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Review article

Tetrazoles: A multi-potent motif in drug design

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A B S T R A C T

The unique physicochemical properties and fascinating bioisosterism of tetrazole scaffolds have received significant attention in medicinal chemistry. We report recent efforts using tetrazoles in drug design strategies in this context. Despite the increasing prevalence of tetrazoles in FDA-approved drugs for various conditions such as cancer, bacterial viral and fungal infections, asthma, hypertension, Alzheimer's disease, malaria, and tuberculosis, our understanding of their structure-activity relationships, multifunctional mechanisms, binding modes, and biochemical properties remains limited. We explore the potential of tetrazole bioisosteres in optimising lead molecules for innovative therapies, discussing applications, trends, advantages, limitations, and challenges. Additionally, we assess future research directions to drive further progress in this field.

1. Introduction

The design and development of molecules for advancement as potential new drugs is a long process that relies on medicinal chemistry. It begins with hit identification, which is optimized into a lead candidate. It then undergoes lead optimization, including improvements in chemical synthesis, identification of the most effective purification methods, and physicochemical characterisation by modern techniques. The novel compounds must be bio-evaluated to assess their improved interactions with biological targets. This conventional approach includes testing the new drug candidates for their potency, biocompatibility, and toxicity and checking their pharmacokinetic profile. Frequently, the improved potency observed *in vitro* is not validated in *vivo* studies, necessitating the redesign of the potential lead molecule to address unexpected limitations. A key component is to enhance the ADME (Absorption, Distribution, Metabolism and Excretion) parameters of established and potent drug candidates through minor structural modifications [1]. One strategy is introducing a bioisostere, a chemical tool used in rational drug design, to eliminate undesirable properties and achieve target selectivity [2]. As such, medicinal chemists often apply the bioisostere concept to convert the molecules containing problematic functional groups into safer, clinically more effective, cost-efficient, and therapeutically appealing drugs. This review presents the use of tetrazoles as bioisosteres drug design and for their further development. Only representative tetrazole-containing drug candidates reported in the literature are described here.

1.1. Preface to tetrazole scaffold

Tetrazole is an unnatural 5-member heterocyclic compound composed of four nitrogen and one carbon atoms, theoretically existing as three tautomeric forms; 1*H*, 2*H* and 5*H* (Fig. 1). The 1*H* and 2*H* tautomers are aromatic with 6 π-electrons, while the 5*H* form is nonaromatic and only theoretical – it has not been observed experimentally [3]. In the solid state, tetrazole exists in the 1*H* form, and in polar solvents such as dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), the 1*H* tautomer is predominant [3]. In the gas phase, the 2*H* form predominates [4]. Tetrazole is the bioisosteric replacement of

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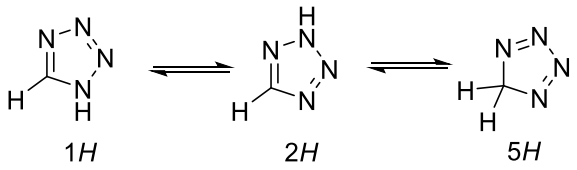
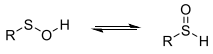


Fig. 1. Tautomers of tetrazole.

Table 1
Examples of bioisosteres of carboxylic acid functional groups.

Bioisostere	Main characteristics
Tetrazole 	The most important characteristics of tetrazole are flatness and acidity, which are very similar to carboxylic acids
Hydroxamic Acids 	Exhibits moderate acidity and strong metal chelating properties. However, metabolism via sulfation and glucuronic acid can lead in the formation of toxic metabolites
Phosphonic Acids 	It has a relatively high acidity and non-planar geometric shape
Sulfonic and Sulfonic Acids 	These are non-planar and have stronger polarity and acidity than carboxylic acid.

carboxylic and amide groups and can improve the metabolic stability and other ADMET properties of compounds containing these groups. Tetrazole derivatives exhibit diverse pharmacological properties against several diseases, including cancer [5], bacterial [6], viral and fungal infections [7], hypertensions [8], and asthma [9]. The tetrazole motif has been a 'hot' bioisosteric group for carboxylic and amide groups in drug discovery and optimization.

1.2. Classification of isosteres

Isosteres refer to functional groups with similar molecular or ionic structures and are usually charged. The moieties have different chemical structures but the same biological properties. Bioisosteres can be classified into two categories: classical and nonclassical. Classical bioisosteres are structurally simple atoms, ions or groups with the same atom numbers and/or the same valence electron numbers, whilst nonclassical bioisosteres are distinct in structure, containing a different number of atoms and show varied steric and electronic properties [10]. Carboxylic acid functional groups are often essential components of pharmacophores, serving as hydrogen bond donors or acceptors [11]. However, the presence of the carboxylic group may influence both toxicity and metabolic stability of drugs [12]. Several bioisosteres have been investigated to retain the benefits of the carboxylic functional group while eliminating their adverse effects, including tetrazoles, hydroxamic acids, and phosphonic acids (Table 1) [13].

1.3. Analysis of tetrazoles publications

The tetrazole motif has emerged as a popular scaffold for drug design in chemical synthesis and medicinal chemistry. The annual count of articles reporting tetrazole derivatives is rising (Fig. 2A), with the United States leading in published reports (Fig. 2B). A notable increase in patents related to tetrazole-containing molecules (Fig. 2C) suggests extensive applications beyond publicly reported findings, potentially as promising drug candidates undergoing confidential development for further clinical trials. A systematic analysis of the current literature highlights medicine, chemistry, biochemistry, and pharmacology as the primary fields for describing tetrazole motifs, with medicinal chemistry being particularly crucial for their application (Fig. 2D). Consequently, the synthesis of tetrazole has been extensively studied using various

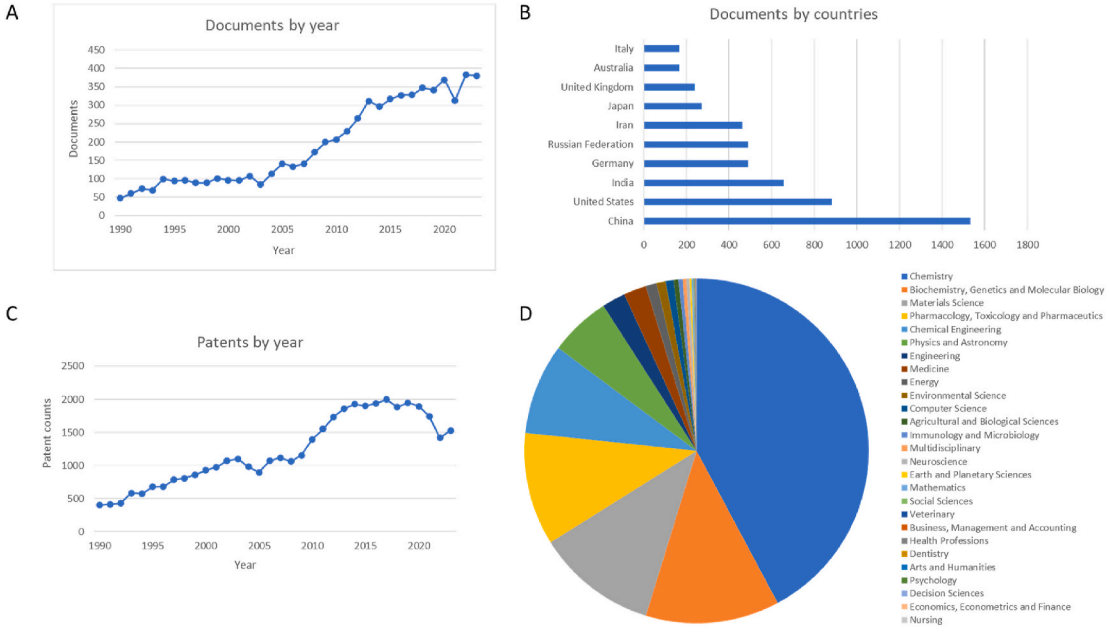


Fig. 2. (A) Number of publications containing "tetrazole(s)" in title and abstract from 1990 to 2023, analysed by Scopus (6511 articles); (B) 10 most published countries/territories containing "tetrazole(s)" in title and abstract (6511 articles); (C) Number of patents containing "tetrazole(s)" from 1990 to 2023, analysed by Lens (41,266 articles) and (D) Documents by subject area analysed by Scopus. Tetrazoles were mainly applied in chemistry, followed by biology and materials science.

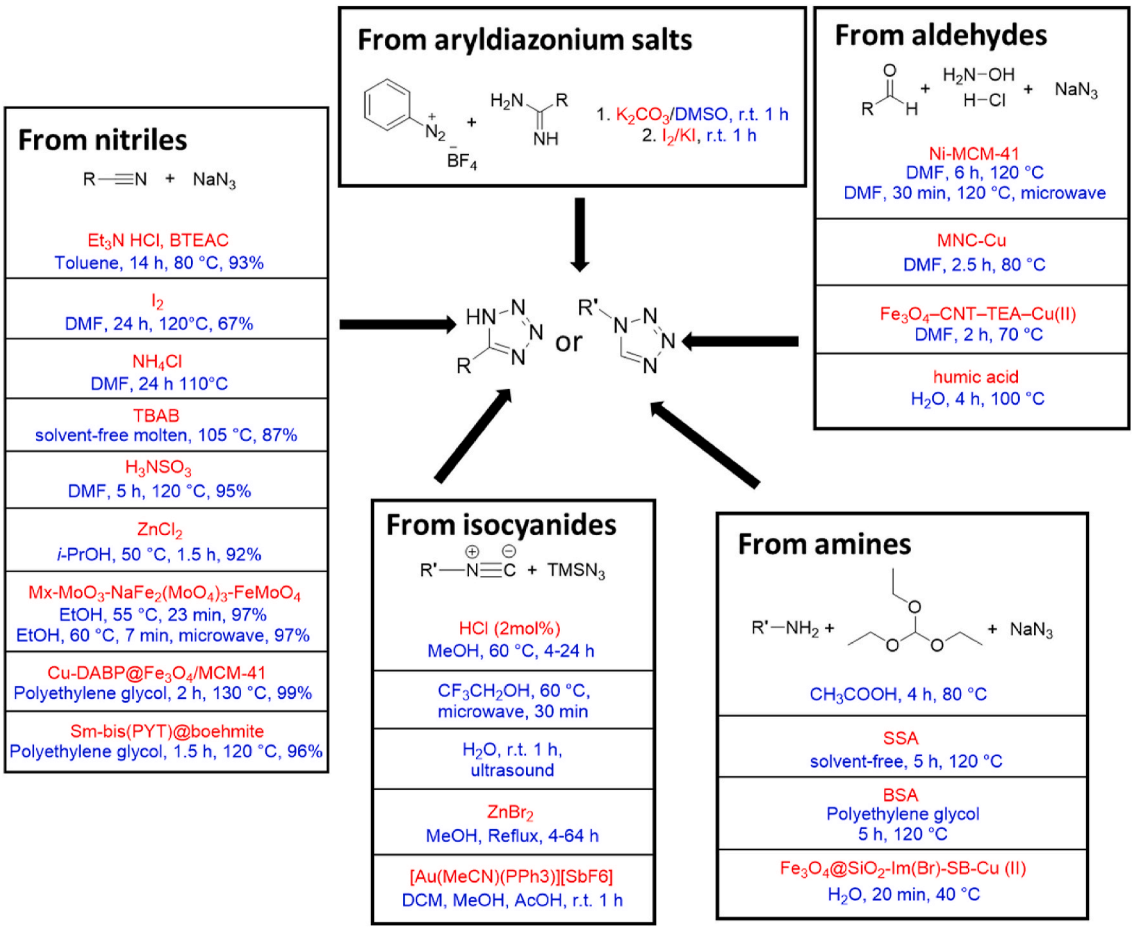


Fig. 3. Substituted tetrazole synthesis can be achieved through various routes involving nitriles, aldehydes, amines, isocyanides and diazonium salts as precursor compounds. The different methods used to produce substituted tetrazole from these starting materials are shown.

starting materials, leading to tetrazole-containing compounds exhibiting multifunctional bioactivities, including antimicrobial [13], anticancer [8], antihypertensive [14], antiasthma [15], anti-inflammatory [16], and anti-HIV properties [17].

