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Benzimidazole chemistry in oncology: recent developments in synthesis, activity, and SAR analysis

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A six-membered benzene ring is fused with a five-membered imidazole ring at positions four and five, generating benzimidazole, the benzo derivative of imidazole and a bicyclic aromatic chemical compound. Benzimidazole is a significant pharmacophore in a variety of physiologically active heterocyclic compounds due to its distinctive characteristics and structural framework. Because benzimidazole is both aromatic and heterocyclic, it interacts with a range of biological targets *via* metal ion interactions, π–π stacking, and hydrogen bonding. Its broad range of medicinal chemistry applications, such as anti-inflammatory, antiviral, antifungal, and anticancer therapies, is based on these interactions. Its significance in the development of potentially novel therapeutic pharmaceuticals is highlighted by the fact that its structural flexibility permits the synthesis of derivatives with targeted bioactivity. Derivatives of benzimidazole have garnered significant research interest as potential anticancer medications. These heterocyclic compounds exhibit a wide range of biological activities, such as DNA interaction, enzyme inhibition, and modulation of cellular pathways crucial to cancer development. Thus, to optimize their therapeutic potential, recent studies have focused on evaluating the structure–activity relationships (SAR) of benzimidazole derivatives. The main topics of this review are the current developments in the synthesis, anticancer activity, and SAR studies of benzimidazole derivatives, which will shed light on the increasing role they play in cancer therapies.

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1 Introduction

According to WHO, deaths due to cancer are predicted to reach 13 million worldwide by 2030.[1,2] Most malignancies are characterized by the uncontrolled growth of undifferentiated cells. Current estimates indicate that one in every five people will develop cancer by the age of 75.[3] Cancer primarily results from the deregulation of key enzymes and proteins that regulate cell division and proliferation.[4,5] However, despite significant advancements in cancer diagnosis and treatment options, many patients do not respond well to therapy, and others relapse after an initial encouraging response. Although chemotherapy is still a crucial component of cancer treatment, the emergence of drug resistance significantly reduces its effectiveness.[6] To combat drug resistance, higher dosages of chemotherapeutic drugs are sometimes necessary, which exacerbates drug-induced toxicities.[7,8] Therefore, there is a critical need to create and develop novel cancer therapies with potent activity while maintaining a high therapeutic index.[9]

Recently, O- and S-based heterocycles have been attracting increasing attention in the discovery of innovative anticancer drugs, following the extensive investigation of nitrogen-based heterocycles as anticancer agents.[10] While heterocyclic compounds with a sulfur atom account for the bulk of FDA-approved drugs, heterocyclic compounds with a nitrogen atom are regarded as the most common type of chemical material utilized in medicinal chemistry.[11,12] Benzimidazole and its derivatives are a family of bioactive compounds with important uses in the pharmaceutical sector.[13] Imidazole, also known as imidazoline, is a heterocyclic molecule[14] classified as

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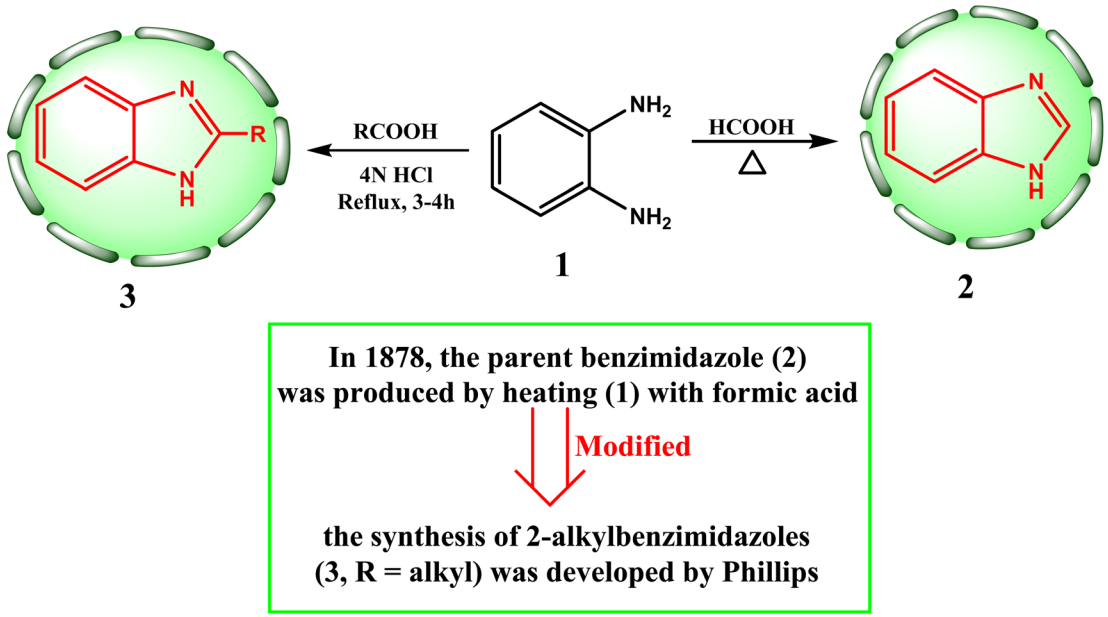
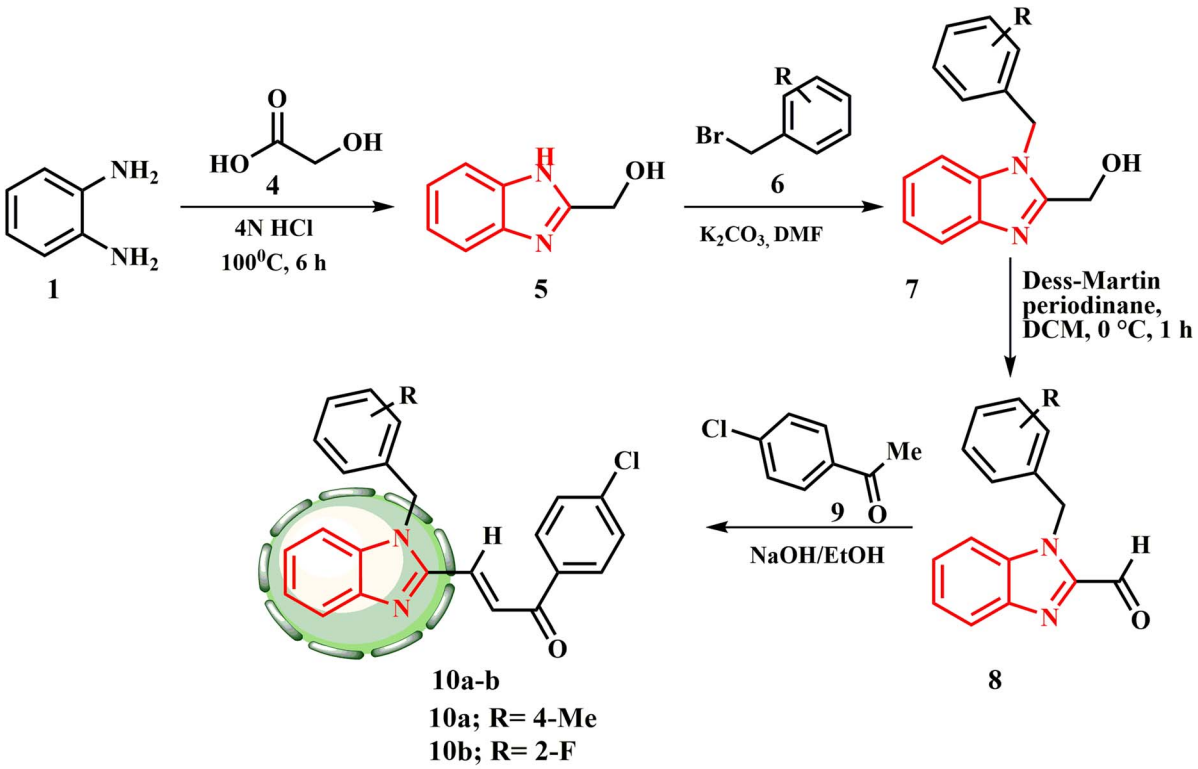


Scheme 1 Primary method for the synthesis of benzimidazole nucleus **2** and its derivative **3**.



Key observation:
1) SAR indicated that chalcone moiety may have a significant role in the inhibition of antiproliferative action of these compounds.

2) The impact of diversification at the R position on the inhibitory activity was found to be inconclusive, as a methyl group or a fluorine atom was moderately tolerated.

Scheme 2 Synthetic route for benzimidazole–chalcone hybrids **10a** and **b**.

an azapyrrole, with two nitrogen atoms separated by a single carbon atom. Historically, this molecule was known as glyoxalin when it was initially synthesized in 1858 by German scientist Heinrich Debus using glyoxal, formaldehyde, and ammonia.[15,16] A six-membered benzene ring is fused with a five-membered imidazole ring at positions four and five to form benzimidazole, the benzo-fused imidazole derivative and a bicyclic aromatic molecule. These substances have antiviral, antifungal, antiparasitic, analgesic, anticancer, and antihistaminic properties, among other medicinal applications. Moreover, benzimidazole derivatives have demonstrated potential in the management of numerous conditions associated with neurology, endocrinology, ophthalmology, and cardiovascular disease.[17]

The benzimidazole nucleus has emerged as a key pharmacophore in cancer research due to its broad cytotoxic potential, adaptive tumor inhibitory mechanisms, and facile synthesis methods for producing a wide range of derivatives. Many bioactive chemicals and anticancer medicines have a benzimidazole motif.[18] The benzimidazole scaffold is crucial in the creation of anticancer medications such as bendamustine, carbendazim, nocodazole, and veliparp. It functions in a number of ways.[19] Benzimidazoles, a structurally distinct class of Topo I poisons that function as DNA minor groove binders, including Hoechst 33258 and Hoechst 33342.[20–23]

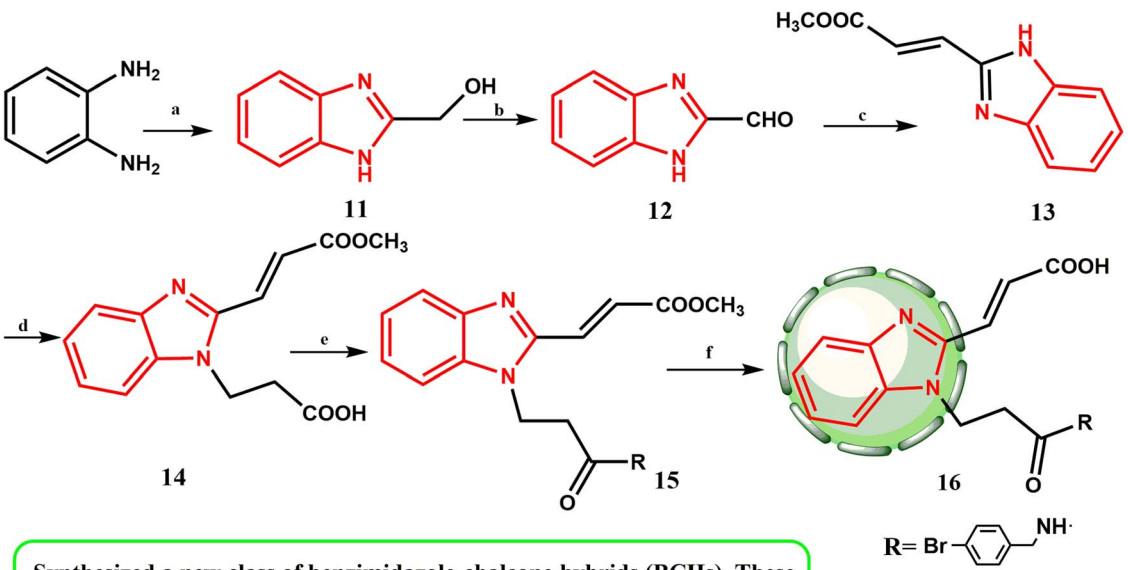
1.1 Techniques that yield benzimidazoles

The synthesis and chemistry of benzimidazoles have been well reviewed in the literature. In general, the majority of key ingredients mentioned previously may be utilized to develop benzimidazoles, as follows:

(1) Phenylenediamines
(2) Acidic compounds
(3) *o*-(*N*-arylamino)arylamine
(4) *o*-Nitro arylamines or *o*-dinitro arenes
(5) *o*-Substituted-*N*-substituted
(6) Imines
(7) Amidines
(8) Heterocyclic scaffolds
(9) Four components

1.1.1. Phenylenediamines. In 1878, the parent benzimidazole (**2**) was produced by heating (**1**) with formic acid.[24] Since then, aliphatic acids have been used to produce a wide variety of benzimidazoles (**2** and **3**). Phillips established the most effective technique for producing 2-alkylbenzimidazoles (**3**, R = alkyl), which involves refluxing equimolar amounts of diamine and aliphatic carboxylic acid in **4** *N* hydrochloric acid for three to four hours (Scheme 1).[24]

As shown in Scheme 2, several benzimidazole–chalcone hybrids **10a** and **b** have been produced.[25] Refluxing *o*-phenylenediamine (**1**) with glycolic acid (**4**) in HCl produced (1*H*-benzo

