Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 3
Open Access

Exploring the Antimicrobial Potential of Pyrimidine and Hydrazone Derivatives: A Comprehensive Review

Garvit Singh[a], Ritika Bhadana[b], Payal[c], Aarti[d], Khushi Quadri[e], Uma*[a,f], Nitin Chauhan[g]

[a]Department of Pharmacy, School of Healthcare and Allied Sciences, G D Goenka University, Sohna,122103.
[b]Dr. A.P.J. Abdul Kalam Technical University, Uttar Pradesh, Lucknow, 226031.
[c]Department of Pharmacy, School of Healthcare and Allied Sciences, G D Goenka University, Sohna,122103.
[d]Department of Pharmacy, SMAS Galgotias University, plot no.2, sector 17-A Yamuna expressway, Greater Noida -201310, Uttar Pradesh, India.
[e]Department of Pharmaceutics, SGT College of Pharmacy, SGT University Gurgaon, Haryana
[f] Department of Pharmacy, Advance institute of Pharmacy, Palwal, Haryana.
[g] School of Pharmaceutical Sciences, Starex University, NH-48, Binola, Gurugram, Haryana.
***Corresponding author:**
Uma
[a]Department of Pharmacy, School of Healthcare and Allied Sciences, G D Goenka University, Sohna,122103,
[f]Department of Pharmacy, Advance institute of Pharmacy, Palwal.

Cite this paper as: Garvit Singh, Ritika Bhadana, Payal, Aarti, Khushi Quadrie, Uma, Nitin Chauhan (2024) Exploring the Antimicrobial Potential of Pyrimidine and Hydrazone Derivatives: A Comprehensive Review. *Frontiers in Health Informatics, 13* (3),7149-7171

Abstract: *Multidrug-resistant bacterial infections have become a major cause of clinical mortality in the twenty-first century, prompting significant efforts to address this issue. The discovery of new antimicrobial compounds and the strategic use of antibacterial drugs with various structures and mechanisms are crucial in combating bacterial resistance. Currently, pyrimidine-containing agents are at the forefront of new antibacterial drug development. Due to their effective activities and diverse mechanisms of action, many pyrimidine-containing heterocyclic compounds have attracted considerable scientific interest. The pyrimidine structure is a vital component of numerous endogenous substances, allowing pyrimidine derivatives to interact with genetic materials, enzymes, and other cellular biopolymers. Researchers have focused on discovering and optimizing pyrimidine derivatives, leading to the identification of many novel compounds with promising profiles. This review summarizes the therapeutic potential of pyrimidine compounds for antimicrobial applications over the past decade, discussing the relationships between the structures of modified pyrimidines and their antimicrobial activity.*

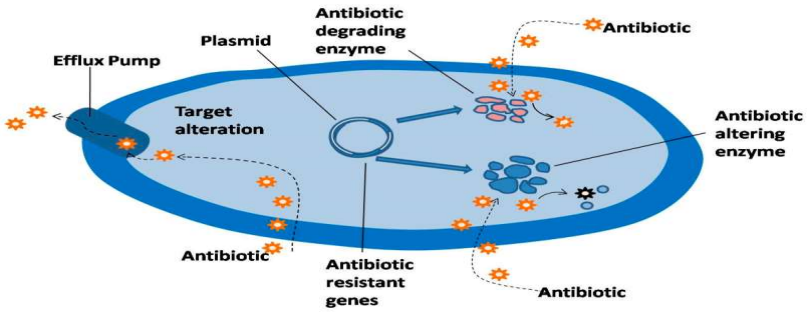
Hydrazide-hydrazone derivatives, found in many bioactive molecules, exhibit a wide range of biological activities, including antibacterial, antitubercular, antifungal, anticancer, anti-inflammatory, anticonvulsant, antiviral, and antiprotozoal effects. Consequently, medicinal chemists synthesize various hydrazide-hydrazones and evaluate their biological activities. Among these, antimicrobial activity is the most commonly reported in scientific literature. This review focuses on the research findings from the last six years (2010–2016) on the antimicrobial activity of hydrazide-hydrazone derivatives, providing a useful guide for developing new hydrazide-hydrazones as potential antimicrobial agents.

Keywords: *Hydrazide, hydrazone, Multidrug-resistant, antibacterial, bacterial infection*

Introduction

Antimicrobial resistance (AMR) poses a significant global public health threat, responsible for 1.27 million deaths in 2019 alone and contributing to a total of 4.95 million deaths. The overuse and misuse of antimicrobials across humans, animals, and plants drive the emergence of drug-resistant pathogens. AMR affects all regions and income levels but disproportionately impacts low- and middle-income countries, exacerbating poverty and inequality. It endangers many medical advancements by making infections harder to treat and increasing the risks associated with surgeries and cancer treatments. The world is grappling with a crisis in both the antibiotics pipeline and access, with inadequate research and development to keep pace with rising resistance. The 2022 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report reveals alarming resistance rates, such as 42% for third-generation cephalosporin-resistant E. coli and 35% for methicillin-resistant Staphylococcus aureus. Resistance is also increasing against last-resort antibiotics like carbapenems, which raises the risk of untreatable infections. Projections by the OECD indicate that resistance to these crucial antibiotics could double by 2035, highlighting the urgent need for robust antimicrobial stewardship and improved surveillance worldwide.

MECHANISM OF ACTION



A Pyrimidine as potential antimicrobial agents

Pyrimidines are a class of organic compounds that play a crucial role in various biological processes, and they have been explored as potential antimicrobial agents due to their ability to inhibit the growth and reproduction of microorganisms. Several pyrimidine derivatives have been investigated for their antimicrobial properties, and they have shown promise against a range of pathogens, including bacteria and fungi.

Structural Diversity: Pyrimidines have a versatile structure, which allows for the synthesis of various derivatives with different functional groups. This structural diversity can be exploited to design compounds with specific antimicrobial properties.

Inhibition of Nucleic Acid Synthesis: Pyrimidines are essential components of nucleic acids (DNA and RNA). Compounds that interfere with the synthesis of nucleic acids by inhibiting enzymes involved in pyrimidine biosynthesis can be effective antimicrobial agents. For example, sulfonamide drugs target dihydropteroate synthase in the folate biosynthesis pathway, which indirectly affects pyrimidine synthesis in bacteria.

Antibacterial Activity: Some pyrimidine derivatives have shown antibacterial activity. For instance, trimethoprim is a well-known antibacterial agent that inhibits dihydrofolate reductase, an enzyme involved in bacterial pyrimidine biosynthesis.

Antifungal Activity: Pyrimidine-based compounds have also been explored for their antifungal properties. Fluconazole, for instance, is an antifungal medication that inhibits the synthesis of ergosterol, a sterol vital for fungal cell membranes.

Resistance and Side Effects: Like all antimicrobial agents, resistance to pyrimidine-based drugs can develop over time. It's essential to use them judiciously to minimize the emergence of resistant strains. Additionally, some pyrimidine derivatives may have side effects and toxicity concerns, so they should be used with caution.

Research and Development: Ongoing research continues to explore new pyrimidine derivatives and their potential as antimicrobial agents. Medicinal chemists are designing molecules with enhanced specificity and reduced toxicity.

Combination Therapy: Pyrimidines are often used in combination with other antimicrobial agents to increase their efficacy and reduce the risk of resistance.

Pyrimidine based antimicrobial agents.

Ismail et al. (2020) synthesized a new series of arylazopyrazolo[1,5-a]pyrimidine derivatives and evaluated their antimicrobial activity. They found that compound 1 had a MIC value of 25 µg/mL against Aspergillus terreus.

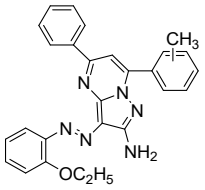
R. Machnikova et al. (2019) created new pyrimidines as potential antibacterial agents using a solid-phase synthetic approach. Their results showed that compound 2 had a MIC value of 12.5µg/mL against Staphylococcus aureus.

Wenneng Wu et al. (2021) synthesized novel pyrimidine analogs and assessed their antimicrobial activity, finding that compound 3 had a MIC value of 10.5µg/mL against the fungal strain Botryosphaeria dothidea.

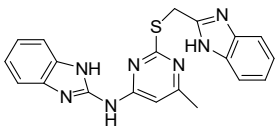
Xue Qian Bai et al. (2019) developed new pyrimidine analogs and tested them for antimicrobial activity, discovering that compound 4 had a MIC value of 2.4µmol/L against Staphylococcus aureus.

Bassyouni F et al. (2021) synthesized novel fused pyrimidine analogs and evaluated their antimicrobial activity, reporting that compound 5 had a MIC value of 5µL against bacterial strains of E. coli.

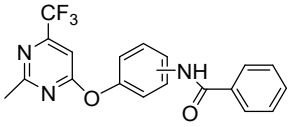
Dofe Vidya S et al. (2018) developed new pyrimidine analogs and tested them for antimicrobial activity. They found that compound 6 exhibited satisfactory potency against bacterial strains with a MIC value of 25µg/mL against Staphylococcus aureus.



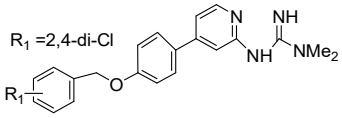
1.
Ismail et al. (2020)



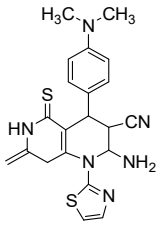
2.
R. Machnikova et al. (2019)



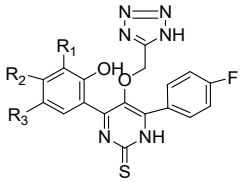
3.
Wenneng Wu et al. (2021)



4.
Xue Qian Bai et al. (2019)



5.
Bassyouni F et al. (2021)



6.
Dofe Vidya S et al. (2018)

Moustafa A. H. et al. (2020) synthesized novel pyrimidine derivatives and tested their antimicrobial activity. Compound 7 exhibited significant potency against S. aureus with a MIC of 0.07 µg/mL.

Ismail et al. (2020) synthesized new pyrimidines as potential antifungal agents, with compound 8 showing a MIC value of 12.5 µg/mL against Candida albicans.

