Al-Salam Journal for Medical Science
Journal Homepage: http://journal.alsalam.edu.iq/index.php/ajbms
E-ISSN: 2959-5398, P-ISSN: 2958-0870

A review of recent developments in pharmaceutical chemistry on biological evolution of tetrazole derivatives

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DOI: https://doi.org/10.55145/ajbms.2025.4.1.001
Received May 2024; Accepted July 2024; Available online August 2024

ABSTRACT: This review sums up the developments in the biological activity of tetrazole active derivatives in recent days. Some of the deliberated derivatives of tetrazole are at present actively scientifically studied; some of them have biological activity that enables them to be studied further in the future as a drug for various biological activities. This review seeks to offer a comprehensive analysis of the efficacy and clinical advantage of biological activity for tetrazole derivatives.

Keywords: Hetrocyclic ,Tetrazole, antibacterial, anticancer, antifungal

1. INTRODUCTION

Tetrazole is a five-membered ring that is doubly unsaturated and contains one carbon atom and four nitrogen atoms. It can function as a precursor for several distinct nitrogen-containing heterocyclic compounds via the Huisgen rearrangement [1]. The medication commonly used as the carboxylic bioisoster, tetrazole, is resistant to many of the biological alterations that affect the liver's capacity to utilize carboxylic acid since it is metabolically stable [2]. Tetrazole can replace carboxylic acid, increase lipophilicity bioavailability, and minimize medication side effects. Various prodrug techniques be mindful of utilized to improve the oral bioavailability of tetrazole drugs [3]. Tetrazole can also interact no covalently with biological targets, and its derivatives have a variety of pharmacological qualities, including anti-Alzheimer's disease effects, antiangiogenic, antibacterial, antiviral, anticancer, antitubercular, antifungal, and antimalarial activities [4-11].

Recently, there has been significant interest in tetrazole compounds as medicinally relevant structures. Tetrazole-derived drugs, including cefamandole, ceftezole, listen, and fasten, have previously been used in medical settings to treat a range of illnesses.

2. Tetrazoles as antibacterial agents

Bacteria are the primary cause of the majority of infections in hospital and community settings, including bloodstream infections, wound infections, pneumonia, and sexually transmitted diseases (STDs) [12]. The tetrazole skeleton is present in some clinically utilized antibacterial medications, suggesting the possibility of tetrazole derivatives as possible antibacterial treatments. Antibiotics are often used for the treatment of bacterial illnesses. Ceftezole has a wide range of antibacterial properties against bacteria of both types. They do this by impeding the creation of bacterial cell walls. These medicines exhibit efficacy even in the presence of drug-resistant illnesses. Tedizolid is a prodrug of the oxazolidinone family, which is a second-generation class of antibiotics. It has been approved to treat acute bacterial infections of the skin and skin structure infections that result from susceptible strains of different Gram-positive bacteria. Tedizolid demonstrates sensitivity to specific organisms that are resistant to other antibiotics because of its unique mechanism of action, distinguishing it from different antibacterial medications in the

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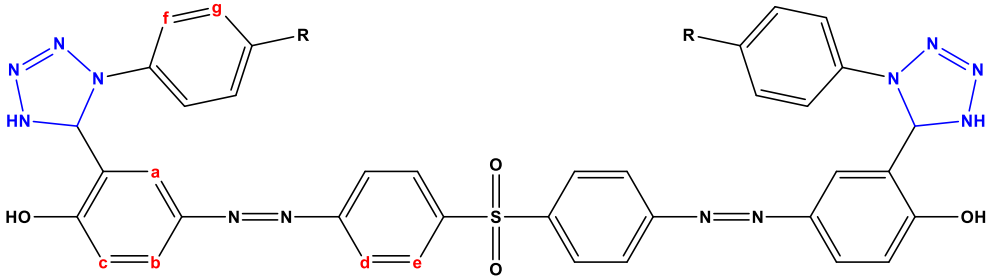
nonoxazolidinone class. Tedizolid has a higher level of effectiveness against methicillin-resistant Staphylococcus aureus (MRSA) compared to linezolid, with a four to sixteen times stronger potency. DA-7867, the amide derivative of tedizolid, has shown significant effectiveness against a wide range of medically significant bacteria, including those that are resistant to conventional treatments. The information above demonstrates tetrazole structures' potential usefulness in developing new antibacterial medications [6].

