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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF PYRAZOLINE BEARING BENZIMIDAZOLE DERIVATIVES AN-UP-TO-DATE-REVIEW

Pushkar Kumar Ray[1], Salahuddin[2], Rajnish Kumar[3], Akhalesh Kumar[4]
[1]Department of Pharmaceutical Chemistry, Noida Institute of Engineering and Technology (Pharmacy Institute), Plot No-19, Knowledge Park-2, Greater Noida Uttar Pradesh-201306, India
[2]sallu_05@yahoo.co.in

ABSTRACT:

Background: Pyrazolines are a heterocyclic compound with a cyclic structure. Pyrazoline is a five-membered ring made up of three carbon and two nitrogen atoms, with just one endocyclic bond and one group of electron-rich nitrogen carriers. Benzimidazole is a heterocyclic aromatic organic compound. Benzene and imidazole are fused to form this bicyclic compound. It's a colorless liquid. In this article, several methods are used to synthesis compound pyrazoline and benzimidazole derivatives with a substantial biological effect.

Objective: Pyrazolines and Benzimidazoles are multifunctional applications. The current review on pyrazoline and benzimidazole derivatives patent literature (1989-2021) describing the introduction, general method, and synthetic scheme on anticancer, anthelmintic, antidiabetic, antimalarial,antiproliferative, antibacterial, anti-histaminic,antitubercular, antinociceptive, and antimicrobial activity have been discussed, also in the general literature area in this review. The research of pyrazoline and benzimidazole derivatives' biological activity has been a fascinating area of pharmaceutical chemistry.

Conclusion: Pyrazolines are a heterocyclic compound with a cyclic structure. Pyrazoline is a five-membered ring made up of three carbon and two nitrogen atoms. A heterocyclic aromatic organic compound, benzimidazoles is a heterocyclic aromatic organic compound. Benzene and imidazole are fused to form this bicyclic compound. Several methods are used to synthesis compound pyrazoline and benzimidazole derivatives with a substantial biological effect. Many approaches can be used to figure out their Synthesis. Numerous Pyrazoline and benzimidazole derivatives have been discovered to have an essential pharmacologic effect on anticancer activity, which has encouraged research in this area. The use of pyrazoline and benzimidazole against a brilliant moiety and has an enormous scope of interest for the researchers to search more and more about this moiety.

KEYWORDS: Pyrazoline; Benzimidazole; Bacteria; Cell lines; Dihydrofolae reductase; Synthetic method.

I. INTRODUCTION:

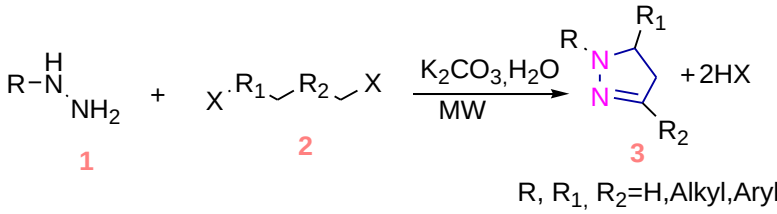
Pyrazolines are heterocyclic compounds that have a wide variety of biological uses. The fluorescent agent pyrazoline, which absorbs light between 300 and 400 nm and induces blue fluorescence, is the most commonly used [1].Pyrazoline is a five-membered ring with just one endocyclic bond and three carbon and two nitrogen atoms [2].Pyrazoline and its derivatives have antimicrobial [3], antiviral [4], antitubercular[5], anti-HIV[6], molluscicidal[7], and cerebroprotective[8].Pyrazoline, also known as dihydropyrazoles, is an electron-rich nitrogenous heterocycle whose chemistry is closely similar to pyrazoles. Pyrazoline derivatives are also electron-rich nitrogenous heterocycles [9]. Sulfinpyrazone, a pyrazoline derivative, is a highly effective uricosuric drug that lowers uric acid levels while increasing urine volume. In contrast, pyrazoline derivatives are used as cannabinoid CB1 receptor reverse agonists in clinical trials [10-11].Axitinib is a pyrazoline-dependent VEGFR second-generation inhibitor used to treat phone cell carcinoma[12]. It binds to the intracellular tyrosine kinase domains of vascular endothelial growth factor receptors (VEGFRs)[13-14-15].

Angiogenesis is blocked, and cells die when the amount of VEGF protein is reduced [16]. GDC-0941 (pictilisibDimethane Sulfonate) is a pyrazoline derivative that is a selective P13k inhibitor. It is currently in the clinical phase -2 and is a promising anticancer agent [17]. Pyrazinamide,9-methoxy pyrazoleacridine (NSC-

366140), is a pyrazoline-fused acridine ring discovered as a potential anticancer drug candidate in phase 2 medical trials [18-19]. Li. *et al.* 2-pyrazoline-based compound defined as a potential anticancer agent [20]. A benzene ring is fused to the 4 and 5 positions of imidazole to form the benzimidazole nucleus, a heterocyclic aromatic system. It can be found in a wide range of naturally occurring compounds and is essential in medicinal chemistry [21-22].Benzimidazoles are a promising class of bioactive heterocyclic compounds with a wide variety of biological functions. This nucleus, in particular, is a vitamin-B12 constituent [23].Benzimidazole ring system can be found in a variety of antioxidants [24-25-26], antiphrastic [27-28]anthelmintic [29], antiproliferative[30], anti-HIV[31], anticonvulsant[32], anti-inflammatory[33-34-35-36], antihypertensive[37-38], antineoplastic[39-40] and antitrichinellosis[41] activities. This experimentation was paired with We've been able to suggest the following after conducting a computational analysis. The molecular mechanisms by which the recent benzimidazole derivatives inhibit 5-HT6R [42]. We examined various benzimidazole substituted compounds as Ang II-AT1 receptor antagonists in this report and other possible clinical applications for this class of compounds [43]. AT1 is the most important vascular receptor for blood pressure control. It is responsible for nearly all Ang II's physiological activities in target cells such as cardiovascular, synaptic, renal, hepatic, endocrine, and others [44]. Various medications can block the RAS at any point in the system, making them useful in treating hypertension [45]. Renin-inhibitors and angiotensin-converting enzyme (ACE) inhibitors were the first RAS blockers to show promise in clinical trials to treat congestive heart failure, renovascular hypertension, and critical hypertension [46-47-48-49].BenzimidazoleAng II receptor antagonists, a form of RAS blocker, have recently been shown in animal and human studies to be safe and effective antihypertensive drugs[50-51-52].

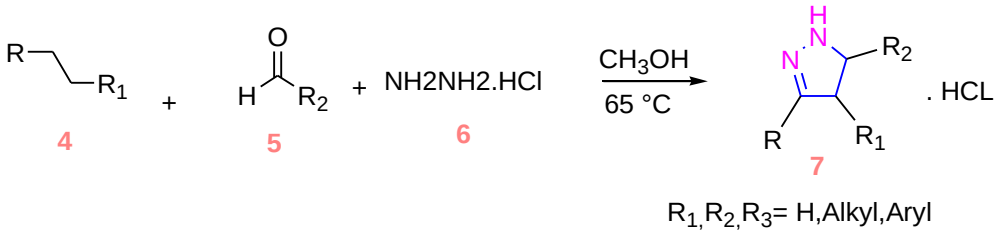
II. GENERAL SYNTHETIC METHOD OF PYRAZOLINE:

2.1 Yuhong. *et al.* Synthesis of nitrogen-containing heterocycles from alkyl dihalides in a single pot and essential amines and hydrazines happens under microwave illumination utilizing a direct and productive cyclo condensation in a liquid antacid medium [53].



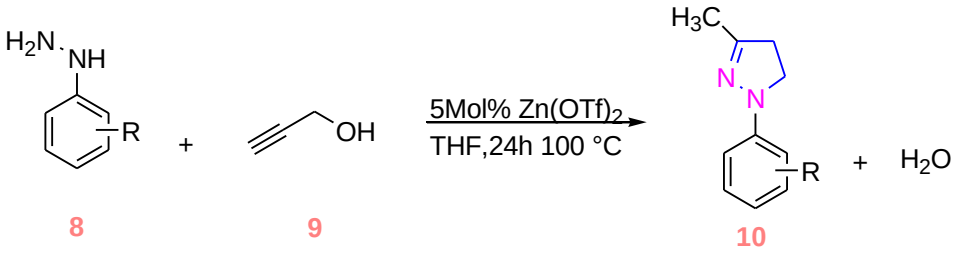
Scheme-1- Synthetic Scheme of Nitrogen contains compound and pyrazoline Derivatives

2.2 Under mild conditions, one-pot builds of aldehydes, ketone, and hydrazine monohydrochloride quickly formed pyrazoline intermediates reported by Lellek. *et.al.*. The expense of a wide range of pyrazoles was controlled in excellent yields using in situ oxidation with bromine. A kinder oxidation convention, on the other hand, bears the expense of 3,4,5-trisubstituted pyrazoles or 3,5-disubstituted by warming pyrazolines in DMSO with oxygen [54].



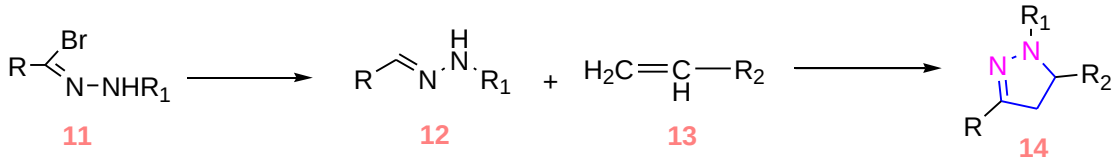
Scheme- 2- One-Pot three-component coupling with Methanol to form Pyrazoline Derivatives

2.3 Alex. *et al.* synthesized novel regioselective aryl-substituted pyrazolines, and pyrazole preparation has also been created. In the presence of a reactant measure of zinc triflate, substituted phenyl hydrazines react to 3-butanol to produce pyrazolineIdenticals[55].



Scheme- 3-Synthetic scheme of pyrazoline Derivatives

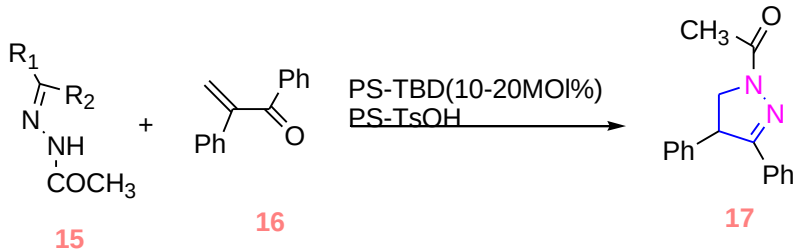
2.4 Various 1,3-diaryl-5-(cyano-, aminocarbonyl-and ethoxy carbonyl-) pyrrolo[3,4-c] 2-pyrazoline pyrazole-4,6-dione and 1,3,4,5-tetraaryl-2-pyrazoline are pyrazole-4,6-dione and 1,3,4,5-tetraaryl-2-pyrazoline, respectively. The reaction of nitrilimine with various dipolarophilic reagents yielded derivatives reported by Yusuf.*et al.*, [56].



R = FC_6H_6 , 2,4 $Cl_2C_6H_3$
R_1 = 4 - $NO_2C_6H_4$
R_2 = 3 - CN,4-$CONH_3$, 5-COOEt

Scheme -4- 1,3-diaryl-5(cyano-aminocarbonyl-andeth-oxycarbonyl-)-2-pyrazoline Derivatives.

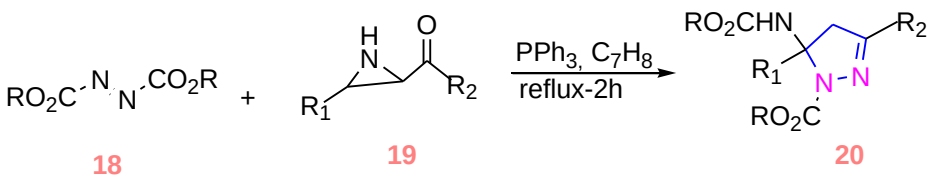
2.5 An organocatalyzed aza-Michael/transamination domino reaction involving a mixture of heterogeneous resin-bound acid/base reagents was used to prepare organically relevant 3,4-substituted pyrazolines somewhere in the range of hydrazones and enones, using a mixture of various resin sure acid/base substance reported by Gembus. *et.al*.,[57].



R_1=($AcNHNH_2$)e, CH_3, C_2H_6, Ph, 4 -$CH_3C_6H_4$
R_2=($AcNHNH_2$)e, H, CH_3

Scheme- 5- Synthesis of Hydrazone and Pyrazoline Derivatives.

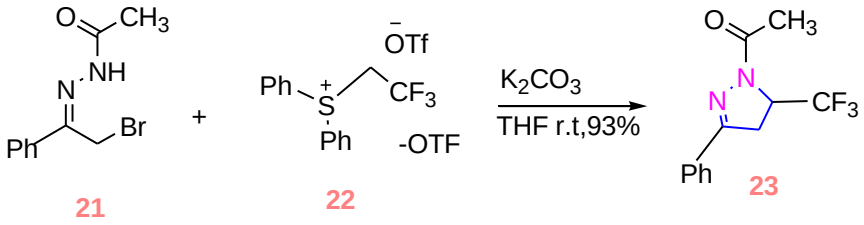
2.6 Cui. *et al.* reported a tale, proficient outfit novel 2-pyrazolines, and specific atom response of 2-acylaziridines with the Huisgen zwitterions. A theoretical domino arrangement mechanism is suggested [58].



R= Et, i-Pr, t-Bu
R_1=C_6H_5, 3,4-$CH_3C_6H_3$, 4-ClC_6H_4, 2-Furyl, 4-$O_2NC_6H_4$
3,4(OCH_2O)C_6H_3, 2-Naphthyl,C_6H_5
R_2=C_6H_5, 4-$CH_3OC_6H_4$, 2-ClC_6H_4, 3-$O_2NC_6H_4$

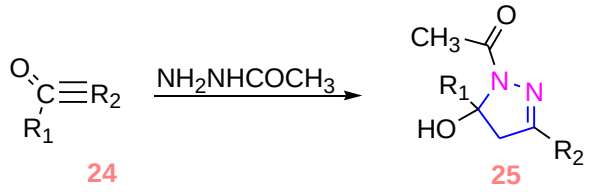
Scheme -6- Synthesis 2-acylaziridines and pyrazoline Derivatives.

2.7 In the field shaped 1,2-diaza-1,3-dienes were utilized informal [4 + 1]-annulation responses with fluorinated sulfur ylides to give 5-(trifluoromethyl) pyrazolines in great yields reported by Wang. *et.al.*, [59].