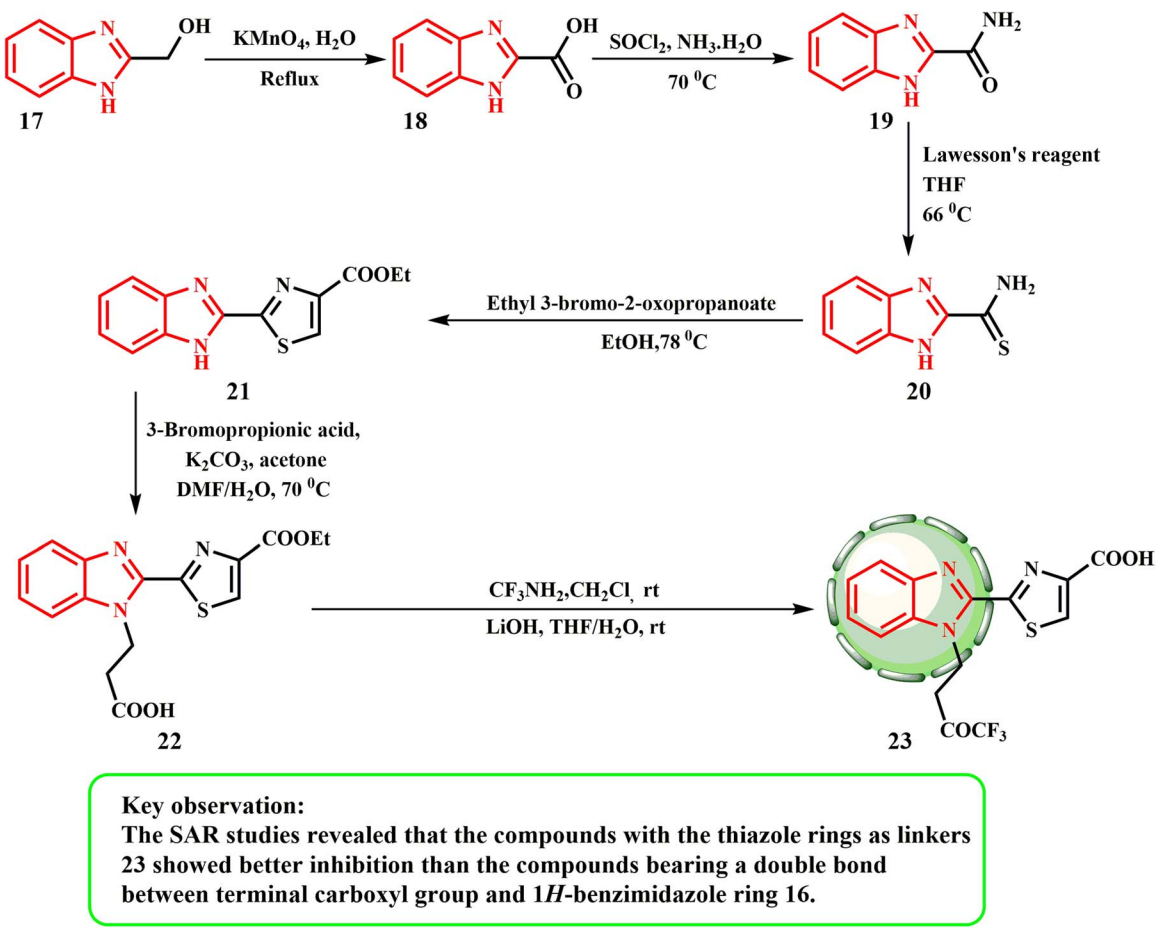


Scheme 3 Synthesis of a new class of BCHs **15** and **16**.

[*d*]imidazol-2-yl)methanol (**5**). **5** and suitable benzyl bromides **6** were used to produce the substituted (1-benzyl-1*H*-benzo[*d*] imidazol-2-yl)methanol (**7**) in the presence of K_2CO_3. Subsequently, the corresponding primary alcohols **7** were oxidized using Dess–Martin reagent to provide substituted-1-benzyl-1*H*-benzo[*d*]imidazole-2-carbaldehydes **8**. Using the Claisen–Schmidt reaction with appropriate acetophenones **9**, target compounds **10a** and **b** were subsequently generated from **8**.

Zhou *et al.*[25] established a novel class of benzimidazole–chalcone hybrids or BCHs. These BCHs demonstrated antiproliferative effects in tumor cell lines and significant inhibitory effects in the Topo II-mediated DNA relaxation assay. One of the main enzymes involved in DNA replication, recombination, and repair is type II topoisomerase (Topo II).[26,27] Condensation and cyclization of *o*-phenylenediamine and glycolic acid produced compound **11** and the synthesis pathway for substances **16**. The oxidation of the C2-hydroxymethyl of **11** with manganese dioxide produced aldehyde product **12**. Intermediate **13** was prepared *via* the Wittig–Horner reaction of aldehydic compound **12** with methyl diethyl phosphonoacetate. Key intermediate **14** was developed by alkylation of **13** with 3-bromopropionic acid. The appropriate amides were produced by reacting carboxylic acid **14** with amines, and then the amides were treated with lithium hydroxide to produce **16**. With an IC_{50} value of 0.64 μM, compound **16** with a 4-Br substituent had the highest Pin1 inhibitory activity, indicating that the bromine atom is preferred, most likely to react with the residues of amino acid to establish an H-halogen link in this way (Scheme 3).

Scheme 4 presents the synthesis of **23**. Potassium permanganate oxidizes **17** to yield 1*H*-benzo[*d*]imidazole-2-carboxylic acid (**18**). The carboxylic acid group of **18** was changed to a carbamoyl group by creating the acyl chloride first, and then reacting it with ammonium hydroxide to produce compound **19**. Using Lawesson's reagent, the carbonyl in chemical **19** was thiolated to produce compound **20**. Compound **20** was condensed and cyclized with ethyl 3-bromo-2-oxopropanoate to produce an intermediate, 2-(1*H*-benzo[*d*]imidazol-2-yl)thiazole **21**. The use of 3-bromopropionic acid to alkylate **21** produced the desired product **22**. Carboxylic acid **22** was combined with amines to form the corresponding amides, which were then reacted with lithium hydroxide to produce the final product **23** (Scheme 4). Wang *et al.*[28] produced derivatives of 1*H*-benzimidazole and assessed their anticancer potential against the human prostate cancer cell line PC-3. With IC_{50} values of 0.64 μM and 0.37 μM, respectively, compounds **16** and **23** showed the greatest inhibitory effects. According to the SAR investigations, compounds **23** with thiazole rings as linkers exhibited



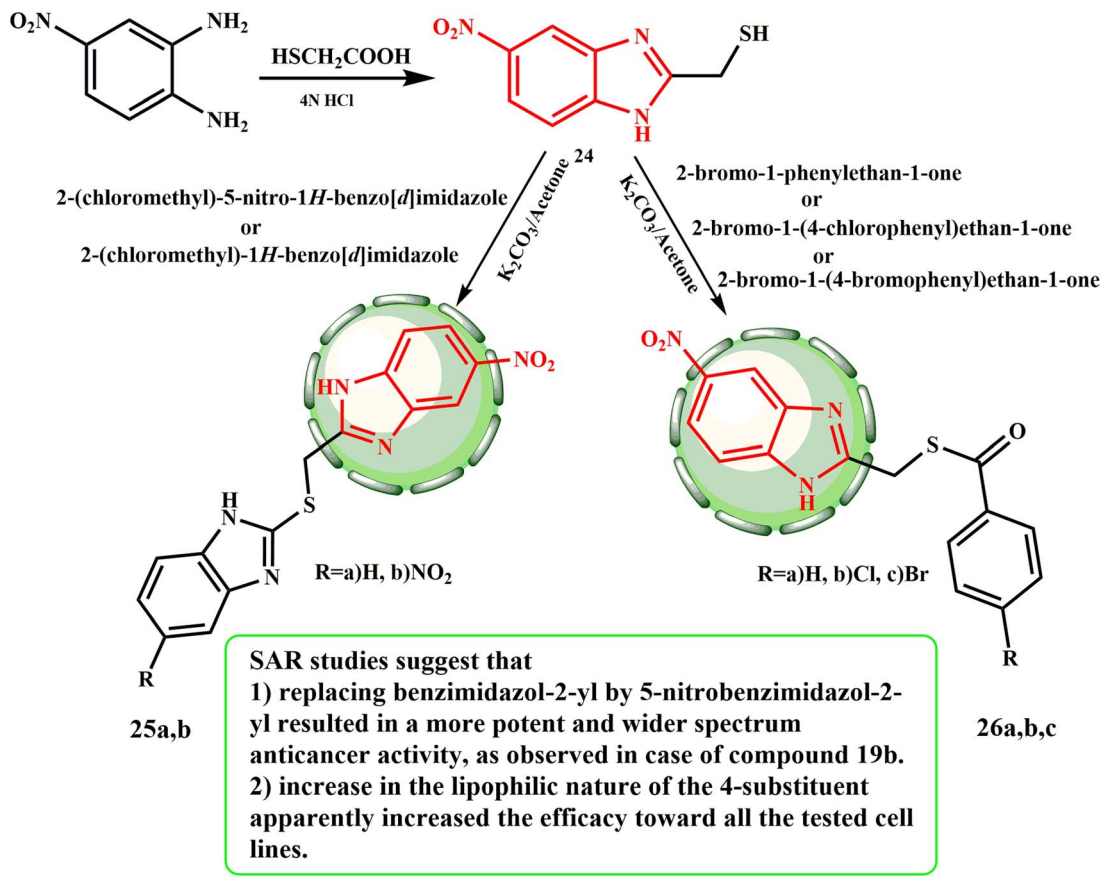
Scheme 4 Synthesis of derivatives of benzimidazole thiazole **22** and **23**.

greater inhibition than **16** with a double bond between the 1*H*-benzimidazole ring and the terminal carboxyl group.

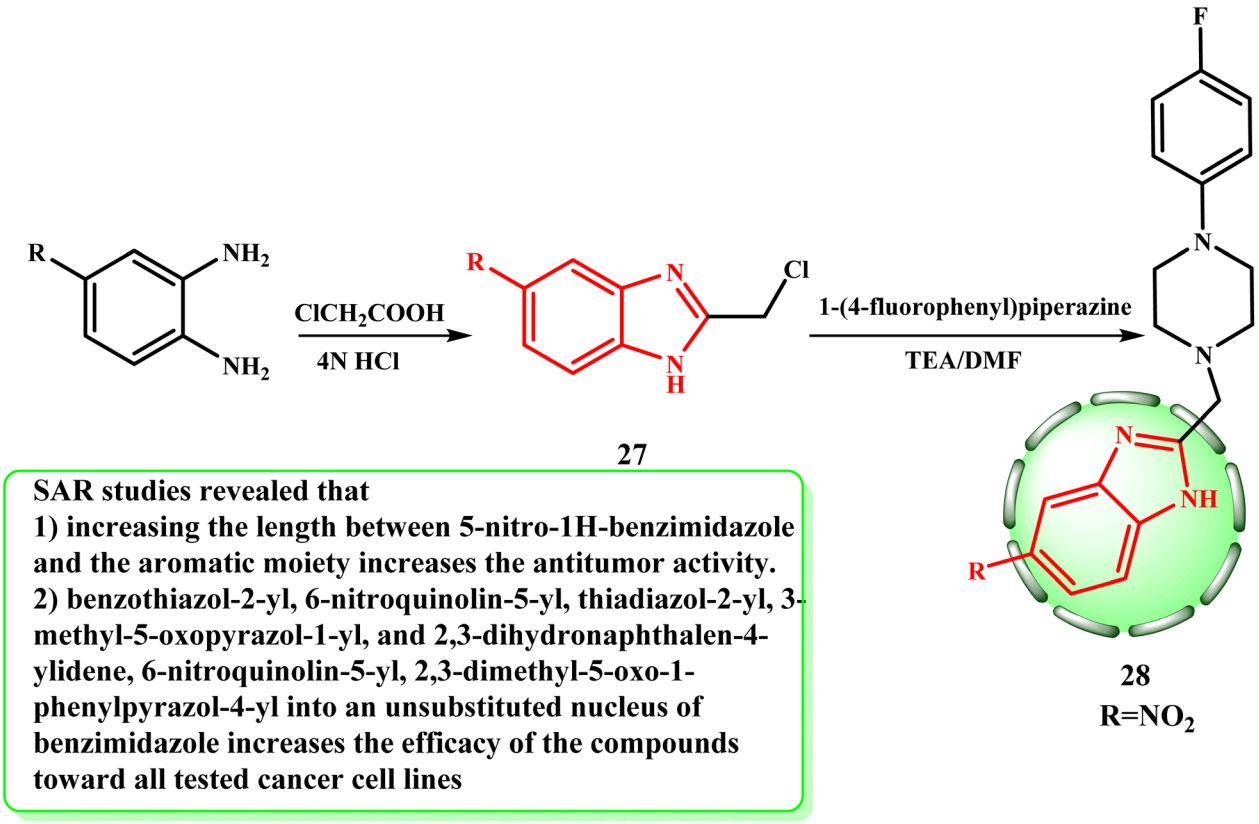
An effective method for creating novel benzimidazoles **25a** and **b** and **26a–c** was accomplished, which began with 2-mercaptomethyl-5-nitro-1*H*-benzimidazole (**24**)[29] (Scheme 5). El-Gohary *et al.*[30] produced new 1*H*-benzimidazole compounds and tested them against human cancer cell lines, including HepG-2 (liver), HCT-116 (colon), and MCF-7 (breast), to determine their anticancer potential. The most promising analogues were determined to be compounds **25b**, **26b**, and **26c**. According to the SAR evaluations, compound **25b** exhibited a more powerful and broad-spectrum anticancer action when 5-nitrobenzimidazol-2-yl was substituted for benzimidazol-2-yl. Furthermore, the improved lipophilicity of the 4-substituent appeared to enhance its effectiveness against all the examined cell lines. Compound **25b**, the 5-nitrobenzimidazol-2-yl homologue, had strong and comprehensive anticancer action. For compounds **26b** and **c** to have anticancer action, the substituent at the 4-position of the phenacyl moiety must be lipophilic. The compounds appeared to be more active against the three examined cell lines as the lipophilicity of the 4-substituent was increased, which the activity following the order of 4-bromophenacyl analog **26c** > 4-chlorophenacyl analog **26b**.

