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Review

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*Review*

# An Overview on the Structure-Activity Relationship in Novel Antimicrobial Thiazoles Clubbed with Various Heterocycles (2017–2022)

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**Abstract:** Antimicrobial resistance is an increasing problem for the global public health. One of the strategies to combat this issue is the synthesis of novel antimicrobials through rational drug design based on extensive structure-activity relationship studies. The thiazole nucleus is a prominent feature in the structure of many authorized antimicrobials, being clubbed with different heterocycles. The purpose of this review is to study the structure-activity relationship in antimicrobial thiazoles clubbed with various heterocycles reported in the literature between 2017 and 2022, in order to offer an overview of the last years in terms of antimicrobial research and provide a helpful instrument for future research in the field.

**Keywords:** thiazole; structure-activity relationship; antimicrobial; heterocycles; hybrid compounds

## 1. Introduction

Antimicrobial resistance (AMR) represents a major threat to the global public health and an increasing challenge to overcome. According to the latest statistics [1], AMR has caused globally 1.27 million deaths alone, with the indiscriminate use of antimicrobials, not only for human but also for livestock, representing the main cause of the problem. Pathogens with the most increased risk for developing resistance are *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and Enterobacteriales to carbapenems and to new molecular entities of newer generation cephalosporins [1].

Strategies in medicinal chemistry for fighting AMR include the total synthesis of well-established antibiotics classes, based on extensive structure-activity relationships of the preexistent antibiotic classes (for example eravacycline), optimization of the physicochemical property space (finafloxacin), knowledge of the target in order to design new scaffolds (avibactam and vaborbactam), synthesis of hybrid compounds with synergistic activity (cadazolid), re-exploration of targets of older antibiotics (griselimycins targeting DnaN, the sliding clamp of DNA polymerase), and targeting the virulence factors (elastase B, lectins A and B of *P. aeruginosa*, quorum-sensing, or transcriptional regulator PqsR) [2].

Thiazole is a five-membered heterocycle, part of the azoles group containing one nitrogen and one sulfur heteroatoms. It is found in a series of authorized antimicrobial drugs, such as aztreonam, various cephalosporins (including the newest cefiderocol), abafungin, isavuconazole, ravuconazole, ethaboxam, and myxothiazol, thus underlining the importance of this nucleus for the antimicrobial activity [3–5]. The effect of the thiazole nucleus on the biological activity of a molecule can be

influenced by clubbing it directly or through a linker with other moieties with pharmacological potential, therefore creating hybrid compounds [6].

Knowledge of qualitative and quantitative structure-activity relationship studies (SAR) has great importance in a rational drug design. Therefore, this review aims to study the structure-activity relationships of novel antimicrobial thiazole clubbed with various heterocycles in hybrid compounds, reported in the last six years, as a helpful tool for further research and development of antimicrobials bearing the thiazole heterocycle. The publications were selected by interrogating Scopus, SpringerLink, PubMed, and EMBASE databases, using "Thiazole AND Hybrid AND Antimicrobial" as search syntax, filtering the results by "Classical Article" filter as article type, and setting the publication date range between 2017 and 2022. A total of 366 results from all four databases were obtained. However, it is important to mention that many of the results were indexed in two or more databases. A bibliometric analysis performed on the selected publications revealed that thiazole in antimicrobial hybrid compounds is a topic of increasing interest in the last three years (Figure 1). Therefore, 45 publications that met the eligibility criteria for this review (synthesis of hybrid compounds bearing the thiazole scaffold clubbed with other heterocycles) were discussed.
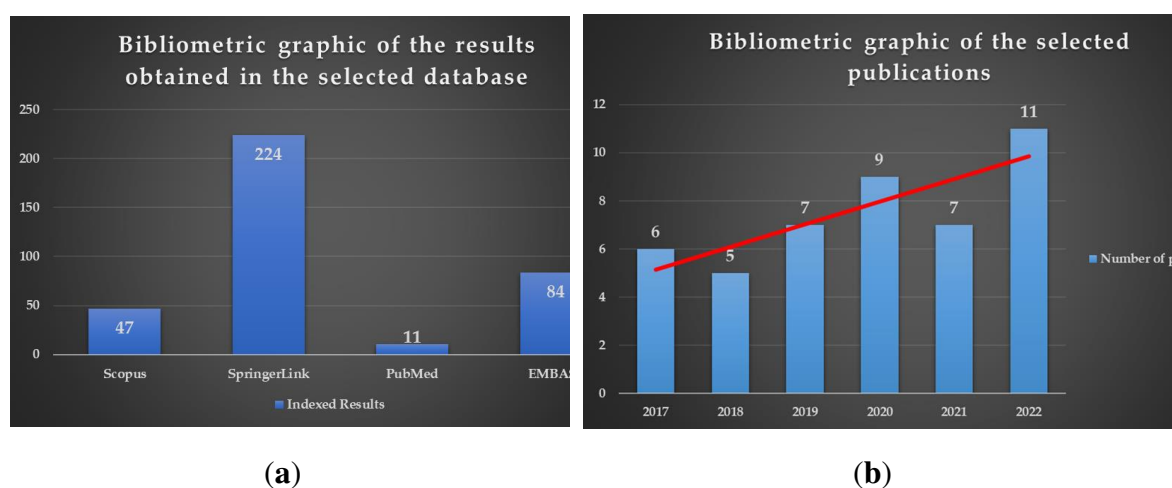


(**a**)                                                        (**b**)

**Figure 1.** (**a**) Bibliometric graphic of the indexed results obtained from Scopus, SpringerLink, PubMed, and EMBASE databases; (**b**) Bibliometric graphic of the selected publications for this review, based on the publication year.

## 2. Structure-Activity Relationships in Antimicrobial Thiazole-based Hybrid Compounds

The selected papers were organized based on the nature of heterocycles that were clubbed with thiazole. Additionally, they were ordered by their size, thus starting with the smallest heterocycles and finishing with polyheterocyclic systems (Figure 2). This offered an overview on how the antimicrobial activity may also be affected by this aspect. It is worth mentioning that no research on antimicrobial thiazoles clubbed with three-membered heterocycles was available in the literature in the specified timeframe. Thus, the classification started with the four-membered group of heterocycles.
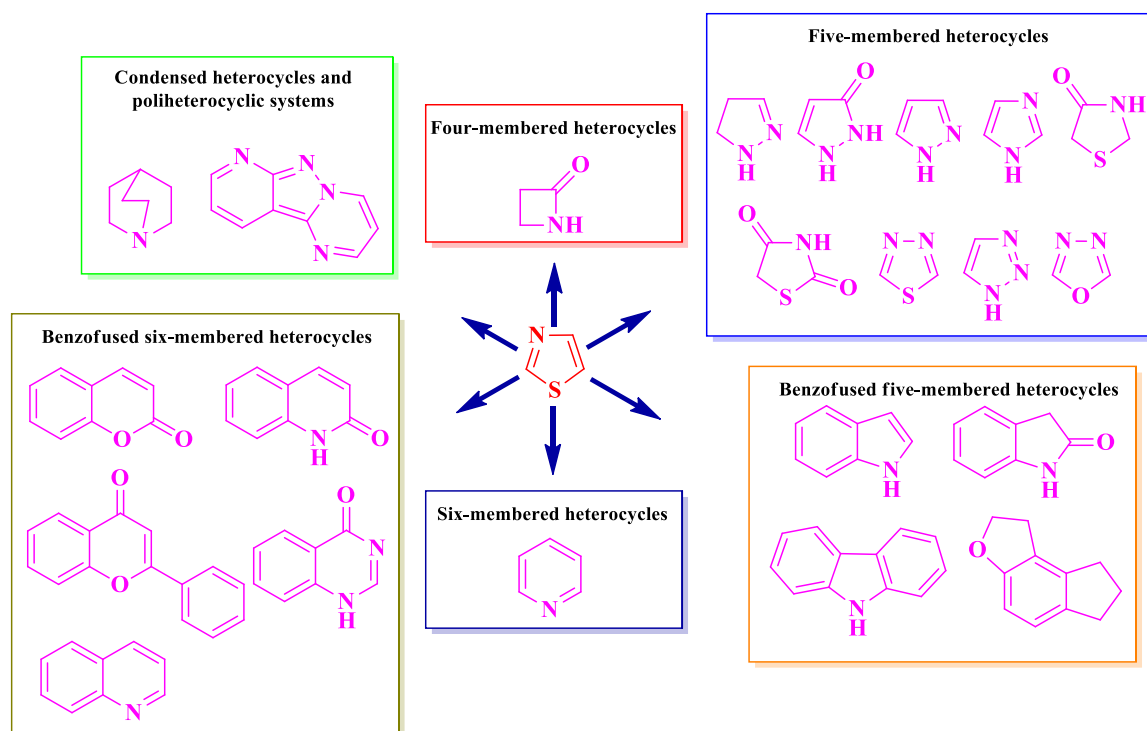
**Figure 2.** Summary of the antimicrobial thiazole-based hybrid compounds from the selected papers.

*2.1. Thiazole Clubbed with Four-Membered Heterocyles*

Four-membered heterocycles are a class of highly reactive and low stability chemical entities, classified in unsaturated heterocycles azetes, oxetenes, thietes, and their saturated derivatives azetidines, oxetanes, and thietanes. The best known and important derivative of this class is the 2-azetidinone. The chemical instability of four-membered heterocycles makes it difficult to use them extensively in medicinal chemistry, hence the reduced number of hybrid compounds available in the literature. Herein, we present the SAR studies in some antimicrobial thiazole clubbed with 2-azetidinone hybrid compounds.

2.1.1. Thiazolyl-Azetidin-2-one Hybrid Compounds

2-Azetidinone is the centerpiece of β-lactam antibiotics and is also found in some β-lactamase inhibitors, like clavulanic acid, sulbactam, and tazobactam, thus making it an essential scaffold in the development of new potential antibacterial molecules [7].

Desai et al. reported the design and synthesis of a series of 4-(quinolin-3-yl)-1-(thiazol-2-yl)-amino-azetidin-2-ones (Figure 3) with two points of variation: the sixth position of the quinoline ring ($R_1$) and the phenyl from the fourth position of the thiazole ring ($R_2$) [8]. Depending on each case, the quinoline ring can be unsubstituted (**1**-**3**) or substituted with a methyl group (**4**-**7**) in the sixth position. Similarly, the thiazole ring can be either unsubstituted (**4**) or substituted with electron-donating (**1**, **5**, and **7**) or electron-withdrawing groups (**2**, **3**, and **6**) in the fourth position [8].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative bacteria and for their antifungal activity against *Candida sp.* and *Aspergillus sp.* strains. The results were quantified as minimal inhibitory concentrations (MICs) [8]. Overall, the compounds were more effective against the Gram-negative strains compared to the Gram-positive ones. Compounds **1-4** and **6** showed the strongest antibacterial activity against *Escherichia coli* MTCC 443 (MICs = 100 μg/mL), while compound **5** was the most efficient against *P. aeruginosa* MTCC 1688 (MIC = 100 μg/mL), but in both cases the activity was inferior to chloramphenicol (MIC = 50 μg/mL) [8].

In terms of antifungal activity, compounds **5** and **7** showed inferior activity (MIC = 200 μg/mL) against *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282, and *A. clavatus* MTCC 1323, compared to nystatin (MIC = 100 μg/mL) [8].

SAR studies in this series showed that $R_2$ substitution was associated with an increased antibacterial activity (Figure 3). Electron-donating groups for both $R_1$ and $R_2$ (**5** and **7**) were associated with antifungal activity [8].

The compounds are potential inhibitors of β-ketoacyl-acyl-carrier protein synthase III, which is an important enzyme in the fatty acid biosynthesis and growth of bacterium, based on the molecular docking studies. No potential mechanism for the antifungal activity was reported [8].
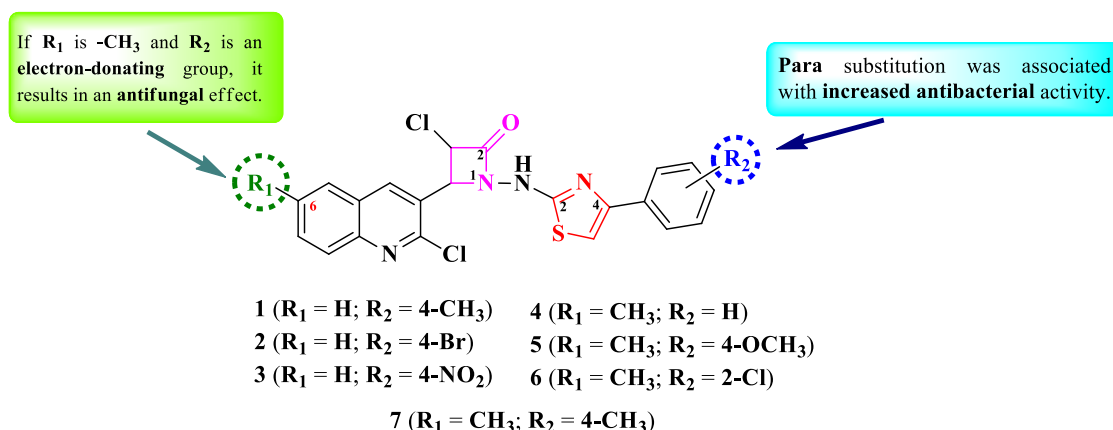


**Figure 3.** SAR studies in antimicrobial 4-(quinolin-3-yl)-1-(thiazol-2-yl)-amino-azetidin-2-one derivatives, reported by Desai et al. [8].

## 2.2. Thiazole Clubbed with Five-Membered Heterocycles

Five-membered heterocycles represent an extensive group of valuable structures for designing pharmacologically active compounds, including antimicrobials. Compared to four-membered heterocycles, they have a significantly greater chemical stability and versatility, which is transposed in their ubiquitarian usage in pharmaceutical research and development.

Based on the literature search of the last six years, we will discuss further the structure-activity relationships in antimicrobial hybrid compounds containing thiazole clubbed with the following five-membered heterocycles and their derivatives: pyrazoline, pyrazolinone, pyrazole, imidazole, thiazolidinone, thiazolidindione, 1,3,4-thiadiazole, 1,2,3-triazole, 1,3,4-oxadiazole, and thioxo-1,3,4-oxadiazole.

### 2.2.1. Thiazolyl-2-Pyrazoline Hybrid Compounds

2-Pyrazoline is an important scaffold in anti-infective drugs, possessing antibacterial, antifungal, antiviral, antiparasitic, and antituberculosis potential [9]. Herein, we present the structure-activity relationship for some series of thiazole linked with 2-pyrazoline derivatives with promising antimicrobial potential, to establish how clubbing these two heterocycles influences the biological activity of the entire molecule.

Based on the found structures, it can be concluded that there is one general scaffold consisting of both heterocycles linked directly, but in different positions. Therefore, there have been identified three types of linking patterns: the fifth position of the thiazole ring to the fifth position of 2-pyrazoline ring [10], the second position of the thiazole ring to the first position of 2-pyrazoline ring [11–16], and the fifth position of the thiazole ring to the third position of 2-pyrazoline ring [17] (Figure 4).
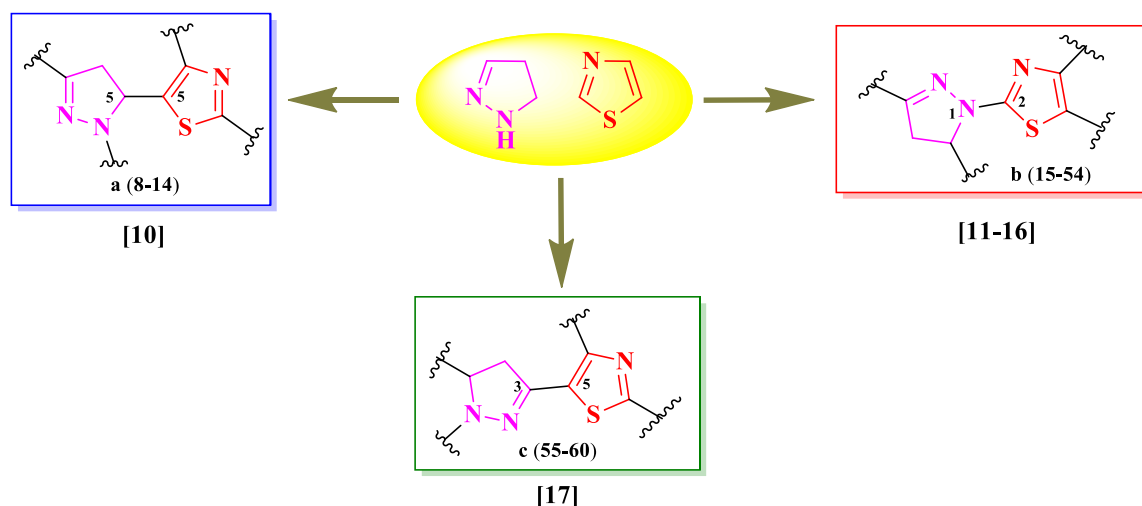
**Figure 4.** The general structures for the series discussed, containing thiazole and 2-pyrazoline rings [10–17].

Cuartas et al. designed four series (**8a-14a**, **8b-14b**, **8c-14c**, **8d-14d**) of 2-($N$-mustard)-5-(2-pyrazolin-5-yl)-thiazoles (Figure 5), with two points of variation: the substituted phenyl from the third position of the 2-pyrazoline (R) and the first position of the 2-pyrazoline ring ($R_1$) [10]. The compounds are bearing a nitrogen mustard moiety, known for its DNA alkylating properties. Depending on each case, $R_1$ can be a carbonylic group (**a** and **b**) or a phenyl ring (**c** and **d**), while R can be hydrogen (**14**), a halogen atom (**8-10**), or etheric groups (**11-13**).

The compounds were tested for their antifungal activity against *Candida sp.* and *Cryptococcus sp.* strains and for their antibacterial activity against Gram-positive and Gram-negative strains. The results were quantified as $IC_{50}$, representing the minimum concentration that inhibits 50% of growth, and MIC [10]. Compounds **8c-14c** ($R_1$ = -$C_6H_5$) and **12d-14d** ($R_1$ = -3,5-di-Cl-$C_6H_3$) showed inferior activity ($IC_{50}$ = 15.6-125 µg/mL) against *Cryptococcus neoformans* ATCC 32264 compared to amphotericin B ($IC_{50}$ = 0.50 µg/mL) [10].

In terms of antibacterial activity, the compounds showed significant effect against vancomycin-intermediate *S. aureus* (VISA) (MICs = 3.25-500 µg/mL), methicillin-susceptible *S. aureus* (MSSA ATCC 25923) (MICs = 62.5-500 µg/mL), methicillin-resistant *S. aureus* (MRSA ATCC 43300) (MICs = 125-500 µg/mL), and *Neisseria gonorrhoeae* ATCC 31426 (MICs = 125-500 µg/mL), compared to penicillin, ceftriaxone, and ciprofloxacin [10].

SAR studies revealed that the nature of the substituents on 2-pyrazoline (**a-d**) and phenyl (**8-14**) were the most important for the antibacterial and antifungal activities (Figure 5) [10]. The phenyl substituent from the first position of the 2-pyrazoline ring (**c**) conferred anticryptococcal activity regardless of the other substituents (**8c-14c**), while 3,5-dichlorophenyl substituent (**d**) was conditioned by electron-donating groups, particularly methoxy (**12d**) or trimethoxy (**13d**) or no substituent at all (**14d**) on the phenyl ring from the third position of the 2-pyrazoline ring. It is worth mentioning that 3,5-dichlorophenyl substituent is found in the structure of some important antifungal azoles like miconazole, ketoconazole, or itraconazole. However, the situation is opposite for the antibacterial activity. The 3,5-dichlorophenyl substituent abolished the antibacterial effect, while for phenyl-substituted derivatives it was very low. The best activity was observed when small substituents in $R_1$ were present, like acetyl (**a**) and formyl (**b**). Another important aspect is that the presence of chloro (**8a** and **8b**), bromo (**9a** and **9b**), and fluoro (**9c**) substituents or no substituents (**14b**) increased the activity against VISA (Figure 5) [10]. No potential target was reported by the authors.
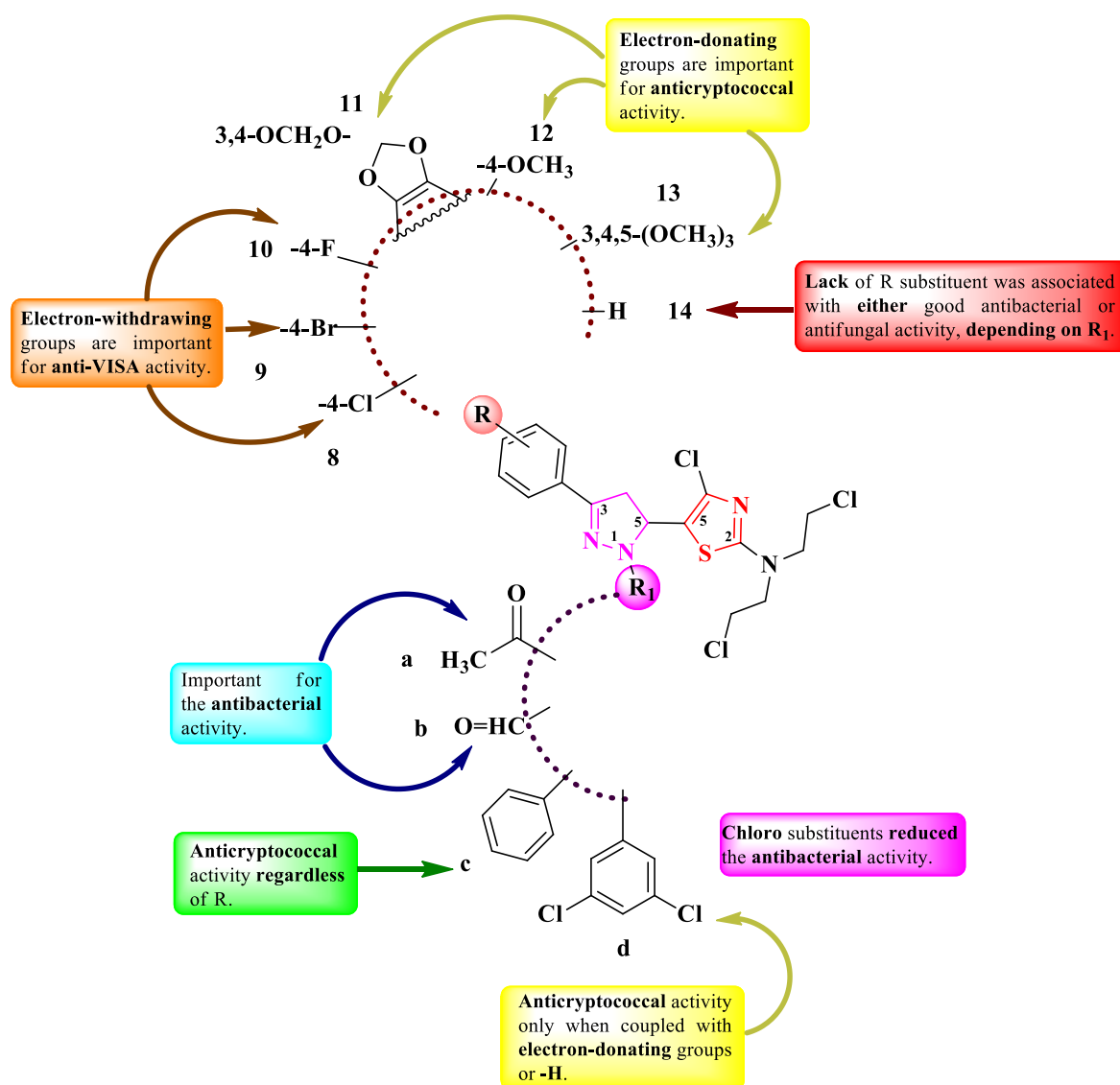
**Figure 5.** SAR studies in antimicrobial 2-(*N*-mustard)-5-(2-pyrazolin-5-yl)-thiazole derivatives, reported by Cuartas et al [10].

Rashdan and Abdelmonsef designed 2-(4-(1-thiazol-2-yl)-2-pyrazolin-3-yl)-1,2,3-triazol-1-yl)-1,3,4-thiadiazole, with a single point of variation: fifth position of the 2-pyrazoline ring (R) (Figure 6) [11].

These compounds were assayed for their antibacterial activity against Gram-positive and Gram-negative bacteria and for their antifungal activity against *C. albicans* [11]. The thiophene substituted compound **15** showed promising results against *E. coli*, *P. aeruginosa*, and *S. aureus* (MICs = 5-10 µg/mL), compared to ciprofloxacin (MICs = 1.25-7 µg/mL) [11].

Concerning the antifungal activity, the same compound showed identic activity to nystatin against *C. albicans* (MIC = 5 µg/mL) [11].

