Research Paper

Insight into Synthetic Progress Aspects of 2-Aminobenzimidazole Derivatives: A Review

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ABSTRACT
Heterocyclic compounds, especially frameworks like 2-aminobenzimidazole, are important in the search and development of novel chemotherapeutics. Besides being common in a wide variety of medications, such a structure exhibits various biological activities like neuroprotective, antiviral, antibacterial, anticancer, and antimalarial properties. Applications include serving as useful tools for targeting disease pathways and thus are of potential interest in future research in the field of medicinal chemistry and pharmacology, notwithstanding challenges such as drug resistance.

Key words: 2-aminobenzimidazole, heterocyclic, anti-cancer, catalyst, imidazole.
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1. Introduction

Heterocyclic compounds are strongly promising for new chemotherapeutics in pharmaceutical drug discovery and development initiatives [1]. Heterocyclic and, most importantly, nitrogen-containing fragments are part of the structure of about 2/3rd of the known drugs utilized in healthcare [2]. One such nitrogen-containing aromatic compound that has a preferred structure and an interesting pharmacophore is benzimidazole (BI). It is a bicyclic structure consisting of a benzo-fused imidazole moiety at the C-4 and C-5 positions of the imidazole moiety [3-5]. BI shows two tautomeric forms [6]. Scientists researching bioorganic chemistry are fascinated by BI compounds because some of them display a range of biological activities [7-9].

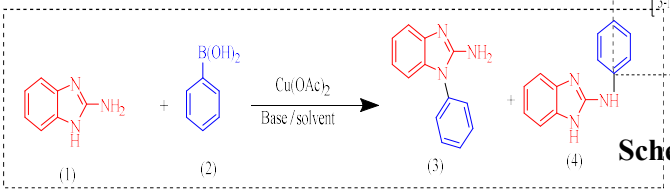
The chemical structure of 2-aminobenzimidazole comprises an imidazole ring and benzene. It's a derivative of benzimidazole in which an amino group has replaced the hydrogen atom [10]. A unique cyclic guanidine component of 2-aminobenzimidazole, which is rich in lone pair electrons and π electrons on three nitrogen atoms, offers various reaction locations for the production of derivatives [11-12]. The guanidine functional group is found in numerous biologically active natural products and several drugs [13]. N-substituted 2-aminobenzimidazoles are heterocyclic products that are known to be essential components of a variety of medical drugs [14-18]. The significance of 2ABI has prompted a combination of theoretical and experimental research on its molecular structure in order to fully understand its chemical and physical characteristics [19-20]. Through hydrogen bonding, a number of 2ABI derivatives have been developed and evaluated to operate as bifunctional organocatalysts. For example, like (2-aminoalkyl)-BIs have been used as chiral organocatalysts in carbonyl compound amination and aldol processes [21]. Few research have reported the synthesis of derivatives of 2-ABZ [22]. The 2-ABZ derivatives show several therapeutic potentials, such as anti-bacterial [23-26], anti-cancer [27-30], anti-diabetic [31-33], anti-fungal [34-35], anti-viral [36-38], anti-protozoal [39-40]. 2-ABZ core is

present in various drugs like pentosidine [41], astemizole [42] and albendazole [43]. Benomyl (fungicide) also contain 2-ABZ scaffold [44].

2. Synthesis of 2-Aminobenzimidazole derivatives

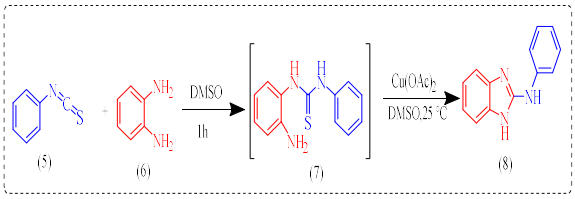
The synthesis of 2-ABZ involves an environmentally friendly process of α-halogenated cyclohexanones reacting with guanidine without the need for transition metals, which is facilitated by NBS/oxone [45]. 2-ABZ can also be synthesized by o-phenylenediamine cyclization using cyanogen bromide or imidoyl dichlorides [46]. In order to boost safety and yield, most recent methods concentrate on mild, scalable, and catalyst-free conditions [47].

Rao et al. (2016) prepared the 1-phenyl-1H-benzo[d]imidazole-2-amine **(3)** and N-phenyl-1H-benzo[d]imidazole-2-amine **(4)**. The coupling of 2-aminobenzimidazole **(1)** and phenylboronic acid **(2)** with Cu(OAc)2 [copper(II)acetate],CsOPiv [cesium pivalate] as base, DMF [dimethylformamide]is employed as solvent, results in compounds (3) and (4) (scheme 1) [48].



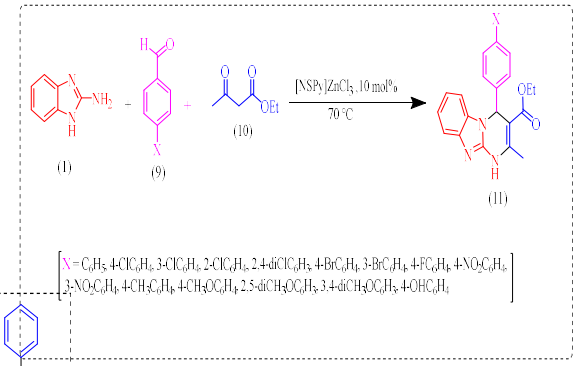
Scheme 1. Synthesis of 1-phenyl-1H-benzo[d]imidazole-2-amine and N-phenyl-1H-benzo[d]imidazole-2-amine

Han et al. (2022) synthesized compound *N*-phenyl-1*H*-benzo[*d*]imidazole-2-amine **(8)** from phenylisothiocyanate **(5)** and *o*-phenylenediamine **(6)**. The thiourea derivative **(7)** was prepared by reaction of **(5)** & **(6)** in the presence of DMSO [dimethyl sulfoxide]. By reacting the catalyst $Cu(OAc)_2$ [Copper(II)acetate] with compound **(7)** at 25°C compound **(8)** was prepared. (Scheme 2) [49].



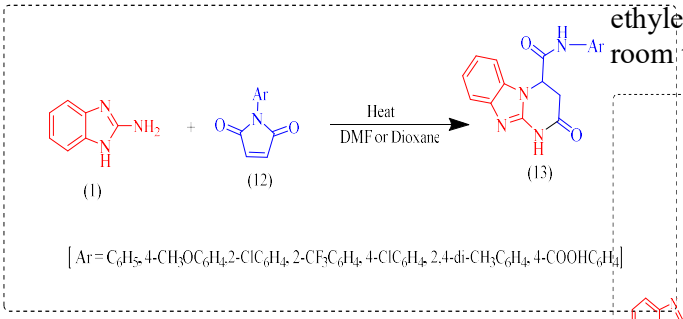
Scheme 2. Synthesis of *N*-phenyl-1*H*-benzo[*d*]imidazole-2-amine

Goudarziafshar et al. (2024) synthesized the 4*H*-pyrimido[2,1-*b*]benzimidazole derivatives **(11)** from 2-aminobenzimidazole **(1)**, aromatic aldehyde **(9)** and ethyl acetoacetate **(10)** in the presence of 10 mol% N-sulfopyridin-1-ium monozinc (II) tri chloride [(NSPy)$ZnCl_3$] at 70 °C temperature under solvent free condition. (Scheme 3) [50].



