HETEROCYCLES, Vol. 102, No. 9, 2021, pp. 1675 - 1728. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 3rd February, 2021, Accepted, 5th March, 2021, Published online, 10th May, 2021
DOI: 10.3987/REV-21-956

SYNTHETIC APPROACHES TOWARD CERTAIN STRUCTURALLY RELATED ANTIMICROBIAL THIAZOLE DERIVATIVES (2010-2020)

Abdelfattah Hassan,[1] Heba A. Hassan,[2] Dalia Abdelhamid,[3] Gamal El-Din A. Abuo-Rahma*

[1]Medicinal Chemistry Department, Faculty of Pharmacy, South Valley University, Qena, Egypt, abdelfattah_hassan@svu.edu.eg
[2]Medicinal Chemistry Department, Faculty of Pharmacy, Minia University, Minia, Egypt, heba.hasan@mu.edu.eg
[3]Medicinal Chemistry Department, Faculty of Pharmacy, Minia University, Minia, Egypt, das184@yahoo.com
[*]Medicinal Chemistry Department, Faculty of Pharmacy, Minia University, Minia, Egypt & Pharmaceutical Chemistry Department, Faculty of Pharmacy, Deraya University, New Minia, Minia, Egypt, gamal.aborahama@mu.edu.eg, +201003069431

Abstract – In the present literature review, we comprehensively discuss different methods of synthesis of published antimicrobial thiazole derivatives in the last decade mainly those which showed antibacterial, antimycobacterial and/or antifungal activity. Owing to the great diversity of thiazole-derived antimicrobial agents, we organized most of them chemically in stipulated classes. In each class, we mentioned common methods of thiazole ring closure and indicated antimicrobial activity of the most active derivatives in clear and simple way.

CONTENTS

1. INTRODUCTION

Thiazole ring is one of the most common heterocycles in biologically active molecules. Thiazole derivatives showed a various biological activities including anticancer,[1] anti-influenza,[2] antiviral,[3] anti-HIV,[4] anti-inflammatory,[5] antidiabetic,[6] antiplatelet,[7] antihypertensive,[8] anti-hyperlipidemic,[9] antileishmanial,[10] and antioxidant.[11]

Nowadays the pharmacy is full of thiazole-derived antibiotics. β-Lactams are widely applied thiazole-containing antibiotics. Thiazolidine is incorporated with β-lactam ring in highly strained bicyclic penam ring in penicillins, which is fundamental for its antibacterial activity (Figure 1). 2-Aminothiazole ring is involved in third and fourth generation cephalosporins to enhance its antibacterial activity against Gram-negative bacteria (Figure 2).[12]

Addition of thiazole moiety on C3 of cephem ring provided a fifth-generation cephalosporin, Ceftaroline which is active against *MRSA*.[13] In November 2019, FDA approved Cefiderocol (Fetroja®) for treatment of severe urinary tract infections in adult patients. One of Cefiderocol characters is 2-aminothiazole ring connected to C3 of cephem ring (Figure 3).[14]

A monobactam antibiotic, Aztreonam contains aminothiazole ring in its side chain, like cephalosporins, so it is active against Gram-negative bacteria.[15] β-Lactamase inhibitors include thiazolidine ring fused with β-lactam ring like Sulbactam and Tazobactam which is used in combination with Ceftolozane (Zerbaxa®) to treat severe abdominal and urinary tract infections (Figure 4).[16]

Other thiazole-containing antimicrobial agents are presented in Figure 5. A classical sulfa drug, Sulfathiazole had been used in its *N*-succinyl form in treatment of GIT infections. Nitazoxanide is a widely used antiprotozoal medication in tropical and warm countries for treatment of protozoa-caused diarrhea in both children and adults. Also, thiazole ring is incorporated in antibacterial agent Cystothiazole A and antifungal agents Abafungin and Ravuconazole.

In the current review, chemically similar compounds were gathered in distinct groups with discussion of

several approaches for thiazole ring closure illustrating different reaction conditions. The antimicrobial activity of the most active derivatives was mentioned based on MIC values against different bacterial, mycobacterial, and fungal strains and comparing the antimicrobial activity of these thiazole compounds with reference drugs. It is worth to mention that the fluctuation in MIC values from one article to other is due to different experimental conditions and using different standard and non-standard stains. Hence, the reported antimicrobial activity of thiazole derivatives expressed in MIC we incorporated as it was mentioned in original article.

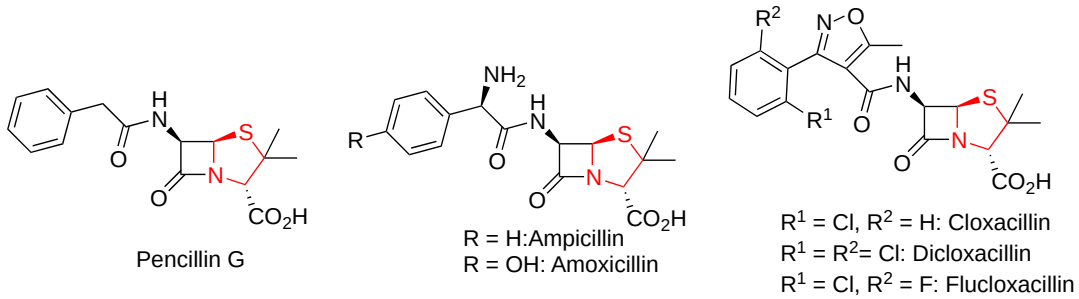


Figure 1. Clinically used penicillin antibiotics

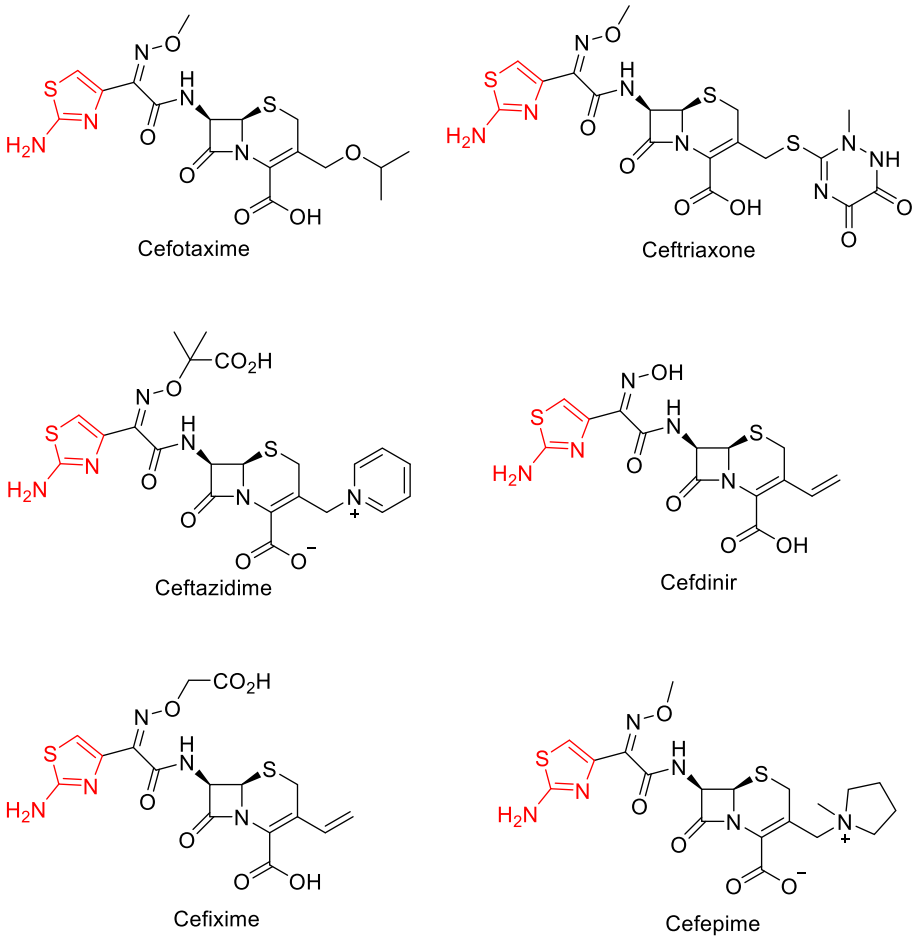


Figure 2. Clinically used third and fourth generation cephalosporin antibiotics

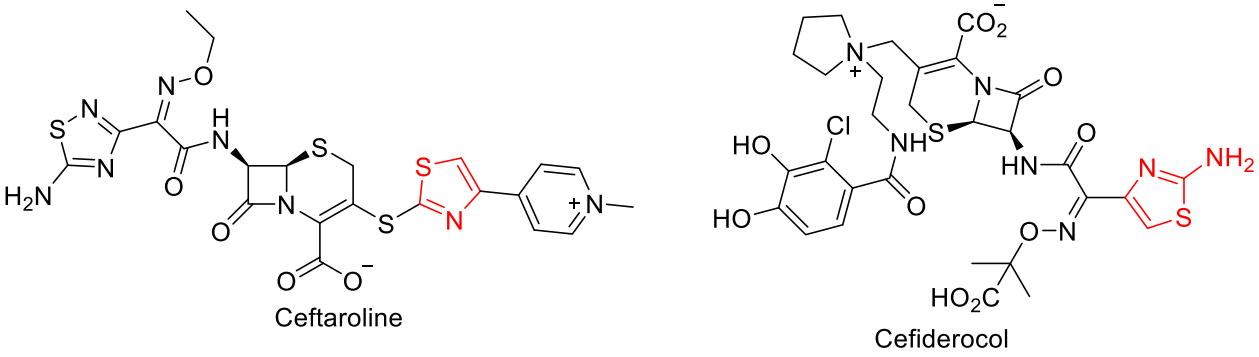


Figure 3. Ceftaroline and Cefiderocol antibiotics

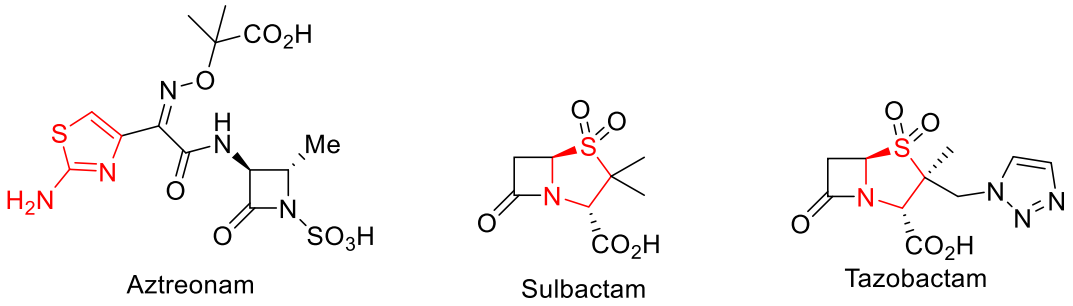


Figure 4. Monobactams and β-lactamase inhibitors

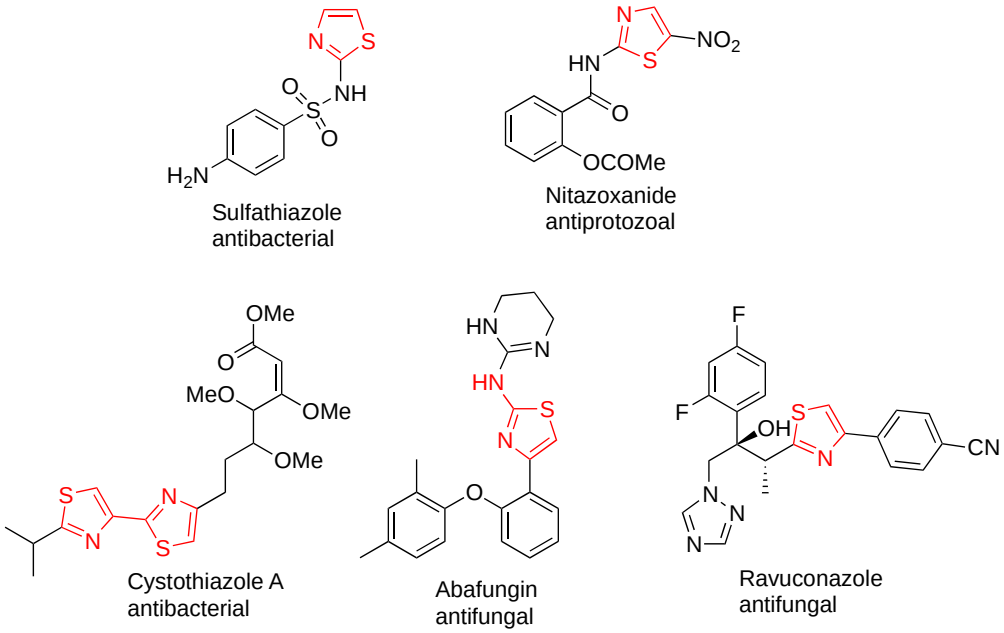
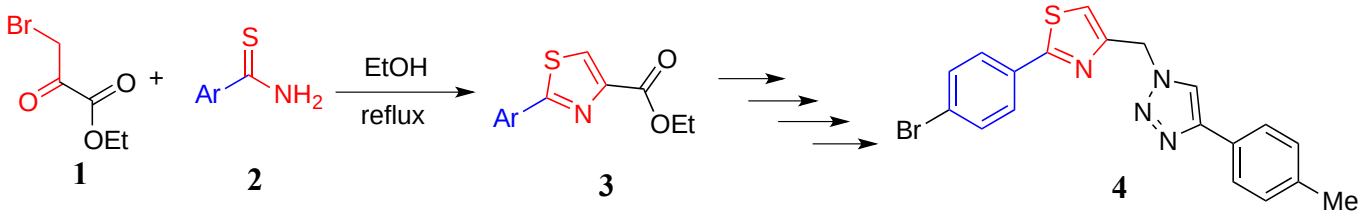


Figure 5. Other thiazole-derived antimicrobial agents

2. SYNTHESIS OF 2-ARYLTHIAZOLES

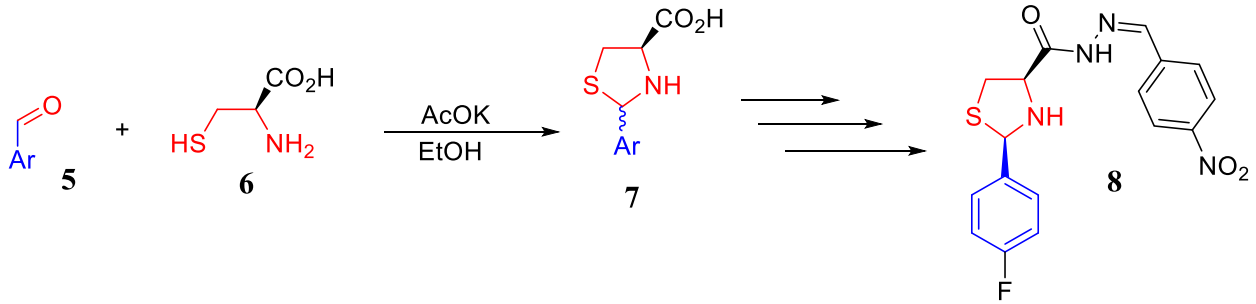
Ethyl 3-bromo-2-oxopropanoate **1** was refluxed with arylthioamide **2** to afford ethyl 2-arylthiazole-4-carboxylate **3** which in turn was utilized by Shinde team[17] to synthesize a group of 2-aryl-4-((4-aryl-1*H*-1,2,3-triazol-1-yl)methyl)thiazoles (Scheme 1). **4** had showed antitubercular activity

against *Mycobacterium tuberculosis* (IC_{50} 4.85 μg/mL) and it was more potent than Rifampicin against *Mycobacterium bovis* as presented by (IC_{50} 0.03 μg/mL). Furthermore, it displayed antibacterial activity against *Escherichia coli*, *Pseudomonas flurescence*, *Staphylococcus aureus* and *Bacillus subtilis*.[17]



Scheme 1. Synthesis of 2-(4-bromophenyl)-4-((4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)methyl)thiazole **4**

2-Phenylthiazolidine-4-carboxylic acid derivatives **7** were obtained by the reaction of different benzaldehyde derivatives **5** with L-cysteine **6** (Scheme 2). After several steps, Nagasree *et al.*[18] succeeded to synthesize and separate a series of two diastereomers (2*R*,4*R*) and (2*S*,4*R*) of each 2-phenyl-*N*′-benzylidenethiazolidine-4-carbohydrazide derivatives and evaluated its antitubercular activity. Generally, (2*R*,4*R*) isomers were found to be more potent than (2*S*,4*R*) isomers. The most active compound was a (2*R*,4*R*) isomer **8** (MIC 1.33 μg/mL) which was more potent than Ethambutol.[18]



Scheme 2. Synthesis of (*2R*,*4R*)-2-(4-fluorophenyl)-*N*′-((*Z*)-4-nitrobenzylidene)thiazolidine-4-carbohydrazide **8**

2-Arylthiazole **9** (Figure 6) showed a comparable antifungal activity to Thifluzamide activity against *Gibberella zeae*, *Phytophythora capsici*, *Sclerotonia sclerotiorum*, *Puccinia sorghi*, and *Erysiphe graminis* (EC_{50} 9.3 μM).[19]

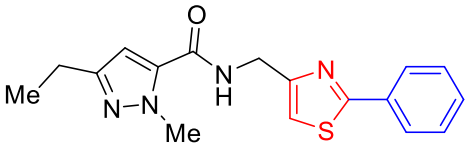
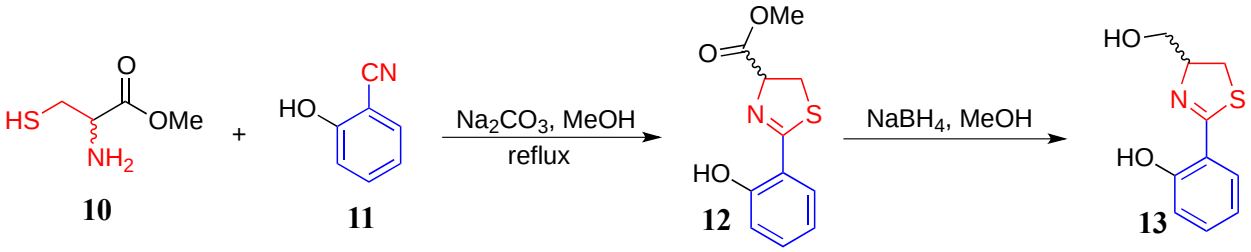


Figure 6. 2-Arylthiazole **9**

Methyl 2-(2-hydroxyphenyl)-4,5-dihydrothiazole-4-carboxylate **12** was synthesized by refluxing methyl cysteinate **10** with 2-hydroxybenzonitrile **11** in methanol in presence of sodium carbonate (Scheme 3). After reduction with sodium borohydride, Two enantiomers of **13** were separated and both enantiomers showed the same activity and were more potent than Ampicillin against all tested strains; *R. solanacearum* (MIC 31.24 µg/mL), *P. syringae* (MIC 7.81 µg/mL), *B. cereus* (MIC 31.24 µg/mL), and *B. subtilis* (MIC 3.91 µg/mL).[20]



Scheme 3. Synthesis of 2-(4-(hydroxymethyl)-4,5-dihydrothiazol-2-yl)phenol **13**

A 2-phenylthiazole hydrazinecarboximidamide derivative **14** (Figure 7) showed antibacterial activity against *MRSA* (MIC 1.3 µg/mL). In addition, it gave synergistic effect with Mupirocin against *MRSA* in skin wounds.[21]

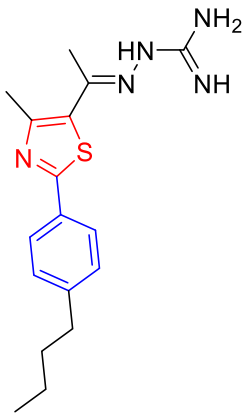
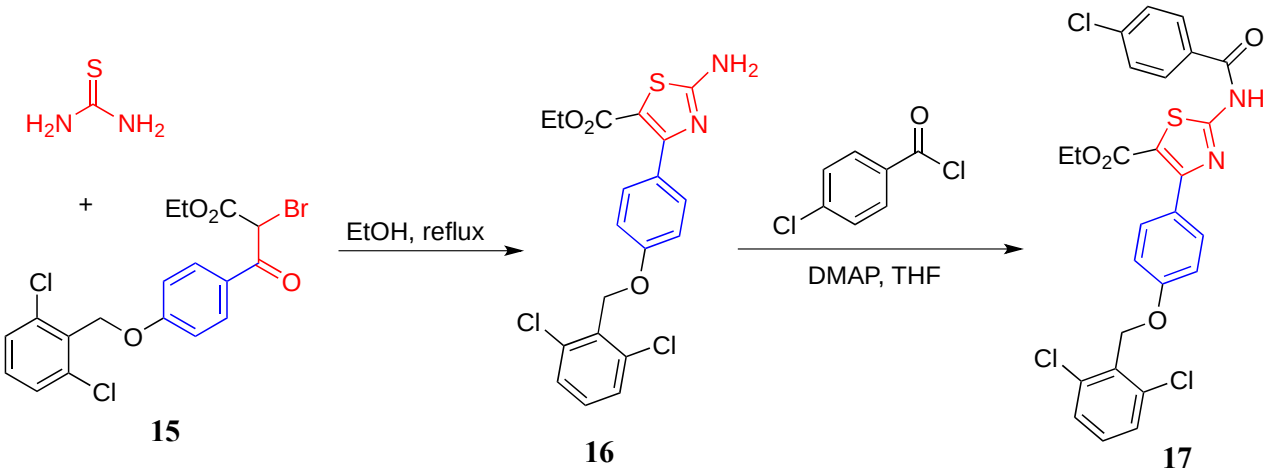


Figure 7. 2-Phenylthiazole hydrazinecarboximidamide **14**

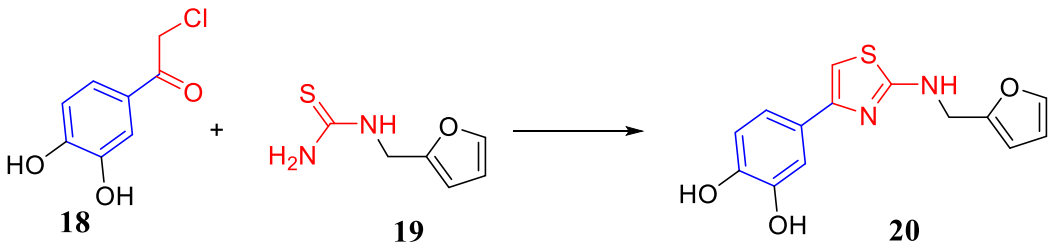
3. SYNTHESIS OF 4-ARYLTHIAZOL-2-AMINES

Although Hantzsch condensation is a classical method for synthesis of 4-arylthiazole-2-amine compounds, it is still broadly used by chemists around the world owing to its simplicity, cheapness, high yield, and widely diversified products. In this method, phenacyl bromides **15** are refluxed with thiourea in ethanol to afford thiazol-2-amine derivatives **16** (Scheme 4). These derivatives were then *N*-acylated to give antitubercular and antibacterial compounds. **17** (MIC 1 µg/mL) showed a comparable antitubercular activity to Isoniazid and a comparable antibacterial activity to Gentamycin against *S. pneumoniae* (MIC 7.12 µg/mL).[22]



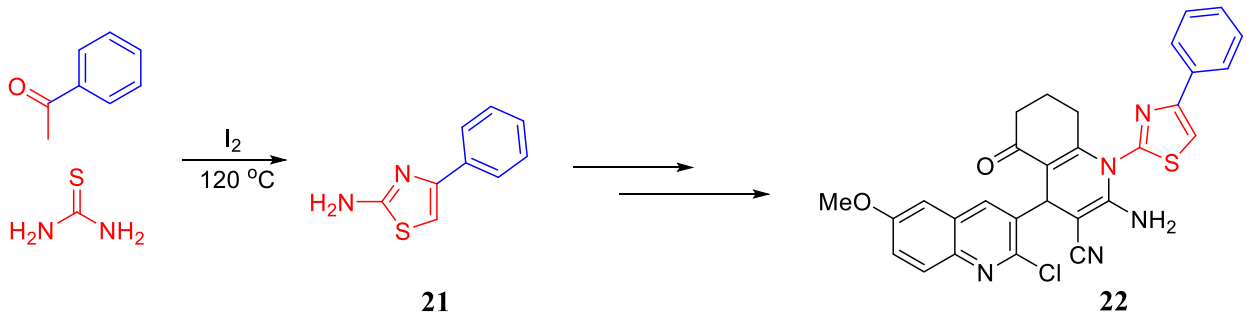
Scheme 4. Synthesis of 4-arylthiazol-2-amine **17**

Similarly, monosubstituted thiourea **19** reacted with phenacyl chloride **18** to afford substituted 2-aminothiazole derivatives (Scheme 5). **20** showed antimicrobial activity against *P. aeruginosa*, *S. aureus*, *S. epidermidis* and *C. albicans* but it was found inactive against *E. coli*, *E. cloacae* and *K. pneumoniae*.[23]



Scheme 5. Synthesis of *N*-substituted 4-arylthiazol-2-amine **20**

Furthermore, A solid phase reaction involving heating acetophenone with thiourea and iodine yielded the well-known 2-amino-4-phenylthiazole intermediate **21** (Scheme 6). After further steps, **22** was synthesized and showed similar antibacterial activity to Ampicillin and Ciprofloxacin against *E. coli*, *B. substilis*, and *S. aureus* and similar antifungal activity to Griseofulvin against *F. oxysporum*, *A. niger*, and *R. oryzae*.[24]



