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Synthesis, Pharmacological Activities, Structure-Activity Relationship of Benzimidazole-Indole Conjugates: A Review

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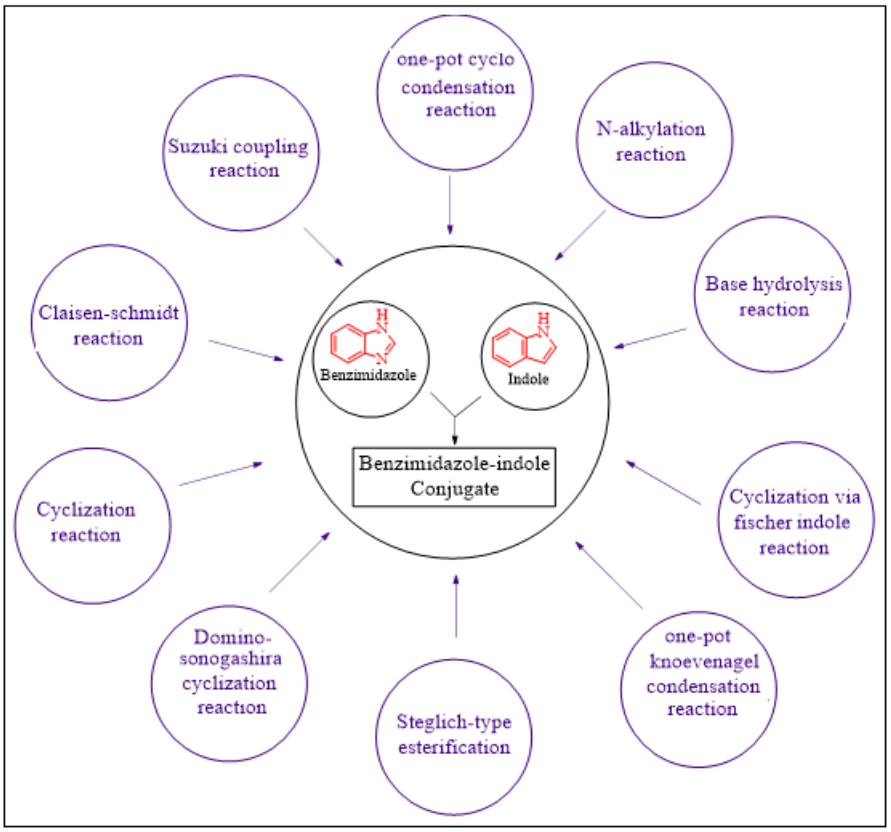
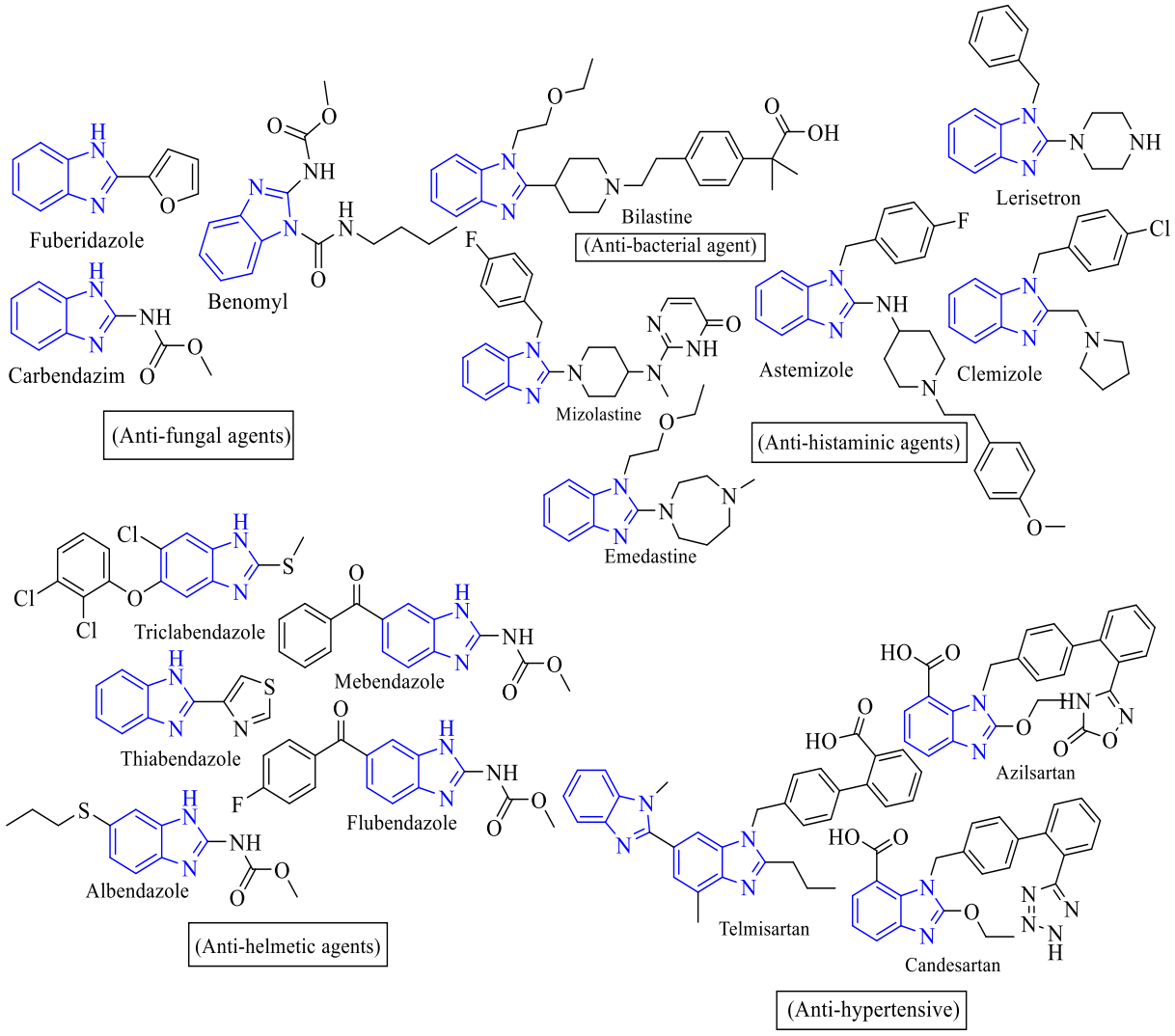
Abstract: ***Benzimidazole–indole conjugates have emerged as an important class of heterocyclic hybrids exhibiting remarkable structural diversity and potent biological activities. The combination of two privileged pharmacophores-benzimidazole and indole- within a single molecular framework enhances their physicochemical properties, target selectivity, and therapeutic potential. Numerous synthetic methodologies have been explored to obtain these conjugates efficiently, including one-pot cyclo-condensation, Suzuki–Miyaura coupling, N-alkylation, base hydrolysis, Claisen–Schmidt condensation, cyclization, domino Sonogashira cyclization, Steglich-type esterification, Knoevenagel condensation, and Fischer indole synthesis. These strategies provide access to a wide variety of benzimidazole–indole scaffolds with diverse substitution patterns under mild and environmentally compatible conditions. Structure–activity relationship (SAR) studies reveal that substitutions on the benzimidazole N^1 position and the indole C^3 or C^5 positions significantly influence anticancer, antimicrobial, antitubercular, and diuretic activities. The conjugation of electron-withdrawing or lipophilic substituents generally enhances biological potency by improving membrane permeability and receptor binding affinity. This review comprehensively summarizes the synthetic strategies, mechanistic pathways, and pharmacological profiles of benzimidazole–indole conjugates, emphasizing their potential as lead compound for novel medicinal product development.***