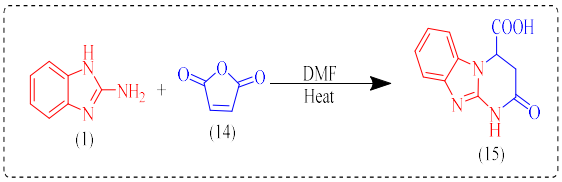
Scheme 3. Synthesis of 4*H*-pyrimido[2,1-*b*]benzimidazole derivatives

Rudenko et al. (2011) synthesized pyrimidobenzimidazole derivatives **(13)** from 2-aminobenzimidazole **(1)** and 1-aryl-1*H*-pyrrole-2,5-dione **(12)** in the presence of dimethylformamide or dioxane by heating. (Scheme 4) [51].



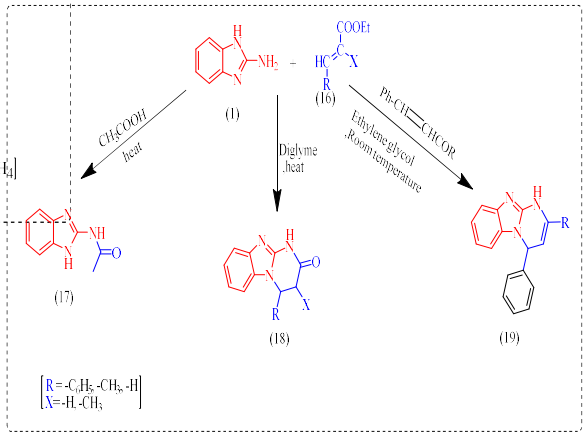
Scheme 4. Synthesis of pyrimidobenzimidazole derivatives

Rudenko et al. (2011) synthesized 2-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrimidine-4-carboxlic acid **(15).** From the reaction of 2-aminobenzimidazole **(1)** and maleic anhydride **(14)** by heating in the presence of DMF [dimethylformamide]. (Scheme 5) [51]



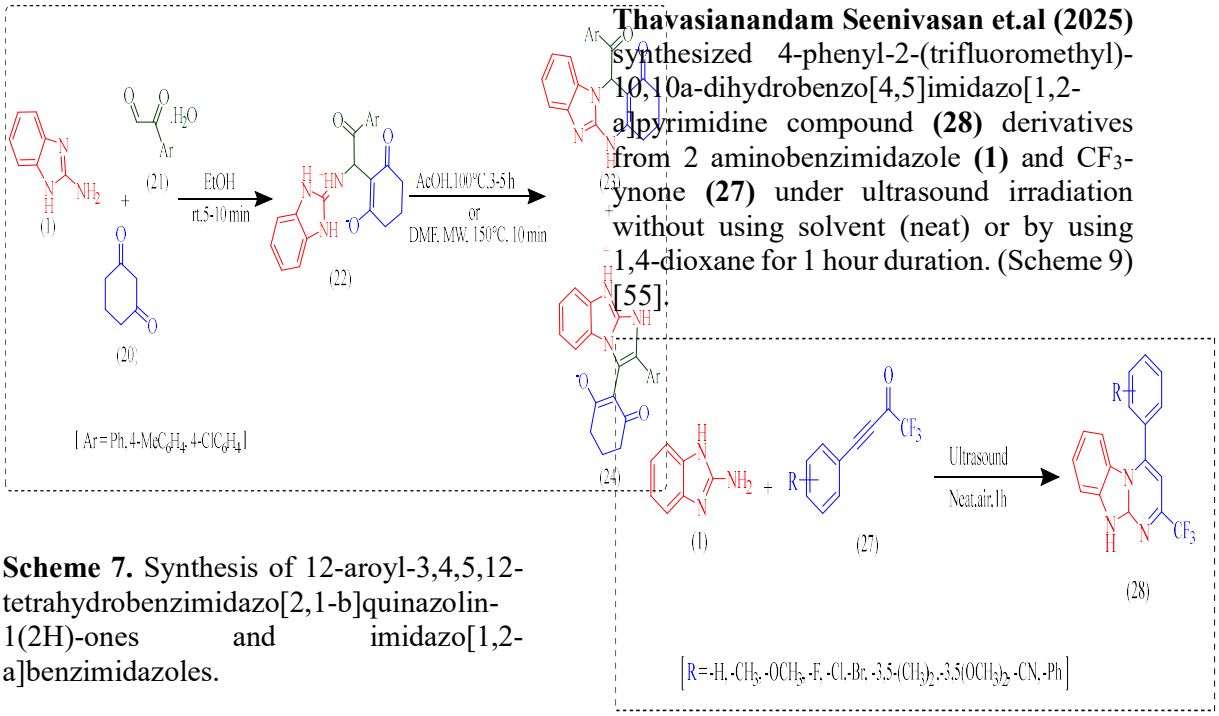
Scheme 5. Synthesis of 2-oxo-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrimidine-4-carboxlic acid

Nawrocka et al. (1998) synthesized 2-Acetylaminobenzimidazole **(17)**, 3,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-2(1*H*)-one derivatives **(18)** and 4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine **(19)** derivatives from 2-aminobenzimidazole **(1)** and ester of α,β-unsaturated acid derivatives **(16)**. The compound **(17)** was synthesized by dissolving **(1)** & **(16)** in glacial acetic acid and was heated for 3-5 h under reflux. Compound **(18)** was synthesized similarly to **(17)** but in the presence of diglyme (solvent). Compound **(19)** was synthesized from **(1)** and **(16)** in the presence of ethylene glycol, it was stirred for 3 days at room temperature. (Scheme 6) [52]



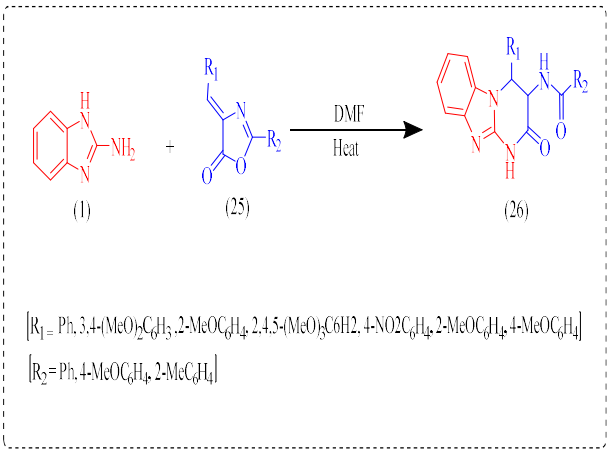
Scheme 6. Synthesizes of 2-Acetylaminobenzimidazole, 3,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-2(1*H*)-one derivatives and 4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine derivatives