Scheme 6. Synthesis of 2-arylthiazole **22**

A *bis*-thiazole derivative **23** (Figure 8) was more potent than Tetracycline against *E. coli* (MIC 15 μg/mL), *Micrococcus luteus* (MIC 0.93 μg/mL), and *B. subtilis* (MIC 7.5 μg/mL).[25]

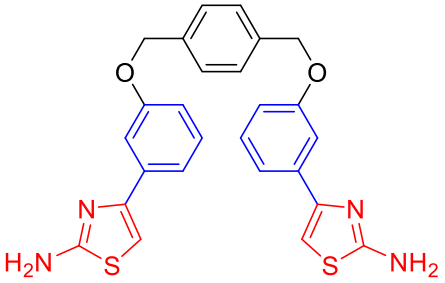


Figure 8. *Bis*-thiazole **23**

24 (Figure 9) showed comparable antibacterial activity to Ciprofloxacin against all tested strains including *E. coli*, *B. subtilis*, *P. aeruginosa*, and *S. aureus*.[26]

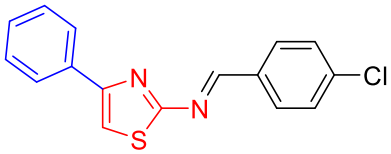
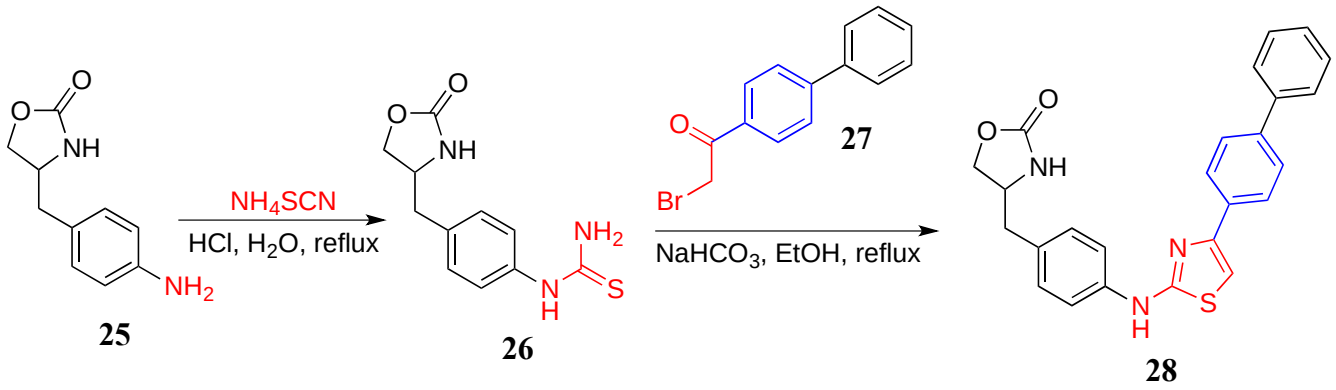


Figure 9. 2-arylthiazol-2-amine **24**

N-Monosubstituted thiourea **26** can be synthesized by refluxing aryl amine **25** with ammonium thiocyanate in aqueous acidic medium that was reacted with phenacyl bromides **27** to afford *N*,4-diarylthiazol-2-amines (Scheme 7). **28** was equipotent to Ciprofloxacin against *B. subtilis* (MIC 6.25 μg/mL) and equipotent to Amphotericin-B against *C. albicans* (MIC 12.5 μg/mL) and *Saccharomyces cerevisiae* (MIC 12.5 μg/mL).[27]



Scheme 7. Synthesis of 2-arylthiazol-2-amine **28**

29 (Figure 9) was more potent than Chloramphenicol against both *Listeria monocytogenes* (MIC 6.25 μg/mL), and *Klebsiella pneumoniae* (MIC 6.25 μg/mL) and it was equipotent to Chloramphenicol against *S. aureus* (MIC 6.25 μg/mL), *Enterococcus faecalis* (MIC 6.25 μg/mL) and *E. coli* (MIC 6.25 μg/mL).[28]

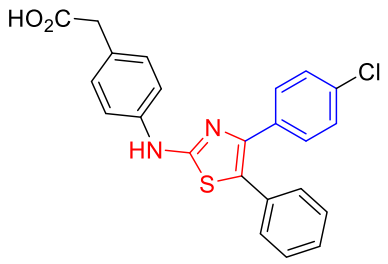
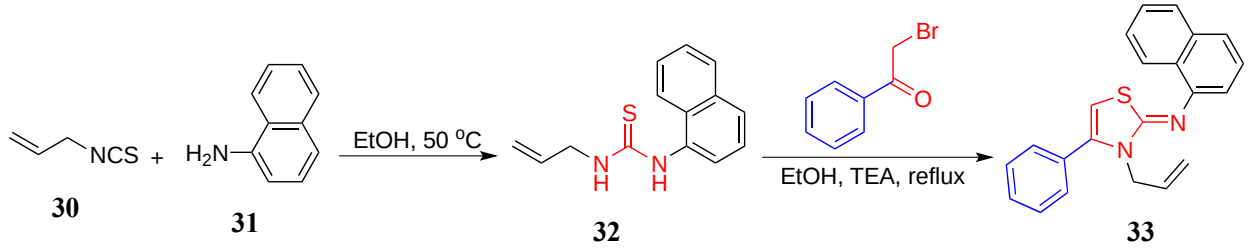


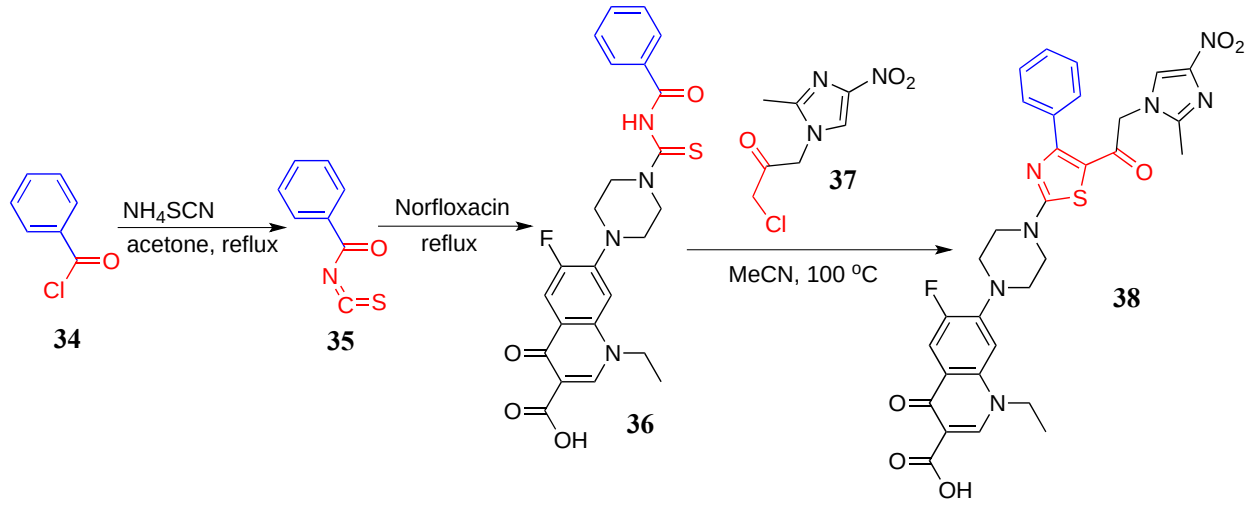
Figure 10. 2-Arylthiazol-2-amine **29**

N,*N*′-Disubstituted thiourea **32** can be synthesized by heating alkyl or allyl isothiocyanate **30** with different aromatic amines **31** in ethanol. Reflux of these disubstituted thioureas with phenacyl bromide afforded thiazol-2(3*H*)-imine derivatives (Scheme 8). **33**exhibited antibacterial activity against *S. enteric*, *M. luteus*, and *B. subtilis*.[29]



Scheme 8. Synthesis of thiazol-2(3*H*)-imine **33**

Recently, another strategy to synthesize substituted thiourea was performed by Ahmed *et al.*[30] (Scheme 9). Reaction of benzoyl chloride **34** with ammonium thiocyanate had afforded benzoyl isothiocyanate **35** which reacted with piperazinyl nitrogen of Norfloxacin to yield *N*,*N*,*N*′-trisubstituted thiourea **36** then was reacted with α-chloroketone **37** to give a trisubstituted thiazole **38**. **38** was more potent than Ciprofloxacin against *P. aeruginosa* (MIC 1.56 µg/mL), *E. faecalis* (MIC 6.25 µg/mL), *S. aureus* (MIC 3.12 µg/mL), and *E. coli* (MIC 3.12 µg/mL).[30]



Scheme 9. Synthesis of 2,4,5- trisubstituted thiazole **38**

An antitubercular 4-arylthiazol-2-amine derivative **39** (MIC = 62.5 μg/mL) (Figure 11) with amino group involved in pyrrolidine ring was synthesized by Belveren *et al.*[31] Reaction of pyrrolidine derivative with benzoyl isothiocyanate gave aminocarbothiolpyrrolidine which reacted with *p*-methoxyphenacyl bromide to give **39**.[31]

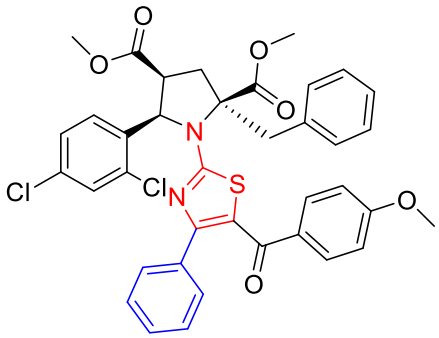


Figure 11. 4-Arylthiazol-2-one **39**

A 4-phenyl-2-(pyrrolidin-1-yl)thiazole derivative **40** (Figure 12) was synthesized recently by Nural *et al.* and it showed antimycobacterial activity (MIC 31.25 μg/mL).[32]

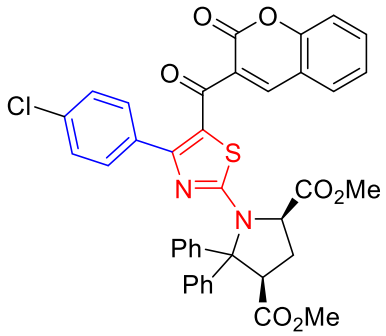
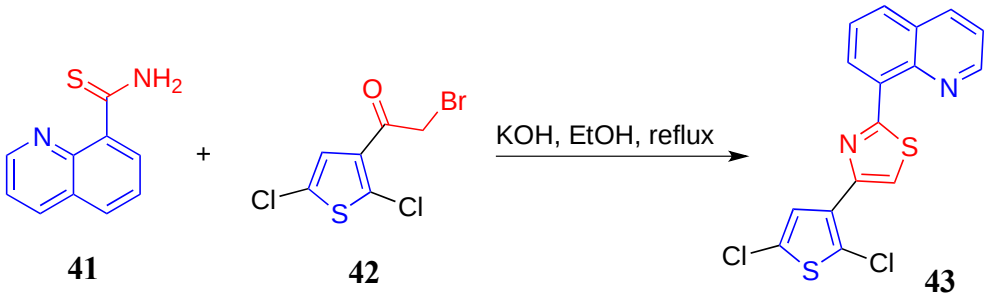


Figure 12. 4-Phenyl-2-(pyrrolidin-1-yl)thiazole **40**

4. SYNTHESIS OF 2,4-DIARYLTHIAZOLES

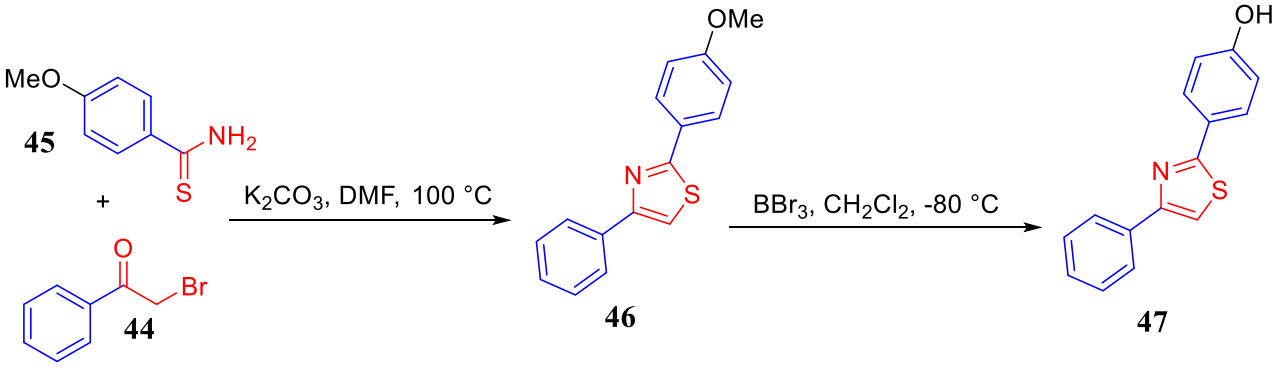
2,4-Diarylthiazoles were synthesized mainly by reaction of phenacyl bromides **41** with thioamides **42**. Sarojini *et al.*[33] synthesized thioamides by heating different aromatic nitriles or carboxamides with phosphorus pentasulfide which are then used as substrates for Hantzsch thiazole synthesis (Scheme 10). Among 5 synthesized compounds, **43** showed the most potent antifungal activity (MIC 6.25-12.5 μg/mL) against *Penicillium marneffei*, *Trichophyton mentagrophytes*, *Aspergillus flovus* and the highest antibacterial activity (MIC 6.25-12.5 μg/mL) against both *S. aureus*, and *K. pneumoniae*.[33]



41 42 43

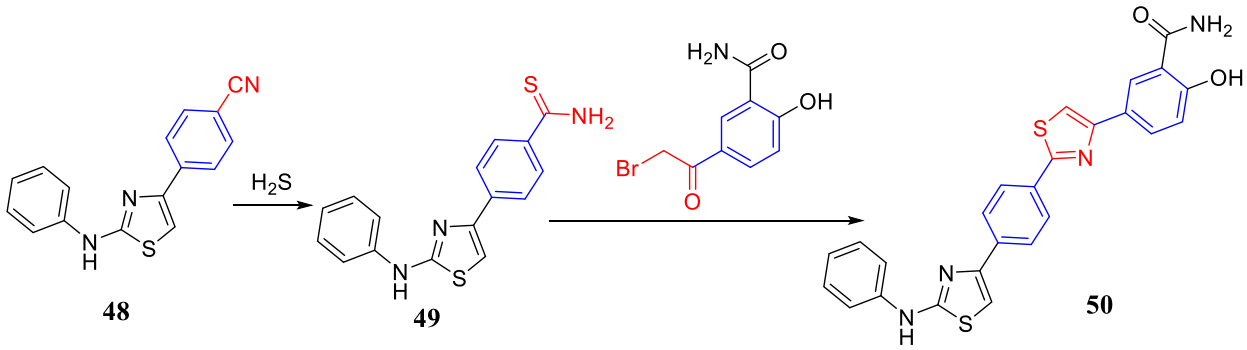
Scheme 10. Synthesis of 2,4-diarylthiazole **43**

In addition, 2,4-diphenylthiazole derivative **46** was formed by heating phenacyl bromide **44** with different benzothioamide derivatives **45** in DMF using potassium carbonate as a base (Scheme 11). **47** exhibited antimicrobial activity (MIC 125-150 µg/mL) against *S. aureus*, *E. coli* and *A. niger*.[34]



Scheme 11. Synthesis of Compound **1**

Thioamides **49** can be obtained from nitrile derivatives **48** via Willgerodt-Kindler reaction, in which iron(II) sulfide, triethylamine and hydrochloric acid were used to liberate hydrogen sulfide. Among 14 compounds synthesized and tested by Bikobo team,[35] **50** displayed the best inhibition values against all Gram-positive and Gram-negative strains and fungi on basis of MIC, MBC and MFC. It was more potent than Spectinomycin against *S. aureus* (MIC 31.25 µg/mL) and *E. faecalis* (MIC 31.25 µg/mL). Moreover, it showed antibacterial activity against *Salmonella typhimurium* (MIC 62.5 µg/mL) and was more potent (MIC 7.81 µg/mL) than Fluconazole against both *C. albicans* and *C. krusei*. Authors believed that its unique antifungal activity is due to presence of hydroxyl (electron donating) and carbamoyl (withdrawing group) (Scheme 12).[35]



Scheme 12. Synthesis of 2,4-diarylthiazole **50**

In the same manner, (1*H*-pyrazol-4-yl)thiazole derivative **51** (Figure 13) was synthesized from 1*H*-pyrazole-4-thioamide derivative and *p*-chlorophenacyl bromide in ethanol. When compared to Chloramphenicol, **51** showed antibacterial activity against *S. aureus* (MIC 128 μg/mL), *E. coli* (MIC 128 μg/mL), *B. subtilis* (MIC 64 μg/mL) and *P. aeruginosa* (MIC 128 μg/mL). And when compared to Nystatin, it is also showed weaker antifungal activity against *A. niger* (MIC 128 μg/mL) and *C. albicans* (MIC 32 μg/mL).[36]

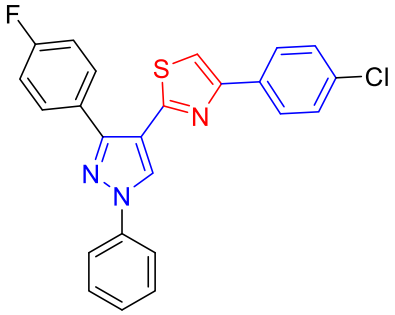


Figure 13. (1*H*-Pyrazol-4-yl)thiazole **51**

52 (Figure 14) is another one 4-(thiazol-2-yl)-1*H*-pyrazol-3-amine derivative, which exerted antibacterial activity against both *S. aureus* and *B. subtilis* and antifungal activity against only *A. niger* with (MIC 128 μg/mL for all strains).[36]

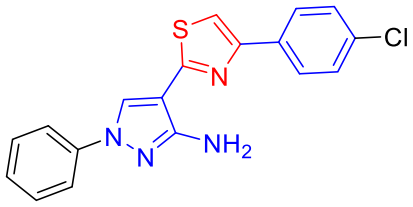


Figure 14. 4-(Thiazol-2-yl)-1*H*-pyrazol-3-amine **52**

Recently, 2-(pyridin-4-yl)thiazole derivative **53** (Figure 15) displayed antibacterial activity, it was more potent than Cefepime against *B. cereus* (MIC 0.01 μg/mL) and equipotent to Amikacin against *S. aureus*

(MIC 0.01 μg/mL). As antifungal, it was more potent than Fluconazole against *C. albicans* (MIC 0.15 μg/mL).[37]

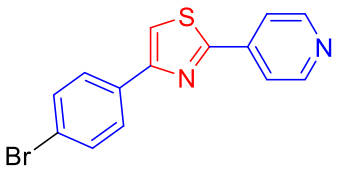
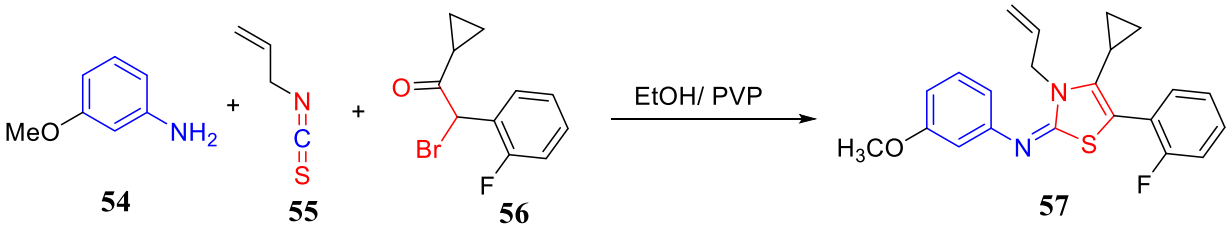


Figure 15. 2-(Pyridin-4-yl)thiazole **53**

5. SYNTHESIS OF 2-(ARYL/ALKYLAMINO)THIAZOLES

Synthesis of *N*-phenylthiazol-2(3*H*)-imines were achieved by one-pot reaction between anilines **54**, isothiocyanates **55** and α-bromoketones **56** (Scheme 13). **57** showed antibacterial activity against *S. enterica*, *M. luteus*, *B. subtilis*, and *P. aeruginosa*.[38]



Scheme 13. Synthesis of *N*-phenylthiazol-2(3*H*)-imine **57**

Additionally, a bis *N*-phenylthiazol-2(3*H*)-imine derivative **58** (Figure 16) exhibited antibacterial activity against *S. enterica*, *M. luteus*, *B. subtilis*, and *P. aeruginosa*.[39]

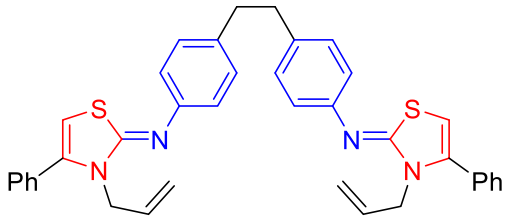
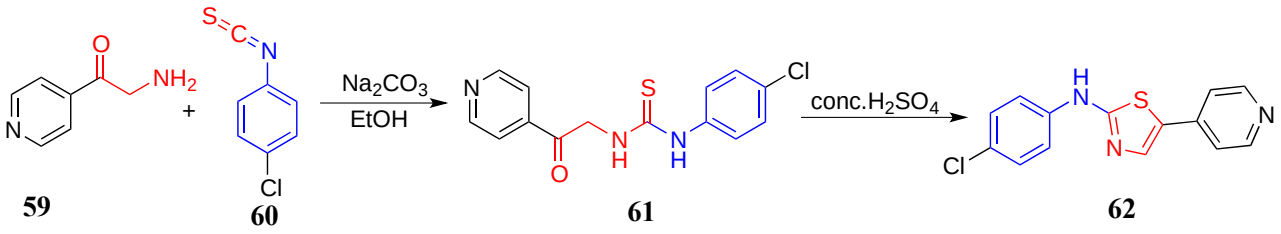


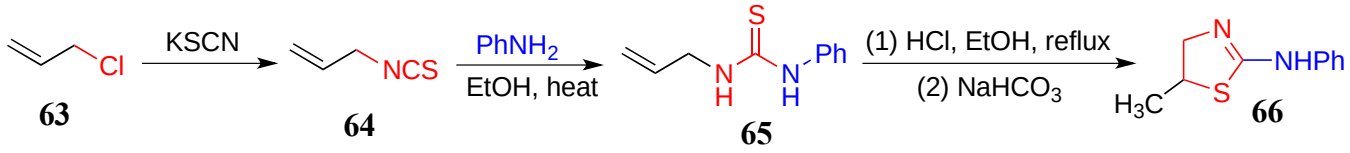
Figure 16. Bis *N*-phenylthiazol-2(3*H*)-imine **58**

Another method to synthesize 2-arylaminothiazoles is to react α-aminoketone **59** with phenylisothiocyanate **60** to afford β-oxothiourea intermediate **61** (Scheme 14). Cyclization with conc. sulfuric acid gave 2-phenylaminothiazole derivative **62**, which showed antibacterial activity against both *B. cereus* (MIC 64 μg/mL) and *S. aureus* (MIC 32 μg/mL).[40]



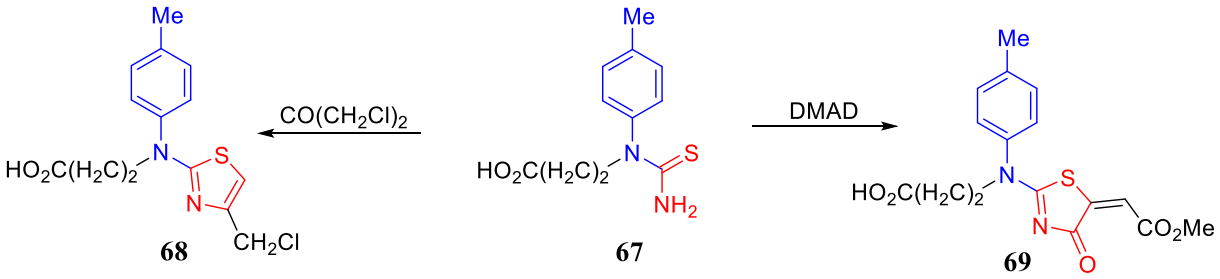
Scheme 14. Synthesis of 2-phenylaminothiazole **62**

Reaction of allyl chloride **63** with potassium isothiocyanate yielded allyl isothiocyanate **64** which reacted with aniline to afford 1-allyl-3-phenylthiourea **65** (Scheme 15). 1-Allyl-3-phenylthiourea **65** was cyclized into thiazole by refluxing in ethanol in presence of HCl and gave **66** after neutralization with a base. **66** showed antibacterial activity comparable to Ofloxacin against *Lactobacillus bulgaricus*, *Yersinia*, and *S. mitis* and antifungal activity comparable to Fluconazole against *A. niger*.[41]



