Antibacterial Activity of Heterocyclic Compounds

Subjects: Chemistry, Medicinal

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Heterocyclic compounds are cyclic compounds which contain the atoms of two discrete elements as representative of their ring(s). They belong to one of the larger classes of organic compounds and also appear more valuable in different fields of chemistry.

heterocyclic compound | medicinal chemistry | infectious disease

1. Heterocyclic Compounds

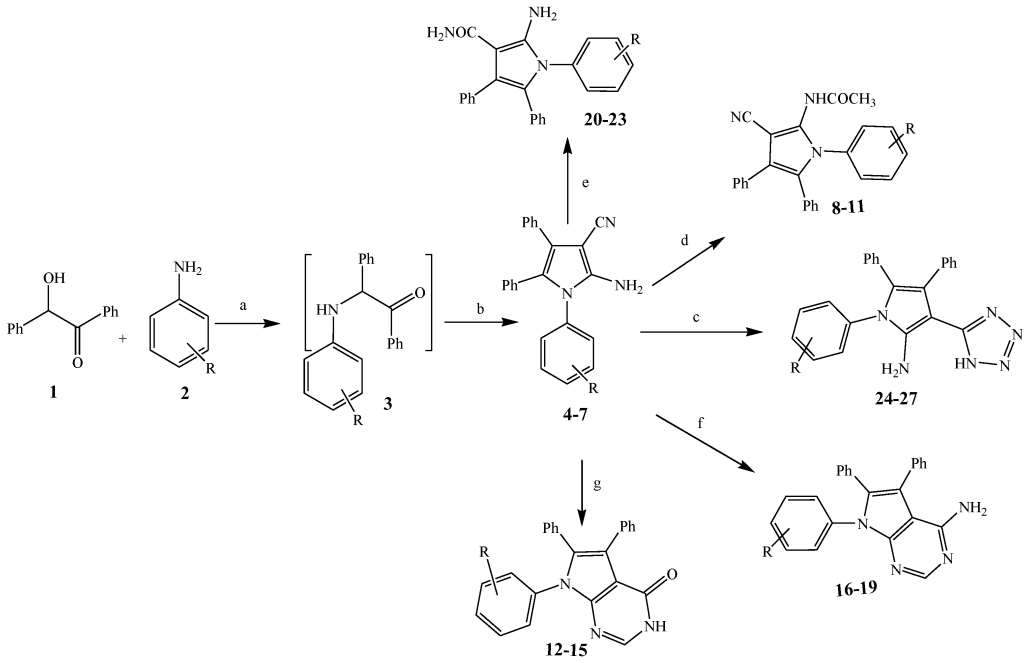
Heterocyclic compounds are cyclic compounds which contain the atoms of two discrete elements as representative of their ring(s). They belong to one of the larger classes of organic compounds and also appear more valuable in different fields of chemistry [1]. These compounds encompass a higher number of drugs, most biomass, nucleic acids, synthetic dyes, and numerous natural products such as alkaloids, herbicides, vitamins, antibiotics, hormones, and pharmaceutics [2]. Heterocyclic compounds have tremendous importance for both organic and medical chemists, and the synthesis of such molecules always remains a challenge from both industrial and academic aspects [3]. Heterocyclic systems with different structures display various biologic activities because of diversities in their molecular structures [4]. All these systems have been used for the composition of unusual drugs due to their unique physicochemical properties. Furthermore, the systems of these compounds have been very attractive in recent times because of both sulfur and nitrogen atoms present in them [5]. In therapeutic perseverance, to deal with the various types of bacterial and fungal infections along with the analysis of cancer, gastric ulcers, and many other diseases, these compounds have been extensively utilized [6].

2. Antibacterial Activity of Heterocyclic Compounds

2.1. Synthesis and Antibacterial Activity of the Pyrrole

The synthesis of various derivatives of pyrrole (**4**–**27**) was carried out by Mohamed et al., 2009 from primary aromatic amines (**2**), benzoin (**1**), and malononitrile (Scheme 1). The synthesized compounds were evaluated in terms of their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Bacillus subtilis,* and *Pseudomonas aeruginosa*. Most of the synthesized compounds exhibited excellent activity against these bacterial strains. Some of them showed similar activity while others were two to four times more or less active than the standard drug, amoxicillin. The activity of compounds **6, 10**, and **15** was almost similar to that of the reference

drug, whereas **17** was found to be two times more active than amoxicillin against *B. subtilis.* Furthermore, the compound **18** against *S. aureus* displayed activity that was lower than amoxicillin, while **21** and **27** were four times more active than amoxicillin. The compound **5** was also more effective against *E. coli* and **16** showed significant activity against *P. aeruginosa*, which was reciprocal to amoxicillin [7].

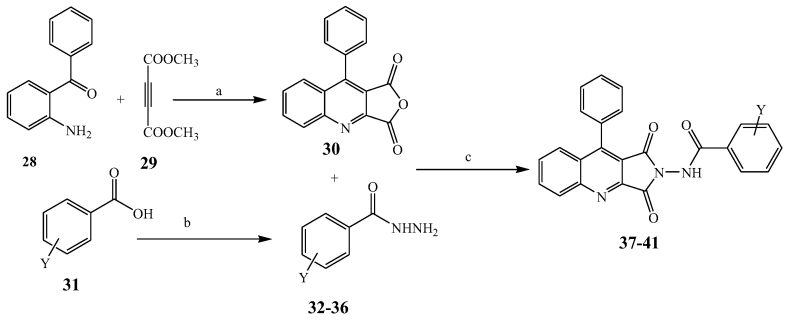


a = Toluene/HCl/Reflux, b = NC-CH2-CN, c = NaN_3/Reflux, d = Ac_2O/Reflux, e = H^+/NH_3, f = $HCONH_2$/Reflux, g = HCOOH/Reflux. **4,8,12,16,20,24**:R = H; **5,9,13,17,21,25**:R = 2-CH_3; **6,10,14,18,22,26**:R = 3-CH_3; **7,11,15,19,23,27**:R = 4-OCH_3.

Scheme 1. Synthetic route of pyrrole and its derivatives (**4**–**27**).