Based on the minimal structural differences between the obtained derivatives, it seems that switching from a bulkier (3-metoxy-4-hydroxy-phenyl in **16**) to a smaller substituent (2-thienyl in **15**) enhanced the activity (Figure 6) [11].

Additionally, compound **15** was a potent inhibitor of SARS-CoV-2 transmembrane serine protease 2 (TMPRSS2), which plays an important role in the disease propagation, based on molecular docking studies [11].
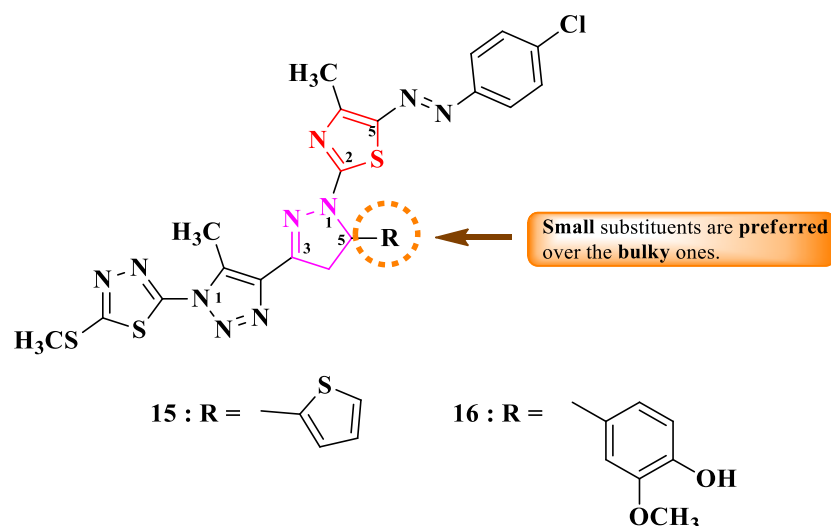
**Figure 6.** SAR study of antimicrobial 2-(4-(1-thiazol-2-yl)-2-pyrazolin-3-yl)-1,2,3-triazol-1-yl)-1,3,4-thiadiazole derivatives, reported by Rashdan and Abdelmonsef [11].

Budak et al. reported the synthesis of a series of 2-(4-(1-(thiazol-2-yl)-2-pyrazolin-3-yl)-phenyl)-methanoisoindol-1,3-dione derivatives. The obtained compounds varied by the substituent in the fifth position of the 2-pyrazoline ring (R), which can be an aryl (**17-23**) or hetaryl ring (**24-25**) (Figure 7) [12].

The compounds were tested for the antimicrobial activity against Gram-positive and Gram-negative bacteria and *C. albicans* ATCC 1213 [12]. The results were quantified by inhibition zone (IZ), through disk diffusion method. All compounds (**17-25**) showed inferior activity against *S. aureus* ATCC 29213 (IZs = 10-19 mm), compared to cefoperazone-sulbactam (IZs = 19-26 mm). Additionally, compound **25** was active against *Proteus vulgaris* KUEN 1329 (IZ = 10 mm), but inferior to the standard drug [12].

SAR studies in this series showed that aryl substitution induced better activity compared to hetaryl substitution (Figure 7). Thus, in the aryl substituted derivatives, para substitution (**17-20**) favorized an overall better activity compared to meta substitution (**21-23**). The position of $R_1$ substituent was found to be more important than their nature, as substitution in para with both electron-withdrawing and electron-donating groups yielded similar activities [12]. In the case of compounds **24** and **25**, bearing 2-thienyl and 2-furanyl substituents, a broader activity spectrum was observed for **24**, which could be attributed to the higher aromaticity of 2-thienyl compared to 2-furanyl substituent, which makes it suitable for the bioisosteric substitution of phenyl rings [12]. No potential target was reported by the authors.
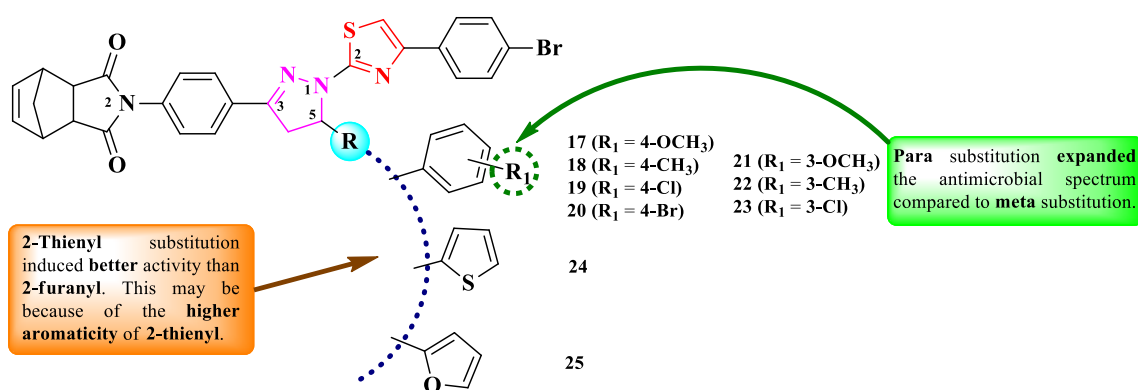


**Figure 7.** SAR studies in antimicrobial 2-(4-(1-(thiazol-2-yl)-2-pyrazolin-3-yl)-phenyl)-methano-isoindol-1,3-dione derivatives, reported by Budak et al [12].

Mansour et al. designed three series of 2-(3-aryl-5-hetaryl-2-pyrazolin-1-yl)-thiazole derivatives (Figure 8), with three points of variation: one is the linking position to the naphthyl ring (**a** = 1-naphthyl or **b** = 2-naphthyl) from the third position of 2-pyrazoline ring and the other two are in the fourth ($R_1$) and fifth positions ($R_2$) of the thiazole ring [13]. Depending on each case, $R_1$ can be a para-halogen substituted phenyl ring (**26** and **27**) or a methyl group (**28-33**), while $R_2$ can be either hydrogen (**26** and **27**) or various acyl substituents (**28-30**) and arenediazo groups (**31-33**) (Figure 8) [13].

The compounds were tested for the antimicrobial activity against Gram-positive and Gram-negative bacteria and various fungal strains [13]. Most of the compounds displayed antibacterial activity against *S. aureus* (IZs = 0.5-2.6 mm) and antifungal activity against *A. flavus* (IZs = 0.5-2.3 mm), but inferior compared to amoxicillin (IZs = 2.2-3.5 mm) and griseofulvin (IZs = 2.1-3.3 mm). Only compounds **27b** and **33a** were active against all the tested microbial strains (*S. aureus*, *Bacillus subtilis*, *K. pneumoniae*, *P. aeruginosa*, *A. fumigatus*, *A. flavus*, *Syncephalastrum racemosum*, *Penicillium expansum*, and *C. albicans*) [13].

SAR studies suggest the activity depends on the nature of $R_1$ and $R_2$ and the linkage 2-pyrazoline ring to the naphthyl group [13]. Thus, in the 4-(*p*-halophenyl)-thiazolyl series (**26a,b** and **27a,b**) (Figure 8), bromo substituent (**27a** and **b**) inactivated the compounds, while the chloro substituent (**26a** and **b**) was responsible for the antibacterial activity, apart from compound **26b**, which displayed activity against all tested bacterial and fungal strains. Therefore, chloro and 2-naphthyl substituents (**26b**) were the best combination for highly active antimicrobials [13].

In the 5-acylthiazolyl series (**28a,b**, **29a,b**, and **30a,b**) (Figure 8), the compounds substituted with acetate (**29a** and **29b**) or anilido (**30a** and **30b**) groups were inactive or had a very low activity only against *A. flavus* (IZ = 0.5 mm) and *P. expansum* (IZ = 0.8 mm), while acetyl substitution (**28a** and **28b**) yielded a moderate antimicrobial activity (IZs = 0.5-1.2 mm) [13].

Finally, in the 5-arendiazothiazolyl series (**31a,b**, **32a,b**, and **33a,b**), the activity depended more on the linkage to the naphthyl group (**a** or **b**) [13]. Thus, the best combination was between *p*-chlorobenzenediazo and 1-naphthyl (**33a**), which was the most active. Combinations between *p*-toluenediazo and 1-naphthyl (**32a**) or benzenediazo and 2-naphthyl (**31b**) yielded inactive molecules (Figure 8) [13]. No potential target was reported by the authors.

Using a similar scaffold, Masoud et al. [14] reported the synthesis of two more series of 2-(3-aryl-5-hetaryl-2-pyrazolin-1-yl)-thiazole derivatives, with two points of variation: (R) linked to the fifth position of 2-pyrazoline ring (**c** = 3,4-dimethoxyphenyl and **d** = 1,3-benzodioxole) and ($R_1$) from the fifth position of thiazole ring [14]. Depending on each case, $R_1$ can be various acyl substituents (**34-36**) or arenediazo groups (**37-39**) (Figure 8).

The antimicrobial effect was assayed using the same strains and positive controls mentioned by Mansour et al [14]. The most notable results for the antibacterial activity were obtained for compounds **36d**, **38d**, and **39c** against *S. aureus* (IZs = 0.9-1.2 mm), compounds **34c**, **35c**, **37c**, **38c**, and **39c** against *K. pneumoniae* (IZs = 1.2-2.0 mm) and *P. aeruginosa* (IZs = 1.0-1.8 mm) [14].

In the case of antifungal activity, the most important results were obtained for compounds **37c**, **38c**, and **39d** against *C. albicans* (IZs = 1.3-2.1 mm), compound **38c** against *A. fumigatus* (IZ = 1.2 mm) and compound **38d** against *A. flavus* (IZ = 2.3 mm) [14].

SAR studies in these compounds suggest that acyl group substitution in position 5 of the thiazole ring (**34c,d**, **35c,d**, and **36c,d**) results in only antibacterial active compounds (Figure 8) [14]. Favorable substituents for the antibacterial activity were acetate (**34c** and **d**), anilido (**35c** and **d**), and acetyl (**36c** and **d**), which was the opposite compared to the compounds by Mansour et al [14].

Arendiazo substitution of the thiazole ring (**37c,d**, **38c,d**, and **39c,d**) expanded the spectrum against both bacterial and fungal strains. In this case, the main difference in the potence was dictated by whether if the substituent from position 5 of the 2-pyrazoline ring was 3,4-dimethoxyphenyl (**c**) or 1,3-benzodioxole (**d**), with the first being more active [14]. No potential target was reported by the authors.

By analyzing the SAR studies in the molecules synthesized by both authors (Figure 8), it seemed that the naphthyl group brought drawbacks to the compounds designed by Mansour et al., as the

antimicrobial potential was reduced compared to the compounds designed by Masoud et al, who replaced it with a 3,4-dimethoxyphenyl moiety. Thus, a higher polarity should be considered when designing novel antimicrobial compounds [13,14].
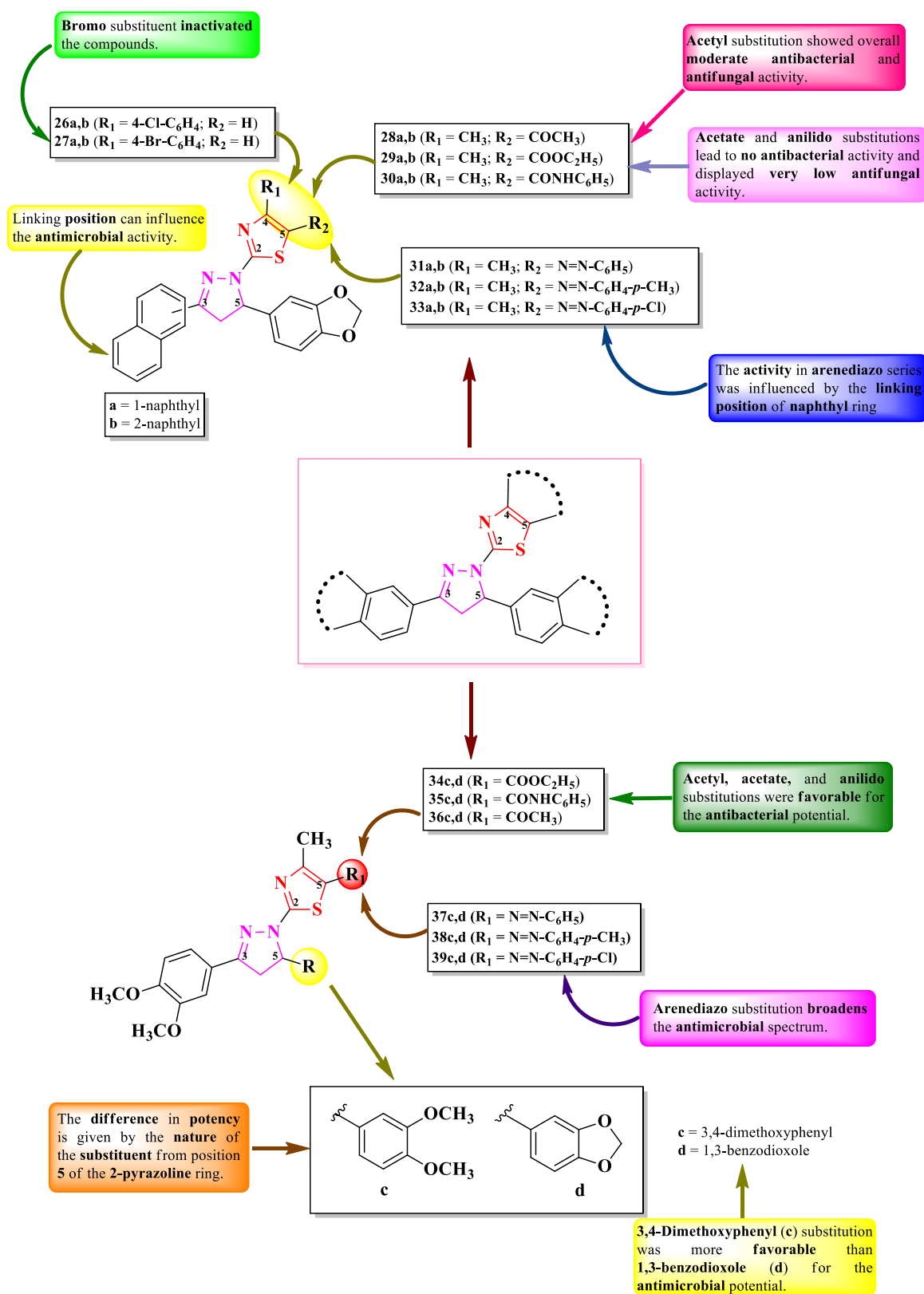


**Figure 8.** SAR studies in the series of antimicrobial 2-(3-aryl-5-hetaryl-2-pyrazolin-1-yl)-thiazole derivatives, synthesized by Mansour et al. [13] and Masoud et al. [14].

Bhandare et al. reported the synthesis of some 2-(2-pyrazolin-1-yl)-thiazoles in which the fourth position of the thiazole ring was linked via a methylene bridge to various thiol- and tioether-containing azoles (1,3,4-oxadiazole and 1,2,4-triazole) (Figure 9) [15].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative strains and for their antifungal activity against *Candida sp.* and *Aspergillus sp.* strains [15]. Overall, all compounds displayed a significant antimicrobial potential. Compounds **42**, **46**, **48**, and **49** showed similar activity (MICs = 0.5-8 μg/mL) against *S. aureus* ATCC 11632, *S. faecalis* ATCC 14506, *K. pneumoniae* ATCC 10031, *E. coli* ATCC 10536, *P. aeruginosa* ATCC 10145, compared to ciprofloxacin (MICs between ≤1 and >5 μg/mL) [15].

Regarding the antifungal activity, the same compounds showed similar activity against *C. tropicalis* ATCC 1369 and *A. niger* ATCC 6275, compared to fluconazole (MICs ≤ 1 μg/mL) [15].

SAR studies pointed out that the heterocyclic tetrad induced promising overall antibacterial and antifungal activities (Figure 9) [15]. The additional aryl substituent (**42**-**46** and **48**-**51**) in the thioether series was essential for the activity. Switching to a hetaryl substituent, 3-pyridinyl (**47**), decreased the activity. The substituents on aryl were also an important factor in determining the antibacterial and antifungal strengths. Thus, a small halogen substituent, like 4-fluoro (**46** and **49**), induced excellent activity, while larger substituents, such as 2-trifluoromethyl (**44**), 4-trifluoromethoxy (**45**), 4- or 5-chloro (**43** and **50**), and 4-bromo (**51**) significantly decreased the activity. Noteworthy, unsubstituted rings (**42** and **48**) also displayed important activity (Figure 9) [15].

These compounds could potentially target DNA gyrase, important for the replication of genetic material in bacteria, and Cytochrome P450 14 $\alpha$-sterol demethylase, important for the synthesis of ergosterol from lanosterol, for the antifungal activity, based on the molecular docking studies [15].
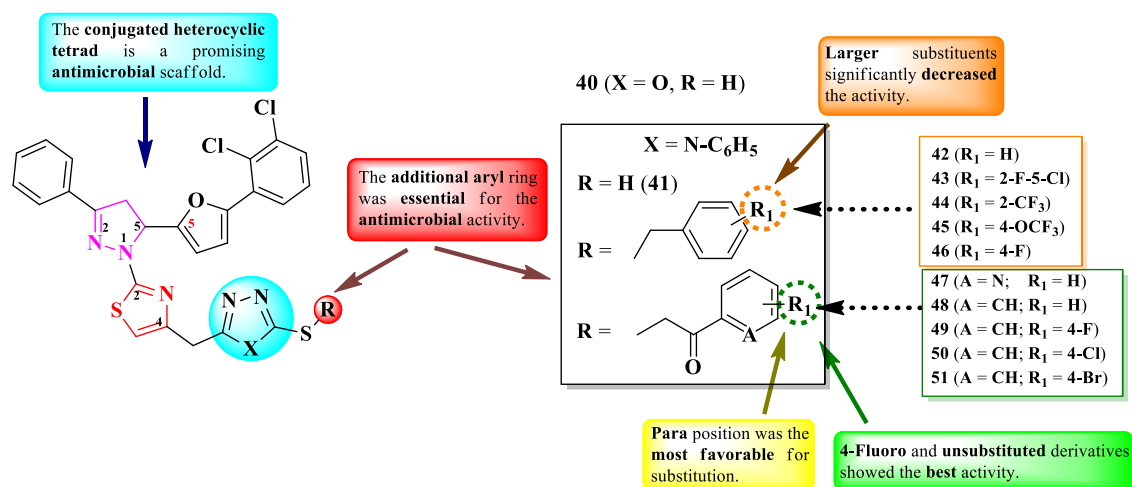


**Figure 9.** SAR studies in antimicrobial 2-(5-(furan-2-yl)-2-pyrazolin-1-yl)-4-methylhetarylthio-thiazole derivatives, reported by Bhandare et al [15].

Abdel-Wahab et al. designed a series of 2-(5-(3-(1,2,3-triazol-4-yl)-pyrazol-4-yl)-2-pyrazolin-1-yl)-thiazole (Figure 10) [16]. These compounds are para substituted on the phenyl ring from the third position of the 2-pyrazoline ring ($R_1$) and have an additional substituent in the fourth position of the thiazole ring ($R_2$).

The compounds were tested for the antimicrobial activity against Gram-positive and Gram-negative bacteria and *C. albicans* NRRL Y-477 [16]. Compounds **52** and **53** showed inferior activity (MIC = 50 μg/mL) against *S. aureus* ATCC 29213 and *K. pneumoniae* ATCC 13883, compared to ciprofloxacin (MIC = 25 μg/mL) [16].

Only compound **54** was active against *C. albicans* (MIC = 200 μg/mL), but the activity was inferior compared to clotrimazole (MIC = 25 μg/mL) [16].

SAR studies in these compounds suggest that identic substitution (**52** and **53**) of both 2-pyrazoline and 1,3-thiazole moieties could be responsible for the antibacterial activity (Figure 10).

Compound **54**, containing an additional 1-(*p*-tolyl)-5-methyl-1,2,3-triazol-4-yl moiety, may induce a closer resemblance to fluconazole than the rest of the compounds, by containing two triazole moieties in its structure, hence the better antifungal activity against *C. albicans* [16]. No potential target was reported by the authors.
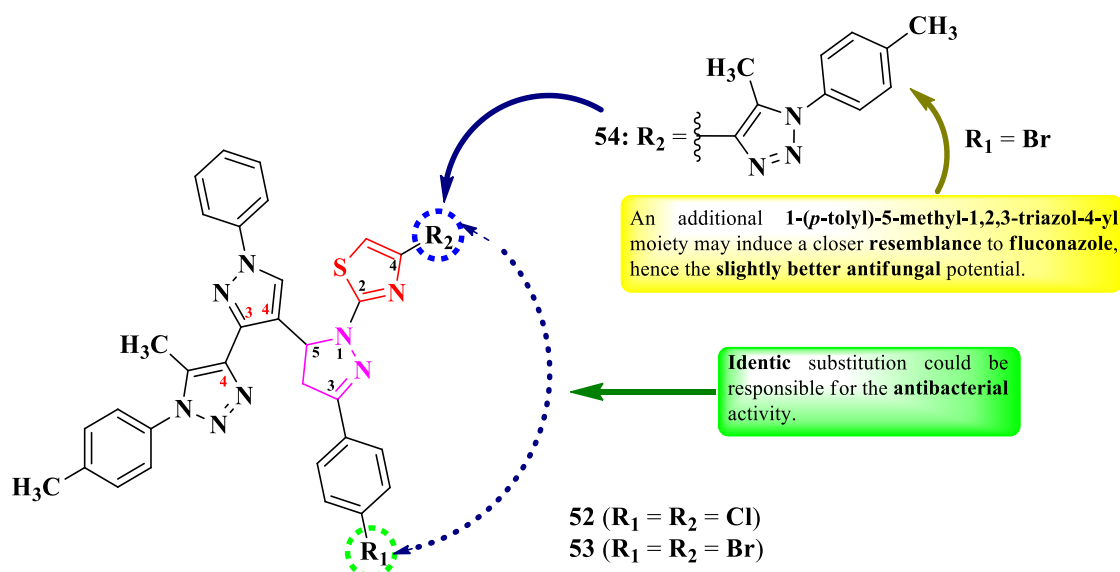


**Figure 10.** Structure-activity relationships in antimicrobial 2-(5-(3-(1,2,3-triazol-4-yl)-pyrazol-4-yl)-2-pyrazolin-1-yl)-thiazole derivatives, reported by Abdel-Wahab et al [16].

Bondock and Fouda designed some 2-(*N*-allyl)-5-(2-pyrazolin-3-yl)-thiazole derivatives with various substituents in the first position of the 2-pyrazoline ring (**55-60**) (Figure 11) [17].

The compounds were tested for the antimicrobial activity against Gram-positive and Gram-negative bacteria and fungal strains [17]. All selected compounds showed similar activities (MICs = 0.03-7.81 μg/mL) against *S. pneumoniae* RCMB 010010 and *S. epidermidis* RCMB 010024, compared to ampicillin (MICs = 0.6-0.24 μg/mL). Compounds **55**, **57**, and **60** showed similar activity (MICs = 0.03-7.81 μg/mL) against *E. coli* RCMB 010052, *P. vulgaris* RCMB 010085, and *K. pneumoniae* RCMB 010093, compared to gentamycin (MICs = 0.03-1.95 μg/mL) [17].

In terms of antifungal activity, which was similar to amphotericin B (MICs = 0.12-7.81 μg/mL), compounds **56-58** and **60** showed results against *A. fumigatus* RCMB 02568 (MICs = 0.12-7.81 μg/mL), while only compounds **57** and **60** were active against *S. racemosum* RCMB 05922 (MICs = 0.24-7.81 μg/mL) [17].