This review is divided into sections with tetrazole synthetical methods, biopotency with antimicrobial, insecticidal, anticancer, and other pharmaceutics classes, all being at their early stage of bioevaluation. The last section is dedicated to reported tetrazole derivatives at the clinical trials and known marketed drugs.

2. Synthetic methods of tetrazole formations

The synthesis of tetrazole was first described by Bladin in 1885. The formation of an azole ring with four nitrogen atoms through the reaction of dicyanophenylhydrazine and nitrous acid was noted; this new heterocyclic ring was named tetrazole [18]. The synthesis of substituted tetrazole from different functional groups including nitrile, isocyanide, aldehyde, amine and aryldiazonium salts is shown in Fig. 3.

2.1. From nitriles

Substituted tetrazole synthesis from nitriles is conventionally conducted in a metal-free environment. As tetrazole cyclization requires activation of the azide for nucleophilic attack, heating is necessary, and thus, high boiling point solvents such as DMF and toluene are used. As shown in Fig. 3, the conventional method usually uses metal-free catalysis to speed up the reaction. Sarngadharan et al., synthesized tetrazole using triethylamine hydrochloride and choline chloride with benzyltriethylammonium chloride (BTEAC) in toluene. This method's advantage was significantly reducing the formation of hazardous hydrazoic acid during reaction [19]. Iodine has also been used to catalyze tetrazole formation [20], as ammonium chloride [21], or molten tetrabutylammonium bromide (TBAB) in a solvent-free method [22]. Sulfamic acid was another efficient catalyst for tetrazole formation, and the advantage was the fast reaction speed [23].

The modern method uses metal-based catalysts to facilitate substituted tetrazole formation by reducing the required temperature and reaction time**.** Vorona et al. reported the formation of tetrazole from thermally unstable nitrile derivatives by using zinc chloride in isopropanol at 50 °C [24]. Taherzad et al., utilized a highly efficient catalyst, novel nanocomposites Mx-MoO_3-α-$NaFe_2(MoO_4)_3$-α-$FeMoO_4$ (M = Al, Co, Ni, and Er), to synthesize tetrazole in a short reaction time (<30 min) [25]. Kikhavani et al. used magnetic MCM-41-supported copper nanoparticles to catalyze tetrazole formation in polyethylene glycol. The catalyst can be easily recovered by an external magnet and recycled in a later reaction [26]. In another report, the synthesis of tetrazole using boehmite nanoparticles supported samarium, a reusable catalyst that can be recycled without reactivation [27].

2.2. From aldehydes

The synthesis of 5-substituted tetrazoles from aldehydes is a multicomponent reaction starting from aldehyde derivatives, hydroxylamine hydrochloride and sodium azide with the help of catalyst (Fig. 3). Nickel supported on MCM-41 has been used as a catalyst to facilitate the synthesis of tetrazoles, with the added advantage of being recyclable for at least 5 cycles without significant weight loss, as it can be easily recovered through filtration. Microwave irradiation can significantly

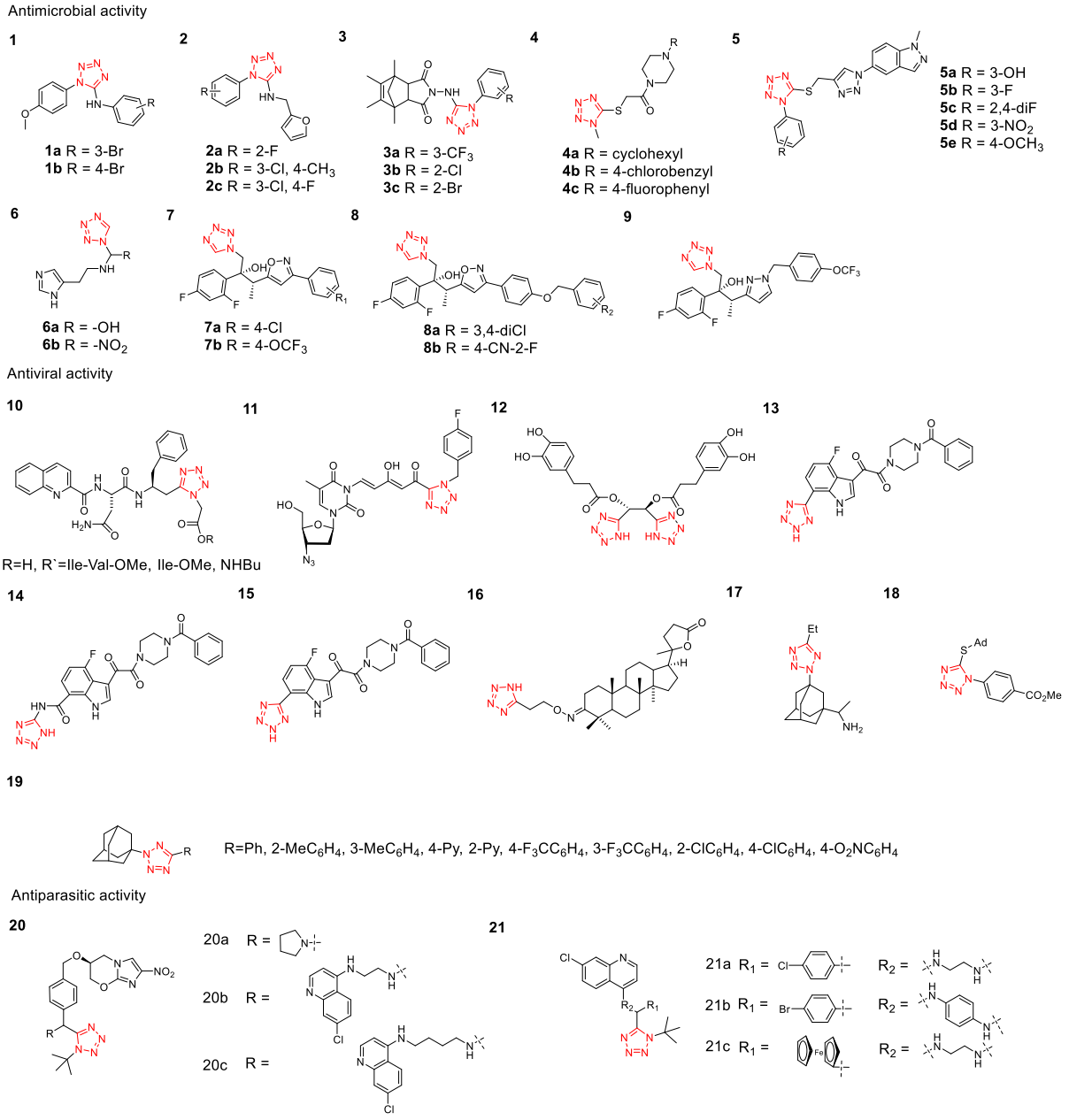


Fig. 4. Published tetrazole-containing antimicrobial, antiviral and antiparasitic agents.

accelerate the reaction rate [28]. Similarly, another two nanocomposites, magnetic nitrogen-doped carbon-based copper (MNC-Cu) and Fe_3O_4–CNT–TEA–Cu (II), were reported as catalyst for tetrazole synthesis, with the catalysts possessing high recoverability and reusability [29,30]. Humic acid has been reported as an inexpensive and environmentally friendly catalyst for tetrazole synthesis in water [31].

2.3. From isocyanides

Isocyanide can be used to synthesize 1-substituted tetrazoles directly (Fig. 3). Jin et al. reported the synthesis of 1-substituted tetrazole from isocyanide and trimethylsilyl azide ($TMSN_3$) in methanol with hydrogen chloride as catalyst [32]. Similarly, this reaction can be conducted in the acidic solvent 2,2,2-trifluoroethanol without using hydrogen chloride [33]. Other Lewis acids, such as zinc bromide [9] and gold ions [34], can also be effective in 1-substituted tetrazole synthesis. Pharande and his co-workers utilized ultrasound-assisted reaction to catalyze tetrazole formation, and the advantage is the mild condition and simple purification method [35].

2.4. From amines

Amine derivatives are another starting material for 1-substituted tetrazole synthesis, and sodium azide and triethyl orthoformate are common reagents for this reaction (Fig. 3). This reaction can be conducted in acetic acid without a catalyst [36]. Alternatively, the use of silica sulfuric acid (SSA) as a catalyst allows for the reaction to be carried out under solvent-free conditions [37] and silica-based boron sulfuric acid (BSA) can be used in polyethylene glycol to enhance the synthesis [38]. Both catalysts can be easily separated by filtration and regenerated at 80 °C for reuse. Nanoparticles can also serve as catalysts; for instance, $Fe_3O_4SiO_2$-Im (Br)-SB-Cu (II) nanoparticles have been used for efficient and recyclable tetrazole synthesis in water, even accommodating thermally unstable starting materials with the reaction conducted at 40 °C

[39].

2.5. From aryldiazonium salts

An efficient one-pot sequential method has been reported for directly synthesizing 2,5-disubstituted tetrazoles using aryldiazonium salts and amidine (Fig. 3) [40]. This method offers the advantage of short reaction time and mild conditions and is readily scalable to gram-scale production.

3. Tetrazole containing drugs against microbes

Tetrazole-containing drugs have emerged as pivotal agents in combating various microbial infections. They serve as potent antimicrobial agents, effectively targeting and inhibiting the growth of bacteria and fungi. Additionally, tetrazoles demonstrate significant antiviral and anti-parasitic activities, showcasing their versatility in addressing various microbial pathogens. Their insecticidal properties further enhance their therapeutic potential, particularly against vector-borne diseases. Beyond their direct antimicrobial actions, tetrazoles are important as drug leads in medicinal chemistry. Their distinctive structural characteristics and bioisosteric properties make them invaluable in drug design, facilitating the development of innovative and targeted therapies against microbial infections.

3.1. Antimicrobial agents containing tetrazole

Antimicrobial resistance has been a significant public health threat due to misuse and overuse of antimicrobials. Antimicrobial resistance directly led to 1.27 million deaths in 2019, and it is estimated that antimicrobial resistance could lead to 10 million deaths by 2050 if no actions are implemented [41]. As such, there is a need to develop novel antibiotics to overcome the current antimicrobial resistance crisis. However, antibiotic discovery is challenging, and no new classes have been marketed since 1987 [42]. Until novel antimicrobials are developed, current antibiotics have been modified to improve their activity and physical-chemical properties to overcome the issue. Tetrazole derivatives has been applied in cephalosporin, oxazolidinone and azole class antibiotics to improve their efficiency and stability as well as permeability [43]. Besides, tetrazole scaffolds have been widely used in novel antimicrobial discoveries, which are summarized in several already published reviews [44–47]. Therefore, to avoid repetition, we focus mainly on the antimicrobial activity of tetrazole derivatives reported since 2020.