Scheme- 7- Synthesis 1-2-diaza-1,3-dines and pyrazoline Derivatives

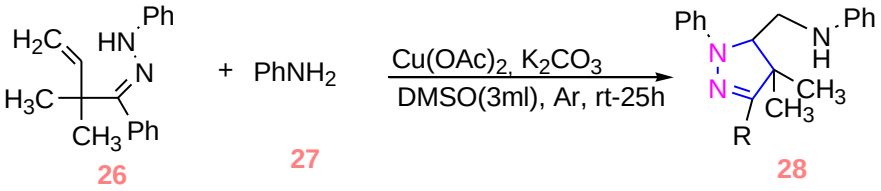
2.8 From the corresponding 2-alkyn-1-ones, various 1-acyl-5-hydroxy-4,5-dihydro-1H-pyrazoles are being synthesized in high yields. In the presence of ICl and Li2CO3 at room temperature, the dihydropyrazoles undergo hydration and iodination, yielding 1-acyl-4-iodo-1H-pyrazoles (scheme-8) reported by Waldo. *et al.*, [60]**.**



R_1= ph, 2-naphthyl, p-FC_6H_4, p-ClC_6H_4, p-BrC_6H_4, p-$Cf_3C_6H_4$, p-NCC_6H_4, P-t-BuC_6H_4, p-$Me_2C_6H_4$, o-MeC_6H_4
R_2=Ph, p-$EtO_2CC_6H_4$, n-Bu

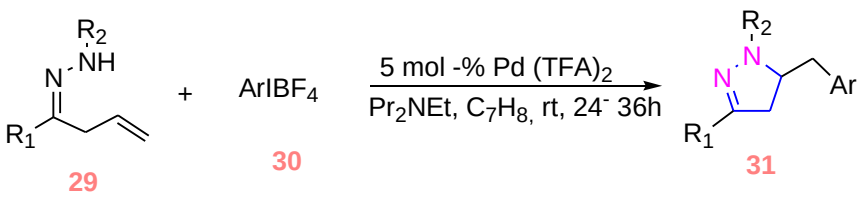
Scheme- 8- Synthesis of pyrazoline Derivatives.

2.9 Under mild response conditions and advantageous copper-catalyzed intramolecular/and intermolecular deamination of beta, gamma-unsaturated hydrazones with simple amines enable productive permission to various nitrogen-containing pyrazolines (Scheme-9) reported by Chen. *et al.*, [61].



Scheme -9-Synthesis of hydrazones with amines to form pyrazoline Derivatives.

2.10 By using an efficient and synchronous arrangement of C(sp3)- N and C(sp3)- C(sp2) derivatives under mellow conditions, a free-ligand, palladium-catalyzed aminoarylation of inactivated alkenes in, Beta-Gamma-unsaturated hydrazones give differently subbed dihydropyrazoles in high yields(scheme-10) reported by Yang. *et al.*, [62].

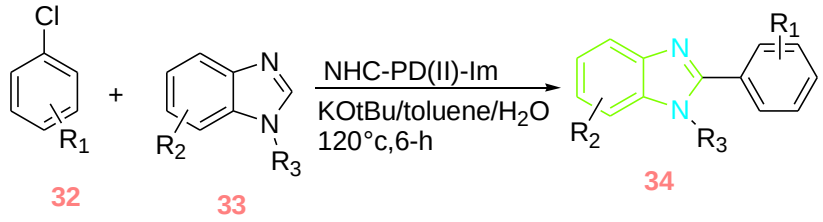


R_1=R_2=H, CH_3, Cl, Br, OCH_3, 4-ClC_6H_4, 2,4,6-MeC_6H_2
Ar = Ph, 4-CN-C_6H_4, 4-Br-C_6H_4, 2-Me-C_6H_4, 1-naphthyl

Scheme- 10- β, γ-unsaturated hydrazone, and pyrazoline Derivatives

III. GENERAL SYNTHETIC METHOD OF BENZIMIDAZOLE:

3.1 The direct C-H bond arylation of (Benz)imidazoles with (hetero)aryl chlorides is made simple and easy by a well-defined NHC-Pd(II)-Im complex. As arylating reagents, various active, unactivated, and deactivated (hetero)aryl chlorides were used to produce 2-(hetero) aryl (Benz)imidazoles in good yields reported by *Zheng. et al.*, [63]**.**

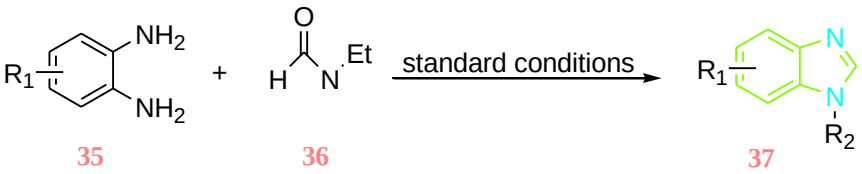


32 33 34

R_1=H, 4-me, 4-OMe, 4-F, 4-Vinyl
R_2= 5,6-Me_2, 5 -Me, 5 -F, 5 -OMe, H
R_3=Me, Benzyl

Scheme-11-Synthesis of Benzimidazole Derivatives.

3.2 Benzimidazoles are generated in good yields using various o-phenylenediamines and N-substituted formamides as C1 sources in a zinc-catalyzed cyclization in the presence of poly (methyl-hydro siloxane) (Scheme-12). It's also possible to make benzoxazole and benzothiazole derivatives reported by Deepak. *et al.*, [64].

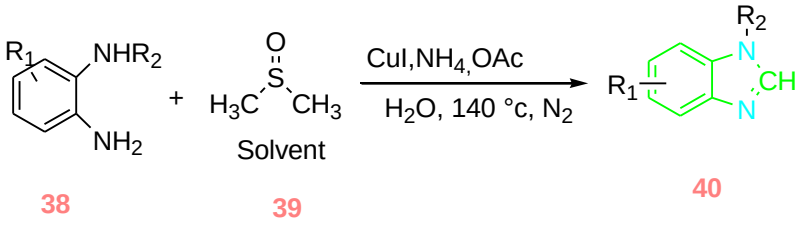


35 36 37

R_1,R_2=H, Me, NO_2

Scheme-12- Synthesis of o-phenylenediamines with N, N-dimethylacetamide.

3.3 Xiaoming. *et al.* reported that 2-unsubstituted benzothiazoles are generated in good isolated yields with good functional group tolerance by a three-component reaction of o-iodoanilines or electron-rich aromatic amines K2S and DMSO. o-phenylenediamines were used in a related reaction to produce 2-unsubstituted benzimidazoles without K2S. DMSO serves as a carbon source, a solvent, and an oxidant [65]**.**

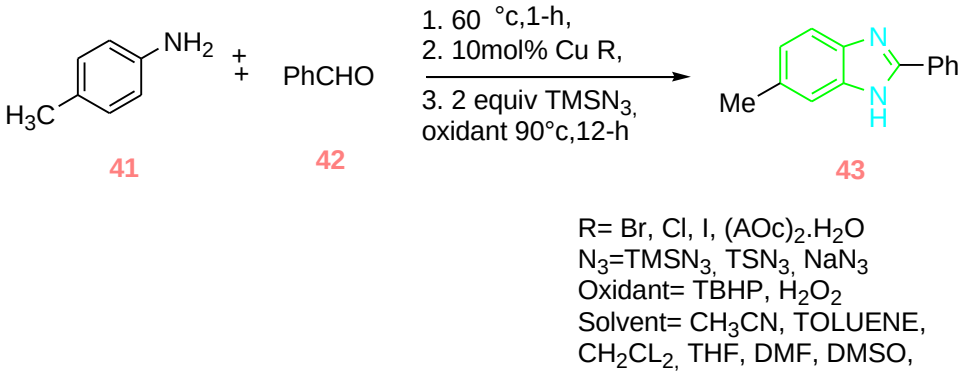


38 39 40

R_1=H, CH_3, OCH_3, F, Cl, Br, $COOCH_3$, CN, NO_2, COPh,
R_2=CH_3, Cl

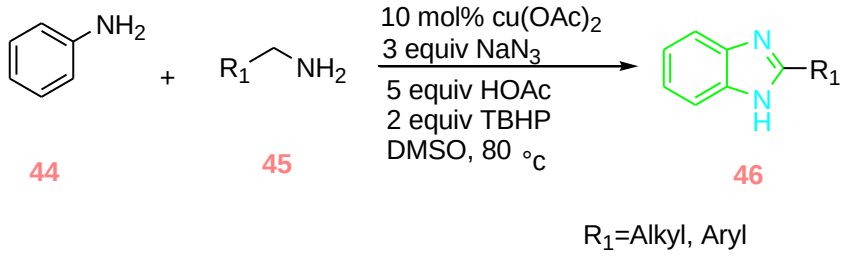
Scheme-13-Synthesis of Benzimidazole Derivatives.

3.4 Mahesh. *et al.* screened a new series of copper-catalyzed amination of N-aryl imines, in which the imine acts as a directing group by chelating to the metal center, viable aryl amines, aldehydes, and azides can be transformed into helpful benzimidazole structural units with a broad substrate variety and diversity as shown in scheme-14[66].



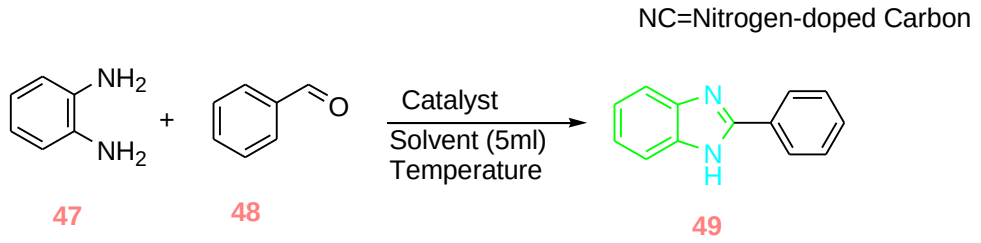
Scheme-14-synthesis of Benzimidazole Derivatives.

3.5 In the presence of TBHP, a domino C-H functionalization, transamination, ortho-selective amination, and cyclization sequence catalyzed by copper(II) provides benzimidazoles through a copper(II)-catalyzed oxidative cross-coupling of anilines, primary alkyl amines, and sodium azide. The reaction has a wide range of substrates and is functional group compatible reported by Mahesh. *et al.*, [67].



Scheme-15- Synthesis of Alkyl, Amines with Aniline.

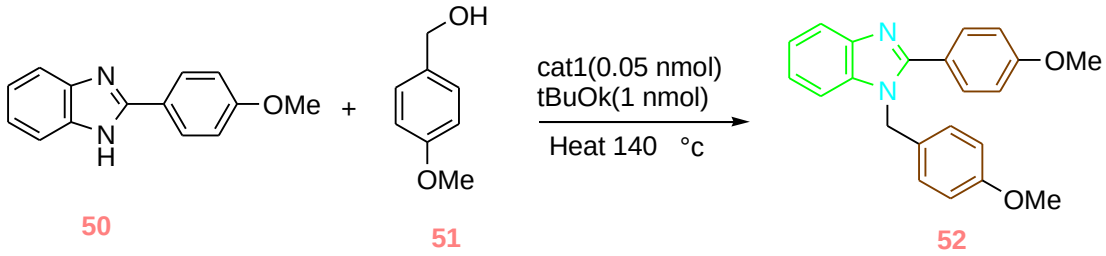
3.6 Under additive- and oxidant-free conditions, a highly recyclable nonnoble cobalt nanocomposite catalysed the coupling of phenylenediamines and aldehydes to produce a wide variety of biologically active benzimidazoles in high yields with strong functional-group tolerance. The catalyst is readily recyclable for subsequent uses reported by Z HU.*et al.*, [68].



Catalyst= CoOx@NC-800, CoOx@NC-700, CoOx@NC-800
, nano-Co_3O_4, Co_3O_4, $CoCl_2$
Solvent=H_2O, THF, DMF, MeOH, EtOH, 1 -4 -dioxane,
MeCN, DMSO

Scheme-16-Synthesis of 2-phenyl-1H-Benzimidazole Derivatives.

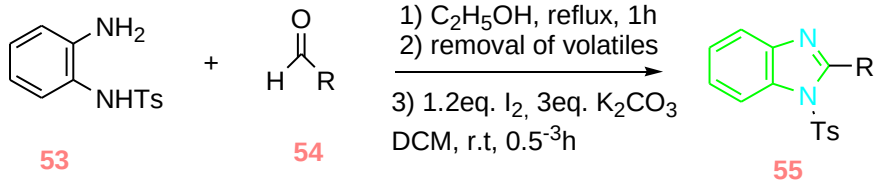
3.7 Das. *et al.* Synthesis of 2-substituted and 1,2-disubstituted benzimidazoles is allowed by an acceptor's dehydrogenative coupling of an aromatic diamine with primary alcohols. A phosphine-free tridentate NNS ligand-derived manganese(I) complex catalyzes the reaction [69].



50 51 52

Scheme-17-Synthesis of N-Alkylation of 2-Substituted Benzimidazole by Cat. 1

3.8 Under simple conditions, a functional intramolecular C-H amidation technique using molecular iodine allows for transition-metal-free cyclization of crude imines for the sequential Synthesis of N-protected benzimidazoles without the need to purify less stable condensation intermediates. Condensation of simple o-phenylenediamine derivatives and a bromine source provided the necessary imine substrates quickly Reported by Zhiyuan. *et al.,* [70].

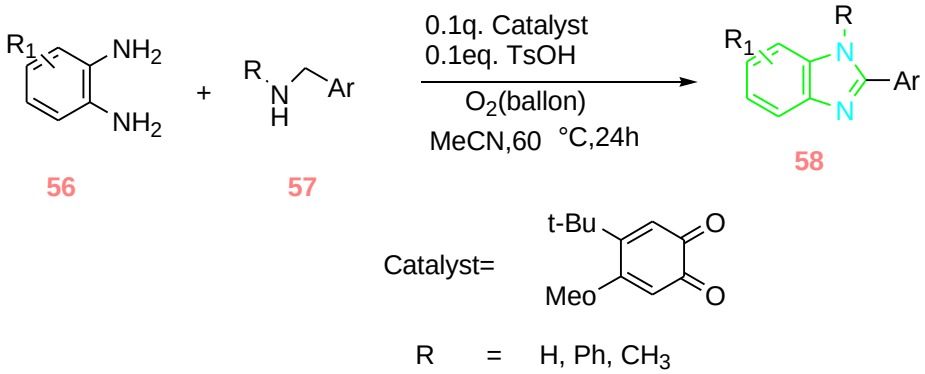


53 54 55

R=Ar, alkyl, CO_2Et

Scheme-18-Synthesis of 1-Tosyl Benzimidazole Derivatives.

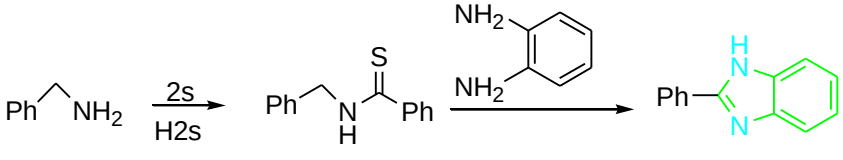
3.9 Under mild conditions and with oxygen as the terminal oxidant, bioinspired ortho-quinone catalysts have been used to oxidatively synthesize benzimidazoles, quinoxalines, and benzoxazoles from primary amines in large yields reported by Zhang. *et al.,* [71].



56 57 58

Scheme-19- Synthesis of Benzimidazole Derivatives.

3.10 The use of elemental sulfur as a traceless oxidizing agent makes the Synthesis of benzazoles from alkylamines and o-hydroxy/amino/mercaptan anilines remarkably simple, solvent-free, and catalyst-free, reported by Nguyen. *et al.,* [72].

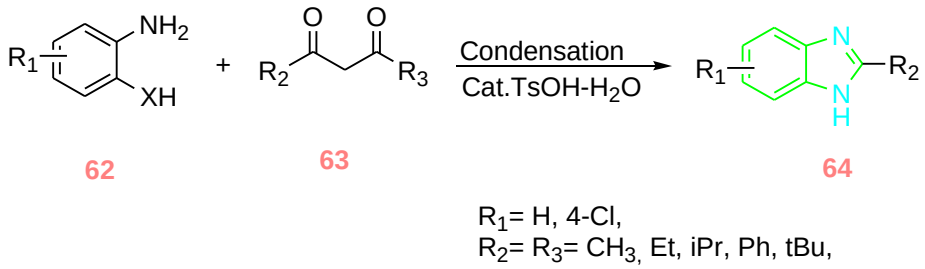


59 60 61

Scheme-20-Synthesis of Benzimidazole Derivatives.

