclines, doxycyclines, and so on). Tetracycline is named after its naphthacene core structure and four aromatic ring structures. depicts the chemical structure of omadacycline, a third-generation tetracycline, and minocycline, with its four aromatic ring core.At least four mechanisms can lead to tetracycline resistance: efflux, ribosomal protection, degradation, and rRNA mutations. It has been demonstrated that tetracyclines have time-dependent activity. [40] Tetracycline efficacy is supported by the pharmacokinetic/pharmacodynamic target area under the curve/MIC (AUC/MIC).

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