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Review

Copper-Coordinated Thiazoles and Benzothiazoles: A Perfect Alliance in the Search for Compounds with Antibacterial and Antifungal Activity

Raúl Colorado-Peralta [1], José Luis Olivares-Romero [2], Sharon Rosete-Luna [1], Oscar García-Barradas [3], Viviana Reyes-Márquez [4], Delia Hernández-Romero [1,*] and David Morales-Morales [5,*]

1 Facultad de Ciencias Químicas, Universidad Veracruzana, Prolongación de Oriente 6, No. 1009, Orizaba C.P. 94340, Veracruz, Mexico; racolorado@uv.mx (R.C.-P.); srosete@uv.mx (S.R.-L.)
2 Instituto de Ecología A.C., Red de Estudios Moleculares Avanzados, Clúster Científico y Tecnológico BioMimic®, Carretera Antigua a Coatepec, No. 351, Xalapa C.P. 91070, Veracruz, Mexico; jose.olivares@inecol.mx
3 Instituto de Química Aplicada, Universidad Veracruzana, Luis Castelazo Ayala S/N, Xalapa C.P. 91190, Veracruz, Mexico; osgarcia@uv.mx
4 Departamento de Ciencias Químico-Biológicas, Universidad de Sonora, Luis Encinas y Rosales S/N, Hermosillo C.P. 83000, Sonora, Mexico; viviana.reyes@unison.mx
5 Instituto de Química, Universidad Nacional Autónoma de México, Cd. Universitaria, Circuito Exterior S/N, Coyoacán C.P. 04510, Ciudad de México, Mexico
* Correspondence: deliahernandez@uv.mx (D.H.-R.); damor@unam.mx (D.M.-M.)

Abstract: Throughout human history, bacteria and fungi have caused infections that are difficult to combat. For this reason, countless research groups have developed novel compounds to solve this problem. Thiazole and benzothiazole are present in different structures with interesting biological effects and are used to develop new effective antimicrobial agents. Moreover, nitrogen atoms that are present in this heterocycle allow for coordination with various metals, forming metal complexes that enhance the biological activity of organic ligands that are often used as commercial drugs. This bibliographical review summarizes the copper complexes that use thiazole and benzothiazole as ligands and that report efficient antimicrobial activity against different bacteria and fungi.

Keywords: thiazole; benzothiazole; copper complexes; heterocycles; azoles; antibacterial; antifungal

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1. Introduction

Heterocycles that contain nitrogen atoms in their structure play an important role in the discovery of new drugs, and such is the case with azoles, which occupy a privileged place in the chemical, biological and medical area due to their contributions to the synthesis of new compounds with therapeutic potential in humans [1]. Among the azoles, we can highlight thiazole (1,3-thiazole), which is one of the most important heterocycles in organic chemistry and in the design of molecules of biological interest [2,3]. This compound is made up of a five-membered unicycle and contains a sulphur atom (hydrogen bond acceptor) in the S1 position and a nitrogen atom (donor of an electron pair) in the N3 position [4,5] (Figure 1). The unsubstituted thiazole has a minimal formula, C_3H_3NS, and is a versatile building block enabling new drug development. It is found in several synthetic substances and in some natural compounds [6,7]. For example, vitamin B_1 (thiamine) contains in its global structure the thiazole nucleus, which serves as an electron trap and participates in the decarboxylation of α-ketoacids and helps the normal functioning of the central nervous system (CNS) due to its role in the synthesis of acetylcholine [8]. In addition, thiazoles are part of various natural products such as alkaloids, steroids, and flavones, among others [9,10].

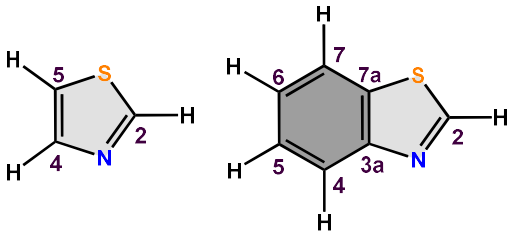

Figure 1. General structure of thiazole and benzothiazole.

1.1. Biological Importance of Thiazoles

Thiazole and its derivatives are among the most prominent compounds in the literature due to their broad spectrum of action, highlighting their activities, which include anti-arthritic, antibacterial, anticancer, anticonvulsant, antifungal, antidiabetic, anti-inflammatory, antiparasitic, anti-Parkinson, antiulcer, antiviral, antithrombotic, and analgesic, among others [11,12]. Compared to other five-membered heterocycles with two heteroatoms, such as oxazole, isoxazole, and isothiazole, thiazole is the most common essential heterocycle in various drugs approved by the US Food and Drug Administration (FDA) [13]. The delocalization of one of the two pairs of electrons on the sulphur atom promotes the aromaticity of the thiazole. The density of the six π electrons (Hückel's rule) reveals that electrophilic substitution occurs at the C5 carbon, while nucleophilic substitution occurs at the C2 carbon [14]. Thiazole is highly reactive due to the acidity of the proton on C2, so it has become an important synthon capable of generating new chemical entities [15]. Thiazole can carry out substitution, cycloaddition, oxidation, arylation, dimerization, and photochemical reactions, among others. These heterocycle modifications have given rise to a variety of novel compounds with a wide range of pharmacological activities [16].

Moreover, there are currently several drugs available that have a thiazole in their structure, including amiphenazole, used in opiate or barbiturate overdose; clomethiazole, a sedative and a hypnotic, anticonvulsant, and anti-anxiety medication; edoxaban, a blood-thinning medication; nitazoxanide, a broad-spectrum antiviral and antiparasitic drug; febuxostat, used to treat gout; lusutrombopag, used for the treatment of thrombocytopenia; mirabegron, used for the treatment of overactive bladder; niridazole, used for the treatment of schistosomiasis; talipexole, used for the treatment of Parkinson's disease; sodelglitazar and tenelgliptin, used to treat type II diabetes; faldaprevir and simeprevir, used for the treatment of hepatitis C; famotidine and nizatidine, used for the treatment of gastroesophageal reflux and peptic ulcers; brecanavir, cobicistat and ritonavir, used for the treatment of human immunodeficiency virus (HIV); and fanetizole, fentiazac, sudoxicam, and meloxicam, anti-inflammatory drugs [17–19] (Figure 2).

In addition to various anticancer drugs such as alpelisib, bleomycin, curacin, dabrafenib, dasatinib, epothilone, ixabepilone, thiazofurin, and vosaroxin, there are various antifungal drugs, such as abafungin, cabemdazole, ethaboxam, isavuconazole, mixothiazole, ravuconazole, and thiabendazole [20–23] (Figure 3).

There are numerous antibiotics of the cephalosporin family (cefcapene, cefdaloxime, cefdinir, cefditoren, cefepime, cefetamet, cefiderocol, cefixime, cefmatilen, cefmenoxime, cefodizime, cefotaxime, cefotiam, cefoselis, cefovecin, cefpirome, cefpodoxime, cefquinome, ceftaroline, ceftazidime, cefteram, ceftibutene, ceftiofur, ceftiolene, ceftizoxime, ceftriaxone, cefuzonam), as well as various antibiotics with diverse structures, such as sulfathiazole, aztreonam, tigemonam, pyrazmonam, carumonam, penicillin and its derivatives (ampicillin and amoxicillin) [24–27], Figure 4.

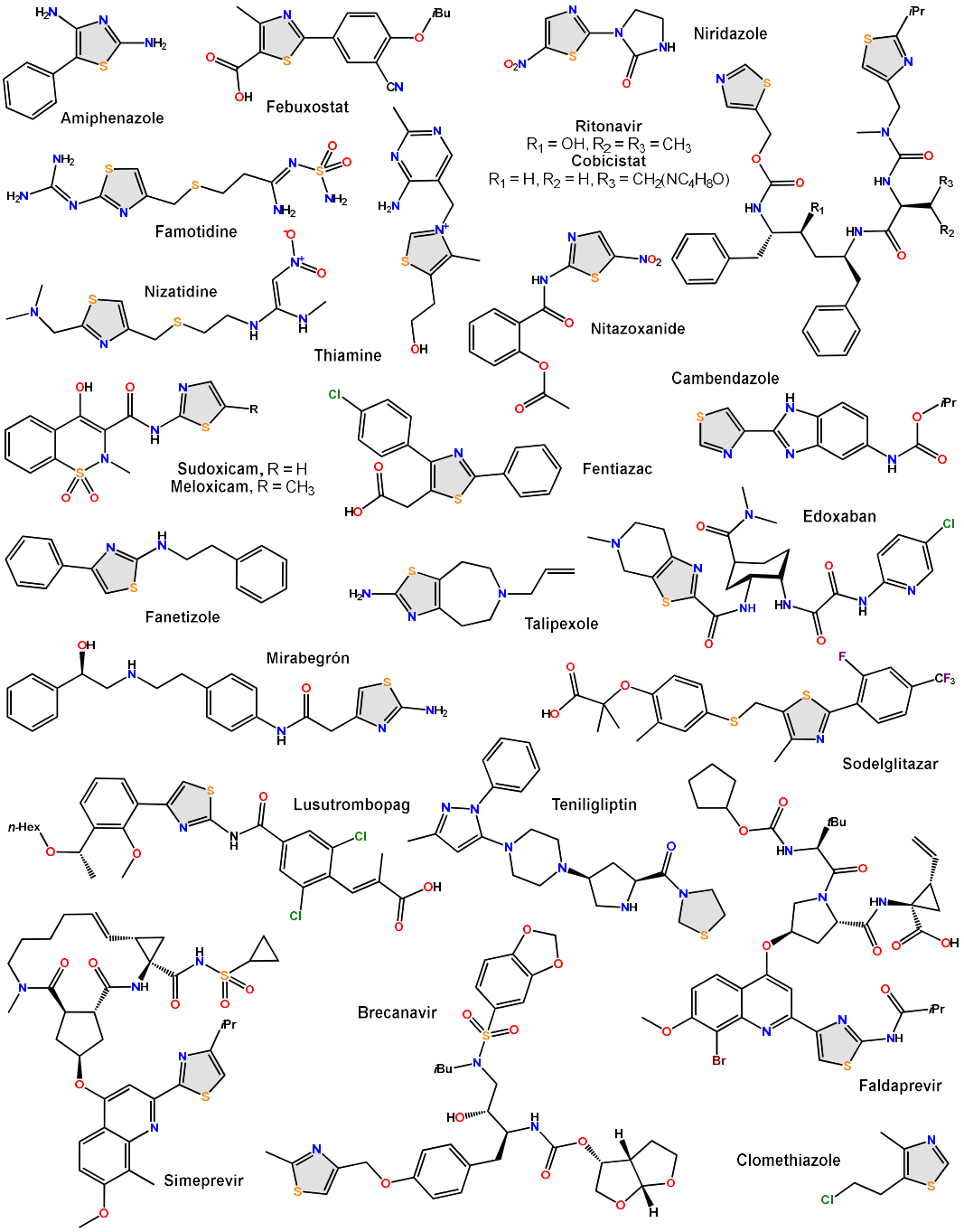

Figure 2. Thiazole-based drugs used in the treatment of various diseases.

1.2. Synthesis and Characterization of Thiazoles

Thiazole synthesis was first reported by Hantzsch and Waber in 1887 and its structure was elucidated by Popp in 1889 [28]. The Hantzsch synthesis is the oldest and most common method for synthesizing thiazoles and consists of the condensation and cyclization of an α-halocarbonyl with various reagents containing the N=C–S fragment (thioamides, thiosemicarbazides, thiosemicarbazones, or thioureas); many thiazoles with substituents at the C2, C4, or C5 positions can be obtained via this method. In 1910, Gabriel reported a new synthetic route for the preparation of thiazoles, for which he used the cyclization of acylaminoacetones using diphosphorus pentasulfide at elevated temperatures; many thiazoles with substituents at the C2 or C5 positions can be obtained via this method. There is another method known as the Cook–Heilborn synthesis, which reacts

α-aminonitriles/α-aminoamides with carbon disulfide, carbonyl oxysulfide, isocyanates, or dithioacid esters; many thiazoles with substituents at the C5 position can be obtained through this method [29,30]. On the other hand, the spectroscopic characterization by ^{1}H NMR (Nuclear Magnetic Resonance) shows chemical shifts for thiazole without substituents at 8.9 ppm (H2), 8.0 ppm (H4) and 7.4 ppm (H5), while the ^{13}C NMR are 154 ppm (C2), 143 pm (C4) and 120 ppm (C5). Ultraviolet-visible (UV-Vis) spectroscopy shows an electronic absorption band with λ_{max} of 235 nm, ε = 3000 L mol^{-1} cm^{-1} [31–34].

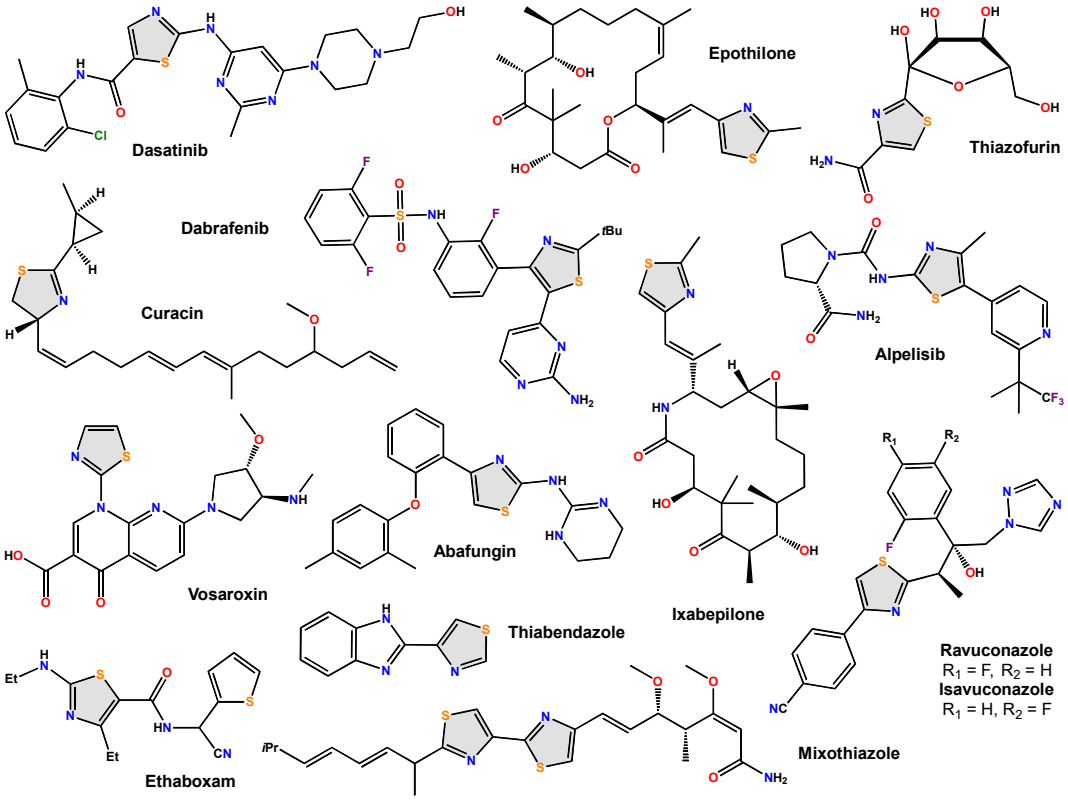

Figure 3. Thiazole-based drugs with anticancer and antifungal activity.

1.3. Biological Importance of Benzothiazoles

Benzothiazole (benzo[d]thiazole) is a heteroaromatic bicyclo consisting of a benzene ring fused at the C4 and C5 positions of the thiazole ring [35–37]. This compound is a privileged scaffold, since in its structure, it has a nitrogen atom in the N3 position and a sulphur atom in the S1 position [38–40]. Benzothiazole with the chemical formula C_7H_5NS has attracted the scientific community's interest due to its potential use in the design of new drugs [41,42]. This planar molecule with electron-rich heteroatoms is part of the structure of luciferin in fireflies and is a constituent of the aroma of blueberries and tea leaves, or of flavour produced by the fungi *A. clavatus* and *P. frondosus* [38,43]. Benzothiazoles contain extended π-delocalized systems capable of binding to DNA molecules [44]. Various pharmacological and biological activities have been conferred on it, among which are anti-arthritic, anti-Azlheimer, antidiabetic, antifungal, antiepileptic, anti-schizophrenia, antihelmintic, and anti-Parkinson, among others [45–51]. Benzothiazole act as the core in various drugs such as dimazole, used as an antifungal agent; ethoxzolamide, used for the treatment of glaucoma and some forms of epilepsy; frentizole, used for rheumatoid arthritis and systemic lupus erythematosus; pramipexole, used for the treatment of Parkinson's disease and Wittmaack-Ekbom syndrome; riluzole, used to treat amyotrophic lateral sclerosis; sibenadet, used for the treatment of chronic obstructive pulmonary disease; thioflavin, used for histological staining and protein aggregation; zopolrestat, used for the treatment of diabetic complications; flutemetamol, used as a radiopharmaceutical in the diagnosis of

Alzheimer's disease; and dithiazanine iodide, which is an anthelmintic for veterinary use and lethal to humans [52–56], Figure 5.

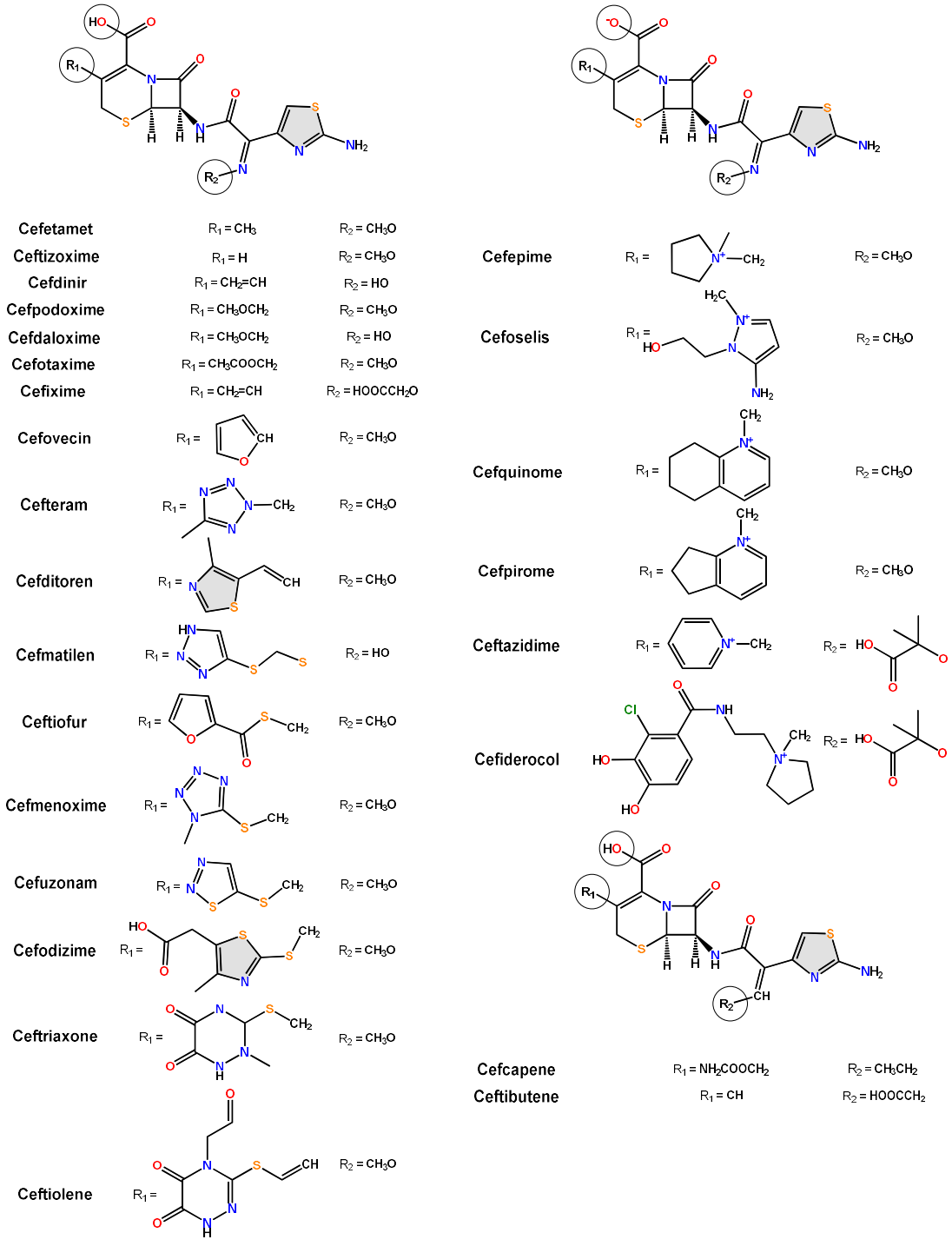

Figure 4. Antibiotics derived from cephalosporins that contain thiazole in their structure.

