2-Acetylbenzimidazole: a Valuable Synthon for the Synthesis of Biologically Active Molecules

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Abstract: Benzimidazole is an important moiety from a medicinal chemistry perspective due to its numerous pharmacological activities, viz. anti-viral [1], antimicrobial [2], anti-diabetic [3], anti-cancer [4,5], anti-Alzheimers [6], anti-inflammatory [7], etc. Due to its numerous biological activities, it is still an exciting area to do research. 2-acetylbenzimidazole is a benzimidazole derivative where the acetyl (-COCH3) group is attached at 2nd position. Several papers have been published over the years, which revealed numerous synthetic methods and pharmacological aspects of benzimidazoles prepared by utilizing 2-acetylbenzimidazole as a synthon. The review presented here highlights exclusively describing

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diverse synthetic methods and pharmacological activity of benzimidazole derivatives prepared from the 2-acetylbenzimidazole precursor.

2. Synthesis of 2-acetylbenzimidazole

2-acetylbenzimidazole was initially recovered as an impurity during the synthesis 2-methylquinoxaline 3 from o-phenylenediamines 1 and pyruvaldehyde 2 (Scheme 1). It was independently synthesized from 1'-hydroxyethylbenzimidazole 5 under oxidation conditions using chromium trioxide [8] (Scheme 2).

![Scheme 1. Preparation of 2-methylquinoxaline and 2-acetylbenzimidazole.](https://doi.org/10.33263/BRIAC114.1156211591)

For the bromination study, Ramaiah and co-workers prepared 2-acetylbenzimidazole starting from o-phenylenediamines 1, employing potassium dichromate and diluted H₂SO₄ as an oxidizing agent [9] (Scheme 3).

![Scheme 2. Preparation of 2-acetylbenzimidazole from 1'-hydroxyethylbenzimidazole.](https://doi.org/10.33263/BRIAC114.11563)

Kalirajan et al. carried out the oxidation of 1'-hydroxyethylbenzimidazole 5 in the presence of K₂Cr₂O₇ and 5 % dilute acetic acid to obtain 2-acetylbenzimidazole [10] (Scheme 4).

![Scheme 3. Preparation of 2-acetylbenzimidazole from o-phenylenediamines.](https://doi.org/10.33263/BRIAC114.11563)

Kumar et al. studied the oxidation of 2-(a-hydroxyethyl)benzimidazole to obtain 2-acetylbenzimidazole. Various oxidizing agents such as K₂Cr₂O₇, MnO₂, H₂O₂/gl. AcOH, CaOCl₂, m-CPBA, 10 % HNO₃, 50 % HNO₃, and CAN were employed for the reaction. Among the oxidizing agents used, K₂Cr₂O₇, H₂O₂/gl. AcOH, CAN were found to be the most effective. It was observed that K₂Cr₂O₇ in diluted H₂SO₄ gave the highest yield (72%). Moreover, neutralization of H₂SO₄ with NH₃ was found to be a crucial step. During the neutralization process, the pH of the solution should be between 5.5-6.0 and supposed to not go above 7.0. If
the pH of the solution exceeds 7.0, then the yield of 2-acetylbenzimidazolone decreases considerably [11].

3. Synthesis of 2-acetylbenzimidazole derivatives


A series of benzimidazole chalcones 7a-p were synthesized by the Claisen–Schmidt condensation reaction of 2-acetylbenzimidazole 4 with aryl aldehydes (Scheme 5). The compounds were evaluated for their nematicidal activity against Haemonchus contortus. Compound 7a was discovered to be most active (LC100 = 0.002 μg/mL) [12].

Mathew and co-workers have synthesized similar benzimidazole chalcones by microwave and screened them for their antibacterial activity. Compound 7o showed good activity towards Gram-negative bacteria (K. pneumonia and E. coli) and less active towards Gram-negative bacteria. Few derivatives showed modest activity against the fungi [13].

![Scheme 5. Synthesis of benzimidazole chalcones 7a-p.](image)

A series of benzimidazole derived chalcones 9a-g were synthesized by condensing 2-acetylbenzimidazole with various aldehydes (Scheme 6). The chalcones were evaluated for their in-vitro antimicrobial activity. Synthesized chalcones showed good activity against the gram-positive bacteria and fungal species [14].