According to SAR studies, substitution of 2-pyrazoline ring with a thiocarbamido group (**57**) favorized the overall antibacterial and antifungal activities (Figure 11), while phenylthiocarbamido group (**58**) only induced good activity against Gram-positive bacteria and *A. fumigatus* [17]. Substitution with a phenyl ring (**56**) induced a moderate antifungal activity (Figure 11). Further expansion of the molecule with a phenylthiazolyl moiety (**59** and **60**) yielded overall medium antibacterial and antifungal activities. The 4-fluorophenyl derivative (**60**) was more potent against *S. epidermidis* RCMB 010024, *P. vulgaris* RCMB 010085, *A. fumigatus* RCMB 02568, and *S. racemosum* RCMB 05922, compared to the compound with unsubstituted phenyl (**59**) [17]. No potential target was reported by the authors.
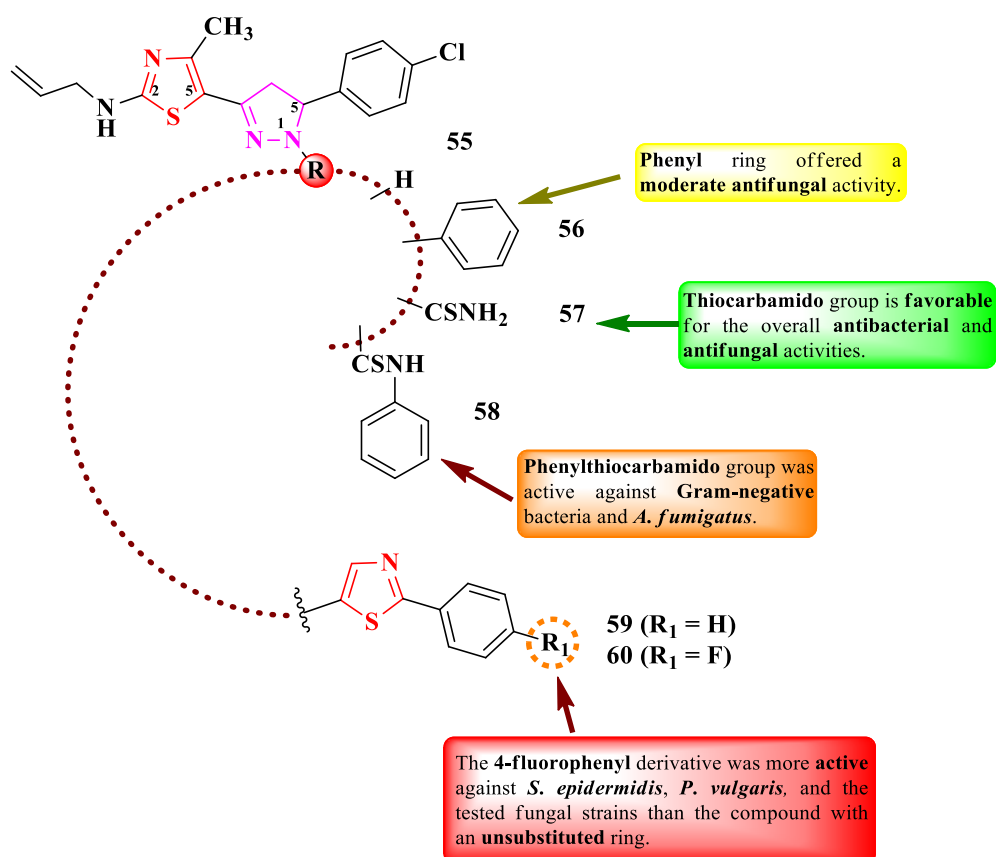
**Figure 11.** SAR studies in antimicrobial 2-(*N*-allyl)-5-(2-pyrazolin-3-yl)-thiazole derivatives, reported by Bondock and Fouda [17].

To conclude the results observed in the analyzed papers (Figure 12), clubbing thiazole with 2-pyrazoline to obtain novel antimicrobials should be considered when aiming for compounds active against Gram-positive bacterial strains, especially against *S. aureus*. Moderate results were observed against Gram-negative bacterial strains, except against *K. pneumoniae*, where the results were promising [13–17].

The antifungal activity was much lower compared to the antibacterial activity. Thus, this scaffold may not be suitable for designing potent antifungals.

Finally, it is worth mentioning that the 2-(2-pyrazolin-1-yl)-thiazole scaffold was the most common and is responsible for the majority of results concerning the antimicrobial activity of hybrid compounds containing thiazole and 2-pyrazoline heterocycles [11–16].
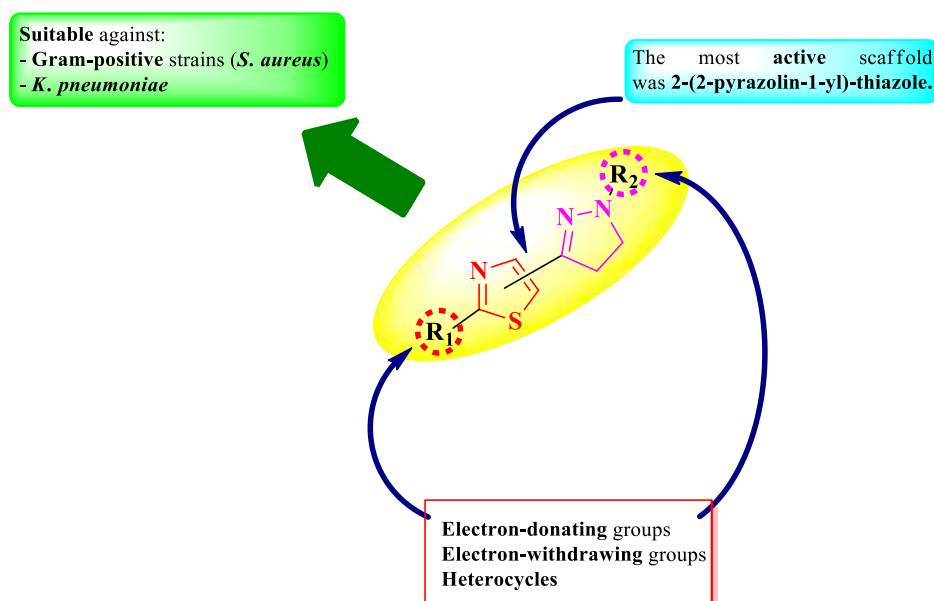
**Figure 12.** Endpoints of designing novel antimicrobial thiazole clubbed with 2-pyrazoline hybrid compounds.

### 2.2.2. Thiazolyl-Pyrazolin-3-one Hybrid Compounds

3-Pyrazolinone is an important scaffold for designing antimicrobial molecules [18], as presented further.

Abu-Melha obtained some *N*-(4-pyrazolin-3-one)-2-thiazolyl-hydrazonomethyl-phenoxyacetamides, with various substituents in the fourth and fifth positions of the thiazole ring (Figure 13), through a multi-step synthesis between *N*-(4-antipyrinyl)-2-chloroacetamide, *p*-hydroxybenzaldehyde, thiosemicarbazide, and various *α*-halogenocarbonyl compounds [19].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative strains and for their antifungal activity [19]. Compounds **61**-**63** showed superior antibacterial activity (MICs = 28-168 µg/mL) on *S. aureus* ATCC 25923, *Salmonella typhimurium* ATCC 14028, and *E. coli* ATCC 25922, compared to chloramphenicol (MICs = 143-152 µg/mL) and cephalothin (MICs = 135-229 µg/mL) [19].

In terms of antifungal activity, compounds **62** and **63** showed superior activity (MICs = 168-172 µg/mL) on *C. albicans* ATCC 10231, compared to cycloheximide (MIC = 254 µg/mL) [19].

Additionally, the compounds can target the penicillin binding proteins 4 (PBP4) from *S. aureus* and *E. coli* for the antibacterial activity, based on the molecular docking studies [19].



61 ($R_1$ = *p*-Cl-$C_6H_4$;    $R_2$ = H)
62 ($R_1$ = $CH_3$;       $R_2$ = $COOCH_3$)
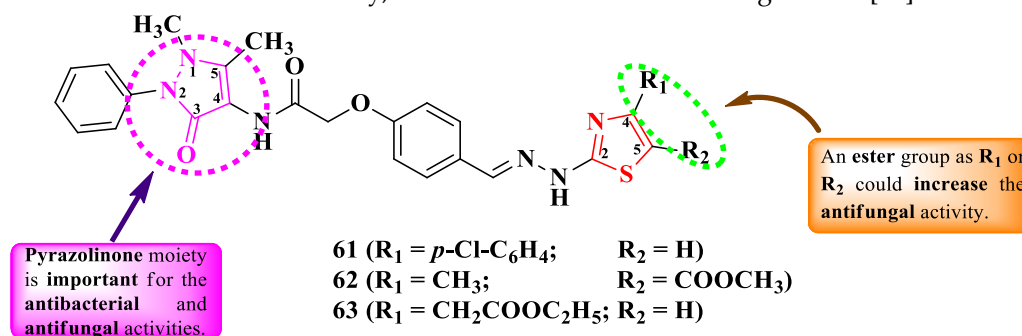63 ($R_1$ = $CH_2COOC_2H_5$; $R_2$ = H)

**Figure 13.** Antimicrobial *N*-(4-pyrazolin-3-one)-2-thiazolyl-hydrazonomethyl-phenoxyacetamides, reported by Abu-Melha [19].

### 2.2.3. Thiazolyl-Pyrazole Hybrid Compounds

Pyrazole bears significant antimicrobial, anthelmintic, and anticancer properties, which makes this heterocycle an important motif when designing novel antimicrobial compounds [20]. Herein, we present the structure-activity relationship in thiazole clubbed with pyrazole compounds with promising antimicrobial potential, in order to establish how clubbing these two heterocycles influences the biological activity.

Based on the found structures, it can be concluded that there were two types of scaffolds used: one in which the thiazole and pyrazole rings are clubbed through a linker, which is a methylylidenehydrazinyl, and the other where both rings are linked directly. For the second type of scaffold, there were two possible linking positions to the pyrazole ring: one in the first position and the other in the third position of the pyrazole ring (Figure 14).
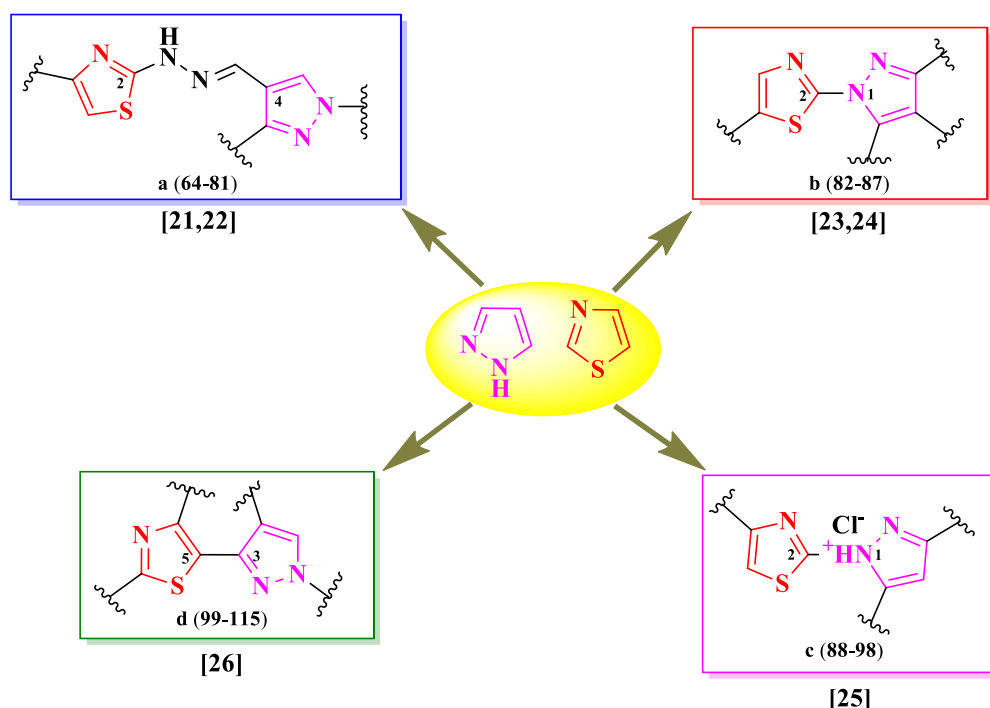


**Figure 14.** The general structures for the series discussed, containing thiazole and pyrazole rings [21–26].

Gondru et al. [21] and Patil et al. [22] synthesized some series of 2-(pyrazol-4-yl)-methylylidenehydrazinyl-thiazoles (Figure 15). These compounds were substituted in the fourth position of thiazole ring with various aryl and hetaryl substituents ($R_1$), in the second position of 2-pyrazoline ring with a benzothiazole or phenyl ring ($R_2$), and in the fifth position with a coumarin (**64**-**69**) or a substituted phenyl ring (**70**-**81**) ($R_3$) (Figure 15).

The compounds were assayed for their antibacterial activity against both Gram-positive and Gram-negative strains and for their antifungal activity against *Candida sp.* and *Aspergillus sp.* strains [21,22]. Compounds **64**, **65**, **67**, and **69** showed inferior activities (MICs = 1.9-7.8 μg/mL) on *S. aureus* MTCC 96 and MTCC 2940, *Micrococcus luteus* MTCC 2470, *K. planticola* MTCC 530, *E. coli* MTCC 739, and *P. aeruginosa* MTCC 2453, compared to ciprofloxacin (MIC = 0.9 μg/mL). Compounds **70**-**81** showed superior activities (MICs = 3.9-18.5 μg/mL) on *S. aureus*, *E. coli*, and *P. aeruginosa*, compared to chloramphenicol (MICs = 24.6-32.8 μg/mL) [21,22].

Concerning the antifungal activity, compounds **64**, **66**, **67**, and **69** showed similar activities (MICs = 7.8 μg/mL) on *C. albicans* MTCC 3017 compared to miconazole (MIC = 7.8 μg/mL). Compounds **70**-**81** showed superior activities on *A. niger* and *C. albicans* (MICs = 3.9-11.3 μg/mL) [21,22].

Additionally, the antibiofilm activity was evaluated on *S. aureus* and *K. planticola* biofilms [21]. Compound **69** presented a promising biofilm inhibition against *S. aureus* MTCC 96 ($IC_{50}$ = 1.8 μM), while compound **67** inhibited the biofilm formation of *S. aureus* MTCC 2940 ($IC_{50}$ = 12 μM) and *K. planticola* MTCC 530 ($IC_{50}$ = 14 μM).

According to the structure-activity relationship study, inserting a strong electron-withdrawing group, particularly nitro, in the para position of the phenyl ring in $R_1$ (**70**, **73**, **76**, and **79**) resulted in an increased overall antibacterial and antifungal activity, while meta substitution was not as favorable (**71**, **74**, **77**, and **80**) (Figure 15). The presence of benzothiazole moiety (**64**-**69**), which is known for its toxicity, could halt any future progress towards leader molecules [21,22].

Compounds **64**-**69** could target dehydrosqualene synthase of *S. aureus*, important for staphyloxanthin biosynthesis, a virulence factor. Based on the molecular docking studies, the coumarin moiety is important for binding to the Lys20 residue, through hydrogen bonds [21].
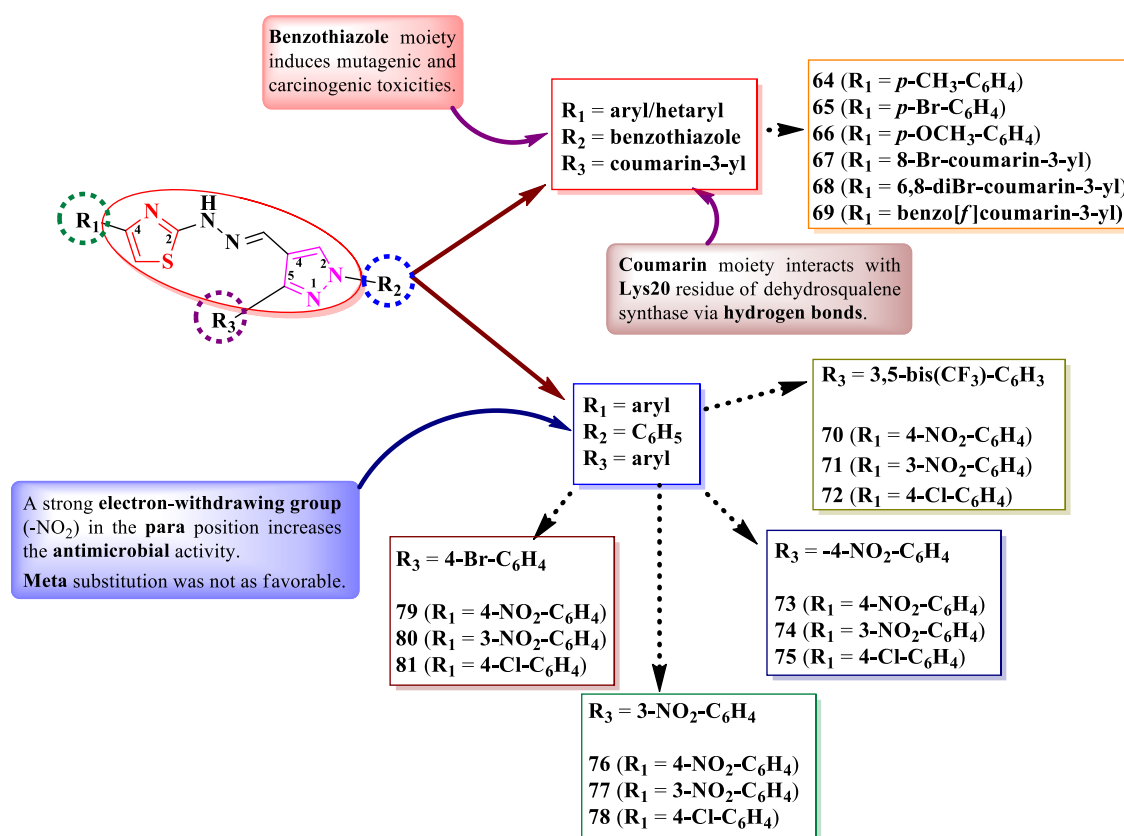


**Figure 15.** SAR studies in antimicrobial 2-(pyrazol-4-yl)-methylylidenehydrazinyl-thiazole derivatves, reported by Gondru et al. [21] and Patil et al. [22].

Abdel-Aziem et al. [23] and Kumar et al. [24] designed some 5-(coumarin-3-yl)-2-(pyrazol-1-yl)-thiazoles. These compounds were halo-substituted in the sixth position of coumarin ring ($R_1$) and variously substituted in the third and fourth positions of the pyrazole ring ($R_2$ and $R_3$) (Figure 16).

The compounds were evaluated for their antibacterial activity, using the agar well diffusion method or MIC assay, against both Gram-positive and Gram-negative strains and for their antifungal activity against *Candida sp.* strains [23,24]. Compounds **82**-**85** showed superior activity on *Enterococcus faecalis* ATCC 29212, compared to chloramphenicol, while compounds **84** and **85** showed superior active *P. aeruginosa* ATCC 27853, compared to cephalotin [23]. Both compounds **86** and **87** showed superior activity (MICs = 15.67-31.25 μM) against *S. aureus* MTCC 3160, *S. pyogenes* MTCC 442, and *E. faecalis* MTCC 439, compared to kanamycin (MICs = 31.25-62.50 μM) [24].

Regarding the antifungal activity, compounds **86** and **87** showed inferior activity (MIC = 61.25 μM) against *C. albicans* NCPF 400034, *C. keyfer* NCPF 410004, *C. krusei* NCPF 44002, and *C. parapsilosis* NCPF 450002, compared to amphotericin B (MICs = 0.78-12.50 μM) [24].

SAR studies showed that small substituents, like methyl (**82**) and hydroxy (**83**), were important for the activity against *E. faecalis*, while the larger substituents, like trifluoromethyl (**84**), against *P. aeruginosa* (Figure 16). Moreover, only the compounds with both $R_1$ and $R_3$ substituents being

electron-withdrawing groups (**86** and **87**) displayed an overall improved antibacterial and antifungal activity. No potential target was reported by the authors [23,24].
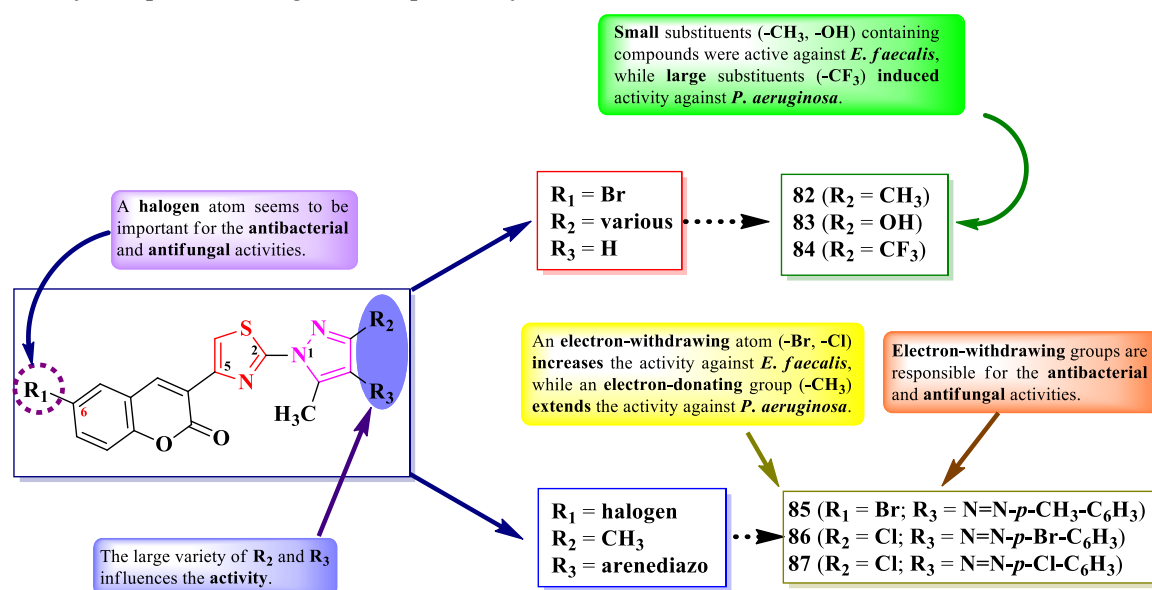


**Figure 16.** SAR studies in antimicrobial 5-(coumarin-3-yl)-2-(pyrazol-1-yl)-thiazole derivatives, reported by Abdel-Aziem et al. [23] and Kumar et al. [24].

Mahmoodi and Ghodsi designed some 2-pyrazolium-thiazol-4-yl salts substituted in the fourth position of the thiazole ring with a coumarin, in the third position of pyrazolium ring with various substituted coumarins ($R_2$-$R_4$), and in the fifth position with various aryl and hetaryl substituents ($R_1$) (Figure 17) [25].

The compounds were tested, using the zone inhibition method, for their antibacterial activity against both Gram-positive and Gram-negative strains and for their antifungal activity against *Aspergillus sp.* strains [25]. Compounds **88-94** and **96** showed inferior activities (IZs = 12-17 mm) against *S. aureus*, *E. coli* and *M. luteus* compared to gentamycin (IZs = 18-21 mm) [25].

Only compound **93** was active (IZs = 16-17 mm) against on *A. niger* and *A. flavus*, but inferior to fluconazole (IZ = 25 mm), in terms of antifungal activity [25].

Nevertheless, the heterogeneity of the results and the lack of activity in MIC terms make it difficult to draw conclusions about potential structure-activity relationships. No potential target was reported by the authors [25].
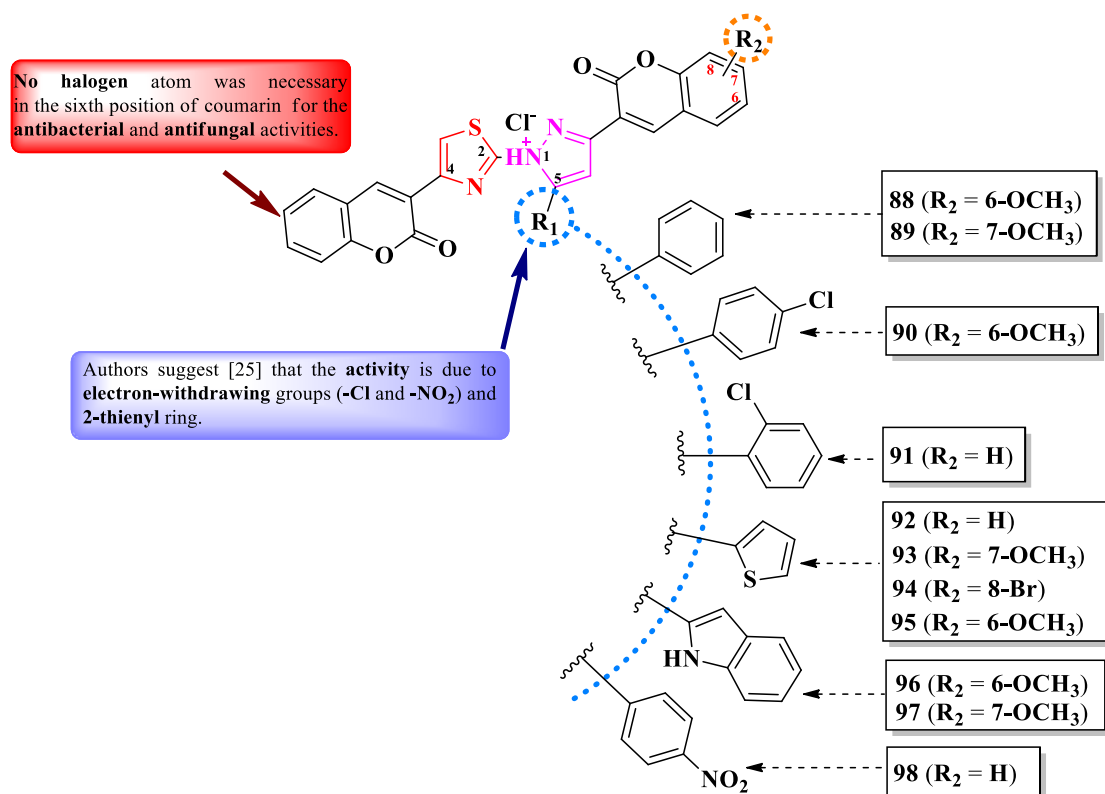
**Figure 17.** Antimicrobial 2-pyrazolium-thiazol-4-yl salts, reported Mahmoodi and Ghodsi [25].