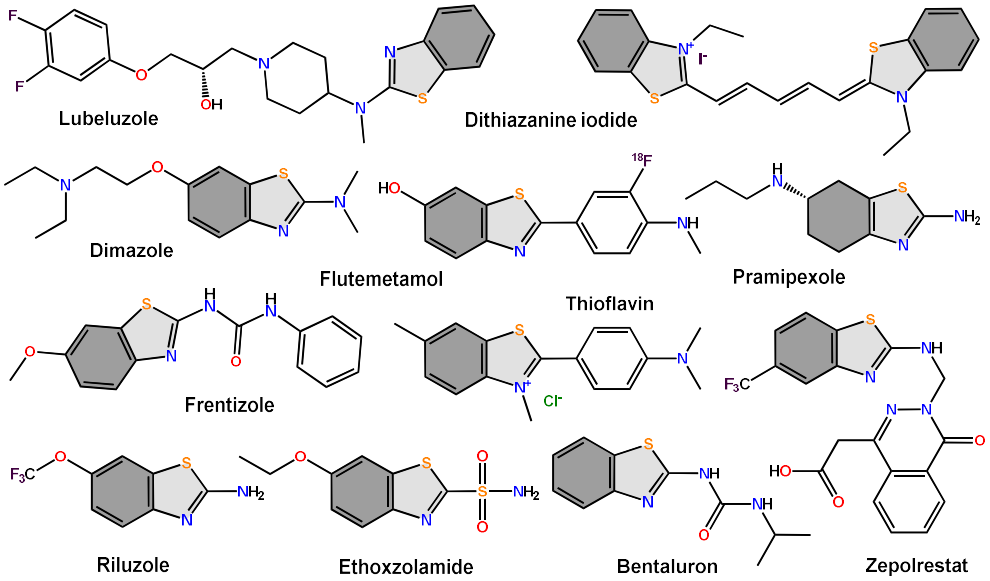

Figure 5. Benzothiazole-based drugs used in the treatment of various diseases.

1.4. Synthesis and Characterization of Benzothiazoles

Various methods have been reported for obtaining benzothiazoles, highlighting mainly the condensation of 2-amino thiophenol with carbonyl compounds (aldehydes, carboxylic acids, esters), nitriles, cyanates, isocyanates, etc., using different reaction conditions and catalysts [57–59]. Finally, spectroscopic characterization by ^{13}C NMR shows chemical shifts for the benzothiazole without substituents at 155 ppm (C2), 123 pm (C4), 126 ppm (C5), 125 ppm (C6), 122 ppm (C7), 153 ppm (C3a) and 134 ppm (C7a). Ultraviolet-visible spectroscopy (UV-Vis) shows a more complex electronic absorption with λ_{max} of 217, 251 nm, (ε = 18,620 L mol^{-1} cm^{-1}, 5500 L mol^{-1} cm^{-1}), 285 nm (ε = 1700 L mol^{-1} cm^{-1}) and 295 nm (ε = 1350 L mol^{-1} cm^{-1}) [60–62].

2. Antibacterial and Antifungal Thiazole-Copper(II) Complexes

Thiazole and benzothiazole heterocycles have been recognized as interesting scaffolds for their promising antimicrobial properties [63–65]. Compared to other five-membered heterocycles such as oxazole and imidazole, the sulphur contained in thiazole and benzothiazole confers small regions of low electron density that may play a role in drug–target interactions. In this work, thiazole and benzothiazole heterocycles that form coordination complexes with copper metal were considered, and their possible use as antibacterial and antifungal agents was analysed.

2.1. Copper Complexes with Monodentate Thiazole Ligands

Sulfathiazole, a sulfa drug, is mainly used in the treatment of respiratory tract and digestive system infections, as well as skin and urinary tract infections [66]. This compound can act as a ligand due to the acidic behaviour of the –SO_2–NH– site, forming an anionic donor supported by the presence of O, N and/or S atoms in the adjacent heterocyclic ring. This drug was used as a ligand, along with the co-ligand *dien* (diethylenetriamine) and the copper(II) atom in the **Tz-01** complex. **Tz-01** crystallized in an orthorhombic crystal system and presented a square dipyramidal geometry. In addition, minimum inhibitory concentrations (MICs) were determined in bacteria (*E. coli*, *P. aeruginosa*, *E. faecalis*, *S. aureus*, and *B. subtilis*) and fungi (*A. niger* and *C. albicans*) using the microdilution method (Appendix A). The antimicrobial activity of **Tz-01** (1–4 µg/mL) was considerably higher than that of free sulfathiazole (8–16 µg/mL for *B. subtilis* and *S. aureus* and was higher than 256 µg/mL for other microbes). The coordination of copper(II) with sulfathiazole markedly strengthens antimicrobial activity [67].

Another monodentate sulfathiazole-based mononuclear coordination complex (**Tz-02**) was obtained; this presented a slightly distorted square pyramidal environment around the copper(II) ion. In addition to sulfathiazole (STz), **Tz-02** contains 1,10-phenanthroline (*phen*) as a secondary ligand. The antimicrobial activity of **Tz-02** and its free ligand against bacteria (*S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli*) and fungi (*C. albicans* and *A. flavus*) was determined using the microdilution technique. MIC values in *S. aureus* did not show antibacterial activity for free ligand and **Tz-02** (>512 µg/mL). However, **Tz-02** showed good antimicrobial activity in the other strains (2–16 µg/mL, respectively) and was superior to free sulfathiazole (4–128 µg/mL). In *P. aeruginosa*, the free ligand and **Tz-02** presented an excellent antimicrobial effect, with MIC values of 1 µg/mL. These MIC values indicated that **Tz-02** was a fairly effective antimicrobial agent [68].

The neutral complex **Tz-03** was obtained with octahedral geometry around the central metal ion. To determine their antibacterial and antifungal activity, the aminothiazole ligand and **Tz-03** were tested against human pathogenic bacteria (*E. coli*, *S. aureus*) and fungi (*A. niger*, *A. flavus*) using the ditch-plate method. **Tz-03** showed a larger zone of inhibition for bacteria (12 mm) and fungi (2–9 mm) than the free ligand (0–5 and 0–6 mm, respectively) [69]. Finally, the antibacterial activity of a new series of coordination complexes (**Tz-04a**–**Tz-04e**) with a distorted octahedral geometry was evaluated against *E. coli*, *B. subtilis* and *B. cereus* using the twofold serial dilution method. The MIC values showed that the complexes exhibited a higher activity (12–100 µg/mL) compared to the starting material (>100 µg/mL). Then, the thiazole ligand is crucial for antimicrobial activity in most cases. They also found that **Tz-04a** and **Tz-04d** exhibited specificity for *B. cereus* (12 µg/mL) and *B. subtilis* (6–12 µg/mL) [70] (Figure 6).

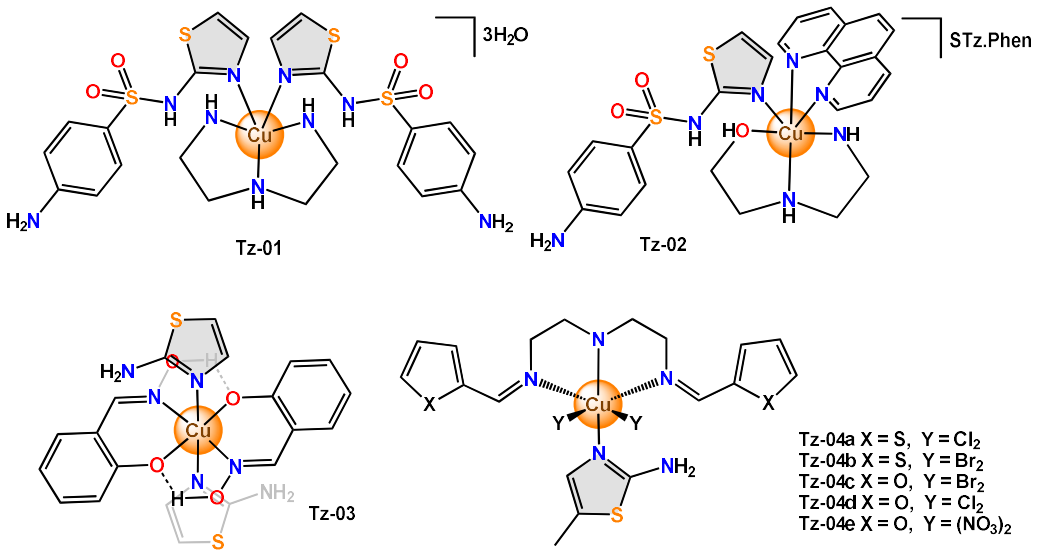

Figure 6. Copper complexes with monodentate thiazole ligands.

2.2. Copper Complexes with Bidentate Thiazole Ligands

On the other hand, coordination complexes that use bidentate ligands that contain different thiazole derivatives in their structure have been reported; such is the case with **Tz-05**, which presented a square planar geometry around the metal centre. In this study, the antimicrobial activity was investigated using the disk diffusion method against the bacteria (*E. coli*, *S. aureus*, *P. aeruginosa*, *B. subtilis*), and the fungi (*C. albicans* and *A. flavus*). **Tz-05** showed excellent antibacterial activities against all four bacterial strains tested (8–13 mm), and against the fungi, it was only active against *C. albicans* (10 mm). In contrast, the free ligand was less active in both bacteria (0–9 mm) and fungi (0–9 mm). The structure–activity relationship (SAR) revealed that the heterocyclic ring and conjugated keto group in chalcones play a crucial role in enhancing antimicrobial activity. The authors reported

that substitution with an electron acceptor (bromide group) increased antimicrobial activity compared to chalcones substituted with an electron donor (methoxy group) [71].

The antimicrobial activity of **Tz-06** was described using a new chalconoid ligand. In this compound, there are keto groups and π-olefin bonds that act as the preferred binding sites for metal ions. In **Tz-06,** the nitrogen atom of the thiazole and the oxygen of the carbonyl group act as effective donors on the metal bond to obtain a complex with a square planar geometry. The antimicrobial activity of the free ligand and **Tz-06** was determined by the disk diffusion method in the bacteria (*E. coli*, *S. aureus*, *P. aeruginosa*, *B. subtilis*) and the fungi (*A. flavus* and *C. albicans*). The zone of inhibition suggests that **Tz-06** showed better antibacterial activity (9–11 mm) than the free ligand (8–9 mm). In addition, the free ligand was found to be inactive against *A. flavus*, but **Tz-06** was active against both fungi with a zone of inhibition of 11 mm [72].

Meloxicam, a non-steroidal anti-inflammatory drug (NSAID), has been used as an organic ligand in coordination complexes to produce better pharmacokinetic and pharmacodynamic properties and to study their chemical characteristics. In **Tz-07**, meloxicam acts in a monobasic bidentate manner and coordinates through the oxygen of the amide and the nitrogen of the thiazole rings, forming a complex with a slightly distorted octahedral geometry. **Tz-07** was tested on several species of bacteria (*E. coli*, *S. aureus*, *S. typhi*, *Citrobacter* and *Listeria*) and fungi (*A. niger* and *P. expansum*) using the disk diffusion method and calculating the value of MIC. **Tz-07** showed highly significant activity against *Citrobacter* (14.5 ± 1.2 mm and MIC value of 0.075 ± 0.01 μg/mL) and *Listeria* (18.6 ± 1.4 mm and MIC value of 0.05 ± 0.007 μg/mL), with moderate antibacterial activity in the other species (0.075–0.1 μg/mL) but without antimicrobial activity in *A. niger* and *P. expansum*. Furthermore, the ligand only presented antibacterial activity in *E. coli* and *Citrobacter* (0.05 ± 0.02 and 0.1 ± 0.03 μg/mL, respectively). The authors related the high antibacterial activity of **Tz-07** with its lipophilic behaviour [73].

On the other hand, **Tz-08** was obtained with two bidentate ligands coordinated to the metal centre and was evaluated in *S. aureus* by the agar diffusion method. **Tz-08** did not show relevant antibacterial activity in *S. aureus*; however, the authors mention that it would be important to test this hexacoordinated copper(II) complex using other microorganism species to prove its potential [74]. The heterobimetallic mixed complexes (**Tz-09a–TZ-09c**) presented an octahedral geometry and were evaluated in the *S. aureus* and *E. coli* strains by the agar disk diffusion method. **Tz-09a** and **Tz-09c** were highly sensitive against *S. aureus*, while the same complexes exhibited resistance against *E. coli*. **Tz-09b** presented resistance against both bacteria. The authors mention that the complexes can be sensitive or resistant due to the lipophilic character of the metal ion in the complexes, which can be increased or decreased by chelation with thiazole ligands and can make the bacterial membrane permeable or impermeable, respectively, for these complexes through the lipid layer of bacterial organisms. Furthermore, the stereochemistry of these complexes plays an important role in antimicrobial activity, which could promote their binding to the *S. aureus* amino acids [75].

Tz-10 was reported to have a distorted octahedral geometry and was tested for its antibacterial activity on *S. aureus*, *B. subtilis*, *E. coli*, and *Streptococcus* and for its antifungal activity on *C. albicans* and *A. niger* by the agar well diffusion method. **Tz-10** showed an antibacterial inhibition zone of 12–15 mm and an antifungal inhibition zone of 8–10 mm, respectively. In addition, the MIC values of **Tz-10** were determined, and ranges of 17–22 μg/mL for antibacterial activity and 13–22 μg/mL for antifungal activity were found, respectively [76]. Sulfathiazole was used again, but this time as a bidentate ligand, and the hexacoordinated copper(II) complex (**Tz-11**) was obtained, which presented a distorted octahedral geometry. The complex was tested in bacteria such as *S. aureus*, *E. coli* and *P. aeruginosa* by determining the MIC value. **Tz-11** showed moderate activity and selectivity, with MIC values of 0.10–0.84 mmol/L in *P. aeruginosa* and *E. coli*, while the free ligand did not show antibacterial activity. The result of **Tz-11** justifies further studies on

the use of this complex in the treatment of skin infections, since it also presented good solubility [77].

Tz-12 was prepared from *N*-(2-thiazolyl)-1*H*-benzotriazole-1-carbothioamide, a polydentate ligand with several coordination sites (benzotriazole, carbothioamide, and thiazole). The thiazole donor sites (N and C-S-) of two ligand molecules were coordinated with a copper(II) ion, obtaining a structure with a square planar geometry. Preliminary biological screening was carried out at 20 mg/mL with *S. aureus* and *E. coli*. The ligand was found to reduce the metabolic growth of the studied bacteria to a different degree and showed better toxicity against *S. aureus* compared to *E. coli*. Coordination of the ligand with copper(II) markedly altered toxicity, with an IC_{50} value of 0.125 µmol/mL (equivalent to 80 µg/mL) [78]. Two new tetracopper(II) (**Tz-13a**–**Tz-13b**) complexes with a square-pyramidal geometry were reported. The in vitro antibacterial activities of **Tz-13a-b** were qualitatively determined by the paper disc method against *S. aureus*, *B. subtilis*, *E. coli*, P. vulgaris and *P. aeruginosa*. Furthermore, the complexes were evaluated by calculating the MIC value using the microdilution broth method. Both complexes showed good antibacterial activity (10–16 mm for **Tz-13a** and 12–20 mm for **Tz-13b**) against the selected microorganisms. In addition, **Tz-13a** presented MIC values in the range of 50 to 180 µM, while **Tz-13b** was in the range of 25 to 140 µM against the selected microorganisms. The authors deduced that the higher activity of **Tz-13b** may be due to the better permeability of the *trans*-oxamido structure of the bacterial cells [79].

In **Tz-14**, the organic ligand was coordinated through the nitrogen atom of the thiazole ring and the amino group linked to C2, and it acted in a bidentate manner. According to the spectroscopic results, the geometry of **Tz-14** was square planar. The disk diffusion method was used to measure the antimicrobial activity of **Tz-14** against different bacteria (*S. pyogenes*, *P. aeruginosa* and *E. coli*) and a fungus (*Candida*). The antibacterial activity of **Tz-14** towards the different microorganisms showed a high to moderate efficiency, with a zone of inhibition of 0.6–1.0 cm, similar to the activity shown by the ligand used. However, **Tz-14** and its ligand did not show inhibition in the *Candida* strain. In this case, the remarkable activity of the ligand may be related to the functional groups in its structure, which may play an important role in its antibacterial potential [80].

In the **Tz-15a**–**Tz-15e** complexes, the authors did not report the structure; however, spectral studies revealed that the ligand is attached to the metal ion through the nitrogen atoms of the azomethine group and the thiazole ring. The effect of the anions on the antibacterial activity of the ligand and its metal complexes against the strains *P. aeruginosa*, *K. pneumoniae*, *S. typhi*, *V. cholera* and *B. megaterium* was examined. The free ligand presented a low zone of inhibition for *K. pneumoniae* and *P. aeruginosa* (2 mm) and a slightly higher one for the other three bacteria (6–8 mm). **Tz-15e** and **Tz-15b** produced a very high inhibition halo for *P. aeruginosa* (28–22 mm) and *K. pneumoniae* (18–12 mm), and in other bacteria, the inhibition halo was low (8–10 mm). **Tz-15d** showed moderate inhibition (6–18 mm) for all bacteria tested. The least effective bactericides were **Tz-15a** (4–8 mm) and **Tz-15c** (2–10 mm). The difference in the antibacterial activity of the **Tz-15a**–**Tz-15e** was related to the anions present in the complexes [81].

For **Tz-16**, the authors did not report the structure; however, the data from the elemental analyses and the determined molecular weight suggest a 1:2 stoichiometry (metal-ligand) and a mononuclear nature of the complex ML_2. The electronic spectrum and the magnetic moment of **Tz-16** suggest a square planar geometry. The antimicrobial activity of the free ligand and **Tz-16** was tested against different bacteria (*S. aureus*, *Bacillus*, *E. Coli* and *Klebsiella*) using the agar diffusion method. A comparative study of the free ligand and **Tz-16** revealed that the copper(II) complex exhibited better antibacterial activity (8–25 mm) than the free ligand (8 mm) [82]. The mixed heterobimetallic complex **Tz-17** possesses a square planar structure conferred by the Schiff base ligand. Its antibacterial activity against various pathogenic bacteria (*E. coli*, *S. aureus*, *P. aeruginosa* and *K. pneumoniae*) was determined using the paper disk diffusion method. The results indicated that the free ligand presented a lower percentage of inhibition for *S. aureus* (27–45%), while with the

other bacteria, the inhibition was 45–64%. However, when the ligand was coordinated with copper(II), it presented 45–82% inhibition in all bacteria; that is, **Tz-17** was more active than the free ligand [83].

