Review

Biginelli Reaction Mediated Synthesis of Antimicrobial Pyrimidine Derivatives and Their Therapeutic Properties

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Abstract: Antimicrobial resistance was one of the top priorities for global public health before the start of the 2019 coronavirus pandemic (COVID-19). Moreover, in this changing medical landscape due to COVID-19, finding new organic structures with antimicrobial and antiviral properties is a priority in current research. The Biginelli synthesis that mediates the production of pyrimidine compounds has been intensively studied in recent decades, especially due to the therapeutic properties of the resulting compounds, such as calcium channel blockers, anticancer, antiviral, antimicrobial, anti-inflammatory or antioxidant compounds. In this review we aim to review the Biginelli syntheses reported recently in the literature that mediates the synthesis of antimicrobial compounds, the spectrum of their medicinal properties, and the structure–activity relationship in the studied compounds.

Keywords: Biginelli reaction; dihydropyrimidininones; catalyst; antimicrobials; antitubercular; antioxidant

1. Introduction

Twelve years after 1881, the year in which the German Arthur Rudolf Hantzsch reported the multicomponent synthesis of dihydropyridine [1], in 1893, the Italian chemist Pietro Biginelli published the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones, by a simple one-pot condensation reaction of an aromatic aldehyde, urea, and ethyl acetoacetate in ethanol solution (Scheme 1) [2,3]. Both reactions proved to be "key methods" for the synthesis of pyridine and pyrimidine derivatives, respectively, which were greatly developed in the following period, especially due to the applications of the synthesized compounds. The Biginelli reaction has been intensively studied in the last two decades, especially due to the applications of synthesized dihydropyrimidinone compounds at the beginning, especially as calcium channel blockers of the nifedipine-type [4], and then as antitumor [5–8], antibacterial, antiviral [9,10], anti-inflammatory [11,12], analgesic [13], anti-Alzheimer [14], or antioxidant [15] compounds.
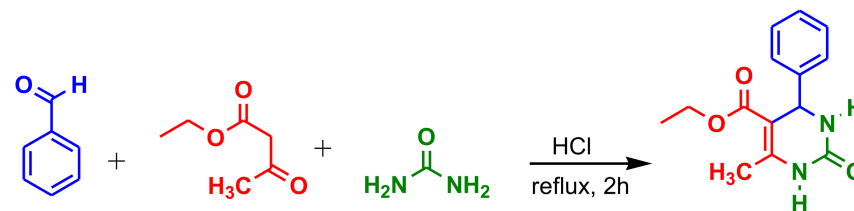
Scheme 1. The Biginelli dihydropyrimidone synthesis.

The synthetic method initially reported by Biginelli has undergone changes, such as the "Atwal-modification" [4,5], and most often, the most efficient catalyst has been sought, which would lead to a higher product yield, milder reaction conditions, and efficient catalyst recovery [16,17]. In the last decade, several improved methods were reported for

the Biginelli synthesis of these compounds, including solvent free synthesis [18], ultrasound radiation [19], microwave irradiation [20], visible light irradiation [21], or using a biocatalyst [22]. Further methods include using various catalysts, such as Bronsted acids, including H_3BO_3 [15], HCOOH [21], p-TsOH-H_2O [23,24], imidazole-1–yl-acetic acid [25], and L-(+)-tartaric acid-dimethylurea [26]; or Lewis acids, including $LiClO_4$, LaI_3, $InCl_3$, $BiCl_3$, $Bi(OTf)_3$, $Mn(OAc)_3$, $Cu(OTf)_2$, $CuCl_2$, $FeCl_3$, $ZrCl_4$, $SnCl_2$, [27–32], $Sr(OTf)_2$ [33], VCl_3 [34], $TaBr_5$ [35], $Ce(NO_3)_3 \cdot 6H_2O$ [36], $ZrO_2/SO_4{}^{2-}$ [37], silica-chloride (SiO_2-Cl) [38], $Sm(ClO_4)_3$ [39], $Y(NO_3)_3 \cdot 6H_2O$ [40], $CeCl_3 \cdot 7H_2O$ [41], $Ce(NH_4)_2(NO_3)_6$ (CAN) [42], $Fe(OTs)_3 \cdot 6H_2O$ [43], $Ca(HSO_4)_2$, $Zn(HSO_4)_2$ [44], $SnCl_2$/nano SiO_2 [45], $Cu(OAc)_2$ [46], copper zirconium phosphate $Cu(OH)_2Zr(HPO_4)_2$ [47], $Sc(OTf)_3$, $Yb(OTf)_3$, and $Zn(OTf)_2$ [48]. Other catalysts of the Biginelli reaction reported in the literature include co-phthalocyanines [49], $NaHSO_4$ [50], zeolites [51,52], clays [53–55], organic polymers [56,57], organic–inorganic mesoporous materials [58], ionic liquids [59–61], etc. [62–64]. Asymmetric Biginelli syntheses have also been developed due to the special importance of the pharmaceutical properties of optically active dihydropyrimidinone compounds [65–67]. For Biginelli synthesis, the literature accepts three plausible mechanisms: through the formation of the imine intermediate, through the formation of the enamine intermediate, and through the formation of the Knoevanagel intermediate [66]. Despite this, it can be assumed that the Biginelli reaction is, in fact, a multicomponent reaction catalyzed by urea through the generation of iminium species, energetically favored route [32,66].

The need to find new compounds with remarkable antimicrobial activities and with a wide range of other therapeutic activities has been stimulated in the last two years by the fact that both patients with severe cases and patients with moderate cases of COVID-19, with or without pneumonia, they received treatments with various antibiotics [68,69]. Therefore, given the various dihydropyrimidinone compounds synthesized through the Biginelli reaction, as well as their various biological properties (Figure 1), in the present study, we aim to present the Biginelli syntheses that led to compounds with antimicrobial properties as well as their therapeutic properties. The database search methodology used in this review was the use of keywords, which can be found in the title, such as Biginelli reaction, pyrimidine derivatives, and Biginelli therapeutic properties, in different websites, such as PubMed, MDPI, Science Direct, Springer, The Royal Society Chemistry, ACS Publications, and Taylor & Francis. The selection of scientific articles for the last ten years was made according to the novelty brought in the Biginelli synthesis, the subsequent synthesis scheme, as well as the therapeutic properties of the reported compounds. In general, articles from the last ten years have been selected.
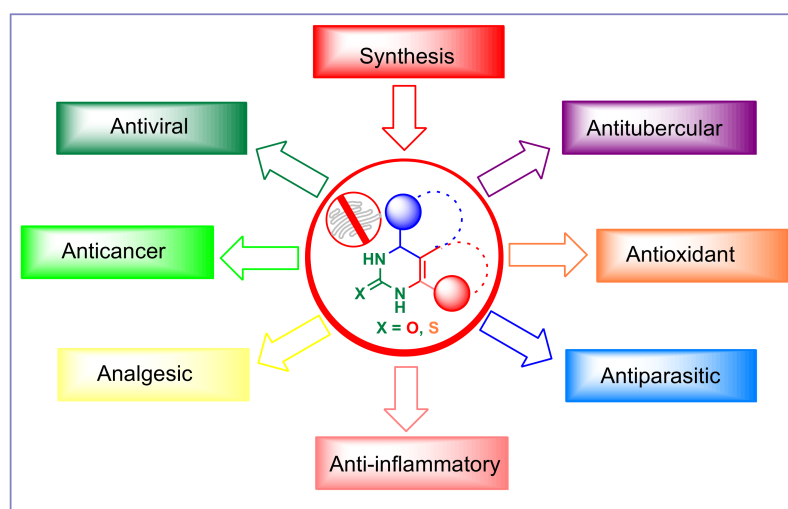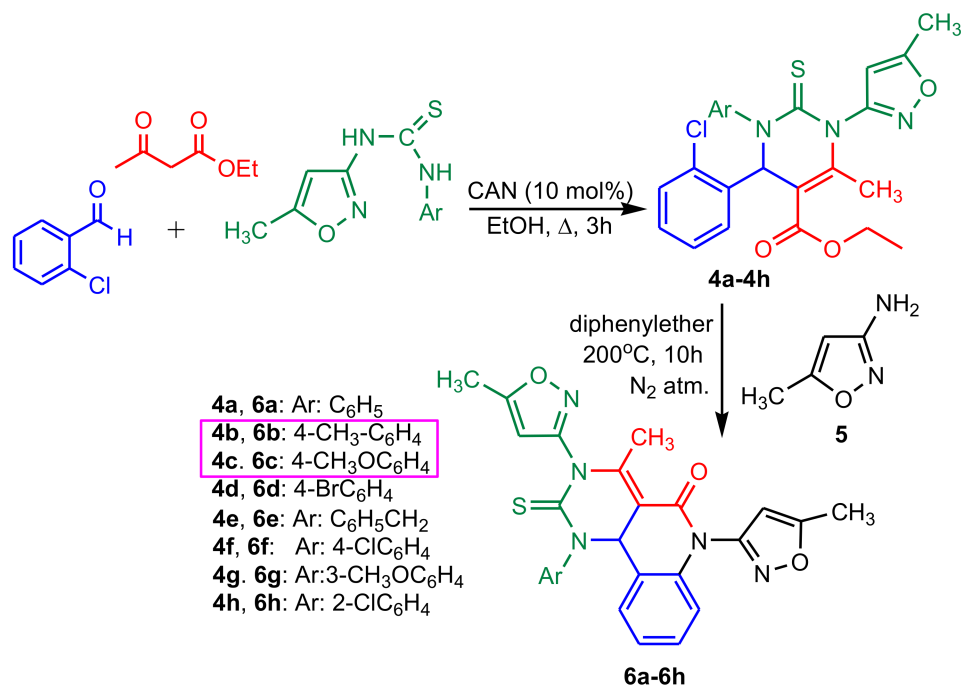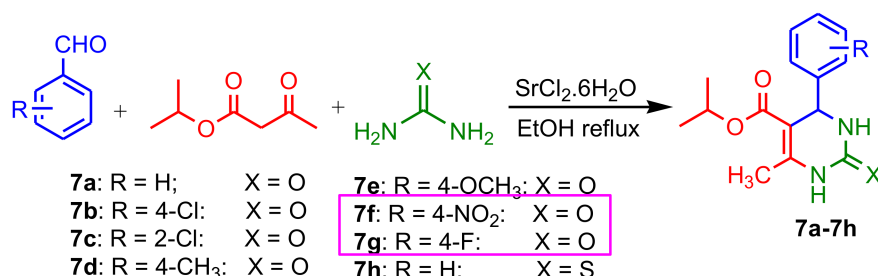

Figure 1. Schematic representation of the synthesis and therapeutical properties of antimicrobial Biginelli mediated Pyrimidine compounds.

2. Biginelli Reaction Mediated Synthesis of Antimicrobial Pyrimidine Derivatives

Kidwai et al. developed a convenient synthetic route for the preparation of quinazolines **2a–2h** by heating equimolar amounts of aldehyde **1a–1d**, 5,5-dimethyl-1,3-cyclohexanedione (dimedone), and urea/thiourea in the absence of solvent and catalyst, under microwave irradiation (Scheme 2) [70]. All compounds **2a–2h** showed antibacterial activity against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 in the concentration range of 0.564 µg mL^{-1} when tested by broth microdilution MIC method using norfloxacin as the standard drug.

Scheme 2. Synthesis of quinazolines **2a–2h** using Biginelli reaction.

Deshmukh et al. reported an efficient one step synthesis of new 2-amino-5-cyano-6-hydroxy-4-arylpyrimidines **3a–3l** by three component Biginelli condensation of aromatic aldehydes, ethyl cyanoacetate, and guanidine hydrochloride in alkaline ethanol (Scheme 3) [71]. All synthesized compounds showed good to excellent activity against tested Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria, but 2-amino-4-hydroxy-6-phenylpyrimidine-5-carbonitrile **3d** was found to be selectively active against Gram-positive bacteria.

3a: 4-N,N(CH$_3$)$_2$C$_6$H$_4$ **3e**: C$_6$H$_4$-CH=CH-   **3i**: 3,4,5(OCH$_3$)$_3$C$_6$H$_2$
3b: 3-NO$_2$-C$_6$H$_4$ **3f**: 3-Cl-C$_6$H$_4$ **3j**: 4-OH-C$_6$H$_4$
3c: 3,4(OCH$_3$)$_2$C$_6$H$_3$ **3g**: 4-OCH$_3$C$_6$H$_4$ **3k**: Thiophene-2-aldehyde
3d: -C$_6$H$_5$ **3h**: 2-NO$_2$-C$_6$H$_4$ **3l**: 2-Cl-C$_6$H$_4$

Scheme 3. Synthesis of 2-amino-5-cyano-6-hydroxy-4-arylpyrimidines **3a–3l**.

Rajanarendar et al. reported Biginelli one-pot condensation of 2-chlorobenzaldehyde, ethyl acetoacetate, and 1-(5-methylisoxazol-3-yl)-3-phenyl thioureas in presence of 10 mol% of ceric ammonium nitrite (CAN) in methanol at 80 °C for 3 h, to obtain isoxazolyl-dihydropyrimidine-thione carboxylates **4a–4h** in 80–90% yields. On heating compound **4** with 3-amino-5-methylisoxazole **5** for 10 h in diphenyl ether at 200 °C under nitrogen atmosphere, new cyclization occurred, yielding 2-thioxo-2,3,6,10b-tetrahydro-1*H*-pyrimido[5,4-c]quinolin-5-one compounds **6a–6h** (Scheme 4) [72]. Compounds **6a–6h** exhibited moderate to good antibacterial activity against *Bacillus subtilis* MTCC 441, *Bacillus sphaericus* MTCC 511, *Staphylococcus aureus* MTCC 96, *Pseudomonas aeruginosa* MTCC 741, *Klebsiella aerogenes* MTCC 39, and *Chromobacterium violaceum* MTCC 2656, and are more active than the standard drug Ciprofloxacin. The antifungal activity of compounds **6a–6h** showed that they are significantly toxic towards all the five tested pathogenic fungi, *Aspergillus niger* MTCC 282, *Chrysosporium tropicum* MTCC 2821, *Rhizopus oryzae* MTCC 262, *Fusarium moniliformae* MTCC 1848, and *Curvularia lunata* MTCC 2030, and they are lethal even at a 100 µg mL^{-1}

concentration. However, compounds **6b** and **6c** exhibited high activity, and they inhibited the growth of fungi to a remarkable extent, which correlated with the presence of methyl and methoxy substituents on the *para* position of the benzene ring.

4a, **6a**: Ar: C_6H_5
4b, **6b**: 4-CH_3-C_6H_4
4c. **6c**: 4-$CH_3OC_6H_4$
4d, **6d**: 4-BrC_6H_4
4e, **6e**: Ar: $C_6H_5CH_2$
4f, **6f**: Ar: 4-ClC_6H_4
4g. **6g**: Ar:3-$CH_3OC_6H_4$
4h, **6h**: Ar: 2-ClC_6H_4

Scheme 4. Synthesis of compounds **4a**–**4h** and **6a**–**6h**.

Chitra et al. reported the synthesis of Biginelli compounds **7a**–**7h** by a one pot cyclo-condensation of aldehydes, isopropyl acetoacetate, and urea/thiourea in ethanol, using strontium chloride hexahydrate as the catalyst (Scheme 5) [73]. Generally, the compounds showed moderate-to-good antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Salmonella typhi*. Only **7f**, which has a *nitro* group at the *para* position, and **7g**, which has a *fluorine* group in the *para* position, are more active than the reference drug Ciprofloxacin. Additionally, the antifungal activity against *Candida albicans*, *Aspergillus flavus*, *Rhizopus*, and *Mucor* of compounds **7f** and **7g** are better than of the standard drug Amphotericin B against all the tested organisms. It is also noted that compounds **7b**–**7g**, which have substituents in the 4-aryl group, are more active than the parent compound **7a** against all the tested fungi.

7a: R = H;   X = O
7b: R = 4-Cl;   X = O
7c: R = 2-Cl;   X = O
7d: R = 4-CH_3; X = O

7e: R = 4-OCH_3; X = O
7f: R = 4-NO_2 X = O
7g: R = 4-F;   X = O
7h: R = H;   X = S

Scheme 5. Synthesis of compounds **7a**–**7h**.

Dabholkar et al. reported the one-step synthesis of dihydropyrimidinones **8a**–**8d** and **9a**–**9d**, using a classic Biginelli synthesis, from thiobarbituric acid, aromatic aldehyde, urea/thiourea in ethanol, and a catalytic amount of HCl (Scheme 6) [74]. All synthesized compounds showed good antibacterial activity against *Staphyllococcus aureus* ATTC-27853, *Corynebacterium diphtheria* ATTC-11913, *Proteus aeruginosa* (recultured) and *Escherichia*

coli ATTC-25922 bacterial strains by the disc diffusion method, considering Ampiciline trihydrate as the standard drug.


8a: R = H;   R' = 4-OCH$_3$ X = S
8b: R = 2-CH$_3$: R' = 4-Cl   X = S
8c: R = 2-NO$_2$: R' = H   X = S
8d: R = 2Cl: R' = 2-OH   X = S

9a: R = H;   R' = 2-OH   X = O
9b: R = 2-CH$_3$: R' = 4-OCH$_3$ X = O
9c: R = 4-Cl: R' = 4-OCH$_3$ X = O
9d: R = 2-Cl: R' = 2-OH   X = O
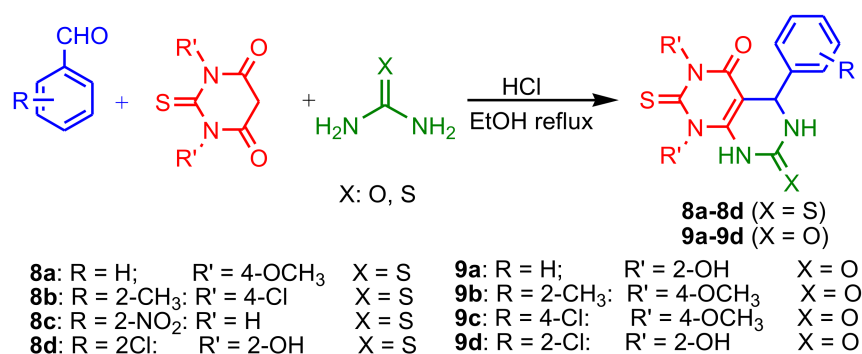
Scheme 6. Synthesis of compounds **8a–8d** and **9a–9d**.

Akhaja et al. proposed a method for the synthesis of 1,3-dihydro-2H-indol-2-ones derivatives **14a–14l** in 4 steps: (1) Biginelli synthesis on CaCl$_2$ catalyst (compounds **10**), (2) synthesis of hydrazides **11**, by treatment of Biginelli compounds with hydrazine hydrate, (3) cyclization to 1,3,4-thiadiazole **12** in concentrated H$_2$SO$_4$ medium, and (4) condensation with various 5-substituted indoline-2,3-dione **13**, in acidic medium, to afford the final compounds **14** (Scheme 7) [75]. Antibacterial activity of all synthesized compounds was screened against *Escherichia coli* MTCC-443, *Pseudomonas aeruginosa* MTCC-1688, Klebsiella pneumonia MTCC-109, *Salmonella typhi* MTCC-98, *Staphylococcus aureus* MTCC-96, Staphylococcus pyogenus MTCC-442, and *Bacillus subtilis* MTCC-441, with Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, and Norfloxacin used as standard antibacterial agents; additionally, antifungal activity was screened against three fungal species, *C. albicans* MTCC 227, *Aspergillus niger* MTCC 282, and *Aspergillus clavatus* MTCC 1323, with Nystatin and Griseofulvin as standard antifungal agents. It was found that compounds **14d** and **14j** (MIC = 62.5–100 µg mL^{-1}), containing a strong electron withdrawing group (F), exhibit excellent activity against all bacterial strains, while **14b** and **14h** (with Br) exhibited comparable activity against Gram-positive strains (MIC = 100–250 µg mL^{-1}), and **14c** and **14i** (with NO$_2$) are highly active against Gram-negative strains (MIC = 100–250 µg mL^{-1}), as compared to standard antibiotic Ampicillin. Additionally, compounds **14d** and **14f** possessed the highest antifungal activity against all fungal strains (100 µg mL^{-1}). It was established that the order of decrease in antibacterial activity, depending on the substituent present at the 5th position of 1H-indole-2,3-diones, is F > NO$_2$ > Br > Cl > H.