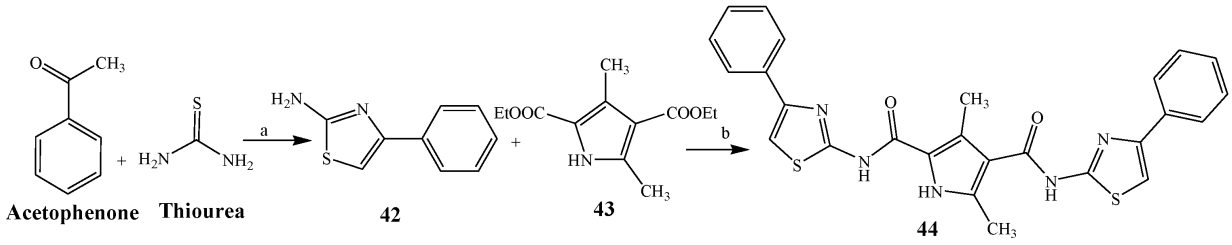
Largani et al., 2017 also synthesized pyrrolo [3,4-b]quinolin-2(3H)-yl)benzamides from benzohydrazide and 9-phenylfuro[3,4-b]quinoline-1,3-dionesas as shown in Scheme 2. The antibacterial activity of compounds **37**–**41** was evaluated against *Staphylococcus aureus*, *E. coli* and *Enterococcus faecalis* which demonstrated vigorous inhibition against these bacterial strains. It was observed that amongst all the targeted compounds, **37** exhibited magnificent activity against *E. faecalis*, *S.* aureus and *E. coli* bacteria with MIC 0.5, 0.25, and 0.25 mg/mL, respectively [8]. The various pyrrole derivatives were prepared (Scheme 3 and Scheme 4) from amino-containing compounds through several steps and their antibacterial activity was evaluated [9]. Compound **42** was synthesized by refluxing acetophenone and thiourea, which was further used for the synthesis of targeted compounds. The synthesized compounds exhibited good antibacterial potential against microbes with an MIC value of 16 µg/mL (**Table 1**). The activity of compound **44** was equipotent correlated with ciprofloxacin against *S. aureus* and *E. coli* [10]. The protected pyrrole ring was synthesized (**46**–**53**) from **45** by reacting with aromatic aldehyde and protected amine. It was revealed that compounds **50**, **51**, and **52** exhibit valuable antibacterial activity against *Pseudomonas putida* bacterial strains. Compound **49** also showed the equivalent inhibitory potential against the tested strains of bacteria. Similarly, **53** and **49** exhibited remarkable antibacterial activity at the range of 32–64 µg/mL [9]. The synthesis of bis-pyrrole (**56**–**60**) through hydrazonoyl halides (Scheme 5) and their evaluation against four different

bacterial strains was reported by Kheder [11]. The synthesized compounds were more active against the positive strains as compared to the negative strains. Furthermore, compound **59** with the Cl group at the *para*-position displayed a high degree of antibacterial activity against *B. subtilis* and *S. aureus*. Similarly, pyrrole derivatives (**64**–**76**) were prepared by a method based on microwave irradiation (Scheme 6) and their antibacterial activity was evaluated against *E. coli* and *S. aureus* [12]. It was also found that the compounds **65** and **71** exhibit significant activity against both *S. aureus* and *E. coli,* while **72** was the least effective. Furthermore, **71** displayed MIC (20 µg/mL in *S. aureus* and *E. coli*) closer to the reference drug, gentamicin. They also explained the SAR of the synthesized compounds, which showed that the substituent 3-formylpyrroles at position C-2 with thiophene (**52**) and pyridine (**50, 51**) had significant antibacterial activity, while 4-pyridyl had a weak response. They further elaborated that the presence of methoxy and ethoxy at positions C-8 and C-6 in the system of chromene increased the efficiency of the compound. The outcome revealed that the substitution at the 2-position of the phenyl ring of the chromene moiety (**72**, **73** and **75**) had the least inhibition of bacterial growth.



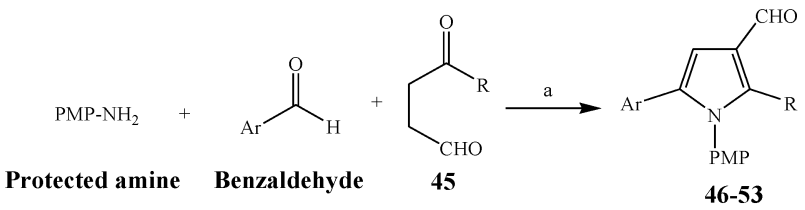
a =EtOH/H⁺/Reflux/KOH/, b = EtOH/H⁺/Reflux/N_2H_4, c = Toluene/Et_3N/Reflux. **32,37**: Y = H; **33,38**:Y = 4-Cl; **34,39**: Y = 4-NO_2; **35,40**: Y = 4-CH_3; **36,41**: Y = 2,4-di-Cl.

Scheme 2. Synthetic route for the synthesis of pyrrole[3,4-b]quinolin-2(3*H*)-yl)bezamide derivatives (**37**–**41**).



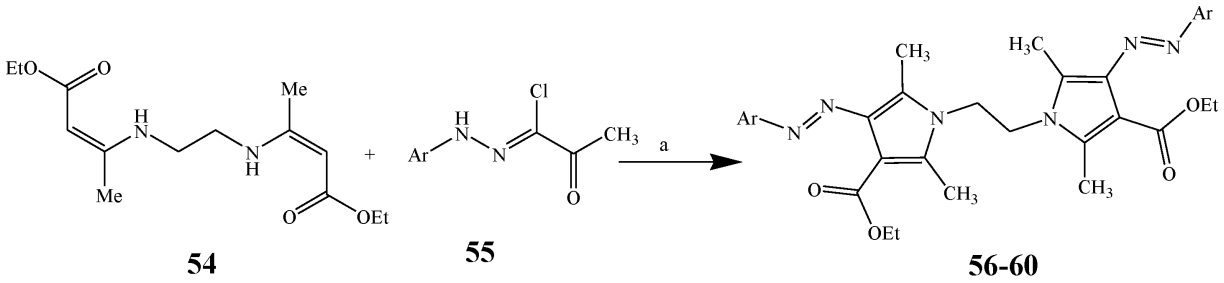
a = EtOH/Reflux, b = EtOH/Reflux.

Scheme 3. Synthetic route of compound **44**.