Petrova et.al (2015) synthesized 12-aroyl-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin- 1(2H)-ones **(23)** and imidazo[1,2-a]benzimidazoles **(24)** from 2-aminobenzimidazole **(1)**, 1,3-cyclohexanedione **(20)** and aryl glyoxals **(21)**. The compounds **(1), (20)** and **(21)** were heated with microwaves in ethanol or acetonitrile at 150°C for 10 minutes which lead in formation of **(23)** and **(24)**. The zwitterionic form compound **(22)** was formed by reaction of **(1), (20)** & **(21)** in the presence of acetic acid at 100°C temperatures. On prolong heating of 3-5h it converts into condensed forms 23 and 24. (Scheme 7) [53].



Scheme 7. Synthesis of 12-aroyl-3,4,5,12-tetrahydrobenzimidazo[2,1-b]quinazolin-1(2H)-ones and imidazo[1,2-a]benzimidazoles.

Chebanov et.al (2004) synthesized N-(oxo-1,2,3,4-tetrahydrobenzo[1,2-*a*]pyrimidine-3-yl)acetamide derivatives **(26)** by heating aminobenzimidazole **(1)** and azlactones **(25)** in the presence of solvent DMF [dimethylformamide]. (Scheme 8) [54]

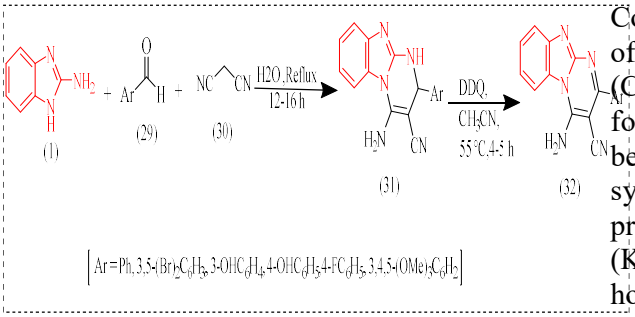


Scheme 8. Synthesis of N-(oxo-1,2,3,4-tetrahydrobenzo[1,2-*a*]pyrimidine-3-yl)acetamide derivatives

Thavasianandam Seenivasan et.al (2025) synthesized 4-phenyl-2-(trifluoromethyl)-10,10a-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine compound **(28)** derivatives from 2 aminobenzimidazole **(1)** and CF_3-ynone **(27)** under ultrasound irradiation without using solvent (neat) or by using 1,4-dioxane for 1 hour duration. (Scheme 9) [55].

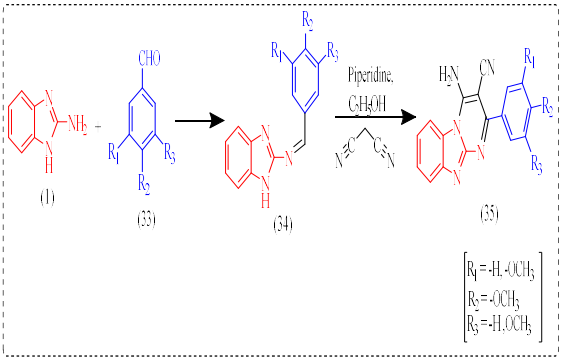
Scheme 9. Synthesis of 4-phenyl-2-(trifluoromethyl)-10,10a-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine

Risley et al. (2014) synthesized 1,2-Dihydropyrimido[1,2-*a*]- benzimidazole **(31)** compound derivatives and Pyrimido[1,2-a]benzimidazole compound **(32)** Derivatives. Firstly 1,2-Dihydropyrimido[1,2-*a*]- benzimidazole **(31)** was prepared using 2-aminobenzimidazole **(1)**, aromatic aldehyde **(29)** and malononitrile **(30)**. They were refluxed for 12-16 hours using water as solvent. 1,2-Dihydropyrimido[1,2-*a*]-benzimidazole **(31)** was then reacted with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and acetonitrile (CH_3CN). They were heated at 55°C for 4-5 hours which gives **(32)**. (Scheme 10) [56]



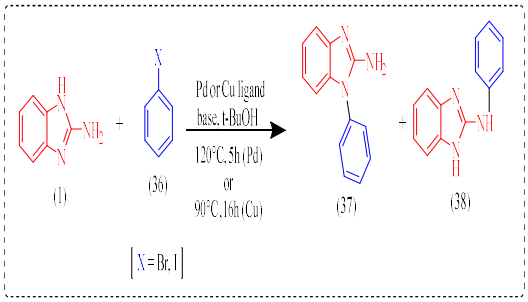
Scheme 10. Synthesis of Pyrimido[1,2-a]benzimidazole

El-Shekeil et al. (2012) synthesized 4-amino-2-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile compound **(35)** derivatives from 2-aminobenzimidazole **(1)** and substituted aldehyde **(33)**. Ethanol was used as solvent & the mixture was refluxed for 24 hours which produces Schiff base compounds **(34)**. These Schiff base compounds **(34)** was then refluxed for 4 h with malanonitrile in the presence ethanol and piperidine which produced compound **(35)**. (Scheme 11) [57]



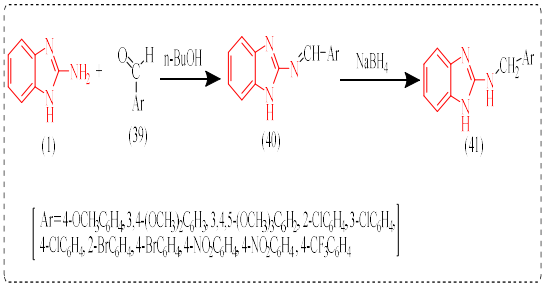
Scheme 11. Synthesis of 4-amino-2-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile

Ueda et al. (2012) synthesized 1-phenyl-1*H*-benzo[*d*]imidazole-2-amine **(37)** and *N*-phenyl-1*H*-benzo[*d*]imidazole-2-amine **(38)** from 2-aminobenzimidazole **(1)** and halobenzene (where, X= I or Br) **(36).** Compound **(37)** was prepared by reaction of **(1)** and **(36)** in the presence of Cu ligand (CuI), base (Cs_2CO_3) and t-butanol at 90°C for 16 hours. Similarly, *N*-phenyl-1*H*-benzo[*d*]imidazole-2-amine **(38)** was synthesized using **(1)** and **(36)** in the presence of Pd ligand ($Pd_2(dba)_3$), base (K_3PO_4) and t-butanol at 120°C for 5 hours.(scheme 12) [58]