Szulczyk et al. reported a new class of tetrazole-containing antitubercular agents (Fig. 4), and compounds **1a** and **1b** showed up to 16-fold more potent growth inhibitory effect against multidrug-resistant *Mycobacterium tuberculosis Spec. 210* compared to first-line tuberculostatics, including isoniazid, rifampicin and ethambutol [48]. Both showed an antimycobacterial selective impact as neither showed antibacterial activity against *Staphylococcus epidermidis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae* and *Proteus vulgaris* (MIC >256 μg/ml). Subsequent modifications were made to the substituted group on the tetrazole ring to enhance its antibacterial activity. Compounds **2a, 2b** and **2c** showed antibacterial activity against several hospital strains, including gram-negative strain *E. coli* and gram-positive strain *S. epidermidis* (MIC 2–32 μg/ml). Compound **2a** was noncytotoxic against mammalian cell lines, indicating the potential application of this tetrazole scaffold as an antibacterial agent [49,50]. Roszkowski et al. reported an imide-tetrazole scaffold exhibiting broad-spectrum antibacterial activity (Fig. 4) [6]. Compounds **3a**, **3b** and **3c** exhibited excellent antibacterial activity against *S. aureus*, *S. epidermidis*, *E. coli* and *P. aeruginosa* (MIC 0.4–25.6 μg/ml) and especially in the case of compound **3c**, it showed a better activity (MIC 0.1–0.2 μg/ml) than ciprofloxacin (MIC 0.125–0.5 μg/ml) against several *S. aureus* strains. A mechanism study determined that these compounds inhibited bacterial gyrase and topoisomerase IV, which could explain their antibacterial activity. Another series of tetrazole--*S*-alkyl derivatives were reported to have antimicrobial activity [51]. Compounds **4a** and **4b** showed antifungal activity (MIC 3.9–7.8 μg/ml) as potent as voriconazole (MIC 3.9 μg/ml) and fluconazole (MIC 7.8 μg/ml) against *Candida krusei*. Compound **4c** exhibited antibacterial activity against *Enterococcus faecalis* with MIC 3.9 μg/ml. Cytotoxicity was tested againstL929 fibroblast cells, and after 48 h of treatment with 100 μM test compounds, **4c** showed 73 % viability, with the other being more than 80 %.

Several 1,2,3-triazolyltetrazole-bearing indazole scaffolds have been reported with potent antimicrobial activity [52]. Compounds **5a-5d** exhibited a broad-spectrum antibacterial activity against gram-positive (*S. aureus*, *Bacillus subtilis*, *Micrococcus luteus*) and gram-negative bacteria (*E. coli*, *P. aeruginosa*) (MIC 5–18 μg/ml) compared with the standard gemifloxacin (MIC 6–10 μg/ml). Compound **5d** also exhibited antifungal activity against *Microsporum gypseum* (MIC 11 μg/ml), as potent as itraconazole (MIC 10 μg/ml). Compound **5e** showed a similar antifungal activity against *Aspergillus flavus* (MIC 10 μg/ml) compared with itraconazole (MIC 8 μg/ml). A tetrazole *N*-Mannich base scaffold is another promising antimicrobial lead structure for future modification [53]. Compounds **6a** and **6b** exhibited a broad-spectrum antibacterial activity against gram-positive strain *S.aureus* (MIC 2–4 μg/ml) and gram-negative strains *E. coli*, *P. aeruginosa*, *K. pneumoniae* and *E. faecalis* (MIC 4–32 μg/ml). Both also showed antifungal activity (MIC 2–32 μg/ml) against *Aspergillus niger*, *Candida albicans*, *Cryptococcus neoformans* and *Microsporum audouinii*. Compound **6b** showed a better antifungal activity (MIC 2 μg/ml) than clotrimazole (MIC 4 μg/ml) against *C. neoformans*. Considering the broad antimicrobial activity and novel structure of compound **6b**, it could be a lead compound for future modifications. Ni et al., reported a tetrazole-isoxazole scaffold as potent antifungal agents [54]. Compounds **7** and **8** (Fig. 4) exhibited broad-spectrum antifungal activity (MIC 0.008–8 μg/ml) against seven fungi including *Candida tropicalis*, *C. albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida auris*, *C. neoformans* and *C. krusei*. Especially, compound **7b** exhibited superior antifungal activity (MIC <0.008 μg/ml) compared to posaconazole, voriconazole and oteseconazole against fluconazole-resistant *C. albicans, C. glabrata* and *C. auris*, and an *in vivo* efficacy study confirmed the broad-spectrum antifungal activity of compound **7b** against *C. albicans* and *C. neoformans* in a ICR mouse of *C. albicans* SC5314 infection. Compound **7b** showed low cytotoxicity, high selectivity index (>4000), and a low risk of drug-drug interactions as no inhibition of human CYP3A4 (IC_{50} > 100 μM), which is responsible for more than 50 % of medicine metabolism. Therefore, compound **7b** was selected for further investigation. The modification was done by replacing the isoxazole core with a pyrazole group (Fig. 4) [7]. Compared with compound **7b**, compound **9** exhibited improved antifungal activity against the seven strains mentioned above with MIC ranging from <0.008 to 0.0625 μg/ml. Among the seven test strains, **9** showed 4-fold, 31-fold and 1000-fold improved antifungal activity against *C. tropicalis*, *C. neoformans* and *C. krusei*, respectively. Compound **9** showed no inhibition of human CYP1A2 and low inhibition of human CYP3A4, which indicates the potential application of tetrazole-pyrazole derivative as an antifungal agent. Compounds **7b** and **9** exhibited good antimicrobial activity and low toxicity, making them promising drug candidates for further clinical trials.

3.2. Antivirals containing tetrazole

It was reported that there were 39 million people living with HIV in 2022 with 630,000 HIV related death [55]. Besides, coronaviruses have raised concern for public health, especially for SARS-CoV-2 infection. Therefore, it is imperative to develop novel and broad-spectrum antiviral agents to face the increasing virus' challenge. The tetrazole moiety is commonly used in the development of antiviral drugs to improve their physico-chemical properties and enhance the activity [56,57],

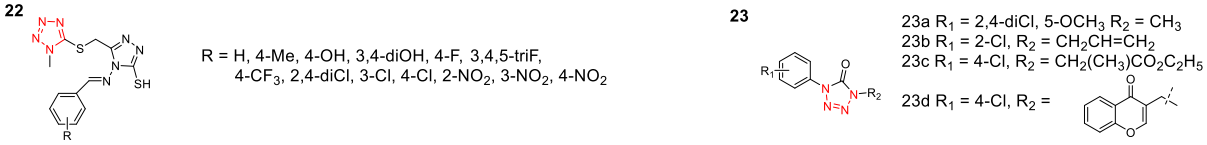


Fig. 5. Tetrazole-based compounds with insecticidal activity.

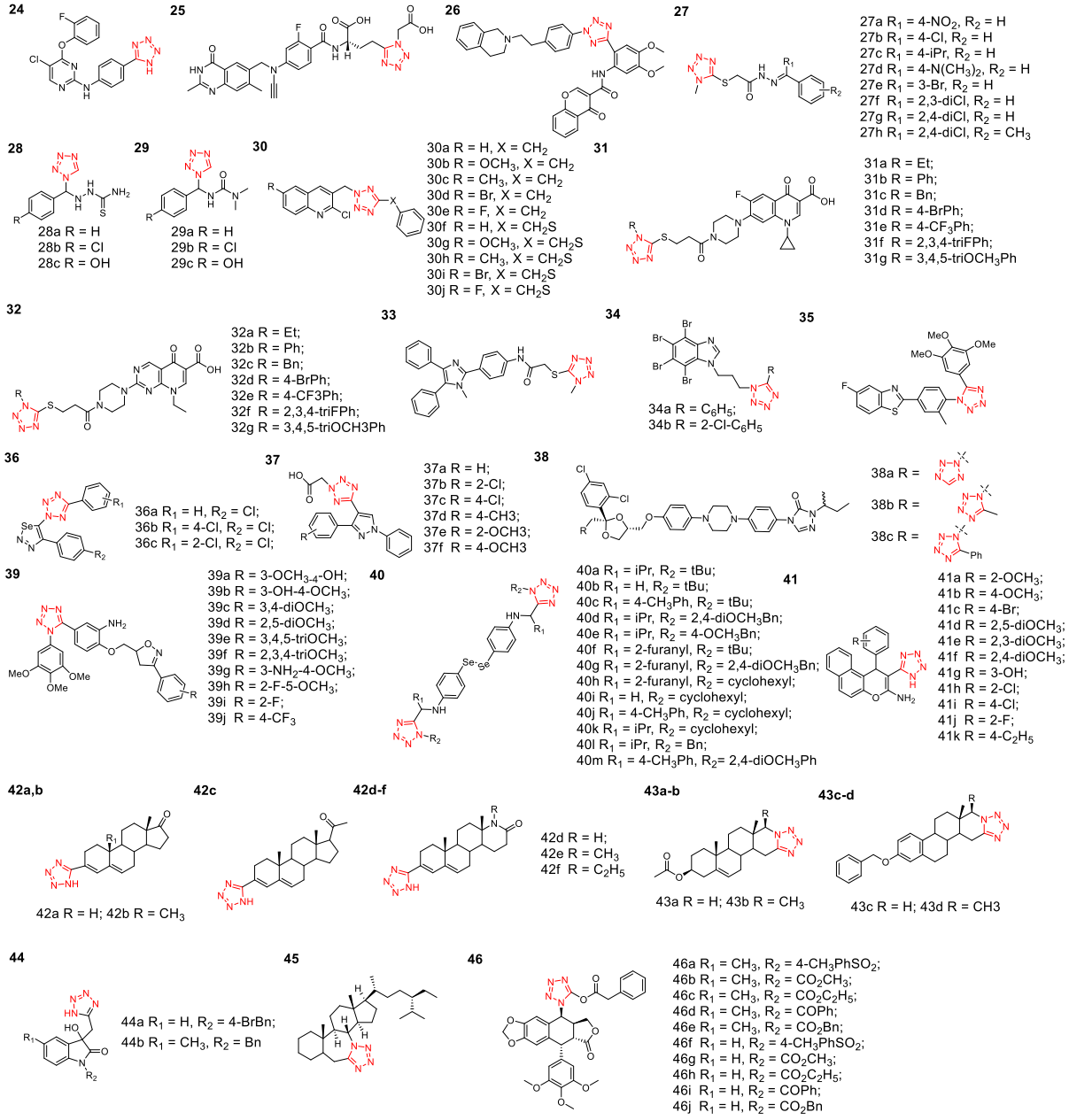


Fig. 6. Selected lead molecules containing a tetrazole moiety with anticancer activity.

especially in modifying natural compounds such as nucleosides, peptides, terpenes, or hybrid molecules containing other pharmacophores (e.g. indolyl, adamantyl) [58,59]. For example, replacing the azide group in the HIV reverse transcriptase inhibitor azidothymidine with tetrazole moiety improves metabolic stability.