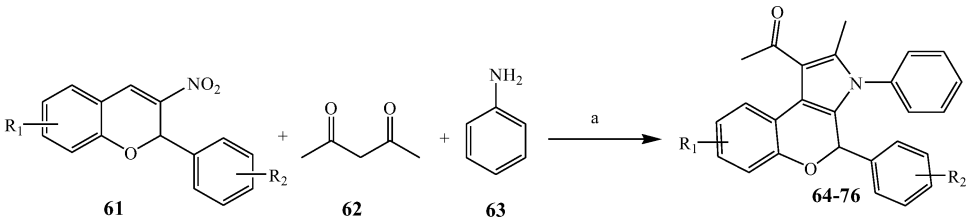
a = DMSO/Proline. **46**:R = 3-NO_2Ph;**47**:R = 4-NO_2Ph;**48**:R = 3-CNPh;**49**:R = 4-CH_3Ph;**50**:R = 3-pyridyl;**51**:R = 4-pyridyl; **52**:R = 2-thiophene;**53**:R = 3-FPh.

Scheme 4. Synthesis of pyrrole from 1,4-dicarbonyls.



a = Reflux. **56**:Ar = Ph;**57**:Ar = 4-MePh;**58**:Ar = 4-OMePh;**59**:Ar = 4-ClPh;**60**:Ar=3-ClPh.

Scheme 5. Synthesis of bis-pyrrole derivatives.

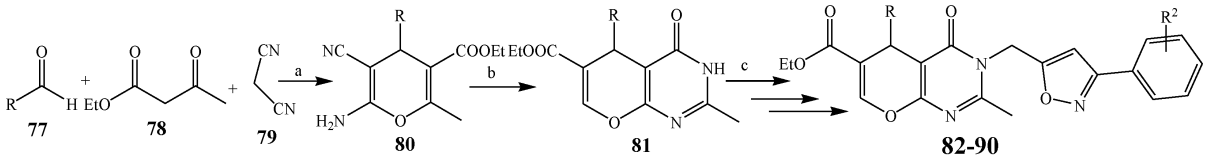


a = Microwave/60W/$FeCl_3$/Toluene. **64**:R_1 = H,R_2 = H;**65**:R_1 = 8-OCH_3,R_2 = H;**66**:R_1 = -OC_2H_5,R_2 = H;**67**:R_1 = 6-Cl,R_2 = H;**68**:R_1 = 6,8-di = Cl,R_2 = H; **69**:R_1 = 6,8-di-Br,R_2 = H;**70**:R_1 = 6-Cl,8-Br,R_2 = H;**71**:R_1 = 6-Br,8-OCH_3,R_2 = H;**72**:R_1 = 6-Br,R_2 = 4-OCH_3; **73**:R_1 = 6-Cl,R_2 = 4-OCH_3;**74**:R_1 = 6-OCH_3,R_2 = H;**75**:R_1 = 8-OC_2H_5,R_2 = H; **76**:R_1 = 6-Br,R_2 = H.

Scheme 6. Synthesis of 2*H*-chromene fused pyrrole derivatives (**64**–**76**).

2.2. Synthesis and Antibacterial Activity of the Pyrimidine

Pyrano[2,3-*d*]pyrimidine-6-carboxylates (**82**–**90**) were synthesized via a multistep reaction (Scheme 7) [13]. The antibacterial activity for the synthesized compounds was checked against Gram-negative (*Klebsiella pneumonia*, *E. coli*) and Gram-positive (*P. aeruginosa*, *S. aureus*) strains using ciprofloxacin as a standard drug. Compounds **80**–**81**, **83**–**85**, **87**, **89** and **90** exhibited exceptional activity, while compounds **83**, **86,** and **88** showed remarkable activity (**Table 1**). They further elaborated that compounds with an electron-withdrawing substituent (–OCH_3 and –NO_2) exhibited maximum activity as compared to compounds with the methyl group [13].

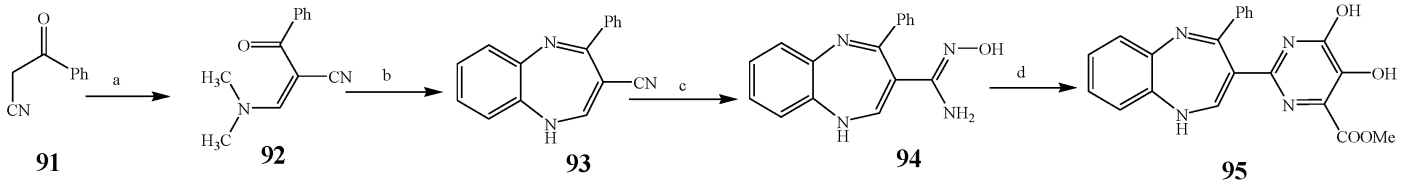


a = Piperdine/EtOH, b = Ac_2O/H^+, c = $NaOCl/Et_3N/K_2CO_3$/Hydrazine. **82**:R = Ph,R_2 = H;**83**:R = 3,4,5-tri-OCH_3-Ph,R_2 = H;**84**:R = 4-CH_3Ph,R_2 = H;**85**:R = 2-thienyl,R_2 = H;**86**:R = H,R_2 = 4-NO_2; **87**:R = H, R_2 = 4-OCH_3; **88**:R = H,R_2 = 4-CH_3;**89**:R = H,R_2 = 4-Cl;**90**:R = H,R_2 = 2-CH_3,3-NO_2.

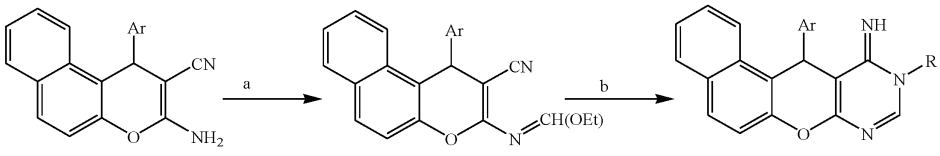
Scheme 7. Synthetic route of pyrimidine from aromatic aldehyde (**82**–**90)**.