3.11 Under oxidant- and metal-free conditions, Brnsted acid-catalyzed cyclization reactions of 2-amino thiophenols and anilines with -diketones give 2-substituted benzothiazoles and benzimidazoles in good yields, reported by

Mayo. *et al.* Under the optimized reaction conditions, various groups such as methyl, Chloro, nitro, and methoxy linked to benzene rings were tolerated [73].

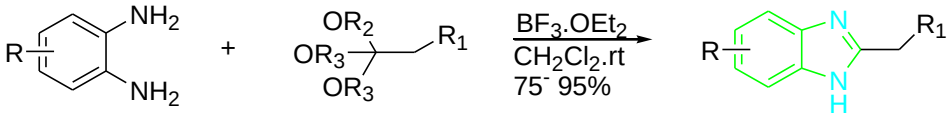


62 63 64

R_1= H, 4-Cl,
R_2= R_3= CH_3, Et, iPr, Ph, tBu,

Scheme-21-Synthesis of Benzimidazole Derivatives.

3.12 In a practical and connective methodology, ortho-substituted anilines react with functionalized orthoesters to produce benzoxazole, benzothiazole, and benzimidazole derivatives reported by Bustug. *et al.* This method's flexibility allows for the development of new heterocycle libraries with multifunctional locations [74].

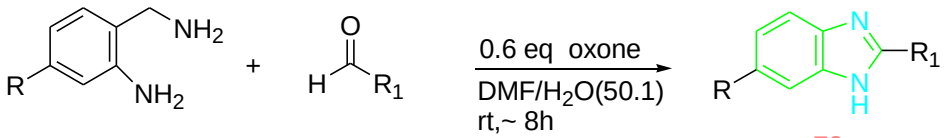


65 66 67

R_1= (CH_2)nX, (CH_2)nCH=CH_2, (CH_2)nCN
R_2 , R_3=Alkyl
R=Cl, Br, CH_3, CO_2CH_3,H

Scheme-22-Synthesis of Benzimidazole Derivatives.

3.13 At room temperature, aromatic, heteroaromatic, and aliphatic aldehydes undergo an oxone-mediated tandem transformation of 2-aminobenzylamines into 2-substituted benzimidazoles. Initial condensation of 2-aminobenzylamine with suitable aldehydes yielded a tetrahydroquinazoline intermediate, which was then subjected to oxone-mediated ring distortion to produce the desired compounds in high yields reported by Hati. *et al.* [75].

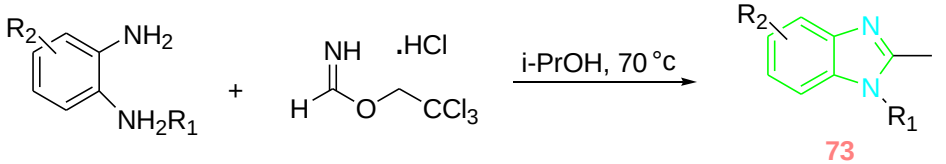


68 69 70

R= H,CH_3, Cl, Br
R_1= Ar, CH_3

Scheme-23-synthesis of Benzimidazole Derivatives.

3.14 Caron. *et al.* synthesized acylating agents 2,2,2-trichloroethyl imitates are used to make benzimidazoles and imidazopyridines under mild conditions in isopropyl alcohol at 70°C. In cases where cyclization was sluggish, the addition of sodium acetate was found to be beneficial. Using the more inert tert-amyl alcohol to react with substrates with low nucleophilicity resulted in better results [76].

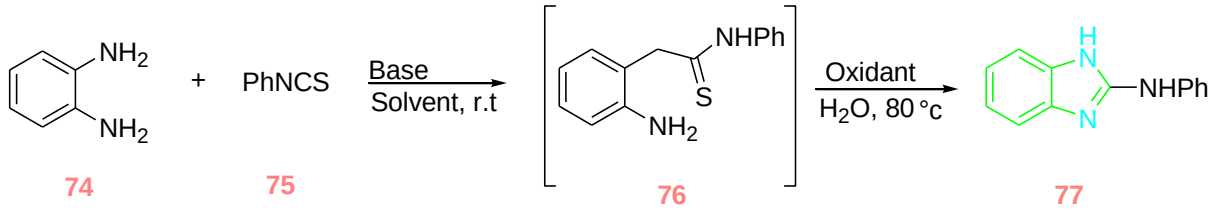


71 72 73

R_1= H,CH_3
R_2= H, 4 -CH_3, 4 -OMe, 3 -Me, 4 -CF_3, 4 -Cl

Scheme-24-Synthesis of Benzimidazole using Imidate.

3.15 Duangkamol. *et al.* reported a reaction of isothiocyanates with ortho-substituted anilines bearing N, N-, N, O-, and N, S-bis-nucleophiles, followed by intramolecular, potassium periodate-mediated oxidative cyclodesulfurization of the in situ produced monothioureas, yields substituted 2-aminobenzazole derivatives in high yields as shown in scheme-25[77].

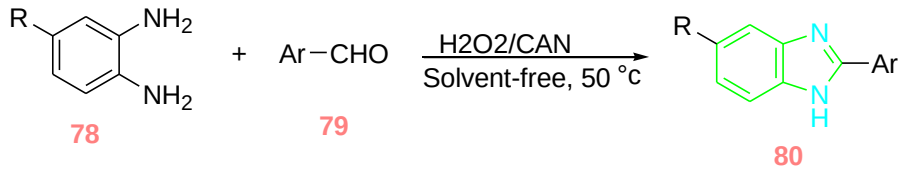


74 75 76 77

Base = $NaHCO_3$, NaOH, K_2CO_3
Solvent =DMSO, THF , H_2O, MeCN, DMF
Oxidant = KIO_4(20),KIO_4(10), KIO_4(5), $NaIO_4$(20), H_2O_2, Oxone,(20), MnO_2

Scheme-25-Synthesis of Benzimidazole Derivatives.

3.16 Bahrami. *et al.*investigated short reaction times, large-scale Synthesis, quick and straightforward isolation of the compounds, excellent chemoselectivity, and excellent yields are among the key benefits of a convenient method for the Synthesis of 2-substituted benzimidazoles and benzothiazoles as shown in scheme-26[78].

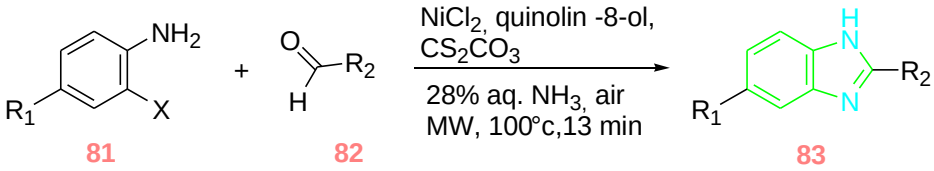


78 79 80

R= H, Me, NO_2
Ar= C_6H_5, 4-$MeOC_6H_4$, 4-HOC_6H_4, 4-MeC_6H_4, 4-(Me)NC_6H_4, 2 -ClC_6H_4, 4 -ClC_6H_4, 3 -$NO_2C_6H_4$, C_6H_5CH=CH, 4 -FC_6H_4, 4 -BrC_6H_4, 4 -$NO_2C_6H_4$, 4 -PhC_6H_4, $OHCC_6H_4$

Scheme-26-Synthesis of 2-Arylbenzimidazoles Derivatives.

3.17 From various 2-haloanilines, aldehydes, and ammonia as nitrogen sources, an effective and convenient Ni-catalyzed C-N bond formation allows excellent yields of various benzimidazoles reported by Fang. *et al.* [79].

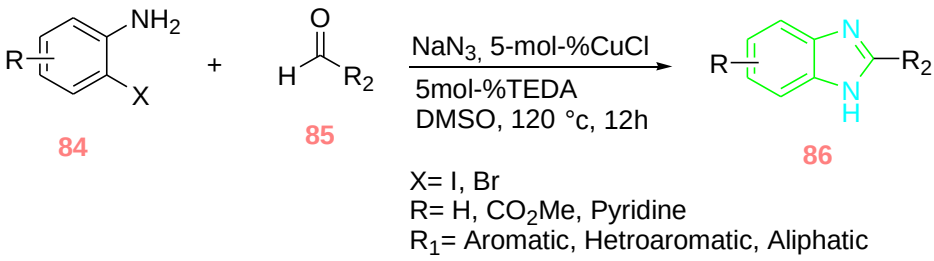


81 82 83

R_1= H, 4-NO_2, 4-Cl, 4-Br, 4-CH_3, 4,5-dichloro
R_2= Ph, 3-pyridyl, 2-FC_6H_4, 2,4-$Me_2C_6H_3$, 4-Tol, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 2-ClC_6H_4, 2-FC_6H_4, 2-HOC_6H_4, 3-FC_6H_4, 3-NCC_6H_4, 3-hydroxy^{-4}-Me-thoxyphenyl, 2-pyridyl, i-pr
X= I, Br

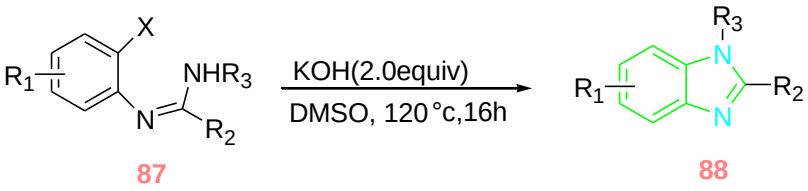
Scheme-27-Synthesis of Benzimidazole Derivatives.

3.18 Benzimidazoles were synthesized in good yields using copper-catalyzed, one-pot, three-component reactions of 2-haloanilines, aldehydes, and NaN3 in DMSO 120°C for 12 hours reported by Kim. *et al.* Many functional groups, such as ester, nitro, and Chloro, were involved in the reaction [80].



Scheme-28-Synthesis of Benzimidazole Derivatives.

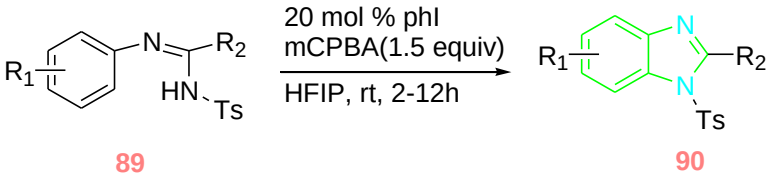
3.19 Baars. *et al.*Synthesized diversely substituted benzimidazoles in good yields is possible thanks to intramolecular N-arylations of amidines induced by potassium hydroxide in DMSO at 120°C [81].



X = F, Cl, Br, I
R_1= F, Cl, Br, Me, CF_3
R_2= Me, Ph, o-tol, ,o-Br-C_6H_4,
p-F-C_6H_4, thiophen^{-2}-yl
R_3= Ph, Me, Bn, PMP

Scheme-29-synthesis of Benzimidazole Derivatives.

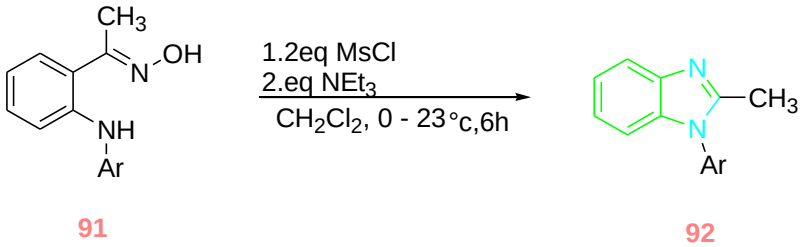
3.2 At room temperature, oxidative C-H amination of N′′-Aryl-N′-tosyl/N′-methylsulfonylamidines and N, N′-bis(aryl)amidines with iodobenzene as a catalyst allows the Synthesis of 1,2-disubstituted benzimidazoles reported by Santhosh. *et al.* The reaction is broadly applicable, and the desired products can be obtained in high yields [82].



R_1= C_6H_5, 4-OMe-C_6H_4, 4-Me-C_6H_4
R_2= Alkyl, Vinyl, Ph

Scheme-30-Synthesis of Benzimidazole Derivatives.

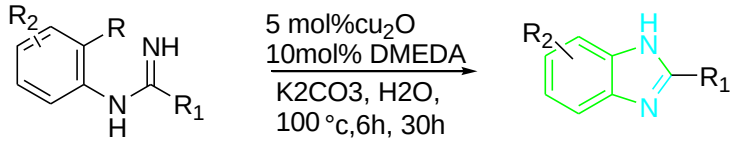
3.21 Depending on the base used in the reaction, various N-aryl-1H-indazoles and benzimidazoles were synthesized in good to excellent yields from typical arylamino oximes. The formation of benzimidazoles was aided by triethylamine, while 2-aminopyridine reported by Brenda helped the construction of N-arylindazoles. *et al.* [83].



Scheme-31-Synthesis of Benzimidazle s usingTriethylamine.

3.22 Peng. *et al.* synthesized a using Cu2O as the catalyst, DMEDA as the ligand, and K2CO3 as the base. A simple, effective, and sustainable intramolecular N-arylation method yields a library of benzimidazoles in high yields.

Surprisingly, the reaction took place entirely in water, making the technique extremely beneficial from an environmental and a financial standpoint [84].

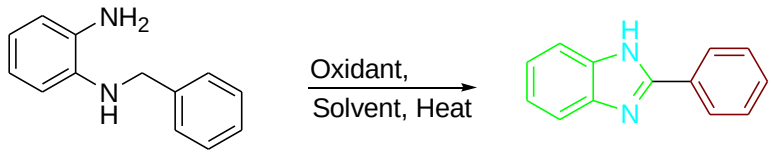


93 94

R =Cl, Br, I
R1 = Aryl, Alkyl
R2 =H, EWG, EDG

Scheme-32-synthesis of Benzimidazole Derivatives.

3.23A metal-free oxidative C-N coupling between the sp3 C-H and free N-H of readily available N1-benzyl/alkyl-1,2-phenylenediamines in the presence of oxygen and TEMPO allows the Synthesis of multisubstituted or fused tetracyclic benzimidazoles reported by Ding. *et al.* [85].

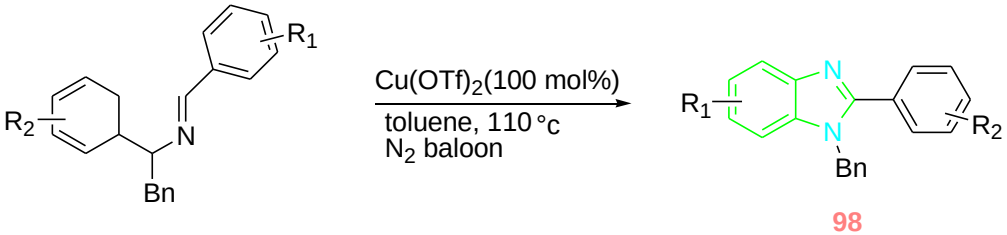


95 96

Oxidant =phI(OAc)$_2$,TEMPO, m-CPBA, $K_2S_2O_8$, CU(OAc)$_2$
Solvent =toluene, DMF, 1,4 -dioxane, acetonitrile

Scheme-33-Synthesis of oxidative C(sp3)-N-Benzyl-1,2-phenylenediamine.