Keywords: Benzimidazole, Benzimidazole-indole conjugate, indole core-compounds, synthetic approach, structure activity relationship (SAR), biological activities

1. Introduction



Benzimidazole was a fused aromatic heterocyclic compound consisting benzene ring condensed with an imidazole nucleus following sp^2 hybridization (mol Formula, wt., and m.p. were $C_7H_6N_2$, 118.14 g/mol & 170–172 °C)[1]. In 1872, A German chemist, Hoebrecker, prepared benzimidazole by reduction of 2-nitroaniline using stannous chloride. Later, several methods of synthesis were developed, including condensation of o-phenylenediamine with carboxylic acids, aldehydes, or their derivatives[2]. The isomeric form was 1H-benzimidazole, shows tautomerism. Proton transfer between the N atom of the imidazole ring leads to 1H- and 3H-tautomers, where the 1H form is more stable & predominant. Benzimidazole was a white to light yellow crystalline solid which freely soluble in polar organic solvents like ethanol, methanol, dimethylformamide, and chloroform but partially soluble in water[3]. The log P value of benzimidazole was 1.44, which shows moderate lipophilicity, which helps it cross biological membranes while still maintaining aqueous solubility and pKa value was 5.55 makes weak base, whereas the pKb value was 8.45, so it acts as both HBD & HBA[4]. Currently, some commercially available medications having benzimidazole nucleus shown in (Fig. **1**)[5]. It undergoes electrophilic substitution due to presence of 5th and 2nd position of the benzene and imidazole ring & reactions with alkyl halides or acyl halides gives *N*-alkyl or *N*-acyl benzimidazoles substitutions. It undergoes nitration, sulfonation, halogenation, and metal-catalyzed cross-coupling reactions, providing hydrogen bonding, metal coordination, and π–π stacking with reactants and make stable derivatives[6]. A notable reaction was the oxidative coupling of o-phenylenediamine with formic acid or aldehydes, producing benzimidazole as a central scaffold[7]. Benzimidazole was act as the anthelmintic drugs[8], anti-fungal activity[9], proton pump inhibitors[10], anti-cancer agents[11], antiviral activity[12], antibacterial activity[13], antihistaminic activity[14], antihypertensive agents[15].



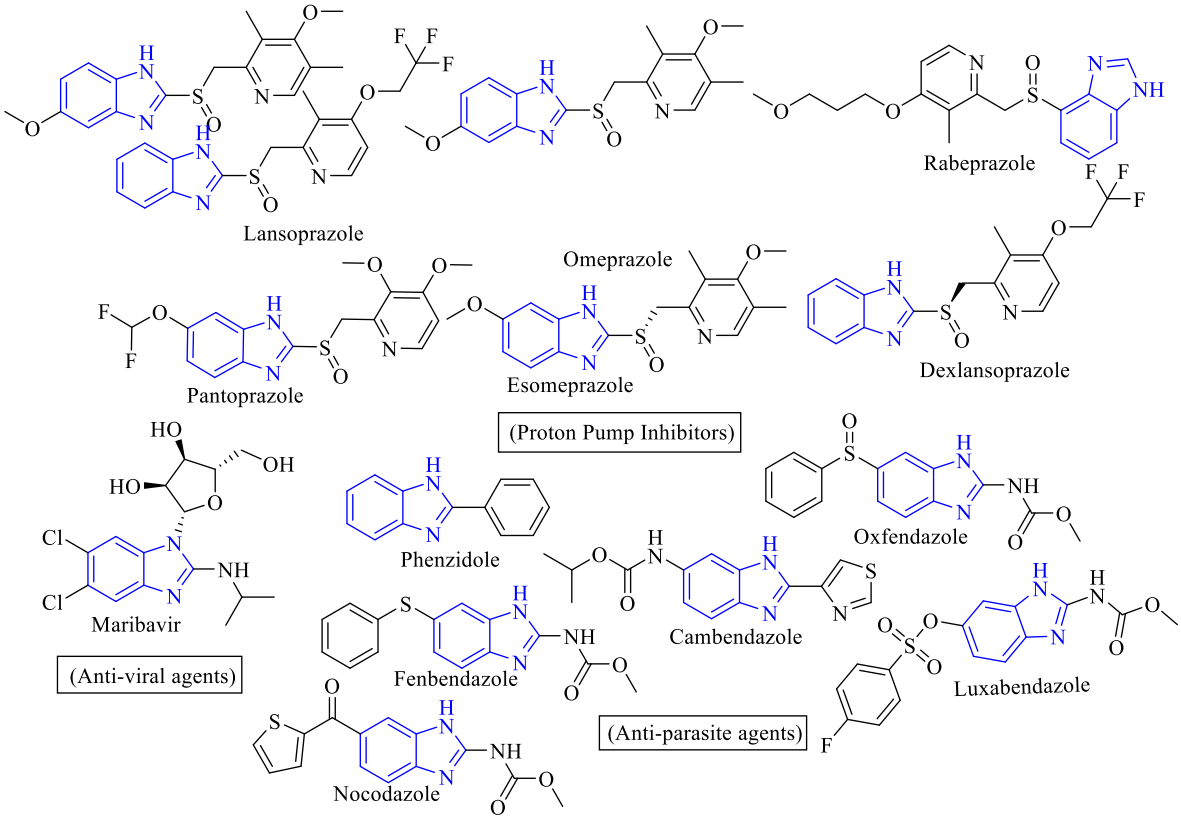


Figure 1: Marketed medications and their pharmacological activity that contain benzimidazole moiety in their molecular structure

Indole consists of a bicyclic aromatic heterocyclic framework in which a benzene ring is fused with a five-membered pyrrole ring (imidazole-like) ring, with the mol. formula C_8H_7N, molar mass 117.16 g·mol^{-1} and a melting point around 52–54 °C [15]. Discovered during 19th-century dye chemistry when Adolf von Baeyer converted indigo into indole, the scaffold quickly became recognized as a privileged nucleus in natural products and drug design [16]. Structurally the indolic nitrogen (N-1) contributes its lone pair to the aromatic 10-π electron system, so indole behaves like pyrrole (aromatic, not a classical Lewis base) and is markedly less basic than aliphatic amines; protonation under strong acidic conditions occurs preferentially at C-3 rather than N-1, and the conjugate-acid pK_a values reported in aqueous media are very low (protonated indole pKa ≈ −2 to −3), while N–H acidity in aprotic solvents (DMSO) corresponds to very high pKa values (~21), meaning deprotonation requires strong bases [17]. Indole is a white to pale yellow crystalline solid with a characteristic odor (at trace levels floral/jasmine; at high concentration fecal), soluble in common organic solvents (ethanol, methanol, chloroform, DMSO) and moderately lipophilic (experimental logP ≈ 2.1–2.3), properties that favour membrane permeability while retaining some aqueous solubility [18]. Chemically, indole undergoes electrophilic substitution predominantly at the C-3 position (the most reactive site) and participates in N-alkylation/acylation under forced conditions. It can be nitrated, halogenated, and engaged in metal-catalyzed cross-couplings to furnish richly substituted derivatives, and strongly basic or strongly acidic conditions can lead to polymerization or degradation [19]. Classical and modern synthetic routes to build the indole core include the Fischer indole synthesis [20], Leimgruber–Batcho [21], Bartoli [22], Reissert [23], Madelung [24], Cadogan–Sundberg [25], and recent transition-metal and aryne-based methods is so accessible to medicinal chemists [26].

