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A Comprehensive Review on Indole as Antibacterial Agents

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ABSTRACT

Indole, a heterocyclic aromatic organic compound, has emerged as a significant scaffold in medicinal chemistry due to its versatile biological activities, notably its antibacterial potential. This review provides a comprehensive analysis of indole and its derivatives as antibacterial agents, emphasizing their mechanisms of action, structure–activity relationships (SAR), and potential clinical applications. Indole-based compounds have demonstrated effectiveness against a broad spectrum of bacterial strains, including multi-drug resistant (MDR) pathogens. Their modes of action include inhibition of bacterial cell wall synthesis, interference with protein and DNA synthesis, disruption of membrane integrity, and inhibition of quorum sensing. Structural modifications at various positions on the indole ring have been shown to enhance antibacterial potency and selectivity, suggesting opportunities for targeted drug design. Furthermore, the review explores the synergy of indole derivatives with existing antibiotics, addressing their role in overcoming resistance mechanisms. The findings underscore the promise of indole as a lead scaffold in the development of next-generation antibacterial agents and highlight the need for further in vivo studies and clinical evaluations to validate their therapeutic potential.

Keywords: Indole, Antibacterial activity, benzopyrrole, heterocyclic compounds

INTRODUCTION

1.1 Indole

Indoles are heterocyclic compounds formed by the fusion of a benzene ring and pyrrole ring. Basic atom of the indole is nitrogen atom which leads for its characterisation[1]. Indole is also known as benzopyrrole which contains benzenoid nucleus and has 10π electrons, two from lone pair on nitrogen and double bonds provide eight electrons which makes them aromatic in nature, the addition of indole nucleus similar to benzene ring, electrophilic substitution occurs readily on indole due to excessive π electronsdelocalisation. Indole is an important heterocyclic system that provides the skeleton to lysergic acid diethylamide [LSD]. Physically they are crystalline colourless in nature with specific odour[2].

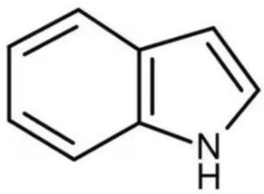


Fig (1): Structure of Indole

Indoles are organic compounds that occur naturally in various plants, animals and microorganisms. Indoles having with an aromatic heterocyclic structure that are widely used in the synthesis of pharmaceutical agents.

Most of them are from marine organisms such as fungi, bacteria, sponges, algae and mollusk.

1.2 Classification

They are classified into:simple indole alkaloids,β-carboline alkaloids, semi terpenoid indole alkaloids, bis-indole alkaloids, monoterpenoid indole alkaloid, prenylated indole and anellated indole.

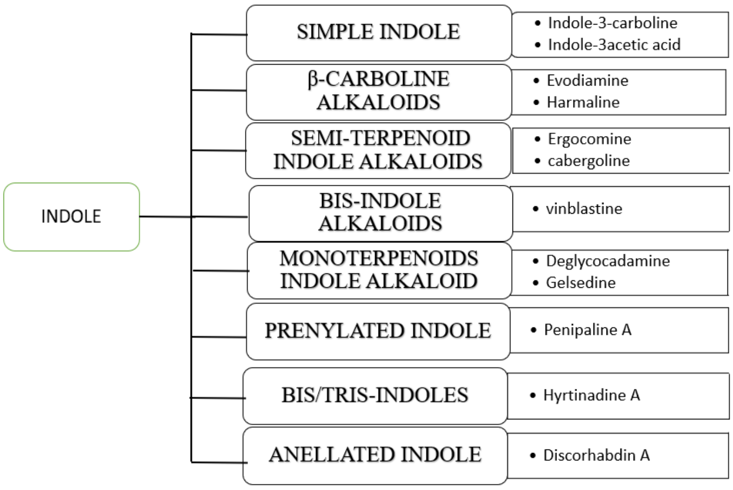
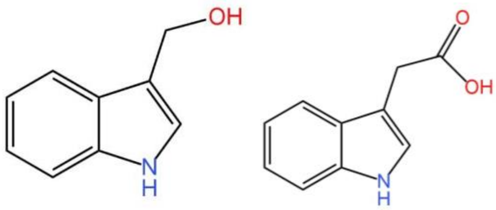