The heterobimetallic complexes (**Tz-18a–Tz-18d**) with the square planar structure were proposed, and the effect of anions (sulphate, nitrate, acetate or oxalate) on antibacterial activity was studied. They were screened against various pathogenic bacteria (*E. coli*, *S. aureus*, *P. aeruginosa* and *K. pneumoniae*) using the paper disk diffusion method. The complex with the nitrate anion (**Tz-18a**) presented the highest percentage of inhibition (82–100%) in *E. coli*., while in *S. aureus*, there was no difference in the percentage of inhibition with respect to the anions used (64–82%). On the other hand, in *P. aeruginosa*, the complex with the acetate anion (**Tz-18d**) presented the highest percentage of inhibition (82–100%). In *K. pneumoniae*, the complexes with nitrate, acetate and oxalate anions presented a higher percentage of inhibition (64–82%). With these evaluations, it was concluded that anions play an important role in the biological behaviour of copper(II) and iron(II) complexes. Some factors, such as solubility, conductivity, dipole moment, and cell permeability mechanism, are influenced by the presence of these anions [84] (Figure 7).

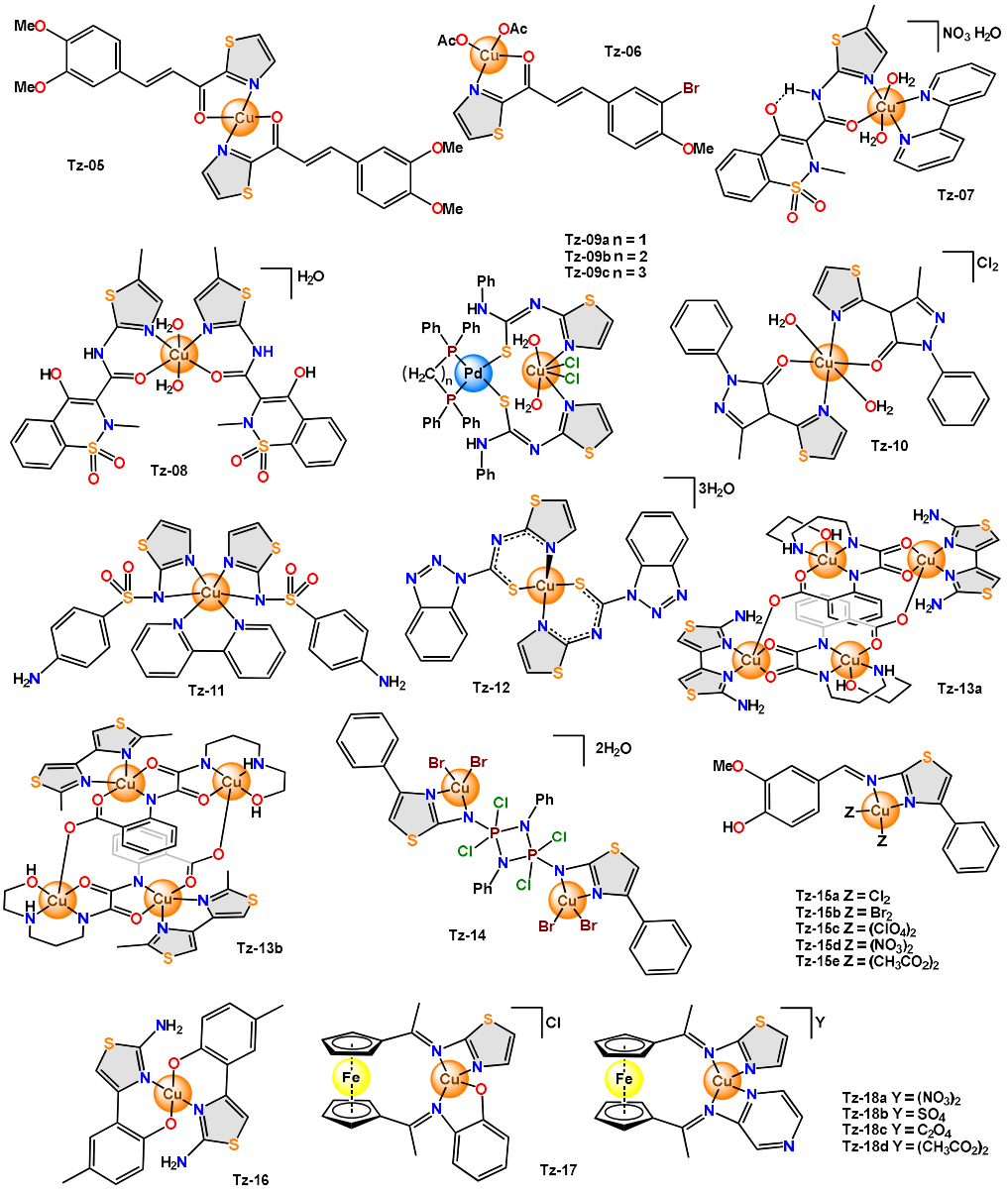

Figure 7. Copper complexes with bidentate thiazole ligands.

In the exploration of novel compounds with antimicrobial activity, complexes with bidentate ligands derived from thiazole have been reported, for example, **Tz-19a** with elongated octahedral geometry and **Tz-19b**, **Tz-20,** and **Tz-21** with distorted square-pyramidal geometry. **Tz-20** is a dinuclear complex, and **Tz-21** is a polymeric complex. Both complexes did not affect the bacterial growth of *P. aeruginosa* and *S. aureus*. However, moderate antifungal activity was observed, especially in the case of **Tz-19b** and **Tz-21,** with MIC values of 31.25 μg/mL for both compounds against *C. albicans* and no significant activity against *C. parapsilosis*. Activity in *C. albicans* was related to the ability to inhibit the hyphal formation of this strain [85].

On the other hand, the combination of L-α-amino acids with various metal ions in the molecular structure of a drug can increase its biocompatibility and antibacterial activity. Because L-α-amino acids are basic structural units of proteins and have the potential to identify the specific sequence of bases through the formation of hydrogen bonds with the nucleic bases in the DNA of bacteria [86]. Therefore, different complexes using L-α-amino acids have been reported. Furthermore, in all these cases, thiabendazole (TBZH), an anthelmintic, is used as a bidentate ligand. The copper(II) complex **Tz-22** presented a distorted square pyramidal geometry in which two equatorial positions are occupied by the secondary ligand Gly-L-Val (N,O) and the other two by the thiabendazole ligand (N,N), while the axial position is occupied by an O atom from H_2O. The antibacterial activity (*B. subtilis*, *S. aureus*, *E. coli* and *P. aeruginosa*) was studied, obtaining the MIC and MBC (minimum bactericidal concentration) values using the microdilution method. **Tz-22** presented good results for the values of MIC (100–320 μg/mL) and MBC (128–512 μg/mL); however, the free ligand did not show any inhibition (MIC 320–512 μg/mL and MBC > 512 μg/mL). The authors mention that the results obtained were consistent with their DNA binding abilities. A change in the properties of the substituent and in the binding sites of the ligand can originate certain modifications in the spatial configuration and density distribution of the electron cloud of the complexes, causing differences in the DNA-binding properties or in the bioactivity [87].

Tz-23a was tested in four bacteria (*S. aureus*, *B. subtilis*, *S. typhi*, and *E. coli*) by the double dilution technique. The MIC value of the ligand was in the range of 320 to 512 μg/mL while for **Tz-23a,** it was in the range of 128–160 μg/mL [88]. **Tz-23b** showed an MIC value of 160 μg/mL in *B. subtilis*, *S. aureus*, *Salmonella*, and *E. coli* [89]. For **Tz-24,** the central copper(II) ion was reported to be penta-coordinated and exhibited a distorted square pyramidal coordination geometry. In vitro antibacterial activity was measured according to the MIC value using the twofold serial tube dilution technique in three microorganisms (*Salmonella*, *B. subtilis* and *S. aureus*). The antibacterial activity of **Tz-24** (128 μg/mL) was better than that of the free ligand (512 μg/mL). The authors consider that the chelating effect caused by bidentate ligands produces greater antimicrobial efficacy compared to the activity caused by complexes with monodentate ligands [86].

Other complexes using mixed ligands were reported, and such was the case with **Tz-25**. This compound crystallized in the triclinic space group and was tested in both *Gram*-positive and *Gram*-negative bacteria. The best results were reported for *B. subtilis* and *E. coli*, with a MIC value of 0.5 μg/mL for both strains, while in *Salmonella*, the MIC value was 2 μg/mL [90]. In all three cases—**Tz-23a**, **Tz-23b**, and **Tz-25**—the authors attributed the result to the ability of the complex to bind to DNA in an intercalated fashion and cleave from pBR322 DNA. In the complexes **Tz-26a**–**Tz-26b**, the resulting coordination geometry was described as slightly distorted trigonal bipyramidal. The complexes were tested against bacteria (*B. subtilis*, *S. aureus*, *Salmonella* and *E. coli*). In addition, the MIC value was determined by the two-fold serial tube dilution method. The results showed that the antibacterial activity of **Tz-26a** (16–64 μg/mL) was better than that of **Tz-26b** (128–256 μg/mL) and that of the free ligand (512 μg/mL). This indicates that the antibacterial activity of the complexes can be attributed predominantly to the synergistic activity of the central copper(II) ion and the ligands in the complexes and the existence of *bipy*

(2,2′-bipyridine) or *phen* (1,10-phenanthroline) co-ligands. Furthermore, the antibacterial activity in **Tz-26a** is in agreement with its DNA binding and cleavage behaviour [91].

Thiabendazole complexes (**Tz-27a**–**Tz-27d**) were obtained from two chelating ligands coordinated to copper(II) centres and exhibited a trigonal bipyramidal geometry. The complexes were tested for their ability to inhibit the growth of *C. albicans* at a concentration of 10 µg/mL, and the results were presented as percentage of cell growth. The free ligand presented a very poor growth inhibition (76%). However, when neutral thiabendazole was coordinated to the copper(II) ion, very potent anti-candida drugs were generated (**Tz-27a** = 54%, **Tz-27b** = 29%, **Tz-27c** = 30%, **Tz-27d** = 19%). In this case, the authors mention that the mode of action of the complexes involves a reduction in the ergosterol content of the fungal cells [92] (Figure 8).

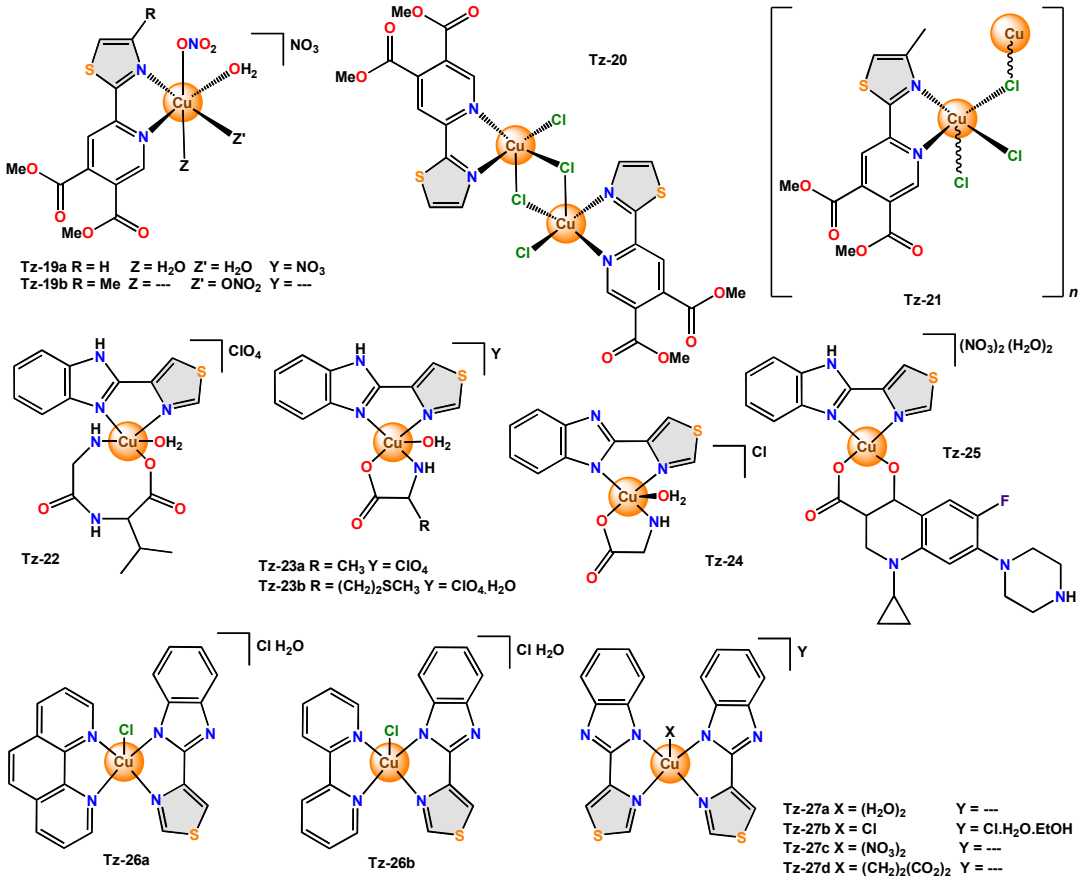

Figure 8. Copper complexes with bidentate thiazole ligands functionalized with pyridine and benzimidazole.

2.3. Copper Complexes with Tridentate Thiazole Ligands

Complexes containing a tridentate thiazole ligand have also been reported, and such is the case with the **Tz-28a**–**Tz-28c** complexes, which were reported as hybrid compounds, since they contain two bioactive moieties: s-triazine and thiazole. The antibacterial and antifungal activity of these compounds was examined in *S. aureus* and *E. coli* bacteria and in *C. albicans* and *A. niger* fungi by the well diffusion method. The results revealed that the complexes showed significant activity against *S. aureus* (16–18 mm) and moderate activity against *E. coli* and both fungi (10–14 mm), while the free ligand did not show antimicrobial activity against *E. coli* and *A. niger* and only moderate activity in *S. aureus* and *C. albicans* (10–12 mm) [93].

Tz-29 with octahedral geometry was tested for antibacterial (*M. luteus* and *E. coli*) and antifungal (*A. niger* and *A. terreus*) activity by the disk diffusion bioassay method. The

results were based on the zone of inhibition for bacteria (16–11 mm) and fungi (17–15 mm), respectively, and were considerably better than those found for the free ligand for bacteria (13–12 mm) and fungi (15–14 mm). The authors mention that metal complexes increased their lipophilic capacity as a result of chelation, which favours their uptake through the lipid membrane of microbes [94]. A bisthiazole derivative was used in the synthesis of **Tz-30**, which exhibited square pyramidal geometry. The antibacterial potential for *E. coli*, *S. aureus* and *P. aeruginosa*, as well as the antifungal potential for *C. albicans*, were determined by agar dilution tests. The MIC value for bacteria was not representative (>32 μg/mL), but in *C. albicans*, the inhibitory activity of **Tz-30** (32 μg/mL) could be higher or similar to that of the free ligand. The authors mention that this result could be associated, almost in part, with the difference in the dipole moments of **Tz-30** and the ligand, which could affect properties that can alter the interaction with the microorganism. In this case, the antimicrobial activity of the bisthiazole compound was related to its lipophilicity [95]. Additionally, **Tz-31** was reported with a tetragonally distorted octahedral geometry and was tested against some bacteria strains (*E. coli*, *P. aeruginosa*, *S. aureus* and *B. subtilis*) by the well diffusion method. Coordination resulted in excellent inhibition in bacteria (40–45 mm), while ligand showed moderate inhibition (30–35 mm) [96].

The antimicrobial activity of the ligand used in the synthesis of the **Tz-32a**–**Tz-32f** complexes (octahedral geometry) was reported using the cup plate method and by the serial dilution technique. The MIC values of the free ligand were found to be in the range of 15–20 mg/mL. In this case, the complexes were tested as insecticides and pesticides and showed a lower poisoning rate than commercial pesticides and insecticides [97,98]. In the case of the complexes **Tz-32g**–**Tz-32i** reportedly with an octahedral geometry, they were tested in vitro against bacteria (*E. coli* and *S. aureus*) using the paper disc method at a concentration of 500 and 1000 ppm and against fungi (*A. flavus* and *A. niger*) using the mycelium dry weight method. The antibacterial data revealed that the copper(II) complexes had greater antibacterial activity at 1000 ppm against *E. coli* (31–35 mm) than that reported against *S. aureus* (23–24 mm). However, better results were obtained in antifungal activity at 1000 ppm for *A. niger* (10(86)–15(80)) and *A. flavus* (16(75)–20(67)) in mg (% inhibition) [99]. Additionally, **Tz-33** was obtained using a Schiff base ligand derived from 2-aminothiazole, and it exhibited a distorted octahedral geometry. The bacteria detection effect of **Tz-33** was tested against *S. aureus*, *B. subtilis*, *P. aeuroginosa*, and *P. vulgaris* by the well-diffusion method with different dilutions (20 μL, 40 μL, and 60 μL). A comparison of the zone of inhibition value of the ligand (10–16 mm) and **Tz-33** (10–18 mm) showed that the metal complex exhibited higher activity than the free ligand [100].

In the copper(II) complex **Tz-34**, the Schiff base acted as a tridentate ligand, and magnetic susceptibility data suggested that the geometric structure of **Tz-34** was square planar. Its antimicrobial activity was examined with different species of bacteria (*B. subtilis*, *S. aureus*, *E. coli* and *P. aeruginosa*) by the well diffusion method at different concentrations (30, 60, 90 μg). As a result, it was detected that **Tz-34** had greater activity (14–20 mm) than the free ligand (13 mm) at 90 μg, highlighting that for *P. aeruginosa*, the ligand did not present activity but that **Tz-34** showed inhibition at 60 μg. (11 mm). The result was related to the greater lipophilic nature of the complex causing a more rapid diffusion of **Tz-34** through the cell membrane or due to the effect of the combined activity of the metal and the ligand [101]. In the case of **Tz-35**, an azo compound was used to functionalize the thiazole, and a tridentate chelating agent was obtained, which was coordinated through the phenolic oxygen atom, the nitrogen atom of the azo group (which is the closest phenyl ring), and from the nitrogen atom of the thiazole ring to form two chelated five-membered rings with a distorted octahedral geometry around the metal centre. The best results were obtained in *Pseudomonas aeruginosa* (>12 mm), but in the other bacteria (*S. aureus*, *Streptococcus*, *Proteus*, *E. coli*), a low and moderate inhibition was obtained (6–12 mm), while the free ligand was slightly more active (6–9 mm) [102].

Tz-36 was reported with a distorted square planar geometry. Antimicrobial activity was determined with the disk diffusion method in bacteria (*S. aureus*, *B. subtilis*, *P. aeruginosa*,

E. coli) and fungi (*C. albicans* and *A. niger*). A comparative study of the zones of inhibition for the free ligand and **Tz-36** showed greater antibacterial activity (10–23 mm) and antifungal activity in *C. albicans* (16 mm) for **Tz-36** with respect to the free ligand (4–18 mm and 11 mm, respectively). The authors concluded that metal ions increased the lipophilic nature of **Tz-36**. Furthermore, Schiff bases may involve the formation of a hydrogen bond through the nitrogen atom of azomethine with the active centres of all constituents, causing interference with normal cellular processes [103].

