Pyridine Compounds with Antimicrobial and Antiviral Activities

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Abstract: In the context of the new life-threatening COVID-19 pandemic caused by the SARS-CoV-2 virus, finding new antiviral and antimicrobial compounds is a priority in current research. Pyridine is a privileged nucleus among heterocycles; its compounds have been noted for their therapeutic properties, such as antimicrobial, antiviral, antitumor, analgesic, anticonvulsant, anti-inflammatory, antioxidant, anti-Alzheimer’s, anti-ulcer or antidiabetic. It is known that a pyridine compound, which also contains a heterocycle, has improved therapeutic properties. The singular presence of the pyridine nucleus, or its one together with one or more heterocycles, as well as a simple hydrocarbon linker, or grafted with organic groups, gives the key molecule a certain geometry, which determines an interaction with a specific protein, and defines the antimicrobial and antiviral selectivity for the target molecule. Moreover, an important role of pyridine in medicinal chemistry is to improve water solubility due to its poor basicity. In this article, we aim to review the methods of synthesis of pyridine compounds, their antimicrobial and antiviral activities, the correlation of pharmaceutical properties with various groups present in molecules as well as the binding mode from Molecular Docking Studies.

Keywords: pyridine; synthesis; heterocyclic compounds; antimicrobial; antiviral

1. Introduction

Pyridine (from the Greek pyr = fire and idine—which is used for aromatic bases) contains a single heteroaromatic ring, which comes from the replacement of a CH group in the benzene ring with the nitrogen atom. Ramsay (1877) synthesizes pyridine for the first time, by the reaction of acetylene with hydrogen cyanide in a red-hot iron tube furnace, this being the first synthesized heterocycle [1]. Arthur Hantzsch later synthesized (1881) pyridine compounds by the synthesis that bears his name, through a multicomponent reaction, starting from a β-ketoester, an aldehyde and ammonia [2,3]. An important role of pyridine is that it is used as an organic solvent or as ligand for coordination complexes [4–8]. The pyridine nucleus is found in many natural products, such as vitamins, alkaloids and coenzymes, as well as in many drugs (Figure 1) and pesticides [9,10]. The recent literature mentions various series of compounds containing the pyridine nucleus, as a unique heterocycle, and with other heterocycles or fused with other heterocycles, which have remarkable antibacterial, antifungal and antiviral properties [1,9–13]. The presence of an additional heterocycle compared to the pyridine one in the bioactive molecule proved to be beneficial in the sense that it intensified the therapeutic properties of the antimicrobial and antiviral ones, and also widened their range [3–8]. Moreover, the presence of certain organic groups, such as amino, hydroxy, methoxy, sulfamide, hydrazide, etc., increase the biological activities of the compounds, as noted in the literature. Moreover, current research has been stimulated by the unexpected evolution of the SARS-CoV-2 pandemic.
(COVID-19), which required new antimicrobial and antiviral agents to treat patients with moderate or severe cases of pneumonia [13].

In the present paper, we aim to review antimicrobial and antiviral pyridine compounds, as well as their methods of synthesis. Their presentation will be based on the complexity of the molecules and their therapeutic properties.

2. Synthesis of Antimicrobial Compounds Containing Only Pyridine Ring

Sarova et al. [14] synthesized three dodecanoic acid derivatives 1–3 with yields of 59–61%, starting from dodecanoic acid in two steps, chlorination with thionyl chloride and reaction with the corresponding aminopyridine (Scheme 1). All compounds possessed good antibacterial activity against B. subtilis, S. aureus and E. coli and antifungal activity against A. niger and C. albicans.

![Scheme 1](image1.png)

Scheme 1. Synthesis of dodecanoic acid pyridines 1–3 [14].

Narang et al. [15] synthesized a series of 18 nicotinic acid benzylidene hydrazide derivatives in three steps with total yields of 60–80% (Scheme 2). The antimicrobial screening results indicated that compounds with nitro (4, 5 and 6) and dimethoxy (7) substituents were the most active ones against tested strains (S. aureus, B subtilis, E coli, C. albicans, and A. niger), some of them having an antimicrobial activity comparable to the standard drugs fluconazole and norfloxacin.

![Scheme 2](image2.png)

Scheme 2. Synthesis of nicotinic acid benzylidene hydrazide derivatives 4–7 [15].
Malhotra et al. [16] synthesized ten substituted Mannich bases 8–17 using a classical Mannich reaction starting from 2-ethoxybenzylidene isonicotinohydrazide, formaldehyde and a secondary amine (Scheme 3). The highest antibacterial activity against Gram-positive species B. subtilis, S. aureus and Gram-negative species P. aeruginosa, E. coli were shown by compounds 12, 15, 16, and 17 (MIC = 6.25–12.5 µg mL⁻¹) with Amoxicillin as standard. Furthermore, these compounds exhibited a high antifungal activity against C. albicans and C. gabrata species (MIC = 12.5 µg mL⁻¹). Judge et al. [17] synthesized isonicotinic acid-1-(substituted phenyl)-ethylidene hydrazides 18–22 by refluxing isonicotinoyl hydrazide with various substituted acetophenones (Scheme 4). Compounds with Br, OCH₃, and Cl groups were highly active antimicrobial agents, all of them exhibiting activities better than the standard compounds norfloxacin and fluconazole.

![Scheme 3](image)

**Scheme 3.** Synthesis of Mannich bases 8–17 [16].

![Scheme 4](image)

**Scheme 4.** Synthesis of isonicotinic acid-1-(substituted phenyl)-ethylidene hydrazides 18–22 [17].

In a similar study, Judge et al. [18] synthesized a series of isonicotinic acid hydrazide derivatives by benzoilation of (E)-N’-benzylideneisonicotinohydrazide compounds (Scheme 5) and found that derivatives 23–27 were the most active antimicrobial agents against the tested strains S. aureus, B. subtilis, E. coli, C. albicans, and A. niger, with MIC between 2.18–3.08 µM mL⁻¹. Eldeab [19] synthesized substituted pyridyl-4-chloro benzoates by microwave-assisted condensation of 2-oxo-1,2-dihydropyridine-3-carbonitriles with 4-chlorobenzoyl chloride under solvent-free conditions or by conventional heating in methylene chloride in the presence of triethylamine. The activity of 3-cyano-5-[(4-hydroxyphenyl)diazenyl]-4-methyl-6-phenylpyridin-2-yl-4-chloro benzoate 28 against B. subtilis and S. aureus was comparable to that of Amikacin, which is used as the standard antibiotic (Figure 2). Karunanidhi et al. [20] isolated 2-(methylthio)pyridine-3-carbonitrile 29 from Persian Shallot (Allium stipitatum Regel.) and screened for its antimicrobial activity. The minimum inhibitory concentrations (MICs) were found to be in the range of 0.5 to 64 µg mL⁻¹ for the tested bacterial strains (A. baumannii, A. iwoffii, Enterobacter sp., E. coli, S. aureus, P. aeruginosa, S. typhi, S. dysenteriae and S. maltophilia) and of 0.25 to 2 µg mL⁻¹ for Candida species (Figure 2). Özgeriş [21] synthesized nicotinoyl compounds 30–34 by reaction of nicotinoyl chloride with potassium thiocyanate or ammonium thiocyanate to get nicotinoyl isothiocyanate, which refluxed with substituted phenethylamines in acetone to yield the nicotinoyl thioureas (Scheme 6). All compounds showed excellent antibacterial activity against the tested bacterial strains S. aureus, E. faecalis, E. coli, A. baumannii, and P. aeruginosa with MIC concentrations of 31.25 to 62.5 µg mL⁻¹. Ragab et al. [22] reported the synthesis of pyridine compounds 36 (by ternary condensation of cyanoacetamide 35, aromatic aldehyde and malononitrile in an equimolar molar ratio 1:1:1 in basic ethanol)
and 37 (by cyclo-condensation of cyanoacetamide 35 with acetylacetone in DMF) with very good antimicrobial activity against all tested strains B. subtilis, S. aureus, E. faecalis, E. coli, P. aeruginosa, S. typhi, C. albicans, and F. oxysporum (MIC = 18–31 μM) (Table 1).

![Scheme 5. Synthesis of isonicotinic acid hydrazide benzoyl derivatives 23–27](image)

![Figure 2. Structure of pyridine compounds 28, 29, 36, 37, and intermediate 35](image)

![Scheme 6. Synthesis of pyridine compounds 30–34](image)

**Table 1.** In vitro antibacterial activity (minimal inhibitory/bactericidal concentrations, MIC and MBC), expressed in μM, for sulfonamides 36 and 37 [22].

| Compound | Test | Gram-Positive | Gram-Negative |
|----------|------|---------------|---------------|
|          |      | B. subtilis   | S. aureus     | E. faecalis   | E. coli       | P. aeruginosa | S. typhi     |
| 36       | MIC  | 16.12         | 5.74          | 11.29         | 22.61         | 90.48        | 11.29        |
|          | MBC  | 30.63         | 10.71         | 19.19         | 36.16         | 171.89       | 19.19        |
| 37       | MIC  | 10.11         | 20.26         | 40.52         | 20.26         | 72.05        | 48.02        |
|          | MBC  | 17.29         | 40.52         | 81.08         | 40.52         | 144.11       | 94.70        |
| Tetracycline | MIC | 70.31         | 140.63        | 140.6         | 35.14         | 140.6        | 7.31         |
|          | MBC  | 91.40         | 196.8         | 210.9         | 42.16         | 196.89       | 98.44        |
Marinescu et al. [23–28] synthesized a series of tetrasubstituted pyridine-N-oxides (octahydroacridines) 38–41, starting from the reaction of 2,2′-methylenebicyclohexanone with formamide at 167–170 °C and the separation of 1,2,3,4,5,6,7,8-octahydroacridine 36 from the reaction mixture (Scheme 7). Oxidation of compound 36 with hydrogen peroxide and acetic acid gave the key intermediate 37, sym-octahydroacridine-10-oxide, which, through reactions of nitration, reduction, alkylation, and hydrolysis, gave the compounds 38, 39, 40, and 41. It was found that antimicrobial activity against the tested pathogens S. epidermidis 1736, S. aureus ATCC 25923, E. faecalis ATCC 29212, B. subtilis 1116, P. aeruginosa 846, K. pneumoniae ESBL+, S. marcescens 0804, C. freundii 1748, E. coli 1576, ESBL+, Salmonella sp. 9246, C. albicans ATCC 10231 increased in the order 40 < 39 < 38 < 41, simultaneously with the decrease of the hydration energy from 0.59, to 1.72, to 3.14 and respectively to 3.76 kcalMol⁻¹.