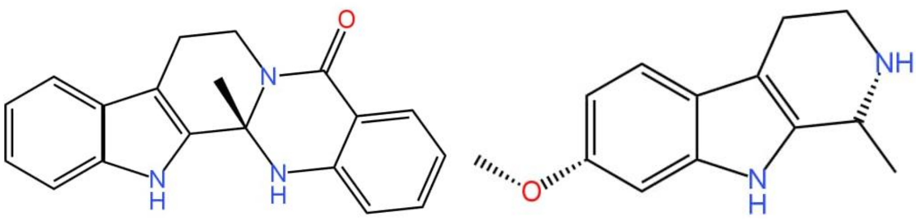
Fig (2): Classification of Indole alkaloids

1.2.1 Simple Indole: Indole is a bicyclic heterocyclic compound consisting of a benzene ring fused to a pyrrole ring,with aromatic nature,the nitrogen lone pair is involved in the aromatic system, making it weakly basic compared to other amine represented in Fig(3). These are derived from amino acids and tryptophan, which originates from the shikimate pathway in plants, bacteria, and fungi.



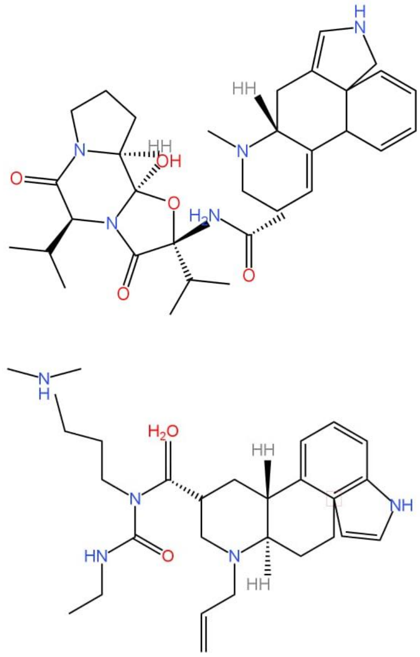
Fig(3): Structures of Indole-3-carbinol, Indole-3-acetic acid

1.2.2 β-carboline alkaloids: are tricyclic structure with an indole fused to a pyridine ring. Basic nitrogen in the pyridine ring allows for protonation,influencing bioactivity represented in Fig (4). These compounds belong to the indole alkaloid family and are structurally related to harmala alkaloids, commonly found in plants. These are derived from tryptophan, an essential amino acid.



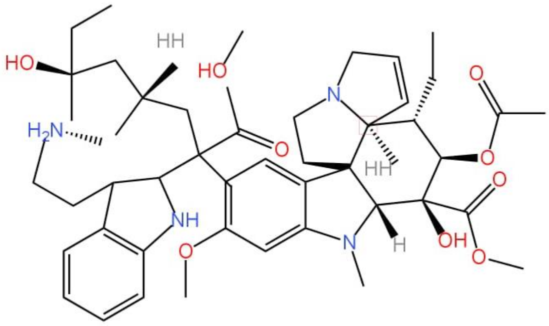
Fig(4): Structures of Evodiamine, Harmaline

1.2.3 Semi-terpenoid indole alkaloids: It contains an indole or β-carboline core fused with terpenoid-derived moieties,retains indole-like aromaticity. Functional groups vary widely, affecting solubility and reactivity Some of the examples are depicted in figure (5).These are derived from tryptophan and partially terpenoid precursors.