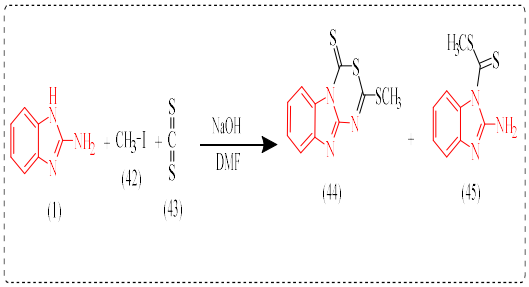
Scheme 12. Synthesis of 1-phenyl-1*H*-benzo[*d*]imidazole-2-amine and *N*-phenyl-1*H*-benzo[*d*]imidazole-2-amine

Nawrocka et al. (2004) synthesized *N*-(1*H*-benzo[d]imidazol-2-yl)methanimine derivatives **(40)** from 2-aminobenzimidazole **(1)** and aromatic aldehydes **(39)** in the presence of butanol. The best approach was found to be heating **(1)** in a 5:1 mixture of absolute ethanol and benzene while glacial acetic acid was present in catalytic concentrations. *N*-methyl-1*H*-benzo[d]imidazol-2-amine derivatives **(41)** were synthesized by the reduction of **(40)** from $NaBH_4$. (Scheme 13) [59]



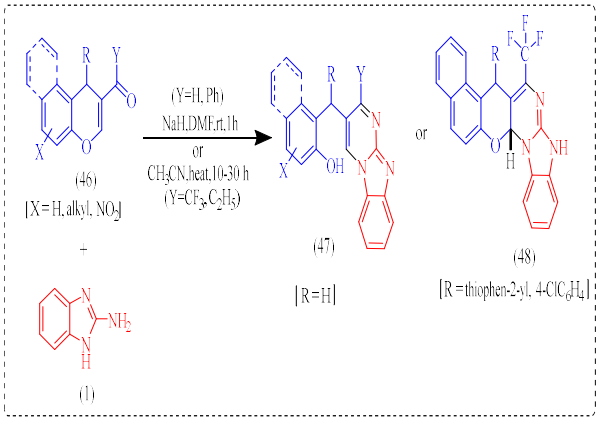
Scheme 13. Synthesis of *N*-(1*H*-benzo[d]imidazol-2-yl)methanimine

Cruz et al. (2014) synthesized 2-Methylthio-4*H*-[1,3,5]thiadiazino[3,4-*a*]benzimidazole-4-thione **(44)** and 2-Aminobenzimidazole-1-carbodithioic acid methyl ester **(45)** in a mixture of 1:3. They were synthesized from reaction of 2-aminobenzimidazole **(1)** with methyl iodide **(42)** and carbon disulfide **(43)** in the presence of base (NaOH) and solvent DMF (Scheme 14) [60].



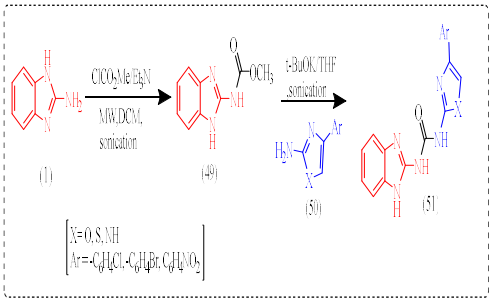
Scheme 14. 2-Methylthio-4*H*-[1,3,5]thiadiazino[3,4-*a*]benzimidazole-4-thione and 2-Aminobenzimidazole-1-carbodithioic acid methyl ester

Osyanin et al. (2021) synthesized pyrimido[1,2-*a*]benzimidazole derivatives **(47)** and 7,13a-dihydro-5*H*-benzo[5',6']chromeno[3',2':5,6] pyrimido[1,2-*a*]benzimidazoles **(48)** from 2-aminobenzimidazole **(1)** and β-carbonyl-substituted 4H-chromenes **(46).** (Scheme 15) [61]**.**



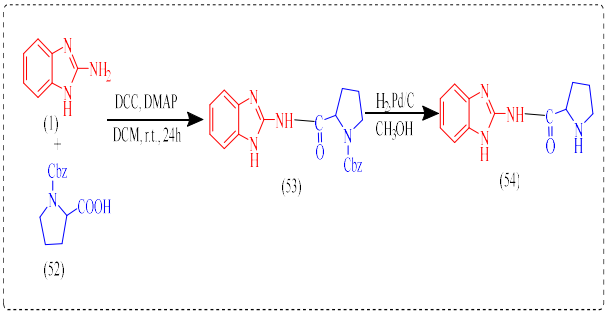
Scheme 15. Synthesis of pyrimido[1,2-*a*]benzimidazole derivatives and 7,13a-dihydro-5*H*-benzo[5',6']chromeno[3',2':5,6] pyrimido[1,2-*a*]benzimidazoles

Nagarjuna et al. (2019) synthesized Benzazolyl azolyl urea derivatives **(51)** from 2-aminobenzimidazole **(1)** . The reaction of (1) with methylchloroformate gives 1*H*-benzo[*d*]imidazole-2-ylcarbamate **(49)**. And by reacting (49) with benzazolyl amine **(50)** gives compound **(51)**. (Scheme 16) [62].

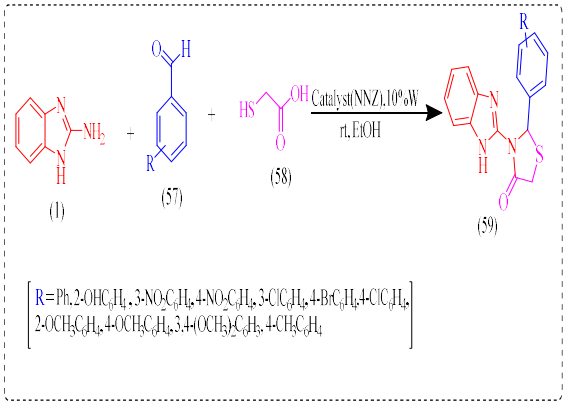


Scheme 16. Synthesis of Benzazolyl azolyl urea derivatives

Tang et al. (2012) synthesized *N*-(1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-2-carboxamide **(54)** from 2-aminobenzimidazole **(1)** and ((benzyloxy)carbonyl)proline **(52)**. The **(1)** and **(52)** were treated with dry dichloromethane at room temperature, which produces benzyl 2-((1H-benzo[d]imidazol-2-yl)carbamoyl)pyrrolidine-1-carboxylate **(53)**. **(53)** was then treated with H_2,Pd/C for removal of protection group (cbz) which produces **(54)** (scheme 17) [63]