Currently, some commercially available medications having indole nucleus shown in (Fig. **2**) [27]. Biologically, indole is ubiquitous has the core of tryptophan, the neurotransmitter serotonin and melatonin, and numerous plant and microbial alkaloids, this natural prevalence underpins the scaffold's presence in many marketed drugs (examples include indomethacin- an NSAID, sumatriptan/almotriptan-antimigraine 5-HT_1 agonists, ondansetron — a 5-HT_3 antagonist, and a broad catalogue of kinase inhibitors, anti-infectives and CNS agents bearing indole or indolyl substituents)[28]. Owing to its planarity, π–stacking ability, H-bonding at N-1, and tunable substitution at C-2 & C-3 and the benzene core structure, indole remains an extremely versatile pharmacophore that supports diverse biological activities and easy derivatization for optimization of potency, selectivity, and ADME properties [29].

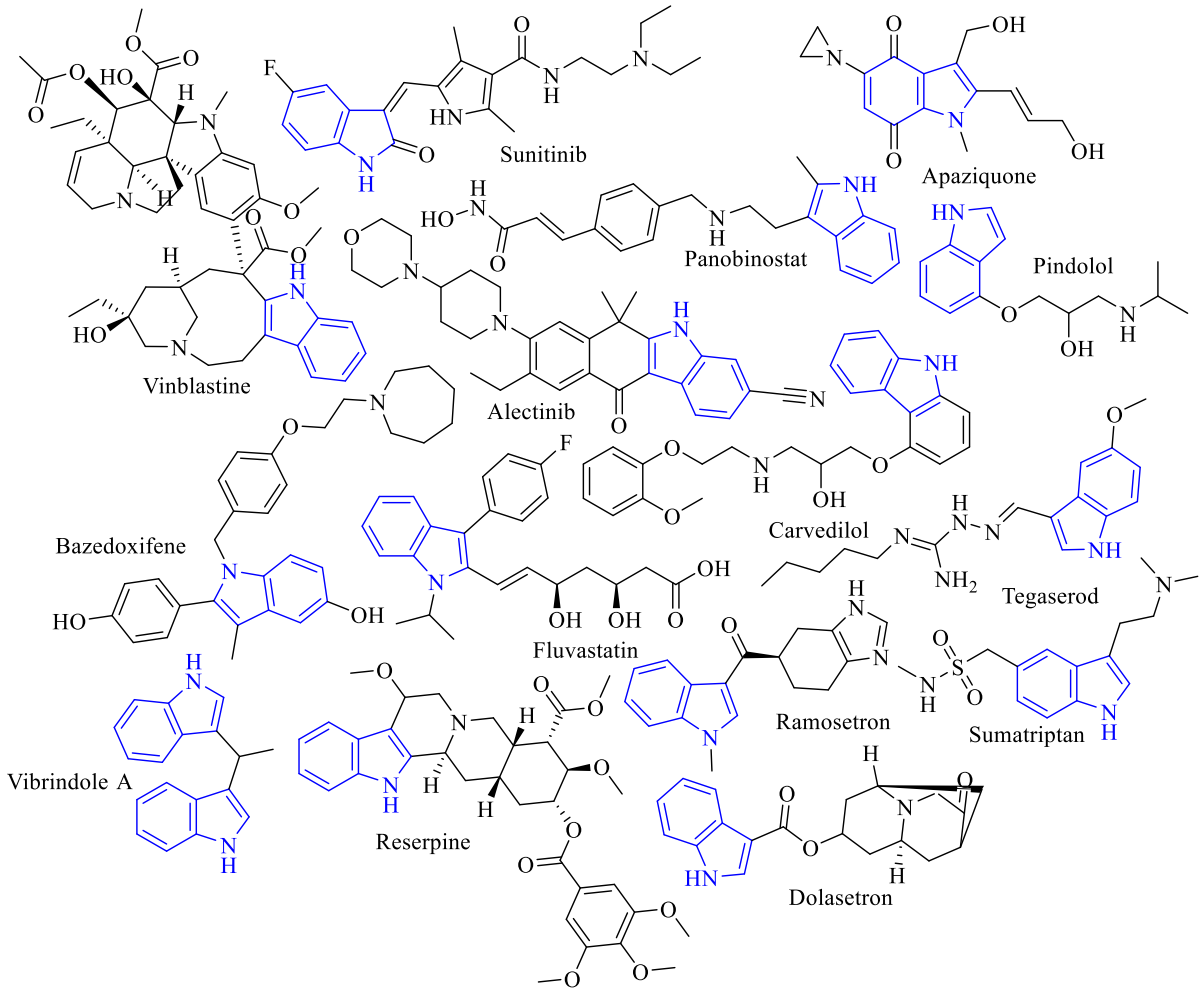


Figure 2: Marketed medications and their pharmacological activity that contain indole moiety in their molecular structure.

The conjugation of two privileged heterocycles, benzimidazole & indole, display synergistic effects attributed multiple aromatic and heteroatom-rich centers that participate in H-bonding, π–π stacking, and hydrophobic interaction, thereby enhance binding-affinity for enzyme active sites and receptor pockets, hybrid molecules gives multi-target modulation, like cancer [30], diabetes [31], neurodegeneration [32], antimicrobial [33], antiviral [34], anti-inflammatory actions [35], and metabolic regulation [36]. Several synthetic approaches have been developed like condensation of o-phenylenediamine with indole-2-carboxylic acids [37], Suzuki–Miyaura [38], Buchwald–Hartwig cross-coupling reactions [39], multicomponent reactions that integrate benzimidazole, indole, and aldehyde fragments in one-pot protocols provide efficient access to structural diversity [40]. Taken together, benzimidazole–indole conjugates represent a powerful class of molecular hybrids with immense therapeutic potential, combining favorable physicochemical profiles, multi-target mechanisms, and broad-spectrum biological activities that can be fine-tuned through modern synthetic methodologies [41].

Table 1: List of (granted) patents on benzimidazole-indole nucleus containing conjugates and its derivatives.