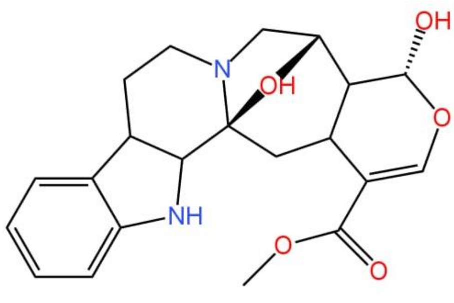
Fig(5): Structures of Ergocornine, Cabergoline

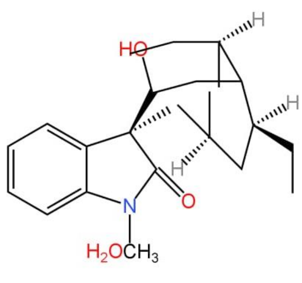
1.2.4 Bis-indole alkaloids: It contains two indole units linked through various bonds, with aromatic nature Fig (6). These are derived from tryptophan, an essential amino acid, commonly found in plants, marine organisms, fungi and bacteria.



Fig(6): Structure of Vinblastine

1.2.5 Monoterpenoid alkaloids: Monoterpene unit linked to a nitrogen-containing alkaloid fused with indole, pyridine, or piperidine rings. These can be aromatic in nature. These are derived from monoterpenes and an amino acid-derived nitrogenous components. (Fig: 7)





Fig(7.1): Deglycocadamine **Fig(7.2):** Gelsedine

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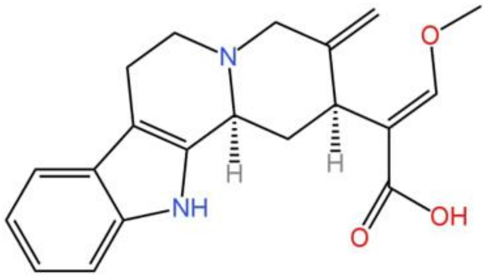
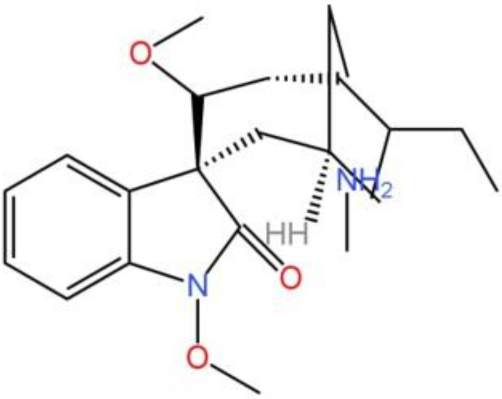
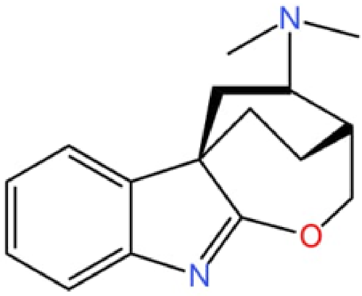
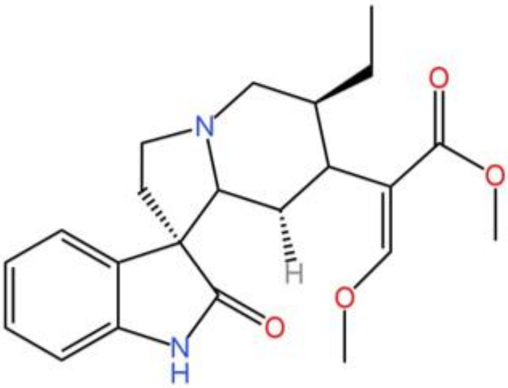


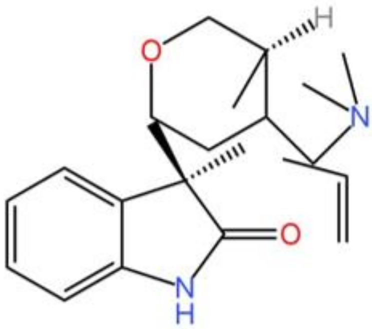
Fig(7.3): Geissoschizic acid





Fig(7.4): Humanthene **Fig(7.5):** Koumine





Fig(7.6): Corynoxine **Fig(7.7):** Gelsemine

1.2.6 Prenylated indoles: It contains an indole core with a prenyl group attached, It can be aromatic in nature depicted in Fig (8). These are derived from indole, usually from tryptophan and prenylgroups,from isoprenoid biosynthesis.

