



ANTIMICROBIAL AGENTS CONTAINING NITROGEN AND SULPHUR HETEROCYCLES AND COMMON PATHOGENIC MICROBES: AN OVERVIEW

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ABSTRACT

The nitrogen and sulphur heterocyclic containing compounds and their derivatives play an important role in medicinal research as antimicrobial agents. Pathogenic microbes used various types of strategies to penetrate into host cells. The several types of mechanisms developed by the microorganisms (fungi, bacteria, and virus), to the penetration into their host cell. The present review mainly highlights the heterocycles containing pyrimidine nucleus important for antimicrobial activity.

Introduction

Antimicrobials have transformed our ability to treat many infectious diseases that were killers only a few decades ago. The increasing use of antimicrobials in humans, animals, and agriculture has resulted in many pathogens developing resistance to these powerful drugs. All major groups of pathogens — viruses, fungi, parasites, and bacteria can become resistant to antimicrobials. Many diseases are increasingly difficult to treat because of the emergence of drug-resistant organisms including: HIV and other viruses; bacteria such as Staphylococci, Enterococci and Escherichia coli; respiratory infections, such as Tuberculosis and Influenza; food-borne pathogens, such as Salmonella and Campylobacter; sexually transmitted organisms such as Neisseria gonorrhoea; fungal infections, such as Candida; and parasites such as Plasmodium falciparum, the cause of malaria. A pathogen is an organism that causes disease. Pathogenic microbes contain certain abilities to cause infections or diseases in hosts during interactions. Virulence factors aggravate the defense mechanisms of the host to establish infections. The nature and type of virulence factors determine the pathogenicity of microorganisms. These virulence factors can be enzymes, toxins, lipids, flagella, exopolysaccharides, quorum sensing, etc. Signaling plays a very important role in pathogenicity which triggers the conformational change of receptors for ligands to reduce or activate the mechanisms. The pathogens such as bacteria and fungus express different sets of virulence genes and transcription factors during infections. The regulation of virulence factors followed the two prime regulatory mechanisms which

includes sigma factors and two-component regulatory systems. Microbial-system-assisted virulence factors can be elucidated at cellular and molecular levels and are useful to develop strategies against microbe-mediated pathogenesis.¹

It is important to remember that:²

- A pathogen is a micro-organism that has the potential to cause disease.
- An infection is the invasion and multiplication of pathogenic microbes in an individual or population.
- Disease is when the infection causes damage to the individual's vital functions or systems.
- An infection does not always result in disease.

Pathogen Types³

There are four most common types of pathogens: viruses, bacteria, fungi, and parasites.

Viruses

Viruses are made up of a piece of genetic code, such as DNA or RNA, and protected by a coating of protein. Once you're infected, viruses invade host cells within your body. They then use the components of the host cell to replicate, producing more viruses. After the replication cycle is complete, these new viruses are released from the host cell. This usually damages or destroys the infected cells. Some viruses can remain dormant for a time before multiplying again. When this happens, a person appears to have recovered from the viral infection, but gets sick again.

Bacteria

Bacteria are microorganisms made of a single cell. They are very diverse, have a variety of shapes and features, and have the ability to live in just about any environment, including in and on your body. Not all bacteria cause infections. Those that can are called pathogenic bacteria.

Fungi

There are millions of different fungal species on Earth. Fungi can be found just about everywhere in the environment, including indoors, outdoors, and on human skin. They cause infection when they overgrow. Fungi cells contain a nucleus and other components protected by a membrane and a thick cell wall. Their structure can make them harder to kill. Some new strains of fungal infections are proving to be especially dangerous, such as *Candida aurus*, and have prompted more research into fungal infections.

Parasites

Parasites are organisms that behave like tiny animals, living in or on a host and feeding from or at the expense of the host. Though parasitic infections are more common in tropical and subtropical regions, they can occur anywhere.

