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A COMPREHENSIVE REVIEW ON PYRIMIDINE AND ITS DERIVATIVES AS POTENTIAL ANTIBACTERIAL AGENTS

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ABSTRACT

Pyrimidine is a fundamental heterocyclic aromatic compound that serves as a key pharmacophore in numerous bioactive molecules. Its derivatives exhibit remarkable antibacterial properties, attributed to their ability to interfere with bacterial DNA replication, protein synthesis, and cell wall biosynthesis. The increasing resistance of bacteria to conventional antibiotics has driven medicinal chemists toward designing novel pyrimidine- based compounds with improved potency and selectivity. The electron density, hydrogen bonding capacity, and molecular orientation of pyrimidine derivatives make them ideal scaffolds for antibacterial drug development. This review provides a comprehensive overview of the structural characteristics, synthetic approaches, mechanisms of antibacterial action, structure–activity relationships, molecular docking insights, and future perspectives of pyrimidine-based antibacterial agents.

KEYWORDS: Pyrimidine, Antibacterial activity, Drug design, Heterocyclic compounds, Docking, SAR.

INTRODUCTION

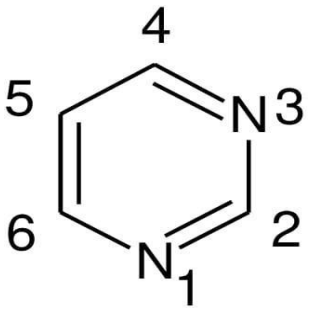
Bacterial infections remain one of the major causes of morbidity and mortality worldwide. The emergence of multidrug-resistant (MDR) bacterial strains has rendered many existing antibiotics less effective, thereby necessitating the search for new chemical entities with novel mechanisms of action.

Pyrimidine, a six-membered heterocycle containing two nitrogen atoms at positions 1 and 3, has emerged as a privileged scaffold in medicinal chemistry due to its versatile biological activities. It forms the structural core of nucleobases like cytosine, thymine, and uracil, making it biocompatible and pharmacologically relevant.

Pyrimidine derivatives have demonstrated wide-ranging pharmacological properties including antibacterial, antifungal, antiviral, anti-inflammatory, and anticancer activities. Modifications in the pyrimidine nucleus or its substitution pattern can yield compounds with enhanced antibacterial profiles. The exploration of pyrimidine derivatives, therefore, provides an efficient pathway to design novel antibacterial agents capable of combating drug resistance.

CHEMICAL STRUCTURE AND CHARACTERISTICS

Pyrimidine ($_4H_4NC_2$) consists of a planar aromatic ring containing two nitrogen atoms at alternate positions. The resonance stabilization within the ring contributes to its aromaticity and chemical stability.



Key Features

Basicity

Pyrimidine is weakly basic due to the electron-withdrawing effect of nitrogen atoms.

Hydrogen Bonding

Capable of forming multiple hydrogen bonds with enzyme active sites.

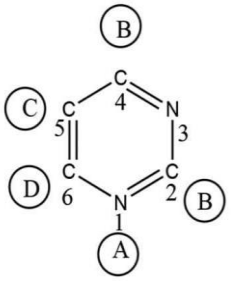
Substitution Potential

The ring allows easy substitution at C-2, C-4, C-5, and C-6 positions, which significantly affects its biological activity.

Bioisosterism

Pyrimidine can act as a bioisostere of benzene or purine in drug design, making it a valuable scaffold for developing novel antibacterial agents.

STRUCTURE ACTIVITY RELATIONSHIP OF PYRIMIDINES



Positions for substitution on pyrimidine ring

- As SAR studies give insights into the molecular properties causing receptor affinity and selectivity, The promising nature of compounds may be attributed to the substitutions at the hydrophobic domain.
- These compounds had electron-withdrawing and donating groups at the ortho, meta, and para position of the hydrophobic aryl ring. In overall, it was noticed that the substituted derivatives have more activity than the other derivatives.
- This may be because of the fact substituted derivatives are better fitted into the receptor site.

Position A

Substitution at five-membered saturated heterocyclic ring leads to anticancer and antiviral activities.