Gomha et al. (2018) created a new series of [1,2,4]triazolo[4,3-a]pyrimidines and evaluated their antibacterial properties. Compound 9 demonstrated a MIC value of 15 µg/mL against Clavibacter michiganensis.

Abd-Allah et al. (2020) synthesized new compounds and screened them for in vitro antibacterial activity, using ciprofloxacin as the control drug. Compound 10 had a MIC value of 22 µg/mL against Pseudomonas aeruginosa.

Buchwald et al. (2021) developed a new pyrimidine derivative through the cross-coupling of 5-bromo-4-(furan-2-yl)pyrimidine and evaluated its antibacterial activity. Compound 11 showed a MIC value of 1.9 µg/mL against Neisseria gonorrhoeae.

Singh et al. (2021) designed, synthesized, and screened a new series of 2,4-disubstituted diarylpyrimidine derivatives for their antibacterial activity. Compound 12 exhibited a MIC value of 12.5 µg/mL against Pseudomonas aeruginosa.

Raju et al. (2019) synthesized a series of novel 1H-pyrrolo[2,3-d]pyrimidine-1,2,3-triazole derivatives and evaluated their in vitro antimycobacterial activity. Compound 13 exhibited a MIC value of 0.78 µg/mL against the Mycobacterium tuberculosis H37Rv strain.

Elhameed et al. (2018) developed a new series of thiazolo[4,5-d]pyrimidine derivatives as antimicrobial agents.

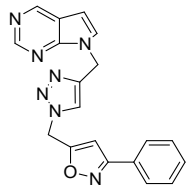
Compound 14 showed a MIC value of 78.12 µg/mL against Aspergillus terreus.

Dofe et al. (2018) synthesized 2-methylpyrimidine-4-ylamine derivatives and assessed their antimicrobial properties. Compound 15 demonstrated a MIC value of 12.5 µg/mL against Bacillus subtilis.

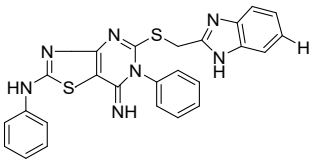
Kayathi et al. (2018) prepared benzoxazolyl/benzothiazolyl/benzimidazolylpyrimidines under ultrasonication with pyridine/dimethylaminopyridine and triethylamine, evaluating their antibacterial activity. Compound 16 had a MIC value of 6.25 µg/mL against Bacillus subtilis.

Verbitskiy et al. (2018) synthesized 5-arylamino-4-(5-nitrofuran-2-yl)pyrimidines using Buchwald–Hartwig cross-coupling with various anilines and found their in vitro antibacterial activity. Compound 17 showed a MIC range between 0.9–15.6 µg/mL against Streptococcus pyogenes.

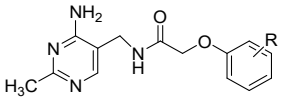
Ebrahimi et al. (2019) synthesized benzo[f]chromeno[2,3-d]pyrimidines via the tandem intramolecular Pinner/Dimroth rearrangement and evaluated their antimicrobial activity against gram-positive bacteria strains. Compound 18 exhibited a MIC value of 0.046 mg/mL against Bacillus cereus.



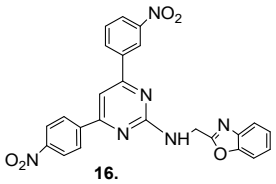
13.
Raju et al. (2019)



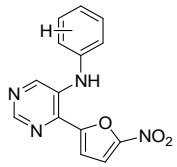
14.
Elhameed et al. (2018)



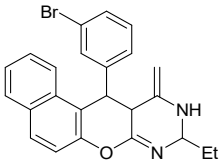
15.
Dofe et al. (2018)



16.
Kayathi et al. (2018)



17.
Verbitskiy et al.(2018)



18.
Ebrahimi et al. (2019)

Machníkova et al. (2019)Synthesized new pyrimidine derivatives and their anti-mycobacterial and antimicrobial activity.MIC value is 0.25 µg/ML of compound 19 againstMycobacterium tuberculosisH37Rv.

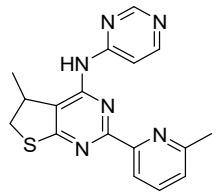
Gohary et al. (2019)Synthesizedanew series of fused pyrazolopyridines were prepared and assessed for antimicrobial activities. MIC value is 78.12 µg/ML of compound 20 against Aspergillus fumigatus.

Mantipally et al. (2019)Designed and synthesized novel homopiperazine linked imidazo[1,2-a]pyrimidine derivatives. They evaluated the antimicrobial property of compound. The value of MIC is 0.86µg/MLof compound 21 against Escherichia coli.

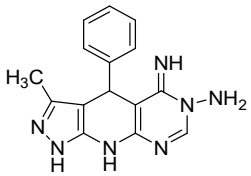
Modi et al. (2019)designed and synthesized and biological evaluation of a new series of pyrazolo[1,5-a]pyrimidine analogues as potential anti-tubercular agents. MIC value is 0.8µg/ML of compound 22against Mycobacterium tuberculosis H37Rv.

Thanh et al.(2019)synthesized 4H-pyrano[2,3-d]pyrimidine as potential anti- mycobacterial. MIC value is 62.5µg/MLof compound 23 compound against Mycobacterium tuberculosis H37Rv.

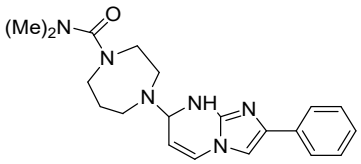
Desai et al (2019)synthesizied pyrimidinthiones in presence of thiourea and easily available catalyst sulfamic acid. Theyevaluate theantimicrobial activity against several bacteria strain.MIC value is12.5 µg/ML of 24 against Escherichia coli.



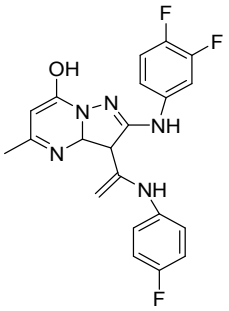
19.
Machníkova et al. (2019)



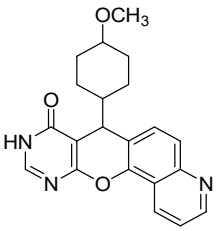
20.
Gohary et al. (2019)



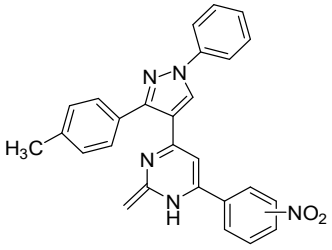
21.
Mantipally et al.(2019)



22.
Modi et al.(2019)



23.
Thanh et al.(2019)



24.
Desai et al (2019)

Ahmedet al.(2020)Synthesized a new Thienopyrimidine Derivatives& tested for antimicrobial activity. They showed the MIC value is 8µg/ml of compound 25 against Bacillus cereus.

Aggarwal et al.(2020)Developed of 7- Aminopyrazolo[1,5-a]pyrimidines as Antibacterial Agent and assessed for antibacterial activities. MIC value is10.8µg/ml of compound 26 against Bacillus cereus.

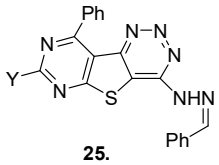
Goffin et al.(2020)Synthesized a series of 1,2,3-triazolo[4,5-d]pyrimidinesand devoid of in vitro antibacterial activity. The value of MIC is 25µg/ml of compound 27 against methicillin-resistant Staphylococcus aureus.

Sui et al.(2020)Synthesized novel type of potential multi-targeting antimicrobial three-component sulfanilamide

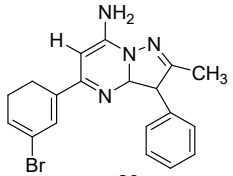
hybrids in combination of pyrimidine and azoles. They evaluate the antimicrobial activity compound. MIC value is 1µg/mL of compound 28 againstEnterococcus Faecalis.

Malasala et al.(2021) Synthesized a new thienopyrimidine derivatives as anti-bacterial agents. The value of MIC is range in between 1.2-105µg/mL of compound 29 against Staphylococcus aureus.

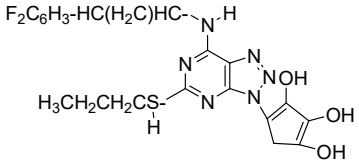
Raniet al.(2021)Synthesized a new isoxazolyl pyrido[2,3-d]pyrimidine derivatives and assessed the antimicrobial activity. MIC value is 7 µg/mL of compound 30 against Pseudomonas aeruginosa.



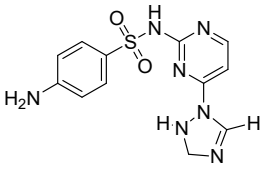
25.
Ahmed et al.(2020)



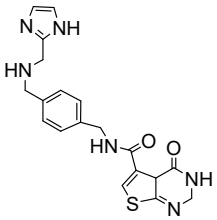
26.
Aggarwal et al (2020)



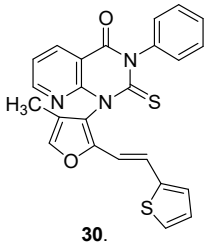
27.
Goffin et al.(2020)



28.
Sui et al.(2020)



29.
Malasala et al (2020)



30.
Rani et al.(2021)

Sattar et al.(2021) SynthesizedPyrano[2,3-d]pyrimidine derivatives and assessed the antimicrobial activity. MIC value is 0.097 µg/ml of compound 31 againstBacillus subtilis.

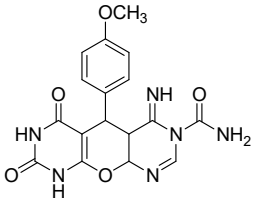
Verma et al.(2021) synthesized 2-(2,3,6,9-tetrahydro-1,3-dimethyl-2,6- dioxo-1H-purin-8-yl)acetonitrile through a moleculer linkingpyridopyrimidine, pyrazolopyridine, and pyranonapthyridine derivatives. They evaluated the antifungal activity of compound. The value of MICis 1.5 µg/ml of compound 32 against Pencillium chrysogenum.

Fares et al.(2018)Synthesized pyrido[2,3-d]pyrimidine derivatives and evaluate the antimicrobial activity. MIC value is 0.98 µg/ml of compound 33 against Streptococcus pneumoniae.

