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Review
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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 various biological activities such as antimicrobial, anti-cancer, anti-diabetic, anti-Alzheimers, and anti-inflammatory, etc. 2-acetylbenzimidazole is exploited to obtain various heterocyclic compounds of pharmacological interest. This review's main motive is to present the literature on 2-acetylbenzimidazole chemistry and provide valuable and up-to-date information for its applications. The present review is carried out by compiling literature from 1964 to 2020 concerning the synthesis and biological aspects of various heterocyclic compounds derived from 2-acetylbenzimidazole. Literature was collected from various online search engines *viz.* Google Scholar, PubMed, Science Direct, Core, and Semantic scholar. 2-acetylbenzimidazole has been successfully employed as a synthon to obtain heterocyclic system viz. oxirane, pyrazoline, thiazole, pyrazole, isoxazoline, isoxazole, pyridine, pyrimidine, thiazine, diazepine, and other miscellaneous rings. 2-acetylbenzimidazole has shown promise for the convenient synthesis of various heterocyclic compounds. The reactions can be carried out on various reactive sites of 2-acetylbenzimidazole, which are the carbonyl group and the amino group. This review will help to explore various heterocyclic compounds and particularly in the synthesis of biologically useful compounds.

Keywords: 2-Acetylbenzimidazole; chalcone; pyrazoline; pharmacology; synthesis.

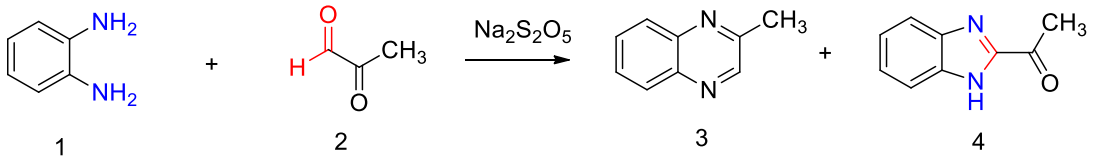
1. Introduction

Benzimidazole, a heterocyclic moiety, consists of benzene and imidazole ring, combined at the 4th and 5th position. It is a very important molecule 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 (-$COCH_3$) group is attached at 2nd position. Given the various pharmacological implications of benzimidazole derivatives, as previously mentioned, it inspires to investigate new synthetic protocol for biologically potent benzimidazoles. 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

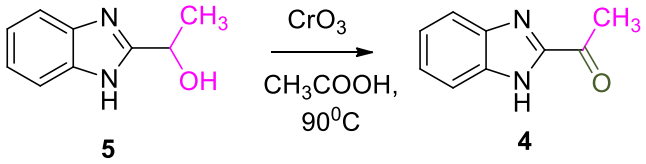
diverse synthetic methods and pharmacological activity of benzimidazole derivatives prepared from the 2-acetylbenzimidazole precursor.

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**).

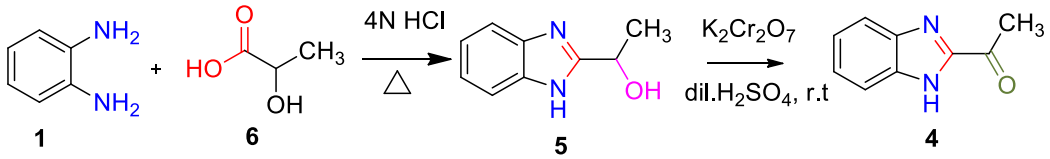


Scheme 1. Preparation of 2-methylquinoxaline and 2-acetylbenzimidazole.



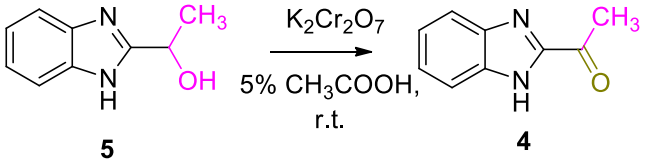
Scheme 2. Preparation of 2-acetylbenzimidazole from 1'-hydroxyethylbenzimidazole.

For the bromination study, Ramaiah and co-workers prepared 2-acetylbenzimidazole starting from o-phenylenediamines **1,** employing potassium dichromate and diluted H_2SO_4 as an oxidizing agent [9] (**Scheme 3**).



Scheme 3. Preparation of 2-acetylbenzimidazole from o-phenylenediamines.

Kalirajan *et al*. carried out the oxidation of 1'-hydroxyethylbenzimidazole **5** in the presence of $K_2Cr_2O_7$, and 5 % dilute acetic acid to obtain 2-acetylbenzimidazole [10] (**Scheme 4**).



Scheme 4. Preparation of 2-acetylbenzimidazole.

Kumar *et al*. studied the oxidation of 2-(α-hydroxyethyl)benzimidazole to obtain 2-acetylbenzimidazole. Various oxidizing agents such as $K_2Cr_2O_7$, MnO_2, H_2O_2/gl. AcOH, $CaOCl_2$, m-CPBA, 10 % HNO_3, 50 % HNO_3, and CAN were employed for the reaction. Among the oxidizing agents used, $K_2Cr_2O_7$, H_2O_2/gl. AcOH, CAN were found to be the most effective. It was observed that $K_2Cr_2O_7$ in diluted H_2SO_4 gave the highest yield (72%). Moreover, neutralization of H_2SO_4 with NH_3 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

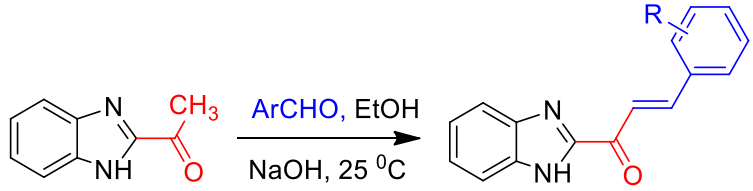
the pH of the solution exceeds 7.0, then the yield of 2-acetylbenzimidazole decreases considerably [11].

3. Synthesis of 2-acetylbenzimidazole derivatives

3.1. Synthesis of chalcones.

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 (LC_{100} = 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].

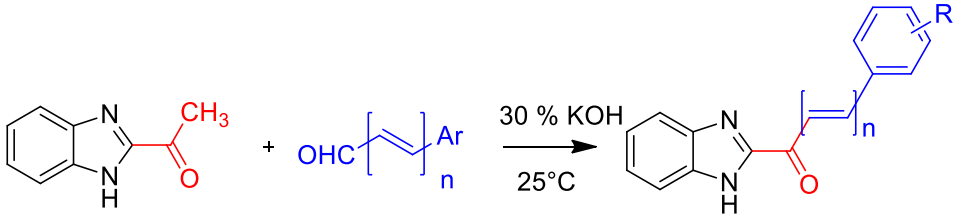


4 **7a-p**

7a-p; R=H, 2-Cl, 3-Cl, 4-Cl, 2-OCH_3, 3-OCH_3, 4-OCH_3, 2-Br, 4-F, 2-CH_3, 3-CH_3, 4-CH_3, 3-NO_2, 4-NO_2, 2-OH, 3-OH

Scheme 5. Synthesis of benzimidazole chalcones **7a-p.**

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].



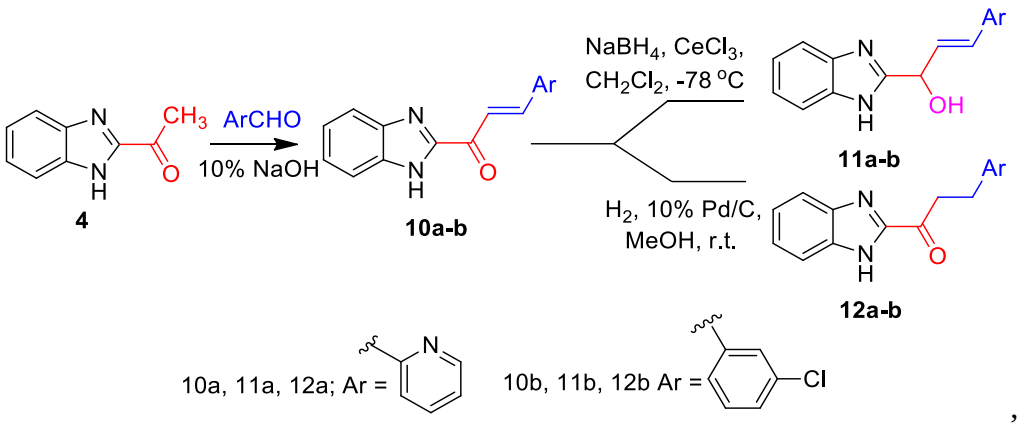
4 **8** **9a-g**

n = 1/2

9a-g; R= H, 3-OCH_3, 4-OCH_3, 2-Cl, 4-Br, 4-CH_3, Furyl

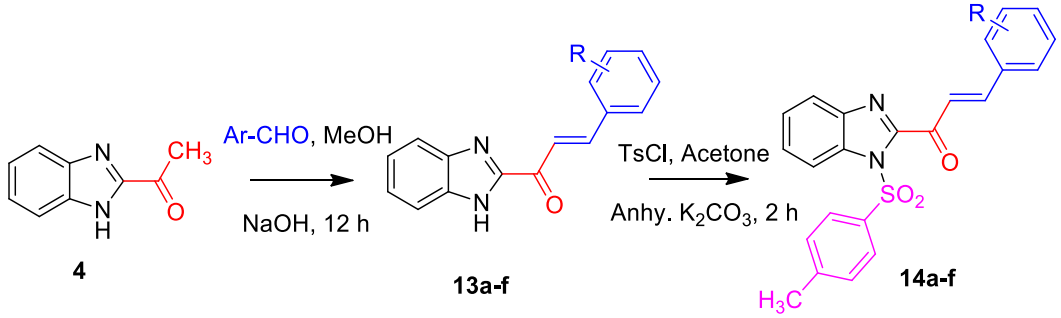
Scheme 6. Synthesis of benzimidazole chalcones **9a-g.**

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 IC_{50} 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.**

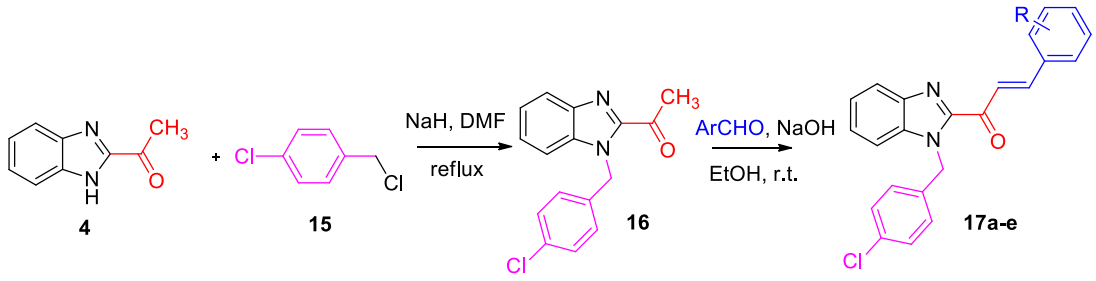
A series of 1-(toluene-4-sulfonyl)-1H-benzimidazol-2-yl]-propen-1-one **14a-f** synthesized by tosylation of benzimidazole chalones **13a-f** using ultrasound (**Scheme 8**) compound **14b** showed moderate inhibition of enzyme glucoamylase. Compounds **14c** and **14e** exhibited excellent activity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



14a-f; R=H, 4-CF_3, 4-OCH_3, 2-Cl, 4-Cl, 4-CH_3

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

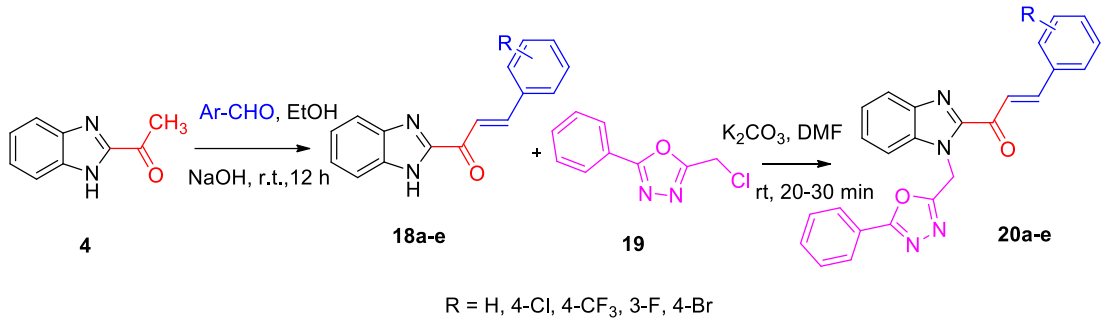
Benzimidazolylchalcones derivatives **16a-d** of chlormidazole were synthesized by reacting different aromatic aldehydes with *N*-(4-chlorobenzyl)-2-acetylbenzimidazole **16** in order to develop new antifungal compounds (**Scheme 9**). The compounds **17a**, **17c**, and **17d** showed significant antifungal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



17a-e; R= H, 3-NO_2, 2-Cl, 5-NO_2, 4-F, 4-Cl

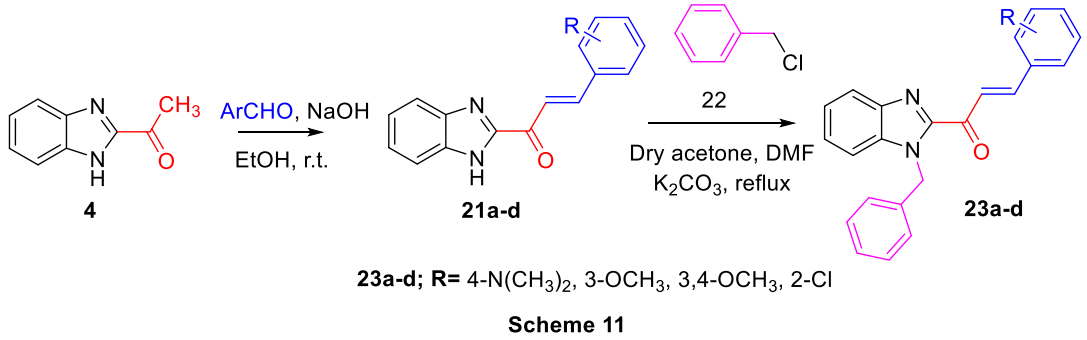
Scheme 9. Synthesis of benzimidazole chalcones **17a-e.**

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 K_2CO_3 (**Scheme 10**). The compounds were found to be moderately active against bacteria and fungi [18].



Scheme 10. Synthesis of benzimidazole chalcones **20a-h.**

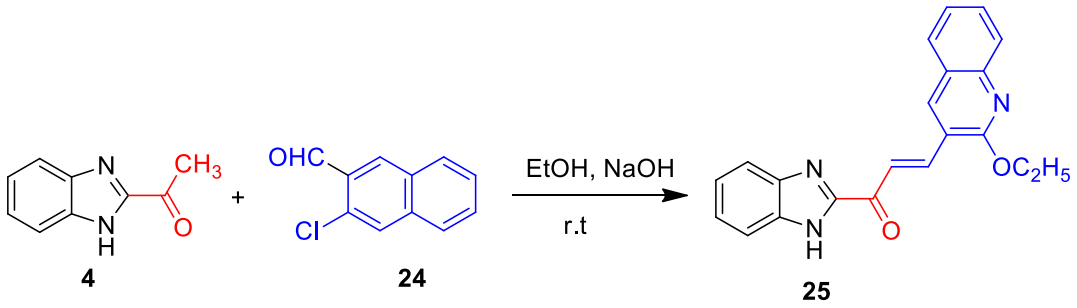
A novel series of 1-benzylbenzimidazole chalcones were synthesized in our laboratory, starting from o-phenylenediamine **1**. Chalcones were prepared by Claisen-Schmidt condensation of **4** with various aromatic aldehydes in the presence of NaOH. Nucleophilic substitution of 1H-Benzimidazole chalcones **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 IC_{50} value of 62.5 µg/mL [19].