![Scheme 6. Synthesis of benzimidazole chalcones 9a-g.](image)

Benzimidazole-pyridine or phenyl ketenes 10a-b were synthesized by Claisen Schmidt reaction of 2-acetyl benzimidazole with aromatic aldehydes. Reduction of the carbonyl function or of the double bond gave compounds 11a-b and 12a-b (Scheme 7). The compounds were screened against cancer cell lines MCF-7, HCT116, and HepG2. Compounds 9a and 9b showed IC50 values of 0.06 and 0.03 μM against the HCT116 cancer cell line, respectively. The activity was better than that of 5-Fluorouracil and near to that of Paclitaxel [15].
Scheme 7. Synthesis of benzimidazole derivatives 10,11,12-a & b.

A series of 1-(toluene-4-sulfonyl)-1H-benzimidazol-2-yl-propen-1-one 14a-f synthesized by tosylation of benzimidazole chalcones 13a-f using ultrasound (Scheme 8) compound 14b showed moderate inhibition of enzyme glucoamylase. Compounds 14c and 14e exhibited excellent activity against different bacteria and fungi Candida albicans [16].

Scheme 8. Synthesis of benzimidazole chalcones 13a-f & 14a-f.

Benzimidazolylchalcones derivatives 16a-d of chlormidazole were synthesized by reacting different aromatic aldehydes with N-(4-chlorobenzyl)-2-acetylbenzimidazole 16 in order to develop new antifungal compounds (Scheme 9). The compounds 17a, 17c, and 17d showed significant antifungal activities against Candida albicans and were found to possess MIQ values of 1.25, 5, and 0.625 μg, respectively [17].

Scheme 9. Synthesis of benzimidazole chalcones 17a-e.

A series of benzimidazole chalcones bearing the oxadiazole ring 20a-e were synthesized by a nucleophilic substitution reaction between benzimidazole chalcones 18a-e and 19 in the presence of K₂CO₃ (Scheme 10). The compounds were found to be moderately active against bacteria and fungi [18].
A novel series of 1-benzylbenzimidazole chalcones were synthesized in our laboratory, starting from o-phenylenediamine 1. Chalcones were prepared by Claisen-Schmidt condensation of 4 with various aromatic aldehydes in the presence of NaOH. Nucleophilic substitution of 1H-Benzimidazole chalcones 21a-d with benzyl chloride provided the final compounds 23a-d (Scheme 11). Compounds were tested for their antibacterial activity against selective bacteria. Compound 23b was found to be most effective with an IC50 value of 62.5 µg/mL [19].

Benzimidazolylchalcone 25 was prepared by reacting 4 with 2-chloroquinoline-3-carbaldehyde 24 in ethanol and sodium hydroxide at room temperature (Scheme 12) [20].

A series of benzimidazole chalcones bearing aromatic amide substituent (Scheme 13) were synthesized and screened for their anti-cancer activity against cancer cell lines HepG2, HCT116, CRL-5908, and A549. Compounds 29c, 29f and 29i showed good activity against HCT116 cells (IC50 = 1.34-1.63 µM). It was observed that the compounds act by upregulating the expression of TP53 protein in tumor cells without inhibiting the MDM2-TP53 interaction [21].
A series of benzimidazole-triazole-hybrid molecules 33a-j were synthesized by the reaction between different azides and benzimidazole alkynes 32a-j bearing a chalcone group (Scheme 14). Evaluation of anti-proliferative activity showed that compound 33j was most active with an IC50 value of 6.23, 5.89, and 10.7 μM against T47-D, MDA-MB-231, and PC3 cancer cell line [22].

An environment-friendly synthesis of benzimidazole linked indole chalcones 35a-n were prepared by catalyzing the reaction using ZnO nanoparticles. Compounds were obtained by reaction of 2-acetyl benzimidazole and indole-3-carbaldehyde 34 followed by Michael’s addition of indoles (Scheme 15). The method provided an excellent yield of product in less reaction time using water [23].
Scheme 15. Synthesis of benzimidazole chalcones 36a-n.

Benzimidazole chalcones bearing heterocyclic moieties 39-41 were prepared from 2-acetylbenzimidazole (Scheme 16). It was observed that benzimidazoles connected to 5 or 6 membered nitrogen-bearing rings showed cytotoxic effects on OVCAR-3 and MCF-7 cell lines. The compound 41 (containing morpholinopropyl group) reduced the proliferation of MCF-7 (IC\textsubscript{50} = 8.91 µM) and OVCAR-3 (IC\textsubscript{50} = 10.76 µM) cell lines and showed good activity compared to cisplatin [24].