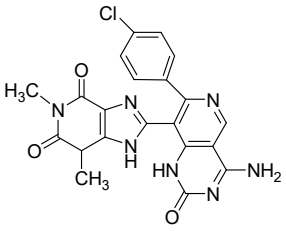
Liu et al.(2018)Synthesized Novel 5H-[1,2,4]oxadiazolo[4,5-a]pyrimidin-5-one derivatives as antibacterial agents. The value of MIC is 3.9 µg/ml of compound 34 against Candida albicans.

Marepu et al.(2018) Synthesized3H-[1,2,3]triazolo[4,5-d]pyrimidinederivatives and evaluated the antimicrobial property of compound. MIC value is50µg/ml of compound 35 againstFusarium recini.

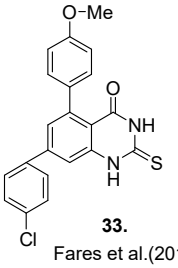
Triloknadh et al.(2018)developed a series of thieno[2,3-d]pyrimidine derivativesand assessed the antimicrobial activity. MIC value is0.01 µg/ml of compound 36 against Bacillus subtilis.



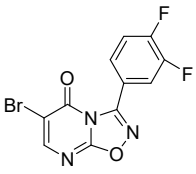
31.
Sattar et al.(2021)



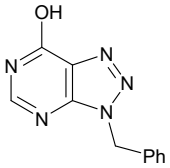
32.
Verma et al.(2021)



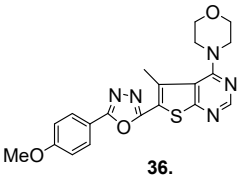
33.
Fares et al.(2018)



34.
Liu et al.(2018)



35.
Marepu et al.(2018)



36.
Triloknadh et al.(2018)

Veeraswamyet al.(2018)synthesized a novel pyrido[2,3-d]pyrimidine derivatives and evaluated the antimicrobial activity. MIC value is 7.8 µg/mlof Compound 37 againstStaphylococcus aureus.

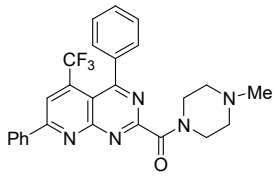
Abdelmoniem et al.(2019)synthesized a novel series of 6,8-dicyanopyrido[1,2-a]thieno[3,2-e]pyrimidine-2-carboxylate and assessed the antimicrobial activity. MIC value30 µg/ml of Compound 38 againstKlebsiella pneumoniae.

Chandrasekaran et al.(2019)synthesized a novel heterofused pyrimidine analogues as effective antimicrobial agent. MIC value is 12.5 µg/mlof compound 39 against Aspergillus niger.

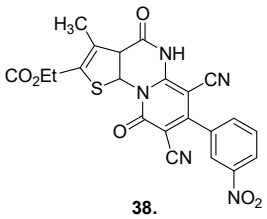
El-serwyet al.(2019)developeda new series of thiopyrimidine-5-carbonitrile derivatives and assessed the antimicrobial activity. The value of MIC is 50 µg/ml of compound40 againstStaphylococcus aureus.

Shaaban et al.(2019)synthesized a series of substituted 3,4-dihydrothieno[2,3-d]pyrimidines asnew potent antimicrobial agents. MICvalue is25 µg/ml of compound 41 against Escherichia coli.

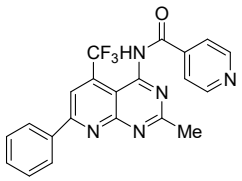
Beyzaeiet al.(2017)synthesizeda new series of 4-imino-5H-pyrazolo[3,4-d]pyrimidin-5-amines as potential antibacterial agents. MIC value is64 µg/ml of compound 42 against Escherichia coli.



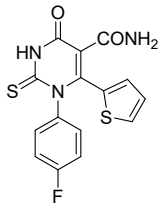
37.
Veeraswamy et al.(2018)



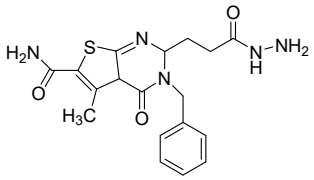
38.
Abdelmoniem et al.(2019)



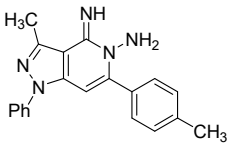
39.
Chandrasekaran et al.(2019)



40.
El-serwy et al.(2019)



41
Shaaban et al.(2019)



42.
Beyzaei et al.(2017)

Dofe et al.(2017)synthesizedaNovel 1,2,3-Triazole-Based Pyrazole and Pyrimidine Derivatives and assessed in vitro for their efficacy as antimicrobial agentsMIC value is 12.5 µg/ml of compound 43 againstBacillus subtilis .

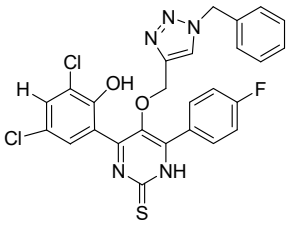
Helal et al.(2017) synthesized a Novel 5-Aminopyrazole, Pyrazolo[1,5-a]pyrimidineAnd carried out the antimicrobial activity. agents MIC value is3.54 µg/ml of compound 44 against Bacillus subtilis .

Pisal et al.(2017)synthesized a number of hybrid molecules containing thienopyrimidinones and thiouracil moieties And carried out the antimicrobial activity. agents MIC value is in the range between7.1±0.91 µg/ml of compound 45 against Mycobacterium tuberculosis H37Ra

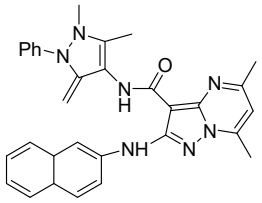
Zesławskaet al.(2017) synthesized four new crystal structures of sulfur and selenium analogues of 2[1H]-pyrimidinone derivatives and assessed the antimicrobial activity. MIC value 3.9 µg/ml of Compound46 againstStaphylococcus aureus.

Zuniga et al.(2017)synthesized triazolopyrimidines as anti-tubercular agents. MIC value is in the range between 3.1 ± 1.3 µg/ml of compound 47against Mycobacterium tuberculosis.

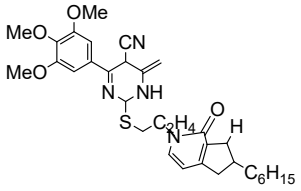
Oruma et al (2017)synthesized a novel tripodal Schiff base ligand, 5-amino-2,4,6-tris(4-carboxybenzimino)-1,3-pyrimidineAnd carried out the antimicrobial activity. agents MIC value is2.29 µg/ml of compound 48 againstCandida albicans.



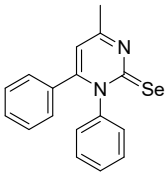
43
Dofe et al.(2017)



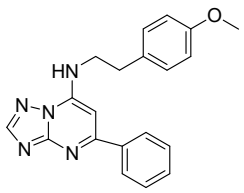
44.
Helal et al.(2017)



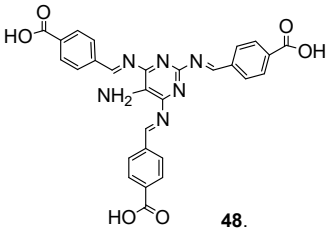
45.
Pisal et al.(2017)



46.
Zeslawska et al.(2017)



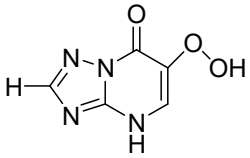
47.
Zuniga et al.(2017)



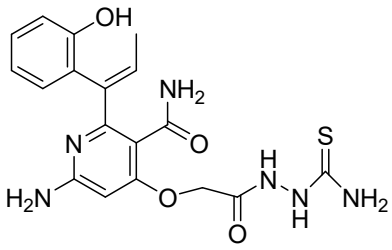
48.
Oruma et al (2017)

Aleam et al (2019)synthesized a series of 1,2,4-triazolo[1,5-a]pyrimidine derivatives assessed the antimicrobial activity. The value of MIC is 1 µg/ml of compound 49 against Methicillin Resistant S. aureus.

Panneerselvam et al (2019)synthesized a new series of antimicrobial thiosemicarbazide substituted pyrimidine derivativesassessed the antimicrobial activity. The value of MIC is 9.8 µg/ml of compound 50 againstKlebsiella pneumonia.



49.
Aleam et al (2019)



50.
Panneerselvam et al (2019

B Hydrazones as potential antimicrobial agents.

Hydrazones are organic compounds that contain a C=N-NH2 functional group. They have been studied for their potential antimicrobial properties, and their derivatives have shown promise as antimicrobial agents. Here are some key points to consider when discussing hydrazones as potential antimicrobial agents:

Chemical Structure: Hydrazones are typically formed by the condensation of a hydrazine compound with a carbonyl compound (aldehyde or ketone). This reaction results in the formation of the C=N-NH2 functional group.

Mechanism of Action: The antimicrobial activity of hydrazones can vary depending on their chemical structure. Some hydrazones have been found to disrupt bacterial cell membranes, while others inhibit specific enzymes or metabolic pathways crucial for microbial growth. This diversity in mechanisms can make hydrazones effective against a wide range of microorganisms.

Types of Hydrazones: There are different types of hydrazones, including aromatic hydrazones and aliphatic hydrazones, which can be synthesized with various substitutions on the hydrazine and carbonyl components. These structural variations can influence their antimicrobial activity.

Antibacterial Properties: Some hydrazones have shown antibacterial activity against a variety of pathogenic bacteria. They can inhibit the growth of bacteria by interfering with their cell walls, cell membranes, or essential enzymes.

Antifungal Properties: Hydrazones have also exhibited antifungal properties. They can target fungal cell membranes or disrupt fungal metabolic pathways, making them potential candidates for antifungal drug development.

Resistance: As with many antimicrobial agents, resistance can develop over time. Microorganisms may develop mechanisms to counteract the effects of hydrazones. This emphasizes the importance of continued research and development of new antimicrobial agents.

Toxicity and Safety: The safety and toxicity profile of hydrazones need to be thoroughly evaluated, especially for potential human use. Assessing their impact on mammalian cells is crucial to determine their suitability as therapeutic agents.

Future Research: Ongoing research is focused on designing and synthesizing hydrazones with improved antimicrobial properties, reduced toxicity, and enhanced selectivity for microbial targets. This involves structural modification and optimization of hydrazones.