Position B

i. Substitution at 2nd position with five or six-membered saturated heterocyclic ring directs to anthelmintic, antiparkinsonian, expectorant activity, and treatment of GI disturbance.
ii. 2nd and 4th position keto group substitution or amino substitution or mixed keto, amino groups substitution leads to anticancer, antiviral, antibacterial, antifungal, and treatment of respiratory tract infection and liver disorder.

Position C

Substitution at 5th position with substituted amine or saturated distal heterocyclic ring or halogen leads to antibacterial and anticancer Activities.

Position D

Fifth and 6th position fused with other heterocyclic ring and o, m, p substituted with aryl ring. This substitution leads to anticancer antiviral, antibacterial, vasodilation, and treatment of UTI.

MECHANISM OF ANTIBACTERIAL ACTION

Pyrimidine derivatives exhibit antibacterial activity through several mechanisms, often depending on the substitution pattern and physicochemical properties.

DNA Gyrase and Topoisomerase Inhibition

Pyrimidine analogs can bind to bacterial DNA gyrase or topoisomerase IV, enzymes responsible for DNA replication and transcription. Inhibition of these enzymes prevents bacterial cell proliferation.

Folate Pathway Inhibition

Certain derivatives mimic the structure of folate intermediates, competitively inhibiting dihydrofolate reductase (DHFR), leading to disruption of bacterial nucleic acid synthesis.

Cell Wall Biosynthesis Interference

Substituted pyrimidines may inhibit peptidoglycan synthesis, weakening bacterial cell walls and causing cell lysis.

Membrane Disruption

Lipophilic pyrimidine derivatives interact with the bacterial membrane, increasing permeability and causing leakage of intracellular contents.

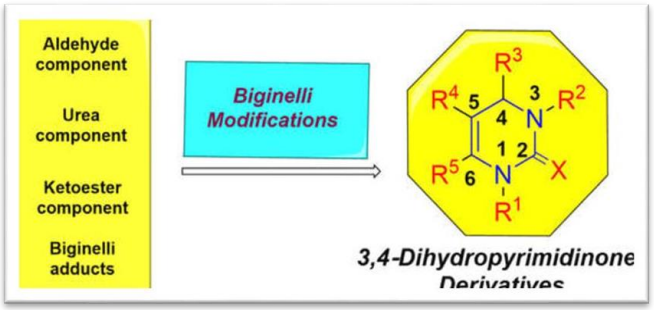
SYNTHETIC APPROACHES FOR PYRIMIDINE DERIVATIVES

Several synthetic strategies have been developed to construct pyrimidine and its derivatives efficiently. The choice of synthesis depends on desired substitution patterns and functional groups.

Classical Methods

Biginelli Condensation

Involves the reaction of β-diketone, aldehyde, and urea (or thiourea) under acidic conditions to form dihydropyrimidinones, which are oxidized to pyrimidines.



Cyclocondensation Reactions

Combination of amidines or guanidines with 1,3-diketones yields substituted pyrimidines.

Modern Green Synthetic Approaches

Microwave-Assisted Synthesis

Reduces reaction time and enhances yield without toxic solvents.

Ultrasound Irradiation

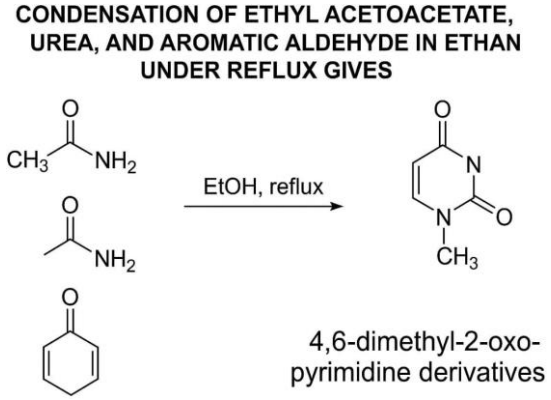
Increases molecular collision and promotes faster ring formation.

Catalyst-Free Solvent Systems

Environmentally sustainable methods producing minimal by-products.

Example Reaction

Condensation of ethyl acetoacetate, urea, and aromatic aldehyde in ethanol under reflux gives 4,6-dimethyl-2-oxo-pyrimidine derivatives with high antibacterial potential.