Kamal et al. reported the Biginelli synthesis of some conformationally flexible dimers of monastrol **15a–15e** and **16a–16e**, using CeCl$_3$.7H$_2$O as catalyst (Figure 2) [76]. Compounds **15a**, **15d**, **15e,** and **16d** exhibited moderate activity against Gram-positive bacteria, such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis*, and Gram-negative bacteria, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

Kaur et al. reported the synthesis of alkylated indeno[1,2-d] pyrimidine-2-thiones **17–26** (**a–d**) in two steps: (i) Biginelli condensation under microwave irradiations to obtain compounds **17–26**, and (ii) alkylation of the 3,4-dihydropyrimidine-2(1H)-thiones with different reactants (Scheme 8) [77]. It was determined in vitro antibacterial activity of the compounds against seven bacterial strains, such as *Bacillus subtilis* MTCC 2451, *Staphylococcus aureus* MTCC 1740, *Staphylococcus epidermidis* MTCC 435, *Escherichia coli* MTCC 443, *Salmonella typhimurium* MTCC 1251, *Pseudomonas fluorescence* MTCC 103, and *Acenetobactor calcoaceticus* MTCC 127, by the agar well diffusion method, and minimal inhibition concentration (MIC) was determined. Table 1 lists the compounds with the best antibacterial activity on at least three tested strains. We note that the ethylated compounds "b" are more biologically active.
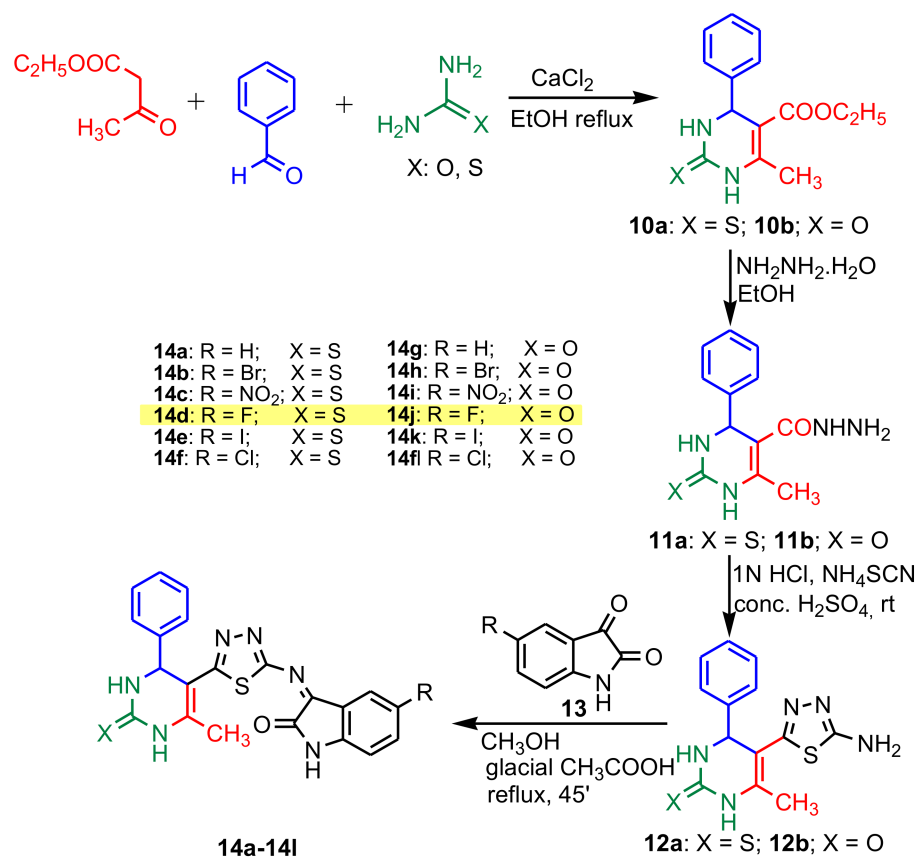
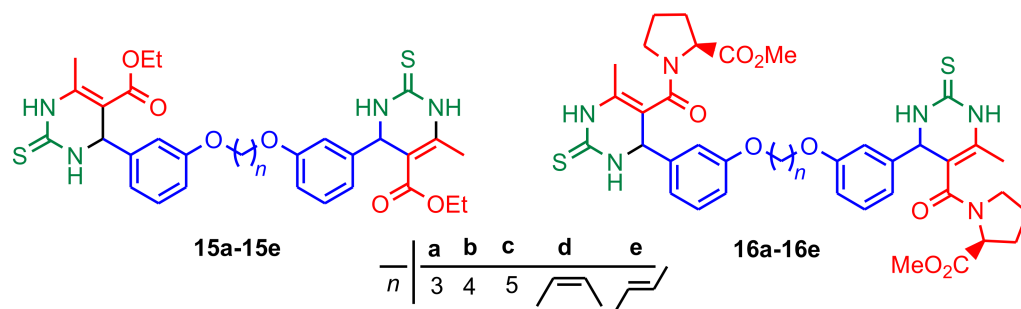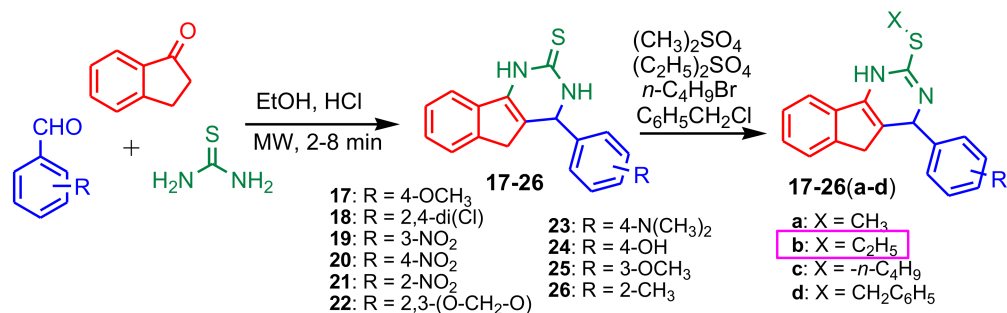**Scheme 7.** Synthesis of compounds **14a–14l**.

**Figure 2.** Chemical structures of the comounds **15a–15e** and **16a–16e**.

Scheme 8. Synthesis of compounds **17–26** and **17–26(a–d)**.

Table 1. Minimum inhibitory concentration of compounds **17–23**.

Compound	Minimum Inhibitory Concentration MIC (μg mL^{-1})						
	PF	**ST**	**SA**	**EC**	**BS**	**SE**	**AC**
17b	15	-	12	-	-	-	55
20a	-	27	54	1	2	2	-
20b	14	1	6	17	21	13	36
23b	14	28	-	-	-	46	-
25b	-	13	26	54	50	20	-

PF: *P. fluorescence*; ST: *S. typhimurium*; SA: *S. aureus*; EC: *E. coli*; BS: *B. subtilis*; SE: *S. epidermidis*; AC: *A. calcoaceticus*.

Kulakov synthesized new 3,4-dihydropyrimidin-2-thiones **28** in two steps: (i) a Biginelli reaction to obtain compounds **27** and (ii) an aminomethylation Mannich reaction to obtain 3,4-dihydropyrimidin-2-thiones grafted with alkaloid cytisine (Scheme 9) [78]. The bioscreening of **28a** revealed its pronounced antibacterial activity against the Gram-positive strains *S. aureus* and *B. subtilis*, weak activity against Gram-negative strains *P. aeruginosa* and *E. coli*, in addition to the fungus *C. albicans*.
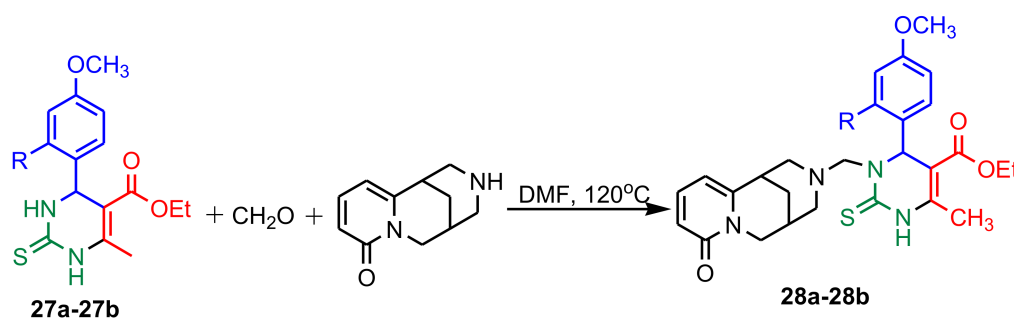
Scheme 9. Synthesis of compounds **28a–28b**.

Alam et al. reported the synthesis of compounds **31a–31n**, using in the first step a Biginelli synthesis to obtain compound **29**, from which, by the nucleophilic attack of the hydrazine hydrate, intermediate **30** resulted. Intermediate **30** was condensed with various aldehydes, resulting in final compounds **31** (Scheme 10) [79]. The minimum inhibitory concentrations (MIC) of the compounds with antimicrobial activities are presented in Table 2. Compound **31e**, which possesses two chlorine atoms, has the best antimicrobial activity at 12.5 μg mL^{-1} against all tested strains.
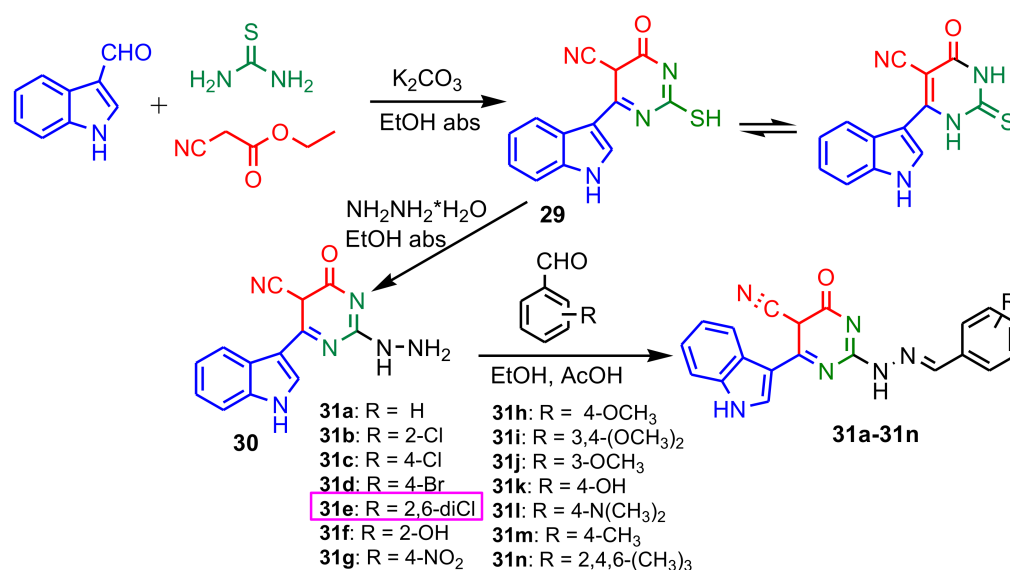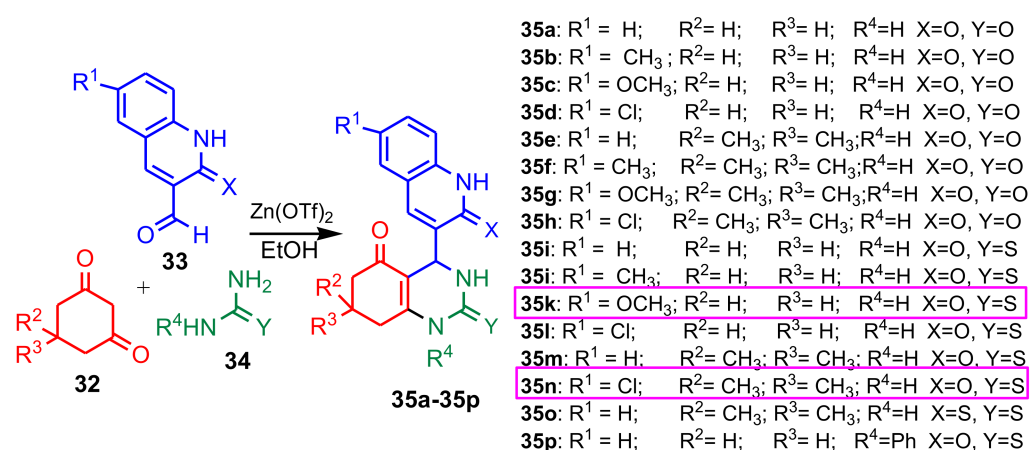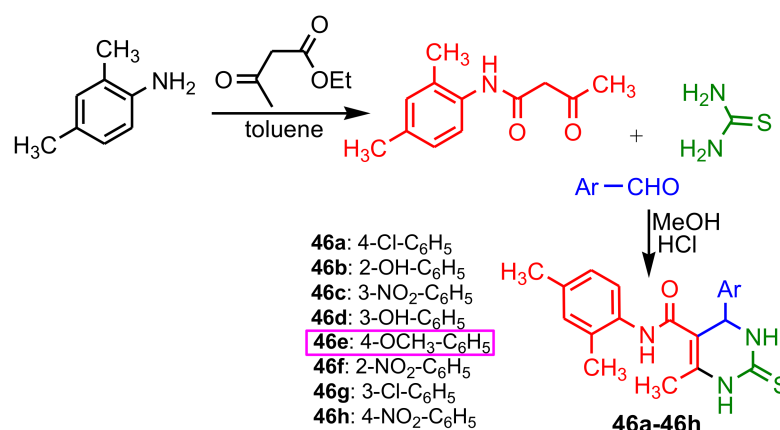

Scheme 10. Synthesis of compounds **31a–31n**.

Table 2. Minimum inhibitory concentration MIC ($\mu g\ mL^{-1}$) of compounds **31**.

Compounds	*Staphylococcus aureus*	*Escherichia coli*	*Rhizopus oryza*	*Penicillium citrum*
31b	50	>100	50	>100
31c	50	50	50	>100
31d	50	50	25	25
31e	12.5	12.5	12.5	12.5
31i	25	25	50	50
Norfloxacin	6.25	6.25	-	-
Fluconazole	-	-	6.25	6.25

Shah and Patel synthesized new octahydroquinazolinone derivatives, using a modified Biginelli synthesis (Scheme 11) and a Lewis acid, zinc triflate, as catalyst [80]. Compounds **35a–35m** were screened for their antibacterial activity against *Bacillus subtilis* MTCC 441, *Clostridium tetani* MTCC 449, *Streptococcus pneumoniae* MTCC 1936, *E. coli* MTCC 443, *Salmonella typhi* MTCC 98, and *Vibrio cholerae* MTCC 3906 as well as for antifungal activity against Aspergillus fumigatus MTCC 3008 and *Candida albicans* MTCC 227. From the screening results, compound **35k** shows excellent antibacterial activity against *E. coli* (MIC = 50 $\mu g\ mL^{-1}$) when compared with ampicillin and equivalent to chloramphenicol (MIC = 50 $\mu g\ mL^{-1}$); compounds **35c**, **35e**, **35f**, **35g**, **35h**, **35i**, and **35l** show comparable antibacterial activity against *E. coli* (MIC = 100 $\mu g\ mL^{-1}$) when compared with ampicillin (MIC = 100 $\mu g\ mL^{-1}$). Compound **35n** shows excellent antibacterial activity against *S. typhi*, *S. pneumoniae*, *V. cholerae*, and *B. subtilis* (MIC = 25–50 $\mu g\ mL^{-1}$) when compared with chloramphenicol (MIC = 50 $\mu g\ mL^{-1}$) and ampicillin (MIC = 100 $\mu g\ mL^{-1}$) and compounds **35o**, **35p** were found to exhibit excellent antibacterial activity against *S. typhi* when compared with ampicillin. (MIC = 100 $\mu g\ mL^{-1}$). Antifungal screening data show that compound **35i** shows excellent antifungal activity (MIC = 100 $\mu g\ mL^{-1}$) against *C. albicans* when compared with nystatin and griseofulvin (MIC = 100 $\mu g\ mL^{-1}$); compounds **35a**, **35c**, **35e–35h**, **35j**, and **35o** show excellent antifungal activity (MIC = 500 $\mu g\ mL^{-1}$) against *C. albicans* when compared with griseofulvin (MIC = 500 $\mu g\ mL^{-1}$).

35a: R^1 = H; R^2= H; R^3= H; R^4=H X=O, Y=O
35b: R^1 = CH_3; R^2= H; R^3= H; R^4=H X=O, Y=O
35c: R^1 = OCH_3; R^2= H; R^3= H; R^4=H X=O, Y=O
35d: R^1 = Cl; R^2= H; R^3= H; R^4=H X=O, Y=O
35e: R^1 = H; R^2= CH_3; R^3= CH_3;R^4=H X=O, Y=O
35f: R^1 = CH_3; R^2= CH_3; R^3= CH_3;R^4=H X=O, Y=O
35g: R^1 = OCH_3; R^2= CH_3; R^3= CH_3;R^4=H X=O, Y=O
35h: R^1 = Cl; R^2= CH_3; R^3= CH_3; R^4=H X=O, Y=O
35i: R^1 = H; R^2= H; R^3= H; R^4=H X=O, Y=S
35i: R^1 = CH_3; R^2= H; R^3= H; R^4=H X=O, Y=S
35k: R^1 = OCH_3; R^2= H; R^3= H; R^4=H X=O, Y=S
35l: R^1 = Cl; R^2= H; R^3= H; R^4=H X=O, Y=S
35m: R^1 = H; R^2= CH_3; R^3= CH_3; R^4=H X=O, Y=S
35n: R^1 = Cl; R^2= CH_3; R^3= CH_3; R^4=H X=O, Y=S
35o: R^1 = H; R^2= CH_3; R^3= CH_3; R^4=H X=S, Y=S
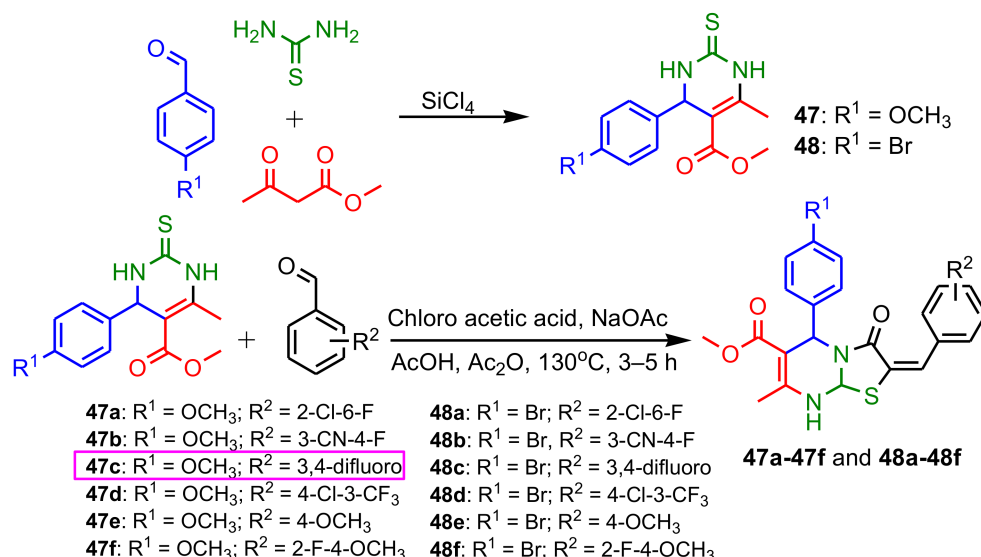**35p**: R^1 = H; R^2= H; R^3= H; R^4=Ph X=O, Y=S

Scheme 11. Synthesis of compounds **35a–35p**.

Youssef and Amin synthesized new compounds **37a–37b** and **38a–38b**, using Biginelli intermediates **36a–36b** obtained by a classical reaction (Scheme 12) [81]. The newly heterocyclic compounds were tested for their antimicrobial activity against *Escherichia coli*, *Pseudomonas putida*, *Bacillus subtilis*, *Streptococcus lactis*, *Aspergillus niger*, *Penicillium* sp., and *Candida albican*s. All compounds showed moderate to slight inhibitory action towards the microorganisms.
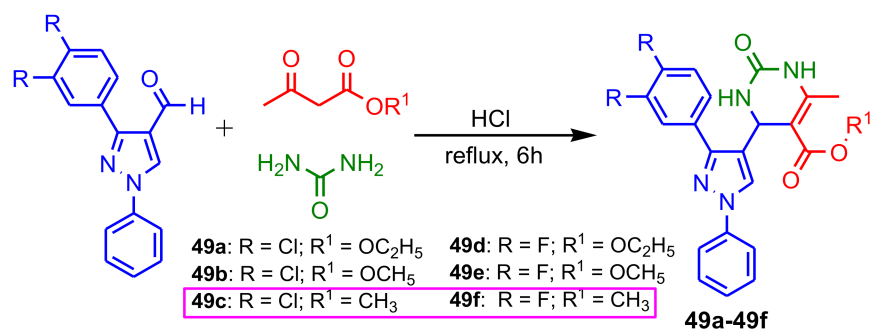
Scheme 12. Synthesis of compounds **36**, **37**, and **38**.

Sedaghati et al. reported synthesis of new Biginelli pyrimidines **39a**–**39b**, **40a**–**40c**, **41**, and **42**, using ferric chloride as Lewis acid (Figure 3) [82]. Compounds **39a** and **42** possessed a significant antibacterial activity (MIC = 128 μg mL^{-1}) against *Staphylococcus aureus* PTCC 1337 and *Pseudomonas aeruginosa* PTCC 1074, respectively. Additionally, compounds **39b**, **40a**, **40b**, **40c**, **41**, and **42** have been shown to be moderate antifungal agents against both *Candida albicans* PTCC 5027 and *Aspergillus niger* 5021 (MIC = 32–128 μg mL^{-1}).

Figure 3. Chemical structures of compounds **39a**–**39b**, **40a**–**40c**, **41** and **42**.

Ghodasara et al. reported the synthesis of Biginelli compounds **43a**–**43d**, the corresponding methylated derivatives **44a**–**44d**, and their oxidized compounds **45a**–**45d** (Scheme 13) [83]. The preliminary in vitro biological activities of the compounds revealed that compounds **43a**, **44d**, **45h**, and **45j** exhibited significant (maximum) antibacterial activities against all bacterial tested strains, *S. aureus* MTCC 96, *E. coli* MTCC 443, and *B. subtilis* MTCC 441, compared with Ampicillin, Chloramphenicol, Ciprofloxacin, and Norfloxacin as standards drug, and against both fungal strains, *C. albicans* MTCC 227 and *A. niger* MTCC 282.