Hydrazones have the potential to serve as antimicrobial agents, targeting a wide range of microorganisms, including bacteria, fungi. However, their development and use as therapeutic agents require further research to ensure efficacy and safety. Additionally, hydrazones should be considered as part of a broader strategy to combat antimicrobial resistance and infectious diseases.

hydrazones based antimicrobial agents.

Abdelrahman et al.**(2021)** synthesized novel hydrazones and evaluated in vitro they carried out the antibacterial properties. The MIC value is 0.49 µg/mL of compound 51 against *Streptococcus pneumoniae.*

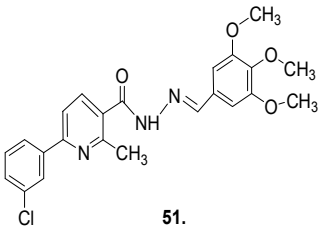
Popiołek et al.(2021) synthesized hydrazones exhibited a wide spectrum of antibacterial activity against tested reference bacteria Thevalue of MIC is 0.98 µg/mL of Compound 52 against Gram-positive bacteria *Staphylococcus epidermidi*s.

Haiba et al.(2021) synthesized hydrazones and they also carried out the antibacterial activity against bacterial strains. They showed that MIC value is 3.125 µg/mL of compound 53 against *Methicillin-resistant Staphylococcus aureus.*

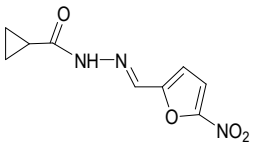
Paruch et al.(2021) synthesized Novel derivatives of 1,2,3-thiadiazole. They carried out the antibacterical activity of compound 54 against *Staphylococcus aureus* (MIC=1.95 µg/ML)

Ajani et al.(2017) synthesized Quinoline Based 4-Hydrazide-Hydrazone Derivatives and assessed the antimicrobial activity. MIC value is 0.39 µg/ml of compound 55 against *Proteus vulgaris.*

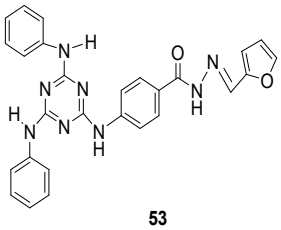
Bera et al.(2017) Synthesized a new pyridinyl thiazole ligand with hydrazone moiety and evaluated its antibacterial property. MIC value is 50 µg/ml of compound 56 against *Salmonella Typhi.*



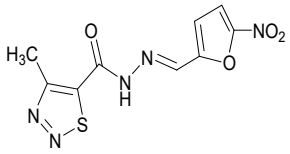
51.
Abdelrahman et al(2021)



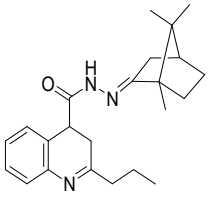
52.
Popioek et al.(2021)



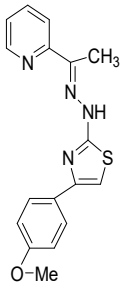
53
Haiba et al. (2021)



54
Paruch et al. (2021)



55
Ajani et al.(2017)



56.
Bera et al.(2017)

Popiołek et al.(2017) Synthesized a Nitrofurazone analogues containing hydrazide-hydrazone moiety and tested for in vitro antimicrobial activity. MIC is 0.002 µg/ml of compound 57 against *Bacillus subtilis.*

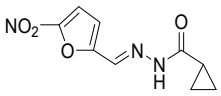
Rawat et al (2017) developed a dipyrromethene derived hydrazones derivatives and evaluated the anti-tubercular activity. MIC is 7.8 µg/ml of compound 58 against *Mycobacterium tuberculosis* H37Rv.

Soliman et al. (2017) Synthesized a novel pyridine and quinolone hydrazone derivatives as potential antimicrobial and antitubercular agents. MIC is 0.39 µg/mL compound 59 against *Mycobacterium tuberculosis* H37Rv.

Zha et al.(2017) developed a series of new benzo[d]thiazole-hydrazones analogues and screened for their in vitro antibacterial and antifungal activities. The value of MIC is in range between 16 ± 1 mg/mL of compound 60 against *Fusarium oxysporum*.

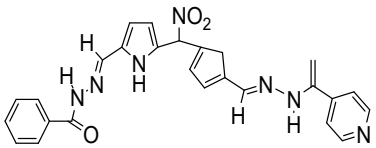
Dantas et al.(2018) They evaluate a series of aminoguanidine hydrazones as antibacterial agents. MIC value is 0.15 µg/ml of compound 61 against *Staphylococcus aureus.*

Wu et al.(2018) Synthesized a series of linezolid analogues containing a hydrazone moiety and evaluated for their antibacterial activity. MIC value is 0.0675 µg/ml of compound 62 against *Methicillin-resistant Staphylococcus aureus.*



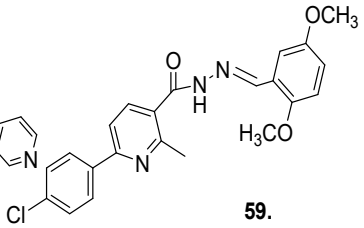
57.

Popiotek et al.(2017)



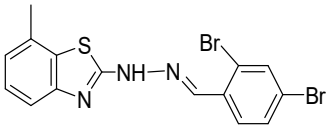
58.

Rawat et al (2017)



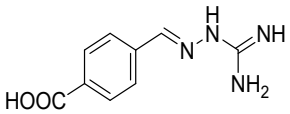
59.

Soliman et al. (2017)



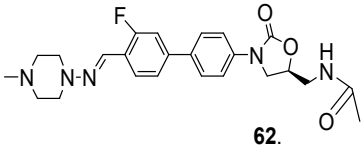
60.

Zha et al. (2017)



61.

Dantas et al.(2018)



62.

Wu et al.(2018)

Zakeyah et al.(2018) Synthesized hydrazone derivatives 4-[3-(2,4- difluorophenyl)-4-formyl-1H-pyrazol-1-yl]benzoic acid and assessed the antimicrobial activity. MIC value is 0.78µM of compound 63 against *Methicillin-resistant Staphylococcus aureus.*

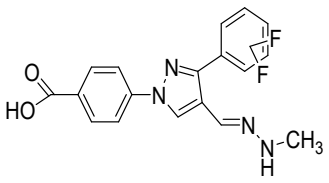
katariya et al.(2019) Synthesized Quinoline Based Hydrazone Analogues and carried out the antimicrobial property. MIC value is 6.25 µg/ml of compound 64 against *Pseudomonas aeruginosa.*

Ozbek et al.(2019) developed a new Sulfonamide-derived hydrazone compounds and assessed the antimicrobial activity. MIC value is 375 µg/ml of compound 65 against *Staphylococcus aureus.*

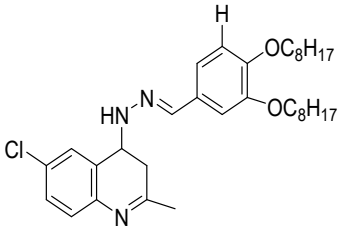
Muluk et al.(2019) Synthesized a series of new hydrazones bearing pyridyl and thiazolyl scaffolds and evaluated for their in vitro antimicrobial activities. MIC value is in the range between 90 ± 0.4 µg/ml of compound 66 against *Bacillus subtilis.*

Celik et al.(2020) synthesized a series of quinoline-2-carbaldehyde hydrazone derivatives and evaluated the antimicrobial activity by the microdilution method. MIC value is 1 µg/ml of compound 67 against *Enterococcus faecalis***.**

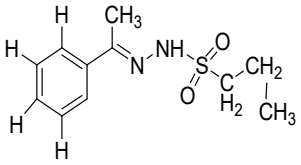
Dkharet al.(2020)developed half sandwich platinum group metal complexes containing pyridyl benzothiazole hydrazones and carried out the antimicrobial activity. MIC value is 0.125 µg/ml of compound 68against *Klebsiella pneumoniae*.



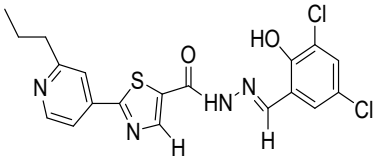
63.
Zakeyah et al.(2018)



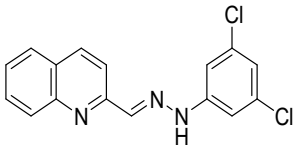
64.
katariya et al.(2019)



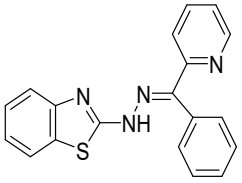
65.
Ozbek et al.(2019)



66.
Muluk et al.(2019)



67.
Celik at al.(2020)



68.
Dkhar et al.(2020)

Popiolek et al.(2020) Synthesized new hydrazide-hydrazones of 5- bromo-2-iodobenzoic acid and evaluated the antimicrobial property. MIC value is125 µg/ml of compound 69 against *Proteus mirabilis*.

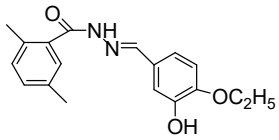
Puskullu et al.(2020) Synthesized quinoline-3-carbaldehyde hydrazone derivative and assessed their antimicrobial activitywith microdilution method. MIC value is 16 µg/ml of compound 70 against *Staphylococcus aureus.*

Trotskoet al.(2020) Synthesizedtwo series of thiazolidine-2,4-dione (TZD) based hybrids with halogenbenzohydrazones and pyridinecarbohydrazones substituents and evaluated their antimycobacterial activity by broth microdilution method. MIC value is 1µg/ml of compound 71 against *Mycobacterium tuberculosis* H37Ra

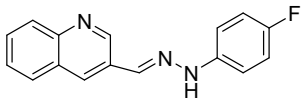
Kratkýet al.(2021) SynthesizedIodinated 1,2-diacylhydrazines and benzohydrazide-hydrazones and their analogues as dual antimicrobial agents. MIC value is 7.97 µg/ml of compound 72 against *Staphylococcus epidermidis*.