MOLECULAR DOCKING AND COMPUTATIONAL STUDIES

Docking studies are essential for understanding the interaction between pyrimidine derivatives and bacterial enzymes.

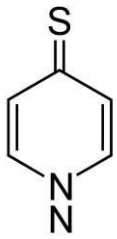
Molecular modeling has revealed that pyrimidine derivatives form π–π stacking and hydrogen bonds with residues in the active sites of DNA gyrase and dihydrofolate reductase.

QSAR (Quantitative Structure-Activity Relationship) analysis helps predict how structural modifications affect antibacterial potency.

In silico ADME (Absorption, Distribution, Metabolism, Excretion) profiling confirms that many pyrimidine derivatives possess favorable pharmacokinetic properties.

Example

2-Thioxopyrimidine derivatives demonstrated strong binding affinity (−8.4 kcal/mol) toward S. aureus DHFR enzyme, supporting their antibacterial efficacy.



2-thioxopyrimidine

RECENT ADVANCEMENTS AND STUDIES

Recent literature highlights several pyrimidine-based compounds with potent antibacterial properties:

Hybrid Pyrimidines

Conjugation of pyrimidine with other pharmacophores such as quinolones, triazoles, or oxadiazoles results in enhanced synergistic effects.

Metal Complexes

Pyrimidine–metal complexes (e.g., Cu, Zn, Co) show increased bacterial inhibition due to improved lipophilicity and redox properties.

Nanoparticle Formulations

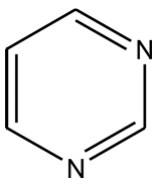
Encapsulation of pyrimidine derivatives in polymeric or lipid nanoparticles enhances solubility, bioavailability, and targeted delivery to infection sites.

Green Synthesis Approaches

Utilizing plant-derived catalysts (e.g., neem extract, lemon peel extract) offers eco-friendly, cost-effective routes to pyrimidine compounds with excellent antimicrobial activity.

RECENT ADVANCES IN ANTIMICROBIAL ACTIVITY OF PYRIMIDINE DERIVATIVES

Pyrimidine nucleus



Pyrimidine is a six-membered aromatic ring that contains two nitrogen atoms at positions 1 and 3.

It forms the basic framework for many biologically active compounds such as anticancer, antiviral, antibacterial, and antifungal agents.

Because of its ability to easily attach different functional groups, pyrimidine acts as a versatile scaffold in medicinal chemistry.

1) 1,2,4-Triazolo[1,5-a]pyrimidine Derivatives

Researcher: Abd El-Aleam et al.

They synthesized a new series of 1,2,4-triazolo[1,5-a]pyrimidine compounds and tested them for antibacterial and antifungal activity.

These derivatives showed excellent results against E. coli, K. pneumoniae, B. pumilus, and B. subtilis, as well as fungi like Candida albicans and Aspergillus niger.

Their performance was comparable to the standard antifungal drug Ketoconazole, showing potential as new antimicrobial agents.

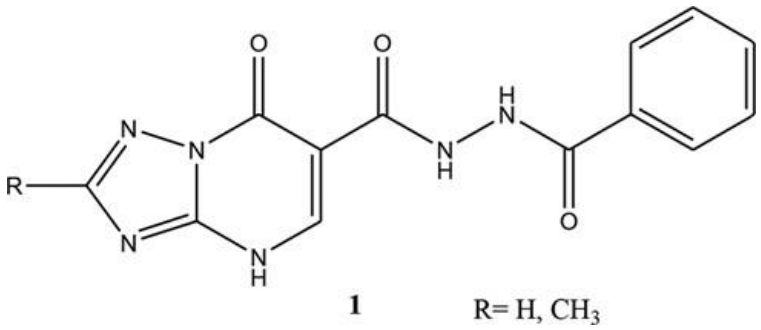


Fig. 1,2,4-Triazolo[1,5-a]pyrimidine Derivatives.

2) Thiosemicarbazide Substituted Pyrimidine Derivatives

Researcher: Alneyadi et al.

They synthesized pyrimidine compounds substituted with 2-hydroxy and 3-chloro thiosemicarbazide groups.