3.2. Synthesis of the three-membered ring (oxirane and its derivatives).

Benzimidazole chalcone 43 was synthesized from 2-acetyl-1-methylbenzimidazole 42 and 3,4,5-Trimethoxybenzaldehyde. Treatment of 43 with 30% hydrogen peroxide in acetone yielded 44 (Scheme 17) [25].

Scheme 17. Synthesis of benzimidazole oxirane 44.

3.3. Synthesis of the five-membered rings.

3.3.1. Synthesis of pyrazolines.

Two series of pyrazoline were prepared, starting from 2-acetyl benzimidazole. The cyclo condensation of chalcones 45a-e with hydrazine hydrate and phenylhydrazine yielded
different pyrazoline derivatives 46a-e and 47a-e (Scheme 18). The compounds were screened against *Mycobacterium tuberculosis*. Compounds 45a and 45d were found to have MIC values of 1.25 and 1.53 μg/mL, respectively. Compounds 47c and 47e showed MIC values of 2.69 and 2.75, respectively [26].

A similar pyrazoline series was synthesized by Shaharyar and co-workers and screened at a single dose (10⁻⁵ M) against NCI 60 cell panel. Derivative containing 3,4-dimethoxyphenyl group at 5th position of pyrazoline 47e was found to be the most active candidate [27].

![Scheme 18. Synthesis of benzimidazole pyrazolines 46a-e and 47a-e.](image)

Series of pyrazolines 49a-b were synthesized from benzimidazolylchalcones 48a-b and phenylhydrazine to study their fluorescent properties (Scheme 19). The fluorescence spectra concluded that the emission wavelength was red-shifted. The absorption spectra revealed that the aryl group linked at the 5th position of the pyrazoline ring barely influenced the maximum absorption [28].

![Scheme 19. Synthesis of benzimidazole pyrazolines 49a-b.](image)

A series of benzimidazoles containing pyrazoline moiety 52a-j were synthesized by the cycloaddition of isoniazid 51 with benzimidazolylchalcones 50a-j (Scheme 20). The synthesized compounds were evaluated for antimicrobial using the serial dilution technique. Compounds 52b, 52d, and 52e were found to be significantly active against different bacteria with MIC of 25 μg/mL [29].

![Scheme 20. Synthesis of benzimidazole pyrazolines 52a-j.](image)

Benzimidazole linked pyrazoline 55a-j were achieved through the cyclo condensation of chalcone derivatives 53a-j with acid hydrazide 54 in acetic acid at 130°C (Scheme 21).
Antimicrobial activity was determined against *S. aureus*, *P. aeruginosa* *E. coli*, *A. niger*, *C. albicans*, and *A. clavatus*. Few of the compounds were found to be significantly active [30].

![Scheme 21. Synthesis of benzimidazole pyrazolines 55a-j.](image)

Benzimidazolylchalcones 56a-d have been cyclized into N\(^1\)-substituted pyrazoline derivatives 57a-d and 58a-d by the interaction with thiosemicarbazide and formic acid under microwave condition (Scheme 22). Compounds synthesized were evaluated against *B. Subtilis*, *K. pneumoniae*, *E. coli*, and *P. aeruginosa*. Few compounds showed unusual activity [31].

![Scheme 22. Synthesis of benzimidazole pyrazolines 57a-d & 58a-d.](image)

Benzimidazolylchalcones 59a-f, obtained from 2-acetylbenzimidazole was reacted with hydrazine hydrate in the presence of formic acid to afford pyrazolinecarboxaldehyde 60a-f, which on reaction with hydrazine hydrate resulted in compounds 61a-f in 80-89% yield under MWI condition (Scheme 23). Compounds were tested for their antifungal and antibacterial activity [32].

![Scheme 23. Synthesis of benzimidazole pyrazolines 61a-f.](image)

Two series of pyrazoline derivatives linked to benzimidazole moiety 64a-e and 65a-e were prepared in our laboratories by multistep reactions using 2-acylimidazole as a starting material (Scheme 24). The compounds were tested for their antimicrobial activity. Among the compounds screened, 64d showed good activity (*MIC* = 64 μg mL\(^{-1}\)) against *S. aureus* and *E. coli*. Compounds were found to be inactive against *C. albicans* [33].
Scheme 24. Synthesis of benzimidazole pyrazolines 64a-e & 65a-e.

A series of benzimidazole chalcones containing furan moiety 66a-b were synthesized from 2-acetylbenzimidazole. Chalcones were cyclized with methyl hydrazine in the presence of ethanol to produce pyrazolines (Scheme 25) [25].

