A Review on Existing Tetracyclines Analogues and Their Pharmacologically Targeted SAR

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ABSTRACT

Background: Tetracyclines belong to a class of broad spectrum antibiotics. Around the globe, they are prescribed to treat various gram negative and gram positive bacterial infections. Once in the cell, they reversibly bind to the receptors which are located on 30S subunit of bacterial ribosome. They act by averting the protein synthesis, in turn, halting the bacterial growth.

Aim and Objectives: The aim of current review is to study tetracyclines, identifying potential activity against infections and highlighting the microbial resistance associated with various analogues.

Material and Method: The data for this review is collected from various databases including Scopus, PubMed, Springer Link and Google Scholar. To ensure the credibility only indexed articles were used in current study.

Result: The outcome of the study has suggested that tetracyclines and number of its analogues show selective bioactivity and strength to the biological targets. Through modification at certain positions, activity of drug is changed substantially. This not only affects therapeutic activity and safety profile but also has influence the bacterial resistance.

Conclusion: As antibiotic resistance amongst bacteria is emerging tremendously, demanding more research. It is still needed to synthesize the novel analogues that would be helpful to cure infections caused by the resistant bacteria. Further these analogues can be tagged with radioisotopes that would be helpful for diagnosis and treatment of infectious diseases.

Keywords: Tetracycline, Structure activity relationship, Pharmacological activity, Analogues, Anti-bacterial.

INTRODUCTION

Tetracyclines are broad spectrum antibiotics which inhibit the microbial protein synthesis by interfering aminoaoyl tRNA and acceptor sites of ribosomes [1]. It exerts its action by binding to 30s ribosomal RNA [2]. It is effective against gram positive and gram negative micro-organisms. Tetracyclines are used widely due to their higher safety profile. It is also used prophylactically against Plasmodium falciparumin...
malaria. It is also used against micro-organisms that are resistant to other antibiotics [3].

**Structure Activity Relationship**

![Figure 1. Structure of tetracycline.](image)

Tetracyclines are linearly fused 6 membered, four carbocyclic ring systems as shown in Figure 1. Among ring C and ring D, one must be aromatic. Unsaturation at positions 2-3 and 11-12 are essential for activity. Presence of keto-enol system at position 1-3 and 11-12 is necessary for activity. Other important structural features in tetracyclines are amino acyl group at position 2, tertiary amine at position 4, diethyl group at position 5 and position 6 having hydroxyl and methyl group [4].

Amide functional group at position 2 should remain unsubstituted for activity, if substitutions are necessary then one hydrogen can be replaced with alkyl amino methyl group as in rolitetracycline [5,6]. Presence of tertiary amines at position 4 is important to keep keto-enol system of ring A intact. Position 4 tertiary amine can bear substituents such as hydrazine, hydroxyl or oxime. Epimerization occur at 5a position [7]. Electrophilic substitution can occur at position 7 & 9 of ring D with nitro group or halogens; halogens probably used mostly because they are less carcinogenic for host [8].

With respect to discovery and development of tetracyclines, chlortetraycline and oxytetracyclines were firstly originated from *Streptomyces aureofaciens* and *Streptococcus rimosus* in 1940s [9,10]. This discovery was followed by synthesis of many semi-synthetic tetracyclines such as minocyclines, methacyclins and doxycyclines [11].

Tetracyclines were first discovered by Dr. Benjamin Dugger of Lederle Laboratories in the mid 1940s as the fermentation product of an unusual golden-colored soil bacterium named as *Streptomyces aureofaciens* [12]. These tetracyclins and their analogues have wide range of activity against microbes. Tigecycline was found to have antibacterial activity [13]. Omadacycline was the first intravenous and orally effective 9-aminomethylcycline in clinical development for use against multiple infectious diseases including acute bacterial skin and skin structure infections (ABSSSI), community-acquired bacterial pneumonia (CABP), and urinary tract infections (UTI). The comparative in vitro activity of omadacycline was determined against a wide range of Gram-positive clinical isolates, including meticillin-resistant *Staphylococcus aureus* (MRSA) [14], vancomycin-resistant *Enterococcus* (VRE), Lancefield groups A and B beta-hemolytic streptococci, penicillin-resistant *Streptococcus pneumonia* (PRSP), and *Haemophilus influenzae* (H. influenzae). The omadacycline MIC90s for MRSA, VRE, and beta-hemolytic streptococci [15].