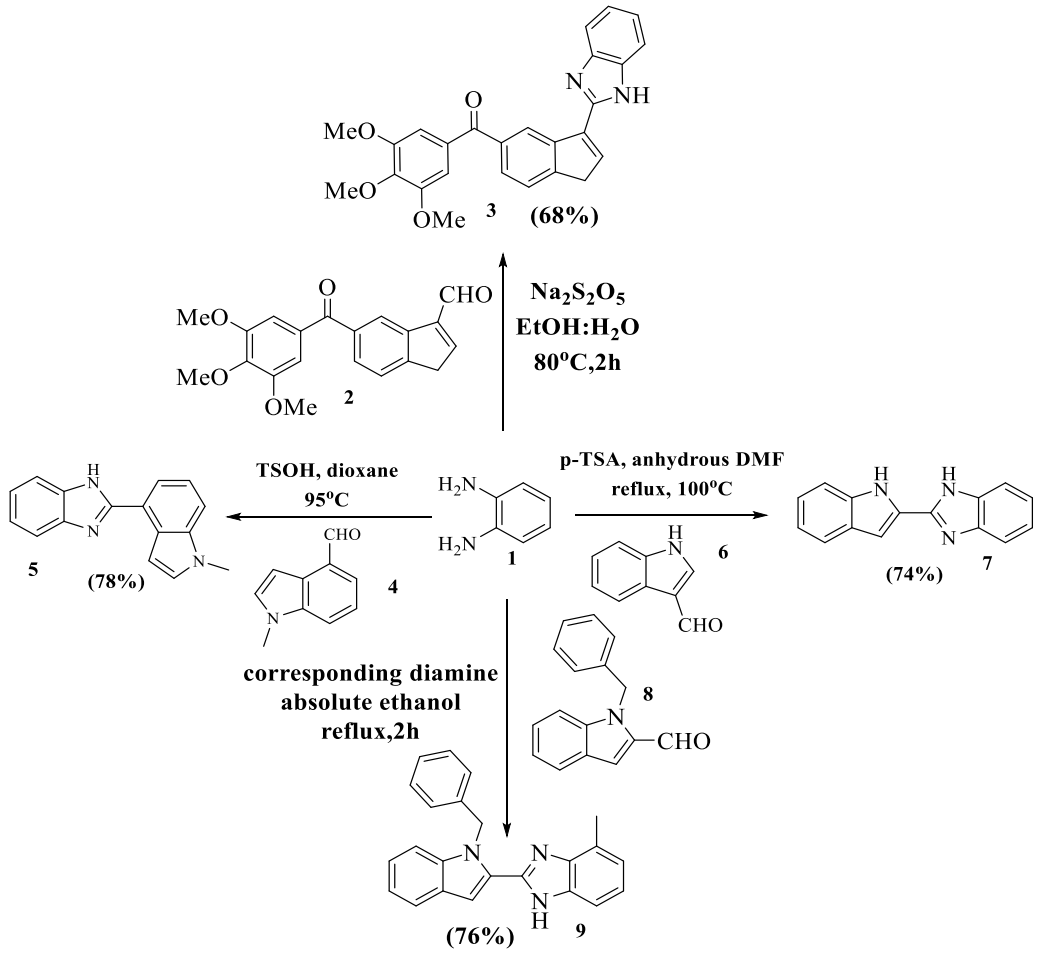
S. No.	Patent No.	Patent Date	Inventors	Descriptions
1	CN-116003390-B [42]	2024/03/08	Yan Jinlong, Wu Yawen, Li Yan	The invention presents an indole-benzimidazole fluorescent probe synthesized in DMF, enabling sensitive colour and fluorescence-based detection of phosgene in aqueous and gaseous forms, with practical test strip applications.
2	US-9475824-B2 [43]	2016/10/25	Zhou Han-jie, Parlati Francesco, Wustrow David	The invention discloses fused pyrimidine compounds featuring indole, benzimidazole, or benzopyrazole-substituted scaffolds that inhibit the p97 AAA proteasome complex, offering potential therapeutic applications in treating cancer and related diseases.
3	CA-2752527-C [44]	2014/09/23	Boezio Alessandro, Cheng Alan c, Coats James R, Copeland Katrina W, Graceffa Russell, Harmange Jean-christophe, Huang Hongbing, La Daniel, Olivieri Philip R, Peterson Emily A, Schenkel Laurie	The invention provides indole-benzimidazole-based compounds as potent PIK kinase, particularly mTOR inhibitors, useful in treating kinase-related diseases such as cancer, along with their pharmaceutical compositions and preparation methods.

4	US-8455516-B2 [45]	2013/06/04	Gochin Miriam, Zhou Guangyan	The invention discloses indole-benzimidazole-based compounds as HIV-1 fusion inhibitors that block viral RNA entry into host cells and show potential against other protein–protein interaction targets.
5	AU-2010216239-B2 [46]	2012/06/14	Boezio Alessandro, Cheng Alan C, Coats James R, Copeland Katrina W, Graceffa Russell, Harmange Jean-christophe, Huang Hongbing, La Daniel, Olivieri Philip R, Peterson Emily A, Schenkel Laurie	The invention presents indole-benzimidazole-based kinase inhibitors, particularly targeting PIK and mTOR pathways, useful in treating kinase-related diseases such as cancer, along with their pharmaceutical formulations and synthesis methods.
6	US-7189739-B2 [47]	2007/03/13	Mavunkel Babu J, Liu David Y, Schreiner George F, Lewicki John A, Perumattam John J	The invention discloses indole-benzimidazole-based compounds and their salts, featuring diverse substituents, useful for treating inflammatory conditions and cardiac failure through targeted structural modifications.
7	US-6689792-B2 [48]	2004/02/10	Kelly Michael G, Kang Young H	The invention presents indole-benzimidazole-based compounds and their salts, designed for central nervous system disorder treatment, offering diverse substitutions and structural variations for enhanced therapeutic potential.
8	US-6130235-A [49]	2000/10/10	Schreiner George F, Mavunkel Babu J, Liu David Y, Lewicki John A	The invention discloses indole-benzimidazole-based compounds and their salts with diverse substitutions, effective in treating inflammatory conditions and cardiac failure through targeted structural configurations and pharmacological activity.

2. Synthetic Approaches for Benzimidazole-Indole Conjugates

2.1 One-pot cyclo-condensation reaction

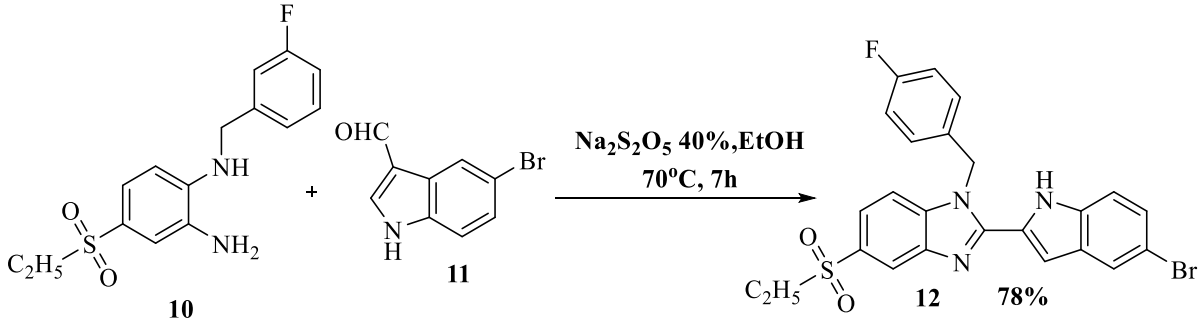
The one-pot cyclo-condensation reaction b/w o-phenylenediamine & indole-based aldehydes serves as an efficient approach for synthesis of benzimidazole-indole compounds under different acid-catalyzed conditions, temp or reflux time to optimize yields shows in (**Scheme 1)**. *Sherif et. al.,* **(2023),** synthesized 2-(1H-indol-2-yl)-1H-benzo[*d*]imidazole **7** by heterocyclic condensation reaction b/w benzene-1,2-diamine **1** & 1H-indole-3-carbaldehyde **6** in the presence of p-toluene sulfonic acid (PTSA) in anhydrous DMF under refluxing conditions at 100ºC gives 74% yield [50]**.** *Mullagiri et. al.*, **(2018),** reported the synthesis of (3-(1H-benzo[d]imidazol-2-yl)-1H-inden-5-yl)(3,4,5-trimethoxyphenyl)methanone **3,** when the compound **1** reacted with 5-(3,4,5-trimethoxybenzoyl)-1H-indene-3-carbaldehyde **2** in the presence of ($Na_2S_2O_5$) sodium metabisulfite in ratio of ethanol & water at 80ºC in 2h reflux condition gives the final compound **3** yield 68% [51]**.** *Singla et. al.,* **(2018),** synthesized 2-(1-benzyl-1H-indol-2-yl)-4-methyl-1H-benzo[d]imidazole **9** by the reaction b/w compound **1** and 1-benzyl-1H-indole-2-carbaldehyde **8** in the presence of corresponding diamine in absolute ethanol solvent & reflux for 2h to gives the final compound **9** yield 76% [52]. *Mavvaji et. al.*, **(2023)**, reported the synthesis of 2-(1-methyl-1H-indol-4-yl)-1H-benzo*[d]*imidazole **5**, when the compound **1** reacted with 1-methyl-1H-indole-4-carbaldehyde **4** under tosylic acid (TsOH) in dioxane solvent at 95ºC with 78% yield [53].