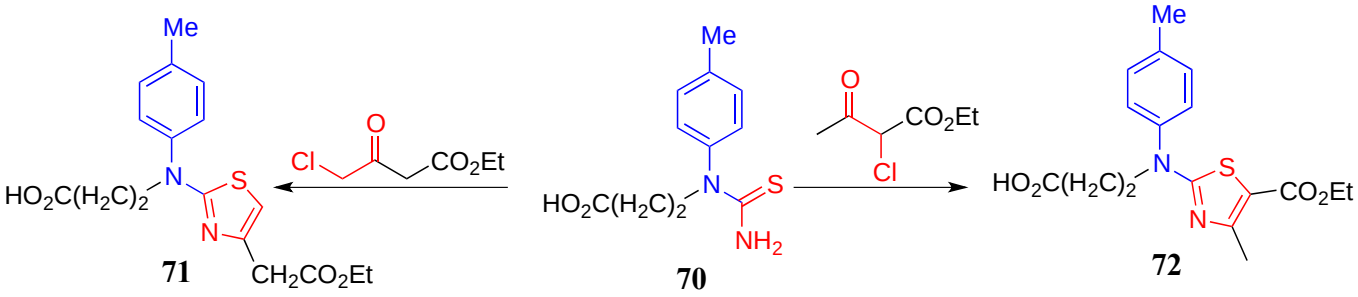
Scheme 15. Synthesis of 5-methyl-*N*-phenyl-4,5-dihydrothiazol-2-amine **66**

Reaction of *N*-phenylthiourea **67** with 1,3-dichloroacetone provided 4-chloromethyl-2-phenylaminothiazole derivative **68**. Moreover, *N*-phenylthiourea **67** reacted with dimethyl acetylenedicarboxylate (DMAD) to afford methyl 2-(4-oxo-2-phenylaminothiazol-5(4*H*)-ylidene)acetate **69** (Scheme 16). Both **68** and **69** showed more potent antifungal activity than Nystatin against *A. niger* with MIC values 1.9 µg/mL, 0.9 µg/mL respectively.[42]



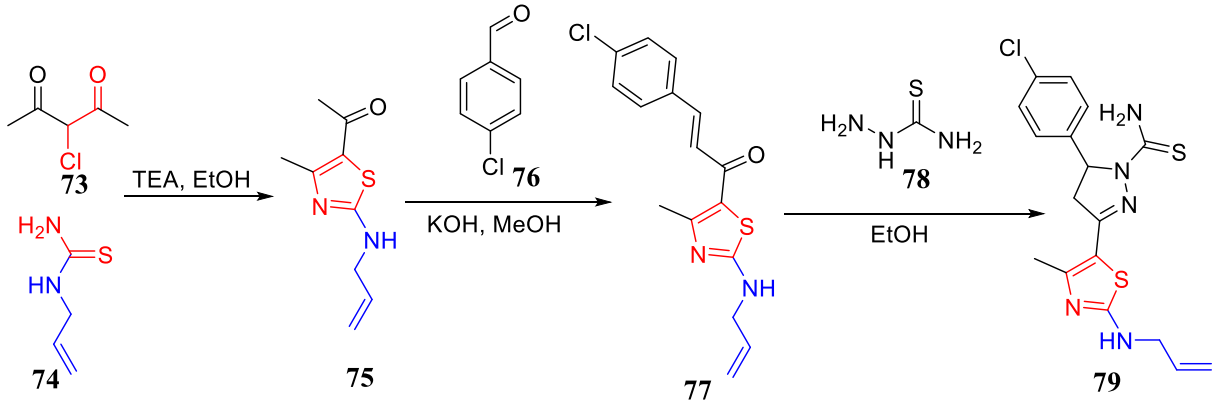
Scheme 16. Synthesis of **68** and **69**

Similarly, reaction of *N*,*N*-disustituted thiourea **70** with ethyl 4-chloroacetoacetate gave ethyl 2-(thiazol-4-yl)acetate derivative **71** while its reaction with 2-chloroacetoacetate gave ethyl 4-methylthiazole-5-carboxylate derivative **72**. **71** was more potent than Nystatin against *A. niger* (MIC 0.9 µg/mL), also it was equipotent to Nystatin against *C. tenuis* (MIC 31.2 µg/mL) (Scheme 17).[42]



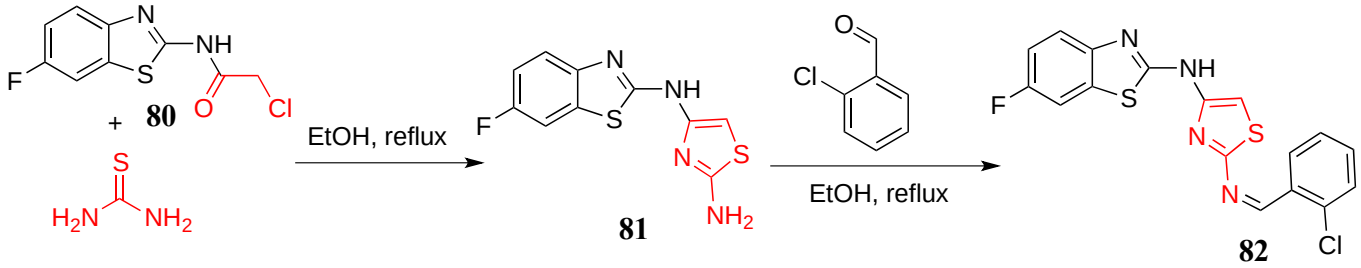
Scheme 17. Synthesis of **71** and **72**

Reaction of 3-chloropentane-2,4-dione **73** with *N*-allylthiourea **74** had yielded 5-acetylthiazole **75** which formed chalcone **77** by condensation with 4-chlorobenzldehyde **76** in presence of KOH as a base (Scheme 18). The formed chalcone **77** was cyclized into pyrazole via reaction with thiosemicarbazide **78** to give 3-(thiazol-5-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide derivative **79**. This compound was more potent than Ampicillin against both *S. pneumoniae* (MIC 0.03 μg/mL) and *B. subtilis* (MIC 0.06 μg/mL) and it was less potent than Ampicillin against *Staphylococcus epidermidis* (MIC 0.12 μg/mL). It was more potent than Gentamycin against *E. coli* (MIC 0.03 μg/mL) and equipotent to Gentamycin against *K. pneumoniae* (MIC 0.03 μg/mL). As antifungal, it was equipotent to Amphotericin B against *Aspergillus fumigatus* (MIC 0.12 μg/mL) and was more potent than Amphotericin B against *Syncephalastrum racemosum* (MIC 0.24 μg/mL).[43]



Scheme 18. Synthesis of 3-(thiazol-5-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **79**

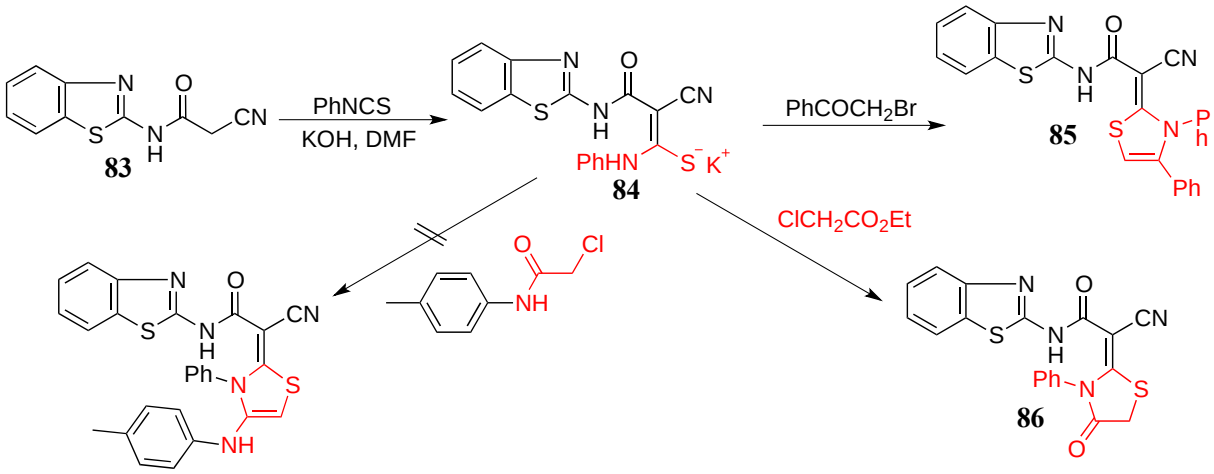
Despite its lower reactivity compared to α-chloroketones, α-chloroamides **80** can also be cyclized by heating with thiourea in ethanol to afford 2-aminothiazoles **81**, which could react with benzaldehydes to yield antimicrobial Schiff bases (Scheme 19). Among a series of Schiff bases that was synthesized by Amnerkar *et al.*, **82** was the most active antimicrobial derivative against *E. coli* (MIC 4 μg/mL), *P. aeruginosa* (MIC 5 μg/mL), *S. aureus* (MIC 11 μg/mL), *B. subtilis* (MIC 4 μg/mL), *C. albicans* (MIC 2 μg/mL), and *A. niger* (MIC 4 μg/mL).[44]



Scheme 19. Synthesis of Schiff base **82**

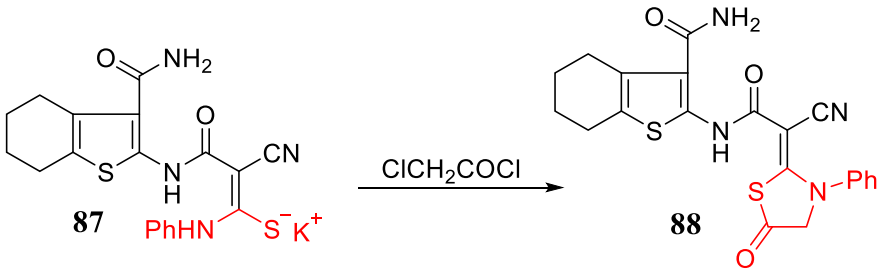
6. SYNTHESIS OF N-PHENYL-2,3-DIHYDROTHIAZOLES

Reaction of cyanoacetamide derivative **83** with phenyl isothiocyanate in DMF affords potassium sulfide salt **84** which was reacted without separation with phenacyl bromide to give vicinal diphenyl (thiazol-2-ylidene)acetamide derivative **85**. In addition, reaction of this potassium sulfide salt with ethyl chloroacetate provided 2-(4-oxo-3-phenylthiazolidin-2-ylidene)acetamide **86**. Intriguingly, Bondock *et al.* reported that there was no reaction occurred between this potassium sulfide salt and 2-chloro-*N*-(*p*-tolyl)acetamide (Scheme 20). **85** showed only antifungal activity against *A. fumigatus* (MIC 6.25 μg/mL) otherwise both compounds gave no noticeable antimicrobial activities (MIC 50-100 μg/mL).[45]



Scheme 20. Synthesis of **85** and **86**

Reaction of potassium sulfide salt **87** with chloroacetyl chloride yielded 2-(5-oxo-3-phenylthiazolidin-2-ylidene)acetamide **88** which showed comparable antimicrobial activity to Ampicillin against *B. theringiensis*, *K. pneumoniae*, *B. fabe*, and *F. oxysporum* (Scheme 21).[46]



Scheme 21. Synthesis of 2-(5-oxo-3-phenylthiazolidin-2-ylidene)acetamide **88**

89 (Figure 17) was synthesized by Fadda *et al.* and evaluated for its antibacterial activity against *B. subtilis*, *S. aureus*, *P. aeruginosa*, and *E. coli*. It showed weak antibacterial activity as compared to Ampicillin.[47]

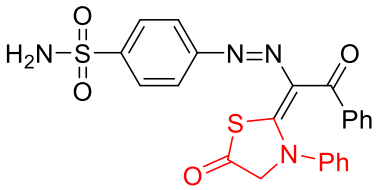
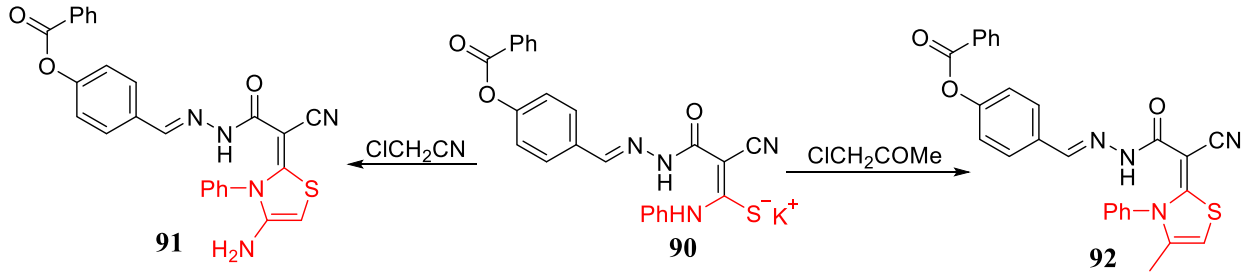


Figure 17. *N*-Phenylthiazolidin-5-one **89**

Reaction of potassium sulfide salt **90** with chloroacetonitrile yielded 2-(4-amino-3-phenylthiazol-2(3*H*)-ylidene)acetohydrazide derivative **91** (Scheme 22). While its reaction with chloroacetone yielded 2-(4-methyl-3-phenylthiazol-2(3*H*)-ylidene)acetohydrazide derivative **92**. The two compounds showed antibacterial activity (MIC 250-500 µg/mL) against both *E. coli* and *S. aureus* bacteria.[48]

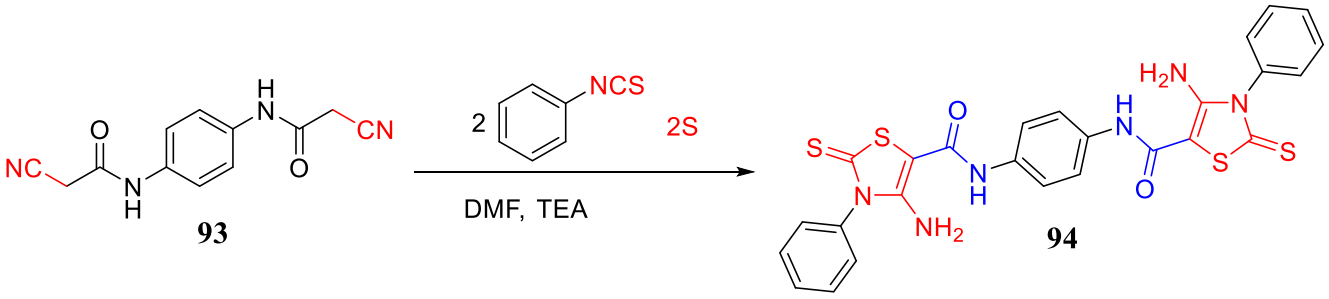


Scheme 22. Synthesis of Compound **2** and Compound **3**

7. SYNTHESIS OF 4-AMINO-2-THIOXO-2,3-DIHYDROTHIAZOLE-5-CARBOXAMIDE

El-Sayeda and Fadda synthesized 4-amino-2-thioxo-2,3-dihydrothiazole-5-carboxamide derivatives by the reaction of cyanoacetamide derivatives **93** with elemental sulfur and phenyl isothiocyanate (Scheme 23). **94** showed a comparable antibacterial activity to both Chloramphenicol and Cephalothin against *S. aureus* (MIC 3.125 µg/mL) and *B. thuringiensis* (MIC 6.25 µg/mL) and it gave comparable antifungal

activity to Cycloheximide against both *F. oxysporum* (MIC 6.25 µg/mL) and *B. fabae* (MIC 6.25 µg/mL), but it showed weaker antibacterial activity against Gram-negative strains (MIC 50-100 µg/mL).[49]



Scheme 23. Synthesis of 4-amino-2-thioxo-2,3-dihydrothiazole-5-carboxamide **94**

95 (Figure 18) is another example of 4-amino-2-thioxo-2,3-dihydrothiazole-5-carbohydrazide derivative which was more potent than Ampicillin against both *S. aureus* (MIC 125 µg/mL) and *E. coli* (MIC 93.7 µg/mL) but displayed minor antifungal activity against *C. albicans* in comparison with Clotrimazole.[50]

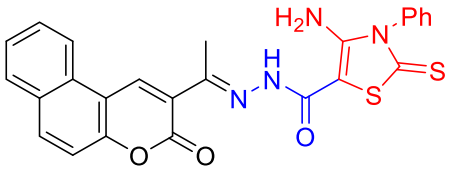
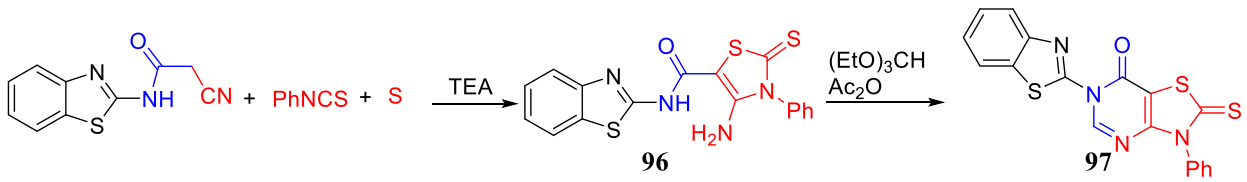


Figure 18. 4-Amino-2-thioxo-2,3-dihydrothiazole-5-carbohydrazide **95**

Moreover, Bondock and coworkers reacted the formed 4-amino-2-thioxo-2,3-dihydrothiazole-5-carboxamide derivative **96** with triethyl orthoformate to form a bicyclic 2-thioxo-2,3-dihydrothiazolo[*4,5-d*]pyrimidin-7(6*H*)-one derivative **97** (Scheme 24). Only **96** was evaluated for its antibacterial and antifungal activity but showed no superior activity compared to Chloramphenicol, Cephalothin and Cycloheximide. Its MIC values were *S. aureus* (MIC 12.5 µg/mL), *P. phaseolicola* (MIC 50 µg/mL), and *F. oxysporum* (MIC 12.5 µg/mL).[45]

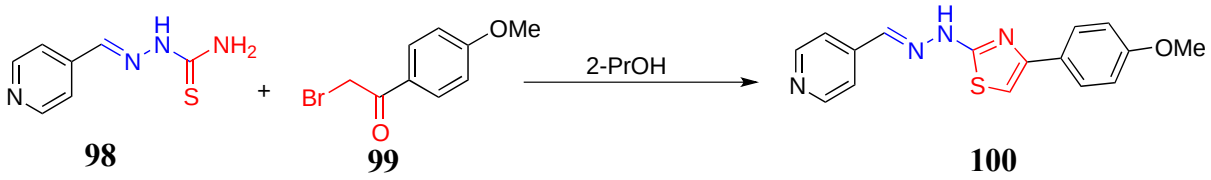


Scheme 24. Synthesis of 4-amino-2-thioxo-2,3-dihydrothiazole-5-carboxamide **96** and 2-thioxo-2,3-dihydrothiazolo[*4,5-d*]pyrimidin-7(6*H*)-one **97**

8. SYNTHESIS OF 2-(2-(ARYL/ALKYLIDENE)HYDRAZINYL)THIAZOLES

This group of compounds represents the most synthesized antimicrobial agents in the last decade. The main method for synthesis of these derivatives is by reaction of thiosemicarbazone with α-bromoketone.

Reaction of thiosemicarbazone derivative **98** with α-bromoketone **99** in isopropyl alcohol yielded 2-(2-arylidenehydrazinyl)thiazole **100** (Scheme 25). **100** was equipotent to Fluconazole against both *C. sake* (MIC 32 µg/mL) and *C. tropicalis* (MIC 16 µg/mL). Moreover, it was more potent than Fluconazole against *C. glabrata* (MIC 0.5 µg/mL), *C. albicans* (MIC 0.125 µg/mL) and *C. krusei* (MIC 16 µg/mL).[51]



Scheme 25. Synthesis of 2-(2-arylidenehydrazinyl)thiazole **100**

Also, 2-(2-benzylidenehydrazinyl)thiazole derivative **101** (Figure 19) had comparable antibacterial activity to Chloramphenicol against *P. aeruginosa* (MIC 32 µg/mL). Also, It exhibited antibacterial activity against *S. aureus* (MIC 32 µg/mL).[52]

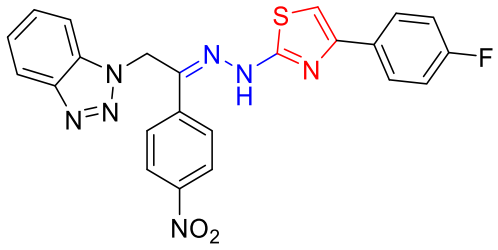


Figure 19. 2-(2-Benzylidenehydrazinyl)thiazole **101**

102 (Figure 20) showed a comparable bacterial growth inhibition to Streptomycin against *B. subtilis*, *S. pneumonia*, *S. aureus*, *E. coli*, and *Pseudomonas* sp.[53]

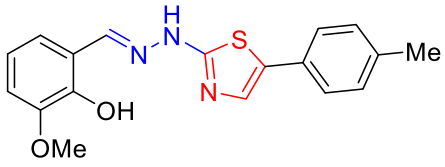


Figure 20. 2-(2-Benzylidenehydrazinyl)thiazole **102**

103 (Figure 21) was more potent than both Ciprofloxacin and Sulbactam/penicillin against *K. pneumoniae* (MIC 0.06 µg/mL), *E. coli* (MIC 0.2 µg/mL), *S. aureus* (MIC 0.08 µg/mL).[55]

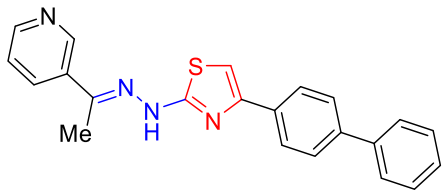


Figure 21. 2-(2-(1-(Pyridin-3-yl)ethylidene)hydrazinyl)thiazole **103**

A 2-(2-(1-(pyridin-2-yl)ethylidene)hydrazinyl)thiazole derivative **104** (Figure 22) showed antimycobacterial activity (MIC 12.5 μg/mL) via inhibition of β-ketoacyl-ACP synthase.[56]

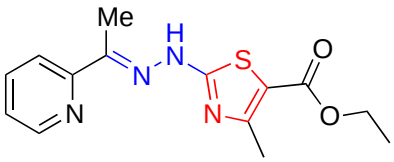


Figure 22. 2-(2-(1-(Pyridin-2-yl)ethylidene)hydrazinyl)thiazole **104**

105 (Figure 23) exhibited antibacterial activity against both Gram-positive and Gram-negative strains including *E. coli*, *P. aeruginosa*, *B. thuringiensis*, and *B. subtilis*. In addition, it was more potent than Kanamycin in inhibition of *E. coli* FabH (IC_{50} 4.9 μM).[57]

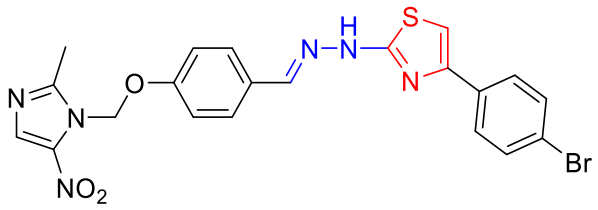


Figure 23. 2-(2-Benzylidenehydrazinyl)thiazole **105**

A 2-hydrazinylthiazole **106** (Figure 24) exhibited antimycobacterial activity (MIC 1.5-6.3 μg/mL) against drug-resistant strains of *M. tuberculosis* including Isoniazid and Rifampicin resistant strains.[54]

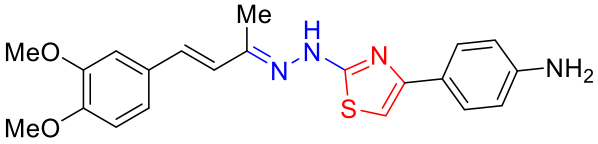


Figure 24. 2-(2-(4-Phenylbut-3-en-2-ylidene)hydrazinyl)thiazole **106**

Compared to Chloramphenicol and Cephalothin, **107** (Figure 25) showed moderate antibacterial activity against both Gram-positive and Gram-negative strains including *E. faecalis*, *S. aureus*, *E. coli*, and *P. aeruginosa*.[58]

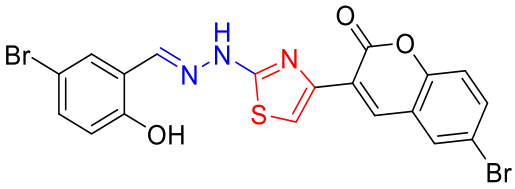
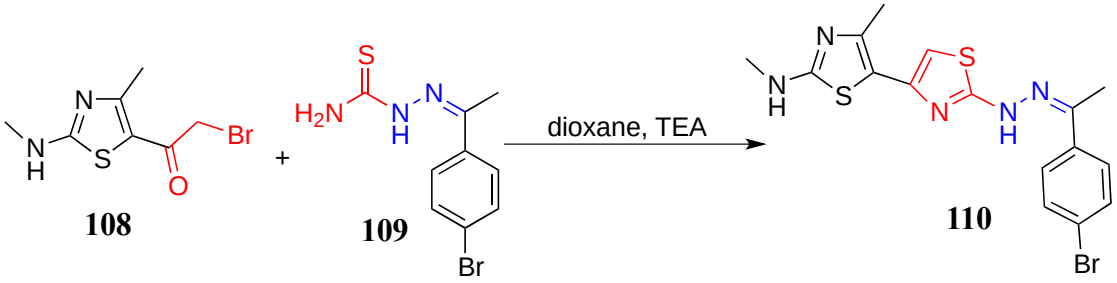