![Scheme 7. Synthesis of 1,2,3,4,5,6,7,8-octahydroacridine-10-oxides 38–41 [23–28].](image)

### 3. Synthesis of Antimicrobial Pyridine Salts

Furdui et al. [29] reported efficient synthesis of symmetrical diquaternary salts by alkylation of 4-[2-(pyridin-4-yl)ethyl]pyridine or 4,4′-bipyridine, with various bromo- or chloro-acetophenone analogues (Scheme 8) and investigated their antimicrobial activity against nine different microorganisms: B. subtilis, B. cereus, S. lutea, R. glutinis, C. utilis, S. cerevisiae, A. niger, G. candidum and P. roqueforti. Compounds 42a–42d, 43a and 43d show efficient inhibitory properties at least against one bacterial strain. Marek et al. [30] synthesized a set of pyridine-4-aldoxime-based quaternary ammonium salts with differing lengths of alkyl side chains 44–50 (Scheme 9). The in vitro antibacterial activity of all compounds was tested on a panel of eight bacterial strains (S. aureus CCM 4516/08, S. aureus MRSA H 5996/08, S. epidermidis HK6966/08, Enterococcus sp. HK14365/08, E. coli CCM 4517, K. pneumoniae D 11750/08, K. pneumoniae J 14368/08, and P. aeruginosa CCM 1961), four yeasts (C. albicans ATCC 44859, C. krusei E28, C. tropicalis 156, C. glabrata 20/I) and four filamentous fungi (Trichosporon asahii 1188, Aspergillus fumigatus 231, Absidia corymbifera 272, Trichophyton mentagrophytes 445). The compounds with an alkyl chain of C12–C16 possessed the best antimicrobial activity of all.
Scheme 8. Synthesis of bis-pyridinium quaternary ammonium salts [29].

Scheme 9. Synthesis of pyridine-4-aldoxime-based quaternary ammonium salts [30].

Brycki et al. [31] performed a Menshutkin reaction between 4-chloromethylpyridine and the N,N-dimethylalkylamines containing 8, 10, 12, 14, 16, 18 carbon atoms in an alkyl chain, respectively in acetonitrile to obtain compounds 51–56 in good yields at room temperature (Scheme 10). The minimal inhibitory concentration (MIC) values of pyridine salts 51–56 against the fungi A. niger, C. albicans, P. chrysogenum range from 0.1 to 12 mM and against bacteria S. aureus, B. subtilis, E. coli, P. aeruginosa range from 0.02 to 6 mM, as can be seen in Table 2.

Scheme 10. Synthesis of pyridine salts 51–56 [31].

Table 2. Antimicrobial activities of compounds 51–56 expressed as MIC values (mM) [31].

| Compound | A. niger | C. albicans | P. chrysogenum | S. aureus | B. subtilis | E. coli | P. aeruginosa |
|----------|----------|-------------|----------------|-----------|-------------|---------|--------------|
| 51       | -        | 12.497      | -              | 6.2485    | 6.2485      | 6.2485  | 6.2485       |
| 52       | 12.499   | 3.125       | 12.4999        | 1.5625    | 1.5625      | 1.5625  | 1.5625       |
| 53       | 1.5625   | 0.7182      | 1.5625         | 0.1953    | 0.1953      | 0.3906  | 0.7812       |
| 54       | 0.3906   | 0.1953      | 0.1953         | 0.0488    | 0.0977      | 0.1953  | 0.1953       |
| 55       | 0.1953   | 0.0976      | 0.1953         | 0.0244    | 0.0244      | 0.0488  | 0.09766      |

Wang et al. [32] showed that pyridinium bromide salts 57–59 (Figure 3) exhibited excellent antibacterial activity against three Gram-negative bacteria Xanthomonas oryzae, Ralstonia solanacearum, and Xanthomonas axonopodis, because of the appropriate balance between hydrophobicity and hydrophilicity in these molecules.
Ali et al. [33] reported synthesis of eight N-alkylated pyridine-based organic salts 60–67 (Scheme 11) and their antibacterial and antibiofilm activities. The best antibacterial activity was shown by compound 66 at the concentration of 100 µg mL\(^{-1}\) with MIC values of 56 ± 0.5% against S. aureus and 55 ± 0.5% against E. coli; followed by salt 65 (MIC = 55 ± 0.5% against E. coli) and 61 (MIC = 55 ± 0.5% against E. coli) at the same concentration. In the antibiofilm activity, salts 65, 60 and 67 inhibited 58 ± 0.4% S. aureus at a concentration of 75 µg mL\(^{-1}\), while 61 inhibited 55 ± 0.5% E. coli at concentration of 100 µg mL\(^{-1}\).

Soukup et al. [34] synthesized five series of pyridinium salts 68a–68c, 69a–69c, 70a–70c, 71a–71c and 72a–72c via an S\(_2\)2 type Menshutkin reaction (Figure 4) with yields of 81–98%. Compound 72c showed a rather versatile efficacy against the whole spectrum of microbes, three Gram-positive (S. aureus C1947, methicillin-resistant S. aureus MRSA C1926, vancomycin-resistant S. aureus Staphylococcus S2484), six Gram-negative strains (E. coli A1235, K. pneumoniae C1950, K. pneumoniae C1934, A. baumannii J3474, Stenotrophomonas maltophilia J3552, Yersinia enterocolitica CNCTC 6230), and eight fungal strains, four yeasts (Candida parapsilosis sensu stricto EXF-8411, Rhodotorula mucilaginosa EXF-8417, Exophiala dermatitidis EXF-8470, Aureobasidium melanogenum EXF-8432) and four filamentous fungi (Bisfilascium dimerum EXF-8427, Penicillium chrysogenum EXF-1818, Aspergillus versicolor EXF-6962, and Aspergillus niger EXF-10185). Anwar et al. [35] reported synthesis of 4-(dimethylamino)pyridinepropylthioacetate 73 (Scheme 12) and effects of 73 coated with gold nanoparticles 73-AuNPs against E. coli (ATCC 8739). The MIC of the Pefloxacin + 73-AuNPs mixture was found to be 25 µg mL\(^{-1}\) as compared to Pefloxacin alone (50 µg mL\(^{-1}\)), which clearly indicates that 73-AuNPs increased the potency of Pefloxacin.

Figure 3. Structure of pyridine salts 57–59 [32].

Figure 4. Structure of pyridine salts 68–72 [34].
Amphotericin B (standard) against Aspergillus fumigates and Syncephalastrum racemosum.

yields (75–96%), using a one-pot four-component condensation of 3-cyanocarbomethylindole, 2-(phenyl(pyridin-2-yl amino)methyl)pyrrolidine-2,5-dione 75 using a classical Mannich reaction between succinimide, aniline, and formaldehyde or benzaldehyde (Figure 5) in good yields (78–80%). Both compounds showed moderate antifungal activity against the antifungal panel (Escherichia coli, Salmonella typhi, and Bacillus subtilis) and antifungal agents (Aspergillus oryzae and Aspergillus fumigates), using Penicillin, Streptomycin, and Amphotericin B as standards.

Figure 5. Structure of Mannich pyrol-pyridine bases 74 and 75 [36].

Scheme 12. Synthesis of 4-(dimethylamino)pyridinepropylthioacetate 73 [35].

4. Synthesis of Antimicrobial Pyridine Compounds Containing a Five-Membered Ring with One or Two Heteroatoms

Tamilvendan et al. [36] synthesized two Mannich pyrol-pyridine bases 1-((pyridin-2-yl amino)methyl)pyrrolidine-2,5-dione 74 and 1-(phenyl(pyridin-2-yl amino)methyl)pyrrolidine-2,5-dione 75 using a classical Mannich reaction between succinimide, aniline, and formaldehyde or benzaldehyde (Figure 5) in good yields (78–80%). Both compounds showed moderate antifungal activity against the antifungal panel (Escherichia coli, Salmonella typhi, and Bacillus subtilis) and antifungal agents (Aspergillus oryzae and Aspergillus fumigates), using Penicillin, Streptomycin, and Amphotericin B as standards.

