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A Review: Synthesis and Antimicrobial Activity of Novel Heterocyclic Derivatives

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Abstract

The antimicrobial activities of newly synthesized compounds were investigated. A diverse set of compounds was synthesized using various synthetic strategies and characterized by spectroscopic methods. The antimicrobial activities of these compounds were assessed against a panel of bacteria and fungi using standard antimicrobial assays such as agar well diffusion and minimum inhibitory concentration. The results demonstrated that several compounds exhibited significant antimicrobial activities against both Gram-positive and Gram-negative bacteria, as well as fungi. Structure-activity relationship studies suggested that specific structural modifications influenced the antimicrobial potency of the compounds. These findings indicate the potential of these novel compounds as effective antimicrobial agents and support further exploration of their therapeutic applications.

Key words: Antimicrobial, Gram-positive & Gram-negative bacteria.

Introduction

Antimicrobial agents are substances that have the ability to inhibit the growth or kill microorganisms, including bacteria, fungi, viruses, and parasites. They play a critical role in the prevention and treatment of infectious diseases. Antimicrobials can be classified into different categories based on their target microorganisms, such as antibacterials (targeting bacteria), antifungals (targeting fungi), antivirals (targeting viruses), and antiparasitics (targeting parasites).There are several mechanisms by which antimicrobials exert their effects. Antibacterials, for example, may target essential components of bacterial cells, such as cell wall synthesis, protein synthesis, DNA replication, or metabolic pathways. Antifungals often target specific components of fungal cells, such as ergosterol synthesis or cell membrane integrity. Antivirals can inhibit viral replication by targeting viral enzymes or proteins involved in viral entry, replication, or release. Antiparasitic drugs may interfere with various aspects of parasite metabolism, growth, or reproduction.

The discovery and development of new antimicrobial agents are of utmost importance due to the emergence and spread of antimicrobial resistance. Over time, microorganisms can develop mechanisms to evade the effects of antimicrobial drugs, rendering them ineffective. Therefore, ongoing research focuses on the identification and development of novel antimicrobial compounds, including natural products, synthetic compounds, and modified derivatives, to combat resistant strains and provide effective treatment options for infectious diseases.

In addition to the development of new antimicrobials, it is crucial to promote responsible and judicious use of these agents to minimize the development of resistance. This includes appropriate prescribing practices, adherence to dosage regimens, and infection prevention measures to reduce the overall

burden of infectious diseases and protect the efficacy of existing antimicrobial agents.

In vitro antimicrobial assay:

The in vitro antimicrobial study of the synthesized bis-pyrimidines was evaluated against Gram +ve bacterial species: S. aureus (MTCC3160), B. subtilis (MTCC441), Gram – ve species: E. coli (MTCC443) and fungus species: A. niger (MTCC281) and C. albicans (MTCC227) by tube dilution technique (Cappuccino and Sherman, 1999). Dilutions of test and reference drug in double strength nutrient broth media I.P. was used for antibacterial study and Sabouraud dextrose broth media I.P. was used for the antifungal study. The stock solution was prepared for the test compounds (q1-q20) and reference drugs (norfloxacin and fluconazole) in dimethyl sulfoxide (DMSO) to get a concentration of 100 µg/mL and this stock solution was used for further tube dilution with six concentration of 50, 25, 12.5, 6.25, 3.125 and 1.562 µg/mL for the antimicrobial study (Pharmacopoeia of India, 2007). The MIC values of synthesized bis-pyrimidine Schiff base derivatives were recorded at different incubation period: 37±1oC (bacterial species) for 24 h, 37±1oC (C. albic albicans) for 48 h and 25±1oC (A. niger) for 7 days and the antimicrobial results have been recorded in terms of minimum inhibitory concentration values in µmol/mL.

In vitro antimicrobial activity:

Antimicrobial activity results indicated particularly; compounds q1, q16, q19 and q20 have shown more promising antimicrobial activity as compared to standard drugs norfloxacin (antibacterial) and fluconazole (antifungal) while other derivatives are moderately active. In the case of Gram +ve antibacterial study, compound q1 was found to be most potent one against B. subtilis with MIC value of 0.83 µmol/mL and compound q20 showed significant activity against S. aureus with MIC value of 0.36 µmol/mL. In the case of Gram -ve bacterial study, compound q16 displayed appreciable antibacterial activity against E. coli. The antifungal activity results indicated that compounds, q1 and q19 (MICca = 0.41 µmol/mL) and compound q16 (MICan = 1.54 µmol/mL) were found to be most effective ones against C. albicans and A. niger respectively. The antimicrobial activity results of synthesized bis-pyrimidine Schiff base derivatives (q19 and q20) depicted them to be more active than standard drugs and may be taken as lead compounds to discover novel antimicrobial agent.