Figure 25. 2-(2-Benzylidenehydrazinyl)thiazole **107**

Althagafi team[59] synthesized **110** by the reaction of α-bromoketone **108** with thiosemicarbazone **109** in dioxane in presence of TEA as a base Scheme 26. **110** displayed antifungal activity similar to

Amphotericin B against *A. niger* (MIC 0.98 µg/mL) and antifungal activity against *Geotricum candidum* (MIC 3.9 µg/mL). It was equipotent to Gentamicin against *K. pneumoniae* (MIC 0.98 µg/mL) and showed antibacterial activity against *S. aureus* (MIC 3.9 µg/mL), *Staphylococcus epidermidis* (MIC 7.81 µg/mL), *B. subtilis* (MIC 31.25 µg/mL), *E. coli* (MIC 1.95 µg/mL), and *S. typhimurium* (MIC 1.95 µg/mL).[59]



Scheme26. Synthesis of 2-(2-benzylidenehydrazinyl)thiazole **110**

111 (Figure 26) was more potent than Ampicillin against both *S. pneumoniae* (MIC 0.03 µg/mL) and *B. subtilis* (MIC 0.06 µg/mL). It was also more potent than Amphotericin B against *Syncephalastrum racemosum* (MIC 0.06 µg/mL). Furthermore, it showed antimicrobial activity against both *K. pneumoniae* (MIC 0.98 µg/mL) and *A. fumigatus* (MIC 0.49 µg/mL).[43]

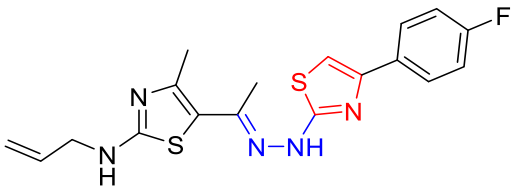


Figure 26. 5-(1-(2-(Thiazol-2-yl)hydrazono)ethyl)thiazol-2-amine **111**

By the same procedures, Biernasiuk *et al.* synthesized a series of 2-methylenehydrazinylthiazoles. **112** (Figure 27) was more potent than Nystatin against both *C. albicans* (MIC 0.06 µg/mL) and *C. krusei* (MIC 0.06 µg/mL). Also, it showed antifungal activity against *C. parapsilosis* (MIC 0.48 µg/mL), *C. tropicalis* (MIC 31.25 µg/mL), *C. inconspicua* (MIC 31.25 µg/mL), *C. lusitaniae* (MIC 7.81 µg/mL), and *C. sake* (MIC 31.25 µg/mL).[60]

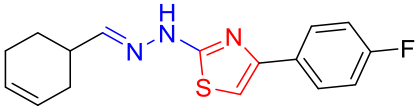


Figure 27. 2-(2-(Cyclohex-3-en-1-ylmethylene)hydrazinyl)thiazole **112**

113 (Figure 28) showed remarkable MIC and MFC values comparable to Fluconazole against C. *albicans* (MIC 3.9 µg/mL), C. *parapsilosis* (MIC 15.62 µg/mL), and C. *zeylanoides* (MIC15.62 µg/mL).[61]

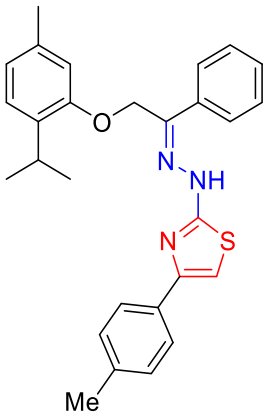


Figure 28. 2-(2-Benzylidenehydrazinyl)thiazole **113**

114 (Figure 29) displayed antibacterial activity against *S. epidermidis* (MIC 1.95 µg/mL) which was similar to Ampicillin and displayed antibacterial activity against both *S. typhimurium* (MIC 3.9 µg/mL), and *K. pneumoniae* (MIC 3.9 µg/mL). While **115** (Figure 30) showed higher antifungal activity than Amphotericin B against *A. niger* and showed higher antifungal activity than Gentamicin against all Gram-negative strains including *S. typhimurium*, *E. coli*, and *K. pneumoniae*, but it failed to show any significant results with Gram-positive strains.[59]

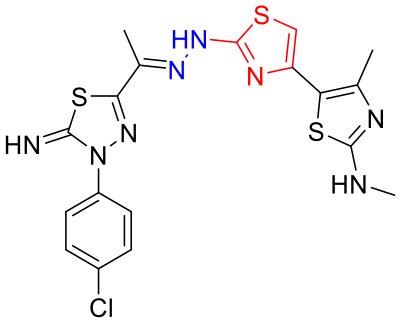


Figure 29. 5-(1-(2-(Thiazol-2-yl)hydrazono)ethyl)-1,3,4-thiadiazol-2(3*H*)-imine **114**

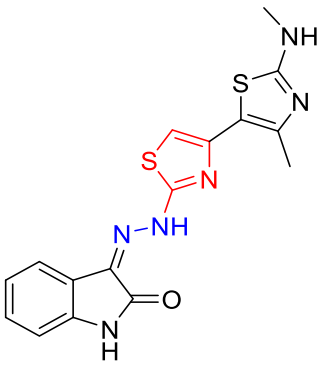


Figure 30. 3-(2-(Thiazol-2-yl)hydrazono)indolin-2-one **115**

116 (Figure 31) exhibited antifungal activity against wide range of *Candida* species including *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. krusei*, *C. tropicalis*, *C. inconspicua*, *C. famata*, *C. guilliermondii*, *C.*

lusitaniae, *C. sake*, and *C. dubliniensis* with MIC values 0.98-1.95 μg/mL. Moreover, it showed inhibitory activity against *Toxoplasma gondii* (IC_{50} 18.08 μg/mL).[62]

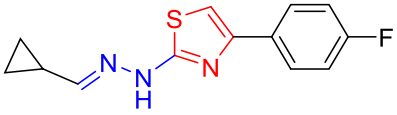


Figure 31. 2-(2-(Cyclopropylmethylene)hydrazinyl)thiazole **116**

117 (Figure 32) exhibited higher antifungal activity than Fluconazole against all tested *Candida* species including *C. albicans* (MIC 0.9 μg/mL), *C. krusei* (MIC 1.9 μg/mL), *C. parapsilosis* (MIC 1.9 μg/mL), *C. tropicalis* (MIC 3.9 μg/mL), *C. gatti* (MIC 0.45 μg/mL), and *C. neoformans* (MIC 0.9 μg/mL).[63]

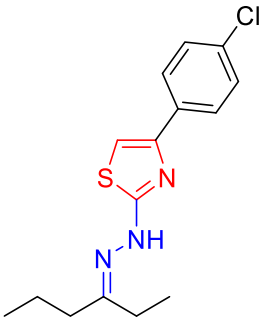


Figure 32. 2-(2-(Hexan-3-ylidene)hydrazinyl)thiazole **117**

118 (Figure 33) showed higher antifungal activity (MIC 0.25 μg/mL) than both Amphotericin B and Fluconazole against resistant *C. neoformans* and *C. gatti* by increasing intracellular reactive oxygen species (ROS). Moreover, it showed synergistic effect with a superoxide generator Menadione.[64]

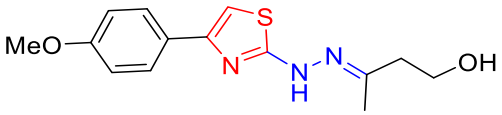


Figure 33. 2-(2-(Butan-2-ylidene)hydrazinyl)thiazole **118**

Although **119** (Figure 34) didn't exert remarkable antibacterial activity against *S. aureus* by itself. However, it augmented the antibacterial activity of Norfloxacin against wild type strain by inhibition of NorA pumps with low cytotoxicity to human cells and decreased the MIC of Norfloxacin to one third.[65]

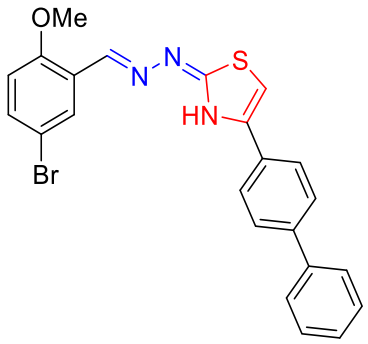


Figure 34. 2-(2-Benzylidenehydrazono)-2,3-dihydrothiazole **119**

In 2018, Ouf *et al.* evaluated the activity of some of 2-hydrazinyl-5-(2-phenylhydrazono)thiazol-4(5*H*)-one derivatives and 5-phenyldiazenyl-2-hydrazinyl-4-phenylthiazole against cutaneous fungi strains. **120** and **121** (Figure 35) were more potent than Fluconazole against *C. albicans* (MIC 2 µg/mL), *M. gypseum* (MIC 4 µg/mL), and *T. mentagrophytes* (MIC 4 µg/mL).[66]

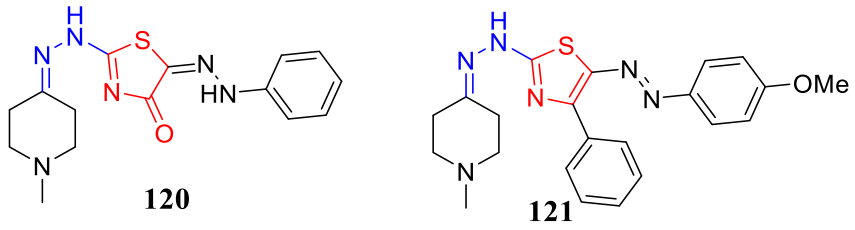
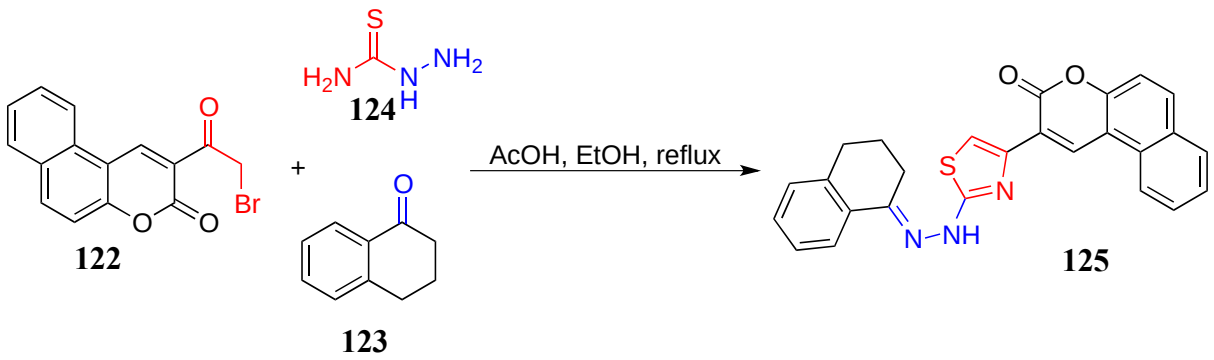


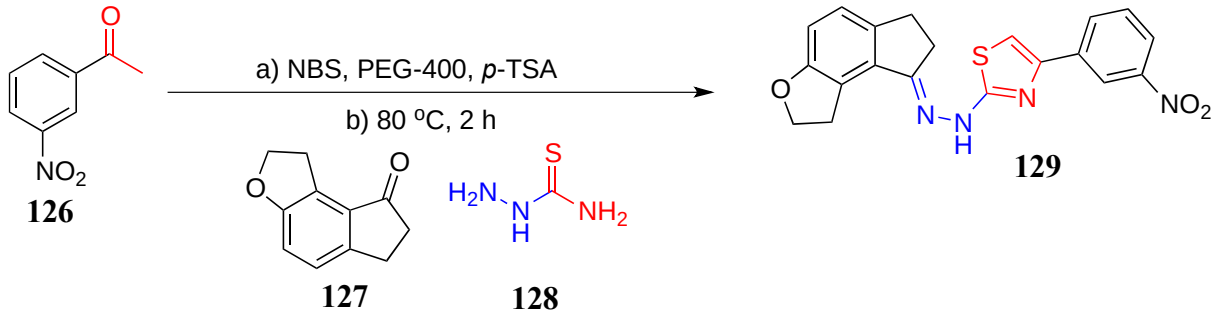
Figure 35. 2-Hydrazinyl-5-(2-phenylhydrazono)thiazol-4(5*H*)-one **120** and 5-phenyldiazenyl-2-hydrazinyl-4-phenylthiazole **121**

In one-pot reaction, **125** was synthesized by refluxing α-bromoketone **122**, 1-tetralone **123** and thiosemicarbazide **124** in ethanol in presence of catalytic amount of acetic acid (Scheme 27). **125** showed antibacterial activity to Gentamycin against both Gram-positive and Gram-negative strains including *S. aureus*, *Bacillus thuringiensis*, *E. coli* and *K. pneumonia*.[67]



Scheme 27. Synthesis of 2-(2-(3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazole **125**

Adole *et al.*[68] introduced a novel one-pot reaction for synthesis of 2-hydrazinylthiazole derivatives from acetophenone derivatives, 1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-one, and thiosemicarbazide. The method was based on heating two flask at 80 ºC, the first was containing (un)substituted acetophenone **126**, NBS, *p*-TSA in PEG-400 and the second flask was containing 1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-one **127** and thiosemicarbazide **128** in PEG-400. After completion of each reaction, the two flasks were mixed without any separation or workup and the resulting mixture was heated again at 80 ºC to yield hydrazinyl thiazole derivatives. All synthesized compounds showed superior antibacterial activity against all tested strains as compared to Ampicillin and also had minimal antifungal activity against both *Rhizopus oryzae* and *Mucor mucedo* as compared to Fluconazole while **129** was equipotent to Fluconazole against both *A. niger* and *C. albicans* (Scheme 28).[68]



Scheme 28. Synthesis of 2-hydrazinylthiazole **129**

Recently, Hublikar *et al.* synthesized a series of 2-(2-allylidenehydrazinyl)thiazole as antimycobacterial agents by one-pot three component reaction. Amongst the synthetic derivatives, **130** (Figure 36) showed the best antimycobacterial activity (MIC 6.5 µg/mL).[69]

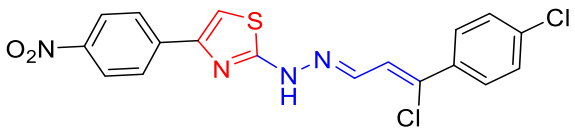


Figure 36. 2-(2-Allylidenehydrazinyl)thiazole **130**

Another series of hydrazinylthiazole derivatives were also synthesized by Chidananda *et al.* from thiosemicarbazone derivatives. **131** (Figure 37) displayed similar antibacterial activity compared to Ampicillin against *E. coli* (MIC 6.25 µg/mL), *P. aeruginosa* (MIC 6.25 µg/mL), and *K. pneumonia* (MIC 6.25 µg/mL) but showed inferior activity against *S. aureus*. Moreover, **132** (Figure 38) exhibited comparable antifungal activity to Itraconazole against *P. marneffei* (MIC 6.25 µg/mL), *T. mentagrophytes* (MIC 6.25 µg/mL) and *A. fumigates* (MIC 6.25 µg/mL) but was not active against *A. flavus*.[70]

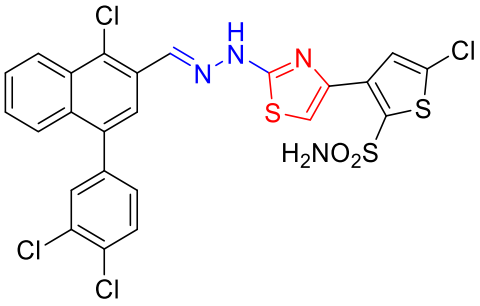


Figure 37. 2-(2-((Naphthalen-2-yl)methylene)hydrazinyl)-4-(thiophen-3-yl)thiazole **131**

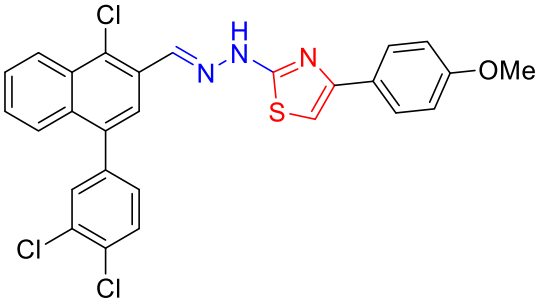


Figure 38. 2-(2-((Naphthalen-2-yl)methylene)hydrazinyl)-4-phenylthiazole **132**

133 (Figure 39) was more potent than Ampicillin against *E. coli* (MIC 62.5 µg/mL), *P. aeruginosa* (MIC 93.7 µg/mL), *S. aureus* (MIC 125 µg/mL) and *B. subtilis* (MIC 125 µg/mL).[71]

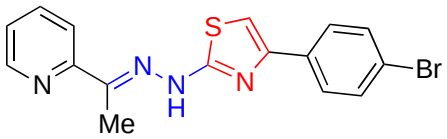


Figure 39. 2-(2-(1-(Pyridin-2-yl)ethylidene)hydrazinyl)thiazole **133**

134 (MIC 6.25 µg/mL) (Figure 40) was equipotent to Fluconazole against all tested fungi strains including *C. albicans*, *C. neoformans*, *A. flavus*, and *C. tropicum*. In addition, it exhibited antibacterial activity against *S. aureus* (MIC 12.5 µg/mL).[72]

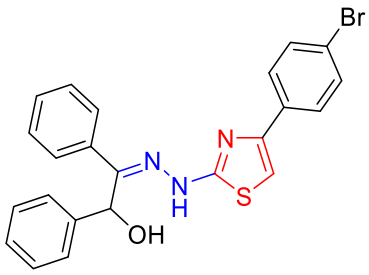


Figure 40. 2-(2-(1,2-Diphenylethylidene)hydrazinyl)thiazole **134**

2-Hydrazono-2,3-dihydrothiazole derivative **135** (Figure 41) was more potent than Streptomycin against both *S. typhi* (MIC 25 µg/mL) and *E. coli* (MIC 6.25 µg/mL) and equipotent against *B. subtilis* (MIC 12.5 µg/mL). It was more potent than Amphotericin B against *C. neoformans* and equipotent against both *C. albicans* and *A. flavus*.[73]

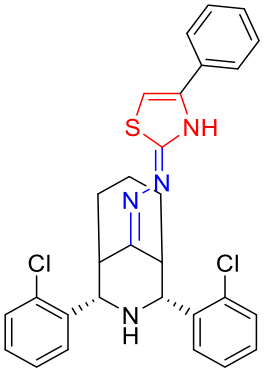
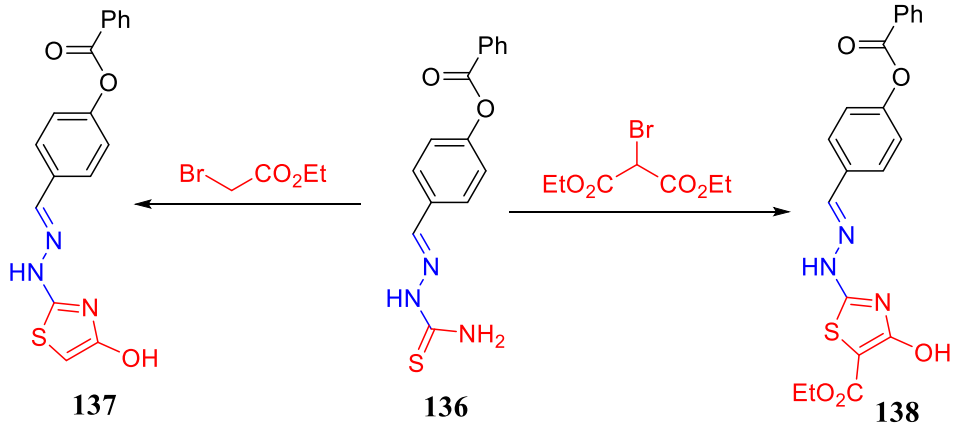


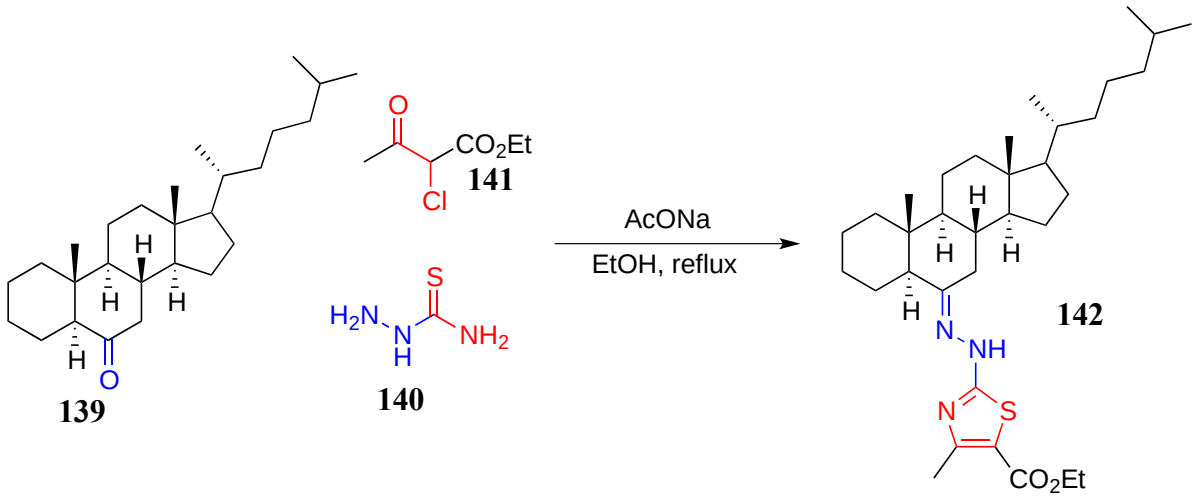
Figure 41. 2-Hydrazono-2,3-dihydrothiazole **135**

In drug design, medicinal chemist tent to replace α-haloketones with α-haloesters. In similar strategy, reaction of thiosemicarbazone **136** with ethyl bromoacetate and diethyl bromomalonate yielded 2-(2-benzylidenehydrazinyl)thiazol-4-ol derivative **137** and ethyl 2-(2-benzylidenehydrazinyl)-4-hydroxythiazole-5-carboxylate **138**, respectively (Scheme 29). These two compounds showed antibacterial activity against both *E. coli* and *S. aureus*.[48]



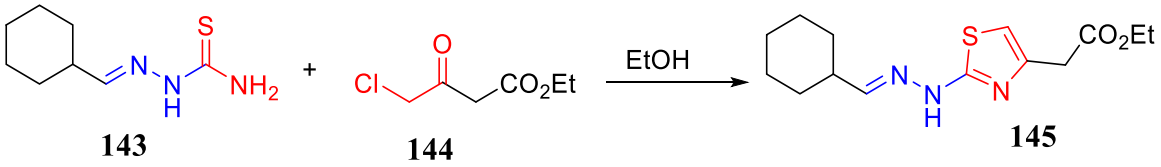
Scheme 29. Synthesis of 2-(2-benzylidenehydrazinyl)thiazol-4-ol **137** and ethyl 2-(2-benzylidenehydrazinyl)-4-hydroxythiazole-5-carboxylate **138**

The antimicrobial 2-hydrazinylthiazole derivative **142** was obtained by three-component one-pot reaction between steroidal ketone **139**, thiosemicarbazide **140** and ethyl 2-chloroacetoacetate **141** (Scheme 30).[74]



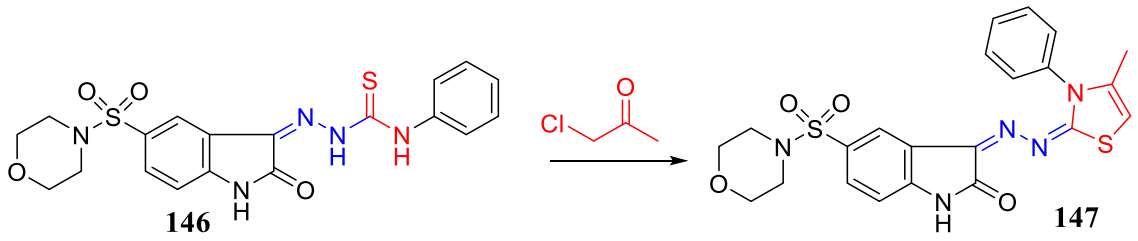
Scheme 30. Synthesis of ethyl 2-hydrazinylthiazole-5-carboxylate **142**

Similarly, reaction of 4-chloroacetoacetate **144** with thiosemicarbazone derivative **143** afforded ethyl 2-(2-hydrazinylthiazol-4-yl)acetate derivative **145** (Scheme 31). The formed 2-hydrazinylthiazole **145** showed remarkable antifungal activity (MIC values: 0.98-15.62 µg/mL) compared to Fluconazole against *Candida* species including C. *albicans, C. parapsilosis, C. sake, C. dubliniensis, C. famata, C. lusitaniae, C. krusei*, and *C. inconspicua*.[75]



Scheme 31. Synthesis of ethyl 2-(2-hydrazinylthiazol-4-yl)acetate **145**

Also, thiosemicarbazones react **146** with chloroacetone to give 2-hydrazono-2,3-dihydrothiazole derivatives **147** (Scheme 32). **147** was equipotent to Ampicillin against both *S. aureus* (MIC 0.06 µg/mL) and *S. epidermidis* (MIC 0.49 µg/mL). In addition, it had a notable activity against both Gram-negative bacteria and some fungi strains which are *P. vulgaris* (MIC 3.9 µg/mL), *K. pneumonia* (MIC 1.95 µg/mL), *S. flexneri* (MIC 0.98 µg/mL), *A. fumigatus* (MIC 3.9 µg/mL), *A clavatus* (MIC 7.8 µg/mL), and *G. candidum* (MIC 0.98 µg/mL).[76]



