Synthesis and Biological Activities of Some 1,2,4-Triazole Derivatives: A Review

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Abstract:

This review is about 1,2,4-triazoles include their synthesis; their physio-chemical properties, SAR, reactions, derivatives. Finally, their biological activities with a demonstrated showing different requirements to achieve different activity.

Key words: Heterocyclic, Triazole, Biological Activities.

مراجعة : التخليق والفعاليات الحيوية لبعض مشتقات 1,2,4-triazoles

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الخلاصة:

تهدف هذه المراجعة الى استعراض صفات مركبات triazoles-1,2,4 الحلقية غير المتجانسة مثل التخليق ، الخواص الفيزيائية والكيميائية ، علاقة التركيب بالفعالية ، التفاعلات والمشتقات الكيميائية. بالاضافة الى ذلك، تم استعراض الفعاليات الحيوية مع ذكر المتطلبات المختلفة للحصول على كل فعالية حيوية.

الكلمات المفتاحية: حلقية غير متجانسة ،التريازول ، الفعاليات الحيوية .

Introduction

Five heterocyclic compounds define as five-membered ring with one or more heteroatom. Heterocyclic compounds offer a wide range of physical, chemical, and biological properties, allowing them being used in a range of applications (1). The s-triazole group is found in a number of well-known medications, including triazolam, alprazolam, and etizolam (2). Triazole is a noteworthy class of heterocyclic compounds that exhibits a wide variety of pharmacological actions. It is a five-membered, di unsaturated ring structure with three nitrogen atoms in a heterocyclic core and is also known as pyrrodiazoles (3). 1,2,4-triazoles and some of their derivatives have anti-inflammatory properties, as well as analgesic, diuretic, bronchodilator, anticancer, antioxidant, and antibacterial properties (4). In the industry, the use of selected 1,2,4-triazole derivatives conferred good stability and heat resistance in many molecular materials, as well as highlighted the corrosion inhibiting capabilities of certain metals (5). Fungicides, bactericidals, and herbicides are all considered 1,2,4-triazoles in agriculture (6). A 1,2,3-triazole ring is a desirable unit because it is resistant to metabolic destruction because oxidative/ Reductive conditions, and enhances

solubility by attaching to biomolecular targets. The pharmacophoric group refers to this ring. It's also found in the structure of drugs like tazobactam and cefatrizine (7). Triazole is a crystalline solid that is white to pale yellow in color and has a mild, distinctive odor. It is soluble in aqueous and alcohol, melts at 120°C, and boils at 260°C. It exists as two isomeric chemical compounds, 1,2,3-triazole and 1,2,4-triazole (Fig.1), both of which have the molecular formula $C_2H_3N_3$ and have a molecular weight of 69.06 (8). The two isomers are as follows (9)

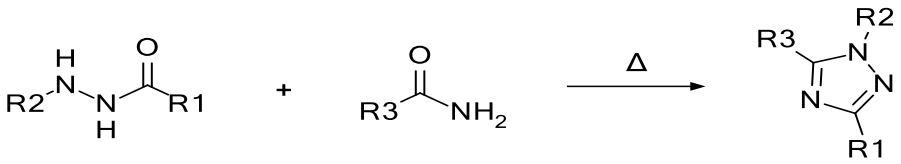
i ii

1,2,4-triazole, (ii) 1,2,3-triazole

Methods of synthesis

Pellizzari Reaction

The Pellizzari reaction is the process of synthesizing 1,2,4-triazole derivatives from a solution of amide and acyl hydrazide. Heating a mixture of formamide and hydrazine hydrochloride with KOH produces 1,2,4-triazole, the compound 2,3,5-triphenyl-1,2,4-triazole was synthesized using benzamide and benzoyl hydrazide, for example high temperature and long time (10)

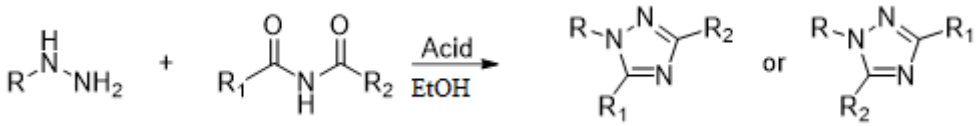


R1, R2, R3: alkyl or aryl

Figure (1): The Pellizzari Reaction.

Einhorn–Brunner reaction

The Einhorn–Brunner reaction is the synthesis of 1,2,4-triazoles via condensation between hydrazines or mono substituted hydrazines and diacylamines in the presence of mild acid at 140°C (11). Using this scenario: 1,5-diphenyl1,2,4-triazole was synthesized from N-formyl benzamide and phenyl hydrazine (12).



R_1, R_2, R_3: alkyl or aryl

Figure (2): Einhorn–Brunner reaction.

Synthesis of 1,2,4- triazoles from nitriles and hydrazonoyl chlorides via 1,3-dipolar cyclo-addition

1,3- dipolar cycloaddition synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from nitriles and hydrazonoyl chlorides is carried out in a single flask (13).