Angelova et al. [37] reported the synthesis of two pyridine-indole compounds 76a and 76b by condensation of nicotinohydrazide with 5-methoxy-1H-indole-3-carbaldehyde or 5-bromo-1H-indole-3-carbaldehyde in an ethanol solution, and evaluated their in vitro antibacterial activity against M. tuberculosis H37Rv (MIC = 1.6989 µM and 2.9139 µM respectively) using isoniazide and ethambutol as reference drugs (Scheme 13). Abo-Salem et al. [38] synthesized a new class of bis(indolyl)pyridines 77 analogues of the marine alkaloid nortopsentin in good yields (75–96%), using a one-pot four-component condensation of 3-cyanocarboxamidylindole, various aldehydes, 3-acetylindole, and ammonium acetate in glacial acetic acid. Moreover, 2,6-bis(1H-indol-3-yl)-4-(benzofuran) pyridine-5-carbonitriles 78 were synthesized via a one-pot four-component condensation of 3-cyanocarboxamidyl indole, 2-acetylbenzofuran, N-substituted-indole-3-aldehydes and ammonium acetate (Scheme 14). Four compounds—77b, 78a, 78c, and 78d—demonstrated good antimicrobial activity against S. aureus, E. coli, and C. albicans, as can be seen in Table 3. All antimicrobial active compounds studied (77b, 78a, 78c, and 78d) revealed favorable binding interactions and binding energy with the binding site of thymidylate kinase (ID: 4QGG) with values ranging from −15.52 to −25.36 kcal mol⁻¹, which is comparable to the native ligand of −24.34 kcal mol⁻¹. Figure 6 revealed the binding mode of the re-docked 78d within the binding pocket of TMPK (Thymidylate kinase, ID: 4QGG). The structures of Thymidylate kinase (TMPK), DNA gyrase subunit B, and DNA topoisomerase IV subunit B were retrieved from the protein data bank at http://www.rcsb.org/pdb (accessed on 1 May 2022) using 4QGG, 6F86, 4HZ5 codes, respectively, and a Gaussian Contact surface were drawn using MOE 2008.10 (Molecular Operating Environment, http://www.chemcomp.com (accessed on 1 May 2022). Mabkhot et al. [39] reported synthesis of thiophene-pyridine compound 80 by reaction of the enaminone 79 with pentane-2,4-dione in glacial acetic acid in the presence of ammonium acetate (Scheme 15). The presence of the pyridine nucleus has been shown to be necessary for better antifungal activity than Amphotericin B (standard) against Aspergillus fumigates and Syncephalastrum racemosum. Moreover, compound 80 revealed a moderate activity towards Geotrichum candidum and Candida albicans. Flefel et al. [40] reported the synthesis of thiophene-pyrazole-pyridine hybrids 82–84, by reaction between thiophene-pyridine 81 and carbonilic compounds (Scheme 16). All synthesized compounds possessed good antimicrobial activity against almost all tested strains,
Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella typhimurium, Aspergillus flavus, and Candida albicans. Figure 7 shows the docked images of the drug candidates 82–84 on the target protein. The results of in silico studies revealed a moderate-to-good pattern of affinity and activity of these compounds on the target protein GlcN-6-P synthase, which is supported by in vitro antimicrobial screenings [40]. In this study, a Lamarckian genetic algorithm contained in AutoDock (version 4.0) was employed for in silico molecular docking studies. Alnassar et al. [41] synthesized phenyldiazenyl pyridone 87 starting from diazopyrazolone 85 in two steps: condensation with 1,3-diphenylpropane-1,3-dione in alkaline ethanol to give intermediate 86, and cyclisation of 86 in acidic medium (Scheme 17). The antibacterial activity revealed that compound 87 was active against two tested strains, Bacillus subtilis ATCC 6633 and Escherichia coli ATCC 25922. Nasr et al.; [42] synthesized izoxazole-pyridone derivatives by refluxing cyanothioacetamide 88 solution with the corresponding arylidene derivatives in absolute ethanol (Scheme 18). All compounds have good antimicrobial activity against all tested strains, S. pneumoniae, B. subtilis, S. epidermidis, E. coli, P. vulgaris, and K. pneumonia. The pyridonethiols 89b and 89c showed double potency of Ampicillin in inhibiting the growth of B. subtilis (MIC = 0.12 µg mL⁻¹ vs 0.24 µg mL⁻¹), while compound 89d was equipotent to Ampicillin against the same bacteria. Kamat et al. [43] reported a synthesis of thiazole-pyridine hybrids 94a–94c in four steps, starting from nicotinonitrile (Scheme 19). The in vitro antimicrobial assay showed that compounds 94 are effective against all tested strains S. aureus, B. subtilis, E. coli, P. aeruginosa, A. flavus, T. atroviridae, P. citranum, and C. albicans with safe pharmacokinetic properties. Patel et al. [44] synthesized two series of pyridine-benzothiazole hybrids 95 and 96, by reaction between 2-[N-(substitutedbenzo thiazolyl)amino]pyridine-3-carbonyl chlorides and 2-(piperazin-1-yl)ethanol or 2,3-dichloropiperazine, respectively with yields of 55–74% (Figure 8). It was found that all compounds have a poor to fair activity against all tested strains, P. aeruginosa, E. coli, S. aureus, B. subtilis, and C. albicans. Sedaghati et al. [45] synthesized novel pyrimidines 97, 98, and 99 by a classic Biginelli reaction, using FeCl₃ as a catalyst (Scheme 20). Most of the compounds had better antifungal than antibacterial activity against the tested microorganisms (E. coli, S. enteritidis, P. aeruginosa, S. aureus, L. monocytogenes, B. subtilis, A. niger, C. albicans). Moderate antifungal agents, 97a, 98a, and 98b were determined among the studied compounds. Yadav et al. [46] reported benzimidazole-pyridine 100 synthesis with weak antimicrobial activity against tested strains, S. aureus, B. subtilis, E. coli, C. albicans, and A. niger, using Ciprofloxacin and Fluconazole as control drugs (Figure 9). Desai et al. [47] reported synthesis of benzimidazole-2-pyridone hybrids 104 using the reactions shown in Scheme 21. Condensation of 1-(1H-benzo[d]imidazol-2-y1)ethanone 101 with 2-hydrazinylacetyl cyanide in alcohol gave hydrazinylacetylcyanide 102, which is cyclized in the second step with 2-(2-hydroxy-benzylidene)malononitrile in the presence of a catalytic amount of piperidine to furnish dihydropyridine-3,5-dicarbonitrile 103. Finally, 103 is condensed with different aryl aldehydes to form the final compounds 104a–104h. Compounds bearing chloro and hydroxy groups exhibit very good to excellent antimicrobial activity against all tested strains, S. aureus, S. pyogenes, E. coli, P. aeruginosa, C. albicans, A. niger, and A. clavatus. A new series of benzimidazole derivatives bearing cyanopyridine and 4-thiazolidinone motifs were synthesized by Desai et al. [48] in four steps, starting by condensation of 1-(1H-benzo[d]imidazol-2-yl)ethanone with aromatic aldehydes to get compounds 105a–105e, which were treated with ammonium acetate and malononitrile to achieve derivatives 106a–106e, produced via a Knoevenagel condensation reaction (Scheme 22). Compounds 106 underwent simple condensation reactions with 3-nitrobenzaldehyde to provide Schiff bases 107a–107e, which in the last step generated final analogs 108a–108e using cyclization with thioglycolic acid. As can be seen in Table 4, the antimicrobial activities of the compounds 108a–108e were good to excellent, compound 108d having better antimicrobial activities than the standards used—Chloramphenicol and Ketoconazole—in most cases, followed by compound 108e, which proves that the presence of the methoxy group and the hydroxy group simultaneously, or, in the case of the methoxy group, leads to a better biological activity. Continuing the research, Desai et al. [49] reported the synthesis of 2-azetidinones 109 from the reaction of compounds 107 with chloroacetyl chloride in
1,4-dioxane. Compounds 109a–109d (Figure 10) showed excellent antimicrobial activity compared to the standards used—Chloramphenicol and Ketoconazole. Furthermore, Rani and Reddy [50] reported the synthesis and antimicrobial activity of pyridine containing substituted phenyl azetidine-2-ones 110. Compounds 3-chloro-1-(4-fluorophenyl)/(4-chlorophenyl)-4-(pyridine-3-yl) azetidine-2-one (110a and 110b) were found to be more potent against all tested strains, S. aureus, B. subtilis, E. coli, P. aeruginosa, A. niger, and P. rubrum. Sarojini et al. [51] reported synthesis of 4-(2,5-dichlorothiophen-3-yl)-2-(pyridin-3-yl) thiazole 112 by reaction of pyridine-4-carboxylicamide 111 with 2-bromo-1-(2,5-dichlorothiophen-3-yl)ethane in ethanolic KOH (Scheme 23). Compound 112 had a weak antimicrobial activity against the tested strains, S. aureus and P. aeruginosa (MIC = 100 µg mL⁻¹), compared to the standard medicine Ampicillin (MIC< 6.5 mL⁻¹). Desai et al. [52] reported the synthesis of pyrazole bearing pyridyl oxadiazole analogues 114a–114e starting from 3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde, in three steps: 1. condensation, with isonicotino hydrazide 113 with formation of hydrazide; 2. cyclization reaction with acetic anhydride under reflux condition, with the formation of the 1,3,4-oxadiazole; 3. Claisen-Schmidt condensation of 1,3,4-oxadiazole intermediate with aromatic aldehydes in ethanolic potassium hydroxide (Scheme 24). All compounds showed considerable inhibition against nearly all of the tested bacteria and fungi as compared to the reference drugs, Chloramphenicol and Griseofulvin, as can be observed in Table 5. Following the same synthetic steps, but starting from 3-(4-fluorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde, Desai et al. [53] synthesized fluorinated pyrazole encompassing pyridyl 1,3,4-oxadiazole motifs 115a–115d (Figure 11). All compounds showed considerable inhibition against nearly all of the tested bacteria, and were proved to be potential antifungal agents, superior to the reference drug (Griseofulvin) at low level of cytotoxic concentrations.

Scheme 13. Synthesis of pyridine-indole compounds 76a and 76b [37].