Scheme 1: Synthesis of benzimidazole-indole derivative from cyclo-condensation reaction.

2.2 Suzuki coupling reaction

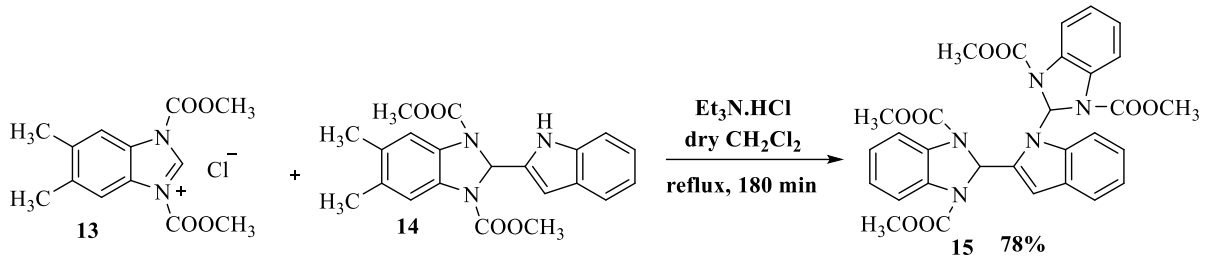
Farag et. al., **(2025),** developed a synthetic route to 2-(5-bromo-1H-indol-2-yl)-5-(ethylsulfonyl)-1-(4-fluorobenzyl)-1H-benzo*[d]*imidazole **12,** when 4-(ethylsulfonyl)-*N*1-(3-fluorobenzyl)benzene-1,2-diamine **10** reacted with 5-bromo-1H-indole-3-carbaldehyde **11** in the presence of 40% Sodium metabisulfite ($Na_2S_2O_5$) in ethanol solvent at 70°C in 7h gives the final compound **12** with 78% yield **(Scheme 2)** [54].



Scheme 2: Synthesis of benzimidazole-indole conjugate by Suzuki coupling reaction.

2.3 *N*-alkylation reaction

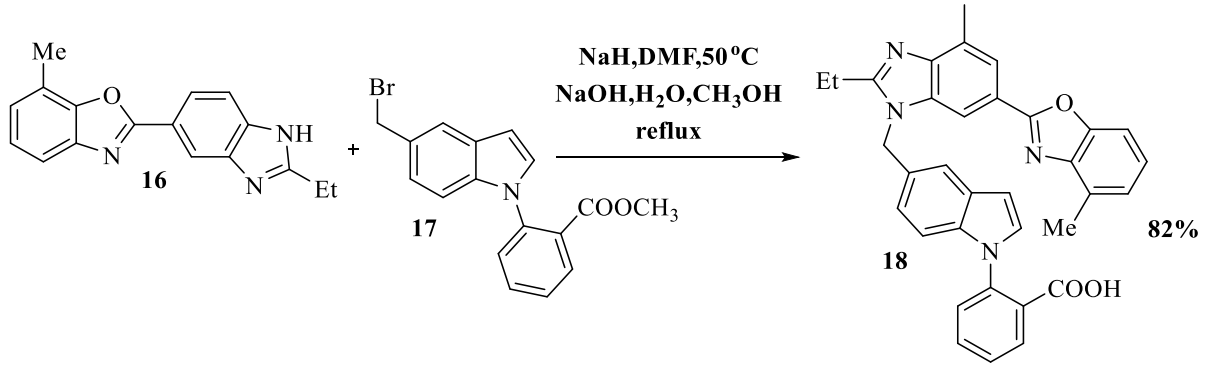
Yordan et. al., **(2025),** carried out the synthesis of *tetra*-methyl 2,2'-(1H-indole-1,2-diyl)*bis*(1H-benzo*[d]*imidazole-1,3(2H)-dicarboxylate) **15**. When 1,3-*bis*(methoxycarbonyl)-5,6-dimethyl-1H-benzo*[d]*imidazol-3-ium chloride **13** reacted with dimethyl 2-(1H-indol-2-yl)-5,6-dimethyl-1H-benzo*[d]*imidazole-1,3(2H)-dicarboxylate **14** undergoes *N*-alkylation reaction in the presence of *tri*-ethylamine hydrochloride in anhydrous chloroform act as solvent reflux for 180min to gives final compound **15** with 78% yield **(Scheme 3)** [55]



Scheme 3: Synthesis of benzimidazole-indole conjugate by *N*-alkylation reaction.

2.4 Base hydrolysis reaction

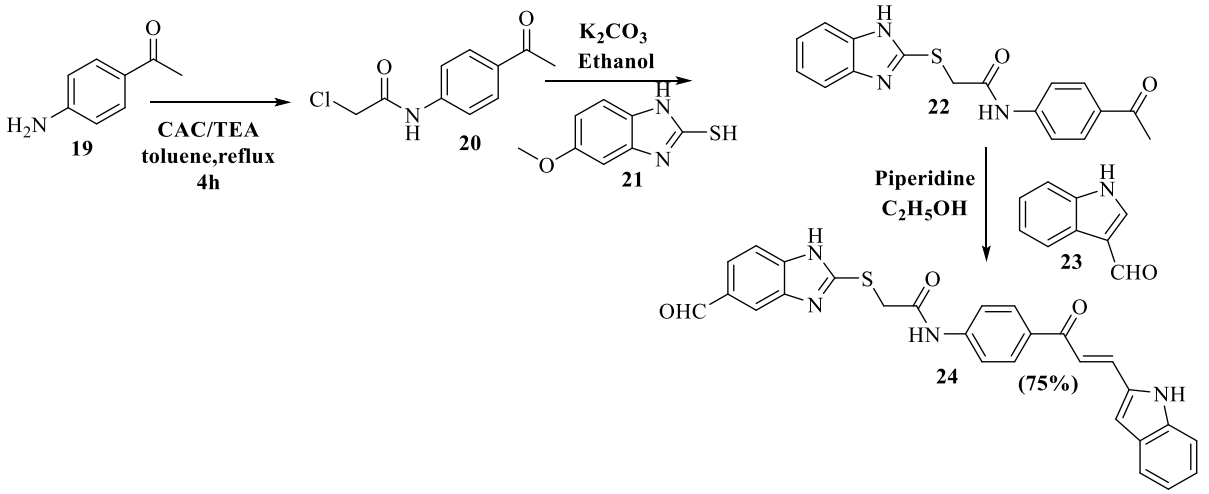
Zhuo et. al., **(2018)** reported the synthesis of 2-(5-((2-ethyl-4-methyl-6-(4-methylbenzo*[d]*oxazol-2-yl)-1H- benzo*[d]* imidazol-1-yl)methyl)-1H-indol-1-yl)benzoic acid **18**. When 2-(2-ethyl-1H-benzo[d]imidazol-5-yl)-7-methylbenzo*[d]*oxazole **16** and methyl 2-(5-(bromomethyl)-1H-indol-1-yl)benzoate **17** in the presence of sodium hydroxide undergoes base hydrolysis & dimethyl formamide act as a solvent at 50°C with NaOH act as a base catalyst in water & methanol act as a solvent gives a final compound **18** with 82% yield **(Scheme 4)** [56].



