

Synthesis and Antimicrobial Evaluation of Substituted Indole Propenones Derived from Anthracenones

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Abstract

A library of structurally diverse indole propenone derivatives was prepared from appropriately substituted anthracenone precursors using a simple and efficient synthetic methodology. The structures of the synthesized compounds were established on the basis of their ^1H NMR spectral data and GC-MS analysis, confirming the formation of the desired products. The prepared derivatives were further subjected to *in vitro* antimicrobial screening against selected bacterial and fungal microorganisms. The results revealed differences in antimicrobial response among the synthesized compounds, indicating that the electronic and structural characteristics of the substituents can affect their biological performance. Derivatives containing halogen and other electron-withdrawing groups demonstrated notable activity against certain tested microorganisms. Overall, the study presents substituted indole propenones as promising heterocyclic frameworks for antimicrobial investigation and provides a convenient synthetic strategy for generating structurally modified analogues for future studies.

Keywords: Indole propenones, Anthracenones, Heterocyclic synthesis, ^1H NMR spectroscopy, GC-MS, Antimicrobial activity; Organic transformation

Introduction

Indole, systematically designated as 1H-benzo[b]pyrrole, is an aromatic bicyclic heterocycle consisting of a six-membered benzene ring fused to a five-membered pyrrole ring. Owing to its distinctive electronic structure and versatile reaction chemistry, indole represents an important structural motif in organic synthesis and medicinal chemistry [1–3]. The compound was first identified in the nineteenth century during investigations of indigo by Adolf von Baeyer. Subsequent studies involving the transformation of indigo into isatin and its successive reduction to oxindole ultimately contributed to the preparation and structural elucidation of indole. Although indole can be obtained through synthetic methods, the indole nucleus and its derivatives occur widely in nature. They have been identified in numerous plant species and families, including *Apocynaceae* and *Rubiaceae*, as well as in *Catharanthus roseus* and *Rauvolfia serpentina*. Indole-containing metabolites have also been reported from marine organisms such as *Aplysina cavernicola* and from microorganisms including *Shewanella algae* [4–6]. From a biosynthetic perspective, indole is closely associated with the shikimate pathway through its role in the formation of L-tryptophan, an aromatic amino acid that serves as a precursor for diverse secondary metabolites in plants, fungi, and microorganisms [7,8].

In humans, numerous naturally occurring indole derivatives are involved in metabolic and physiological processes and perform important biological functions. Serotonin (5-hydroxytryptamine) is an indole-derived monoamine neurotransmitter distributed throughout the central and peripheral nervous systems, blood, and cardiovascular tissues. It participates in several physiological processes, including regulation of smooth-muscle tone, vascular function, memory, mood, and sleep. Serotonergic signaling is mediated through multiple receptor subtypes, and alterations in serotonin metabolism and neurotransmission have been associated with several neurological and neurodegenerative disorders, including Alzheimer's and Parkinson's diseases. Consequently, modulation of serotonergic receptors and enzymes involved in serotonin metabolism, particularly monoamine oxidase (MAO), has been investigated as a potential therapeutic strategy [8–10].

Melatonin, another biologically important indole derivative, is synthesized from serotonin and plays a central role in the regulation of circadian rhythms, sleep–wake cycles, and photoperiodic responses. Because of these physiological properties, melatonin and related compounds have

been extensively investigated for the management of sleep and circadian-rhythm disturbances [8–10]. β -Carboline alkaloids, which can be biosynthetically derived from L-tryptophan, constitute another important class of indole-related natural products. Their structural diversity, arising from variations in substitution patterns and ring fusion, contributes to a broad range of pharmacological activities, particularly within the central nervous system [7,8,11].

Among clinically important indole-containing natural products, vincristine and vinblastine, obtained from *Catharanthus roseus*, are prominent anticancer agents. These alkaloids exert their cytotoxic effects primarily by binding to tubulin and interfering with microtubule dynamics, thereby disrupting mitotic spindle formation and arresting dividing cells during mitosis. Vincristine is widely used in the treatment of acute lymphoblastic leukemia and several other malignancies, whereas vinblastine has applications in the treatment of Hodgkin lymphoma and other cancers. The diverse biological activities of these naturally occurring indole derivatives demonstrate the considerable pharmacological importance of the indole framework and its derivatives [12–14].

In the present study, a series of substituted indole propenone derivatives was synthesized and investigated for their antimicrobial potential. The indole propenone framework was selected as the principal structural motif because of its chemical versatility and reported biological significance. The synthesized derivatives were evaluated against selected microbial strains to examine the influence of structural substitution on antimicrobial activity. The findings may provide useful insights into the development of structurally modified indole-based compounds with potential applications in future antimicrobial drug discovery.

Material and Methods

All chemicals used in the experiments were of analytical reagent (AR) grade. Analytical thin-layer chromatography (TLC) was carried out on Merck pre-coated silica gel 60 F254 aluminium sheets. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded in CDCl_3 on a 500 MHz spectrometer with tetramethylsilane (TMS) serving as the internal standard.