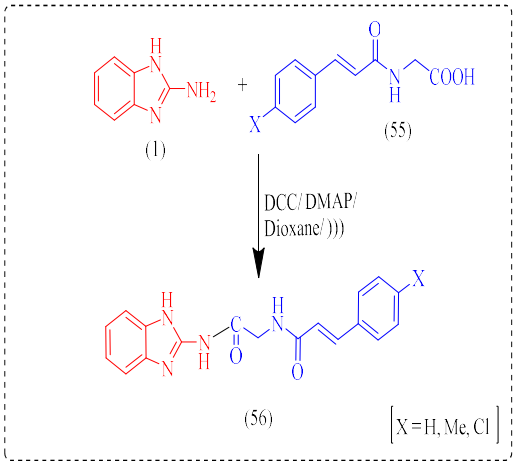


Scheme 17. Synthesis of *N*-(1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-2-carboxamide



Scheme 19. Synthesis of 3-(1H-benzo[d]imidazol-2-yl)-2-phenylthiazolidin-4-one

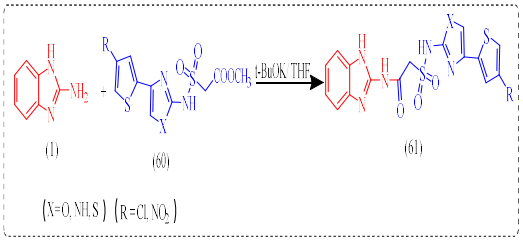
Sowdari et al. (2019) synthesized *E-N*-((1H-benzimidazol-2-ylcarbamoyl)methyl) cinnamamide **(56)** derivatives from 2 aminobenzimidazole **(1)** and 2-(cinnamamido)acetic acid **(55)** by ultrasonication in the presence of N,N-dimethylpyridin-4-amine (DMAP); N,N'-dicyclohexylcarbodiimide (DCC) and in dioxane (scheme 18) [64].



Scheme 18. Synthesis of *E-N*-((1H-benzimidazol-2-ylcarbamoyl)methyl) cinnamamide

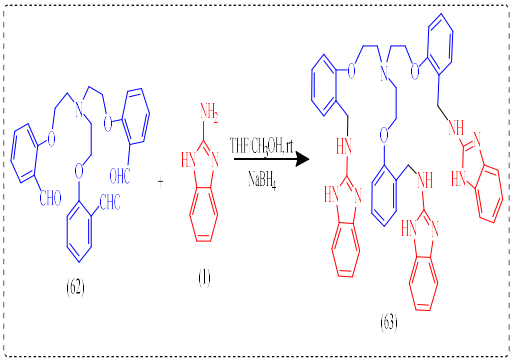
Kalhor et al. (2018) synthesized 3-(1H-benzo[d]imidazol-2-yl)-2-phenylthiazolidin-4-one **(59)** derivatives from 2-aminobenzimidazole **(1)** aromatic aldehyde **(57)** and 2-mercaptoacetic acid **(58).** The compounds **(1), (57)** & **(58)** was mixed in ethanol and stirred for 5 min in the presence of catalyst **NNZ** (Ni(II) ion stabilized on zeolite-Y). (scheme 19) [65].

Rajeswari et al. (2019) synthesized N-(1H-benzo[d]imidazol-2-yl)-2-sulfamoylacetamide derivatives **(61)** from 2-aminobenzimidazole **(1)** and methyl 2-(*N*-(5-(tetrahydrothiophen-2-yl)-3*H*-pyrrol-2-yl)sulfamoyl)acetate derivatives **(60)** in the presence of potassium tert-butoxide in tetrahydrofuran. Where (R = Cl or NO_2) and (X = O, NH or S) (Scheme 20) [66].



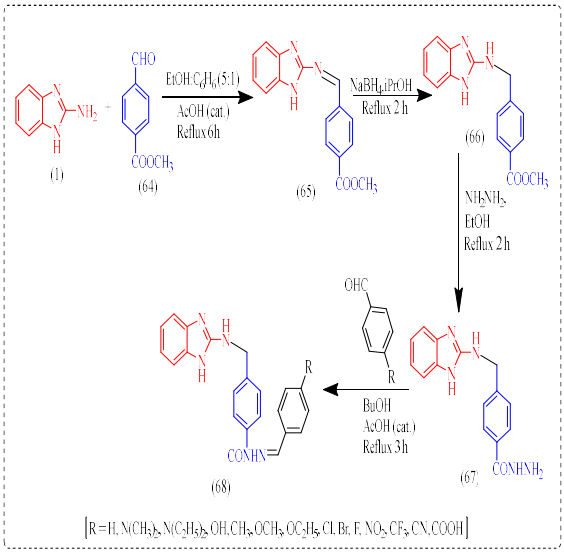
Scheme 20. Synthesis of N-(1H-benzo[d]imidazol-2-yl)-2-sulfamoylacetamide

Singh et al. (2007) synthesized *N*-(2-(2-(bis(2-(2-(((1*H*-benzo[*d*]imidazol-2-yl)amino)methyl)phenoxy)ethyl)amino)ethoxy)benzyl)-1*H*-benzo[*d*]imidazol-2-amine **(63)** from 2-aminobenzimidazole **(1)** and 2,2',2''-((nitrilotris(ethane-2,1-diyl))tris(oxy))tribenzaldehyde **(62)** in THF & methanol mixture as solvent and toluenesulfonic acid was used in catalytic amount. (Scheme 21) [67]



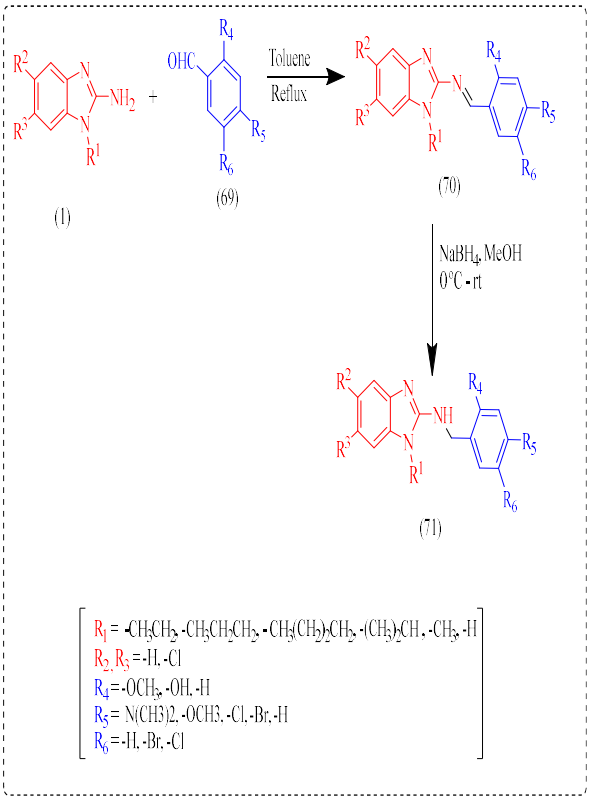
Scheme 21. Synthesis of *N*-(2-(2-(bis(2-(2-(((1*H*-benzo[*d*]imidazol-2-yl)amino)methyl)phenoxy)ethyl)amino)ethoxy)benzyl)-1*H*-benzo[*d*]imidazol-2-amine