Scheme 4: Synthesis of benzimidazole-indole conjugate by base hydrolysis

2.5 Claisen–Schmidt condensation reaction

Naraboli et. al., **(2017),** synthesized *(E)-N*-(4-(3-(1H-indol-2-yl) acryloyl)phenyl)-2-((5-formyl-1H-benzo[d]imidazol-2-yl)thio)acetamide **24.** First, 1-(4-aminophenyl)ethan-1-one reacted with chloro-acetyl chloride/triethyl amine in toluene act as a solvent reflux for 4 hr to gives *N*-(4-acetylphenyl)-2-chloroacetamide **20,** further compound **20** reacted with 5-methoxy-1H-benzo*[d]*imidazole-2-thiol **21** under potassium carbonate in ethanol gives 2-((1H-benzo[d]imidazol-2-yl)thio)-*N*-(4-acetylphenyl)acetamide **22,** then compound **22** reacted with 1H-indole-3-carbaldehyde **23** undergoes claisen–schmidt condensation reaction under the presence of piperidine (base catalyst) in ethanol gives final compound **24** with 75% yield **(Scheme 5)** [57].

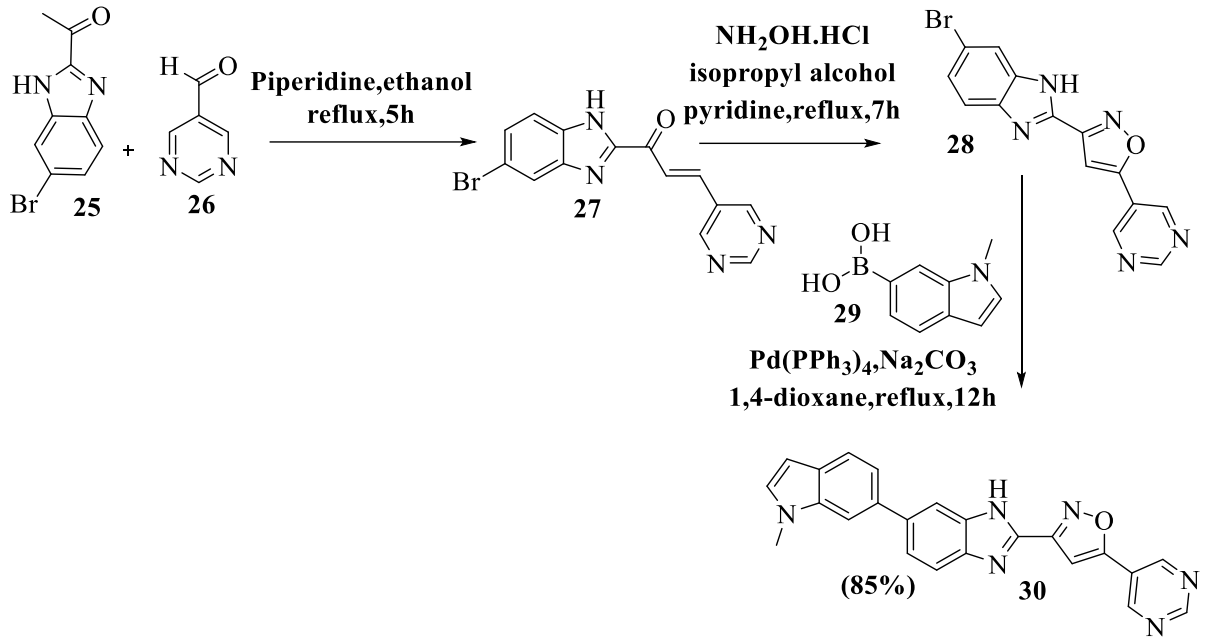


Scheme 5: Synthesis of benzimidazole-indole derivative by Claisen-schmidt condensation reaction.

2.6 Cyclization reaction

Karuna et. al., **(2022),** reported the synthesis of 3-(6-(1-methyl-1H-indol-6-yl)-1H-benzo*[d]*imidazol-2-yl)-5-(pyrimidin-5-yl)isoxazole **30.** First 2-acetyl-6-bromo-1H-benzo*[d]*imidazol-4-ylium **25** reacted pyrimidine-5-carbaldehyde **26** under piperidine act as base catalyst in ethanol reflux for 5hr gives *(E)*-1-(5-bromo-1H-

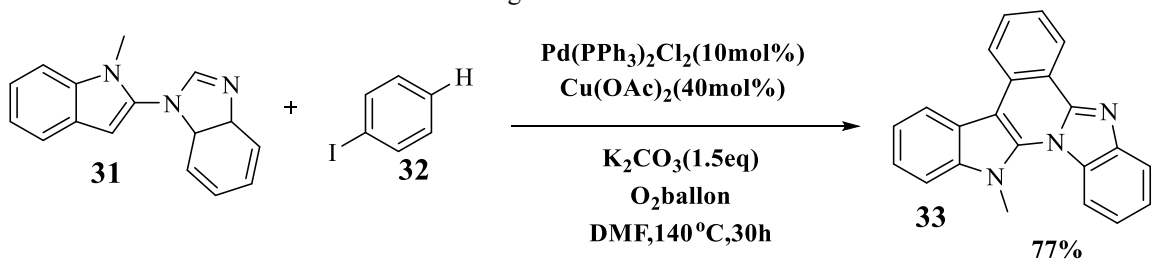
benzo*[d]*imidazol-2-yl)-3-(pyrimidin-5-yl)prop-2-en-1-one **27,** further reacted with hydroxylamine hydrochloride in isopropyl alcohol act as solvent & pyridine as base catalyst reflux for 7h gives 3-(6-bromo-1H-benzo[d]imidazol-2-yl)-5-(pyrimidin-5-yl)isoxazole **28** undergoes cyclization then reacted with (1-methyl-1H-indol-6-yl)boronic acid **29** in the presence of *tetra*-kis(triphenylphosphine)palladium catalyst & sodiumcarbonate in 1,4-dioxane act as solvent & reflux for 12h to gives final compound **30** with 85% yield **(Scheme 6)** [58].



Scheme 6: The synthesis of benzimidazole-indole conjugate by Knoevenagel condensation reaction.

2.7 Domino Sonogashira–cyclization reaction

Pathi et. al., **(2023),** achieved the synthesis of 14-methyl-14H-benzo[4,5]imidazo[2,1-a]indolo[2,3-c]isoquinoline **33**. When 1-(1-methyl-1H-indol-2-yl)-3a,7a-dihydro-1H-benzo[d]imidazole **31** reacted with iodobenzene undergoes domino sonogashira–cyclization reaction catalysed by *di*-chlorobis(triphenylphosphine)palladium(II) (10mol%) with Copper(II) acetate (40mol%) in (K_2CO_3) potassium carbonate in dimethylformamide solvent at 140°C in 30h gives the final compound **33** with 77% yield **(Scheme 7)** [59].



Scheme 7: Synthesis of benzimidazole-indole conjugate by Domino Sonogashira-cyclization reaction.