They prepared tetrazole compounds from the Schiff base. They tested it with 4th type of bacteria and found that the tetrazole compounds are more effective and have more antibacterial activity than the Schiff base from which they were derived. Two tetrazole compounds have higher activity against these four bacteria, whereas compounds [F3, F4] demonstrated greater efficacy at the lowest inhibitory concentration against Pseudomonas aeruginosa. Compound [F3] demonstrated the maximum inhibition against Streptococcus faecalis at the lowest inhibitory concentration, but compound [F4] demonstrated greater efficacy against Staphylococcus aureus and E. coli [13].



[F3, F4]

FIGURE 1. - Tetrazole antibacterial chemicals' structure [14]

They synthesized fourteen novel tetrazole Antibacterial activity of analogs 5a–g and 8a–g derivatives was assessed against six bacterial strains; three of the strains were Gram-positive (Bacillus megaterium, Bacillus subtilis, Micrococcus luteus), and the other three were Gram-negative (Pseudomonas aeruginosa, Salmonella typhi, Escherichia coli). The strains were tested against pipemidic acid, ciprofloxacin, and streptomycin B. These synthesized showed different antibacterial activity from active to moderate antibacterial activity against these six microorganisms. Still, compounds 5e and 5f show the best antibacterial activity Among all examined tetrazole derivatives; this is due to electron-withdrawing groups on tetrazole rings like (fluoro, bromine, trifluoromethyl). For further study, they tested 5a–g derivatives for MIC on the same bacterial strains.

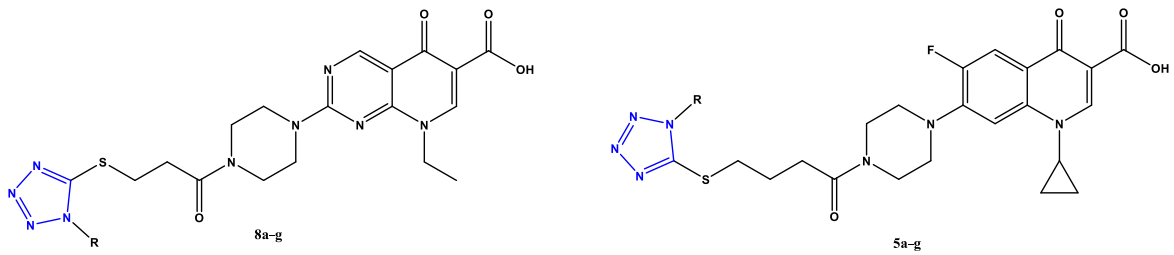
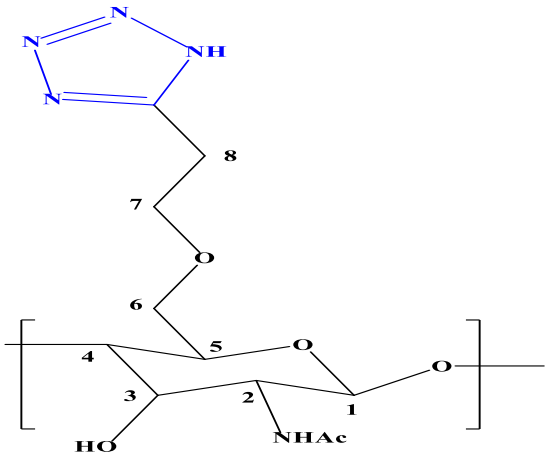


FIGURE 2. - Tetrazole antibacterial chemicals' structure [15]

Novel chitin polymers, which included tetrazole rings in their derivatives, were produced and evaluated in vitro to determine their antibacterial characteristics. These polymers displayed varying molecular weights, ranging from high to low, as well as different degrees of substitution, ranging from high to low. The tetrazole derivatives that were created were tested in a laboratory setting to determine their effectiveness in killing bacteria, namely S. aureus and E. coli. Prior to this, the antibacterial characteristics of chitosan tetrazole compounds were also investigated and evaluated. The findings of this research indicate that chitin tetrazole derivatives had greater antibacterial efficacy compared to chitosan derivatives, even when their molecular weights and substitution levels were similar. Chitin has more hydrophobicity compared to chitosan, resulting in a more pronounced capacity to form hydrophobic interactions with bacterial cells. Consequently, chitin compounds have greater efficacy in killing bacteria. The chitin tetrazole derivatives of moderate molecular weight exhibited the most potent antibacterial action.