Scheme 32. Synthesis of 2-hydrazono-2,3-dihydrothiazole **147**

Using similar procedures, Biernasiuk *et al.* synthesized a series of 2-hydrazinylthiazole compounds. **148** (Figure 42) had a notable antifungal activity and was more potent than Nystatin against a variety of fungi strains including *C. albicans* (MIC 0.03 μg/mL), *C. parapsilosis* (MIC 0.03 μg/mL), *C. krusei* (MIC 0.015 μg/mL), *C. inconspicua* (MIC 0.06 μg/mL), and *C. lusitaniae* (MIC 0.06 μg/mL).[60]

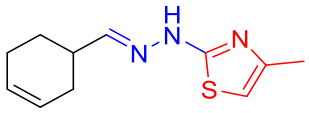
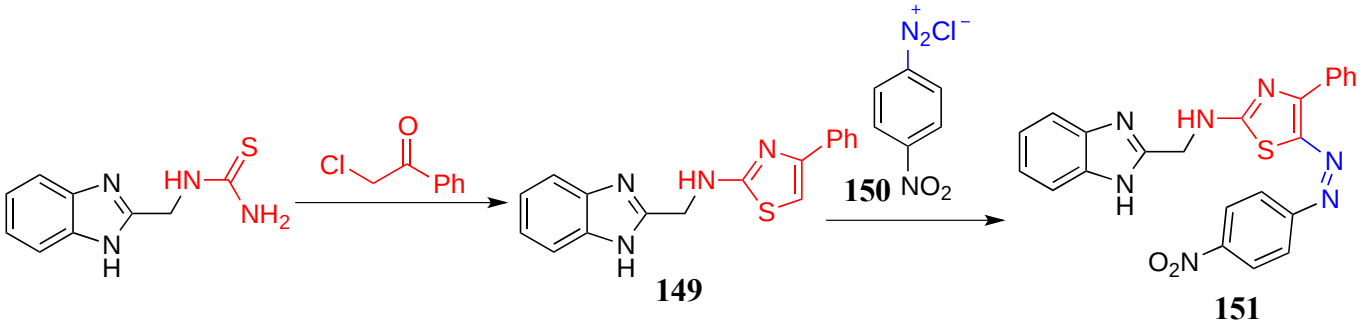


Figure 42. 2-(2-(Cyclohex-3-en-1-ylmethylene)hydrazinyl)thiazole **148**

9. SYNTHESIS OF 4/5-DIAZENYLTHIAZOLES

Reaction of 4-nitrobenzenediazonium chloride **150** with active methylene of 4-phenylthiazol-2-amine **149** derivative yielded antibacterial agent 5-diazenyl-4-phenylthiazol-2-amine **151** (Scheme 33) showed antibacterial activity against *E. coli* (MIC 16 μg/mL) and *S. aureus* (MIC 28 μg/mL). 5-diazenylthiazol-2-amine **152** (Figure 43) showed antibacterial activity against *E. coli* (MIC 14 μg/mL).[77]



Scheme 33. Synthesis of **151**

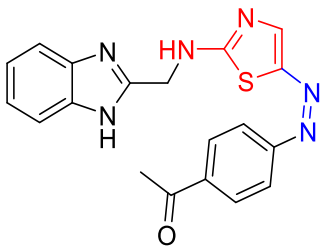
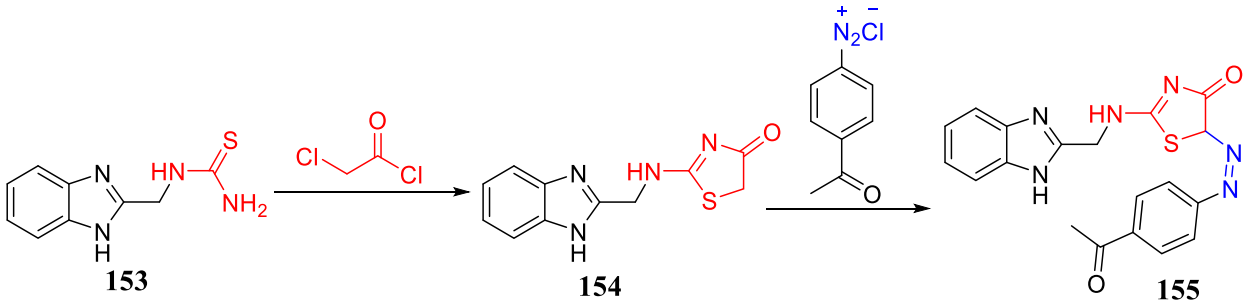


Figure 43. 5-Diazenylthiazol-2-amine **152**

Chloroacetyl chloride reacted with *N*-alkylated thiourea **153** to form 2-(alkylamino)thiazol-4(5*H*)-one **154** (Scheme 34), which upon reaction with 4-acetylbenzenediazonium chloride formed 2-alkyylamino-5-diazenylthiazol-4(5*H*)-one derivative **155** that showed antibacterial activity against *S. aureus* (MIC 27 μg/mL).[77]



Scheme 34. Synthesis of 2-alkyylamino-5-diazenylthiazol-4(5*H*)-one **155**

4-(2-(*p*-Tolyl)hydrazono)thiazolidin-5-one derivative **156** (Figure 44) was synthesized by coupling of 4-methylbenzenediazonium chloride with active methylene of thiazolidin-5-one. It showed comparable antimicrobial activity to Ampicillin against *B. theringiensis*, *K. pneumoniae*, *B. fabe*, and *F. oxysporum*.[46]

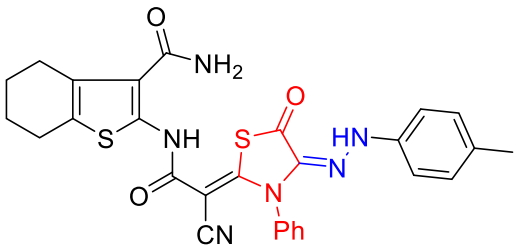


Figure 44. 4-(2-(*p*-Tolyl)hydrazono)thiazolidin-5-one **156**

The related 4-hydrazinylthiazole derivative **157** (Figure 45) was more potent than Ciprofloxacin and Ofloxacin against all tested strains including *S. aureus*, *B. subtilis*, *S. epidermidis*, *E. coli*, and *P. aeruginosa* with MIC 1.281 µg/mL for all strains. Also, it was more potent than Fluconazole against both *C. albicans* (MIC 1.582 µg/mL), and *A. niger* (MIC 1.281 µg/mL).[78]

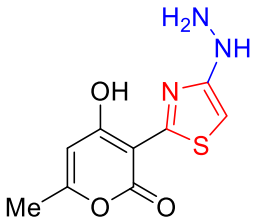
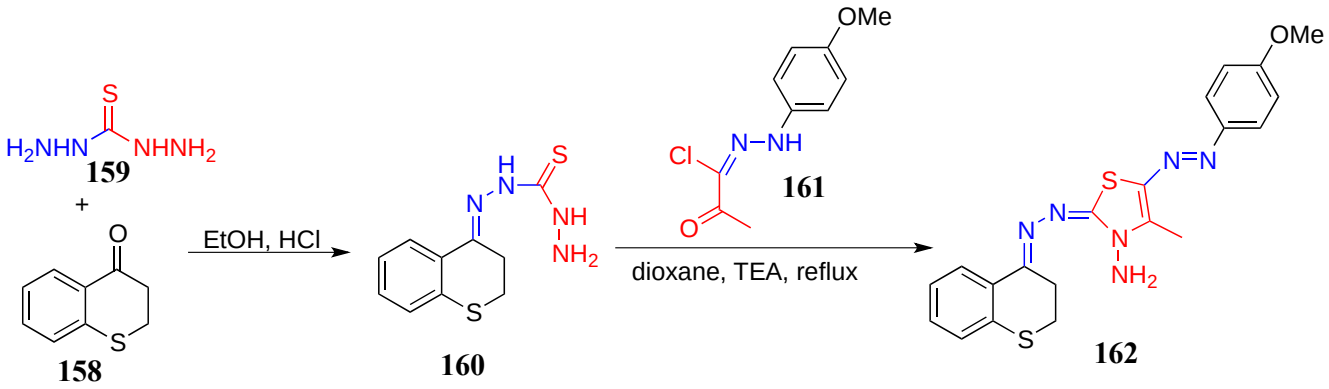


Figure 45. 4-Hydrazinylthiazole **157**

10. SYNTHESIS OF 5-DIAZENYL-2-HYDRAZONOTHIAZOLES

Reaction of ketone **158** with thiocarbohydrazide **159** gave *N*′-substituted hydrazinecarbothiohydrazide **160** which in turn reacted with hydrazonoyl chloride derivative **161** to afford 5-diazenyl-2-hydrazonothiazol-3(2*H*)-amine **162** showed comparable antibacterial activity to Ampicillin against *B. subtilis* (MIC 1.95 µg/mL). And showed superior activity than Amphotericin B against *S.*

racemosum (MIC 0.49 µg/mL) (Scheme 35). In addition, it showed antimicrobial activity against *P. aeruginosa* (MIC 1.95 µg/mL), *E. coli* (MIC 0.12 µg/mL), *A. fumigatus* (MIC 0.24 µg/mL), and *Geotricum candidum* (MIC 0.12 µg/mL).[79]



Scheme 35. Synthesis of 5-diazenyl-2-hydrazonothiazol-3(2*H*)-amine **162**

Another 5-diazenyl-2-hydrazinylthiazole **163** (Figure 46) was equipotent to Ampicillin against *E. coli* (MIC 125 µg/mL). It was more potent than Ampicillin against both *P. aeuroginosa* (MIC 125 µg/mL) and *B. subtilis* (MIC 187.5 µg/mL).[71]

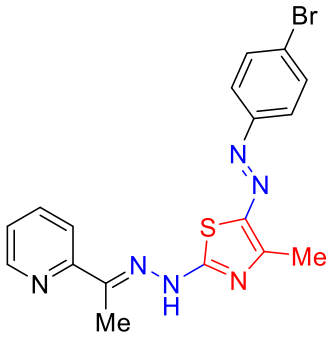


Figure 46. 5-Diazenyl-2-hydrazinylthiazole **163**

164 (Figure 47) was equipotent to Ampicillin against *S. pneumoniae* (MIC 0.12 µg/mL) and it was equipotent to Gentamycin against both *E. coli* (MIC 1.95 µg/mL) and *K. pneumoniae* (MIC 0.03 µg/mL). It was more potent than Ampicillin against *B. subtilis* (MIC 0.06 µg/mL) but equipotent to Amphotericin B against *S. racemosum* (MIC 7.81 µg/mL).[43]

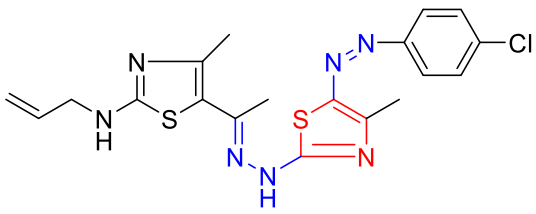


Figure 47. 5- Diazenyl-2-hydrazinylthiazole **164**

Reaction of thiosemicarbazone derivative with 2-oxo-*N*-phenylpropanehydrazonoyl chloride afforded **165** (Figure 48). Comparing to Chloramphenicol, it showed high antibacterial activity against both *E. faecalis* and *S. aureus*.[58]

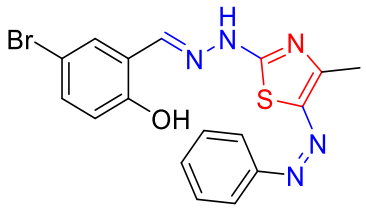


Figure 48. 5-Diazenyl-2-hydrazinylthiazole **165**

166 (Figure 49) was synthesized by Abdel-Galil *et al.* and it displayed antibacterial activity against both *E. coli* (MIC 750 µg/mL) and *S. aureus* (MIC 375 µg/mL).[48]

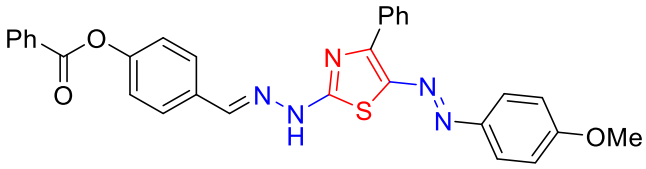


Figure 49. 5-Diazenyl-2-hydrazinylthiazole **166**

167 (Figure 50) was synthesized by Fadda *et al.* and evaluated for its antibacterial activity comparing to Ampicillin against *B. subtilis*, *S. aureus*, *P. aeruginosa*, and *E. coli*.[47]

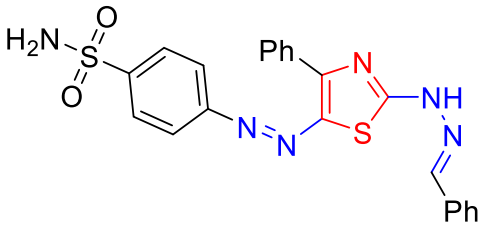
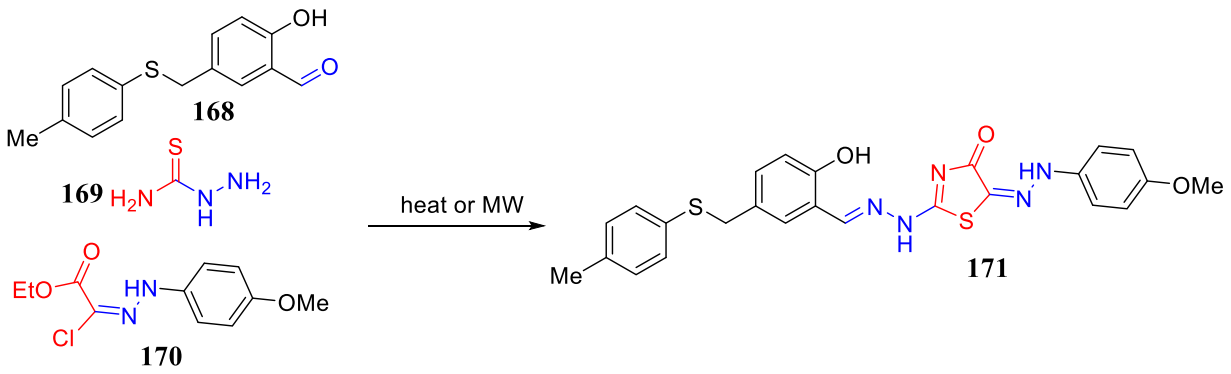


Figure 50. 5-Diazenyl-2-hydrazinylthiazole **167**

In 2020, Sanad and his two colleagues succeeded to synthesize 2-benzylidene-hydrazinyl-5-hydrazonothiazol-4(5*H*)-ones **171** without catalyst through neat one-pot three-component reaction between aldehyde **168**, thiosemicarbazide **169** and hydrazonyl chlorides **170** (Scheme 36). **171** was the best compound with more superior antibacterial activity than Ampicillin and Gentamycin against Gram-positive and Gram-negative bacteria, respectively with MIC values *S. aureus* (MIC 3.9 µg/mL), *S. mutans* (MIC 7.8 µg/mL), *K. pneumoniae* (MIC 3.9 µg/mL), and *E. coli* (MIC 15.6 µg/mL). The unique antibacterial activity of **171** was owed to inhibition of MurB enzyme.[80]

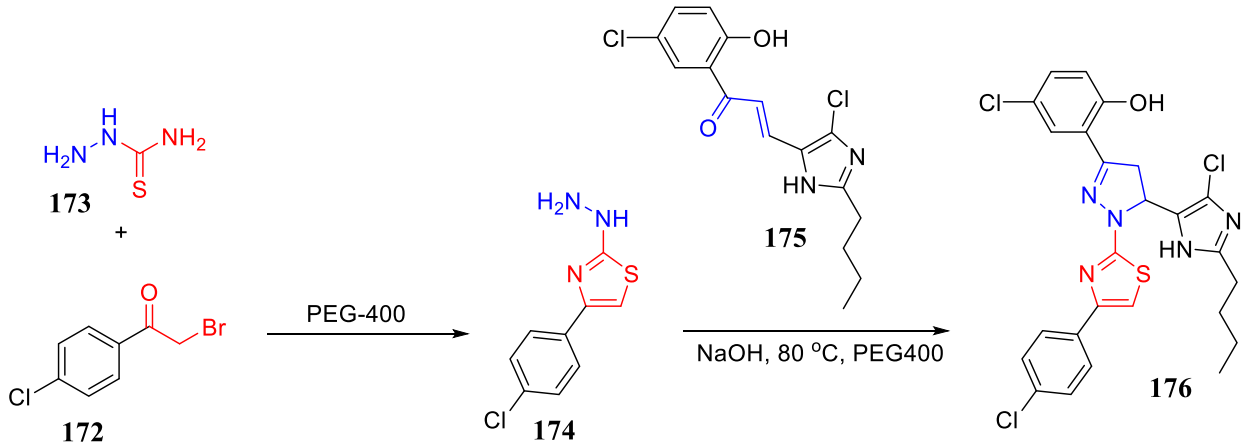


Scheme 36. Synthesis of 2-benzylidene-hydrazinyl-5-hydrazonothiazol-4(5*H*)-one **171**

11. SYNTHESIS OF (4,5-DIHYDRO-1H-PYRAZOL-1-YL)THIAZOLES

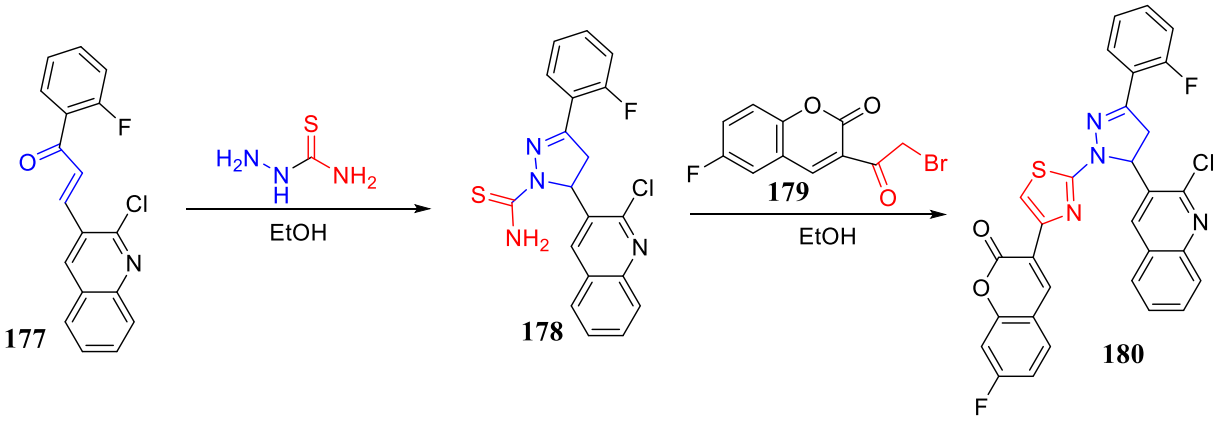
Because of the promising antimicrobial activity of both thiazole and pyrazole, medicinal chemists all over the world synthesized numerous (4,5-dihydro-1*H*-pyrazol-1-yl)thiazole derivatives and assessed their bioactivity as antibacterial and antifungal agents. The main reactants for synthesis of these agents are α-bromoketones, chalcones and thiosemicarbazides. The reactions differed in solvent, order of addition of reactants and whether the reaction was one-pot or multistep.

Dawane and his team had used PEG-400 as a solvent in the reaction of *p*-chlorophenacyl bromide **172** with thiosemicarbazide **173** to afford 4-(4-chlorophenyl)-2-hydrazinylthiazole **174**, which in turn reacted with different chalcones **175** in PEG-400 in presence of sodium hydroxide to yield a series of active antimicrobial compounds (Scheme 37). One of these compounds is **176** (MIC 25 µg/mL) which was equipotent to Tetracycline against all tested bacterial strains including *E. coli*, *S. aureus* and *B. subtilis*. It was also equipotent to Nystatin against all tested fungal strains including *A. niger*, *Trichoderma virdea*, *C. albicans*, *Penicillium chrysogenum* and *Fusarium moniliforme*.[81]



Scheme 37. Synthesis of 2-(4,5-dihydro-1*H*-pyrazol-1-yl)thiazole **176**

Ansari and Khan started first by the reaction of chalcones **177** with thiosemicarbazide to give 4,5-dihydro-1*H*-pyrazole-1-carbothioamide derivatives **178** which then reacted with α-bromoketones **179** to afford a series of (4,5-dihydro-1*H*-pyrazol-1-yl)thiazoles (Scheme 38). Among this series fluorinated **180** was the most active against Gram-positive bacteria (MIC 50 µg/mL) including *S. aureus*, *E. faecalis*, *S. epidermidis*, *B. subtilis* and *B. cereus*. and against Gram-negative bacteria (MIC 50-75 µg/mL) including *E. coli*, *P. aeruginosa*, *K. pneumonia*, *B. bronchiseptica* and *P. vulgaris*. In addition to its antifungal activity (MIC 50 µg/mL) against *C. albicans*, *A. niger*, *A. flavus*, *M. purpureous* and *P. citrinum*.[82]



Scheme 38. Synthesis of 2-(4,5-dihydro-1*H*-pyrazol-1-yl)thiazole **180**

Furthermore, Bondock and Fouda synthesized 2-(4,5-dihydro-1*H*-pyrazol-1-yl)-5-phenylthiazoles via one-pot reaction by refluxing chalcone, phenacyl bromide and thiosemicarbazide in ethanol in presence of small amount of conc. HCl. The synthesized **181** (Figure 51) was equipotent to Ampicillin against *S. pneumoniae* (MIC 0.12 µg/mL). Also, it exhibited antimicrobial activity against *B. subtilis* (MIC 1.95 µg/mL), *S. epidermidis* (MIC 7.81 µg/mL), and *E. coli* (MIC 31.25 µg/mL).[43]

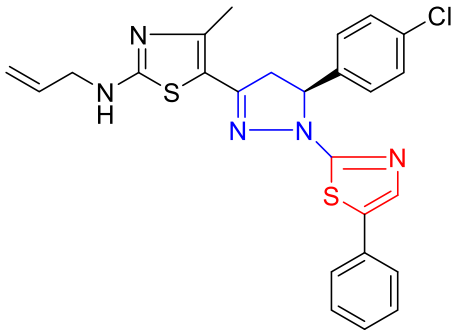


Figure 51. 2-(4,5-Dihydro-1*H*-pyrazol-1-yl)-5-phenylthiazole **181**

Another (4,5-dihydro-1*H*-pyrazol-1-yl)thiazole derivative **182** (Figure 52) showed antimicrobial activity against several bacterial and fungal strains including *S. aureus*, *P. vulgaris*, *B. subtilis*, *P. aeruginosa*, *C. albicans* and *E. coli*.[83]

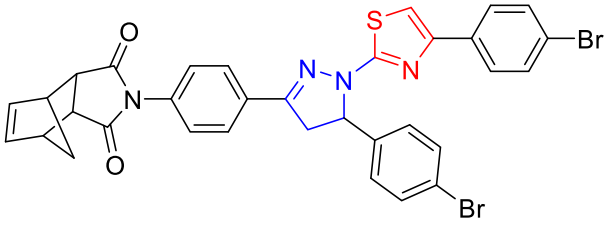


Figure 52. 2-(4,5-Dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazole **182**

Gautam *et al.* succeeded to synthesize a series of (4,5-dihydro-1*H*-pyrazol-1-yl)thiazoles by one step condensation of 2-benzylidene-1-tetralones, thiosemicarbazide and phenacyl bromides in presence of trifluoroethanol and conc. HCl. **183** (Figure 53) showed comparable microbial growth inhibition to both **S**treptomycin and Ketoconazole against *S. aureus*, *P. aeruginosa*, *C. albicans*, and *Aspergillus niger*.[84]

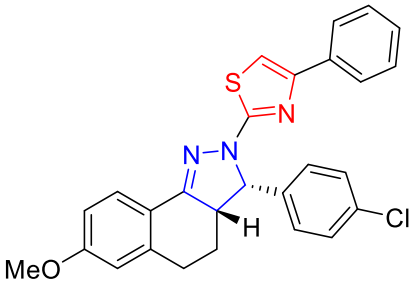


Figure 53. 2-(4,5-Dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazole **183**

Recently, Elewa *et al.* synthesized another series of (4,5-dihydro-1*H*-pyrazol-1-yl)thiazole derivatives. **184** (MIC 1.25 µg/mL) (Figure 54) displayed comparable antibacterial activity to Amoxicillin against *S. aureus* and it exhibited higher antifungal activity than Griseofulvin against *A. fumigatus*.[85]