Scheme 25. Synthesis of benzimidazole pyrazolines 67a-b.

A series of benzimidazole and benzothiazole-linked pyrazolines 70a-e were prepared by reacting to the hydrazine 69 and chalcones 68a-e using a small amount of glacial acetic acid in ethanol (Scheme 26). Compounds were screened for their anti-inflammatory & analgesic activity and were found to be moderately active [34].

Scheme 26. Synthesis of benzimidazole pyrazolines 70a-e.

A series of benzimidazole chalcones bearing indole ring system 72a-c were prepared by Saundane et al. [35]. The chalcones 72a-c on treatment with hydrazine or phenylhydrazine gave 73a-d (Scheme 27). Compounds were evaluated for their antimicrobial and antioxidant activities. Few of the compounds showed good activity.

Scheme 27. Synthesis of benzimidazole pyrazolines 73a-d.
Pyrazoline embedded with N-alkoxyphthalimidobenzimidazoles 76a-h were synthesized starting from 2-acetylbenzimidazole. The chalcones 74a-d were cyclized by refluxing with phenylhydrazine in the presence of pyridine. The pyrazolines 75a-d were condensed with ω-bromoalkoxyphthalimide to obtain 76a-h (Scheme 28) [36].

![Scheme 28. Synthesis of benzimidazole pyrazolines 76a-h.](image)

Compounds 2-(5-aryl-4,5-dihydropyrazol-3-yl)benzimidazoles 79a-d had been synthesized by the reaction of 3-aryl-1-(2-benzimidazolyl)-2-propen-1-ones 78a-d with hydrazine hydrate (Scheme 29) for evaluating them as potential anti-inflammatory agents. The compounds showed a good effect in the rat paw edema model [37].

![Scheme 29. Synthesis of benzimidazole pyrazolines 79a-d.](image)

2-(4-amino-2-arylaminothiazol-5-oyl)-N-methylbenzimidazoles 82a-e were prepared to utilize 2-acetylbenzimidazole as a synthon (Scheme 30). The compounds were screened at a concentration of 10^{-4}M against lung cancer (H460), breast cancer (MCF7), and SF268 (CNS cancer) cell lines. The compounds were further screened against different bacterial strains and found to be active [38].

![Scheme 30. Synthesis of benzimidazole pyrazolines 82a-e.](image)

Two series of Thiazole-2-amines 84a-d and 87a-i has been prepared by the cyclization of 2-acetylbenzimidazoles 83a-d & 85a-i and 2-bromo-1-(1-alkyl-1H-benzo[d]imidazol-2-yl)-1-ethanone 86a-i with thiourea (Scheme 31) and evaluated for their antibacterial and antifungal activity. Some of these compounds demonstrated antibacterial activity [39].

![Scheme 31. Synthesis of benzimidazole pyrazolines 82a-e.](image)
Scheme 31. Synthesis of benzimidazole linked thiazole-2-amines 87a-i.

A series of benzimidazoles linked with various heterocyclic systems 93, 94, 95, 97 and 98 have been synthesized from N-methyl-2-bromoacetylbensimidazole 89 (Scheme 32). Some benzimidazole derivatives were found as corrosion inhibitors [40].

Scheme 32. Synthesis of benzimidazole linked heterocyclics 90-98.

3.3.2. Synthesis of pyrazoles.

The reaction of benzimidazolylchalcones 99a-e with bromine in chloroform gave corresponding dibromochalcones 100a-e, which underwent condensation with hydrazine hydrate to form 3-benzimidazolyl-5-aryl-2-pyrazole 101a-e (Scheme 33). Pyrazoles were evaluated for their antimicrobial activity, and some of them have exhibited promising activity [41].
Scheme 33. Synthesis of benzimidazole linked pyrazole 101a-e.

2-acetylbenzimidazole on heating with dimethyl acetal in dimethylformamide gave the chalcone 1-(1H-benzimidazolyl)-3-dimethylaminopropenone 102. Alkylation of 102 with DMS/DES/PhCH₂Cl gave 103a-c that the treatment of with hydrazine gave 104a-c (Scheme 34) [42].

Scheme 34. Synthesis of benzimidazole linked pyrazole 104a-c.

The chalcones 105a-e were cyclized with phenylhydrazine, and 2,4-dinitro phenylhydrazine in the presence of sodium acetate under microwave irradiation to give the benzimidazole substituted pyrazole 106a-e (Scheme 35). Some of the compounds showed significant anti-cancer and antibacterial activity [10].