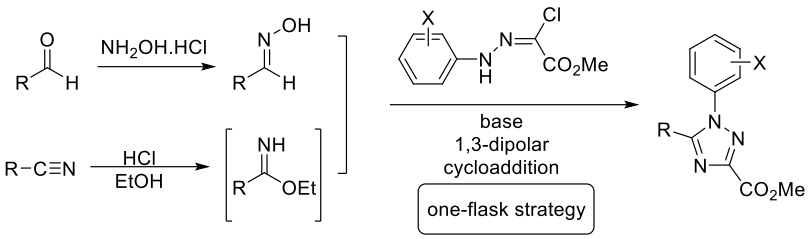


Figure (3): Synthesis of 1,2,4-triazole derivatives.

The reaction can be applied to both aromatic and al aliphatic nitriles with N-arylhy-drazonoyl chlorides having different substitution on the phenyl group (14). A reasonable 1,3-dipolar cycloaddition mechanism was suggested for the reaction of imidate (resulted from nitrile) with nitrilimine (resulted from hydrazonoyl) chloride in one flask to generate the proposed 1,2,4-triazole (15).

Synthesis of 1,2,4-triazoles via copper-catalyzed domino nucleophilic substitution/oxidative cyclization

The first strategy is based on a Cu-catalyzed domino intermolecular nucleophilic substitution/ring closure between two molecules of amidine HCl in a single flask (16). This is a one pot which involves the formation of two bonds A copper-catalyzed domino reaction involving two molecules of an imidate hydrochloride and an ammonium source can also yield 3,5-diaryl-1,2,4-triazoles in one pot (17). Two carbon-nitrogen bonds and one nitrogen-nitrogen bond are formed in a single synthetic step using this approach (18).

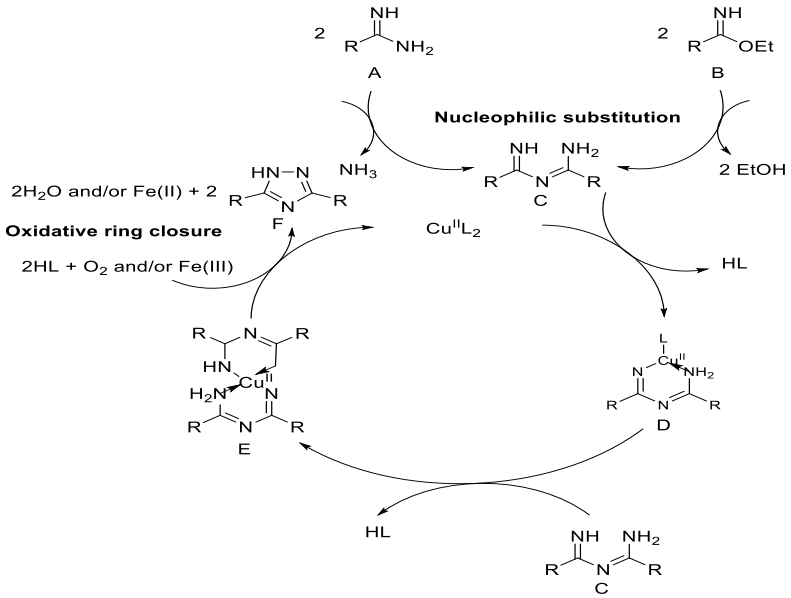


Figure (4): General scheme for Synthesis of 1,2,4-triazoles via copper-catalyzed domino nucleophilic substitution/oxidative cyclization

Synthesis of 1,2,4-triazoles by microwave-assisted N-acylation of amide derivatives and the consecutive reaction with hydrazine hydrochlorides

For the synthesis of 1,3,5-trisubstituted-1,2,4-triazoles, N-acylation of amides and cyclization with hydrazines is considered one of the finest procedures (19). Reactions were carried out under mild conditions within a short time and yielding good product yields. The synthesis can alternatively be done in a one-pot sequential reaction utilizing K_2CO_3 or H_2SO_4 and microwave irradiation to

benzamide with acetic anhydride to produce N-acylate benzamide (20). The process was completed in 3 minutes to the application of microwave irradiation (as a source of energy) (21).

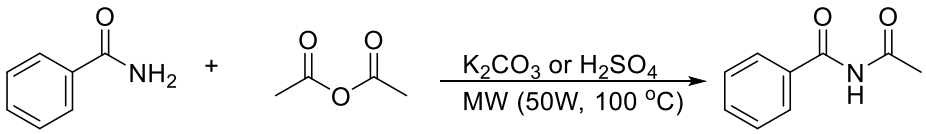


Figure (5): Synthesis of N-acylate benzamide.

Pyridine use a catalyst to help producing a purer 1,2,4-triazoles in some situations. The synthesis could be improved by utilizing phenylhydrazine HCl, a greater power of microwave irradiation power (300 W), and a higher temperature (200 °C) (22).