The present study used 2-chloromethyl-1*H*-benzimidazole **27** (ref. 31) as the starting materials to produce novel benzimidazoles **28** employing a straightforward, effective, and repeatable approach with a simple work-up procedure (Scheme 6). In the following way, the appropriate **27** reacts with 1-(4-fluorophenyl)piperazine in DMF when triethylamine is present to produce 2-(aryl amino)methyl-benzimidazole **28**. El-Gohary *et al.*[32] developed and evaluated a variety of 1*H*-benzimidazole derivatives for their anticancer characteristics. The MTT assay was used to screen the derivatives against the HepG-2 (liver), HCT-116 (colon), and MCF-7 (breast) cancer cell lines. Compound **28** exhibited the strongest activity against all the cell lines, in accordance with the results. The cytotoxic tests of the compounds revealed that they were less active than the reference medication, 5-fluorouracil. According to SAR investigations, the anticancer activity increased with the length of the contact between the aromatic moiety and 5-nitro-1*H*-benzimidazole.[32]

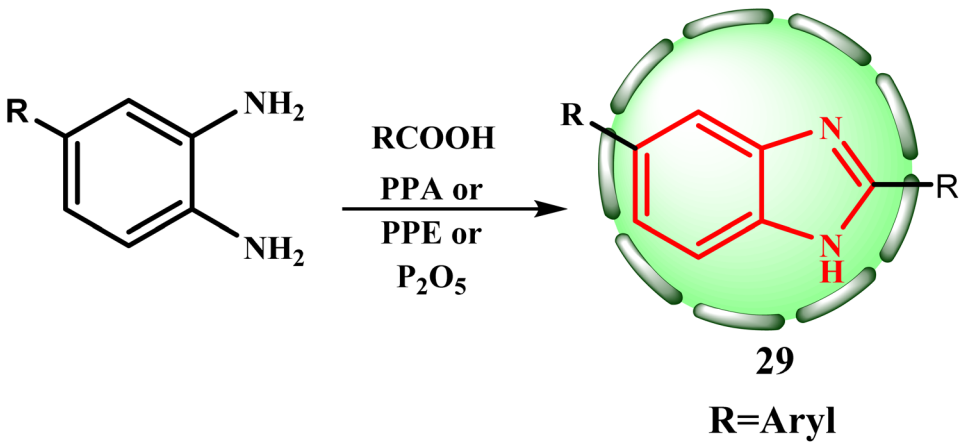
The proposed mechanistic route for the formation of benzimidazoles by reacting a derivative of *o*-phenylene diamine with an organic acid has already been studied.[24,33] Furthermore, the role of hydrochloric acid in the reaction has also been investigated.[24,34] The catalytic action of hydrochloric acid is explained by the protonation of oxygen, which activates the carboxyl group. The reaction intermediate is an addition product, which is produced when the carbonyl group of the protonated acid is attacked by the shared electron pair of a nitrogen. Nevertheless, the researchers concluded that the generation of the monoacyl



Scheme 5 Synthesis of novel benzimidazoles **25a** and **b** and **26a–c**.



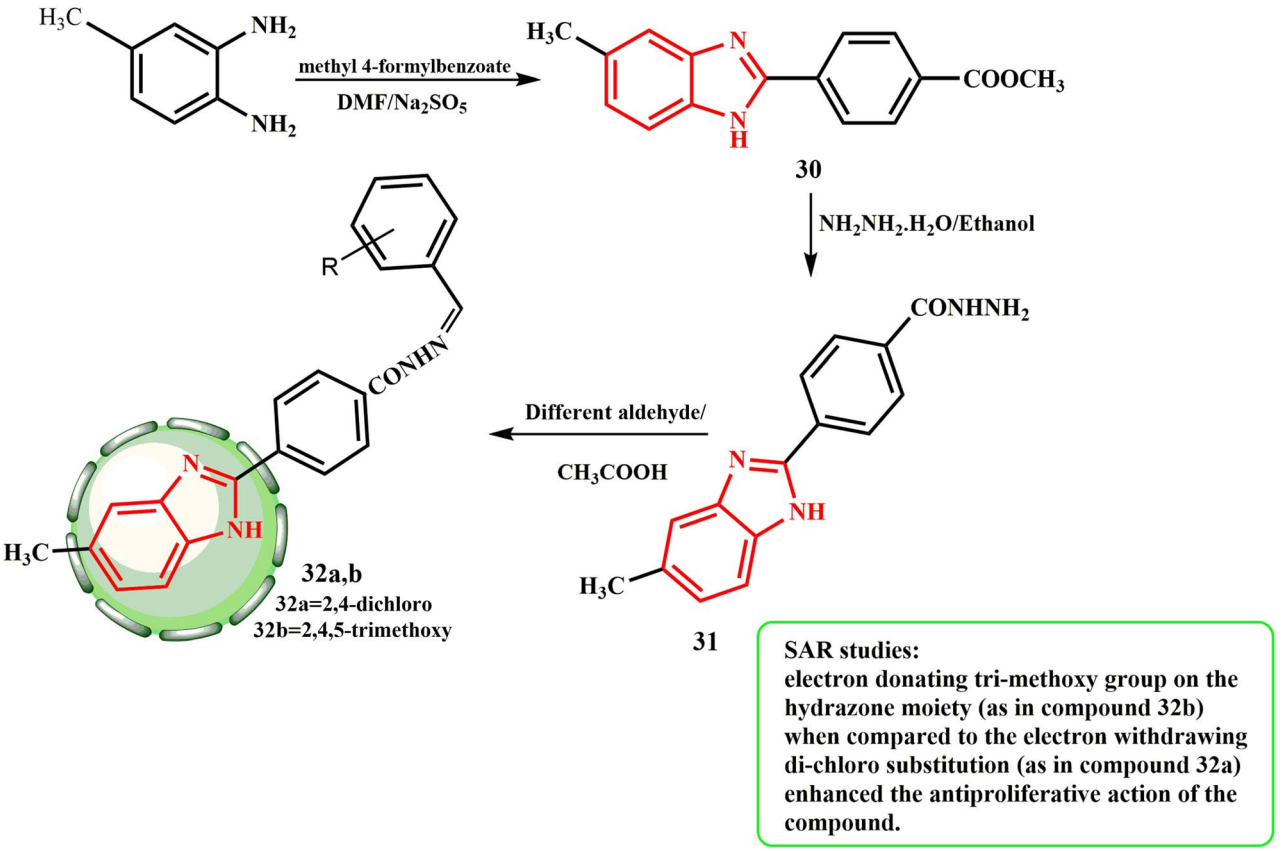
Scheme 6 Synthesis of target 2-(aryl amino)methyl-benzimidazole **28**.



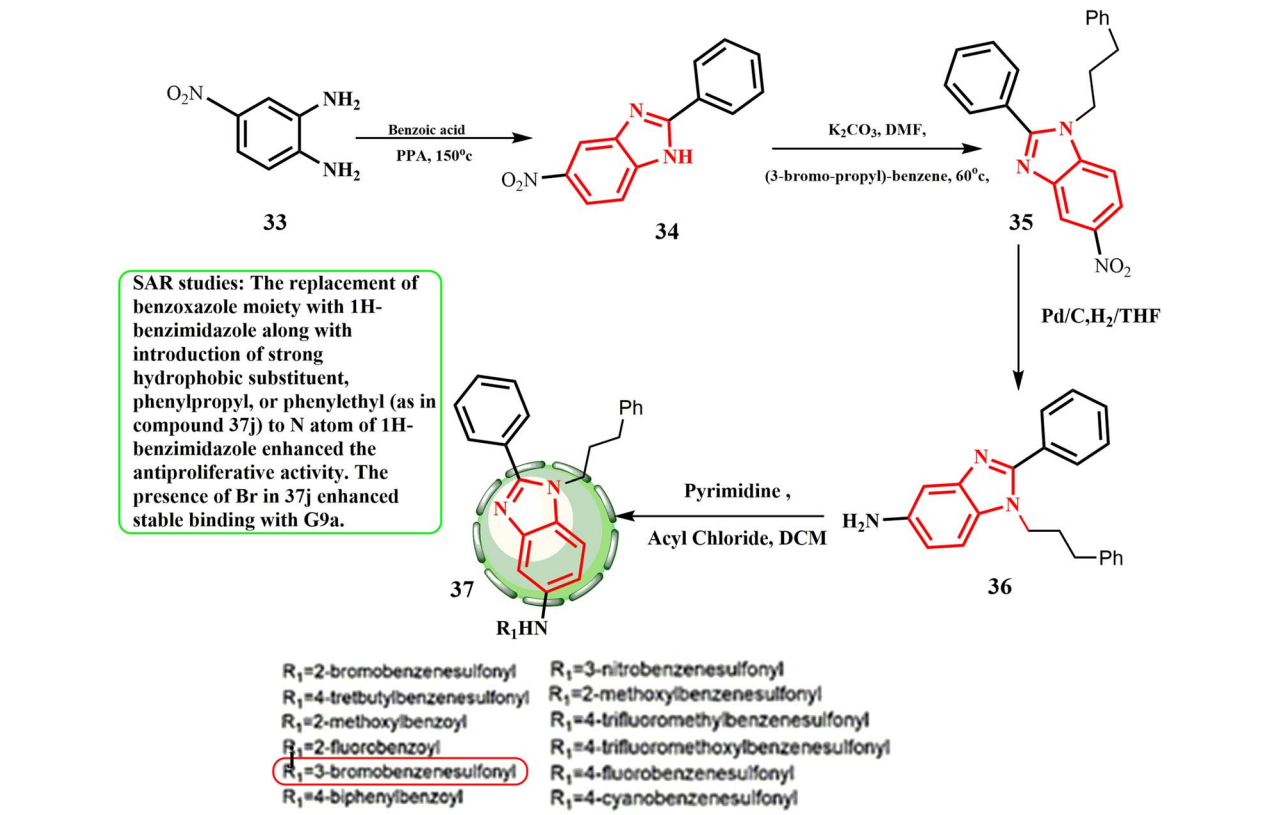
Scheme 7 Synthetic route for the formation of 2-arylbenzimidazole **29**.

derivative was a necessary step in the benzimidazole ring building process.[24,34] It has been reported that heating aromatic carboxylic acids with *o*-phenylene diamine in a sealed tube at 180–190 °C produces good yields of 2-arylbenzimidazoles (**29**, R = Ar). An improved method for producing 2-arylbenzimidazoles **29** from aromatic carboxylic acid uses polyphosphate ester (PPE) or polyphosphoric acid (PPA) as a dehydrator. As an alternative, phosphorus pentoxide has also been documented to function as a dehydrator in the process of producing a derivative of 2-arylbenzimidazole (Scheme 7).[34]

Scheme 8 shows the preparation of certain *N*′-(substituted-benzylidene)-4-(5-methyl-1*H*-benzimidazol-2-yl)benzohydrazide derivatives **32a** and **b** for the analysis. Three steps were used to get the targeted synthetic substances. Firstly, methyl-4-formylbenzoate and 5-methyl-1,2 phenylenediamine were mixed equimolarly in DMF with $Na_2S_2O_5$ to yield **30**. Compound **31** was produced by refluxing a mixture of ethanolic solution of hydrazine hydrate and **30**, which occurred in approximately seven hours. The desired compounds **32a** and **b** were obtained *via* condensation of hydrazide with different substituted