Scheme 13. Synthesis of compounds **43a**–**43d**, **44a**–**44d**, and **45a**–**5d**.

Godhani et al. reported the Biginelli synthesis of compounds **46a**–**46h** (Scheme 14) and their antimicrobial activities [84]. Compounds **46b**, **46g**, and **46h** showed good activity against *E. coli* MTCC 443 bacteria (MIC = 324.7–405.7 μM L^{-1}), while compound **46e** showed excellent activity against *E. coli* (MIC = 202.93 μM L^{-1}). Additionally, compounds **46b** and **46e** showed good activity against *P. aeruginosa* MTCC 1688. Compounds **46a**, **46b**, **46c**, **46d**, **46f**, **46g**, and **46h** showed moderate activity against *S. aureus* MTCC 96, with MIC = ranging from 649.4 to 811.75 μM L^{-1}. Compounds **46b**, **46e**, and **46f** showed good activity against *S. pyogenus* MTCC 442 (MIC = 324.7–405.87 μM L^{-1}).

Scheme 14. Synthesis of compounds **46a–46h**.

Umesha et al. synthesized in two steps compounds **47a–47f** and **48a–48f** (Scheme 15) [85]. Compound **48c** showed the best antimicrobial activity against all tested strains, four bacterial strains, *S. aureus*, *B. subtilis*, *S. typhi*, and *E. coli*, and two fungal strains, *A. niger* and *C. albicans*, but the other compounds also had good antimicrobial activities.

47a: R¹ = OCH₃; R² = 2-Cl-6-F
47b: R¹ = OCH₃; R² = 3-CN-4-F
47c: R¹ = OCH₃; R² = 3,4-difluoro
47d: R¹ = OCH₃; R² = 4-Cl-3-CF₃
47e: R¹ = OCH₃; R² = 4-OCH₃
47f: R¹ = OCH₃; R² = 2-F-4-OCH₃

48a: R¹ = Br; R² = 2-Cl-6-F
48b: R¹ = Br, R² = 3-CN-4-F
48c: R¹ = Br, R² = 3,4-difluoro
48d: R¹ = Br, R² = 4-Cl-3-CF₃
48e: R¹ = Br, R² = 4-OCH₃
48f: R¹ = Br, R² = 2-F-4-OCH₃

Scheme 15. Synthesis of compounds **47a–47f** and **48a–48f**.

Viveka et al. synthesized compounds **49a–49f** by a Biginelli reaction (Scheme 16) [86]. The antibacterial screening results revealed that acetyl-substituted pyrimidinone compounds **49c** and **49f** showed a broad spectrum of antimicrobial activity against *E. coli*, *P. aeruginosa*, and *K. pneumonia* (6.25 µg mL⁻¹), comparable with the standard Streptomycin (6.25 µg mL⁻¹). A gradual decrease in the activity against the tested strains was noticed, with the introduction of ethoxy **49a** and **49d** and methoxy **49b** and **49e** groups, in place of acetyl substituent.

Raj et al. reported the synthesis of dihydropyrimidinones **50a–50e**, by a Biginelli reaction using Zn(ClO₄)₂ as catalyst (Scheme 17) [87]. In vitro antibacterial studies of dihydropyrimidones **50a–50e** were carried out against *Escherichia coli* MTCC 119, *Shigella flexneri* MTCC 1457, *Pseudomonas aeruginosa* MTCC 741, and *Staphylococcus aureus* MTCC 740 strains, by disk-diffusion assay. Antifungal evaluations were also carried out against two fungal strains, *Geotrichum candidum* MTCC 3993 and *Candida albicans* MTCC 227 (Table 3). From the determined MIC values, it can be said that compound **50a** had the best antimicrobial activity against all the strains tested.

Scheme 16. Synthesis of compounds **49a–49f**.
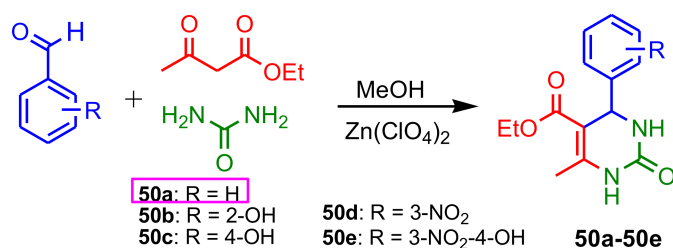
Scheme 17. Synthesis of compounds **50a–50e**.

Table 3. In vitro antibacterial activities of compounds **50a–50e**.

Compounds	MIC (μg mL^{-1})					
	Sa	**Pa**	**Sf**	**Ec**	**Gc**	**Ca**
50a	15 ± 1	30 ± 0.5	71	72 ± 2	40 ± 1	99 ± 1
50b	15	>100	>100	>100	60 ± 3	>100
50c	20 ± 3	18 ± 1	73	75 ± 2	>100	99 ± 1
50d	80 ± 4	82 ± 2	>100	90 ± 4	>100	>100
50e	90 ± 2	91 ± 2	>100	85 ± 4	>100	>100

Sa: *S. aureus* MTCC 740; Pa: *P. aeruginosa* MTCC 741; Sf: *S. flexneri* MTCC 1457; Ec: *E. coli* MTCC 119; Gc: *G. candidum* MTCC 3993; CA: *C. albicans* MTCC 227.

Gein et al. reported the synthesis of new N,6-diaryl-4-methyl-2-oxo- 1,2,3,6-tetrahydro-pyrimidine-5-carboxamides by a Biginelli reaction (Scheme 18) [88]. Compounds **51–61** showed weak antimicrobial activity against *S. aureus*, E.coli, and *C. albicans* (MIC = 250–1000 μg mL^{-1}) considering dioxidine and fluconazole as standards, but good antibacterial activities for compound **53** (MIC = 250 μg mL^{-1}), considering Chloramine B as standard (MIC = 250–500 mg mL^{-1}).
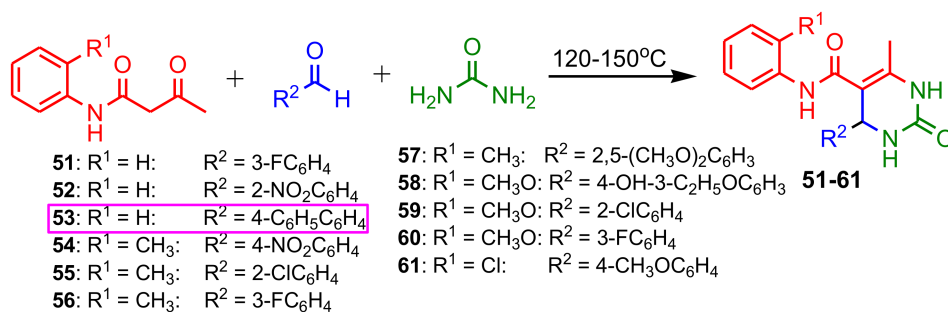
Scheme 18. Synthesis of compounds **51–61**.

Khalifa et al. reported the synthesis of compounds **62a–62d** and **63**, using a Biginelli intermediate reaction (Figure 4) [89]. Compound **62d** exhibited inhibition versus all kinds of bacterial (*Staphylococcus aureus*, *Salmonella typhimurium* and *Pseudomonas aeruginosa*) and

fungal strains (*Candida albicans* and *Aspergillus flavus*). Additionally, compounds **62a–62c** possessed good antimicrobial activities.

62a: R = H
62b: R = OCH₃
62c: R = F
62d: R = N(CH₃)₂
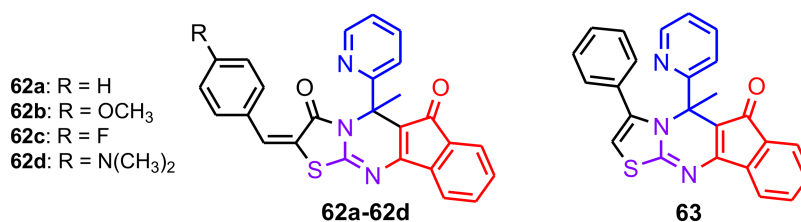
62a-62d   **63**

Figure 4. Chemical structures of compounds **62a–62d** and **63**.

Ahmad et al. reported the synthesis of some 2-amino-1,4-dihydropyrimidines by a Biginelli reaction, starting from guanidine HCl, benzaldehyde, and ethyl acetoacetate in DMF, and SnCl₂·2H₂O or NaHCO₃ as catalyst, under ultrasonic irradiation [90].

The good antibacterial activities of compounds **64**, **65**, and **66** (Figure 5), against *S. aureus*, *B. subtilis*, *E. coli*, and *S. typhi*, as well as the theoretical studies, have shown that these compounds may have acceptable pharmacokinetic/drug-like properties.

64: R¹ = H: R² = Ph;   R³ = Ph
65: R¹ = 2-ClC₆H₄;   R² = OEt;   R³ = OEt
66: R¹ = 4-ClC₆H₄;   R² = OEt;   R³ = OEt
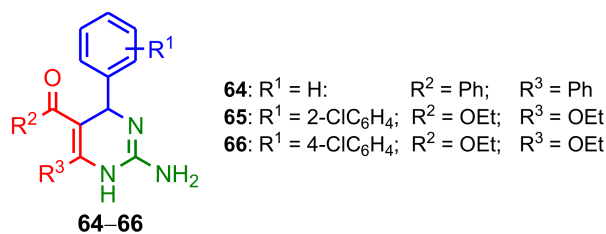
64–**66**

Figure 5. Chemical structures of compounds **64**–**66**.

Ramachandran et al. reported the syntheses of dihydropyrimidinones **67** and **68** using solvent-free grindstone chemistry method catalyzed by CuCl₂·2H₂O and HCl (Scheme 19) [91]. All the synthesized compounds exhibited significant activity against pathogenic bacteria *Salmonella typhi* and *Staphylococcus aureus*. These dihydropyrimidinone (DHPM) derivatives also focus on the bacterial ribosomal A site RNA as a drug target. Series of docking studies were also performed for human 40S rRNA as a target. It was found that amikacin drug exhibited higher binding affinity than compound **68e**, which showed relatively low binding affinity towards human rRNA site (Figure 6).

67a: R = H;   Z = O   **68a**: R = H;   Z = S
67b: R = 3-Cl;   Z = O   **68b**: R = 3-Cl;   Z = S
67c: R = 4-OCH₃;   Z = O   **68c**: R = 4-OCH₃;   Z = S
67d: R = 2-NO₂;   Z = O   **68d**: R = 2-NO₂;   Z = S
67e: R = 2,3-OCH₂O-; Z = O   **68e**: R = 2,3-OCH₂O-; Z = S
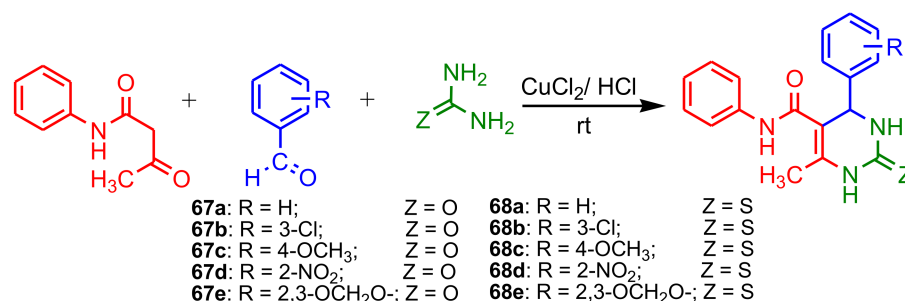
Scheme 19. Synthesis of compounds **67a–67e** and **68a–68e**.

Desai and Bhatt reported the synthesis of compounds **72a–72c**, using, in the first step, a Biginelli reaction in the presence of SnCl₂·2H₂O catalyst to obtain compound **69**, which, in the presence of hydrazine hydrate, resulted in a hydrazide **70**, from which Schiff bases **71a–71c** were obtained by reaction with aromatic aldehydes. Cyclization of compounds **71** in the presence of triethylamine provided the desired β-lactams **72a–72c**, as shown in Scheme 20 [92]. Compounds **72a–72c** exhibited outstanding antimicrobial properties

against almost all tested strains *S. aureus*, *S. pyogenes*, *E. coli*, *P. aeruginosa*, *C. albicans*, *A. niger*, and *A. clavatus* with MIC = 12.5–50 µg mL^{-1} for antibacterial activities and 25–100 µg mL^{-1} for antifungal activities, respectively.
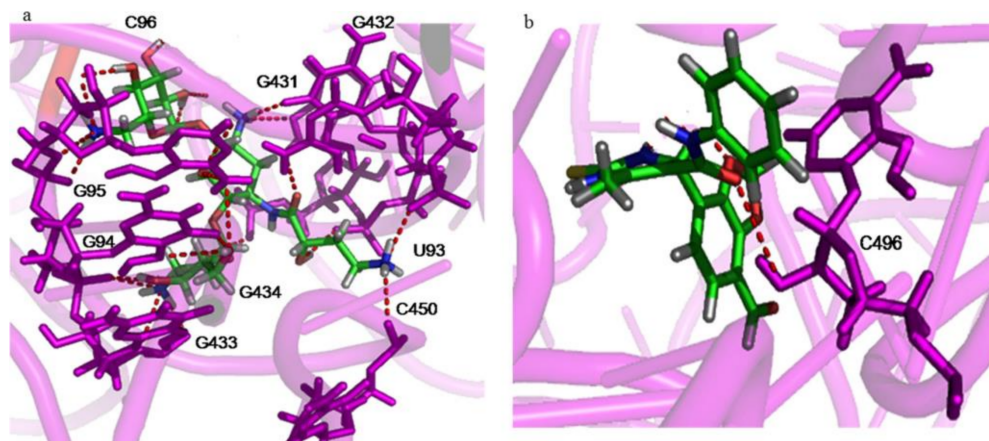
Figure 6. Extra precision Glide docking of human rRNA (3J3D) with (**a**) amikacin and (**b**) compound **68e**.
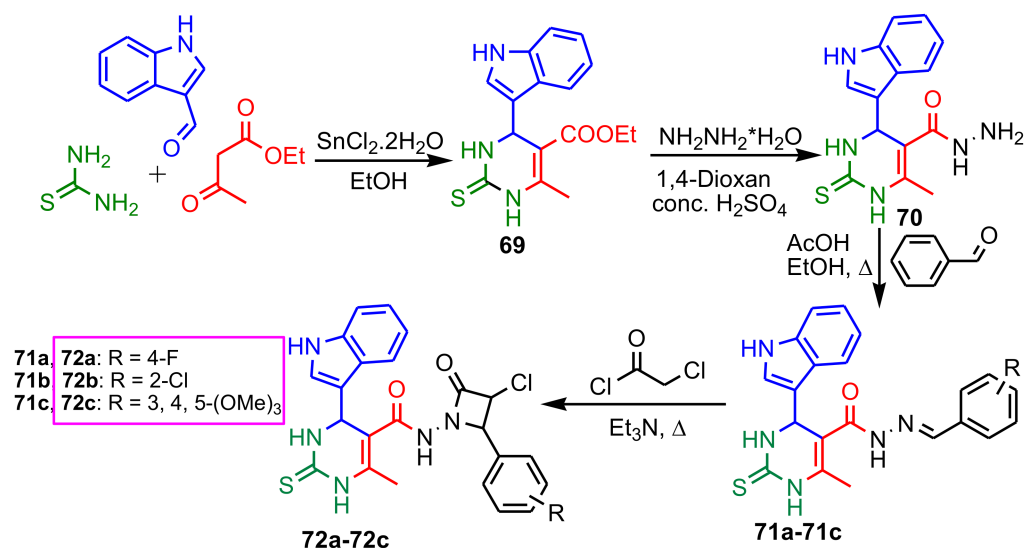
Scheme 20. Synthesis of compounds **71a**–**71c** and **72a**–**72c**.

Attri et al. synthesized dihydropyrimidinones by a Biginelli reaction with triethylammonium acetate ionic liquid as catalyst [93]. Compounds **73a**–**73c** (Figure 6) showed the good antibacterial activity against all bacteria *Escherichia coli* MTCC 443, *Staphylococcus aureus* MTCC 3160, *Pseudomonas aeruginosa* MTCC 2581 and *Klebsiella pneumoniae* MTCC 7028, which could possibly be due to the presence of halogen atom in the molecules. Wani et al. reported the synthesis of Flucytosine analogues **74a**–**74b** and **75a**–**75b** obtained by the classic Biginelli reaction as efficient antifungal agents against *C. albicans* (Figure 7) [94]. Thus, bis-derivatives **75a**–**75b** were found to be more efficacious than their corresponding mono analogues **74a**–**74b**. Compound **75b** with two pyrimidithione rings showed high synergy with amphotericin-B and fluconazole, both followed by compounds **75a**, **74b**, and **74a**.
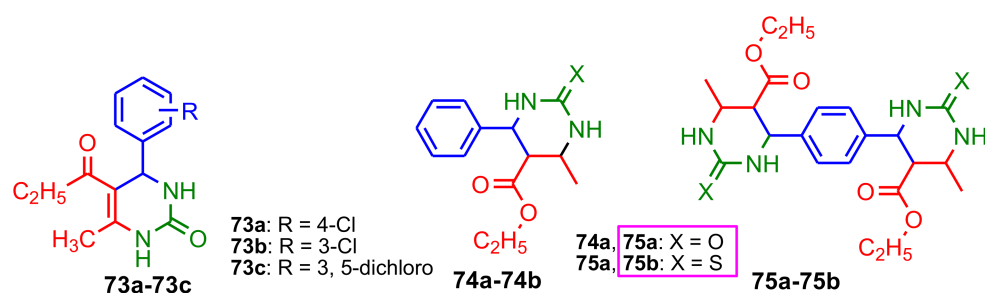
Figure 7. Chemical structures of compounds **73a**–**73c**, **74a**–**74b**, and **75a**–**75b**.

Rani et al. synthesized compounds **76a**–**76e** by a Biginelli reaction from 3-oxo-N-phenylbutanamide, guanidine nitrate, an aldehyde, and HCl as catalyst [95] (Scheme 21), and compounds **77a**–**77e**, from the reaction of derivatives **76** with 6-(hydroxymethyl)-tetrahydro-2H-pyran-2,3,4,5-tetraol, ethyl acetoacetate, and monochloroacetic acid. It was found that compounds **77a** and **77b** had significant activity against *S. aureus* (MIC = 2.14×10^{-2} μM mL^{-1}), and compound **77c** was most potent against *B. subtilis* (MIC = 0.58×10^{-2} μM mL^{-1}). Compound **77e** displayed more potent activity against *E. coli* (MIC = 1.10×10^{-2} μM mL^{-1}), and compound **77d** was found to be most potent against *C. albicans* and *A. niger* (MIC = 1.04×10^{-2} μM mL^{-1}).

76a, **77a**: R = 3-Br
76b, **77b**: R = 4-Br
76c, **77c**: R = 3-Br-6-OH

76d, **77d**: R = 3-Cl
76e, **77e**: R = 2-OC$_2$H$_5$-4-OH
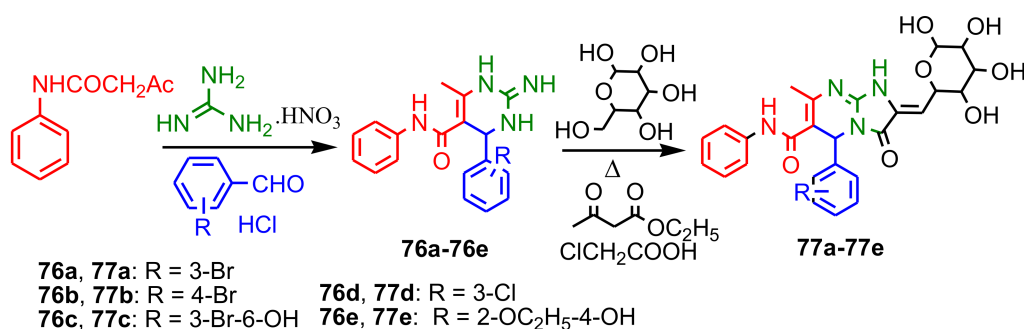
Scheme 21. Synthesis of compounds **76a**–**76e** and **77a**–**77e**.

Allam synthesized pyrazolopyrimidinone based dihydropyrimidinones **78a**–**78f** by a green Biginelli procedure catalyzed by CuCl$_2$·2H$_2$O (Figure 8) [96]. All compounds had good antibacterial activities against *B. subtilis*, *E. coli*, *K. pneumonia*, and *S. aureus*. Foroughifar et al. reported that tetrahydropyrimidine **79**, synthesized by a Biginelli reaction with DABCO (1,4-Diazabicyclooctane) as catalyst, had good antimicrobial activities against all tested strains *S. aureus*, *S. epidermidis*, *Bacillus cereus*, *K. pneumoniae*, *E. coli*, and *P. aeruginosa* [97].