Karunnanidhiet al.(2021) Synthesized a Novel thiomorpholine tethered isatin hydrazones as potential inhibitors against Mycobacterium tuberculosis. MIC value is 7.0 µg/ml of compound 73 against *Mycobacterium tuberculosis H37Ra.*

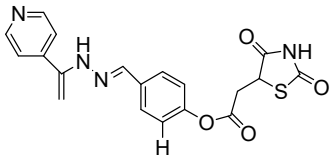
Singh et al.(2021) Synthesizedisatin hydrazone schiff base conjugated organosilicon compounds and evaluated the antimicrobial property. MIC value is 7.8 µg/ml of compound 74 against *Streptococcus pyogenes*.



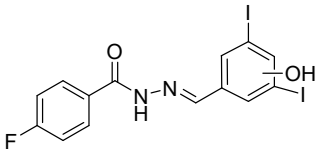
69.
Popiolek et al.(2020)



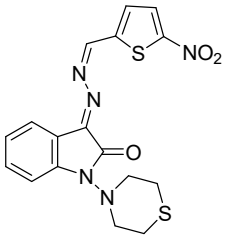
70.
Puskullu et al.(2020)



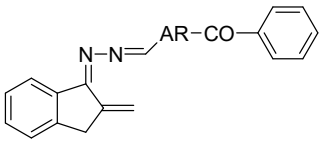
71.
Trotsko·et al.(2020)



72.
Kratký et al.(2021)



73.
Karunnanidhi et al.(2021)



74.
Singh et al.(2021)

Conclusion

Pyrimidines and their derivatives show significant promise as antimicrobial agents, effective against a wide range of bacterial and fungal pathogens. Their structural diversity allows for the creation of various compounds with targeted antimicrobial properties, enhancing their versatility in treating infections. Modifying the pyrimidine structure with different functional groups enables the development of new drugs with improved specificity and reduced toxicity. Pyrimidines can disrupt nucleic acid synthesis by targeting key enzymes in their biosynthesis, such as sulfonamides and trimethoprim inhibiting dihydropteroate synthase and dihydrofolate reductase, respectively.

The antibacterial activity of pyrimidine derivatives has been notable against pathogens like Staphylococcus aureus, Escherichia coli, and Mycobacterium tuberculosis. They also exhibit significant antifungal properties, with compounds like fluconazole targeting ergosterol synthesis in fungi. However, resistance development to pyrimidine-based drugs is a concern, necessitating cautious use to prevent the emergence of resistant strains. Some pyrimidine derivatives may pose side effects and toxicity risks, emphasizing the need for thorough evaluation and monitoring.

Ongoing research is crucial to discovering new pyrimidine derivatives with enhanced antimicrobial properties. Medicinal chemists are working on designing molecules that offer better efficacy and lower toxicity. Additionally, combining pyrimidines with other antimicrobial agents can improve their effectiveness and reduce resistance risks. Notable compounds with significant antimicrobial activity include Compound 2 (MIC 12.5 µg/mL against Staphylococcus aureus), Compound 5 (MIC 5 µL against E. coli), Compound 12 (MIC 12.5 µg/mL against Pseudomonas aeruginosa), Compound 13 (MIC 0.78 µg/mL against Mycobacterium tuberculosis H37Rv), Compound 19 (MIC 0.25 µg/mL against Mycobacterium tuberculosis H37Rv), Compound 1 (MIC 25 µg/mL against Aspergillus terreus), Compound 3 (MIC 10.5 µg/mL against Botryosphaeria dothidea), Compound 8 (MIC 12.5 µg/mL against Candida albicans), and Compound 31 (MIC 0.097 µg/mL against Bacillus subtilis). The continuous exploration and development of pyrimidine derivatives are essential for advancing their role as effective antimicrobial agents. With ongoing research, pyrimidines have the potential to significantly expand the arsenal of drugs available to combat microbial infections.

Hydrazones and their derivatives exhibit significant potential as antimicrobial agents due to their versatile chemical structure and diverse mechanisms of action. Formed by the condensation of hydrazine with carbonyl compounds, hydrazones can disrupt bacterial cell membranes, inhibit enzymes, or interfere with metabolic pathways, making them effective against a wide range of microorganisms. Both aromatic and aliphatic hydrazones can be synthesized with various substitutions, influencing their antimicrobial activity. Notable antibacterial properties have been observed against pathogenic bacteria such as Streptococcus pneumoniae, Staphylococcus epidermidis, Methicillin-resistant Staphylococcus aureus, and Mycobacterium tuberculosis. Additionally, hydrazones have shown antifungal activity, targeting fungal cell membranes and metabolic pathways.

However, resistance to hydrazone-based antimicrobial agents can develop, emphasizing the need for continuous research to develop new and effective compounds. The safety and toxicity of hydrazones must be thoroughly evaluated to ensure their suitability for therapeutic use, particularly their impact on mammalian cells. Future research should focus on designing hydrazones with improved antimicrobial properties, reduced toxicity, and enhanced selectivity for microbial targets through structural modification and optimization. Notable compounds demonstrating significant antimicrobial activity include Compound 51 (MIC 0.49 µg/mL against Streptococcus pneumoniae), Compound 52 (MIC 0.98 µg/mL against Staphylococcus epidermidis), Compound 53 (MIC 3.125 µg/mL against Methicillin-resistant Staphylococcus aureus), Compound 55 (MIC 0.39 µg/mL against Proteus vulgaris), and Compound 57 (MIC 0.002 µg/mL against Bacillus subtilis). Hydrazones hold promise in the broader strategy to combat antimicrobial resistance and infectious diseases, and their continued development and research are essential for advancing their therapeutic potential.

REFERENCE

1. Ismail, M. M., Khalifa, M. M., El-Sehrawi, H. M., & Sabour, R. (2022). Design, synthesis and antimicrobial evaluation of new arylazopyrazole and arylazopyrazolo [1, 5-a] pyrimidine derivatives. Polycyclic Aromatic Compounds, 42(5), 2245-2262.
2. Beyzaei, H., Aryan, R., Moghaddam-Manesh, M., Ghasemi, B., Karimi, P., Delarami, H. S., & Sanchooli, M. (2017). Evaluation and structure-activity relationship analysis of a new series of 4-imino-5H-pyrazolo [3, 4-d] pyrimidin-5-amines as potential antibacterial agents. Journal of Molecular Structure, 1144, 273-279.
3. Dofe, V. S., Sarkate, A. P., Shaikh, Z. M., & Gill, C. H. (2017). Ultrasound-Mediated Synthesis of Novel 1, 2, 3-Triazole-Based Pyrazole and Pyrimidine Derivatives as Antimicrobial Agents. Journal of Heterocyclic Chemistry, 54(6), 3195-3201.
4. Helal, M. H., Salem, M. A., & Aly, H. M. (2017). Synthesis, Antimicrobial Activity and Molecular Modeling of Some Novel 5-Aminopyrazole, Pyrazolo [1, 5-a] pyrimidine, Bispyrazole and Bispyridone Derivatives Containing Antipyrinyl Moiety. Journal of Heterocyclic Chemistry, 54(5), 2614-2626.
5. Pisal, M. M., Nawale, L. U., Patil, M. D., Bhansali, S. G., Gajbhiye, J. M., Sarkar, D., ... & Borate, H. B. (2017). Hybrids of thienopyrimidinones and thiouracils as anti-tubercular agents: SAR and docking studies. European Journal of Medicinal Chemistry, 127, 459-469.
6. Żesławska, E., Korona-Głowniak, I., Szczesio, M., Olczak, A., Żylewska, A., Tejchman, W., & Malm, A. (2017). Structural analysis and antimicrobial activity of 2 [1H]-pyrimidinethione/selenone derivatives. Journal of Molecular Structure, 1142, 261-266.
7. Zuniga, E. S., Korkegian, A., Mullen, S., Hembre, E. J., Ornstein, P. L., Cortez, G., ... & Parish, T. (2017). The synthesis and evaluation of triazolopyrimidines as anti-tubercular agents. Bioorganic & Medicinal Chemistry, 25(15), 3922-3946.
8. Raju, K. S., AnkiReddy, S., Sabitha, G., Krishna, V. S., Sriram, D., Reddy, K. B., & Sagurthi, S. R. (2019). Synthesis and biological evaluation of 1H-pyrrolo [2, 3-d] pyrimidine-1, 2, 3-triazole derivatives as novel anti-tubercular agents. Bioorganic & medicinal chemistry letters, 29(2), 284-290.