These compounds exhibited strong antibacterial activity against E. coli and Pseudomonas aeruginosa, with the best compound showing MIC value of 1.10 µg/mL, indicating high potency.

The results proved that thiosemicarbazide substitution improves the antimicrobial strength of pyrimidine derivatives.

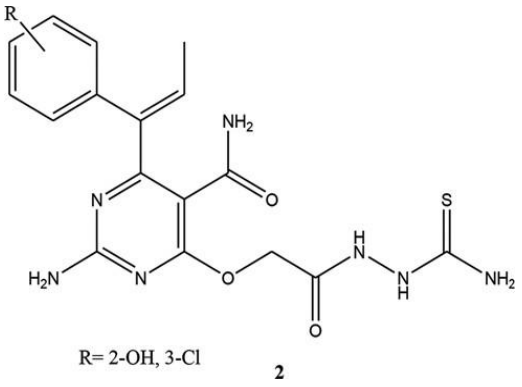


Fig: Thiosemicarbazide Substituted Pyrimidine Derivatives.

3) Benzazole Acrylonitrile-Based Pyrimidine Derivatives

Researcher: Mantapally et al.

They developed benzazole acrylonitrile-pyrimidine derivatives and studied their antibacterial potential.

When tested with amoxicillin, these compounds showed enhanced antibacterial activity. Molecular docking studies confirmed that they bind to bacterial enzyme targets, possibly inhibiting cell-wall synthesis, which explains their strong antibacterial action.

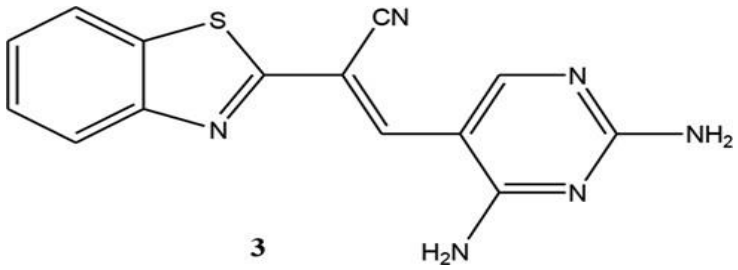


Fig. Benzazole Acrylonitrile-Based Pyrimidine Derivatives.

4) Homopiperazine-Linked Imidazo[1,2-a]pyrimidine Derivatives

Researcher: Al-Bogami et al.

They synthesized imidazo-pyrimidine derivatives linked with a homopiperazine ring under solvent-free, mechanochemical conditions using magnesium oxide catalyst.

These derivatives displayed broad-spectrum antimicrobial activity, effective against both bacteria and fungi.

The presence of the homopiperazine ring improved cell permeability and biological activity, making these compounds promising for future antimicrobial drug development.

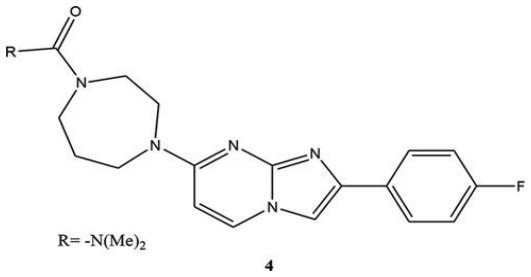


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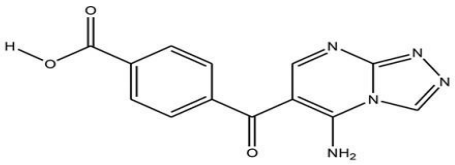
Fig. Homopiperazine-Linked Imidazo[1,2-a]pyrimidine Derivatives.

5) Triazolo[4,3-a]pyrimidines and Imidazo[1,2-a]pyrimidine Derivatives

Researcher: Mourad et al.

They prepared a new group of triazolo and imidazo fused pyrimidine derivatives and tested them for antibacterial activity against Pseudomonas aeruginosa and Staphylococcus aureus. These compounds showed strong antibacterial results, and some also displayed antifungal activity.

Their broad-spectrum nature indicates that fused triazolo and imidazo rings enhance pyrimidine's antimicrobial potential.