78a: R^1 = H;   R^2= H;   R^3= Et;   X=O
78b: R^1 = H;   R^2= OMe; R^3= Et;   X=O
78c: R^1 = H;   R^2= OEt; R^3= Et;   X=S
78d: R^1 = H;   R^2= OEt; R^3= Me;   X=S
78e: R^1 = OMe ; R^2= OMe; R^3= Et;   X=S
78f: R^1 = OMe ; R^2= OMe; R^3= Me;   X=S
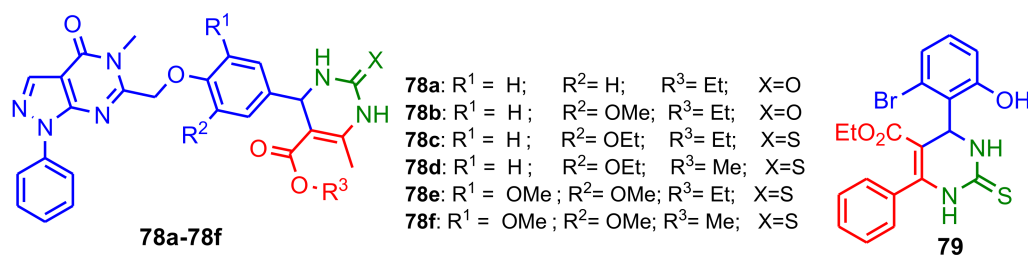
Figure 8. Chemical structures of compounds **78a**–**78f** and **79**.

Naik et al. reported the synthesis of a new of 3,4-dihydropyrimidinone-coumarin analogues **80** and **81** (Scheme 22) as a new class of antibacterial agents [98]. The 3,4-dihydropyrimidinone-coumarins were evaluated for their in vitro antibacterial studies against Staphylococcus aureus, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*

by Broth micro dilution method (Table 4). All compounds exhibited excellent antibacterial activity against *S. aureus* - bold values (MIC = 0.2–6.25 μg mL^{-1}), but in the case of *B. subtilis*, all compounds were less active. The efficacy of substituent at C-6 position decreased in the order -CH$_3$ > -7,8-Benzo > -Cl > -OCH$_3$ (**b** > **e** > **c** >**a**). Similarly, compounds **81a**, **81c**, and **81e** were highly active against *E. coli*, whereas the other compounds showed significantly less activity.

80a: R = 6-OCH$_3$;   X = O
80b: R = 6-CH$_3$;   X = O
80c: R = 6-Cl;   X = O
80d: R = 7-Me;   X = O
80e: R = 7-8-Benzo;   X = O
81a: R = 6-OCH$_3$;   X = S
81b: R = 6-CH$_3$;   X = S
81c: R = 6-Cl;   X = S
81d: R = 7-Me;   X = S
81e: R = 7-8-Benzo;   X = S
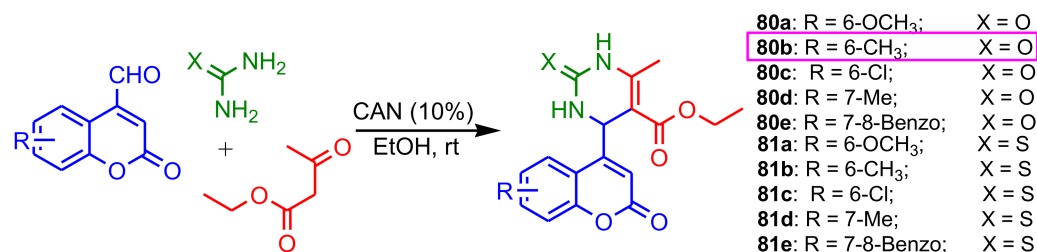
Scheme 22. Synthesis of compounds **80a**–**80e** and **81a**–**81e**.

Table 4. In vitro antibacterial activity (MIC) of compounds **80a**–**80e** and **81a**–**81e**.

Compound	Minimum Inhibitory Concentrations (MIC) (μg mL^{-1})			
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
80a	**0.4**	12.5	50	100
80b	**0.8**	100	50	25
80c	3.12	100	25	50
80d	**0.2**	50	12.5	100
80e	**0.4**	100	25	25
81a	**0.4**	100	**1.6**	100
81b	**0.8**	50	25	100
81c	**0.8**	50	**0.4**	100
81d	6.25	50	25	100
81e	**0.4**	100	**0.4**	100
Ciprofloxacin	2	2	2	<4

Hamdi et al. synthesized 3,4-dihydropyrimidinones **82a**–**82e** by a modified Biginelli-type reaction with various metallophthalocyanines **83**–**85** as reusable heterogeneous as catalysts (Figure 9) [99]. The antimicrobial activity of compounds **82a**–**82e** was evaluated against *Micrococcus luteus* LB 14110, *Staphylococcus aureus* ATCC 6538, *Listeria monocytogenes* ATCC 19117, and *Salmonella typhimurium* ATCC 14028, but significant antimicrobial activity (MIC = 312 μg mL^{-1}) was observed against *M. luteus*.

82a: R = H
82b: R = 3-CH$_3$
82c: R = 4-Br
82d: R = 4-NO$_2$
82e: R = 3-OCH$_3$

82a-82e

83: M = Co
84: M = Zn
85: M = Cu
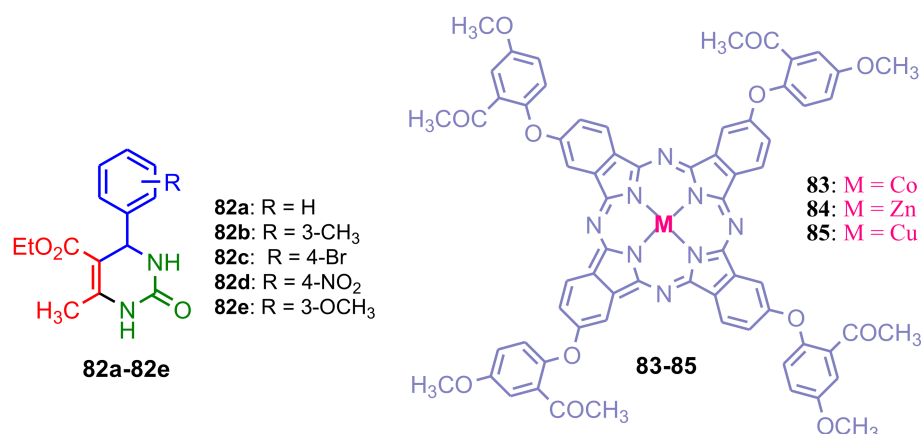
83-85

Figure 9. Chemical structures of compounds **82a**–**82e** and **83**–**85**.

Youssef et al. synthesized 6-amino-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine- 5-carbonitrile derivatives **86a–86d** by Biginelli reaction of aromatic aldehydes, malononitrile, and thiourea in alcoholic sodium ethoxide solution [100]. The reaction of each **86** with monobromomalononitrile in ethanolic potassium hydroxide solution yielded, in each case, a single product, **87a–87d**. By refluxing each **87** with carbon disulphide, the corresponding compounds **88a–88b** were obtained. Finally, heating compounds **87** with formic acid yielded **89a–89b** (Figure 10). Compounds **86a**, **86b**, **87a**, **87b**, **88a**, and **89a** showed moderate to slight inhibitory action against the tested strains *Escherichia coli*, *Pseudomonas putida*, *Bacillus subtilis*, *Streptococcus lactis*, *Aspergillus niger*, *Penicillium* sp., and *Candida albicans*.

86a, 87a: R = 4-Cl
86b, 87b: R = 4-OCH₃
86c. 87c: R = 4-F
86d, 86d: R = 4-NO₂
88a, 89a: R = 4-Cl
88b, 89b: R = 4-OCH₃
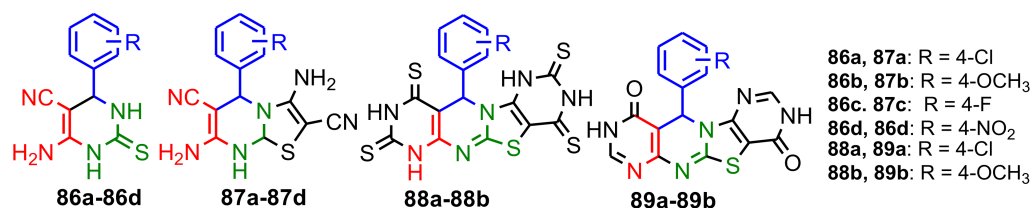
Figure 10. Chemical structures of compounds **86**, **87**, **88**, and **89**.

Viveka et al. reported the Biginelli synthesis of 3,4-dihydropyrimidinones **90a–90c**. Reaction of each compound **90** with pyrazole **91** gave thiazolo[2,3-b] dihydropyrimidinones **92a–92c** (Scheme 23) [101]. As observed in Table 5, compounds **92a–92c** show good antibacterial activity against all the tested species (MIC = 3.12–25 µg mL^{-1}).

90a, 92a: R = 3-F-4-CH₃
90b, 92b: R = 2,5-(OCH₃)₂
90c. 92c: R = 4-OCH₃
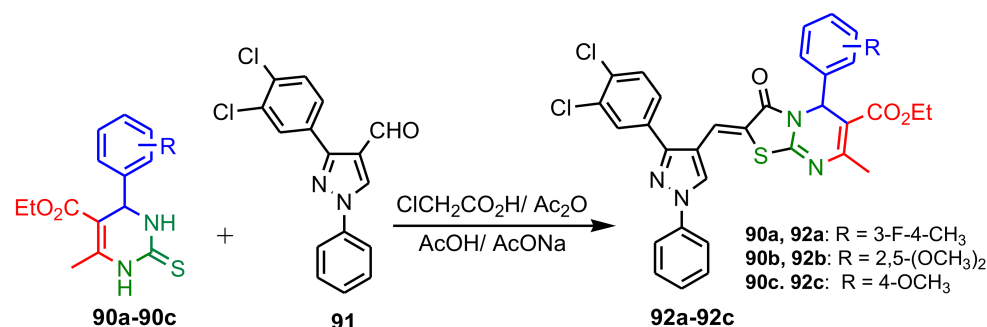
Scheme 23. Synthesis of compounds **90a–90c** and **92a–92c**.

Table 5. In vitro antibacterial activity (MIC) of compounds **92a–92c**.

Compound	Minimum Inhibitory Concentrations (MIC) (µg mL^{-1})			
	E. coli	*S. aureus*	*P. aeruginosa*	*K. pneumoniae*
92a	3.12	3.12	12.5	6.25
92b	3.12	6.25	12.5	3.12
92c	6.25	25	6.25	6.25
Streptomycin	2.8	2.5	3.8	2.8

Huseynzada et al. reported Biginelli synthesis catalyzed by Cu(OTf)₂ of dihydropyrimidines, their regioselective oxidation, and their antibacterial properties [102]. Compounds **93** and **94** showed the highest inhibitory effect against *A. baumanii* and *S. aureus*, with a value of 62.5 µg mL^{-1} (Figure 11).

Gondru et al. reported the synthesis of a series of newly fused thiazolo[2,3-b] pyrimidinones **97** by reaction between Biginelli intermediates **95** and 3-(2-oxo-2H- chromen-3-yl)-1-aryl-1H-pyrazole-4-carbaldehyde (Scheme 24) [103] **96**. All compounds exerted significant in vitro antibacterial activity against almost all the tested bacterial strains with MICs ranging from 1.56 − 12.5 µg mL^{-1} (Table 6). Compound **97d** displayed inhibitory efficacies and a broader antibacterial spectrum than that of the reference drugs.

Compound **97d** exhibited excellent inhibiting activity than the standard streptomycin (MIC = 6.25 µg mL^{-1}) and equipotent to that of penicillin (MIC = 1.562 µg mL^{-1}) against *S. aureus* and *B. subtilis* with MIC values 1.56 µg mL^{-1}, being almost as active as the standard drug (MIC = 3.12 µg mL^{-1}) against Gram-positive *S. epidermidis* (MIC = 3.12 µg mL^{-1}). Compounds **97c** and **97e** could effectively inhibit the growth of *S. aureus* with MIC values (MIC = 1.56 and 3.12 µg mL^{-1}, respectively) and *P. aeruginosa* (MIC = 6.25 µg mL^{-1}). Compounds **97a**, **97b**, **97c** and **97e** have shown bioactivity against *P. aeruginosa* (MIC = 6.25 µg mL^{-1}), which was better than penicillin. Compounds **97g** and **97h** showed significant activity against *S. aureus* (MIC = 3.12 µg mL^{-1}).
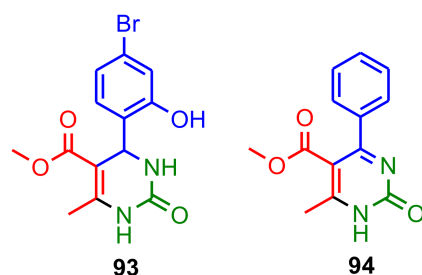
Figure 11. Chemical structures of compounds **93** and **94**.
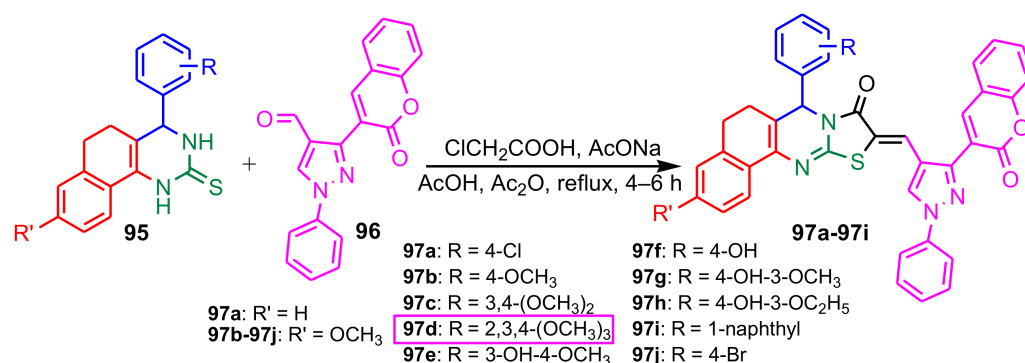
Scheme 24. Synthesis of compounds **97a–97j**.

Table 6. In vitro antibacterial activity (MIC) of compounds **97a–97i**.

Compounds	Minimum Inhibitory Concentrations (MIC) (µg mL^{-1})					
	S. aureus	*B. subtilis*	*S. epidermitis*	*E. coli*	*K. pneumoniae*	*P. aeruginosa*
97a	-	-	50 ± 0.22	-	50 ± 0.63	6.25 ± 0.21
97b	25 ± 0.62	25 ± 0.46	12.5 ± 0.90	50 ± 0.32	50 ± 0.79	6.25 ± 0.79
97c	1.56 ± 0.22	12.5 ± 0.71	12.5 ± 0.3	12.5 ± 0.44	12.5 ± 0.58	6.25 ± 0.15
97d	1.56 ± 0.35	1.56 ± 0.45	3.12 ± 0.66	6.25 ± 0.70	6.25 ± 0.40	12.5 ± 0.23
97e	3.12 ± 0.28	6.25 ± 0.19	12.5 ± 0.37	50 ± 0.68	6.25 ± 0.30	6.25 ± 0.16
97f	6.25 ± 0.49	6.25 ± 0.33	12.5 ± 0.38	50 ± 0.42	12.5 ± 0.22	12.5 ± 0.50
97g	3.12 ± 0.28	12.5 ± 0.42	12.5 ± 0.31	25 ± 0.20	50 ± 0.40	12.5 ± 0.36
97h	3.12 ± 0.19	6.25 ± 0.20	12.5 ± 0.45	6.25 ± 0.43	12.5 ± 0.22	6.25 ± 0.38
97i	-	-	-	12.5 ± 0.25	-	25 ± 0.55
Streptomycin	6.25 ± 0.25	6.25 ± 0.70	3.125 ± 0.45	6.25 ± 0.82	3.125 ± 0.96	1.562 ± 0.69
Penicillin	1.56 ± 0.21	1.562 ± 0.65	3.125 ± 0.22	12.5 ± 0.35	6.25 ± 0.88	12.5 ± 0.74

New selenoxotetrahydropyrimidines **98a–98g** were synthesized by Biginelli reaction of ethyl acetoacetate, substituted aromatic aldehydes and selenourea (Scheme 25) in ethanol in the presence of HCl under microwave irradiation [104]. The results of antibacterial evaluation indicated that compounds **98a** and **98e** are active against Gram-positive bacteria *Pseudomonas fluorescens*, while compounds **98b** and **98d** exhibited significant an-

tibacterial activity against Gram-negative bacteria *Klebsellia pneumoniae* and *Escherichia coli*, respectively (Table 7). Only compound **98f** was active against both Gram-negative and Gram-positive strains, namely *Pseudomonas aeruginosa* and *Staphylococcus pyrogens*. Additionally, compounds **98c** and **98g** possessed antifungal activity against *Aspergillius janus* and *Penicillium glabrum*. In conclusion, all compounds showed inhibitory effects with a minimum inhibitory concentration of 8 µg mL^{-1}.

98a: R = H
98b: R = 4-OCH$_3$
98c: R = 3-NO$_2$
98d: R = 4-OH
97e: R = 3-OCH$_3$-4-OH
97f: R = 2,3-OCH$_2$O
97g: R = 2,4-Cl$_2$
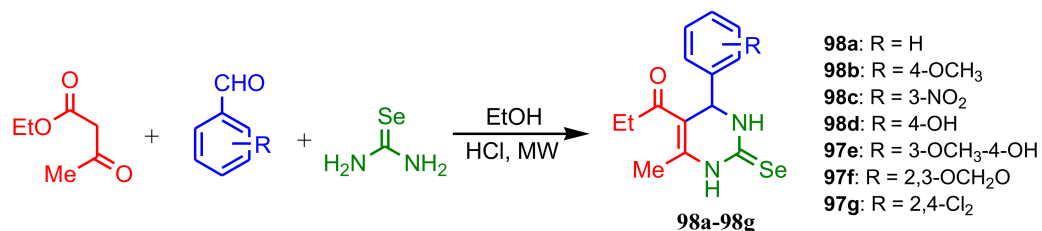
Scheme 25. Synthesis of compounds **98a–98g**.

Table 7. In vitro antibacterial activity (MIC) (µg mL^{-1}) of compounds **98a–98g**.

Comp.	Gram-Positive Bacteria				Gram Negative Bacteria				Fungi			
	Ec	Kp	Pa	Pf	Sa	Bs	Sp	Aj	Pg	An	Fo	As
98a	32	16	32	**8**	32	32	16	32	32	32	16	16
98b	32	**8**	32	16	16	32	32	32	16	32	32	16
98c	16	32	32	32	32	16	16	**8**	16	16	16	16
98d	**8**	32	16	32	32	16	32	32	16	3	32	32
98e	32	32	32	**8**	32	32	64	16	16	16	16	16
98f	16	16	**8**	32	16	16	8	32	16	32	32	32
98g	32	32	16	16	32	32	32	16	**8**	16	32	16
Amoxicilin	4	4	4	4	2	2	4	2	-	-	-	-
Fluconazole	-	-	-	-	-	-	-	-	2	2	2	2

Ec: *Escherichia coli*; Kp: *Klebsiella pneumoniae*; Pa: *Pseudomonas aeruginosa*; Pf: *Pseudomonas fluorescens*; Sa: *Staphylococcus aureus*; Bs: *Bacillus subtilis*; Sp: *Staphylococcus pyrogens*; Aj: *Aspergillus janus*; Pg: *Penicillium glabrum*; An: *Aspergillus niger*; Fo: *Fusarium oxysporum*; As: *Aspergillus sclerotioum*.

Devineni et al. developed a Biginelli-type reaction of substituted thiazol-2-amines, 2-(4-nitrophenyl)acetonitrile, and aromatic aldehydes, promoted by heterogeneous catalyst SiO$_2$-ZnBr$_2$ and diisopropylethylamine (DIPEA) as base, for the synthesis of 2,5-substituted-6-(4-nitrophenyl)-5H-thiazolo[3,2-a]pyrimidin -7-amines **99** and **100** (Scheme 26) [105]. All compounds were tested against four bacterial strains, *Staphylococcus aureus* ATCC 43300, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 27853, and *Escherichia coli* ATCC 25922, as well as on three fungal strains *Aspergillus flavus* MTCC-1884, *Fusarium oxysporum* MTCC-1755, and *Candida albicans* ATCC 2091. Few of the synthesized compounds showed activity in the MIC range 6.25–25.0 µg mL^{-1}, which was close to that of the standard drugs, tetracycline and amphotericin B (MIC = 3.125–6.25 µg mL^{-1}). Compounds **99c** and **100c**, containing the dimethylamino group, showed good activity against all the tested species, in particular *B. subtilis* and *P. aeruginosa* (MIC = 6.25 µg mL^{-1}).

99: R^1 = Et; **100**: R^1 = H
99a, 100a: R^2 = 3-NO$_2$
99b, 100b: R^2 = 3-Cl
99c, 100c: R^2 = 4-NMe$_2$
99d, 100d: R^2 = 2,3-OCH$_2$O
99e, 100e:: R^2 = 3,5-(OCH$_3$)$_2$-4-OH
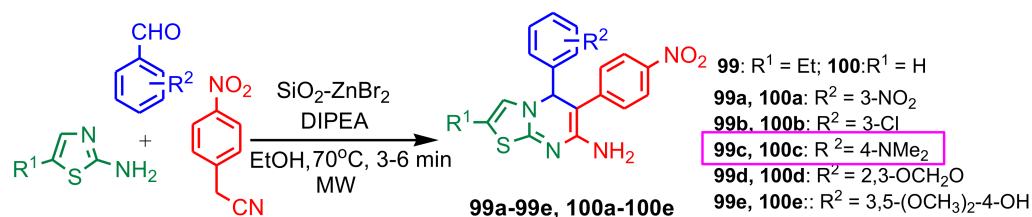
Scheme 26. Synthesis of compounds **99a–99e** and **100a–100e**.

Gein et al. reported that reaction of dimedone with a mixture of 5-aminotetrazole monohydrate and substituted aromatic aldehyde taken in an equimolar ratio without solvent and catalyst at a temperature of 160–170 °C for 5–10 min afforded 9-aryl-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-b]quinazolin-8(4H)-ones **101** (Figure 12) [106]. All compounds were found to have low antibacterial and antifungal activity (MIC > 1000 µg mL^{-1}).