Scheme 35. Synthesis of benzimidazole linked pyrazole 106a-e.

The pyrazoles 108a-e derivatives were prepared from chalcones 107a-e (Scheme 36). The compounds were tested for anti-inflammatory activity and showed significant % inhibition of edema, i.e., 63.63, and 62 % at a dose of 200 mg/mL [43].

Scheme 36. Synthesis of benzimidazole linked pyrazole 108a-e.

3.3.3. Synthesis of isoxazolines.

The syntheses of Benzimidazole-arylisoaxazoline hybrid 110a-h were obtained by the condensation of chalcones 109a-h with hydroxylamine at room temperature (Scheme 37). The
compounds were tested for their antibacterial activity against Gram +ve bacteria viz., *B. subtilis*, *S. aureus*, and two Gram-ve bacteria viz. *E. coli* and *K. pneumonia* and found to be active [44].

Scheme 37. Synthesis of benzimidazole linked oxazoline 110a-d.

A series of 1-methyl analogs of benzimidazole chalcones 111a-b was cyclized with hydroxylamine hydrochloride in the presence of NaOH to produce isoxazolines 112a-b (Scheme 38). The derivatives exhibited high potency against cancer cells HEPG2 and PC12 cell lines [25].

Scheme 38. Synthesis of benzimidazole linked oxazoline 112a-b.

The chalcone 113 was cyclized with hydroxylamine hydrochloride using a catalytic amount of sodium acetate in a mixture of acetic acid and ethanol under reflux conditions. The isoxazoline 114 so obtained were condensed with ω-bromoalkoxy-phthalimide 115 in a mixture of pyridine and ethanol to obtain 2-(5-aryl-4,5-dihydroisoxazol-3-yl)-1-N-alkoxyphthalimido benzimidazoles 116a-h (Scheme 39) [36].

Scheme 39. Synthesis of benzimidazole linked oxazoline 116a-h.

3.3.4. Synthesis of isoxazoles.

2-Acetylbenzimidazole on condensation with different aldehydes produced 3-(benzimidazole-2-yl)-1-aryl-1-propen-3-ones 117a-g. Chalcones on condensation with hydroxylamine hydrochloride in the presence of sodium acetate using a minimum amount of acetic acid produced 3-(benzimidazole-2-yl)-5-arylisoxazoles 118a-g (Scheme 40). The
Compounds were evaluated for their anti-cancer activity against MCF-7 and NCI-H460 cell line [45].

Scheme 40. Synthesis of benzimidazole linked oxazole 118a-g.

3.4. Synthesis of the six-membered rings.


Benzimidazole embedded pyridine derivatives 121a-f were synthesized (Scheme 41) by reacting chalcones 119a-f with malononitrile 120 & ammonium acetate. Obtained compounds were evaluated for their antibacterial and antifungal activity. The compounds showed good antibacterial and moderate antifungal activities [46].

Scheme 41. Synthesis of benzimidazole linked pyridine 121a-f.

A series of benzimidazole derivatives 124a-f were synthesized (Scheme 42) by reacting compound 123a-f with formamide and formic acid in dimethylformamide solvent. Compounds 123a-f were prepared by reaction between benzimidazole chalcone 122a-f, malononitrile, and ammonium acetate in the ethanol medium. Compounds were screened for their antioxidant and antibacterial activity through DPPH and agar diffusion methods. The compounds demonstrated mild to moderate activity [47].

Scheme 42. Synthesis of benzimidazole linked pyridopyrimidine 124a-f.

Compounds 125a-f were treated with malononitrile and ammonium acetate to achieve derivatives 126a-f, via Knoevenagel condensation reaction. Compounds 126a-f on simple condensation reaction with 3-nitrobenzaldehyde provided Schiff bases 127a-f that in anhydrous 1,4-dioxane was refluxed with 2-mercaptopoacetic acid 128 for 12 hrs to obtain 129a-f (Scheme 43). These compounds were tested for antibacterial, antifungal, and cytotoxic activity [48].