Misra et al., 2018 reported the synthesis of pyrimidine derivatives with 1,5-benzodiazepines under microwave conditions using 1,4-diazabicyclo[2.2.2]octane and dimethyl acetylenedicarboxylate, as shown in Scheme 8. The antibacterial results indicated that compound **95** had exhibited persuasive inhibitory activity against *E. coli* and *S. aureus* with IC_{50} values of 300 and 200 µg/mL, respectively [14]. The synthesis of (benzo[1][2]chromeno[2,3-*d*]pyrimidine (**96**–**106**) (Scheme 9) was reported by Ameli et al., 2017, while their anti-infectious activity was checked against *S. aureus*, *B. subtilis*, *E. coli* and *Salmonella typhimurium.* Compounds **100**–**106** showed high activity while **96-99** remained moderate (MIC > 250). These results suggested that the pyrimidine moiety plays a significant role in antibacterial activity. Compounds **101**, **102**, **105** and **106** whose aryl groups have a Cl or OH group, displayed greater inhibitory effects against *E. coli*, *S. aureus*, *S. typhimurium* and *B. subtilis* strains which may have the potential to bind the compounds to corresponding receptors [15]. The 2,4-disubstituted-6-thiophenyl-pyrimidine as antibacterial agents was prepared by Fang et al., 2019 and the route of synthesis is presented in Scheme 10. It is estimated that among compounds **116**–**123**, the most potent were **118**, **117** and **123** with 5 µg/mL MIC compared to vancomycin and methicillin (**Table 1**). On the other hand, the inhibitory effect was weak against *E. coli* which may be due to the lower penetrating capacity of the synthesized compounds to the outer Gram-negative bacterial membrane [16]. The results further showed the presence of the group at the 2nd position of pyrimidine pivotal activity. The cyclo-condensation protocol was also reported for the synthesis of the bis-2-phenylpyrimidines compound from β-ketoester, benzamidine hydrochloride, and dihaloalkanes as shown in Scheme 11 [17]. The *in vitro* antibacterial activity of the synthesized compounds **126**–**134** was also studied against *Salmonella enterica* ATCC 13312, *E. coli* ATCC 25922, *Micrococcus luteus* ATCC 29213, *B. subtilis* ATCC 29213, and *S. aureus* ATCC 29213. The results showed that compounds **126**–**134** had good activities towards *B. subtilis*, *S. enterica* and *M. luteus,* while most of the compounds against *S. aureus* showed a weak response [17]. Pyrimidine (**140**–**149**) and oxadiazole (**150**–**159**) were prepared by Triloknadh et al., 2018 as shown in Scheme 12 [18]. Among all the synthesized compounds, **150**, **154**, **155a**, and **156** exhibited vigorous activity with 0.0125 to 0.0412 mg/mL values of MIC, which were higher than gentamicin (MIC = 0.0212 to 0.0422 mg/mL). Compound **141** displayed dominant activity across three strains (*P. aeruginosa*, *B. subtilis* and *S. aureus*) with 0.0124, 0.0120, and 0.0311 mg/mL MIC values, respectively (**Table 1**). Moreover, if the methoxy group was moved from position 3 to position 4 (**140**), it may lead to the reduction of activity across the strains. In addition, methyl, cyano, and bromo substitutions enhanced the activity. Andrews et al., 2017 described the synthesis of the pyrimidine derivatives (**161**–**170**), (**171**–**180**) as represented in Scheme 13. The *in vitro* antibacterial activity of the recently synthesized

compounds was screened against *E. coli*, *S. aureus* and *P. aeruginosa* by agar well disk diffusion technique. The antibacterial activity data showed that compounds **161**–**170** had lower inhibition than compounds **171**–**180** [19].

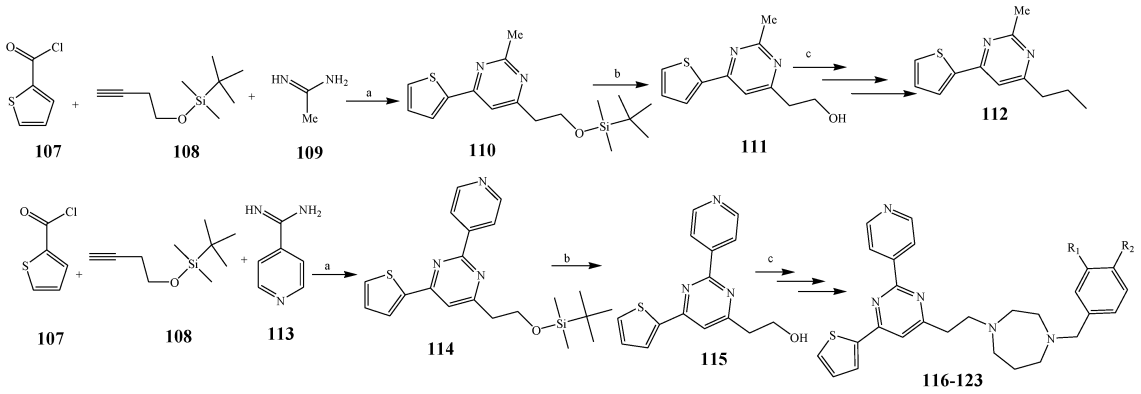


Scheme 8. Synthesis of pyrimidine derivatives of 1,5-benzodiazepine from benzoylacetonitrile.



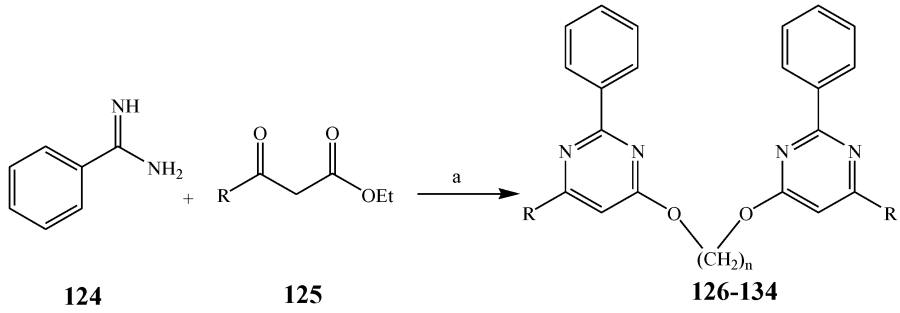
a = $HC(OEt)_3/Ac_2O$/Reflux, b = MeOH/R-NH_2. **96**:Ar = 3-NO_2Ph;**97**:Ar = 4-OHPh;**98**:Ar = 4-ClPh;**99**:Ar = 2-ClPh;**100**:Ar = 3-NO_2Ph,R = Me;**101**:Ar = 4-OHPh, R = Me;**102**:4-ClPh,R = Me;**103**:Ar = 3-NO_2Ph,R = Benzyl;**104**:Ar = 3-NO_2Ph,R = Ph,**105**:Ar = 4-OHPh,R = Ph,**106**:Ar = 2-Cl-C_6H_4,R = Ph.