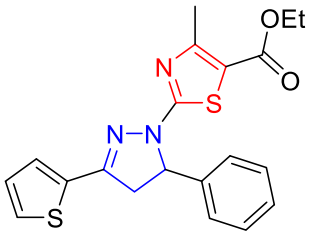
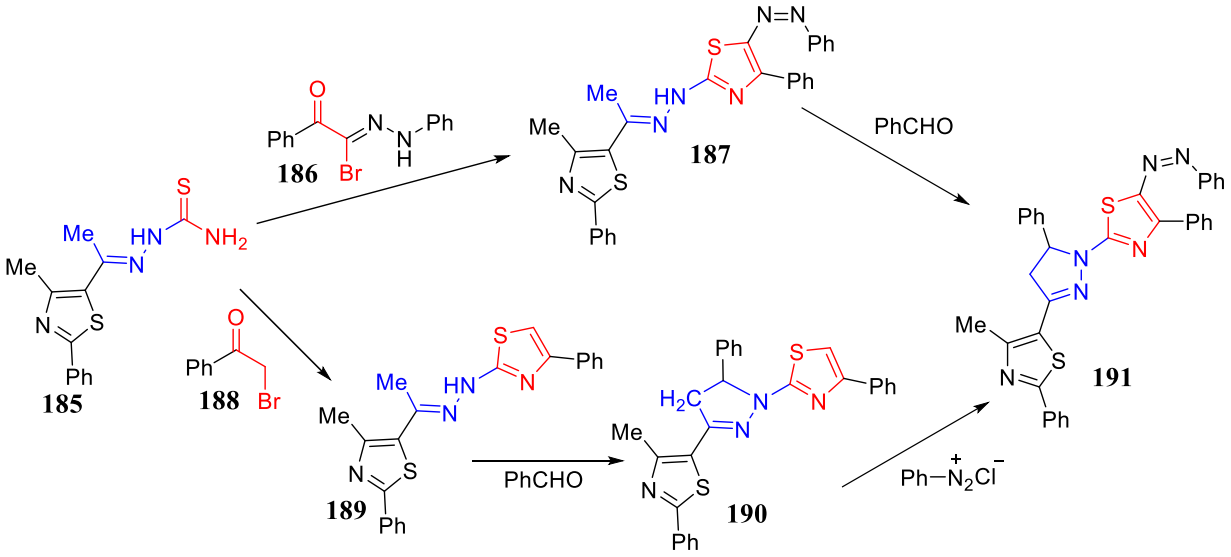


Figure 54. Ethyl 2-(4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carboxylate **184**

Abdelhamid and his colleagues synthesized 2-(4,5-dihydro-1*H*-pyrazol-1-yl)-5-(phenyldiazenyl)thiazole derivative **191** by two different pathways (Scheme 39). The first one was to react thiosemicarbazone **185** with 2-oxo-*N*,2-diphenylacetohydrazonoyl bromide **186** followed by cyclization by condensation with benzaldehyde with the produced 2-hydrazinyl-5-(phenyldiazenyl)thiazole **187**. The second method was to react phenacyl bromide **188** with thiosemicarbazone **185** to yield 2-hydrazinylthiazole derivative **189** which condensed with benzaldehyde to form 2-(5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole derivative **190** which finally react through its active methylene with phenyldiazonium chloride.[86]



Scheme 39. Synthesis of 2-(4,5-dihydro-1*H*-pyrazol-1-yl)-5-(phenyldiazenyl)thiazole **191**

192 (Figure 55) was the most active antimicrobial compound among a series of 2-(4,5-dihydro-1*H*-pyrazol-1-yl)-5-diazenylthiazoles which were recently synthesized and evaluated for antibacterial and antifungal activity.[85]

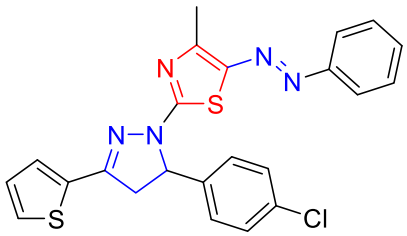
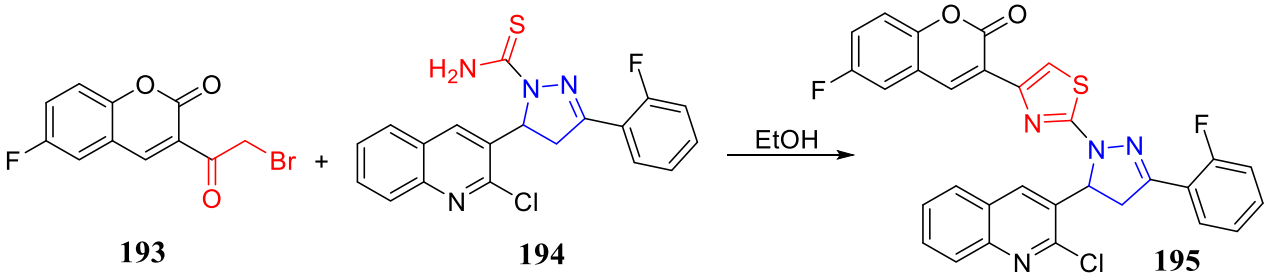


Figure 55. 2-(4,5-Dihydro-1*H*-pyrazol-1-yl)-5-diazenylthiazole **192**

When substituted thiosemicarbazide is involved in cyclic form like pyrazole-1-carbothioamide **194** reacts with α-bromoketone **193**, it will yield pyrazolylthiazole derivative **195** (Scheme 40). It exhibited antibacterial activity (MIC 50 µg/mL) against *S. aureus*, *E. faecalis*, *S. epidermidis*, *B. subtilis*, and *B. cereus*.[82]



Scheme 40. Synthesis of 2-(4,5-dihydro-1*H*-pyrazol-1-yl)thiazole **195**

By the same method, Aggarwal *et al.* synthesized a series of (*R*)-1-(thiazol-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazol-5-ol derivatives. **196** (Figure 56) was the most active antibacterial compound against *S. aureus* (MIC 16 μg/mL), *S. epidermidis* (MIC 64 μg/mL), *K. aerogenes* (MIC 8 μg/mL), *E. coli* (MIC 2 μg/mL), *P. mirabilis* (MIC 4 μg/mL), and *P. aeruginosa* (MIC 32 μg/mL).[87]

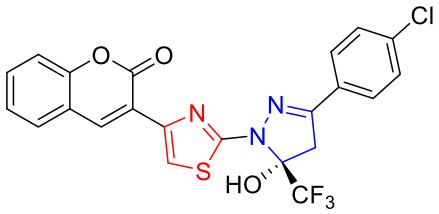


Figure56. (*R*)-1-(Thiazol-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazol-5-ol **196**

The structurally related 2-(1*H*-pyrazol-1-yl)thiazoles were also synthesized and evaluated for their antimicrobial activity. In 2015, Kumar *et al.* refluxed the previously mentioned (*R*)-1-(thiazol-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazol-5-ol derivatives with sodium carbonate in ethanol to afford 2-(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)thiazoles. **197** (Figure 57) exhibited antibacterial activity against both *S. aureus* (MIC 32 μg/mL), and *B. subtilis* (MIC 32 μg/mL).[88]

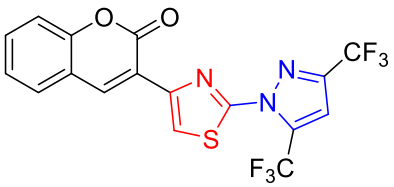
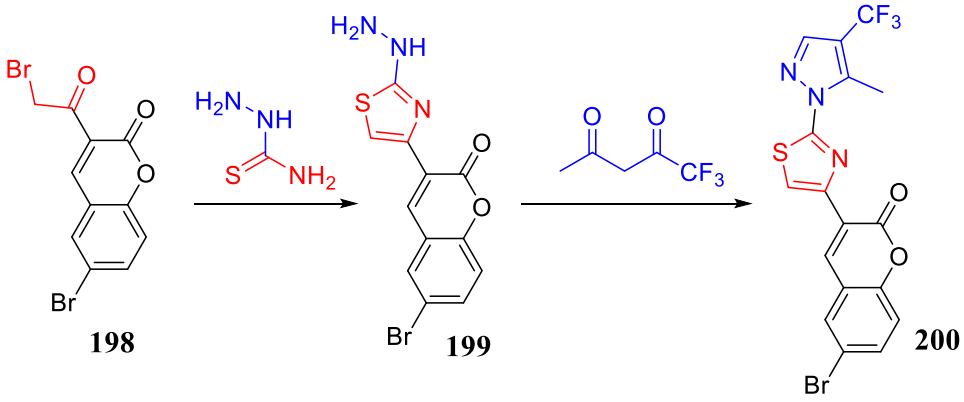


Figure 57. 2-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)thiazole **197**

Reaction of α-bromoketone **198** with thiosemicarbazide afforded 2-hydrazinylthiazole **199** (Scheme 41), which reacted with trifluoroacetylacetone to give 2-(5-methyl-4-(trifluoromethyl)-1*H*-pyrazol-1-yl)thiazole derivative **200**, showed comparable bacterial growth inhibition to Cephalothin against *P. aeruginosa*.[58]



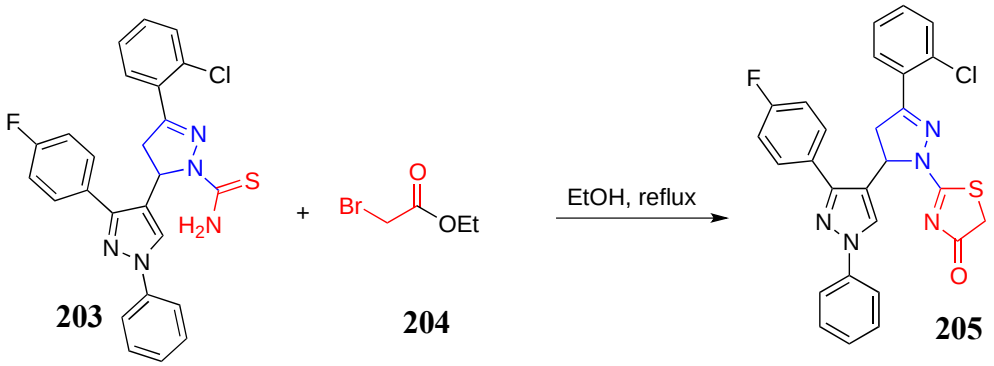
Scheme 41. Synthesis of 2-(5-methyl-4-(trifluoromethyl)-1*H*-pyrazol-1-yl)thiazole **200**

By totally different method, Gaikwad *et al.* reacted 2-(2-alkylidenehydrazinyl)thiazoles **201** with phosphorus oxychloride in DMF to yield 1-thiazol-2-yl-1*H*-pyrazole-4-carbaldehyde derivative **202** (Scheme 42). It showed antimicrobial activity (MIC 128 µg/mL) against *E. coli*, *P. aeruginosa*, *A. niger*, and *C. albicans*.[36]

Scheme 42. Synthesis of 1-thiazol-2-yl-1*H*-pyrazole-4-carbaldehyde **202**

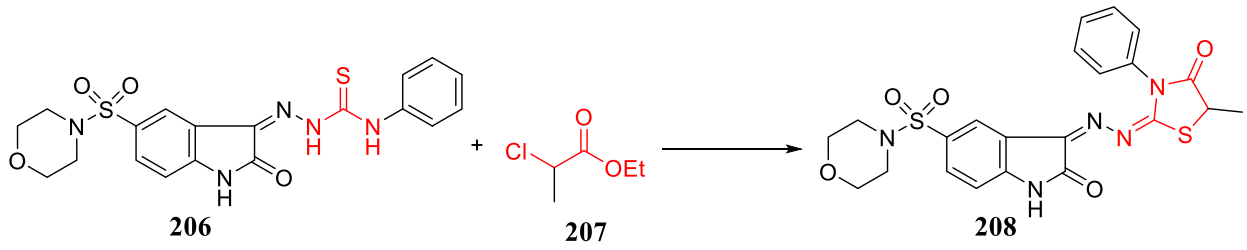
12. SYNTHESIS OF THIAZOL-4(5*H*)-ONES AND THIAZOLIDINE-2,4-DIONES

Reaction of thiourea derivatives with α-haloesters rather than α-haloketones afforded thiazol-4(5*H*)-ones. Reaction of 4,5-dihydro-1*H*-pyrazole-1-carbothioamides **203** with ethyl bromoacetate **204** yielded 2-(4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one derivatives (Scheme 43). **205** (MIC 25-100 µg/mL) was more potent than Ampicillin against *E. coli*, *S. aureus* and *S. pyogenes* and equipotent against *P. aeruginosa*. In addition, it was more potent than Griseofulvin against *C. albicans*, *A. niger* and *A. clavatus*.[89]



Scheme 43. Synthesis of 2-(4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one **205**

Reaction of *N*-substituted thiosemicarbazones **206** with ethyl 2-chloropropanoate **207** afforded 5-methyl-2-hydrazono-3-phenylthiazolidin-4-one derivatives (Scheme 44). **208** was more potent than Ampicillin against both *S. aureus* (MIC 0.03 µg/mL) and *S. epidermidis* (MIC 0.12 µg/mL), equipotent to Ampicillin against *S. flexneri* (MIC 0.49 µg/mL) and it was less potent than Ampicillin against *B. subtilis* (MIC 0.03 µg/mL), *P. vulgaris* (MIC 3.9 µg/mL), and *K. pneumonia* (MIC 0.98 µg/mL). Moreover, it was more potent than Amphotericin B against *G. candidum* (MIC 0.12 µg/mL) and it was equipotent to Amphotericin B against both *A. fumigatus* (MIC 0.98 µg/mL) and *A. clavatus* (MIC 1.95 µg/mL).[76]



Scheme 44. Synthesis of 5-methyl-2-hydrazono-3-phenylthiazolidin-4-one **208**

Antibacterial derivatives, 2-(2-benzylidenehydrazinyl)thiazol-4(5*H*)-one **209** and 2-(2-benzylidenehydrazinyl)-5-(2-phenylhydrazone)thiazol-4(5*H*)-one **210** (Figure 58) were obtained by the reaction of thiosemicarbazone with ethyl 2-chloroacetate and ethyl 2-chloro-2-(2-phenylhydrazono)acetate respectively.[58]

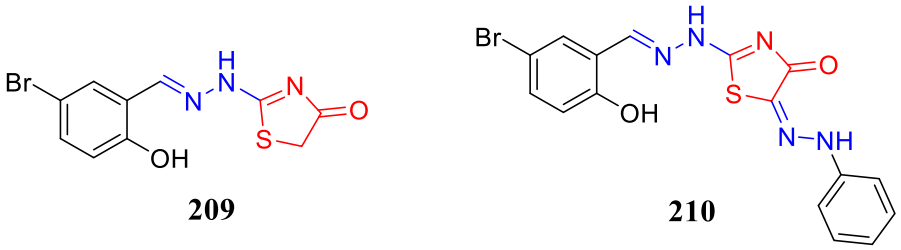
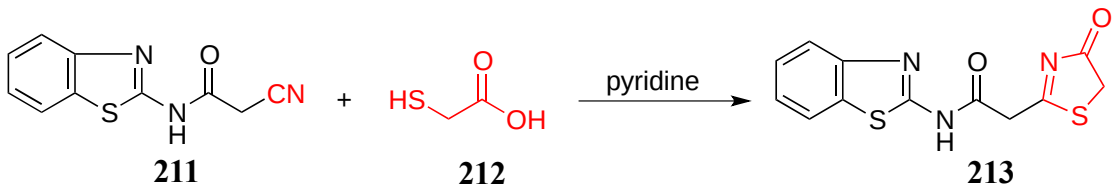


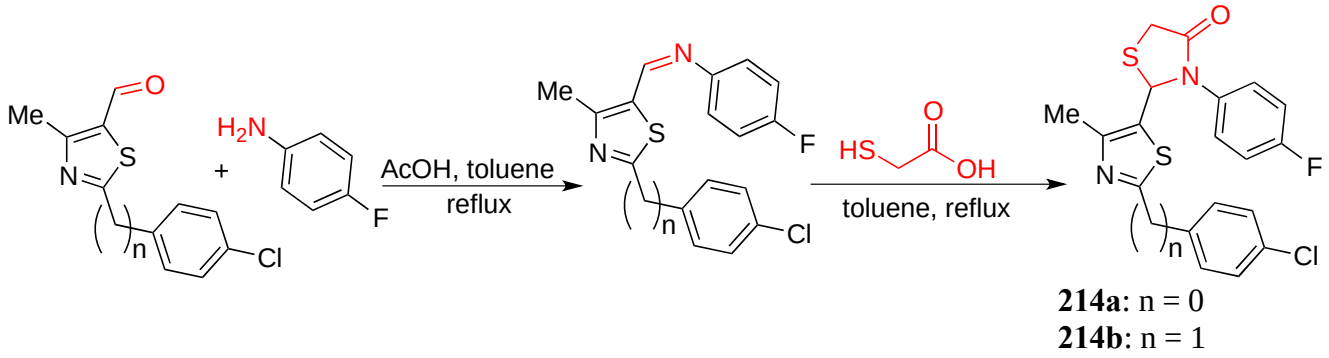
Figure 58. 2-(2-Benzylidenehydrazinyl)thiazol-4(5*H*)-one **209** and 2-(2-benzylidenehydrazinyl)-5-(2-phenylhydrazono)thiazol-4(5*H*)-one **210**

Thioglycolic acid is another key start for synthesis of thiazolidin-4-ones and thiazol-4(5*H*)-ones. Reaction of cyanoacetamide derivative **211** with thioglycolic acid **212** in pyridine yields 4-oxo-4,5-dihydrothiazole derivative **213** (Scheme 45). **213** was equipotent to both Chloramphenicol and Cephalothin against a Gram-negative strain *P. fluorescens* (MIC 6.25 µg/mL). In addition, it showed antimicrobial activity against *S. aureus* (MIC 25 µg/mL), *S. pyogenes* (MIC 25 µg/mL), *P. phaseolicola* (MIC 100 µg/mL), *F. oxysporum* (MIC 100 µg/mL), and *A. fumigatus* (MIC 50 µg/mL).[45]



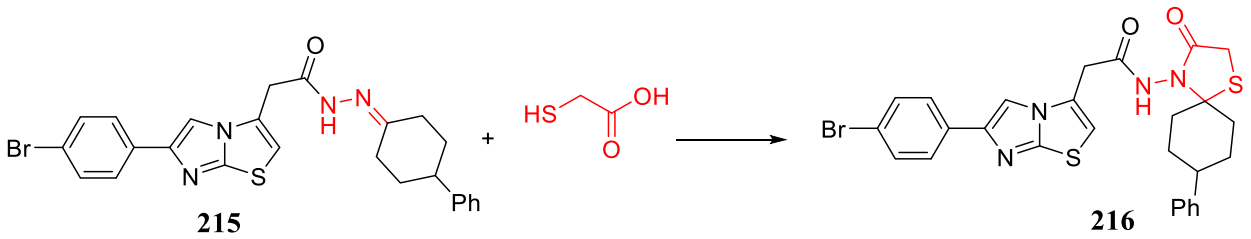
Scheme 45. Synthesis of 4-oxo-4,5-dihydrothiazole **213**

By the same method, Shelke *et al.* synthesized a series of 3-phenyl-2-(thiazol-5-yl)thiazolidin-4-ones and evaluated the antimicrobial activity (Scheme 46). **214a** (n = 0) was the most active antibacterial compound against both *E. coli* (MIC 6.25 µg/mL) and *S. aureus* (MIC 12.5 µg/mL). While **214b** (n = 1) was the most active antifungal compound (MIC 6.25 µg/mL) against *C. albicans* and *A. niger*.[90]



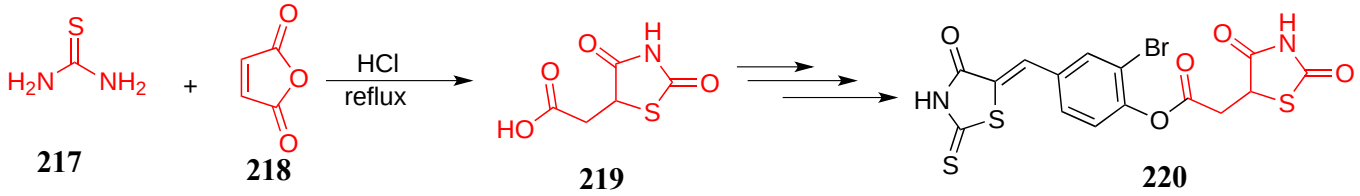
Scheme 46. 2-(Thiazol-5-yl)-3-(4-fluorophenyl)thiazolidin-4-ones **214a**,**b**

Reaction of thioglycolic acid with *N*′-cyclohexylideneacetohydrazide derivative **215** afforded spiro-thiazolidin-4-one derivative **216** (Scheme 47). **216** showed antimycobacterial activity (MIC 0.854 μg/mL).[91]



Scheme 47. Synthesis of spiro-thiazolidin-4-one **216**

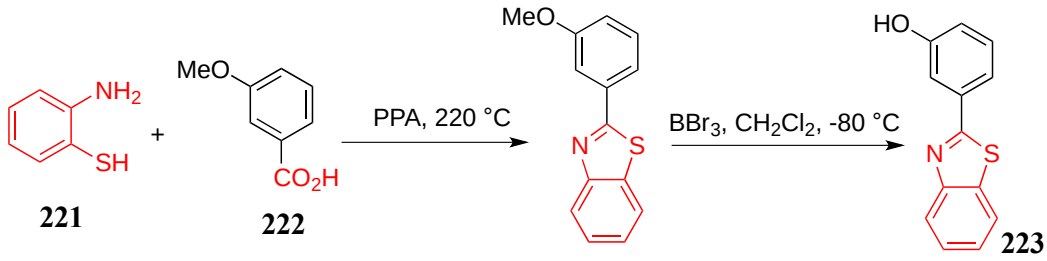
Through a unique pathway, reaction of thiourea **217** with maleic anhydride **218** afforded 2,4-dioxothiazolidin-5-ylacetic acid **219** (Scheme 48). After multistep synthesis, a series of antibacterial 2,4-dioxo-1,3-thiazolidin-5-ylacetate esters was synthesized by Trotsko team. **220** is one of the most active compounds with antibacterial activity against Gram-positive bacteria including *S. aureus* (MIC 31.25 μg/mL), *S. epidermidis* (MIC 125 μg/mL), *B. subtilis* (MIC 62.5 μg/mL), *B. cereus* (MIC 62.5 μg/mL), and *Micrococcus luteus* (MIC 125 μg/mL) but showed no activity against a Gram-negative strain *Proteus mirabilis*.[92]



Scheme 48. Synthesis of 2,4-dioxo-1,3-thiazolidin-5-ylacetate ester **220**

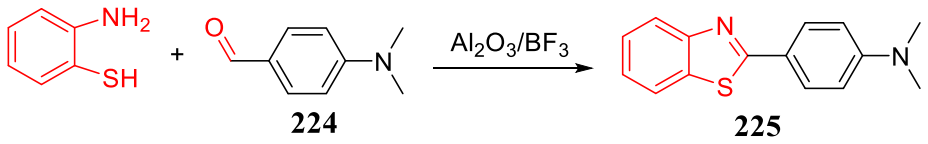
13. SYNTHESIS OF BENZOTHIAZOLES

2-Aminothiophenol is used by many research teams to synthesize benzothiazole-derived antimicrobial agents. Sadek *et al.* succeeded to synthesize benzimidazole derivative 2-phenylbenzothiazole **223** by heating 2-aminothiophenol **221** with substituted benzoic acid **222** in polyphosphoric acid followed by demethylation by boron tribromide (Scheme 49). **223** displayed antimicrobial activity against *S. aureus* (MIC 50 µg/mL), *E. coli* (MIC 75 µg/mL) and *A. niger* (MIC 50 µg/mL).[34]



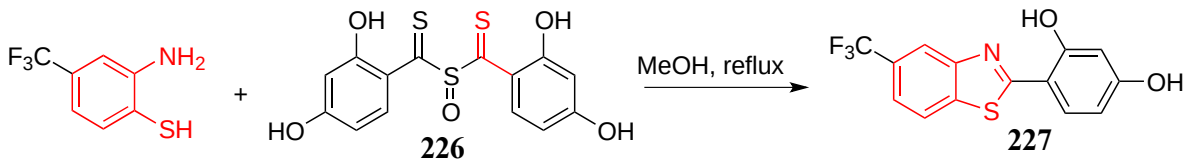
Scheme 49. Synthesis of 2-phenylbenzothiazole **223**

Similarly, benzothiazole antibacterial agents were synthesized by reacting 2-aminothiophenol with appropriate aldehyde **224** using nano-γ-Al_2O_3/BF_3 as a catalyst (Scheme 50). **225** showed antifungal activity against a broad range of strains including *C. albicans*, *C. dubliniensis*, *C. glabrata*, *C. parapilopsis*, *C. tropicalis*, *A. clavatus*, *Exophiala dermatitidis*, *M. canis*, *T. rubrum*, *E. flucusom* with MIC value 8-64 µg/mL.[93]