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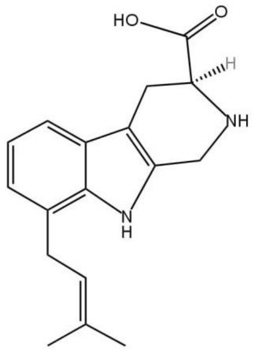

Fig (8): Penipaline A

.**1.2.7 Bis/tris-indoles:** It contains two (bis) or three (tris) indole units linked together, It can be aromatic in nature. Example is depicted in Fig (9). These are derived from tryptophan and biosynthetically derived from two or three building blocks.

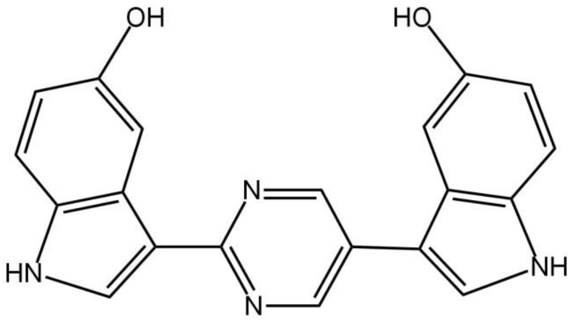

Fig (9): Hyrtinadine A

1.2.8 Anellated indoles: Indole is fused with additional rings, fusion can occur at different positions which retains indole aromaticity, influencing electrophilic substitution Fig (10). These are derived from tryptophan or indole, where the indole core is fused with non-prenylated-derived heterocyclic ring.

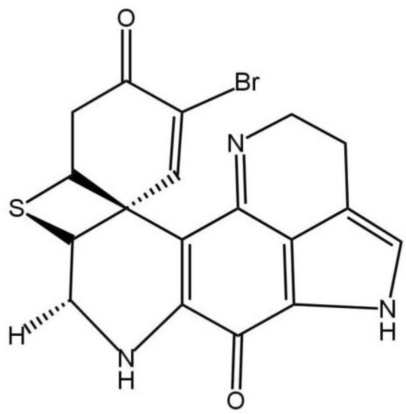

Fig (10): Discorhabdin A

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1.3 Biological activity of indole

These compounds have broad biological activity such as anxiolytic anticonvulsant antiviral anti-inflammatory antiparasitic antibacterial antiarrhythmic and anti-tumour properties most of them are from Marine organisms such as fungi bacteria sponge and algae.[3]

This also plays a beneficiary role in anti-cancer activity. Marine organisms give the novel secondary metabolites this is the research which has been intensively investigated in last few decades these indole alkaloids not only possess the intrinsic structure features but also wide range of biological activity including antimicrobial biological activities like antibacterial activity.[4]

Due to the reason researchers had interest to synthesise different scaffolds of indole for screening pharmacological activities they are different natural compounds which contain indole as parent nucleus like for example tryptophan in the degradation of tryptophan is higher plant leads to the production of indole free Acetic Acid hormone the derivatives of indole have diverse biological and clinical application.[5]

Over the decades the use of antibiotics has improved Public Health the bacteria developed drug resistance rapidly to most antibiotics due to improper use of antibiotics by Rapid emergence of drug resistance bacteria used antibiotic treatment to fight against bacterial infections benzimidazoles and indoles are natural compounds aromatic heterocyclic structures are used for pharmaceutical synthesis and modification.

Indole pharmacological active bicyclic heterocyclic is used to enhance antibacterial properties and indole nucleus is used to enhance the activity of numerous anti-tumour antimicrobial, antibacterial, antiviral and anti-HIV agent. Indole quinazoline-6,12 dione that show that it has potential antibacterial activity[6].