Scheme 9. Synthesis of new benzo[1][2]chromeno[2,3-*d*]pyrimidines (**100**–**106**).



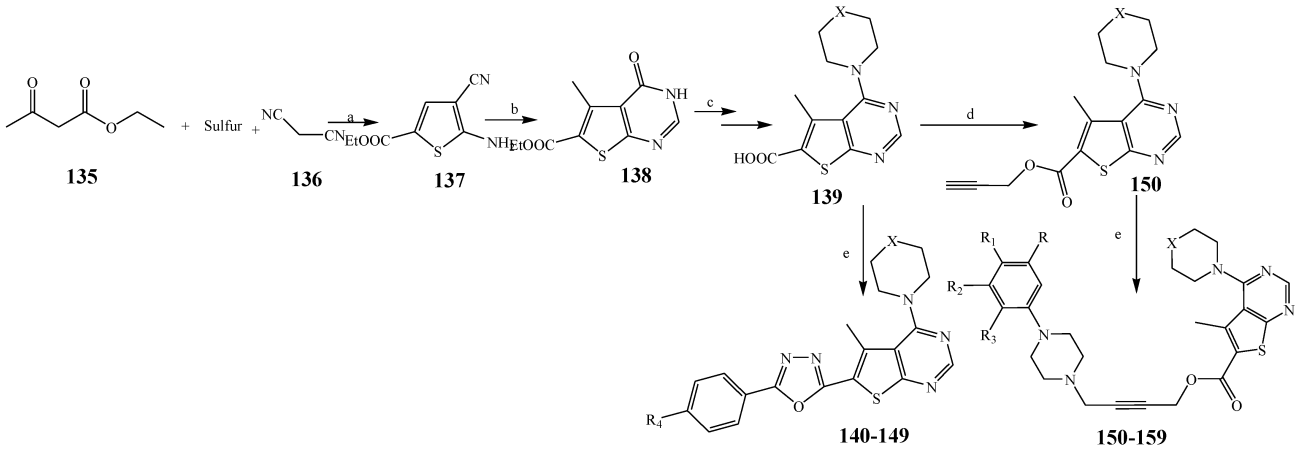
a = (i) 2 mol% $Pd(PPh_3)_2Cl_2$/4 mol% CuI/NEt_3/tetrahydrofuran (THF)/rt 1–2 h and (ii) Na_2CO_3, reflux 14 h; b = Conc. HCl/MeOH/rt 2 h; c= PPh_3/CBr_4/THF/rt 3–4 h/various amines/ACN/rt 24 h/TFA/DCM,. **116**:R_1 = H,R_2 = H;**117**:R_1 = H,R_2 = iPrH;**118**:R_1 = H,R_2 = tBuH;**119**:R_1 = H,R_2 = F;**120**:R_1 = F,R_2 = H;**121**:R_1 = F,R_2 = F;**122**:R_1 = H,R_2 = Br;**123**:R_1 = H,R_2 = CF_3.

Scheme 10. Synthesis of pyrimidine using acetamidine and isonicotinamidine.



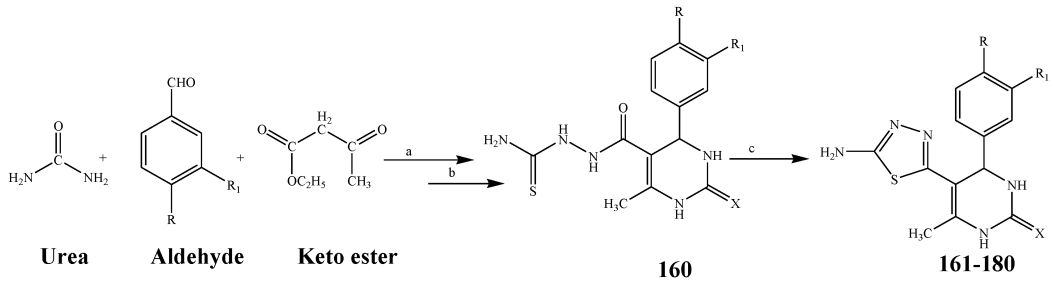
a = DMF/K_2CO_3/heat. **126**:R = Me,n = 4;**127**:R = Me,n = 5; **128**:R = Me, n = 6; **129**:R = Pr,n = 4; **130**:R = Pr,n = 5; **131**:R = Pr,n = 6; **132**:R = Ph,n = 4;**133**:R = Ph,n = 5;**134**:R = Ph,n = 6.

Scheme 11. Synthesis of bis-pyrimidines (**126**–**134**).



a = EtOH/NEt_3/Reflux, b = HCOOH/Reflux, c = $POCl_3$/Reflux/Piperidine/EtOH/NaOH, d = DMF/Propargyl bromide/K_2CO_3, e = amine, **140**:X = O,R_4 = H;**141**:X = O,R_4 = Me;**142**:X = O,R_4 = OMe;**143**:X = O,R_4 = NO_2;**144**:X = O,R_4 = Cl;**145**:X = CH_2,R_4 = H;**146**:X = CH_2,R_4 = Me;**147**:X = CH_2,R_4 = OMe;**148**:X = CH_2,R_4 = NO_2;**149**:X = CH_2,R_4 = Cl;**150**:X = O,R_4 = H;**151**:X = O,R_4 = Me;**152**:X = O,R_4 = OMe;**153**:X = O,R_4 = NO_2;**154**:X = O,R_4 = Cl;**155**:X = CH_2,R_4 = H;**156**:X = CH_2,R_4 = Me; **157**:X = CH_2,R_4 = OMe;**158**:X = CH_2,R_4 = NO_2;**159**:X = CH_2,R_4 = Cl.

Scheme 12. Synthesis of thieno[2,3-*d*]pyrimidine-alkyne.