R: H, 4-CH$_3$; 4-t-Bu; 2-OCH$_3$;
3,4-(CH$_3$O)$_2$; 2,5-(CH$_3$O)$_2$;
2-Cl; 4-OCH$_3$; 4-Br; 4-NO$_2$

101
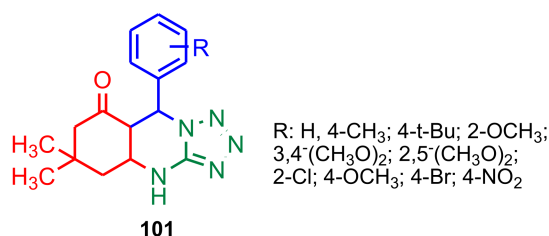
Figure 12. Chemical structures of compounds **101**.

Afradi reported the synthesis of 3,4-dihydropyrimidines **102a**–**102d** using Mn$_{0.5}$Fe$_{0.25}$Ca$_{0.25}$Fe$_2$O$_4$@starch@aspartic acid magnetic nanoparticles (MNPs) as a new nanocatalyst in a solvent free synthesis (Scheme 27) [107]. The main advantages of the Biginelli reaction in the presence of catalyst Mn$_{0.5}$Fe$_{0.25}$Ca$_{0.25}$Fe$_2$O$_4$@starch@aspartic acid magnetic nanoparticles (MNPs) are: short reaction time, high yield, and the green and novel nature of the nanocatalyst. All synthesized compounds possessed good antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538 and *Staphylococcus epidermidis* ATCC 12228) and Gram-negative bacteria (*Pseudomonas aeruginosa* ATCC 9027 and *Escherichia coli* ATCC 8739).

Ar = 2-Furyl
2-pyrrolyl
2-thiophenyl
4-pyridyl
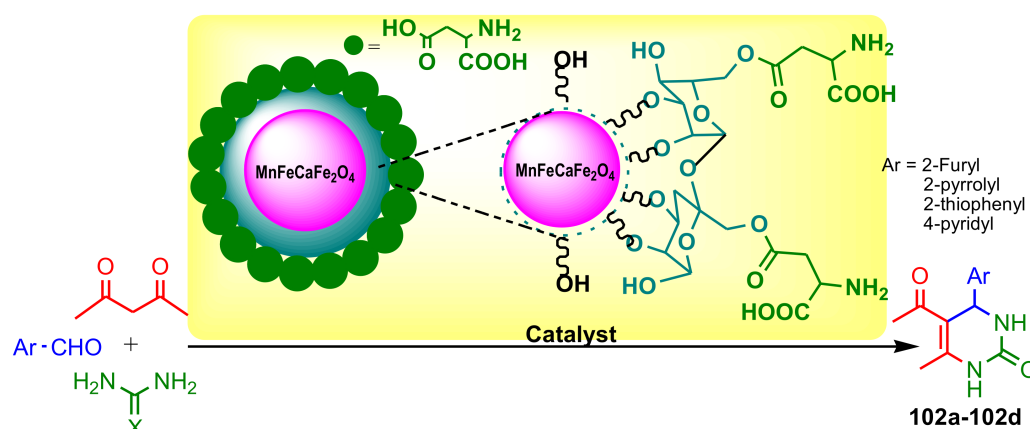
102a-102d

Scheme 27. Synthesis of the compounds **102a**–**102i** catalyzed by MnFeCaFe$_2$O$_4$@starch@aspartic acid MNPs.

Jadhav et al. reported the diisopropyl ethyl ammonium acetate (DIPEAc)-promoted Biginelli protocol by a successive one-pot three-component reaction of aldehydes, ethyl-cyanoacetate/ethyl acetoacetate, and thiourea/urea to afford pharmacologically promising 1,2,3,4-tetrahydropyrimidines in high yields at room temperature [108]. All compounds were evaluated against four bacterial *Streptococcus pyogenes*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and two fungal *Candida albicans*, *Aspergillus niger* strains with Ampicillin and Griseofulvin as standard drugs. Compounds **103a**, **103b**, and **103c** showed satisfactory antibacterial activity against all four bacterial pathogens due to the presence of withdrawing groups (-NO$_2$ and -CF$_3$) and electron-donating groups (-OH and -OCH$_3$) in the molecule (Figure 13, Table 8). In addition, **103b** showed good antibacterial activity against the Gram-positive strains, *P. aeruginosa*, *E. coli*, *S. aureus*, and *S. pyogenes*, which can be significantly correlated with the presence of -OH and -OCH$_3$ groups in the

molecule. Additionally, compounds **103d**, **103e**, and **103f** showed potent activities against all the tested fungal strains. The best antimicrobial values are marked in bold in Table 8.
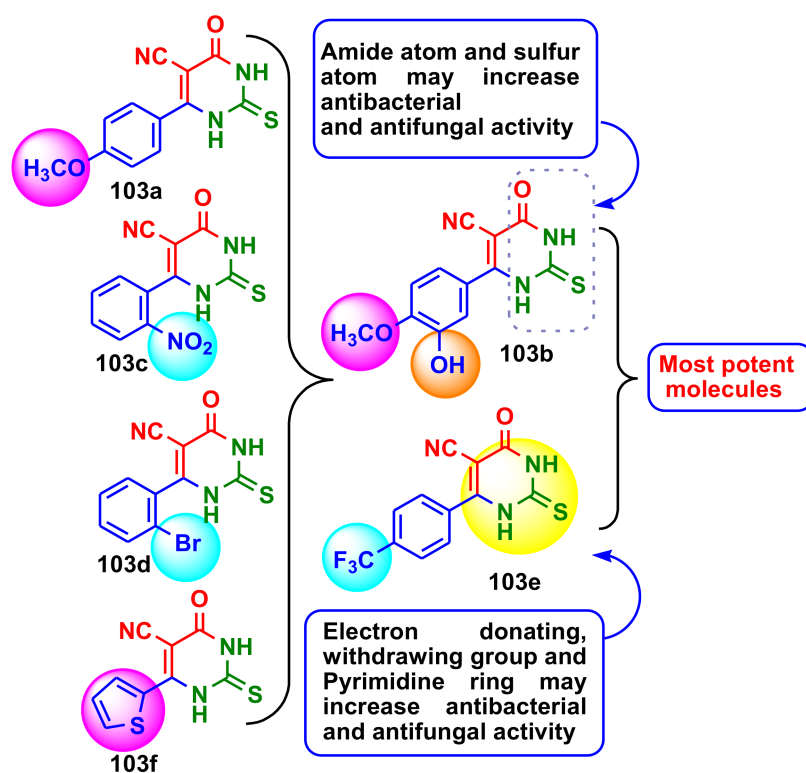
Figure 13. Structure−activity relationship of compounds **103a–103f**.

Table 8. In vitro antibacterial activity (MIC) (μg mL^{-1}) of compounds **103a–103f**.

Compounds	Minimum Inhibitory Concentrations (MIC) (μg mL^{-1})					
	E. coli	*P. aeruginosa*	*S. aueus*	*S. pyogenes*	*C. albicans*	*A. niger*
103a	**50**	**25**	500	**50**	500	250
103b	**50**	**12.5**	**25**	250	100	250
103c	**12.5**	**25**	100	**50**	500	250
103d	100	500	100	100	100	**25**
103e	500	500	500	250	**12.5**	50
103f	100	100	250	**50**	50	100
Ampicillin	50	50	200	200	-	-
Griseofulvin	-	-	-	-	500	100

Desai et al. carried out a convenient synthesis of 20 pyrimidinthiones in the presence of thiourea and catalyst sulfamic acid (Scheme 28) [109]. Synthesized bacteria *Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 1688, *Staphylococcus aureus* MTCC 96, and *Streptococcus pyogenes* MTCC 442 and fungi *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282, and *Aspergillus clavatus* MTCC 1323 using serial dilution method. The antimicrobial activity of compounds **104a**, **104b**, and **104c** showed the best activity (of all compounds - bold values) against all tested strains (Table 9).
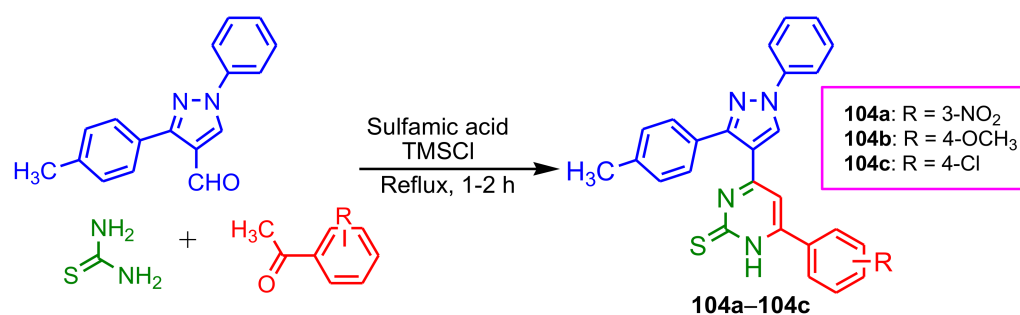
Scheme 28. Synthesis of compounds **104a–104c**.

Table 9. In vitro antibacterial activity (MIC) (μg mL^{-1}) of compounds **104a–104c**.

Compound	Bacteria				Fungi		
	Ec	Pa	Sa	Sp	Ca	An	Ac
104a	**12.5**	250	250	250	1000	250	250
104b	100	200	500	200	**12.5**	**50**	500
104c	100	250	**12.5**	**12.5**	500	1000	1000
Ciprofloxacin	25	25	50	50	-	-	-
Nystatin	-	-	-	-	100	100	100

Ec: *Escherichia coli*; Pa: *Pseudomonas aeruginosa*; Sa: *Staphylococcus aureus*; Sp: *Streptococcus pyogenes*; Ca: *Candida albicans*; An: *Aspergillus niger*; Ac: *Aspergillus clavatus*.

New 1,2,3,4-tetrahydropyrimidines **105** were synthesized by Biginelli reaction starting from the desirable aldehyde, benzyl 3-oxobutanoate, urea, and Co(HSO$_4$)$_2$ (Scheme 29) [110]. Antibacterial activity of the compounds was tested against bacterial strains *S. aureus*, *P. aeruginosa*, *E. coli* and *S. flexneri*. Compounds **105a–105d** showed significant growth inhibition at 40.6, 21.7, 37.8, and 19.9 μg mL^{-1} concentrations, respectively, against *S. aureus* and maximum activity at 34.0, 17.8, 101.4, and 52.4 μg mL^{-1}, respectively, against *E. coli*.
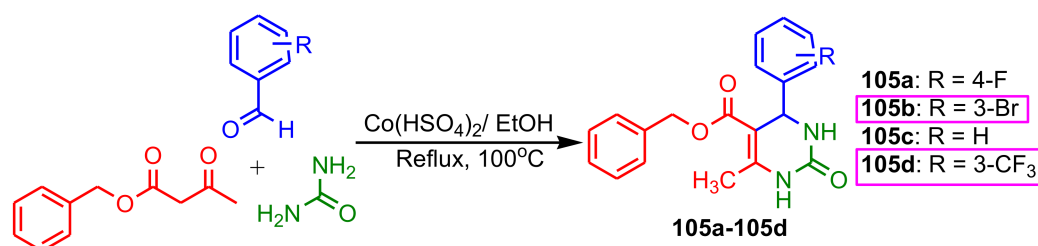
Scheme 29. Synthesis of compounds **105a–105d**.

Rajitha et al. synthesized new 3-substituted 5-phenylindeno-thiazolopyrimidinones in two steps (Scheme 30) [111]. The first reaction is a poly(4-vinylpyridinium)hydrogen sulfate catalyzed Biginelli reaction to produce **106**, and the second is a condensation with phenacyl bromide to give **107**. Among the analogs, 4-methoxyphenyl-5-phenylindeno[1,2-d]thiazolo [3,2-a]pyrimidin-6(5H)-one showed good activity against a bacterium, Staphylococcus aureus (MIC = 25 μg mL^{-1}), and a fungus, *Aspergillus niger* (zone of inhibition 20 mm).

Sethiya et al. reported the eco-friendly synthesis of pyrimidine derivatives **108a–108g** by the reaction of aromatic aldehydes, 2-aminobenzothiazole and dimedone in the presence of thiamine hydrochloride (Vitamine B$_1$) as organocatalyst (Scheme 31) [112]. Molecular docking studies were performed on the synthesized compounds using *Staphylococcus aureus* dihydropteroate synthase (saDHPS) (6CLV) and DNA gyrase (1KZN) proteins. Compound **108e** was found to be the most potent and showed good binding interactions and the highest docking score against both proteins, 1KZN and 6CLV (Figure 14).
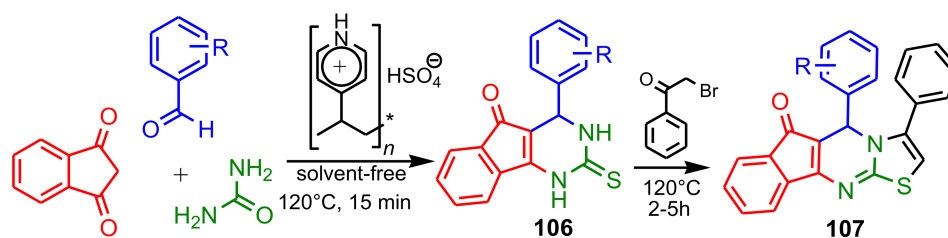
Scheme 30. Synthesis of compounds **106** and **107**.
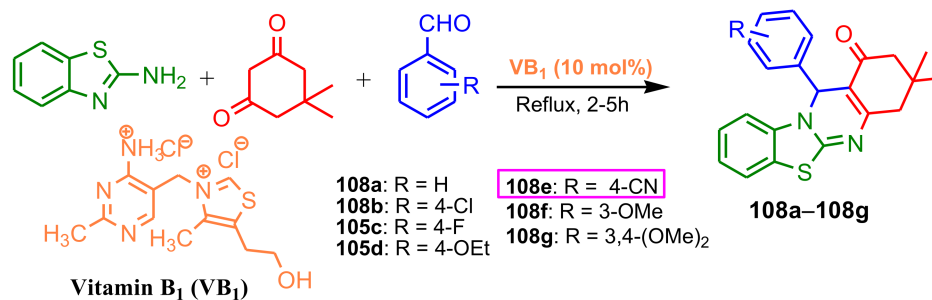
Scheme 31. Synthesis of compounds **108a–108g**.
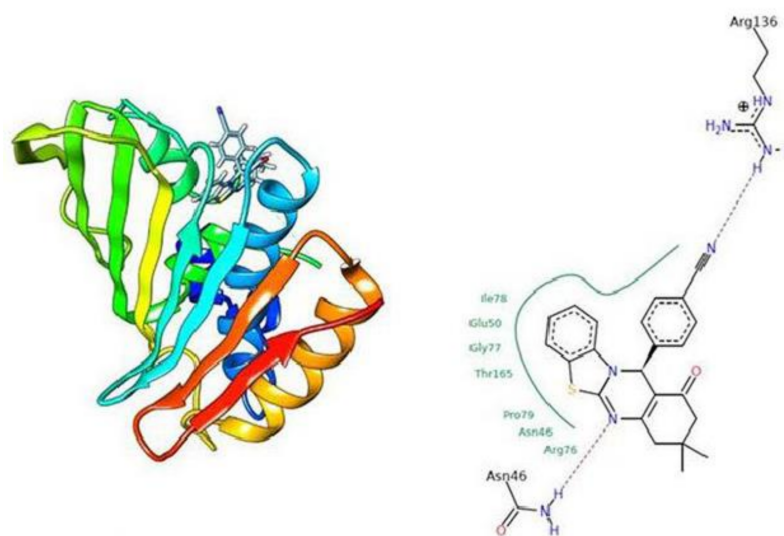
Figure 14. 3D and 2D interaction plots of docked compound **108e** within the binding cavity of 1KZN.

A series of 3,4-dihydropyrimidin-2(1H)-thione compounds were synthesized from the 1-(4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidin-5-yl)ethanone **109**, as can be seen in Scheme 32 [113]. Compounds **110b**, **111b**, **112**, and **113b** were the most potent against the tested microorganisms *Staphylococcus aureus* AUMC B.54, *Bacillus cereus* AUMC B.52, *Escherichia coli* AUMC B.53, *Pseudomonas aeruginosa* AUMC B.73, *Candida albicans* AUMC 214, and *Aspergillus flavus* AUMC 1276 (Table 10). It was stated that presence of certain electron donating groups, such as -Cl and -OCH$_3$, may increase the antimicrobial activity of the compounds. These results are in line with similar results in the literature [114,115].
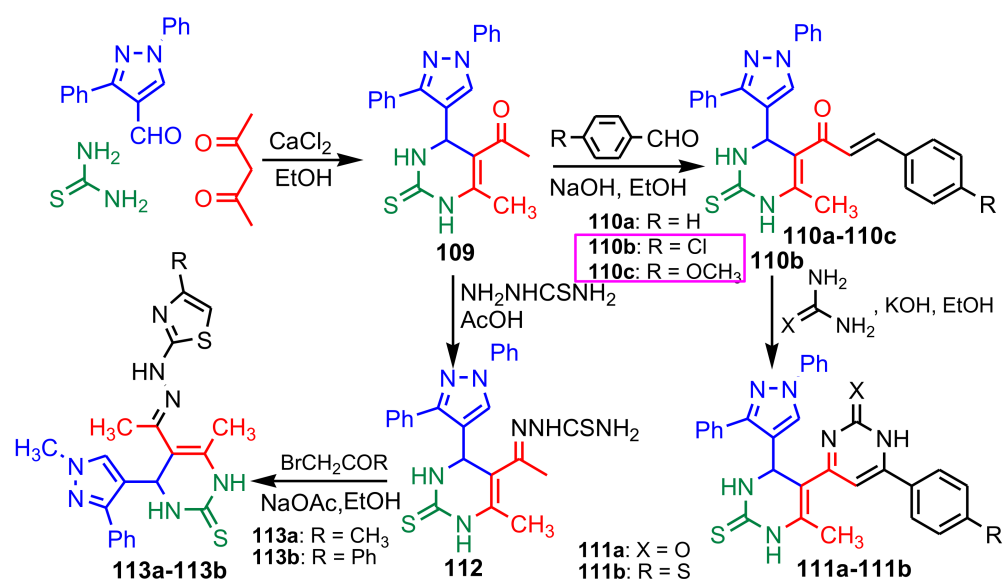
Scheme 32. Synthesis of compounds **109**, **110a–110c**, **111a**, **111b**, **112**, **113a**, and **113b**.

Table 10. In vitro antibacterial activity (MIC) (μg mL^{-1}) of compounds **109–113**.

Compounds	Diameter of Zone of Inhibition (mm)/% Inhibition with Reference to Standard					
	S. aueus	*B. cereus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. flavus*
109	15 (46)	19 (49)	22 (81)	14 (82)	-	-
110a	9 (50)	-	-	-	-	-
110b	13 (72)	16 (66)	31 (>100)	23 (>100)	11 (39)	27 (64)
110c	10 (55)	13 (54)	15 (56)	-	-	-
111a	12 (66)	9 (37)	13 (48)	-	-	21 (50)
111b	19 (>100)	29 (>100)	33 (>100)	26 (>100)	10 (36)	36 (86)
112	11 (61)	35 (>100)	11 (41)	8 (47)	-	-
113a	12 (66)	10 (42)	13 (48)	8 (47)	19 (68)	26 (62)
113b	22 (>100)	29 (>100)	37 (>100)	24 (>100)	-	44 (>100)
Chloramphenicol	18	24	27	17	-	-
Clotrimazole	-	-	-	-	28	42

3. Biginelli Reaction Mediated Synthesis of Antitubercular Pyrimidine Derivatives

Tuberculosis, resulting from infection by the bacterium *Mycobacterium tuberculosis*, is a major worldwide health problem [116]. Approximately 2 million people die every year. The emergence of multi-drug resistance has forced the development of new structural classes of antitubercular agents, with several of them showing promising activity against *M. tuberculosis* [117]. Virsodia et al. synthesized new N-phenyl-6- methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamides using the Biginelli reaction by reacting acetoacetanilide derivatives, substituted aldehydes, and urea in methanol with a catalytic amount of HCl. Compound **114** showed 65% inhibition of *M. tuberculosis*, the best antitubercular activity (Figure 15). Additionally, 3D-QSAR studies are reported. Trivedi et al. reported the synthesis of 30 dihydropyrimidines by a classical Biginelli reaction and their in vitro antitubercular activity against *Mycobacterium tuberculosis* H37Rv [118]. Two compounds, **115a** and **115b**, with MIC of 0.02 μg mL^{-1} against *M. tuberculosis*, were found to be the most active of all and more potent than isoniazid. Akhaja et al. found that compound **14d** displayed promising antitubercular activity compared to standards Rifampicin and Izoniazid [75].
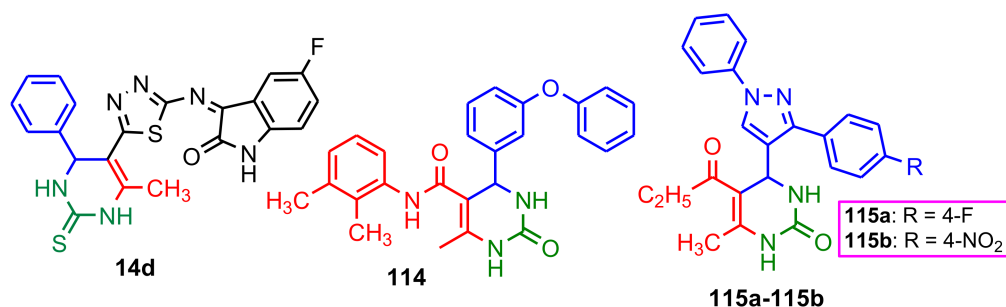
Figure 15. Chemical structure of compounds **14d**, **114**, **115a**, and **115b**.