Özkay et al. (2011) synthesized 4-(1H-benzimidazol-2-yl aminomethyl)-N'-(4-substituted benzylidene) benzohydrazides derivatives **(68)** from 2-aminobenzimidazole **(1)** and methyl 4-formylbenzoate **(64)**. Compound 4-(1H-benzimidazol-2-yl-iminomethyl) benzoate **(65)** was prepared by reacting **(1) & (64)** in a mixture of ethanol and benzene (5:1) and catalytic amount of GAA (glacial acetic acid). Compound **(65)** was then reduced to 4-(1H-benzimidazol-2-yl-aminomethyl) benzoate (**66)** by $NaBH_4$ in isopropanol. The compound **(66)** was treated with hydrazine hydrate (80%) in absolute ethanol which gave 4-(1H-benzimidazol-2-yl aminomethyl) benzohydrazide **(67)**. The reaction of **(67)** with aromatic aldehyde in the presence of butanol and GAA gave compound **(68)**. (Scheme 22) [68]



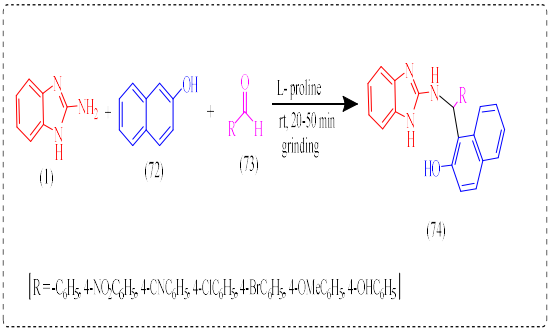
Scheme 22. Synthesis of 4-(1H-benzimidazol-2-yl aminomethyl)-N'-(4-substituted benzylidene) benzohydrazides

Nieto-Meneses et.al (2018) synthesized N-benzyl-1H-benzimidazol-2-amine derivatives **(71)** from 2-aminobenzimidazole **(1)** and aromatic aldehyde derivatives **(69)**. The compounds **(1)** and **(69)** were reacted in the presence of toluene which gives (*E*)-*N*-(1*H*-benzo[*d*]imidazol-2-yl)-1-phenylmethanimine derivatives (**70)**. Compound (70) was reduced by $NaBH_4$ in the presence of methanol which gives **(71)**. (Scheme 23) [69]



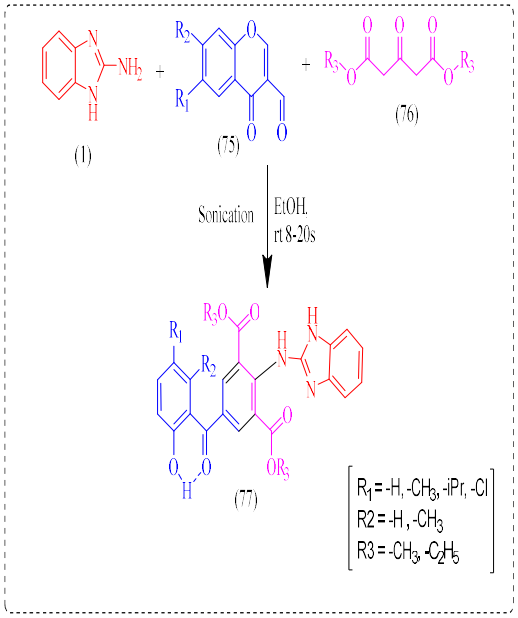
Scheme 23. Synthesis of N-benzyl-1H-benzimidazol-2-amine

Javanshir et al. (2010) synthesized 2'-aminobenzimidazolophenylmethylnaphthols derivatives **(74)** from 2-aminobenzimidazole **(1)**, 2-naphthol **(72),** and aromatic aldehyde **(73)** in the presence of L-proline and the mixture was grind for 20-50 mins. (Scheme 24) [70]



Scheme 24. Synthesis of 2'-aminobenzimidazolophenylmethylnaphthols

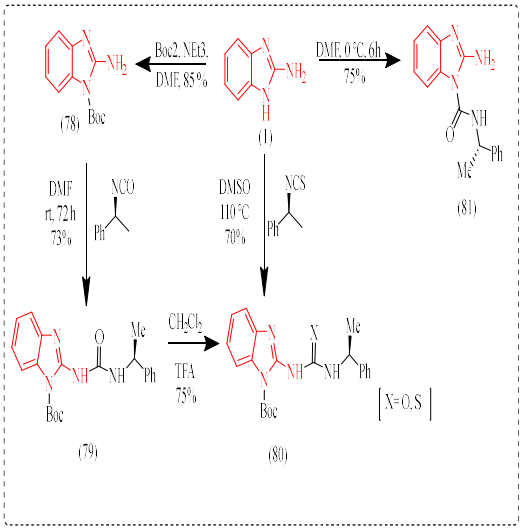
Eleftheriadis et al. (2015) synthesized 2-(1*H*-benzimidazol-2-ylamino)-5-(2-hydroxyaroyl)isophthalate deriavtives **(77)** from 2-aminobenzimidazole **(1)**, 3-formylchromone derivatives **(75)** and Acetonedicarboxylate derivatives **(76)** in the presence of ethanol under ultrasound irradiation. (Scheme 25) [71]



Scheme 25. Synthesis of 2-(1*H*-benzimidazol-2-ylamino)-5-(2-hydroxyaroyl)isophthalate

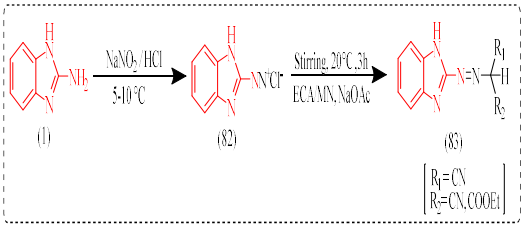
Lafzi et al. (2021) synthesized the Boc-protected urea derivative **(79)**, thiourea derivative **(80)** and urea derivative **(81)**. First, compound **(1)** reacts with triethylamine and di-tert-butyl dicarbonate (Boc_2O) in DMF to give the N-Boc-protected intermediate **(78)**. The latter on reaction with isocyanate or isothiocyanate reagents to provide compound **(79)** and **(80)** derivatives. The compound **(81)** was obtained after reaction with DMF at 0°C for 6 h. the reaction of compound **(79)** with trifluoroacetic acid (TFA) in

dichloromethane also gives compound **(80)**. (Scheme 26) [72]



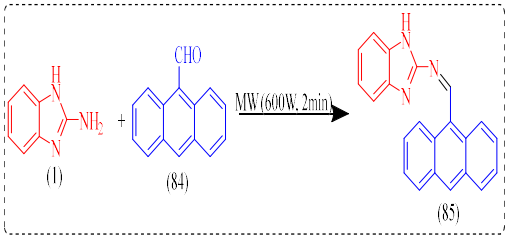
Scheme 26. Synthesis of Boc-protected urea derivative, thiourea derivative and urea derivative.