Tz-37 was obtained using cefotaxime, a third-generation cephalosporin, as a ligand. With the data acquired from the electronic spectra, the authors found that the complex has a distorted square planar geometry. Microbiological screening was tested on *S. aureus*, *E. coli*, *K. pneumoniae*, *S. enteritidis*, *P. mirabilis*, and *P. aeruginosa*. **Tz-37** exhibited superior antibacterial activity (38–54 mm) with respect to the free ligand (30–50 mm), except for *P. aeruginosa*. The authors commented that cephalosporins undergo metal-catalyzed solvolytic degradation via beta-lactam ring opening. However, in this case, the antibacterial activity was preserved or increased, perhaps because the metal complex of beta-lactam antibiotics changes the stereochemistry required in the solvolytic reactions of the enzyme surface [104]. On the other hand, it is important to highlight that the structure used in this article was obtained after using density functional theory (DFT) calculations [105].

For **Tz-38a**–**Tz-38i**, the electronic spectral data, together with the magnetic moment, suggested a distorted octahedral geometry for the complexes. The antibacterial activity of the ligand and its complexes against *S. typhi* was tested using the serial dilution technique.

The MIC values for the ligands were in the range of 20–26 µg/mL, while the values of the complexes were in the range of 10–15 µg/mL; that is, the complexes enhanced the antibacterial activity compared to the initial ligands [106] (Figure 9).

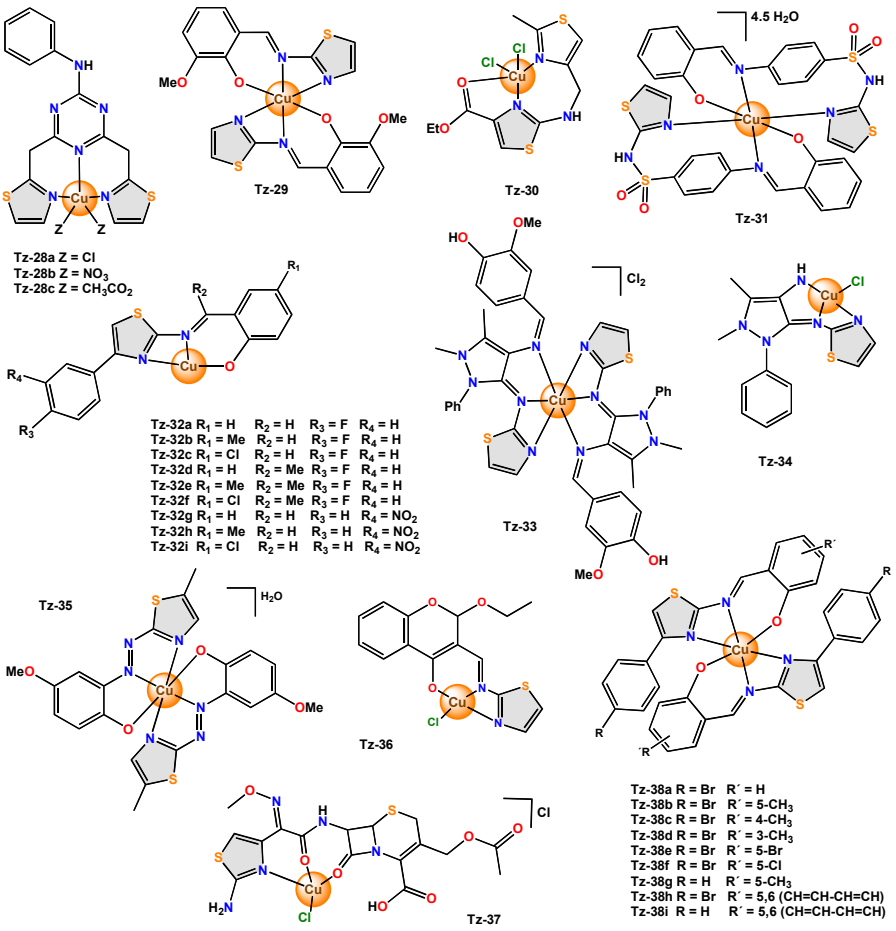

Figure 9. Copper complexes with tridentate thiazole ligands.

2.4. Copper Complexes with Tetradentate Thiazole Ligands

Finally, different complexes with tetradentate ligands have been reported, and such is the case with the functionalized thiazole with several donor sites that was used to obtain the **Tz-39** binuclear complex with an octahedral geometry. The ligand and **Tz-39** were evaluated by the disk diffusion method against bacterial strains (*S. aureus* and *E. coli*) and fungal strains (*C. albicans*). **Tz-39** did not show antimicrobial activity against the bacteria and fungi used. The authors mention that the negative effects of antimicrobial activity may be due to the fact that these compounds do not diffuse through the cell wall of the bacteria and, therefore, cannot interrelate with their biological process, or they can be dispersed and inactivated by bacterial enzymes [107].

The combination of sulfathiazole and an azo dye in the ligand allowed for obtaining the **Tz-40** binuclear complex. The antibacterial (*S. typhi*murium, *S. aureus*) and antifungal (*C. albicans*, *A. fumigates*) activities were examined utilizing the agar diffusion technique. The ligand was inactive against all organisms tested; however, the complex displayed good activity against *S. aureus* and *C. albicans* within the inhibition zones of 9.03 mm and 11.97 mm, respectively. The researchers conclude that the improved activity of **Tz-40** could be explained based on Overton's concept and Tweedy's chelation theory. Furthermore, the action mode of **Tz-40** could be related to the formation of hydrogen bonds between the compounds and the cellular centres, interfering with common cellular processes. In addition, the free ligand and **Tz-40** could disturb the respiration process in the cell and thus exclude the formation of proteins and cause limitations in the development of the organism [108].

On the other hand, the capacity of Schiff bases and sulfonamide derivatives was also used to obtain the binuclear copper chelate **Tz-41**, which exhibited an octahedral geometry. **Tz-41** was examined against bacteria (*E. coli* and *S. aureus*) and fungi (*C. albicans* and *A. fumigates*) by the agar well diffusion method. The result showed the same inhibition zone for **Tz-41** and the free ligand in *E. coli* (15 mm), and it was even lower in *C. albicans* (13 mm and 15 mm), with no activity in *S. aureus* and *A. fumigates* [109]. **Tz-42** was reported as a mononuclear complex consisting of a Schiff base-type tetradentate ligand and a central copper atom with square planar geometry. Then, the antibacterial activity (*E. coli*, *P. aeruginosa*, *B. subtilis* and *S. aureus*) was tested by the well diffusion method at different concentrations (30, 60, 90 µg). The results showed that **Tz-42** had higher activity (14–22 mm) than the free ligand (0–15 mm) at 90 µg. The authors suggested that this may be due to the higher lipophilic nature of **Tz-42,** which enhanced its diffusion through the cell membrane due to the combined activity between the metal and the ligand [110].

The metal complex **Tz-43** with a square planar geometry around the central metal ion was tested against pathogenic bacteria ((*E. coli*, *P. aeruginosa*, *B. subtilis* and *S. aureus*) and one fungal specie (*C. albicans*) by the well diffusion method. **Tz-43** displayed higher antibacterial activity (13–23 mm) than the free ligand (12–14 mm) and much better fungal activity (20 and 14 mm, respectively). The in silico DNA results revealed that **Tz-43** was bound to DNA through hydrogen bonds [111] (Figure 10).

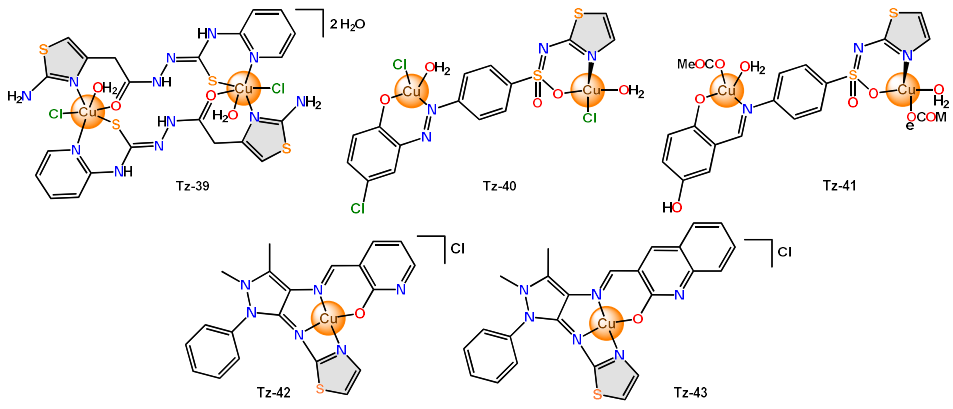

Figure 10. Copper complexes with tetradentate thiazole ligands.

3. Antibacterial and Antifungal Benzothiazole-Copper(II) Complexes

3.1. Copper Complexes with Monodentate Benzothiazole Ligands

The compound 2-Aminobenzothiazole and its simple metal complexes are well known for their possible biological activities, which include antimicrobial, anticancer, antifungal, anti-inflammatory, anthelmintic, antiulcer, and antitumor, among others [112]. The 2-aminobenzothiazole derivatives contain three nucleophilic sites (N, S, NH_2); all or some of them could be potential coordination sites. Nevertheless, the ligand is capable of binding to the metal centres through the endocyclic nitrogen atom instead of the other two, possibly coordinated with the NH_2 group or the sulphur atom present in the same molecule, as can be seen in the following works reported in the literature.

The benzothiazole used in **Btz-01** contains three potential coordination sites (endocyclic nitrogen, exocyclic nitrogen, and sulphur). Between the three nucleophilic centres, the endocyclic nitrogen is the most basic and easily coordinates with the metal ion, producing a complex with an octahedral geometry. The antibacterial activity of **Btz-01** was evaluated by the well assay, and the MIC value was calculated. The antifungal activity was also determined by the agar tube dilution method. Moderate bioactivities were observed against the pathogenic bacteria *E. sakazkii* and *S. aureus* (11 mm), with MIC values of 250 μg/mL, and lower bioactivity was obtained in *E. coli* and *K. pneumoniae* (16 and 9 mm), with MIC values of 500 μg/mL. For the free ligand, the inhibition zones were in the range of 7–10 mm, and the MIC values were in the range of 250–1000 μg/mL. Antifungal efficacy against *A. flavous*, *A. niger*, *A. fumigatus*, and *F. oxysporium* was also measured, and **Btz-01** was found to be more active against *A. flavous* and *F. oxysporium* (15.6 μg/mL) compared to the free ligand (62.5 and 31.25 μg/mL, respectively). In the case of *A. niger* (62.5 μg/mL) and *A. fumigatus* (31.25 μg/mL), the behaviour was the same for both the free ligand and for **Btz-01** [113].

In **BTz-02**, the benzothiazole coordinated with the copper ion by monodentate bonding and the crystal structure showed a distorted square pyramidal structure. Intermolecular hydrogen bonds between the carboxylate group and the amino molecules play an important role in stabilizing the crystal structure. The antimicrobial activity (*S. aureus*, *E. coli*, *E. faecalis*, *C. krusei*, *C. parapisilosis*) was evaluated by the well diffusion method at a concentration of 10 mg/mL. The ligand only showed antibacterial activity in *E. faecalis* and *E. coli* (2 and 4 mm, respectively) and did not display antifungal activity. However, **Btz-02** showed moderate activity against *E. faecalis* and *E. coli* (2 and 3 mm, respectively), and no activity against *S. aureus* was observed. The antifungal results showed that **Btz-02** had no activity against *C. krusei*, but showed modest activity against *C. parapisilosis* (2 mm) [112].

In **Btz-03**, **Btz-04a** and **Btz-04b**, two benzothiazoles were coordinated with copper, forming mononuclear and binuclear complexes depending on the reaction conditions. The three complexes were tested for their antibacterial effect on *E. coli* and *S. aureus* and for their antifungal activity in *R. mucilaginosa*, *C. albidosimilis*, *P. citrinum* and *A. niger* by the double serial dilution method, and the MIC value was calculated. All three complexes showed moderate antibacterial effects between 10 and 20 μg/mL. However, the antifungal effects were significant between 1 and 10 μg/mL. The MIC values were better than those reported for the free ligand between 1 and 50 μg/mL. With these results, the complexes could be selected as good antifungal candidates [114].

Considering that the change in the structure of the substituent at the C2 position of the benzothiazole commonly results in a change in its bioactivity, the derivatives **Btz-05a**–**Btz-05b** were synthesized. These compounds were reported with a square planar geometry and were evaluated for their antibacterial (*S. aureus*, *S. pyogenus*, *E. coli* and *P. aeruginosa*) and antifungal (*C. albicans*, *A. niger*, *A. clavatus*) activity by the broth dilution method. The bioassays showed specific activity in the inhibition of the growth of the four bacteria studied (62.5–200 μg/mL). Meanwhile, in the fungicidal activity, **Btz-05a**–**Btz-05b** did not show significant activity (500–1000 μg/mL). In general, **Btz-05a**–**Btz-05b** exhibited better antibacterial activity (125–500 μg/mL) than their free ligands [115] (Figure 11).

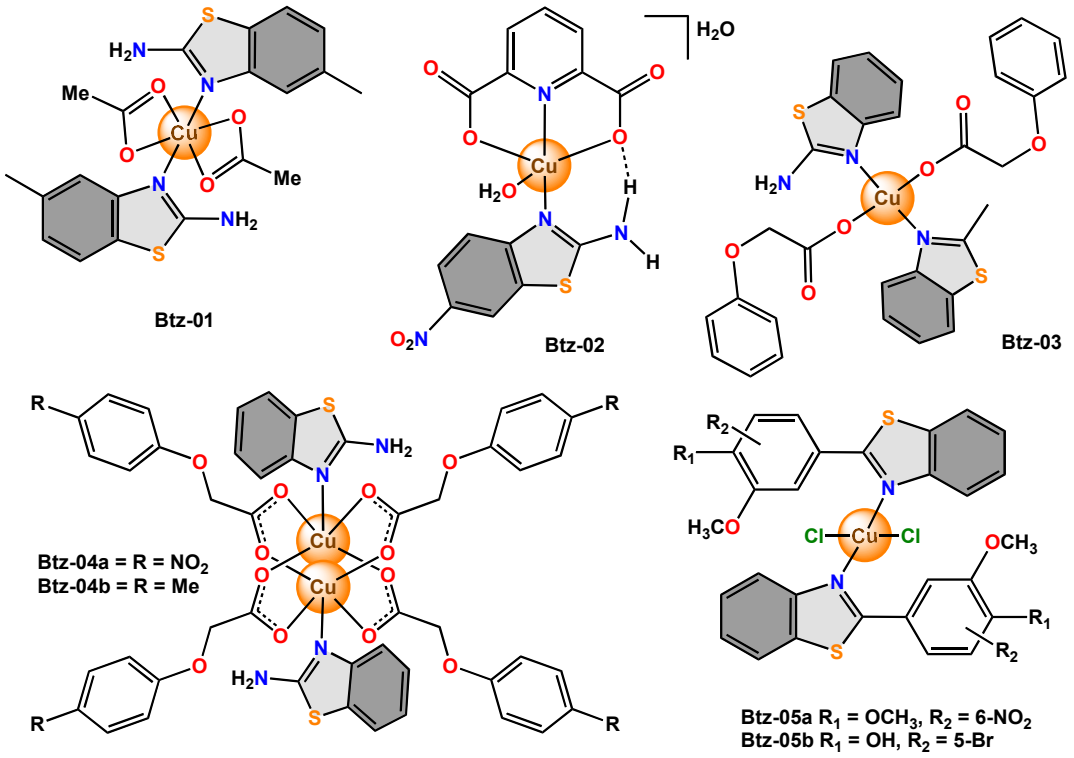

Figure 11. Copper complexes with monodentate benzothiazole ligands.

3.2. Copper Complexes with Bidentate Benzothiazole Ligands

Benzothiazole and its derivatives are of great interest due to their coordination capacity, which is favoured by the delocalized π system in their structures. These compounds are capable of binding to molecules of biological interest, such as DNA, through π–π interactions [115]. In this sense, the antimicrobial activity of bidentate complexes derived from benzothiazole has been reported. In **Btz-06** it was reported that the ligand acted as a bidentate agent that coordinated through the nitrogen atoms of the benzothiazole fragment, and it was also reported that the complex adopted a square planar geometry. The antimicrobial potential of **Btz-06** was evaluated against bacteria (*B. subtilis*, *S. aureus*, *K. oxytoca*, *E. coli*, *P. mirabilis* and *P. aeruginosa*) and fungi (*A. niger*, *A. flavus* and *R. stolonifera*) by the agar diffusion method at 250 µg/mL and by the MIC value. In general, **Btz-06** exhibited moderate-to-good antimicrobial activity against the test microbes; an inhibition halo of 14–21 mm for bacteria and 18–23 mm for fungi was obtained, but there was no effect on *S. aureus*. In the case of the free ligand, lower antimicrobial activity was presented against the test microbes; an inhibition halo of 7–12 mm for bacteria and 7–10 mm for fungi was obtained, but there was no effect on *P. aeruginosa* and *S. aureus*. The MIC value of the free ligand was in the range of 80–100 µg/mL for both microorganisms, and that of **Btz-06** was in the range of 10–90 µg/mL for bacteria and 30–100 µg/mL for fungi [116].

In 2015, two new copper(II) complexes, **Btz-07** and **Btz-08**, were reported. The authors found that **Btz-07** was mononuclear and had a distorted square pyramidal geometry. **Btz-08** was a thiocyanate bridged species in which each copper(II) ion adopted an irregular octahedral geometry. **Btz-08** is composed of discrete centrosymmetric neutral dimeric units. Two ligand moieties are connected via two thiocyanate (N,S) bridges end-to-end to form the dimeric unit, in which the thiocyanate ion is nearly linear. The next step was the evaluation of the antibacterial activity against *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli*. The best bioactivity results were with 1 mg/mL and demonstrated that both complexes have a broad spectrum of antibacterial activity against all bacteria tested (14–20 mm). In contrast, the free ligand displayed modest bioactivity (11–14 mm) towards all bacteria, even at high

doses. In general, **Btz-07** and **Btz-08** were active against *S. aureus* and *B. subtilis* and less bioactive against *P. aeruginosa* and *E. coli* [117].

For **Btz-09a**-**Btz-09b**, in the single crystal XRD analysis, a distorted tetrahedron was found around the central metal ion for both complexes. Then, the antibacterial activity was tested against *S. aureus*, *B. cereus* and *S. typhi* using the diffusion method. The inhibition zone of the ligand free is smaller (14–18 mm) than that of **BTz-09a** (14–24 mm) and **Btz-09b** (15–21 mm). These results showed that **Btz-09a**-**Btz-09** were more bioactive than the free ligand. The authors mention that in metal complexes, the metal ion polarity is probably reduced to a greater degree, and the increased delocalization of electrons over the entire chelate ring improves the lipophilicity of the complex and increases the penetration of the complexes into the lipid membrane of microorganisms [118].