Scheme 11

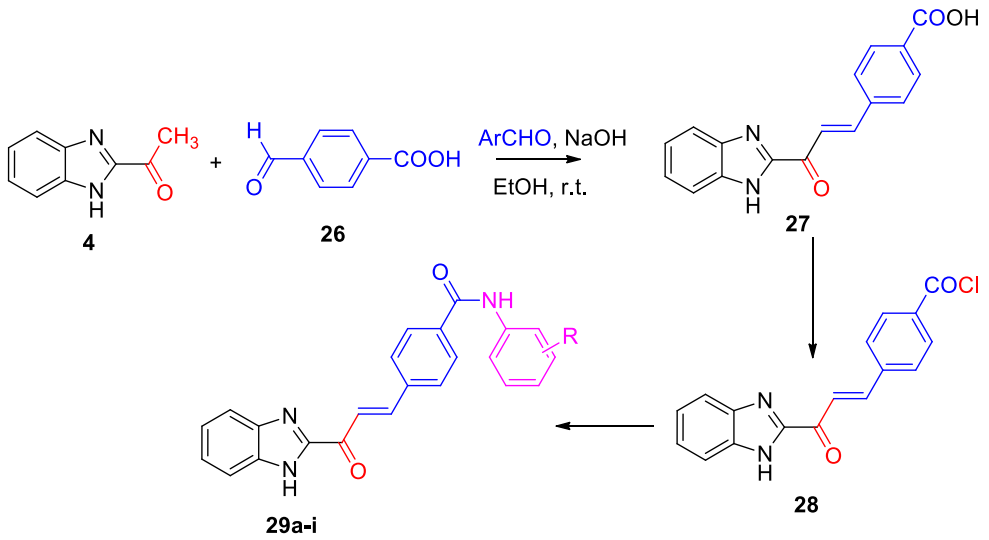
Scheme 11. Synthesis of benzimidazole chalcones **23a-d.**

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



Scheme 12. Synthesis of benzimidazole chalcone **25.**

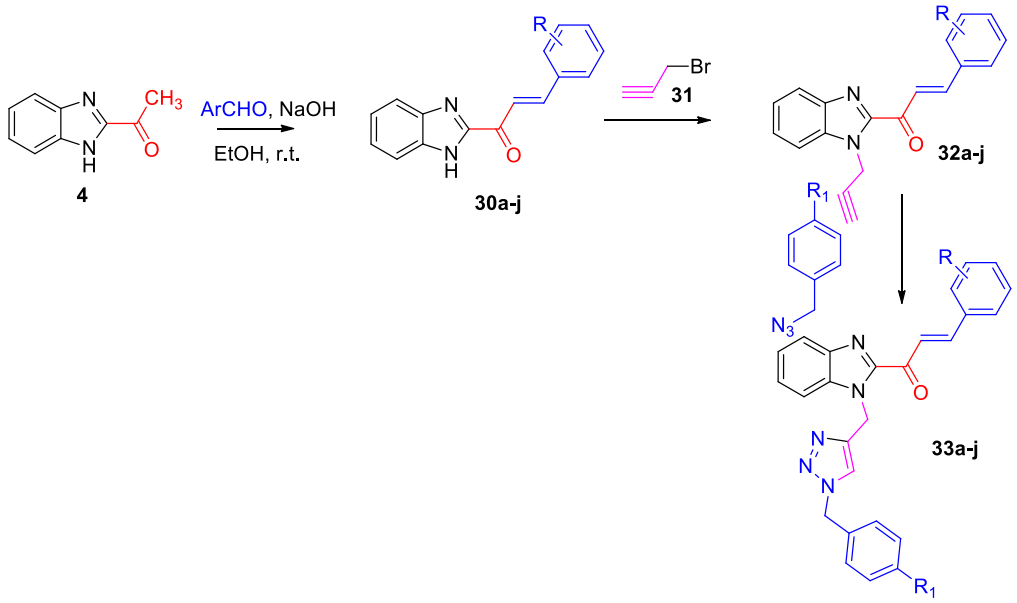
A series of benzimidazole chalcones bearing aromatic amide substituent (**Scheme 13**) were synthesized and screened for their anti-cancer activity against cancer cell lines HepG2, HCT116, CRL-5908, and A549. Compounds **29c**, **29f** and **29i** showed good activity against HCT116 cells (IC_{50} = 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].



29a-i; R= H, 2-CH_3, 3-CH_3, 4-CH_3, 2-Cl, 3-Cl, 4-Cl, 2-OCH_3, 3-OCH_3

Scheme 13. Synthesis of benzimidazole chalcones **29a-i.**

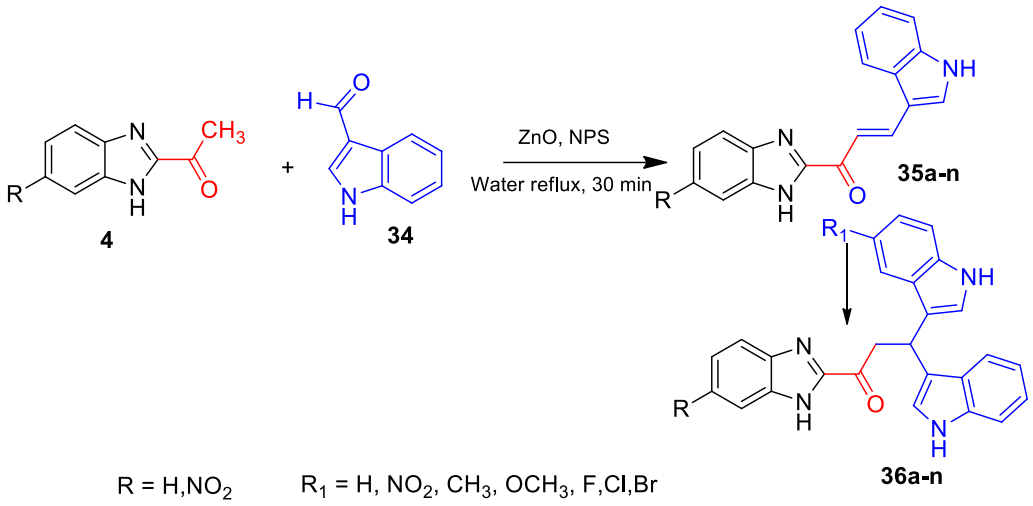
A series of benzimidazole-triazole-hybrid molecules **33a-j** were synthesized by the reaction between different azides and benzimidazole alkynes **32a-j** bearing a chalcone group (**Scheme 14**). Evaluation of anti-proliferative activity showed that compound **33j** was most active with an IC_{50} value of 6.23, 5.89, and 10.7 µM against T47-D, MDA-MB-231, and PC3 cancer cell line [22].



33a; R=4-CH_3, R_1=OCH_3 33b; R=4-Cl, R_1=OCH_3, 33c; R=4-Br, R_1=OCH_3 33d; R=4-CH_3, R_1=H 33e; R=4-Br, R_1=H 33f; R=4-Cl, R_1=CH_3 33g; R=H, R_1=CH_3 33h; R=4-Br R_1=CH_3 33i; R=4-OCH3 R_1=CH_3 33j; R=2-Cl R_1=H

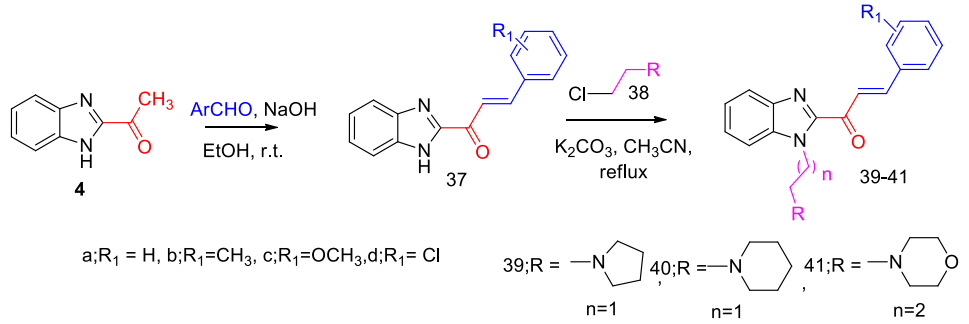
Scheme 14. Synthesis of benzimidazole chalcones **33a-j.**

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.**

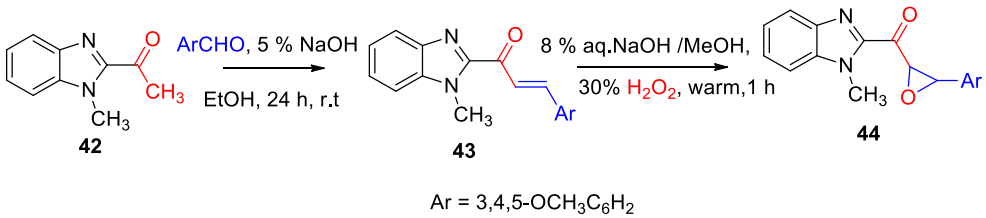
Benzimidazole chalcones bearing heterocyclic moieties **39-41** were prepared from 2-acetylbenzimidazole (**Scheme 16**). It was observed that benzimidazoles connected to 5 or 6 membered nitrogen-bearing rings showed cytotoxic effects on OVCAR-3 and MCF-7 cell lines. The compound **41** (containing morpholinopropyl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



Scheme 16. Synthesis of benzimidazole chalcones **39-41.**

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.**

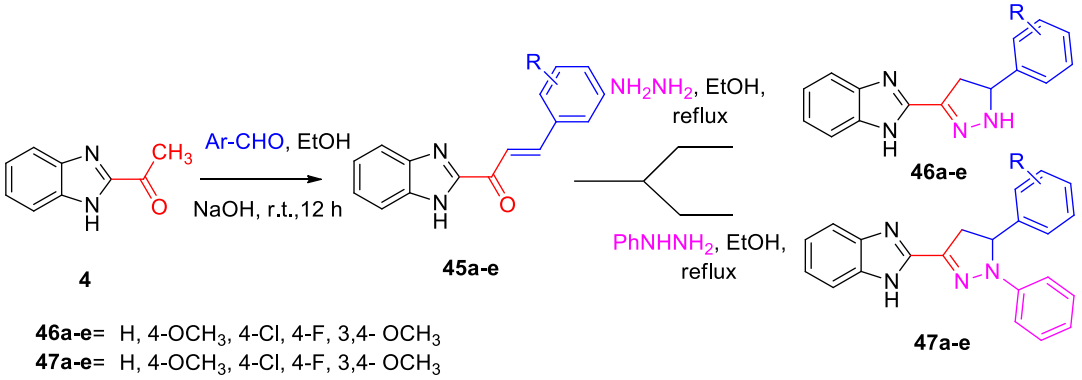
3.3. Synthesis of the five-membered rings.

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

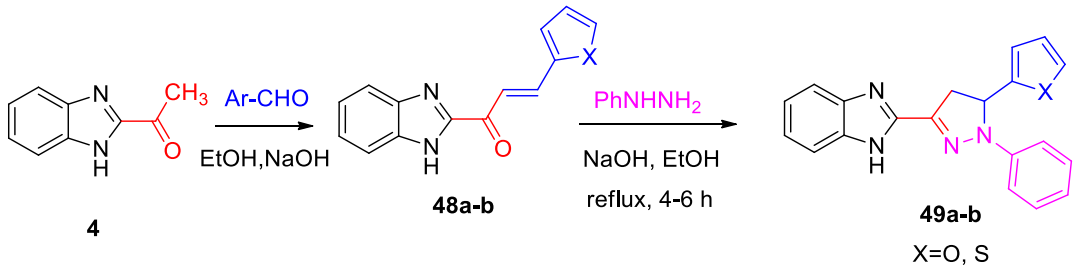
different pyrazoline derivatives **46a-e** and **47a-e** (**Scheme 18**). The compounds were screened against *Mycobacterium tuberculosis*. Compounds **45a** and **45d** were found to have MIC values of 1.25 and 1.53µg/mL, respectively. Compounds **47c** and **47e** showed MIC values of 2.69 and 2.75, 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. Derivativecontaining 3,4-dimethoxyphenyl group at 5thposition of pyrazoline **47e** was found to be the most active candidate [27].



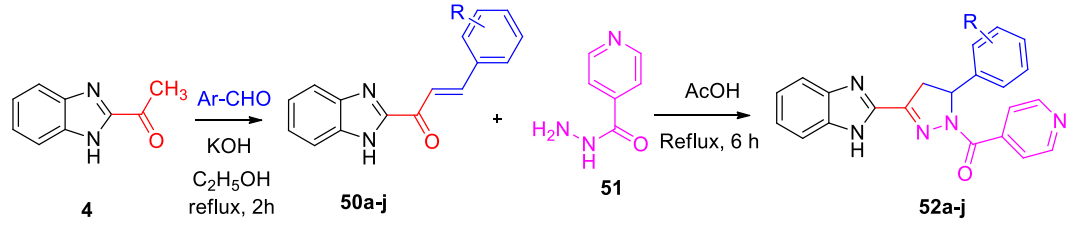
Scheme 18. Synthesis of benzimidazole pyrazolines **46a-e** and **47a-e.**

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.**

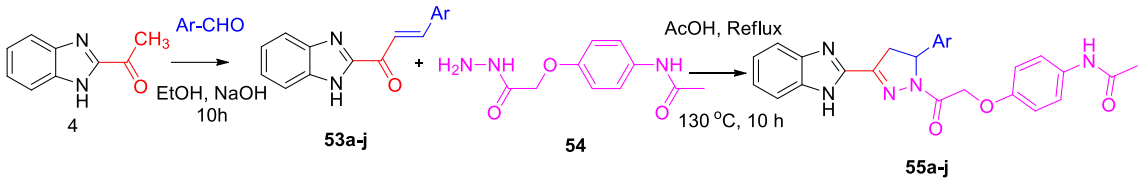
A series of benzimidazoles containing pyrazoline moiety **52a-j** were synthesized by the cycloaddition of isoniazid **51** with benzimidazolylchalcones **50a-j** (**Scheme20**). The synthesized compounds were evaluated for antimicrobial using the serial dilution technique. Compounds **52b**, **52d**, 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.**

Benzimidazole linked pyrazoline **55a-j** were achieved through the cyclo condensation of chalcone derivatives **53a-j** with acid hydrazide **54** in acetic acid at 130ºC (**Scheme 21**).

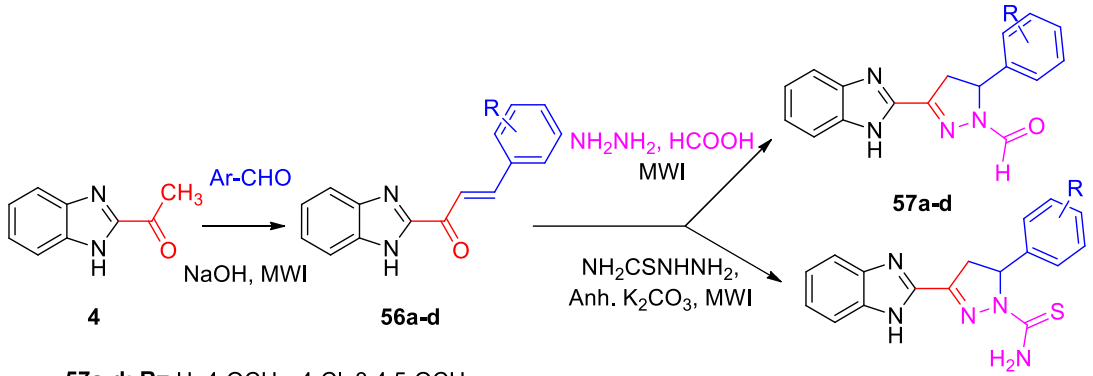
Antimicrobial activity was determined against *S. aureus*, *P. aeruginosa E. coli*, *A. niger*, *C. albicans*, and *A. clavatus*. Few of the compounds were found to be significantly active [30].