Scheme 14. Synthesis of bis(indolyl)pyridines 77a–77d and 78a–78e [38].
Table 3. Minimum inhibitory concentrations (MIC, µg mL\(^{-1}\)) and minimum bactericidal concentrations (MBC, µg mL\(^{-1}\)) of the most active bis(indolyl)pyridines [38].

| Compounds | Pathogenic Microorganisms |
|-----------|--------------------------|
|           | S. aureus ATCC 6538 | E. coli ATCC 25922 | C. albicans ATCC 10231 |
|           | MIC | MBC | MIC | MBC | MIC | MBC |
| 77b       | 78.125 | 312.5 | 312.5 | 1250 | 78.13 | 312.5 |
| 78a       | 39.06 | 625 | 312.5 | 625 | 39.06 | 156.25 |
| 78c       | 312.5 | 625 | 625 | 1250 | 39.06 | 78.13 |
| 78d       | 9.766 | 19.53 | 312.5 | 1250 | 19.53 | 19.53 |

Figure 6. (A) The binding mode of the re-docked ligand within the binding pocket of TMPK (ID: 4QGG). The re-docked ligand shows superimposed on the same position as the native ligand (yellow, stick) with the same orientation. The two ligands show the same H-bonds profile with Gln101, Arg48, and Ser97 (white, stick). (B) The binding mode of compound 78d (pink, stick) within the binding pocket of TMPK (ID: 4QGG). Compound 78d shows π-cation interactions and two H-bound acceptors with the amine acid residue Arg92 (yellow, stick) [38].

Scheme 15. Synthesis of thiophene-pyridine compound 80 [39].

Scheme 16. Synthesis of thiophene-pyrazole-pyridine compounds 82–84 [40].
Figure 7. Docking into the active site of glucosamine-6-phosphate (GlcN-6-P) synthase (PDB ID: 2VF5). (A) Docked poses of compounds 82–84 on the GlcN-6-P; (B) the interaction the compound 84 and GlcN-6-P [40].

Scheme 17. Synthesis of phenyldiazenyl pyridone 87 [41].

Scheme 18. Synthesis of isoxazol-pyridonethiols 89a–89d [42].

Scheme 19. Synthesis of thiazole-pyridine hybrids 94a–94c [43].
Figure 8. Structures of pyridine-benzothiazole hybrids 95 and 96 [44].

Scheme 20. Synthesis of pyrimidines 97, 98 and 99 [45].

Figure 9. Structure of benzimidazole-pyridine 100 [46].

Scheme 21. Synthesis of benzimidazole-2-pyridone hybrids 104a–104h [47].
1. 1,4-dioxane, reflux, 8h

yield: 60-65%

2. (CH₃CO)₂, reflux, 5h

yield: 60-65%

3. EtOH, KOH, reflux, 7h

yield: 60-65%

Scheme 22. Synthesis of benzimidazole-cyanopyridine—thiazolidinones 108a–108e [48].

Table 4. In vitro antimicrobial screening results of compounds 108a–108e.

| Compound | Gram-Positive Bacteria | Gram-Negative Bacteria | Fungi |
|----------|------------------------|------------------------|-------|
|          | Sa | Sp | Ec | Pa | Ca | An | Ac |
| 108a     | 100 | 62.5 | 62.5 | 50 | 250 | 100 | 100 |
| 108b     | 250 | 100 | 100 | 100 | 50 | 50 | 50 |
| 108c     | 100 | 50 | 50 | 50 | 250 | 100 | 100 |
| 108d     | 50 | 25 | 12.5 | 25 | 50 | 25 | 12.5 |
| 108e     | 25 | 50 | 50 | 50 | - | - | - |
| Chloramphenicol | 50 | 50 | 50 | 50 | - | - | - |
| Ketoconazole | - | - | - | - | 50 | 50 | 50 |

Sa: Staphylococcus aureus MTCC 96; Sp: Staphylococcus pyogenes MTCC 442; Ec: Escherichia coli MTCC 443; Pa: Pseudomonas aeruginosa MTCC 1688; Ca: Candida albicans MTCC 227; An: Aspergillus niger MTCC 282; Ac: Aspergillus clavatus MTCC 1323.

Figure 10. Structure of benzimidazole-pyridine 109a–109d and 110a–110e [49,50].

Scheme 23. Synthesis of 4-(2,5-dichlorothiophen-3-yl)-2-(pyridin-3-yl)thiazole 112 [51].
Scheme 24. Synthesis of pyrazole bearing pyridyl oxadiazole analogues 114a–114e [52].

Table 5. Antimicrobial activity (MIC values in μg mL⁻¹) of analogues 114a–114e.

| Compound   | Gram-Positive Bacteria | Gram-Negative Bacteria | Fungi |
|------------|------------------------|------------------------|-------|
|            | Sa         | Sp | Ec | Pa | Ca | An | Ac |
| 114a       | 50         | 25 | 25 | 50 | 50 | 50 | 50 |
| 114b       | 25         | 25 | 25 | 25 | 50 | 25 | 25 |
| 114c       | 50         | 50 | 50 | 50 | 50 | 50 | 50 |
| 114d       | 25         | 50 | 25 | 25 | 50 | 25 | 50 |
| 114e       | 12.5       | 25 | 25 | 12.5 | 25 | 12.5 | 25 |
| Chloramphenicol | -  | -  | -  | -  | -  | -  | -  |
| Griseofulvin     | -  | -  | -  | -  | -  | 500 | 100 |

Sa: Staphylococcus aureus MTCC 96; Sp: Staphylococcus pyogenes MTCC 442; Ec: Escherichia coli MTCC 443; Pa: Pseudomonas aeruginosa MTCC 1668; Ca: Candida albicans MTCC 227; An: Aspergillus niger MTCC 282; Ac: Aspergillus clavatus MTCC 1323.

Figure 11. Pyridyl-pyrazole-1,3,4-oxadiazoles 115a–115d [53].

5. Synthesis of Antimicrobial Pyridine Compounds Containing a Five-Membered Ring with Three Heteroatoms

Murty et al. [54] synthesized 1,3,4-oxadiazoles–pyridines 117a–117c through an oxidative C–O coupling by direct C–H bond activation of N-aroyl-N-arylidinehydrazines 116a–116c using a catalytic quantity of CuO nanoparticles (Scheme 25). Compound 117a showed broad-spectrum antibacterial activity for all tested strains, E. coli, B. subtilis, M. luteus, K. pneumoniae MIC 37.5 μg mL⁻¹, and compounds 117a and 117b exerted antifungal activity better than standard drug, Cycloheximide.

Scheme 25. Synthesis of 1,3,4-oxadiazoles–pyridines 117a–117c [54].
Krishna et al. [55] synthesized compound 120 in two steps: alkylation of 4-hydroxy-2H-chromen-2-one 118 to give ester 119, which by condensation reaction with (Z)-N’-hydroxyisonicotinimidamide under reflux temperature for 24 h, gave 4-[(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)methoxy]-coumarin 120 (Scheme 26). Compounds 121 and 122 were synthesized by similar reactions (Figure 12) and showed good antibacterial activity against S. aureus and E. coli, and pyridines 120–122 presented better antifungal activity than that of standard drug, Clotrimazole. Bhardwaj et al. [56] synthesized pyridine imidazo[2,1b]-1,3,4-thiadiazoles 125a–125e in two steps, from pyridine-2,5-dicarboxylic acid 123, through intermediate 124 (Scheme 27). All compounds were found to be promising candidates against tested strains, B. pumilus, S. aureus, V. cholera, E. coli, P. mirabilis, P. aeruginosa and C. albicans. Panda and Jain [57] synthesized pyridine-triazoles 127a–127k by a condensation reaction between 3-hydrazinylpyridine 126, the corresponding aldehyde and ammonium acetate in acetic acid at 25 °C (Scheme 28). Minimum inhibitory concentrations (MIC, Table 6) showed excellent antimicrobial activity of compounds 127i–127k, substituted with trimethoxyphenyl, furanyl and thiophenyl, as well as good activity of compounds 127b, 127d, 127g and 127h. Table 3 marked green the values identical to those of the standard medicines used, Ciprofloxacin and Miconazole. Morsy et al. [58] synthesized 1,2,3-triazole nucleosides based on functionalized nicotinonitriles 131a–131b and 132, via [2 + 3]-dipolar-cycloaddition of terminal acetylenes 128a–128b, 129 and 1-azidoglucose 130 (Figure 13) in the presence of copper (I) ions generated from copper(II) sulfate and sodium L-(+)-ascorbate. Compounds 131a–131b and 132 showed good in vitro antibacterial activity against Staphylococcus aureus ATCC 6538, Micrococi luteus ATCC 10240, Pseudomonas aeruginosa ATCC 9027, Escherichia coli ATCC 10536, Candida albicans ATCC 10231, and Aspergillus niger ATCC 16404.

![Scheme 26. Synthesis of 4-[(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)methoxy]-coumarin 120 [55].](image1)

![Figure 12. Structure of 1,2,4-oxadiazol-coumarin-pyridines 121 and 122.](image2)

![Scheme 27. Synthesis of imidazo[2,1b]-1,3,4-thiadiazoles 120a–120e [56].](image3)
Scheme 28. Synthesis of pyridine-triazoles 127a–127k [57].

