DESIGN, SYNTHESIS AND CHARACTERIZATION OF 1,4-DIHYROPYRIDINE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

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Abstract

A novel series 1,4-dihyropyridine via one-pot four-component reaction of 3-(p-substituted phenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde, Malononitrile, diethyl acetylenedicarboxylate, and aryl amine to produce excellent yield without further purification. The product's composition has been identified by spectrum studies. Synthesized substances were screened for in vitro antimicrobial activity. The substance's antibacterial and antifungal activity was good in some cases.

Keywords: One-pot multicomponent reaction, 1,4-DHP's, pyrazole aldehyde Antimicrobial activity.

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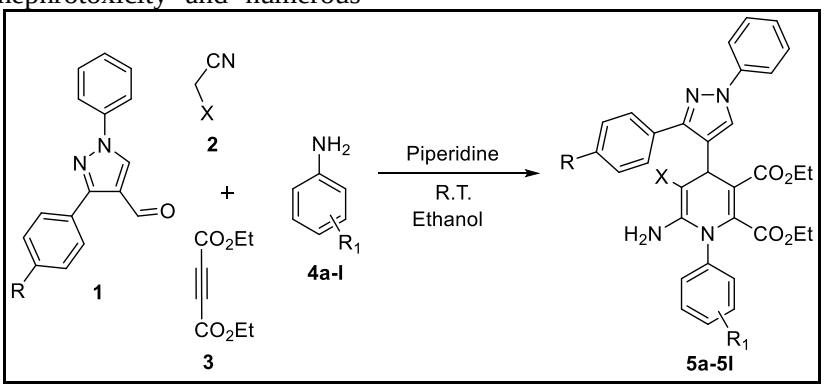
DOI: 10.53555/ecb/2022.11.01.37

INTRODUCTION

The needs of the highest chemical structures to privileged molecules have newly reported to the attention of current chemical synthesis and drug development.[1][2][3] It is believed that multicomponent reaction (MCRs), which combines three or more components in a single reaction flask to produce a final result. [4][5] As a result, these reactions follow the fundamentals of green chemistry and demonstrate excellent properties including atom efficiency, synthetic dispersion, bond productivity, short synthesis times, and minimum workup and purification procedures.[6][7][8]

These frameworks design and synthesis of compounds with potential biological and chemical characteristics in the pharmaceuticals.[9][10] Among 1,4-DHPs are widely distributed in nature with a substantial impact on not needed number of sectors, including the compound, chemical, medical applications.[11]. Fungi are a significant important pathogen and are immune to many drugs used to treat it.[12] Amphotericin B, a polyene antifungal drug, is used with caution due to its significant nephrotoxicity and numerous other side effects.[13] In the medical field, triazole derivatives like fluconazole[14] and voriconazole[15][16] are frequently used to treat fungus[17] illnesses, although medication resistance is a major issue.[18]

There are numerous methods for synthesizing 1,4-DHPs. In the literature, it is mentioned that N-aryl-1,4-DHPs[19][20] can be created through a one-pot reaction involving aryl amines, diethyl acetylenedicarboxylate, and benzaldehydes, and that N-alkyl-1,4DHPs[21] can be created through a region-selective [4+2] cyclization of 1-aryl-4-phenyl-1azadienes.[22] Here, we present a practical and efficient technique for the synthesis of highly substituted dihydropyridines via four-component reactions involving malononitrile and its derivatives at ambient temperature, ethanol as the solvent, arylamines, Diethylacetylenedicarbox ylate, and 3-(p-substituted phenyl)-1-phenyl-1H-pyrazole-4carbaldehyde.[8] This study is a continuation of our ongoing efforts to develop unique synthetic processes for the multicomponent synthesis of diverse heterocycles. (Scheme-1)



Scheme-1

Table 1: PHYSICAL DATA OF SUBSTITUTED 1,4-DIHYROPYRIDINE (5a-5l)