55a-j= H, 2-Cl, 4-Cl, 2-OH, 4-OH, 3-Br, 3-NO_2, 3-OCH_3, 4-OCH_3, 4-NO_2

Scheme 21. Synthesis of benzimidazole pyrazolines **55a-j.**

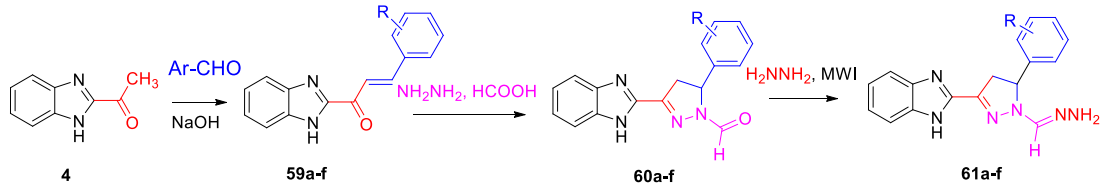
Benzimidazolylchalcones **56a-d** have been cyclized into N^1-substituted pyrazoline derivatives **57a-d** and **58a-d** by the interaction with thiosemicarbazide and formic acid under microwave condition (**Scheme 22**). Compounds synthesized were evaluated against *B. Subtilis*, *K. pneumonae, E. coli,*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



57a-d; R= H, 4-OCH_3, 4-Cl, 3,4,5-OCH_3
58a-d; R= H, 4-OCH_3, 4-Cl, 3,4,5-OCH_3

Scheme 22. Synthesis of benzimidazole pyrazolines **57a-d & 58a-d.**

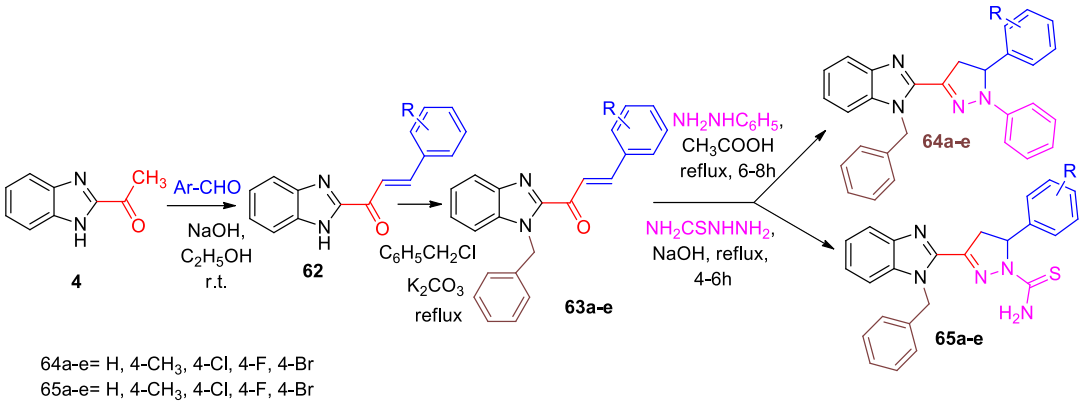
Benzimidazolylchalcones **59a-f,** obtained from 2-acetylbenzimidazole was reacted with hydrazine hydrate in the presence of formic acid to afford pyrazolinecarboxaldehyde **60a-f,** which on reaction with hydrazine hydrate resulted in compounds **61a-f** in 80-89% yield under MWI condition (**Scheme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



61a-f; R= H, 4-Cl, 4-OH, 3,4-OCH_3, 3,4,5-OCH_3, 4-N(Me)2

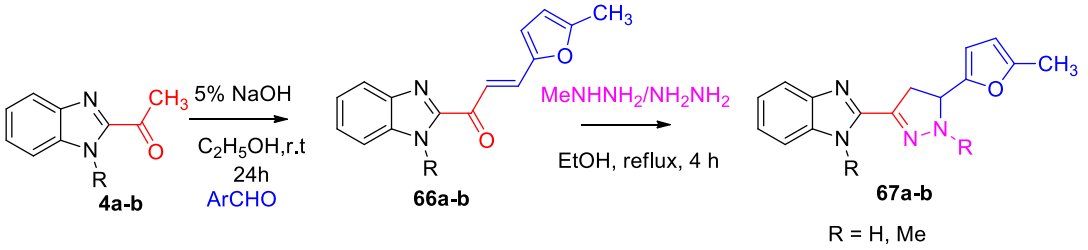
Scheme 23. Synthesis of benzimidazole pyrazolines **61a-f.**

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



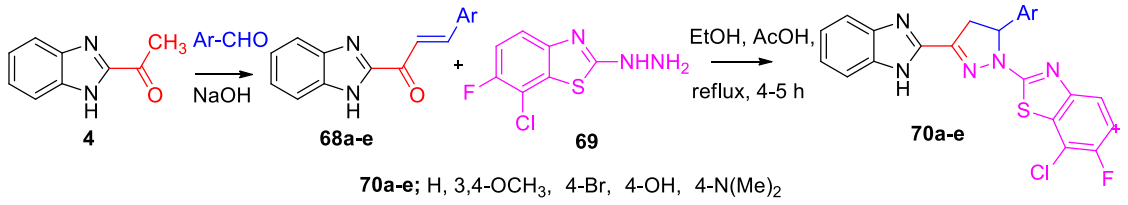
Scheme 24. Synthesis of benzimidazole pyrazolines **64a-e & 65a-e.**

A series of benzimidazole chalcones containing furan moiety **66a-b** were synthesized **67a-b** from 2-acetylbenzimidazole**.** Chalcones were cyclized with methyl hydrazine in the presence of ethanol to produce pyrazolines (**Scheme 25**) [25].



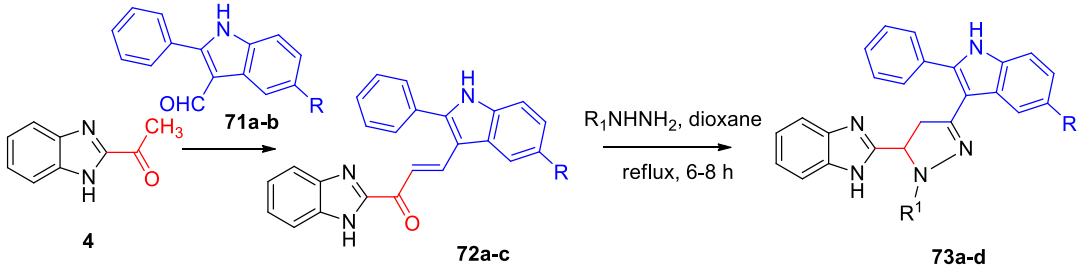
Scheme 25. Synthesis of benzimidazole pyrazolines **67a-b.**

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].



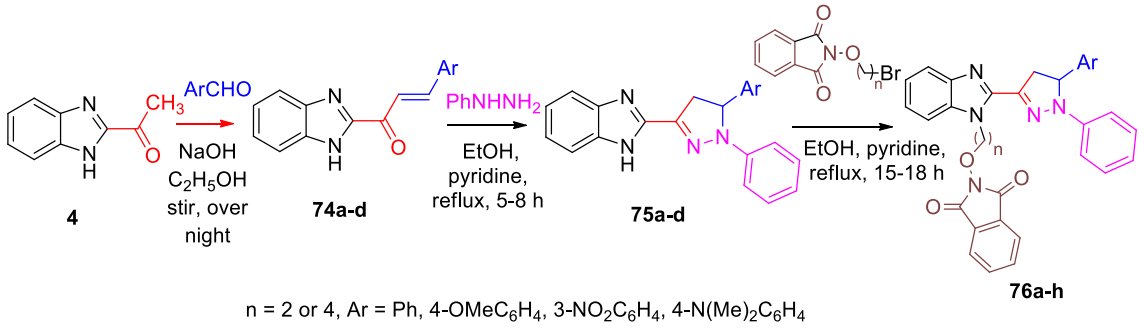
Scheme 26. Synthesis of benzimidazole pyrazolines **70a-e.**

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.



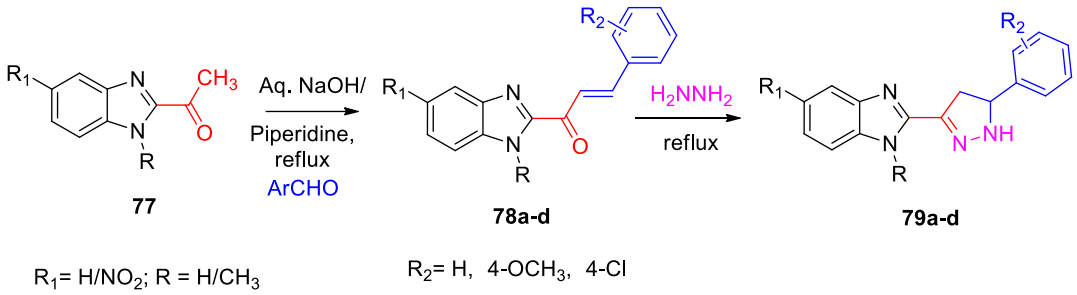
Scheme 27. Synthesis of benzimidazole pyrazolines **73a-d**.

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].



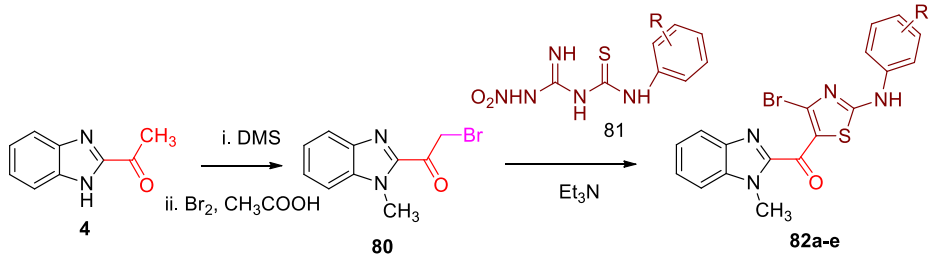
Scheme 28. Synthesis of benzimidazole pyrazolines **76a-h.**

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].



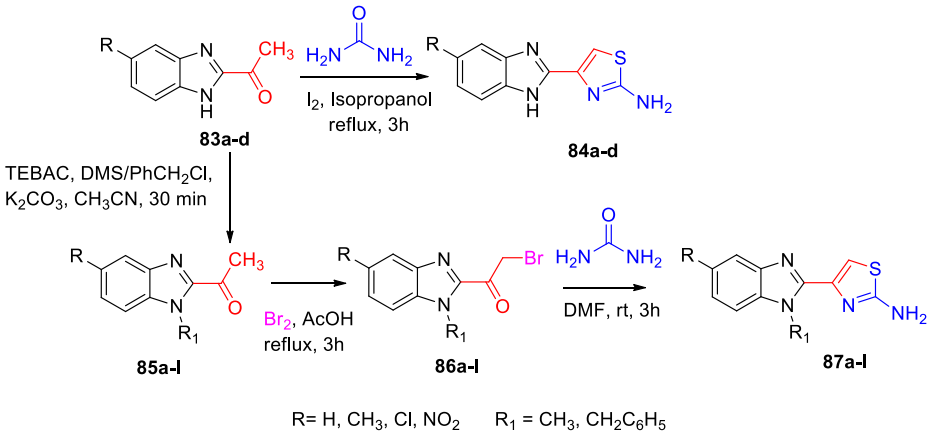
Scheme 29. Synthesis of benzimidazole pyrazolines **79a-d.**

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].



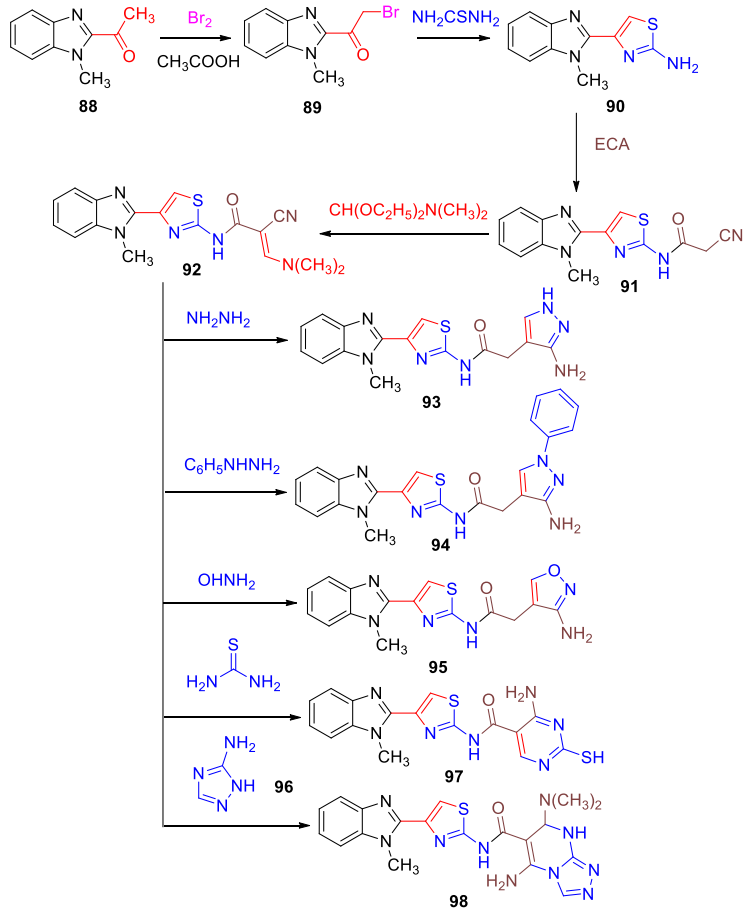
Scheme 30. Synthesis of benzimidazole pyrazolines **82a-e.**

Two series of Thiazole-2-amines **84a-d** and **87a-i** has been prepared by the cyclization of 2-acetylbenzimidiazoles **83a-d** & **85a-i** and 2-bromo-1-(1-alkyl-1*H*-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 linked thiazole-2-amines **87a-i.**

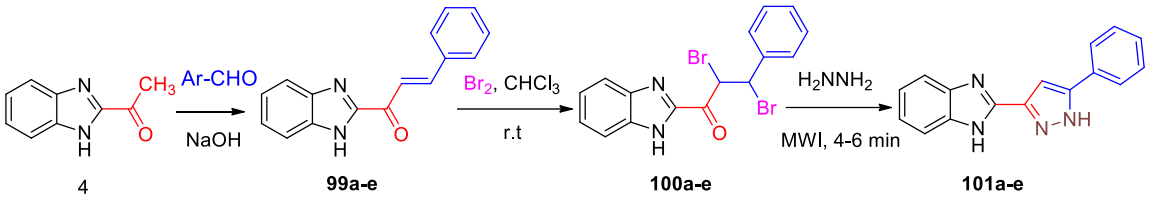
A series of benzimidazoles linked with various heterocyclic systems 93, 94, 95, 97 and 98 have been synthesized from *N*-methyl-2-bromoacetylbenzimidazole **89** (**Scheme 32**). Some benzimidazole derivatives were found as corrosion inhibitors [40].