Table 6. Antimicrobial activity (MIC values in µg mL⁻¹) of pyridine triazoles 122a–122k [56].

| Compd. | Bacterial Strains | Fungal Strains |
|--------|------------------|----------------|
|        | Sa               | Bs             | Ec | St | Kp | An | Afu | Afl | Ca |
| 127a   | 12.5             | 25             | 25 | 12.5 | 12.5 | 12.5 | 50  | 50  | 12.5 |
| 127b   | 12.5             | 12.5           | 25 | 25  | 6.25 | 12.5 | 6.25 | 25  | 6.25 |
| 127c   | 12.5             | 25             | 12.5 | 12.5 | 12.5 | 25  | 25  | 25  | 25  |
| 127d   | 6.25             | 12.5           | 6.25 | 12.5 | 25  | 25  | 25  | 25  | 25  |
| 127e   | 25               | 25             | 25  | 25  | 12.5 | 25  | 25  | 25  | 25  |
| 127f   | 25               | 25             | 12.5 | 25  | 12.5 | 25  | 25  | 25  | 25  |
| 127g   | 12.5             | 25             | 12.5 | 50  | 6.25 | 6.25 | 25  | 25  | 12.5 |
| 127h   | 12.5             | 12.5           | 6.25 | 25  | 6.25 | 6.25 | 25  | 12.5 | 12.5 |
| 127i   | 6.25             | 12.5           | 6.25 | 25  | 12.5 | 6.25 | 6.25 | 6.25 | 6.25 |
| 127j   | 6.25             | 12.5           | 6.25 | 25  | 12.5 | 6.25 | 6.25 | 6.25 | 6.25 |
| 127k   | 6.25             | 12.5           | 6.25 | 25  | 6.25 | 6.25 | 12.5 | 12.5 | 6.25 |
| Ciprofloxacine | 6.25             | 6.25           | 6.25 | 6.25 | 6.25 | 6.25 | -   | -   | -   |
| Miconazole   | -               | -              | -   | -   | -   | 6.25 | 12.5 | 6.25 | 6.25 |

Sa: Staphylococcus aureus MTCC 096; Bs: Bacillus subtilis MTCC 441; Ec: Escherichia coli MTCC 443; St: Salmonella typhi MTCC 733; Klebsiella pneumoniae MTCC 432; An: Aspergillus niger MTCC 282; Afl: Aspergillus fumigatus MTCC 543; Afu: Aspergillus flavus MTCC 277; Ca: Candida albicans MTCC 227.

Figure 13. Structures of compounds 128–132 [58].

6. Synthesis of Antimicrobial Pyridine Compounds Containing a Six-Membered Ring with One, Two, or Three Heteroatoms or Macrocycles

Deng et al. [59] synthesized (S)-2-((ethy1(2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)amino)ethyl-2-((picolinamido)propanoate 134 in six steps, from 5-amino-3,4-dihydroquinolin-2(1H)-one 133 (Scheme 29). Compound 134 showed moderated activity gainst all tested strains. S. aureus, MRSA, B. subtilis, B. proteus, E. coli, P. aeruginosa, C. albicans, C. mycoderma, S. cerevisiae, C. neoformans, and A. flavus, considering Streptomycin and Fluconazole as standards. Ranjbar-Karimi and Poorfreidoni [60] reported the reaction of pentafluoropyridine 135a with 2-((7-chloroquinolin-4-yl) amino)ethan-1-ol 136 in the presence of
potassium carbonate in CH₃CN, to give 7-chloro-N-(2-((perfluoropyridin-4-yl)oxy)ethyl)-quinolin-4-amine **138a**. Moreover, the reaction of N¹-(7-chloroquinolin-4-yl) ethane-1,2-diamine **136** with 2,3,5,6-tetrafluoro-4-phenylsulphonyl pyridine **135b** in the presence of potassium carbonate in CH₃CN, gave N¹-(7-chloroquinolin-4-yl)-N²-(3,5,6-trifluoro-4-(phenylsulphonyl)pyridin-2-yl)ethane-1,2-diamine **139a** in a high yield. Similar reactions occurred to give products **138b, 139b, 140, and 141**, respectively in good yields (75–80%) (Scheme 30). Compounds **138a, 138b, 139a, and 141** showed moderate antibacterial activity against Gram-positive bacterium, *S. aureus*. Myangan and Raval reported [61] synthesis of azetidinyl-3-quinazolin-4-one hybrids **143a–143h** from N-(2-(chloromethyl)-4-oxoquinazolin-3(4H)-yl)isonicotinamide **142** in three steps: (1) synthesis of intermediate hydrazides by reflux with hydrazine in ethanol; (2) synthesis of Schiff bases by condensation of hydrazides with aldehydes in ethanol and acetic acid; and (3) synthesis of final azetidines **143** by reaction of Schiff bases with chloroacetylchloride in dry benzene, in the presence of triethylamine (TEA) (Scheme 31). The antibacterial activity data indicate that the analogs with halogen and nitro substituents emerged as promising antimicrobials, showing better to moderate activity, while analogs bearing chloro and methoxy substituent showed better antifungal activities, see bold compounds (Table 7). Saleh et al. [62] synthesized pyridine-fluorophenyl[1,3,5]triazines **148a–148b** starting from 2,4,6-trichloro-1,3,5-triazine **144**, and pyridin-3-amines **145**, via intermediates **146** and **147**, and by using in the last step a Suzuki coupling reaction (Scheme 32). Compounds **148a and 148b** showed excellent antibacterial activity against *S. epidermidis*, with MIC values of 16 µg mL⁻¹ and 32 µg mL⁻¹, respectively, taking Streptomycin sulfate as standard (MIC > 16 µg mL⁻¹). Solankie and co-workers reported [63] that compound **149** (Figure 14) exhibited promising antibacterial activity against *Micrococcus flavus* with a zone of inhibition value (iv) of 7 mm, which was slightly less active than the standard Ampicillin (iv = 8mm) [54]. Rajavelu and Rajkumar reported [64,65] synthesis of triazino-oxacalixarenes **150** and **151** and their good antibacterial activity against E. coli (MIC = 50 µg mL⁻¹). These oxacalixarenes were docked against the covalent acyl enzyme PDB: 1PW8, and the most potent compound **151** exhibited a good docking score, glide energy, a strong hydrogen bond and hydrophobic interactions with the amino acids in the active pocket. Moreover, oxacalixarene **151** showed strong hydrogen bond interactions with Ser 62, Asn 161, Thr301, and Tyr306 and hydrophobic interactions with Thr116, Phe 120, Thr123, Tyr159, Trp 233, Arg 285, Gln 303, and Asn 327, as seen in Figure 15. The computational work (molecular docking) for the oxacalixarenes used the Schrodinger software version 9.0 for the molecular docking.

**Scheme 29.** Synthesis of tetrahydroquinolin-pyridine **134** [59].

**Scheme 30.** Synthesis of quinoline-pyridine compounds **136–141** [60].
Scheme 31. Synthesis of azetidinyl-3-quinazolin-4-one hybrids 143a–143h [61].

Table 7. Minimal inhibition concentration (µg mL⁻¹) of hybrids 143a–143h [61].

| Compd. | Gram-Positive Bacteria | Gram-Negative Bacteria | Fungal Strain |
|--------|------------------------|------------------------|---------------|
|        | Ec | Pa | Kp | St | Sa | Sp | Bs | Ca | An | Ac |
| 143a   | 200 | 125 | 200 | 200 | 250 | 250 | 100 | 1000 | 500 | 500 |
| 146b   | 100 | 200 | 250 | 200 | 200 | 250 | 200 | 500 | 1000 | 1000 |
| 143c   | 250 | 250 | 100 | 500 | 500 | 500 | 500 | 200 | 200 | 250 |
| 143d   | 150 | 150 | 200 | 200 | 100 | 125 | 100 | 500 | >1000 | >1000 |
| 143e   | 250 | 250 | 500 | 250 | 500 | 200 | 200 | 1000 | >1000 | >1000 |
| 143f   | 250 | 250 | 250 | 250 | 200 | 250 | 250 | 500 | >1000 | >1000 |
| 143g   | 500 | 500 | 62.5 | 500 | 125 | 200 | 250 | 200 | 250 | 200 |
| 143h   | 50 | 100 | 100 | 100 | 250 | 100 | - | - | - | - |
| Ampicillin | - & - | - & - | - & - | - & - | - & - | - & - | - & - | - & - | - & - | - & - |
| Griseofulvin | - & - | - & - | - & - | - & - | - & - | - & - | - & - | - & - | - & - | - & - |
| Ec: E. coli (MTCC443); Pa: P. aeruginosa (MTCC1688); Kp: K. pneumoniae (MTCC109); St: S. typhi (MTCC98); Sa: S. aureus (MTCC96); Sp: S. pyogenus (MTCC442); Bs: B. subtilis (MTCC441); Ca: C. albicans (MTCC227); An: A. niger (MTCC282); Ac: A. clavatus (MTCC1323).

Scheme 32. Synthesis of pyridine-fluorophenyl[1,3,5]triazines 143a–143b [62].

Figure 14. Structures of compounds 144–146 [63–65].
Figure 15. (a) Binding of oxacalixarene 151 with the covalent acyl enzyme (PDB ID: 1PW8). (b) The oxacalixarene substrate 151 bound to the binding site of quadruple mutant, showing the fitting of the test oxacalixarene on the substrate surface.

7. Synthesis of Antimicrobial Macroyclic Pyridine Compounds

Al-Salahi et al. [66] synthesized N2,N6-bis[1-hydrazinyl-1-oxopropan-2-yl]pyridine-2,6-dicarboxamide 153, in three steps from pyridine-2,6-dicarboxylic acid 152. Reaction of 153 with 1,2,4,5-benzenetetracarboxylic acid dianhydride or 1,4,5,8-naphthalene tetracarboxylic acid dianhydride in refluxing acetic acid afforded the corresponding macrocyclic octaamide-tetraimide chiral pyridine derivatives 154 and 155, respectively (Scheme 33). Table 8 shows that compounds 154 and 155 had significant antimicrobial activities against all tested strains, B. subtilis, S. aureus, E. coli, and C. albicans. Using a similar synthesis strategy, Abd El-Salam et al. [67] synthesized chiral macrocyclic polyamides 156, 157 and 158a–158f (Figure 16). As can be seen in Table 9, except for compounds 158b, 158d (against B. subtilis) and 158c and 158e (against S. aureus), the activities of the tested compounds against the Gram-positive bacteria are slightly higher than that of the reference drug Ampicillin. Compounds 156 and 158a also had better inhibitory activity than Ampicillin against E. coli. The antifungal activity of compounds 156–158 was moderate considering the standard drug Ketoconazole.