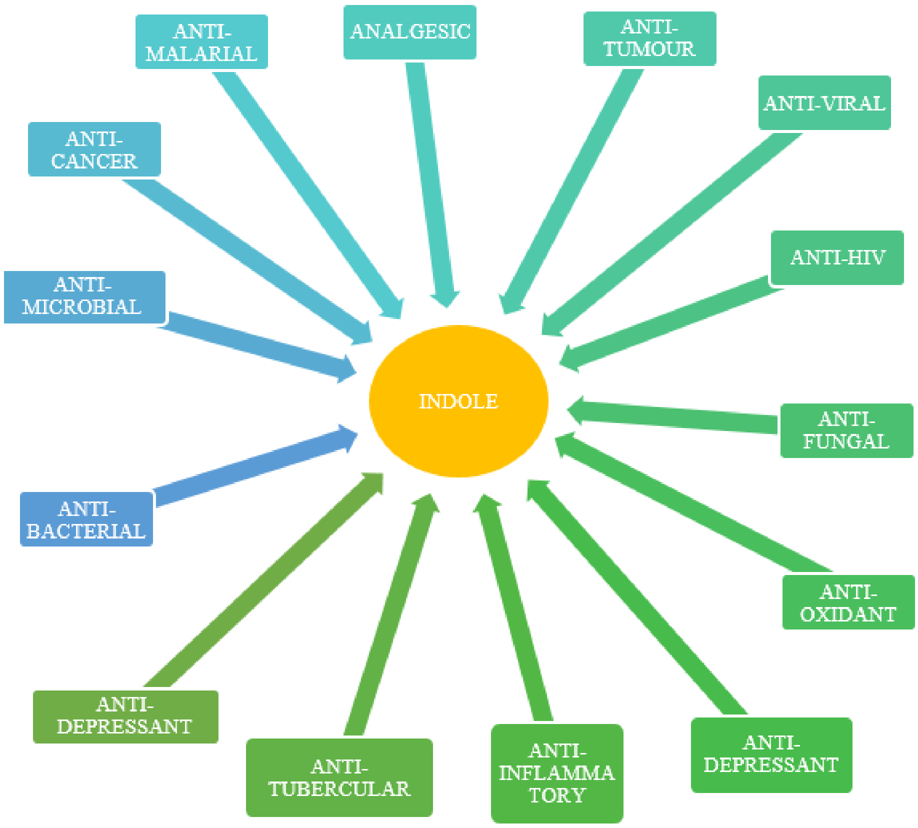

Fig 11: Broad varieties of medicinal properties for Indole

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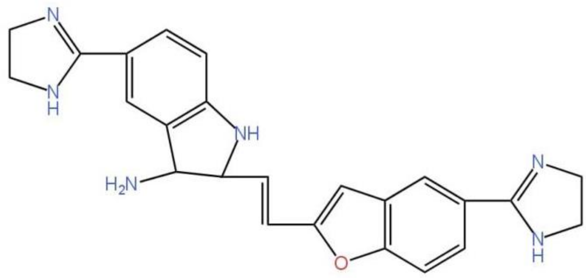
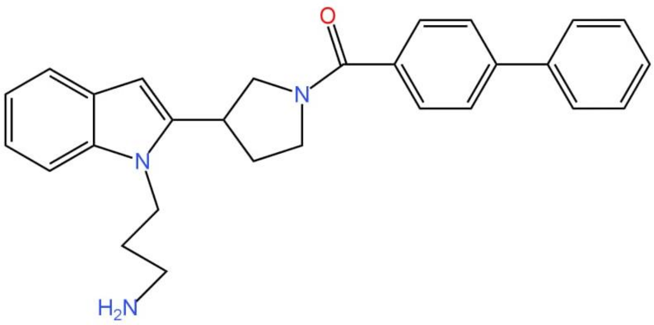
1.4 Reported indole as antibacterial agents