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

3.3.2. Synthesis of pyrazoles.

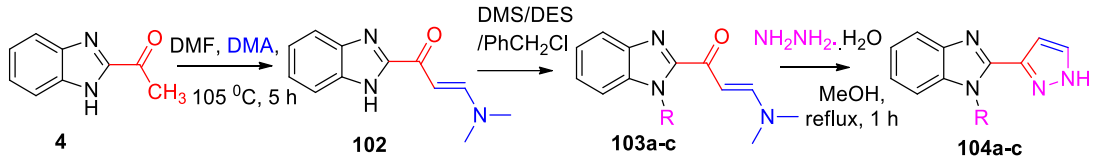
The reaction of benzimidazolylchalcones **99a-e** with bromine in chloroform gave corresponding dibromochalcones **100a-e**, which underwent condensation with hydrazine hydrate to form 3-benzimidazolyl-5-aryl-2-pyrazole **101a-e** (**Scheme 33**). Pyrazoles were evaluated for their antimicrobial activity,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



101a-e= H, 4-OCH_3, 3,4,5-OCH_3, 4-Cl, 4-OH

Scheme 33. Synthesis of benzimidazole linked pyrazole **101a-e.**

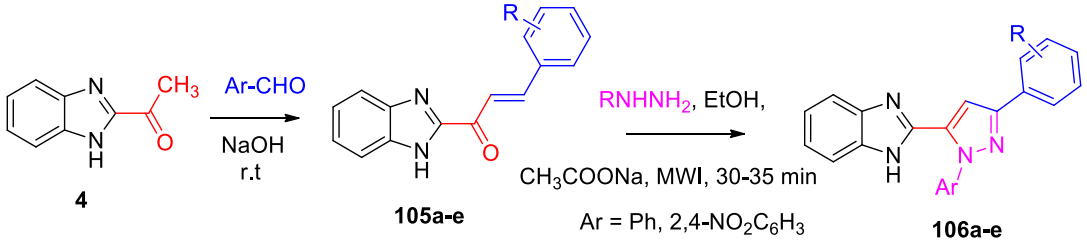
2-acetylbenzimidazole on heating with dimethyl acetal in dimethylformamide gave the chalcone 1-(1H-benzimidazolyl)-3-dimethylaminopropenone **102.** Alkylation of **102** with DMS/DES/$PhCH_2Cl$ gave **103a-c** that the treatment of with hydrazine gave **104a-c** (**Scheme 34**) [42].



R = Me, C_2H_5, $PhCH_2$

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

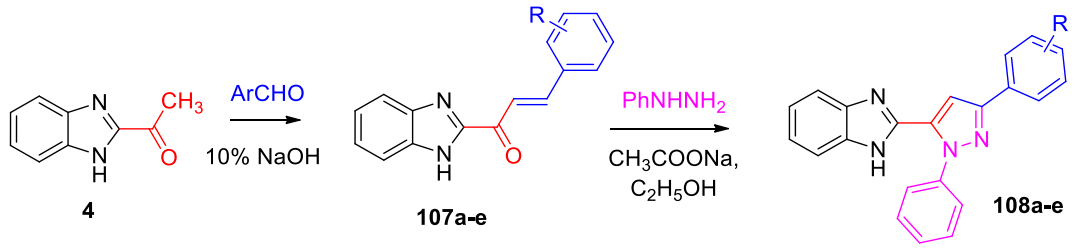
The chalcones **105a-e** were cyclized with phenylhydrazine, and 2,4-dinitro phenylhydrazine in the presence of sodium acetate under microwave irradiation to give the benzimidazole substituted pyrazole **106a-e** (**Scheme 35**). Some of the compounds showed significant anti-cancer and antibacterial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



106a-e = H, 4-OCH_3, 2-Cl, 4-Cl, 2,4-Cl

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].



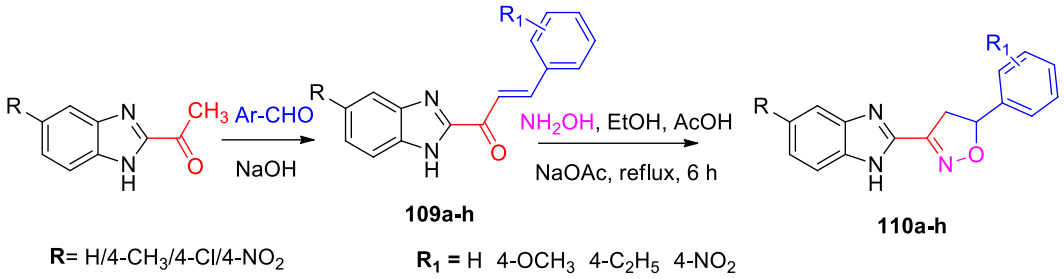
108a-e = 4-Cl, 3-Br, 4-$N(Me)_2$, 3-Cl, 4-OH

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

3.3.3. Synthesis of isoxazolines.

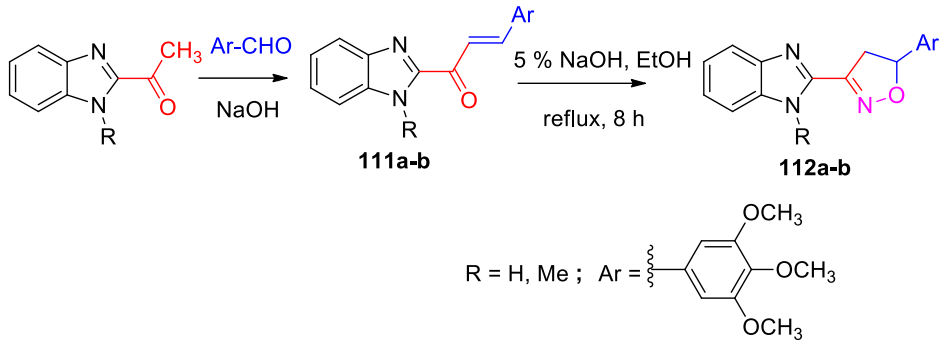
The syntheses of Benzimidazole-arylisoxazoline hybrid **110a-h** were obtained by the condensation of chalcones **109a-h** with hydroxylamine at room temperature (**Scheme 37**). The

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].



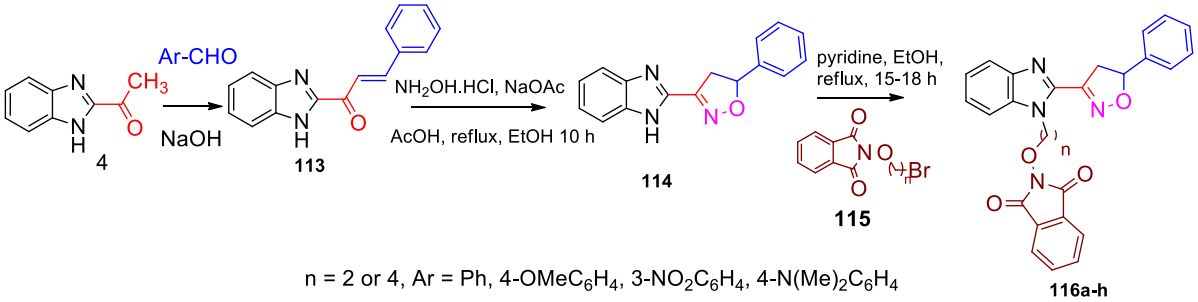
Scheme 37. Synthesis of benzimidazole linked oxazoline **110a-d.**

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 PC12cell 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].

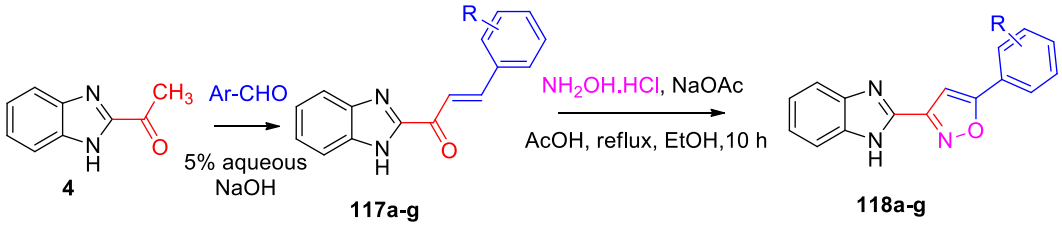


Scheme 39. Synthesis of benzimidazole linked oxazoline **116a-h.**

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].



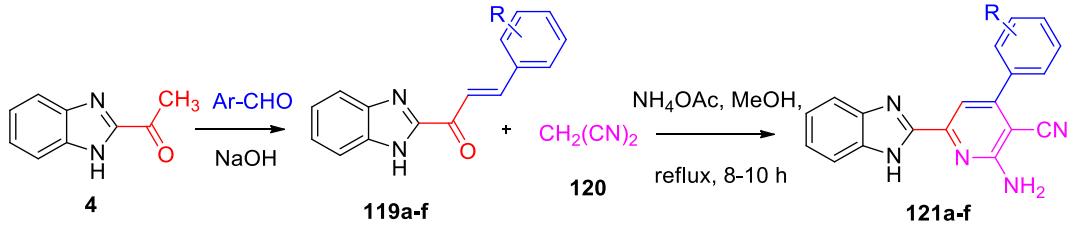
118a-g = H 4-CH3 4-OCH_3 2-Cl 4-Cl 2-NO_2 4-SCH_3

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

3.4. Synthesis of the six-membered rings.

3.4.1. Synthesis of pyridine and its derivative.

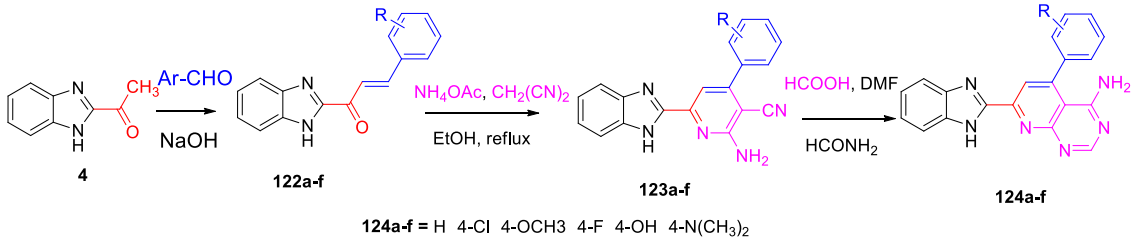
Benzimidazole embedded pyridine derivatives **121a-f** were synthesized (**Scheme 41**) by reacting chalcones **119a-f** with malononitrile **120** & ammonium acetate. Obtained compounds were evaluated for their antibacterial and antifungal activity. The compounds showed good antibacterial and moderate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



121a-f = H 4-Cl 4-OCH_3 3,4-OCH_3 3,4,5-OCH_3 4-$N(CH_3)_2$

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

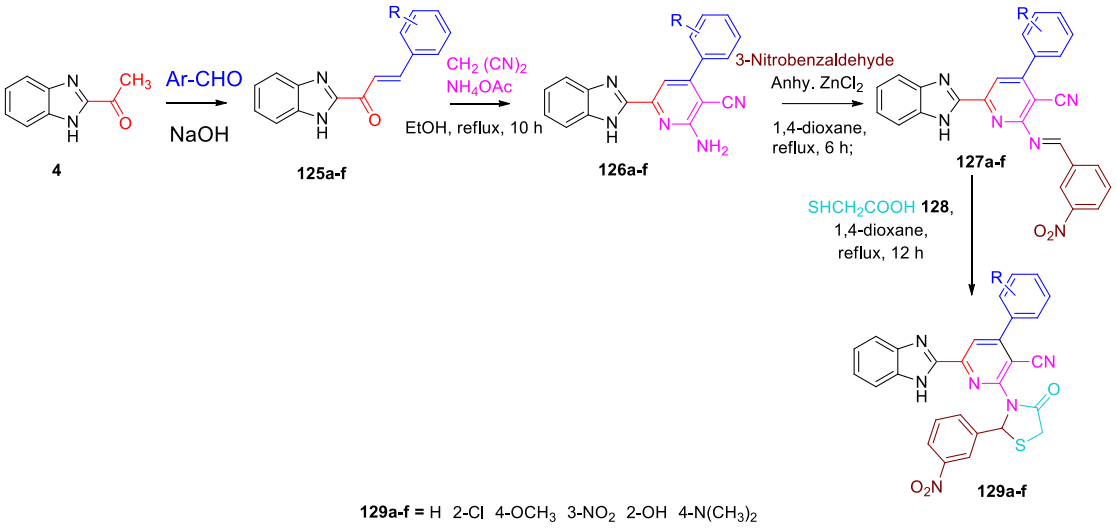
A series of benzimidazole derivatives **124a-f** were synthesized (**Scheme 42**) by reacting compound **123a-f** with formamide and formic acid in dimethylformamide solvent. Compounds **123a-f** were prepared by reaction between benzimidazole chalcone **122a-f**, malononitrile, and ammonium acetate 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].



124a-f = H 4-Cl 4-OCH3 4-F 4-OH 4-$N(CH_3)_2$

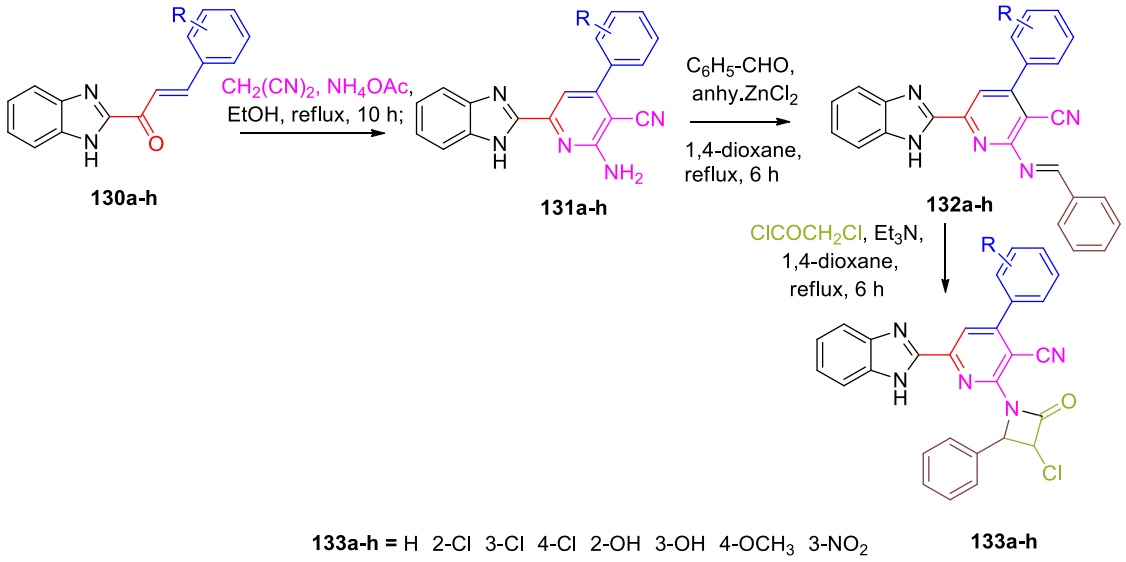
Scheme 42. Synthesis of benzimidazole linked pyridopyrimidine **124a-f.**

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-mercaptoacetic acid **128** for 12 hrs to obtain **129a-f** (**Scheme 43**). These compounds were tested for antibacterial, antifungal, and cytotoxic activity [48].



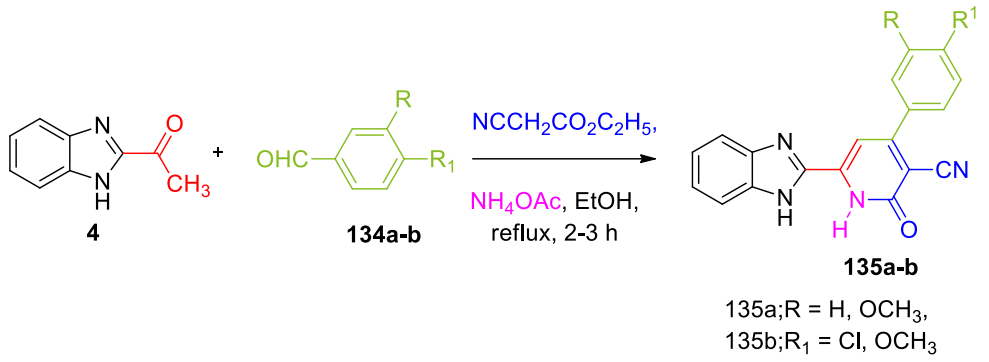
Scheme 43. Synthesis of benzimidazole linked pyridine **129a-f.**

Desai *et al.* [49] prepared benzimidazole-pyridine-azetidine hybrid **133a-h** (**Scheme 44**), stating from 2-acetyl benzimidazole through chalcone intermediates **130a-h.** Chalcone derivatives were condensed with malononitrile in the presence of ammonium acetate to afforded **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.