Scheme 33. Syntheses of pyridine macrocyclic pyridine compounds 154 and 155 [66].
Table 8. Antimicrobial activities of the compounds 154 and 155 [66].

| Compound         | Inhibition Zone in mm (at 50 μg mL⁻¹) |
|------------------|---------------------------------------|
|                  | B. subtilis | S. aureus | E. coli | C. albicans |
| 154              | 19          | 24        | 20      | 16          |
| 155              | 20          | 22        | 21      | 15          |
| Ciprofloxacin    | 23          | 23        | 25      | -           |
| Ketoconazole     | -           | -         | -       | 25          |

Figure 16. Structures of compounds 151, 152 and 153a–153f [67].

Table 9. Antimicrobial activities of the compounds 156–158 [67].

| Compound | Inhibition Zone in mm (at 50 μg mL⁻¹) |
|----------|---------------------------------------|
|          | B. subtilis | S. aureus | E. coli | C. albicans | A. niger |
| 156      | 1.55        | 1.60      | 0.80    | 0.65        | 1.60    |
| 157      | 1.35        | 1.75      | 0.60    | 0.75        | 1.90    |
| 158a     | 1.45        | 1.45      | 0.80    | -           | 1.60    |
| 158b     | 0.90        | 1.30      | -       | 0.65        | 1.70    |
| 158c     | 1.80        | 1.25      | 0.60    | -           | 1.80    |
| 158d     | 0.85        | 1.30      | 0.75    | 0.65        | 1.95    |
| 158e     | 1.80        | 1.25      | 0.70    | 0.60        | 1.65    |
| 158f     | 1.60        | 1.45      | 0.70    | 0.55        | 1.75    |
| Ampicillin| 1.15        | 1.30      | 0.75    | -           | 2.50    |
| Ketoconazole| -           | -         | -       | 0.80        | 2.30    |

8. Synthesis of Fused Pyridines with Other Heterocycles with Antimicrobial Properties

Chandak et al. [68] synthesized pyrazolo[3,4-b]pyridines 159–161 by reaction between 3-substituted-(5-amino-1H-pyrazol-1-yl)benzenesulfonamide and appropriate trifluoro methyl-β-diketone (Scheme 34). Compound 159 was found to be the most potent analogue exhibiting a moderate antibacterial activity against Gram-positive bacteria, S. aureus and B. subtilis, while 160 and 161 exhibited moderate antifungal activity against S. cerevisiae and C. albicans, respectively (Table 10). Altalbawy [69] reported a reaction between compound 162 with 2-chloro-N-(4-bromophenyl) acetamide, in ethanolic sodium ethoxide solution at room
temperature to give 4,4′-(5-methyl-1-phenyl-1H-pyrazole-3,4-diyl)bis-6-(2-furyl) thieno[2,3-b]pyridine-2-carboxamide [163] (Scheme 35). Compound [163] had moderate antimicrobial activity against *E. coli* and *C. albicans* strains. Jose et al. [70] synthesized imidazo[4,5-c]pyridines [166a–166c] from substituted 3,4-diamino pyridine and carboxylic acids in the presence of DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) mediated by T3P (anhydride of propane phosphonic acid) (Scheme 36). All compounds displayed a promising antimicrobial activity compared to control antibiotic, Streptomycin and antifungal drug, Fluconazole. Porbea et al. [71] reported synthesis of new sulfonamide isoxazolo[5,4-b]pyridines [167a–167b] by reaction between aryl sulfonic chlorides and amines (Figure 17). Both compounds showed moderate antibacterial activity against *E. coli* and *P. aeruginosa*. Reen et al. [72] prepared 2-(substituted-phenyl)oxazolo[4,5-b]pyridines [169a–169h] using a one pot synthetic strategy in quantitative yield by reaction between 2-amino-3-hydroxy pyridine [168] and substituted benzoic acids in the presence of silica-supported perchloric acid (Scheme 37). As can be seen in Table 11, three compounds ([169c, 169f, 169g]) possessed strong antibacterial activity against all the four strains, with the best activity profile against *S. aureus*, and the other five compounds were found to be moderately active against all the tested strains of bacteria. Ali [73] reported synthesis of pyrazolo[3,4-b]pyridine [170] by treatment of 5-amino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-3-(methylthio)-1H-pyrazole-4-carbonitrile with benzoyl acetone in basic medium (Figure 16). Compound [170] showed moderate antimicrobial activity against tested strains, *S. ureus*, *S. epidermidis*, *E. coli*, and *A. fumigatus*. El-Borai et al. [74] reported that compound 5-(4-chlorobenzoyl)-1-phenyl-3-(pyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6(7H)-one [171] exhibited strong activity against *E. coli*, *E. cloaca*, and *Serratia*. Appna et al. [75] synthesized pyrido[2,3-d]pyrimidines [173a–173c] in four steps from ethyl 2-amino-6-(trifluoromethyl) nicotinate [172] (Scheme 38). All compounds exhibited significant antimicrobial activities against tested strains, *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. krusei*, and *Issatchenka honeoisis*. Patel et al. [76] reported synthesis of pyridoquinolones [175–180] from substituted aniline, substituted phenyl thioureas and 4-amino-N-(substitutedphenyl) benzenesulfonylamine (Scheme 39). The structure–activity relationship study for pyridoquinolones demonstrated that both electron withdrawing as well as eletrodonating groups at the phenyl ring increase the antimicrobial activity. Furthermore, the presence of chloro and hydroxy groups at the C–6 position showed a similar activity. Activities of amides increased in order: thioureido amides < sulfonamides < amides. Antibacterial activities increased in order: *P. aeruginosa* < *S. aureus* < *B. subtilis* < *E. coli*.

Scheme 34. Synthesis of pyrazolo[3,4-b]pyridines 159–161 [68].

Table 10. Minimum inhibitory concentration (MIC) in μg mL−1 of compounds 159–161.

| Compound | *S. aureus* | *B. subtilis* | *S. cerevisiae* | *C. albicans* |
|----------|------------|--------------|----------------|--------------|
| 159      | 32         | 32           | 128            | 64           |
| 160      | 32         | 64           | 64             | 64           |
| 161      | 128        | 128          | 32             | 32           |
| Ciprofloxacin | 5          | 5            | -              | -            |
| Amphotericin-B     | -          | -            | 20             | 20           |
Scheme 35. Synthesis of thieno[2,3-b]pyridine 163 [69].

Scheme 36. Synthesis of imidazo[4,5-c]pyridines 166a–166c [70].

Figure 17. Structures of compounds 167a, 167b, 170, and 171 [71,73,74].

Scheme 37. Synthesis of oxazolo[4,5-b]pyridines 169a–169h [72].

Table 11. MIC values (in µg mL^{-1}) of oxazolo[4,5-b]pyridine derivatives 169a–169h [72].

| Compound | Gram-Positive Bacteria | Gram-Negative Bacteria |
|----------|------------------------|------------------------|
|          | *S. aureus* ATCC 2943  | *B. subtilis* ATCC 6633 | *E. coli* ATCC 13067 | *P. diminuta* MTCC 3361 |
| 169a     | 6.25                   | 25                     | 50                     | 25                     |
| 169b     | 6.25                   | 12.5                   | 25                     | 25                     |
| 169c     | 3.125                  | 6.25                   | 25                     | 12.5                   |
| 169d     | 12.5                   | 12.5                   | 50                     | 25                     |
| 169e     | 6.25                   | 25                     | 50                     | 50                     |
| 169f     | 1.56                   | 3.125                  | 12.5                   | 6.25                   |
| 169g     | 3.125                  | 6.25                   | 12.5                   | 12.5                   |
| 169h     | 12.5                   | 25                     | 50                     | 25                     |
| Ampicillin | 6.25               | 12.5                   | 50                     | 25                     |
| Streptomycin | 12.5              | 25                     | 50                     | 25                     |
Scheme 38. Synthesis of pyrido[2,3-d]pyrimidines 173a–173c [75].

Scheme 39. Synthesis of pyridoquinolone 175–180 [76].

Brahmbhatt et al. [77] synthesized coumarin-indenopyridine 183 using Krohnke’s conditions (Scheme 40), by the reaction of 3-coumarinylmethylpyridinium salts 181a–181b with appropriate 2-arylidene-1-indanones 182a–182b. Compounds 183a and 183b were the most potent against S. aureus and B. subtilis, respectively, while the rest of the compounds have moderate antibacterial and antifungal activity considering Ampicillin as standard. Salem et al. [78] reported the synthesis of ethyl 3-amino-4-(furan-2-yl)-6-(naphthalen-1-yl)furo[2,3-b]pyridine-2-carboxylate 184 using a one-pot four-component reaction. Compound 184 has a moderate antibacterial activity against E. coli and S. aureus considering Tetracycline as standard (Figure 18). Youssoufi et al. [79] reported the synthesis of 4H-pyrimido[2,1-b]benzothiazoles 185a–185h from curcumin and their antimicrobial activities against S. aureus, S. typhi, P. aeruginosa, E. coli, B. cereus, and P. rettgeri bacteria. All compounds
showed moderate to high antibacterial activities (Table 12). Flefel et al. [80] reported the synthesis of compounds 187–192 in good yields (51–79%) from pyridine 186 using the pathways showed in Scheme 41. All synthesized compounds showed moderate to good antibacterial and antifungal activities against tested strains, S. aureus, B. subtilis, E. coli, S. typhimurium, A. flavus, and C. albicans, as compared to standard reference drugs, Gentamycin and Ketoconazole. El-Sayed et al. [81] reported that tetrazolo[1,5-a]pyridine derivative 193 and thienopyridine 194, synthesized from 6-ethoxy-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile, have good antimicrobial activities against S. aureus, B. cereus, E. coli, P. aeruginosa, A. flavus, and A. niger as compared to standard drugs, Cefotaxime and Dermatin (Figure 19).