BTz-10 is a copper(II) chelate and has a square planar geometry. This compound was evaluated against *S. aureus*, *E. coli*, and *K. pneumoniae* Although Btz-10 was successfully characterized, no data was obtained indicating acceptable bioactivity against the bacteria tested. The authors suggested that the concentration used was not sufficient to inhibit bacterial growth [119]

Btz-11 was described as a coordinated compound with a slightly distorted square pyramid geometry. **Btz-11** was tested on *E. coli*, *Salmonella*, *B. subtilis* and *S. aureus* and showed good antibacterial activities against these microorganisms (160–256 μg/mL) compared to the free ligand (1024 μg/mL). In the words of the authors, the biological activity can be attributed mainly to the synergistic enhancement of the central ion and the free ligand. In general, the MIC value results for **Btz-11** follow the trend of *E. coli* (160 μg/mL), *S. aureus* (200 μg/mL), *B. subtilis* (256 μg/mL), *Salmonella* (256 μg/mL) [120].

Sulphur-containing compounds are found in all cells of the body and are essential for life [121]. There are several medical conditions for which sulphur derivatives could be used therapeutically [122]. In this context, other complexes have been reported that use sulphur atoms in addition to benzothiazole as part of the main ligand. **Btz-12** with a square planar geometry was used as an antibacterial agent against *E. coli*, *S. aureus*, *B. subtilis* and *P. aeruginosa* by the cup plate method. **Btz-12** was active against *E. coli*, *S. aureus*, and *B. subtilis* (8–10 mm), and no inhibition was detected against *P. aeruginosa*. The free ligand was active in *E. coli* and *B. subtilis* but with increases in the inhibition zone (13 mm) with respect to **Btz-12** [123]. **Btz-13** with a square planar geometry was tested in vitro against pathogenic bacteria (*E. coli* and *S. aureus*) and fungi (*C. albicans*) by the agar streak dilution method to determine the MIC value. The antibacterial and antifungal activity also showed that the free ligand possessed better bioactivity against bacteria (4.68 and 3.12 μg/mL) and fungi (1.56 μg/mL) compared to **Btz-13** (75, 50 μg/mL for bacteria and 37.5 μg/mL for *C. albicans*) [124].

In the case of **Btz-14a** and **Btz-14b**, the copper(I) centre presented a tetrahedral geometry. Antimicrobial tests of free ligands and coordination complexes were performed on multi-resistant bacteria isolated from dogs under clinical conditions (*E. coli*, *Proteus*, *P. aeruginosa* and *S. aureus*). Furthermore, the compounds were tested against bacterial strains (*E. coli*, *P aeruginosa*, *S. aureus*) and fungi (*C. krusei*, *C. albicans*). In bacteria isolated under clinical conditions, **Btz-14a** and **Btz-14b** did not show antibacterial activity, while both ligands showed antimicrobial activity in *E. coli* and *P. aeruginosa* (10 mg/mL). In the bacterial strains, Btz-14a showed antimicrobial activity in *S. aureus* (10 mg/mL), while the free ligand (R=H) was active in *P. aeruginosa*, *S. aureus*, *C. krusei* and *C. albicans* (2.5–20 mg/mL). **Btz-14b** showed antimicrobial activity in *S. aureus* and *P. aeruginosa* (10 mg/mL), while the free ligand (R = CH_3) was active in *P. aeruginosa*, *S. aureus*, *C. krusei* and *C. albicans* (5–10 mg/mL). The authors mention that the ligands can be recommended for preclinical detection [125,126]. On the other hand, another ligand was reported but using chlorine as a substituent in the C3 and C5 positions of the phenyl ring. However, in the analyses of the IR spectra, it was shown that the C=N bond of the benzothiazole was not involved in the coordination complex [127].

In the case of **Btz-15**, its potential as an antibacterial (*S. aureus*, *B. cereus*, *M. roseus*) and antifungal (*A. flavus*, *A. niger*, *P. chrysogenum*) agent was evaluated by the disk diffusion method. **Btz-15** showed a slight increase in the inhibition zones (7–13 mm) with respect to the free ligand (4–12 mm). The antimicrobial activity of **Btz-15** stood out in *M. roseus* and *A. niger* (13 and 10 mm), and it was inactive in *A flavus* [128].

The results obtained with these investigations that include more sulphur atoms to the main ligand could be related to the studies that indicate that sulphur compounds regulate the potential toxic effects of metal ions such as copper [129–132] (Figure 12).

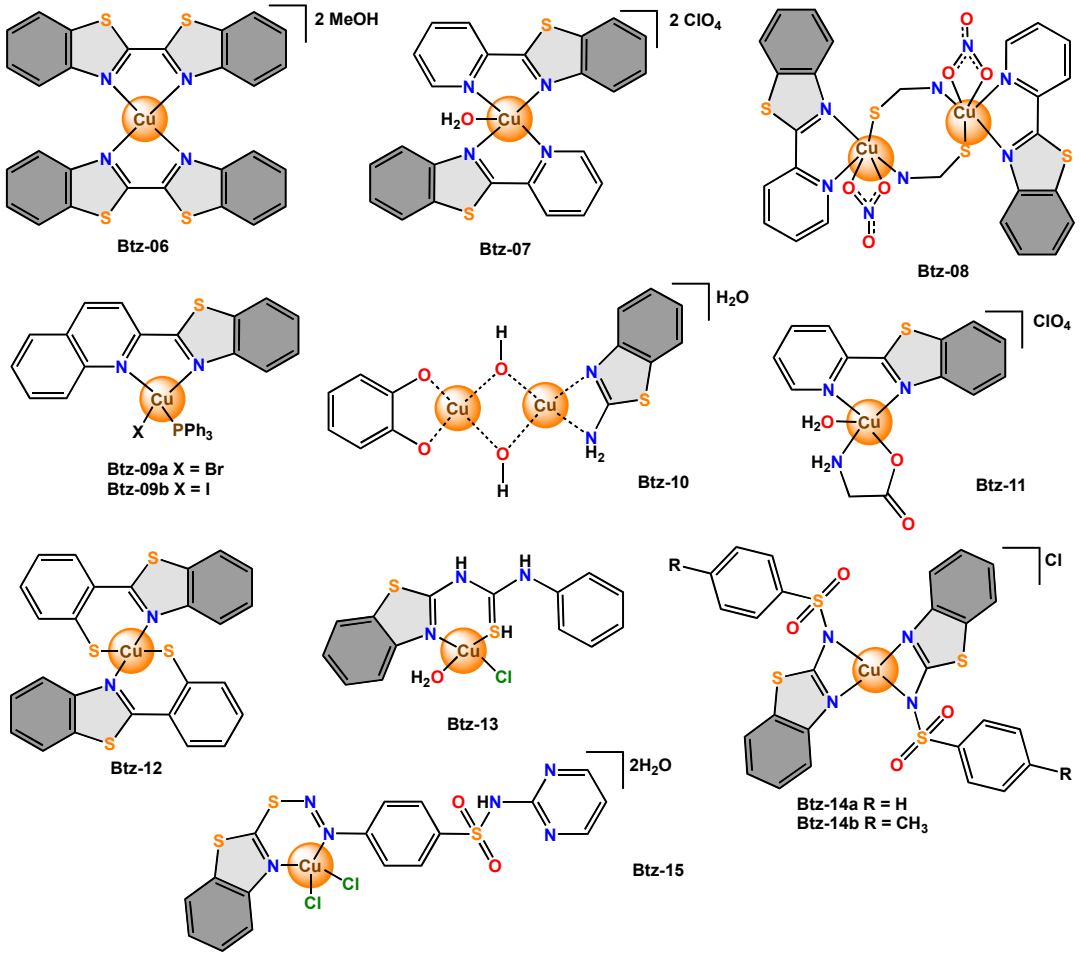

Figure 12. Copper complexes with bidentate benzothiazole ligands.

Schiff bases have versatile applications for the treatment of numerous diseases [133,134], and their metal complexes have shown significant biological activity [135]. In this context, different Schiff bases containing benzothiazole in their structure have been used in order to form adducts between the copper ion and some of the following functional groups: the nitrogen of a Schiff base (azomethine or imine group) and the nitrogen of a hydrazone or the nitrogen of a benzothiazole, to potentiate its antimicrobial activity. In addition, numerous investigations have reported that heterocyclic rings containing sulphur, nitrogen, and/or oxygen are responsible for the biological activity of Schiff bases and their metal complexes. Furthermore, it has been confirmed that chelation in these compounds, to a large extent, is also responsible for such activity [136,137].

Recent research compared the use of benzothiazole derivatives containing the hydrazone moiety and different substituents on the aromatic rings. The purpose was to determine the form of coordination of these ligands and their influence on biological activity. The authors reported different copper complexes with bidentate and tridentate ligands as in **Btz-16**, **Btz-22**–**Btz-24** [138], **Btz-17a**, **Btz-17b**, **Btz-20** [139], and even using mixed ligands

as in **Btz-18**, **Btz-19**, **Btz-25** [140]. The complexes presented different distorted geometries; for example, **Btz-16** and **Btz-22a** were pseudotetrahedral; **Btz-17a** and **Btz-17b** were octahedral; **Btz-18**, **Btz-20**, **BTz-22b**, **Btz-23a**, **Btz-23b** and **Btz-25** were square pyramidal; and **Btz-19** and **Btz-24** were square planar. Moreover, in the IR spectrum, the absorption band of the NH group disappears, indicating the tautomeric form of the **Btz-16**, **Btz-19**, **Btz-20** and **Btz-24** complexes. In all cases, for antimicrobial activity, 10 µL of a 10^{-4} M solution of each complex was used against bacteria (*E. coli*, *P. aeruginosa*, *Staphylococcus coagulase-positive*, *Streptococcus β-hemolytic type A*, *Streptococcus β-hemolytic type B* and *S. aureus*) and fungi (*C. albicans*). The ligand used in the synthesis of **Btz-16**, **Btz-17a**, **Btz-17b** and **Btz-20** with methoxy and amino groups as substituents on the phenyl ring did not show antimicrobial activity. Ligands used in the synthesis of **Btz-18**, **Btz-19** and **Btz-22**–**Btz-25** with dimethylamino and hydroxyl groups as substituents on the phenyl ring were weak inhibitors (0–3 mm). Nevertheless, all the complexes were biologically active. The most active bidentate ligand complexes were **Btz-17a**, **Btz-18** and **Btz-19** (2–5 mm), and the most active tridentate ligand complexes were **Btz-22a**, **Btz-24** and **Btz-25** (1–5 mm). The authors mention that it is possibly due to the more rapid diffusion of these metal complexes through the cell membrane.

On the other hand, **Btz-21** was tested as an antibacterial and antifungal agent by the agar diffusion method. **Btz-21** showed good antibacterial activity against *E. coli* and *B. subtilis*, with inhibition zones of 2.5 and 2.0 mm, respectively. The study of antifungal activity showed inhibition zones of 1.6 and 1.4 mm against *A. niger* and *A. flavus*, respectively. Nonetheless, the free ligand showed antimicrobial activity only in *B. subtilis*, with an inhibition halo of 1.1 mm [141] (Figures 13 and 14).

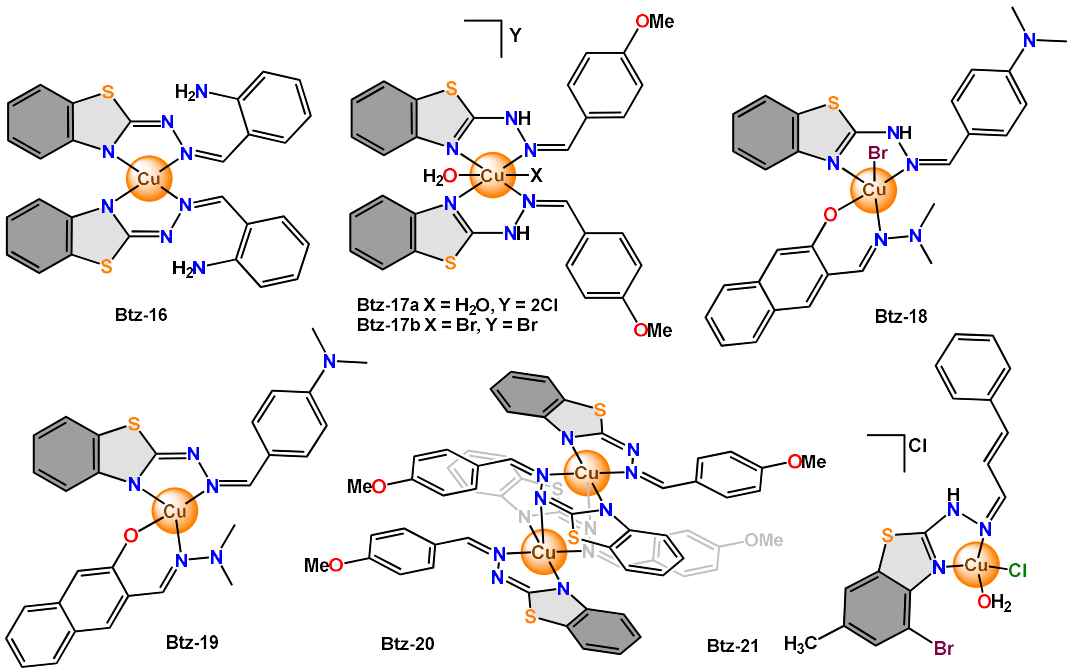

Figure 13. Copper complexes with bidentate benzothiazole ligands functionalized with hydrazine moieties.

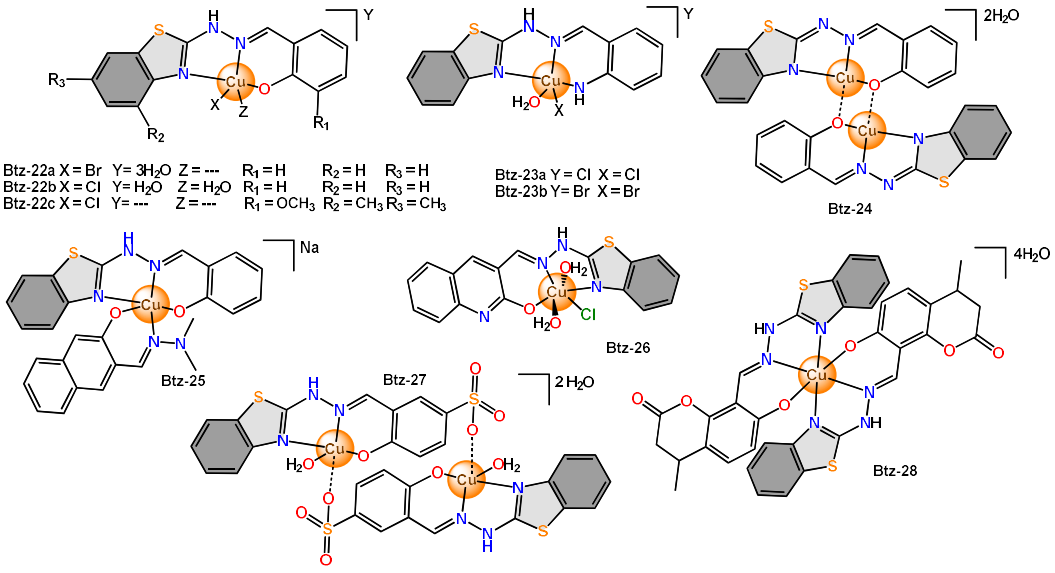

Figure 14. Copper complexes with tridentate benzothiazole ligands functionalized with hydrazine moieties.

3.3. Copper Complexes with Tridentate and Tetradentate Benzothiazole Ligands

Tridentate complexes have been reported by different research groups and have been used as antimicrobial agents. For example, **Btz-26** with an octahedral geometry was screened against bacteria (*E. coli* and *P. aeruginosa*) and fungi (*A. niger* and *Cladosporium*). The results showed good bioactivity against fungi (58.3 and 122.2% inhibition) but less activity against bacteria (9.37 and 13.79% inhibition). **Btz-26** was chosen for studies evaluating the value of MIC in fungi at a concentration of 250 µg, presenting 25% and 100% inhibition in *A. niger* and *Cladosporium*, respectively. The authors commented that the increased activity of **Btz-26** *versus* free ligand is due to chelation, which favours its infiltration through the lipid layers of the cell membrane [142]. Continuing with the search for bioactive copper complexes, the synthesis of **Btz-22c** containing a tridentate Schiff base-type ligand was reported. Structural analysis revealed that **Btz-22c** had a tetrahedral geometry. The antibacterial analysis of this complex (*E. coli*, *S. thyphi*, *S. aureus*, *B. subtilis*, *Erwinia*, *Xanthomonas*) was performed, as well as the evaluation of the antifungal activity (*A. niger*, *P. chrysogenum*, *F. moniliform* and *A. flavus*) by the agar cup method. Inhibition experiments in bacteria showed an inhibition zone of 11–23 mm for **Btz-22c** and 5–15 mm for the free ligand. Although in the antifungal test no activity was observed for *F. moniliform*, moderate activity was shown for the other fungi studied [143].

A new Schiff base type ligand was used to obtain **Btz-27**, which is a dinuclear copper complex that adopts a pentacoordinate quasi-square pyramidal geometry. The complex was bioassayed as an antibacterial (*S. aureus*, *B. cereus*, *E. coli*, *P. aeruginosa*) and as an antifungal (*C. albicans*) agent using the agar disk diffusion method. The inhibition zone showed that the free ligand did not have any bioactivity, and that *E. coli* and *P. aeruginosa* bacteria were not inhibited by **Btz-27**. In addition, inhibition zones of 25 and 30 mm were obtained for the bacteria *S. aureus* and *B. cereus*, respectively, and the yeast *C. albicans* presented an inhibition zone of 25 mm. MIC showed activity for *S. aureus*, *B. cereus* and *C. albicans*, with values of 0.5, 1 and 4 mg/mL, respectively. The authors mention that lipophilicity, which controls the rate of entry into the cell, is influenced by coordination. In addition, the good results for *S. aureus* and *B. cereus* could be associated with the absence of the outer membrane, which acts as a barrier to penetration [144].

Btz-28 with octahedral geometry was proposed as a candidate for the evaluation of antibacterial (*S. aureus* and *E. coli*) and antifungal (*C. albicans* and *A. fumigatus*) activity by the broth microdilution method. In addition, a study of antituberculous activity (*Mycobacterium tuberculosis*) was carried out using the microplate Alamar blue assay (MABA) method. The

results showed good activity against *S. aureus* and *E. coli* bacteria (3.12 and 12.5 μg/mL, respectively) and *C. albicans* and *A. fumigatus* fungi (12.5 and 25 μg/mL, respectively) compared to the free ligand (25–50 μg/mL). The antituberculous activity (0.8 μg/mL) also obtained better results for the complex compared to the free ligand (1.6 μg/mL) [145] (Figures 13 and 14).

Btz-29 with octahedral geometry was proposed as a candidate to test its antimicrobial activity against bacteria (*M. luteus* and *E. coli*) and fungi (*A. niger* and *A. terreus*) using the disk diffusion bioassay method. **Btz-29** showed higher activity in both bacteria (15 and 21 mm) and fungi (20 and 17 mm) compared to the free ligand also in both bacteria (12 and 15 mm) and fungi (14 and 12 mm). The author mentioned that the presence of benzothiazole resulted in the formation of metal complexes with higher biological activity than that of their original ligands. Furthermore, **Btz-29** was stable, and its antimicrobial properties could help reduce or inhibit pathogen growth [94]. **Btz-30** with an octahedral geometry was tested in bacteria (*S. aureus*, *S. epidermis*, *P. aeruginosa*, *Streptococcus*, *E. coli*, *Klebsiella* sp.) and fungi (*C. albicans*) by employing the disk diffusion method. **Btz-30** showed slightly higher antimicrobial activity against pathogenic bacteria (11–16 mm) and the yeast *C. albicans* (11 mm) compared to the free ligand on bacteria (10–15 mm) and fungi (10 mm). The highest values of 16 mm in the inhibition zone for **Btz-30** were observed for *S. aureus* and *Streptococcus* sp. [146].