Sr No.	Compound Code	R	R_1	X	Time (h)	Yield %	M.P. (°C)
1	5a	H	H	CN	11	85	168-170
2	5b	H	4-F	CN	8	92	176-178
3	5c	H	2,4-F	CN	9	87	139-141
4	5d	H	4-Cl	CN	8.5	90	172-174
5	5e	CH_3	H	CN	10	88	164-166
6	5f	CH_3	4-F	CN	8.5	95	176-178
7	5g	CH_3	2,4-F	CN	8	89	143-145
8	5h	H	H	COOEt	11	83	83-85
9	5i	H	4-F	COOEt	9	86	97-99
10	5j	CH_3	H	COOEt	10	88	91-93
11	5k	CH_3	4-Cl	COOEt	10	90	105-107
12	5l	CH_3	4-F	COOEt	10	87	101-103

EXPERIMENTAL

All the reagents were purchased from Sigma-Aldrich and Spectrochem chemicals and used without further purification. Reaction was monitored by thin-layer chromatography precoated silica gel-G plates G60 F254 (E-Merck Co.) by using solvent system and vizulized in UV light. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FT-IR-8400 instrument cm^{-1}(KBr). The NMR spectra were recorded (^{1}H NMR 400 MHz & ^{13}C 101 MHz NMR) on a Bruker Avance 400MHz spectrometer and chemical shifts were expressed in δ ppm using MeOD, $CDCl_3$ and DMSO-d^6 using as a solvents and TMS as internal reference. The mass spectra recorded on Ultraperfomance LC/MS electrospray (+) ionization; mass range 100-1500 Da, 30-V cone voltage.

General procedure for the synthesis of Diethyl 6-amino-5-(cyano or carboxylate)-1(substituted-phenyl)-4-(1-phenyl-3-(sub.Phenyl)-1H-pyrazol-4-yl)-1,4-dihydropyridine2,3-dicarboxylate derivatives (5a-5l): A mixture of 3-(p-substituted phenyl)-1-phenyl-1Hpyrazole-4-carbaldehyde (1 mmol), Malononitrile or Ethyl cynoacetate (1 mmol), and piperidine (1 mmol) were stirred in 4 mL ethanol at room temperature for 15 minutes; Then aromatic amine (1 mmol) and diethyl acetylenedicarboxylate (1 mmol) in 2 mL ethanol was stirred for appropriate time. The reaction was monitored by Thin-layer chromatography (Hexane: Ethyl acetate; 7:3). After the completion of the reaction, the reaction mixture was poured into chilled water to precipitate out the product was filtered off and dried. The crude product was recrystallized in hot ethanol to give pure as white solid product. All the synthesized compounds were found to be white solid or off-white solid. The synthesis of the compounds (5a–5l) (yield 83–95%) was similarly.

Diethyl 6-amino-5-cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-1-phenyl-1,4dihydropyridine-2,3-dicarboxylate (5a): MP: 168-170 ºC, FT-IR (KBr cm^{-1}): 3749.74, 3471.98, 3379.40, 3055.35, 2985.91, 2816.16, 2484.40, 2183.49, 1967.46, 1890.30, 1735.99, 1705.13, 1581.68, 1496.81, 1396.51, 1327.07, 1234.48, 1103.32, 1010.73, 771.55, 686.68, 617.24, 532.37; MS: m/z 560.5 $(M+H)^+$.

Diethyl 6-amino-5-cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-1,4dihydropyridine-2,3-dicarboxylate (5b): MP: 176-178 ºC, FT-IR (KBr cm^{-1}): 3757.46, 3471.98, 3379.40, 3055.35, 2978.19, 2569.27, 2353.23, 2183.49, 1743.71, 1705.13, 1581.68, 1504.53, 1411.94, 1203.62. 1103.32, 1018.45, 802.41, 686.68, 547.82; ^{1}H NMR (400 MHz, DMSO-d^6) δ ppm 8.47 (s, 1H), 7.98-7.96 (d, 2H), 7.79-7.78 (d, 2H), 7.54 (m,7H), 7.36(d,3H), 5.67 (s,2H), 4.89 (s,1H), 3.86-3.84 (m,4H), 0.89-0.81 (dt,6H); ^{13}C NMR (101 MHz, DMSO-d^6) δ ppm 165.17, 164.28, 162.78, 161.82, 151.30, 150.92, 141.32, 139.84, 133.93, 133.90, 133.84, 131.91, 131.88, 130.01, 128.84, 128.40, 127.92, 126.75, 121.73, 118.72, 116.85, 116.62, 104.82, 61.88, 60.68, 59.76, , 36.24, 29.26, 13.96, 13.63; MS: m/z 578.4 $(M+H)^+$.