Trivedi et al. reported synthesis of phenothiazine-pyrazolo[3,4-d]pyrimidines **116a**–**116h** by Biginelli reaction in the presence of P_2O_5 as catalyst (Scheme 33) [119]. Compounds **116b**, **116d**, and **116f** exhibited excellent antitubercular activity with percentage inhibition of 93, 91, and 96, respectively, at a minimum inhibitory concentration (MIC) < 6.25 μg mL^{-1}, whereas compounds **116a**, **116c**, **116e**, **116g**, and **116h** exhibited moderate to good antitubercular activity, with a percentage inhibition of 75, 68, 74, 54, and 63, respectively, at MIC > 6.25 μg mL^{-1}.
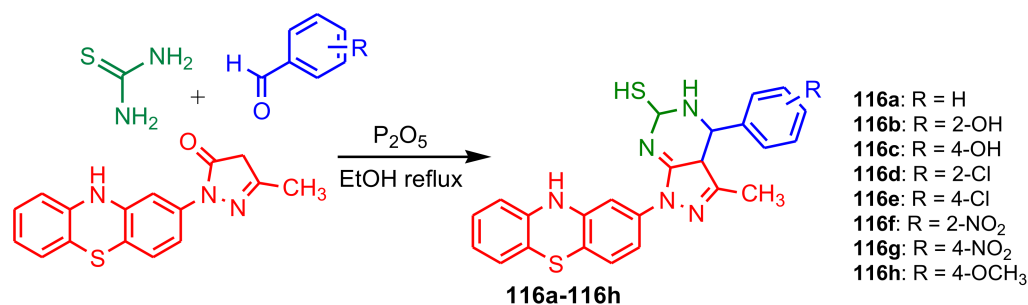
Scheme 33. Synthesis of compounds **116a**–**116h**.

Yadlapalli implemeted a Biginelli reaction for the synthesis of 4-aryl-3,4-dihydro-2(1H)-pyrimidone esters possessing lipophilic carbamoyl groups [120]. Compounds **117a** and **117b**, with a MIC value of 0.125 and 0.25 μg mL^{-1}, were found to be the most potent in the series (Figure 16). Ambre et al. reported the synthesis of 16 compounds, 4-(substituted) phenyl-2-thioxo-3,4-dihydro-1H- chromino[4,3-d]pyrimidin-5-one and 4-(substituted) phenyl-3,4-dihydro-1H- chromino[4,3-d]pyrimidine-2,5-dione analogs as antitubercular agents by a classical. Biginelli reaction between a substituted aldehyde, 6-substituted-4-hydroxy coumarin, urea (or thiourea), and p-toluenesulfonic acid as catalyst. Compounds **118a** and **118b**, with MIC of 59% and 61%, respectively, were found to be the most potent in these series [121].
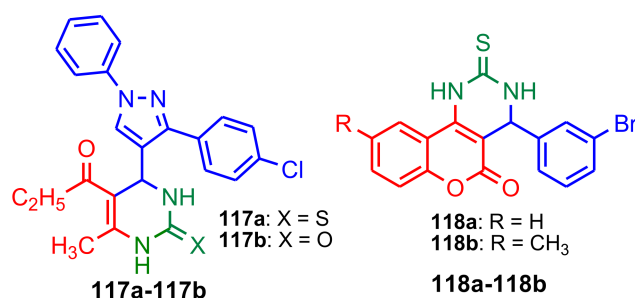
Figure 16. Chemical structure of compounds **117a**–**117b**, **118a**–**118b**.

Chikhale et al. synthesized a series of N-(benzo[d]thiazol-2-yl)-6-methyl -4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine -5-carboxamide by a Biginelli reaction (Scheme 34) [122].

It was found that compounds **119a–119d** exhibited an MIC between 0.08 and 0.09 μM, which is found to be better than the standard reference Isoniazid with MIC of 0.2 μM. The very good antitubercular activity was correlated with the presence of the fluorine atom in the molecule.
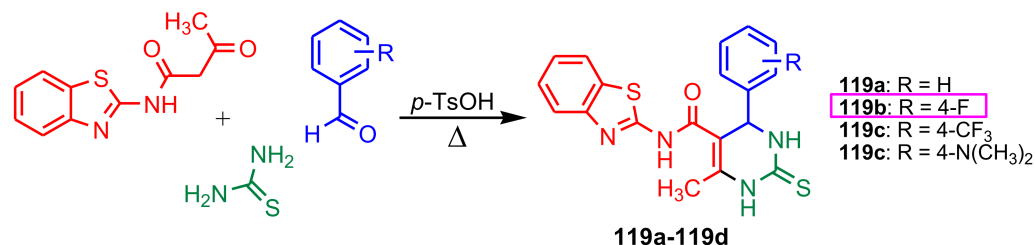
Scheme 34. Synthesis of compounds **119a–119d**.

4. Antioxidant Activity of Antimicrobial Pyrimidine Derivatives

Youseff et al. found that compounds **37a** and **37b** showed considerable inhibitory activity in the hemolysis assay (Table 11) [81]. Compounds **37c** and **37d** (Figure 17) showed moderate antioxidant and inhibitory activity (Table 12). Additionally, the antioxidant assay by ABTS method showed that compounds **37a**, 37**b**, **37c**, and **37d** showed potent antioxidant activity.

Table 11. Antioxidant assays by erythrocyte hemolysis (A/B).

Compound	Absorbance of Sample (A)	Hemolysis (%)
Complete hemolysis with distilled water (B)	0.660	-
37a	0.035	5.22
37b	0.031	4.68
37c	0.045	6.92
37d	0.051	8.02
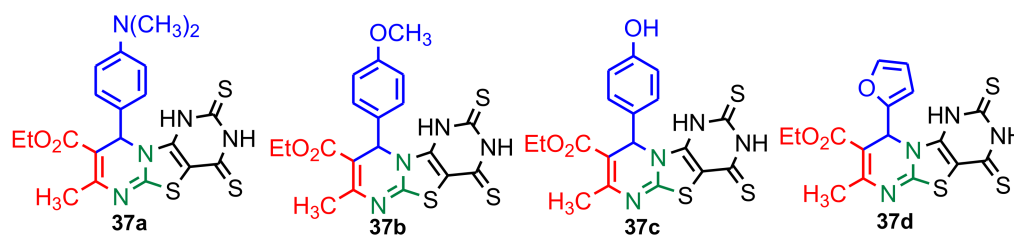
Figure 17. Chemical structure of compounds **37a–37d**.

Table 12. Antioxidant assays by ABTS method (Abs. (control) − Abs.(test)/Abs.(control) × 100).

Compound	Absorbance of Sample (A)	Inhibition (%)
ABTS control	0.54	0
Ascorbic acid	0.06	88.8
37a	0.10	81.5
37b	0.12	77.7
37c	0.15	72.2
37d	0.13	75.9

Viveka et al. reported compounds **49c** (89.41%) and **49f** (83.34%) exhibited excellent DPPH radical scavenging activity, as compared to glutathione (89.09%) [86]. Attri et al. reported that that compounds **73a–73c** possess good-to-moderate antioxidant activity in comparison to the standard gallic acid and quercetin [93]. Rani et al. reported that

compounds **77f** and **77g** exhibited excellent in vitro antioxidant activity due to the presence of electron releasing groups on benzylidene portion (Figure 18) [95].
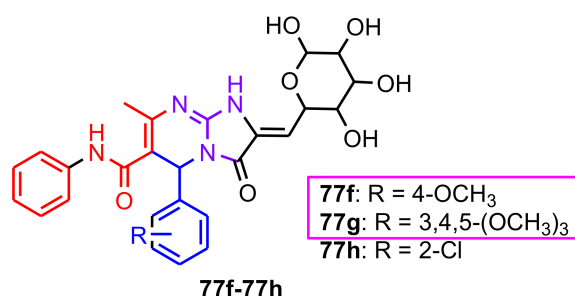
Figure 18. Chemical structures of compounds **77f**–**77h**.

5. Anticancer Activity of Antimicrobial Pyrimidine Derivatives

Yadlapalli reported that compound **117a**, with excellent antitubercular activity against MTB H37Rv, showed moderate anticancer activity against MCF-7 breast cancer cell lines [120]. Compound **77h** was found to be the most potent anticancer agent (IC_{50} = 57.65 mg mL^{-1}) of all compounds **77** at a dose of 10^{-4} M against human breast (MCF-7) cancer cell line and was comparable with Adriamycin as the standard [95]. Gondru et al. showed that derivatives **97a**, **97g**, **97h**, and **97j** have shown moderate antiproliferative potency against the HepG2 tumor cell line with an average percentage of inhibition, ranging from 39.09 to 40.35 at cell lines [103].

6. Anti-Inflammatory Activity of Antimicrobial Pyrimidine Derivatives

Gelatinases are present in the physiologic system and play a key role in inflammation and autoimmunity states. Activated inflammatory cells and dermal fibroblasts can express several proteinases designated as matrix metalloproteinases (MMPs) able to degrade all connective tissue macromolecules [98]. Among these are gelatinases, e.g., MMP-2 and MMP-9, which, together with interstitial collagenase, have been assumed to be of importance in connective tissue remodeling after inflammation. The obtained results revealed that all compounds **80a**–**80e** and **81a**–**81e** were highly active against MMP-2 (72 kDa gelatinase A). Similarly, the compounds **80e**, **81a**, **81b**, **81d**, and **81e** were highly active against MMP-9 (92 kDa gelatinase B), whereas the compounds **80b** and **80d** showed slight inhibitory activity, and rest of the compounds were not active against MMP-9 (Table 13).

Table 13. The in vitro anti-inflammatory results of compounds **80a**−**80e** and **81a**−**81e** with % bands and % inhibition of MMP-2 and MMP-9.

Compound	% Bands of MMP		% Inhibition of MMP	
	MMP-9	MMP-2	MMP-9	MMP-2
80a	20	10	**80**	90
80b	15	05	**85**	95
80c	100	15	-	85
80d	30	05	70	95
80e	10	04	**90**	96
81a	100	18	-	82
81b	90	13	10	87
81c	100	15	-	85
81d	70	20	30	80
81e	05	10	**95**	90
Tetracycline	00	00	100	100

Alam et al. screened compounds **31a**–**31n** for their anti-inflammatory activity using Winter et al. method. The results showed inhibition of edema ranging from 32.72% to

71.14%. The compounds **31c**, **31d**, and **31e** (Scheme 10) showed 65.45%, 67.07%, and 71.14%, respectively, inhibition of edema [79]. From the anti-inflammatory activity result analysis, Viveka et al. observed that compounds **92a**, **92b**, **92d**, **92e**, **92f**, **92g**, and **92h** showed good activity, with 67.61 to 85.33% inhibition of the edema (Figure 19). The compounds **92a** (85.33), **92d** (81.32), and **92h** (80.75) showed potent anti-inflammatory activity compared with the other test compounds and are comparable with the standard, indomethacin (86.76). This emphasizes the presence of the 3F-4CH$_3$- substituted phenyl ring on the 5th position of the 3-oxothiazolopyrimidine nucleus in this pyrazole series [101]. Additionally, El-Emary et al. found that compounds **110b** and **112b** (Scheme 29) had the most anti-inflammatory activity, comparable to that of Indomethacin [113].

92a: R = 3-F-4-CH$_3$ R^1 = Cl; R^2 = Cl
92b: R = 2,5-(OCH$_3$)$_2$ R^1 = Cl; R^2 = Cl
92d: R = 3-F-4-CH$_3$ R^1 = F; R^2 = F
92e: R = 2,5-(OCH$_3$)$_2$ R^1 = F; R^2 = F
92f: R = 3-F-4-CH$_3$ R^1 = Cl; R^2 = H
92g: R = 3-F-4-CH$_3$ R^1 = F; R^2 = H
92h: R = 2,5-(OCH$_3$)$_2$ R^1 = F; R^2 = H
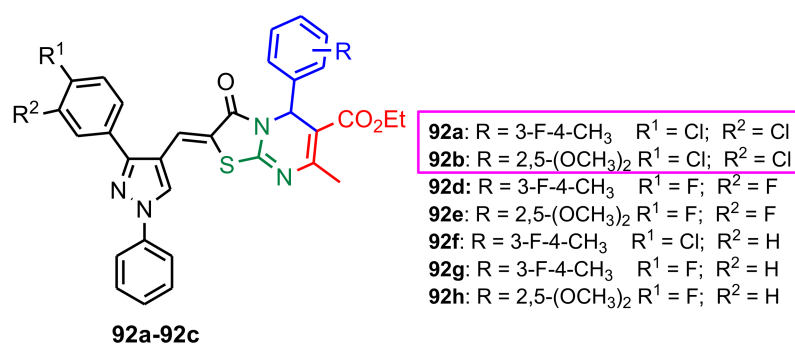
92a-92c

Figure 19. Chemical structures of compounds **92a**, **92b**, **92e**–**92h**.

7. Analgesic Activity of Antimicrobial Pyrimidine Derivatives

Alam et al. reported that compounds **31c**, **31d**, and **31e** with analgesic activity (expressed as % protection) of 44.35%, 47.01%, and 50.36%, respectively, have analgesic properties, considering Indomethacin as the standard (60.30%) [79]. Khalifa et al. reported the descending order of the central analgesic potencies of compounds **62e**–**62g** after 90 min, as compared to Tramadol, which were 97.2, 97.2, 89.0, and 78.0% for compounds **62e**, **62f**, **62g**, and **62b**, respectively (Figures 4 and 20) [84]. Gein et al. reported that all studied compounds **51**–**61** (Scheme 16) were found to have high analgesic activity, as compared with sodium Metamizole (47.7%) or Nimesulide (75.5%) with analgesic activity between 60.8% and 84.0% [88].
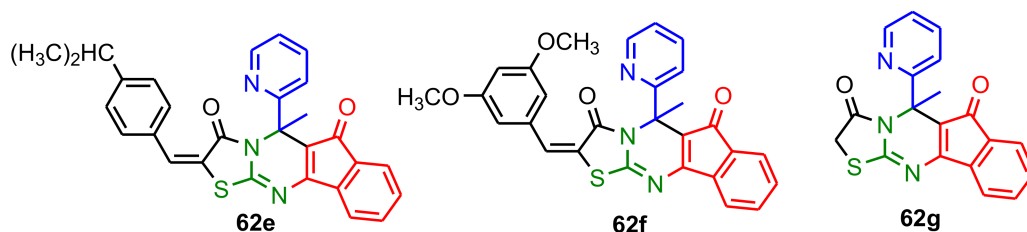
Figure 20. Chemical structures of compounds **62e**, **62f**, and **62g**.

8. Antiviral Activity of Antimicrobial Pyrimidine Derivatives

Umesha et al. reported the antiviral studies for the selected compounds, in which **48a** exhibited 73.69% and 54.42% of inhibition of buffalopox and camelpox viruses, respectively (Scheme 15) [85]. The calculated docking (ΔE) and binding (ΔG) energies of **47a** were −54.2 and −8.7 kcal Mol^{-1}, respectively, whereas for compound **48a**, the calculated energy values were −58.6 and −10.4 kcal Mol^{-1}, respectively. An O4 oxygen atom of compound **47a** exhibited long-distance (3.24 Å) hydrogen-bond interactions with the N atom of the residue Met414 of human IMPDH, and most of the atoms of the molecule showed hydrophobic interactions with Cys331, Met70, His93, Asn94, and Cys95 (Figure 21A). Compound **4a** exhibited at least three different long-distance hydrogen-bond interactions. An O1 atom showed with the NH$_2$ atom of Arg259 with a distance of 3.06 Å, an O3 atom showed

with the NE2 atom of His93 with a distance of 2.87 Å, and a Cl atom showed with the O atom of Pro69 with a distance of 2.87 Å (Figure 21B). Additionally, other atoms of the molecule showed several important hydrophobic interactions against Asp256, Asn94, Met414, Asp71, and Tyr411 with different distances. These results showed that the relatively higher antiviral activity of compound **48a** than **47a** may due to lower docking and binding energies, as well as higher hydrogen and hydrophobic interactions.
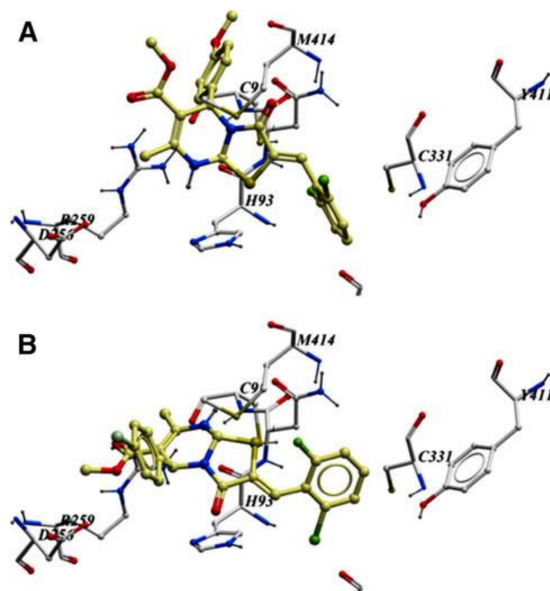
Figure 21. Intermolecular interactions with of the compounds **47a** (**A**) and **48a** (**B**) (Scheme 13) at the active site of human inosine monophosphate dehydrogenase (IMPDH) type II (PDB ID: 1NFB), where Cys331 is the catalytic residue. Both compounds exhibited imperative hydrogen bonding with a number of explicit residues of the active site of IMPDH.

Razzaghi-Asl et al. reported that trifluoromethyl group at the meta-position of phenyl ring provided a potent anti-HIV-1 property to the compound **105d** (Scheme 29) [110]. Similarly, compounds bearing nitro **105e**, fluorine **105f**, bromine **105b**, and chlorine **105h** groups at the meta-position as well as chlorine and nitro groups at para- and meta-positions **105i** (Figure 22) of phenyl were less potent, with an inhibition rate of P24 expression (%) in 100 μM of 52.25, 10.67, 12.93, 50.21, and 61.43, respectively. The presence of fluorine at meta position showed better anti-HIV-1 activity than the para-position **105d** (10.67 vs. 4.75% in 100 μM).

105e: R = 3-NO$_2$
105f: R = 3-F
105h: R = 3-Cl
105i: R = 4-Cl-3-NO$_2$
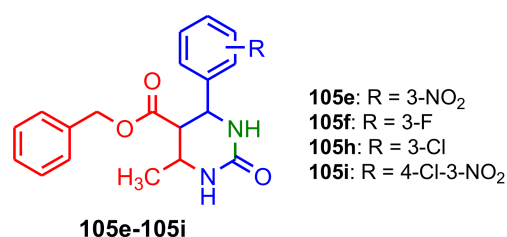
105e-105i

Figure 22. Chemical structures of compounds **105e**, **105f**, **105h** and **105i**.

9. Antiparasitic Activity of Antimicrobial Pyrimidine Derivatives

Rajanarendar reported that compounds **6b** and **6d** are proved to be lethal for mosquito larvae, with LC$_{50}$ concentration, representing the concentration in ppm that killed 50%, of 0.85 and 0.88, respectively (Scheme 4) [72]. Thus, pyrimidine compounds **6b** and **6d** can be useful as more toxic substances to kill mosquito larvae. Fatima et al. reported the synthesis of three Biginelli compounds **120**, **121**, and **122** more potent than the standard

drug Chloroquine against K1 strains of P. falciparum, with an IC$_{50}$ (μg mL^{-1}) of 0.56, 0.5 and 0.5, respectively (Figure 23) [123]. These compounds with three different pharmacophores have potential to be exploited in medicinal chemistry.
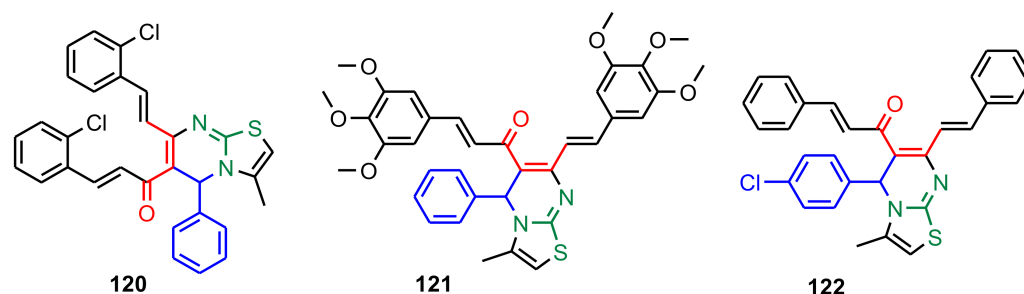

Figure 23. Chemical structures of compounds **120**, **121**, and **122**.