Murthy et al. (2013) synthesized 2-diazo-benzimidazole derivatives **(83)** from 2-aminobenzimidazole **(1)**. 2-ABZ **(1)** was dissolved in HCl at 5-10 ℃ then sodium nitrate was added which gives diazonium salt derivative **(82)**. Ethylcyanoacetate (ECA) or malanonitrile (MN) in the presence of NaOAc were added to the above solution while stirring for 3-4h at 20℃ for the production of compound **(83)** derivatives. (Scheme 27) [73].



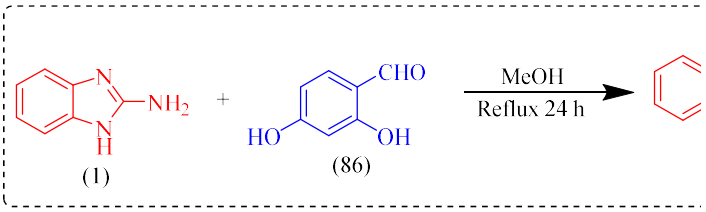
Scheme 27. Synthesis of 2-diazo-benzimidazole derivatives

Sreerama et al. (2025) synthesized (*Z*)-1-(anthracen-9-yl)-*N*-(1*H*-benzo[*d*]imidazol-2-yl)methanimine **(85)** from 2-aminobenzimidazole **(1)** and anthracene-9-carbaldehyde **(84)** at 600 W for 2 minutes in microwave oven. (Scheme 28) [74]



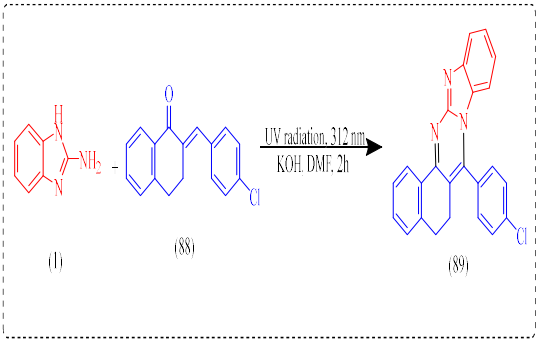
Scheme 28. Synthesis of (*Z*)-1-(anthracen-9-yl)-*N*-(1*H*-benzo[*d*]imidazol-2-yl)methanimine

El-wakiel et al. (2015) synthesized 4-(((1H-benzo[d]imidazol-2-yl)imino)methyl)benzene-1,3-diol **(87)** from 2-aminobenzimidazole **(1)** and 2,4-dihydroxybenzaldehyde **(86)** in the presence of methanol. The mixture was refluxed for 24 h. (Scheme 29) [75]



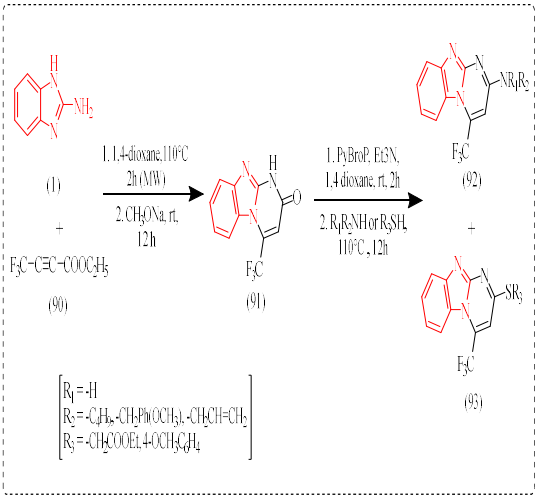
Scheme 29. Synthesis of 4-(((1H-benzo[d]imidazol-2-yl)imino)methyl)benzene-1,3-diol

Devipriya et al. (2019) synthesized 7-(4-chlorophenyl)-5,6-dihydrobenzo[*h*]benzo[4,5]imidazo[2,1*b*]quinazoline **(89)** from 2-aminobenzimidazole **(1)** and (*E*)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(*2H*)-one **(88)** in the presence of KOH and DMF at 312 nm for 2 hours under UV irradiation. (Scheme 30) [76]



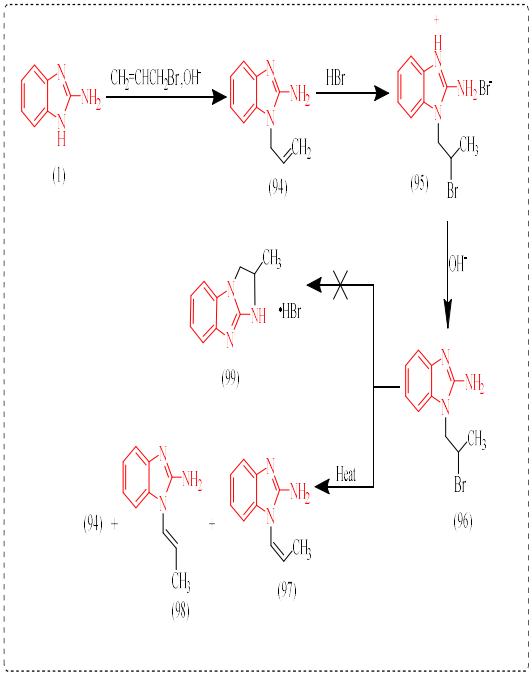
Scheme 30. Synthesized of 7-(4-chlorophenyl)-5,6-dihydrobenzo[*h*]benzo[4,5]imidazo[2,1 *b*]quinazoline

Jismy et al. (2019) synthesized 7-amino 5-trifluoromethyl imidazo[1,2-a]pyrimidines (92) & 2-thiolated-4-trifluoromethyl benzo [4,5]imidazo[1,2-a]pyrimidines (93) from 2 aminobenzimidazole (1). 4-(trifluoromethyl)benzo[4,5]imidazo[1,2-a]pyrimidin-2(1H)-one (91) was synthesized from (1) and fluorinated alkyne (90). (Scheme 31) [77]



Scheme 31. Synthesis of 7-amino 5-trifluoromethyl imidazo[1,2-a]pyrimidines & 2-thiolated-4-trifluoromethyl benzo [4,5]imidazo[1,2-a]pyrimidines