Nalawade et al. designed a series of 2-phenyl-5-(4-hetaryl-pyrazol-3-yl)-thiazoles (Figure 18) [26].

The compounds were tested, using the well diffusion method, for the antibacterial activity against Gram-positive and Gram-negative strains and for the antifungal activity against three types of strains [26]. All tested compounds (**99**-**115**) showed inferior activity (IZs = 9.6-14.4 mm) against *E. coli* and *S. epidermidis*, compared to streptomycin (IZs = 18.52-25.0 mm). In terms of antifungal activity, all compounds were active (IZs = 13.0-22.3 mm) against *C. albicans* NCIM 3100, *A. niger* ATCC 504, and *Rhodotorula glutinis* NCIM 3168, but inferior to fluconazole (IZs = 18.35-25.30 mm) and ravuconazole (IZs = 20.15-28.64 mm).

The antifungal activity was further evaluated through MIC screening [26]. Eleven compounds (**99**-**119**) emerged as promising anti *A. niger* agents (MICs = 31.25 μg/mL), with similar activity compared to ravuconazole (MICs = 7.81-31.25 μg/mL). Twelve compounds (**100**, **102**-**106**, **110**-**115**) were moderately active against *R. glutinis* (MICs = 62.5 μg/mL) and only one (**101**) against *C. albicans* (MIC = 62.5 μg/mL), but with inferior activity compared to fluconazole (MIC = 7.81 μg/mL) and ravuconazole.

Structure-activity relationship in these compounds implies that the best activity against *A. niger* was in the presence of methyl (**101**-**103**) or fluoro (**104**-**108** and **111**) as substituents on the phenyl ring directly linked to thiazole, while bulkier substituents, such as chloro (**108**, **112**, and **113**) and bromo (**109**, **110**, and **113**-**115**), were associated with a lower activity (Figure 18). This was opposite in the case of anti *R. glutinis* activity.

The antifungal activity of these compounds can be attributed to their capacity to target lanosterol 14α-demethylase, based on the molecular docking studies. No potential target was reported by the authors for the antibacterial activity [26].
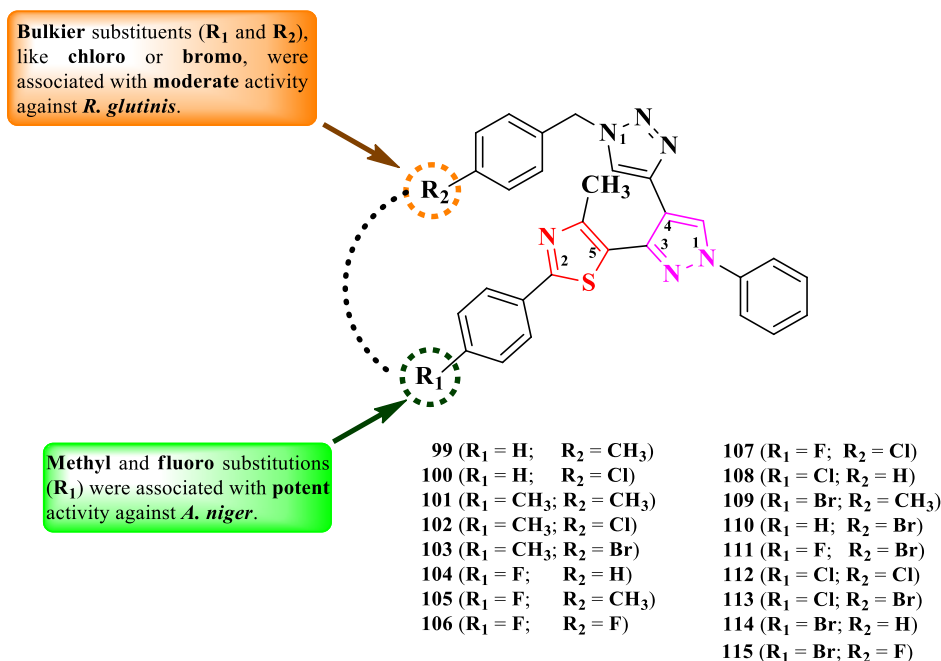
**Figure 18.** SAR studies in antimicrobial 2-phenyl-5-(4-hetaryl-pyrazol-3-yl)-thiazoles, reported by Nalawade et al. [26].

To conclude the results observed in the analyzed papers (Figure 19), clubbing thiazole with pyrazole to obtain novel antimicrobials seems to expand the activity spectrum, compared to 2-pyrazoline. Pyrazole-containing compounds displayed antibacterial activity against Gram-positive and Gram-negative strains, while the antifungal activity got increasingly better. However, it should be noted that additional structural elements, such as a hydrazine linker or a supplementary heterocycle, like coumarin or 1,2,3-triazole, could significantly influence the antimicrobial activity. For example, coumarin-containing compounds were only active against Gram-positive bacterial and fungal strains, while 1,2,3-triazole-containing compounds were potent antifungal agents.

Based on the provided results, the general structure-activity relationship studies of antimicrobial 3-(2-(pyrazol-1-yl)-thiazol-4-yl)-coumarins and 2-pyrazolium-thiazol-4-yl salts could be formulated as follows: a halogen atom, bromo or chloro, in the sixth position of the coumaryl moiety enhances, but is not essential (as observed in the pyrazolium series, Figure 17), the antimicrobial potential, while the nature of the substituents from pyrazole or pyrazolium moieties influences the spectrum. Thus, compounds containing electron-withdrawing groups had a larger span of activity compared to those containing electron-donating groups, covering both Gram-positive and Gram-negative bacterial strains, as well as fungal strains.

Nevertheless, clubbing pyrazole with 1,3-thiazole is a promising research hypothesis when designing novel antifungals.
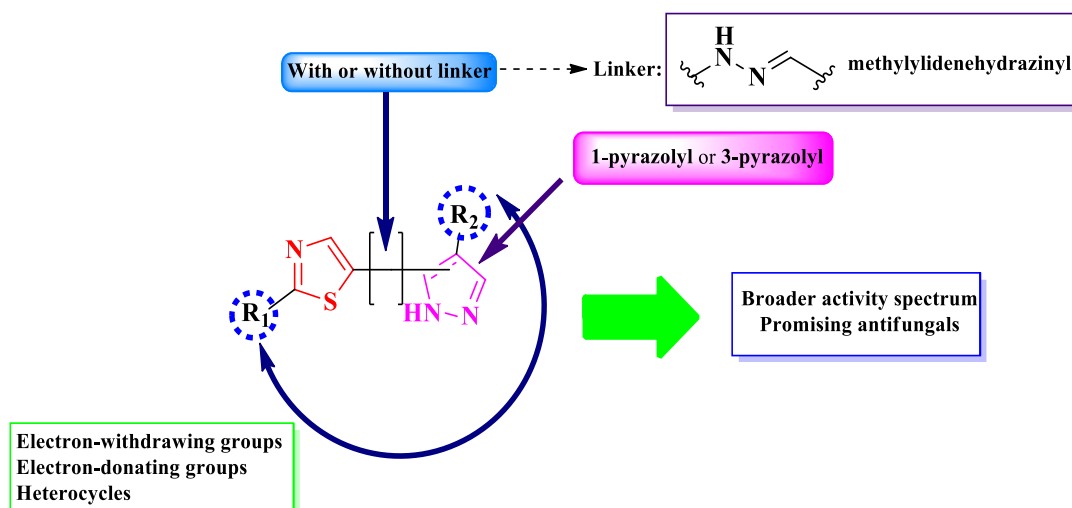
**Figure 19.** Endpoints of designing novel antimicrobial thiazole clubbed with pyrazole hybrid compounds.

## 2.2.4. Thiazolyl-Imidazole Hybrid Compounds

Imidazole is frequently present in various bioactive compounds. Besides the potent activity against fungal strains, imidazole is found in compounds with various effects, such as antibacterial, antituberculosis, antiviral, antiparasitic or anticancer [27].

Nikalje et al. reported the synthesis of some 2-(2,4,5-triphenyl-imidazol-1-yl)-thiazoles, variably substituted in the second position of imidazole ring (Figure 20) [28]. The general structure of these series was rationally designed by using the thiazole heterocycle from abafungin, isavuconazole, and ravuconazole, the imidazole heterocycle and the two phenyl rings from clotrimazole, flutrimazole, and bifonazole.

The compounds were tested for their antifungal activity against multiple strains. The activity was quantified using $MIC_{80}$, which is the minimal inhibitory concentration for 80% inhibition of growth. Among the synthesized compounds, those containing either electron-donating groups (**116**-**119**) or nitro (**120**) on the aryl showed superior activity, in most cases, against *C. albicans* NCIM 3471 and *C. glabrata* NCYC 388 ($MIC_{80}$ = 0.2-0.35 μg/mL), *Fusarium oxysporum* NCIM 1332 ($MIC_{80}$ = 20-35 μg/mL), *A. flavus* NCIM 539 ($MIC_{80}$ = 35-50 μg/mL), *A. niger* NCIM 1196 ($MIC_{80}$ = 40-45 μg/mL), and *C. neoformans* NCIM 576 ($MIC_{80}$ = 5-10 μg/mL), compared to miconazole and fluconazole ($MIC_{80}$ between 0.5 μg/mL and >64 μg/mL). The antifungal activity of these compounds can be attributed to their capacity to target lanosterol 14α-demethylase, based on the molecular docking studies [28].
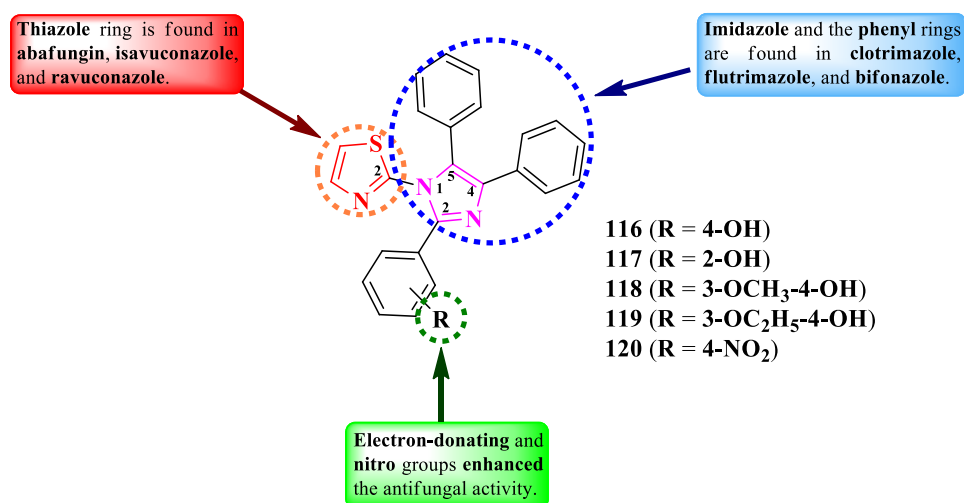


**Figure 20.** Design of antifungal 2-(2,4,5-triphenyl-imidazol-1-yl)-thiazoles, reported by Nikalje et al. [28].

2.2.5. Thiazolyl-Thiazolidin-4-one Hybrid Compounds

Thiazolidin-4-one is another versatile five-membered heterocycle, used in designing novel antibacterial compounds, one important direction being the development of antituberculosis compounds [29].

Othman et al. designed a series of novel 2-(thiazol-2-yl)-*N*-thiazolidin-4-ones, variably substituted in the second position of thiazolidin-4-one ring (Figure 21) [30].

The compounds were tested for their antibacterial activity against sensitive (ATCC 25177 H37Ra), MDR (multidrug resistant, ATCC 35822), and XDR (extended drug resistant, RCMB 2674) strains of *Mycobacterium tuberculosis* and various bronchitis causing bacteria [30]. Five compounds (**121**-**125**) showed equal or inferior activity against the sensitive strain, compared to isoniazid (MIC = 0.12 μg/mL). Three compounds (**121**, **123**, and **125**) showed activity against the MDR strain (MICs = 1.95-7.81 μg/mL), and one (**123**) against the XDR strain (MIC = 7.81 μg/mL). Concerning the antibacterial activity, all five compounds showed similar activity (MICs = 0.48-7.81 μg/mL) against *Mycoplasma pneumoniae* ATCC 15531, *S. pneumoniae* ATCC 1659, and *K. pneumoniae* ATCC 43816, while four compounds (**123** and **125**-**127**) showed similar activity against *Bordetella pertussis* ATCC 9340 (MICs = 1.95-7.81 μg/mL), compared to azithromycin (MICs = 0.49-7.81 μg/mL).

SAR studies showed that the activity on *M. tuberculosis* sensitive strain was favorably influenced by the presence in para position of halo-substituents (**123** and **125**) or methoxy substituents (**121**, **122**, and **124**). Monosubstitution (**121**, **123**, and **125**) was associated with MDR antituberculosis activity. Supplementary, the presence of a voluminous halogen in the fourth position (**123**) was associated with XDR antituberculosis activity, most likely due to increased molecular lipophilicity (Figure 21) [30].

Concerning the activity against bronchitis causing bacteria, SAR studies showed that the best antibacterial activity was associated with the grafting of methoxy groups in meta position (**122** and **124**) (Figure 21) [30].

Molecular docking studies showed that the compounds can target the enoyl-acyl carrier protein reductase InhA of *M. tuberculosis*, important for the type II fatty acids biosynthesis. The inhibition is enhanced by the substituent from the fourth position of the thiazole, the carbonyl of the ester group binding to the target through an accepting hydrogen bond. The inhibitory activity on InhA was further confirmed by *in vitro* studies [30].
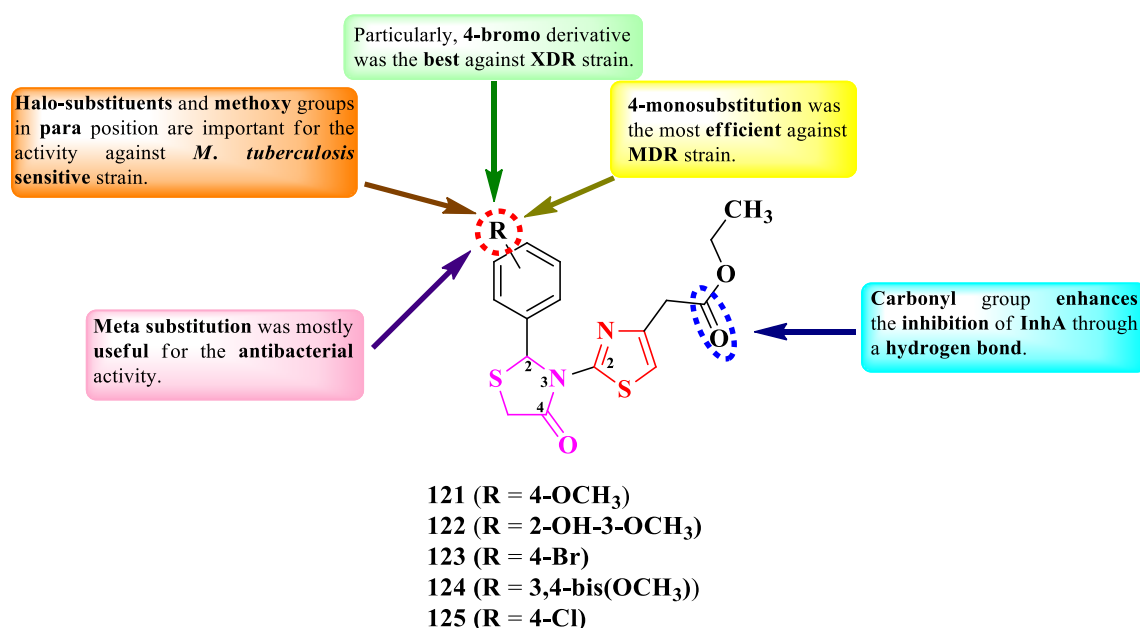


121 (R = 4-OCH$_3$)
122 (R = 2-OH-3-OCH$_3$)
123 (R = 4-Br)
124 (R = 3,4-bis(OCH$_3$))
125 (R = 4-Cl)

**Figure 21.** SAR studies in antibacterial 2-(thiazol-2-yl)-*N*-thiazolidin-4-one derivatives, reported by Othman et al. [30].

Abo-Ashur et al. reported the synthesis of a series of 2-(thiazol-2-yl)-imino-thiazolidin-4-ones (Figure 22) [31].

The compounds were tested for their antituberculosis activity, with six compounds (**128**-**133**) presenting similar activity (MICs = 0.78-3.12 μg/mL) to isoniazid (MIC = 0.78 μg/mL), against *M. tuberculosis* RCMB 010126 [31].

The antibacterial activity was also tested against Gram-positive and Gram-negative strains [31]. Three compounds (**130**, **131**, and **134**) showed excellent activity against *S. aureus* RCMB 010028 and *P. aeruginosa* RCMB 010043 (MICs = 0.49-0.98 μg/mL) and six compounds (**130-134**) against *E. coli* RCMB 010052 (MICs = 0.49-0.98 μg/mL), compared to ciprofloxacin (MICs = 1.95-3.90 μg/mL) [31].

With respect to the antifungal activity, which was tested against *Candida* and *Aspergillus* strains, two compounds showed superior activity (**130** and **134**) against *A. fumigatus* (MICs = 0.49 μg/mL), and four compounds (**127**, **130**, **131**, and **134**) against *C. albicans* (MICs = 0.49 μg/mL), compared to amphotericin B (MICs = 0.98-1.95 μg/mL) [31].

SAR studies in these series suggest that a halogen (**126** and **129**) or methoxy (**127**, **131**, and **132**) substituent grafted on the phenyl ring ($R_2$) is essential for the antituberculosis, antibacterial, and antifungal activities (Figure 22). Advantageous for these activities were also the bioisosteric substitution of the phenyl ring with a 3-pyridinyl (**134**) and the grafting of an additional morpholinyl ring (**128** and **130**) [31]. No potential target was reported by the authors.
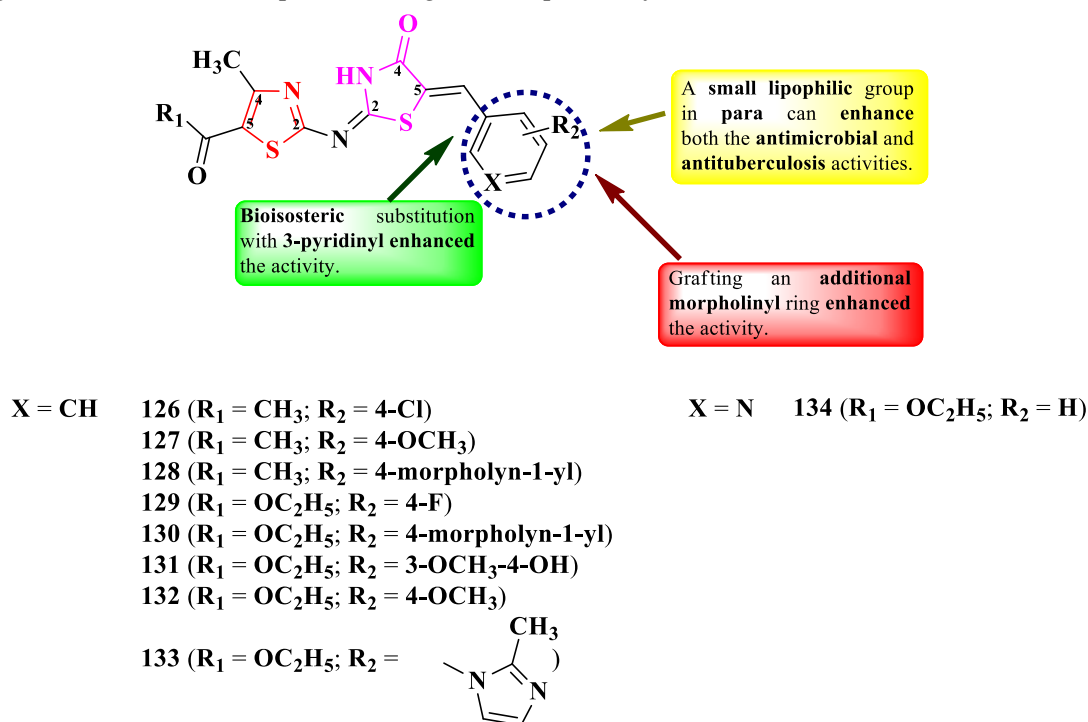


X = CH        **126** ($R_1$ = $CH_3$; $R_2$ = **4-Cl**)                                    X = N        **134** ($R_1$ = $OC_2H_5$; $R_2$ = **H**)
                  **127** ($R_1$ = $CH_3$; $R_2$ = **4-OCH$_3$**)
                  **128** ($R_1$ = $CH_3$; $R_2$ = **4-morpholyn-1-yl**)
                  **129** ($R_1$ = $OC_2H_5$; $R_2$ = **4-F**)
                  **130** ($R_1$ = $OC_2H_5$; $R_2$ = **4-morpholyn-1-yl**)
                  **131** ($R_1$ = $OC_2H_5$; $R_2$ = **3-OCH$_3$-4-OH**)
                  **132** ($R_1$ = $OC_2H_5$; $R_2$ = **4-OCH$_3$**)

                  **133** ($R_1$ = $OC_2H_5$; $R_2$ = )

**Figure 22.** SAR studies in antimicrobial 2-(thiazol-2-yl)-imino-thiazolidin-4-one derivatives, reported by Abo-Ashur et al. [31].

### 2.2.6. Thiazolyl-Thiazolidindione Hybrid Compounds

Widely known for the antidiabetic activity in glitazones, the thiazolidinedione heterocycle was also used in designing new antibacterial, antifungal, antiretroviral, antituberculosis, and anticancer compounds [32].

Alegaon et al. designed a series of antimicrobial 2-(thiazolidin-2,4-dion-3-yl)-*N*-(thiazol-2-yl)acetamides (Figure 23). The active methylene from the fifth position of the thiazolidin-2,4,-dione ring was derivatized (R) with various aromatic and heteroaromatic aldehydes through Knoevenagel condensations [33].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative strains and for their antifungal activity against various fungal strains [33]. Five compounds

(**135**-**139**) showed inferior activity (MICs = 4-32 µg/mL) against *S. aureus* ATCC 25923, *E. faecalis* ATCC 35550, *E. coli* ATCC 35218, and *P. aeruginosa* ATCC 25619, compared to ciprofloxacin (MICs = 2 µg/mL) [33].

Concerning the antifungal activity, the same compounds showed inferior activity against *C. albicans* ATCC 2091, *A. flavus* NCIM 524, *A. niger* ATCC 6275, and *C. neoformans* (clinical isolate), compared to ketoconazole (MICs = 1-2 µg/mL) [33].

SAR studies underlined that the substitution of the arylidene moiety from the fifth position of thiazolidin-2,4-dione ring with electron-donating groups, especially methoxy (**136-138**), enhanced the overall antibacterial and antifungal activities (Figure 23). Bioisosteric substitution of the phenyl ring with 2-furanyl (**139**) also favorized the antibacterial and antifungal activities. The substitution with electron-withdrawing groups, such as nitro or cyano, almost abolished both activities [33].

These compounds could potentially target the ATP binding domain of bacterial DNA gyrase B and the fungal lanosterol 14α-demethylase, according to the molecular docking studies [33].
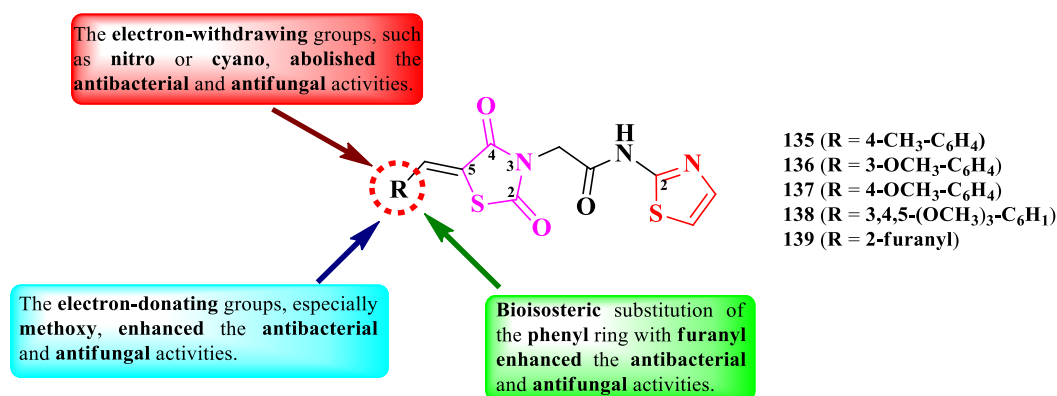


**Figure 23.** SAR studies in antimicrobial 2-(thiazolidin-2,4-dion-3-yl)-*N*-(thiazol-2-yl)acetamides, reported by Alegaon et al. [33].