Characterization Techniques

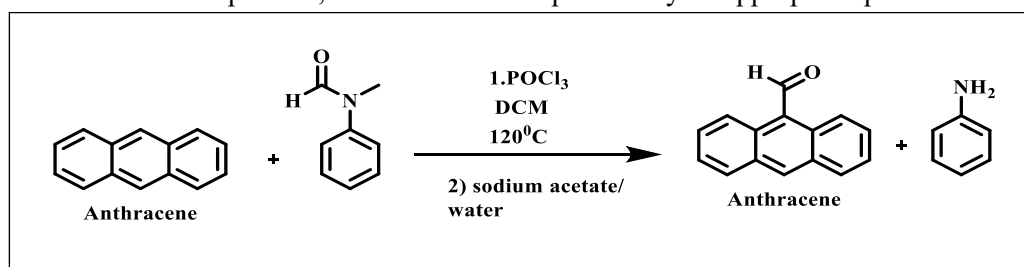
The structure of synthesized compounds was determined by chemical properties elemental analysis and spectral data. ^1H -NMR spectra were recorded on Bruker Avance Neo 500 MHz spectrometer using CDCl_3 solvent and TMS as internal standards at SAIF, Punjab University, Chandigarh (India). Chemical shifts are expressed in ppm. Mass spectrums were recorded on Thermo Scientific TSQ 8000 Gas Chromatogram

Experimental

Synthesis of Anthracenones

The Vilsmeier–Haack reaction was employed for the functionalization of the activated aromatic ring using phosphorus oxychloride (POCl_3) in the presence of a formamide reagent such as dimethylformamide (DMF). Under the reaction conditions, the formamide and POCl_3 generate a reactive iminium electrophile that undergoes electrophilic substitution on the activated aromatic substrate. Subsequent hydrolysis during work-up affords the corresponding aryl aldehyde or ketone. After completion of the reaction, the reaction mixture was subjected to an aqueous work-up, and the aniline side product was removed by washing the organic layer with dilute hydrochloric acid [15].

Aniline was converted into water-soluble anilinium chloride and transferred to the aqueous phase, whereas the desired organic product remained in the organic layer. The organic phase was subsequently washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product, which was further purified by an appropriate purification method.

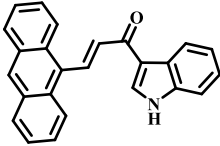
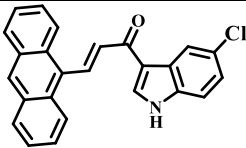
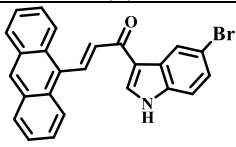


Scheme 1. Synthesis of Anthracenones

General Reaction for synthesis of Substituted Indole Propenones

The reaction between 10-anthraldehyde and 3-acetylindole will be carried out in presence of KOH in ethanol for 14 h. and substituted indole propanone will be formed. The progress of reaction will be encountered by TLC.

Table 1. Structural Analysis

Sr. No	Structure of Products	Structural analysis by ^1H NMR and GCMS
1	 (a)	^1H NMR (500MHz, CDCl_3): δ 12.0 (s, 1H), 8.69-8.32 (m, 16 H) GCMS: Cal m/z: 347.42 Found m/z: 347.40
2	 (b)	^1H NMR(500MHz, CDCl_3): δ 12.02 (s, 1H), 8.71-8.35 (m, 15H) GCMS: Cal m/z: 381.86 Found m/z: 381.80
3	 (c)	^1H NMR(500MHz, CDCl_3): δ 12.09 (s, 1H), 8.70-8.39 (m, 15H) GCMS: Cal m/z: 426.31 Found m/z: 426.28

Biological Investigation of Substituted Indole Propenones

Antimicrobial Properties

The synthesized substituted indole propenone derivatives were screened for their antimicrobial activity against selected bacterial and fungal strains using an in vitro agar diffusion assay. The compounds were evaluated at a predetermined concentration, and antimicrobial efficacy was determined by measuring the diameter of the inhibition zones in millimetres. The derivatives displayed variable antimicrobial responses across the tested microorganisms, indicating that the nature and position of substituents on the indole propenone scaffold influence their biological activity. Among the synthesized compounds, halogen-substituted derivatives exhibited comparatively higher inhibitory effects against selected microbial strains. These findings demonstrate that structural modification of the indole propenone framework can significantly affect its antimicrobial properties [16].

Compound	Substituent	<i>S. aureus</i> (mm)	<i>E. coli</i> (mm)	Activity
a	H	12	10	Moderate
b	4-Cl	16	14	Good
c	4-Br	18	16	Good

Conclusion

The synthesized substituted indole propenones (3a–c) represent a structurally relevant class of compounds with promising antimicrobial potential. Incorporation of chloro and bromo substituents on the aromatic ring produced noticeable changes in the antimicrobial response, indicating the influence of halogen substitution on biological activity. The observed results suggest that appropriate modification of the indole propenone scaffold can enhance its interaction with microbial targets and contribute to improved inhibitory effects. Overall, these findings provide useful preliminary evidence for the antimicrobial potential of substituted indole propenones and may serve as a basis for further structural optimization and development of indole-based compounds for future medicinal chemistry studies.

Conflict of Interest: Authors have declared that no competing interests exist.

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