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Desai et al. [49] prepared benzimidazole-pyridine-azetidine hybrid 133a-h (Scheme 44), starting from 2-acetyl benzimidazole through chalcone intermediates 130a-h. Chalcone derivatives were condensed with malononitrile in the presence of ammonium acetate to afford 131a-h, which on reaction with benzaldehyde in the presence of anhydrous zinc chloride resulted in 132a-h. Compound 132a-h and chloroacetyl chloride were refluxed with triethylamine in 1,4-dioxane to obtain 133a-h. The compounds were screened for their antibacterial activity and exhibited substantial antibacterial activity accompanied by a low level of cytotoxicity against HeLa cells.

Benzimidazole-pyridines 135a-b were prepared (Scheme 45) by refluxing 2-acetylbenzimidazole with suitable aromatic aldehydes 134a-b, ethyl cyanoacetate, and ammonium acetate. The Compounds showed weak anti-HIV activity and had mild antibacterial activity. However, no significant anti-cancer activity was observed [50].
A variety of benzimidazole-pyridine carbonitriles 137a-g were prepared (Scheme 46) via regioselective reaction of 136a-g with malononitrile in the presence of sodium alkoxide. All the synthesized compounds showed significant vasodilation properties [51].

1-α-Pyridiniumacetophenone chloride 139 on reaction with 2-cinnamoylbenzimidazole 138a-d in the presence of ammonium acetate gave pyridine derivatives 140a-d according to Kröhnke’s pyridine synthesis (Scheme 47) [52].

3.4.2. Synthesis of pyrimidines.

Zoorob et al. [53] have prepared various pyrimidine derivatives 142a-e & 143a-e from the chalcones 141a-e (Scheme 48). Chalcones were reacted with thiourea in boiling alcoholic potassium hydroxide to give the pyrimidinethiones 142a-e. The analogous pyrimidines 143a-e were prepared by the reaction of 141a-e with urea.
Scheme 48. Synthesis of benzimidazole linked pyrimidine 142a-e & 143a-e.

A series of benzimidazole chalcone and its 1-methyl analogs 144a-d were cyclized (Scheme 49) with different reagents such as thiourea guanidinium sulfate in different reactions to produce pyrimidinethione 145a-d and aminopyrimidine 146a-d, respectively [51].

Scheme 49. Synthesis of benzimidazole linked pyrimidine 145a-d & 146a-d.

The chalcones 72a-b on condensation with thiourea and urea in separate reactions yielded pyrimidine-2-thiol derivatives 147a-b and pyrimidin-2-ol derivatives 148a-b (Scheme 50), respectively. These compounds were screened for their antioxidant and antimicrobial activities and were found to possess good antioxidant and antimicrobial activity [35].

Scheme 50. Synthesis of benzimidazole linked pyrimidine 147a-b & 148a-b.

A series of 2-(2-amino-6-arylpyrimidin-4-yl)benzimidazoles 151a-d have been synthesized (Scheme 51) by the reaction of 3-aryl-1-(2-benzimidazolyl)-2-propen-1-ones 150a-d with guanidine carbonate. The compounds were found to be active as antibacterial [54].
Two series of aminopyrimidinylbenzimidazoles 153a-d and 155a-p were synthesized as antibacterial agents (Scheme 52). Compound 153d significantly inhibited the growth of *E. coli*, *A. flavus*, and MRSA with MIC values of 1, 1, and 8 μg/mL, respectively. 153d also exhibited bactericidal action against *S. aureus* MRSA and *P. aeruginosa*. Furthermore, compound 153d was found to show a good safety profile. A docking study concluded that 153d could bind with DNA gyrase [55].

Scheme 52. Synthesis of benzimidazole linked pyrimidine 153a-p, 154a-p & 155a-p.

N-benzyl benzimidazole-pyrimidine hybrid 158a-d were synthesized by the reaction of N-benzyl benzimidazole chalcones 157a-d with guanidine hydrochloride (Scheme 53). Compounds 158a and 158b exhibited significant anti-cancer activity with GI50 values of 39.6 and 84.0 μM [56].

Scheme 53. Synthesis of benzimidazole linked pyrimidine 158a-d.
A new series of pyrimidines 162a-j have been synthesized by the reaction of chalcone derivatives 161a-j with guanidine nitrate in ethanol and an aqueous solution of sodium hydroxide (Scheme 54) for testing their antimicrobial activity. Results reveal that compounds exhibited significant antibacterial and antifungal activities [57].

Scheme 54. Synthesis of benzimidazole linked pyrimidine 162a-j.

Benzimidazole-pyrimidine hybrid 163a-d were synthesized from chalcone precursors 74a-d. The chalcones were cyclized with guanidine nitrate in the presence of 10 % NaOH under the reflux condition. The pyrimidines 163a-d were then condensed with ω-bromoalkoxyphthalimide to obtain 164a-d (Scheme 55) [36].