### 2.2.7. Thiazolyl-1,3,4-Thiadiazole Hybrid Compounds

The versatility of 1,3,4-thiadiazole heterocycle comes from its ability to act as a hydrogen binding domain, as a two-electron donor system and as a bioisosteric replacement of thiazole. Thus, it is a valuable moiety for designing novel antimicrobial, anticancer, and antiprotozoal compounds [34].

Using the artificial intelligence, Stokes et al. repurposed an antidiabetic compound, SU-3327, which acts as a c-Jun N-terminal protein kinase (JNK) inhibitor, into a promising antibacterial molecule called halicin. Structurally, halicin (**140**) contains a 5-nitrothiazole and a 2-amino-1,3,4-thiadiazole, linked in the 2,5' positions by a thioether group (Figure 24) [35,36].

Halicin displayed broad antibacterial activity against *E. coli* (MIC = 2 µg/mL), *M. tuberculosis*, carbapenem-resistant Enterobacteriaceae and *A. baumanii*, but no activity against *P. aeruginosa* [35]. Further studies for the assessment of the antibacterial potential were reported by other authors as well [36,37].

Booq et al. tested halicin with significant results against *S. aureus* ATCC BAA-977 (MIC = 16 µg/mL), *E. coli* ATCC 25922 (MIC = 32 µg/mL), *A. baumanii* ATCC BAA-747 (MIC = 128 µg/mL), and *A. baumanii* MDR isolate (MIC = 256 µg/mL) bacterial strains [36]. Hussain et al. obtained promising results when assayed halicin against strains of *E. faecalis* and *E. faecium* (MICs = 4-8 µg/mL) [37]. Moreover, halicin showed proof of antibiofilm potential, alone and also in synergism with other molecules, as reported by some authors [38,39]. Currently, there are no ongoing clinical trials for testing halicin on humans.

The unique mechanism of action, which implies the disruption of membrane electrochemical gradient, pH modification and upregulation of iron acquisition genes, makes it difficult to acquire resistance. It is also possible that halicin may act as a siderophore prior to pH alteration [35].
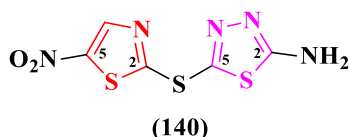
**(140)**

**Figure 24.** Structure of halicin.

### 2.2.8. Thiazolyl-1,2,3-Triazole Hybrid Compounds

1,2,3-Triazole is the most stable among heterocycles with three adjacent nitrogen atoms and it can be found in variable bioactive compounds, including antibacterial, antifungal, antimalarial, and anticancer agents [40]. Herein, we present the structure-activity relationship in thiazole clubbed with 1,2,3-triazole compounds with promising antimicrobial potential, to establish how clubbing these two heterocycles could potentially influence the biological activity.

Based on the found structures, it can be concluded that there were two types of scaffolds used: one in which the thiazole and 1,2,3-triazole rings are linked directly, but with different linking positions (**a**-**b**) [41,42], and the other one in which the rings are clubbed through various linkers and variable linking positions (**c**-**e**) [43–45] (Figure 25).
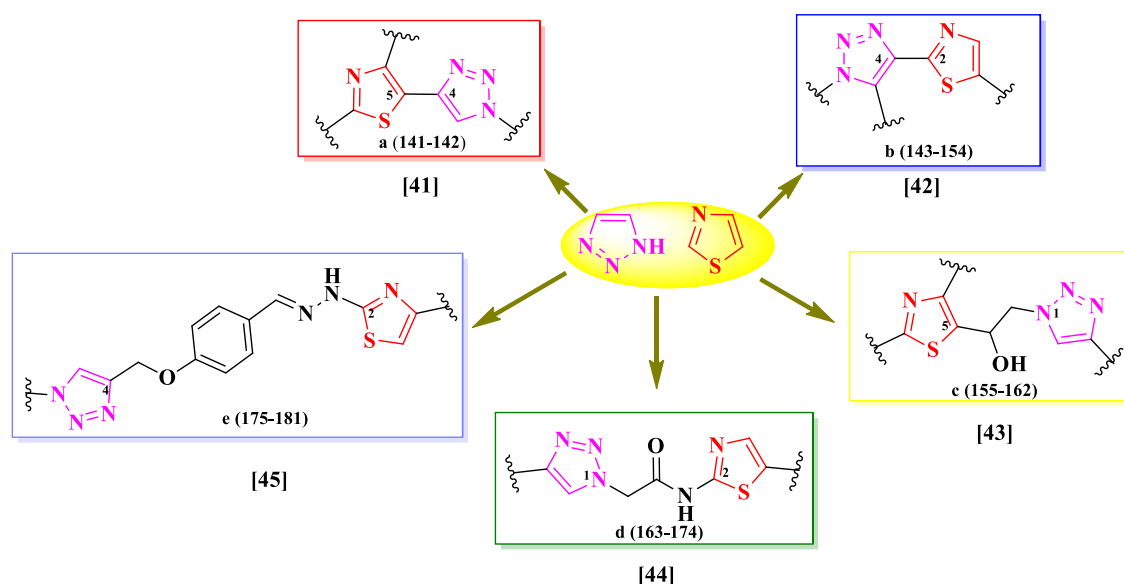


**Figure 25.** The general structures for the series discussed, containing thiazole and 1,2,3-triazole rings [41–45].

Shinde et al. reported the design of novel antituberculosis 5-(1,2,3-triazol-4-yl)-thiazoles, substituted in the second position of the thiazole ring with various aryl substituents (Figure 26) [41].

The antituberculosis activity was tested against *M. tuberculosis* H37Ra (ATCC 25177), using rifampicin ($IC_{50}$ = 0.002 µg/mL and $MIC_{90}$ = 0.75 µg/mL) as reference. The activity of the compounds was quantified using both $IC_{50}$ and $MIC_{90}$. While most of the compounds were very active in terms of $IC_{50}$ values (0.58-8.23 µg/mL) [41], only two compounds (**141** and **142**) were active in terms of $MIC_{90}$ values (2.22 µg/mL and 4.71 µg/mL), the activity being inferior to rifampicin [41].

SAR studies show that fluoro substitution of the benzyl group linked to 1,2,3-triazole is responsible for the antituberculosis activity (Figure 26) [41]. However, this boost in the activity only took place when the other phenyl ring was either unsubstituted (**141**) or 3-methyl substituted (**142**). Double halogen substitution was associated with a decrease in the activity [41].

These compounds can potentially target enoyl acyl carrier protein reductase, which is an important enzyme in the fatty acid biosynthesis and growth of mycobacteria, based on the molecular docking studies [41].
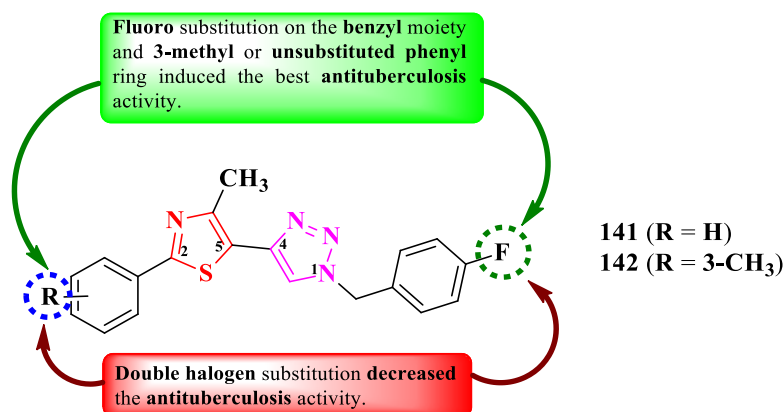
**Figure 26.** SAR studies in antituberculosis 5-(1,2,3-triazol-4-yl)-thiazoles, reported by Shinde et al. [41].

Mahale et al. synthesized a series of 2-(1,2,3-triazol-4-yl)-thiazole derivatives, substituted on the first position of 1,2,3-triazole ring ($R_1$) and the fifth position of thiazole ring ($R_2$) with aryl substituents (Figure 27) [42].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative strains and for their antifungal activity against *Candida sp.* and *Aspergillus sp.* strains [42]. Compounds **144**, **146**, **148**, and **150**-**154** were equally active (MIC = 0.5 μg/mL) against *E. coli* ATCC 25922 and *S. aureus* ATCC 25923, compared to streptomycin (MIC = 0.5 μg/mL).

Concerning the antifungal activity, compounds **143**-**145**, **147**, **149**, and **150** were equipotent (MIC = 0.5 μg/mL) against *C. albicans* MTCC 2977 and *A. niger* MCIM 545, compared to griseofulvin (MIC = 0.5 μg/mL) [42].

SAR studies suggest that substitution with predominantly electron-withdrawing groups, like nitro and halogen atoms, provide an antibacterial effect to the molecules, while the antifungal effect can be achieved using electron-donating, such as methyl and methoxy, and electron-withdrawing groups in both positions (Figure 27). No potential target was reported by the authors [42].
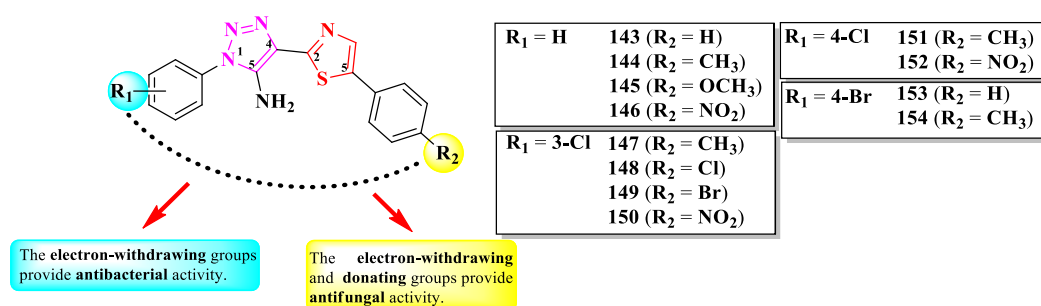


**Figure 27.** SAR studies in antimicrobial 2-(1,2,3-triazol-4-yl)-thiazole derivatives, reported by Mahale et al. [42].

Jagadale et al. designed a series of 1-(thiazol-5-yl)-2-(1,2,3-triazol-1-yl)-ethanol derivatives, substituted in the second position of the thiazole ring ($R_1$) and the fourth position of the 1,2,3-triazole ring ($R_2$) with various aryl substituents (Figure 28) [43].

The compounds were tested for the antibacterial activity against Gram-positive and Gram-negative strains and for the antifungal activity against various strains [43]. Compounds **156**-**158** showed inferior activity (MIC = 62.5 μg/mL) against *S. epidermidis* NCIM 2178, compared to streptomycin (MIC = 7.81 μg/mL) [43].

Regarding the antifungal activity, compounds **155** and **159**-**162** were inferior against *A. niger* (ATCC 504) compared to fluconazole (MIC = 7.81 μg/mL), but similar to ravuconazole (MIC = 31.25

μg/mL). Additionally, compound **158** displayed activity against *R. glutinis* (MIC = 62.5 μg/mL) too, but inferior to both reference compounds [43].

SAR studies suggest that substitution with 4-chloro (**160-162**) and 4-fluoro (**159**) in $R_1$, as well as unsubstituted phenyl (**155**) are responsible for the activity against *A. niger* (Figure 28). Fluoro substitution of only one (**156-157**, and **160**) or both (**158**) of the phenyl rings was associated with antibacterial activity against *S. epidermidis*. Double 4-fluorophenyl substitution induced activity against *S. epidermidis*, *A. niger*, and *R. glutinis*, as seen in compound **158**. No potential target was reported by the authors [43].
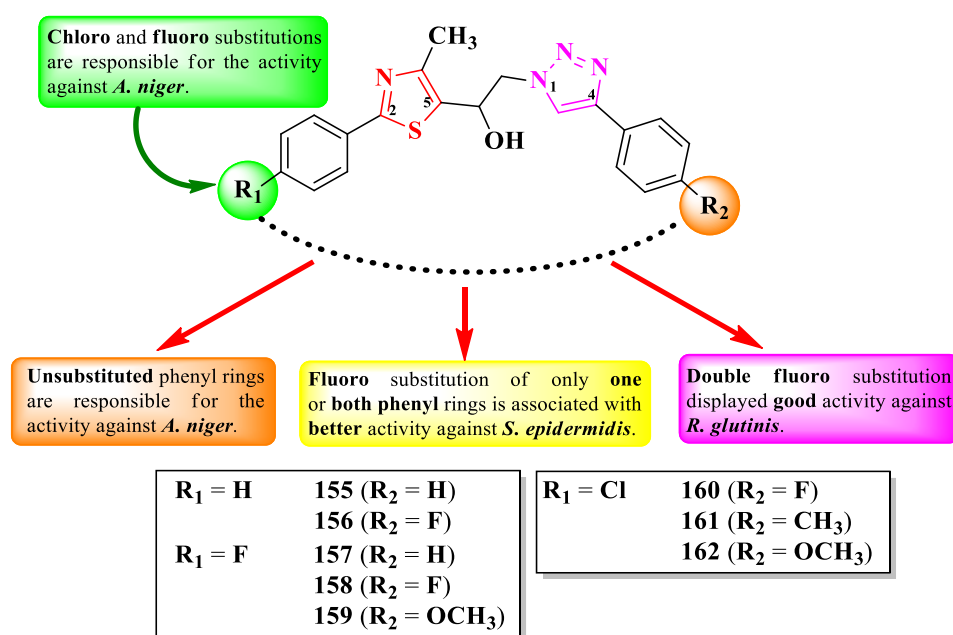


**Figure 28.** SAR studies in antimicrobial 1-(thiazol-5-yl)-2-(1,2,3-triazol-1-yl)-ethanol derivatives, reported by Jagadale et al. [43].

Poonia et al. designed some 2-(1,2,3-triazol-1-yl)-*N*-(thiazol-2-yl)-acetamides and 2-(1,2,3-triazol-1-yl)-*N*-(benzothiazol-2-yl)-acetamides, para-substituted on the phenyl-ureidomethyl moiety, linked to the fourth position of 1,2,3-triazole ring (Figure 29) [44].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative strains and for their antifungal activity against *Candida sp.* and *Rhizopus sp.* strains [44]. All compounds (**163-174**) showed superior activity (MICs = 0.0074-0.0333 μmol/mL) against *C. albicans* MTCC 183 and *Rhizopus oryzae* MTCC, compared to fluconazole (MIC = 0.0408 μmol/mL) [44].

Concerning the antibacterial activity, four compounds (**165**, **170**, **173**, and **174**) showed noteworthy activity. Compounds **165** and **170** showed inferior activity (MICs = 0.0287-0.0299 μmol/mL) against *E. coli* MTCC 1654 and *S. aureus* MTCC 3160, compared to ciprofloxacin (MIC = 0.0094 μmol/mL). Compounds **170** and **173** showed inferior activity (MICs = 0.0257-0.0299 μmol/mL) against *P. fluorescens* MTCC 664, compared to the reference drug, while compound **174** showed superior activity (MIC = 0.0071 μmol/mL). Lastly, compound **171** was the most active against *Bacillus endophyticus* (MIC = 0.0257 μmol/mL), but still inferior to the reference drug [44].

Based on the SAR studies, the insertion of thiazole or benzothiazole rings increased the antifungal activity, compared to the phenylureidopropargyl precursors and fluconazole (Figure 29) [44]. For the antibacterial activity, bromo (**165**, **169**, and **173**) and methoxy (**166**, **170**, and **171**) substitutions, as well as the annulation of the thiazole ring (**171-174**) were the most important [44].

These compounds act as antifungals by targeting sterol 14-$\alpha$ demethylase, according to the molecular docking studies [44].
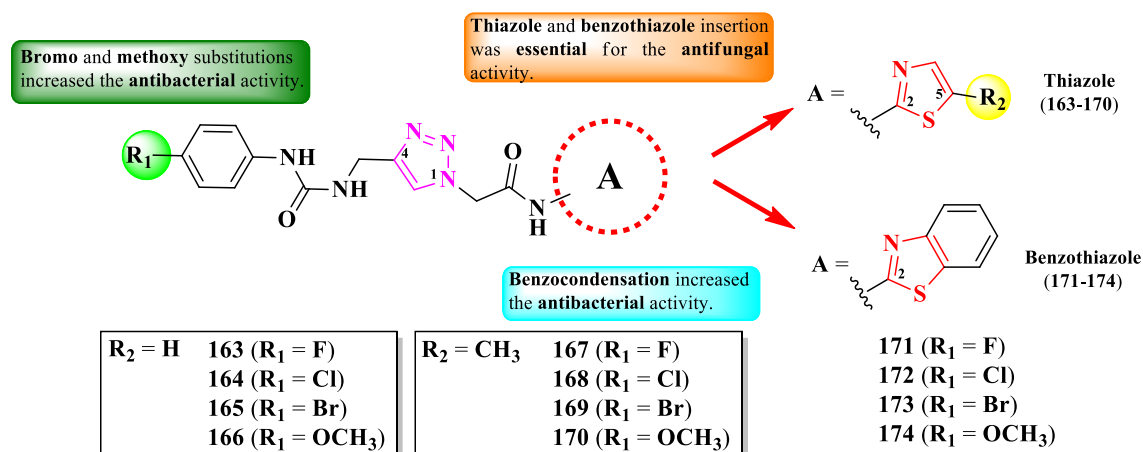
**Figure 29.** SAR studies in antimicrobial 2-(1,2,3-triazol-1-yl)-*N*-(thiazol-2-yl)-acetamides and 2-(1,2,3-triazol-1-yl)-*N*-(benzothiazol-2-yl)-acetamides, reported by Poonia et al. [44].

Gondru et al. reported the synthesis of two series of 2-(1,2,3-triazol-4-yl-methoxybenzylidenehydrazinyl)-thiazoles, substituted on the fourth position of thiazole ring with aryl and hetaryl substituents (Figure 30) [45]. They used para-hydroxybenzaldehyde as starting material, of which the phenolic hydroxyl group was etherified with a substituted 1,2,3-triazole moiety, while the carbonylic group was derivatized to the corresponding hydrazonothiazoles [45].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative strains and for their antifungal activity against various *Candida sp.* and *Issatchenkia sp.* strains [45]. Compounds **175**-**181** showed inferior activity (MICs = 2.8-15.7 μM) against *S. aureus* MTCC-96, *S. aureus* MLS16 (MTCC 2940), *M. luteus* MTCC 2470, *K. planticola* MTCC 530, *E. coli* MTCC 739, and *P. aeruginosa* MTCC 2453, compared to ciprofloxacin (MIC = 2.7 μM) [45].

Concerning the antifungal activity, compounds **176**-**180** showed superior activity (MICs = 5.9-14.2 μM) against *C. albicans* MTCC 183, MTCC 854, and MTCC 3018, *C. aaseri* MTCC 1962, *C. glabrata* MTCC 3019, and *Issatchenkia hanoiensis* MTCC 4755, compared to miconazole (MIC = 18.7 μM) [45].

According to the SAR studies, 4-methoxyphenyl (**175**), benzo[f]coumarinyl (**176**), and 8-methoxycoumarinyl (**177**), 6-bromo-8-methoxycoumarinyl (**178**), and 8-bromocoumarinyl (**179**) substitutions were associated with antibacterial activity against *S. aureus* (Figure 30) [45]. The presence of the coumarin heterocycle was important for the antifungal activity, especially against *C. albicans* MTCC 183 strain. By replacing the methoxy group from the coumarin ring with an ethoxy group or introducing electron-withdrawing groups, like chloro and nitro, in both 6- and 8- positions of the coumarin, cancelled the antibacterial effect, but not the antifungal one. No potential target was reported by the authors [45].
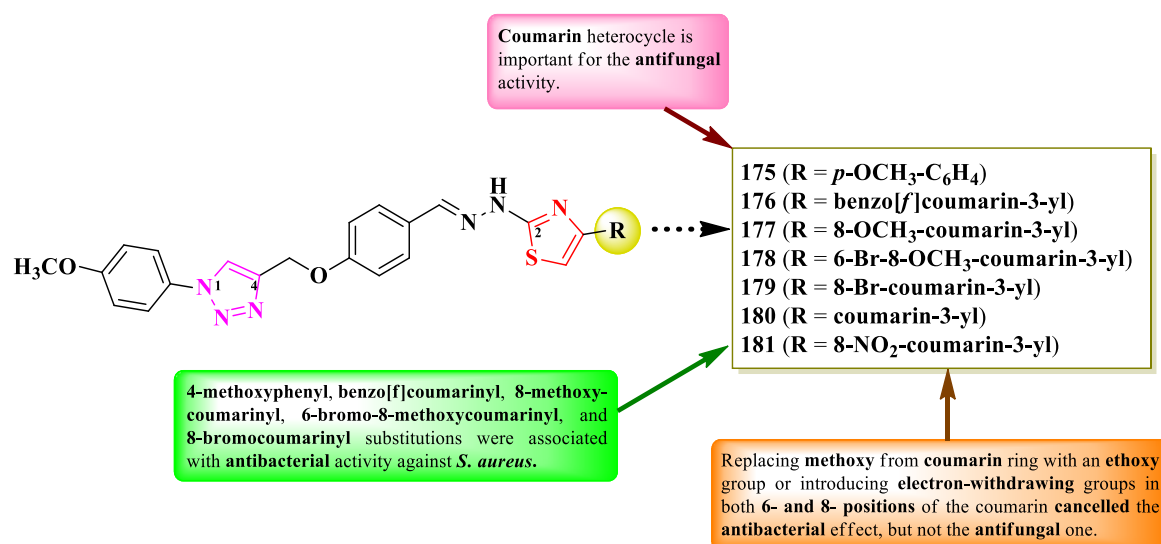
**Figure 30.** SAR studies in antimicrobial 2-(1,2,3-triazol-4-yl-methoxybenzylidenehydrazinyl)-thiazoles, reported by Gondru et al. [45].

In conclusion, 1,2,3-triazole heterocycle is a versatile moiety for designing novel antimicrobial compounds with broad activity spectrum. As observed in the presented studies, clubbing with thiazole resulted in potent compounds against a large variety of pathogen strains, including mycobacteria.

A prominent feature of the presented compounds was the presence of substituted phenyl rings, linked directly to the heterocycles or through a linker. Thus, the difference between compounds' activity were mostly attributed to these substituents. By far, the most used substituents in these compounds were halogens, methyl and methoxy groups [41–45]. A summary of the structure-activity relationships in antimicrobial 1,3-thiazole clubbed with 1,2,3-triazole hybrid compounds is presented in Figure 31.
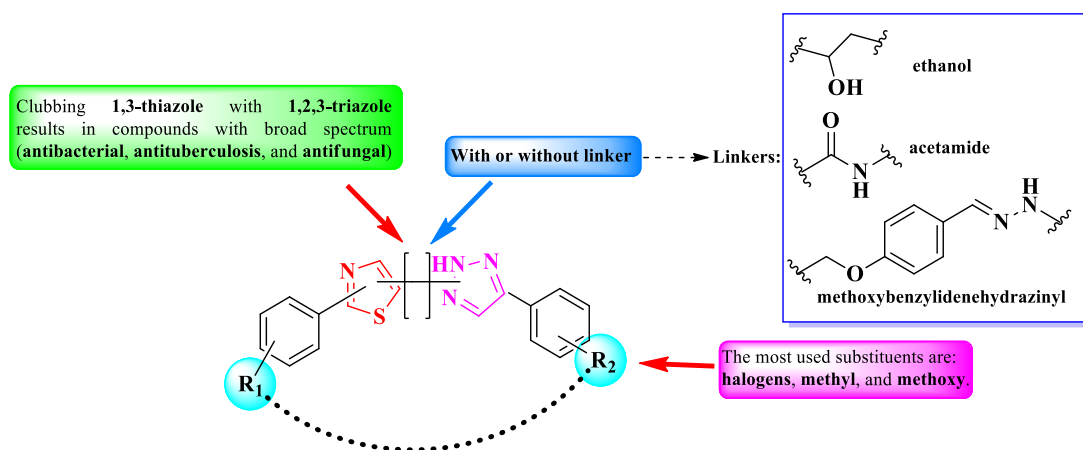


**Figure 31.** Endpoints of designing novel antimicrobial 1,3-thiazole clubbed with 1,2,3-triazole hybrid compounds.

### 2.2.9. Thiazolyl-1,3,4-Oxadiazole Hybrid Compounds

Similarly to the previously mentioned heterocycles containing three heteroatoms, the 1,3,4-oxadiazole ring can be found in a plenitude of compounds with various biological activities, including anticancer, antibacterial, antifungal, and antiviral effects. This heterocycle can act as bioisostere for the carbonyl group and can be used in the structure of a molecule as a flat aromatic linker to ensure an adequate orientation [46].