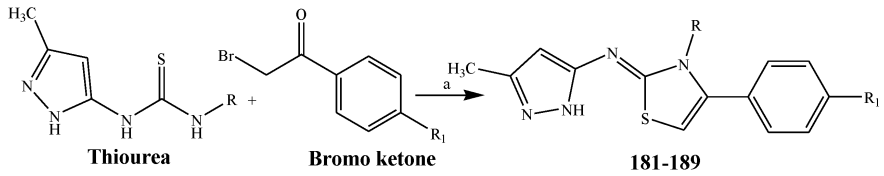
a = EtOH/Reflux, b = Acetone/Reflux/Thiourea, c = H^+/Reflux. **161**:X = O,R = H,R_1 = H;**162**:X = O,R = Cl,R_1 = H;**163**:X = O,R = $N(CH_3)_2$,R_1 = H;**164**:X = O,R = H,R_1 = NO_2;**165**:X = O, R = OH,R_1 = H;**166**:X = O,R = H,R_1 = H;**167**:X = O,R = Cl,R_1 = H;**168**:X = O,R = $N(CH_3)_2$,R_1 = H;**169**:X = O,R = H,R_1 = NO_2;**170**:X = O,R = OH,R_1 = H;**171**:X = S,R = H,R_1 = H;**172**:X = S,R = Cl,R_1 = H;**173**:X = S,R = $N(CH_3)_2$,R_1 = H;**174**:X = S,R = H,R_1 = NO_2;**175**:X = S,R = OH,R_1 = H;**176**:X = S,R = H,R_1 = H;**177**:X = S,R = Cl,R_1 = H;**178**:X = S,R = $N(CH_3)_2$,R_1 = H;**179**:X = S,R = H,R_1 = NO_2;**180**:X = S,R = OH,R_1 = H.

Scheme 13. Synthesis of 3,4-dihydro-5-(5-mercapto-4*H*-1,2,4-triazol-3-yl)-6-methyl-4-phenyl pyrimidin-2(1*H*)-one (**161**–**180**).

2.3. Synthesis and Antibacterial Activity of the Thiazole

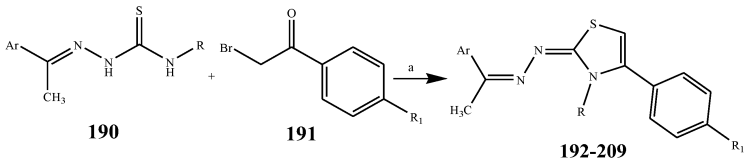
The thiazole derivatives (**181**–**189**), such as 3-substituted-4-aryl-2-[(1-phenylethylidene)hydra-zono]-2,3-dihydrothiazoles and 4-Aryl-2-[2-(1-substituted ethylidene) hydra-zinyl]-thiazoles were prepared through the reaction of bromoacetophenones and (ethylidene)hydrazinecarbothioamides (Scheme 14 and Scheme 15) [20]. Compounds **192**–**209** were evaluated against different Gram-positive and Gram-negative strains of bacteria such as *K. pneumonia*, *P. aeruginosa*, *S. aureus*, and *E. coli* using reference drugs. The results concluded that compounds **192**, **194**, **195**, **200** and **205** had remarkable activity against *E. coli*. Furthermore, compounds **195**, **192**, **196**, **200**, **209** and **207** reported the promising antibacterial activity against *K. pneumonia,* which is greater than ciprofloxacin. Compounds **192**, **194**, **195**, **200**, **205** and **207** exhibited excellent activity against *P. aeruginosa*, which was higher as compared to ciprofloxacin. Moreover, **196**, **200**, **205**, **207** and **209** displayed several folds of activity against *S. aureus.* It was indicated from the results that the existence of a phenyl ring at thiosemicarbazones is necessary for significant activity. Similarly, the allyl, benzyl and phenyl group on the *N*-position of thiazole (**207, 209** and **205**) was associated with a significantly high degree of activity [20]. Thirty thiazole derivatives (**213**–**242**) were synthesized by Zha et al., 2019 as represented in Scheme 16. *In vitro* antibacterial studies of compounds were carried out against *B. subtilis*, *S. aureus*, *K. pneumonia* and *E. coli*. The results explained that compounds **231** and **232** demonstrated valuable activity against all the bacterial strains, while compounds **226** and **227** revealed good activity against *E. coli*, *S. aureus* and *B. subtilis* because of the existence of an electron-donating (-OCH_3 and -OH) moiety in the molecule [21]. Similarly, Abdel-Galil et al., 2018 reported the synthesis of a series of scaffolds of heterocyclic compounds that contain thiazolidin-5-one and thiazole rings from 4-formylphenyl benzoate precursor (Scheme 17). Antibacterial activity of the synthesized compounds was performed against *S. aureus* and *E. coli*. The results reported that compounds **244**, **245** and **248** exhibited dominant antibacterial activity against the *S. aureus* bacterial strain, while **6** displayed exceptional activity against *E. coli*. Moreover, compounds **251**, **250** and **246** demonstrated acceptable activity across the positive strain and compounds **244** and **247** revealed good activity against the negative strain (**Table 1**). The existence of ethoxy, methyl, amino, azo, hydroxyl, or methoxy groups assimilated with phenylbenzoate, cyanoacetyl hydrazine, and carbamothioylhydrazone moiety in the derivatives of thiazole depicted excellent antibacterial activity. Furthermore, the presence of an electron-withdrawing group rather than an electron-donating group in compound **249** reduced the activity. The compound **248** showed the excellent antibacterial activity against *S. aureus* and *E. coli* bacterial strains, which may be due to the –CH_3 group at the 4th position of thiazole [22]. The synthesis of thiazoles from allyl thiourea as given in Scheme 18 was carried out by Khare, et al., 2016. All the synthesized compounds (**253**–**258**) exhibited moderate activity [23]. Beyzaei, et al., 2017 illustrated the synthesis of 4-thiazolylpyrazole (**264**–**269**) compounds from the modified Hantzsch method, in the presence of catalyst MgO nanoparticles as represented in Scheme 19. An evaluation of the *in vitro* antibacterial activity of the synthesized compounds was also performed against 21 bacteria. Compounds **264** to **269** of 4-thiazolylpyrazoles exhibited inhibition activities against *S. agalactiae*, *P. aeruginosa* and *S. pneumoniae*. In comparison with the other compounds, thiazoles **265** and **269** were potent against eight pathogenic bacterial strains, and as such they appeared as one of the effective broad-

spectrum agents [24]. Mohamed et al., 2018 reported the synthesis of thiazole derivatives as shown in Scheme 20 and observed that the derivative of **272** had greater antibacterial activity. This may be due to the thiazole's molecular structure and also the existence of the NH group, which helps the adsorption of a compound onto the surface of bacteria, perforation into their cell membrane, and finally eradication of the membrane, causing the death of bacteria [25]. Seven unique derivatives of pleuromutilin with the moiety of thioether and thiazole-5-carboxamide (**277**–**283**) were prepared by Wang et al., 2011 as represented in Scheme 21. The *in vitro* antibacterial activity of the synthesized compounds was evaluated against two positive strains of bacteria viz. *S. aureus* ATCC26112 and *S. aureus* SC. The compounds exhibited valuable activity against the bacteria and it can be examined that the bacterial strain of *S. aureus* was more susceptible than *S. aureus* [26].