Diethyl 6-amino-5-cyano-1-(2,4-Difluorophenyl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)-1,4dihydropyridine-2,3-dicarboxylate (5c): MP: 139-141 ºC, ^{1}H NMR (400 MHz, DMSOd^6) δ ppm 8.52(s,1H), 8.12 (s, 1H), 7.96 (s,1H), 7.80-7.75 (d,2H), 7.64-7.51 (m, 4H), 7.46– 7.44 (d,1H), 7.36–7.24 (d,1H), 5.99 (s,1H), 4.85-4.80 (d,1H), 3.87-3.78 (d, 2H), 0.92 – 0.81 (dt, 6H); ^{13}C NMR (101 MHz, DMSO-d^6) δ ppm 165, 162.77, 159.17, 150.96, 150.74, 140.98, 139.73, 130.31, 130.01, 128.93, 128.54, 128.10, 127.35, 127.10, 119.85, 118.62, 118.40, 105.86, 62.20, 61.01, 60.76, 36.24, 31.21; MS: m/z 596.5 $(M+H)^+$.

Diethyl 6-amino-5-cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-1-(4-chlorophenyl)-1,4dihydropyridine-2,3-dicarboxylate (5d): MP: 172-174 ºC, ^{1}H NMR (400 MHz, DMSOd^6): δ ppm 8.45 (s, 1H), 7.96–7.94 (m, 2H), 7.76–7.75 (m, 2H), 7.59– 7.50 (m, 6H), 7.47-7.45 (m,3H), 7.36-7.33 (t,1H), 5.69 (s,2H), 4.88 (s,1H), 3.88–3.81(m, 4H), 0.90-0.86 (t,3H), 0.820.78(t,3H); MS: m/z 594.5 $(M+H)^+$.

Diethyl 6-amino-5-cyano-1-phenyl-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1,4dihydropyridine-2,3-dicarboxylate (5e): MP: 164-166 ºC, FT-IR (KBr cm^{-1}): 3468.3, 3356.5, 3054.6, 2987.5, 2372.5, 2176.8, 2126.4, 1992.3, 1891.6, 1729.5, 1645.6, 1587.3, 1500.3, 1449.9, 1371.7, 1326.9, 1243.1, 1108.9, 957.9, 823.7, 751.1, 695.1; ^{1}H NMR (400 MHz, DMSO-d^6) δ ppm 8.37 (s, 1H), 7.93–7.91 (m, 2H), 7.64-7.62 (d,2H), 7.54-7.52(d,2H), 7.51-7.50 (d,3H), 7.47 (s,1H), 7.39–7.37 (m, 2H), 7.36-7.30 (d,3H), 5.46 (s, 2H), 4.84 (s, 1H), 3.88-3.77 (d,2H), 3.76-3.69 (m, 2H), 2.50-2.39 (s, 3H), 0.84-0.82 (dt,6H); MS: m/z 572.7 $(M)^+$.

Diethyl 6-amino-5-cyano-1-(4-fluorophenyl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)1,4-dihydropyridine-2,3-dicarboxylate (5f): MP: 176-178 °C, ^{1}H NMR (400 MHz, DMSO-d^6) δ ppm 8.40 (s,1H), 7.94-7.92(d,2H), 7.63-7.61 (d,2H), 7.54-7.50(t,2H), 7.477.44(d,2H), 7.43-7.30(t,5H), 5.61 (s, 2H), 4.83 (s, 1H), 3.87-3.81(d,1H), 3.79–3.72 (m, 2H), 2.39(s, 3H), 0.88–0.82 (dt,6H); MS: m/z 592.5 $(M+H)^+$.