10. Conclusions

This review summarizes the recent Biginelli syntheses of pyrimidine compounds with antimicrobial properties, as well as their biological activities mentioned in the literature. Regarding the Biginelli synthesis of pyrimidine compounds, the presentation clearly shows that the catalyst has an important role in the development of the reaction and in obtaining a high yield. Derivatization of Biginelli compounds leads in most cases to compounds with stronger antimicrobial properties than the initial Biginelli dihydropyrimidines. Additionally, the presence of another heterocycle in the final molecules, such as pyrazole, thiazole, isoxazole, imidazole, benzothiazole, phenothiazine, 1,3,4-thiadiazole, coumarin, chromene, indole, and quinoline, potentiate the antimyrobial activity of pyrimidine compounds. In general, thiopyrimidine compounds have a stronger antimicrobial activity than pyrimidinone compounds. Selenopyrimidine compounds generally have better antimicrobial activity than pyrimidinone. Additionally, the presence of certain groups grafted on the benzimidazole and pyrazole nuclei, such as -NO$_2$, -CN, -F, -CF$_3$, -CN, -COOCH$_3$, -NHCO, -CHO, Cl, -OH, OCH$_3$, OC$_2$H$_5$, and -N(CH$_3$)$_2$, increases the antimicrobial activity of the compounds [124–127]. However, there are quite a few studies performed on the structure–properties relationship for these compounds, as well as few studies of molecular mechanics, DFT, through which to achieve the directed synthesis of some biologically active molecules. Therefore, we hope that this article will be a starting point for conducting new theoretical studies and syntheses of new compounds for the synthesis of improved antimicrobial compounds that possess other biological activities.

References

1. Hantzsch, A. Condensations produkte aus Aldehydammoniak und ketonartigen Verbindungen. *Ber. Der Dtsch. Chem. Ges.* **1881**, *14*, 1637–1638. [CrossRef]
2. Biginelli, P. Aldehyde-urea derivatives of aceto-and oxaloacetic acids. *Gazz. Chim. Ital.* **1893**, *23*, 360–413.
3. Kappe, C.O. 100 years of the Biginelli dihydropyrimidine synthesis. *Tetrahedron* **1993**, *49*, 6937–6963. [CrossRef]
4. Kappe, C.O. Biologically active dihydropyrimidones of the Biginelli-type—A literature survey. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052. [CrossRef]
5. Fatima, A.; Braga, T.C.; Neto, L.S.; Terra, B.S.; Oliveira, B.G.F.; da Silva, D.L.; Modolo, L.V. A mini-review on Biginelli adducts with notable pharmacological properties. *J. Adv. Res.* **2015**, *6*, 363–373. [CrossRef] [PubMed]

6. Silva, G.C.O.; Correa, J.R.; Rodrigues, M.O.; Alvim, H.G.O.; Guido, B.C.; Gatto, C.C.; Wanderley, K.A.; Fioramonte, M.; Gozzo, F.C.; de Souzad, R.O.M.A.; et al. The Biginelli reaction under batch and continuous flow conditions: Catalysis, mechanism and antitumoral activity. *RSC Adv.* **2015**, *5*, 48506. [CrossRef]

7. Liu, Y.; Liu, J.; Zhang, R.; Guo, Y.; Wang, H.; Meng, Q.; Sun, Y.; Liu, Z. Synthesis, Characterization, and Anticancer Activities Evaluation of Compounds Derived from 3,4-Dihydropyrimidin-2(1*H*)-one. *Molecules* **2019**, *24*, 891. [CrossRef] [PubMed]

8. Li, Y.; Tan, T.; Zhao, Y.; Wei, Y.; Wang, D.; Chen, R.; Tao, L. Anticancer Polymers via the Biginelli Reaction. *ACS Macro Lett.* **2020**, *9*, 1249–1254. [CrossRef]

9. Rani, J.; Kumar, S.; Saini, M.; Mundlia, J.; Verma, P.K. Biological potential of pyrimidine derivatives in a new era. *Res. Chem. Intermed.* **2016**, *42*, 6777–6804. [CrossRef]

10. Kaur, R.; Chaudhary, S.; Kumar, K.; Gupta, M.K.; Rawal, R.K. Recent synthetic and medicinal perspectives of dihydropyrimidinones: A review. *Eur. J. Med. Chem.* **2017**, *132*, 108–134. [CrossRef]

11. Mokale, S.N.; Shinde, S.S.; Elgire, R.D.; Sangshetti, J.N.; Shinde, D.B. Synthesis and anti-inflammatory activity of some 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4424–4426. [CrossRef]

12. Gireesh, T.; Kamble, R.R.; Kattimani, P.P.; Dorababu, A.; Manikantha, M.; Hoskeri, J.H. Synthesis of Sydnone Substituted Biginelli Derivatives as Hyaluronidase Inhibitors. *Arch. Pharm. Chem. Life Sci.* **2013**, *346*, 645–653. [CrossRef] [PubMed]

13. Sawant, R.; Sarode, V. Synthesis, Spectral Characterization and Analgesic Activity of 2-Methylthio-1,4-Dihydropyrimidines. *Iran. J. Pharm. Res.* **2011**, *10*, 733–739.

14. Bais, J.; Benedetti, F.; Berti, F.; Cerminara, I.; Drioli, S.; Funicello, M.; Regini, G.; Vidali, M.; Felluga, F. One Pot Synthesis of Micromolar BACE-1 Inhibitors Based on the Dihydropyrimidinone Scaffold and Their Thia and Imino Analogues. *Molecules* **2020**, *25*, 4152. [CrossRef]

15. Ismaili, L.; Nadaradjane, A.; Nicod, L.; Guyon, C.; Xicluna, A.; Robert, J.F.; Refouvelet, B. Synthesis and antioxidant activity evaluation of new hexahydropyrimido[5,4-c]quinoline-2,5-diones and 2-thioxohexahydropyrimido[5,4-c]quinoline-5-ones obtained by Biginelli reaction in two steps. *Eur. J. Med. Chem.* **2008**, *43*, 1270–1275. [CrossRef]

16. Panda, S.S.; Khanna, P.; Khanna, L. Biginelli Reaction: A Green Perspective. *Curr. Org. Chem.* **2012**, *16*, 507–520. [CrossRef]

17. Chopda, L.V.; Dave, P.N. Recent Advances in Homogeneous and Heterogeneous Catalyst in Biginelli Reaction from 2015-19: A Concise Review. *Chem. Sel.* **2020**, *5*, 5552–5572. [CrossRef]

18. Dondoni, A.; Massi, A. Parallel synthesis of dihydropyrimidinones using Yb(III)-resin and polymer-supported scavengers under solvent-free conditions. A green chemistry approach to the Biginelli reaction. *Tetrahedron Lett.* **2001**, *42*, 7975–7978. [CrossRef]

19. Zhang, X.; Li, Y.; Liu, C.; Wang, J. An efficient synthesis of 4-substituted pyrazolyl-3,4-dihydropyrimidin-2(1H)-(thio)ones catalyzed by Mg(ClO4)$_2$ under ultrasound irradiation. *J. Mol. Catal. A* **2006**, *253*, 207–211. [CrossRef]

20. Ahn, B.J.; Gang, M.S.; Chae, K.; Oh, Y.; Shin, J.; Chalg, W. A microwave-assisted synthesis of 3,4-dihydropyrimidin-2-(1H)-ones catalyzed by FeCl3-supported Nanopore Silica under solvent-free conditions. *J. Ind. Eng. Chem.* **2008**, *14*, 401–405. [CrossRef]

21. Devthade, V.; Kamble, G.; Ghugal, S.G.; Chikhalia, K.H.; Umare, S.S. Visible Light-Driven Biginelli Reaction over Mesoporous g-C3N4 Lewis-Base Catalyst. *Chem. Sel.* **2018**, *3*, 4009–4014. [CrossRef]

22. Gulati, S.; Singh, R.; Prakash, R.; Sangwan, S. One-pot three component synthesis of substituted dihydropyrimidinones using fruit juices as biocatalyst and their biological studies. *PLoS ONE* **2020**, *15*, e0238092. [CrossRef] [PubMed]

23. Cheng, J.; Qi, D.Y. An efficient and solvent-free one-pot synthesis of dihydropyrimidinones under microwave irradiation. *Chin. Chem. Lett.* **2007**, *18*, 647–650. [CrossRef]

24. Tayebee, R.; Ghadamgahi, M. Solvent free one-pot multi-component synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones catalyzed by mesoporous NH$_4$H$_2$PO$_4$/MCM-41 as an environmentally friendly, cheap, and effective catalyst. *Arab. J. Chem.* **2017**, *10* (Suppl. S1), S757–S764. [CrossRef]

25. Kargar, M.; Hekmatshoar, R.; Mostashari, A.; Hashemi, Z. Efficient and green synthesis of 3,4-dihydropyrimidin- 2(1*H*)-ones/thiones using imidazol-1-yl-acetic acid as a novel, reusable and water-soluble organocatalyst. *Catal. Commun.* **2011**, *15*, 123–126. [CrossRef]

26. Gore, S.; Baskaran, S.; Koenig, B. Efficient synthesis of 3,4-dihydropyrimidin-2-ones in low melting tartaric acid-urea mixtures. *Green Chem.* **2011**, *13*, 1009–1013. [CrossRef]

27. Paraskar, A.S.; Dewkar, G.K.; Sudalai, A. Cu(OTf)$_2$: A reusable catalyst for high-yield synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. *Tetrahedron Lett.* **2003**, *44*, 3305–3308. [CrossRef]

28. Naeimi, H.; Rashid, Z.; Zarnani, A.-H.; Ghahremanzadeh, R. Nanocrystalline magnesium oxide: An efficient promoter and heterogeneous nano catalyst for the one-pot synthesis of pyrazolotriazoles in green medium. *J. Nanopart. Res.* **2014**, *16*, 2416. [CrossRef]

29. Gohain, M.; Prajapati, D.; Sandhu, J.S. A Novel Cu-catalysed Three-component One-pot Synthesis of Dihydropyrimidin-2(1*H*)-ones Using Microwaves under Solvent-free Conditions. *Synlett* **2004**, 235–238. [CrossRef]

30. Simon, C.; Constantieux, T.; Rodriguez, J. Utilisation of 1,3-Dicarbonyl Derivatives in Multicomponent Reactions. *Eur. J. Org. Chem.* **2004**, 4957–4980. [CrossRef]

31. Yadav, J.S.; Reddy, B.V.S.; Sridhar, P.; Reddy, J.S.S.; Nagaiah, K.; Lingaiah, N.; Saiprasad, P.S. Green Protocol for the Biginelli Three-Component Reaction: Ag$_3$PW$_{12}$O$_{40}$ as a Novel, Water-Tolerant Heteropolyacid for the Synthesis of 3,4-Dihydropyrimidinones. *Eur. J. Org. Chem.* **2004**, 552–557. [CrossRef]

32. De Souza, R.O.M.A.; da Penha, E.T.; Milagre, H.M.S.; Garden, S.J.; Esteves, P.M.; Eberlin, M.N.; Antunes, O.A.C. The Three-Component Biginelli Reaction: A Combined Experimental and Theoretical Mechanistic Investigation. *Chem. Eur. J.* **2009**, *15*, 9799–9804. [CrossRef]

33. Su, W.; Li, J.; Zheng, Z.; Shen, Y. One-pot synthesis of dihydropyrimidiones catalyzed by strontium(II) triflate under solvent-free conditions. *Tetrahedron Lett.* **2005**, *46*, 6037–6040. [CrossRef]

34. Sabitha, G.; Reddy, G.S.K.K.; Reddy, K.B.; Yadav, J.S. Vanadium(III) chloride catalyzed Biginelli condensation: Solution phase library generation of dihydropyrimidin-(2H)-ones. *Tetrahedron Lett.* **2003**, *44*, 6497–6499. [CrossRef]

35. Ahmed, N.; van Lier, J.E. TaBr5-catalyzed Biginelli reaction: One-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones under solvent-free conditions. *Tetrahedron Lett.* **2007**, *48*, 5407–5409. [CrossRef]

36. Adib, M.; Ghanbary, K.; Mostofi, M.; Ganjali, M.R. Efficient Ce(NO₃)₃·6H₂O-Catalyzed Solvent-Free Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones. *Molecules* **2006**, *11*, 649–654. [CrossRef]

37. Angeles-Beltrán, D.; Lomas-Romero, L.; Lara-Corona, V.H.; González-Zamora, E.; Negrón-Silva, G. Sulfated Zirconia-Catalyzed Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones (DHPMs) Under Solventless Conditions: Competitive Multicomponent Biginelli vs. Hantzsch Reactions. *Molecules* **2006**, *11*, 731–738. [CrossRef]

38. Karade, H.N.; Sathe, M.; Kaushik, M.P. Synthesis of 4-Aryl Substituted 3,4-Dihydropyrimidinones Using Silica-chloride Under Solvent Free Conditions. *Molecules* **2007**, *12*, 1341–1351. [CrossRef] [PubMed]

39. Liu, C.-J.; Wang, J.-D. Ultrasound-Assisted Synthesis of Novel 4-(2-Phenyl-1,2,3-Triazol-4-yl)-3,4-Dihydropyrimidin-2(1H)-(Thio)ones Catalyzed by Sm(ClO₄)₃. *Molecules* **2010**, *15*, 2087–2095. [CrossRef]

40. Nandurkar, N.S.; Bhanushali, M.J.; Bhor, M.D.; Bhanage, B.M. Y(NO₃)₃·6H₂O: A novel and reusable catalyst for one pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions. *J. Mol. Catal. A Chem.* **2007**, *271*, 14–17. [CrossRef]

41. Zych, A.J.; Wang, H.-J.; Sakwa, S.A. Synthesis and Suzuki-Miyaura reactions of 5-halo-3,4-dihydropyrimidin-2(1H)-ones. *Tetrahedron Lett.* **2010**, *51*, 5103–5105. [CrossRef]

42. Karade, H.N.; Acharya, J.; Kaushik, M.P. An efficient and rapid dehydrogenation of 4-aryl-3,4-dihydropyrimidin-2(1H)-ones (DHPMs) using CAN/HCl. *Tetrahedron Lett.* **2012**, *53*, 5541–5543. [CrossRef]

43. Starcevich, J.T.; Laughlin, T.J.; Mohan, R.S. Iron(III) tosylate catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones via the Biginelli reaction. *Tetrahedron Lett.* **2013**, *54*, 983–985. [CrossRef]

44. Niknam, K.; Zolfigol, M.A.; Hossieninejad, Z.; Daneshvar, N. Efficient synthesis of 3,4-dihydropyrimidin-2(1H)-one using metal hydrogen sulfates M(HSO₄)n as catalyst under solvent free conditions. *Chin. J. Catal.* **2007**, *28*, 591–595. [CrossRef]

45. Safaei Ghomi, J.; Teymuri, R.; Ziarati, A. A green synthesis of 3,4-dihydropyrimidine-2(1H)-one/thione derivatives using nanosilica-supported tin(II) chloride as a heterogeneous nanocatalyst. *Monatsh. Chem.* **2013**, *144*, 1865–1870. [CrossRef]

46. Kathing, C.; Rani, J.W.S.; Singh, N.G.; Tumtin, S.; Nongrum, R.; Nongkhlaw, R. One-pot synthesis of 3,4-Dihydropyrimidin-2(1H)-ones catalysed by cupric acetate under solvent-free conditions. *J. Chin. Chem. Soc.* **2014**, *61*, 1254–1258. [CrossRef]

47. Karimi, H. Copper Zirconium Phosphate as an Efficient Catalyst for Multi-component Reactions in Solvent-Free Conditions. *Iran. J. Sci. Technol. Trans. Sci.* **2018**, *42*, 219–235. [CrossRef]

48. Popovics-Tóth, N.; Tajti, Á.; Hümpfner, E.; Bálint, E. Synthesis of 3,4-Dihydropyrimidin-2(1H)-one-phosphonates by the Microwave-Assisted Biginelli Reaction. *Catalysts* **2021**, *11*, 45. [CrossRef]

49. Medyouni, R.; Elgabsi, W.; Naouali, O.; Romerosa, A.; Al-Ayed, A.S.; Baklouti, L.; Hamdi, N. One-pot three-component Biginelli-type reaction to synthesize 3,4-dihydropyrimidine-2-(1H)-ones catalyzed by Co phthalocyanines: Synthesis, characterization, aggregation behavior and antibacterial activity. *Spectrochim. Acta A* **2016**, *167*, 165–174. [CrossRef]

50. Gein, V.L.; Zamaraeva, T.M.; Dmitriev, M.V. Sodium hydrogen sulfate as a catalyst for the synthesis of N,4-diaryl-6-methyl-1-methyl(phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides via the Biginelli reaction. *Chem. Heterocycl. Comp.* **2018**, *54*, 177–182. [CrossRef]

51. Moosavifar, M. An appropriate one-pot synthesis of dihydropyrimidinones catalyzed by heteropoly acid supported on zeolite: An efficient and reusable catalyst for the Biginelli reaction. *Compt. Rend. Chim.* **2012**, *15*, 444–447. [CrossRef]

52. Shahid, A.; Ahmed, N.S.; Saleh, T.S.; Al-Thabaiti, S.A.; Basahel, S.N.; Schwieger, W.; Mokhtar, M. Solvent-Free Biginelli Reactions Catalyzed by Hierarchical Zeolite Utilizing a Ball Mill Technique: A Green Sustainable Process. *Catalysts* **2017**, *7*, 84. [CrossRef]

53. Bentahar, S.; Taleb, M.A.; Sabour, A.; Dbik, A.; El Khomri, M.; El Messaoudi, N.; Lacherai, A.; Mamouni, R. Potassium Fluoride-Modified Clay as a Reusable Heterogeneous Catalyst for One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones. *Russ. J. Org. Chem.* **2019**, *55*, 1423–1431. [CrossRef]

54. Torres-Méndez, C.E.; López-Mayorga, B. Copper supported on acid-activated vermiculite as an efficient and recyclable catalyst for the Biginelli reaction: A green approach. *Clay Miner.* **2020**, *55*, 271–280. [CrossRef]

55. Bosica, G.; Cachia, F.; De Nittis, R.; Mariotti, N. Efficient One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones via a Three-Component Biginelli Reaction. *Molecules* **2021**, *26*, 3753. [CrossRef] [PubMed]

56. Diarjani, E.S.; Rajabi, F.; Yahyazadeh, A.; Puente-Santiago, A.R.; Luque, R. Copper Tridentate Schiff Base Complex Supported on SBA-15 as Efficient Nanocatalyst for Three-Component Reactions under Solventless Conditions. *Materials* **2018**, *11*, 2458. [CrossRef] [PubMed]

57. Akbarzadeh, P.; Koukabi, N. Synthesis and characterization of the immobilized polythiophene on magnetic carbon nanotube as a prominent catalyst for the synthesis of dihydropyrimidinone and octahydroquinazolinone derivatives. *Res. Chem. Intermediat.* **2020**, *46*, 4955–4969. [CrossRef]

58. Farooq, S.; Alharthi, F.A.; Alsalme, A.; Hussain, A.; Dar, B.A.; Hamid, A.; Koul, S. Dihydropyrimidinones: Efficient one-pot green synthesis using Montmorillonite-KSF and evaluation of their cytotoxic activity. *RSC Adv.* **2020**, *10*, 42221. [CrossRef]

59. Freitas, E.F.; Souza, R.Y.; Passos, S.T.A.; Dias, J.A.; Dias, S.C.L.; Neto, B.A.D. Tuning the Biginelli reaction mechanism by the ionic liquid effect: The combined role of supported heteropolyacid derivatives and acidic strength. *RSC Adv.* **2019**, *9*, 27125. [CrossRef]

60. Liu, Z.; Ma, R.; Cao, D.; Liu, C. New Efficient Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones Catalyzed by Benzotriazolium-Based Ionic Liquids under Solvent-Free Conditions. *Molecules* **2016**, *21*, 462. [CrossRef] [PubMed]

61. Zhang, Y.; Wang, B.; Zhang, X.; Huang, J.; Liu, C. An Efficient Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-Ones and Thiones Catalyzed by a Novel Brønsted Acidic Ionic Liquid under Solvent-Free Conditions. *Molecules* **2015**, *20*, 3811–3820. [CrossRef] [PubMed]

62. Mohammadi, B.; Behbahani, F.K. Recent developments in the synthesis and applications of dihydropyrimidin-2(1*H*)-ones and thiones. *Mol. Divers.* **2018**, *22*, 405–446. [CrossRef]

63. Nagarajaiah, H.; Mukhopadhyay, A.; Moorthy, J.N. Biginelli reaction: An overview. *Tetrahedron Lett.* **2016**, *57*, 5135–5149. [CrossRef]

64. Shumaila, A.M.A.; Al-Thulaia, A.A.N. Mini-review on the synthesis of Biginelli analogs using greener heterogeneous catalysis: Recent strategies with the support or direct catalyzing of inorganic catalysts. *Synth. Commun.* **2019**, *49*, 1613–1632. [CrossRef]

65. Heravi, M.M.; Asadi, S.; Lashkariani, B.M. Recent progress in asymmetric Biginelli reaction. *Mol. Divers.* **2013**, *17*, 389–407. [CrossRef]

66. Heravi, M.M.; Moradi, R.; Mohammadkhani, L.; Moradi, B. Current progress in asymmetric Biginelli reaction: An update. *Mol. Divers.* **2018**, *22*, 751–767. [CrossRef]

67. Guo, Y.; Gao, Z.; Wang, K.; Li, J.; Bi, X.; Guo, L.; Liu, H.; Shi, E.; Xiao, J. Chiral Spirocyclic Phosphoric Acid-Catalyzed Synthesis of 4-Alkyl-3,4-dihydropyrimidin-2(1*H*)-one Derivatives by Asymmetric Biginelli Reactions. *Asian J. Org. Chem.* **2020**, *9*, 626–630. [CrossRef]