Btz-31 is a copper(II) complex whose structural analysis revealed a distorted square pyramidal geometry. The antibacterial activity of **Btz-31** against bacteria (*S. epidermidis* and *A. baumannii*) was studied. The authors reported that they did not observe inhibition zones in the cultures when using the free ligand. Nevertheless, when using **Btz-31**, inhibition zones of 8 mm and 12 mm were shown for *A. baumannii* and *S. epidermidis*, respectively. However, the authors reported that the antibacterial efficacy was diffusion-limited due to the low solubility of **Btz-31** in aqueous biological media. In addition, they mentioned that bacteria have a modest electronegative surface potential and allow easy cell penetration in the case of cationic complexes compared to their neutral analogues, such as **Btz-31** [147]. **Btz-32** with an octahedral geometry was used to evaluate the antimicrobial activity against pathogenic bacteria (*S. aureus*, *Enterococcus*, *S. viridans*, *E. coli*, *P. aeruginosa* and *K. pneumoniae*) and fungi (*A. niger* and *A. flavus*). The results showed that **Btz-32** had modest antibacterial activity (9–12 mm), slightly better than the free ligand (6–12 mm). The study of the antifungal activity also showed that **Btz-32** had more bioactivity (62.2–68.9%) than the free ligand (48.9–56.7%). This result suggested that **Btz-32** had antibacterial activity by inhibiting the multiplication process of microbes by obstructing their active sites. It was also observed that **Btz-32** exhibited a higher bioactivity against *A. niger* than *A. flavus*, and the authors explained that the difference in the activity of **Btz-32** against the tested microbes was influenced by the impermeability of microbe cells or by differences in the ribosomes of microbial cells [148].

On the other hand, **Btz-33** was described as a monomeric complex with octahedral geometry. Therefore, a bioassay of **Btz-33** and the free ligand was carried out by analysing an antibiogram to determine its antibacterial activity. Antibiograms showed that the free ligand was inactive in *E. coli*, but there was an improvement in the inhibitory activity of **Btz-33** [149]. **Btz-34** was reported as a phenoxyde bridged tetranuclear copper(II) complex. This compound presented an octahedral geometry and was tested in bacteria (*P. aeruginosa*, *S. aureus*) and fungi (*A. niger* and *C. albicans*) at different concentrations (5–100 μg/mL). In general, the antimicrobial activity of **Btz-34** was higher than that of the free ligand. The best results were found in *P. aeruginosa*, *S. aureus*, and *C. albicans* at concentrations of 50 μg/mL. Furthermore, it was highly active in *A. niger* at concentrations of 5 μg/mL, even up to twenty times more than the ligand [150]. **Btz-35** was a reported binuclear complex with a square pyramidal geometry and was tested in bacteria (*P. aeruginosa* and *B. cirroflagellosus*) and fungi (*A. niger* and *C. albicans*) by the cup plate method. **Btz-35** presented low inhibition in *P. aeruginosa* (5.2%) but high antimicrobial inhibition in *B. cirroflagellosus*, *A. niger* and *C. albicans* (61.9 to 260%) [151] (Figure 15).

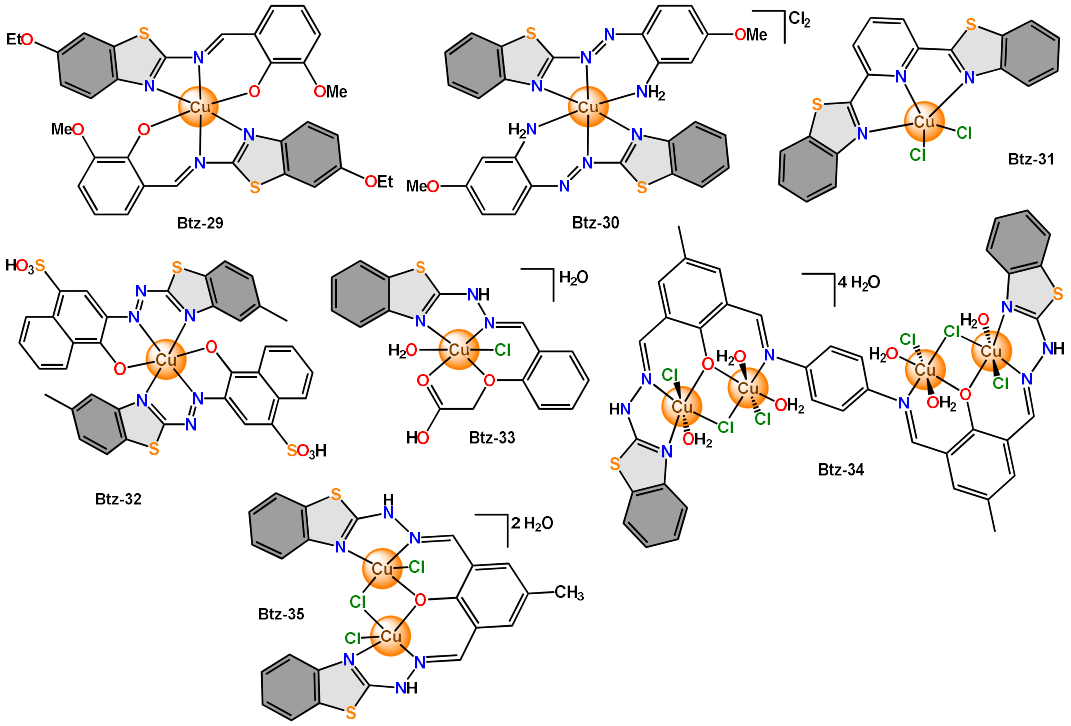

Figure 15. Copper complexes with diverse tridentate and tetradentate benzothiazole ligands.

The enhanced antimicrobial activity of metal complexes containing thiazole or benzothiazole as ligands could be based on Overtone's concept and Tweedy's chelation theory. Overtone discovered that molecules with greater lipid solubility penetrate the cell more quickly. Consequently, lipid solubility is an essential factor that must be controlled to enhance antimicrobial properties. Additionally, Tweedy proposed that the partial distribution of the positive charge of the metal ion with the free ligand and the overlap of the M-L orbitals considerably reduce the polarity of the metal ion. Furthermore, it increases the delocalization of electrons over the entire complex system and improves the lipophilicity of the complex. This increases the cell permeability of the complex through the cell membrane and blocks the growth of the microorganism. For this reason, the ligands have lower antimicrobial activity compared to thiazole and benzothiazole-derived copper complexes [152]. Additionally, aspects such as solubility, conductivity, electronic density, membrane penetrability, concentration, size molecular and stereochemistry have an effect on the development of the activity of complexes on microorganisms [75].

4. General Remarks

In recent decades, the antimicrobial activity of a greater number of thiazole complexes and a smaller number of benzothiazole complexes has been studied. In both cases, few complexes with monodentate ligands have been reported. On the one hand, most of the thiazole complexes analysed have been cationic in nature, and the most widely used counterion has been chloride and nitrate. On the other hand, most of the benzothiazole complexes analysed have been neutral in nature, and the few cases of cationic nature use chloride as a counterion. The copper atom geometry in thiazole complexes was square planar, while in benzothiazole complexes, it was both octahedral and square planar.

It was observed that when both the new compounds and already established drugs are used as chelating agents or organic ligands, the antimicrobial activity is potentiated exponentially. Sulfathiazole and thiabendazole were the most studied drugs as organic ligands, adding different co-ligands to improve the solubility of the copper complexes obtained. In such cases, *bipy* and *phen* helped to improve the antimicrobial activity. In

addition, the complexes obtained from metal copper coordinated to the drugs derived from benzothiazole is still a seldom explored field.

The most commonly used thiazoles as organic ligands had amine, sulphonamide, amide and imine groups as substituents in the C2 position (Schiff bases). This functionalization allowed them to obtain more coordination points with the copper atom. However, there are few reported examples with substituents at the C4 position, and even less common at the C5 position of the thiazole ring. In the case of benzothiazole, the hydrazone-type substituent in the C2 position of the ring has been the most used, since it allowed for the obtaining of ligands of greater denticity that are more selective to coordinate with the copper ion.

5. Conclusions

As multi-resistant infections have severely increased, current research groups are exploring new treatment options and strategies to combat bacteria and fungi. These approaches include improving the solubility of existing drugs or synthesizing new drugs with a greater capacity to attack these microorganisms. Metal complexes are a great strategy because they have different modes of action and because they can adopt a variety of coordination geometries and redox states, improving the lipophilicity and cell permeability of the complex. In this way, the complexes can reach the internal organelles and DNA to finally block the growth of microorganisms.

Thiazole and benzothiazole derivatives are widely known as highly important scaffolds for obtaining molecules with numerous biological activities. The ability of these heterocycles to coordinate with the copper ion has allowed for the obtaining of different monodentate, bidentate, tridentate and tetradentate complexes with antimicrobial activity. In addition, different research groups have shown that the coordination of these heterocycles with the copper ion improves lipid solubility, and their coordination complexes penetrate the cell more quickly, enhancing their antimicrobial activity.

In general, it was observed that the complexes with benzothiazole showed a greater antifungal capacity compared to the activity shown by the complexes with thiazole. Changes in the binding sites of the ligand to the metal change the configuration and distribution of electron density, modifying its bioactivity. In both cases, their antimicrobial capacity depends on their lipid solubility to penetrate the membrane; this is explained by the Overtone concept and Tweedy's theory of chelation.

The organic ligands with thiazole and benzothiazole are sufficiently active, for which a greater number of complexes without co-ligands have been reported. Nonetheless, in cases where co-ligands have been used, very good results have been reported. For complexes with thiazole, antimicrobial activity has been reported in different bacteria, both Gram + and Gram—,and no preference is observed in the inhibition of this type of bacteria. However, there is a positive effect when modifying the counterion used in the cationic complexes, highlighting the activity of the complexes with nitrate and chloride. The antifungal activity has been less reported with respect to the antibacterial activity. Nevertheless, in most cases, very good activity has been reported in the *C. albicans* strain.

Additionally, the biological activity of benzothiazole derivatives has been reported in different bacteria, both Gram + and Gram -. In these cases, the antimicrobial activity decreased with the use of monodentate ligands or with the use of ligands with a greater number of sulphur atoms. There are very few reports of substituted benzothiazole ligands on the aromatic ring (C4-C7 positions). However, the few examples showed that the electro donor groups (alkoxy and alkyl) potentiate the biological activity. Metals other than copper have been used, such as zinc, cobalt or nickel, showing very good antimicrobial activity. Nonetheless, the study of copper-based systems is even broader today.

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Abbreviations

Abbreviation	Meaning
Bipy	2,2′-Bipyridine
CNS	Central nervous system
MABA	Microplate Alamar blue assay
MBC	Minimum bactericidal concentration
MIC	Minimum inhibitory concentration
MTT	(3-[4,5-Dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide)
NSAIDs	Non-steroidal anti-inflammatory drug
phen	1,10-phenanthroline
STz	Sulfathiazole
TBZH	Thiabendazole

Appendix A

Table A1. Species of microorganisms mentioned in the review.

Species	Short Name	Long Name
Gram-positive	B. cirroflagellosus	*Bacillus cirroflagellosus*
	B. subtilis	*Bacillus subtilis*
	B. cereus	*Bacillus cereus*
	B. megaterium	*Bacillus megaterium*
	E. faecalis	Enterococcus *faecalis*
	Listeria	*Listeria*
	M. tuberculosis	*Mycobacterium tuberculosis*
	M. luteus	*Micrococcus luteus*
	M. roseus	*Micrococcus roseus*
	S. aureus	*Staphylococcus aureus*
	S. pyogenus	*Streptococcus pyogenes*
	S. epidermidis	*Staphylococcus epidermidis*
	S. viridans	*Streptococcus viridans*
	S. coagulase	*Staphylococcus coagulase*
	S. β-hemolytic	*Streptococcus β-hemolytic*
Gram-negative	*A. baumannii*	*Acinetobacter baumannii*
	Citrobacter	*Citrobacter*
	E. coli	*Escherichia coli*
	E. sakazkii	*Enterobacter sakazakii*
	Erwinia	*Erwinia*
	K. oxytoca	*Klebsilla oxytoca*
	K. pneumoniae	*Klebsiella pneumoniae*
	P. aeruginosa	Pseudomonas aeruginosa
	P. mirabilis	*Proteus mirabilis*
	P. vulgaris	*Proteus vulgaris*
	S. enteriditis	*Salmonella enteriditis*
	S. thyphi	*Salmonella typhi*
	V. Cholera	*Vibrio cholerae*
	Xanthomonas	*Xanthomonas*
Fungi	*A. clavatus*	*Aspergillus clavatus*
	A. flavus	*Aspergillus flavus*
	A. niger	*Aspergillus niger*
	A. terreus	*Aspergillus terreus*
	A. fumigates	*Aspergillus fumigates*
	C. albicans	*Candida albicans*
	C. krusei	*Candida krusei*
	C. parapisilosis	*Candida parapisilosis*
	Cladosporium	Cladosporium
	C. albidosimilis	*Cryptococcus albidosimilis*
	F. moneliforme	*Fusarium moniliforme*
	P. citrinum	*Penicillium citrinum*
	P. frondosus	*Polyporus frondosus*
	P. chrysogenum	*Penicillium chrysogenum*
	P. expansum	*Penicillium expansum*
	R. stolonifer	*Rhizopus stolonifer*
	R. mucilaginosa	*Rhodotorula mucilaginosa*

References

1. Sharma, P.C.; Bansal, K.K.; Sharma, A.; Sharma, D.; Deep, A. Thiazole-containing compounds as therapeutic targets for cancer therapy. *Eur. J. Med. Chem.* **2020**, *188*, 112016. [CrossRef]
2. Al-Ghorbani, M.; Alghamdi, H.A.; Khanum, S.A. A review on anticancer potential of thiazole-heterocyclic hybrid compounds. *Eur. J. Biomed. Pharm. Sci.* **2018**, *5*, 122–128.
3. Zhang, Z.; Shu, B.; Zhang, Y.; Deora, G.S.; Li, Q.-S. 2,4,5-Trisubstituted thiazole: A privileged scaffold in drug design and activity improvement. *Curr. Top. Med. Chem.* **2020**, *20*, 2535–2577. [CrossRef]
4. Abdu-Rahem, L.R.; Ahmad, A.K.; Abachi, F.T. Synthesis and medicinal attributes of thiazole derivatives: A review. *Syst. Rev. Pharm.* **2021**, *12*, 290–295.
5. Ayati, A.; Emami, S.; Moghimi, S.; Foroumadi, A. Thiazole in the targeted anticancer drug discovery. *Future Med. Chem.* **2019**, *11*, 1929–1952. [CrossRef]
6. Guemues, M.; Yakan, M.; Koca, I. Recent advances of thiazole hybrids in biological applications. *Future Med. Chem.* **2019**, *11*, 1979–1998. [CrossRef] [PubMed]
7. Sharma, D.; Bansal, K.K.; Sharma, A.; Pathak, M.; Sharma, P.C. A brief literature and review of patents on thiazole related derivatives. *Curr. Bioact. Compd.* **2019**, *15*, 304–315. [CrossRef]
8. Qureshi, A.; Pradhan, A. Short review on thiazole derivative. *J. Drug Deliv. Ther.* **2019**, *9*, 842–847.
9. Verma, R.S.; Gupta, S.K.; Jaiswal, S.; Dwivedi, A.K. A review on thiazole based compounds & it's pharmacological activities. *World J. Pharm. Res.* **2020**, *9*, 577–589.
10. Khatik, G.L.; Datusalia, A.K.; Ahsan, W.; Kaur, P.; Vyas, M.; Mittal, A.; Nayak, S.K. A retrospect study on thiazole derivatives as the potential antidiabetic agents in drug discovery and developments. *Curr. Drug Discov. Technol.* **2018**, *15*, 163–177. [CrossRef] [PubMed]
11. Kashyap, A.; Adhikari, N.; Das, A.; Shakya, A.; Ghosh, S.K.; Singh, U.P.; Bhat, H.R. Review on synthetic chemistry and antibacterial importance of thiazole derivatives. *Curr. Drug Discov. Technol.* **2018**, *15*, 214–228. [CrossRef] [PubMed]
12. Kumawat, M.K. Thiazole containing heterocycles with antimalarial activity. *Curr. Drug Discov. Technol.* **2018**, *15*, 196–200. [CrossRef]
13. Kumar, A.; Kumar, P.; Shravya, H. Thiazole derivatives as potential antidiabetic agents. *Rasayan J. Chem.* **2021**, *Special Issue*, 175–179. [CrossRef]
14. Nayak, S.; Gaonkar, S.L. A review on recent synthetic strategies and pharmacological importance of 1,3-thiazole derivatives. *Mini-Rev. Med. Chem.* **2019**, *19*, 215–238. [CrossRef] [PubMed]
15. Mishra, C.B.; Kumari, S.; Tiwari, M. Thiazole: A promising heterocycle for the development of potent CNS active agents. *Eur. J. Med. Chem.* **2015**, *92*, 1–34. [CrossRef] [PubMed]
16. Arshad, M.F.; Alam, A.; Alshammari, A.A.; Alhazza, M.B.; Alzimam, I.M.; Alam, M.A.; Mustafa, G.; Ansari, M.S.; Alotaibi, A.M.; Alotaibi, A.A.; et al. Thiazole: A versatile standalone moiety contributing to the development of various drugs and biologically active agents. *Molecules* **2022**, *27*, 3994. [CrossRef]
17. Fatima, Y.; Dayal, M.S.; Lal, T.S.; Ahmad, I. Thiazole core: A restorative target in the discovery of potent anti-cancer agents. *Indian J. Adv. Chem. Sci.* **2021**, *9*, 268–274.
18. Petrou, A.; Fesatidou, M.; Geronikaki, A. Thiazole ring—A biologically active scaffold. *Molecules* **2021**, *26*, 3166. [CrossRef]
19. Jain, S.; Pattnaik, S.; Pathak, K.; Kumar, S.; Pathak, D.; Jain, S.; Vaidya, A. Anticancer potential of thiazole derivatives: A retrospective review. *Mini-Rev. Med. Chem.* **2018**, *18*, 640–655. [CrossRef]
20. Shelar, U.B. Thiazole an attractive scaffold for development of anticancer agent: A review. *Int. J. Pharm. Pharm. Res.* **2022**, *24*, 311–321.
21. Varghese, N.; Jacob, J.; Mythri, M.; Nija, B.; Sheeba Jasmine, T.S. Synthesis of thiazole derivatives-a review. *World J. Pharm. Pharm. Sci.* **2016**, *5*, 624–636.
22. Sharma, D.; Sharma, V.; Sharma, A.; Goyal, R.; Tonk, R.K.; Thakur, V.K.; Sharma, P.C. Green chemistry approaches for thiazole containing compounds as a potential scaffold for cancer therapy. *Sustain. Chem. Pharm.* **2021**, *23*, 100496. [CrossRef]
23. Farghaly, T.A.; Alsaedi, A.M.R.; Alenazi, N.A.; Harras, M.F. Anti-viral activity of thiazole derivatives: An updated patent review. *Expert Opin. Ther. Pat.* **2022**, *32*, 791–815. [CrossRef]
24. Sharma, D.; Malhotra, A.; Bansal, R. An overview of discovery of thiazole containing heterocycles as potent GSK-3b inhibitors. *Curr. Drug Discov. Technol.* **2018**, *15*, 229–235. [CrossRef] [PubMed]
25. Agarwal, S.; Kalal, P.; Gandhi, D.; Prajapat, P. Thiazole containing heterocycles with CNS activity. *Curr. Drug Discov. Technol.* **2018**, *15*, 178–195. [CrossRef] [PubMed]
26. Chhabria, M.T.; Patel, S.; Modi, P.; Brahmkshatriya, P.S. Thiazole: A review on chemistry, synthesis and therapeutic importance of its derivatives. *Curr. Top. Med. Chem.* **2016**, *16*, 2841–2862. [CrossRef]
27. Morigi, R.; Locatelli, A.; Leoni, A.; Rambaldi, M. Recent patents on thiazole derivatives endowed with antitumor activity. *Recent Pat. Anti-Cancer Drug Discov.* **2015**, *10*, 280–297. [CrossRef]
28. Chugh, V.; Pandey, G.; Rautela, R.; Mohan, C. Heterocyclic compounds containing thiazole ring as important material in medicinal chemistry. *Mater. Today Proc.* **2022**, *69 (Pt. 2)*, 478–481. [CrossRef]
29. Borcea, A.-M.; Ionut, I.; Crisan, O.; Oniga, O. An overview of the synthesis and antimicrobial, antiprotozoal, and antitumor activity of thiazole and bisthiazole derivatives. *Molecules* **2021**, *26*, 624. [CrossRef]