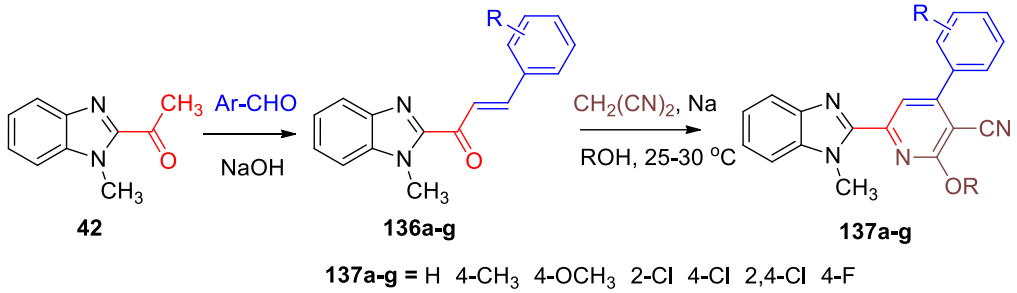
Scheme 44. Synthesis of benzimidazole linked pyridine **133a-h.**

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].



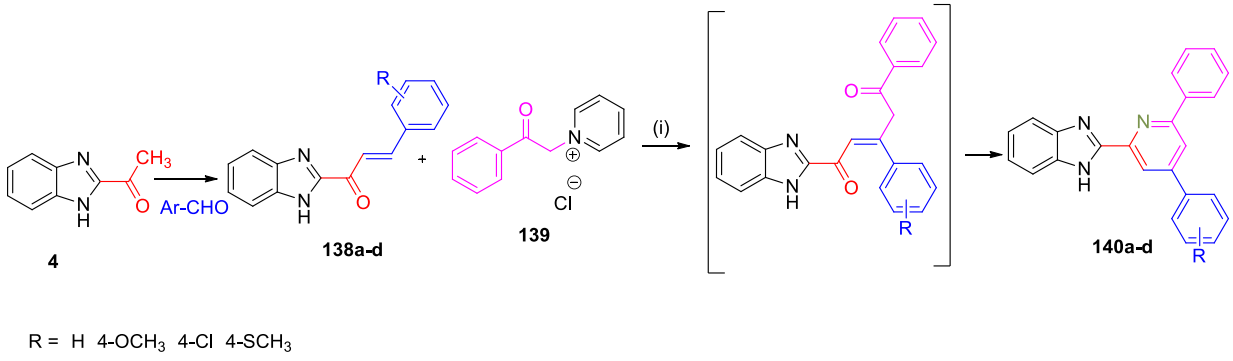
Scheme 45. Synthesis of benzimidazole linked pyridine **135a-b.**

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].



Scheme 46. Synthesis of benzimidazole linked pyridine **137a-g.**

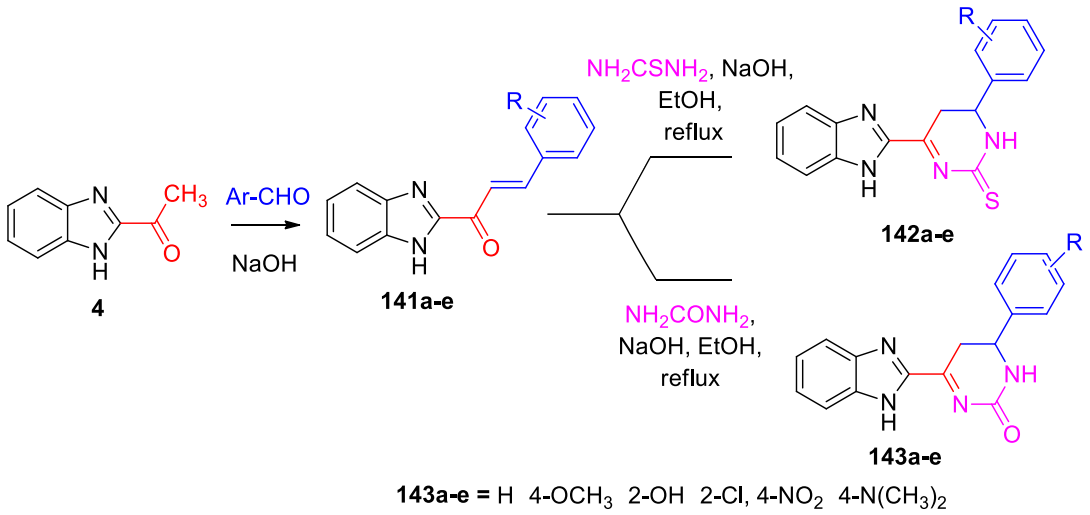
1-α-Pyridiniumacetophenone chloride **139** on reaction with 2-cinnamoylbenzimidazole **138a-d** in the presence of ammonium acetate gave pyridine derivatives **140a-d** according to Kröhnke's pyridine synthesis (**Scheme 47**) [52].



Scheme 47. Synthesis of benzimidazole linked pyridine **140a-d.**

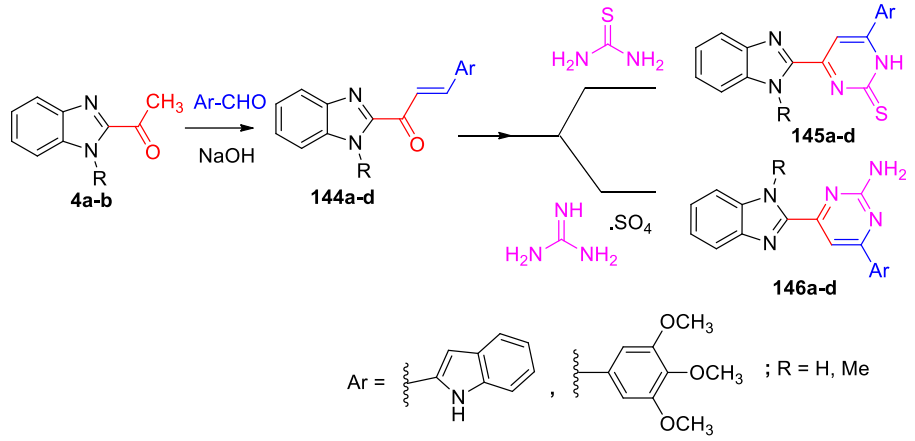
3.4.2. Synthesis of pyrimidines.

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.



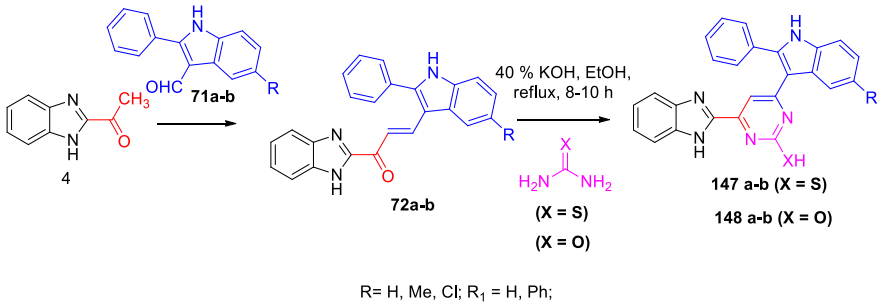
Scheme 48. Synthesis of benzimidazole linked pyrimidine **142a-e & 143a-e.**

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].



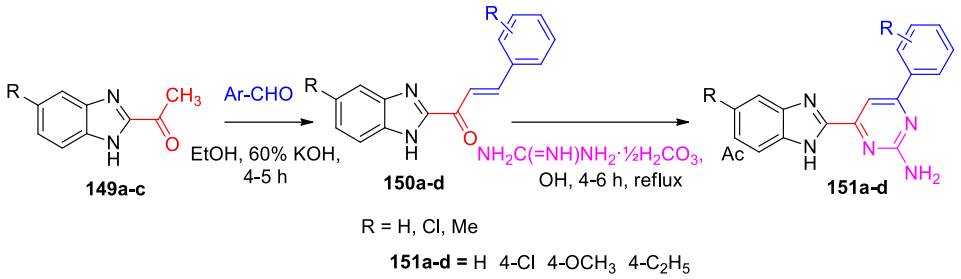
Scheme 49. Synthesis of benzimidazole linked pyrimidine **145a-d & 146a-d.**

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].



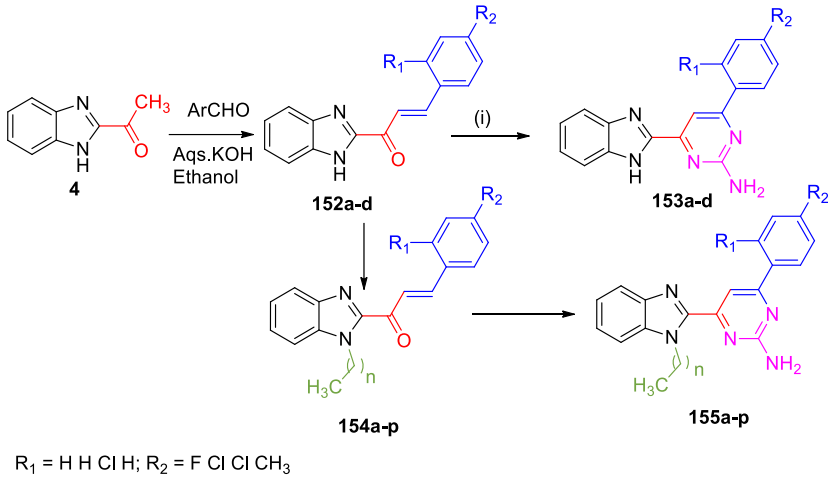
Scheme 50. Synthesis of benzimidazole linked pyrimidine **147a-b & 148a-b.**

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].



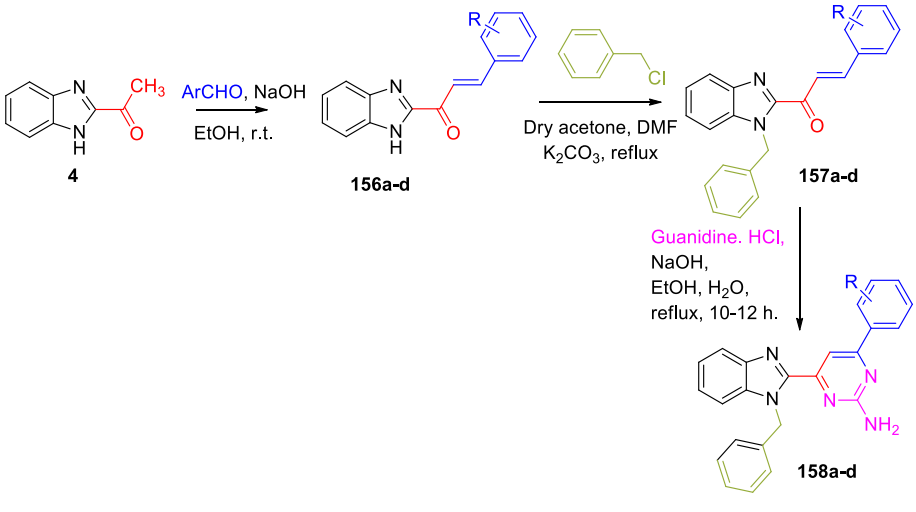
Scheme 51. Synthesis of benzimidazole linked pyrimidine **151a-d.**

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].



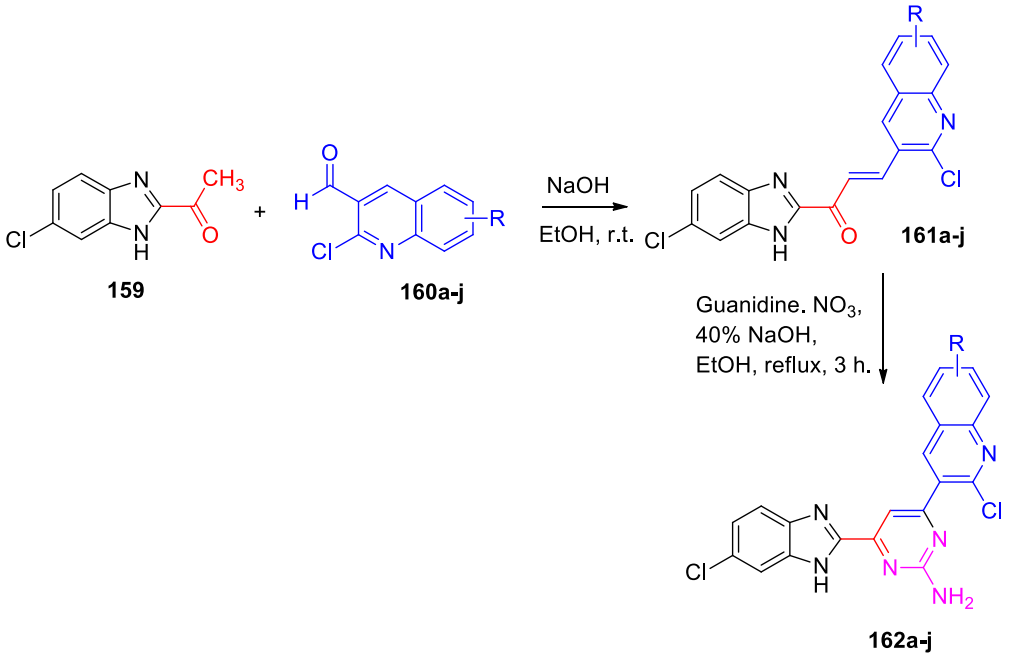
Scheme 52. Synthesis of benzimidazole linked pyrimidine **153a-p, 154a-p & 155a-p.**

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 GI_{50} values of 39.6 and 84.0 μM [56].



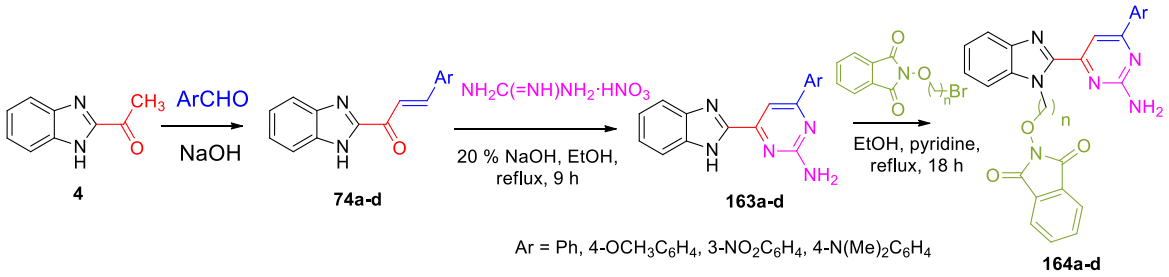
Scheme 53. Synthesis of benzimidazole linked pyrimidine **158a-d.**

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].