**Scheme 40.** Synthesis of pyridoquinolone 183a–183b [77].

**Figure 18.** Structures of compounds 184 and 185a–185h [78].

**Table 12.** MIC values of 4H-pyrimido[2,1-b]benzothiazoles 185a–185h [79].

| Compd. | S. aureus | S. typhi | P. aeruginosa | E. coli | B. cereus | P. rettgeri |
|--------|-----------|----------|---------------|---------|-----------|------------|
| 185a   | 20        | 20       | 10            | -       | 5         | 20         |
| 185b   | 20        | -        | 20            | -       | 5         | -          |
| 185c   | -         | -        | 20            | 10      | 5         | -          |
| 185d   | -         | 10       | 10            | 5       | 2.5       | 10         |
| 185e   | -         | 10       | 5             | 10      | 2.5       | 10         |
| 185f   | 1.25      | 20       | 10            | 5       | 2.5       | -          |
| 185g   | 20        | -        | -             | 10      | 5         | 20         |
| 185h   | -         | -        | 20            | 20      | 5         | 10         |
| Ciprofloxacin | 1.25     | 2.5      | 1.25          | 1.25    | 0.62      | 1.25       |
Scheme 41. Synthesis of compounds 187–192; reagent and conditions: (i) ClCH₂CH₂Cl, DMF, heat; (ii) CH₃COCH₂COCH₃, EtOH, heat; (iii) CH₃(COOEt)₂, EtOH, heat; (iv) NCCH₂CO₂Et, EtOH, heat; (v) PhCOCH₂CO₂Et, EtOH, heat; (vi) 1-CH₃COCH₂CO₂Et, EtOH, heat. [80]

Scheme 42. Synthesis of compounds 196–198 [82].

Figure 19. Structures of compounds 193 and 194 [81].

El-Deen et al. [82] reported the synthesis of the pyridothienopyrimidine derivatives 196–198 in good yields (70–81%) from compounds 195a–195b, as can be seen in Scheme 42. The in vitro evaluation of these compounds against six strains of both Gram-positive (S. aureus, B. Subtilis, B. cereus) and Gram-negative (E. coli, S. typhimurium, P. aeruginosa) bacteria compared with Amoxicillin trihydrate as a reference drug showed a significant antibacterial activity for all compounds, especially against Gram-negative strains, with MIC values ranging from 7.81 to 62.5 µg mL⁻¹.
Antimicrobial Properties (Scheme 43). All compounds showed high antimicrobial activities against *Escherichia coli* Minimum inhibitory concentrations (MICs) of compounds 200a–200e in high yields from reactions of 3-acetyl pyridine 199 with aromatic amines and triphenylphosphite in the presence of lithium perchlorate as a catalyst (Scheme 43). All compounds showed high antimicrobial activities against *Escherichia coli* and *Staphylococcus aureus* ATCC25292, *Candida albicans*, and *Saccharomyces cerevisiae*, at low concentrations (10–100 µg mL⁻¹, Table 13).

Scheme 43. Synthesis of phosphorus containing pyridines 200a–200e [83].

### Table 13. Minimum inhibitory concentrations (MICs) of α-aminophosphonates 200a–200e.

| Compound         | Minimum Inhibitory Concentrations (MICs) (µg mL⁻¹) |
|------------------|-----------------------------------------------|
|                  | *E. coli* | *S. aureus* | *B. subtilis* | *C. albicans* | *S. cerevisiae* |
| 200a             | 100       | 10          | 10            | 10            | 10             |
| 200b             | 10        | 10          | 10            | 10            | 10             |
| 200c             | 10        | 50          | 10            | 10            | 10             |
| 200d             | 10        | 10          | 10            | 10            | 10             |
| 200e             | 10        | 10          | 10            | 10            | 10             |
| Ciprofloxacin    | 5         | 5           | 5             | -             | -              |
| Amphotericin B   | -         | -           | -             | 15            | 15             |
Sekhar et al. [84] synthesized phosphorylated nucleosides 202a–202b from the reaction between compound 201 and the corresponding pyridines (Scheme 44). Both compounds 202a–202b exhibited better activity on *Staphylococcus aureus* when compared to standard, Gentamycin. Devineni et al. [85] synthesized compounds 205a–205d by reaction of 2-amino-2,3-dihydro-1H-2A3-[1–3]diazaphosphol(4,5-b)pyridin-2-one 203 and compounds 204 (Scheme 45). Urea derivatives 205a, 205b, 205c, and 205d showed growth of inhibition against all the tested bacterial strains *B. cereus* ATCC 11778, *S. faecalis* MTCC 0459, *E. coli* ATCC 9637, and *P. marginalis* MTCC-2758.

![Scheme 44. Synthesis of phosphorus containing pyridines 202a–202b [84].](image)

Kumar et al. [86] synthesized organoselenium imidazo[1,2-a]pyridines compounds 207a–207c in four steps, starting with 2-aminopyridines 206a–206b (Scheme 46). Compounds 207a and 207c were observed to exhibit antibacterial activity with an MIC value of 2.48 µg mL\(^{-1}\) and 10.41 µg mL\(^{-1}\) respectively, against Gram-negative bacteria *E. coli*. These observed activities, in particular the one observed for compound 207a against *E. coli*, have been found to be more potent as compared to the few reports concerning antimicrobial activity of selenide-based compounds in the literature so far and quite similar to the Rifampicin (standard). Compound 207b was found to be exhibiting multi-spectrum activity against *A. fumigates*, *C. krueri*, *A. niger*, and *C. parapsilosis* with observed MIC values of 9.96, 9.96, 19.93, and 19.93 µg mL\(^{-1}\) respectively.

![Scheme 45. Synthesis of phosphorus containing pyridines 202a–202b [85].](image)

Abdelattif et al. [87] synthesized organo-selenium compounds 210a–210c starting from 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile 208, in two steps (Scheme 47). Selanone 210c was found to be the most potent antibacterial agent against all tested strains, *S. aureus*, *S. pyogenes*, *E. coli*, and *P. aeruginosa*, as well as a good antifungal agent, against *C. albicans*, *A. niger*, and *A. clavatus*. A computational study of selenium compounds
was performed for prediction of ADME properties by the QikProp3.2 tool available in Schrödinger 9.0 version (USA) and Molinspiration online property calculation toolkit to understand whether the compounds have the optimum pharmacokinetic properties to enter higher phases of the drug development process or not. It was found that compound 210c displayed the highest energy interaction (−8.48 KcalMol⁻¹) within the binding pocket in the molecular docking study, as can be seen in Figure 20. Fontaine et al. [88] reported the synthesis of the boronic pyridines 212a and 212b (Scheme 48), which showed a 4-fold increase in activity compared to 6-(benzylxoxy)pyridin-3-ylboronic acid. Furthermore, they emerged as potential Staphylococcus aureus NorA inhibitors as they potentiate the activity of Ciprofloxacin and Norfloxacin, have no significant intrinsic antibacterial activity, show a reduced cytotoxicity, and do not inhibit the mammalian P-gp efflux pump.

Figure 20. 3D interaction of selenium compound 210c with 1kzn protein [87].

Scheme 48. Synthesis of boron containing pyridines 211a–211b [88].

10. Synthesis of Antitubercular Pyridine Compounds

Tuberculosis (TB) remains a major threat to global public health, with at least 10 million new cases and 1.2 million deaths in 2019. The high incidence and mortality rates of TB can be attributed to the capacity of its etiological agent, intracellular bacterium Mycobacterium tuberculosis (MTb), to adapt to and survive in the aggressive physiological environment within the host [89]. The need for new tuberculostatic agents arises due to bacterial resistance to first-line drugs: Isoniazid (INH), Rifampicin (RIF), Ethambutol (ETH), Streptomycin (STR), and Pyrazinamide (PYR).

Navarrete-Vázquez et al. [90] synthesized 4-(5-substituted-1,3,4-oxadiazol-2-yl)pyridines 214a and 214b from INH and acid chlorides (Scheme 49). Compound 214a showed 10
and 20 times more potency than INH and STR, respectively, against the INH-resistant *M. tuberculosis* CIBIN 112 strain. Moreover, this compound was 27 times more active than ETH. Compound 214b showed the same behavior as 214a against this strain.

Scheme 49. Synthesis of (1,3,4-oxadiazol-2-yl)pyridines 214a–214b [90].

Patel et al. [91] reported two series of compounds 215 and 216 with poor activity against *M. tuberculosis* when compared with Rifampicin (Figure 21). Furthermore, compounds showed a very good activity against *C. albicans* and possessed moderate to poor activity against *A. niger* and *A. clavatus* when compared to the standard, Griseofulvin. Sangani et al. [92] reported the synthesis of pyrido[1,2-a]benzimidazole derivatives 219a–219c, via a base-catalyzed microwave-assisted multicomponent cyclocondensation reaction (Scheme 50). Evaluation of antitubercular activity shows that compounds 219b and 219c were found to have better antitubercular activity when compared to standards Isoniazid and Rifampicin, and compound 219a appeared as the promising antimicrobial compound with a significant antitubercular activity.

Figure 21. Structures of compounds 215 and 216.

Scheme 50. Synthesis of pyrido[1,2-a]benzimidazole derivatives 219a–219c [92].

Rathod et al. [93] synthesized a series of INH compounds 220a–220d and 221a–221d using multicomponent reactions in good yields (80–94%), as can be seen in Scheme 51. Electron-withdrawing groups were reported to increase the anti-TB activity [94,95]. Compound 220c (R1 = H) showed an MIC value of 3.12 μg mL\(^{-1}\), the minimum inhibitory concentration of 220a (R1 = Cl) was estimated at 6.25 μg mL\(^{-1}\), and the MIC value of 221a (R1 = Cl) was 12.5 μg mL\(^{-1}\). The other compounds were moderately active (MIC 50 μg mL\(^{-1}\)) against *M. tuberculosis* H37Rv in comparison to the standard antitubercular
drugs isoniazid (INH), pyrazinamide (PZA), streptomycin (STM), and ciprofloxacin (CPF), as can be seen in Table 14.