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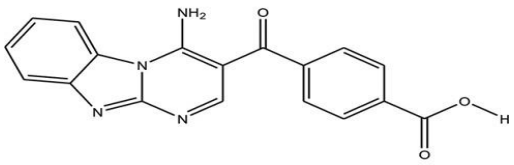

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Fig. Triazolo[4,3-a]pyrimidines and Imidazo[1,2-a]pyrimidine Derivatives.

7) Oxazole Condensed Pyrimidine Derivatives

Researcher: Dole et al.

They synthesized oxazole-fused pyrimidine derivatives using a simple and eco-friendly method.

These compounds showed promising antibacterial and antifungal activity, especially against Candida albicans and Aspergillus niger.

The presence of the oxazole ring improved biological activity, proving that ring condensation increases effectiveness.

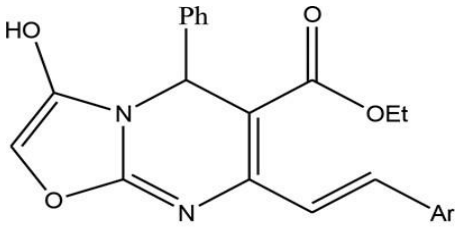

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Fig. Oxazole Condensed Pyrimidine Derivatives.

8) Fused Pyrimidine Derivatives Possessing a Trifluoromethyl Moiety

Researcher: Arun et al.

They prepared novel pyrido[2,3-d]pyrimidine compounds that included trifluoromethyl groups to boost antimicrobial activity.

These compounds exhibited excellent antibacterial performance against Pseudomonas aeruginosa, Staphylococcus aureus, and Bacillus subtilis.

The trifluoromethyl group improved cell permeability and drug-likeness, making these compounds more potent.

	R_1	R_2
b	4-ClPh	H
d	CH_3	H
j	NH_2	3-CF_3PhN=N

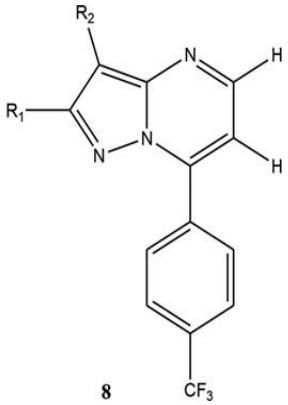

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Fig. Fused Pyrimidine Derivatives Possessing a Trifluoromethyl Moiety.

9) Thioyrimidine Derivatives

Researcher: Mohamed et al.

A new set of thioyrimidine derivatives was synthesized and screened for antifungal and antibacterial properties.

Among them, certain compounds (10 and 11) showed notable activity comparable to standard antibiotics such as Amphotericin B and Ciprofloxacin.

This revealed that sulfur-containing pyrimidines play an important role in enhancing antimicrobial efficiency.

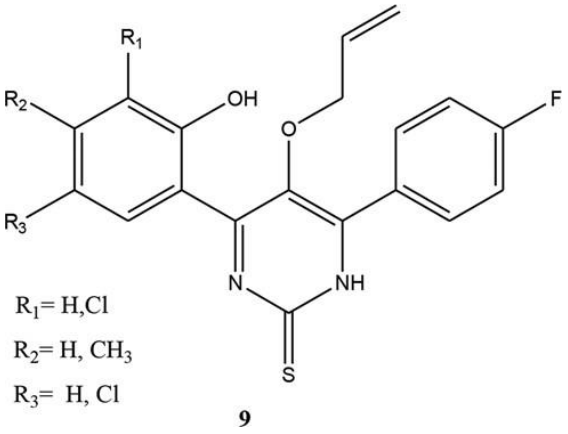

Fig. Thioyrimidine Derivatives.

10) Pyrido [2,3-d] pyrimidine Derivatives

Researcher: Andrews et al.

They developed pyrido-fused pyrimidine derivatives and compared their effects against several bacteria.

The newly synthesized compounds showed strong inhibition zones against Gram-positive and Gram-negative organisms.

This study proved that pyrido fusion increases antibacterial activity due to enhanced aromatic stability and electronic distribution.