| Table 1. Sources, Structures, Pharmacological Activities of Natural Tetracyclines. |
|---|---|---|---|
| **Sources** | **Structures** | **Pharmacological Activity** | **Substitutions** |
| Chlotetracyclines [16] | ![Chlotetracycline](image) | Antibacterial activity (Primarily act at 30s / tRNA ribosome). Used in conjunctivitis in cats, dogs and horses [47]. | Cl group at position 7 |
| Oxytetracycline [17] | ![Oxytetracycline](image) | Primary target is 30s / tRNA ribosome and exhibit antibacterial activity. | OH at 5th position |
Demeclocycline [18]
- Antibacterial (bind to 30s ribosomal RNA)
- CI group at position 7 and removal of CH₃ at position 6.

Doxurubicin [19]
- Exerts its anticancer effect by apoptosis and oxidative Stress mechanism.
- Substitution at 1 & 9 position.

### Table 2. Sources, Structures, Pharmacological Activities of Semisynthetic tetracyclines.

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<thead>
<tr>
<th>Sources</th>
<th>Structures</th>
<th>Pharmacological Activity</th>
<th>Substitutions</th>
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<tbody>
<tr>
<td>Doxycycline [20]</td>
<td>![image]</td>
<td>Anticancer (apoptosis and oxidative Stress mechanism), veterinary medicine, Respiratory tract and intestinal diseases of poultry [47].</td>
<td>OH group at 5th position and deoxylation at 6th position</td>
</tr>
<tr>
<td>Meclocycline [22]</td>
<td>![image]</td>
<td>Antifungal (Oxidative Stress) Lonophore and Chelating Mechanism</td>
<td>Substitution at 7 position.</td>
</tr>
<tr>
<td>Methacyclin [23]</td>
<td>![image]</td>
<td>Antifungal (Oxidative Stress) Lonophore and Chelating Mechanism</td>
<td>Methylene group at 6th position &amp; OH at 5th position</td>
</tr>
<tr>
<td>Minocycline [24]</td>
<td>![image]</td>
<td>Anticancer (apoptosis and oxidative Stress mechanism), veterinary medicine, canine brucellosis [47].</td>
<td>Addition of Dimethylamino at 7th position &amp; removal of CH₃ &amp; OH group at position 6th</td>
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<tbody>
<tr>
<td>Rolitetracyclin [25]</td>
<td><img src="image" alt="Rolitetracyclin" /></td>
<td>Antibacterial (bind to 30s ribosomal RNA)</td>
<td>Pyrrolidine ring at 2nd position</td>
</tr>
<tr>
<td>Epi-ANhydrochlorotetracycline [26]</td>
<td><img src="image" alt="Epi-ANhydrochlorotetracycline" /></td>
<td>Antibacterial (Atypical Mechanism) Primary Target is not Bacterial Ribosomal</td>
<td>Substitution at 7 position.</td>
</tr>
</tbody>
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Table 3. Sources, Structures, Pharmacological Activities of Synthetic Tetracyclines.
Medicinal Importance of Tetracyclines

Tetracyclines are broad spectrum antibiotics because its activity is being evaluated against wide array of bacterial infections [32]. Tetracyclines have been used immensely in the prophylaxis and treatment of bacterial infections as they are inexpensive and broad spectrum antimicrobials [33]. Tetracyclines are predominately a low-cost alternative among other antibiotics. Interestingly, certain type of tetracycline has recently been used in prevention of cancer recurrence by inhibiting such enzymes and processes that usually stimulate growth of cancerous cells [34, 6]. These drugs may show potential for long-term management of some types of cancers [11, 35].

Radioprotective Activity

Kwanghee and coworkers in 2009 conducted a research to recognize medicinal agents that shield body tissues from detrimental effects of radiation therapy. They tested radioprotective activity of tetracyclines and fluoroquinolones in murine lymphocyte rat model which were subjected to total body irradiation. Results manifested that tetracyclines and fluoroquinolones exhibited marked radioprotective activity owing to their planar ring structure. Tetracyclines also averted injurious affects of radiations on human lymphoid cells by preventing DNA strand breakdown. These findings proved that tetracyclines have tremendous potential in reducing radiotherapy damage on normal tissues [36].

Tumor Detection

Radio isotopes of tetracyclines has been developed and used in localized tumor detection. Tetracycline radioisotope 99mTc has been successfully employed in external scanning of tumor lesions in rabbits, mice, rats and humans [37].