In vitro anticancer activity:

The in vitro anticancer activity of synthesized bis-pyrimidine derivatives was carried out against human colorectal cancer cell line (HCT-116 (ATCC CCL-247) and the results are presented in Table 2. Anticancer screening results revealed that in general bis-pyrimidine Schiff bases exhibited good anticancer potential against human colorectal cancer cell line, especially, compounds q1 (IC50 = 0.18 µmol/mL) displayed anticancer activity more than the reference drug 5-fluorouracil (IC50 = 0.35 µmol/L).

Experimental Work

Synthesis of 6,6'-(1,4-phenylene)bis(4-(4-bromophenyl)pyrimidin-2-amine) analogues:
The cyclization of bis-chalcone I, 3,3'-(1,4-phenylene)bis(1-(4-bromophenyl) prop-2-en-1-one) to yield bis-pyrimidine (int-II, (6,6'-(1,4-phenylene)bis(4-(4- Chapter 6. Series - iv Synthesis and antimicrobial activity of novel heterocyclic derivatives Page 86 bromophenyl)pyrimidin-2-amine) was effected with guanidine hydrochloride. The reaction of bis-pyrimidine with corresponding substituted aldehyde resulted in the formation of title compounds with appreciable yields. The synthesized compounds were characterized by the determination of their physicochemical properties, spectral and elemental analyses, which are in agreement with the proposed molecular structures" of bis-pyrimidine derivatives.

Synthesis of 3,3'-(1,4-phenylene)bis(1-(4-bromo-phenyl)prop-2-en-1-one
The reaction mixture of 1-(4-bromophenyl) ethanone (0.02 mol) and terephthalaldehyde (0.01 mol) was stirred for 2-3 h in ethanol "(5-10 mL) followed by drop wise addition of

sodium hydroxide solution (10 mL 40%) with constant stirring at room temperature till a dark yellow mass was obtained. The reaction mixture was allowed to stand overnight at room temperature and was then poured into ice cold water and acidified with hydrochloric acid and the precipitated 3,3'-(1,4-phenylene) bis(1-(4-bromophenyl)prop-2-en-1-one was filtered, dried and recrystallized from methanol.

Synthesis of 6,6'-(1,4-phenylene)bis(4-(4-bromo-phenyl)pyrimidin-2-amine)

The solution of 3,3'-(1,4-phenylene)bis(1-(4-bromo-phenyl)prop-2-en-1-one (0.01 mol) (synthesized in previous step a) in ethanol (80 mL) was added with 0.01 mol of potassium hydroxide and 40 mL of 0.50 M solution of guanidine hydrochloride and refluxed for 5-6 h at 50 oC (temp). The reaction mixture was then cooled and acidified with few drops of hydrochloric acid (20 mL of 0.5 M solution) and the resultant precipitate of 6,6'-(1,4-phenylene) bis(4-(4-bromo-phenyl)pyrimidin2-amine was separated dried and recrystallized from methanol.

Structure activity relationship (SAR)

The structure activity relationship for antimicrobial and anticancer potentials of synthesized bis-pyrimidine derivatives can be deduced as follow:

Antimicrobial activity

a) Presence of tri-methoxy group at benzylidene portion of compound enhanced the antimicrobial potential against E. coli and C. albicans.

b) Substitution by α-bromo-cinnamaldehyde enhanced the antifungal activity against A. niger, than the other synthesized derivatives.

c) Presence of mono-nitro group at meta-position is responsible in improving the antibacterial activity against S. aureus, whereas, para–NO2 (Compound 13y) and ortho-NO2 showing less activity against S. aureus Substitution by 5-bromo-2-hydroxybenzaldehyde enhanced the antibacterial potential against B. subtilis.

Aim and Objectives

Aim and Objectives of the research on the antimicrobial activity of novel compounds aim to contribute to the advancement of antimicrobial strategies and the development of effective agents against drug-resistant microorganisms.

Conclusion

In conclusion, the antimicrobial activity of novel compounds, particularly heterocyclic derivatives, holds significant promise in addressing the global challenge of antimicrobial resistance. The synthesis and evaluation of these compounds have provided valuable insights into their potential as effective antimicrobial agents. Through the exploration of structure-activity relationships, it has been possible to optimize their antimicrobial efficacy and develop compounds with potent activity against a wide range of microorganisms.

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