Peptidomimetics with the nonhydrolysable tetrazol-1,5-diyl **10** are HIV protease inhibitors (IC_{50} = 18 μM) [60]. Tetrazole-containing nucleoside analog **11** displays similar activity with low toxicity [61]. In addition, L-chicoric acid derivatives with tetrazol-5-yl fragments have anti-HIV activity. Compound **12** (Fig. 4) is the most promising compound with better values of activity (EC_{50} = 0.06 μM) than L-chicoric acid (EC_{50} = 0.81 μM) [62]. Further, derivatives of amino acids and peptides containing tetrazole can possess activity, *inter alia,* against hepatitis C protease [56,63]. Moreover, tetrazole-containing 4-fluoro-1-H-indoles (**13, 14**) are highly effective with low cytotoxicity [64,65], and **15** is active against the tropic virus [66]. Dammarane-type

triterpenoid **16** [67], as well as tetrazole derivatives with the adamantanyl moiety (**17**–**19**) exhibit potent activity against H1N1 influenza A virus [65,68]. Interestingly, some exhibit superior activity compared to the well-known rimantadine and its derivatives while being less toxic [68]. Besides, combinations of tetrazoles with 1,2,3-triazoles have demonstrated inhibition of the main protease of SARS-CoV-2 [69].

3.3. Anti-parasitic activity of tetrazole derivatives

Parasites live on or inside another organism (host) and derive nutrients at the host's expense. Parasitic diseases are a significant global health concern, particularly in developing countries with limited access to clean water and healthcare facilities. They account for approximately 30 % of the world's population. Some common parasitic diseases include malaria (affecting over 200 million people per year), schistosomiasis (affecting 1.5 billion people globally), and soil-transmitted helminthiasis (affecting over 240 million people worldwide). As the impact of parasitic infections on global health is significant, there is an urgent need to design drugs for treatment strategies. Indeed, quinoline-based compounds bearing tetrazole moieties are essential antimalarial drugs. Combining quinolines' antimalarial effects with tetrazole substituents enhances drug efficacy and reduces resistance (compounds **20**–**21** in Fig. 4). These compounds offer improved bioavailability and targeted delivery and inhibit multiple stages of the *Plasmodium* parasite, promising advanced and effective malaria treatments [43,70,71].

4. Insecticidal activity of tetrazole derivatives

Tetrazole-containing compounds exhibited insecticidal activity, positioning them as valuable agents in insect pest management. They demonstrate efficacy against diverse insect species, offering promising solutions for sustainable and effective insect control strategies. As such, hybrid compounds such as (1-methyl-1H-tetrazol-5-yl)thiomethyl)-4H-1,2,4-triazole-5-thiol derivatives (compound **22** in Fig. 5) are good examples of compounds with activity against *Plodia inter-Punctella*, also known as Indian meal moth or pantry moth [72]. Compound **23** showed good insecticide activity against *Tetranychus cinnabarinus* at 250 mg/L with at least 98.6 % killing [73].

5. Antiproliferative agents containing tetrazole

Cancer is a leading cause of mortality worldwide, regardless of the level of countries' wealth. It counts for nearly 10 million annual deaths worldwide, i.e. 1 in 6 deaths [74]. Despite hundreds drugs and immune therapies for cancer, they have severe drawbacks due to the lack of differentiation between normal and cancer cells [75]. In addition, cancer cells become resistant to chemotherapeutic agents to an alarming level due to multidrug resistance [76]. Hybrid molecules could offer a solution by integrating tetrazoles with pharmacophores that possess anticancer properties. This innovative strategy holds the potential for developing advanced anti-cancer candidates that enhance efficacy and lower toxicity [76]. Some representative compounds are collected in Fig. 6, but most have only been screened in cancer cell lines, which needs more investigations for their toxicity in normal cells. The tetrazole-pyrimidine hybrids **24** (Fig. 6, IC_{50} = 0.012 nM) have strong inhibitory activity against aurora kinase A (AKA), IC_{50} = 0.012–0.438 nM. Notably, the overexpression of this kinase is observed in several cancers [77]. The tetrazole-pyrimidone **25** has high activity towards thymidylate synthase (TS) enzyme (IC_{50} = 2.4 nM) and L1210 cell (IC_{50} = 1.2 μM, Fig. 6) [62]. Encequidar (HM30181, **26,** Fig. 6) is a novel promising P-glycoprotein inhibitor (P-gp - multidrug resistance protein 1/MDR1) that enhances the oral bioavailability of Pgp substrate drugs (e.g. paclitaxel) [78]. Interestingly, encequidar is significantly more potent (IC_{50} = 35.4 nM) than tariquitar, another new-generation P-gp inhibitor [79].

Arshad et al. identified that tetrazole-hydrazone hybrids **27** exhibit efficacy against the MCF-7 breast cancer cell line, as well as moderate activity against the A549 cell line (lung adenocarcinoma) with an IC_{50} range of 100–800 μM when compared to cisplatin (IC_{50} = 31.6 μM), with **27b** (Fig. 6) as a lead compound (IC_{50} = 100 μM). It demonstrated acceptable cytotoxicity against the NIH3T3 cell line (IC_{50} = 2100 μM) [80,81]. Ahamed et al. identified tetrazole-thiosemicarbazides **28** (especially **28a**, Fig. 6) as being more active than the tetrazole-urea analogs **29** towards liver (HepG2), cervical (HeLa), and breast (MCF-7) cancer cell lines (Fig. 6) [82].

Potent tetrazole-quinolone hybrids such as 3-[(5-benzyl/benzylthio-2H-tetrazol-2-yl)methyl]- 2-chloro-6-substituted quinolines are shown as **30** (Fig. 6). The tetrazole-phenyl linker has a favourable, whilst thio- – disfavourable influence on the activity. The attachment of the methoxy group for the *R* position results in improved activity (**30b**, Fig. 6) against several cancer cell lines. The order of electron-donating groups is as follows: methoxy > hydrogen > methyl > bromo > fluoro [83]. These structure-activity relationship with primary cytotoxicity data created a base for further investigations. In addition, the ciprofloxacin-tetrazoles **31** and pipemidic acid tetrazoles **32** showed antiproliferative activity against cervix (SiHa), breast (MDAMB-231), and pancreatic carcinoma cell lines, with some showing superior effects compared to tamoxifen. Compounds **31d-g**, bearing substituents on the tetrazole moiety, were more potent than their analogs **32d-g** (Fig. 6) with enhanced growth inhibition [84,85].

Ozkay et al. synthesized tetrazole-imidazole **33** hybrids (IC_{50} = 4.5 μM) with anti-proliferation activity against breast (MCF-7) and colon (HT-29) cancer cell lines comparable to cisplatin (IC_{50} = 2.6 μM) (Fig. 6), [86]. In addition, Chojnacka et al. designed tetrazole-containing benzimidazole and benzotriazole derivatives. Compound **34** exhibited high toxicity on leukemia cell lines (CCRF-CEM) and lower cytotoxicity towards breast cancer cell lines (MCF-7). Increasing the compound concentration (25 μM) and treatment time to 48 h caused near complete loss of cell viability (<1 %) in CCRF-CEM cell line [87]. Rao et al. studied tetrazole-benzothiazole hybrids **35**, derivatives of the natural compound combretastatin A-4, with promising activity (IC_{50} = 0.24–31.62 μM). While combretastatin A-4 is an effective antimitotic agent from the South African willow tree, it suffers from light-induced isomerisation. Tetrazole-based analogs, **35**, displayed notable activity against various cancer types but were generally less potent than combretastatin A-4. Thus, the development of derivatives incapable of isomerisation were needed. The replacement of the olefin bridge by a five-membered heterocyclic linker was one of the strategies investigated. Tetrazole-based analogs (**35**, IC_{50} = 0.24–3.23 μM, Fig. 6) demonstrated anti-proliferative activity to human prostate (DU-145), cervix (HeLa), lung (A549), liver (HepG2), and breast (MCF-7) cancer cell lines. However, they were similar to or less active than combretastatin A-4 (IC_{50} = 0.005–0.069 μM) [88].

Kanakaraju et al. synthesized tetrazole-1,2,3-selenadiazole hybrids **36**: molecules **36a-c** (IC_{50} = 43.19–74.78 μM) displayed considerable activity towards liver (Hep G2) and breast (MCF-7) cancers, while other derivatives were inactive. The most active **36b** (IC_{50} = 43.19 μM when R_1═Cl, and 74.78 μM when R_2═Cl) was not inferior to cisplatin (IC_{50} = 33.69 and 21.69 μM, respectively, Fig. 6) [89]. Ravula et al. indicated tetrazole-pyrazole hybrids **37** (IC_{50} = 6.43–86.26 μM) active against colon (HT-29) and prostate (PC-3) cancers when activity order, in the context of substituents, is chloro > methoxy > methyl. Besides, substituent location also has relevance – para-is more suitable than ortho-position. Compound **37c** (IC_{50} = 6.43 μM, Fig. 6) is the most active molecule with bio-properties similar to Doxorubicin (IC_{50} = 2.24 μM, Fig. 6) [90]. Pasunooti et al. indicated that itraconazole derivatives **38** inhibited human umbilical vein endothelial cell proliferation through inducing Niemann-Pick C phenotype and blocking AMPK/mechanistic target of rapamycin signaling [91]. Notably, new molecules are more active than Itraconazole, which is a significant drawback related to its potent inhibition of human liver cytochrome P450 3A4 (CYP3A4), which can result in severe drug-drug interactions with other anticancer

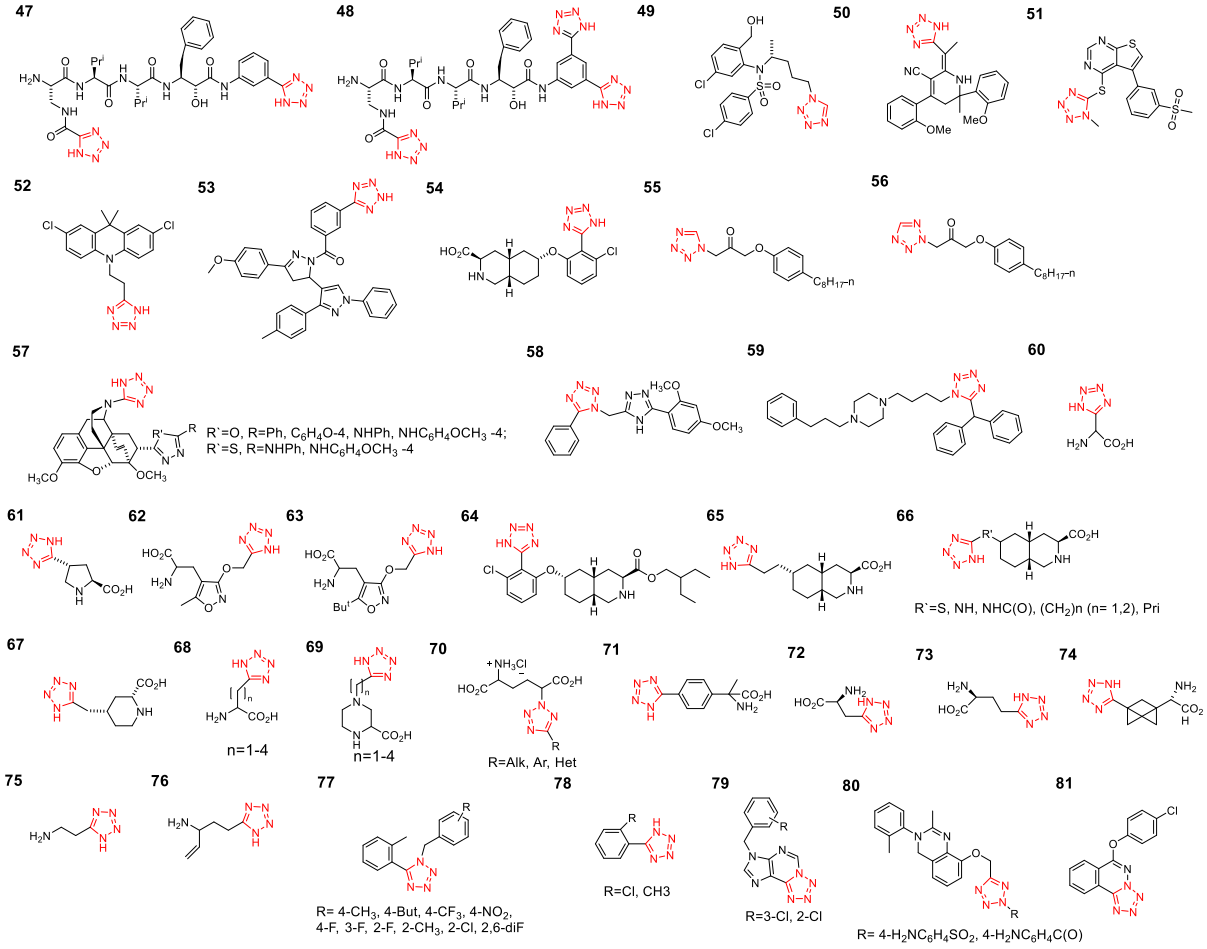


Fig. 7. Selected lead molecules containing tetrazole moiety with action on the central nervous system.