Three main types of parasites can cause disease in humans. These include:

- Protozoa, which are single-celled organisms that can live and multiply in your body
- Helminths, which are larger, multi-celled organisms that can live inside or outside your body and are commonly known as worms
- Ectoparasites, which are multi-celled organisms that live on or feed off your skin, including some insects, such as ticks and mosquitos

They can be spread several ways, including through contaminated soil, water, food, and blood, as well as through sexual contact and via insect bites.

Pathogenic bacteria are bacteria that can cause disease.⁴ This article deals with human pathogenic bacteria. Although most bacteria are harmless or often beneficial, some are pathogenic, with the number of species estimated as fewer than a hundred that are seen to cause infectious diseases in humans.⁵ By contrast, several thousand species exist in the human digestive system. One of the bacterial diseases with the highest disease burden is tuberculosis, caused by *Mycobacterium tuberculosis* bacteria, which kills about 2 million people a year, mostly in sub-Saharan Africa. Pathogenic bacteria contribute to other globally important diseases, such

as pneumonia, which can be caused by bacteria such as *Streptococcus* and *Pseudomonas*, and foodborne illnesses, which can be caused by bacteria such as *Shigella*, *Campylobacter*, and *Salmonella*. Pathogenic bacteria also cause infections such as tetanus, typhoid fever, diphtheria, syphilis, and leprosy. Pathogenic bacteria are also the cause of high infant mortality rates in developing countries. Fungal infections of the skin are caused by dermatophytes, such as *Trichophyton rubrum*, *Trichophyton tonsurans*, *Trichophyton mentagrophytes*, *Microsporum canis*, *Epidermophyton floccosum*, *Microsporum gypseum*, and *Trichophyton verrucosum*. Most fungal skin infections, such as tinea pedis and tinea cruris, respond to topical therapy, although widespread or chronic infections that do not respond to local measures may require systemic treatment. The evaluation of the antifungal activity can be performed *in vitro* or *in vivo*.⁶⁻⁸

The heterocycles containing nitrogen and sulfur containing heterocyclic compounds possess a wide spectrum of pharmacological/biological activities.

Vaghasia SJ. et. al. (2007) synthesized and determined antimicrobial activity of thiazolo[5,4-d]pyrimidine. The synthesis of thiazolo [5,4-d] pyrimidines can be achieved from different 5- thiazolidinones, 2-butyl-1H-imidazole-5-carbaldehyde and thiourea using microwave irradiation within 5 min. The structures of the products were supported by FTIR, PMR and mass spectral data. The *in vitro* antimicrobial activity of the synthesized thiazolo [5, 4-d] pyrimidines, having substituents at the 1- and 3-positions, were determined by the cup-plate method against several standard strains chosen to define the spectrum and potency of the new compounds. The antimicrobial activities of the thiazolo [5,4-d] pyrimidines are compared with those of known chosen standard drugs, viz. ampicillin, chloramphenicol, ciprofloxacin, norfloxacin and griseofulvin. .

Ronsisvalle G. et. al. (2006) synthesized and determined the antifungal activity of pyrazole[3,4-d]pyrimidines and imidazo[4,5-d]pyrimidines. Some pyrimidines, pyrazolo[3,4-d]pyrimidines and imidazo[4,5-d]pyrimidines bearing the 5-nitro- and 5-aminothienyl-2-sulfide functionalities on the pyrimidine nucleus were synthesized and evaluated for their antifungal activity against several strains of yeasts and dermatophytes

Wetzel B. et. al. (2006) synthesized and determined antimicrobial activity of pyrimidinylureidocephalosporins. A new pyrazolo [3, 4-d] pyrimidine derivative was synthesized and its antifungal activity evaluated *in vitro* against mycelial and yeast cells of *Candida albicans*.

Ismail KA. et. al. (2006)¹² synthesized and determined antimicrobial activity of some tetramethylenethieno [2, 3-d] pyrimidine derivatives. A series of tetramethylenethieno[2,3-d]pyrimidine derivatives has been synthesized and tested for its antimicrobial properties. All the synthesized compounds were found to exhibit *in vitro* antibacterial and/or antifungal activity.