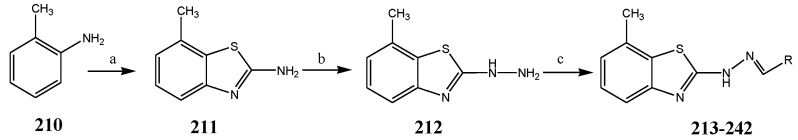
a = EtOH/Reflux. **181**:R = Ph,R_1 = H;**182**:R = $PhCH_2$,R_1 = H;**183**:R = Alyl,R_1 = H;**184**:R = Ph,R_1 = Br;**185**:R = $PhCH_2$,R_1 = Br;**186**:R = Allyl,R_1 = Br;**187**:R = Ph,R_1 = Ph;**188**:R = $PhCH_2$,R_1 = Ph;**189**:R = Allyl,R_1 = Ph.

Scheme 14. (Thiazol-2-yl)pyrazol-5-amines from pyrazolylthioureas and ω-bromoacetophenones.



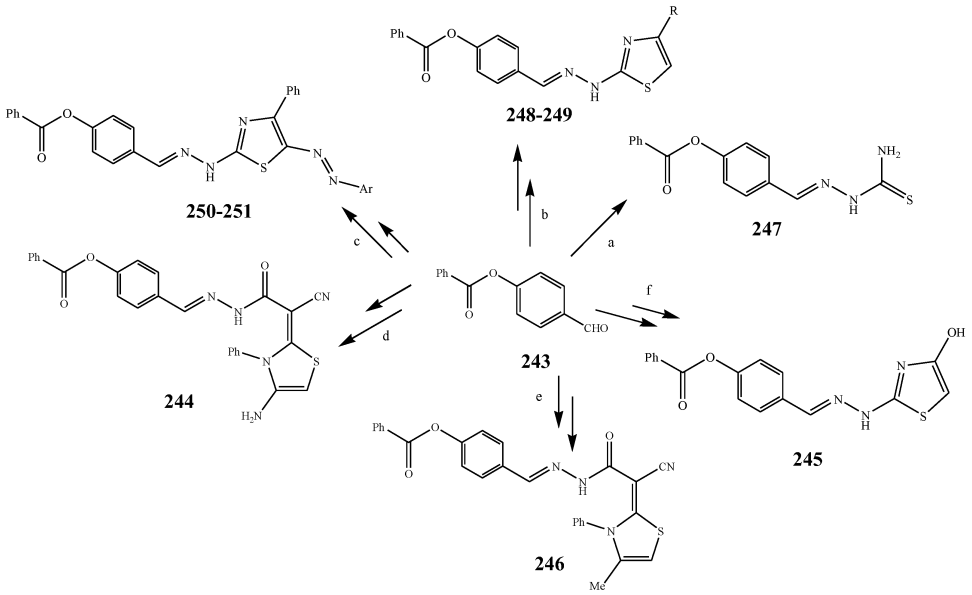
192:Ar = Ph,R = H,R_1 = H;**193**:Ar = Furan-2-yl,R = H,R_1 = H;**194**:Ar = Pyridin-3-yl,R = H,R_1 = H;**195**:Ar = Ph,R = H,R_1 = Br;**196**:Ar = Furan-2-yl,R = H,R_1 = Br;**197**:Ar = Pyridin-3-yl,R = H,R_1 = Br;**198**:Ar = Ph,R = H,R_1 = Ph;**199**:Ar = Furan-2-yl,R = H,R_1 = Ph;**200**:Ar = Pyridin-3-yl,R = H,R_1 = Ph;**201**:Ar = Ph,R = Ph,R_1 = H;**202**:Ar = Ph,R = $PhCH_2$,R_1 = H;**203**:Ar = Ph,R = allyl,R_1 = H;**204**:Ar = Ph,R = Ph,R_1 = Br;**205**:Ar = Ph,R = $PhCH_2$,R_1 = Br;**206**:Ar = Ph,R = Allyl,R_1 = Br;**207**:Ar = Ph,R = Ph,R_1 = Ph;**208**:Ar = Ph,R = $PhCH_2$,R_1 = Ph;**209**:Ar = Ph,R = alyl,R_1 = Ph.

Scheme 15. Synthetic route of compounds (**192**–**209**).



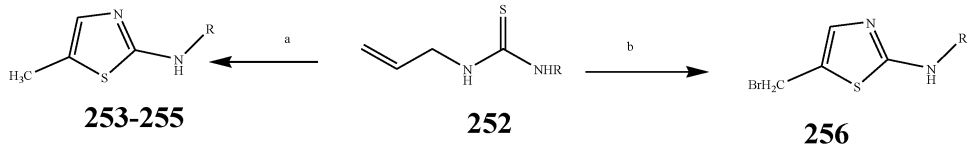
a = NH_4SCN/Br_2/Glacial acetic acid, b = Hydrazine/HCl, c = Aldehydes/Acetic acid/Reflux. **213**:R = Ph;**214**:R = 4-Cl-Ph;**215**:R = 4-NO_2-Ph;**216**:R = 4-F-Ph;**217**:R = 4-Br-Ph;**218**:R = 4-OH-Ph;**219**:R = 4-OMe-Ph;**220**:R = 2,4-di-Cl-Ph;**221**:R = 2,4-di-NO_2-Ph;**222**:R = 2,4-di-F-Ph;**223**:R = 2,4-di-Br-Ph;**224**:R = 2,4-di-OMe-Ph;**225**:R = 3-OH,4-OMe-Ph;**226**:R = 3-Br,4-OH-Ph;**227**:R = 3-F,4-OH-Ph;**228**:R = 3-OMe,4-OH,5-Br-Ph;**229**:R = 3,4,5-tri-OMe-Ph;**230**:R = 3,4-di-OH,5-Br-Ph;**231**:R = 1-benzyl-4-methylbenzene;**232**:R = 1-(benzyloxy)-4-methylbenzene;**233**:R = Pyridine;**234**:R = 4-Me-Ph;**235**:R = 2,4-di-OH-Ph;**236**:R = 2-methylbutane;**237**:R = Pr;**238**:R = Pent;**239**:R = Furan-2-yl;**240**:R = Thiophene-2-yl;**241**:R = Pyrrole-2-yl; **242**:R = Indole-2-yl.