Yuan W., Yu Z.,et al. (2019) has reportedthe activity of benzimidazole and indole-core based derivatives have activity against various microbials,thetri-substituted benzimidazole derivatives and indole derivatives can inhibit the growth of bacterial strain such as M.tuberculosis, s.aureusandB.subtiliswhich have been reported in previous studies.[7]

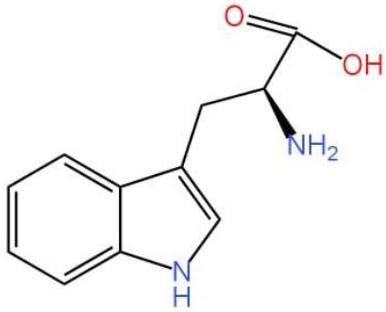


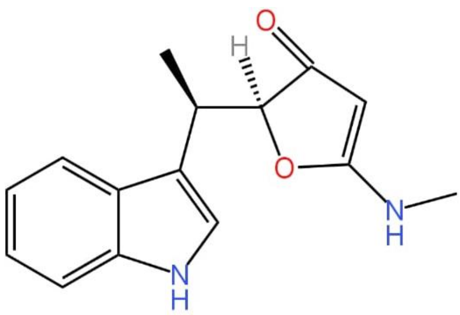
Indole derivatives 1 MIC:1.95µ/ml

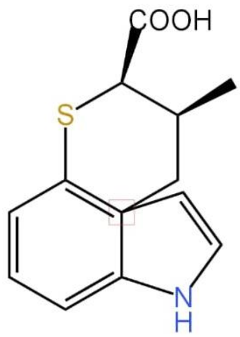


Indole derivatives 2 MIC:0.05µ/ml

Zhang, S., Qiu, X., Wang, R., Sun, L., Zhu, Z., Shan, G., & Li, Z. (2020).Studiedthe emergence of drug resistance bacteria has occurred due to excessive use of treatment of bacterial infection both in human and animals the significant damage to human health is due to antibiotic resistanceChuangxinmycin and indolmycinare natural products which are isolated from actinoplanesand streptomyces Albus from African strain, Chuangxinmycin has activity against the range of gram positivebacteria examples staphylococcus aureus.indolmycin have some resemblance to Chuangxinmycinand it was reported that they have antibacterial activity against staphylococci and pathogenic bacteria it showed that it is not active against Indolmycin.[8]







L-tryptophanMIC:2.8µ/ml Indolmycin MIC:0.5-2µg/ml Chuangcinmycin MIC:4-8µg/ml

Sneha Bince, Shreyas S. Dindorkar, Anshul Yadav. (2022) had reportedqinazoline-6,12 dione show that it has potential antibacterial activity against both gram positive andgram negativebacteria. The significance of indolebased derivatives as an antibacterial agent against a methicillin-resistance variant of *s.aureus*.The potential biological activities as potent antibacterial agent has been shown by cyclopentane heterocyclic derivatives of 1,3,4-oxadizole and 1,2,4-triazole. The compounds used in therapeutics in enhancing biological activity, including anti-convulsant, fungicidal, antitubercular, antimicrobial, anti-tumour and antibacterial agents. The in-vitro antibacterial activity of 1,2,4-triazole derivatives against drug resistance of pathogen has been investigated. 1,2,4-Triazole-3-thione-ciprofloxacin, one of the 1,2,4-triazole shows higher activity than parent ciprofloxacin, it has been shown that introduction of an indole moiety to 1,3,4-oxidazole and 1,2,4-triazole compound increase antibacterial activity. green approach for synthesizing indole modified derivatives of 1,3,4-oxidazole and 1,2,4-triazole with several substituent and examined their potential activity. Antibacterial activity was evaluated against s.aureus and Escherichia coli,,the synthesis of indole-2-carboxylic acid and it was investigated its antimicrobial activity against five pathogenic strains. The theoretical methods for chemical reactivity and biological activity examined for antibacterial drugs.[9]