Kumaraswamy MN. et. al. (2006) synthesized and determined antimicrobial activity of 2-mercapto-4-substituted-naphtho [2, 1- b] furo [3, 2- d] pyrimidines. 2-Hydroxy-1-naphthonitrile on treatment with different α -haloketones affords corresponding 2-acyl-3-aminonaphtho [2, 1- b] furans. The compounds on reacting with ammonium thiocyanate and benzoyl chloride produce N-acyl-N1-(2-acylnaphtho[2,1- b]furan)thiourea, which on further refluxing with sodium hydroxide yield 2-mercapto-4-acylnaphtho[2,1- b]furo [3,2-d] pyrimidines. These on stirring with chloroacetic acid give S- (4-acylnaphtho [2, 1- b] furo [3, 2-d] pyrimidine)-mercaptoacetic acid. The structures of newly synthesized compounds have been established by elemental analysis and spectral studies. In addition, they have been screened for antimicrobial, diuretic, and antiinflammatory activities.

Emam HA. et. al. (2006) synthesized and determined antimicrobial activity of chloropyrimidine novel naphtho[2,1-b]pyran, pyrano[2,3-d]pyrimidine and pyrano[3,2-e][1,2,4]triazolo[2,3-c]-pyrimidine derivatives. The synthesis of new naphtho[1',2':5,6]pyrano[2,3-d]pyrimidines and related heterocycles has been reported. The key intermediate 3-amino-8-bromo-1- (p-methoxyphenyl)-1H-naphtho [2, 1-b] pyran-2-carbonitrile was obtained in one pot synthesis by treating alpha-cyanocinnamionitrile with 6-bromo-2-naphthol. Antimicrobial activity was shown for some of the synthesized compounds.

Jerzy C. et. al. (2006) synthesized and determined antimicrobial activity of pyrimidine 5-terpeno derivatives. The pyrimidine terpenoderivatives were tested on seven selected bacterial strains: *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*. Antifungal tests were also carried out on *Candida albicans*. Some interesting microbiological results were obtained, both antibacterial and antifungal.

Michal G. et. al. (2005) synthesized and determined antimicrobial activity of some imidazo [1,2- α] pyrimidine derivatives. A series of 75 imidazo [1, 2- α]pyrimidine derivatives were synthesized. The *in vitro* antibacterial activity of these compounds and their corresponding α -bromoketones against a variety of gram (+), gram (-) bacteria and Mycobacterium species is reported. Some of the prepared derivatives exhibited potent antimicrobial activity.

Zaki ME. et. al. (2005) synthesized and determined antimicrobial activity of some fused heterocyclic pyrroles. Pyrrole derivatives were used as precursors for the preparation of pyrrolo [2, 3-d] pyrimidine derivatives. Also, the formation and structure of different pyrrolotriazolopyrimidine derivatives were discussed.

Bolte M. et. al. (2004) synthesized and determined antimicrobial activity of 3-nitroso-2-phenylimidazo [1, 2- α] pyrimidine. The title compound, C₁₂H₈N₄O, is of pharmacological interest. It contains an imidazo [1, 2- α] pyrimidine heterocycle, carrying a nitroso group in position 3 and a phenyl group in position 2. Both substituents are almost coplanar with the heterocycle.