1a–c

FIGURE 3.- Tetrazole antibacterial chemicals' structure [16]

Table 1. -inhibition activity of (F3-F4) compounds

compounds	Type of Bactria	Inhibition activity
F3,F4	Pseudomonas aeruginosa	High
F4	Staphylococcus aureus and E. coli	High
F3	Streptococcus faecalis	High

Table 2. -inhibition activity of this compounds against gram(+) and gram (-)

compounds	standard	Gram(-)	Gram(+)	Inhibition activity
5a–g	ciprofloxacin, streptomycin B and pipemidic acid	Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa	Bacillus subtilis, Bacillus megaterium, Micrococcus luteus	Significant
8a–g	ciprofloxacin, streptomycin B and pipemidic acid	Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa	Bacillus subtilis, Bacillus megaterium, Micrococcus luteus	Moderate
5e - 5f	ciprofloxacin, streptomycin B and pipemidic acid	Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa	Bacillus subtilis, Bacillus megaterium, Micrococcus luteus	High

3. Tetrazoles as agents against cancer

If present trends persist, over 100 million individuals will perish during the next decade. Among these fatalities, cancer-related deaths would contribute to an annual toll of 9 million, thus burdening the global healthcare system significantly [16]. Letrozole, a tetrazole derivative, is already being used in different types of cancer, typically following tamoxifen failure and resection. Letrozole is a nonsteroidal aromatase inhibitor that inhibits aromatase's ability to produce estrogens by binding to its cytochrome P450 unit's heme competitively and reversibly. Encequidar (HM30181) has shown a significant increase, ranging from 20 to 50 times, in its ability to inhibit P-glycoprotein (P-gp) compared to tariquidar. Additionally, it successfully prevented the movement of paclitaxel across MDCK monolayers. Encequidar is a novel P-gp blocking of the latest generation that is currently in development with the aim of enhancing the oral absorption of substances that are substrates of P-gp. In rats, it can potentially boost the co-administration of paclitaxel's oral bioavailability by more than 12 times [17].

TIAN Ye and coworkers [5] have designed and synthesized a series of derivatives from diary biuret, including a tetrazole moiety. Using the MTT test, each target chemical's in vitro anti-tumor activity was assessed against the HT-29, MCF-7, HepG2, and A549 cell lines. Most showed recognizable anti-tumor activity, and four of these compounds (4a, 4c, four h, and 7a) were superior to the sorafenib drug. Compound 4h showed more potent action than the

medication sorafenib in all the cancer cells that were evaluated. Compound 4c had the most remarkable efficacy in suppressing the proliferation of HepG2 cells. Additionally, in an in vitro experiment, they both demonstrated excellent metabolic stability. Compounds 4c and 4h show promise as future development prospects. Compound 4c had the most remarkable efficacy in suppressing the proliferation of HepG2 cells. notably, these compounds also showed increased sensitivity to HepG2 cancer cells, suggesting that they could be effective treatments for hepatocellular carcinoma [18].