drugs. However, tetrazole-contained derivatives show lower inhibition on CYP3A4 and significant inhibition of human umbilical vein endothelial cell (HUVEC) proliferation (IC_{50} = 73–124 nM; IC_{50} for itraconazole is 170 nM). The introduction of methyl (**38b**) or phenyl (**38c**) on the tetrazole scaffold decreased the activity but increased CYP3A4 inhibition in comparison to the unsubstituted compound (**38a**). In addition, **38a** is the most active promising anticancer agent (IC_{50} = 73 nM). Noteworthy, its regioisomer is less active [92].

Kamal et al. synthesized isoxazoline-tetrazoles **39** (IC_{50} = 1.22–3.22 μM), which showed anti-cancer activity in the breast (MDA-MB-231) and lung adenocarcinoma (A549) cell lines *in vitro*. Compounds **39i-k** (IC_{50} = 1.22–2.40 μM), containing electron-withdrawing groups, exhibited a superior anticancer effect compared to **39a-h** (IC_{50} = 1.51–3.62 μM), which have electron-donating groups (Fig. 6). These molecules inhibit tubulin polymerisation, potentially serving as novel tubulin polymerisation inhibitors [93]. Shaaban et al. identified diselenide-tethered dimers **40** (IC_{50} = 2–88 μM), with **40d** as a lead compound (Fig. 6), that displayed cytotoxicity to the liver cancer cell lines (HepG2, IC_{50} 2 μM), but less cytotoxicity to lung fibroblast cell line (WI-38, IC_{50} 64 μM), and were more active than 5-fluorouracil (IC_{50} = 3–8 μM) [94].

The tetrazole-benzochromene hybrids **41**, with the most potent **41f** (IC_{50} = 15–26 μM, Fig. 6) - the same level as that of 5-fluorouracil, showed improved activity (IC_{50} = 10–17 μM) on cancer cell lines of breast (MCF-7 and SKBR-3), colon (Caco-2), and cervix (HeLa). The dimethoxy-substituted phenyl ring confers activity and potency: dimethoxy > methoxy > fluoro > chloro > bromo [76,95]. Aggarwal et al. examined steroid-tetrazoles as inhibitors of 5alpha-reductase in the context of benign prostate hyperplasia. Hybrid **42c** (Fig. 6) is a potent dual inhibitor for 5-alpha-reductase type 1 and 5-reductase type 2 isoenzymes (IC_{50} = 547 and 15.6 nM, respectively), with activity like finasteride (IC_{50} = 204.20 μg mL^{-1}). The increased inhibition against 5alpha-reductase type 2 was observed in hybrids: **42c** (IC_{50} = 15.6 nM) > **42a,b** (IC_{50} = 83.8 nM) > **42d-f** (IC_{50} = 157–273 nM). Compounds **42b** and **42e-f** have a slightly better activity (IC_{50} = 174.40–195.10 μg mL^{-1}) than finasteride (IC_{50} = 15.6 nM) towards prostate cancer DU-145 cells (Fig. 6) [96].

Hybrids **43a,b** (IC_{50} = 12.63 and 4.58 μM) are more active than their analogs **43c,d** (IC_{50} = 56.23 and 25.45 μM, respectively) against breast cancer cell line (MCF-7), while **43c,d** (IC_{50} = 11.09–78.96 μM) were more potent on a prostate cancer cell line (PC3) and myelogenous leukemia 35 (K562) compared to **43a** (IC_{50} = 65.45–100 μM) [97]. Compound **43c** (Fig. 6) exhibits greater potency (IC_{50} = 15.32 μM) against a prostate cancer cell line compared to doxorubicin (IC_{50} = 95.61 μM), indicating its potential for further development. Most importantly, compound **43a-d** showed no antiproliferative activity against normal fetal lung fibroblast (MRC-5) cells at highest test concentration (IC_{50} > 100 μM). Hou et al. evaluated tetrazole-isatin hybrids **44** (IC_{50} = 4.26–100 μM, Fig. 6) as quite effective against diverse cancers such as breast (BT549 and MDA MB231), prostate (PC3 and DU145) and ovarian (PA1) cancer cell lines. Compounds **44a** and **44b** had good activity (IC_{50} = 10.13 and 7.01 and 11.71 and 4.26 μM against PC3 and DU145, respectively) towards prostate cells that was a few times better than 5-fluorouracil, and compound **44a** showed a less toxicity on human normal prostate epithelial (RWPE-1) cells (IC_{50} 75.97 μM) [75,97]. The 7-alpha-aza-B-homo stigmast-5-eno [7*a*,7-*d*]tetrazole **45** (Fig. 6) exhibited anticancer activity against HCT116 (IC_{50} = 4.58 μM) and HepG2 (IC_{50} = 4.82 μM) cancer cell lines, which is similar to

doxorubicin (IC_{50} = 2.60 and 2.85 μM, respectively) and showed no inhibition to human lung fibroblast HFL1 at highest test concentration 25 μM [98]. Tetrazole-podophyllotoxin hybrids **46,** with **46e** (Fig. 6) as a lead agent (IC_{50} = 2.48–4.85 μM, Fig. 6), were active against diverse cancer cell lines, such as SK-N-SH, A549, HeLa and MCF-7 (IC_{50} = 2.4–9.44 μM, in comparison: activity of doxorubicin is 6.13–12.34 μM) [99,100].

Given the discussed advantages, there is a robust foundation for developing tetrazole-containing anticancer drugs. Several have FDA approval, others are in clinical trials, and many are undergoing initial bio-evaluation.

6. Other classes of pharmaceutics containing tetrazole groups

Tetrazole containing compounds exhibit multifaceted actions, from influencing the central nervous system to combating inflammation and oxidative stress. From analgesics to antidepressants, anti-inflammatory agents to anti-thrombotics, they hold promise across various therapeutics. They also show benefits in cardiovascular health, diabetes management, asthma, including their role as protein modifiers for elucidating intricate biological mechanisms. In this chapter, we mainly focus on the published tetrazole-containing drug candidates and approved drugs will be summarized in chapter 7. These are described further below.

6.1. Action on the central nervous system

Tetrazole-containing compounds have been used to treat neurological diseases for several decades [64]. Neurological disorder-related deaths have increased by ~40 % over the past three decades and are projected to double by 2050. Current treatments offer limited benefits and often cause severe side effects [101]. The beta-amyloid peptide, a critical factor in Alzheimer's disease [102], is produced from its precursor by two enzymes. Beta-secretase is a primary target for therapeutic agents, while acetylcholinesterase and butyrylcholinesterase inhibition can alleviate Alzheimer's symptoms [64]. Tetrazole compounds are promising inhibitors of beta-secretase. Pentapeptides **47** and **48** containing terminal tetrazol-5-yl moieties are good examples (IC_{50} = 4.8 and 1.2 nM, respectively, Fig. 7) [103,104]. The 5-unsubstituted 1H-tetrazole derivatives **49** and some 1,5-disubstituted tetrazoles (IC_{50} = 0.51 nM), in the group of heterocyclic and acyclic N-alkyl sulfonamide derivatives, are effective inhibitors of gamma-secretase, which is involved in beta-amyloid synthesis [105]. Compound **50** (Fig. 7) is a selective butyrylcholinesterase inhibitor, with activity similar to donepezil and neostigmine (IC_{50} = 0.290 μM, Fig. 7) [106].

Phosphatidylinositol-5-phosphate 4-kinase, type II ɣ (PIP4Kɣ), is described as a potential target for Huntington disease, an autosomal dominant neurodegenerative disorder with practically no curative or preventative treatment strategies. NCT-504 (**51**, Fig. 7) is under preclinical studies as an allosteric inhibitor of PIP4Kɣ [107]. Moreover, the compounds in the pre-clinical phase, such as K+ channel activator ML-6733 (**52**, Fig. 7) [108] and Ca + channel inhibitor BTT-369 (**53**, Fig. 7) are noteworthy [109].

6.1.1. Analgesic drugs

Tetrazol-5-ylphenoxydecahydroisoquinoline, such as lead compound LY545694, **54** (Fig. 7) exhibit analgesic activity as glutamate receptor antagonists based on two pain models (both GluK1 and GluA2 receptors) [110]. Isomers 1-tetrazolyl-1-aryloxypropan-2-ones, including **55** and **56**, are potent fatty acid amide hydrolase inhibitors with IC_{50} = 0.039 and 0.010 μM, respectively. Fatty acid amide hydrolyses the endocannabinoid anandamide; thus, inhibiting it can elevate brain anandamide levels, resulting in analgesic and anxiolytic effects [111]. Morpholine alkaloid compounds act as analgesics targeting opioid receptors with N-(tetrazol-1H-5-yl)-6,14-endoethenotetrahydrothebaine derivatives showing promising analgesic activity, with **57** as a notable example [112]. Compound **58**, a binuclear heterocyclic compound with 1,2,4-triazole and tetrazole groups, showed activity comparable to ibuprofen (Fig. 7) [113].

6.1.2. Antidepressant activity

Compounds with an alkylated tetrazole can inhibit monoamine oxidase A, offering potential antidepressant and antianxiety effects [114,115]. Monoamine neurotransmitters, like dopamine, norepinephrine, and serotonin, are crucial in neuropsychiatric disorders [116] with serotonin and norepinephrine targeted for depression [116–118], despite their slow initial effect and associated complications [119]. The low remission rate of depression may be due to the slow onset of conventional treatments. A suggested strategy to enhance drug efficacy is combining dopamine with selective serotonin reuptake inhibitors or dual reuptake inhibitors [120,121]. Triple reuptake inhibitors, which target serotonin, norepinephrine, and dopamine reuptake, are gaining interest for their potential to boost dopamine neurotransmission, a feat not achieved by conventional methods [118].

Tetrazole-containing compounds show promise in inhibiting the reuptake of these neurotransmitters. Paudel et al. proposed guidelines for designing such inhibitors, highlighting the importance of linker carbon number (n) between tetrazole and piperidine and suggesting potential compounds for treating neuropsychiatric disorders beyond depression [120,121]. Compound **59** (Fig. 7) showed potent inhibitory effects against three reuptake transporters (IC_{50}, 158.7 nM for 5-HT; 99 nM for NE; 97.5 nM for DA).