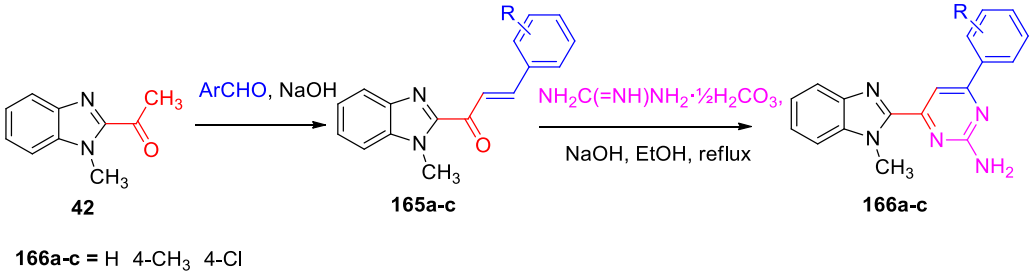
Scheme 54. Synthesis of benzimidazole linked pyrimidine **162a-j.**

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.**

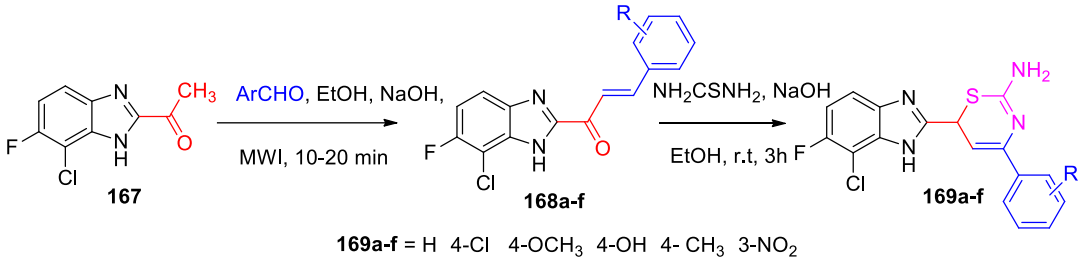
A series of benzimidazole-pyrimidine **163a-d** have been synthesized (**Scheme 56**) by the reaction of chalcones **74a-d** with guanidine carbonate for evaluating them as potential anti-inflammatory agents. Compounds showed good anti-inflammatory activity in the carrageenan-induced rat paw edema model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

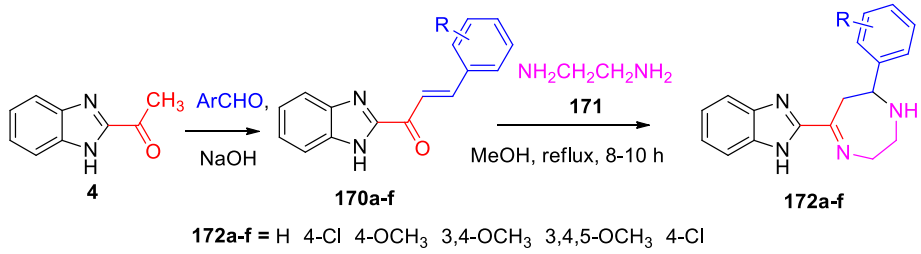


Scheme 57. Synthesis of benzimidazole linked pyrimidine **169a-f.**

3.5. Synthesis of the seven-membered rings.

3.5.1. Synthesis of diazepine.

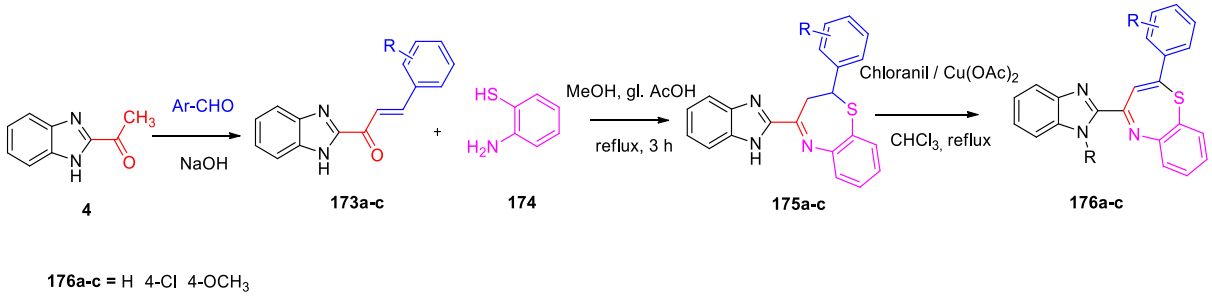
The benzimidazolylchalcones **170a-f** on treatment with ethylenediamine **171** afforded the diazepines **172a-f** under MWI condition (**Scheme 58**). The compounds were evaluated for antibacterial and antifungal activity in vitro. It was observed that all the compounds possess promising activity [59].



Scheme 58. Synthesis of benzimidazole linked diazepine **172a-f.**

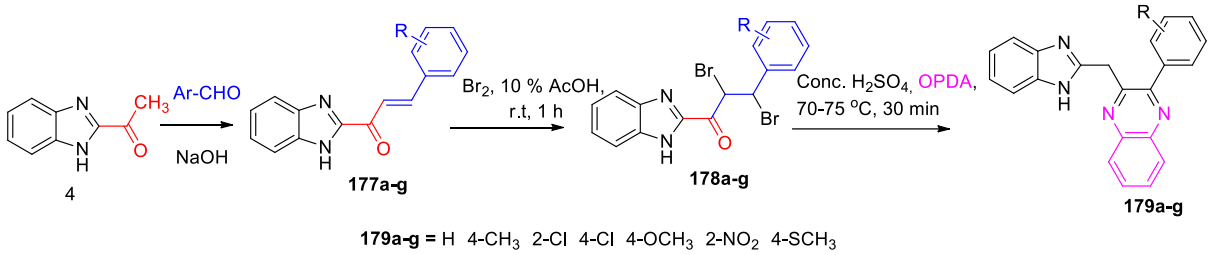
3.5.2. Synthesis of fused rings.

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.**

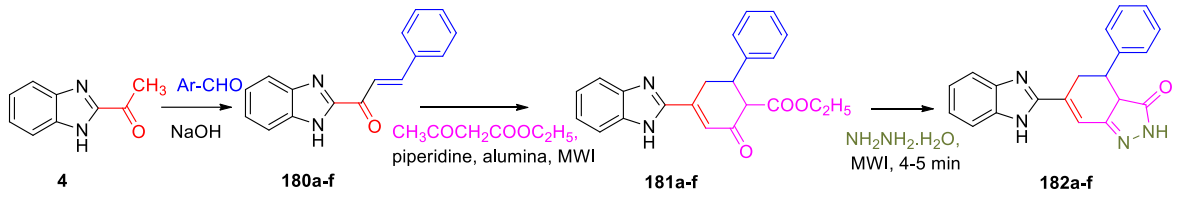
The chalcones **177a-g** on treatment with bromine in acetic acid gave dibromo derivatives **178a-g** which reacted with an o-phenylene diamine in sulphuric acid to furnish 2-(benzimidazol-2-yl-methyl)-3-arylquinoxazolines **179a-g** (**Scheme 60**) [46].



179a-g = H 4-CH_3 2-Cl 4-Cl 4-OCH_3 2-NO_2 4-SCH_3

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

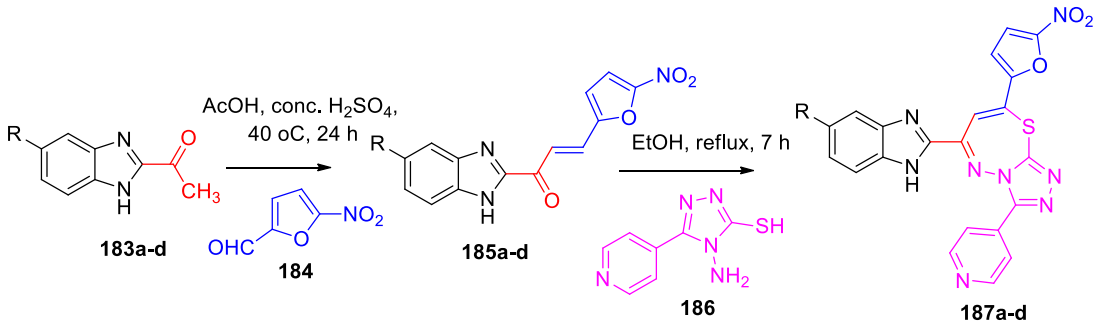
Benzimidazolylchalcones **180a-f** on reaction with ethyl acetoacetate in the presence of basic alumina gave 6-carboethoxy-3-benzimidazolyl-5-arylcyclohexenones **181a-f,** which on treatment with hydrazine hydrate gave benzimidazole linked indazoles **182a-f** under microwave-assisted condition (**Scheme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



182a-f = H 4-Cl 4-OCH_3 3,4-OCH_3 3,4,5-OCH_3 4-Cl

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

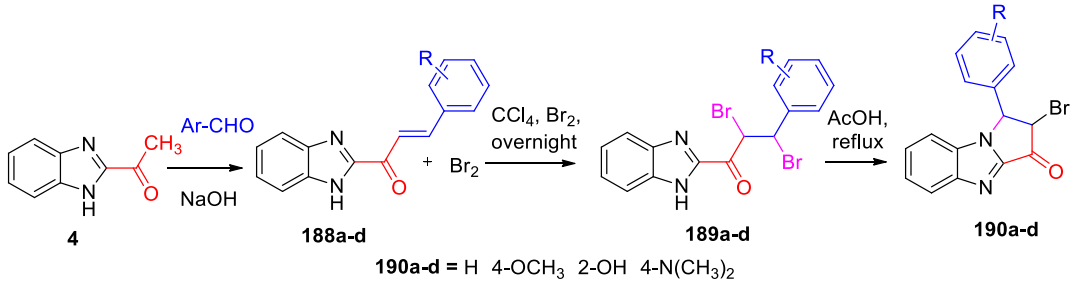
2-acetyl benzimidazoles **183a-d** on condensation reaction with 5-nitro furfural **184** at room temperature leads to the formation of chalcones **185a-d**. These compounds on cyclo condensation reaction with triazole derivative **186** afforded benzimidazole linked triazolo[3,4-*b*][1,3,4]thiadiazepines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



187a-d = H 4-Cl 4-CH_3 4- NO_2

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[l,2-a]benzimidazoles **190a-d** (**Scheme 63**) [53].



190a-d = H 4-OCH_3 2-OH 4-$N(CH_3)_2$

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

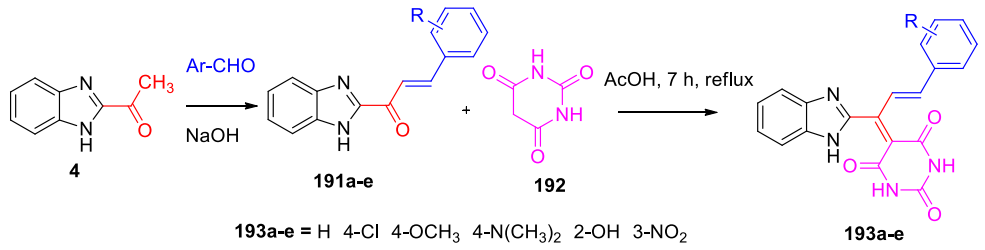
3.6. Synthesis of Miscellaneous compound.

A series of (2E)-1-(H-benzimidazol-2-yl)-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].

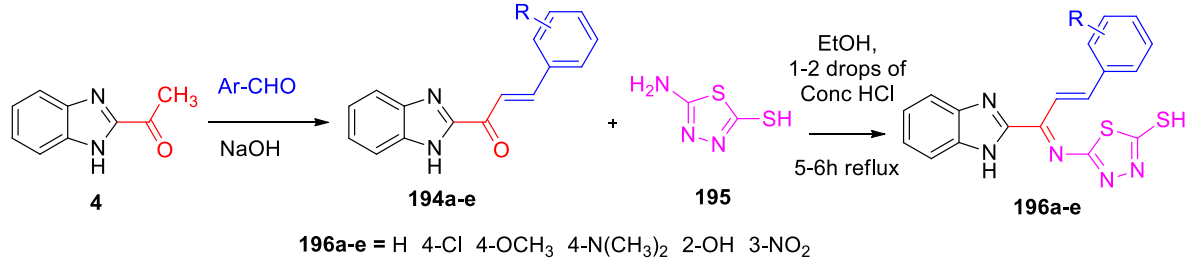
The synthesized compounds **193 a-e** also showed good antidepressant activity at a dose of 20 mg/kg. The compounds **193 a-e** considerably reduced the duration of immobility times [66].



Scheme 64. Synthesis of benzimidazole linked barbitone **193a-e.**

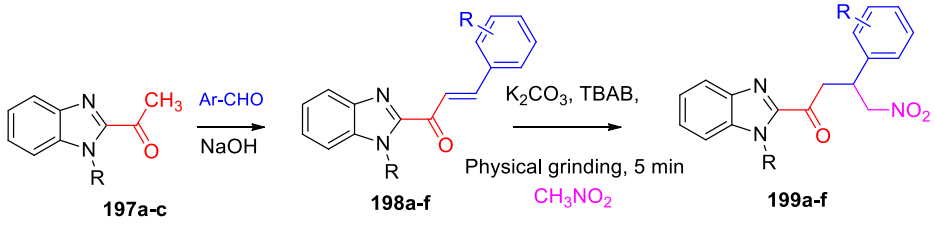
A series of some novel imines **196a-e** were prepared (**Scheme 65**) by an acid-catalyzed nucleophilic addition reaction between 5-amino-1,3,4-thiadiazole-2-thiol **195** and heteroaryl chalcones **194a-e** (**Scheme 65**). The compounds were screened for their antiulcer activity in the pylorus-ligated 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.**

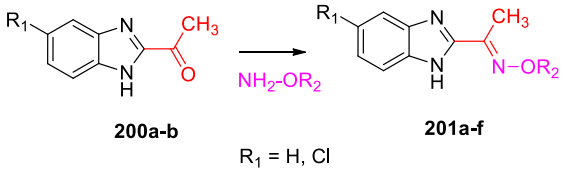
Dubey *et al.* [69] investigated the Michael addition of various α, β- unsaturated benzimidazole chalcones **198a-f** with nitromethane under solvent-free conditions in the presence of K_2CO_3 and TBAB as the surface catalyst by simple physical mixing in a mortar and pestle at room temperature gave the respective adducts **199a-f** in good yields (**Scheme 66**).



199a-f = H 4-Cl 4-OCH_3 4-CH_3 4-SCH_3 4-F

Scheme 66. Synthesis of benzimidazole derivatives **199a-f.**

2-acetyl-1*H*-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].

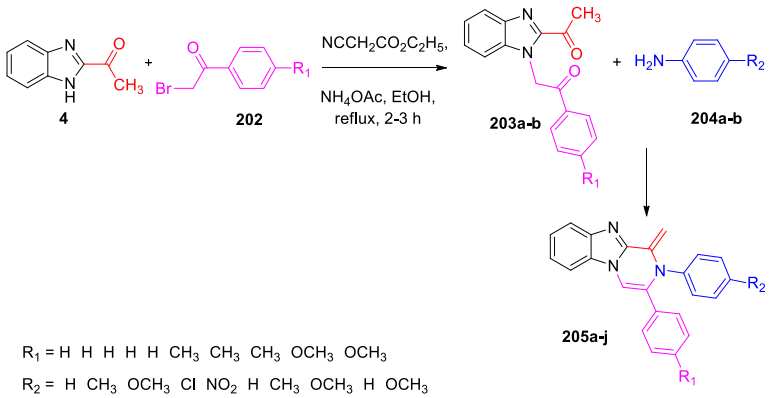


R_1 = H, Cl

R_2 = CH_3 C_2H_5 n-C_4H_9 $CH_2C_6H_5$ 4-$FC_6H_4CH_2$ 4-$ClC_6H_4CH_2$

Scheme 67. Synthesis of benzimidazole derivatives **201a-f.**

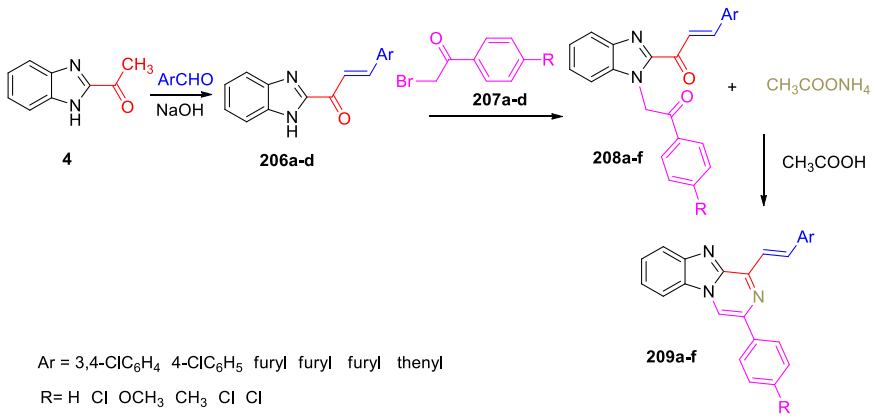
Dihydropyrazino[1,2-*a*]benzimidazole **205a-j** and 1-(2-arylvinyl)-3-arylpyrazino[1,2-*a*]benzimidazole **206a-j** were synthesized (**Scheme 68 and 69**), and their anti-cancer and anti-HIV activities were determined. The compounds did not show anti-HIV activity, whereas significant anti-cancer activity was observed against leukemia cell lines [71].