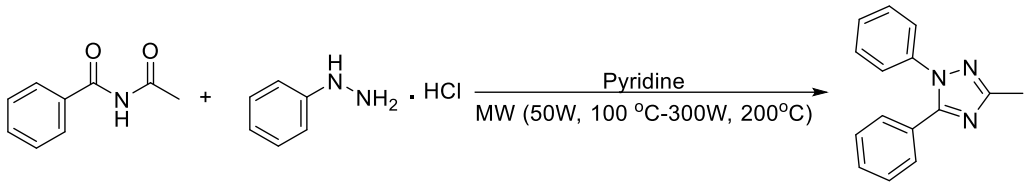


Figure (6): Synthesis of 1,2,4-triazole derivatives.

N-arylation of 1H-1,2,4-triazole

The use of prominent facet CuO nanoparticles as a catalyst for 1,2,4-triazoles N-arylation at room temperature with aryl iodides under ligand-free conditions is reported as a simple, efficient technique and economic method (23). The catalyst was reusable, and a wide range of substrates were successfully reacted. Because of the broad breadth of this catalyst, researchers are looking into transformations using less reactive azoles such as pyrazole and imidazole (24). Several azole derivatives are found to be successful in combining with aryl iodide to produce the necessary N-arylated products in high yields (25).

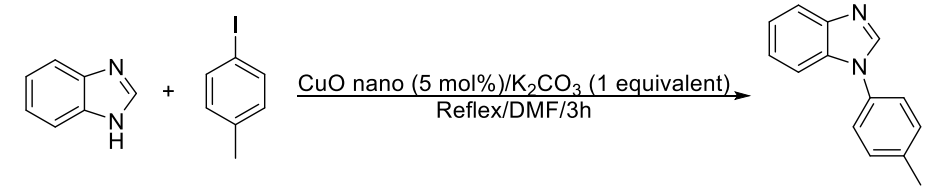


Figure (7): General equation of N-arylation of 1H-1,2,4-triazole.

Biological activities of 1,2,4-triazoles

The chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives attracted a lot of attention and have been use in a wide application in life. A number of 1,2,4-triazoles have been included into a diverse range of therapeutically interesting drug competitors that have the following qualities (26):

Antibacterial activity

Gram- negative and Gram-positive bacterial strains were inoculated with 1,2,4-triazole compounds newly synthesised for their ability to suppress growth *in vitro*.

Drug-resistant strains (e.g., MRSA, VRE) should be tested for possible antibacterial properties of newly discovered compounds. Some derivatives have also shown antituberculosis action, as evidenced by numerous investigations (27).

Triazole hybrides of quinolone antibacterial agents

A considerable number of 1,2,4-triazole combinations with fluoroquinolone medicines have been combined into therapeutically promising drug candidates (1). It has been shown that novel nalidixic acid derivatives with antimicrobial activity, such as 1,2,4 triazole-3-thione derivatives 1-2 (Figure 9), have antibacterial effects on both Gram-positive (*B. subtilis, S. aureus)* and Gram-negative bacteria (*P. aeruginosa, E. coli and K. pneumonia)* (1). The MIC of 16 g/mL for the azomethine derivatives against *P. aeruginosa* was shown to be highly active. If the 2-phenyl ring has a chloro-substituent (compound 2) than compounds 1 and 3, showed the greatest antibacterial effectiveness against all tested microbes, compared to streptomycin, which had an MMIC of 2–15 mg/ml.