According to Lee et al., Indole derivatives are prominent for both prokaryotic and eukaryotic communities Indole belongs to a group of phytochemicals, which are naturally occurring plant compounds and related to micro-organisms prevention, indole is a type of aromatic compound composed of benzene ring fused with a pyrrole ring. Over eighty five species of gram positive and gram negative bacteria produce indole with many functions in bacterial signalling. indole acts as a natural proton ionophore because of its primary activity to inhibition the cell division in the biological process, indole plays a crucial role in several bacterial phenotypes and eukaryotic immunities, indole has been reported to modify biofilm formation and persister formation in Escherichia coli.[18]

Monte et al. Studied and evaluated the antibacterial activities of four phytochemicals, namely hydroxycoumarin, indole-3-carbinol, salicylic acid and saponin against Escherichia coli and staphylococcus aureus, either as planktonic cells or as biofilms Additionally,the four phytochemicals were used as combination therapy with three antibiotics to evaluate any synergistic impact.[17]

In the same way Lee.et.al, studied thirty six different indole derivatives with the aim of certaining new compounds which could prevent bacterial persister and biofilm formation by gram negative Escherichia coli and gram positive s.aureusfour halogenated indoles (5-iodoindole ,4-fluroindole,7-chloroindole and 7-bromoindole).[10]

Kemp et al.confirmed the current investigation on the signalling molecule indole as a target for Quorum-sensing inhibition (QSI)and the application of indole derivatives called indole 3-carboxaldehdye (ICA).[16]

Ahmed T. Sulaiman and Susan W. Sarsam. (2020) has reported thatindole is a heterocyclic compound and is formed naturally in various form and is widely distributed in the biological system several indolebased biomolecules occurs with different effects such as serotonin (5-hydroxytryptamine) a neurotransmitter, melatonin the sleep hormone, tryptamine and related amino acid tryptophan.Indole also based on natural alkaloids, exhibiting important pharmacological properties that have been successfully isolated among them vinblastine and vincristine. Indole propionic acid (IPA) is a plant auxin that plays a crucial role in various developmental processes throughout the growth cycle of the plant in human,IPA is detected in serum and cerebrospinal fluid.[11]

Jasiewicz, B.; Babijczuk, K.; Warżajtis, B.; Rychlewska, U.; Starzyk, J.; Cofta, G.; Mrówczyńska, L. (2023) reported synthetic indoles are promising therapeutic agents and exhibiting antiviral, antibacterial, anti-inflammatory and anti-depressantactivities.Many of them have been approved as drugs such as indomethacin, pindolol,indapamide. The indole structure is also present in the indole -3-carbinol,an important agent, the indole moiety is widely distributed in nature.[12]

Shah, M., Kumar, A., Singh, A. K., Singh, H., Narasimhan, B., & Kumar, P. (2023)Discoverd antibacterial agents have played a crucial role in extending human lifespan,but irrational use of these agents led to the rise of bacterialresistance.Resistance,is associated with overuse or misuse of antibacterial drugs in humans,animal farming and agriculture and is an increasingly, severe worldwide problem. Indole is a key scaffold in drug design,commonly found in many pharmaceutically relevant compounds.An indole nucleus is present in compounds involved in research aimed and evaluating new products that posses beneficial biological properties such as anti-fungal,anti-tubercular,anti-inflammatory,anti-psychotic,anti-cancer,anti-microbial,anti-oxidant,anti-convulsant,anti-leishmanial and anti-depressant activities.[13]

Liu, H.-B., Lauro, G., O'Connor, R. D., Lohith, K., Kelly, M., Colin, P., Bifulco, G., & Bewley, C. A. (2017)has summarized the two indole alkaloids have been successfully isolated from a deep-water specimen of Topsentiasptulongicin is the first example of a natural product containing a bis-indolemethane linked to an imidazole group.[14]