Diethyl 6-amino-5-cyano-1-(2,4-Difluorophenyl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4yl)-1,4-dihydropyridine-2,3-dicarboxylate (5g): MP: 143-145 °C, ^{1}H NMR (400 MHz, DMSO-d^6) δ ppm 8.47 (s,1H), 8.07(s,1H), 7.93 (m,4H), 7.67–7.54 (m,3H), 7.32-7.23 (d,4H), 5.93 (s,2H), 4.81-4.76 (d, 1H), 3.85-3.78 (d,4H), 2.39 (s,3H), 0.90–0.83 (dt,6H).

Triethyl 6-amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-1-phenyl-1,4-dihydropyridine-2,3,5-tricarboxylate (5h): MP: 83-85 °C, FT-IR (KBr cm^{-1}): 3765.17, 3680.30, 3464.27, 3271.38, 3055.35, 2985.91, 2885.60, 1890.30, 1735.99, 1658.84, 1589.40, 1496.81, 1327.07, 1211.34, 1103.32, 1018.45, 817.85, 763.84, 694.40, 632.67, 509.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (s,1H), 7.81-7.80(dd,2H), 7.75-7.73 (m,2H), 7.48–7.46 (m,4H), 7.22-7.19 (m,2H), 6.14 (s,1H), 5.39(s,1H) 4.04-3.92(m,2H), 3.90-3.84(m,2H), 3.76-3.77(m,2H), 2.44 (s,3H), 1.06–0.90 (m,9H); MS: m/z 607.45 $(M)^+$.

Triethyl 6-amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-1,4dihydropyridine-2,3,5-tricarboxylate (5i): MP: 97-99 °C, MS: m/z 625.69 $(M)^+$.

Triethyl 6-amino-1-phenyl-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1,4dihydropyridine-2,3,5-tricarboxylate (5j): MP: 91-93 °C, FT-IR (KBr cm^{-1}): 3780.60, 3671.73, 3464.27, 3263.66, 3055.35, 2978.19, 1905.73, 1681.98, 1597.11, 1504.53, 1381.08, 1327.07, 1211.34, 1103.32, 1018.45, 964.44, 833.28, 756.12, 686.68, 617.24, 516.94; ^{1}H NMR (400 MHz, MeOD) δ ppm 8.09 (s,1H), 7.93-7.92(d,2H), 7.79-7.77 (m,2H), 7.54–7.51 (m,8H), 7.49-7.45 (m,2H), 7.36-7.32 (m,2H), 5.38(s,1H) 4.01-3.98(m,2H), 3.85-3.80(m,2H), 3.83-3.74(m,2H), 1.30–0.95 (m,9H); MS: m/z 621.22 $(M)^+$.

Triethyl 6-amino-1-(4-chlorophenyl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1,4dihydropyridine-2,3,5-tricarboxylate (5k): MP: 105-107 °C, FT-IR (KBr cm^{-1}): 3718.88, 3649.44, 3464.27, 3271.38, 2978.19, 2229.79, 1890.30, 1735.99, 1597.11, 1496.81, 1327.07, 1211.34, 1103.32, 1018.45, 964.44, 833.28, 756.12, 694.40, 509.22, 447.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (s,1H), 7.81-7.80(dd,2H), 7.75-7.73 (m,2H), 7.48–7.46 (m,4H), 7.22-7.19 (m,2H), 6.14 (s,1H), 5.39(s,1H) 4.04-3.92(m,2H), 3.90-3.84(m,2H), 3.76-3.77(m,2H), 2.44 (s,3H), 1.06–0.90 (m,9H); MS: m/z 655.45 $(M)^+$.

Triethyl 6-amino-1-(4-fluorophenyl)-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1,4dihydropyridine-2,3,5-tricarboxylate (5l): MP: 101-103 °C, MS: m/z 639.69 $(M)^+$.