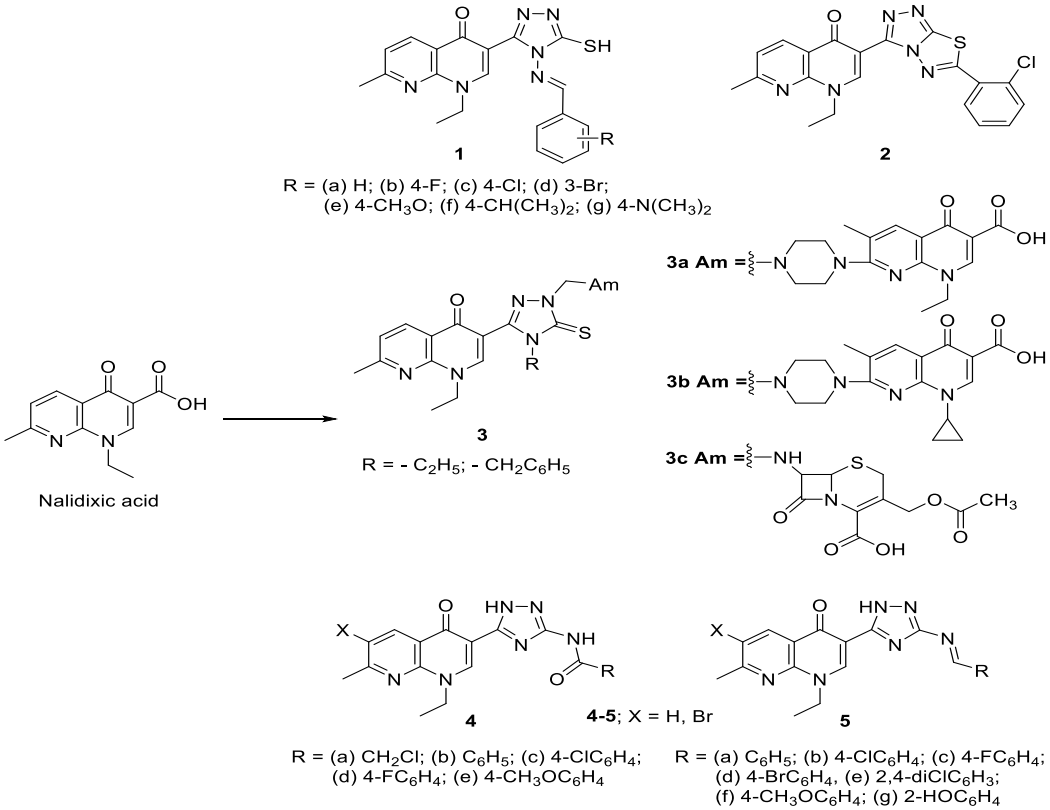


Figure (8): 1,2,4-triazole-3-thione derivatives.

1.1.1. 1,2,4-Triazoles as anti-tubercular agents

Most people who get TB get it from Mycobacterium tuberculosis, which is responsible for the disease in around a third of the world's population. This bacteria's proliferation is inhibited by a number of medications that have been developed specifically for this purpose. A

multidrug regimen is the only treatment option for TB infections right now (28).

UNICEF and WHO have initiated directly observed treatment short courses (DOTS) to combat long-term non-adherence and multidrug resistance (MDR) or XDR. Anti-tuberculosis properties have been discovered in a collection of pyridine-1,2,4-triazole derivatives that were produced by researchers (29). Using rifampicin as a reference medication, Rode *et al.* reported the synthesis and biological activity of novel 3-aryl-5-(alkylthio)-1H-1,2,4-triazoles derivatives in 2016 (30). Twenty-five produced compounds of triazole derivatives showed promising anti-TB activity in the dormant stage and 20 compounds in the active stage, according to the anti-mycobacterial activity data. The anti-TB activity of compounds 69 (IC50 = 0.03 g/mL) and 70 (IC50 = 0.89 g/mL) was exceptional (31).

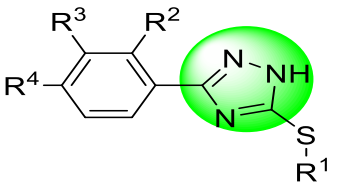


Figure 9: General structure of anti TB 1,2,4-triazole.

It has been reported that Dixit and his colleagues have developed hybrid triazole compounds for the treatment of multiple-resistant *M. tuberculosis*. They created a verapamil/thioridazine hybrid (TZ). When tested against *M. tuberculosis*, compounds 71-74 had MIC values as low as 8, 4, 32, and 64 g/ml. They hypothesised that the synergistic action of these chemicals would lead to increased potency and decreased toxicity (32).

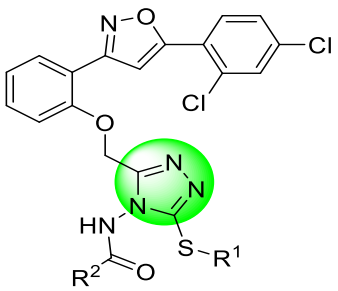


Figure 10: General structure of compounds (74-71).

Antifungal Activity

Antifungal drugs such as voriconazole and fluconazole, which have been approved by the FDA, are the major antifungal agents used to treat invasive fungal diseases. Antifungal triazoles directly inhibit the 14a-lanosterol demethylase (CYP51) in CYP450, which results in the inhibition of sterol biosynthesis in cell membranes (33). When Wang *et al.* made and tested phenyl-pyrazole and piperazine thiones in 2016, they discovered that they were effective antifungal agents. To compare the percent concentration inhibition of mycelium rate of growth with the positive controls carbendazim, triadimefon and chlorothalonil, the synthesised compounds were tested against six fungi (34). Maximum age inhibition percentages of 75% and 91.8 percent were found for 1,2,4-triazole thione 65. Compound 65 was the most effective of the bis-1,2,4 triazole thiones against *Rhizoctonia cerealis*, with a maximum inhibition of 83.9 percent (35).

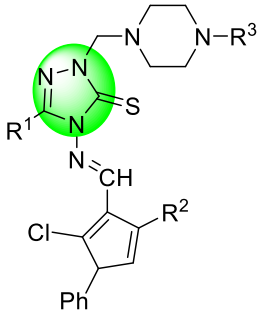


Figure 10: General structure of antifungal 1,2,4-triazoles.