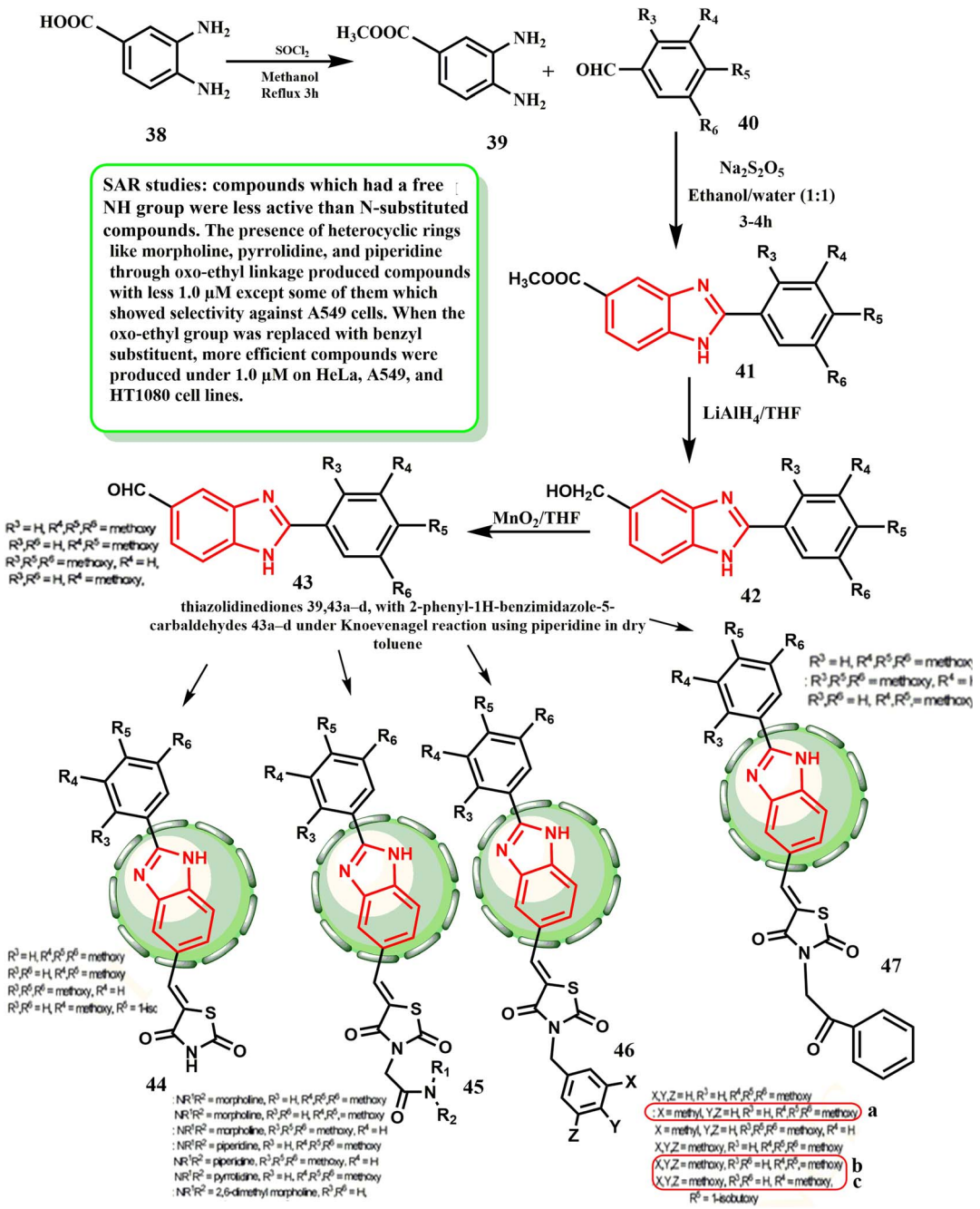
Scheme 8 Preparation of certain *N*′-(substituted-benzylidene)-4-(5-methyl-1*H*-benzimidazol-2-yl)benzohydrazide derivatives **32a** and **b**.



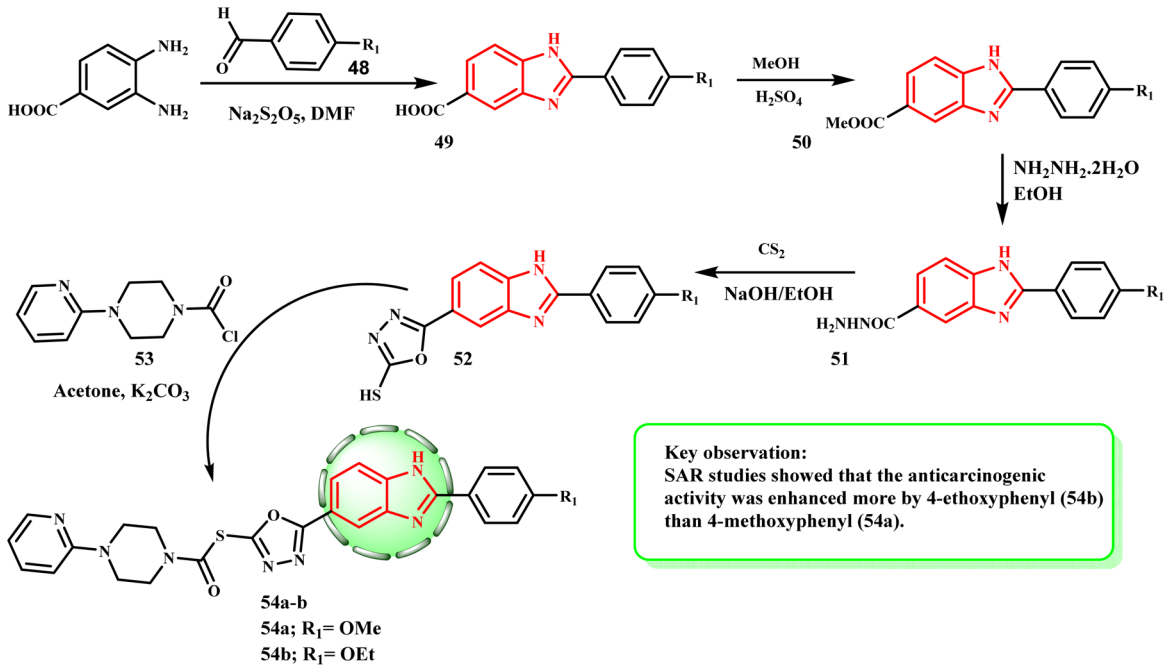
Scheme 9 Synthesis of benzimidazole derivatives **37**.

benzaldehydes. Compounds **32a** and **b** were discovered to exhibit significant effectiveness against a number of cancer cell lines, preventing their proliferation by 50–84%.[35] SAR studies revealed that the antiproliferative action of compound **32b** was enhanced by the presence of tri-methoxy as an electron-donating group on hydrazone, as opposed to the electron-drawing di-chloro substitution in **32a**.

Scheme 9 shows that commercially produced 4-nitrobenzene-1,2-diamine (**33**) was employed as the starting material for the synthesis of benzimidazole derivatives **37**. In polyphosphoric acid (PPA), **33** first interacted with benzoic acid to produce **34**, which then combined with (3-bromo-propyl)-benzene to produce intermediate **35** in the presence of K_2CO_3. Amino intermediate **36** was produced by reducing intermediate **35** with Pd/C in THF. Essential compounds **37** were obtained by treating amine **36** with suitable acyl chlorides or sulfonyl chlorides and triethylamine in dichloromethane. After various screening rounds, **37j** was shown to be an effective G9a antagonist ($IC_{50} = 1.32$ μM), which caused the MCF-7 cancer cell line to undergo autophagy ($IC_{50} = 5.73$ μM), where increased

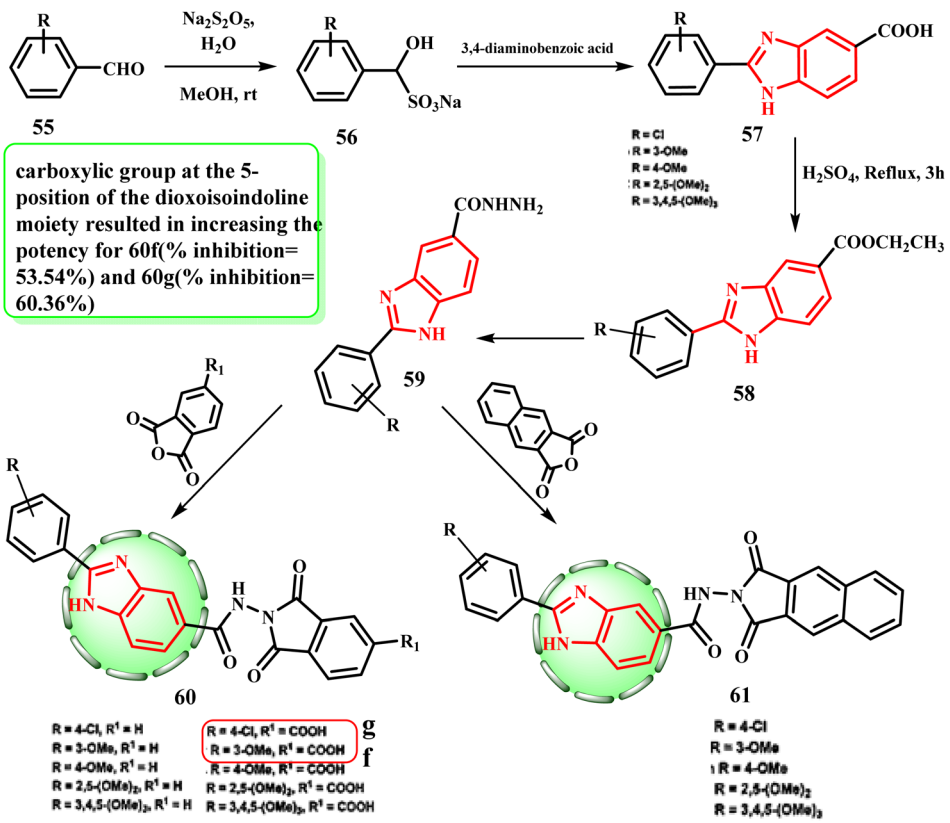


Scheme 10 Approach for the synthesis of benzimidazole-thiazolidinediones 46a–c.

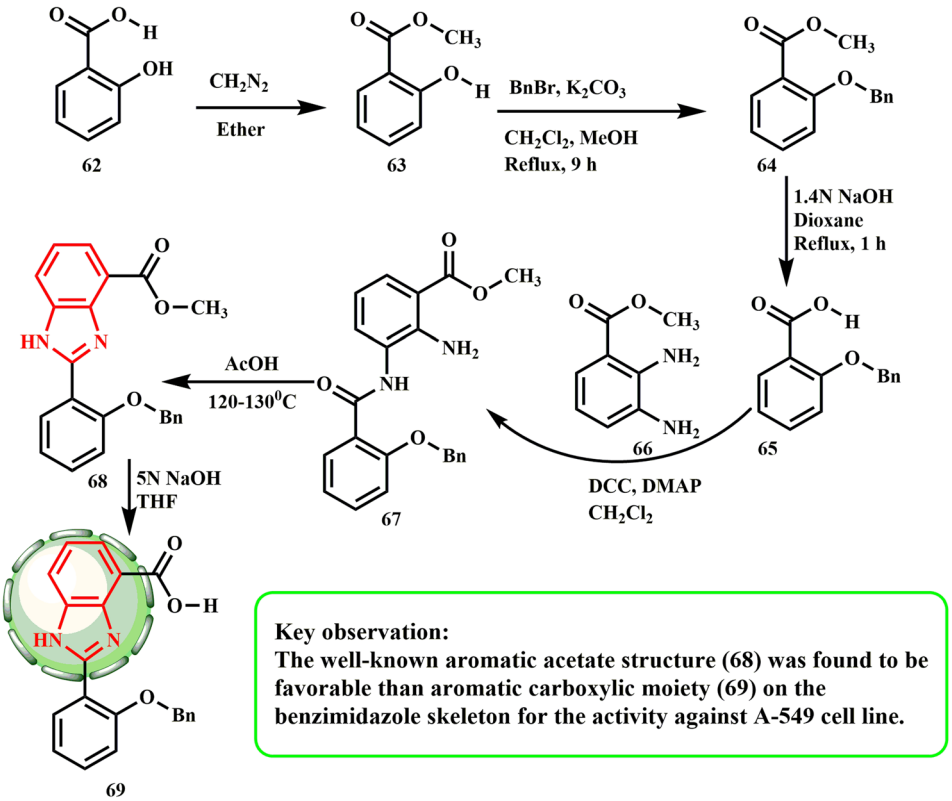


Scheme 11 Synthesis of compounds 54a and b.

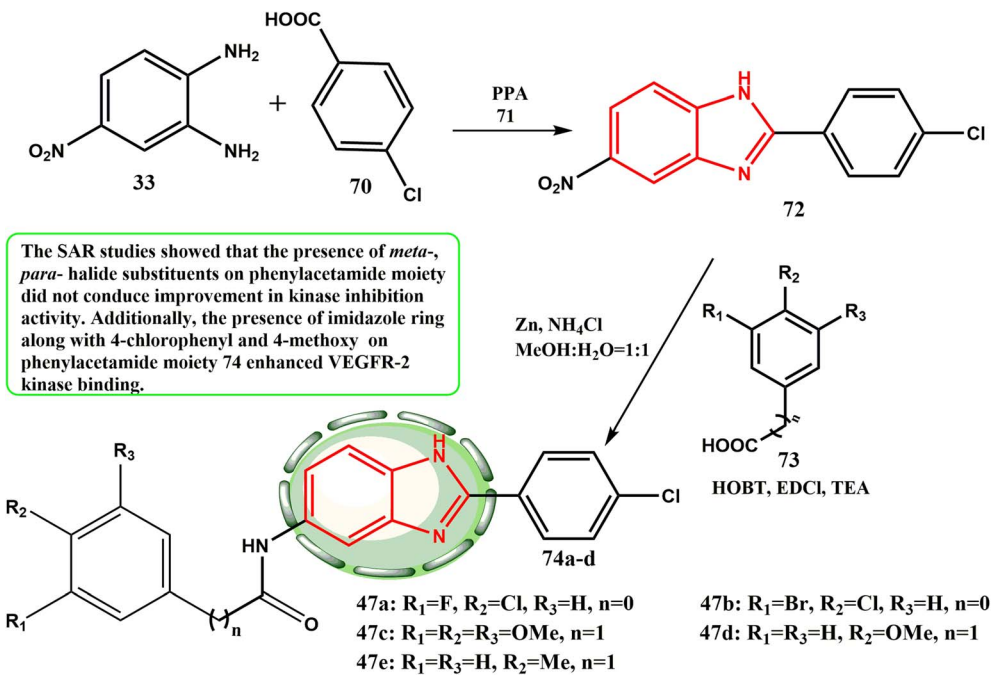
concentrations caused the MCF-7 cells to undergo apoptosis.[36] The antiproliferative action was increased by the addition of a moiety containing 1*H*-benzimidazole and a potent hydrophobic substituent, phenylpropyl (found in compound **37j**), to the *N* atom of 1*H*-benzimidazole. Stable binding with G9a was improved by the presence of Br in **37j**.