3.24A simple method for converting N-benzyl bisarylhydrazones and bisaryloxime ethers to functionalized N-benzyl bisarylhydrazones and bisaryloxime ethers. Under neutral conditions, the C-H functionalization/C-N/C-O bond formation in 2-Aryl-N-benzylbenzimidazoles and 2-arylbenzoxazoles is mediated by copper(II) reported by Guru. *et al.* At room temperature, cyclization occurs on substrates with either electron-donating or electron-withdrawing substituents [86].

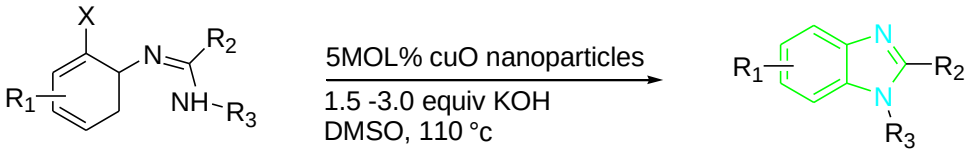


97 98

R_1=R_2= EWG,EDG

Scheme-34- Synthesis of copper-mediated cyclization of N-benzyl BisaryIhyrazones.

3.25 Copper(II) oxide nanoparticles in DMSO under air catalyze the intramolecular cyclization of o-bromoaryl derivatives, resulting in an experimentally simple, general, practical, and ligand-free synthesis of substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles reported by Saha. *et al.* Without losing its activity, the heterogeneous catalyst can be recovered and recycled [87].



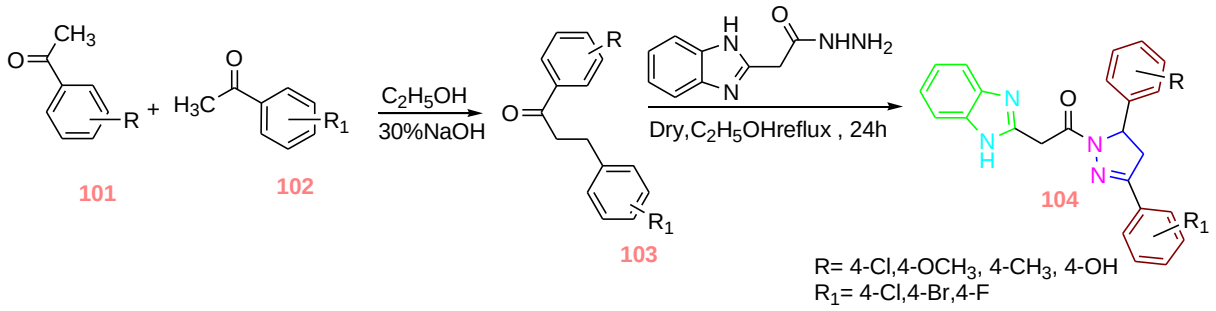
99 100

R_1= H,Br, Cl, CH_3, OMe
R_2= CH_3, Ph, morphine, pyrrolidine, piperazine
R_3= alkyl, aryl
X =Br,I

Scheme-35-synthesis of Benzimidazole Derivatives.

IV. POTENTIAL TARGET FOR PYRAZOLINE BEARING BENZIMIDAZOLE DERIVATIVES AND SYNTHETIC SCHEME:

4.1 Md. Jawaid.Akhtar*et al.* investigated the synthesis of 2-(1H-benzo[d]imidazole-2-yl)-1-(3,5-bisbenzo[d]imidazole-2-yl)-1-(3,5-bisbenzo[d]imidazole-2-yl)-1-(3,5-bisbenzo[d]imidazole-2- (4-chlorophenyl) ethenone (-4,5-dihydro-1H-pyrazol-1-yl) (94), A new order of compound pyrazoline attached to Benzimidazole was synthesised by cyclo condensation reaction with one–pot multiple component reaction in absolute ethanol. All of the compounds studied tested against five cancer cell lines MCF-7, MDA-MB231, As49, HaCaT, and HePG2. Among the synthesized compound derivatives (104) are more potent. The R group substituted with the chlorine group at position 4, and the R1 group is substituted with the chlorine group at position four, as shown in scheme-36[88].

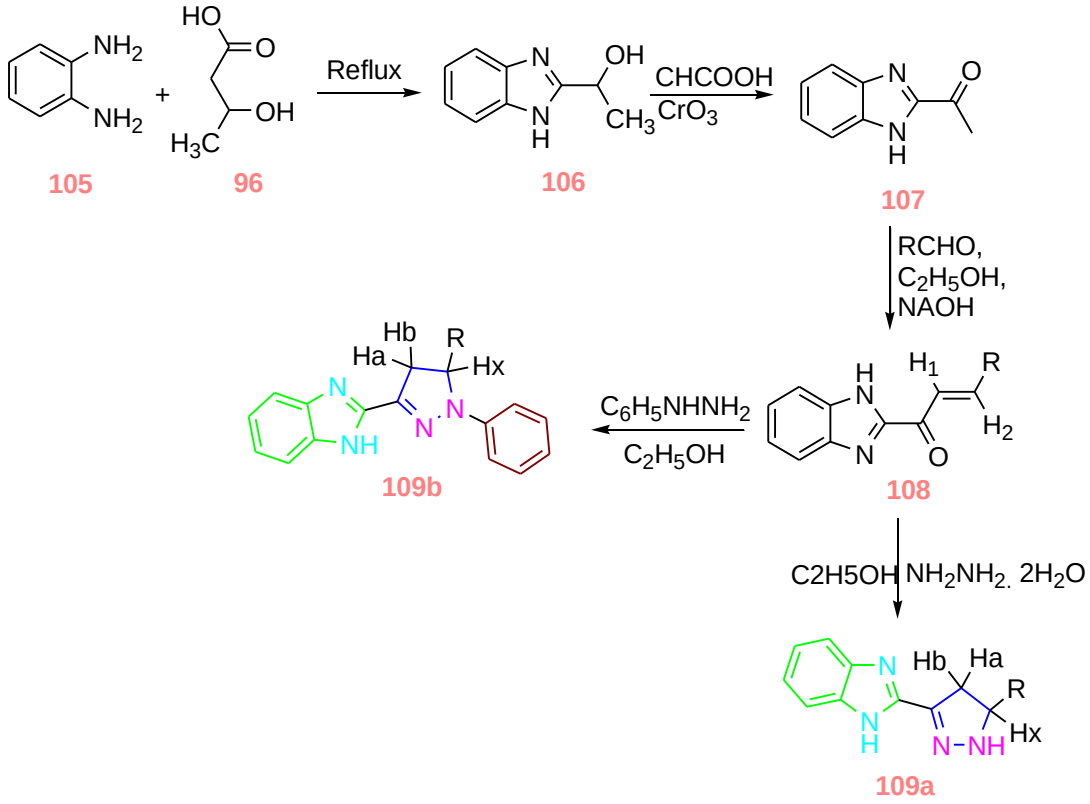


101 102 103 104

R= 4-Cl,4-OCH_3, 4-CH_3, 4-OH
R_1= 4-Cl,4-Br,4-F

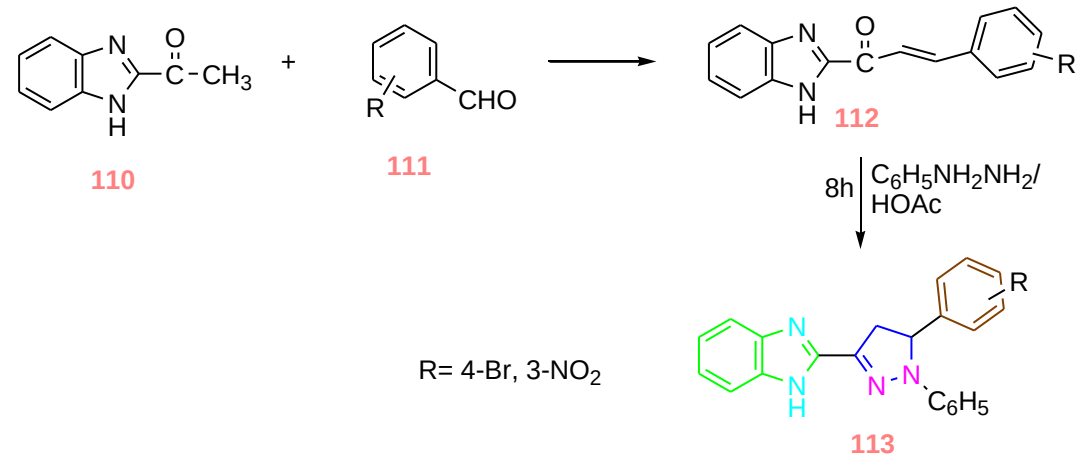
Scheme-36-Synthesis of Pyrazoline Bearing Benzimidazole Derivatives.

4.2 Shahryar *et al.* reported an anticancer activity and synthesized a new compound, Benzene 1,2-diamine with 4-hydroxypentan-2-one, and screened for their anticancer activity against CCRF-CEM, A549, Colon -205, SF-268, M14, MCF-7, and Many cancers cell lines and other derivatives showed moderate anticancer activity. Among the synthesized compound derivatives (109b) found to be more potent because if R group substituted with dimethoxy phenyl at positions 3 & 4, as shown in scheme-37[89].



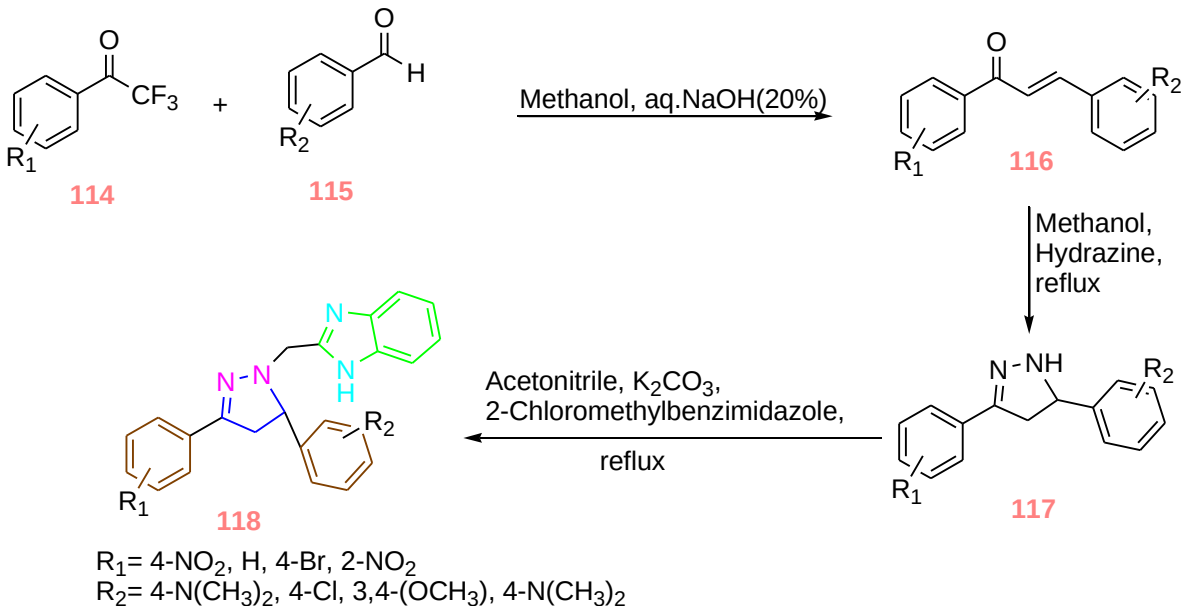
Scheme-37-Synthesis of 2-Acetyl pyrazoline Bearing Benzimidazole Derivatives.

4.3 Yousef. *et al.* synthesized a compound 1-phenyl-2 pyrazolines were obtained by reacting the chalcones with phenylhydrazine in acetic acid and evaluated for their anthelmintic activity against the mortality of earthworm. Among the synthesized compounds, 3-(Benzimidazole-2-yl)-5-(substituted phenyl)-1-phen-yl-2-pynzolines (113) were found to be more potent if R substituted with Bromine group at 4-position as shown in scheme-38[90].



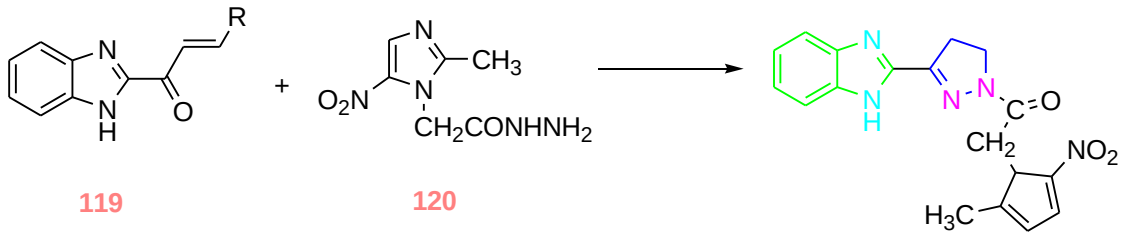
Scheme-38-Synthesis of Pyrazoline Bearing Benzimidazole Derivatives.

4.4 Farhat. *et al.*synthesized a novel compound 2-((3,5-diaryl-4,5-dihydro-1H-pyrazol-1-yl) methyl)-1H-benzo[d]imidazole (118) and evaluated for their antidiabetic activity via α-glucosidase enzyme inhibition assay and IC50 value of these potent compound 50.06 µm. Among the series of compound derivatives (118) were more potent, If R1 substituted with Hydrogen and if R2 substituted with chlorine at 4th position as shown in scheme-39[91].



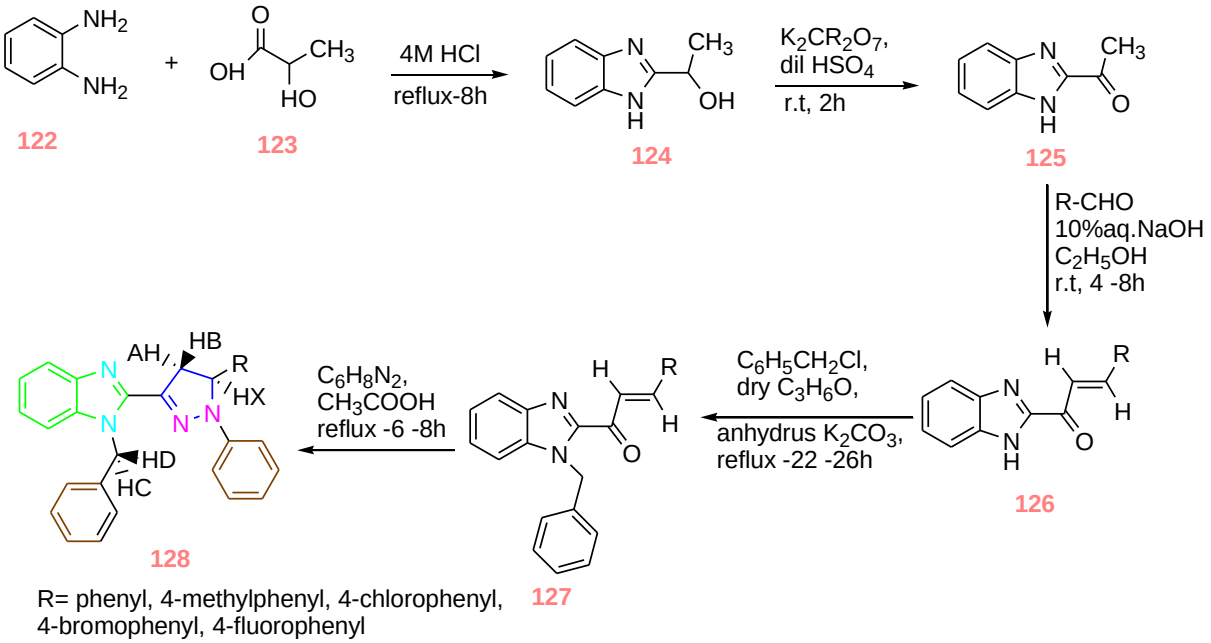
Scheme-39-Synthesis of Pyrazoline Bearing benzimidazole Derivatives.