Anticancer Activity

Leezenberg and Wesseling in 1979 carried out a retrospective research on 218 cancer patients. These patients were stricken by nasopharyngeal cancer. This study was aimed to evaluate effects of tetracyclines therapy on life span of patients. Results revealed that patients who received tetracyclines not only lived longer but tetracyclines also improved the detrimental effects of methotrexate. It is believed tetracyclines exert this action owing to inhibition of mitochondrial protein synthesis [38].

A study revealed that tetracyclines regulated gene delivery system along with radiation therapy employed in prostate cancerous rat model, developed tumor immunity in cancerous rats and augmented immune response [39].

Prevention of Corneal Ulceration

Tetracyclines are used as prophylactic treatment for corneal ulceration after severe optical damage. They exert their action by inhibiting protein degradation through its suppressive action on neutrophil collagenase, alpha 1 antitrypsin degradation and through its anti-oxidant activity [40].

Antimicrobial Activity

Analogs of tetracyclines also show promising antimicrobial activity. 9- substituted analogues of tetracyclines were synthesized by reaction of organotin reagent with salt of C-9 diazonium tetrafluoroborate tetracyclines. These analogues show significant activity against other antibiotic resistant infections [41].

Tetracycline is used in variety of bacterial infections of different body organs such as respiratory pathway, urinary pathway, intestine, reproductive organs, lymph nodes, and skin etc [42]. Many sexually transmitted diseases (STDs) including syphilis, gonorrhea, or chlamydia and also acute acne are treated by these analogues [43]. A wide range of gram positive and gram negative bacteria e.g. Brucella, Coxiella Burnetii, Rickettsiae rickettsii, Chlamydia trachomatis, Mycoplasma pneumoniae, Chlamydiae species, Helicobacter pylori etc are treated by tetracyclines [44].

Treatment for Acne

The growth suppression of an anaerobic organism, Cutibacterium acnes, demonstrated by the tetracyclines makes this class of drug important for the treatment of moderate and severe acne. Moreover, the anti-inflammatory effect of tetracyclines is an added advantage for the acne lesions [43, 45, 46].

Veterinary Use

Several analogues of tetracyclines including minocycline, methacycline and doxycycline were considered harmful for veterinary use. It was found out that minocycline and doxycycline were rather effective in treatment of animal diseases. These tetracyclines have high lipid solubility that explain its better pharmacokinetic profile that is improved absorption and distribution which may results in efficient antimicrobial activity. Doxycycline excretes
through intestine; it is useful in renal impairment situations. Doxycycline is used in intestinal and respiratory tract infections in poultry. Minocycline is used in combination with streptomycin in treatment of canine brucellosis [47].

Miscellaneous Uses
Tetracyclines are useful in treatment of number of diseases such as relapsing fever, syphilis, pneumonia, throat irritation; bacterial urinary tract infection, anthrax, Rocky mountain spotted fever, sinus irritation and congestion, chronic slow progressing ulcerative granulomatous disease [48]. The infections induced by direct contact with the infected animals and adulterated edibles are also treated with antibiotics. Tetracycline can be served as a substitute for penicillin or other antibiotics in cases of severe infections like Anthrax, Listeria, Clostridium. Actinomyces, and others [49]. Tetracyclines are used in treatment of bones and also used for calcification of cartilage [12, 50].

Precautions
The intake of milk, dairy products that contain calcium, iron, antacids, or aluminum salts should be avoided at least 2 hours before or 6 hours after using antacids when using this therapy [51]. Dose of tetracyclines should be taken with water and one hour before or two hours after meals [52, 53].

CONCLUSION
Tetracyclines belong to a class of broad spectrum antibiotics. Worldwide, they are recommended to cure various gram negative and gram positive bacterial infections. They exert their action by reversibly binding to 30S subunit of bacterial ribosome. Tetracyclines analogues are commonly used because of their availability and cost effectiveness especially in developing countries. The structure-activity-relationship (SAR) studies of tetracyclines shows the selective bioactivity and strength to the biological targets which makes this class of medicinal compounds able to label with radioisotopes and providing outstanding results in detection and treatment of localized tumors. Furthermore, advanced methods of therapy has been introduced against infectious lesions includes radiotherapy by using the radioisotopes of tetracyclines. In time to come, more radiolabeled tetracyclines analogues can be derivatized for diagnosis and treatment of infectious diseases.

REFERENCES

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