Scheme 12 Synthesis of *N*-(1,3-dioxo-isoindol-2-yl)-2-phenyl-1*H*-benzo[*d*]imidazole derivatives 60 and 61.



Scheme 13 Synthesis of benzimidazole analogues 68 and 69.



Scheme 14 Procedure for the preparation of 2-arylbenzoimidazole derivatives 74a–d.

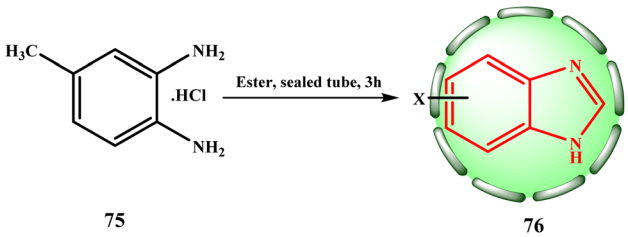
Scheme 10 describes the approach for the synthesis of benzimidazole-thiazolidinediones **46a–c**. The Knoevenagel condensation reaction was used to produce the final products **46a–c** in a convergent manner. In the presence of sodium metabisulfite, 3,4-diaminobenzoic acid (**38**) was natively altered to its methyl ester **39**, which subsequently interacted with various substituted benzaldehydes **40** to yield 1*H*-benzo[*d*] imidazole-5-carboxylates **41**. Lithium aluminum hydride was

used to decrease the ester functionalities in **41**, resulting in alcohols **42**, which were subsequently oxidized to their respective aldehydes **43**. Compounds **46a–c** were created by employing the Knoevenagel reaction to react different thiazolidinediones with 2-phenyl-1*H*-benzimidazole-5-carbaldehydes **43** in dry toluene containing piperidine. Both conventional and microwave-assisted synthesis were used to carry out the Knoevenagel condensation reaction for the synthesis of compounds **46a–c**. Compounds **46a–c** exhibited satisfactory cytotoxicity to prostate, cervical, bone, and lung cell lines (IC_{50} = 0.096–0.63 μM).[37] According to SAR evaluations, with the exception of a few that demonstrated selectivity against A549 cells, compounds with IC_{50} values less than 1.0 μM were generated when heterocyclic rings such as morpholine, pyrrolidine, and piperidine were present *via* an oxo-ethyl linkage. On the HeLa, A549, and HT1080 cell lines, more effective compounds were generated at 1.0 μM when the oxo-ethyl group was substituted out for a benzyl substituent. On almost all the screened cancer cell lines, derivatives such as **46b** that had 3,4,5-trimethoxybenzyl substitution at the tail produced higher active molecules at concentrations below 1.0 μM. By contrast, derivative **46a**, which included a 3-methyl benzyl moiety on the thiazolidinedione tail, was more effective against all cancer cell lines at 1.78 μM. The most powerful derivative, **46c**, has benzimidazole replaced with 4-isobutoxy-3-methoxy.

Scheme 11 displays the procedure used to synthesize compounds **54a** and **b**. Using sodium bisulphite in DMF, 4-substituted benzaldehyde **48** reacted with 3,4-diaminobenzoic acid (**38**) to produce 2-(4-substituted-phenyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid (**49**) derivatives in the first step. A simple esterification procedure transformed molecule **49** into methyl ester **50**, which was then reacted with hydrated-hydrazine to yield 2-(4-substituted-phenyl-6-carbohydrazide)-1*H*-benzo[*d*]imidazole (**51**). Hydrazide derivative **51** was converted to 2-(4-substituted-phenyl)-6-(5-mercapto-1,3,4-oxadiazol-2-yl)-1*H*-benzo[*d*]imidazole derivative (**52**) by reacting with carbon disulfide in boiling basic medium of ethanol and NaOH. Compound **52** and acetylated piperazine derivative **53** reacted in acetone at the last reaction step to yield 2-((5-(2-(4-substituted-phenyl)-1*H*-benzo[*d*]imidazol-6-yl)-1,3,4-oxadiazol-2-yl)thio)-1-(4-substituted-piperazin-1-yl) derivatives of ethane-1-on (**54a** and **b**). Çevik *et al.*[38] produced a variety of 1*H*-benzimidazole-oxadiazole compounds and tested them against HeLa, MCF-7, A549, HepG-2, and C6 human cancer cell lines *in vitro* to determine their anticancer properties. By inhibiting topoisomerase I, compounds **54a** (IC_{50} = 0.224 ± 0.011 μM) and **54b** (IC_{50} = 0.205 ± 0.010 μM) demonstrated the strongest antiproliferative action against the HeLa cancer cell line when doxorubicin (14.280 mM) was used as the standard medication. However, the majority of the derivatives demonstrated effective antiproliferative activity. The above-mentioned MTT experiment results supported our hypothesis that compounds **54a** and **b** would be more potent than Hoechst 33342 (0.306 mM) due to their potential for effective activity and reduced toxicity.

Several aryl aldehyde sodium bisulfates adduct **56** were reacted with the benzoic acid derivative to produce the initial document 2-substituted-benzimidzole-5-carboxylic acids **57**. Then, benzimidazole derivatives **57** were converted into the ester congeners **58** by a reaction with ethanol in the presence of sulphuric acid. Hydrazide derivatives **59** were generated when **58** reacted with hydrazine hydrate. Lastly, the target hybrids **60** were generated by allowing hydrazides **59** and acid anhydrides to react in acetic acid (Scheme 12).[39] Series **60** was produced by adding a carboxylic group to the dioxoisoindoline moiety at position 5, which increased the potency of **60f** (% inhibition = 53.54%) and **60g** (% inhibition = 60.36%).

Derivatives of benzimidazoles were synthesized and reported by Huang *et al.* Salicylic acid (**62**) was first esterified by diazomethane to produce methyl salicylate **63**, which allowed the



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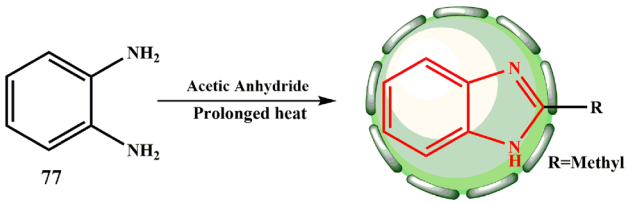
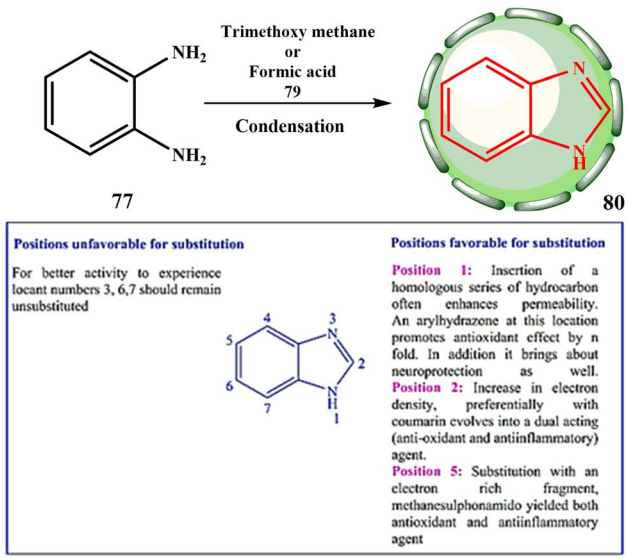
Scheme 15 Method for the preparation of 5-methyl benzimidazole (**76**).



77 78

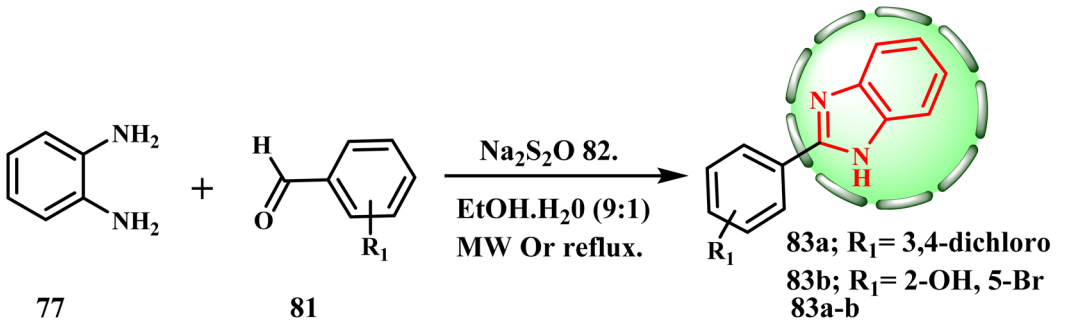
Scheme 16 Synthesis of -2-methylbenzimidazole (**78**).



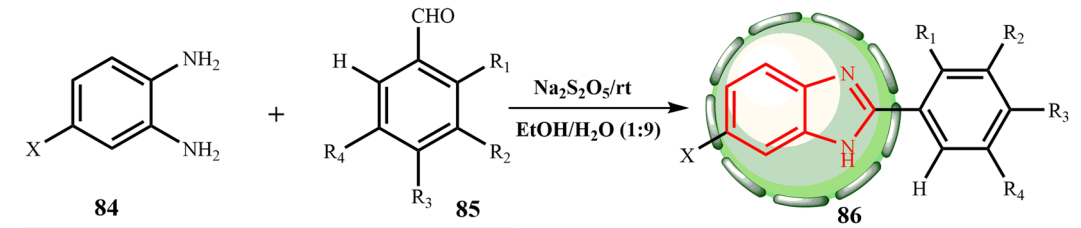
Scheme 17 Synthesis of BZ **80**.

production of the desired derivatives. After being treated with benzyl bromide and potassium carbonate, the hydroxyl group of **63** was protected with benzyl ether to yield **64**.[40] The saponification reaction then changed component **64** into carboxylic acid **65**. After treating compound **65** with dicyclohexylcarbodiimide, amide **67** was produced, which was further transformed into benzimidazole **68** through cyclization–dehydration by refluxing in acetic acid.[41] Lastly, 5 M NaOH was used to saponify compound **68**, yielding compound **69** (Scheme 13). Benzoimidazole-4-metylacetate, **68** (A549, IC_{50} 70 μM), was found to be more effective than benzoimidazole-4-carboxylic acid, **69** (A549, IC_{50} 87 μM) in the anticancer screening tests.[42,43]

Scheme 14 shows the main procedure for the preparation of 2-arylbenzoimidazole derivatives. The readily available starting material **33** was reacted with substituted benzoic acid **70** in polyphosphoric acid (PPA) (**71**) at 150 °C for 10–15 h to yield the 2-arylbenzoimidazole intermediate **72**.[44] The nitro group was reduced to generate an amino intermediate, which was then reacted with substituted aromatic carboxylic acids **73** at 20 °C for 2–4 h with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) and hydroxy benzotriazole (HOBt) as a condensing agent and triethanolamine[45] as a base to obtain **74a–d**. According to the CAM experiment, compound **74d** demonstrated a great level of angiogenesis inhibition (79% inhibition per 10 nM per egg),



Scheme 18 Synthesis of substituted 1*H*-benzimidazole derivatives **83a** and **b**.



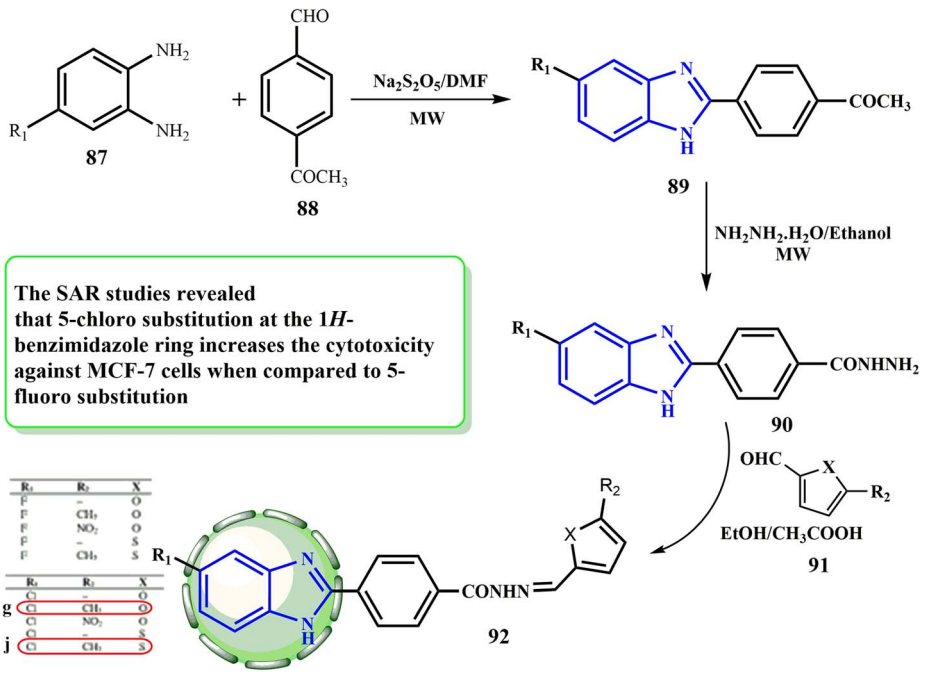
Compound	X	R_1	R_2	R_3	R_4
86a	H	H	OH	H	H
86b	H	H	H	OH	H
86c	H	OCH_3	H	H	OCH_3
86e	H	H	OCH_3	OCH_3	OCH_3
86f	H	H	H	$N(CH_3)_2$	H
86g	H	NO_2	H	H	H
86h	H	H	OCH_3	OH	H
86i	H	H	H	$-OCH_2-C_6H_5$	H

Scheme 19 Synthesis of 2-(substituted-phenyl) benzoimidazole derivatives **86**.