As reported in the literature, the 5-thioxo-1,3,4-oxadiazole heterocycle can be found in a series of anticancer and antimicrobial compounds [47–49], thus making this heterocycle an important contender for designing novel antimicrobials.

Some series of 2-thiazolyl-5-mercapto-1,3,4-oxadiazoles, either linked through a methylene linker between the fourth position of thiazole ring and the second position of 1,3,4-oxadiazole ring (Figure 33), or directly linked between the fifth position of thiazole ring and the second position of 1,3,4-oxadiazole ring (Figure 34), were synthesized [50,51].

The compounds exist in two tautomeric forms (Figure 32). The existing data [52] show that the thione tautomer (**II**) is more stable in the solid state, while in solution the thiol tautomer (**I**) is predominant. The existence of thiol-thione tautomerism was valorized by obtaining the corresponding thioether derivatives (Figure 33) and Mannich bases (Figure 34) [50,51].
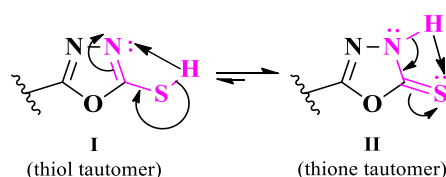


**I**
(thiol tautomer)

**II**
(thione tautomer)

**Figure 32.** The thiol-thione tautomerism [52].

Athar Abbasi et al. described the synthesis of 2-(thiazol-4-yl)-5-thio-1,3,4-oxadiazoles, capable of urease inhibition, thus offering an alternative potential treatment to *Helicobacter pylori* infections (Figure 33) [50].

The inhibitory activity was tested using thiourea ($IC_{50}$ = 21.11 ± 0.12 μM) as reference. Based on the results ($IC_{50}$ = 2.17 ± 0.41 μM) and molecular docking studies, compound **182** (Figure 33) presented the best binding affinity (-8.40 kcal/mol), among all synthesized and tested compounds, and was able to bind to the active site of the enzyme [50].

By integrating all the obtained information, it could be concluded that the fluorine atom forms two halogen-metal bonds with the nickel active center of urease. The potential inhibition of urease was influenced by the type and position of the halogen atom, on the benzyl moiety linked to the sulfur atom. The fluorine atom in para position (**182**) was the most advantageous for the inhibition. For chlorine, meta position was favorable, while for bromine was either ortho or para position. One more important aspect observed was that an unsubstituted benzyl moiety yielded the weakest inhibitory capacity, therefore the presence of a halogen substituent was essential for urease inhibition [50].



Factors that affect the binding capacity:
- the presence of a **substituent** is **essential**
- **size** of the halogen group **(F > Cl > Br)**
- **position** on the benzyl moiety

**182 (R = 4-F)**

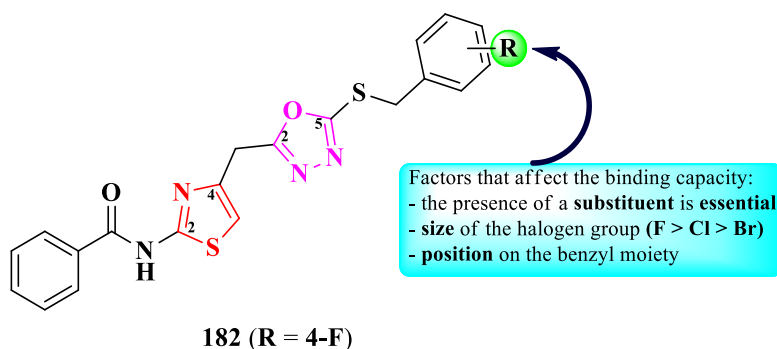**Figure 33.** SAR studies in 1,3-thiazole clubbed in 2-(thiazol-4-yl)-methylene-5-thio-1,3,4-oxadiazoles urease inhibitors, reported by Athar Abasi et al. [50].

Desai et al. designed a series of 2-(thiazol-5-yl)-5-mercapto-1,3,4-oxadiazole Mannich bases. These compounds are variably substituted on the anilino moiety linked to the fourth position of the 1,3,4-oxadiazole ring, through a methylene bridge (Figure 34) [51].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative bacterial strains and for their antifungal activity against *Candida sp.* and *Aspergillus sp.* strains [51]. Compounds **183**, **184**, and **187** showed superior activity against *E. coli* MTCC 443, *P. aeruginosa* MTCC 1688, and *S. pyogenes* MTCC 442, compared to ampicillin (MICs = 100-250 μg/mL) [51].

Concerning the antifungal activity, compounds **185** and **186** showed superior activity (MICs = 25-50 μg/mL) against *C. albicans* (MTCC 227) and *A. niger* (MTCC 282), compared to griseofulvin (MICs = 100-500 μg/mL) [51].

SAR studies implied that the most active antibacterial compounds had electron-withdrawing groups, such as nitro (**187**) and fluoro (**183**-**184**), while the most active antifungal compounds had electron-donating groups, such as methoxy (**185**-**186**) (Figure 34). No potential target was reported by the authors [51].
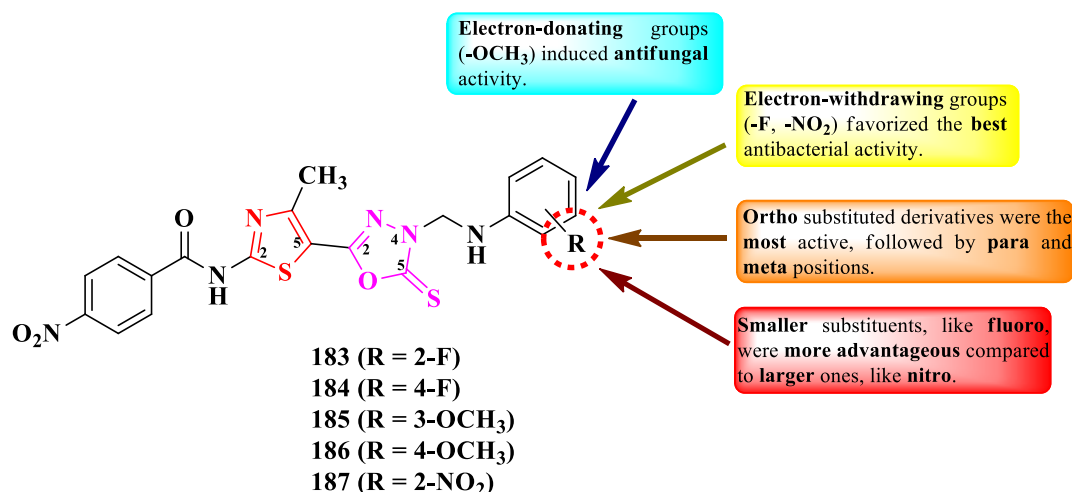


**Figure 34.** SAR studies in antimicrobial 2-(thiazol-5-yl)-5-mercapto-1,3,4-oxadiazoles, reported by Desai et al. [51].

## 2.3. Thiazole Clubbed with Five-Membered Benzofused Heterocycles

Benzofusion of heterocycles leads to an increase in lipophilicity and electron-withdrawing character, which could be advantageous in drug design. Additionally, benzofused heterocycles constitute bioisostere alternatives to naphthalene, which can facilitate better binding to a potential target [53].

Based on the literature search of the last six years, we will discuss further the structure-activity relationship in antimicrobial hybrid compounds containing thiazole clubbed with the following five-membered heterocycles and their derivatives: indole, carbazole, indolin-2-one, and tetrahydroindenofuran.

### 2.3.1. Thiazolyl-Indole and Thiazolyl-Carbazole Hybrid Compounds

The antimicrobial properties of carbazole derivatives were known since the isolation of carbazole alkaloids from *Murraya koenigii* leaves [54]. Similarly, indole naturally occurs in various alkaloids with antimicrobial properties [55–57]. Since then, these heterocycles have been increasingly used in the design of synthetic novel antimicrobials.

Zhao et al. reported the design of a novel series of antimicrobial thiazole clubbed with either indole or carbazole hybrid compounds, containing a ferrocene scaffold (Figure 35) [58].

The antibacterial activity was assayed against *S. aureus*, *E. coli*, and *P. aeruginosa*, using ciprofloxacin as reference (MIC = 15.625 μg/mL). Only three compounds (**188**-**190**) showed good activity against *E. coli* (MIC = 31.25 μg/mL), while the activities against the other strains were poor (MICs = 125-250 μg/mL) [58].

SAR studies in these series suggest that the introduction of a second heterocycle on the 4-ferrocenylthiazole scaffold, indole or carbazole, significantly decreased the antibacterial activity

(Figure 35), compared to the 4-ferrocenyl-2-*N*-anilinothiazole series. No potential target was reported by the authors [58].
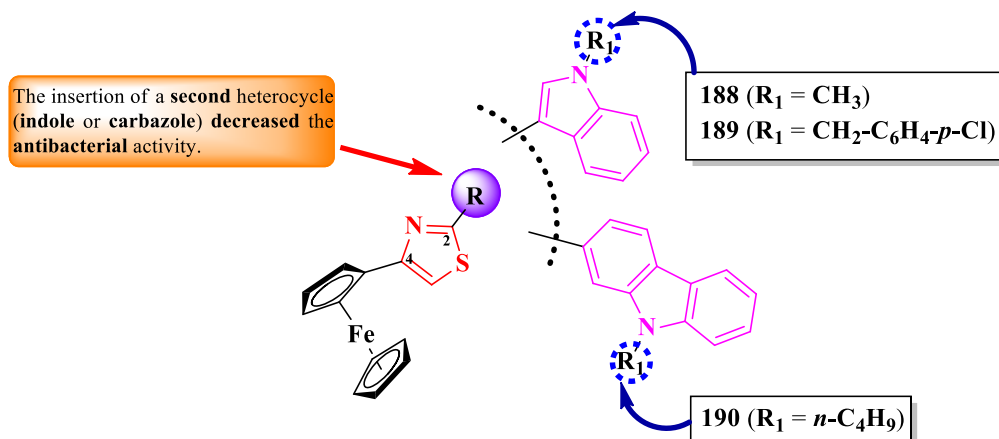


**Figure 35.** SAR studies in antibacterial 4-ferrocenylthiazoles clubbed with indole or carbazole, reported by Zhao et al. [58].

### 2.3.2. Thiazolyl-Indolin-2-one Hybrid Compounds

Indolin-2-one derivatives are ubiquitous compounds found in the human body. They possess various biological activities, including antioxidant, antimicrobial, and antiproliferative activities [59].

Starting from 5-(piperazin-1-yl)-sulfonylindolin-2,3-dione, Alzahrani et al. obtained some clubbed thiazole Schiff bases and thiazolin-4-one compounds as dihydrofolate reductase (DHFR) inhibitors and anti-quorum sensing (QS) agents (Figure 36) [60].

They derivatized the carbonyl group from the third position of indolin-2,3-dione by either condensation with 2-*N*-anilino-thiazolin-4-one or with different aminothiazoles and hydrazonothiazoles (Figure 36, **191**-**194**) [60].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative bacterial strains and for their antifungal activity against *C. albicans* ATCC 10213 [60]. Compounds **191**, **193**, and **194** showed superior activity (MICs = 1.9-15.6 μg/ml) against *S. aureus* ATCC 25923 and ATCC 29213, *E. faecalis* ATCC 29212, *E. coli* ATCC 35218, *P. aeruginosa* ATCC 9027 and PAR.36, and *S. typhimurium* ATCC 14028, compared to levofloxacin (MICs = 8.1-130 μg/mL). Furthermore, compounds **191**, **192**, and **194** inhibited the *E. faecalis* QS system at low concentrations and presented $IC_{50}$ values of DHFR inhibition in the submicromolar range (0.04-0.28 μM), which were similar to methotrexate ($IC_{50}$ = 0.061 μM) [60].

Regarding the antifungal activity, as it was expected, the compounds had inferior activity against *C. albicans* (**192**, MIC = 62.5 μg/ml), compared to nystatin (MIC = 3.9 μg/mL) [60].

SAR studies in these series can be constructed on four levels. The first level is the nature of the bond between the indolin-2-one ring and the thiazolin-4-one- or thiazole-containing fragments (Figure 36). Compound **191**, containing an ethenyl bond (-C=C-), showed antibacterial activity against *S. aureus* and *P. aeruginosa* (MIC = 12.5 μg/mL), while compounds **192**-**194**, containing an imine bond (-C=N-), showed both antibacterial and antifungal activities against a broader spectrum, including *E. faecalis*, *E. coli*, *S. typhimurium*, and *C. albicans* [60].

The second level is based on the nature of the azole heterocycle. As observed on the previous level, the compound containing a thiazolin-4-one ring had a narrower activity spectrum compared to the compounds containing the thiazole ring (Figure 36) [60].

The third level is based on the distance between the indolin-2-one ring and the thiazole ring. As the distance between the two rings grows, so does the antibacterial activity. Compound **192**, in which the rings are directly linked through an imine bond, had the weakest activity among all three imino compounds (MIC = 62.5 μg/mL). Compound **193** had registered better activity when the imino bond was swapped with a hydrazono one (MIC = 7.8 μg/mL), while introducing a benzensulfonamide

moiety in compound **194** resulted in the best antibacterial activity (MICs = 1.9-7.8 μg/mL). An additional sulfonamide group will increase the antibacterial activity, which is the last level of the SAR studies in these series (Figure 36) [60].

It should be noted that replacing the methyl from the piperazine ring with a phenyl decreased the antibacterial activity (Figure 36) [60].
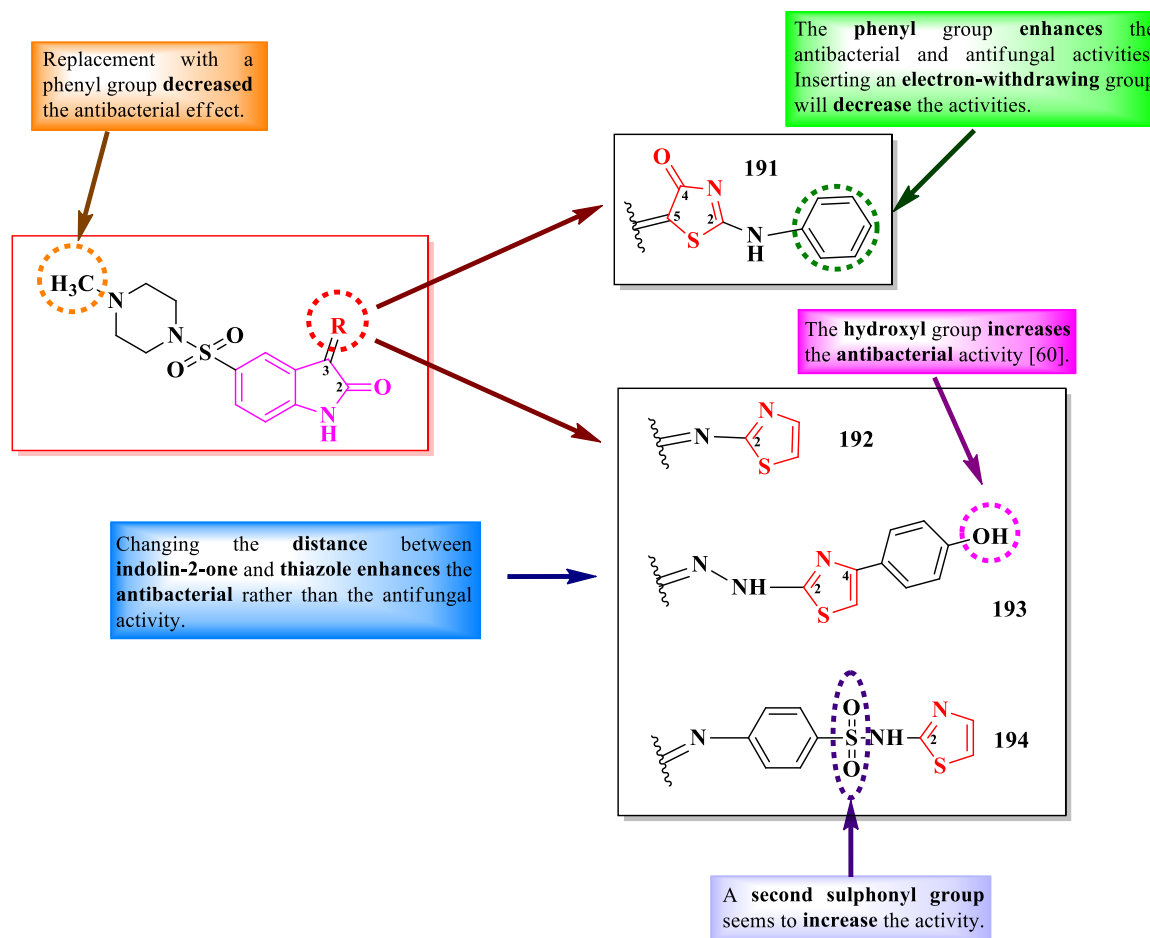


**Figure 36.** SAR studies in antimicrobial thiazole clubbed with indolin-2-one compounds, reported by Alzahrani et al. [60].

### 2.3.3. Thiazolyl-Tetrahydroindenofuran Hybrid Compounds

Indenofurans are rare occurring in nature compounds, found in *Anisodus tanguticus* species. These compounds are mostly known for their antioxidant properties, but there have been reports about their antibacterial potential [61,62].

Adole et al. designed a series of 2-(2-tetrahydroindenofuranylidene)-hydrazinylthiazoles, substituted in the fourth position of the thiazole ring with various aryl groups (Figure 37) [63].

The compounds were tested for the antibacterial activity against Gram-negative strains and for the antifungal activity against various strains [63]. Compounds **195-197** showed inferior activity (MICs = 15.62-31.25 μg/mL) against *E. coli* and *Shigella boydii*, compared to ampicillin (MICs = 1.95-3.9 μg/mL).

Concerning the antifungal activity, compounds **195-199** showed similar activity (MICs = 1.95-15.62 μg/mL) against *R. oryzae*, *Mucor mucedo*, *A. niger*, and *C. albicans*, compared to fluconazole (MICs = 0.97-1.95 μg/mL) [63].

SAR studies in these compounds underline that the para substitution with bulky substituents was associated with overall good antibacterial and antifungal activities (Figure 37). The meta substitution may be useful in enhancing the antifungal effect, compound **198** being twice or thrice

more active than the para substituted compounds**.** It is also worth mentioning that fluoro substitution (**199**) is beneficial for the antifungal activity, but not for the antibacterial [63]. Switching from phenyl to naphthyl in the fourth position of thiazole ring decreased the overall antibacterial and antifungal activities and it should be avoided. No potential target was reported by the authors [63].
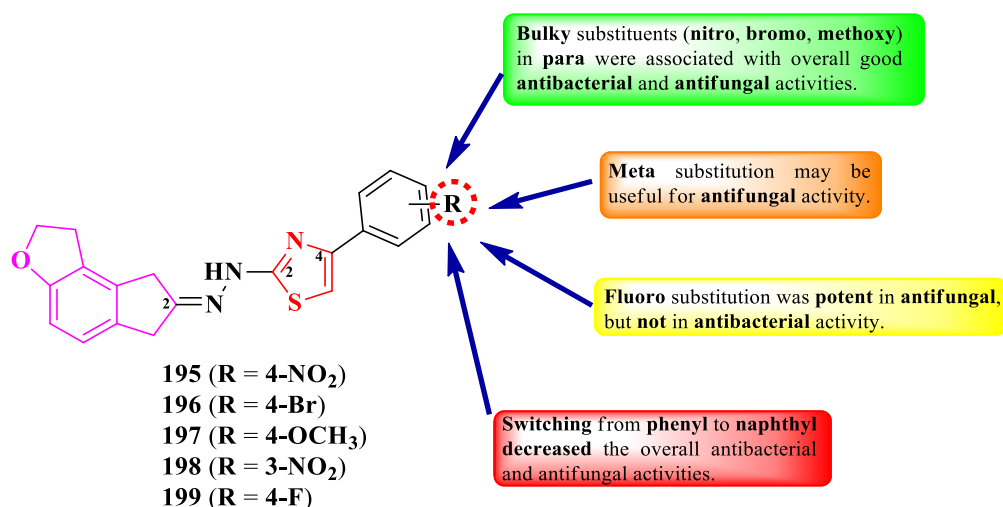


**Bulky** substituents (**nitro**, **bromo**, **methoxy**) in **para** were associated with overall good **antibacterial** and **antifungal** activities.

**Meta** substitution may be useful for **antifungal** activity.

**Fluoro** substitution was **potent** in **antifungal**, but **not** in **antibacterial** activity.

**Switching** from **phenyl** to **naphthyl** **decreased** the overall antibacterial and antifungal activities.

**195 (R = 4-NO₂)**
**196 (R = 4-Br)**
**197 (R = 4-OCH₃)**
**198 (R = 3-NO₂)**
**199 (R = 4-F)**

**Figure 37.** Structure-activity relationships in antimicrobial 2-(2-tetrahydroindenofuranylidene)-hydrazinylthiazoles, reported by Adole et al. [63].

### *2.4. Thiazole Clubbed with Six-Membered Heterocycles*

The six-membered heterocyclic compounds are numerous and versatile in terms of structure and bioactivity. Based on the literature research in the last years, only thiazole clubbed with pyridine antimicrobials were reported [64–67]. Thus, we present the SAR studies only for them.

### 2.4.1. Thiazolyl-Pyridine Hybrid Compounds

Pyridine is a privileged heterocycle found in a large variety of antimicrobial compounds, either as a sole heterocycle or together with other heterocycles. There have been reports that noted an additional heterocycle to pyridine may have the potential to enhance its biological activity [68].

Muluk et al. and Patil et al. designed some 2-(4-pyridyl)-thiazoles as potential DNA gyrase and lumazine synthase inhibitors [64–66]. These compounds are substituted in the fourth position of the thiazole ring with aryl or hetaryl substituents, linked to the thiazole ring via an acylhydrazonomethylene or $\alpha,\beta$-unsaturated carbonyl linker (R2) (Figure 38). There is a supplementary substituent in the second position of the pyridine ring, which is ethyl or propyl, depending on the starting thiocarbamide fragment (-CN=S) for the Hantzsch synthesis, ethionamide or prothionamide [64–66].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative strains and for their antifungal activity against *Candida sp.* and *Aspergillus sp.* strains [64–66]. Compounds **200**-**204**, **208**, and **209** showed inferior activity (MICs = 18-170 μg/mL) against *S. typhi* ATCC 9207, *E. coli* ATCC 8739, *E. aerogenes* ATCC 13048, *S. aureus* ATCC 6538, and *P. aeruginosa*, compared to tetracycline (MICs = 3.0-20 μg/mL) and streptomycin (MIC = 30 μg/mL) [64–66].

Concerning the antifungal activity, the same compounds showed inferior activity (MICs = 60-280 μg/mL) against *C. albicans* ATCC 10231, compared to fluconazole (MIC = 30 μg/mL) [64–66].

SAR showed that by bioisosteric substitution of the phenyl ring with a furan heterocycle (**204** and **208**) (Figure 38), the antibacterial and antifungal activities increased. Substitution with electron-withdrawing groups was favorable for the overall antibacterial and antifungal activities. The presence of a 2-nitro group (**200**) was favorable for the activity on *E. aerogenes* and the 3,5-dichloro substitution (**203**) for the activity on *C. albicans*, this being in agreement with the presence of this substituent in some important antifungal azoles like miconazole, ketoconazole, or itraconazole. The

elimination of the methyl group from the fifth position of the thiazole ring (R₃) did not affect the overall antibacterial and antifungal activities [64–66].

In order to establish the importance of the position by which the pyridine ring is linked to the thiazole one, Eryılmaz et al. synthesized two series of 2-(2/4-pyridyl)-thiazoles, substituted in the fourth position of the thiazole ring with aryl or hetaryl substituents (Figure 38) [67].

The compounds were tested for the antibacterial activity against Gram-positive and Gram-negative strains and for the antifungal activity against *C. albicans* ATCC 10231 [67]. Both 2-pyridyl (**213**-**217a**) and 4-pyridyl (**213**-**217b**) series showed inferior activity (MICs = 0.01-5.7 mM) against *E. coli* W3110, *P. aeruginosa* ATCC 27853, and *S. aureus* ATCC 6538P, compared to cefepime (MICs = 0.001-0.06 mM) and amikacin (MICs = 0.01-0.02 mM). The 4-pyridyl series (**b**) showed better activity (MICs = 0.01-4.7 mM) compared to 2-pyridyl series (**a**) (MICs = 1.2-5.7 mM) [67].