68. Nasir, N.; Rehman, F.; Omair, S.F. Risk factors for bacterial infections in patients with moderate to severe COVID-19 case: A-control study. *J. Med. Virol.* **2021**, *93*, 4564–4569. [CrossRef]

69. Marinescu, M. Synthesis of Antimicrobial Benzimidazole–Pyrazole Compounds and Their Biological Activities. *Antibiotics* **2021**, *10*, 1002. [CrossRef]

70. Kidwai, M.; Saxena, S.; Khan, M.K.R.; Thukral, S.S. Synthesis of 4-aryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydro quinazoline-2-one/thione-5-one derivatives and evaluation as antibacterials. *Eur. J. Med. Chem.* **2005**, *40*, 816–819. [CrossRef] [PubMed]

71. Deshmukh, M.B.; Salunkhe, S.M.; Patil, D.R.; Anbhule, P.V. A novel and efficient one step synthesis of 2-amino-5-cyano-6-hydroxy-4-arylpyrimidines and their anti-bacterial activity. *Eur. J. Med. Chem.* **2009**, *44*, 2651–2654. [CrossRef]

72. Rajanarendar, E.; Reddy, M.N.; Murthy, K.R.; Reddy, K.G.; Raju, S.; Srinivas, M.; Praveen, B.; Rao, M.S. Synthesis, antimicrobial, and mosquito larvicidal activity of 1-aryl-4-methyl-3,6-bis-(5-methylisoxazol-3-yl)-2-thioxo-2,3,6,10b-tetrahydro-1*H*-pyrimido[5,4-c]quinolin-5-ones. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6052–6055. [CrossRef]

73. Chitra, S.; Devanathan, D.; Pandiarajan, K. Synthesis and in vitro microbiological evaluation of novel 4-aryl-5-isopropoxycarbonyl-6-methyl-3,4-dihydropyrimidinones. *Eur. J. Med. Chem.* **2010**, *45*, 367–371. [CrossRef]

74. Dabholkar, V.V.; Ravi, T.D. Synthesis of Biginelli products of thiobarbituric acids and their antimicrobial activity. *J. Serb. Chem. Soc.* **2010**, *75*, 1033–1040. [CrossRef]

75. Akhaja, T.N.; Raval, J.P. 1,3-dihydro-2*H*-indol-2-ones derivatives: Design, Synthesis, in vitro antibacterial, antifungal and antitubercular study. *Eur. J. Med. Chem.* **2011**, *46*, 5573–5579. [CrossRef]

76. Kamal, A.; Shaheer, M.M.; Bajee, S.; Azeeza, S.; Faazil, S.; Ramakrishna, S.; Naidu, V.G.M.; Vishnuwardhan, M.V.P.S. Synthesis and biological evaluation of conformationally flexible as well as restricted dimers of monastrol and related dihydropyrimidones. *Eur. J. Med. Chem.* **2011**, *46*, 3274–3281. [CrossRef]

77. Kaur, R.; Bansal, M.; Kaur, B.; Mishra, T.; Bhatia, A. Synthesis of 4-aryl-4,5-dihydro-1H-indeno[1,2-d]pyrimidines by Biginelli condensation and their antibacterial activities. *J. Chem. Sci.* **2011**, *123*, 443–451. [CrossRef]

78. Kulakov, I.V. Synthesis and biological activity of 3,4-dihydropyrimidin-2-thione of aminomethylene derivatives based on the alkaloid cytisine. *Chem. Nat. Comp.* **2011**, *47*, 597–599. [CrossRef]

79. Alam, M.M.; Akhter, M.; Husain, A.; Marella, A.; Tanwar, O.P.; Ali, R.; Hasan, S.M.; Kumar, H.; Haider, R.; Shaquiquzzaman, M. Anti-inflammatory and antimicrobial activity of 4,5-dihydropyrimidine-5-carbonitrile derivatives: Their synthesis and spectral elucidation. *Acta Pol. Pharm.* **2012**, *69*, 1077–1085. [PubMed]

80. Shah, P.M.; Patel, M.P. Zn(OTf)2-catalyzed three component, one-pot cyclocondensation reaction of some new octahydroquinazolinone derivatives and access their bio-potential. *Med. Chem. Res.* **2012**, *21*, 1188–1198. [CrossRef]

81. Youssef, M.M.; Amin, M.A. Microwave Assisted Synthesis of Some New Thiazolopyrimidine, Thiazolodipyrimidine and Thiazolopyrimidothiazolopyrimidine Derivatives with Potential Antioxidant and Antimicrobial Activity. *Molecules* **2012**, *17*, 9652–9667. [CrossRef]

82. Sedaghati, B.; Fassihi, A.; Arbabi, S.; Ranjbar, M.; Memarian, H.R.; Saghaie, L.; Omidi, A.; Sardari, A.; Jalali, M.; Abedi, D. Synthesis and antimicrobial activity of novel derivatives of Biginelli pyrimidines. *Med. Chem. Res.* **2012**, *21*, 3973–3983. [CrossRef]

83. Ghodasara, H.B.; Trivedi, A.R.; Kataria, B.; Patel, B.G.; Shah, V.H. Synthesis and antimicrobial evaluation of novel substituted pyrimidine scaffold. *Med. Chem. Res.* **2013**, *22*, 6121–6128. [CrossRef]

84.   Godhani, D.R.; Dobariya, P.B.; Jogel, A.A.; Sanghani, A.M.; Mehta, J.P. An efficient synthesis, characterization, and antimicrobial screening of tetrahydropyrimidine derivatives. *Med. Chem. Res.* **2014**, *23*, 2417–2425. [CrossRef]

85.   Umesha, K.; Sarojini, B.K.; Darshan Raj, C.G.; Bhanuprakash, v.; Yogisharadhya, R.; Raghavendra, R.; Khan, M.T.H. In vitro and in silico biological studies of novel thiazolo [3,2-a]pyrimidine-6-carboxylate derivatives. *Med. Chem. Res.* **2014**, *23*, 168–180. [CrossRef]

86.   Viveka, S.; Madhu, L.N.; Nagaraja, G.K. Synthesis of new pyrazole derivatives via multicomponent reaction and evaluation of their antimicrobial and antioxidant activities. *Monatsh. Chem.* **2015**, *146*, 1547–1555. [CrossRef]

87.   Raj, T.; Billing, B.K.; Kaur, N.; Singh, N. Design, synthesis and antimicrobial evaluation of dihydropyrimidone based organic–inorganic nanohybrids. *RSC Adv.* **2015**, *5*, 46654. [CrossRef]

88.   Gein, V.L.; Zamaraeva, T.M.; Fedotov, A.Y.; Balandina, A.V.; Dmitriev, M.V. Synthesis, Structure, and Antimicrobial Activity of N,6-Diaryl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides. *Russ. J. Gen. Chem.* **2016**, *86*, 2437–2441. [CrossRef]

89.   Khalifa, N.M.; Nossier, E.S.; Al-Omar, M.A.; Amr, A.E. Synthesis, Reactions, and Antimicrobial Activity of Some Novel Fused Thiazolo[3,2-a]pyrimidine-5H-indeno[1,2-d]pyrimidine Derivatives. *Russ. J. Gen. Chem.* **2016**, *86*, 1948–1953. [CrossRef]

90.   Ahmad, M.J.; Hassan, S.F.; Nisa, R.U.; Ayub, K.; Nadeem, M.S.; Nazir, S.; Ansari, F.L.; Qureshi, N.A.; Rashid, U. Synthesis, in vitro potential and computational studies on 2-amino-1,4-dihydropyrimidines as multitarget antibacterial ligands. *Med. Chem. Res.* **2016**, *25*, 1877–1894. [CrossRef]

91.   Ramachandran, V.; Arumugasamy, K.; Singh, S.K.; Edayadulla, N.; Ramesh, P.; Kamaraj, S.K. Synthesis, antibacterial studies, and molecular modeling studies of 3,4-dihydropyrimidinone compounds. *J. Chem. Biol.* **2016**, *9*, 31–40. [CrossRef] [PubMed]

92.   Desai, N.C.; Bhatt, M.J. Catalytic synthesis and antimicrobial activity of N-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-4-(1H-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides. *Heterocycl. Commun.* **2016**, *22*, 131–136. [CrossRef]

93.   Attri, A.; Bhatia, R.; Gaur, J.; Arora, B.; Gupta, A.; Kumar, N.; Choi, E.H. Triethylammonium acetate ionic liquid assisted one-pot synthesis of dihydropyrimidinones and evaluation of their antioxidant and antibacterial activities. *Arab. J. Chem.* **2017**, *10*, 206–214. [CrossRef]

94.   Wani, M.Y.; Ahmad, A.; Kumar, S.; Sobral, A.J.F.N. Flucytosine analogues obtained through Biginelli reaction as efficient combinative antifungal agents. *Microb. Pathog.* **2017**, *105*, 57–62. [CrossRef] [PubMed]

95.   Rani, J.; Saini, M.; Kumar, S.; Verma, P.K. Design, synthesis and biological potentials of novel tetrahydroimidazo[1,2-a]pyrimidine derivatives. *Chem. Cent. J.* **2017**, *11*, 16. [CrossRef] [PubMed]

96.   Allam, M.; Bhavani, A.K.D.; Vodnala, S. The New Green Procedure for Pyrazolopyrimidinone Based Dihydropyrimidinones and Their Antibacterial Screening. *Russ. J. Gen. Chem.* **2017**, *87*, 2712–2718. [CrossRef]

97.   Foroughifar, N.; Beromi, S.K.; Pasdar, H.; Shahi, M. Synthesis of Some New Tetrahydropyrimidine Derivatives as Possible Antibacterial Agents. *Iran. J. Pharm. Res.* **2017**, *16*, 596–601. [PubMed]

98.   Naik, N.S.; Shastri, L.A.; Joshi, S.D.; Dixit, S.R.; Chougala, B.M.; Samundeeswari, S.; Holiyachi, M.; Shaikh, F.; Madar, J.; Kulkarni, R.; et al. 3,4-Dihydropyrimidinone-coumarin analogues as a new class of selective agent against S. aureus: Synthesis, biological evaluation and molecular modelling study. *Bioorg. Med. Chem.* **2017**, *25*, 1413–1422. [CrossRef]

99.   Hamdi, N.; Medyouni, R.; Bilel, H.; Mansour, L.; Romerosa, A. An Efficient One-Pot Protocol for the Synthesis of Substituted 3,4-Dihydropyrimidin-2(1H)-ones Using Metallophthalocyanines (MPcs) as Potent Heterogeneous Catalysts: Synthesis, Characterization, Aggregation and Antimicrobial Activity. *Molecules* **2017**, *22*, 605. [CrossRef]

100.   Youssef, A.M.S.; Fouda, A.M.; Faty, R.M. Microwave assisted synthesis of some new thiazolopyrimidine and pyrimidothiazolopyrimidopyrimidine derivatives with potential antimicrobial activity. *Chem. Cent. J.* **2018**, *12*, 50. [CrossRef]

101.   Viveka, S.; Nagaraja, G.K.; Shama, P.; Basavarajaswamy, G.; Rao, K.P.; Sreenivasa, M.Y. One pot synthesis of thiazolo[2,3-b]dihydropyrimidinone possessing pyrazole moiety and evaluation of their antiinflammatory and antimicrobial activities. *Med. Chem. Res.* **2018**, *27*, 171–185. [CrossRef]

102.   Huseynzada, A.E.; Jelch, C.; Akhundzada, H.V.N.; Soudani, S.; Nasr, C.B.; Israyilova, A.; Doria, F.; Hasanova, U.A.; Khankishiyeva, R.F.; Freccero, M. Synthesis, crystal structure and antibacterial studies of dihydropyrimidines and their regioselectively oxidized products. *RSC Adv.* **2021**, *11*, 6312. [CrossRef]

103.   Gondru, R.; Peddi, S.R.; Manga, V.; Khanapur, M.; Gali, R.; Sirassu, N.; Bavantula, R. One-pot synthesis, biological evaluation and molecular docking studies of fused thiazolo[2,3-b]pyrimidinone pyrazolylcoumarin hybrids. *Mol. Div.* **2018**, *22*, 943–956. [CrossRef] [PubMed]

104.   Samdhian, V.; Bhatia, S.K.; Kaur, B. Cell-Viability Analysis Against MCF-7 Human Breast Cell Line and Antimicrobial Evaluation of Newly Synthesized Selenoxopyrimidines. *Russ. J. Org. Chem.* **2019**, *55*, 1041–1046. [CrossRef]

105.   Devineni, S.R.; Madduri, T.R.; Chamarthi, N.R.; Liu, C.Q.; Pavuluri, C.M. An efficient microwave-promoted three-component synthesis of thiazolo[3,2-a]pyrimidines catalyzed by SiO_2–$ZnBr_2$ and antimicrobial activity evaluation. *Chem. Heterocycl. Compd.* **2019**, *55*, 266–274. [CrossRef]

106.   Gein, V.L.; Prudnikova, A.N.; Kurbatova, A.A.; Dmitriev, M.V.; Novikova, V.V.; Rudakova, I.P.; Starikov, A.L. Three-Component Reaction of Dimedone with Aromatic Aldehydes and 5-Aminotetrazole. *Russ. J. Gen. Chem.* **2019**, *89*, 881–885. [CrossRef]

107.   Afradi, N.; Foroughifar, N.; Pasdar, H.; Qomi, M. Aspartic-acid-loaded starch-functionalized Mn–Fe–Ca ferrite magnetic nanoparticles as novel green heterogeneous nanomagnetic catalyst for solvent-free synthesis of dihydropyrimidine derivatives as potent antibacterial agents. *Res. Chem. Intermed.* **2019**, *45*, 3251–3271. [CrossRef]

108. Jadhav, C.K.; Nipate, A.S.; Chate, A.V.; Songire, V.D.; Patil, A.P.; Gill, C.H. Efficient Rapid Access to Biginelli for the Multicomponent Synthesis of 1,2,3,4-Tetrahydropyrimidines in Room-Temperature Diisopropyl Ethyl Ammonium Acetate. *ACS Omega* **2019**, *4*, 22313–22324. [CrossRef] [PubMed]

109. Desai, N.C.; Joshi, S.B.; Jadeja, K.A. A one-pot multicomponent Biginelli reaction for the preparation of novel pyrimidinthione derivatives as antimicrobial agents. *J. Heterocycl. Chem.* **2020**, *57*, 791–795. [CrossRef]

110. Razzaghi-Asl, N.; Kamrani-Moghadam, M.; Farhangi, B.; Vahabpour, R.; Zabihollahi, R.; Sepehri, S. Design, synthesis and evaluation of cytotoxic, antimicrobial, and anti-HIV-1 activities of new 1,2,3,4-tetrahydropyrimidine derivatives. *Res. Pharm. Sci.* **2019**, *14*, 155–166. [CrossRef] [PubMed]

111. Rajitha, G.; Arya, C.G.; Janardhan, B.; Laxmi, S.V.; Ramesh, G.; Kumari, U.S. 3-Aryl/Heteryl-5-Phenylindeno[1,2-*d*]thiazolo[3,2-*a*]pyrimidin-6(5*H*)-ones: Synthesis, Characterization, and Antimicrobial Investigation. *Russ. J. Bioorg. Chem.* **2020**, *46*, 612–619. [CrossRef]

112. Sethiya, A.; Soni, J.; Manhas, A.; Jha, P.C.; Agarwal, S. Green and highly efficient MCR strategy for the synthesis of pyrimidine analogs in water via C–C and C–N bond formation and docking studies. *Res. Chem. Intermed.* **2021**. [CrossRef]

113. El-Emary, T.I.; Abdel-Mohsena, S.A.; Mohamed, S.A. An Efficient Synthesis and Reactions of 5-Acetyl-6-Methyl-4-(1,3-Diphenyl-1*H*-Pyrazol-4-yl)-3,4-Dihydropyrmidin-2(1*H*)-Thione as Potential Antimicrobial and Anti-Inflammatory Agents. *Russ. J. Bioorg. Chem.* **2021**, *47*, 561–571. [CrossRef]

114. Marinescu, M.; Berea, E.B.; Neculae, A.V.F.; Stavarache, C.E.; Hanganu, A.; Zalaru, C.M.; Marton, G.I. Synthesis, biological screening and DFT studies of the new tetrahydropyrimidine-benzo[d]imidazol compounds. *Arch. Chem. Res.* **2018**, *19–20*, 2. [CrossRef]

115. 115. Marinescu, M.; Zălaru, C.-M.; Hanganu, A.; Stavarache, C.; Marton, G.I. Synthesis, Spectral Characterization Antimicrobial Activity and DFT Studies of Some Tetrahydropyrimidinones. *Proceedings* **2020**, *57*, 52. [CrossRef]

116. Vickers, C.F.; Silva, A.P.G.; Chakraborty, A.; Fernandez, P.; Kurepina, N.; Saville, C.; Naranjo, Y.; Pons, M.; Schnettger, L.S.; Gutierrez, M.G.; et al. Structure-based design of MptpB inhibitors that reduce multidrug-resistant mycobacterium tuberculosis survival and infection burden in vivo. *J. Med. Chem.* **2018**, *61*, 18337–18352. [CrossRef]

117. Virsodia, V.; Pissurlenkar, R.R.S.; Manvar, D.; Dholakia, C.; Adlakha, P.; Shah, A.; Coutinho, E.C. Synthesis, screening for antitubercular activity and 3D-QSAR studies of substituted N-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamides. *Eur. J. Med. Chem.* **2008**, *43*, 2103–2115. [CrossRef]

118. Trivedi, A.R.; Bhuva, V.R.; Dholariya, B.H.; Dodiya, D.K.; Kataria, V.B.; Shah, V.H. Novel dihydropyrimidines as a potential new class of antitubercular agents. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6100–6102. [CrossRef]

119. Trivedi, A.R.; Dholariya, B.H.; Vakhariya, C.P.; Dodiya, D.K.; Ram, H.K.; Kataria, V.B.; Siddiqui, A.B.; Shah, V.H. Synthesis and anti-tubercular evaluation of some novel pyrazolo[3,4-d]pyrimidine derivatives. *Med. Chem. Res.* **2012**, *21*, 1887–1891. [CrossRef]

120. Yadlapalli, R.K.; Chourasia, O.P.; Vemuri, K.; Sritharan, M.; Perali, R.S. Synthesis and *in vitro* anticancer and antitubercular activity of diarylpyrazole ligated dihydropyrimidines possessing lipophilic carbamoyl group. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2708–2711. [CrossRef]

121. Ambre, P.K.; Pissurlenkar, R.R.S.; Wavhale, R.D.; Shaikh, M.S.; Khedkar, V.M.; Wan, B.; Franzblau, S.G.; Coutinho, E.C. Design, synthesis, and evaluation of 4-(substituted)phenyl-2-thioxo-3,4-dihydro-1*H*-chromino[4,3-d]pyrimidin -5-one and 4-(substituted)phenyl-3,4-dihydro-1*H*-chromino[4,3-d]pyrimidine-2,5-dione analogs as antitubercular agents. *Med. Chem. Res.* **2014**, *23*, 2564–2575. [CrossRef]

122. Chikhale, R.; Menghani, S.; Babu, R.; Bansode, R.; Bhargavi, G.; Karodia, N.; Rajasekharan, M.V.; Paradkar, A.; Khedekar, P. Development of selective DprE1 inhibitors: Design, synthesis, crystal structure and antitubercular activity of benzothiazolylpyrimidine-5-carboxamide. *Eur. J. Med. Chem.* **2015**, *96*, 30–46. [CrossRef] [PubMed]

123. Fatima, S.; Sharma, A.; Saxena, R.; Tripathi, R.; Shukla, S.K.; Pandey, S.K.; Tripathi, R. Tripathi, R.P. One pot efficient diversity oriented synthesis of polyfunctional styryl thiazolopyrimidines and their bio-evaluation as antimalarial and anti-HIV agents. *Eur. J. Med. Chem.* **2012**, *55*, 195–204. [CrossRef] [PubMed]

124. Marinescu, M.; Cinteza, L.O.; Marton, G.I.; Chifiriuc, M.C.; Popa, M.; Stanculescu, I.; Zalaru, C.M.; Stavarache, C.E. Synthesis, density functional theory study and in vitro antimicrobial evaluation of new benzimidazole Mannich bases. *BMC Chem.* **2020**, *14*, 45. [CrossRef]

125. Marinescu, M.; Tudorache, D.G.; Marton, G.; Zalaru, C.M.; Popa, M.; Chifiriuc, M.C.; Stavarache, C.; Constantinescu, C. Density functional theory molecular modeling, chemical synthesis, and antimicrobial behaviour of selected benzimidazole derivatives. *J. Mol. Struct.* **2017**, *1130*, 463–471. [CrossRef]

126. Marinescu, M.; Cinteza, L.O.; Marton, G.; Măruţescu, L.; Chifiriuc, M.C.; Constantinescu, C. Density functional theory molecular modeling and antimicrobial behaviour of selected 1,2,3,4,5,6,7,8-octahydroacridine-N(10)-oxides. *J. Mol. Struct.* **2017**, *1144*, 14–23. [CrossRef]

127. Zalaru, C.; Dumitrascu, F.; Draghici, C.; Tarcomnicu, I.; Tatia, R.; Moldovan, L.; Chifiriuc, M.C.; Lazar, V.; Marinescu, M.; Nitulescu, G.; et al. Synthesis, spectroscopic characterization, DFT study and antimicrobial activity of novel alkylaminopyrazole derivatives. *J. Mol. Struct.* **2018**, *1156*, 12–21. [CrossRef]