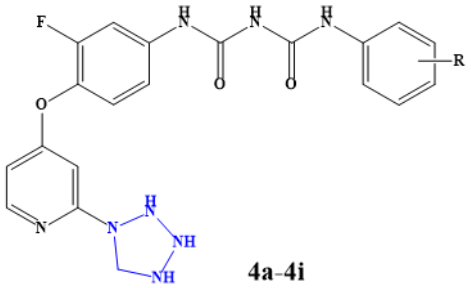


FIGURE 4.- Tetrazole antibacterial chemicals' structure

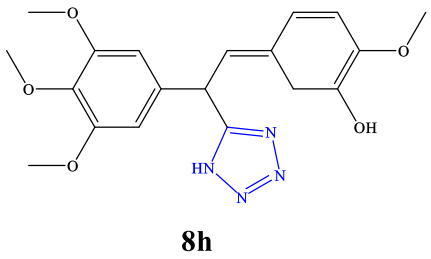


FIGURE 5.- Tetrazole antibacterial chemicals' structure

Tetrazole anticancer compound structure, as reported in a study [19] Synthase the tetrazole analog based isoxazolines and pyrazolines derivatives, they study the effect of substitution on activity against cancer cells. Compounds 5c, which has a fluoro group, and 5g, which has a methyl group, shown exceptional efficacy against the lung cancer cell line. Additionally, compounds 5b with a chloro group and compound 5c with a fluoro group demonstrated noteworthy action against Additionally, HepG2 and compound 5c showed exceptional efficacy against MCF-7. Compounds 6a-h, which are based on tetrazole, had modest activity against A549, while compound 6g, which possesses a methyl group that donates electrons, was the most effective among the synthesized variants. We then went on to investigate how substituents on the phenyl ring affected the proliferative activity of ants. After that, they carried on investigating how substitution affected the phenyl ring while taking anti-proliferative action into account. Certain derivatives demonstrated excellent cytotoxicity against the A549, MCF-7, and HepG2 cell lines. Comparable to CA-4, compounds 5b and 5c showed an anti-proliferative activity. According to an in-vitro investigation, isoxazolines and pyrazolines based on tetrazole may have model structural resources for the future development of innovative therapeutic medicines.

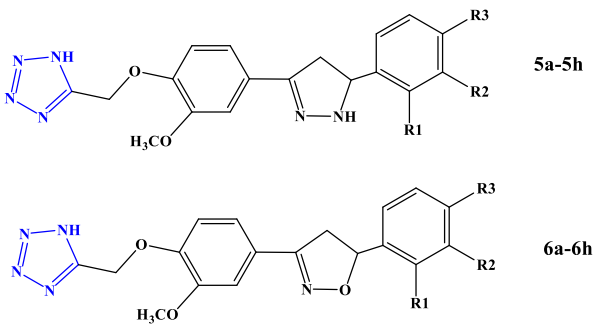
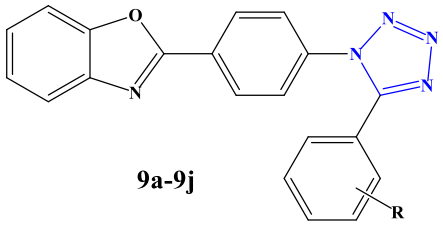


FIGURE 6.- Tetrazole antibacterial chemicals' structure

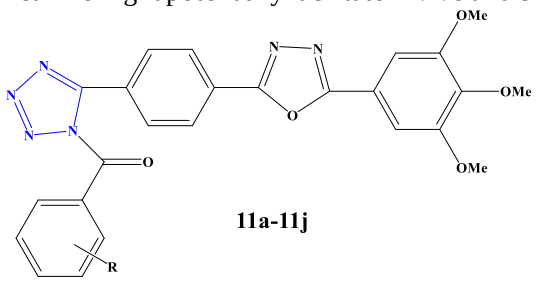
Structure of tetrazole anticancer compounds reported in research [20]. The in vitro cytotoxicity of a new set of tetrazole compounds 9a–9j, is evaluated after their synthesis. These substances were tested against four distinct cancer cell lines: A-549 (lung cancer), MCF-7 (breast cancer), KB (oral cancer), and Hop62 (carcinoma of the mouth). Good anticancer activity is shown by compounds 9b and 9g, especially against different cancers. Adriamycin served as a favorable reference point. The substances showed promising anticancer properties.



9a-9j

FIGURE 7.- Tetrazole antibacterial chemicals' structure

Tetrazole anticancer compound structure as reported in a study [21], compounds synthesized exhibited higher anticancer activity. Compound 11c exhibited strong anti-cancer effects against the different cell lines. The 1,3,4-oxadiazole fused tetrazole amides 11a-j were created and tested for their ability to inhibit cancer cell growth using the MTT assay. The positive control used was doxorubicin. Most of the compounds exhibited superior anticancer efficacy and greater safety when compared to the conventional medication, doxorubicin. Substance 11d demonstrated significant anticancer effects on A549, MDA-MB-231, and MCF-7 cell lines. Compound 11b exhibited superior efficacy against the different cell lines. The molecule that demonstrated remarkable anticancer effects was compound 11c. One day, the very powerful chemical 11c might potentially facilitate in vivo and clinical studies.