6.1.3. Convulsant/analeptic action

(R,S)-(tetrazol-5-yl)glycine **60** (Fig. 7) has similar properties but influences the action of neuronal excitatory glutamate receptors. It is a selective *N*-methyl-*D*-aspartate receptor agonist [122,123]. *Trans*-4-(-tetrazol-5-yl)proline (LY300020) (**61**), IC_{50} = 3.4 μM as well as tetrazol-5-ylmethoxy derivatives of alanine **62**–**63** (with IC_{50} = 17 and 80 μM, respectively) have specific affinity for alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors and may be potential activators of the central nervous system (Fig. 7) [124]. In the context of AMPA receptors, Dasolampanel etibutil (**64**), has completed phase II clinical trial, is either an AMPA or kainate receptor antagonist, which could be a potential drug in chronic pain [125].

6.1.4. Anticonvulsant activity

Tetrazol-5-ylethyldecahydroisoqui-nolinecarboxylic acid (tezampanel, LY-293558) (**65**), kainate (GluK1)/AMPA receptor antagonist, has significant neuroprotective and anticonvulsant effects and has completed phase II clinical trial [126]. Its derivative (**66**) also displays anticonvulsant activity. *Cis*-4-(tetrazol-5-ylmethyl)piperidine-2-carboxylic acid (LY2333053, **67**) is a selective ionotropic N-methyl-*d*-aspartate (NMDA) glutamate receptor antagonist (IC_{50} = 100 nM) [127]. Tetrazolyl derivatives of amino acids **68**–**69** have slightly worse properties (IC50 = 1–10 μM) towards NMDA receptors [128]. 2-aminoadipic acid derivative containing the 5-*R*-tetrazol-2-yl substituent at position 5 (**70**) was identified as a low-toxic NMDA receptor antagonist [129]. (*R, S*)-alpha-methyl-[4-(1H-tetrazol-5-yl)phenyl]glycine (**71**), L-2-amino-3-(1H-tetrazol-5-yl)propionic acid (**72**), L-2-amino-4-(1-H-tetrazol-5-yl)butyric acid (**73**), and 2-[3'-(1H-tetrazol-5-yl)bicyclo [1.1.1]pent-1-yl]glycine (**74**) are examples of metabotropic glutamate receptor antagonists (mGlu) [130,131]. Tetrazolylalkylamines, such as GABA analogs **75** (Fig. 7) or 4-aminohex-5-enoic acid analogs (**76**), which exhibit strong interaction with GABA aminotransferase, are promising anticonvulsant agents [132]. 1-benzyl-5-(*o*-tolyl)-1H-tetrazoles are potential anticonvulsants. Compound **77** has high anticonvulsant activity and low neurotoxicity. NH-unsubstituted tetrazoles bearing an aryl or substituted benzyl group at the cyclic carbon atom, such as 5-aryl tetrazoles (**78**), are the most promising anticonvulsant agents [133]. 7-Benzyl-7H-tetrazolo [1,5-g]purines are potential

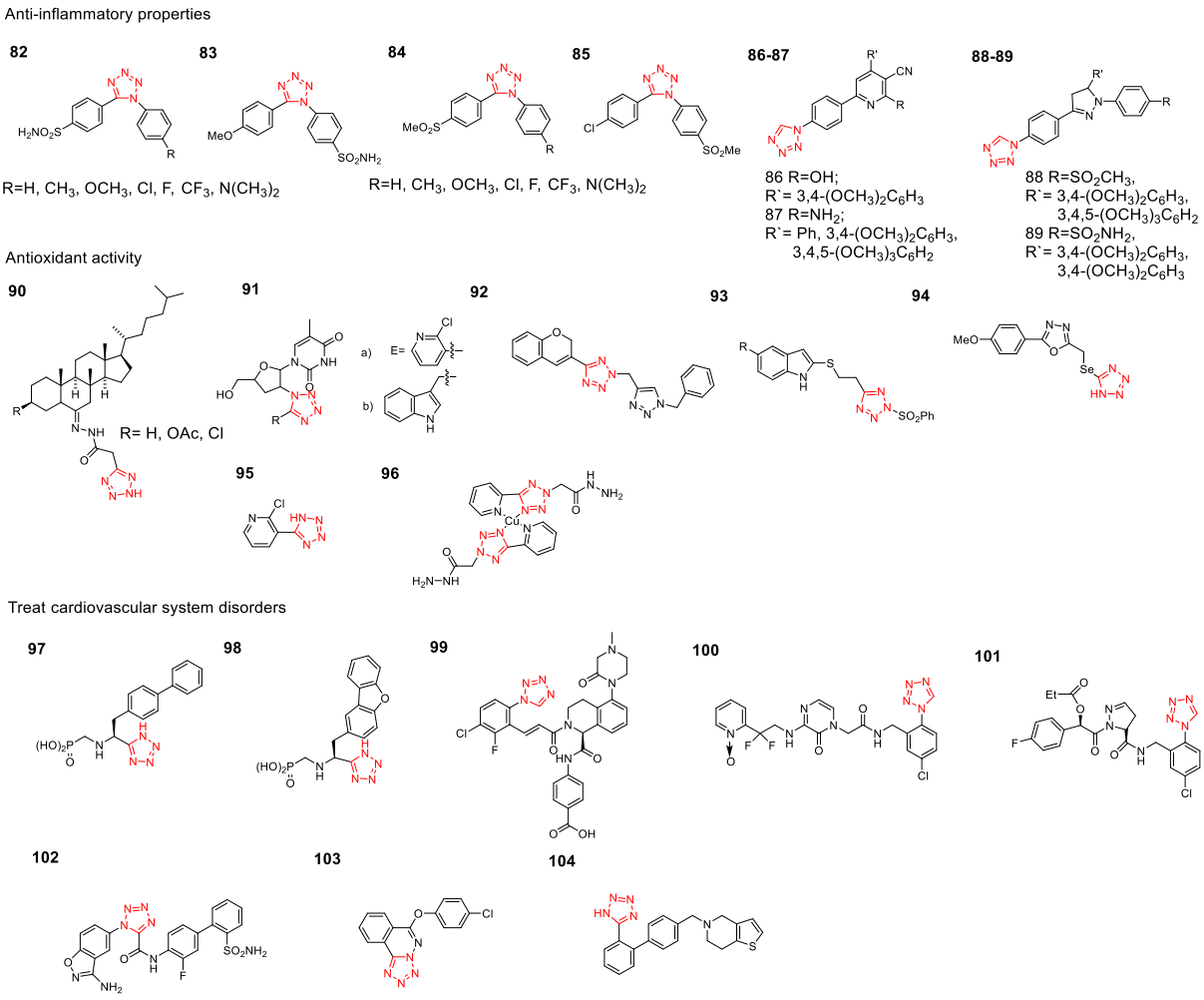


Fig. 8. Selected lead molecules containing tetrazole moiety with anti-inflammatory and antioxidant activities and to treat cardiovascular system disorders.

anticonvulsants and antidepressants. 7-(3-chlorobenzyl)-7H-tetrazolo [1,5-g]purine (**79**) has a better profile (ED_{50} 28.9 mg/kg, protective index 15.8) than carbamazepine (ED_{50} 11.8 mg/kg, protective index 6.4) [134]. Compound **80** is the most promising anticonvulsant drug among tetrazole-containing *o*-tolylquinazolines [10]. 4-(4-chlorophenoxy)-1,2-dihydrotetrazolo [5,1-*a*]phthalazine (QUAN-0808, **81**) is a potential drug with strong anticonvulsant and antidepressant effects that exhibits low neurotoxicity. It has other beneficial properties, including anti-inflammatory, anticoagulant, and antithrombotic activities [135].

6.2. Anti-inflammatory properties

The substitution of a tetrazole in place of a carboxyl group can improve anti-inflammatory activity [136]. The tetrazole scaffold attached to sulfanilamide benzotriazole shows improved anti-inflammatory effects compared to paracetamol, and the anti-nociceptive activity is comparable to pentazocine [137]. Tetrazole-containing compounds act as inhibitors of cyclooxygenases (COX), enzymes involved in synthesizing prostaglandins, prostacyclins and thromboxanes. Compounds **82**–**85** (Fig. 8) mainly inhibit the COX-2 isomer. This inhibition is a key mechanism for the anti-inflammatory activity of non-steroidal anti-inflammatory drugs. The activity of 1, 5-diaryl tetrazoles depends on the nature and positions of substituents in the benzene rings (IC_{50} < 1.5 μM) [138–140]. Polynuclear heterocyclic compounds with tetrazolyl groups, specifically **86**–**89** (Fig. 8), are promising COX-1 or COX-2 inhibitors, showing activity comparable to diclofenac and indomethacin [16].

6.3. Antioxidant activity

Tetrazole analogs of steroids **90** [141], anomalous nucleosides (tetrazolylthymidines) **91** (IC_{50} = 25.87 μg ml^{-1}) [142], 1,2,3-triazolylmethyltetrazoles **92** [143], benzimidazole derivatives **93** [144], 1,3,4-oxadiazole **94** [145], tetrazol-5-ylpyridines **95** (IC_{50} = 27.63 μg ml^{-1}) [146], and copper complex **96** (IC_{50} = 2.82 μg ml^{-1}) [146], reveal potential antioxidant activity. Interestingly, the action of **91** and **95** is similar to butylhydroxytoluene, while **96** (Fig. 8) shows the best antioxidant activity in comparison to butylhydroxytoluene (IC_{50} = 22.92 μg ml^{-1}) [64].

6.4. Treatment of cardiovascular system disorders

Tetrazoles have gained attention for their potential therapeutic applications in treating cardiovascular system disorders. These compounds exhibit diverse pharmacological properties, including vasodilatory effects, antihypertensive actions, and antiplatelet activity. Their unique chemical structure and multifunctional mechanisms make them promising candidates for cardiovascular disease management and treatment, particularly anti-hypertensives and antithrombotics.

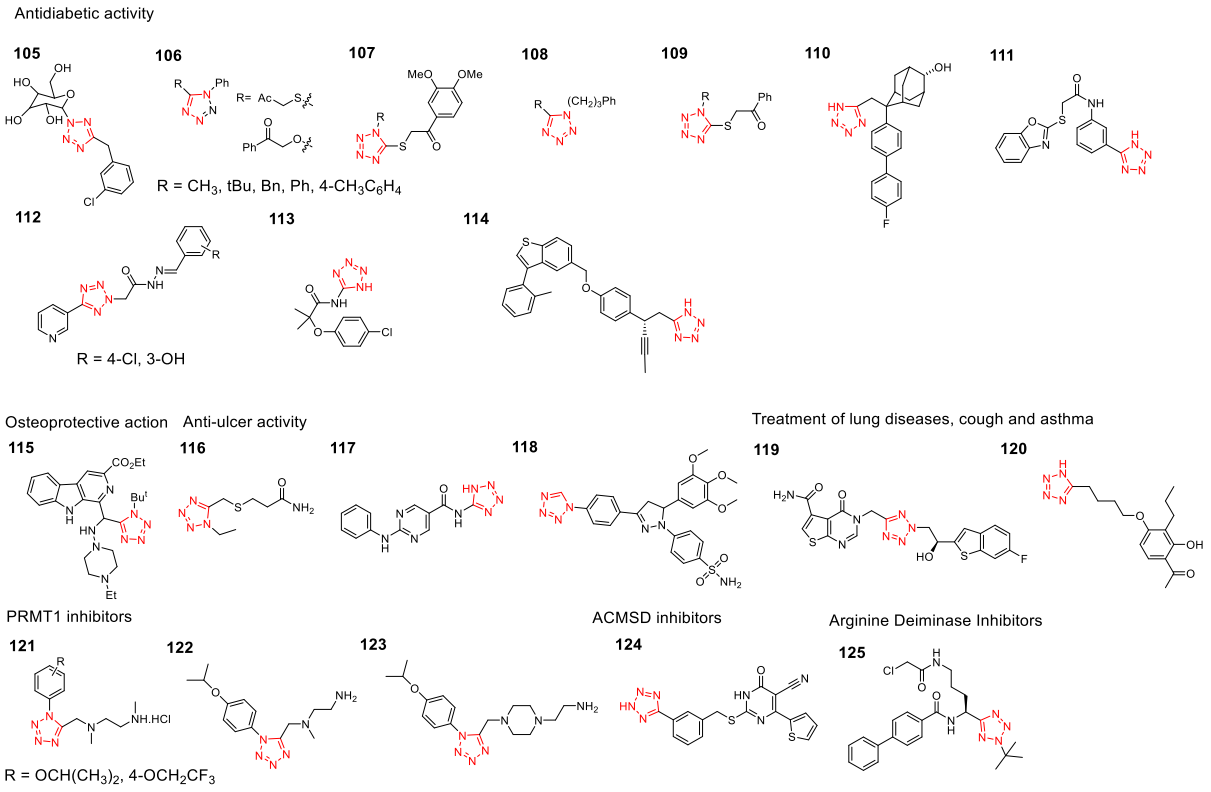


Fig. 9. Selected lead molecules containing tetrazole moiety with other activities.