Concerning the antifungal activity, both series showed superior activity against *C. albicans* compared to fluconazole, the 4-pyridyl series showed better activity (MICs = 0.15-1.2 mM) than 2-pyridyl series (MICs = 0.15-2.8 mM) [67].

Based on these results, 4-pyridyl had a better influence on the antibacterial and antifungal activities compared to 2-pyridyl. This can be due to the better capacity of the compounds to interact with a potential target through hydrogen bonds or ionic bonds, which may be difficult in 2-pyridyl series, due to the steric hinderances [67].

Some of the compounds can express their antibacterial activity by targeting DNA gyrase, important for the replication of genetic material in bacteria, while some of the compounds express the antifungal activity by targeting lumazine synthase, a key enzyme in the biosynthesis of riboflavin in fungi [64,65].
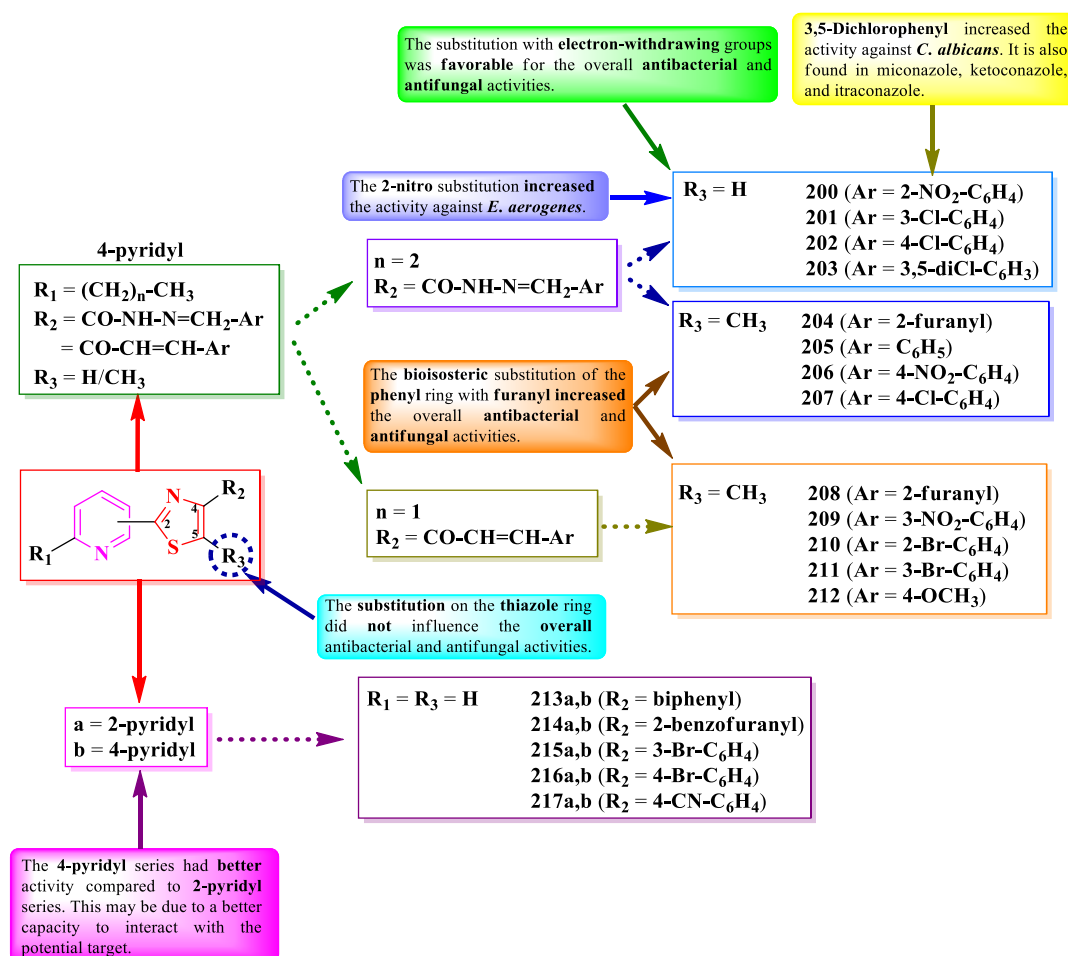


**Figure 38.** Structure-activity relationships in antimicrobial 2-pyridyl-thiazoles, reported by Muluk et al. [64,65], Patil et al. [66], and Eryılmaz et al. [67].

In conclusion, clubbing thiazole with pyridine to design potent antimicrobials in the presented cases depends mostly on the nature of the used substituents, which were mainly electron-withdrawing substituents (nitro and halogens). Based on the obtained results, the spectrum is narrower and the activity is lower compared to hybrid compounds containing five-membered heterocycles, such as pyrazole or triazole. Thus, clubbing an additional heterocycle may be helpful, however there was no similar study performed in the selected timeframe for this paper to support our hypothesis.

### 2.5. Thiazole Clubbed with Six-Membered Benzofused Heterocycles

Based on the literature search of the last six years, we will discuss further the structure-activity relationship in antimicrobial hybrid compounds containing thiazole clubbed with the following six-membered heterocycles and their derivatives: coumarin, flavone, quinoline, quinoline-2(1*H*)-one, and quinazolin-4(3*H*)-one.

### 2.5.1. Thiazolyl-Coumarin Hybrid Compounds

The coumarin heterocycle is found in some authorized antimicrobials (novobiocin and chlorobiocin) [69], thus making this moiety veritable for designing novel antimicrobials. Herein, we present the SAR studies in antimicrobial thiazole clubbed with coumarin compounds.

Yusufzai et al. reported the design and synthesis of some bis-coumarin derivatives (series I). In this series, the 4-(3-coumaryl)-thiazoles are linked to a second coumarin heterocycle by a methylylidenhydrazinyl bridge in the second position of the thiazole ring (Figure 39) [70].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative strains and for their antituberculosis activity against the H37Rv strain (ATCC 25618) [70]. Compounds **218**-**220**, **222**, **224**, **226**, and **227** showed similar activities (MICs = 31.25-62.5 μg/mL) against *E. coli*, *E. aerogenes*, *S. typhi*, *S. pneumoniae*, and *S. aureus*, compared to streptomycin (MICs = 31.25-62.5 μg/mL), kanamycin (MICs = 62.5-125 μg/mL), and vancomycin (MICs = 31.25-250 μg/mL) [70].

Regarding the antituberculosis activity, compounds **218**-**220**, **222**-**225**, **227**, and **228** showed inferior activity (MIC = 50 μg/mL) compared to isoniazid (MIC = 0.0781 μg/mL) [70].

SAR studies in these compounds suggest that the substitution of the second coumarin unit ($R_2$) with a nitro group (**221** and **226**) abolished the antituberculosis activity and severely decreased the antibacterial activity (Figure 39) [70]. Bromo (**227**) and methoxy (**218-220** and **223**-**225**) substitutions on the same coumarin were advantageous for both activities, while hydroxy substitution (**228**) was by far the best for the activity against all tested strains (MICs = 31.25-62.5 μg/mL). Coumarin heterocycles may also have a significant contribution to the activity, as all compounds displayed different degrees of potency, but none of them was completely inactive. No potential target was reported by the authors [70].

Another attempt to obtain urease inhibitors against *H. pylori* was reported by Salar et al., who designed a series of 4-(3-coumaryl)-thiazoles, in which they replaced the second coumarin heterocycle with an aromatic structure (series II) (Figure 39) [71].

The inhibitory capacity of the compounds was compared to acetohydroxamic acid ($IC_{50}$ = 27 ± 0.5 μM) [71]. The most active compound (**229**) had a better inhibitory activity than acetohydroxamic acid ($IC_{50}$ = 16.29 ± 1.1 μM). Other results worth mentioning were registered by compounds **230** ($IC_{50}$ = 76.41 ± 0.1 μM), **231** ($IC_{50}$ = 77.67 ± 1.5 μM), and **232** ($IC_{50}$ = 71.21 ± 1.6 μM) [71].

Structure-activity relationships in this series reflect the importance of fluoro, chloro, hydroxy, and methoxy substitutions for the urease inhibition, as well as their relative position on the aryl ring (Figure 39). Thus, 2-fluoro (**231**), 2-hydroxy (**232**), 2-hydroxy-5-fluoro (**229**), and 2-chloro-3-methoxy (**231**) substitutions were the most advantageous for the inhibition [71].

Molecular docking studies further emphasized the capacity of these compounds to inhibit urease by binding to its active site [71].
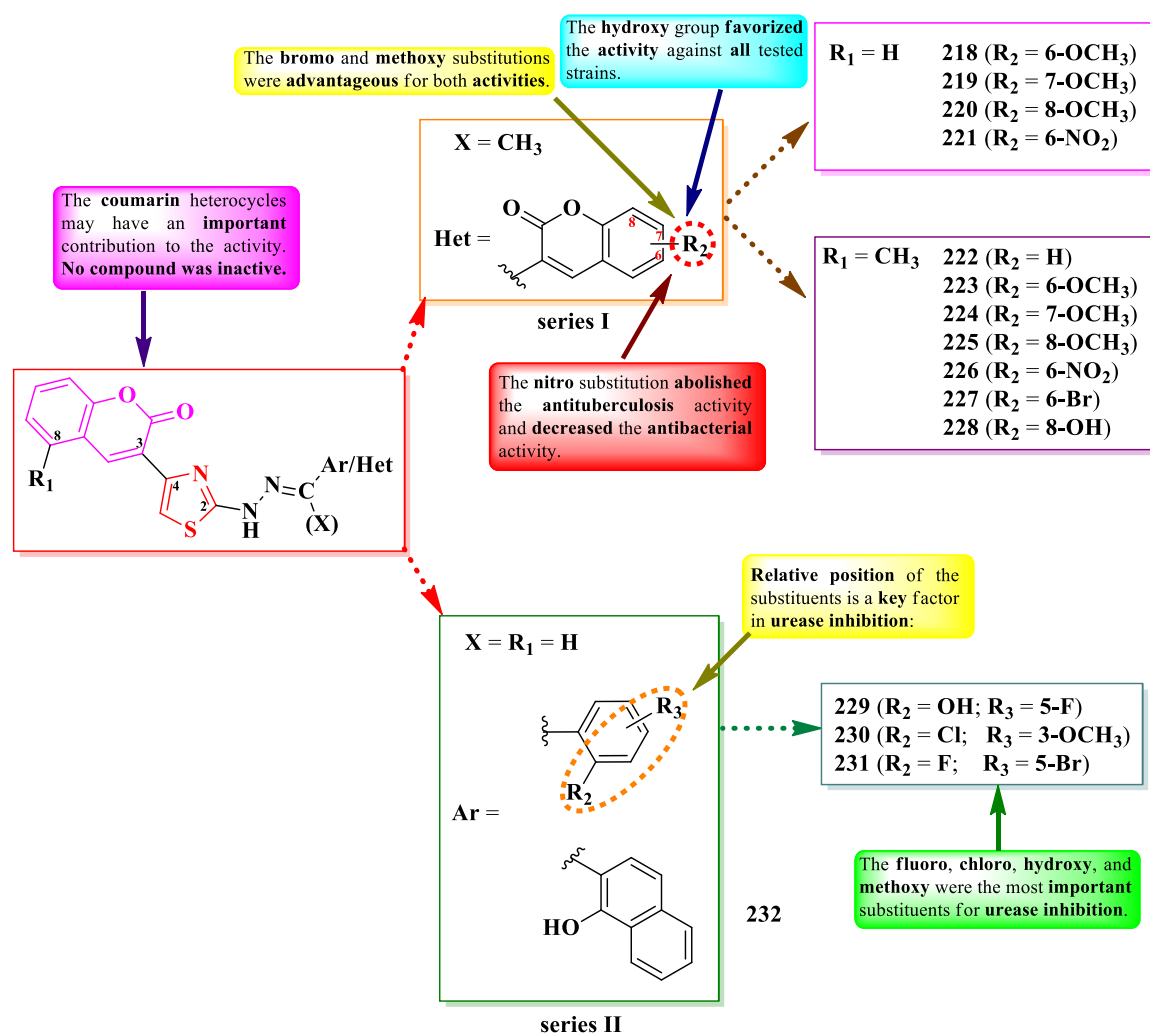
**Figure 39.** SAR studies in antimicrobial 4-(3-coumaryl)-2-hydrazinylthiazoles, reported by Yusufzai et al. [70] and Salar et al. [71].

Hu et al. designed two series of antibacterial 2-(8-(1-oxoprop-2-en-2-yl)-oxycoumarinyl)-thiazoles, substituted on the $\alpha,\beta$-unsaturated carbonyl linker with aryl or hetaryl substituents (Figure 40) [72].

The compounds were tested for the antibacterial activity against Gram-positive and Gram-negative strains. Compounds **237-242** showed superior activity (MICs = 0.004-0.0016 mM) against MRSA (*S. aureus* N315), *E. coli* ATCC 25922, and *E. faecalis*, compared to norfloxacin (MICs = 0.025-0.050 mM) [72].

SAR studies in these series of compounds underline the selectivity confined by the two major substituents, phenyl and indole, towards MRSA, *E. coli*, and *E. faecalis* (Figure 40) [72]. The substituents on these rings influence the antibacterial activity. In the phenyl series, 4-nitro (**234**) and 2,4-dichloro (**233**) groups influenced the activity towards MRSA, while 4-methyl (**236**) against *E. coli*. The 4-methoxy (**235**) substitution was the most advantageous against both strains [72].

In the indole series, small alkyl chains (**241** and **242**) selectively influenced the activity against *E. faecalis*. As reported by the authors, the bis-*N*-(2-hydroxyethyl) groups are important for the development of some antiparasitic and antifungal drugs (Figure 40) [72].

These compounds can express the antibacterial activity by targeting DNA gyrase, based on the molecular docking studies [72].
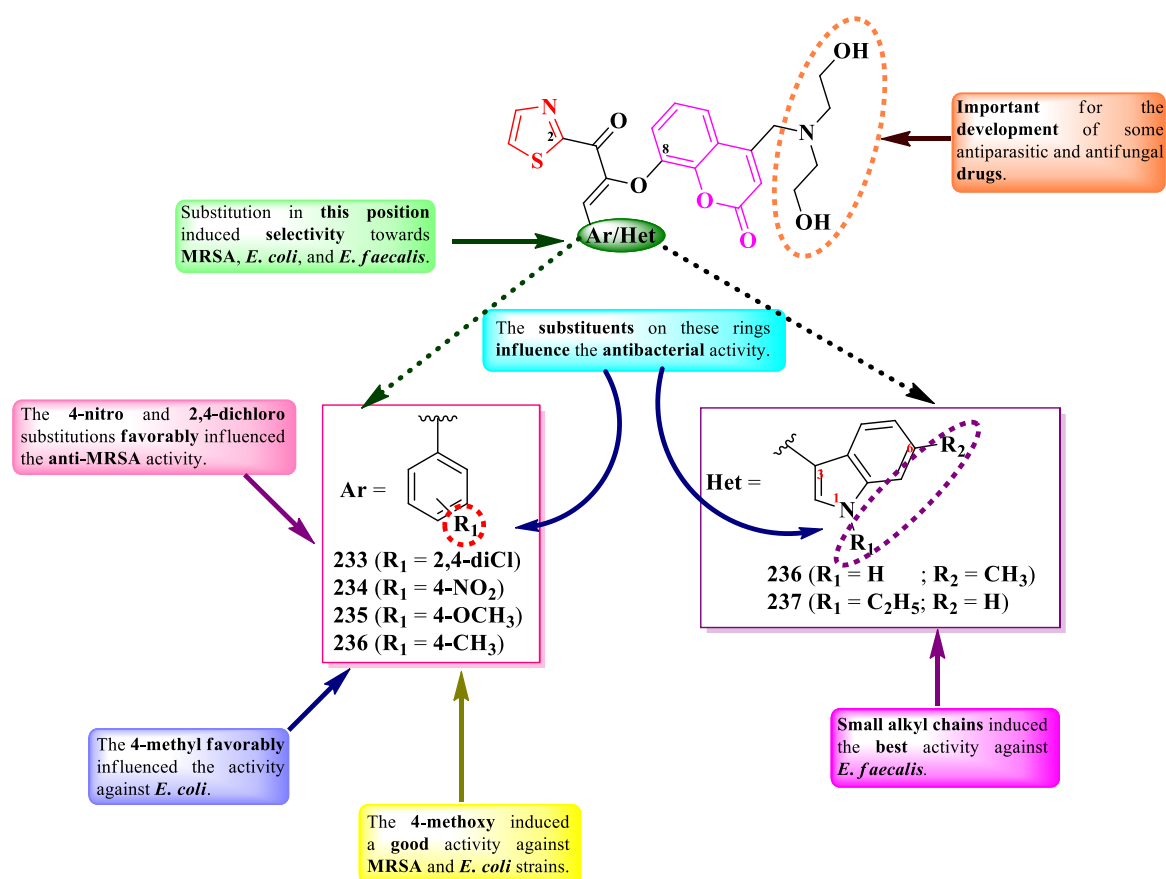
**Figure 40.** SAR studies in antibacterial 2-(8-(1-oxoprop-2-en-2-yl)-oxycoumarinyl)-thiazoles, reported by Hu et al. [72].

In conclusion, the clubbing of thiazole with coumarin resulted in very potent antibacterial and antifungal agents against a broad spectrum of pathogen strains, including even MRSA and mycobacteria.

The broad spectrum was also demonstrated in other hybrid compounds bearing a coumarin heterocycle, previously mentioned in this paper [21,23–25,45].

The coumarin heterocycle should be taken into consideration when designing novel antibacterials against problematic strains, like MRSA.

### 2.5.2. Thiazolyl-Flavone Hybrid Compounds

Flavones are part of the large family of flavonoids, a widely distributed class of natural polyphenolic compounds. These impressive compounds exhibit a large variety of biological activities, including antimicrobial, antioxidant, and anticancer activities, thus constituting an attractive scaffold for drug design [73].

Zhao et al. reported the design and synthesis of a series of antistaphylococcal 2-(7-aminoethoxyflavonyl)-thiazoles, substituted on the fifth position of the thiazole ring with various aryl substituents (Figure 41) [74].

The compounds were tested for the antistaphylococcal activity against 40 clinical isolates (DPHS001 to DPHS040) of *S. aureus*, one MRSA strain (ATCC 43300), and one MSSA strain (ATCC 29213). Out of the 40 clinical isolates, 35 were mecA-positive (DPHS001 to DPSH035), (mecA = the gene complex responsible for altered penicillin-binding protein (PBP2a) synthesis and methicillin resistance), and 5 were mecA-negative (DPHS036 to DPHS040) [74].

Only three compounds (**238**-**240**) were active against the tested clinical isolates. The antibacterial activity was higher against MSSA and mecA-negative strains (MICs = 31.2-125 µg/mL) than against

MRSA and mecA-positive strains (MICs = 31.2-500 µg/mL. The most active was compound **238**, with good activity against all tested strains (MICs = 31.2-125 µg/mL) [74].

SAR studies in these compounds showed that for the nitro derivatives, 4-nitro substitution (**240**) increased the antistaphyloccocal activity, while 2- and 3-nitro substitutions inactivated the compounds (Figure 41) [74]. For the chloro derivatives, 2-chloro substitution (**238**) induced activity against all tested strains, while 3-chloro (**239**) only against MSSA and mecA-negative strains. 4-Chloro and other substituents, such as fluoro, hydroxy, and methyl inactivated the compounds [74].

These compounds express their antistaphylococcal activity by targeting DNA gyrase. Their inhibitory capacity was evaluated in comparison to novobiocin (IC$_{50}$ = 0.8-3.23 µg/mL) [74]. Six compounds presented promising inhibitory capacity: IC$_{50}$ = 23.45-38 µg/mL against DPHS001 DNA gyrase and IC$_{50}$ = 12.21-31.34 µg/mL against DPHS0036 DNA gyrase. Molecular docking studies showed that 4-nitro derivative **240** was able to block the ATP binding site of DNA gyrase [74].
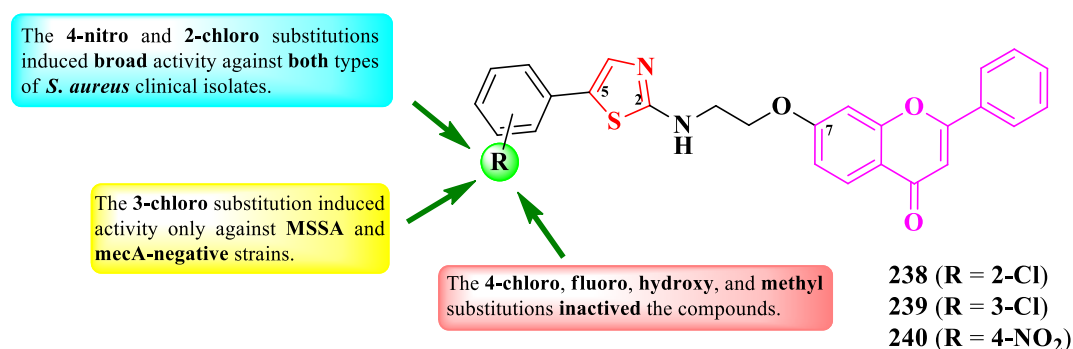


**Figure 41.** SAR studies in antistaphylococcal 2-(7-aminoethoxyflavonyl)-thiazoles, reported by Zhao et al. [74].

### 2.5.3. Thiazolyl-Quinoline and Thiazolyl-Quinolone Hybrid Compounds

Quinoline and quinolinone are heterocycles found in some antimalarial drugs, such as quinine, and antibacterial compounds, as part of the fluoroquinolones class. Thus, they should be taken into consideration when designing novel antimicrobial compounds [75]. Herein, we report the structure-activity relationship of antimicrobial thiazoles clubbed with quinolines and quinoline-2(1*H*)-ones.

Ammar et al. reported the synthesis of some 2-(quinolin-3-yl-methylenehydrazinyl)-thiazoles, substituted in the fourth and fifth positions of the thiazole ring (Figure 42) [76].

The compounds were tested for their antibacterial activity against sensitive and multidrug resistant bacterial strains and against some fungal strains [76]. Compounds **241**-**243** showed superior activity (MICs = 0.97-27.77 µg/mL) against *S. aureus*, *E. faecalis*, *E. coli*, *P. aeruginosa*, and *S. typhi* sensitive strains, compared to tetracycline (MICs = 15.62-62.5 µg/mL) [76]. Regarding the multidrug resistant strains, these compounds showed similar activity against *S. aureus* (ATCC 33591), *E. coli* (BAA-196), and *P. aeruginosa* (BAA-2111), compared to vancomycin (MICs = 0.78-1.95 µg/mL) and ciprofloxacin (MICs = 1.38-3.9 µg/mL) [76].

Concerning the antifungal activity, compounds **241**-**243** showed similar activity (MICs = 7.81-62.5 µg/mL) against *C. albicans* and *F. oxysporum*, compared to amphotericin B (MICs = 15.62-31.25 µg/mL) [76].

SAR studies in these compounds underline the importance of a substituent in para position of the phenyl ring from the fourth position of thiazole ring, as the unsubstituted thiazole compound had low antibacterial and antifungal activities (Figure 42) [76]. The nature of the substituent was as important too, since the hydroxy derivative (**242**) had better activity compared to the chloro derivative (**241**). The importance of electron-donating groups can be seen in compound **243**, where the phenyl ring was replaced with methyl [76].

These compounds express their antibacterial activity by targeting DHFR. Compound **242** showed better inhibitory capacity (IC$_{50}$ = 10.02 ± 1.05 µM) than trimethoprim (IC$_{50}$ = 18.25 ± 0.65 µM) [76].

The **para phenyl** substitution was **important** for the **antibacterial** and **antifungal** activities.

**241** ($R_1$ = 4-Cl-$C_6H_4$; $R_2$ = H)
**242** ($R_1$ = 4-OH-$C_6H_4$; $R_2$ = H)
**243** ($R_1$ = $CH_3$; $R_2$ = N=N-$C_6H_3$-*p*-$CH_3$)

The **electron-donating** groups had better activity compared to the **electron-withdrawing** ones.
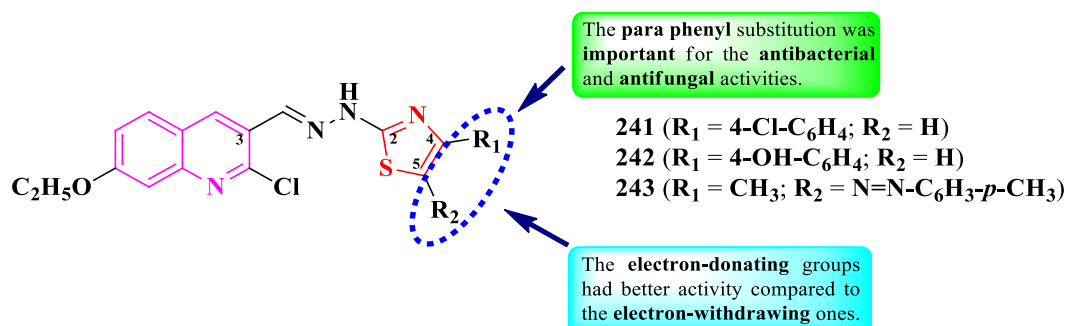
**Figure 42.** SAR studies in antimicrobial 2-(quinolin-3-yl-methylenehydrazinyl)-thiazoles, reported by Ammar et al. [76].