4.5 Krishnakumar. *et al.* synthesized a series of 1-[3-(1H-Benzoimidazol-2-yl)-4, 5-dihydro-pyrazol-1-yl]-2-(2-methyl-5-nitro-imidazol-1-yl)-ethanone derivative (121) and screened for their antimalarial activity against dihydrofolate reductase enzyme. In this series of compound 1-[3-(1H-benzoimidazol-2-yl)-5-(4-fluoro-phenyl)-4, 5- dihydro-pyrazol-1-yl]-2-(2-methyl-5-nitro-imidazol-1- yl)-ethanone(121) were found to be more potent activity as shown in scheme-40[92].



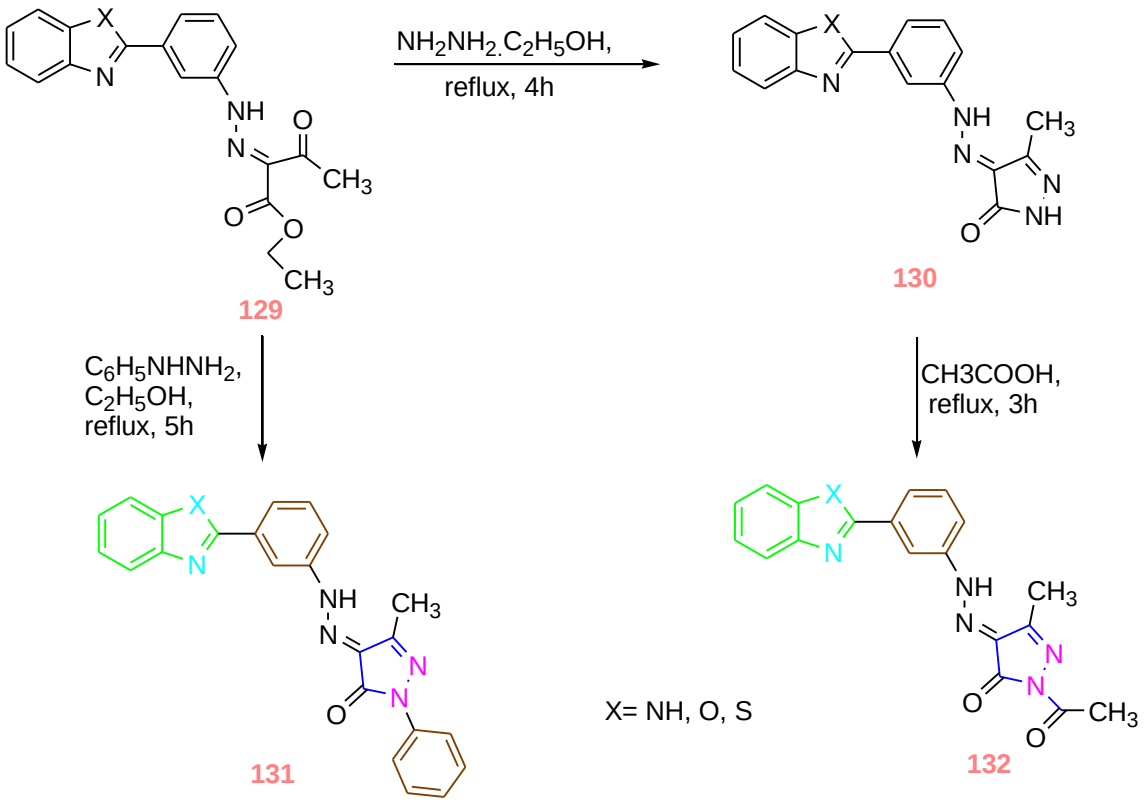
Scheme-40- Synthesis of 1-[3-(1H-Benzoimidazol-2-yl)-4, 5-dihydro-pyrazol-1-yl]-2-(2-methyl-5-nitro-imidazol-1-yl)-ethanone

4.6 Gopal.*et al.* synthesized a series of novel compound 1-benzyl-2-(1-substituted-5-aryl-4,5-dihydro-1H-pyrazol-3-yl)- -1H-benzimidazoles (128) and screened for their In-vitro antibacterial activity against *S. aureus*, *B. Subtilis* (gram-positive bacteria), *E. coli*, *P. Aeruginosa* (gram-negative bacteria), *C. Albicans*(fungi) and MIC value of these bacteria 64, 128, 64, 256, 256µmmL-1. Among the synthesized compound (128) found to be more potent, If R is substituted with fluorophenyl at four positions as shown in scheme-41[93].



Scheme-41-Synthesis of 1-benzyl-2-(1-substituted-5-aryl-4,5-dihydro-1H-pyrazol-3-yl)- -1H-benzimidazoles.

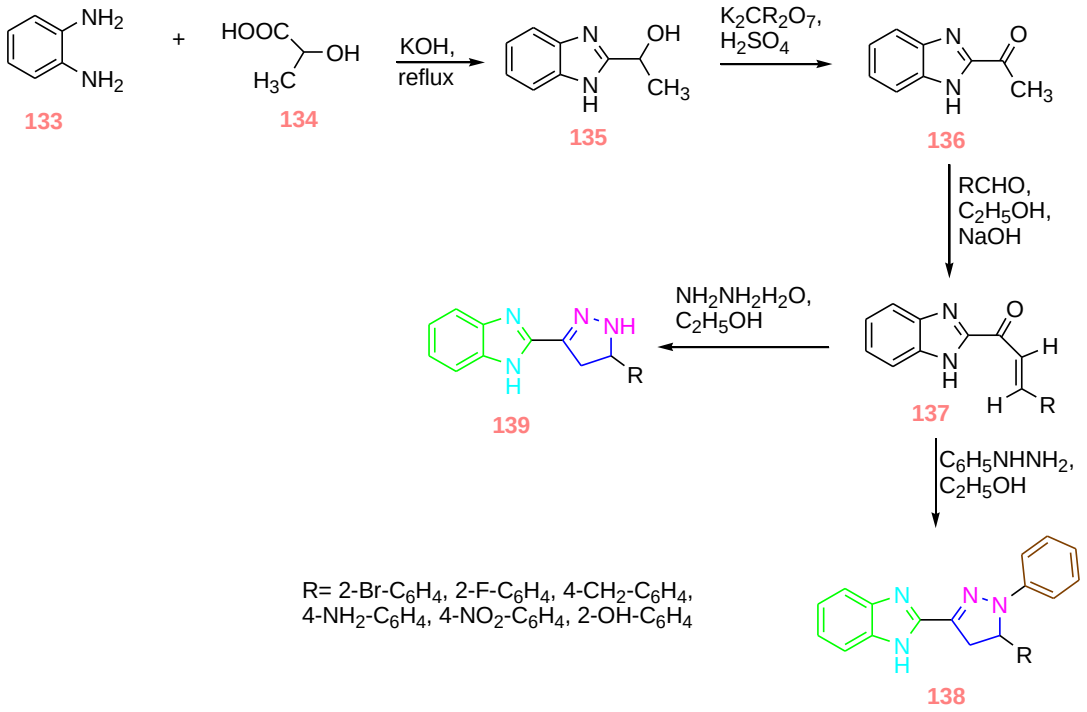
4.7 Mohamed. *et al.* Investigated a series of novel benzothiazole/benzoxazole and benzimidazole substituted pyrazoline derivatives and screened for their In vitro antiproliferative activity against MCF-7, A549 cell lines, and COX-1, COX-2 enzyme.Among the synthesized compound 4-[3-(Benzothiazol-2-yl)-phenyl)hydrazono]-5-methyl-2-phenyl-2,4-dihydropyrazol-3-one(132) and 2-Acetyl-4-[(3-(1H-benzimidazol-2-yl)-phenyl]hydrazono-5- methyl-2,4-dihydropyrazol-3-one (131) were found to be more potent as shown in scheme-42[94].



Scheme-42-Synthesis of benzothiazole/benzoxazole and benzimidazole substituted pyrazoline Derivatives.

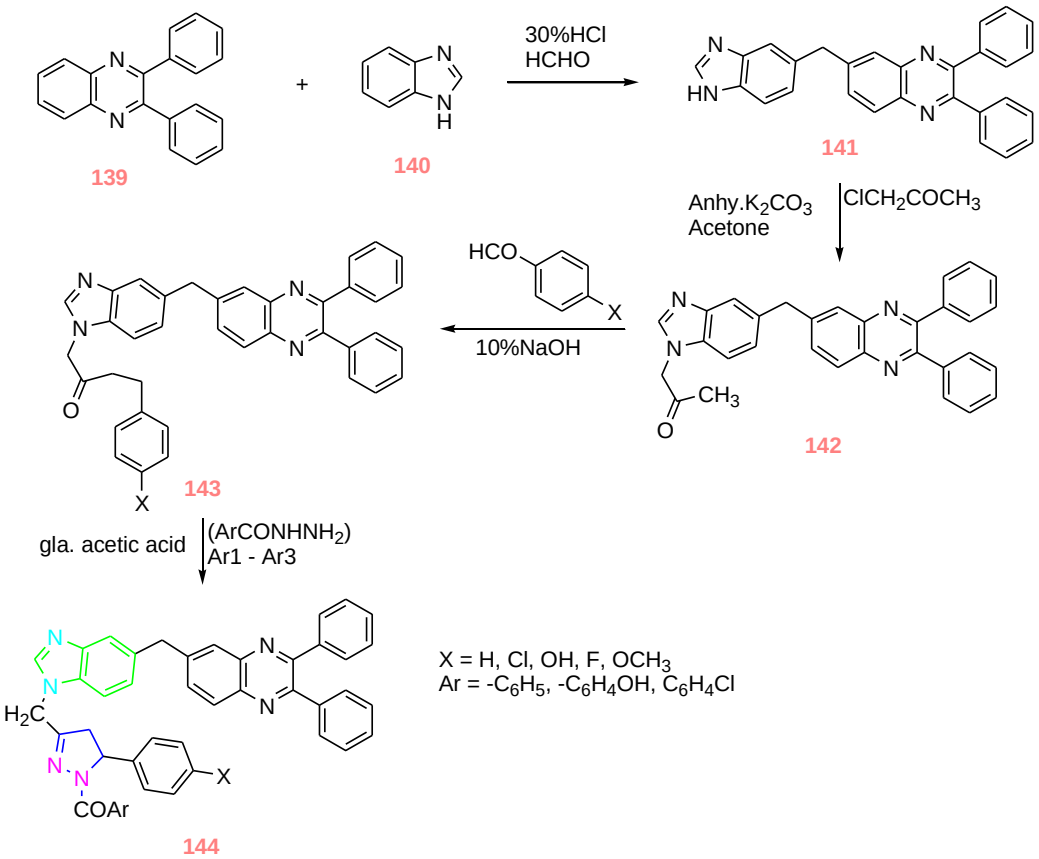
4.8 Soni. *et al.* synthesized a series of novel substituted pyrazoline bearing benzimidazole derivativesand evaluated them for their anthelmintic activity against *Pheretimaposthuman* using standard compound albendazole. Among the synthesized compounds 2-[5-(1H-Benzoimidazol-2-yl)-4H-pyrazol-3-yl]-4-hydroxy-benzaldehyde (139) and

4-(2-Amino-ethyl)-2-[5-(1H-benzoimidazol-2-yl)-4H-pyrazol-3-yl]-benzalde (138) were found to be more potent activity as shown in scheme-43[95] .



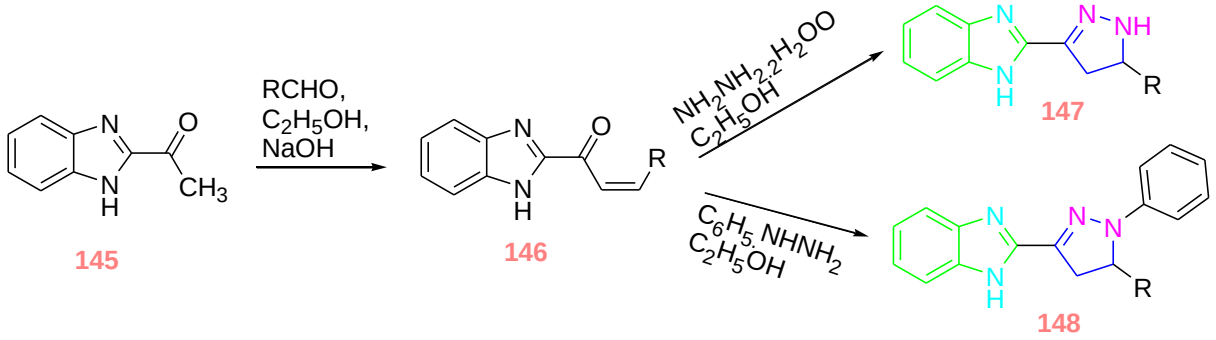
Scheme-43-Synthesis of pyrazoline substituted benzimidazole Derivatives.

4.9A new series of novel compound 6-((1-((1-benzyl-4, 5-dihydro-5-phenyl-1H-pyrazol-3-yl) methyl)-1H Benzo [d]imidazol-5-yl) methyl)-2, 3-diphenylquinoxaline(144) reported by Sridevi.*et al.* and evaluated for their anti-histaminic agents against histaminic activity. Among the synthesized compounds, Derivatives (144) were found to be more potent if X substitute with chlorine group or Ar was substituted with chlorophenyl, as shown in scheme-44[96].



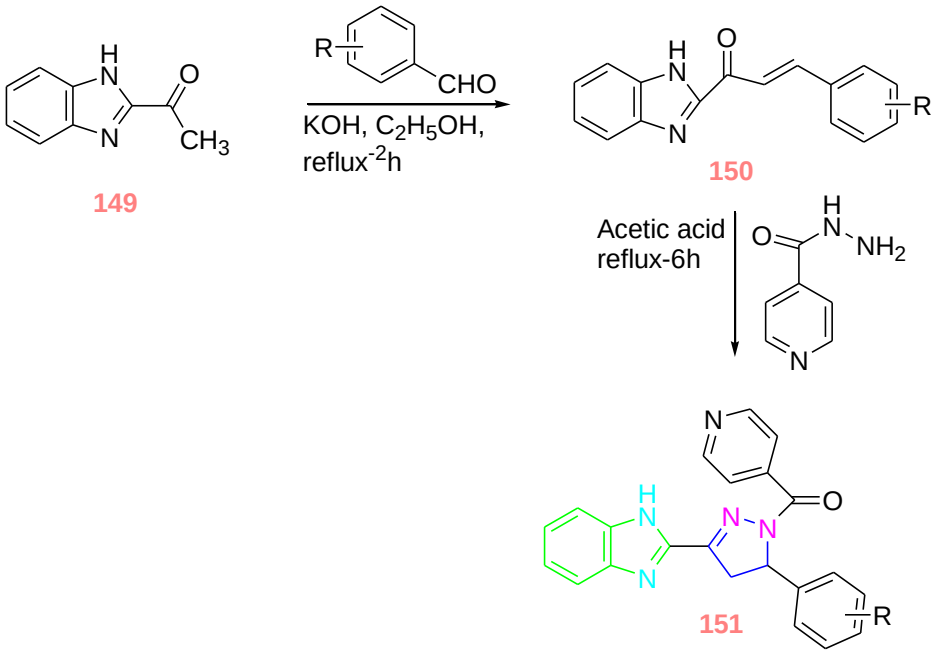
Scheme-44- Synthesis of pyrazoline bearing Benzimidazole Derivatives.