30. Hassan, A.; Hassan, H.A.; Abdelhamid, D.; El-Din, A.; Abuo-Rahma, G. Synthetic approaches toward certain structurally related antimicrobial thiazole derivatives. *Heterocycles* **2021**, *102*, 1675–1728. [CrossRef]
31. Mishra, I.; Mishra, R.; Mujwar, S.; Chandra, P.; Sachan, N. A retrospect on antimicrobial potential of thiazole scaffold. *J. Heterocycl. Chem.* **2020**, *57*, 2304–2329. [CrossRef]
32. Singh, A.; Malhotra, D.; Singh, K.; Chadha, R.; Bedi, P.M.S. Thiazole derivatives in medicinal chemistry: Recent advancements in synthetic strategies, structure activity relationship and pharmacological outcomes. *J. Mol. Struct.* **2022**, *1266*, 133479. [CrossRef]
33. Namitha, T.H.; Nair, S.S.; Kumar, A.; Vinod, B.; Daisy, P.A. A review on synthesis and biological activity of thiazole and its derivatives. *Int. J. Pharm. Sci. Rev. Res.* **2021**, *70*, 29. [CrossRef]
34. Joule, J.A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; John Wiley & Sons, Ltd.: Chichester, UK, 2010; pp. 13–17.
35. Abd El-Meguid, E.A.; Naglah, A.M.; Moustafa, G.O.; Awad, H.M.; El Kerdawy, A.M. Novel benzothiazole-based dual VEGFR-2/EGFR inhibitors targeting breast and liver cancers: Synthesis, cytotoxic activity, QSAR and molecular docking studies. *Bioorg. Med. Chem. Lett.* **2022**, *58*, 128529. [CrossRef]
36. Zhilitskaya, L.V.; Shainyan, B.A.; Yarosh, N.O. Modern approaches to the synthesis and transformations of practically valuable benzothiazole derivatives. *Molecules* **2021**, *26*, 2190. [CrossRef]
37. Qadir, T.; Amin, A.; Salhotra, A.; Sharma, P.K.; Jeelani, I.; Abe, H. Recent advances in the synthesis of benzothiazole and its derivatives. *Curr. Org. Chem.* **2022**, *26*, 189–214. [CrossRef]
38. Keri, R.S.; Patil, M.R.; Patil, S.A.; Budagupi, S. A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry. *Eur. J. Med. Chem.* **2015**, *89*, 207–251. [CrossRef]
39. Irfan, A.; Batool, F.; Zahra, N.; Syeda, A.; Islam, A.; Osman, S.M.; Nocentini, A.; Alissa, S.A.; Supuran, C.T. Benzothiazole derivatives as anticancer agents. *J. Enzyme Inhib. Med. Chem.* **2020**, *35*, 265–279. [CrossRef]
40. Sharma, P.C.; Bansal, K.K.; Deep, A.; Pathak, M. Benzothiazole derivatives as potential anti-infective agents. *Curr. Top. Med. Chem.* **2017**, *17*, 208–237. [CrossRef]
41. Agarwal, D.K.; Agarwal, S.; Gandhi, D. Benzothiazole: A versatile synthetic auxillary for antiepileptic drugs. *Chem. Biol. Interface* **2018**, *8*, 135–137.
42. Patel, T.; Siva Subramaniam, N.; Eshrath; Divya, C. Benzothiazole: A molecule with broad spectrum of antimicrobial activity. *World J. Pharm. Pharm. Sci.* **2017**, *6*, 566–576.
43. Lihumis, H.S.; Alameri, A.A.; Zaooli, R.H. A review on recent development and biological applications of benzothiazole derivatives. *Prog. Chem. Biochem. Res.* **2022**, *5*, 147–164. [CrossRef]
44. Elamin, M.B.; Elaziz, A.A.E.S.A.; Abdallah, E.M. Benzothiazole moieties and their derivatives as antimicrobial and antiviral agents: A mini-review. *Int. J. Res. Pharm. Sci.* **2020**, *11*, 3309–3315. [CrossRef]
45. Raju, G.N.; Sai, K.B.; Chandana, K.; Rao, N.R. Benzothiazole: Unique and versatile scaffold in the field of cancer. *J. Chem. Pharm. Res.* **2015**, *7*, 286–293.
46. Pathak, A.K.; Saroj, R. Clinical efficacy of benzothiazole in antitumor activity: A recent trends. *World J. Pharm. Pharm. Sci.* **2020**, *9*, 796–838.
47. Nivatya, H.K.; Singh, A.; Verma, R.; Varshney, S. Review on: Synthesis and biological evaluation of different benzothiazole derivatives. *World J. Pharm. Pharm. Sci.* **2018**, *7*, 865–881.
48. Srivastava, A.; Mishra, A.P.; Chandra, S.; Bajpai, A. Benzothiazole derivative: A review on its pharmacological importance towards synthesis of lead. *Int. J. Pharm. Sci. Res.* **2019**, *10*, 1553–1566. [CrossRef]
49. Midhula, C.C.; Marathakam, A.; Baijika, P.; Shadiha, S.K. A short review on synthesis and its medicinal significance of 1,3 benzothiazole derivatives. *World J. Pharm. Res.* **2018**, *7*, 1–11.
50. Asif, M.; Imran, M. A mini-review on pharmacological importance of benzothiazole scaffold. *Mini-Rev. Org. Chem.* **2021**, *18*, 1086–1097. [CrossRef]
51. Kumar, A.; Mishra, A.K. Advancement in pharmacological activities of benzothiazole and its derivatives: An up to date review. *Mini-Rev. Med. Chem.* **2021**, *21*, 314–335. [CrossRef]
52. Tariq, S.; Kamboj, P.; Amir, M. Therapeutic advancement of benzothiazole derivatives in the last decennial period. *Arch. Pharm.* **2019**, *352*, 1–17. [CrossRef]
53. Agarwal, S.; Gandhi, D.; Kalal, P. Benzothiazole: A versatile and multitargeted pharmacophore in the field of medicinal chemistry. *Lett. Org. Chem.* **2017**, *14*, 729–742. [CrossRef]
54. Abrol, S.; Bodla, R.B.; Goswami, C. A comprehensive review on benzothiazole derivatives for their biological activities. *Int. J. Pharm. Sci. Res.* **2019**, *10*, 3196–3209. [CrossRef]
55. Bhat, M.; Belagali, S.L. Structural activity relationship and importance of benzothiazole derivatives in medicinal chemistry: A comprehensive review. *Mini-Rev. Org. Chem.* **2020**, *17*, 323–350. [CrossRef]
56. Banerjee, S.; Payra, S.; Saha, A. A review on synthesis of benzothiazole derivatives. *Curr. Organocatalysis* **2017**, *4*, 164–181. [CrossRef]
57. Popli, J.V.; Kumbhare, M.R.; Suran, A.R.; Bhalerao, M.R.; Agrawal, P.A. Benzothiazole analogues and their biological aspects: A review. *Indian J. Chem. Sect. B.* **2021**, *60B*, 1659–1669.
58. Gao, X.; Liu, J.; Zuo, X.; Feng, X.; Gao, Y. Recent advances in synthesis of benzothiazole compounds related to green chemistry. *Molecules* **2020**, *25*, 1675. [CrossRef] [PubMed]

59. Sulthana, S.; Pandian, P. A review on Indole and Benzothiazole derivatives its importance. *J. Drug Deliv. Ther.* **2019**, *9*, 505–509. [CrossRef]
60. Shaista, A.; Amrita, P. Benzothiazole—A magic molecule. *Int. J. Pharm. Sci. Res.* **2017**, *8*, 4909–4929. [CrossRef]
61. Nangare, A.K.; Chavan, A.N.; Avhad, U.R.; Lodha, G.S.; Kolate, N.S.; Ransing, B.J.; Bura, A. Benzothiazole analogs synthesis by using different types of reaction. *Eur. J. Biomed. Pharm. Sci.* **2017**, *4*, 221–225.
62. Satyadev, S.A.; Prasad, Y.R.; Avupati, V.R.; Aparna, K.; Rudru, M.J. A review on benzothiazole—A versatile scaffold in the field of pharmaceutical chemistry. *Int. J. Pharm.* **2016**, *6*, 150–158.
63. Cascioferro, S.; Parrino, B.; Carbone, D.; Schillaci, D.; Giovannetti, E.; Cirrincione, G.; Diana, P. Thiazoles, their benzofused systems, and thiazolidinone derivatives: Versatile and promising tools to combat antibiotic resistance. *J. Med. Chem.* **2020**, *63*, 7923–7956. [CrossRef]
64. De, S.; Aamna, B.; Sahu, R.; Parida, S.; Behera, S.K.; Dan, A.K. Seeking heterocyclic scaffolds as antivirals against dengue virus. *Eur. J. Med. Chem.* **2022**, *240*, 114576. [CrossRef]
65. Tratrat, C. Benzothiazole as a promising scaffold for the development of antifungal agents. *Curr. Top. Med. Chem.* 2023; *ahead of print*. [CrossRef]
66. Fatima, A.; Pooja, K.; Savita, S.; Singh, M.; Verma, I.; Siddiqui, N.; Javed, S. Quantum chemical, experimental spectroscopic, Hirshfeld surface and molecular docking studies of the anti-microbial drug sulfathiazole. *J. Mol. Struct.* **2021**, *1245*, 131118. [CrossRef]
67. Öztürk, F.; Bulut, İ.; Bekiroğlu, Y.; Bulut, A. Spectroscopic, structural, electrochemical and antimicrobiological studies of Cu(II)-sulfathiazole complex with diethylenetriamine ligand. *Polyhedron* **2016**, *119*, 420–428. [CrossRef]
68. Öztürk, F.; Aycan, T.; Çon, A.H. Spectroscopic, structural characterization and magnetic studies of Cu(II)-sulfathiazole complex with 1,10-phenanthroline and N-(2-hydroxyethyl)-ethylenediamine ligands. *J. Mol. Struct.* **2020**, *1202*, 127220. [CrossRef]
69. Joshi, S.R.; Pachling, S.P.; Habib, S.I. Metal complexes of salisylaldoxime: Preparation characterization and biological activity. *Inorg. Chem. Indian J.* **2014**, *9*, 102–108.
70. Chaviara, A.T.; Cox, P.J.; Repana, K.H.; Papi, R.M.; Papazisis, K.T.; Zambouli, D.; Kortsaris, A.H.; Kyriakidis, D.A.; Bolos, C.A. Copper(II) Schiff base coordination compounds of dien with heterocyclic aldehydes and 2-amino-5-methyl-thiazole: Synthesis, characterization, antiproliferative and antibacterial studies. Crystal structure of CudienOOCl$_2$. *J. Inorg. Biochem.* **2004**, *98*, 1271–1283. [CrossRef] [PubMed]
71. Johnson, J.; Yardily, A. Co(II), Ni(II), Cu(II), and Zn(II) metal complexes of chalcone: Synthesis, characterization, thermal, antimicrobial, photocatalytic degradation of dye and molecular modeling studies. *Appl. Organomet. Chem.* **2022**, *36*, e6465. [CrossRef]
72. Johnson, J.; Yardily, A. Spectral, modeling and biological studies on a novel (E)-3-(3-bromo-4-methoxyphenyl)-1-(thiazol-2-yl)prop-2-en-1-one and some bivalent metal(II) complexes. *J. Mol. Struct.* **2021**, *1244*, 130991. [CrossRef]
73. Sadeek, S.A.; Abd El-Hamid, S.M.; Mohamed, A.A.; Zordok, W.A.; El-Sayed, H.A. Spectroscopic characterization, thermogravimetry, density functional theory and biological studies of some mixed-ligand complexes of meloxicam and 2,2′-bipyridine with some transition metals. *Appl. Organomet. Chem.* **2019**, *33*, e4889. [CrossRef]
74. Franzé, J.A.; Carvalho, T.F.; Gaglieri, C.; Caires, F.J.; Bannach, G.; Castro, R.C.; Treu-Filho, O.; Ionashiro, M.; Mendes, R.A. Synthesis, characterization, thermal and spectroscopic studies and bioactivity of complexes of meloxicam with some bivalent transition metals. *J. Therm. Anal. Calorim.* **2017**, *127*, 1393–1405. [CrossRef]
75. Aziz, N.M.; Abdullah, B.H. Synthesis, cytotoxicity, antibacterial activity and molecular modeling study of new mono, homo and heterobimetallic complexes of palladium(II) with some transition metal ions containing the ligands N-phenyl-N′-(2-thiazolyl)thiourea and diphosphines $Ph_2P(CH_2)nPPh_2$ (Where n = 1–3). *Indian J. Chem. A.* **2019**, *58*, 772–782.
76. Mohammed, S.R.; Ganganaik, K.; Halehatti, S.B.; Yuvaraj, T.C.M.; Manjunath, B. Synthesis of 3-methyl-1phenyl-4-(thiazol-2-yl)-1H-pyrazol-5(4H)-one via Sandmeyer reaction and their transition metal complexes; spectral, XRD, cytotoxicity, molecular docking and biological evaluation. *Der Pharma Chem.* **2017**, *9*, 19–26.
77. Nunes, J.H.B.; de Paiva, R.E.F.; Cuin, A.; da Costa Ferreira, A.M.; Lustri, W.R.; Corbi, P.P. Synthesis, spectroscopic characterization, crystallographic studies and antibacterial assays of new copper (II) complexes with sulfathiazole and nimesulide. *J. Mol. Struct.* **2016**, *1112*, 14–20. [CrossRef]
78. Mansour, A.M. Thermal, spectral, DFT and biological activity evaluation of Co(II), Ni(II) and Cu(II) complexes of N,S-chelated benzotriazole ligand. *J. Therm. Anal. Calorim.* **2016**, *123*, 571–581. [CrossRef]
79. Li, X.; Li, X.-J.; Li, Y.-T.; Wu, Z.-Y.; Yan, C.-W. Syntheses and structure of tetracopper(II) complexes with an N-benzoate-N′-[3-(2-hydroxylethylammino)propyl]oxamide ligand: Reactivity towards DNA, cytotoxic and antimicrobial activities. *New. J. Chem.* **2012**, *36*, 2472–2483. [CrossRef]
80. Alaghaz, A.-N.M.A.; Elbohy, S.A.H. New tetrachlorocyclodiphosph(V)azane complex of Co(II), Ni(II), and Cu(II): Preparation, characterization, solid state electrical conductivity and biological activity studies. *Phosphorus Sulfur.* **2008**, *183*, 2000–2019. [CrossRef]
81. Ashalekshmi, V.S.; Mohanan, K. Synthesis, characterization and antibacterial activity of copper (II) complexes with N-vanillidene-2-amino-4-phenylthiazole. *Asian J. Chem.* **2008**, *20*, 623–628. [CrossRef]
82. Badwaik, V.B.; Mahale, R.G.; Bevhade, J.B.; Aswar, A.S. Synthesis, characterization, thermal, electrical and antibacterial studies of complexes of bivalent metal ions. *J. Indian Chem. Soc.* **2005**, *82*, 777–780.