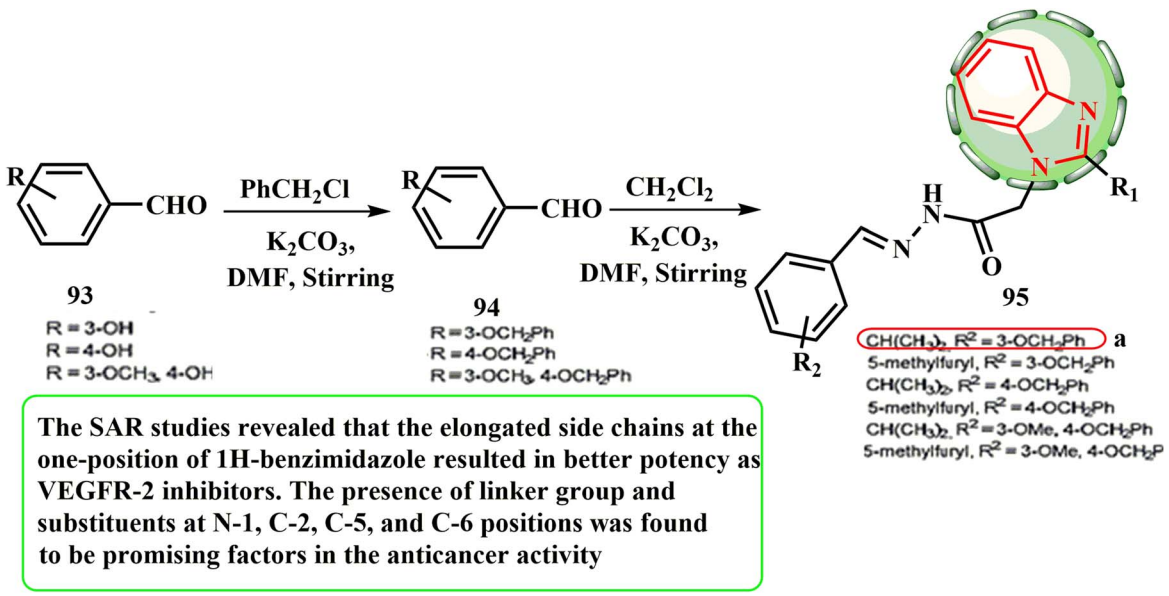
demonstrating the highest level of VEGFR-2 kinase inhibitory activity (51.4 nM IC_{50}), and effective anti-proliferative potencies against HepG-2 and HUVEC cells (1.47 μM and 2.57 μM, respectively).[46] According to the SAR investigations, the phenylacetamide moiety *meta*- and *para*-halide substitutes did not increase the kinase inhibitory activity. Furthermore, the imidazole ring and 4-chloroyphenyl together with the 4-methoxyphenylacetamide moiety in compound **74d** improved VEGFR-2 kinase binding.

Other benzimidazoles were synthesized similarly. Niementowski started by producing 5-methyl benzimidazole (**76**, X = 5-methyl) by the condensation of equimolar amounts of **75** and ethyl formate at 225 °C in a sealed tube for three hours to investigate the reaction between 4-methyl-*o*-phenylenediaminehydrochloride (**75**) and esters (Scheme 15).[24,34]

Although a shorter treatment only produced *N*,*N*′-diacetylphenylenediamine (Scheme 16), the further treatment of **77** with acetic anhydride produced 2-methyl benzimidazole (**78**, R



Scheme 20 Synthesis of target compounds **92**.



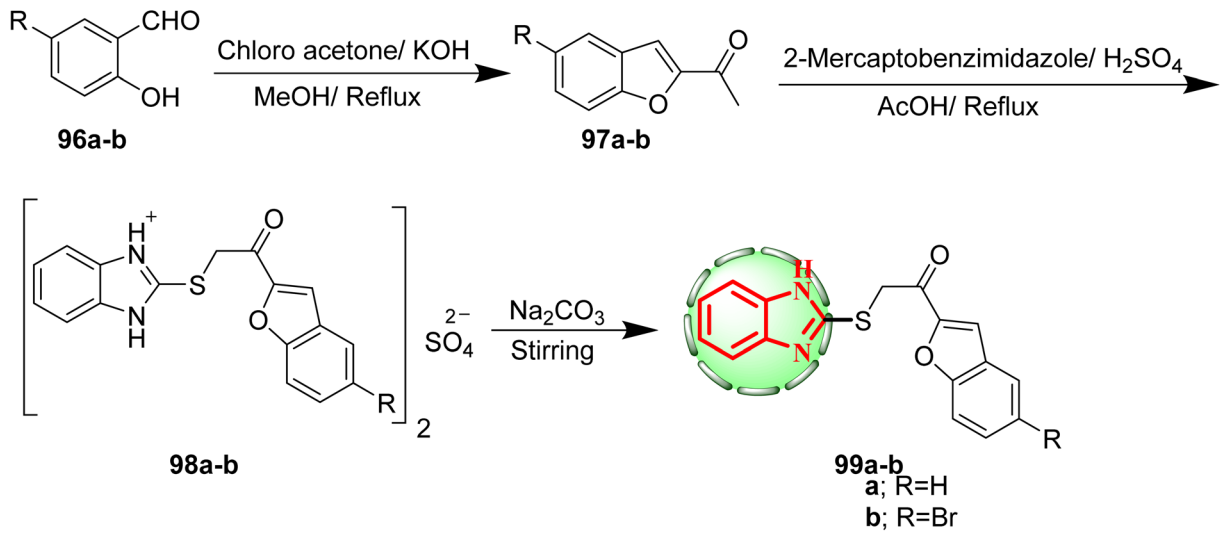
Scheme 21 Synthetic protocol for benzimidazole hybrids **95**.

= CH_3). Reinhardt found that the 2-methylbenzimidazole yields from 1% and 2% acetic anhydride were increased using diluted hydrochloric acid.[24,34,47]

With the help of the scientific research by Hoebrecker[48] in a six year period, scientists Banerjee[49] set the foundation for existing medical chemistry research by discovering a novel heterocyclic molecule (basic structure and synthesis shown in Scheme 17). BZ is the name of this substance.

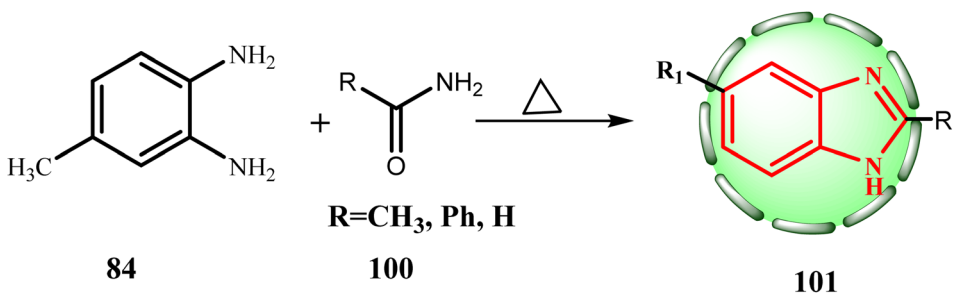
The synthesis and cytotoxic potential of 1*H*-benzimidazole scaffolds were examined by Pham *et al.* *N*,2,6-trisubstituted 1*H*-benzimidazole derivatives **83a** and **b** were prepared from benzene-1,2-diamine derivative 77. There are two steps in the synthetic process (Scheme 18). Firstly, using microwave assistance for the heating requirement, benzene-1,2-diamine derivative 77 was condensed with substituted aromatic aldehyde **81** to produce 2,6-disubstituted 1*H*-benzimidazole derivatives **83a** and **b**. Then, using the non-selective (positive) control involved in paclitaxel (PTX) in the MTT assay, we evaluated the anticancer activity of compounds **83a** and **b** on five cancer cell lines including hepatocellular carcinoma cell line (HepG-2), human breast cancer cell lines (MDA-MB-231 and MCF-7), the aggressive and highly malignant rhabdomyosarcoma cell line (RMS), and colon carcinoma cell line (C-26). Among the synthesized compounds, compounds **83a** (3,4-dichloro) and **83b** (5-bromo-2-hydroxy) demonstrated the greatest anticancer activity against all the tested cell lines.[50]

Given that $Na_2S_2O_5$ dissolves readily in an EtOH–H_2O mixture (9 : 1 v/v) as the medium for the manufacture of benzimidazole derivatives, the oxidation reaction to yield 2-phenyl benzimidazole derivatives **86** can occur at room temperature, as illustrated in Scheme 19. Huynh *et al.*[51] produced 2-(substituted-phenyl)benzimidazole derivatives by reacting *ortho* phenylenediamines with benzaldehydes and using sodium metabisulphite as an oxidant. Three human cancer cell lines, A549, MDA-MB-231, and PC-3, were used to test these substances for their anticancer activities. The functioning of the phenyl ring system at 2-position, the biochemical properties of the cell lines, and electron-withdrawing and -donating groups



The SAR studies revealed that combining 2-thiobenzimidazole with 2-acetylbenzofuran and 4-aminoacetophenone, resulted in maximum cytotoxic action.
It was observed that benzo fused heterocyclic acetyl derivatives exhibited maximum anticancer activity whereas the addition of 5-5-bromo substituent suppressed its activity.

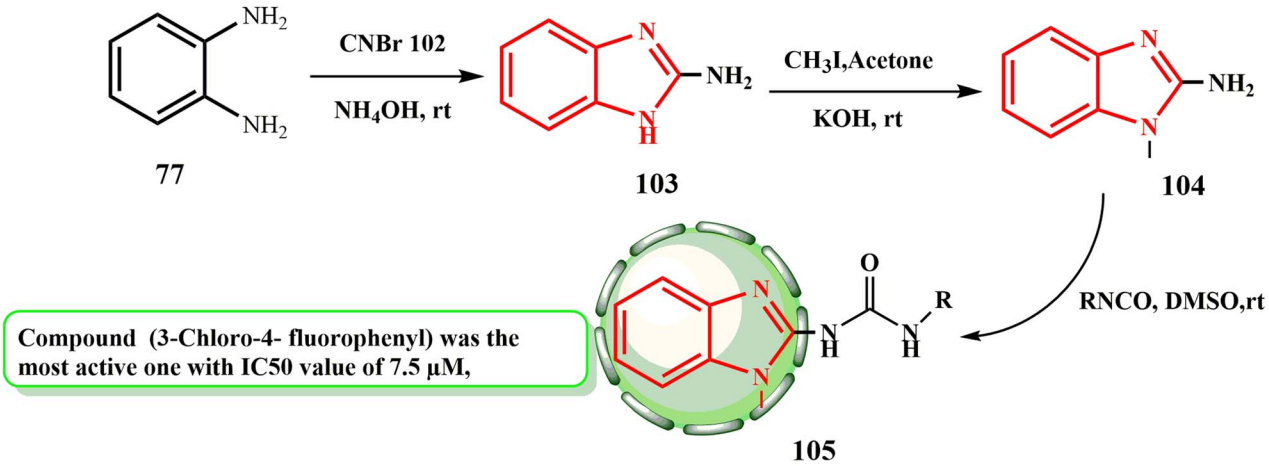
Scheme 22 Synthesis of benzimidazole-linked 2-acetylbenzofuran derivatives **99a** and **b**.

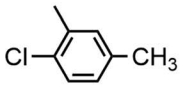
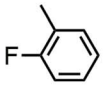
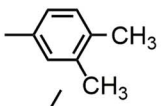
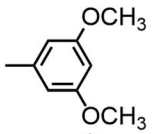
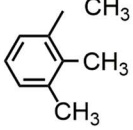
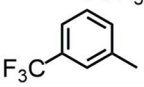
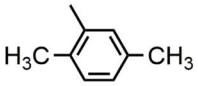
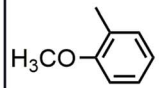
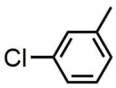
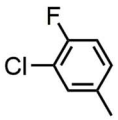


Scheme 23 Synthesis route to target compounds **101**.