BIOLOGICAL ACTIVITY

Antibacterial and antifungal activities: The in-vitro antibacterial evaluation of the recently produced compounds towards gram-positive bacteria were studied Bacillus subtilis and Staphylococcus aureus, two gram-negative bacteria Microbroth dilution method antifungal activity against Aspergillus niger and Aspergillus flavus against Escherichia coli and Pseudomonas aeruginosa.[23] The most widely used medications for its antibacterial and antifungal properties are ampicillin, streptomycin, and nystatin.[24] As a neutriant medium, Mueller Hinton Broth was used to grow bacteria, whereas Sabouraud Dextrose Broth was used to grow fungus. The inoculum concentration again for test strain was changed to 108 CFU/mL while analyzing the turbidity. The serial dilutions were made for the main and secondary screening. To make the standard solution (2000 µg/mL), the study chemicals and standard medications were mixed two times each. The produced compounds were screened at concentrations of 1000, 500, 250 and 125 µg/mL, respectively. The compounds that made it through this preliminary investigation and were shown to be effective received further research. In secondary screening, concentrations of 200 µg/mL, 100 µg/mL, 50 µg/mL, 25 µg/mL, 12.5 µg/mL, and 6.25 µg/mL have been used. The inoculation wells spent the night being incubated at 37 °C in a humid atmosphere. At the greatest dilution that totally stopped the process, a minimum inhibition zone is measured (MIC).[25][26]

The MIC values reveale that some of the newly synthesized compounds showed moderate to good inhibition. Compound 5g showed moderate activity against bacillus subtilis and both of the fungal strains. Compound e shows good activity against S. aureus, Enterobacter aerogenes and A.

flavus strains, while Compound 5f shows good to excellent activity against both the fungal strains. Compound 1h showed moderate activity against bacillus subtilis and E. coli bacterial strains. All other compounds showed poor activities against all bacterial and fungal strains.

RESULTS AND DISCUSSION

Chemistry: Diethyl 6-amino-5-(cyano/carboxy late)-1-(substituted-phenyl)-4-(1-phenyl3-(sub. phenyl)-1H-pyrazol-4-yl)-1,4-dihydropyridine-2,3-dicarboxylate derivatives were mention in **Scheme 5a-5l.** Substituted 3-(p-substituted phenyl)-1-phenyl-1H-pyrazole-4carbaldehyde derivatives were prepared by different acetophenone derivatives and phenyl hydrazine in presence of gl.AcOH in ethanol as solvent.[27] Then further vilsmeier haack reaction to form 3-(p-substituted phenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde. 3-(psubstituted phenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde was reacted with malononitrile, various amine and DEAD in presence of piperidine in ethanol at ambient temperature for appropriate time to afford targeted compound **5a-5l** high yield(83-95%).[28],[29] The compounds of the produced 1,4-Dihydropyridine determined by FT-IR, ^{1}H NMR, ^{13}C NMR, MS data.

Biological activity: The produced compounds shown moderately good inhibition, according to the MIC values. The compounds 5b, 5c, 5d, 5f, 5g and 5j showed good antibacterial activity. Compounds 5c, and 5g shown good antifungal activity against all fungal strains, according to the MIC values for antifungal activity. The produced compounds (5a-5l) antimicrobial activity data are showed in Table-2.

Table-2: Antibacterial and antifungal activity of 1,4-dihydropyridine derivatives **5a-5l.**

	Antibacterial MIC (µg mL^{-1})				Antifungal MIC (µg mL^{-1})	
Compound	Bacillus megaterium	Staphylococcus aureus	Enterobacter aerogenes	Pseudomonas aeruginosa	Aspergillus flavus	Aspergillus niger
Streptomycin	-	-	50	50	-	-
Ampicillin	100	100	-	-	-	-
Nystatin	-	-	-	-	100	100
5a	1000	1000	1000	1000	1000	1000
5b	500	1000	1000	1000	1000	1000
5c	1000	1000	1000	500	500	125
5d	500	1000	1000	1000	500	500
5e	1000	1000	1000	1000	1000	500
5f	1000	500	500	1000	1000	1000
5g	1000	500	1000	500	500	1000
5h	1000	1000	1000	1000	1000	1000
5i	1000	1000	1000	1000	1000	1000
5j	500	1000	1000	1000	500	1000
5k	1000	1000	1000	1000	1000	1000
5l	1000	1000	1000	1000	1000	1000

CONCLUSION

In summary, an atom efficient for synthesizing one-pot, four component protocol highly functionalized 1,4-DHP's via Knoevenagel, Michael and intramolecular nucleophilic additions at ambient temperature. The synthesized compounds was elucidation by ^{1}H & ^{13}C NMR, FT-IR and Mass spectral analysis and All the synthesized compounds were tested against common drugs for their antibacterial and antifungal properties. The evaluated antibacterial and antifungal strains showed the good activity against compounds 5c and 5g substituent.