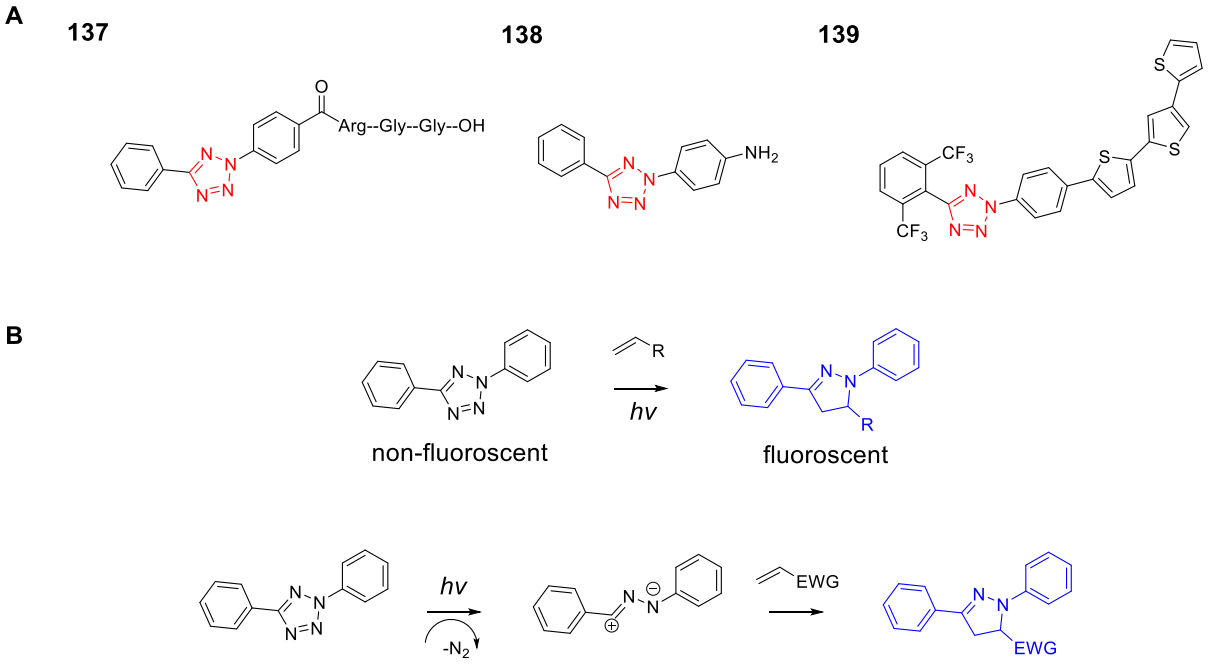


Fig. 10. (A) Selected molecules containing tetrazole moiety as protein-label; (B) general photoclick reaction procedure and the potential mechanism.

6.4.1. Anti-hypertensive activity

Most commercially available tetrazole-containing anti-hypertensive drugs are angiotensin II AT1 receptor antagonists [56,63,147,148]. Tetrazole-based compounds also have different mechanisms of action. They inhibit conversions of the bicyclic peptide endothelin-1, a potent vasoconstrictor, to its active form. Here, endothelin-converting enzyme-like Zn-dependent peptidase is a target. Compound CGS26303 **97** (IC_{50} = 0.9 nM) and its derivative CGS34043 **98** (IC_{50} = 6 nM) are worth noting due to their long-lasting action and high selectivity [149,150].

6.4.2. Anti-thrombotic action

Tetrazole derivatives act as important thrombin inhibitors that are used in the treatment of thromboembolic disorders. Notably, one

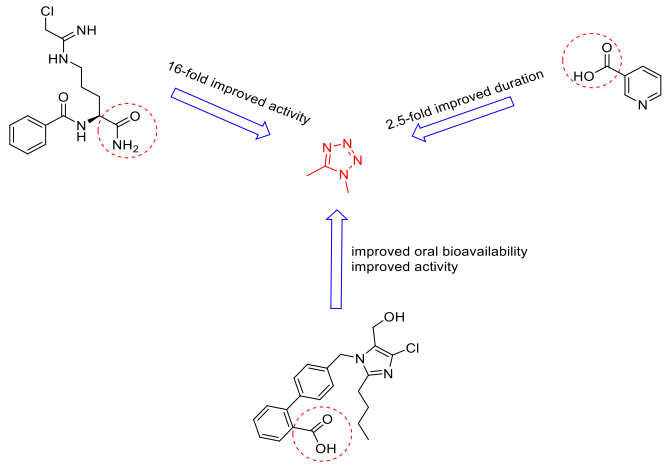


Fig. 11. Advantages of introducing tetrazole motif.

compound (BMS-962212, **99**) is under clinical trials [151]. Both 1-(4-chlorophenyl)tetrazole derivative (**100**) and AZD8165 **101** (Fig. 8) are good examples of potential lead molecules [152,153]. 1-aryl- and 1-hetaryl tetrazoles inhibit serine protease fXa, which triggers the conversion of prothrombin to thrombin. **102** was reported as a lead compound, while **103** – as an antithrombotic and anticoagulant compound [154,155]. Conversely, 5-[2-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5,6,7-tetrahydro-thieno [3,2-*c*]pyridine (**104**), a bioisostere of 4-(6,7-dihydro-4H-thieno [3,2-*c*]pyridin-5-ylmethyl)biphenyl-2-carboxylic acid, reveals high platelet aggregation inhibitory activity similar to clopidogrel [156].

6.5. Anti-diabetic activity

Tetrazole-containing compounds have gained attention for their potential role in anti-diabetic activity. These compounds exhibit promising pharmacological properties that may help in managing type-2 diabetes. Some tetrazole derivatives have been found to enhance insulin sensitivity, improve glucose uptake by cells, and reduce blood glucose levels. They may also exert antioxidant and anti-inflammatory effects, which are beneficial in preventing diabetes-related complications. As such, tetrazole-based compounds **105**–**111**, as well as a series of C- and N-aryl-5-R-tetrazoles (**106**–**108**) and 1-R-5-sulfanyltetrazoles (**109**), are considered as potential 11-beta-hydroxysteroid dehydrogenase (11beta-HSD1) inhibitors, in the treatment of type-2 diabetes. In a group of adamantylmetyl-substituted tetrazoles, **110** (Fig. 9) is the most promising compound (IC_{50} = 3.7 nM) [157–159]. N-[3-(1H-Tetrazol-5-yl)phenyl]-2-(benzo[*d*]oxazol-2-yl)thioacetamide (**120**) revealed the highest activity (IC_{50} = 4.48 μM) against protein tyrosine phosphatase 1B (PTP1B) [160].

Tetrazole-bearing glycoside derivatives have shown potential as inhibitors of sodium-dependent glucose co-transporters [157]. A lead compound, 2-[5-(3-chlorobenzyl)-2H-tetrazol-2-yl]-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol (**114**) has been identified. Polynuclear heterocyclic compounds with 3-pyridyltetrazol-6-yl and aryl groups linked by an acetohydrazide linker were assessed, with **112** demonstrating the highest activity [160]. Notably, compound **113** was highlighted as a bioisostere of clofibric acid, being less toxic and greater activity (IC_{50} = 10 μM) than both the acid and its ethyl ester [161,162]. Compound **114** is particularly noteworthy for its potential as a GPR40 receptor agonist in studies on the anti-diabetic activity of tetrazole-substituted benzo [*b*]thiophene derivatives [163].

6.6. Osteoprotective action

Tetrazole-containing compounds have demonstrated osteoprotective effects, showing potential in preventing and treating bone-related disorders and promoting bone health through various pharmacological mechanisms. In this context, the tetrazole-based compound **115** has activity similar to the natural bone-sparing hormone 17-beta-estradiol [164].

6.7. Anti-ulcer activity

Tetrazole-containing compounds have shown promising anti-ulcer activity, suggesting their potential as therapeutic agents in treating and preventing gastric ulcers and related gastrointestinal disorders. Tetrazole-based compounds with anti-inflammatory and cytoprotective properties have been studied for their potential anti-ulcer effects. Uchuda et al. tested tetrazole alkanamides in the context of their gastric mucosal protective activity. 3-[(1-ethyl-5-tetrazoyl)methylthio]propionamide (**116**) was identified as the most potent [165]. Likewise, Terashima et al. showed that *N*-(1H-tetrazol-5-yl)-2-anilino-5-pyrimid inecarboxamides (**117**) had anti-ulcer activities and identified new compound leads with excellent gastric mucosal protection and gastric anti-secretion activities [166]. Ulcerogenic potential of new tetrazole derivatives was evaluated by Lamie et al. **118** showed a similar activity in ulcer index compared to Celecoxib [16].

6.8. Treatment of lung diseases, cough and asthma

Tetrazole-containing compounds have shown potential in treating lung diseases, cough, and asthma. They exhibit anti-inflammatory properties and bronchodilatory effects, making them valuable candidates for managing respiratory conditions. Their ability to modulate pathways involved in lung inflammation and airway constriction highlights their therapeutic promise in respiratory disorders. Transient receptor potential (TRP) channels are a class of voltage-gated ion channels on the plasma membrane. Transient receptor potential ankyrin 1 (TRPA1) is popular as a sensor for environmental irritants causing pain, cold or itch. TRPA1 is triggered by reactive, electrophilic stimuli and non-reactive compounds implicated in cough related to asthma, chronic pulmonary obstructive disease, idiopathic pulmonary fibrosis, and post-viral and chronic idiopathic cough. Tetrazole derivatives **119** (Fig. 9) can play the role of TRPA1 inhibitors in treating idiopathic lung disorders and cough [167]. Tomelukast (**120**) is an anti-asthma tetrazole derivative with anti-inflammatory and bronchodilatory properties, and its role cannot be ignored [168].