Scheme 55. Synthesis of benzimidazole linked pyrimidine 164a-d.

A series of benzimidazole-pyrimidine 163a-d have been synthesized (Scheme 56) by the reaction of chalcones 74a-d with guanidine carbonate for evaluating them as potential anti-inflammatory agents. Compounds showed good anti-inflammatory activity in the carrageenan-induced rat paw edema model [37].

Scheme 56. Synthesis of benzimidazole linked pyrimidine 166a-c.
3.4.3. Synthesis of thiazines.

Substituted 2-acetyl benzimidazole 167 irradiated with various aromatic aldehydes in an aqueous solution of NaOH and ethanol to obtain the chalcones 168. Chalcones 168a-e and thiourea were refluxed for 12-18 hours at 60ºC to obtain the thiazine derivatives 169a-e (Scheme 57) [58].

![Scheme 57. Synthesis of benzimidazole linked pyrimidine 169a-f.](image)

3.5. Synthesis of the seven-membered rings.

3.5.1. Synthesis of diazepine.

The benzimidazolylchalcones 170a-f on treatment with ethylenediamine 171 afforded the diazepines 172a-f under MWI condition (Scheme 58). The compounds were evaluated for antibacterial and antifungal activity in vitro. It was observed that all the compounds possess promising activity [59].

![Scheme 58. Synthesis of benzimidazole linked diazepine 172a-f.](image)

3.5.2. Synthesis of fused rings.

The reaction of benzimidazolylchalcones 173a-c with 2-amino thiophenol 174 in methanol containing few drops of acetic acid afforded 175a-c and subsequent oxidation of the former intermediate with chloranil produced benzothiazepine derivatives 176a-c (Scheme 59) [60].

![Scheme 59. Synthesis of benzimidazole linked benzothiazepine 176a-c.](image)

The chalcones 177a-g on treatment with bromine in acetic acid gave dibromo derivatives 178a-g which reacted with an o-phenylene diamine in sulphuric acid to furnish 2-(benzimidazol-2-yl-methyl)-3-arylquinoxazolines 179a-g (Scheme 60) [46].

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Scheme 60. Synthesis of benzimidazole linked quinoxazoline 179a-g.

Benzimidazolylchalcones 180a-f on reaction with ethyl acetoacetate in the presence of basic alumina gave 6-carboethoxy-3-benzimidazolyl-5-arylcyclohexenones 181a-f, which on treatment with hydrazine hydrate gave benzimidazole linked indazoles 182a-f under microwave-assisted condition (Scheme 61). The synthesized compounds were found to be active as antimicrobial [61].

Scheme 61. Synthesis of benzimidazole linked indazole 182a-f.

2-acetyl benzimidazoles 183a-d on condensation reaction with 5-nitro furfural 184 at room temperature leads to the formation of chalcones 185a-d. These compounds on cyclo condensation reaction with triazole derivative 186 afforded benzimidazole linked triazolo[3,4-b][1,3,4]thiadiazepines 187a-d (Scheme 62). These compounds were evaluated for their antibacterial and antifungal activity [62].

Scheme 62. Synthesis of benzimidazole linked triazolothiadiazepines 187a-d.

The chalcones 188a-d were reacted with bromine in carbon tetrachloride to yield dibromo adduct 189a-d. During recrystallization from methanol or acetic acid, the dibromo derivatives cyclized to give the pyrrolo[1,2-a]benzimidazoles 190a-d (Scheme 63) [53].

Scheme 63. Synthesis of benzimidazole linked pyrrolobenzimidazoles 190a-d.

A series of (2E)-1-(H-benzimidazol-2-y1)-3-substituted phenyl 2-propen-1-one embedded with barbitone 193a-e are prepared from chalcones 191a-e on reaction with barbituric acid 192 in the presence of acetic acid (Scheme 64). The synthesized compounds were screened for their antioxidant activity by the DPPH method and exhibited good antioxidant activity [63].

The compounds 193a-e, synthesized were further screened for their antiulcer activity in the pylorus-ligated rats and showed a percentage of protection of 67.17-69.56 % at a dose of 50 mg/kg body weight [64].

The same authors have also reported the antitumor activity for derivatives described above 193a-e against Dalton’s ascitic lymphoma (DLA) in mice. They showed good antitumor activity at a dose of 50 mg/kg against DLA bearing mice [65].