9. Abd Elhameed, A. A., El-Gohary, N. S., El-Bendary, E. R., Shaaban, M. I., & Bayomi, S. M. (2018). Synthesis and biological screening of new thiazolo [4, 5-d] pyrimidine and dithiazolo [3, 2-a: 5′, 4′-e] pyrimidinone derivatives as antimicrobial, antiquorum-sensing and antitumor agents. Bioorganic Chemistry, 81, 299-310.
10. Dofe, V. S., Sarkate, A. P., Shaikh, Z. M., Jadhav, C. K., Nipte, A. S., & Gill, C. H. (2018). Ultrasound-assisted synthesis of novel pyrazole and pyrimidine derivatives as antimicrobial agents. Journal of Heterocyclic Chemistry, 55(3), 756-762.
11. Gomha, S. M., Mohamed, A. M., Zaki, Y. H., Ewies, M. M., & Elroby, S. A. (2018). Structural Elucidation and Antimicrobial Evaluation of Novel [1, 2, 4] Triazolo [4, 3-a] pyrimidines and Pyrido [2, 3-d][1, 2, 4] triazolo [4, 3-a] pyrimidinones. Journal of Heterocyclic Chemistry, 55(5), 1147-1156.
12. Kayathi, N. B., Sowmya, D. V., Adivireddy, P., & Venkatapuram, P. (2018). Synthesis of benzazolyl pyrimidines under ultrasonication and their antimicrobial activity. Journal of Heterocyclic Chemistry, 55(4), 1024-1032.
13. Fares, M., Abd El Hadi, S. R., Eladwy, R. A., Shoun, A. A., Abdel-Aziz, M. M., Eldehna, W. M., ... & Keller, P. A. (2018). An improved synthesis of pyrido [2, 3-d] pyrimidin-4 (1 H)-ones and their antimicrobial activity. Organic & Biomolecular Chemistry, 16(18), 3389-3395.
14. Liu, X., Song, X., Liu, Y., Xie, M., Yu, W., Yan, S., ... & Jin, Y. (2018). Novel 5H-[1, 2, 4] oxadiazolo [4, 5-a] pyrimidin-5-one derivatives as antibacterial and anticancer agents: Synthesis and biological evaluation. Tetrahedron letters, 59(42), 3767-3772.
15. Oruma, U. S., Ukoha, P. O., Rhyman, L., Elzagheid, M. I., Obasi, L. N., Ramasami, P., & Jurkschat, K. (2018). Synthesis, characterization, antimicrobial screening, and computational studies of a tripodal schiff base containing pyrimidine unit. Journal of Heterocyclic Chemistry, 55(5), 1119-1129.
16. Triloknadh, S., Rao, C. V., Nagaraju, K., Krishna, N. H., Ramaiah, C. V., Rajendra, W., ... & Suneetha, Y. (2018). Design, synthesis, neuroprotective, antibacterial activities and docking studies of novel thieno [2, 3-d] pyrimidine-alkyne Mannich base and oxadiazole hybrids. Bioorganic & Medicinal Chemistry Letters, 28(9), 1663-1669.
17. Veeraswamy, B., Madhu, D., Dev, G. J., Poornachandra, Y., Kumar, G. S., Kumar, C. G., & Narsaiah, B. (2018). Studies on synthesis of novel pyrido [2, 3-d] pyrimidine derivatives, evaluation of their antimicrobial activity and molecular docking. Bioorganic & Medicinal Chemistry Letters, 28(9), 1670-1675.
18. Verbitskiy, E. V., Baskakova, S. A., Natal'ya, A. G., Natal'ya, P. E., Natal'ya, V., Kungurov, N. V., ... & Chupakhin, O. N. (2018). New 5-arylamino-4-(5-nitrofuran-2-yl) pyrimidines as promising antibacterial agents. Mendeleev Communications, 28(4), 393-395.
19. Ebrahimi, Z., Davoodnia, A., Motavalizadehkakhky, A., & Mehrzad, J. (2019). Synthesis of benzo [f] chromeno [2, 3-d] pyrimidines via the tandem intramolecular Pinner/Dimroth rearrangement and their antibacterial and antioxidant evaluation. Organic Preparations and Procedures International, 51(4), 357-367.
20. Abdelmoniem, A. M., Ghozlan, S. A., Abdelwahab, H. M., & Abdelhamid, I. A. (2019). 2-Cyano-N-(thiophen-2-yl) acetamide in Heterocyclic Synthesis: Synthesis and Antibacterial Screening of Novel Pyrido [1, 2-a] thieno [3, 2-e] pyrimidine-2-carboxylate Moieties. Journal of Heterocyclic Chemistry, 56(9), 2637-2643.
21. Machníková, R., Janovská, L., & Brulikova, L. (2020). Solid-phase synthetic approach towards new pyrimidines as potential antibacterial agents. Journal of Molecular Structure, 1200127101.
22. Abd El-Aleam, R. H., George, R. F., Hassan, G. S., & Abdel-Rahman, H. M. (2020). Synthesis of 1, 2, 4-triazolo [1, 5-a] pyrimidine derivatives: Antimicrobial activity, DNA Gyrase inhibition and molecular docking. Bioorganic Chemistry, 94, 103411.

23. Chandrasekaran, B., Cherukupalli, S., Karunanidhi, S., Kajee, A., Aleti, R. R., Sayyad, N., ... & Karpoormath, R. (2019). Design and synthesis of novel heterofused pyrimidine analogues as effective antimicrobial agents. Journal of Molecular Structure, 1183, 246-255.
24. El-Gohary, N. S., Hawas, S. S., Gabr, M. T., Shaaban, M. I., & El-Ashmawy, M. B. (2019). New series of fused pyrazolopyridines: Synthesis, molecular modeling, antimicrobial, antiquorum-sensing and antitumor activities. Bioorganic Chemistry, 92, 103109.
25. El-serwy, W. S., Mohamed, H. S., El-serwy, W. S., Mohamed, N. A., Kassem, E. M., Nossier, E. S., & Shalaby, A. S. G. (2019). Molecular docking study of newly synthesized thiopyrimidines as antimicrobial agents targeting DNA gyrase enzyme. Journal of Heterocyclic Chemistry, 56(7), 2027-2035.
26. Figueiredo, J., Serrano, J. L., Soares, M., Ferreira, S., Domingues, F. C., Almeida, P., & Silvestre, S. (2019). 5-Hydrazinylethylidenepyrimidines effective against multidrug-resistant Acinetobacter baumannii: Synthesis and in vitro biological evaluation of antibacterial, radical scavenging and cytotoxic activities. European Journal of Pharmaceutical Sciences, 137, 104964.
27. Krátký, M., Konečná, K., Brablíková, M., Janoušek, J., Pflégr, V., Maixnerová, J., ... & Vinšová, J. (2021). Iodinated 1, 2-diacylhydrazines, benzohydrazide-hydrazones and their analogues as dual antimicrobial and cytotoxic agents. Bioorganic & medicinal chemistry, 41, 116209.
28. Mantipally, M., Gangireddy, M. R., Gundla, R., Badavath, V. N., Mandha, S. R., & Maddipati, V. C. (2019). Rational design, molecular docking and synthesis of novel homopiperazine linked imidazo [1, 2-a] pyrimidine derivatives as potent cytotoxic and antimicrobial agents. Bioorganic & medicinal chemistry letters, 29(16), 2248-2253.
29. Modi, P., Patel, S., & Chhabria, M. (2019). Structure-based design, synthesis and biological evaluation of a newer series of pyrazolo [1, 5-a] pyrimidine analogues as potential anti-tubercular agents. Bioorganic Chemistry, 87, 240-251.
30. Panneerselvam, T., & Mandhadi, J. R. (2020). Microwave assisted synthesis and antimicrobial evaluation of novel substituted thiosemicarbazide derivatives of pyrimidine. Journal of Heterocyclic Chemistry, 57(8), 3082-3088.
31. Shaaban, O. G., Issa, D. A., El-Tombary, A. A., Abd El Wahab, S. M., Wahab, A. E. A., & Abdelwahab, I. A. (2019). Synthesis and molecular docking study of some 3, 4-dihydrothieno [2, 3-d] pyrimidine derivatives as potential antimicrobial agents. Bioorganic Chemistry, 88, 102934.
32. Thanh, N. D., Ha, N. T. T., Le, C. T., Van, H. T. K., Toan, V. N., & Toan, D. N. (2019). Synthesis, biological evaluation and molecular docking study of 1, 2, 3-1H-triazoles having 4H-pyrano [2, 3-d] pyrimidine as potential Mycobacterium tuberculosis protein tyrosine phosphatase B inhibitors. Bioorganic & Medicinal Chemistry Letters, 29(2), 164-171.
33. Desai, N. C., Joshi, S. B., & Jadeja, K. A. (2020). A one-pot multicomponent Biginelli reaction for the preparation of novel pyrimidinthione derivatives as antimicrobial agents. Journal of Heterocyclic Chemistry, 57(2), 791-795.
34. Ahmed, M., Sayed, M., Saber, A. F., Hassanien, R., Kamal El-Dean, A. M., & Tolba, M. S. (2022). Synthesis, characterization, and antimicrobial activity of new thienopyrimidine derivatives. Polycyclic Aromatic Compounds, 42(6), 3079-3088.
35. Aggarwal, R., Singh, G., Kumar, V., Masan, E., & Jain, P. (2020). Development of 7-Aminopyrazolo [1, 5-a] pyrimidines as Anti-Candida and Antibacterial Agents. Organic Preparations and Procedures International, 53(1), 42-51.
36. El-Etrawy, A. A. S., & Sherbiny, F. F. (2021). Design, synthesis, biological assessment and molecular docking studies of some new 2-Thioxo-2, 3-dihydropyrimidin-4 (1H)-ones as potential anticancer and antibacterial agents. Journal of Molecular Structure, 1225, 129014.