6.9. Protein arginine methyltransferases inhibitor

Protein arginine methyltransferases (PRMTs) can catalyze protein arginine methylation and influence numerous cellular processes, including transcriptional regulation, RNA splicing, cell growth, and differentiation [169]. The dysregulation of PRMT type 1 is involved in various diseases - especially cancer, diabetes, renal and cardiovascular diseases, and pulmonary fibrosis [169–172]. As such, there is a need to develop new inhibitors due to the weak potency of current agents against PRMT1. Sun et al. developed, through computer-aided drug design, 1,5-substituted tetrazole derivatives **121**–**123** (Fig. 9) as strong inhibitors of PRMT1 [173].

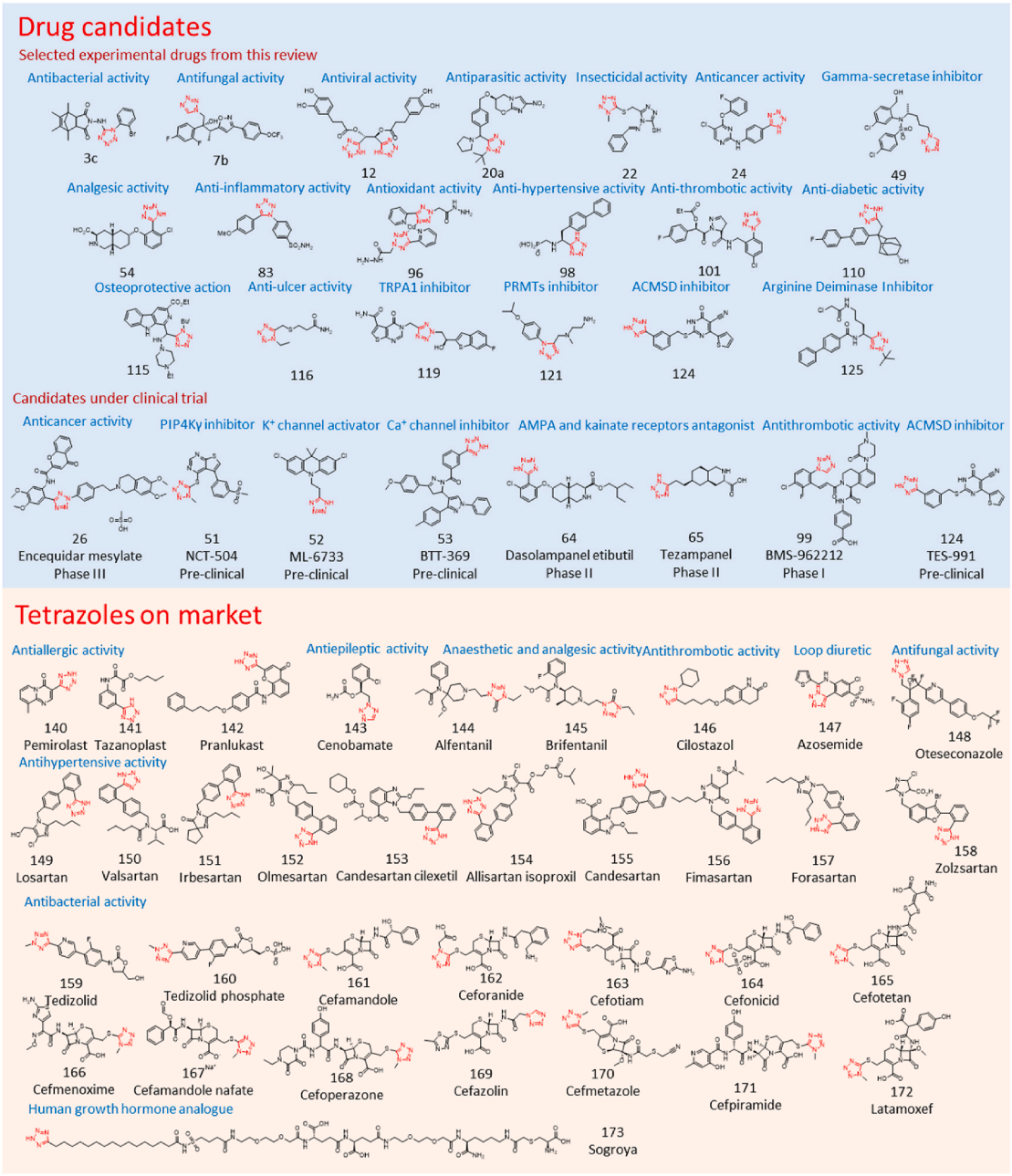


Fig. 12. Tetrazoles on the market and potential tetrazole-containing drug candidates. The drug candidates presented in the upper part have been described in the previous chapters, while drugs on the market presented in the lower part are a summary of the commercially available drugs with their brand names provided.

6.10. α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase inhibitor

TES-991 (**124**, Fig. 9) is the first low nanomolar (IC_{50} 3 nM) α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD) inhibitors to increase intracellular NAD + level through limiting production of the NAD + precursor quinolinic acid, thus providing protection to kidney and liver [174,175]. Compound **124** now is under pre-clinical trial for the treatment of metabolic dysfunction-associated steatotic liver disease (MASLD).

6.11. Protein arginine deiminase inhibitors

Protein arginine deiminase (PAD) catalyses the hydrolysis of arginine to form citrulline and is a target for autoimmune diseases. Compound **125** exhibited inhibitory activity against U2OS cells with EC_{50} 10 μM [176].

6.12. Protein-labelling to facilitate mode of action study

The photoclick reaction of 2,5-diaryl tetrazoles has many applications in bio-medicinal chemistry. It will become a powerful tool soon due to its unique features, such as the very good stability of the substrate in the physiological environment, low toxicity, and fluorogenicity of the cycloaddition with dipolarophiles, leading to efficient sensing of specific biomolecules. The main application is bioorthogonal labelling of proteins, but they are used in modifying nucleic acid structures by developing efficient photoaffinity labels, all to study specific biological targets of new potential drugs to determine their mechanism of action. They could also be helpful in the development of innovative

biomaterials (e.g. hydrogels). More specifically, the 2,5-diaryl tetrazoles play the role of fluorogenic sensors to detect biological molecules in the native environment or to decode their bio-properties. Examples of tetrazoles (**126**–**128**) employed in photoreactivity studies are presented in Fig. 10A [177]. The reaction starts from the formation of 1,3-nitrile imine dipole in the presence of UV light and then reacts with substituted ethene to afford fluorescent product 2,5-diaryl pyrazoline (Fig. 10B) [178].

7. Specific examples of beneficial effects of tetrazole incorporations

A class of lipolysis inhibitors (Fig. 11) with a replacement of the carboxylic group with tetrazole can extend the duration of the inhibitory effect by 2.5-fold in a model in dogs [179]. This enhancement was achieved by improving metabolic stability by the tetrazole motif [180]. Moreover, tetrazole groups exhibit an increased membrane penetration due to its lipophilicity. Thus, peptide-based protein arginine deiminase inhibitor was optimized by replacing the amide bond with tetrazole (Fig. 11), which showed an up to 16-fold improved potency of tetrazole derivatives compared to its parent counterpart and this improvement could be explained by the compounds' increased cell permeability from a more lipophilic tetrazole group [176].

Losartan is a tetrazole-containing medicine commercially available to treat hypertension and diabetic nephropathy by blocking angiotensin II receptors [7]. The parent compound (Fig. 12) showed good inhibitory activity *in vitro* (IC_{50} 0.23 μM), probably because of the binding of the carboxylic group to the positive charge in all receptors, but poor bioavailability in a rat model, which could be explained by the metabolic instability of carboxylic acid. Thus, further optimization was conducted based on carboxylic groups to increase stability and bioavailability. Amide-type isosteres (e.g. carboxamide, sulfonamide and their derivatives) can increase the activity. This improvement is enhanced when a high acidity group is used, but unfortunately, it failed to improve bioavailability due to the limited stability. Tetrazole was selected to replace the carboxylic group because it has a similar PKa to the carboxylic group, and its 4-nitrogen-containing aromatic ring could have a better interaction with positive charge in receptors and its high metabolic stability. Fig. 12 presents selected compounds in this review and all drug candidates currently in ongoing clinical trials (top of the figure) and all tetrazole-containing marketed drugs (bottom of the figure).

8. Conclusion, limitations & future perspectives

8.1. Conclusion

Tetrazole is a pivotal scaffold for drug design in both chemical synthesis and medicinal chemistry. Medicinal chemistry emerges as the leading field exploiting the diverse bio-activities of tetrazole compounds, from anti-microbial and anti-cancer properties to anti-hypertensive, anti-asthma and anti-inflammatory activities, to treat neurological diseases and many others, to mention only the most important examples. The escalating number of publications and patents centred on tetrazole derivatives, with the United States at the forefront, demonstrates its growing significance and potential applications. The multifunctional properties of tetrazole derivatives indicate promising potential for therapeutic applications.

8.2. Limitations

There are many synthetic approaches for making tetrazole-containing compounds. However, very little is mentioned in the literature about their proper bio-evaluation and comparisons of drug candidates with and without the tetrazole moiety. Tetrazole compounds still face challenges in stability, solubility, and target specificity. There is a need for strategies that include systematic tetrazole-containing compound synthesis modifications for monitoring their bio-stability, innovative formulations for solubility, structural adjustments to reduce toxicity, and innovative drug delivery and re-purposing for broader therapeutic potential.

8.3. Future perspectives

The synthesis of tetrazoles from diverse starting materials will continue to be a research focus. Advancements could yield novel tetrazole derivatives with enhanced pharmacological benefits and fewer side effects. Additionally, there is a demand for a comprehensive investigation of tetrazole's role in improving drug stability/bioavailability/safety and permeability. It is imperative to present more evidence of observed pharmacokinetic or efficacy improvement by introducing the tetrazole component. All future structure-activity relationship, SAR, studies should focus on the changes done in the area of the tetrazole incorporation to make it methodical by replacing in each synthetic approach only one fragment/group/moiety in the compound's core. Then, compounds with and without tetrazole in the molecule structure should be compared in bio-investigation. Such a comprehensive study could provide a clear explanation of the vital role of the tetrazole isostere in biomolecules.

CRediT authorship contribution statement

Ye Yuan: Writing – original draft, Visualization, Software. **Muzi Li:** Writing – original draft, Investigation, Conceptualization. **Vasso Apostolopoulos:** Writing – review & editing. **John Matsoukas:** Writing – review & editing. **Wojciech M. Wolf:** Writing – review & editing. **Mark A.T. Blaskovich:** Writing – review & editing, Conceptualization. **Joanna Bojarska:** Writing – original draft, Formal analysis, Conceptualization. **Zyta M. Ziora:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Abbreviations used

ACMSD	α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase
ADME	Absorption, distribution, metabolism and excretion
AKA	Aurora kinase a

AMPA	Alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
BSA	Boron sulfuric acid
BTEAC	Benzyltriethylammonium
COX	Cyclooxygenases
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
GABA	Gamma-aminobutyric acid
HUVEC	Human umbilical vein endothelial cell
MASLD	Metabolic dysfunction-associated steatotic liver disease
MGlu	Metabotropic glutamate receptor antagonists
MNC-Cu	Magnetic nitrogen-doped carbon-based copper
NMDA	N-methyl-*d*-aspartate
PAD	Protein arginine deiminase
PIP4Kγ	Phosphatidylinositol-5-phosphate 4-kinase, type ii γ
PRMTs	Protein arginine methyltransferases
SSA	Silica sulfuric acid
TBAB	Tetrabutylammonium bromide
TMSN3	Trimethylsilyl azide
TRP	Transient receptor potential
TRPA1	Transient receptor potential ankyrin 1
TS	Thymidylate synthase

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