Sue, K., Cadelis, M.M., Rouvier, F., Bourguet-Kondracki, M.-L., Brunel, J.M., & Copp, B.R. (2024) Discovered activity of 5-bromo indole 3 glyoxamido spermine exhibited intrinsic anti-microbial activity towards Gram positive bacteria and Fungi and increased the action of doxycycline towards the gram negative bacteria such as Pseudomonas aeruginisa and over up bacterial membrane.,The compound class had red blood cells properties that promoted the explanation of analogous set of indole-3-acetamido polyamine conjugates, indole-3-acetamido polyamines had exhibited hemolytic properties.[15]

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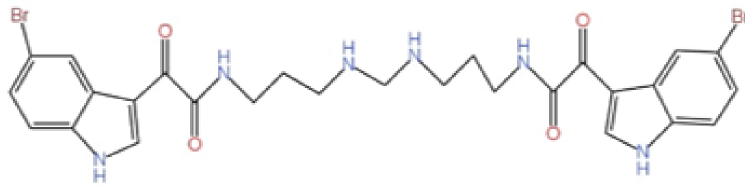
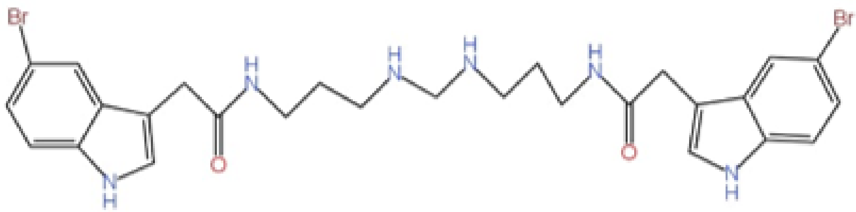
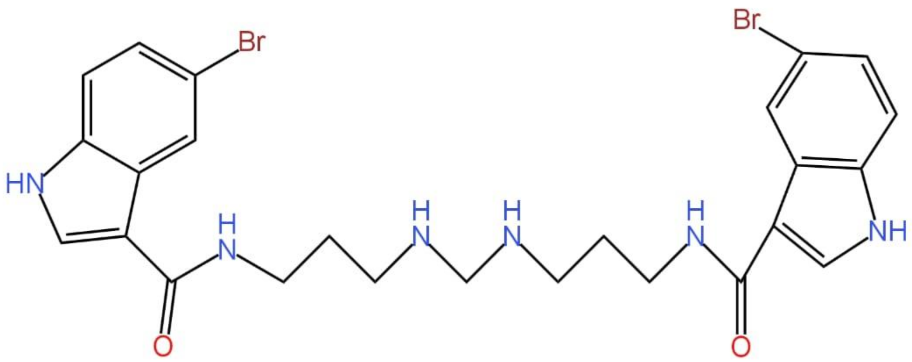


5-bromo-substituted indole 3glyoxylamido



Indole 3-acetamido derivatives



Indole 3-carboxamido derivatives

CONCLUSION:

The structural versatility and biological richness of indole and its derivatives underscore their immense potential as antibacterial agents in the fight against drug-resistant pathogens. As evidenced by both natural and synthetic indole-based compounds, these heterocycles exhibit a broad spectrum of antibacterial activities through diverse mechanisms, including the inhibition of biofilm formation, disruption of bacterial cell membranes, and interference with essential metabolic pathways. The wide occurrence of indole alkaloids in marine and terrestrial organisms, coupled with advancements in chemical synthesis, has enabled the development of novel analogues with improved potency and specificity. Notably, the incorporation of indole moieties into other pharmacophores has enhanced the antibacterial efficacy of several therapeutic agents, offering promising leads for next-generation antibiotics. Despite significant progress, further research is needed to optimize pharmacokinetic properties, reduce toxicity, and validate in vivo efficacy. Continued exploration of indole scaffolds guided by structure–activity relationship studies and green synthetic approaches holds promise for the development of effective and sustainable antibacterial therapies to counter the global threat of antimicrobial resistance.

ACKNOWLEDGEMENTS:

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ABBREVATIONS:

QSI: Quorum sensing inhibition

ICA: Indole-3-carboxaldehyde

IPA: Indole-propionic acid

LSD: Lysergic acid diethylamide

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