37. Goffin, E., Jacques, N., Musumeci, L., Nchimi, A., Oury, C., Lancellotti, P., & Pirotte, B. (2020). Synthesis of ticagrelor analogues belonging to 1, 2, 3-triazolo [4, 5-d] pyrimidines and study of their antiplatelet and antibacterial activity. European Journal of Medicinal Chemistry, 208, 112767.
38. Ismail, M. M., Khalifa, M. M., El-Sehrawi, H. M., & Sabour, R. (2022). Design, synthesis and antimicrobial evaluation of new arylazopyrazole and arylazopyrazolo [1, 5-a] pyrimidine derivatives. Polycyclic Aromatic Compounds, 42(5), 2245-2262.
39. Magoulas, G. E., Kalopetridou, L., Ćirić, A., Kritsi, E., Kouka, P., Zoumpoulakis, P., ... & Calogeropoulou, T. (2021). Synthesis, biological evaluation and QSAR studies of new thieno [2, 3-d] pyrimidin-4 (3H)-one derivatives as antimicrobial and antifungal agents. Bioorganic Chemistry, 106, 104509.
40. Sui, Y. F., Li, D., Wang, J., Bheemanaboina, R. R. Y., Ansari, M. F., Gan, L. L., & Zhou, C. H. (2020). Design and biological evaluation of a novel type of potential multi-targeting antimicrobial sulfanilamide hybrids in combination of pyrimidine and azoles. Bioorganic & Medicinal Chemistry Letters, 30(6), 126982.
41. Malasala, S., Polomoni, A., Ahmad, M. N., Shukla, M., Kaul, G., Dasgupta, A., ... & Nanduri, S. (2021). Structure based design, synthesis and evaluation of new thienopyrimidine derivatives as anti-bacterial agents. Journal of Molecular Structure, 1234, 130168.
42. Rani, N. V., & Kunta, R. (2021). PEG-400 promoted a simple, efficient and eco-friendly synthesis of functionalized novel isoxazolyl pyrido [2, 3-d] pyrimidines and their antimicrobial and anti-inflammatory activity. Synthetic Communications, 51(8), 1171-1183.
43. Abd El-Sattar, N. E., El-Adl, K., El-Hashash, M. A., Salama, S. A., & Elhady, M. M. (2021). Design, synthesis, molecular docking and in silico ADMET profile of pyrano [2, 3-d] pyrimidine derivatives as antimicrobial and anticancer agents. Bioorganic Chemistry, 115, 105186.
44. Verma, V. A., Halu, B., Saundane, A. R., & Meti, R. S. (2022). Synthesis, Biological Validation, and Docking Studies of Novel Purine Derivatives Containing Pyridopyrimidine, Pyrazolopyridine, and Pyranonapthyridine Rings. Polycyclic Aromatic Compounds, 42(6), 3694-3716.
45. Wu, W., Lan, W., Wu, C., & Fei, Q. (2021). Synthesis and antifungal activity of pyrimidine derivatives containing an amide moiety. Frontiers in chemistry, 9, 695628.
46. Bai, X. Q., Li, C. S., Cui, M. Y., Song, Z. W., Zhou, X. Y., Zhang, C., ... & Jiang, T. Y. (2020). Synthesis and molecular docking studies of novel pyrimidine derivatives as potential antibacterial agents. Molecular Diversity, 24, 1165-1176.
47. Bassyouni, F., Tarek, M., Salama, A., Ibrahim, B., Salah El Dine, S., Yassin, N., ... & Abdel-Rehim, M. (2021). Promising antidiabetic and antimicrobial agents based on fused pyrimidine derivatives: molecular modeling and biological evaluation with histopathological effect. Molecules, 26(8), 2370.
48. Ahmed, M., Sayed, M., Saber, A. F., Hassanien, R., Kamal El-Dean, A. M., & Tolba, M. S. (2022). Synthesis, characterization, and antimicrobial activity of new thienopyrimidine derivatives. Polycyclic Aromatic Compounds, 42(6), 3079-3088.
49. Machníková, R., Janovská, L., & Brulikova, L. (2020). Solid-phase synthetic approach towards new pyrimidines as potential antibacterial agents. Journal of Molecular Structure, 1200, 127101.
50. Abd-Allah, W. H., Osman, E. E. A., Anwar, M. A. E. M., Attia, H. N., & El Moghazy, S. M. (2020). Design, synthesis and docking studies of novel benzopyrone derivatives as antimicrobial. Bioorganic Chemistry, 98, 103738.
51. Ajani, O. O., Iyaye, K. T., Audu, O. Y., Olorunshola, S. J., Kuye, A. O., & Olanrewaju, I. O. (2018). Microwave assisted synthesis and antimicrobial potential of quinoline-based 4-hydrazide-hydrazone Derivatives. Journal of Heterocyclic Chemistry, 55(1), 302-312.
52. Ismail, M. M., Khalifa, M. M., El-Sehrawi, H. M., & Sabour, R. (2022). Design, synthesis and antimicrobial evaluation of new arylazopyrazole and arylazopyrazolo [1, 5-a] pyrimidine derivatives. Polycyclic Aromatic Compounds, 42(5), 2245-2262.

53. Popiołek, Ł., & Biernasiuk, A. (2017). Synthesis and investigation of antimicrobial activities of nitrofurazone analogues containing hydrazide-hydrazone moiety. Saudi Pharmaceutical Journal, 25(7), 1097-1102.
54. Rawat, P., Singh, R. N., Niranjan, P., Ranjan, A., & Holguín, N. R. F. (2017). Evaluation of antituberculosis activity and DFT study on dipyrromethane-derived hydrazone derivatives. Journal of Molecular Structure, 1149, 539-548.
55. Abdelrahman, M. A., Salama, I., Gomaa, M. S., Elaasser, M. M., Abdel-Aziz, M. M., & Soliman, D. H. (2017). Design, synthesis and 2D QSAR study of novel pyridine and quinolone hydrazone derivatives as potential antimicrobial and antitubercular agents. European Journal of Medicinal Chemistry, 138, 698-714.
56. Zha, G. F., Leng, J., Darshini, N., Shubhavathi, T., Vivek, H. K., Asiri, A. M., ... & Qin, H. L. (2017). Synthesis, SAR and molecular docking studies of benzo [d] thiazole-hydrazones as potential antibacterial and antifungal agents. Bioorganic & medicinal chemistry letters, 27(14), 3148-3155.
57. Dantas, N., de Aquino, T. M., de Araújo-Júnior, J. X., da Silva-Júnior, E., Gomes, E. A., Gomes, A. A. S., ... & Junior, F. J. B. M. (2018). Aminoguanidine hydrazones (AGH's) as modulators of norfloxacin resistance in Staphylococcus aureus that overexpress NorA efflux pump. Chemico-Biological Interactions, 280, 8-14.
58. Wu, Y., Ding, X., Ding, L., Zhang, Y., Cui, L., Sun, L., ... & Zhao, Y. (2018). Synthesis and antibacterial activity evaluation of novel biaryloxazolidinone analogues containing a hydrazone moiety as promising antibacterial agents. European Journal of Medicinal Chemistry, 158, 247-258.
59. Zakeyah, A. A., Whitt, J., Duke, C., Gilmore, D. F., Meeker, D. G., Smeltzer, M. S., & Alam, M. A. (2018). Synthesis and antimicrobial studies of hydrazone derivatives of 4-[3-(2, 4-difluorophenyl)-4-formyl-1H-pyrazol-1-yl] benzoic acid and 4-[3-(3, 4-difluorophenyl)-4-formyl-1H-pyrazol-1-yl] benzoic acid. Bioorganic & medicinal chemistry letters, 28(17), 2914-2919.
60. Katariya, K. D., Shah, S. R., & Reddy, D. (2020). Anticancer, antimicrobial activities of quinoline based hydrazone analogues: Synthesis, characterization and molecular docking. Bioorganic Chemistry, 94, 103406.
61. Özbek, N., Özdemir, Ü. Ö., Altun, A. F., & Şahin, E. (2019). Sulfonamide-derived hydrazone compounds and their Pd (II) complexes: Synthesis, spectroscopic characterization, X-ray structure determination, in vitro antibacterial activity and computational studies. Journal of Molecular Structure, 1196, 707-719.
62. Muluk, M. B., Ubale, A. S., Dhumal, S. T., Rehman, N. N., Dixit, P. P., Kharat, K. K., ... & Haval, K. P. (2020). Synthesis, anticancer and antimicrobial evaluation of new pyridyl and thiazolyl clubbed hydrazone scaffolds. Synthetic Communications, 50(2), 243-255.
63. Celik, I., Erol, M., Puskullu, M. O., Uzunhisarcikli, E., Ince, U., Kuyucuklu, G., & Suzen, S. (2022). In vitro and in silico studies of quinoline-2-carbaldehyde hydrazone derivatives as potent antimicrobial agents. Polycyclic Aromatic Compounds, 42(4), 1942-1958.
64. Dkhar, L., Banothu, V., Kaminsky, W., & Kollipara, M. R. (2020). Synthesis of half sandwich platinum group metal complexes containing pyridyl benzothiazole hydrazones: Study of bonding modes and antimicrobial activity. Journal of Organometallic Chemistry, 914, 121225.
65. Popiołek, Ł., Patrejko, P., Gawrońska-Grzywacz, M., Biernasiuk, A., Berecka-Rycerz, A., Natorska-Chomicka, D., ... & Wujec, M. (2020). Synthesis and in vitro bioactivity study of new hydrazide-hydrazones of 5-bromo-2-iodobenzoic acid. Biomedicine & Pharmacotherapy, 130, 110526.
66. Puskullu, M. O., Celik, I., Erol, M., Fatullayev, H., Uzunhisarcikli, E., & Kuyucuklu, G. (2020). Antimicrobial and antiproliferative activity studies of some new quinoline-3-carbaldehyde hydrazone derivatives. Bioorganic Chemistry, 101, 104014.
67. Trotsko, N., Golus, J., Kazimierczak, P., Paneth, A., Przekora, A., Ginalska, G., & Wujec, M. (2020). Synthesis and antimycobacterial activity of thiazolidine-2, 4-dione based derivatives with

halogenbenzohydrazones and pyridinecarbohydrazones substituents. European journal of medicinal chemistry, 189, 112045.
68. Krátký, M., Konečná, K., Brablíková, M., Janoušek, J., Pflégr, V., Maixnerová, J., ... & Vinšová, J. (2021). Iodinated 1, 2-diacylhydrazines, benzohydrazide-hydrazones and their analogues as dual antimicrobial and cytotoxic agents. Bioorganic & medicinal chemistry, 41, 116209.
69. Karunanidhi, S., Chandrasekaran, B., Karpoormath, R., Patel, H. M., Kayamba, F., Merugu, S. R., ... & Mahlalela, M. C. (2021). Novel thiomorpholine tethered isatin hydrazones as potential inhibitors of resistant Mycobacterium tuberculosis. Bioorganic Chemistry, 115, 105133.
70. Singh, G., Kalra, P., Singh, A., Sharma, G., Espinosa-Ruíz, C., & Esteban, M. A. (2021). A quick microwave preparation of isatin hydrazone schiff base conjugated organosilicon compounds: Exploration of their antibacterial, antifungal, and antioxidative potentials. Journal of Organometallic Chemistry, 953, 122051.
71. Abdelrahman, M.A.; Salama, I.; Gomaa, M.S.; Elaasser, M.M.; Abdel-Aziz, M.M.; Soliman, D.H. Design, synthesis and 2D QSAR study of novel pyridine and quinolone hydrazone derivatives as potential antimicrobial and antitubercular agents. Eur. J. Med. Chem. 2017, 138, 698–714.
72. Popiołek, Ł., & Biernasiuk, A. (2017). Synthesis and investigation of antimicrobial activities of nitrofurazone analogues containing hydrazide-hydrazone moiety. Saudi Pharmaceutical Journal, 25(7), 1097-1102.
73. Haiba, N. S., Khalil, H. H., Moniem, M. A., El-Wakil, M. H., Bekhit, A. A., & Khattab, S. N. (2019). Design, synthesis and molecular modeling studies of new series of s-triazine derivatives as antimicrobial agents against multi-drug resistant clinical isolates. Bioorganic Chemistry, 89, 103013.
74. Trotsko, N., Golus, J., Kazimierczak, P., Paneth, A., Przekora, A., Ginalska, G., & Wujec, M. (2020). Synthesis and antimycobacterial activity of thiazolidine-2, 4-dione based derivatives with halogenbenzohydrazones and pyridinecarbohydrazones substituents. European journal of medicinal chemistry, 189, 112045.