ACKNOWLEDGEMENTS

Authors are thankful to Shri M. & N. Virani Science College, Rajkot for providing research facilities & Atmiya in-vitro testing Laboratory, Rajkot for antimicrobial activity studies. We also thankful to SHODH-ScHeme of Development High quality research, Education Department, Gujarat State.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES:

1. V. H. Reddy *et al.*, "Environmentally benign one-pot multicomponent synthesis of 1 ,
2. 4-dihydropyridine derivatives applying montmorillonite K10 as reusable catalyst," vol. 55, no. 1, pp. 60–65, 2019.
3. N. M. Thumar, A. A. Kaneria, M. Vadodaria, and K. Ladva, "Synthesis, Characterization and Biological Evaluation of some Novel Pyrazolo[1,5-a]Pyrimidine Derivatives," *Int. Lett. Chem. Phys. Astron.*, vol. 65, pp. 11–26, 2016.
4. J. Kolb, B. Beck, M. Almstetter, S. Heck, E. Herdtweck, and A. Dömling, "New MCRs: The first 4-component reaction leading to 2,4-disubstituted thiazoles," *Mol. Divers.*, vol. 6, no. 3–4, pp. 297–313, 2003.
5. B. M. Trost, "Times to The Atom Economy A Search for Synthetic Efficiency," *Science (80-.).*, vol. 254, pp. 1471–1477, 1991.
6. A. B. Pandit, M. M. Savant, and K. D. Ladva, "An Efficient One-Pot Synthesis of Highly Substituted Pyridone Derivatives and Their Antimicrobial and Antifungal Activity," *J. Heterocycl. Chem.*, vol. 55, no. 4, pp. 983–987, 2018.
7. M. M. Khan, Saigal, S. Khan, S. Shareef, and M. Danish, "Organocatalyzed Synthesis and Antifungal Activity of Fully Substituted 1,4-Dihydropyridines," *ChemistrySelect*,
8. vol. 3, no. 24, pp. 6830–6835, 2018.
9. S. Pal, L. H. Choudhury, and T. Parvin, "One-pot multicomponent reactions for the efficient synthesis of highly functionalized dihydropyridines," *Synth. Commun.*, vol. 43, no. 7, pp. 986–992, 2013.
10. S. S. Kauthale, S. U. Tekale, V. P. Pagore, K. G. Huge, and R. P. Pawar, "One pot multicomponent synthesis of functionalized pyridines using morpholine organobase at ambient temperature," *Eur. Chem. Bull.*, vol. 8, no. 3, pp. 71–77, 2019.
11. D. V. Smil *et al.*, "Novel HDAC6 isoform selective chiral small molecule histone deacetylase inhibitors," *Bioorganic Med. Chem. Lett.*, vol. 19, no. 3, pp. 688–692, 2009.
12. M. A. El-hashash and S. S. Shaban, "Synthesis and biological assessment of novel cyanopyridine derivatives," *Synth. Commun.*, vol. 49, no. 16, pp. 2073–2085, 2019.
13. A. Trivedi, D. Dodiya, B. Dholariya, V. Kataria, V. Bhuva, and V. Shah, "Synthesis and biological evaluation of some novel 1,4-dihydropyridines as potential antitubercular agents," *Chem. Biol. Drug Des.*, vol. 78, no. 5, pp. 881–886, 2011.
14. C. C. Lai, C. K. Tan, Y. T. Huang, P. L. Shao, and P. R. Hsueh, "Current challenges in the management of invasive fungal infections," *J. Infect. Chemother.*, vol. 14, no. 2, pp. 77–85, 2008.
15. F. C. Odds, A. J. P. Brown, and N. A. R. Gow, "Antifungal agents: Mechanisms of action," *Trends Microbiol.*, vol. 11, no. 6, pp. 272–279, 2003.
16. X. Liu *et al.*, "Synergistic antifungal effect of fluconazole combined with licofelone against resistant Candida albicans," *Front. Microbiol.*, vol. 8, no. NOV, pp. 1–13, 2017.
17. E. S. Dodds Ashley, G. A. Weinberg, and D. J. Krysan, "Voriconazole therapeutic drug monitoring," *J. Pediatric Infect. Dis. Soc.*, vol. 3, no. 3, pp. 270–271, 2014.
18. F. C. Odds, "Genomics, molecular targets and the discovery of antifungal drugs," *Rev. Iberoam. Micol.*, vol. 22, no. 4, pp. 229–237, 2005.
19. M. Richardson and C. Lass-Flörl, "Changing epidemiology of systemic fungal infections," *Clin. Microbiol. Infect.*, vol. 14, no. SUPPL. 4, pp. 5–24, 2008.
20. D. Allen, D. Wilson, R. Drew, and J. Perfect, "Azole antifungals: 35 years of invasive fungal infection management," *Expert Rev. Anti. Infect. Ther.*, vol. 13, no. 6, pp. 787–798, 2015.
21. M. P. S. Ishar *et al.*, "Facile, regioselective [4 + 2] cycloaddition involving 1-aryl-4phenyl-1-azadienes and allenic esters: An efficient route to novel substituted 1-aryl-4phenyl-1,4-dihydropyridines," *Org. Lett.*, vol. 3, no. 14, pp. 2133–2136, 2001.
22. S. Sarkar, D. K. Das, and A. T. Khan, "RSC Advances dihydropyridines in a highly chemoselective manner utilizing a multicomponent reaction (MCR) strategy †," *RSC Adv.*, vol. 4, pp. 53752–53760, 2014.
23. N. Kerru, S. Maddila, and S. B. Jonnalagadda, "A Facile and Catalyst-Free Microwave-Promoted Multicomponent Reaction for the Synthesis of Functionalised 1,4-Dihydropyridines With Superb Selectivity and Yields," *Front. Chem.*, vol. 9, no. March, pp. 1–7, 2021.
24. T. Aghaalizadeh and F. Nasiri, "Regioselective four-component synthesis of new tetrazolo[1,5-a]quinoline-based 2-amino-1,4-dihydropyridine and pyridin-2(1H)-one