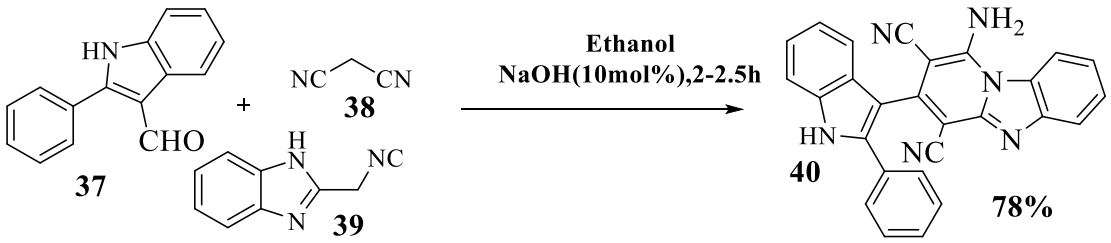
2.8 Steglich-type esterification

Ding et. al., **(2019),** reported the synthesis of (1-methyl-1H-benzo*[d]*imidazol-2-yl)methyl 1H-indole-3-carboxylate **36**. When (1-methyl-1H-benzo*[d]*imidazol-2-yl)methanol **34** reacted with 1H-indole-3-carboxylic acid **35** undergoes steglich-type esterification in the presence of *N,N'*-dicyclohexylcarbodiimide & 4-(dimethylamino)pyridine with *tetra*-hydrofuran act as a solvent, reflux at room temp for 7-9h gives final compound **36** with 47% yield **(Scheme 8)** [60].

Scheme 8: Synthesis of benzimidazole-indole derivative by Steglich-type esterification reaction.

2.9 One pot Knoevenagel condensation reaction

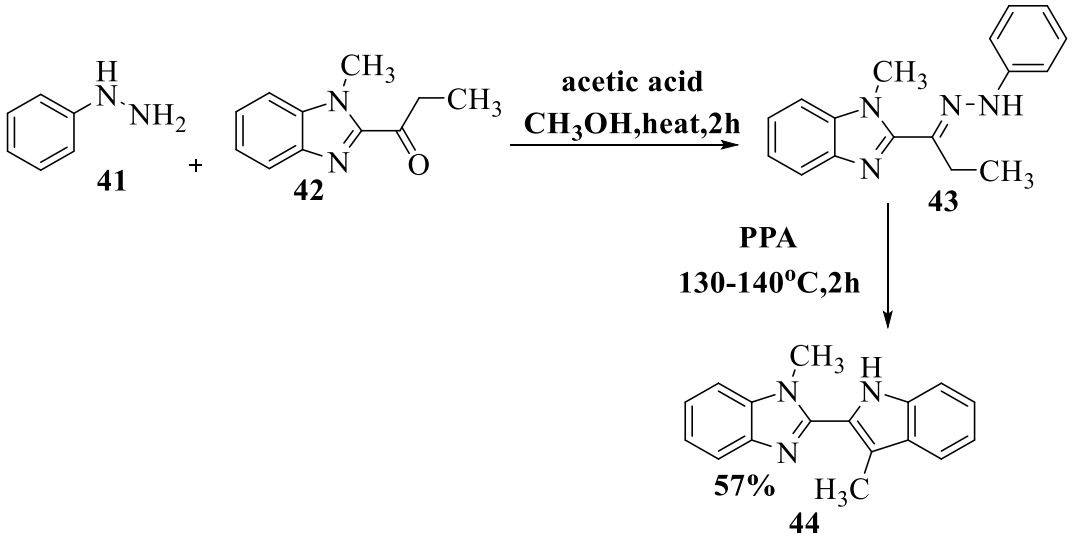
Kathrotiya et. al., **(2013),** reported the synthesis of 1-amino-3-(2-phenyl-1H-indol-3-yl)benzo[4,5]imidazo[1,2-a]pyridine-2,4-dicarbonitrile **40** by one-pot Knoevenagel condensation reaction between 2-phenyl-1H-indole-3-carbaldehyde **37,** malononitrile **38** and 2-(isocyanomethyl)-1H-benzo*[d]*imidazole **39** in the presence of sodium hydroxide (10mol%) act as base catalyst in ethanol solvent reflux for 2-2.5h gives final compound with 78% yield **(Scheme 9)** [61].



Scheme 9: Synthesis of benzimidazole-indole conjugate by one-pot Knoevenagel condensation reaction.

2.10 cyclization via Fischer-indole reaction

Babu et. al., **(2014),** synthesized 1-methyl-2-(3-methyl-1H-indol-2-yl)-1H-benzo*[d]*imidazole **44** by cyclization via Fischer-indole reaction in which phenylhydrazine **41** reacted with 1-(1-methyl-1H-benzo*[d]*imidazol-2-yl)propan-1-one **42** catalysed by acetic acid in methanol as solvent, heat the reaction for 2h gives *(E)*-1-methyl-2-(1-(2-phenylhydrazono)propyl)-1H-benzo*[d]*imidazole **43,** further reacted with polyphosphoric acid at 130-140°C for 2h to gives a final compound **44** with 57% yield **(Scheme 10)** [62].



Scheme 10: Synthesis of benzimidazole-indole conjugate by cyclization *via* fischer-indole reaction.

3. Pharmacological Activities

3.1 Anticancer activity

Satija et. al., **(2021),** reported 2-(5-bromo-1H-indol-3-yl)-5-(ethylsulfonyl)-1-(4-fluorobenzyl)-1H-benzo*[d]*imidazole **45** and evaluated their anti-cancer activity against MCF-7 and HEPG2 cell lines. Microarray expression profiling, gene enrichment analyses (GSEA), LINCS analysis and suggested that these indole-benzimidazole derivatives, alter the ER target gene expression and an integrated stress response was induced in a dose-related manner with IC50 value was 170.28 ± 10.22µM. (Fig. **3**) showed the Structure-Activity Relationship of the derivative **45** [63].

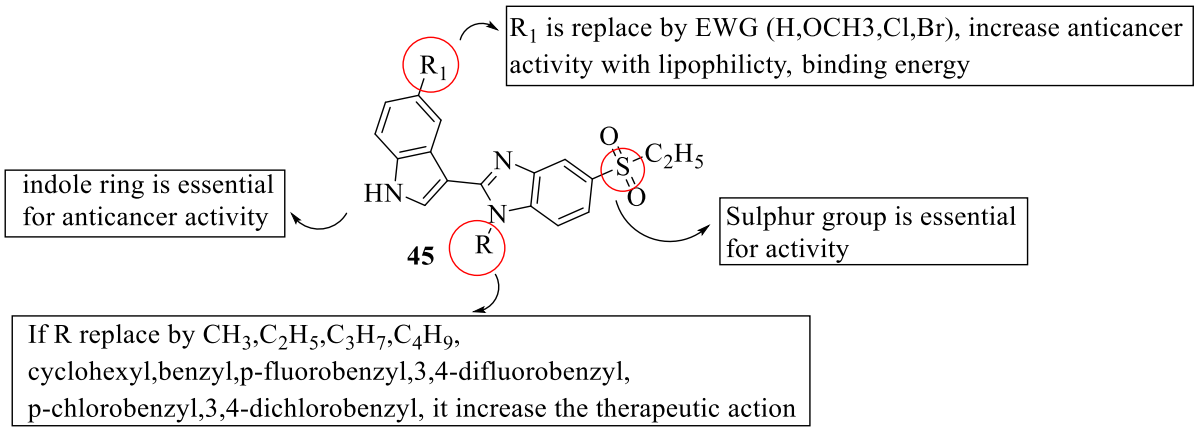


Figure 3: Compounds with anti-cancer effects that contain the benzimidazole ring with indole moiety: structure-activity relationship