R_1 = H H H H H CH_3 CH_3 CH_3 OCH_3 OCH_3

R_2 = H CH_3 OCH_3 Cl NO_2 H CH_3 OCH_3 H OCH_3

Scheme 68. Synthesis of benzimidazole derivatives **205a-j.**

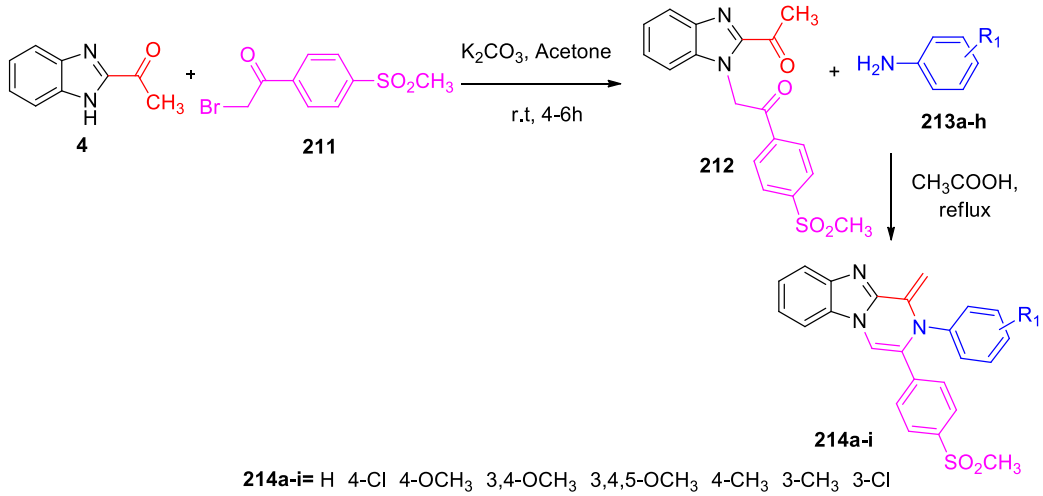


Ar = 3,4-ClC_6H_4 4-ClC_6H_5 furyl furyl furyl thenyl

R= H Cl OCH_3 CH_3 Cl Cl

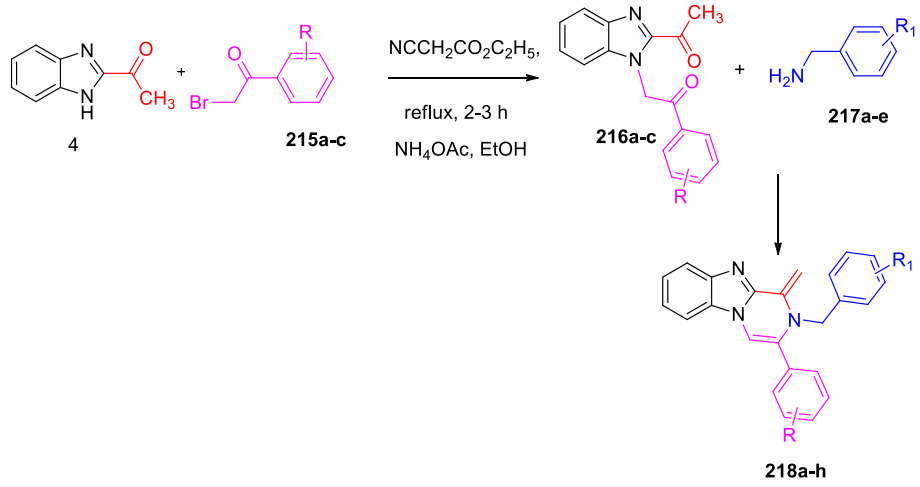
Scheme 69. Synthesis of benzimidazole derivatives **209a-f.**

Pyrazino[1,2-*a*]benzimidazole derivatives **214a-i** possessing the SO_2CH_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 [72].



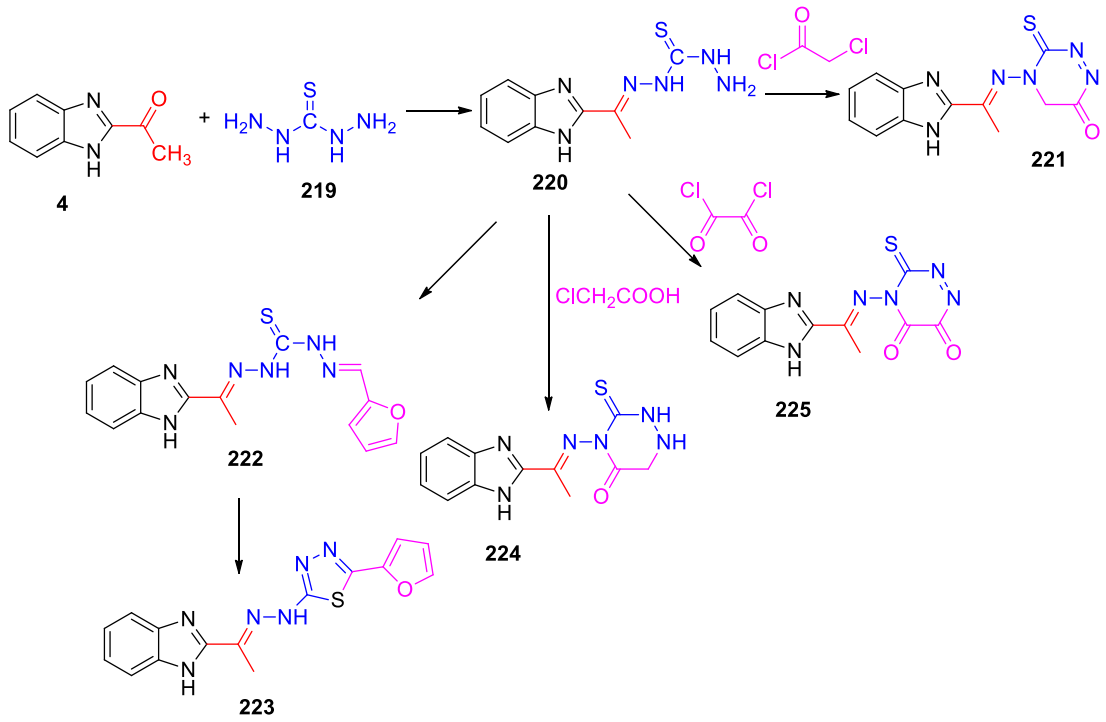
Scheme 70. Synthesis of benzimidazole derivatives **214a-i.**

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** [73].



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].



Scheme 72. Synthesis of benzimidazole derivatives **221-225.**

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

1. Kanwal, A.; Ahmad, M.; Aslam, S.; Naqvi, S.A.R.; Saif, M.J. Recent Advances in Antiviral Benzimidazole Derivatives: A Mini Review. *Pharm. Chem. J.* **2019**, *53*, 179-187, https://doi.org/10.1007/s11094-019-01976-3.

2. Yogita, B.; Manjinder, K.; Gulshan, B. Antimicrobial Potential of Benzimidazole Derived Molecules. *Mini-Rev. Med. Chem.* **2019**, *19*, 624-646, https://doi.org/10.2174/1389557517666171101104024.
3. Taha, M.; Rahim, F.; Zaman, K.; Selvaraj, M.; Uddin, N.; Farooq, R.K.; Nawaz, M.; Sajid, M.; Nawaz, F.; Ibrahim, M.; Khan, K.M. Synthesis, α-glycosidase inhibitory potential and molecular docking study of benzimidazole derivatives. *Bioorg. Chem.* **2020**, *95*, 103555, https://doi.org/10.1016/j.bioorg.2019.103555.
4. Md. Jawaid, A.; Mohammad Shahar, Y.; Vinod Kumar, S.; Ahsan Ahmed, K.; Zulphikar, A.; Haider, M.D.R.; Ankita, P. Recent Progress of Benzimidazole Hybrids for Anticancer Potential. *Curr. Med. Chem.* **2020**, *27*, 5970-6014-, https://doi.org/10.2174/0929867326666190808122929.
5. Vemana, H.P.; Barasa, L.; Surubhotla, N.; Kong, J.; Ha, S.S.; Palaguachi, C.; Croft, J.L.; Yoganathan, S.; Dukhande, V.V. Benzimidazole scaffolds as potential anti-cancer agents: Synthesis and Biological evaluation. *The FASEB Journal* **2019**, *33*, 618-646, https://doi.org/10.1096/fasebj.2019.33.1_supplement.646.18. -
6. Hayrettin Ozan, G.; Açelya, M.; Mustafa Fethi, S.; Ilkay Erdogan, O. Benzimidazole-derived Compounds Designed for Different Targets of Alzheimer's Disease. *Curr. Med. Chem.* **2019**, *26*, 3260-3278, https://doi.org/10.2174/0929867326666190124123208.
7. Bukhari, S.N.A.; Lauro, G.; Jantan, I.; Fei Chee, C.; Amjad, M.W.; Bifulco, G.; Sher, H.; Abdullah, I.; Rahman, N.A. Anti-inflammatory trends of new benzimidazole derivatives. *Future Med. Chem.* **2016**, *8*, 1953-1967, https://doi.org/10.4155/fmc-2016-0062.
8. Cheeseman, G.W. 2-Acetylbenzimidazole. Royal Soc Chemistry Thomas Graham House, Science Park, Milton Rd, Cambridge: 1964; 4645.
9. Ramaiah, K.; Dubey, P.K.; Ramanatham, J.; Grossert, J.S.; Hooper, D.L. ChemInform Abstract: An Unusual Resistance to α-Bromination by Arylacetyl Compound: Studies on Bromination of 2-Acetylbenzimidazoles and Their Subsequent Reactions with Sulfur Nucleophiles — Synthesis of Novel β-Ketosulfone Derivatives of Benzimidazoles. *ChemInform* **1999**, *30*, https://doi.org/10.1002/chin.199941120.
10. Kalirajan, R.; Rathore, L.; Jubie, S.; Gowramma, B.; Gomathy, S.; Sankar, S. Microwave assisted synthesis of some novel pyrazole substituted benzimidazoles and evaluation of their biological activities. *Indian J. Chem. Sect. B* **2011**.
11. Kumar, P.K.; Dubey, P.K. Studies on preparation of 2-Acetylbenzimidazole. *Der Pharma Chemica* **2012**, *4*, 1292-1295.
12. Ouattara, M.; Sissouma, D.; Koné, M.W.; Menan, H.E.; Touré, S.A.; Ouattara, L. Synthesis and anthelmintic activity of some hybrid Benzimidazolyl-chalcone derivatives. *Tropical Journal of Pharmaceutical Research* **2011**, *10*, 767-775, https://doi.org/10.4314/tjpr.v10i6.10.
13. Mathew, B.; Unnikrishnan, G.; Shafeer, V.P.; Muhamed, M.C.; Femina, P. Microwave assisted synthesis, physicochemical properties and antimicrobial activity of benzimidazole chalcones. *Der Pharma Chemica* **2011**, *3*, 627-631.
14. Babu, I.; Selvakumar, S. An Antibacterial, Antifungal and Anthelmintic Evaluations of Some Synthesized Chalcone Derived Benzimidazoles. *Biosciences Biotechnology Research Asia* **2013**, *10*, 891-896.
15. Wu, L.-t.; Jiang, Z.; Shen, J.-j.; Yi, H.; Zhan, Y.-c.; Sha, M.-q.; Wang, Z.; Xue, S.-t.; Li, Z.-r. Design, synthesis and biological evaluation of novel benzimidazole-2-substituted phenyl or pyridine propyl ketene derivatives as antitumour agents. *Eur. J. Med. Chem.* **2016**, *114*, 328-336, https://doi.org/10.1016/j.ejmech.2016.03.029
16. Meshram, G.; Vala, V.; Wagh, P.; Deshpande, S. Ultrasound accelerated synthesis of novel benzimidazole derived chalcones as glucosidases inhibitor and antimicrobial agents. *Indian J. Chem. Sect. B* **2016**, *55*, 613-623.
17. Sissouma, D.; Ouattara, M.; Kone, M.W. Synthesis and antifungal activities of some benzimidazolyl-chalcones, analogues of chlormidazole. *African Journal of Pharmacy and Pharmacology* **2015**, *9*, 418-423. https://doi.org/10.5897/ajpp2014.4171.
18. Meshram, G.A.; Vala, V.A. Synthesis, characterization, and antimicrobial activity of benzimidazole-derived chalcones containing 1,3,4-oxadiazole moiety. *Chemistry of Heterocyclic Compounds* **2015**, *51*, 44-50, https://doi.org/10.1007/s10593-015-1653-1.
19. Padhy, G.; Panda, J.; Behera, A. Synthesis and characterization of novel benzimidazole chalcones as antibacterial agents. *Der Pharma Chemica* **2016**, *8*, 235-241.
20. Abdel-Motaal, M.; Almohawes, K.; Tantawy, M.A. Antimicrobial evaluation and docking study of some new substituted benzimidazole-2yl derivatives. *Bioorg. Chem.* **2020**, *101*, 103972, https://doi.org/10.1016/j.bioorg.2020.103972.
21. Wu, L.; Yang, Y.; Wang, Z.; Wu, X.; Su, F.; Li, M.; Jing, X.; Han, C. Design, Synthesis, and Biological Evaluation of Aromatic Amide-Substituted Benzimidazole-Derived Chalcones. The Effect of Upregulating TP53 Protein Expression. *Molecules* **2020**, *25*, 1162., https://doi.org/10.3390/molecules25051162.
22. Djemoui, A.; Naouri, A.; Ouahrani, M.R.; Djemoui, D.; Lahcene, S.; Lahrech, M.B.; Boukenna, L.; Albuquerque, H.M.T.; Saher, L.; Rocha, D.H.A.; Monteiro, F.L.; Helguero, L.A.; Bachari, K.; Talhi, O.; Silva, A.M.S. A step-by-step synthesis of triazole-benzimidazole-chalcone hybrids: Anti-cancer activity in human cells+. *J. Mol. Struct.* **2020**, *1204*, 127487, https://doi.org/10.1016/j.molstruc.2019.127487.