derivatives using nano-ZnO catalysis," *Mol. Divers.*, vol. 22, no. 4, pp. 907–917, 2018.
25. A. Ahamed, I. A. Arif, M. Mateen, R. Surendra Kumar, and A. Idhayadhulla,
26. "Antimicrobial, anticoagulant, and cytotoxic evaluation of multidrug resistance of new 1,4-dihydropyridine derivatives," *Saudi J. Biol. Sci.*, vol. 25, no. 6, pp. 1227–1235, 2018.
27. P. Mehta and P. Verma, "Antimicrobial activity of some derivatives of 1,4dihydropyridines," *J. Chem.*, vol. 2013, no. 2 mL, pp. 6–10, 2013.
28. M. Yusuf, Shehneela, and B. Singh, "Synthesis and Antimicrobial Evaluation of New Pyrrolo-isoxazolidine Derivatives," *Asian J. Chem.*, vol. 31, no. 1, pp. 220–228, 2019.
29. D. Pansuriya, K. Menpara, N. Kachhadiya, J. Menpara, and K. Ladva, "Synthesis, characterization and in-vitro biological evaluation of urea analogue of tetrazolo[1,5a]pyrimidine," *Der Pharma Chem.*, vol. 7, no. 10, pp. 212–218, 2015.
30. R. Dnyanpeeth, "Synthesis and Pharmacological Activities of 4-carboxaldehyde and Its Aldimines Derivatives," vol. 20, no. 7, pp. 5037–5045, 2008.
31. R. Ramesh, M. Arivazhagan, J. G. Malecki, and A. Lalitha, "Improved One-Pot, FourComponent Strategy to Access Functionalized Dihydropyridines by Using 4-(N, NDimethylamino)pyridine as a Catalyst," *Synlett*, vol. 29, no. 14, pp. 1897–1901, 2018.
32. S. Tabassum, S. Govindaraju, R. U. R. Khan, and M. A. Pasha, "Ultrasound mediated, green innovation for the synthesis of polysubstituted 1,4-dihydropyridines," *RSC Adv.*, vol. 6, no. 35, pp. 29802–29810, 2016.