Antiviral Activity

For viral infections, a wide variety of antiviral drugs are available, but these agents have limitations like a limited spectrum of action, drug resistant strains and inability to combat latent viruses. Since this is the case, newer antiviral drugs must be developed that have a broader antiviral spectrum and are not susceptible to drug resistance (36). For the first time, Chudinov *et al.* synthesized and tested ribavirin analogues for treatment of herpes simplex, hepatitis C, syphilis and influenza A viruses. No toxic effects were observed at the highest concentration of the synthesized analogues (1250 M). Compound 68 was the most active of the synthesized analogues, with an EC50 value of 19 M (37).

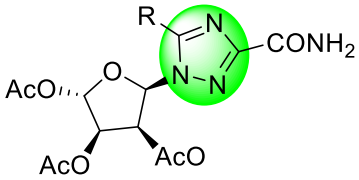


Figure (11): Structure of compound 68.

Anticancer Activity

They were inspired to develop many drugs, one of which is the cancer-fighting agent thiazoles. There are numerous heterocyclic rings containing nitrogen atoms in both natural and synthetic products, which have powerful anticancer properties against a wide range of human cancer cell lines (38). Letrozole is an aromatase inhibitor-containing triazole structural unit used to treat cancer. It has been found that the most important subclass of bioactive 5-membered heterocyclic organic compounds for medicinal chemistry is 1,2,4-thiadiazoles, which show significant biological actions such as cyclooxygenase inhibitors, human leukemia (39). 3,5-bis(pyridin-3-yl)-1,2,4 - thiadiazole (2) is an aromatase inhibitor and is used to treat a variety of cancer types (40).

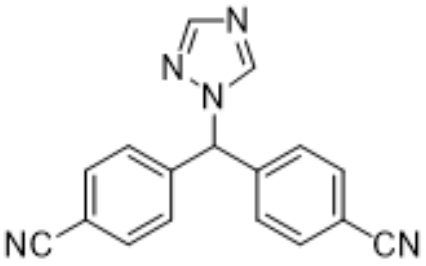


Figure 12: Structure of letrozole.

Structure activity relationships of triazole derivatives

SAR such as triazoles, it can highlight the concept and benefit of using triazoles in compounds (41). Triazoles can be employed for stabilization because have multi electron pair in nitrogen atoms, chain lengthening, drug receptor interactions, activity, structural lengthening, and even degradation prevention. As a result, each chemical should be investigated separately (42). Azoles are antifungal medicines that work by inhibiting the enzyme lanosterol 14-demethylase (CYP51), which is involved in fungi's sterol production. Itraconazole, fluconazole, posaconazole and voriconazole are all orally active azoles that have a broad spectrum of activity against yeasts and filamentous fungus (43). Azole medicines have been utilized as first-line antifungal treatments because of their broad antifungal spectrum, higher efficacy, and lower toxicity (44). A robust a structure-activity model connections time and money could be factors helpful in designing and surveying novel azoles, which are a major family of significant antifungal medicines (45). Important structural properties for future investigations in the field can be obtained,

modelled, and summarized from other triazoles that have already been produced (46). All azole medicines, in general, share the same basic model, which includes A heme binding group, side chain A, side chain B, and a three-atom connector (47).

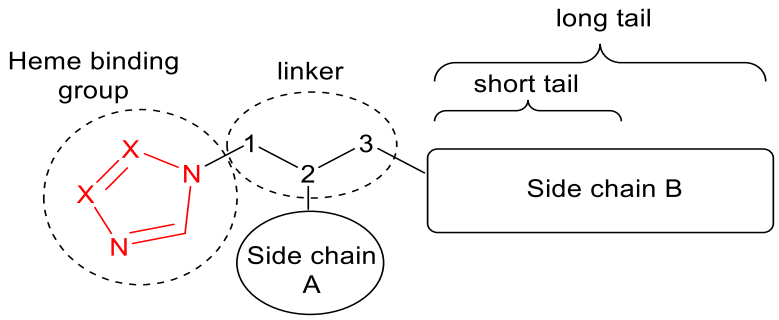


Figure (13): General structure of antifungal 1,2,4-triazoles.

A. Heme binding groups

CYP51 enzyme lanosterol 14-demethylase (CYP51) is a member of the CYP51 family of cytochrome P450 enzymes, which is responsible for the antifungal activity of azoles (48). Iron in the triazole ring of the azole medicines can be substituted for the sixth coordination position of the iron in lanosterol's 14-demethylase cofactor. Ergosterol production in fungus is regulated by the 14 a-demethylation of lanosterol (49). Ergosterol levels in cell membranes drop when CYP51 is inhibited. As a result, the lipid bilayer becomes less fluid and fungal growth is slowed. The 14 a-methyl-3,6-diol produced from 14-methyl-fecosterol is one of the hazardous metabolites that accumulates when CYP51 is inhibited (50). The heme ring is essential for the azole group's antifungal activity without any modification that attach to the linker with N-1 atom. The porphyrin active site is bounded by triazole or tetrazole rings, with the iron of the active site aligned with the length of its coordinated bond. (43). Adding a simple or bulky group to the N-4 of the triazole may have an effect on its activity because it prevents the triazole from attaching to the heme (51). Triazole compounds also contain:

B. The three atoms linker:

A three-atom linker is only one of several possible configurations for this linker. There is a particular gap between the arms of the structure, resulting in higher potency, because of this three-atom configuration (52).