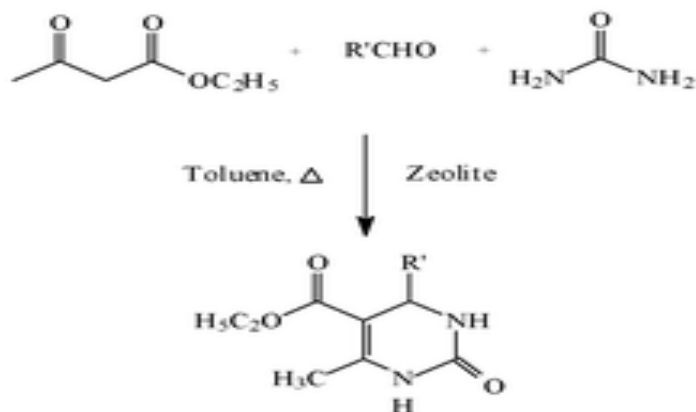
Fanaki N. et. al. (2003) synthesized and determined antimicrobial activity of novel pyrimidine-2, 4-diones and 2-thioxo-pyrimidine-4-ones. Two novel series of pyrimidine derivatives have been prepared, namely; 3, 6-disubstituted perhydropyrimidine-2, 4-diones as well as 3, 6-disubstituted 2-thioxo-perhydropyrimidine-4-ones. The anticancer as well antimicrobial activities of these compounds and their open-chain counterparts have been determined.

Gossnitzer E. et. al. (2002) synthesized and determined antimicrobial activity of selected s-trans-6-aryl-4-isopropyl-2-[2-[(E)-1-phenylalkylidene]-(E)hydrazino] -1,4-dihydropyrimidine hydrochlorides. The antimicrobial activity was evaluated against representative Gram-negative and Gram-positive bacteria, and against the pathogenic yeast *Candida albicans*. The tested title compounds showed weak antibacterial activity against Gram-positive bacteria, and one compound was active against *Candida albicans*.

Sarg MT. et. al. (2002) synthesized and determined antimicrobial activity of pyrimidines, 1,2,4-triazolo[4,3- a]pyrimidin-7-ones and pyrimidino[2,1- c][1,2,4]triazin-8-ones.

Jun L., et. al. (2002) synthesized 3, 4-dihydropyrimidinones from the aldehyde, β -keto ester and urea in ethanol, using ferric chloride hexahydrate or nickel chloride hexahydrate as the catalyst, is described. Compared with the classical Biginelli reaction conditions, this new method offers better yields and shorter reaction time.

Radha Rani V., et. al. (2001) reported zeolite catalyzed, single step and environment friendly process for the synthesis of dihydropyrimidinones, a pharmacologically important class of compounds. Reusability of the catalyst and the ease of separation of pure product, selectively and in high yields in comparison to the classical Biginelli reaction, are a few of the unique features of this process.



Baraka AM et. al. (2000) synthesized and determined antimicrobial activity of some substituted 1H-pyrazolyl-thiazolo [4, 5-d] pyrimidines. The synthesis of two novel series of structurally related 1H-pyrazolyl derivatives of thiazolo [4, 5-d] pyrimidines is described. All the newly synthesised compounds were examined for their *in vitro* antimicrobial activity against Escherichia coli, as an example of Gram negative bacteria, Staphylococcus aureus as an example of Gram positive bacteria, and Candida albicans as a representative of fungi.

Balkan A et. al. (2000) synthesized and determined antimicrobial activity of thiazolo [4, 5-d] pyrimidine derivatives. In this study, by starting from ethyl 4-amino-2,3-dihydro-3-phenyl-2-thioxothiazole-5-carboxylate, three compounds having 2,3-dihydro-3-phenyl-5-mercapto-6-alkyl/phenyl-2-thioxothiazolo[4,5-d]pyrimidin-7(6H)-one structure and their 5-(4'-nonsubstituted/-substituted benzoylmethyl) thio derivatives were synthesized. The antimicrobial activities of the synthesized compounds were investigated against some bacteria and fungi using the microdilution method. 2,3-Dihydro-3,6-diphenyl-5-(4'-bromobenzoylmethyl)thio-2-thioxothiazolo [4,5-d]pyrimidin-7(6H) one possessing remarkable activity against Gram-positive bacteria and yeast like fungi was found to be the most active compound in this series.