4.10 ShaharYar. *et al.* synthesized a compound 1-(1H-benzimidazol-2-yl)-3-(substituted phenyl)-2-propen-1-one were reacting with hydrazine hydrate and phenylhydrazine to get pyrazoline and phenyl pyrazoline derivatives as shown in scheme-45 and evaluated for their In-vitro antitubercular activity against Mycobacterium tuberculosis H37Rv strain(ATCC-27294) using Microplate Alamar Blue Assay (MABA). Among the synthesized compound, 2- [5-(4- fluorophenyl)-1-phenyl-4,5-dihydro-1H-3-pyrazolyl]-1H-benzimidazole (148) found to be a more potent activity[97].



Scheme-45-Synthesis of Pyrazoline bearing Benzimidazole Derivatives.

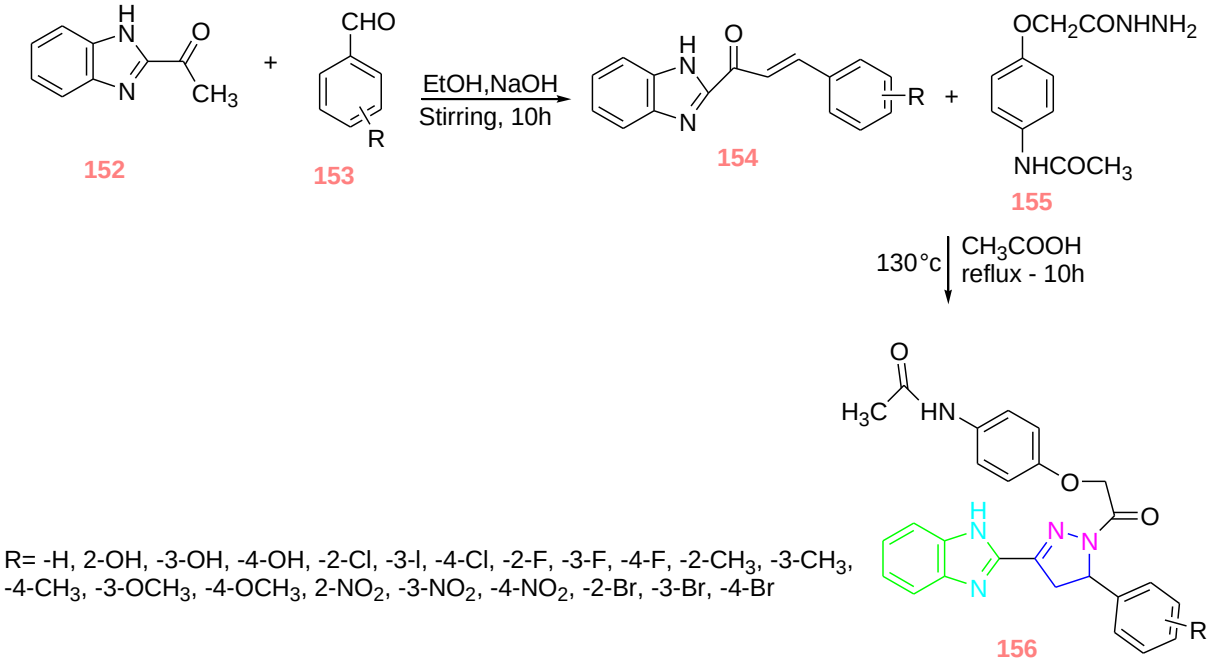
4.11 Desai. *et al.* reported a series of the novel (3-(1H-benzo[d]imidazol-2-yl)-5-(aryl)-4,5-dihydro-1H-pyrazol-1-yl) (pyridin-4-yl) methanone (151) and evaluated for their antimicrobial activity against gram-negative bacteria (E. coli-MTCC-443, P. Aeruginosa-MTCC-1688) and gram-positive bacteria (S. aureus-MTCC-96, S. Pyogenes-MTCC-442, C. Albicans-MTCC-227, A. niger-MTCC-282, A. Clavatus-MTCC-1323). Among the synthesized compound (3-(1H-Benzo[d]imidazol-2-yl)-5-(4-hydroxyphenyl)-4,5- dihydro-1H-pyrazol-1-yl) -(pyridin-4-yl) methanone (151) were found to be more potent as shown in scheme-46[98].



Scheme 46: synthesis of pyrazoline bearing Benzimidazole Derivatives.

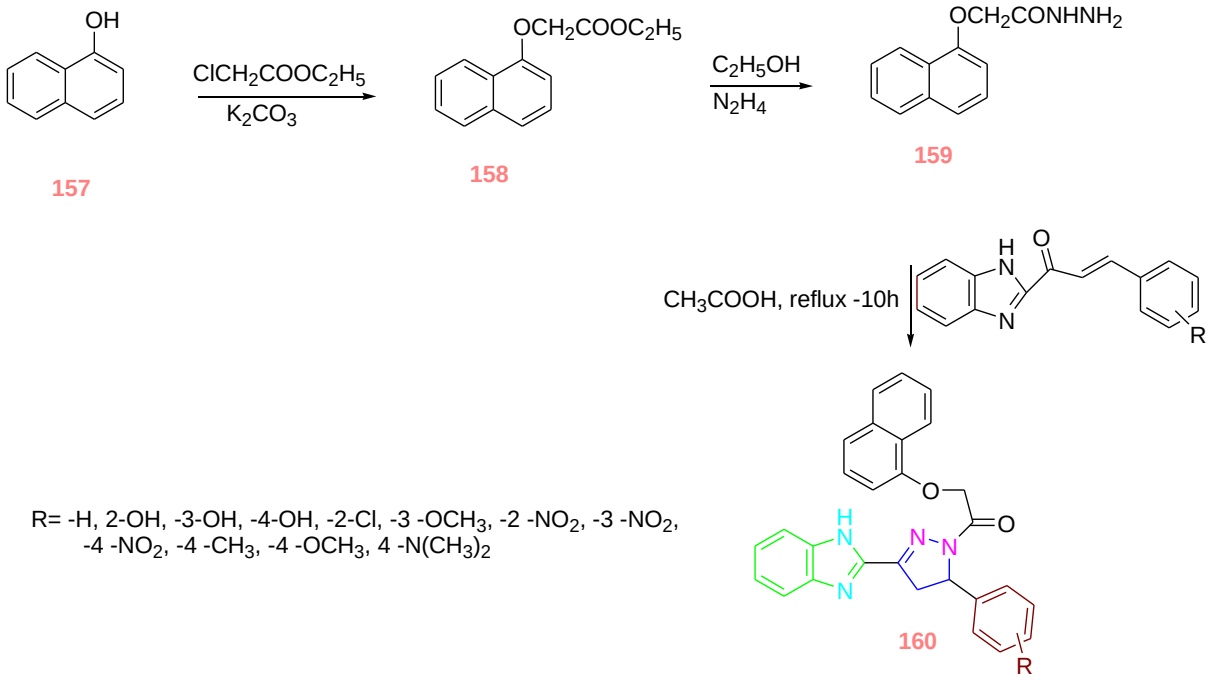
4.12 Desai. *et al.* reported a series of novel N-(4-(2-(3-(1H-benzo[d]imidazol-2-yl)-5-(aryl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) phenyl) acetamides (156) and screened for their antimicrobial activity against Gram-

positive bacteria (S. aureus(MTCC-96), S. pyogenes(MTCC-442) and Gram-negative bacteria (E. coli-(MTCC-443), P. aeruginosa(MTCC-1688) . From all the series of compound N-(4-(2-(3-(1H-benzo[d]imidazol-2-yl)-5-(3-fluorophenyl)- 4,5-dihydro-1H-pyrazol-1-yl)-2- oxoethoxy) phenyl) acetamide (156) were found to be more potent activity as show in scheme-47[99].



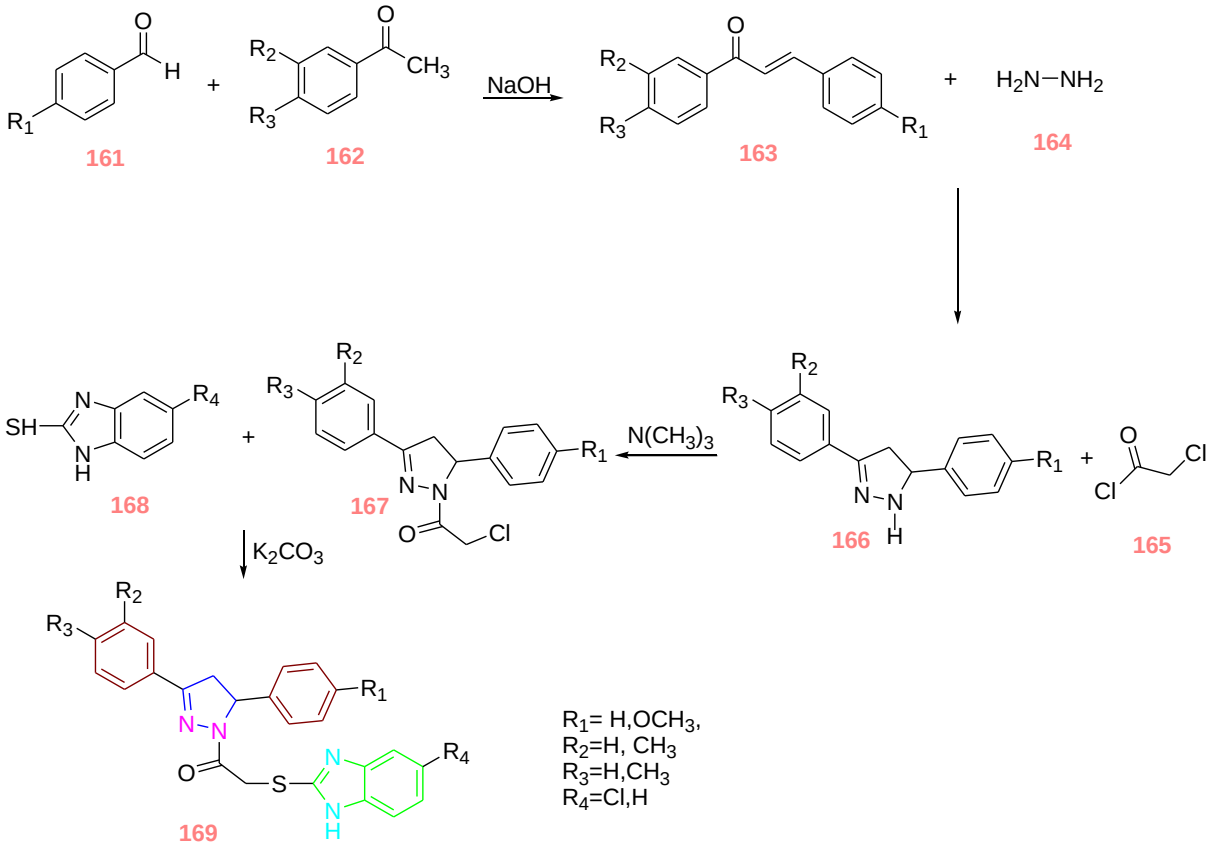
Scheme-47-Synthesis of Pyrazoline Bearing Benzimidazole Derivatives.

4.13 Desai. *et al.* synthesized a novel compound 1-(3-(1H-benzoimidazol-2-yl)-5-aryl-4-5dihydro-1H-pyrazol-1-yl)-2-(napthalene-1-yloxy) ethanones (160)and evaluated for their antimicrobial activity against strains of fungi (C. Albicans, A. niger, and A. Clavatus) and gram-positive bacteria (S. aureus, S. pyogenes) and gram-negative bacteria (E. coli, P. aeruginosa). Among the synthesized compound 1-(3-(1H-benzoimidazol-2-yl)-5-(4-methoxyphenyl-4-5dihydro-1H-pyrazol-1- yl)-2-(napthalen-1-yloxy) ethanone (160) found to be more potent activity as shown in scheme-48 [100].



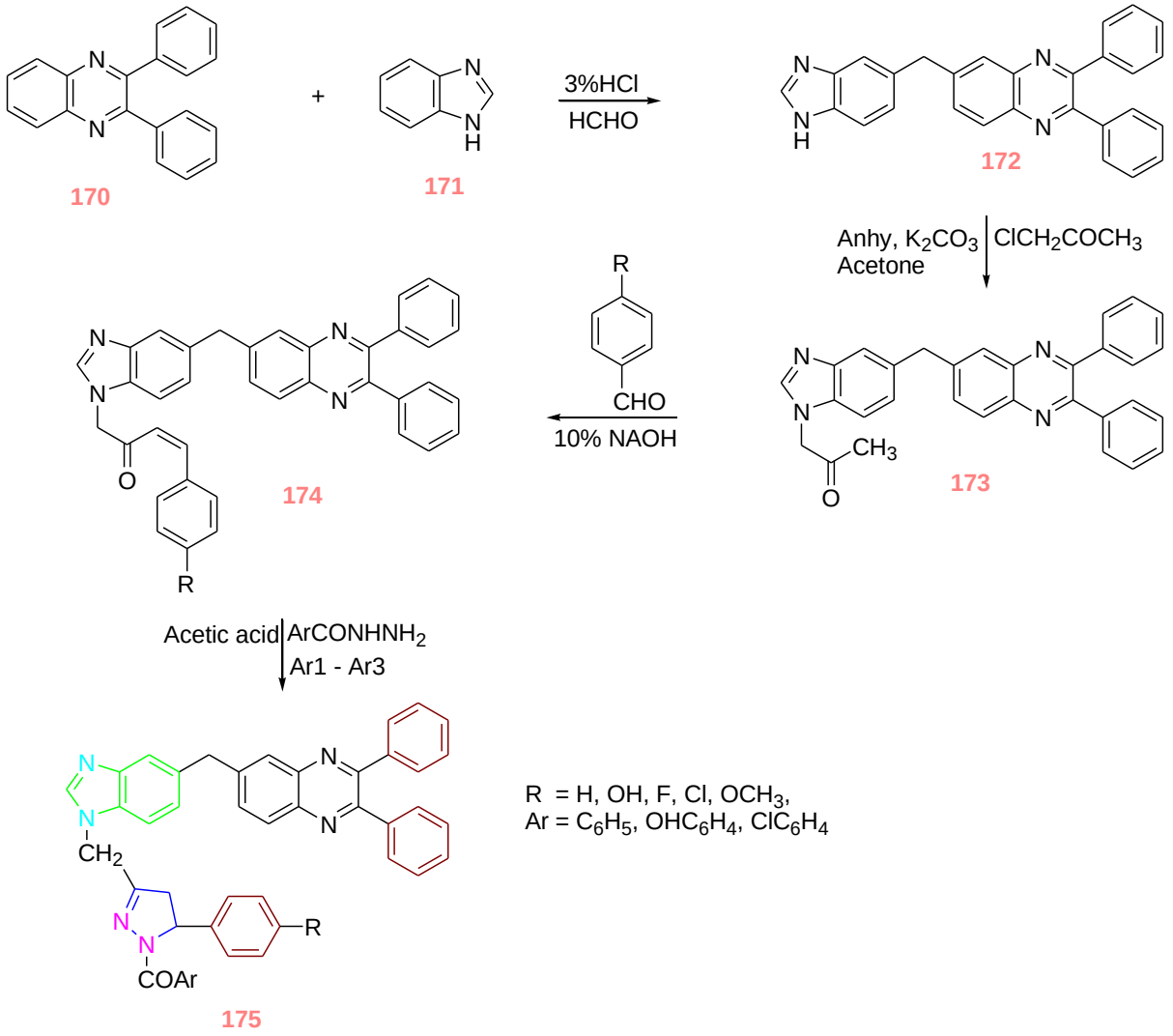
Scheme-48-synthesis of Pyrazoline Bearing Benzimidazole Derivatives.