There are few exceptions to this rule, including clotrimazole analogues and vinyl imidazole derivations, for which carbon is the linker group's number one atom (53).

In the linker, the majority of the atoms are carbon-2 and carbon-3. The carbons chirality has a significant impact on the antifungal action (54).

For example:

- Adding a hydroxyl group to C-2, for example, has various advantages, including increased potency via water and an indirect H-bond molecules in Enhanced pharmacokinetics, the active site, and water solubility, as well as more stable and better tolerated metabolism (55). Several prodrugs, such fluconazole phosphate ester, voriconazole, and ravuconazole phosphate ester, should also complete the C-2 substitution. (56).
- C-3 could benefit from the addition of a methyl group.

Lanosterol's C-13 binding pocket is filled by the methyl group attached to side-chain B, which goes in the antiperiplanar direction of side-chain A. There is also the necessary activity in other substituents such as CH (double bond with C-3) and two F or two methyl (non-chiral C-3) (57).

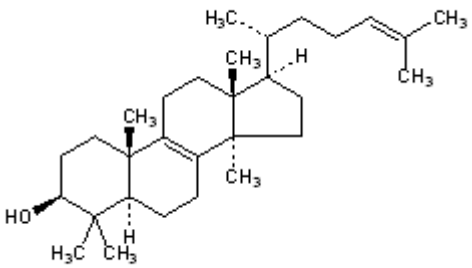


Figure (14): Structure of Lanosterol.

An oxygen, sulphur, or NR2 (such as miconazole) may be C-3, which retains antifungal action and also conformational limitation of the structure, such as di-oxalene (C-2 and C-3) (ketoconazole or itraconazole). The other pharmacokinetic features are not enhanced by them (58).

Side chain A

Aside from the lanosterol 17-alkyl chain and the hydrophobic tunnel that it occupies of halogenated phenyl is important for the inhibitory impact of side chain A (59).

Y132, for example, has a stacking interaction with it (a conserved amino acid found in fungi).

Only groups bigger than chlorine in C-2 and C-6, which have weak steric adherence and diminish the inhibitors binding affinity in the active site, are acceptable substitutions of the phenyl ring (60).

Atoms of fluorine in C-2 and C-4 have a stronger potency than those in C-1 and C-2. Instead of substituting 4-fluorophenyl, additional big bulky groups could be used to retain the molecule's capacity to inhibit CYP51 in the para position. (42).

Side chain B.

When optimising side chain B, one could develop potent and favourable pharmacokinetic features solely with this side chain's optimization in mind. In third-generation and hybrid structures, this side chain has been subjected to a wide range of alterations (61). Commonly, a linker attaches to the tree atom linker C-3, and antifungal activity ranges from other types of linkers here. Studying the antifungal properties of these compounds has shown that they are well-tolerated and can be used as linkages, but the antifungal activity is reduced by ester, esteramide, and NHR (62).

The aforementioned linkers could be used to link modifications to the target protein's deep binding cleft, which can form a variety of significant hydrophobic, steric, and H-bond interactions (63). Fluconazole, ravuconazole, and voriconazole are examples of short-tail structures with potential small changes to the linkage (64). When small hydrophobic, electron-rich, and electron-withdrawing groups in ortho- or para-positions join a phenyl or heteroaromatic ring to the linker (such as –CNs and chlorinated heteroaromatic rings), potency is increased through possible steric and hydrophobic interactions (65).

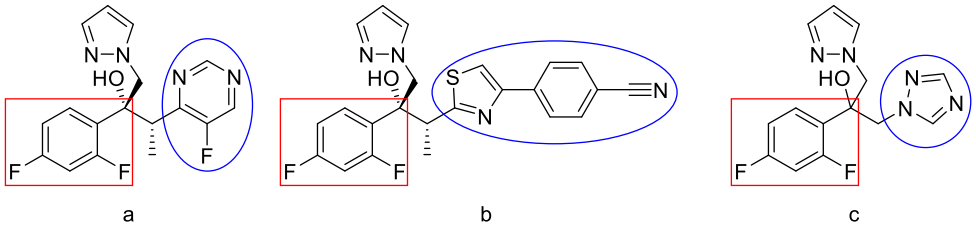


Figure (15): (a) voriconazole, (b) ravuconazole, (c) fluconazole.

As an example, a fluorine on the pyrimidine ring of the voriconazole and the fungus Tyr122 establish an H-bond contact. While M-position substitutions are detrimental to activity. Oxygen (ether, carbonyl) or Nitrogen (NR2) may be used as an H-bond acceptor substitution in long-tail structures like itraconazole and posaconazole, at the para-position of the para-phenyl ring. (66). This substitution in figure 16 appears in some active sites, to form an H-bond with a residue. Another aromatic group This H-bond acceptor group binds to steric and Van der Waals contacts in the active site. (67).