3.2 Antimicrobial activity

Mendogralo et. al., **(2023),** synthesized 5-bromo-2-(5-bromo-1H-indol-3-yl)-1H-benzo[d]imidazole **46** and their anti-microbial therapeutic activity was evaluated by determining the minimum inhibitory concentration (MIC) using the serial dilution method. against four bacterial strains, namely against Staphylococcus aureus ATCC 25923, Staphylococcus aureus ATCC 43300 (MRSA), Mycobacterium smegmatis (mc(2)155/ATCC 700084), and Candida albicans ATCC 10231, after this result found that the compound **46** are more potent towards Staphylococcus aureus ATCC 25923 (MIC value= 0.98 µg/ML), Staphylococcus aureus ATCC 43300 (MRSA) (MIC value= 7.8 µg/ML) and moderately potent towards the Mycobacterium smegmatis (mc(2)155/ATCC 700084) (MIC value= 125 µg/ML) , Candida albicans ATCC 10231 (MIC value= 15.6 µg/ML), compare with std reference (Amikacin) for their antimicrobial therapeutic action. The compound **46** Structure Activity-Relationship is shown in (Fig. **4**) **[64]**.

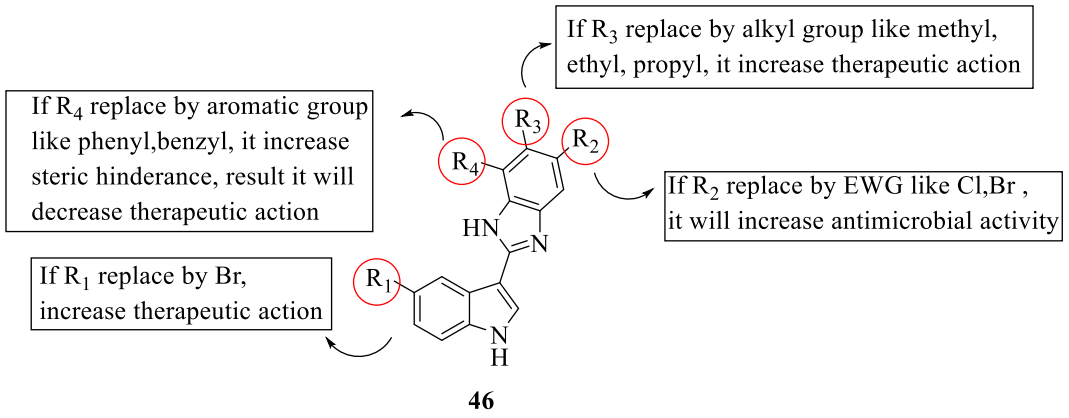


Figure 4: Compounds with anti-microbial effects that contain the benzimidazole ring with indole moiety: structure-activity relationship.

3.3 Antitubercular activity

Brishty et. al., **(2021),** reported 2-(1-((1-(2-chlorophenyl)-1H-1,2,3-triazol-5-yl)methyl)-1H-indol-3-yl)-1H-benzo*[d]*imidazole **47** by conventional & microwave-assisted methods & evaluated for invitro anti-tubercular activity against M.tuberculosis H37Rv strain. The Compound **47** showed prominent antitubercular activity with MIC values in the range of 3.125–6.25µg/ml. The compound **47** Structure Activity-Relationship is shown in Fig **5 [65].**

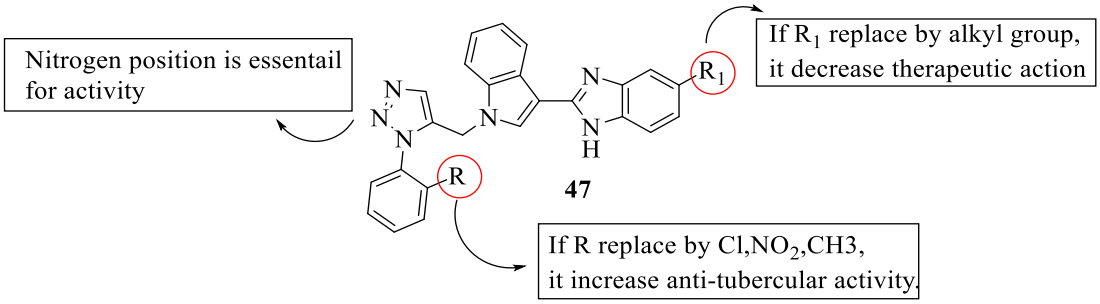


Figure 5: Compounds with anti-tubercular effects that contain the benzimidazole ring with indole moiety: structure-activity relationship.

3.4 Diuretic activity

Keri et. al., **(2014),** reported 5-chloro-2-(1H-indol-2-yl)-1H-benzo*[d]*imidazole **48** and screened for diuretic activity by Lipschitz method. Compounds **48** showed significant increase in urine volume (LV=2) and also urine excretion of Na+ and K+. The compound **47** Structure Activity-Relationship is shown in **Fig 6 [66]**.

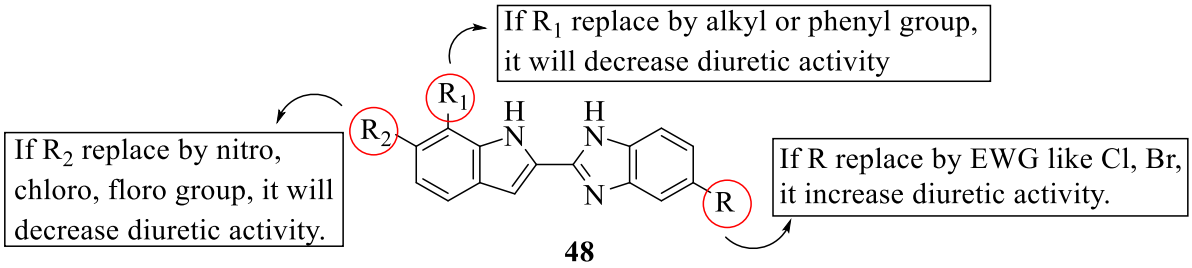


Figure 6: Compounds with diuretic effects that contain the benzimidazole ring with indole moiety: structure-activity relationship.

4. Conclusion

Benzimidazole–indole conjugates represent a promising and versatile class of bioactive heterocycles, successfully integrating two pharmacophoric units known for their broad pharmacological relevance. A variety of synthetic approaches—such as one-pot cyclo-condensation, Claisen–Schmidt condensation, Suzuki coupling, domino Sonogashira cyclization, Steglich-type esterification, Knoevenagel condensation, and Fischer indole synthesis—have been utilized to construct these conjugates with improved yield, selectivity, and operational simplicity. The development of these methodologies demonstrates continuous progress toward greener, more sustainable, and cost-effective synthetic routes. SAR analysis of benzimidazole–indole derivatives reveals that structural modifications at both heterocyclic rings can fine-tune their pharmacodynamic and pharmacokinetic properties. Compounds bearing halogen, nitro, or alkoxy substituents, as well as conjugated π-systems, often display enhanced anticancer, antimicrobial, antitubercular, and diuretic effects.

Overall, the synthesis and biological evaluation of benzimidazole–indole conjugates have established them as potent molecular frameworks for medicinal chemistry research. Continued exploration of new catalytic systems, hybridization strategies, and computational SAR modeling will further facilitate the design of next-generation benzimidazole–indole-based therapeutics with improved efficacy and selectivity.

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