4.14 Zafer. *et al.* Synthesized a novel 1-[(benzazole-2-yl) thioacetylamino]-3,5-diaryl-2-pyrazoline Derivatives and evaluated for their antinociceptive activity against chemical and thermal noxious stimuli. Among the synthesized compound derivatives (169) found to be more potent if R1 substituted with hydrogen group and R2 substituted with a methyl group and R3 substituted with a methyl group, and R4 substituted with chlorine group as shown in scheme-49[101].



Scheme-49-Synthesis of 1-[(benzazole-2-yl)thioacetylamino]-3,5-diaryl-2-pyrazoline Derivatives.

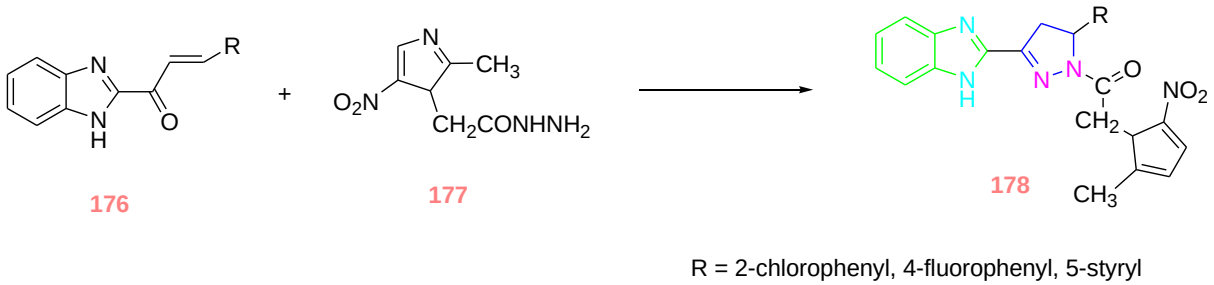
4.15 Sridevi. *et al.* synthesized a compound methylene bridge that connects 2,3-diphenyl quinoxalin (170) and benzimidazole (171), allowing for acetylation. The acetylated substance (166) is used to make chalcones by reacting with various aromatic aldehydes (174). Different phenyl pyrazolobenzimidazolequinoxaline derivatives were obtained by refluxing chalcones with substituted acid hydrazide derivatives (175) and were more potent if R was substituted with hydroxide group and Ar substituted with phenyl group as shown in scheme-50[102].



170 171 172 173 174 175

Scheme-50-Synthesis of phenylpyrazolobenzimidazoloquinoxaline Derivatives.

4.16 Krishnakumar. *et al.* reported a novel compound 1-[3-(1H-Benzoimidazol-2-yl)-4, 5-dihydro-pyrazol-1-yl]-2-(2-methyl-5-nitro-imidazol-1-yl)-ethanone (178) and screened for their antimalarial activity against dihydrofolate reductase. Among the synthesized compound (178) found to be more potent, If R group substituted with the chlorophenyl group as shown in scheme-51[103].



176 177 178

R = 2-chlorophenyl, 4-fluorophenyl, 5-styryl

Scheme-51-Synthesis of 1-[3-(1H-Benzoimidazol-2-yl)-4, 5-dihydro-pyrazol-1-yl]-2-(2-methyl-5-nitro-imidazol-1-yl)-ethanone.

V. CONCLUSION:

Pyrazolines are a heterocyclic compound with a cyclic structure. Pyrazoline is a five-membered ring made up of three carbon and two nitrogen atoms, with just one endocyclic bond and one group of electron-rich nitrogen carriers. benzimidazole is a heterocyclic aromatic organic compound. Benzene and imidazole are fused to form this bicyclic compound. It's a colorless liquid. In this article, several methods are used to synthesis compound pyrazoline and benzimidazole derivatives with a beneficial biological effect. Pyrazolines and Benzimidazoles are multifunctional

applications. The current review on pyrazoline and benzimidazole derivatives patent literature (1989-2021) describing the introduction, general method, and synthetic scheme on anticancer, anthelmintic, antidiabetic, antimalarial,antiproliferative, antibacterial, anti-histaminic,antitubercular, antinociceptive, and antimicrobial activity have been discussed, also in the general literature area in this review. The research of pyrazoline and benzimidazole derivatives' biological activity has been a fascinating area of pharmaceutical chemistry. Numerous Pyrazoline and benzimidazole derivatives have been discovered to have an essential biological effect on anticancer activity, which has encouraged research in this area. The use of pyrazoline and benzimidazole against a brilliant moiety and has an enormous scope of interest for the researchers to search more and more about this moiety.

CONFLICT OF INTEREST:

The authors confirm that this article is content has no conflict of interest.

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REFERENCES:

1. Ziauddina HM, Zameera M, Hingoleb SS, Baseera MA. An introduction of some novel
2. pyrazolines to synthetic chemistry and antimicrobial studies. *J. Chem*. 2010; **2:** 441-5.
3. Babu VH, Sridevi CH, Joseph A, Srinivasan KK. Synthesis and biological evaluation of some novel pyrazolines. *Ind.J. of Pharmaceutical Sciences*. 2007; **69,**470.
4. Azarifar D, Shaebanzadeh M. Synthesis and characterization of new 3, 5-dinaphthyl substituted 2-pyrazolines and study of their antimicrobial activity. molecules. 2002; **7,**885-95.
5. Kumar S, Bawa S, Drabu S, Kumar R, Gupta H. Biological activities of pyrazoline derivatives-A recent development. Recent patents on anti-infective drug discovery. 2009; **4,**154-63.
6. Ali MA, Shaharyar M, Siddiqui AA. Synthesis, structural activity relationship and anti-tubercular activity of novel pyrazoline derivatives. *Eur. J. of med. chem*. 2007; **42,**268-75.
7. Rizvi SU, Siddiqui HL, Johns M, Detorio M, Schinazi RF. Anti-HIV-1 and cytotoxicity studies of piperidyl-thienylchalcones and their 2-pyrazoline derivatives. *Med. Chem. Research.*2012;**21**,3741-49.
8. Mishriky N, Asaad FM, Ibrahim YA, Girgis AS. New 2-pyrazolines of anticipated molluscicidal activity. *Die Pharmazie*. 1996; **51,**544-48.
9. Kawazura H, Takahashi Y, Shiga Y, Shimada F, Ohto N, Tamura A. Cerebroprotective effects of a novel pyrazoline derivative, MS-153, on focal ischemia in rats. *The Jap. J. of Pharmacology*. 1997; **73,**317-24.
10. Li JT, Zhang XH, Lin ZP. An improved synthesis of 1, 3, 5-triaryl-2-pyrazolines in acetic acid aqueous solution under ultrasound irradiation. *Beilstein.J. of org. chem***.** 2007;**3**, 13.
11. Nehra B, Rulhania S, Jaiswal S, Kumar B, Singh G, Monga V. Recent advancements in the development of bioactive pyrazoline derivatives. *Europ.J. of Med Chem*. 2020; 112666.
12. Chorvat RJ, Berbaum J, Seriacki K, McElroy JF. JD-5006 and JD-5037: peripherally restricted (PR) cannabinoid-1 receptor blockers related to SLV-319 (Ibipinabant) as metabolic disorder therapeutics devoid of CNS liabilities. *Bio.org & med. chemletr.* 2012 ;**22**,6173-80.
13. Upadhyay N, Tilekar K, Loiodice F, Anisimova NY, Spirina TS, Sokolova DV, Smirnova GB, Choe JY, Meyer-Almes FJ, Pokrovsky VS, Lavecchia A. Pharmacophore hybridization approach to discover novel pyrazoline-based hydantoinanalogs with anti-tumor efficacy. *Bio.org. Chem*.2021;**107**,104527.
14. Karkkainen MJ, Petrova TV. Vascular endothelial growth factor receptors in the regulation of angiogenesis and lymphangiogenesis. *Oncogene*. 2000;**19**,5598-05.
15. Morabito A, De Maio E, Di Maio M, Normanno N, Perrone F. Tyrosine kinase inhibitors of vascular endothelial growth factor receptors in clinical trials: current status and future directions. *The oncologist*. 2006; **11,**753-64.
16. El-Miligy MM, Abd El Razik HA, Abu-Serie MM. Synthesis of piperazine-based thiazolidinones as VEGFR2 tyrosine kinase inhibitors inducing apoptosis. *Future med.chem*. 2017 ;**9**,1709-29.
17. Sharma R, Kumar R, Kodwani R, Kapoor S, Khare A, Bansal R, Khurana S, Singh S, Thomas J, Roy B, Phartyal R. A review on mechanisms of anti tumor activity of chalcones. Anti-Cancer Agents in*Med. Chem(Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*. 2016 ;**16**,200-11.
18. P. Schoffski, S. Cresta, I.A. Mayer, H. Wildiers, S. Damian, S. Gendreau, € I. Rooney, K.M. Morrissey, J.M. Spoerke, V.W. Ng, S.M. Singel, E. Winer, A phase Ib study of pictilisib (GDC-0941) in combination with paclitaxel, with and without bevacizumab or trastuzumab, and with letrozole in advanced breast cancer, Breast Cancer Res. 20 (2018), 3-6.
19. Chang LC, Lin HY, Tsai MT, Chou RH, Lee FY, Teng CM, Hsieh MT, Hung HY, Huang LJ, Yu YL, Kuo SC. YC-1 inhibits proliferation of breast cancer cells by down-regulating EZH 2 expression via activation of c-C bl and ERK. *British. J. of pharmacology*. 2014 ;**171**,4010-25.
20. Ramaswamy B, Mrozek E, Kuebler JP, Bekaii-Saab T, Kraut EH. Phase II trial of pyrazoloacridine (NSC# 366140) in patients with metastatic breast cancer. *Investigational new drugs*. 2011; **29,**347-51.
21. Li QS, Shen BN, Zhang Z, Luo S, Ruan BF. Discovery of Anticancer Agents from 2-Pyrazoline-Based Compounds. *Current medicinal chemistry*. 2020 **,**2-6.
22. Wang M, Han X, Zhou Z. New substituted benzimidazole derivatives: A patent review (2013–2014). *Expert opinion on therapeutic patents.*2015; **25,**595-12.
23. Gaba M, Mohan C. Development of drugs based on imidazole and benzimidazole bioactive heterocycles: recent advances and future directions. *Med. Chem. Research.*2016; **25,**173-10.
24. O'Neil MJ, Smith A, Heckelman PE, Budavari S. The merck index-An encyclopedia of chemicals, drugs, and biologicals. whitehouse station, NJ: Merck and Co. Inc. 2001;**767**,4342.
25. Ayhan-Kılcıgil G, Kus C, Özdamar ED, Can-Eke B, Iscan M. Synthesis and antioxidant capacities of some new benzimidazole derivatives. Archiv der Pharmazie: *An Int. J. Pharmaceutical and Med. Chem*. 2007; **340,**607-11.

26. Kus C, Ayhan-Kilcigil G, Eke BC. Synthesis and antioxidant properties of some novel benzimidazole derivatives on lipid peroxidation in the rat liver. *Archives of pharmacal research.*2004; **27,**156-63.

27. Ateş-Alagöz Z, Kuş C, Çoban T. Synthesis and antioxidant properties of novel benzimidazoles containing substituted indole or 1, 1, 4, 4-tetramethyl-1, 2, 3, 4-tetrahydro-naphthalene fragments. *J. of enzyme inhibition and med. chem*. 2005; **20,**325-31.

28. Navarrete-Vázquez G, Cedillo R, Hernández-Campos A, Yépez L, Hernández-Luis F, Valdez J, Morales R, Cortés R, Hernández M, Castillo R. Synthesis and antiparasitic activity of 2-(trifluoromethyl) benzimidazole derivatives. *Bio. &med.chem. letters*. 2001; **11,**187-90.

29. Katiyar SK, Gordon VR, McLaughlin GL, Edlind TD. Antiprotozoal activities of benzimidazoles and correlations with beta-tubulin sequence. *Antimicrobial agents and chemotherapy*. 1994;**38**,2086-90.

30. Ravina E, Sanchez-Alonso R, Fueyo J, Baltar MP, Bos J, Iglesias R, Sanmartin ML. Antiparasitic activity of some New Caledonian medicinal plants. Arzneim. Forsch. 1993; **43**,684-94.

31. Garuti L, Roberti M, Malagoli M, Rossi T, Castelli M. Synthesis and antiproliferative activity of some benzimidazole-4, 7-dione derivatives. *Bio & med. chem letters*. 2000; **10**,2193-95.

32. Rao A, Chimirri A, De Clercq E, Monforte AM, Monforte P, Pannecouque C, Zappalà M. Synthesis and anti-HIV activity of 1-(2, 6-difluorophenyl)-1H, 3H-thiazolo [3, 4-a] benzimidazole structurally-related 1, 2-substituted benzimidazoles. Il Farmaco. 2002; **57,**819-23.

33. Chimirri A, De Sarro A, De Sarro G, Gitto R, Zappala M. Synthesis and anticonvulsant properties of 2, 3, 3a, 4-tetrahydro-1H-pyrrolo [1, 2-a] benzimidazol-1-one derivatives. Il Farmaco. 2001**; 56,**821-26.

34. Thakurdesai PA, Wadodkar SG, Chopade CT. *Pharmacologyonline* 2007; 1, 314–329.

35. Le HT, Lemaire IB, Gilbert AK, Jolicoeur F, Yang L, Leduc N, Lemaire S. Histogranin-like antinociceptive and anti-inflammatory derivatives of o-phenylenediamine and benzimidazole. *Journal of Pharmacology and Experimental Therapeutics*. 2004; **309,**146-55.

36. Lackner TE, Clissold SP. Bifonazole. Drugs. 1989; **38,**204-25.

37. Ersan S, Nacak S, Noyanalpan N, Yeşilada E. Studies on analgesic and anti-inflammatory activities of 1-dialkylaminomethyl-2-(p-substituted phenyl)-5-substituted benzimidazole derivatives. *Arzneimittel-forschung*. 1997; **47,**834-36.

38. Serafin B, Borkowska G, Główczyk J, Kowalska I, Rump S. Potential antihypertensive benzimidazole derivatives. *Polish.J. of pharmacology and pharmacy*. 1989,**41**,89-96.

39. Kubo K, Inada Y, Kohara Y, Sugiura Y, Ojima M, Itoh K, Furukawa Y, Nishikawa K, Naka T. Nonpeptide angiotensin II receptor antagonists. Synthesis and biological activity of benzimidazoles. *J. of med. chem*. 1993;**36**,1772-84.

40. Abdel-hafez AA. Benzimidazole condensed ring systems: New synthesis and antineoplastic activity of substituted 3, 4-dihydro-and 1, 2, 3, 4-tetrahydro-benzo [4, 5] imidazo [1, 2-a] pyrinnidine derivatives. *Archives of pharmacal research.*2007; **30,**678-84.

41. Ram S, Wise DS, Wotring LL, McCall JW, Townsend LB. Synthesis and biological activity of certain alkyl 5-(alkoxycarbonyl)-1H-benzimidazole-2-carbamates and related derivatives: a new class of potential antineoplastic and antifilarial agents. *J. of med. chem.*1992; **35,**539-47.