Scheme 50. Synthesis of 2-phenylbenzothiazole **225**

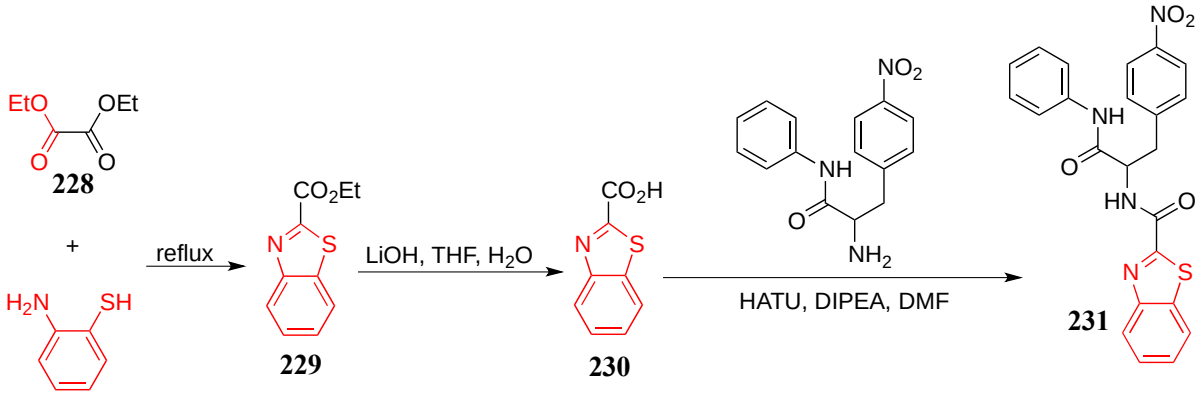
2-Phenylbenzothiazoles were also synthesized by the raction of 2-aminothiophenol with sulfinylbis((2,4-dihydroxyphenyl)methanethione) **226** (Scheme 51). **227** showed antibacterial activity against *S. epidermidis* (MIC 12.5 µg/mL), *S. aureus* (MIC 12.5 µg/mL), *B. subtilis* (MIC 12.5 µg/mL), and *M. luteus* (MIC 6.25 µg/mL).[94]



Scheme 51. Synthesis of 2-phenylbenzothiazole **227**

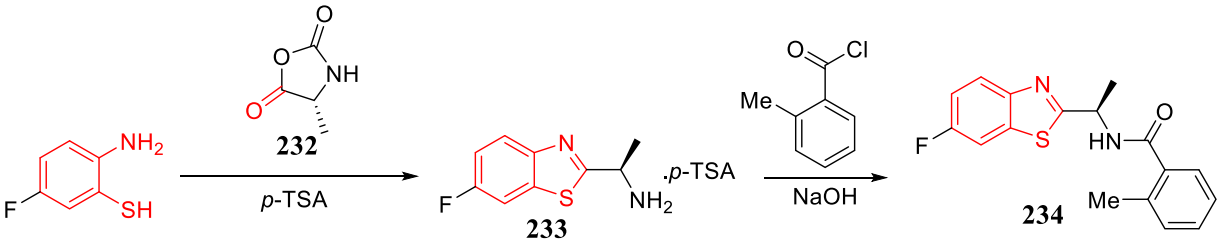
Ethyl benzothiazole-2-carboxylate **229** was synthesized by refluxing *o*-aminothiophenol with diethyl oxalate **228** (Scheme 52) which was hydrolyzed to corresponding acid **230**. Amidation of acid **230** was

achieved by reaction with amine using HATU as coupling agent and DIPEA as base to afford benzothiazole-2-carboxamides. **231** exhibited a comparable bacterial growth inhibition to Chloramphenicol against *S. aureus*.[95]



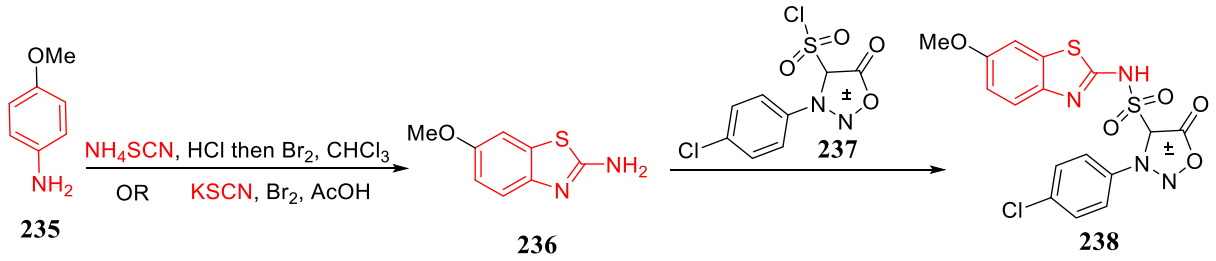
Scheme 52. Synthesis of benzothiazole-2-carboxamide **231**

Reaction of *D*-alanine with phosgene gave a reactive compound, (*R*)-4-methyloxazolidine-2,5-dione **232** which was utilized to synthesize (*R*)-1-(6-fluorobenzo[*d*]thiazol-2-yl)ethan-1-amine **234** by reaction with 2-amino-5-fluorothiophenol (Scheme 53). The reaction of benzothiazole derivative **233** with 2-methylbenzoyl chloride yielded **234** which showed antibacterial activity. Furthermore, it showed a comparable antifungal activity to Amphotericin B against *C. albicans* (MIC 50 µg/mL), *C. glabrata* (MIC 25 µg/mL), and *C. tropicalis* (MIC 50 µg/mL).[96]



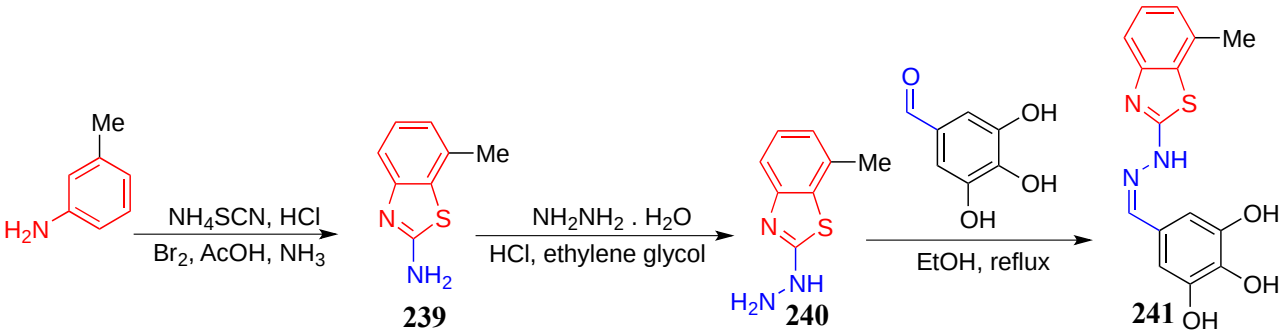
Scheme 53. Synthesis of (*R*)-1-(6-fluorobenzo[*d*]thiazol-2-yl)ethan-1-amine **234**

Asundaria and Patel had synthesized 2-aminobenzothiazoles by two methods, the first is by reaction of different anilines **235** with ammonium thiocyanate in presence of HCl to afford *N*-phenylthiourea which was then was cyclized by stirring with bromine in chloroform. The second method is one step reaction of anilines with potassium thiocyanate and bromine in acetic acid. The yielded 2-aminobenzothiazoles **236** reacted with 4-(chlorosulfonyl)sydnones **237** to give antibacterial derivatives (Scheme 54). **238** showed antibacterial activity against *S. aureus* (MIC 64 µg/mL), *B. subtilis* (MIC 16 µg/mL), *E. coli* (MIC 32 µg/mL), and *P. aeruginosa* (MIC 32 µg/mL).[97]



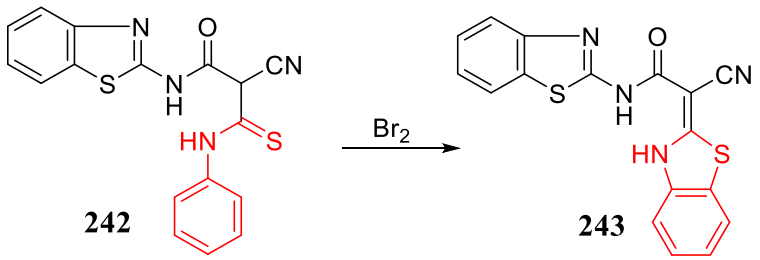
Scheme 54. Synthesis of *N*-(benzothiazol-2-yl)-5-oxo-1,2,3-oxadiazolidine-4-sulfonamide **238**

Zha *et al.* succeeded to synthesize 2-methylenehydrazinylbenzothiazole derivatives by totally different method. Firstly, 2-aminobenzothiazole **239** was reacted with hydrazine hydrate in ethylene glycol in presence of HCl to give the corresponding 2-hydrazinylbenthothiazole **240** (Scheme 55), which then reacted with different aliphatic and (hetero)aromatic aldehydes to afford the 2-methylenehydrazinylbenzothiazole. **241** was more potent than Chloramphenicol against *S. aureus*, *B. subtilis*, *E. coli*, *K. pneumoniae*, and *MRSA* with MIC values 15-24 µg/mL. It was also more potent than Ketoconazole against *A. niger*, *F. moniliforme*, and *F. oxysporum* with MIC values 22-28 µg/mL.[98]



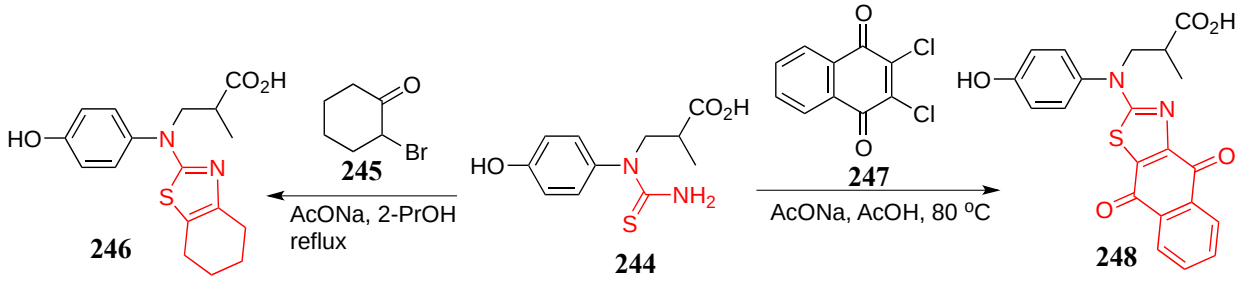
Scheme 55. Synthesis of 2-methylenehydrazinylbenzothiazole **241**

Bondock *et al.* were able to cyclize 3-(phenylamino)-3-thioxopropanamide derivative **242** into 2-(benzo[*d*]thiazol-2(3*H*)-ylidene)acetamide derivative **243** by reaction with bromine in ethyl acetate in presence of pyridine (Scheme 56). **243** showed antibacterial activity against Gram-positive bacteria including *S. aureus* and *S. pyogenes* with MIC values 25 µg/mL for both strains. But it showed less activity against both Gram-negative bacteria and fungi.[45]



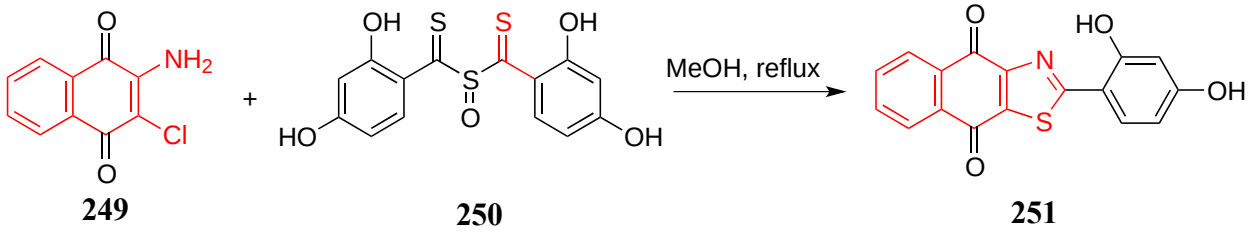
Scheme 56. Synthesis of 2-(benzo[*d*]thiazol-2(3*H*)-ylidene)acetamide **243**

Parašotas *et al.* synthesized new series of antibacterial agents (Scheme 57) through reaction of *N*,*N*-disubstituted thiourea derivative **244** with 2-bromocyclohexan-1-one **245** to yield *N*,*N*-disubstituted (4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-yl)amine **246**. Reaction of *N*,*N*-disubstituted thiourea derivative **244** with 2,3-dichloronaphthalene-1,4-dione **247** gave *N*,*N*-disubstituted (4,9-dioxo-4,9-dihydronaphtho[2,3-*d*]thiazol-2-yl)amine **248**.[99]



Scheme 57. Synthesis of *N*,*N*-disubstituted (4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-yl)amine **246** and *N*,*N*-disubstituted (4,9-dioxo-4,9-dihydronaphtho[2,3-*d*]thiazol-2-yl)amine **248**

Synthesis of benzothiazole was also achieved by reaction of 2-amino-3-chloronaphthalene-1,4-dione **249** with sulfinylbis((2,4-dihydroxyphenyl)methanethione) **250** (Scheme 58). **251** was more potent than Ampicillin against all tested strains including *S. epidermidis* (MIC 0.78 µg/mL), *S. aureus* (MIC 0.78 µg/mL), *B. subtilis* (MIC 0.78 µg/mL), and *M. luteus* (MIC 0.156 µg/mL).[94]



Scheme 58. Synthesis of 2-(2,4-dihydroxyphenyl)naphtho[2,3-*d*]thiazole-4,9-dione **251**

A benzothiazole derivative **251** (Figure 59) showed antibacterial activity against highly resistant strains including *MRSA* (MIC 1.5 µg/mL), *VREF* (MIC 1.5 µg/mL), and *NDM-1 E. coli* (MIC 3 µg/mL), and multidrug resistant *P. aeruginosa* (MIC 6 µg/mL) through its ability to disturb FtsZ protein.[100]

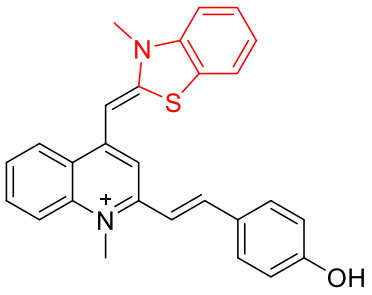
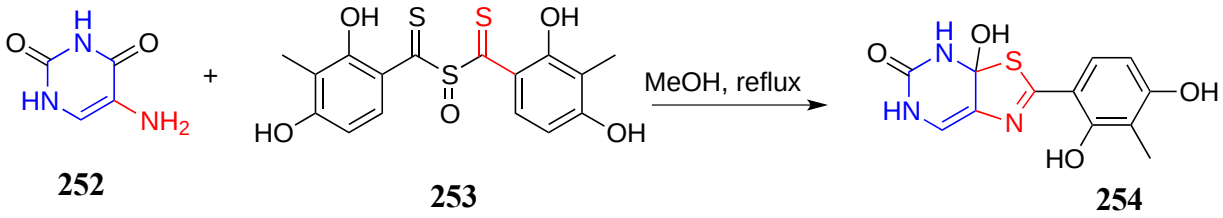


Figure 59. 2-(Quinolin-4-yl)methylene)-2,3-dihydrobenzo[*d*]thiazole **251**

14. SYNTHESIS OF HETEROCYCLOTHIAZOLES

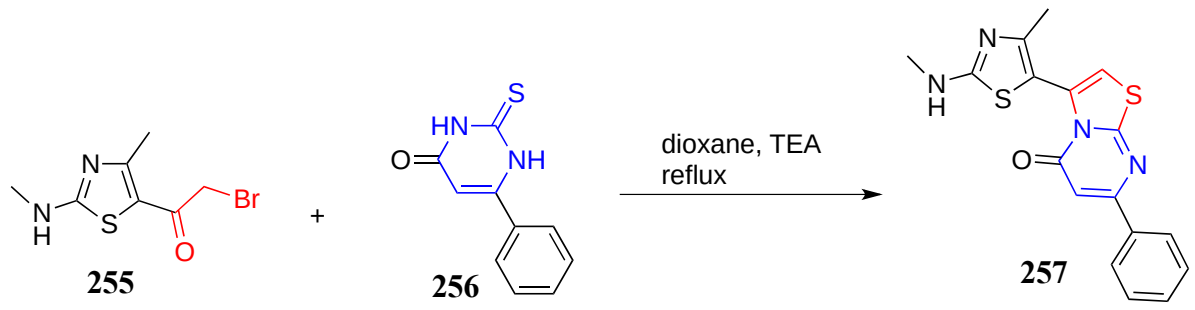
Reaction of 5-aminopyrimidine-2,4(1*H*,3*H*)-dione **252** with sulfinylbis((2,4-dihydroxy-3-methylphenyl)methanethione) **253** afforded 3a-hydroxy-3a,6-dihydrothiazolo[5,4-*d*]pyrimidin-5(4*H*)-one derivative **254** (Scheme 59). **254** was more potent than Ampicillin against *M. luteus* (MIC 3.13 μg/mL). Furthermore, it was equipotent to Ampicillin against *S. epidermidis* (MIC 6.25 μg/mL), *S. aureus* (MIC 3.13 μg/mL), and *B. subtilis* (MIC 3.13 μg/mL).[94]



252 **253** **254**

Scheme 59. Synthesis of 3a-hydroxy-3a,6-dihydrothiazolo[5,4-*d*]pyrimidin-5(4*H*)-one **254**

When thiourea is incorporated in cyclic form it gives a bicyclothiazole structure, as an example reaction of 2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one derivative **256** with α-bromoketone **255** gives thiazolo[3,2-*a*]pyrimidin-5-one **257** (Scheme 60). **257** was equipotent to Amphotericin B in its antifungal activity against both *A. niger* (MIC 0.98 μg/mL) and *Geotricum candidum* (MIC 0.49 μg/mL). Additionally, its antibacterial activity against Gram-positive strains **257** was equipotent to Ampicillin against both *S. aureus* (MIC 0.98 μg/mL) and *S. epidermidis* (MIC 1.95 μg/mL). Comparing to Gentamicin, **257** showed similar potency against both *E. coli* (MIC 0.49 μg/mL) and *K. pneumoniae* (MIC 0.98 μg/mL).[59]



255 **256** **257**

Scheme 60. Synthesis of thiazolo[3,2-*a*]pyrimidin-5-one **257**

A 6,7,8,9-tetrahydro-5*H*-thiazolo[2,3-*b*]quinazoline derivative **258** (Figure 60) showed remarkable MIC and MBC values when compared to both Ampicillin and Ciprofloxacin against *S. aureus* (MIC 1 μg/mL), *B. subtilis* (MIC 1 μg/mL), *M. luteus* (MIC 2 μg/mL), *E. coli* (MIC 2 μg/mL), and *P. aeruginosa* (MIC 4 μg/mL).[101]

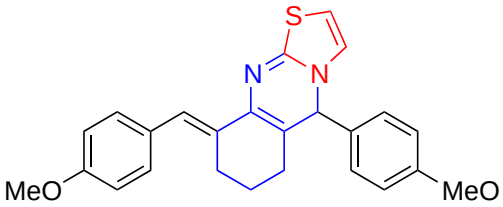
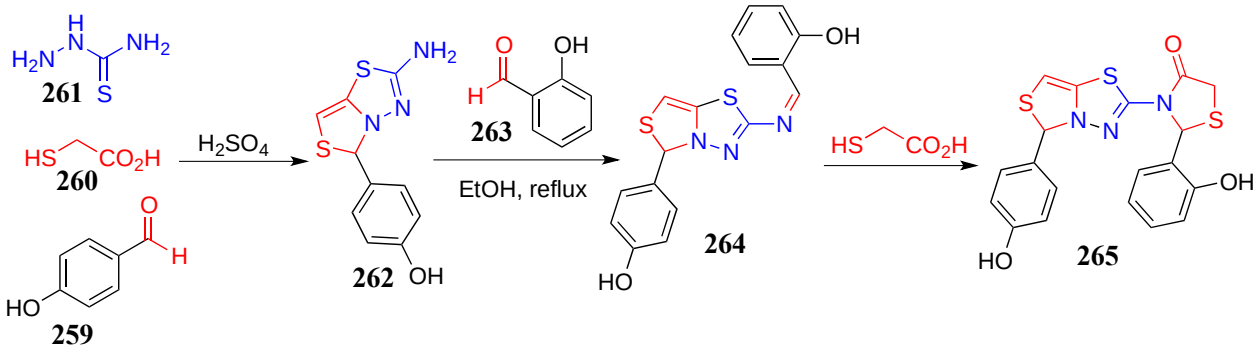


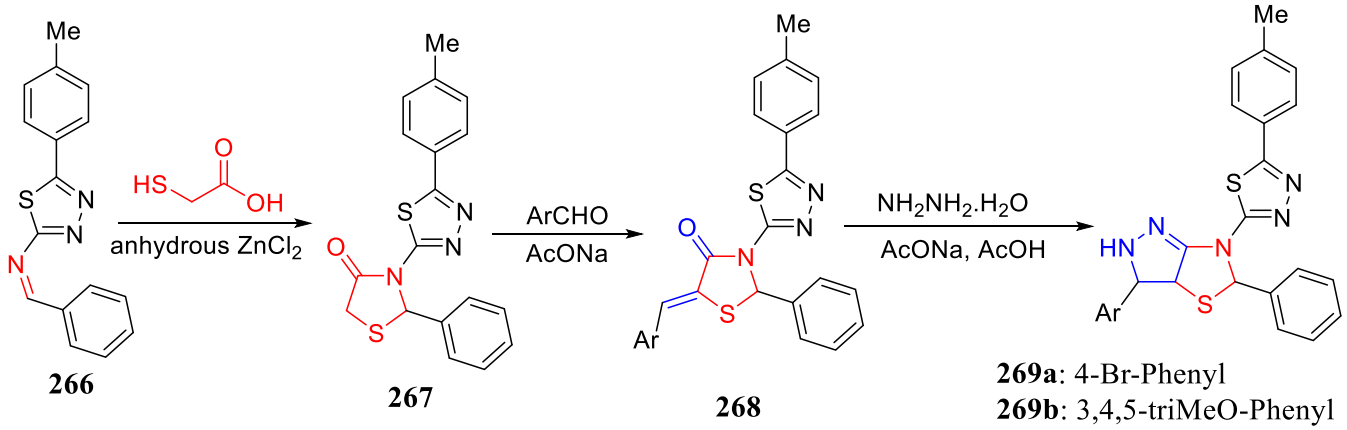
Figure 60. 6,7,8,9-Tetrahydro-5*H*-thiazolo[2,3-*b*]quinazoline **258**

5*H*-Thiazolo[4,3-*b*][1,3,4]thiadiazol-2-amine derivative **262** was synthesized by a three components one-pot reaction between *p*-hydroxybenzaldehyde **259**, thioglycolic acid **260** and thiosemicarbazide **261** (Scheme 61). The product **262** was reacted with *o*-hydroxybenzaldehyde **263** to yield a Schiff base **264** which cyclized using thioglycolic acid to form 3-(5*H*-thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl)thiazolidin-4-one derivative **265**. Both **264** and **265** displayed more antitubercular activity than Streptomycin and similar to that of Pyrazinamide with MIC 3.125 µg/mL for both compounds.[102]



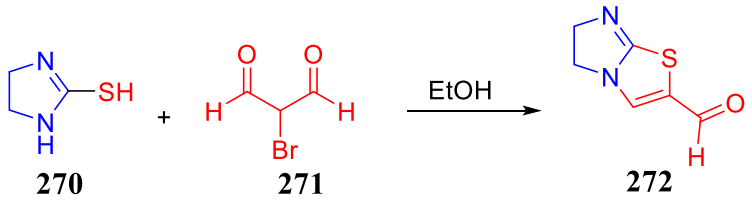
Scheme 61. Synthesis of Schiff base **264** and
3-(5*H*-thiazolo[4,3-*b*][1,3,4]thiadiazol-2-yl)thiazolidin-4-one **265**

Seelam and Shrivastava used anhydrous zinc chloride to cyclize Schiff base **266** by thioglycolic acid to form thiazolidin-4-one intermediate **267** (Scheme 62). By Knoevenagel condensation, thiazolidin-4-one reacted with different substituted benzaldehyde to afford 5-benzylidenethiazolidin-4-one derivatives **268**, which in turn reacted with hydrazine hydrate to give 3-phenyl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*]thiazoles **269a,b**. **269a** (Ar = 4-bromophenyl) (MIC 3.125 µg/mL) was more potent than Streptomycin against *B. thuringiensis*, *E. coli*, and *P. aeruginosa* and it was equipotent to Streptomycin against *B. subtilis*. Furthermore, **269a** (MIC 3.125 µg/mL) exhibited the highest antitubercular activity among all tested compounds. On the other hand, **269b** (Ar = 3,4,5-trimethoxyphenyl) (MIC 3.125 µg/mL) was equipotent to Treflucan against *C. albicans*, *B. fabae*, and *F. oxysporam*.[103]



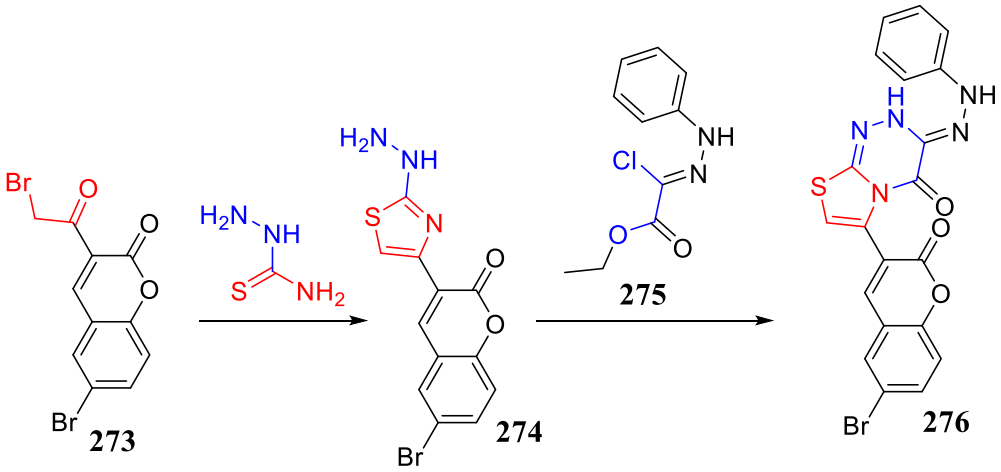
Scheme 62. Synthesis of 3-phenyl-3,3a,5,6-tetrahydro-2*H*-pyrazolo[3,4-*d*]thiazoles **269a,b**

Antibacterial agent 5,6-dihydroimidazo[2,1-*b*]thiazole-2-carbaldehyde **272** was synthesized by the reaction of imidazolidine-2-thione **270** with malonaldehyde **271** in ethanol (Scheme 63).[104]



Scheme 63. Synthesis of 5,6-dihydroimidazo[2,1-*b*]thiazole-2-carbaldehyde **272**

Reaction of α-bromoketone **273** with thiosemicarbazide afforded 2-hydrazinylthiazole **274** (Scheme 64). 2-Hydrazinylthiazole **274** was reacted with 2-chloro-2-hydrazonoacetate derivative **275** to yield 3-hydrazono-2,3-dihydro-4*H*-thiazolo[2,3-*c*][1,2,4]triazin-4-one **276** which showed antimicrobial activity against both *E. faecalis* and *P. aeruginosa*.[58]



Scheme 64. Synthesis of 3-hydrazono-2,3-dihydro-4*H*-thiazolo[2,3-*c*][1,2,4]triazin-4-one **276**

15. CONCLUSION

The aforementioned structurally related groups of thiazole derivatives showed promising antimicrobial activity including antibacterial, antimycobacterial and antifungal activities. The 4-triazolylmethylthiazole derivative, **4** was more potent than Rifampicin against *Mycobacterium bovis* (IC_{50} 0.03 μg/mL). The 2-phenylthiazole hydrazinecarboximidamide derivative, **14** showed antibacterial activity against *MRSA* (MIC 1.3 μg/mL). The thiazole/fluoroquinolone hybrid, **38** was more potent than ciprofloxacin against *Pseudomonas aeruginosa* (MIC 1.56 μg/mL). The 2-pyridinylthiazole derivative, **53** was more potent than Cefepime against *Bacillus cereus* (MIC 0.01 μg/mL). The 2-phenylaminothiazole derivative, **69** showed more potent antifungal activity than Nystatin against *Aspergillus niger* with (MIC 0.9 μg/mL). The 3-thiazolylpyrazole-1-carbothioamide derivative, **79** was more potent than Ampicillin against both *Streptococcus pneumoniae* (MIC 0.03 μg/mL) and *Bacillis subtilis* (MIC 0.06 μg/mL). The 2-arylidenehydrazinylthiazole, **100** was more potent than Fluconazole against *Candida albicans* (MIC 0.125 μg/mL). Another 2-arylidenehydrazinylthiazole, **103** was more potent than both Ciprofloxacin and Sulbactam/penicillin against *Klebsiella pneumoniae* (MIC 0.06 μg/mL). The benzothiazole derivative, **251** showed antibacterial activity against highly resistant strains including *MRSA* (MIC 1.5 μg/mL), *VREF* (MIC 1.5 μg/mL), and *NDM-1 Escherichia coli* (MIC 3 μg/mL). So, we see that this arrangement of antimicrobial thiazole agent can help medicinal chemists for more in silico pharmacophore studies and structure-based drug design towards more specified and potent antimicrobial thiazoles.