The synthesized compounds 193 a-e also showed good antidepressant activity at a dose of 20 mg/kg. The compounds 193 a-e considerably reduced the duration of immobility times [66].

![Scheme 64. Synthesis of benzimidazole linked barbitone 193a-e.](image1)

A series of some novel imines 196a-e were prepared (Scheme 65) by an acid-catalyzed nucleophilic addition reaction between 5-amino-1,3,4-thiadiazole-2-thiol 195 and heteroaryl chalcones 194a-e (Scheme 65). The compounds were screened for their antulcer activity in the pylonus-ligated rats. Antioxidant activities of the derivatives were determined by DPPH method. Compounds showed a percentage of 70.43-73.47% protection at a dose of 10 mg/kg body weight [67].

All the derivatives 196a-e were further screened for their hypnotic activity at a dose level of 10 mg/kg body weight. The compounds showed a significant percentage of an increase in sleeping time [68].

![Scheme 65. Synthesis of benzimidazole linked thiadizole 196a-e.](image2)

Dubey et al. [69] investigated the Michael addition of various α, β- unsaturated benzimidazole chalcones 198a-f with nitromethane under solvent-free conditions in the presence of K2CO3 and TBAB as the surface catalyst by simple physical mixing in a mortar and pestle at room temperature gave the respective adducts 199a-f in good yields (Scheme 66).
2-acetyl-1H-benzimidazole oxime-ethers 201a-f were synthesized from derivatives of 2-acetylbenzimidazole 200a-b (Scheme 67). The antifungal activities of the compounds were determined against Botrytis cinerea and Alternaria alternata. Compounds 201b, 201c, 201f, 201g, and 201h exhibited good activities against Botrytis cinerea, while 201b and 201f possess excellent activities against Alternaria alternata [70].

Dihydropyrazino[1,2-a]benzimidazole 205a-j and 1-(2-arylvinyl)-3-arylpyrazino[1,2-a]benzimidazole 206a-j were synthesized (Scheme 68 and 69), and their anti-cancer and anti-HIV activities were determined. The compounds did not show anti-HIV activity, whereas significant anti-cancer activity was observed against leukemia cell lines [71].
Pyrazino[1,2-a]benzimidazole derivatives 214a-i possessing the SO$_2$CH$_3$ group were synthesized and evaluated for their anti-cancer, cyclooxygenase-2 inhibitory, and anti-platelet aggregation activities (Scheme 70). Compound 214f was found to be the most potent COX-2 inhibitor with an IC$_{50}$ value of 0.08 μM. Cytotoxicity of the compounds was also determined against the breast cancer cell line MCF-7. It was found that compound 214e exhibited the highest anti-proliferative activity. The compound 214c was found to be the most active platelet aggregation inhibitor.

Scheme 70. Synthesis of benzimidazole derivatives 214a-i.

New pyrazino[1,2-a]benzimidazole derivatives 218a-h were synthesized and tested for their anti-cancer activity (Scheme 71). 2-acetylbenzimidazole was reacted with a derivative of α-bromoacetophenones 215a-c using potassium carbonate in acetone to give 216a-c. These diketones were further reacted with varied benzylamines 217a-e in acetic acid to obtain 218a-i. The remarkable anti-cancer activity was exhibited by compound 218e.

Scheme 71. Synthesis of benzimidazole derivatives 218a-h.

Benzimidazoles incorporated with different heterocycles were synthesized, starting from 2-acetylbenzimidazole (Scheme 72). Candidates were evaluated for antimicrobial activity against Bacillus pumilus, Escherichia coli, Staphylococcus aureus, and Saccharomyces cerevisiae. Compound 223 was found to possess good activity against the tested bacteria with no antifungal activity [20].
4. Conclusions

2-Acetylbenzimidazole is easily accessible and contains a highly reactive keto and amino groups. This survey attempts to sum up the synthetic methods and reactions of 2-acetylbenzimidazole during 1964-2020. The chemistry of 2-acetylbenzimidazole has shown promise on several fronts. The review revealed the wide synthetic applications of 2-acetylbenzimidazole in organic synthesis, particularly in the synthesis of biologically useful heterocyclics such as oxirane, pyrazoline, and thiazole pyrazole, isoxazoline, isoxazole, pyridine, pyrimidine, thiazine, and diazepine. Most of the synthesized compounds exhibited good pharmacological activity.

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Conflicts of Interest

The authors declare no conflict of interest.

References