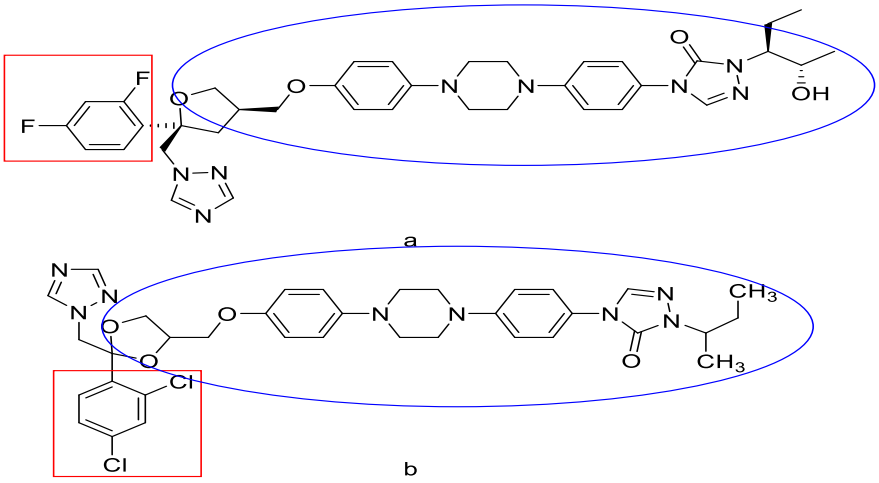


Figure (16): (a) Itraconazole and (b) Posaconazole.

Triazole derivatives bind quickly to a number of enzymes and receptors due to their unusual structure, which includes three nitrogen atoms and an electron-rich system (68). Compound AA was shown to be the most powerful of the 1,2,4-triazole compounds examined, capable of reducing viral plaques by 50% at an 80 mM dose to neutralize herpes simplex virus-1 (HSV-1) (69). Furthermore, compound AA had greater selectivity than acyclovir (>200 mM vs. 80 mM) (37). The primary notion behind AA is that it can make numerous hydrogen bonds in the HSV-1 thymidine kinase active site (70). Furthermore, the triazole plays two important roles in this compound: despite its participation in H-bonding, it also adds stability to the complex and acts to grow the compound in order to fit the key groups to the active sites (71).

The presence of two R arms prevents the ester and pyrimidine groups from being degraded by pH (72).

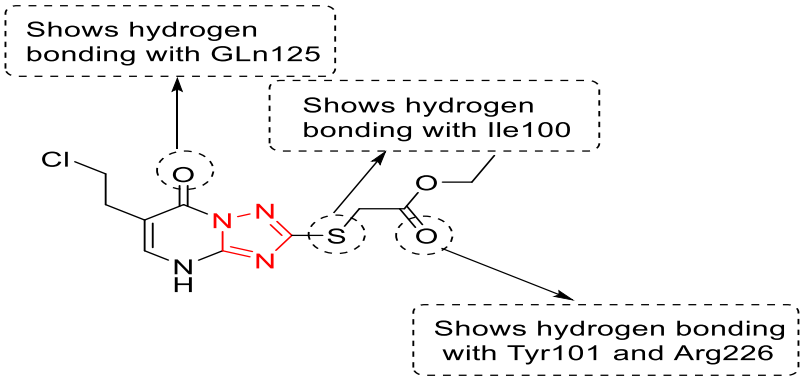
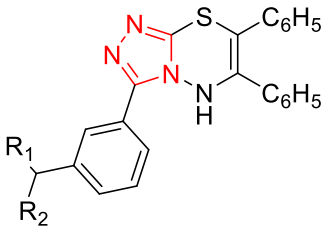


Figure (17): Structure of triazole derivative.

It has been reported that a number of 1,2,4-triazolo [4,3]-quinoxaline derivatives can be prescribed as antimicrobial and antiviral agents after being synthesised (73).

The 1,2,4-triazolo [3,4] [1,3,4] thiadiazines were synthesised and tested for antiviral activity against JEV and HSV-1. Compound AB (ED50 7.8 mg/mL) demonstrated reasonable activity against JEV with 50% inhibition and therapeutic index value of 32 (74).



R_1 = H
R_2 = 2-phenyl-3-methyl-quinazolin(3H)4-one

Figure (18): Structure of triazole derivative.

There are two R arms in the core of this compound, just like the AA compound. However, it is different from the former in that it has thiopyridazine rings instead of pyrimidine, which is more effective. It was discovered that the AC compounds showed potent antiviral properties against coxsackievirus B3 (CVB3) and enterovirus 71 (EV71) after a screening of 44 chiral triazole derivatives (75). In comparison to ribavirin (SI: 15), they demonstrated a higher level of action.