23. Dasari, G.K.; Sunkara, S.; Gadupudi, P.C.R. Green and ecofriendly synthesis of indole-condensed benzimidazole chalcones in water and their antimicrobial evaluations. *J. Heterocycl. Chem.* **2020**, *57*, 1201-1210, https://doi.org/10.1002/jhet.3856.
24. Hsieh, C.-Y.; Ko, P.-W.; Chang, Y.-J.; Kapoor, M.; Liang, Y.-C.; Chu, H.-L.; Lin, H.-H.; Horng, J.-C.; Hsu, M.-H. Design and synthesis of benzimidazole-chalcone derivatives as potential anti-cancer agents. *Molecules* **2019**, *24*, 3259, https://doi.org/10.3390/molecules24183259.
25. Nofal, Z.M.; Soliman, E.A.; Abd El-Karim, S.S.; El Zahar, M.I.; Srour, A.M.; Sethumadhavan, S.; Maher, T.J. Novel benzimidazole derivatives as expected anti-cancer agents. *Acta Pol. Pharm.* **2011**, *68*, 519-534.
26. Yar, M.S.; Abdullah, M.M.; Majeed, J. In vitro anti-tubercular screening of newly synthesized benzimidazole derivatives. *World Acad. Sci. Engr. Tech* **2009**, *55*, 593-599.
27. Shaharyar, M.; Abdullah, M.M.; Bakht, M.A.; Majeed, J. Pyrazoline bearing benzimidazoles: Search for anti-cancer agent. *Eur. J. Med. Chem.* **2010**, *45*, 114-119, https://doi.org/10.1016/j.ejmech.2009.09.032.
28. Cao, X.Q.; Lin, X.H.; Zhu, Y.; Ge, Y.Q.; Wang, J.W. The optical properties, synthesis and characterization of novel 5-aryl-3-benzimidazolyl-1-phenyl-pyrazoline derivatives. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* **2012**, *98*, 76-80, https://doi.org/10.1016/j.saa.2012.08.036.
29. Desai, N.C.; Pandya, D.D.; Joshi, V.V.; Rajpara, K.M.; Vaghani, H.V.; Satodiya, H.M. Synthesis, characterization and antimicrobial screening of hybrid molecules containing benzimidazole-pyrazole and pyridine nucleus. *Med. Chem. Res.* **2012**, *21*, 4463-4472, https://doi.org/10.1007/s00044-012-9990-4.
30. Desai, N.C.; Pandya, D.D.; Kotadiya, G.M.; Desai, P. Synthesis and characterization of novel benzimidazole bearing pyrazoline derivatives as potential antimicrobial agents. *Med. Chem. Res.* **2014**, *23*, 1474-1487, https://doi.org/10.1007/s00044-013-0756-4.
31. Rajora, J.; Yadav, J.; Kumar, R.; Srivastava, Y.K. ChemInform Abstract: Microwave Assisted Transformation of Benzimidazolyl Chalcones into N1-Substituted Pyrazolines and Evaluation of Their Antimicrobial Activities. *ChemInform* **2010**, *41*. https://doi.org/10.1002/chin.201047119.
32. Rajora, J.; Srivastava, Y. Eco friendly microwave assisted synthesis of some 3-benzimidazolyl -5- aryl-2-pyrazolin -1- carboxaldehyde hydrazones as potent antimicrobial agents. *Rasayan Journal of Chemistry* **2009**, *2*, 641-644.
33. Padhy, G.K.; Panda, J.; Behera, A.K. Synthesis and characterization of novel benzimidazole embedded 1, 3, 5-trisubstituted pyrazolines as antimicrobial agents. *J Serbian Chem. Soc.* **2017**, 82, 985–993, https://doi.org/10.2298/JSC160604089P.
34. Sharmila, A.; Shivakumar, B.; Gaviraj, E.N. Synthesis and evaluation of new pyrazolines of benzimidazole as potent analgesic and anti-inflammatory agents. *Der Pharma Chemica* **2016**, *8*, 33-37.
35. Saundane, A.R.; Mathada, K.N. Synthesis, characterization, and biological evaluation of some new chalcones containing indole moiety and their derivatives. *Monatshefte für Chemie - Chemical Monthly* **2016**, *147*, 1291-1301.
36. Bapna, A.; Ojha, S.; Talesara, G.L. ChemInform Abstract: Facile Synthesis of Alkoxyphthalimide-Derivatized Benzimidazole-Assembled Pyrazoles, Pyrimidines and Isoxazoles, via Common Intermediate Chalcone. *ChemInform* **2008**, *39*, https://doi.org/10.1002/chin.200846118.
37. Sawhney, S.N.; Vir, D.; Gupta, A. Synthesis and Antiinflammatory Activity of Some 2-(5-Aryl-4, 5-dihydropyrazol-3-yl)-and 2-(2-Amino-6-arylpyrimidin-4-yl) benzimidazoles. *ChemInform* **1991**, *22*, 1107–1112.
38. Paul, S.S.P.; Yardily, A.; Rajasekharan, K.N.; Abbs Fen Reji, T.F. ChemInform Abstract: Synthesis of Anticancer Compounds 2-(4-Amino-2-arylaminothiazol-5-oyl)-N-methylbenzimidazoles. *ChemInform* **2013**, *44*, https://doi.org/10.1002/chin.201330144.
39. Malla Reddy, V.; Ravinder Reddy, K. Synthesis and Antimicrobial Activity of Some Novel 4- (1H-Benz[d]imidazol- 2yl)-1,3-thiazol-2-amines. *Chem. Pharm. Bull* **2010**, 58, 953–956, https://doi.org/10.1248/cpb.58.953.
40. Eldebss, T.M.A.; Farag, A.M.; Shamy, A.Y.M. Synthesis of Some Benzimidazole-based Heterocycles and their Application as Copper Corrosion Inhibitors. *J. Heterocycl. Chem.* **2019**, *56*, 371-390, https://doi.org/10.1002/jhet.3407.
41. Rajora, J.; Srivastava, Y. Synthesis and antimicrobial activities of some benzimidazolyl pyrazoles. *Rasayan Journal of Chemistry* **2009**, *2*, 655-658.
42. Kumar, K.; Hemasunder, G.; Naidu, A.; Dubey, P.K. Alkylation studies on pyrazolyl and isoxazolyl benzimidazoles. *Indian J. Heterocycl. Chem.* **2011**, *20*, 393-398.
43. Arora, R.; Kaur, A.; Gill, N.S. Analgesic and anti-inflammatory activity of some newly synthesized novel pyrazole derivatives of benzimidazole. *Curr. Res. Chem* **2012**, *4*, 76-87, https://doi.org/10.3923/crc.2012.76.87.
44. Reddy, V.M.; Reddy, K.R. Synthesis and biological evaluation of some novel-3-(5-substituted benzimidazol-2-yl)-5-arylisoxazolines. *Chin. Chem. Lett.* **2010**, *21*, 1145-1148, https://doi.org/10.1016/j.cclet.2010.06.017.
45. Vekariya, N.A.; Khunt, M.D.; Parikh, A.R. Synthesis of Isoxazoles and Quinoxalines as Potential Anti-cancer Agents. *ChemInform* **2003**, *34*, https://doi.org/10.1002/chin.200322165.

46. Yadav, J.S.; Srivastava, Y.K. A facile synthesis and antimicrobial activity of some new 2-subsituted benzimidazole derivatives carrying pyridine. *Der Chemica Sinica* **2011**, *2*, 1-7.
47. Maheswaran, N.; Saleshier, M.F.; Mahalakshmi, K.; Sureshkannan, V.; Parthiban, N.; Reddy, K.A. Synthesis And Characterisation Of 7-(1 H-Benzimidazol-2-Yl)-5-(Substituted Phenyl) Pyrido[2, 3-D] Pyrimidin-4-Amine For Their Biological Activity. *International Journal of Chemical Sciences* **2012**, *10*, 43-51.
48. Desai, N.C.; Pandya, D.D.; Bhatt, K.A.; Kotadiya, G.M.; Priyanka, D. Synthesis, antimicrobial, and cytotoxic activities of novel benzimidazole derivatives bearing cyanopyridine and 4-thiazolidinone motifs. *Med. Chem. Res.* **2014**, *23*, 3823-3835, https://doi.org/10.1007/s00044-014-0971-7.
49. Desai, N.C.; Pandya, D.D.; Kotadiya, G.M.; Desai, P. Synthesis, antimicrobial and cytotoxic activity of 2-azetidinone derivatives of pyridyl benzimidazoles. *Med. Chem. Res.* **2014**, *23*, 1725-1741, https://doi.org/10.1007/s00044-013-0775-1.
50. Rida, S.M.; El-Hawash, S.A.M.; Fahmy, H.T.Y.; Hazzaa, A.A.; El-Meligy, M.M.M. Synthesis of novel benzofuran and related benzimidazole derivatives for evaluation ofin vitro anti-HIV-1, anti-cancer and antimicrobial activities. *Arch. Pharmacal Res.* **2006**, *29*, 826-833, https://doi.org/10.1007/BF02973901.
51. Nofal, Z.M.; Srour, A.M.; El-Eraky, W.I.; Saleh, D.O.; Girgis, A.S. Rational design, synthesis and QSAR study of vasorelaxant active 3-pyridinecarbonitriles incorporating 1H-benzimidazol-2-yl function. *Eur. J. Med. Chem.* **2013**, *63*, 14-21, https://doi.org/10.1016/j.ejmech.2013.01.042.
52. Dubey, P.K.; Kumar, C.R.; Reddy, P.V.V. Syntheses of 1-alkyl-2-(substituted-2-pyridyl) benzimidazoles. *Indian J. Chem. Sect. B* **2003**, 42, 2115–2118.
53. Zoorob, H.H.; Hammouda, H.A.; Ismail, E. Study of the Reactivity of 2-Cinnamoylbenzimidazole towards Thiourea, Urea, Hydrazines and Hydroxylamine Hydrochloride. *Zeitschrift für Naturforschung B* **1977**, *32*, 443-446, https://doi.org/10.1515/znb-1977-0419.
54. Ravinder Reddy, K.; Malla Reddy, V.; Srinivas, B. Synthesis And Characterization Of Some Novel 2-[(5-Aryl)-4, 5-Dihydro-1h-Pyrazole-3-Yl]-1h-Benzimidazoles With Antimicrobial Activity. *International Journal of Pharmaceutical Sciences and Drug Research* **2014**, *6*.
55. Liu, H.-B.; Gao, W.-W.; Tangadanchu, V.K.R.; Zhou, C.-H.; Geng, R.-X. Novel aminopyrimidinyl benzimidazoles as potentially antimicrobial agents: Design, synthesis and biological evaluation. *Eur. J. Med. Chem.* **2018**, *143*, 66-84, https://doi.org/10.1016/j.ejmech.2017.11.027.
56. Padhy, G.K.; Panda, J.; Behera, A.K. Synthesis and Characterization of Novel N-Benzylbenzimidazole Linked Pyrimidine Derivatives as Anticancer Agents. *Indian J. Pharm. Educ. Res.* **2019**, *53*, S129–S134, https://doi.org/10.5530/ijper.53.2s.57.
57. Madawali, I.M.; Kalyane, N.V.; Gaviraj, E.N.; Shivakumar, B. Synthesis and Antimicrobial activity of some new Pyrimidines of 6-chlorobenzimidazoles. *Oriental Journal of Chemistry* **2018**, *34*, 1633, http://dx.doi.org/10.13005/ojc/340358.
58. Gayathri, B.; Hipparagi, S.M.; Ramjith, U.S.; Jacob, C.M. Microwave Assisted Synthesis of Fluoro, Chloro 2-Substituted Benzimidazole Thiazine Derivatives for Antibacterial and Analgesic Activities. *Int. J. Res. Pharm. Sci.* **2016**, 2, 146–158.
59. Yadav, J.S.; Srivastava, Y. An efficient microwave assisted synthesis of some novel 1, 4 dizepine derivatives as possible antimicrobial agents. *Rasayan Journal of Chemistry* **2010**, *3*, 726-730.
60. Dubey, P.K.; Naidu, A.; Kumar, C.R.; Reddy, P.V.V. Preparation of 4-(1-alkyl-benzo [d] imidazole-2-yl)-2-phenyl-2, 3 dihydrobenzo (b)[1, 4] thiazepines. *Indian J. Chem. Sect. B* **2003**, 42, 1701–1705.
61. Yadav, J.S.; Rajora, J.; Srivastava, Y.K. Some transformations of benzimidazolyl chalcones using MAOS protocol—a green approach. *Arch Appl Sci Res* **2011**, *3*, 192-198.
62. Malla Reddy, V.; Ravinder Reddy, K. Synthesis and Antibacterial Activity of Some Novel 6-(1H-benz[d]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro [1,2, 4] triazolo [3,4-b][1,3,4] thiadiazepines. *Chem. Pharm. Bull* **2010**, 58, 1081–1084, http://dx.doi.org/10.1248/cpb.58.1081.
63. Mathew, B.; Suresh, A.J.; Anbazhagan, S. Microwave Assisted Synthesis, Physico-chemical Properties and Antioxidant Activity of a,b-Unsaturated Benzimidazole Derivatives Incorporated with Baritone Moiety. *Asian J. Chem.* **2013**, *25*, 1853-1856, https://doi.org/10.14233/ajchem.2013.13187.
64. Mathew, B.; Suresh, J.; Anbazhagan, S. Synthesis and PASS-assisted in silico approach of some novel 2-substituted benzimidazole bearing a pyrimidine-2, 4, 6(trione) system as mucomembranous protector. *J. Pharm. Bioallied Sci.* **2013**, *5*, 39-43, https://doi.org/10.4103/0975-7406.106563.
65. Mathew, B.; Suresh, J.; Vinod, D. Antitumour activity of 5-[(2E)-1-(1H-benzimidazol-2-yl)-3-substituted phenylprop-2-en-1-ylidene] pyrimidine-2,4,6(1H,3H,5H)-triones against Dalton's ascitic lymphoma in mice. *Med. Chem. Res.* **2013**, *22*, 3911-3917, https://doi.org/10.1007/s00044-012-0407-1.
66. Mathew, B.; Suresh, J.; Anbazhagan, S. Development of novel (1-H) benzimidazole bearing pyrimidine-trione based MAO-A inhibitors: Synthesis, docking studies and antidepressant activity. *Journal of Saudi Chemical Society* **2016**, *20*, S132-S139, https://doi.org/10.1016/j.jscs.2012.09.015.
67. Mathew, B.; Suresh, J.; Anbazhagan, S.; Chidambaranathan, N. Discovery of some novel imines of 2-amino, 5-thio, 1,3,4-thiadiazole as mucomembranous protector. Synthesis, antioxidant activity and in silico PASS approach. *Journal of Saudi Chemical Society* **2016**, *20*, S426-S432, https://doi.org/10.1016/j.jscs.2013.01.002.

68. Mathew, B.; Suresh, J.; Anbazhagan, S.; Devaraji, V. Hypnotic Profile of Imines from Benzimidazole Chalcones: Mechanism of Synthesis, DFT Studies and in silico Screening. *Cent. Nerv. Syst. Agents Med. Chem.* **2013**, *13*, 207-216, https://doi.org/10.2174/18715249146661404061359 30.
69. Dubey, P.K.; Reddy, P.V.V.; Srinivas, K. An Expeditious "Green" Michael Addition of Nitro Methane to Benzimidazole Chalcones in the Presence of TBAB as Surface Catalyst. *Lett. Org. Chem.* **2007**, *4*, 445-447, https://doi.org/10.2174/157017807781467533.
70. Jiang, L.; Wang, H.; Mu, W.; Ji, Z.; Cao, P. Synthesis and Fungicidal Activity of 2-Acetyl-6-(un)substituted-1H-benzimidazole Oxime-ethers. *Chin. J. Chem .* **2011**, *29*, 539-543, https://doi.org/10.1002/cjoc.201190119.
71. Demirayak, Ş.; Abu Mohsen, U.; Çağri Karaburun, A. Synthesis and anti-cancer and anti-HIV testing of some pyrazino[1,2-a]benzimidazole derivatives. *Eur. J. Med. Chem.* **2002**, *37*, 255-260, https://doi.org/10.1016/S0223-5234(01)01313-7.
72. Azami Movahed, M.; Daraei, B.; Shahosseini, S.; Esfahanizadeh, M.; Zarghi, A. Design, synthesis, and biological evaluation of new pyrazino[1,2-a]benzimidazole derivatives as selective cyclooxygenase (COX-2) inhibitors. *Arch. Pharm.* **2019**, *352*, 1800265, https://doi.org/10.1002/ardp.201800265.
73. Demirayak, Ş.; Yurttaş, L. Synthesis and anti-cancer activity of some 1,2,3-trisubstituted pyrazinobenzimidazole derivatives. *J. Enzyme Inhib. Med. Chem.* **2014**, *29*, 811-822, https://doi.org/10.3109/14756366.2013.858142.