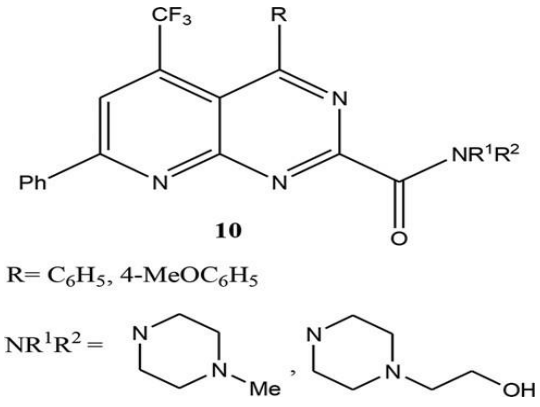

Fig: Pyrido[2,3-d]pyrimidine Derivatives.

11) Hydrazino Pyrimidine Derivative

Researcher: Khalil et al.

They prepared hydrazino-substituted pyrimidines and studied their biological potential.

These compounds displayed significant antibacterial activity against Staphylococcus aureus

and Escherichia coli.

The hydrazine group (-$NHNH_2$) helped improve binding with bacterial proteins, explaining their enhanced effect.

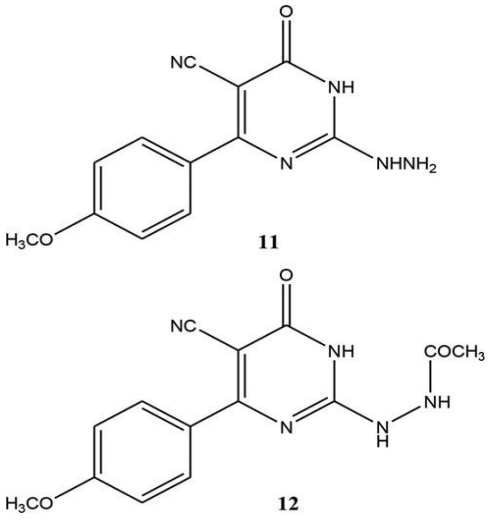

Fig: Hydrazino Pyrimidine Derivative.

Pyrimidine Derivatives with Antibacterial Activity

Derivative	Substitution/Modification	Active Against	Reported Activity
4,6-Dimethyl-2-phenylpyrimidine	Aromatic substitution	E. coli, S. aureus	Moderate antibacterial activity
2-Thiopyrimidine derivatives	Sulfur substitution at position 2	P.aeruginosa, Bacillus subtilis	Strong antibacterial activity
4,6-Diarylpyrimidine derivatives	Aryl groups at 4 and 6 positions	Staphylococcus aureus	Comparable to standard drugs
Pyrimidinone derivatives	Oxygen substitution	E. coli, Klebsiella pneumoniae	Inhibition of bacterial DNA synthesis

Advantages of Pyrimidine Scaffold

- Structural similarity to biological nucleotides
- High potential for substitution to improve potency
- Good pharmacokinetic and metabolic stability
- Effective against resistant bacterial strains

Limitations

- Some derivatives show low solubility in aqueous media
- Toxicity at higher doses in vivo
- Need for optimization to enhance selectivity and minimize resistance

Future Perspectives

- Pyrimidine continues to be a promising nucleus for antibacterial drug design. Future research should focus on:Structure-activity relationship (SAR) optimization
- Combination therapy with existing antibiotics
- Green synthesis and nano-drug delivery systems
- Evaluation against multi-drug resistant (MDR) bacterial strains

APPLICATIONS OF PYRIMIDINE DERIVATIVES

Therapeutic Applications

Antibacterial, antifungal, antiviral, anti-inflammatory, anticancer, and anti-HIV agents.

Drug Design

Serve as building blocks for next-generation antibiotics.

Diagnostic Tools

Certain fluorescent pyrimidine analogs are used in biological imaging.

Pharmaceutical Formulations

Used in developing topical antibacterial creams and oral tablets.

CONCLUSION

Pyrimidine derivatives represent a promising class of heterocyclic compounds in the field of antibacterial drug discovery. Their structural flexibility allows extensive modification to improve potency and reduce resistance. Pyrimidine derivatives have proven to be effective antibacterial agents with multiple mechanisms of action. Their structural flexibility allows the synthesis of a wide range of potent analogs. The development of pyrimidine-based drugs can significantly contribute to overcoming the global challenge of bacterial resistance. Continued research in this area may yield safer and more effective therapeutic agents in the near future.

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