83. Chohan, Z.H.; Praveen, M. Synthesis, characterization, coordination and antibacterial properties of novel asymmetric 1,1′-disubstituted ferrocene-derived Schiff-base ligands and their Co(II), Cu(II), Ni(II) and Zn(II) complexes. *Appl. Organomet. Chem.* **2001**, *15*, 617–625. [CrossRef]
84. Chohan, Z. Antibacterial copper(II) complexes of 1,1′-symmetric ferrocene-derived Schiff-base ligands: Studies of the effect of anions on their antibacterial properties. *Appl. Organomet. Chem.* **2002**, *16*, 17–20. [CrossRef]
85. Andrejevic, T.P.; Aleksic, I.; Pockaj, M.; Kljun, J.; Milivojevic, D.; Stevanovic, N.L.; Nikodinovic-Runic, J.; Turel, I.; Djuran, M.I.; Glisic, B.D. Tailoring copper(II) complexes with pyridine-4,5-dicarboxylate esters for anti-*Candida* activity. *Dalton Trans.* **2021**, *50*, 2627–2638. [CrossRef] [PubMed]
86. Chen, J.Y.; Ren, X.X.; Mao, Z.W.; Le, X.Y. Synthesis, characterization, and antibacterial activities of two new copper(II) glycinate complexes incorporating 2-(4′-thiazolyl) benzimidazole/2-(2-pyridyl) benzimidazole. *J. Coord. Chem.* **2012**, *65*, 2182–2191. [CrossRef]
87. Qi, Y.Y.; Liu, Y.X.; Gan, Q.; Xiong, Y.H.; Mao, Z.W.; Le, X.Y. Three new mixed-ligand copper(II) complexes containing glycyl-l-valine and N, N-aromatic heterocyclic compounds: Synthesis, characterization, DNA interaction, cytotoxicity and antimicrobial activity. *Appl. Organomet. Chem.* **2018**, *32*, e4126. [CrossRef]
88. Zhu, L.; Lu, Y.; Ou, Z.; Le, X. Synthesis, characterization, antibacterial activities and DNA interaction of ternary copper(II) complex with 2-(4′-thiazolyl) benzimidazole and L-alaninate. *J. South China Agric. Univ.* **2012**, *33*, 574–579. [CrossRef]
89. Lu, Y.-M.; Ou, Z.-B.; Liu, H.-F.; Le, X.-Y. Syntheses, characterization, antibacterial activities of ternary copper (II) complexes with 2-(4′-thiazolyl) benzimidazole/2-(2-pyridyl) benzimidazole and L-methionine and their interaction with DNA. *Chin. J. Inorg. Chem.* **2011**, *27*, 704–710.
90. Ren, X.-X.; Wang, C.-X.; Lu, Y.-M.; Zhuang, C.-X.; Le, X.-Y. Synthesis, antibacterial activities of copper (II) complexes with ciprofloxacin and TBZ or HPB and their DNA interactions. *Chin. J. Inorg. Chem.* **2010**, *26*, 891–898.
91. Ren, X.; Chen, J.; Le, X. Antibacterial activities and nuclease properties of two new ternary copper(II) complexes with 2-(4′-thiazolyl)-benzimidazole and 2,2′-bipyridine/1,10-phenanthroline. *Chin. J. Chem.* **2011**, *29*, 1380–1388. [CrossRef]
92. Devereux, M.; McCann, M.; Shea, D.O.; Kelly, R.; Egan, D.; Deegan, C.; Kavanagh, K.; McKee, V.; Finn, G. Synthesis, antimicrobial activity and chemotherapeutic potential of inorganic derivatives of 2-(4′-thiazolyl)benzimidazole{thiabendazole}: X-ray crystal structures of $[Cu(TBZH)_2Cl]Cl.H_2O.EtOH$ and $TBZH_2NO_3$ (TBZH=thiabendazole). *J. Inorg. Biochem.* **2004**, *98*, 1023–1031. [CrossRef] [PubMed]
93. Vathanaruba, M.; Johnson, R.S.; Princess, R.; Tharmaraj, P. Pharmacological and molecular docking studies of new copper (II) complexes of N^2-phenyl-N^4,N^6-di(thiazol-2-yl)-1,3,5-triazine-2,4,6-triamine. *J. Mol. Struct.* **2022**, *1253*, 132275. [CrossRef]
94. Noreen, S.; Sumrra, S.H. Aminothiazole-linked metal chelates: Synthesis, density functional theory and antimicrobial studies with antioxidant correlations. *ACS Omega* **2021**, *6*, 33085–33099. [CrossRef]
95. Velluti, F.; Acevedo, A.; Serra, G.; Ellena, J.; Borthagaray, G.; Facchin, G.; Scarone, L.; Alvarez, N.; Torre, M.H. Novel bisthiazole ligand and its copper(II) complex with unusual seven membered ring: Synthesis, characterization, experimental and theoretical study of the effect of ligand flexibility, and antimicrobial activity. *Polyhedron* **2021**, *209*, 115490. [CrossRef]
96. Reiss, A.; Cioateră, N.; Dobrițescu, A.; Rotaru, M.; Carabet, A.C.; Parisi, F.; Rotaru, P.; Gănescu, A.; Dăbuleanu, I.; Spînu, C.I.; et al. Bioactive Co(II), Ni(II), and Cu(II) complexes containing a tridentate sulfathiazole-based (ONN) Schiff base. *Molecules* **2021**, *26*, 3062. [CrossRef] [PubMed]
97. Muthal, B.N.; Raut, B.N.; Tekale, A.S. Synthesis and characterization of transition metal ion (Co^{II}, Ni^{II}, Cu^{II} & Zn^{II}) complexes of Schiff bases derived from aminothiazole and their biological activity. *Int. J. Chem. Stud.* **2016**, *4*, 78–82.
98. Muthal, B.N. Synthesis of new schiff bases and their transition metal complexes (Co^{II}, Ni^{II}, Cu^{II} & Zn^{II}) and their characterization stability constant and microbial activities. *Pharm. Innov. J.* **2017**, *6*, 72–76.
99. Muthal, B.N. Transition metal ion Co^{II}, Ni^{II}, Cu^{II} & Zn^{II} complexes of tridentate ligands (NNO) their synthesis, characterization and biological activities. *Pharm. Innov. J.* **2017**, *6*, 90–95.
100. Kumaran, J.S.; Muthukumaran, J.; Jayachandramani, N.; Mahalakshmi, S. Synthesis, characterization, in silico DNA studies and antibacterial evaluation of transition metal complexes of thiazole based pyrazolone Schiff base. *J. Chem. Pharm. Res.* **2015**, *7*, 1397–1409.
101. Kumaran, J.S.; Priya, S.; Gowsika, J.; Jayachandramani, N.; Mahalakshmi. Synthesis, spectroscopic characterization, in silico DNA studies and antibacterial activities of copper(II) and zinc(II) complexes derived from thiazole based pyrazolone derivatives. *Res. J. Pharm. Biol. Chem. Sci.* **2013**, *4*, 279–287.
102. Al-Adilee, K.J.; Fanfon, D.Y. Preparation, spectral identification and analytical studies of some transition metal complexes with new thiazolylazo ligand and their biological activity study. *J. Chem. Chem. Eng.* **2012**, *6*, 1016–1028.
103. Kalanithi, M.; Kodimunthiri, D.; Rajarajan, M.; Tharmaraj, P. Synthesis, characterization and biological activity of some new VO(IV), Co(II), Ni(II), Cu(II) and Zn(II) complexes of chromone based NNO Schiff base derived from 2-aminothiazole. *Spectrochim. Acta A* **2011**, *82*, 290–298. [CrossRef]
104. Anacona, J.R.; Silva, G.D. Synthesis and antibacterial activity of cefotaxime metal complexes. *J. Chil. Chem. Soc.* **2005**, *50*, 447–450. [CrossRef]
105. Zhuravlev, E.V.; Alekseev, V.G.; Feofanova, M.A.; Ryasenskii, S.S. Complexation of Cu(II) with cefotaxime in NaCl solution. *Russ. J. Inorg. Chem.* **2016**, *61*, 877–879. [CrossRef]

106. More, P.G.; Bhalvankar, R.B. Synthetic, spectral, thermal and antibacterial studies on copper(II) and zinc(II) complexes using NNO donor Schiff bases. *J. Indian. Chem. Soc.* **2004**, *81*, 13–17. [CrossRef]
107. Fayed, T.A.; Gaber, M.; Abu El-Reash, G.M.; El-Gamil, M.M. Structural, DFT/B3LYP and molecular docking studies of binuclear thiosemicarbazide copper(II) complexes and their biological investigations. *Appl. Organomet. Chem.* **2020**, *34*, e5800. [CrossRef]
108. Saad, F.A.; El-Ghamry, H.A.; Kassem, M.A. Synthesis, structural characterization and DNA binding affinity of new bioactive nano-sized transition metal complexes with sulfathiazole azo dye for therapeutic applications. *Appl. Organomet. Chem.* **2019**, *33*, e4965. [CrossRef]
109. Al-Fahemi, J.H.; Khedr, A.M.; Althagafi, I.; El-Metwaly, N.M.; Saad, F.A.; Katouah, H.A. Green synthesis approach for novel benzenesulfonamide nanometer complexes with elaborated spectral, theoretical and biological treatments. *Appl. Organomet. Chem.* **2018**, *32*, e4460. [CrossRef]
110. Priya, S.; Kumaran, J.S.; Jayachandramani, N.; Mahalakshmi, S. Antibacterial studies of transition metal complexes of tetradentate thiazole based Schiff base. *Am. J. Pharm. Tech. Res.* **2013**, *3*, 607–616.
111. Kumaran, J.S.; Priya, S.; Muthukumaran, J.; Jayachandramani, N.; Mahalakshmi, S. Synthesis, characterization and biological studies of Cu(II), Co(II), Ni(II) and Zn(II) complexes of tetradentate Schiff base ligand. *J. Chem. Pharm. Res.* **2013**, *5*, 56–69.
112. Ílkimen, H.; Yenikaya, C.; Gülbandilar, A.; Sari, M. Synthesis and characterization of a novel proton salt of 2-amino-6-nitrobenzothiazole with 2,6-pyridinedicarboxylic acid and its metal complexes and their antimicrobial and antifungal activity studies. *J. Mol. Struct.* **2016**, *1129*, 25–33. [CrossRef]
113. Gul, Z.; Din, N.U.; Khan, E.; Ullah, F.; Tahir, M.N. Synthesis, molecular structure, anti-microbial, anti-oxidant and enzyme inhibition activities of 2-amino-6-methylbenzothiazole and its Cu(II) and Ag(I) complexes. *J. Mol. Struct.* **2020**, *1199*, 126956. [CrossRef]
114. Gu, H.B.; Wang, Z.Y.; Chen, W.Y. Copper(II) complexes bearing 2-amino benzothiazole and phenoxyacetic acid derivatives: Coordination modes and antimicrobial activity. *Chin. J. Inorg. Chem.* **2012**, *28*, 591–600.
115. Maru, M.; Shah, M.K. Synthesis, physico-chemical studies and antimicrobial evaluation of novel 2-(substituted aryl)-1H-benzo[d]thiazoles and their metal(II) chloride complexes. *Int. J. Pharm. Pharm. Sci.* **2012**, *4*, 388–391.
116. Omaka, O.; Ekennia, A.C.; Njoku, N.N.; Onwudiwe, D.C. Nickel(II) and copper(II) complexes of 2,2′-bibenzo[*d*]thiazole: Synthesis, characterization and biological studies. *Appl. Organomet. Chem.* **2018**, *32*, e4241. [CrossRef]
117. Ghosh, M.; Layek, M.; Fleck, M.; Saha, R.; Bandyopadhyay, D. Synthesis, crystal structure and antibacterial activities of mixed ligand copper(II) and cobalt(II) complexes of NNS Schiff base. *Polyhedron* **2015**, *85*, 312–319. [CrossRef]
118. Meghdadi, S.; Amirnasr, M.; Mirhashemi, A.; Amiri, A. Synthesis, characterization and X-ray crystal structure of copper(I) complexes of the 2-(2-quinolyl)benzothiazole ligand. Electrochemical and antibacterial studies. *Polyhedron* **2015**, *97*, 234–239. [CrossRef]
119. El-Zweay, R.S.; El-Ajaily, M.M.; Ben-Gweirif, S.F.; Maihub, A. Preparation, characterization and antibacterial activity of some mixed ligand chelates. *J. Chem. Soc. Pak.* **2013**, *35*, 67–71.
120. Yanmei, L.; Yongheng, C.; Zhibin, O.; Shi, C.; Chuxiong, Z.; Xueyi, L. Synthesis, antibacterial activities and nuclease properties of ternary copper(II) complex containing 2-(2′-pyridyl)benzothiazole and glycinate. *Chin. J. Chem.* **2012**, *30*, 303–310. [CrossRef]
121. Battin, E.E.; Brumaghim, J.L. Antioxidant activity of sulfur and selenium: A review of reactive oxygen species scavenging, glutathione peroxidase, and metal-binding antioxidant mechanisms. *Cell Biochem. Biophys.* **2009**, *55*, 1–23. [CrossRef]
122. Zhao, C.; Rakesh, K.P.; Ravidar, L.; Fang, W.Y.; Qin, H.L. Pharmaceutical and medicinal significance of sulfur (SVI)-Containing motifs for drug discovery: A critical review. *Eur. J. Med. Chem.* **2019**, *162*, 679–734. [CrossRef]
123. Ammar, R.A.; Alturiqi, A.S.; Alaghaz, A.-N.M.A.; Zayed, M.E. Synthesis, spectral characterization, quantum chemical calculations, in vitro antimicrobial and DNA activity studies of 2-(2′-mercaptophenyl) benzothiazole complexes. *J. Mol. Struct.* **2018**, *1168*, 250–263. [CrossRef]
124. Jambi, M.S. Quantum, characterization and spectroscopic studies on Cu(II), Pd(II) and Pt(II) complexes of 1-(benzo[d]thiazol-2-yl)-3-phenylthiourea and its biological application as antimicrobial and antioxidant. *J. Mol. Struct.* **2017**, *1143*, 217–228. [CrossRef]
125. Obasi, N.L.; Benedict, O.C.O.; Ukoha, P.O.; Anaga, A.O. Synthesis, characterization, and antimicrobial screening of N-(benzothiazole-2 yl)benzenesulphonamide and its Cu(I), Ni(II), Mn(II), Co(II), and Zn(II) complexes. *E-J. Chem.* **2012**, *9*, 2354–2370. [CrossRef]
126. Obasi, L.N.; Okoye, C.O.B.; Ukoha, P.O.; Chah, K.F. Synthesis, characterization and antimicrobial screening of N-(benzothiazol-2-yl)-4-methylbenzenesulphonamide and its Cu(I), Ni(II), Mn(II), Co(II) and Zn(II) complexes. *Asian J. Chem.* **2013**, *25*, 2369–2376. [CrossRef]
127. Obasi, L.N.; Okoye, C.O.B.; Ukoha, P.O.; Chah, K.F. Synthesis, characterization, and antimicrobial screening of N-(benzothiazol-2-yl)-2,5-dichlorobenzenesulphonamide and its Cu(I), Ni(II), Mn(II), Co(III) and Zn(II) complexes. *Asian J. Chem.* **2013**, *25*, 2199–2207. [CrossRef]
128. Awad, I.M.A.; Osman, A.H.; Aly, A.A.M. Heterocyclo-substituted sulfa drugs: Part XII. Mercapto-S-azo-benzothiazol dyes and their metal complexes. *Phosphorus Sulfur.* **2003**, *178*, 1339–1352. [CrossRef]
129. Ramoutar, R.R.; Brumaghim, J.L. Investigating the antioxidant properties of oxo-sulfur compounds on metal-mediated DNA damage. *Main Group Chem.* **2007**, *6*, 143–153. [CrossRef]
130. Atmaca, G. Antioxidant effects of sulfur-containing amino acids. *Yonsei Med. J.* **2004**, *45*, 776–788. [CrossRef] [PubMed]

131. Mukwevho, E.; Ferreira, Z.; Ayeleso, A. Potential role of sulfur-containing antioxidant systems in highly oxidative environments. *Molecules* **2014**, *19*, 19376–19389. [CrossRef] [PubMed]
132. Battin, E.E.; Brumaghim, J.L. Metal specificity in DNA damage prevention by sulfur antioxidants. *J. Inorg. Biochem.* **2008**, *102*, 2036–2042. [CrossRef]
133. Alfonso-Herrera, L.A.; Rosete-Luna, S.; Hernández-Romero, D.; Rivera-Villanueva, J.M.; Olivares-Romero, J.L.; Cruz-Navarro, J.A.; Soto-Contreras, A.; Arenaza-Corona, A.; Morales-Morales, D.; Colorado-Peralta, R. Transition metal complexes with tridentate Schiff bases (O N O and O N N) derived from salicylaldehyde: An analysis of their potential anticancer activity. *ChemMedChem* **2022**, *17*, e202200367. [CrossRef]
134. de Fátima, Â.; de Paula Pereira, C.; Olímpio, C.R.S.D.G.; de Freitas Oliveira, B.G.; Franco, L.L.; da Silva, P.H.C. Schiff bases and their metal complexes as urease inhibitors–a brief review. *J. Adv. Res.* **2018**, *13*, 113–126. [CrossRef] [PubMed]
135. Uddin, M.N.; Ahmed, S.S.; Alam, S.R. Biomedical applications of Schiff base metal complexes. *J. Coord. Chem.* **2020**, *73*, 3109–3149. [CrossRef]
136. Ashraf, T.; Ali, B.; Qayyum, H.; Haroone, M.S.; Shabbir, G. Pharmacological aspects of Schiff base metal complexes: A critical review. *Inorg. Chem. Commun.* **2023**, *150*, 110449. [CrossRef]
137. Malik, M.A.; Dar, O.A.; Gull, P.; Wani, M.Y.; Hashmi, A.A. Heterocyclic Schiff base transition metal complexes in antimicrobial and anticancer chemotherapy. *MedChemComm* **2018**, *9*, 409–436. [CrossRef]
138. Cálinescu, M.; Ion, E.; Georgescu, R.; Negreanu-Pîrjol, T. Synthesis and spectroscopic, antibacterial and antifungal studies on copper (II) complexes with 2-benzothiazolyl hydrazones. *Rev. Roum Chim.* **2008**, *53*, 911–919.
139. Cálinescu, M.; Ion, E.; Emandi, A.; Georgescu, R.; Negreanu-Pîrjol, T. Magnetic, optical and biological studies on copper (II) complexes with 2-benzothiazolyl hydrazones. II. *Rev. Chim.* **2008**, *59*, 1322–1326. [CrossRef]
140. Ion, E.; Cálinescu, M.; Emandi, A.; Badea, V.; Negoiu, D. Copper (II) complex compounds with mixed hydrazone ligands. *Rev. Chim.* **2008**, *59*, 12–16. [CrossRef]
141. Bhagat, S.M.; Deshpande, M.N. Synthesis and antimicrobial activity of some transition metal ion chelates of 2-(cinnamyl)-4-bromo-6-methyl benzothiazolyl hydrazones. *J. Chem. Pharm. Res.* **2012**, *4*, 1454–1456.
142. Kurdekar, G.S.; Mudigoudar, P.S.; Kulkarni, N.V.; Budagumpi, S.; Revankar, V.K. Synthesis, characterization, antibiogram and DNA binding studies of novel Co(II), Ni(II), Cu(II), and Zn(II) complexes of Schiff base ligands with quinoline core. *Med. Chem. Res.* **2011**, *20*, 421–429. [CrossRef]
143. Swamy, D.K.; Pachling, S.P.; Bhagat, T.M. Synthesis, characterization, antibacterial and antifungal studies on metal complexes with benzothiazolyl hydrazone. *Rasāyan J. Chem.* **2012**, *5*, 208–213.
144. Hosseini-Yazdi, S.A.; Mirzaahmadi, A.; Khandar, A.A.; Eigner, V.; Dušek, M.; Mahdavi, M.; Soltani, S.; Lotfipour, F.; White, J. Reactions of copper(II), nickel(II), and zinc(II) acetates with a new water-soluble 4-phenylthiosemicarbazone Schiff base ligand: Synthesis, characterization, unexpected cyclization, antimicrobial, antioxidant, and anticancer activities. *Polyhedron* **2017**, *124*, 156–165. [CrossRef]
145. Jawoor, S.S.; Patil, S.A.; Toragalmath, S.S. Synthesis and characterization of heteroleptic Schiff base transition metal complexes: A study of anticancer, antimicrobial, DNA cleavage and anti-TB activity. *J. Coord. Chem.* **2018**, *78*, 271–283. [CrossRef]
146. Dahi, M.A.; Jarad, A.J. Synthesis, characterization and biological evaluation of thiazolyl azo ligand complexes with some metal ions. *J. Phys.* **2020**, *1664*, 012090. [CrossRef]
147. Chakraborty, I.; Pinto, M.; Stenger-Smith, J.; Martinez-Gonzalez, J.; Mascharak, P.K. Synthesis, structures, and antibacterial properties of Cu(II) and Ag(I) complexes derived from 2,6-bis(benzothiazole)-pyridine. *Polyhedron* **2019**, *172*, 1–7. [CrossRef]
148. Al-khafagy, A.H. Synthesis, characterization, and biological study of some new metal-azo chelate complexes. *J. Chem. Pharm. Res.* **2016**, *8*, 296–302.
149. Netalkar, P.P.; Kamath, A.; Netalkar, S.P.; Revankar, V.K. Desing, synthesis and DNA binding activities of late first-row transition metal(II) complexes of bi-functional tri—And tetratopic imines. *Spectrochim. Acta A.* **2012**, *97*, 762–770. [CrossRef]
150. Kamath, A.; Kulkarni, N.V.; Netalkar, P.P.; Revankar, V.K. Phenoxide bridged tetranuclear Co(II), Ni(II), Cu(II) and Zn(II) complexes: Electrochemical, magnetic and antimicrobial studies. *Spectrochim. Acta A.* **2011**, *79*, 1418–1424. [CrossRef]
151. Annigeri, S.M.; Naik, A.D.; Gangadharmath, U.B.; Revankar, V.K.; Mahale, V.B. Symmetric binuclear complexes with an 'end-off'compartmental Schiff base ligand. *Transit. Metal Chem.* **2002**, *27*, 316–320. [CrossRef]
152. Panchal, P.K.; Parekh, H.M.; Pansuriya, P.B.; Patel, M.N. Bactericidal activity of different oxovanadium(IV) complexes with Schiff bases and application of chelation theory. *J. Enzym Inhib. Med. Chem.* **2006**, *21*, 203–209. [CrossRef] [PubMed]