75. Ali, B. H. (1983). Some pharmacological and toxicological properties of furazolidone. *Veterinary Research Communications, 6*(1), 1-11.
76. Al-Sharifi, H., & Patel, H. S. (2012). Synthesis, spectral investigation and biological evaluation of novel hydrazones derivative of substituted 1,2-dihydropyrimidine ring. *Der Pharma Sinica, 3*(3), 305-311.
77. Backes, G. L., Neumann, D. M., & Jursic, B. S. (2014). Synthesis and antifungal activity of substituted salicylaldehyde hydrazones, hydrazides and sulfohydrazides. *Bioorganic & Medicinal Chemistry, 22*(18), 4629-4636.
78. Bala, S., Uppal, G., Kajal, A., Kamboj, S., & Sharma, V. (2013). Hydrazones as promising lead with diversity in bioactivity-therapeutic potential in present scenario. *International Journal of Pharmaceutical Sciences Review and Research, 18*(1), 65-74.
79. Chatterjee, S. N., & Ghosh, S. (1979). Mechanism of action of furazolidone: Inter-strand cross-linking in DNA & liquid holding recovery of Vibrio cholerae cells. *Indian Journal of Biochemistry & Biophysics, 16*(3), 125-130.
80. Cihan-Üstündağ, G., & Çapan, G. (2012). Synthesis and evaluation of functionalized indoles as antimycobacterial and anticancer agents. *Molecular Diversity, 16*(3), 525-539.
81. Coates, A., Hu, Y., Bax, R., & Page, C. (2002). The future challenges facing the development of new antimicrobial drugs. *Nature Reviews Drug Discovery, 1*(11), 895-910.
82. Coelho, T. S., Cantos, J. B., Bispo, M. L. F., Gonçalves, R. S. B., Lima, C. H. S., da Silva, P. E. A., & Souza, M. V. (2012). In vitro anti-mycobacterial activity of (E)-N'-(monosubstituted-benzylidene) isonicotinohydrazide derivatives against isoniazid-resistant strains. *Infectious Disease Reports, 4*, e13.
83. Çakır, B., Dağ, Ö., Yıldırım, E., Erol, K., & Şahin, M. F. (2001). Synthesis and anticonvulsant activity of some hydrazones of 2-[(3H)-oxobenzoxazolin-3-yl-aceto]hydrazide. *Journal of Faculty of Pharmacy of Gazi University, 18*(2), 99-106.

84. Çıkla, P., Küçükgüzel, S. G., Küçükgüzel, İ., Rollas, S., De Clercq, E., Pannecouque, C., Andrei, G., Snoeck, R., Şahin, F., & Bayrak, Ö. F. (2010). Synthesis and evaluation of antiviral, antitubercular and anticancer activities of some novel thioureas derived from 4-aminobenzohydrazide hydrazones. *Marmara Pharmaceutical Journal, 14*(1), 13-20.
85. Doğan, H. N., Duran, A., Rollas, S., Şener, G., Armutak, Y., & Keyer-Uysal, M. (1998). Synthesis and structure elucidation of some new hydrazones and oxadiazolines anticonvulsant activities of 2-(3-acetyloxy-2-naphtyl)-4-acetyl-5-substituted-1,3,4-oxadiazolines. *Medical Science Research, 26*(10), 755-758.
86. Popiołek, Ł., Stefańska, J., Kiełczykowska, M., Musik, I., Biernasiuk, A., Malm, A., & Wujec, M. (2016a). Synthesis, dissociation constants, and antimicrobial activity of novel 2,3-disubstituted-1,3-Thiazolidin-4-one derivatives. *Journal of Heterocyclic Chemistry, 53*(2), 393–402. https://doi.org/10.1002/jhet.2383
87. Popiołek, Ł., Biernasiuk, A., & Malm, A. (2016b). Design, synthesis, and in vitro antimicrobial activity of new Furan/Thiophene-1,3-Benzothiazin-4-one hybrids. *Journal of Heterocyclic Chemistry, 53*(2), 479–486. https://doi.org/10.1002/jhet.2401
88. Popiołek, Ł., & Biernasiuk, A. (2016a). Hydrazide-hydrazones of 3-methoxybenzoic acid and 4-tert-butylbenzoic acid with promising antibacterial activity against Bacillus spp. *Journal of Enzyme Inhibition and Medicinal Chemistry*. https://doi.org/10.1080/14756366.2016.1170012
89. Popiołek, Ł., & Biernasiuk, A. (2016b). Design, synthesis, and in vitro antimicrobial activity of hydrazide-hydrazones of 2-substituted acetic acid. *Chemical Biology & Drug Design, 88*(6), 873–883. https://doi.org/10.1111/cbdd.12782
90. Rambabu, N., Dubey, P. K., Ram, B., & Balram, B. (2015). Synthesis, characterization and antimicrobial activity of some novel hydrazone derivatives of anacardic acid. *Der Pharma Chemica, 7*(4), 90–97.
91. Rasras, A. J. M., Al-Tel, T. H., Al-Aboudi, A. F., & Al-Qawasmeh, R. A. (2010). Synthesis and antimicrobial activity of cholic acid hydrazone analogues. *European Journal of Medicinal Chemistry, 45*(6), 2307–2313. https://doi.org/10.1016/j.ejmech.2010.01.039
92. Rollas, S., & Küçükgüzel, Ş. G. (2007). Biological activities of hydrazone derivatives. *Molecules, 12*(8), 1910–1939. https://doi.org/10.3390/12081910
93. Rutkauskas, K., Mickevičius, V., Kantminienė, K., Stasevych, M., Komarovska-Porokhnyavets, O., Musyanovych, R., & Novikov, V. (2013). Synthesis and antimicrobial activity of 1,3-disubstituted pyrrolidinones with hydrazone and naphthoquinone moieties. *Chemija, 24*(1), 74–80.
94. Satyanarayana, G. V., Rao, V. L., Chary, M. T., Ram, B., Balram, B., & Chinmaiyee, V. (2014). Synthesis and antimicrobial activity of novel hydrazone derivatives of 4-(4-chlorophenyl)cyclohexanecarboxylic acid. *Journal of Applied Chemistry, 3*(3), 1232–1238.
95. Şenkardes, S., Kaushik-Basu, N., Durmaz, İ., Manvar, D., Basu, A., Atalay, R., & Küçükgüzel, Ş. G. (2016). Synthesis of novel diflunisal hydrazide-hydrazones as anti-hepatitis C virus agents and hepatocellular carcinoma inhibitors. *European Journal of Medicinal Chemistry, 10*, 301–308. https://doi.org/10.1016/j.ejmech.2015.11.058
96. Shirinzadeh, H., Altanlar, N., Yucel, N., Ozden, S., & Suzen, S. (2011). Antimicrobial evaluation of indole-containing hydrazone derivatives. *Zeitschrift für Naturforschung C, 66*(5-6), 340–344. https://doi.org/10.1515/znc-2011-5-615
97. Siddiqui, A. I. S. M., Macedo, T. S., Moreira, D. R. M., Leite, A. C. L., Soares, M. B. P., & Azam, A. (2014). Design, synthesis and biological evaluation of 3-[4-(7-chloro-quinolin-4-yl)-piperazin-1-yl]-propionic acid hydrazones as antiprotozoal agents. *European Journal of Medicinal Chemistry, 75*, 67–76. https://doi.org/10.1016/j.ejmech.2014.01.031

98. Sreedhar, P., Srinivas, G., & Raju, R. M. (2016). Synthesis and antibacterial activity of N-substituted-1-benzyl-1H-1,2,3-triazole-carbohydrazide derivatives. *Pharmaceutical Chemistry Journal, 8*(10), 173–178.
99. Sriram, D., Yogeeswari, P., Vyas, D. R. K., Senthilkumar, P., & Srividya, P. B. (2010). 5-Nitro-2-furoic acid hydrazones: design, synthesis and in vitro antimycobacterial evaluation against log and starved phase cultures. *Bioorganic & Medicinal Chemistry Letters, 20*(14), 4313–4316. https://doi.org/10.1016/j.bmcl.2010.06.010
100. Tejeswara, R. A., Polkam, N., Rayam, P., Sridhara, J., Garikapati, N. S., Kotapalli, S. S., Ummanni, R., & Anireddy, J. S. (2016). Design, synthesis and biological activity evaluation of novel pefloxacin derivatives as potential antibacterial agents. *Medicinal Chemistry Research, 25*(5), 977–993. https://doi.org/10.1007/s00044-016-1513-1
101. Unissa, A. N., Hanna, L. E., & Swaminatha, S. (2016). A note on derivatives of isoniazid, Rifampicin, and pyrazinamide showing activity against resistant Mycobacterium tuberculosis. *Chemical Biology & Drug Design, 87*(4), 537–550. https://doi.org/10.1111/cbdd.12675
102. Velezheva, V., Brennan, P., Ivanov, P., Koronienko, A., Lyubimov, S., Kazarian, K., Nikonenko, B., Majorov, K., & Apt, A. (2016). Synthesis and antituberculosis activity of indole-pyridine derived hydrazides, hydrazide-hydrazones, and thiosemicarbazones. *Bioorganic & Medicinal Chemistry Letters, 26*(5), 978–985. https://doi.org/10.1016/j.bmcl.2016.01.005
103. World Health Organization. (2010). *Treatment of tuberculosis guidelines* (4th ed.). Geneva: World Health Organization.
104. Xaiver, J. J. F., Krishnasamy, K., & Sankar, C. (2012). Synthesis and antibacterial, antifungal activities of some 2r,4c-diaryl-3-azabicyclo[3.3.1]nonan-9-one-4-aminobenzoyl hydrazones. *Medicinal Chemistry Research, 21*(2), 345–350. https://doi.org/10.1007/s00044-011-9531-1
105. Yadagiri, B., Holagunda, U. D., Bantu, R., Nagarapu, L., Guguloth, V., Polepally, S., & Jain, N. (2014). Rational design, synthesis and anti-proliferative evaluation of novel benzosuberone tethered with hydrazide–hydrazones. *Bioorganic & Medicinal Chemistry Letters, 24*(20), 5041–5044. https://doi.org/10.1016/j.bmcl.2014.08.069