Litim et al. designed some 2-(quinolin-3-yl)- and 2-(quinolinon-3-yl)-thiazoles, in which the heterocycles are linked by an α-aminophosphonate group (Figure 43). The obtained compounds are substituted on the hexatomic heterocycles with methyl or methoxy groups and on the fifth position of the thiazole ring with a phenyl or coumarinyl ring. Additionally, the quinoline derivatives are substituted on the third position with hydroxy or chloro substituents [77].

The compounds were tested for their antibacterial activity against sensitive and drug resistant bacterial strains and for their antifungal activity against *C. albicans* [77]. Compounds **244**-**250** showed similar or lower activity (MICs = 0.25-128 μg/mL) against *S. aureus* ciprofloxacin resistant (cipro R), ATCC 25923, and ATCC 6538, *E. faecalis* vancomycin resistant (vanco R) and ATCC 29212, *E. coli* ATCC 25922, ESBL (extended spectrum beta-lactamase), cipro R, colistin resistant (mcr-1), and ATCC 8739, *P. aeruginosa* VIM-2 and ATCC 9027, *A. baumanii* NDM-1 and OXA-23, *E. cloacae* fosfomycin resistant (fos R), *K. pneumoniae* (carbapenem-resistant and carbapenem-sensitive), *Serratia marcescens*, *S. typhi* 14028, and *Citrobacter sp.*, compared to imipenem, ciprofloxacin, and amikacin (MIC = 2 μg/mL) [77].

Concerning the antifungal activity, compounds **244**-**250** showed similar or lower activity (MICs = 0.25-32 μg/mL) against *C. albicans* compared to fluconazole (MIC = 2 μg/mL) [77].

According to the SAR studies, quinolone compounds showed better activity (MICs = 0.25-256 μg/mL) than quinoline derivatives (MICs = 0.25-512 μg/mL) (Figure 43) [77]. The inhibitory effect was also related to the type of substituent on the α-aminophosphonate moiety, with 5-(3-coumarinyl)-thiazole being more active than 5-phenylthiazole substituent [77].

The presence of both 2-hydroxyquinoline and 5-(coumarin-3-yl)-thiazole moieties in the same molecule (compounds **248**-**249**) favored the antibacterial activity against *E. faecalis* vanco R and *A. baumanni* NDM 1. The combination between quinolone and 5-phenylthiazole moieties (**247**) showed potential activity against *E. faecalis* ATCC 29212, *E. cloacae* fos R, and *K. pneumoniae* carbapenemase-producing bacteria, while the combination between quinolone and 5-(coumarin-3-yl)-thiazole moieties (**244**-**246**) favored the antibacterial activity against *E. faecalis* vanco R and *E. coli* ESBL. No potential target was reported by the authors [77].
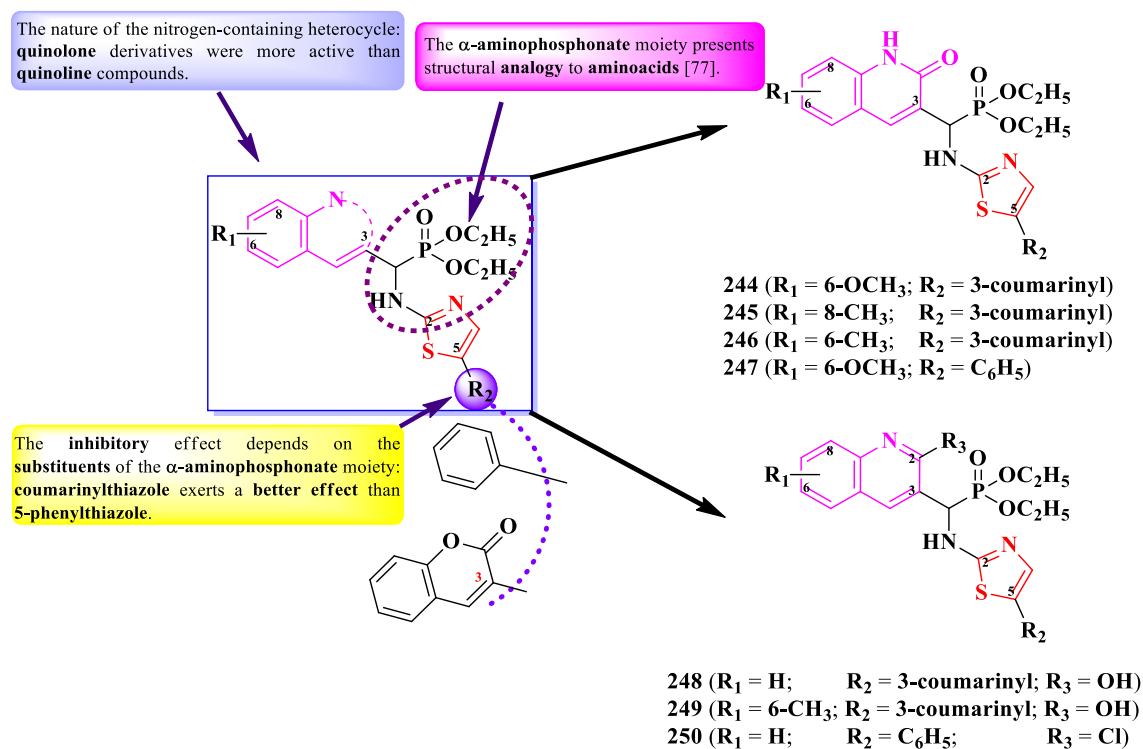
**Figure 43.** SAR studies in antimicrobial 2-(quinolin-3-yl)- and 2-(quinolinon-3-yl)-thiazoles, reported by Litim et al. [77].

### 2.5.4. Thiazolyl-Quinazolones Hybrid Compounds

Quinazolones are found in compounds with a wide range of activities, including antibacterial, antifungal, anti-HIV, antimalarial, and antituberculosis activities [78]. Herein, we report the structure-activity relationship in antimicrobial thiazoles clubbed with quinazolones.

Desai et al. designed and synthesized antibacterial 2-(quinazolon-3-yl)-thiazole Mannich bases, directly linked to a substituted 5-thioxo-1,3,4-oxadiazole heterocycle (series I), as DNA gyrase inhibitors as it was predicted by the molecular docking studies (Figure 44) [79].

In a similar manner, Wang et al. reported the identification of thiazole quinazolones, in which the two heterocycles are linked by an $\alpha,\beta$-unsaturated carbonyl group (series II), as lactate dehydrogenase (LDH) inhibitors (Figure 44) [80].

The inactivation of LDH by compound **254** was supported by molecular docking studies. Important for the interaction with the target were the 7-chloro substituent, which formed hydrophobic bonds with Ile241 residue, the thiazole ring, which formed $\pi$-alkyl bonds with Ile25 and Val30 residues, and the two carbonyl groups and sulfur atom, which interacted through hydrogen bonds with Asn137 residue [80].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative strains. Compounds **251**-**253** showed inferior activity (MICs = 50-150 μg/mL) against *S. aureus* MTCC-96, *E. coli* MTCC-443, and *P. aeruginosa* MTCC-1668, compared to gentamycin (MICs = 0.05-1 μg/mL) [79]. Compound **254** showed superior activity (MIC = 1 μg/mL) against *E. coli* and *P. aeruginosa* compared to norfloxacin (MIC = 4 μg/mL) [80].

Compound **254** produced inappreciable hemolysis, compared to the other tested compounds [80]. It showed synergistic effect in combination with norfloxacin and displayed different mechanisms of action including the blocking of biofilm formation, favoring the ROS generation in the bacterial cell, distortion of the bacterial metabolism by lactate dehydrogenase (LDH) inactivation, and intercalating into the bacterial DNA, which all could be responsible for a low bacterial resistance [80].

SAR studies on the series I compounds showed that the presence of an electron-withdrawing group on the anilino moiety linked by a methylene bridge to the 1,3,4-oxadiazole ring favorized the antibacterial activity (Figure 44) [79].

Based on the SAR studies on series II, 7-chloro substitution is important for the antibacterial effect, as well as an large electron-withdrawing group, like trifluoromethyl, linked on the benzylidene moiety (Figure 44) [80].
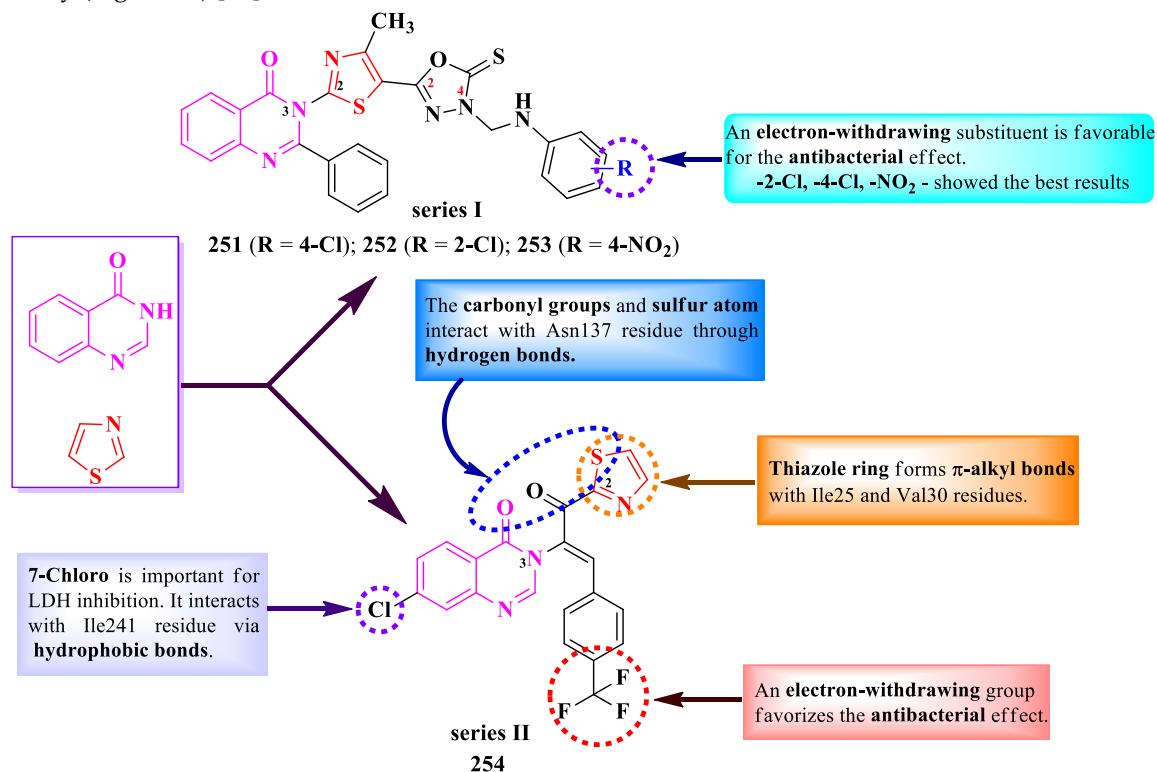


**Figure 44.** SAR studies in antibacterial quinazolonyl-thiazoles, reported by Desai et al. [79] and Wang et al. [80].

## 2.6. Thiazole Clubbed with Condensed Heterocycles

Condensed heterocycles are moieties that result from fusing two or more heterocycles into compact structures with enhanced properties. Based on the literature research, examples of condensed heterocycles clubbed with thiazole are quinuclidine, thiazolopyrimidines, pyrido-thiazolopyrimidines, and pyrazolo-thiazolopyrimidines [81,82]. Herein, we report the SAR studies of antimicrobial thiazole clubbed with condensed heterocycles.

### 2.6.1. Thiazolyl-Quinuclidine Hybrid Compounds

Quinuclidine is found in the structures of natural compounds extracted from *Cinchona* species as alkaloids, as well as in semisynthetic authorized antibacterials, namely quinupristin [83].

Łączkowski et al. designed a series of 2-(quinuclidin-3-ylidene)-hydrazonothiazoles, with a large potential of biological activities, including antibacterial and antifungal ones. These compounds are substituted in the fourth position of the thiazole ring with various aryl substituents (Figure 45) [81].

The compounds were tested for their antibacterial activity against Gram-positive and Gram-negative strains and for their antifungal activity against *Candida sp.* strains [81]. Compounds **255**-**260** showed similar or inferior activity (MICs = 0.48-500 µg/mL) against *S. aureus* ATCC 6538, ATCC 25923, and ATCC 43300, *S. epidermidis* ATCC 12228, *M. luteus* ATCC 10240, *E. coli* ATCC 25922, *P. mirabilis* ATCC 12453, *K. pneumoniae* ATCC 13883, *S. thyphimurium* ATCC 14028, and *B. bronchiseptica* ATCC 4617, compared to ciprofloxacin (MICs = 0.004-0.98 µg/mL) [81].

Regarding the antifungal activity, compounds **255**-**260** showed inferior activity (MICs = 1.95-125 μg/mL) against *C. albicans* ATCC 2091 and ATCC 10231, *C. parapsilosis* ATCC 22019, *C. glabrata* ATCC 90030, and *C. krusei* ATCC 14243, compared to nystatin (MICs = 0.24-0.48 μg/mL) [81].

According to SAR studies, substitutions with halogens (**255**, **256**, **258**, and **259**), large electron-withdrawing groups (**260**), and methyl (**257**) were the most advantageous for the overall antibacterial and antifungal activities (Figure 45) [81]. The bromo (**263**) substitution induced the best antifungal activity, the iodo substitution (**264**) induced the best activity against Gram-positive bacterial strains, and trifluoromethyl group (**265**) favorized the overall antibacterial and antifungal activities. The substitution with larger groups, such as amides, sulfonamides, or large heterocycles like coumarin decreased the activity, while additional substitutions on the thiazole ring cancelled the effect [81].

These compounds express their antibacterial activity by targeting DNA gyrase and the antifungal activity by targeting secretory aspartyl proteinase, important for the fungal pathogenesis, based on the molecular docking studies [81].
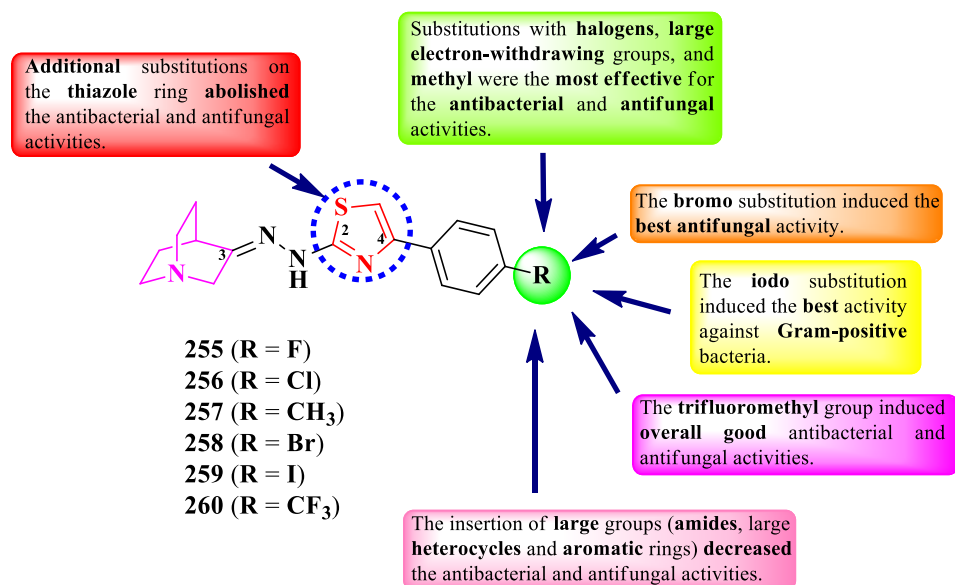


**Figure 45.** SAR studies in antimicrobial 2-(quinuclidin-3-ylidene)-hydrazonothiazoles, reported by Łączkowski et al. [81].

### 2.6.2. Thiazole Clubbed with Polyheterocyclic Systems

An important strategy for the design of bioactive compounds is represented by the obtention of some polyheterocyclic systems, as they combine the biological activities of each of their components into compact structures.

Abdel-Latif et al. designed and synthesized thiazole-based polyheterocyclic systems, containing pyrimidine, pyridine, triazole, benzimidazole, and pyrazole heterocycles, as new antibacterial compounds (Figure 46) [82].

Starting from 3-cyano-thiazolo[3,2-*a*]pyrimidinone (**261**), they obtained some polyheterocyclic systems by annelation with pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidin-4-amine (**a**), benzo[4,5]imidazo[1,2-*a*]pyrimidin-4-amine (**b**), pyrazolo[1,5-*a*]pyrimidin-7-amine (**c**), [1,2,4]triazolo[3,4-*a*]pyrimidin-5-amine (**d**), 4,5-dihydro-1*H*-pyrazol-3-amine (**e**), and pyridines-2,6-diamine substituted in the ninth position (**f**, **262**-**263**). Other series contained isolated heterocycles as thiazol-2-yl-pyridinone derivatives (**g**) (Figure 46) [82].

The activity of the compounds was assayed against *S. aureus* and *E. coli*, using the agar diffusion method and determination of the inhibition zone, compared to ampicillin (IZs = 24-27 mm, 100%) [82]. Compounds 2**61**-2**63** showed similar activity with the reference against *S. aureus* (IZs = 20-22 mm, 83.3-91.7%) and *E. coli* (IZs = 22-23 mm, 81.48-85.18%) [82].

Despite the heterogeneity of the synthesized molecules, some SAR studies can be underlined based on their antibacterial potential (Figure 46) [82]. A first difference can be noticed based on how

the thiazole is linked to the rest of the system. Condensed thiazolo[3,2-*a*]pyrimidinones (**a**-**f**) displayed stronger activity than isolated thiazol-2-yl-pyridinones (**g**) [82].

Concerning the polycondensed heterocyclic systems, differences occur in the number of annulated rings. The activity decreased by supplementary annulation. The best results were obtained for the bicyclic compound **261** (IZ = 22 mm and 91,7% against *S. aureus*, while IZ = 23 mm and 85,18% against *E. coli*), with tetra- (**c**, **d**) and pentacyclic (**a**, **b**) compounds having very low or no activity (Figure 46) [82]. In the tricyclic compounds (**e**, **f**), pyrazolo-thiazolo[3,2-*a*]pyrimidinone (**e**) derivatives, containing azole rings, had lower activity compared to the pyrido-thiazolo[3,2-*a*]pyrimidinone (**f**) derivatives, containing azine rings (Figure 46) [82].

The activity was also influenced by the nature of the substituents present in the pyrido-thiazolo[3,2-*a*]pyrimidinone derivatives. Compound **262**, containing a 9-cyano substituent, displayed better activity (IZ = 21 mm and 87,5% against *S. aureus*, while IZ = 23 mm and 85,18% against *E. coli*) than compound 2**63**, containing a 9-ethoxycarbonyl substituent (IZ = 20 mm and 83,3% against *S. aureus*, while IZ = 22 mm and 81,48% against *E. coli*) (Figure 46). No potential target was reported by the authors [82].
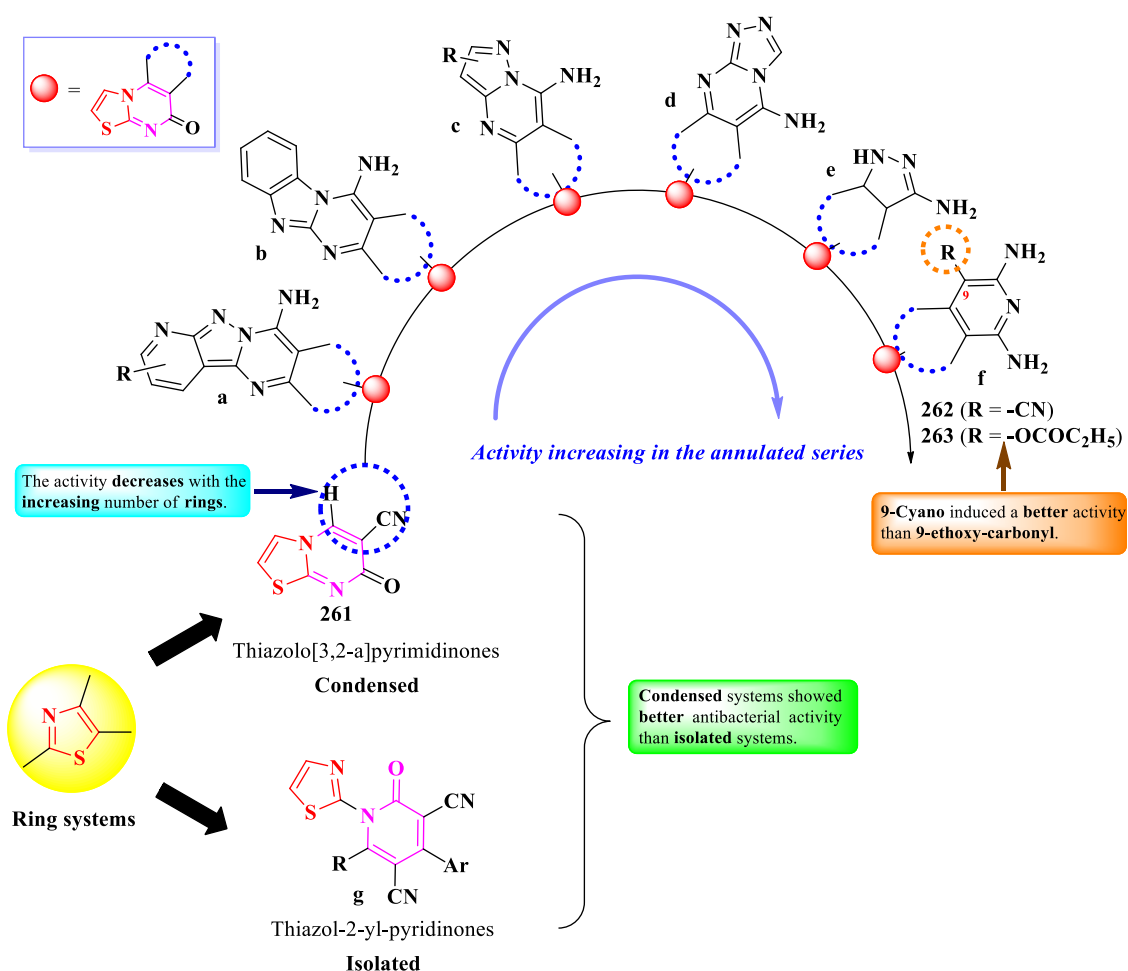


**Figure 46.** SAR studies in antibacterial 1,3-thiazole clubbed with polyheterocyclic systems, reported by Abdel-Latif et al. [82].

## 3. Conclusions

Thiazole is an important heterocycle for drug design, not only for antibacterials and antifungals, but also for many other pharmacological classes. Approaching a rational design in novel drugs development allows for a faster progress and effectiveness. Therefore, a rational approach for drug discovery is the optimization based on structure-activity relationships.

Based on the observations drawn in this review, it is easy to notice that each compound behaves differently based on its structure. However, they can exhibit the same pharmacological effect but with different potency. Thus, this work aimed to collect and visualize the SAR studies in some of the reported antimicrobial scaffolds of hybrid thiazolic compounds, as a mean to observe the structural heterogeneity that can induce the antimicrobial activity.

Thiazole clubbing with various heterocycles had different results depending on the other heterocycle(s). Pyrazoline-clubbed antimicrobials expressed activity against Gram-positive bacteria and *K. pneumoniae*, while using pyrazole the activity was extended against fungal strains, similar with imidazole. Hybrid thiazoles clubbed with thiazolidinone were promising antituberculosis compounds, while clubbing with triazole covered all three types of activity, antibacterial, antifungal, and antituberculosis. A lower potency was observed in hybrid compounds with pyridine, but this was not transposable to the benzofused heterocycles quinoline and quinolone. Similarly to triazole, coumarin is another veritable scaffold for designing novel antimicrobials. Also, high importance should be allocated to the substituents used in each scaffold.

The observations made in this work could provide a valuable scientific material in the design of novel antimicrobials in future research.

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