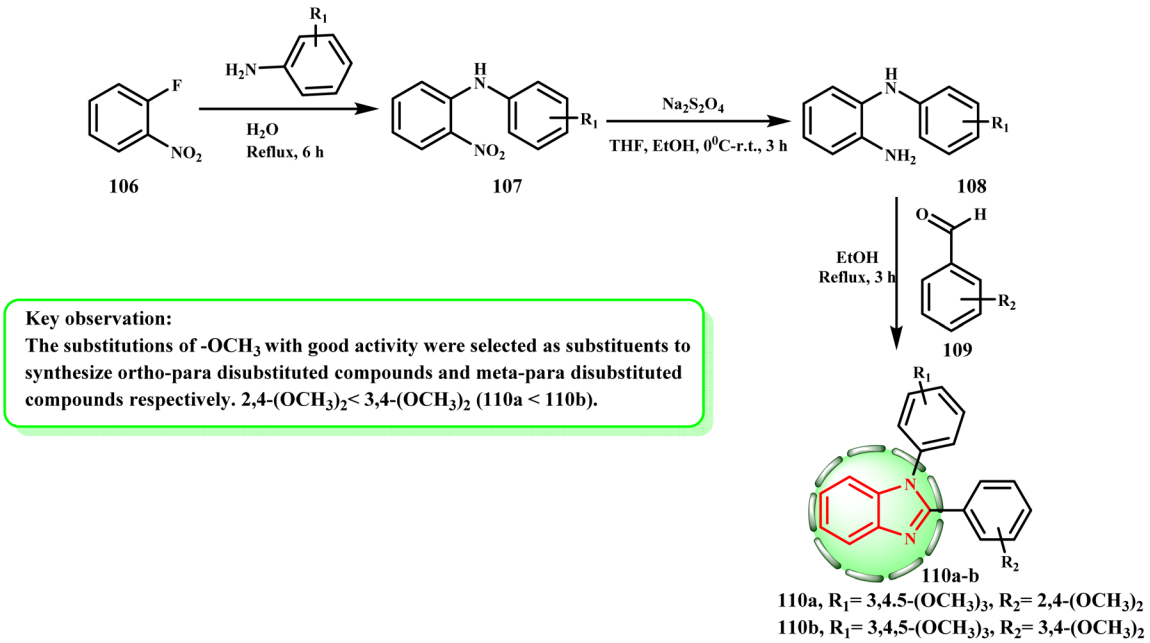
on the benzimidazole scaffold were shown to be associated with variations in the IC_{50} values. We established additional benzimidazole derivatives with various substituents on the 2-phenyl ring system, such as –OH, $–NO_2$, $–CF_3$, –I, –OMe, $–NMe_2$, and $–OCH_2–C_6H_5$, in parallel to provide more information about the impact of the electron-donating and withdrawing groups on the phenyl ring at the 2-position as well as on the benzimidazole frame. Remarkably, the bioactivities of compounds **86** on the A549 and PC-3 cell lines showed that the methyl group at position 5 is crucial in enhancing their bioactivities (**86a** > **86b** > **86c** > **86e** > **86f** > **86g** > **86h** > **86i**).

Scheme 20 illustrates the three-step synthesis of target compounds **92** used in this investigation. Following the procedure outlined in the literature, the substrates, 1-(4-(5-substituted-1*H*-benzo[*d*]imidazol-2-yl)phenyl)ethan-1-ones (**89**) and 4-(5-substituted-1*H*-benzo[*d*]imidazol-2-yl)benzohydrazides (**90**), were created.[52] Condensation of the hydrazide with diverse substituted benzaldehydes **91** (ref. 53) led to the related arylidene hydrazides **92**. Çevik *et al.*[54] produced a variety of 4-(5-substituted-1*H*-benzimidazol-2-yl)-*N*/-((5-substitutedthiophen/furan-2-yl)methylene)benzohydrazides (**92**) and used the MTT assay to evaluate them for their ability to kill A549 and MCF-7 (breast) cancer cell lines, using cisplatin as a (+ve) control. The normal NIH/3T3 cell line was also employed to check the synthesized synthetic substances. Compound **92g** exhibited no effect on the normal cell line, while it had the maximum cytotoxic potential in the A549 cell line (IC_{50} against A549 = 0.316 μM). Compared to cisplatin, compound **92j** (IC_{50} = 0.0316 μM) exhibited the most potent selective cytotoxicity against the MCF-7 cell line. In comparison to 5-fluoro substitution, SAR investigations demonstrated that 5-chloro substitution at the 1*H*-benzimidazole ring improved the cytotoxicity against MCF-7 cells.

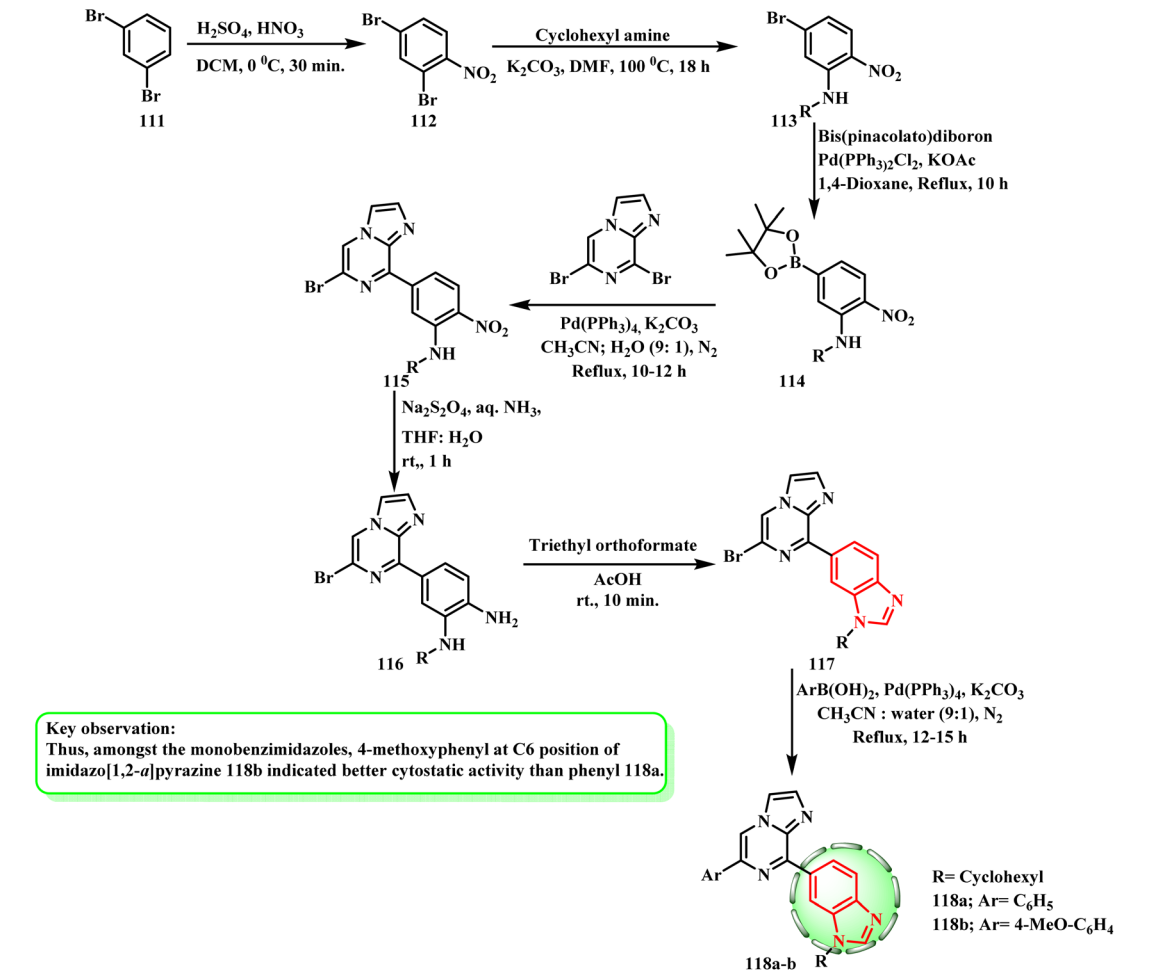


Compound	R	Compound	R
105a		105f	
105b		105g	
105c		105h	
105d		105i	
105e		105j	

Scheme 24 Synthesis of benzimidazole–urea derivatives **105**.



Scheme 25 General synthesis of compounds 110a and b.



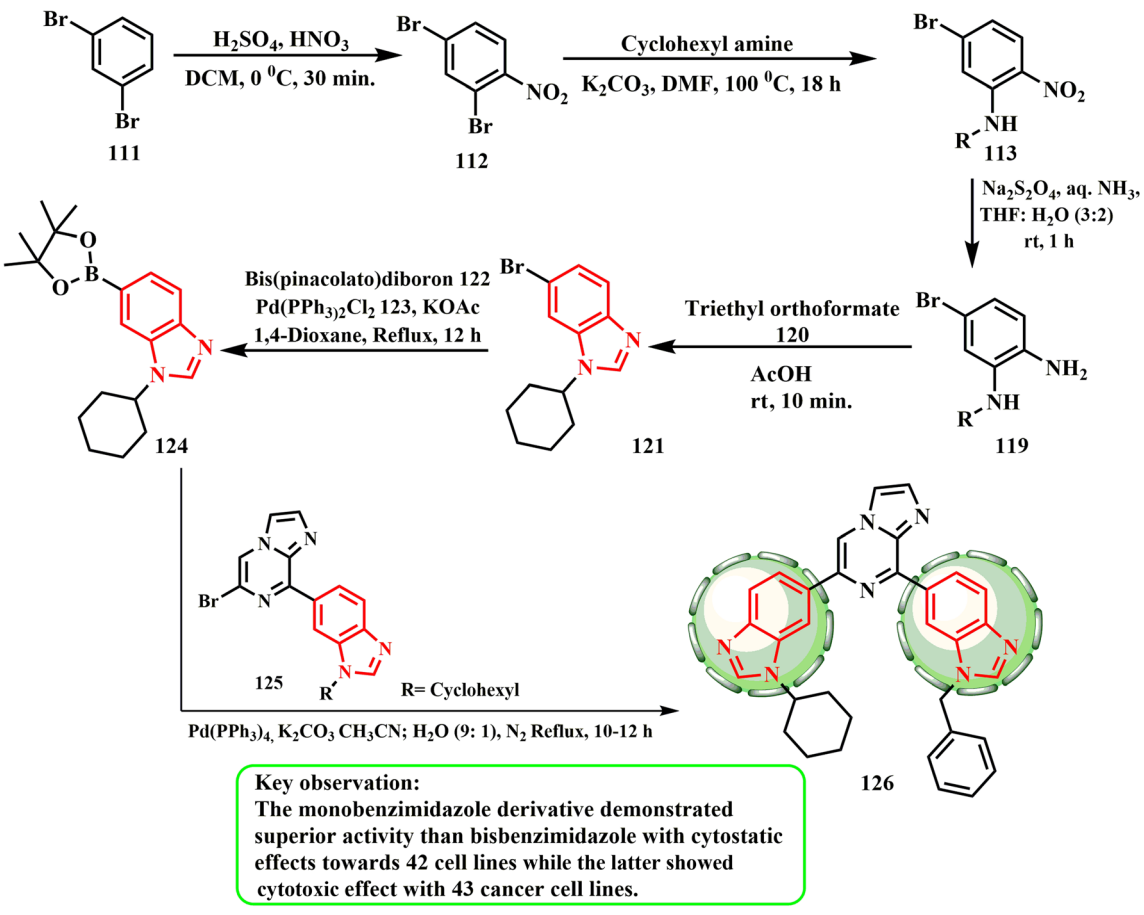
Scheme 26 Synthesis of mono benzimidazole derivatives 117 and 118a and b.

The appropriate benzyloxybenzaldehyde **94** was produced by reacting 4-hydroxybenzaldehyde (**93**) with benzyl chloride to synthesize target compounds **95** (Scheme 21). Abdel-Mohsen *et al.*[55] investigated the effects of a novel class of 1,2-disubstituted 1*H*-benzimidazoles as VEGFR-2 inhibitors on the HepG-2 hepatocellular carcinoma cell line. According to the results, sorafenib (IC_{50} = 10.99 μM) had lower cytotoxic activity than one of the created hybrids, **95** (IC_{50} = 1.98 μM). According to the SAR evaluations, the elongated side chains of 1*H*-benzimidazole at the one position resulted in activity as a VEGFR-2 inhibitor. It was discovered that the presence of a linker and substituents at positions N-1, C-2, C-5, and C-6 is promising in the anticancer action.

1.1.2. Acidic compounds. As shown in Scheme 22, the appropriate 2-acetylbenzofurans (**97**) were produced by cyclizing salicylaldehyde (**96**) with chloroacetone in the presence of potassium hydroxide.[56] 2-Substituted thiobenzimidazole sulfate salts (**98**) were produced when compounds (**97**) and 2-mercaptobenzothiazole reacted in acidic medium of two equivalents of conc. sulfuric acid using the modified procedure described by Abdel-Aziz *et al.*[57] At room temperature and to provide the appropriate free bases **99**, the free molecules were liberated from the sulfate salts by neutralizing through stirring with an $NaHCO_3$ solution. With sunitinib serving as the reference medication (IC_{50} = 0.18 μM), compound **99** demonstrated excellent inhibitory efficacy against the A498 human kidney cancer cell line (IC_{50} = 6.97 μM).[58] Mixing 2-thiobenzimidazole with 2-acetylbenzofuran and 4-aminoacetophenone had the most cytotoxic effect, according to the SAR investigations. Benzo-fused heterocyclic acetyl derivatives were shown to have the strongest anticancer activity, but the addition of a 5-bromo substituent reduced this activity.

Niementowski heated free base **84** with appropriate amides **100** to produce methyl benzimidazole (**101**, R_1 = 5 (6)1-methyl, R = H, CH_3, or Ph) (Scheme 23).