Table 14. In vitro antitubercular activity of compounds 220a and 221 in comparison to some reference drugs.

| Compound     | MIC (µg mL⁻¹) | Growth Inhibition, % |
|--------------|---------------|----------------------|
| 220a         | 6.25          | 75                   |
| 220b         | 25            | 65                   |
| 220c         | 3.12          | 80                   |
| 220d         | 25            | 65                   |
| 221a         | 12.5          | 70                   |
| 221b         | 50            | 50                   |
| 221c         | 50            | 60                   |
| 221d         | 50            | 50                   |
| Isoniazid    | 0.6125        | -                    |
| Pyrazinamide | 3.125         | -                    |
| Streptomycin | 6.25          | -                    |
| Ciprofloxacin| 3.125         | -                    |

11. Synthesis of Antiviral Pyridine Compounds

In recent years, several important viral infections have emerged and antiviral chemotherapeutic agents are not sufficiently effective in clinic, leading to serious human diseases and mortality. Therefore, novel antiviral candidates are urgently desirable, which is undoubtedly essential for the therapy of various fatal viral infections. Pyridine compounds are obtaining importance in the field of medicinal chemistry because of the broad spectrum of their physiological activities. In this part of the review is highlighted antiviral behavior of pyridine compounds [96]. The pandemic of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents an unprecedented challenge to identify effective drugs for prevention and treatment [97].

Balzarini et al. [98] reported the synthesis of pyridine N-oxide derivatives and the inhibitory effect of these compounds on human SARS and feline infectious peritonitis coronavirus in cell culture. Thus, compounds 222 and 223 were the most interesting compounds that had a comparable (potent) activity against both SARS-CoV and feline coronavirus FIPV strain (EC₅₀: 1.7–4.2 mg L⁻¹), being poorly cytotoxic (Figure 22). Furthermore, they reported that a lack of the oxide moiety proved detrimental for anti-SARS-CoV and anti-FIPV activity, as none of the tested compounds was antivirally active at subtoxic concentrations [99].
Continuing their research, the Ghaleb group [100] found the structural conditions that N-oxides must meet in order to have an increased antiviral activity, which is shown in Figure 23. In this study, pyridine N-oxide 223 with SARS-CoV inhibitory activity was selected for a further 3D-QSAR studies. From 3D QSAR, molecular docking modeling, it was found that compound 224 is more potent than chloroquine and hydroxychloroquine against SARS-CoV-2. Moreover, 223 shows an excellent stability to inhibit the main protease 3CLpro of CoV-2 and also has excellent bioavailability and no toxicity results. In this study, Surflex-Dock was used for molecular docking using SYBYL-X.2.0 software The crystal structure of COVID-19 main protease was downloaded from Protein Data Bank in Europe (PDB ID: 6LU7).

Ghosh et al. [101] reported synthesis of 5-chloro-4-methylpyridin-3-yl-1H-indole-4-carboxylate 227 from 5-chloro-4-methylpyridin-3-ol 225 and 1H-indole-4-carboxylic acid 226 in the presence of EDC (1-ethyl-3-carbodiimide hydrochloride) and DMAP (4-dimethyl aminopyridine) using dichloromethane as solvent (Scheme 52). Compound 227 exhibited potent antiviral activity (EC$_{50}$ ~ 2.2 µM) against SARS-CoV-2 3CLpro, which was comparable to antiviral medicine Remdesivir. The authors demonstrate that the antiviral activity of a compound is not because of misleading cytostatic effects or cytotoxic effects but due to an apparent destructive “antiviral effect.” The determined high-resolution X-ray structures of compounds bound to SARS-CoV 3CLpro and SARS-CoV-2 3CLpro enzymes revealed that catalytic Cys145 formed a covalent bond with the indole carbonyl group. Furthermore, the indole rings of the inhibitor formed π−π stacking interactions with the imidazole ring of His41, a residue that must move substantially before, during, and after reaction with the inhibitors (Figure 24). X-ray data of the compounds were indexed, integrated, and scaled using the HKL2000 software package.

**Figure 22.** Structures of compounds 222, 223, and 224.

**Figure 23.** Different regions that can increase or decrease the antiviral activity [100].
Table 15. In vitro inhibition of the growth on respective cell lines of adenovirus 5, herpesvirus 1, coxsackievirus B5, and echovirus 7 [102].

| Compound | Adenovirus 5 | Herpesvirus 1 | Coxsackievirus B5 | Echovirus 7 |
|----------|--------------|--------------|------------------|-------------|
| 230a     | >100         | >100         | 1.7 ± 1.6        | 3.2 ± 3.3   |
| 230b     | 15.2 ± 31.4  | >100         | 2.7 ± 4.6        | 0.03 ± 0.21 |
| 230c     | >100         | 56.7 ± 61.3  | 4.3 ± 3.1        | 0.63 ± 0.38 |

Salem et al. [103] reported the synthesis of compound 231 by cyclisation of ethyl 2-(3-cyano-4-(furan-2-yl)-6-(naphthalen-1-yl)pyridin-2-yl)oxy)acetate in the presence of alcoholic KOH 10% at reflux and compound 232 by refluxing 4-(furan-2-yl)-2- hydrazinyl-6-(naphthalen-1-yl) nicotinonitrile with POCl₃ and PCl₅, in a water bath (Figure 25). Compounds 231 and 232 showed antiviral activity against rotavirus Wa strain and adenovirus.
type 7. Compound 231 showed a 60% and 53.3% reduction in viral titer with rotavirus Wa strain and adenovirus type 7, respectively. Compound 232 showed 53.3% and 50% reduction with rotavirus Wa strain and adenovirus type 7, respectively. Sekhar et al. [84] reported that compounds 202a and 202b (Scheme 44) exhibited the better antiviral activities against Newcastle disease virus (NDV) in embryonated chicken eggs by vanishing of virus at the sixth titer (1/32). Abu-Hashem et al. [104] reported the synthesis of compounds 234a and 234b by reaction of 233a and 233b, respectively, with triethoxy-methane (Scheme 54). The data revealed that isothio chromeno-triazolopyrimidines 234a and 234b have promising in vitro antiviral activity against herpes simplex virus-1 (HSV-1) and human immunodeficiency virus-1 (HIV-1).

From the literature reports presented, we can highlight the following aspects related to the interaction of pyridine compounds, which determine the selectivity of antimicrobial action:

- Another heterocycle (pyrazole, imidazole, thiazole, pyrimidine, benzimidazole, indole, etc.) on pyridine compounds improves antimicrobial or antiviral activities. In pyridinium salts it was found that an appropriate balance between hydrophobicity and hydrophilicity or an alkyl chain of C12–C16 improves the antimicrobial activity. Moreover, the presence of certain groups grafted on pyridine nuclei, such as -F, -Cl, -OH, -CF3, OCH3, -N(CH3)2, -NHCO, -COOCH3, -CHO, -NO2, and -CN, increases the antimicrobial and antiviral activity of the compounds. As is shown, the positions of the substituents on the pyridine molecule are also very important for the antimicrobial and antiviral activity of the compounds. Additionally, the binding linker between pyridine and another heterocycle is important for their antimicrobial and antiviral activity. Additionally, the antimicrobial activity is improved if the molecule contains linker groups such as carbonyl (CO), amide (NHCO), thioamide (NHCS), or other heteroatoms. It is also noted that pyridine compounds containing P, Se, and B, generally have an improved antimicrobial activity compared to those with only heterocyclic rings.

From the literature reports presented, we can highlight the following aspects related to the interaction of pyridine compounds, which determine the selectivity of antimicrobial action:
a favorable binding interaction with Thymidylate kinase (ID: 4QG), within the binding pocket of TMPK, determines a good antimicrobial activity of bis (1H-indol-3-yl)-pyridine 78d, against S. aureus, E. coli, and C. albicans strains;

affinity and activity of thiophene-pyridines 82–84 on the target protein GlcN-6-P synthase is supported by in vitro antimicrobial screenings against almost all tested strains, S. aureus, B. subtilis, E. coli, S. typhimurium, A. flavus, and C. albicans;

The good antimicrobial activity of triazino-oxacalixarenes 150 and 151 against E. coli is due to a good covalent interaction with acyl enzyme PDB: 1PW8;

3D interaction of selenium compound 210c with 1kzn protein, the lower hydrophobicity, higher topological polar surface area, lower dipole moment, high H-bonding acceptor and donor, and in-silico absorption percentage of it expalicit its highest antimicrobial activity against all tested strains, S. aureus, S. pyogenes, E. coli, P. aeruginosa, as well as a good antifungal agent, against C. albicans, A. niger, and A. clavatus;

3D QSAR, molecular docking modeling showed that pyridine-N-oxide 223 shows an excellent stability to inhibit the main protease 3CLpro of CoV-2 and also has excellent bioavailability and no toxicity results;

the excellent antiviral activity of compound 227 (EC50~2.2 µM) against SARS-CoV-2 3CLpro comparable to antiviral medicine Remdesivir is due to binding of the compound to SARS-CoV 3CLpro and SARS-CoV-2 3CLpro enzymes, which revealed that catalytic Cys145 formed a covalent bond with the indole carbonyl group, and also indole rings of inhibitor formed π−π stacking interactions with the imidazole ring of His41. It is once again confirmed that the cleavage of SARS-CoV-2 polyproteins by 3CLpro (3-Chymotrypsin-like protease) is facilitated by a Cys145–His41 catalytic dyad [105].

We hope that this review will be useful for the synthesis of other pyridine compounds with antimicrobial and antiviral properties, in order to help the current situation of the pandemic, with the infection with SARS-CoV-2.

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