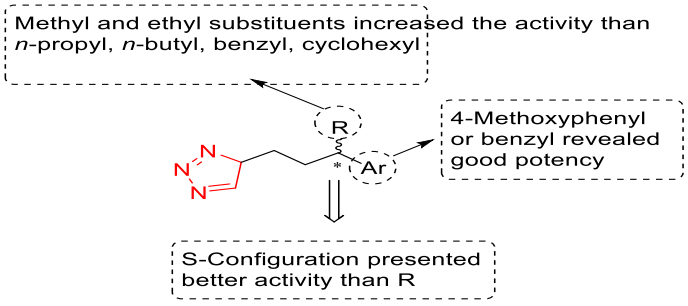


Figure (19): Compound AC.

SAR studies showed that Benzyl units (Ar) or 4-methoxyphenyl short alkyl chains (R) were found to be favourable for antiviral activity in SARs (76). The introduction of 1,2,4-triazole contributes to the H-bonding as well as to the overall compound's stability. [1,2,4]pyrimidin-5 (4H)-ones like AD compound have been evaluated for antiviral ability against human enteroviruses such as (Cox

B3), (Cox B1), Poliovirus 3, and Human Rhinovirus 14, 21, and 71 (77). Compound AD is a promising lead compound for developing broad spectrum anti-enterovirus drugs (78).

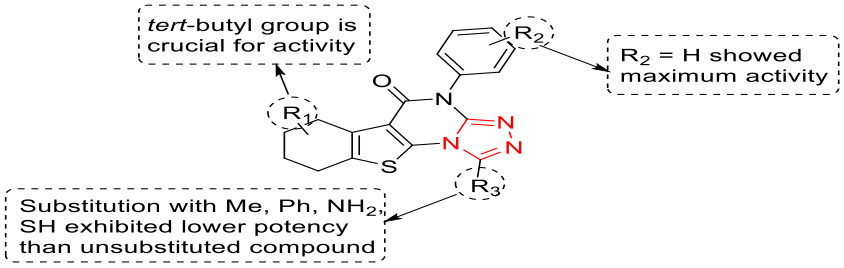


Figure (20): Structure of triazole derivative.

A decrease in the Triazole's activity and potency may be attributed to the introduction of some bulky groups to the triazole, which may hinder the Triazole's capacity to share hydrogen bonds. Also, triazole is used to stabilise the compound by electro-resonance forces and to increase the molecule's size (79). Studying the 1,2,4-triazole SARs as anti-TB shows the main characteristics of these compounds.

Compounds have a number of key characteristics, such as:

- 1,2,4-triazole ring, which is crucial for the action and binding of TB to intracellular targets. Attaching or adding -NO_2 to the Triazole group's third carbon improves binding, which in turn improves this role's high-limit performance. However, Triazole and NO_2 both have poor TB activity, resulting in the formation of new groups (80).
- Links atoms range from 2-methyl to 5-methyl groups, which are the other component. The nitro-triazole ring is sandwiched between this group and the sulfamido group. Several investigations have demonstrated that the aerobic anti-TB activity is diminished when the length of the linker group is decreased (from a 4-methylene to a 2-methylene and 3-methylene) (79). While several antitubercular agents are available, two compounds, BC and BB, have the most potent antitubercular action against both hypoxic and aerobic strains of TB.

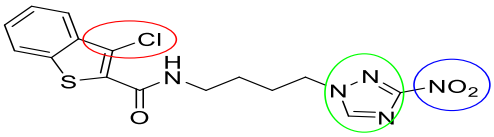


Figure (21): Compound BB.

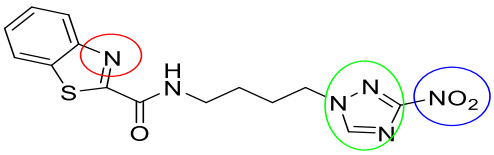


Figure (22): Compound BC.

- Bulky-withdrawing groups, such as phenyloxyphenylacetamides, propanamide analogues, benzyloxy group are crucial for the binding and activity of the medication against Mtb (81).

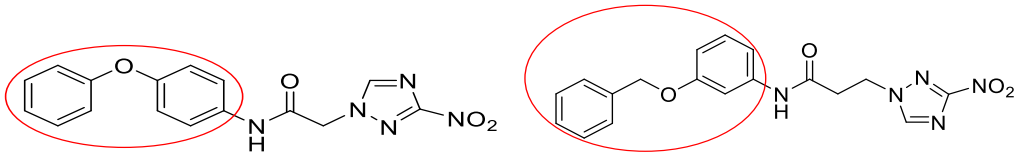


Figure (23): Synthesis of triazole derivatives.

Conclusions

1,2,4-triazoles derivatives have a wide range of biological activities, which are thought to be pharmacologically essential to the nucleus. The chemistry of triazoles and their heterocyclic derivatives has gotten a lot of attention in recent years because of their synthetic and biological relevance. Many 1,2,4-triazole-containing ring systems, for example, have been incorporated into a wide range of therapeutically promising drug candidates.

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