Scheme 16. Synthetic routes of various thiazoles.



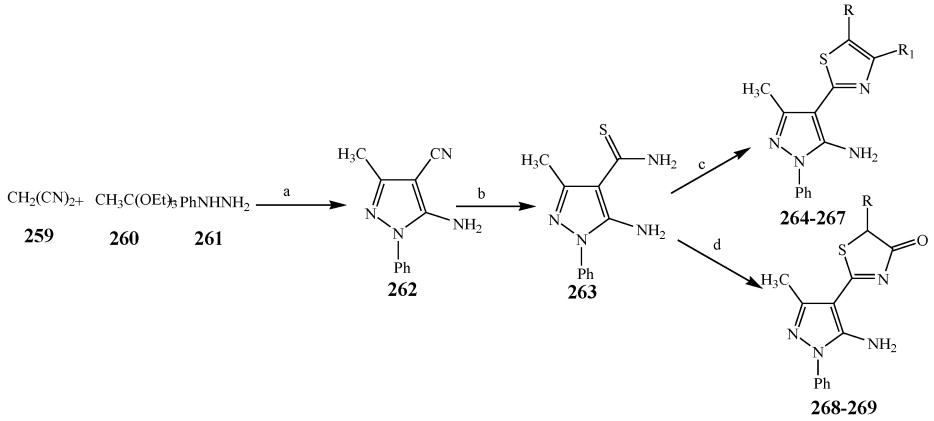
a = EtOH/NH_2-NH-CS-NH_2, b = EtOH/NH_2-NH-CS-NH_2/RCOCH$_2$Clc = EtOH/NH_2-NH-CS-NH_2/Ph-CO-C(Cl)N_2H-Ar, d = EtOH/PhNCS/DMF/KOH/Cl-CH_2CN, e = EtOH/PhNCS/DMF/KOH/CH_3COCH$_2$Cl. **248**:R = Me;**249**:R = Ph;**250**:Ar = MePh;**251**:Ar = OMePh.

Scheme 17. Synthetic routes of thiazole.



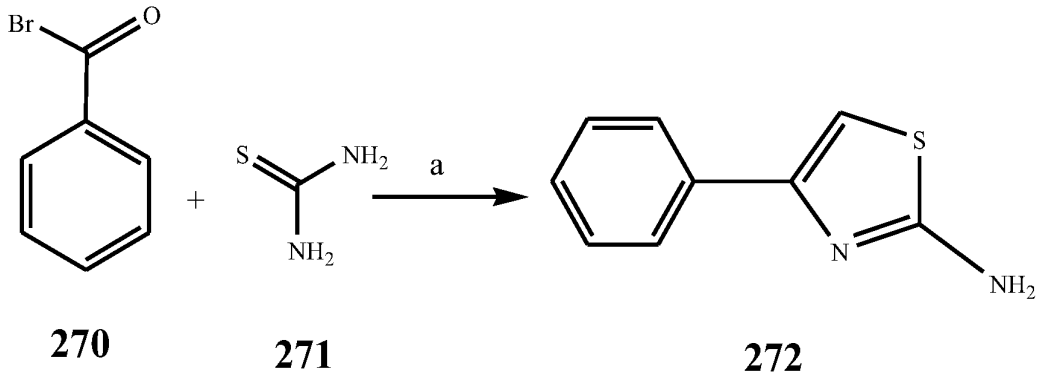
a = EtOH/HCl/Reflux, b = Br_2/$CHCl_3$. **253**:R = Ph;**254**:R = Cl-Ph;**255**:R = Me-Ph;**256**:R = Pyridine.

Scheme 18. Synthesis of thiazole from thiourea (**253**–**256**).

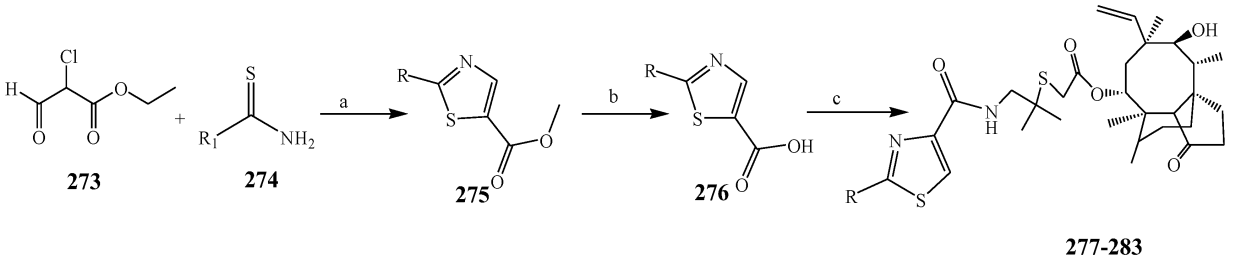


a = EtOH/Reflux, b = EtOH/P_4S_{10}, c = DMF/$NaHCO_3$/MgO-NP/Heat/α-bromo-ester, d = DMF/Na-HCO_3/MgO-NP/Heat/α-bromo-ketone. **264:**R = H,R_1 = Me;**265:**R = COMe,R_1 = Me;**266:**R = COOEt,R_1 = Me;**267:**R = H,R_1 = COOEt;**268:**R = H;**269:**R = Me.

Scheme 19. Total synthesis of 4-thiazolylpyrazoles.



Scheme 20. Synthetic routes of substituted thiazole.



a = Toluene/$MgSO_4$/Heat, b = EtOH/NaOH/Reflux, c = Et_3N/Pleuromutilin/Reflux. **277:**R = H; **278:**R = Me; **279:**R = Ph; **280:**R = 4-MePh; **281:**R = 3-MePh; **282:**R = 4-OMePh; **283:**R = 3,5-di-OMePh.

Scheme 21. The synthetic route to thiazole having pleuromutilin moiety.

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