Sriram D et. al. (1996) synthesized and determined antimicrobial activity of Schiff and Mannich bases of isatin and its derivatives with pyrimidine. Isatin and its derivatives have been reacted with 4-(4'-chlorophenyl)-6-(4''-methyl phenyl)-2-aminopyrimidine to form Schiff bases and the N-Mannich bases of these compounds were synthesized by reacting them with formaldehyde and several secondary amines. Investigation of antimicrobial activity of the compounds was made by the agar dilution method against 28 pathogenic bacteria, eight pathogenic fungi and anti-HIV activity against replication of HIV-1 (III B) in MT-4 cells. The compounds are significantly active against bacteria and fungi.

Ghozlan HA et. al. (1996) synthesized and determined antimicrobial activity of thiazolo [4, 5-d] pyrimidine derivatives. Some novel thiazolo [4, 5-d] pyrimidines containing 6-arylideneamino, 2-dicyanomethylidene, 2-(cyanoethoxy carbonyl) methylidene or 2-hydrazono moieties were synthesized. The prepared compounds were tested *in vitro* for their antibacterial, antifungal, anti-HIV and anticancer activities. Most of them showed promising antifungal activity, but only a few compounds exhibited anticancer activity.

Onnis Vet. al. (1995) synthesized and determined antimicrobial activity of new thioxopyrimidines. A convenient and simple synthesis of some new thioxopyrimidines was developed starting from 3-amino-3-(dialkylamino)propanethioamide derivatives. The prepared compounds were assayed *in vitro* for antimicrobial activity and found practically inactive.

Cocco MT et. al. (1995) synthesized and determined antimicrobial activity of 2-mercapto-3-(N-aryl) pyrimido [5, 4-c] cinnolin-4-(3H)-ones. Ten new substituted 2-mercapto-3-(N-aryl) pyrimido [5, 4-c] cinnolin-4-(3H)-ones were prepared by refluxing substituted 4-aminocinnolin-3-carboxylic acid with substituted arylisothiocyanate in anhydrous pyridine. These derivatives were evaluated for their antimicrobial and anti-inflammatory activities. Some of the compounds possess potent antimicrobial activity.

Fellahi Y et. al. (1995) synthesized and determined antimicrobial activity of 2-substituted, 2-diarylethyl-4, 6-dichloropyrimidine derivatives. Fluorinated 4-imino-3, 5, 7-trisubstituted pyrido [2, 3-d] pyrimidine-2 (1H)-thiones were prepared by 2-amino-3-cyano-4, 6-disubstituted-pyridines and appropriate arylisothiocyanates. The antibacterial activity of all the pyrido [2,3-d]-pyrimidines has been evaluated and found active against *S.aureas*.

Salas JM et. al. (1992) synthesized and determined antimicrobial activity of zinc, cadmium, and mercury complexes of 5,7-dimethyl-[1,2,4] triazolo [1,5] pyrimidine. A study of the antimicrobial activity of the complexes shows that the compounds display activity against two strains.

Cocco MT et. al. (1992) synthesized and determined antimicrobial activity of some imidazo [1, 2-a] pyrimidine derivatives. A series of 75 imidazo [1, 2-a] pyrimidine derivatives were synthesized. The *in vitro* antibacterial activity of these compounds and their corresponding alpha-bromoketones against a variety of gram (+), gram (-) bacteria and Mycobacterium species is reported. Some of the prepared derivatives exhibited potent antimicrobial activity.

Auzzi G et. al. (1989) synthesized and determined antimicrobial activity of 3-(1, 3, 4-thiadiazol-2-yl) pyrazolo [1, 5-a] pyrimidine derivatives. The synthesis of some 3-(1,3,4-thiadiazol-2-yl)pyrazolo[1,5-a]-pyrimidine derivatives is performed by reacting 2-(3-amino-1,2-dihydro-5-oxo-5H-pyrazol-4-yl)-1,3,4-thiadiazoles with 2,4-pentanedione, ethyl 3-oxobutyrate and diethyl ethoxymethylenemalonate. The antimicrobial activity of the synthesized compounds was reported

Conclusion

Based on literature, In this review we focused on pathogenic microbes and searching potential bioactive, effective therapeutic agent as antimicrobial compounds.

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