11a-11j

FIGURE 8.- Tetrazole antibacterial chemicals' structure

Table 3. -anti-tumor activity of this compounds

compounds	Standard drug	Cell line markers	Anti-tumor activity
4a, 4c, 4h and 7a	sorafenib	HT-29, MCF-7, HepG2 and A549	more potent
8g and 10a		MV4-11	Less effective
8h and 10b		MV4-11	More effective
11a-j	Doxorubicin	A549, MDA MB-231 and MCF-7	Exhibited

4. Tetrazoles as antifungal agents

Invasive fungal infections pose a substantial risk to very ill adult and pediatric patients, leading to around 1.35 million deaths worldwide [22]. The discovery of new antifungal medications is crucial because of the negative consequences associated with existing antifungal therapies and the rise of drug-resistant fungi, which may make the treatment of fungal illnesses more challenging. Oteseconazole (VT-1161) is a tetrazole-pyridine hybrid that selectively blocks the activity of cytochrome P51 in fungi, as compared to existing therapy alternatives. It has higher efficacy, fewer side effects, and improved selectivity. Oteseconazole is the first medication licensed by the US FDA to treat recurrent vulvovaginal candidiasis, making it a potentially best-in-class therapy choice for affected patients. In addition, oteseconazole shows great promise in combating other fungal infections, such as those that are resistant to azoles [23]. A variant of oteseconazole called Quilseconazole (VT-1129) similarly inhibits cytochrome P51, specifically in fungi. As a potentially effective oral medication, Quilseconazole may be able to combat Cryptococci meningitis, a potentially fatal fungal, transplant recipients, and HIV-positive individuals. Quilseconazole has been classified by the FDA as a

qualified infectious illness medication and has been awarded fast-track designation as an orphan medicine for Cryptococci meningitis.

Łukowska-Chojnacka, E. and coworkers reported of Synthesis of Tetrazole derivatives are assessed for their antifungal activity and contain the compounds benzothiazole, benzoxazole, and azole ring. It was also discovered here that the cell wall architecture can be altered by the benzoxazole derivative 5c. They noticed that the benzoxazole derivative 5c's benzene ring's chlorine substituents (4-Cl) may be involved in this mechanism. According to preliminary studies, benzoxazole antifungal activity against Candida albicans can be effectively combined with fluconazole at supra-MIC doses. The benzoxazole derivatives 5c and 5d exhibit no harmful effects on the invertebrate host, G. mellonella, while demonstrating action against Candida albicans. This observation may provide valuable insights into the potential therapeutic applications of these compounds [24].

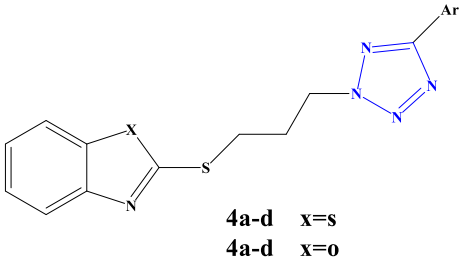


FIGURE 9.- Tetrazole antibacterial chemicals' structure

Each new imine compound was treated with sodium azide chemical to get the unique five-membered heterocyclic, which are Tetrazole derivatives O6–O10. At an average of the zone of inhibition of 14.0 mm, O6 is the best derivative that has shown a much stronger influence to block the growth of Candida guilliermondii [25].

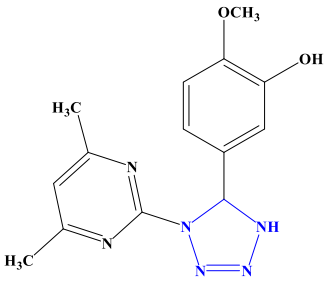


FIGURE 10.- Tetrazole antibacterial chemicals' structure

Table 4. -anti-fungal activity of this compounds

Compounds	Type of fungal	activity
5c-5d	C. albicans	exhibited
O6-O10	Candida guilliermondii	Significant

4. CONCLUSION

Tetrazole, a carboxylic acid bioisoster, plays a crucial role in the creation of new medications. A variety of compounds containing Tetrazoles, including tomelukast, irbesartan, valsartan, and others, have already been utilized in clinical settings due to their medical and pharmacy properties. Moreover, certain Tetrazoles have shown encouraging pharmacological effects against Alzheimer's disease, malaria, tuberculosis, and viruses, both in laboratory settings and in living organisms. This indicates their potential for use in treating and eliminating a wide range of diseases.

Funding

None

ACKNOWLEDGEMENT

The authors would like to thank the anonymous reviewers for their efforts.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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