

## REVIEW ARTICLE

# Indole/isatin-containing hybrids as potential antibacterial agents

Feng Song<sup>1,2</sup>  | Zhenghua Li<sup>1</sup> | Yunqiang Bian<sup>1</sup> | Xiankai Huo<sup>3</sup> | Junman Fang<sup>2</sup> | Linlin Shao<sup>2</sup> | Meng Zhou<sup>2</sup>

<sup>1</sup>Shandong Key Laboratory of Biophysics, Institute of Biophysics, Dezhou University, Dezhou, Shandong, China

<sup>2</sup>School of Life Sciences, Dezhou University, Dezhou, Shandong, China

<sup>3</sup>Department of Medical Imaging, Dezhou People's Hospital, Dezhou, Shandong, China

**Correspondence**

Feng Song, Shandong Key Laboratory of Biophysics, Institute of Biophysics, Dezhou University, Dezhou, 253023 Shandong, China. Email: sfeng-08@163.com

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**Abstract**

The emergence and worldwide spread of drug-resistant bacteria have already posed a serious threat to human life, creating the urgent need to develop potent and novel antibacterial drug candidates with high efficacy. Indole and isatin (indole-2,3-dione) present a wide structural and mechanistic diversity, so their derivatives possess various pharmacological properties and occupy a salient place in the development of new drugs. Indole/isatin-containing hybrids, which demonstrate a promising activity against a panel of clinically important Gram-positive and Gram-negative bacteria, are privileged scaffolds for the discovery of novel antibacterial candidates. This review, covering articles published between January 2015 and May 2020, focuses on the development and structure–activity relationship (SAR) of indole/isatin-containing hybrids with potential application for fighting bacterial infections, to facilitate further rational design of novel drug candidates.

**KEYWORDS**

antibacterial, drug resistance, hybrid compounds, indole, isatin, structure–activity relationship

## 1 | INTRODUCTION

Gram-positive and Gram-negative pathogens are the most common infections responsible for various diseases such as lower respiratory tract infections, urinary tract infections, intra-abdominal infections, and skin and soft tissue infections.<sup>[1,2]</sup> Antibiotics play indispensable roles in the treatment of bacterial infections, but the frequent and inappropriate application of antibiotics contributes to the fast spread of antibiotic resistance, which results in the reduced effectiveness of empiric antimicrobial treatment.<sup>[3–6]</sup> Antibiotic resistance has been considered as an alarming concern in Europe (59%), followed by Southeast Asia (18%), Western Pacific (12%), the Americas (6%), and Africa (6%), and over 700,000 deaths occur annually worldwide due to antibiotic resistance.<sup>[7,8]</sup> Thus, drug-resistant bacteria have already posed a serious threat to human health, and it is imperative to deliver potent and novel antibacterial drug candidates.

Indole and isatin (indole-2,3-dione; Figure 1), which present a wide structural and mechanistic diversity, could bind to multiple enzymes and receptors with high affinity and play roles in various biological processes

like cellular growth, motility, nutrient acquisition, stress response, biofilm formation, and defense. Consequently, indole/isatin derivatives possess various pharmacological properties such as antibacterial,<sup>[9,10]</sup> anticancer,<sup>[11,12]</sup> antifungal,<sup>[13,14]</sup> antimalarial,<sup>[15,16]</sup> antiviral,<sup>[17,18]</sup> and antitubercular<sup>[19,20]</sup> activities. Therefore, indole/isatin derivatives are privileged scaffolds for the development of novel drugs. Among them, indole/indole-containing hybrids are endowed with potential activity against diverse clinically important Gram-positive (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Enterococcus faecium*, and *Enterococcus faecalis*) and Gram-negative (*Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*) bacteria, including drug-resistant pathogens such as methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *S. epidermidis* (MRSE), vancomycin-resistant *S. aureus* (VRSA), vancomycin-resistant *E. faecalis* (VRE), and extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Enterobacter*, demonstrating their potential as useful tools for the development of novel antibacterial agents that are active against both drug-sensitive and -resistant pathogens.<sup>[21,22]</sup>

This review covers the recent advances of indole/isatin-containing hybrids as potential antibacterial agents, covering articles published