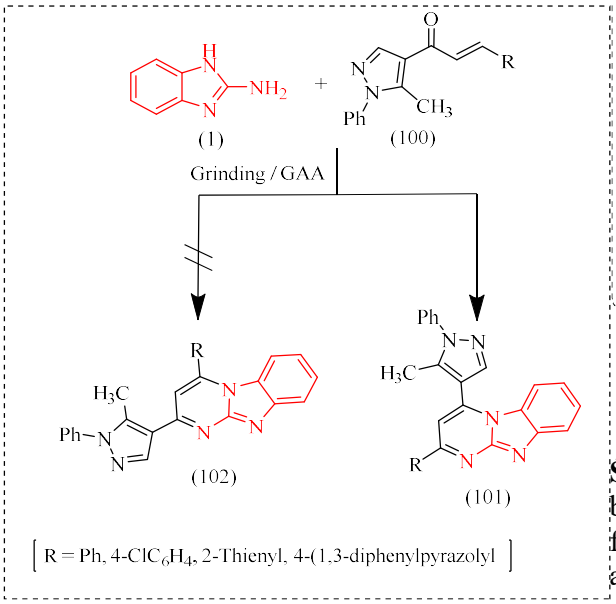
Anisimova et al. (2011) synthesized cis- and trans-isomeric 2-amino-1-(prop-2-en-1-yl)-1*H*-benzimidazoles **(97)** and **(98)** from 2-aminobenzimidazole **(1).** On reaction of compound **(1)** with allyl bromide in the presence of acetone and base (NaOH or KOH), compound 1-allyl-2-aminobenzimidazole **(94)** was synthesized. By heating **(94)** with 48% hydrobromic acid gave 2-amino-1 (2-bromopropyl)-1H-benzimidazole hydrobromide **(95). (95)** was then treated with aq. Ammonia which gave 1-(2-bromopropyl)-1*H*-benzo[*d*]imidazol-2-amine **(96)**. On heating in xylene **(95)** gave **(94)**, **(97)** and **(98).** Even after thermolysis of **(95)** in the presence of triethylamine 2-methyl-2,3-dihydro-1H-benzo[d]imidazo[1,2-a]imidazole hydrobromide **(99)** was not produced. (Scheme 32) [78]



Scheme 32. synthesis of cis- and trans-isomeric 2-amino-1-(prop-2-en-1-yl)-1*H*-benzimidazoles

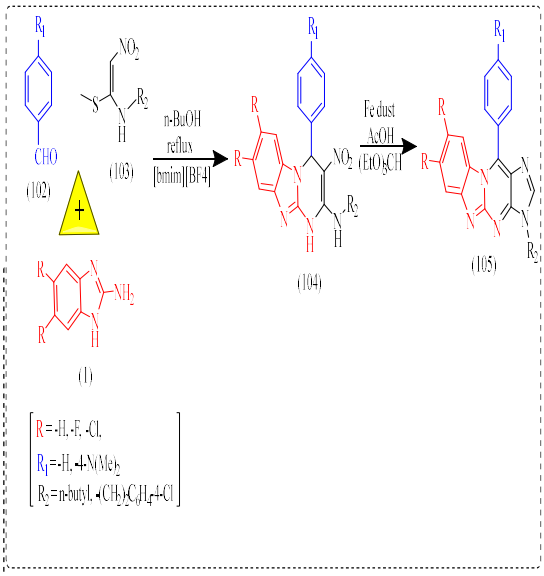
El-Hashash et al. (2017) synthesized 4-(5-methyl-1-phenyl-1*H*-pyrazol 4-yl)-2-aryl/or heteroaryl benzo[4,5] imidazo[1,2-a] pyrimidine derivatives **(101)** from 2-aminobenzimidazole **(1)** and pyrazolyl

chalcones **(100). (1) & (100)** were ground via mortar in the presence of glacial acetic acid in catalytic amount at room temperature which gave **(101)** not 2-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)benzo[4,5]imidazo[1,2-a]pyrimidine derivatives **(102).** (Scheme 33) [79]



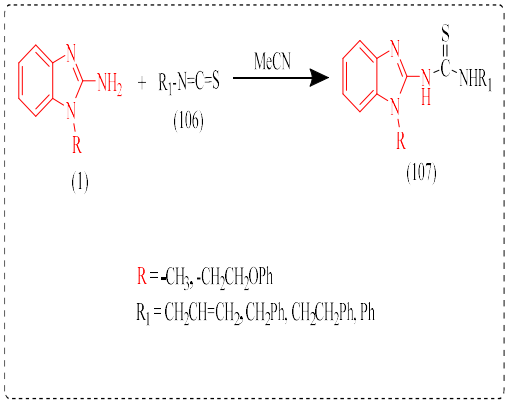
Scheme 33. Synthesis of 4-(5-methyl-1-phenyl-1*H*-pyrazol 4-yl)-2-aryl/or heteroaryl benzo[4,5] imidazo[1,2-a] pyrimidine

Fedotov et al. (2020) synthesized tetracyclic benzimidazopurine derivatives **(105)** from 2-aminobenzimidazole **(1),** aromatic aldehyde derivatives **(102)** and *N*-alkyl-1-(methylthio)-2-nitroethylene-1-amine derivatives **(103). (1), (102)** & **(103)** were reacted by heating in n-butanol for three hours and adding 10 mol% [BMIM][BF4] which gave nitro-containing benzimidazopyrimidines **(104)**. On reacting **(104)** with Fe dust in the presence of triethyl orthoformate and acetic acid mixture tetracyclic benzimidazopurine derivatives **(105)** were synthesized. (Scheme 34) [80]



Scheme 34. Synthesis of tetracyclic benzimidazopurine

Śmiechowska et al. (2010) synthesized 2-benzimidazolylthiourea derivatives **(107)** from 2-aminobenzimidazole derivatives **(1)** and Isothiocyanate derivatives **(106)** in the presence of acetonitrile (MeCN) at 50°C was stirred for 2-6 hours**.** (Scheme 35) [81]



Scheme 35. Synthesis of 2-benzimidazolylthiourea

Conclusion

The current review paper consists of a wide range of easy access to synthetic materials, the development of new chemotherapeutic drugs is still heavily dependent on heterocyclic compounds, especially 2-aminobenzimidazole derivatives.

Advancements in green synthesis techniques and the clarification of structure-activity relationships have really paved the way for the design of potent derivatives with enhanced effectiveness and safety profiles. More multidisciplinary research involving medicinal chemistry, pharmacology, and computational tools is required to utilize their therapeutic potential fully and accelerate clinical translation.

CRediT author statement

Tarun Sharma: Writing the paper**; Salahuddin:** Conceptualization**; Rajnish Kumar:** Methodology**.**

Ethical approval and consent to participate

Not Applicable

Human and animal rights

Not Applicable

Consent for publication

Not applicable. The study does not contain data from any person.

Availability of data and materials

All data generated during this review are included in this published article.

Conflict of interest

The author(s) declared no conflict of interest, financial or otherwise.

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