ORCID

Abdelfattah Hassan https://orcid.org/0000-0001-8539-662X

Gamal El-Din A. Abuo-Rahma https://orcid.org/0000-0003-3908-1832

REFERENCES

1. A. M. Omar, J. Bajorath, S. Ihmaid, H. M. Mohamed, A. M. El-Agrody, A. Mora, M. E. El-Araby, and H. E. A. Ahmed, *Bioorg. Chem.*, 2020, **101**, 103992.
2. A. Lamut, M. Gjorgjieva, L. Naesens, S. Liekens, K. E. Lillsunde, P. Tammela, D. Kikelj, and T. Tomašič, *Bioorg. Chem.*, 2020, **98**, 103733.
3. I. P. Singh, S. Gupta, and S. Kumar, *Med. Chem.*, 2020, **16**, 4.
4. A. Rauf, M. K. Kashif, B. A. Saeed, N. A. Al-Masoudi, and S. Hameed, *J. Mol. Struct.*, 2019, **1198**, 126866.
5. A. Khan, A. Diwan, H. K. Thabet, M. Imran, and M. A. Bakht, *Molecules*, 2020, **25**, 2002.
6. S. Mor and S. Sindhu, *Med. Chem. Res.*, 2020, **29**, 46.
7. Z. L. Pi, J. Sutton, J. Lloyd, J. Hua, L. Price, Q. M. Wu, M. Chang, J. Zheng, R. Rehfuss, C. S. Huang, R. R. Wexler, and P. Y. S. Lam, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 4206.

8. I. Drapak, B. Zimenkovsky, L. Perekhoda, M. Suleyman, H. Yeromina, N. Skaletska, N. Seredynska, and A. Demchenko, *Pharmacia*, 2019, **66**, 181.
9. P. Makadia, S. R. Shah, H. Pingali, P. Zaware, D. Patel, S. Pola, B. Thube, P. Priyadarshini, D. Suthar, M. Shah, S. Giri, C. Trivedi, M. Jain, P. Patel, and R. Bahekar, *Bioorg. Med. Chem.*, 2011, **19**, 771.
10. F. H. A. Leite, P. B. G. da Silva Santiago, T. Q. Froes, J. da Silva Filho, S. G. da Silva, R. M. Ximenes, A. R. de Faria, D. J. Brondani, J. F. de Albuquerque, and M. S. Castilho, *Eur. J. Med. Chem.*, 2016, **123**, 639.
11. Asma, B. Kalluraya, N. Manju, and C. L. Sharath, *J. Heterocycl. Chem.*, 2020, **57**, 3105.
12. R. Fontana, S. Valisena, and G. Cornaglia, *J. Chemother.*, 1996, **8**, 23.
13. S. Mermer, T. Turhan, E. Bolat, S. Aydemir, T. Yamazhan, H. Pullukcu, B. Arda, H. Sipahi, S. Ulusoy, and O. R. Sipahi, *J. Glob. Antimicrob. Resist.*, 2020, **22**, 147.
14. Y. R. Lee and S. Yeo, *Clin. Drug Investig.*, 2020, **40**, 901.
15. L. A. Barbee and M. R. Golden, *J. Antimicrob. Chemother.*, 2020, **75**, 1685.
16. D. Shortridge, M. A. Pfaller, J. M. Streit, and R. K. Flamm, *J. Glob. Antimicrob. Resist.*, 2020, **21**, 60.
17. V. Shinde, P. Mahulikar, P. C. Mhaske, L. Nawale, and D. Sarkar, *Res. Chem. Intermed.*, 2018, **44**, 1247.
18. K. P. Nagasree, M. M. K. Kumar, Y. R. Prasad, D. Sriram, and P. Yogeeswari, *Indian J. Chem.*, 2018, **57B**, 538.
19. Z. Yan, A. Liu, M. Huang, M. Liu, H. Pei, L. Huang, H. Yi, W. Liu, and A. Hu, *Eur. J. Med. Chem.*, 2018, **149**, 170.
20. F. Tan, B. Shi, J. Li, W. Wu, and J. Zhang, *Molecules*, 2015, **20**, 20118.
21. H. Mohammad, M. Cushman, and M. N. Seleem, *PLOS ONE*, 2015, **10**, e0142321.
22. X. Lu, X. Liu, B. Wan, S. G. Franzblau, L. Chen, C. Zhou, and Q. You, *Eur. J. Med. Chem.*, 2012, **49**, 164.
23. V. V. Odaryuk, N. I. Burakov, L. V. Kanibolotskaya, A. L. Kanibolotskii, I. D. Odaryuk, N. Y. Lebedeva, E. N. Poddubnaya, and A. N. Shendrik, *Pharm. Chem. J.*, 2015, **49**, 96.
24. N. K. Shah, N. M. Shah, M. P. Patel, and R. G. Patel, *Chin. Chem. Lett.*, 2012, **23**, 454.
25. N. O. Mahmoodi, J. Parvizi, B. Sharifzadeh, and M. Rassa, *Arch. Pharm.*, 2013, **346**, 860.
26. V. JishaMol, K. Binsalma, M. Vivek, and V. Rubeena, *Indo Am. J. Pharm. Res.*, 2017, **4**, 1944.
27. K. Kaur, V. Kumar, V. Beniwal, V. Kumar, N. Kumar, V. Sharma, and S. Jaglan, *Med. Chem. Res.*, 2016, **25**, 2237.
28. H. K. Gençer, *Çukurova Med. J.*, 2017, **42**, 741.

29. J. A. Shiran, A. Yahyazadeh, M. Mamaghani, and M. Rassa, *J. Mol. Struct.*, 2013, **1039**, 113.
30. A. Ahmed, K. I. Molvi, H. M. Patel, R. Ullah, and A. Bari, *J. Infect. Public Health*, 2020, **13**, 472.
31. S. Belveren, H. A. Dondas, M. Ülger, S. Poyraz, E. García-Mingüens, M. Ferrándiz-Saperas, and J. M. Sansano, *Tetrahedron*, 2017, **73**, 6718.
32. Y. Nural, *Monatsh. Chem.*, 2018, **149**, 1905.
33. B. K. Sarojini, B. G. Krishna, C. G. Darshanraj, B. R. Bharath, and H. Manjunatha, *Eur. J. Med. Chem.*, 2010, **45**, 3490.
34. B. Sadek, M. M. Al-Tabakha, and K. M. S. Fahelelbom, *Molecules*, 2011, **16**, 9386.
35. D. S. N. Bikobo, D. C. Vodnar, A. Stana, B. Tiperciuc, C. Nastasă, M. Douchet, and O. Oniga, *J. Saudi Chem. Soc.*, 2017, **21**, 861.
36. N. D. Gaikwad, S. V. Patil, and V. D. Bobade, *J. Heterocycl. Chem.*, 2013, **50**, 519.
37. S. Eryılmaz, E. Türk Çelikoğlu, Ö. İdil, E. İnkaya, Z. Kozak, E. Mısır, and M. Gül, *Bioorg. Chem.*, 2020, **95**, 103476.
38. J. Abbasi Shiran, A. Yahyazadeh, M. Mamaghani, B. M. Yamin, J. Albadi, F. Shirini, and M. Rassa, *Synth. Commun.*, 2015, **45**, 1520.
39. J. A. Shiran, A. Yahyazadeh, B. M. Yamin, M. Mamaghani, and H. Kiyani, *Heterocycles*, 2015, **91**, 123.
40. M. Kalhor, M. Salehifar, and I. Nikokar, *Med. Chem. Res.*, 2014, **23**, 2947.
41. R. Khare, J. Sharma, and A. Sharma, *Russ. J. Gen. Chem.*, 2016, **86**, 702.
42. B. Grybaitė, R. Vaickelionienė, M. Stasevych, O. Komarovska-Porokhnyavets, K. Kantminienė, V. Novikov, and V. Mickevičius, *ChemistrySelect*, 2019, **4**, 6965.
43. S. Bondock and A. M. Fouda, *Synth. Commun.*, 2018, **48**, 561.
44. N. D. Amnerkar, B. A. Bhongade, and K. P. Bhusari, *Arab. J. Chem.*, 2015, **8**, 545.
45. S. Bondock, W. Fadaly, and M. A. Metwally, *Eur. J. Med. Chem.*, 2010, **45**, 3692.
46. M. Gouda, M. Berghot, G. E. Abd El-Ghani, and A. Khalil, *Eur. J. Med. Chem.*, 2010, **45**, 1338.
47. A. A. Fadda, A. M. El-badraw, H. M. Refat, and E. Abdel-Latif, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2016, **191**, 778.
48. E. Abdel-Galil, E. B. Moawad, A. El-Mekabaty, and G. E. Said, *Synth. Commun.*, 2018, **48**, 2083.
49. E. H. El-Sayed and A. A. Fadda, *J. Heterocycl. Chem.*, 2018, **55**, 2251.
50. H. M. Refat and A. Fadda, *Eur. J. Med. Chem.*, 2013, **70**, 419.
51. F. Chimenti, B. Bizzarri, A. Bolasco, D. Secci, P. Chimenti, A. Granese, S. Carradori, M. D'Ascenzio, D. Lilli, and D. Rivanera, *Eur. J. Med. Chem.*, 2011, **46**, 378.
52. N. D. Gaikwad, S. V. Patil, and V. D. Bobade, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3449.
53. M. H. Sherif, I. M. Eldeen, and E. O. Helal, *Res. Chem. Intermed.*, 2013, **39**, 3949.

54. G. A. Hampannavar, R. Karpoormath, M. B. Palkar, M. S. Shaikh, and B. Chandrasekaran, *ACS Med. Chem. Lett.*, 2016, **7**, 686.
55. A. A. Hassan, Y. R. Ibrahim, E. M. El-Sheref, M. Abdel-Aziz, S. Bräse, and M. Nieger, *Arch. Pharm.*, 2013, **346**, 562.
56. P. Makam, R. Kankanala, A. Prakash, and T. Kannan, *Eur. J. Med. Chem.*, 2013, **69**, 564.
57. Y.-J. Qin, P.-F. Wang, J. A. Makawana, Z.-C. Wang, Z.-N. Wang, G. Yan, A.-Q. Jiang, and H.-L. Zhu, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 5279.
58. A. Abdel-Aziem, B. S. Baaiu, A. W. Elbazzar, and F. Elabbar, *Synth. Commun.*, 2020, **50**, 2522.
59. I. Althagafi, N. El-Metwaly, and T. A. Farghaly, *Molecules*, 2019, **24**, 1741.
60. A. Biernasiuk, M. Kawczyńska, A. Berecka-Rycerz, B. Rosada, A. Gumieniczek, A. Malm, K. Dzitko, and K. Z. Łączkowski, *Med. Chem. Res.*, 2019, **28**, 2023.
61. A. I. Pricopie, I. Ionut, G. Marc, A. M. Arseniu, L. Vlase, A. Grozav, L. I. Găină, D. C. Vodnar, A. Pîrnău, B. Tiperciuc, and O. Oniga, *Molecules*, 2019, **24**, 3435.
62. K. Z. Łączkowski, N. Konklewska, A. Biernasiuk, A. Malm, K. Sałat, A. Furgała, K. Dzitko, A. Bekier, A. Baranowska-Łączkowska, and A. Paneth, *Med. Chem. Res.*, 2018, **27**, 2125.
63. C. I. Lino, I. G. de Souza, B. M. Borelli, T. T. S. Matos, I. N. S. Teixeira, J. P. Ramos, E. M. de Souza Fagundes, P. de Oliveira Fernandes, V. G. Maltarollo, S. Johann, and R. B. de Oliveira, *Eur. J. Med. Chem.*, 2018, **151**, 248.
64. N. P. de Sá, C. M. de Lima, C. I. Lino, P. J. S. Barbeira, L. de Matos Baltazar, D. A. Santos, R. B. de Oliveira, E. Mylonakis, B. B. Fuchs, and S. Johann, *Antimicrob. Agents Chemother.*, 2017, **61**, e02700-16.
65. P. S. Pereira, M. d. C. A. d. Lima, P. P. M. Neto, C. D. d. M. Oliveira-Tintino, S. R. Tintino, I. R. d. A. Menezes, J. F. d. Oliveira, P. Marchand, H. D. M. Coutinho, M. d. D. Rodrigues, and T. G. d. Silva, *Bioorg. Med. Chem.*, 2019, **27**, 3797.
66. S. A. Ouf, S. M. Gomha, M. Eweis, A. S. Ouf, and I. A. Sharawy, *Bioorg. Med. Chem.*, 2018, **26**, 3287.
67. R. Deshineni, R. Velpula, R. Ragi, and G. K. Chellamella, *Indian J. Chem.*, 2016, **55B**, 1415.
68. V. A. Adole, R. A. More, B. S. Jagdale, T. B. Pawar, and S. S. Chobe, *ChemistrySelect*, 2020, **5**, 2778.
69. M. Hublikar, V. Kadu, J. K. Dublad, D. Raut, S. Shirame, P. Makam, and R. Bhosale, *Arch. Pharm.*, 2020, e2000003.
70. N. Chidananda, B. Poojary, V. Sumangala, N. S. Kumari, and Unnikrishnan, *Med. Chem. Res.*, 2014, **23**, 3979.
71. R. E. Khidre, S. R. El-Gogary, and M. S. Mostafa, *J. Heterocycl. Chem.*, 2017, **54**, 2511.

72. S. Bharti, G. Nath, R. Tilak, and S. Singh, *Eur. J. Med. Chem.*, 2010, **45**, 651.
73. R. Ramachandran, P. Parthiban, M. Rani, S. Jayanthi, S. Kabilan, and Y. T. Jeong, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 6301.
74. A. Ansari, A. Ali, M. Asif, M. A. Rauf, M. Owais, and Shamsuzzaman, *Steroids*, 2018, **134**, 22.
75. K. Z. Łączkowski, K. Motylewska, A. Baranowska-Łączkowska, A. Biernasiuk, K. Misiura, A. Malm, and B. Fernández, *J. Mol. Struct.*, 2016, **1108**, 427.
76. A. Farag, *Drug Res.*, 2015, **65**, 373.
77. M. E. Khalifa, A. A. Gobouri, F. M. Kabli, T. A. Altalhi, A. S. Almalki, and M. A. Mohamed, *Molecules*, 2018, **23**, 3285.
78. J. K. Kapoor, R. Prakash, A. Kumar, D. Saini, and L. Arora, *J. Heterocycl. Chem.*, 2018, **55**, 899.
79. T. A. Farghaly, M. A. Abdallah, M. A. Khedr, and H. K. Mahmoud, *J. Heterocycl. Chem.*, 2017, **54**, 2417.
80. S. M. Sanad, A. A. Ahmed, and A. E. Mekky, *Arch. Pharm.*, 2020, **353**, 1900309.
81. B. S. Dawane, S. G. Konda, G. G. Mandawad, and B. M. Shaikh, *Eur. J. Med. Chem.*, 2010, **45**, 387.
82. M. I. Ansari and S. A. Khan, *Med. Chem. Res.*, 2017, **26**, 1481.
83. Y. Budak, U. M. Kocyigit, M. B. Gürdere, K. Özcan, P. Taslimi, İ. Gülçin, and M. Ceylan, *Synth. Commun.*, 2017, **47**, 2313.
84. P. Gautam, D. Gautam, and R. Chaudhary, *J. Heterocycl. Chem.*, 2016, **53**, 294.
85. S. I. Elewa, E. Mansour, I. F. Nassar, and A. A. Mekawey, *Russ. J. Bioorg. Chem.*, 2020, **46**, 382.
86. A. O. Abdelhamid, E. K. Abdelall, N. A. Abdel-Riheem, and S. A. Ahmed, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2010, **185**, 709.
87. R. Aggarwal, S. Kumar, P. Kaushik, D. Kaushik, and G. K. Gupta, *Eur. J. Med. Chem.*, 2013, **62**, 508.
88. S. Kumar, R. Aggarwal, and C. Sharma, *Synth. Commun.*, 2015, **45**, 2022.
89. N. Desai, V. Joshi, K. Rajpara, H. Vaghani, and H. Satodiya, *J. Fluorine Chem.*, 2012, **142**, 67.
90. S. H. Shelke, P. C. Mhaske, M. Nandave, S. Narkhade, N. M. Walhekar, and V. D. Bobade, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 6373.
91. E. Gürsoy, E. D. Dincel, L. Naesens, and N. U. Güzeldemirci, *Bioorg. Chem.*, 2020, **95**, 103496.
92. N. Trotsko, U. Kosikowska, A. Paneth, M. Wujec, and A. Malm, *Saudi Pharm. J.*, 2018, **26**, 568.
93. B. B. F. Mirjalili, S. Kabnadideh, K. Zomorodian, L. Zamani, M. Faghih, Z. Haghighijoo, and S. Kananizadehgan, *J. Pharm. Res. Int.*, 2017, **19**, 1.
94. J. Matysiak, R. Los, A. Malm, M. M. Karpińska, U. Głaszcz, B. Rajtar, M. Polz-Dacewicz, M. Trojanowska-Wesołowska, and A. Niewiadomy, *Arch. Pharm.*, 2012, **345**, 302.
95. M. Bhat, S. Belagali, N. H. Kumar, and S. M. Kumar, *Res. Chem. Intermed.*, 2017, **43**, 361.

96. V. Pejchal, M. Pejchalová, and Z. Růžičková, *Med. Chem. Res.*, 2015, **24**, 3660.
97. S. Asundaria and K. Patel, *Pharm. Chem. J.*, 2012, **45**, 725.
98. G.-F. Zha, J. Leng, N. Darshini, T. Shubhavathi, H. Vivek, A. M. Asiri, H. M. Marwani, K. Rakesh, N. Mallesha, and H.-L. Qin, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 3148.
99. I. Parašotas, K. Anusevičius, R. Vaickelionienė, I. Jonuškienė, M. Stasevych, V. Zvarych, O. Komarovska-Porokhnyavets, V. Novikov, S. Belyakov, and V. Mickevičius, *ARKIVOC*, 2018, **iii**, 240.
100. N. Sun, Y.-J. Lu, F.-Y. Chan, R.-L. Du, Y.-y. Zheng, K. Zhang, L.-Y. So, R. Abagyan, C. Zhuo, Y.-C. Leung, and K.-Y. Wong, *Front. Microbiol.*, 2017, **8**, 855.
101. W. D. Alrohily, M. E. Habib, S. M. El-Messery, A. Alqurshi, H. El-Subbagh, and E.-S. E. Habib, *Microb. Pathog.*, 2019, **136**, 103674.
102. H. Malipeddi, A. A. Karigar, V. R. Malipeddi, and M. S. Sikarwar, *Trop. J. Pharm. Res.*, 2012, **11**, 611.
103. N. Seelam and S. Shrivastava, *J. Saudi Chem. Soc.*, 2016, **20**, 33.
104. B. C. Yallur, U. Katrahalli, P. M. Krishna, and M. D. Hadagali, *Spectrochim. Acta, Part A*, 2019, **222**, 117192.

Abdelfattah Hassan is an Assistant Lecturer of Medicinal Chemistry at South Valley University, Qena, Egypt. He received his Master's degree from Minia University, Minia, Egypt. He obtained his Bachelor's degree with honors from Assiut University, Assiut, Egypt. He is interested in design and synthesis of heterocyclic small molecules with potential biological activities, especially triazole, thiazole, pyrazole, benzimidazole, quinoline, phthalazine, and pyrimidine. His current research focuses on the development of novel small molecules for treatment of cancer via targeting cellular signaling pathways mainly tyrosine kinase inhibition. He has published several articles in international peer-reviewed journals in the field of bioorganic and medicinal chemistry.

Heba A. Hassan is an Assistant Professor of Pharmaceutical/Medicinal Chemistry at Minia University, Egypt. She was born in Minia at 1981, Egypt. She received her PhD through collaborative studies between Minia University and Wake Forest University (NC, USA) under the supervision of Prof. Bruce King and Prof. Hassan Farag. She obtained her Bachelor's and Master's degrees in Excellent with honors from Minia University, Egypt. She is interested in research on the design and synthesis of different heterocyclic hybrid molecules with potential biological activities, especially oxadiazole, triazole quinoline, fluoroquinolone derivatives, and histone deacetylase inhibitors. She has supervised a number of PhD and Master theses. She has published till now more than 20 articles in high-impact international peer-reviewed journals in the field of bioorganic and medicinal chemistry.

Dalia Abdelhamid is an Associate Professor of Organic and Medicinal chemistry in the Faculty of Pharmacy - Minia University. Dalia's research interests include design and synthesis of drug molecules as well as polymer therapeutics. Her current research focuses on the development of novel molecules for treatment of cancer via interference with various pathways underlying cancer. This included inhibition of STAT3 phosphorylation, inhibition of tubulin dimerization, and induction of Caspase-3 dependent apoptosis. Dalia received a Bachelor of Pharmaceutical Sciences from Cairo University - Egypt (excellent, honors). Afterwards she was awarded an Egyptian Government Scholarship for funding her MsC and PhD degrees at The Ohio state University - USA from where she where graduated. She worked as Postdoctoral Associate at Rutgers, The State University of New Jersey – USA, where she designed and formulated polymer-based nanoparticles. In 2015 she received a Postdoctoral Fellowship from The World Academy of Sciences–University Putra Malaysia then was awarded a Postdoctoral Fellowship from the Egyptian Council of Higher Education at University of Ottawa - Canada in 2017.

Gamal El-Din A. Abuo-Rahma is a Professor of Pharmaceutical/Medicinal Chemistry at Minia University, Egypt. He was born in 1967 at Assiut, Egypt. He received his PhD through collaborative studies between Minia University and Bonn University under the supervision of Prof. Jochen Lehmann and Prof. Ali El-Emam. He obtained his Bachelor's and Master's degrees with honors from Assiut University, Egypt. He is interested in research on the design and synthesis of small molecules with potential biological activities, especially nitric oxide donor hybrids, quinoline, fluoroquinolone derivatives, and histone deacetylase inhibitors. He has supervised a number of PhD and Master theses. He has published till now more than 75 articles in high-impact international peer-reviewed journals in the field of bioorganic and medicinal chemistry.