42. MavrovaaT, Denkova P, Tsenov YA, Anichina KK, Vutchev DI. Synthesis and antitrichinellosis activity of some bis (benzimidazol-2-yl) amines. *Bio& med. chem*. 2007 ;**15**,6291-97.

43. De La Fuente T, Martín-Fontecha M, Sallander J, Benhamú B, Campillo M, Medina RA, Pellissier LP, Claeysen S, Dumuis A, Pardo L, López-Rodríguez ML. Benzimidazole derivatives as new serotonin 5-HT6 receptor antagonists. Molecular mechanisms of receptor inactivation. *J. of med. chem*. 2010 **;53**,1357-69.

44. Akazawa H, Yasuda N, Komuro I. Mechanisms and functions of agonist-independent activation in the angiotensin II type 1 receptor. *Molecular and cellular endocrinology.*2009; **302,**140-47.

45. De Gasparo M, Catt KJ, Inagami T, Wright JW, Unger TH. International union of pharmacology. XXIII. The angiotensin II receptors. *Pharmacological reviews*. 2000; **52,**415-72.

46. Laragh JH. Historical perspective on renin system blockade in the treatment of hypertension. *American journal of hypertension*. 1992;**5** ,207S-08S.

47. Captopril Multicenter Research Group**. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *J. of the American College of Cardiology*. 1983**; 2,**755-63.

48. SOLVD Investigators*. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *New England J. of Medicine*. 1991; **325,**293-02.

49. Case DB, Atlas SA, Marion RM, Laragh JH. Long-term efficacy of captopril in renovascular and essential hypertension. *The American. J. of cardiology*. 1982;**49**,1440-46.

50. Consensus Trial Study Group*. Effects of enalapril on mortality in severe congestive heart failure. *New England J. of Medicine.* 1987 ;**316**,1429-35.

51. Timmermans PB, Wong PC, Chiu AT, Herblin WF. Nonpeptide angiotensin II receptor antagonists. *Trends in pharmacological sciences*. 1991 ;**12**,55-62.

52. Timmermans PB, Carini DJ, Chiu AT, Duncia JV, Price Jr WA, Wells GJ, Wong PC, Wexler RR, Johnson AL. Angiotensin II receptor antagonists. From discovery to antihypertensive drugs. *Hypertension*. 1991**; (5_supplement), III**,136-42.

53. Wong PC, Price WA, Chiu AT, Duncia JV, Carini DJ, Wexler RR, Johnson AL, Timmermans PB. Nonpeptide angiotensin II receptor antagonists. VIII. Characterization of functional antagonism displayed by DuP 753, an orally active antihypertensive agent. *J. of Pharmacology and Experimental Therapeutics*. 1990**,252**,719-25.

54. Yuhong J, Varma RS. queous N-heterocyclization of primary amines and hydrazines with dihalides: microwave-assisted syntheses of N-azacycloalkanes, isoindole, pyrazole, pyrazolidine, and phthalazine derivatives. *The J. of Org. Chem.*2006; **71,**135-41.

55. Lellek V, Chen CY, Yang W, Liu J, Ji X, Faessler R. An Efficient Synthesis of Substituted Pyrazoles from One-Pot Reaction of Ketones, Aldehydes, and Hydrazine Monohydrochloride. Synlett. 2018 ;**29**,1071-75.

56. Alex K, Tillack A, Schwarz N, Beller M. Zinc-catalyzed synthesis of pyrazolines and pyrazoles via hydrohydrazination. *Org. Letters*. 2008;**10**,2377-79.

57. Yusuf M, Jain P. Synthetic and biological studies of pyrazolines and related heterocyclic compounds. *Arabian J. of Chem*. 2014; **7,**553-96.

58. Gembus V, Bonnet JJ, Janin F, Bohn P, Levacher V, Brière JF. Synthesis of pyrazolines by a site isolated resin-bound reagents methodology. *Org&biomolecular chem*. 2010**;8**,3287-93.

59. Cui SL, Wang J, Wang YG. Facile access to pyrazolines via domino reaction of the Huisgen zwitterions with aziridines. *Org Letters.*2008 ;**10**,13-16.

60. Wang Z, Yang Y, Gao F, Wang Z, Luo Q, Fang L. Synthesis of 5-(Trifluoromethyl) pyrazolines by Formal [4+ 1]-Annulation of Fluorinated SulfurYlides and Azoalkenes. *Org letters*. 2018,**20**,934-37.

61. Waldo JP, Mehta S, Larock RC. Room temperature icl-induced dehydration/iodination of 1-acyl-5-hydroxy-4, 5-dihydro-1 h-pyrazoles. A selective route to substituted 1-acyl-4-iodo-1 h-pyrazoles. *The J. of org. chem*. 2008 ;**3**,6666-70.

62. Chen M, Wang LJ, Ren PX, Hou XY, Fang Z, Han MN, Li W. Copper-catalyzeddiamination of alkenes of unsaturated ketohydrazones with amines. *Org letters*. 2018; **20,**510-13.

63. Yang MN, Yan DM, Zhao QQ, Chen JR, Xiao WJ. Synthesis of dihydropyrazoles via ligand-free Pd-catalyzed alkene aminoarylation of unsaturated hydrazones with diaryliodonium salts. *Org letters*. 2017 ;**19**,5208-11.

64. Gu ZS, Chen WX, Shao LX. N-heterocyclic carbene-palladium (II)-1-methylimidazole complex-catalyzed direct C–H bond arylation of (Benz) imidazoles with aryl chlorides.*The J. of org. chem*. 2014;**79**,5806-11.

65. Nale DB, Bhanage BM. N-substituted formamides as C1-sources for the synthesis of benzimidazole and benzothiazole derivatives by using zinc catalysts. *Synlett***.** 2015 ;**26**,2835-42.
66. Zhu X, Zhang F, Kuang D, Deng G, Yang Y, Yu J, Liang Y. K2S as Sulfur Source and DMSO as Carbon Source for the Synthesis of 2-Unsubstituted Benzothiazoles. *Org. letters*. 2020;**22,** 3789-93.
67. Mahesh D, Sadhu P, Punniyamurthy T. Copper (I)-catalyzedregioselective amination of N-aryl imines using TMSN3 and TBHP: a route to substituted benzimidazoles. *The J. of org.chem*. 2015 ;**80**,1644-50.
68. Mahesh D, Sadhu P, Punniyamurthy T. Copper (II)-catalyzed oxidative cross-coupling of anilines, primary alkyl amines, and sodium azide using TBHP: a route to 2-substituted benzimidazoles. *The J. of org.chem*.2016 ;**81**,3227-34.
69. Hu Z, Zhao T, Wang M, Wu J, Yu W, Chang J. I2-Mediated Intramolecular C–H Amidation for the Synthesis of N-Substituted Benzimidazoles. *The J. of org chem*. 2017;**82**,3152-58.
70. Das K, Mondal A, Srimani D. Selective synthesis of 2-substituted and 1, 2-disubstituted benzimidazoles directly from aromatic diamines and alcohols catalyzed by molecularly defined nonphosphine manganese (I) complex. *The J. of org. chem*. 2018 ,**83**,9553-60.
71. Hu Z, Zhao T, Wang M, Wu J, Yu W, Chang J. I2-Mediated Intramolecular C–H Amidation for the Synthesis of N-Substituted Benzimidazoles. *The J. of org. chem*. 2017 ;**82**,3152-58.
72. Zhang R, Qin Y, Zhang L, Luo S. Oxidative synthesis of benzimidazoles, quinoxalines, and benzoxazoles from primary amines by ortho-quinone catalysis. *Org. letters.*2017 ;**19**,5629-32.
73. Nguyen TB, Ermolenko L, Dean WA, Al-Mourabit A. Benzazoles from aliphatic amines and o-amino/mercaptan/hydroxyanilines: elemental sulfur as a highly efficient and traceless oxidizing agent. *Org. letters*. 2012 ;**14**,5948-51.
74. Mayo MS, Yu X, Zhou X, Feng X, Yamamoto Y, Bao M. Convenient synthesis of benzothiazoles and benzimidazoles through Brønsted acid catalyzed cyclization of 2-amino thiophenols/anilines with β-diketones. *Org. letters*. 2014; **16,**764-67.
75. Bastug G, Eviolitte C, Marko IE. Functionalized orthoesters as powerful building blocks for the efficient preparation of heteroaromatic bicycles. *Org. letters*. 2012;**14**,3502-05.
76. Hati S, Kumar Dutta P, Dutta S, Munshi P, Sen S. Accessing benzimidazoles via a ring distortion strategy: an oxone mediated tandem reaction of 2-Aminobenzylamines. *Org. letters*. 2016;**18**,3090-93.
77. Caron S, Jones BP, Wei L. Preparation of substituted benzimidazoles and imidazopyridines using 2, 2, 2-trichloroethyl imidates. Synthesis.2012 ;**44**,3049-54.
78. Duangkamol C, Phakhodee W, Pattarawarapan M. Potassium Periodate Mediated Oxidative Cyclodesulfurization toward Benzofused Nitrogen Heterocycles. Synthesis. 2020l;**52**,1981-90.
79. Bahrami K, Khodaei MM, Naali F. Mild and highly efficient method for the synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles. *The J.oforg.chem*.2008 ;**73**,6835-37.
80. Ke F, Zhang P, Xu Y, Lin X, Lin J, Lin C, Xu J. Microwave-Assisted Nickel-Catalyzed Synthesis of Benzimidazoles: Ammonia as a Cheap and Nontoxic Nitrogen Source. *Synlett*.2018 ;**29**,2722-26.
81. Kim Y, Kumar MR, Park N, Heo Y, Lee S. Copper-catalyzed, one-pot, three-component synthesis of benzimidazoles by condensation and C–N bond formation. *The J. of org.chem*.2011; **76**,9577-83.
82. Baars H, Beyer A, Kohlhepp SV, Bolm C. Transition-metal-free synthesis of benzimidazoles mediated by KOH/DMSO. *Org. letters*. 2014; **16,536**-39.
83. Alla SK, Kumar RK, Sadhu P, Punniyamurthy T. Iodobenzenecatalyzed C–H amination of N-substituted amidines using m-chloroperbenzoic acid. *Org. letters*. 2013 ;**15**,1334-37.
84. Wray BC, Stambuli JP. Synthesis of N-arylindazoles and benzimidazoles from a common intermediate. *Org. letters*. 2010 ;**12**,4576-79.
85. Peng J, Ye M, Zong C, Hu F, Feng L, Wang X, Wang Y, Chen C. Copper-catalyzed intramolecular C− N bond formation: A straightforward synthesis of benzimidazole derivatives in water. *The J. of org. chem*. 2011; **76,716**-19.
86. Xue D, Long YQ. Metal-free TEMPO-promoted C (sp3)–H amination to afford multisubstitutedbenzimidazoles. *The J. of org. chem*. 2014 ;**79**,4727-34.
87. Guru MM, Ali MA, Punniyamurthy T. Copper-Mediated Synthesis of Substituted 2-Aryl-N-benzylbenzimidazoles and 2-Arylbenzoxazoles via C–H Functionalization/C–N/C–O Bond Formation. *The J. of org. chem*.2011**; 76**,5295-08.
88. Saha P, Ramana T, Purkait N, Ali MA, Paul R, Punniyamurthy T. Ligand-free copper-catalyzed synthesis of substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles. *The J.of org. chem*. 2009;**74**,8719-25.
89. Akhtar MJ, Khan AA, Ali Z, Dewangan RP, Rafi M, Hassan MQ, Akhtar MS, Siddiqui AA, Partap S, Pasha S, Yar MS. Synthesis of stable benzimidazole derivatives bearing pyrazole as anticancer and EGFR receptor inhibitors. *Bio. -org Chem*.2018; **78,**158-69.
90. Shaharyar M, Abdullah MM, Bakht MA, Majeed J. Pyrazoline bearing benzimidazoles: search for anticancer agent.*Europ .J.of med. chem*. 2010 ;**45**,114-19.
91. Youset MY, Eisa HM, Nasr MN, El-Bialy SA. Synthesis and anthelmintic properties of new benzimidazoles. ALEXANDRIA JOURNAL OF PHARMACEUTICAL SCIENCES. **1996**; **10**,155-58.
92. Ibraheem F, Ahmad M, Ashfaq UA, Aslam S, Khan ZA, Sultan S. Synthesis, molecular docking and anti-diabetic studies of novel benzimidazole-pyrazoline hybrid molecules*Pak. J. of pharmaceutical sciences.***2020**; **33**,847-54.
93. Lohidakshan K, Rajan M, Ganesh A, Paul M, Jerin J. Pass and Swiss ADME collaborated in silico docking approach to the synthesis of certain pyrazoline spacer compounds for dihydrofolate reductase inhibition and antimalarial activity. ||| *Bang. J.of Pharmacology*|||.2018**;13**,23-29.
94. Krishna Padhy G, Panda J, Behera AK. Synthesis and characterization of novel benzimidazole embedded 1, 3, 5-trisubstituted pyrazolines as antimicrobial agents. *arXiv e-prints*. **2020**, arXiv-2005; 2-7.
95. Abdelgawad MA, Bakr RB, Omar HA. Design, synthesis and biological evaluation of some novel benzothiazole/benzoxazole and/or benzimidazole derivatives incorporating a pyrazole scaffold as antiproliferative agents. *Bio-org.chem*. 2017 ;**74**,82-90.
96. soni,N.Gangwar,A.&Soni.N.Synthesis of molecular docking studies in vitro anthelmintic activities of novel substituted pyrazole bearing benzimidazole derivatives
The pharma .J. , 2019;**8**, 327-32
97. Sridevi CH, Balaji K, Naidu A, Sudhakaran R. Synthesis of some phenylpyrazolobenzimidazoloquinoxaline derivatives as potent antihistaminic agents. E-Journal of Chemistry.2010 ;**7(1)**,234-38.
98. Yar MS, Abdullah MM, Majeed J. In vitro anti-tubercular screening of newly synthesized benzimidazole derivatives. *World Acad. Sci. Engr. Tech*. 2009 ;**55**,593-99.
99. Desai NC, Pandya DD, Joshi VV, Rajpara KM, Vaghani HV, Satodiya HM. Synthesis, characterization and antimicrobial screening of hybrid molecules containing benzimidazole-pyrazole and pyridine nucleus. *Med.Chem. Research*. 2012;**21**,4463-72.
100. Desai NC, Pandya DD, Kotadiya GM, Desai P. Synthesis and characterization of novel benzimidazole bearing pyrazoline derivatives as potential antimicrobial agents. *Med. Chem. Research*. 2014;**23**,1474-87.
101. Desai NC, Pandya D, Vaja D. Synthesis and antimicrobial activity of some heterocyclic compounds bearing benzimidazole and pyrazoline motifs. *Med. Chem. Research*. **2018** ;**27**,52-60.
102. Kaplancikli ZA, Turan-Zitouni G, Özdemir A, Can ÖD, Chevallet P. Synthesis and antinociceptive activities of some pyrazoline derivatives. *Europ. J. of med. chem*. 2009; **44**,2606-10.

103. Sridevi C, Balaji K, Naidu A, Suthakaran R. Synthesis of some phenylpyrazolobenzimidazoloquinoxaline derivatives. *Ori. J. of Chem*. 2009;**25**,325-29.
104. Lohidakshan K, Rajan M, Ganesh A, Paul M, Jerin J. Pass and Swiss ADME collaborated in silico docking approach to the synthesis of certain pyrazoline spacer compounds for dihydrofolate reductase inhibition and antimalarial activity. ||| *Bang. J. of Pharmacology*|||. 2018;**3**,23-29.