Here, we describe how we produced benzimidazole–urea derivatives **105**. The reaction of *O*-phenylene diamine (77) and cyanogen bromide (**102**) in methanol at room temperature produced 2-aminobenzimidazole (**103**) in 88% yield by ammonium hydroxide workup (Scheme 24). Compound **105j** (3-chloro-4-fluorophenyl) was the most active compound against a liver cancer cell lines (HepG-2), with an IC_{50} value of 7.5 μM. The anticancer activity of the other compounds followed the order of **105d** > **105a** > **105b** > **105e** > **105c** > **105g** > **105f**. The anticancer activity of the other compounds followed the sequence of **105a** > **105b** > **105d** > **105i** > **105f** > **105h** > **105g** with IC_{50} values in the range of 2.4–38.5 μM, among which compound **105j** was the most effective (IC_{50} = 1.9 μM) against non-small lung cancer (A549).[59]

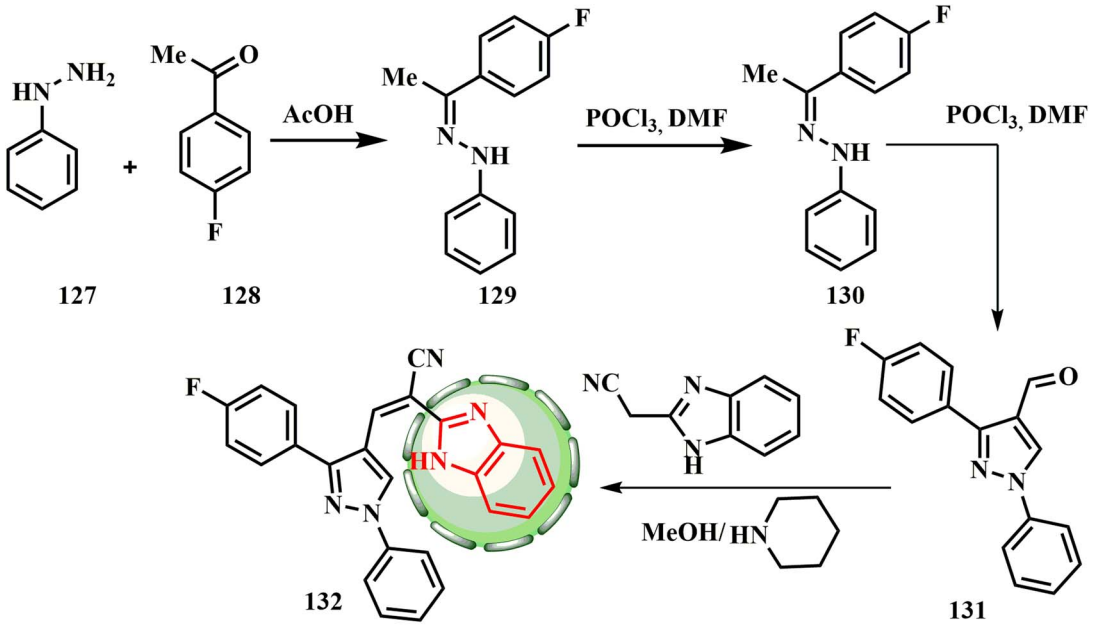


Scheme 27 Schematic of the route for the synthesis of bisbenzimidazole **126**.

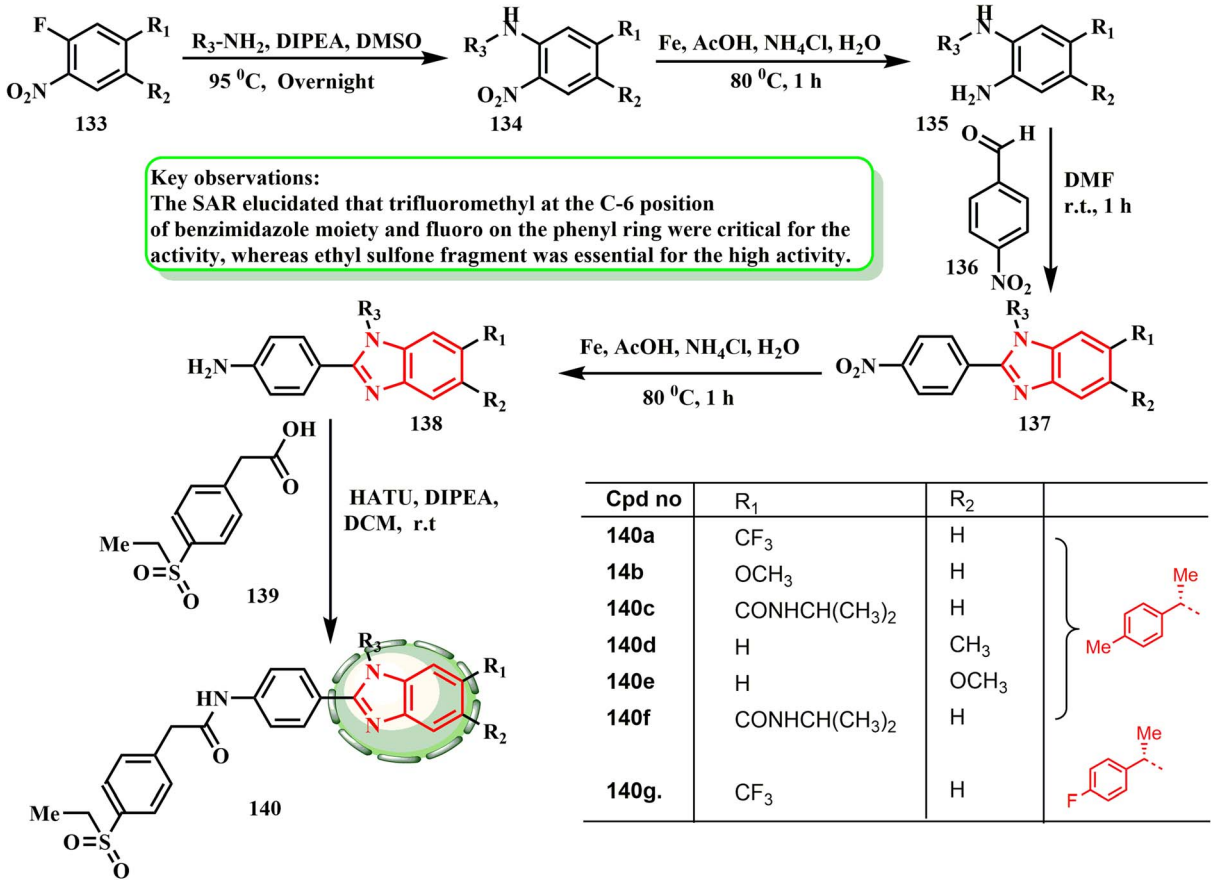
1.1.3. *o*-(*N*-Arylamino)arylamines. The production and cytotoxic potential of novel 1,2-diarylbenzimidazole analogues were examined by Zhang *et al.* Following the general procedure indicated in Scheme 25, compounds **110a** and **b** were synthesized by refluxing *o*-fluoronitrobenzene (**106**), neutralizing it with $NaHCO_3$, and then obtaining analogue **107**. After dissolving compound **107** in a mixed solution of ethanol and tetrahydrofuran, the reduction process was initiated by the addition of $Na_2S_2O_4$ solution. Following $NaHCO_3$ alkalization, compounds **108** were produced. Imidazole rings **110a** and **b** were finally formed by refluxing compounds **108** with substituted benzaldehyde **109** after they had been dissolved in anhydrous ethanol. Compound **110b** demonstrated minimal toxicity to normal cells and maximum anticancer activity against HeLa, HepG-2, A549, and MCF-7 cells, with IC_{50} values of 1.71 ± 0.14, 0.71 ± 0.07, 2.41 ± 0.31, and 1.94 ± 0.08 μM, respectively.[60] The impact of double substitution on activity was also considered. To develop *ortho–para* disubstituted compounds and *meta–para* disubstituted compounds, respectively, $-OCH_3$ with excellent activity was chosen as the substituent, where **110a** < **110b** = 2,4-$(OCH_3)_2$ < 3,4-$(OCH_3)_2$. As a result, 3,4-$(OCH_3)_2$ had the best activity in *meta–para* disubstitution, which had higher activity than *ortho–para* disubstitution.

After being nitrated with sulfuric and nitric acids, the commercially available 1,3-dibromobenzene (**111**) was converted to **112**, which was then selectively replaced with cyclohexylamine in DMF to produce **113**. Bis(pinacolato) diboron was used to boronate **113** in the presence of $Pd(PPh_3)_2Cl_2$ and KOAc, producing **114**. Suzuki–Miyaura cross-coupling of **114** with dibromo-imidazo[1,2-*a*]pyrazine[61,62] and $Pd(PPh_3)_4$ afforded compound **115** together with traces of disubstituted products. Amines **116** were obtained by reducing the derivatives with $Na_2S_2O_4$ in ammonia. Then, triethyl orthoformate was cyclized in acetic acid to produce intermediate **117**. Using $Pd(PPh_3)_4$ and K_2CO_3, Suzuki reactions of the intermediates with unsubstituted and substituted phenylboronated were performed in $CH_3CN : H_2O$, yielding **118a** and **b** (ref. 63) (Scheme 26). Mono benzimidazole derivatives **118a** and **b** showed specific effectiveness against subpanels of melanoma, colon, leukemia, and central nervous system (GI_{50} = 0.31–0.39 μM). Therefore, 4-methoxyphenyl at the C6 position of imidazo[1,2-*a*]pyrazine **118b** showed superior cytostatic activity compared to phenyl **118a** among the mono benzimidazoles.

The commercially available 1,3-dibromobenzene (**111**) was nitrated to produce **112**, which was then replaced with cyclohexylamine in DMF to produce **113**. After reducing **113** with $Na_2S_2O_4$ in ammonia to yield **119**, the corresponding benzimidazole **121** was obtained by cyclization with triethyl orthoformate (**120**) in acetic acid. Bis(pinacolato)diboron (**122**) was used to boronate the derivative in the presence of $Pd(PPh_3)_2Cl_2$ (**123**) and KOAc, yielding **124**. Using $Pd(PPh_3)_4$ and K_2CO_3, Suzuki–Miyaura cross-coupling of benzimidazole boronated

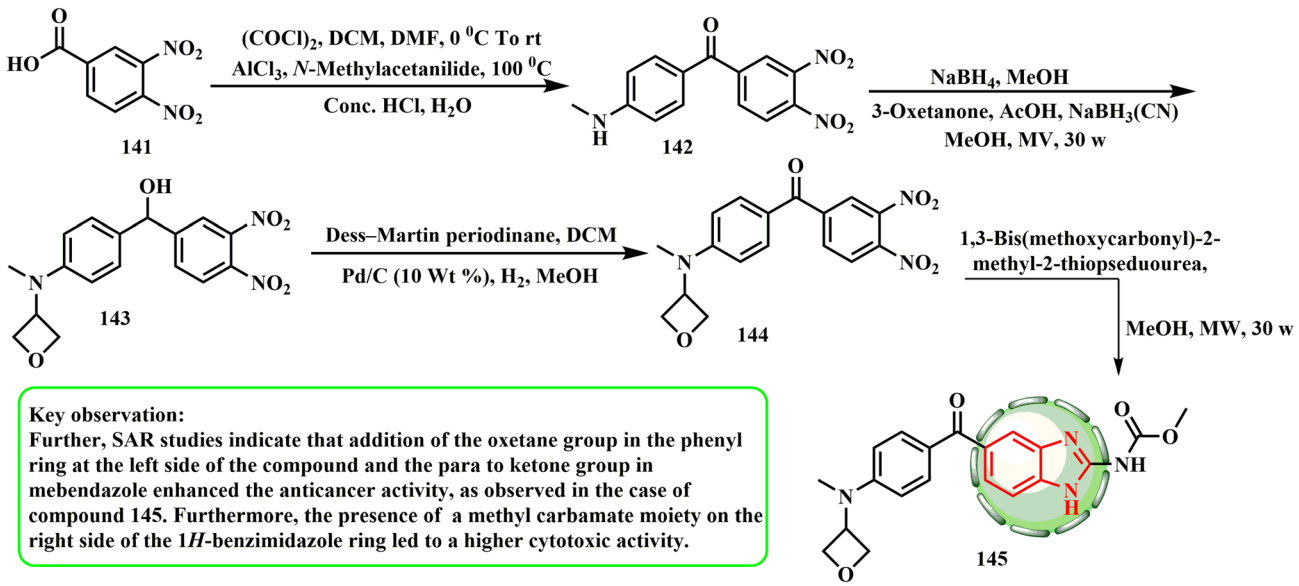


Scheme 28 Synthesis of benzimidazole–tethered pyrazole 132.



Cpd no	R_1	R_2	
140a	CF_3	H	
14b	OCH_3	H	
140c	$CONHCH(CH_3)_2$	H	
140d	H	CH_3	
140e	H	OCH_3	
140f	$CONHCH(CH_3)_2$	H	
140g.	CF_3	H	

Scheme 29 Synthesis of benzimidazole derivatives **140a–g**.



Scheme 30 Synthesis of (1*H*-benzo[*d*]imidazol-2-yl)carbamate analogue **145**.

125 with intermediate **124** was carried out to yield **126** (Scheme 27). All the screened cell lines showed the cytotoxicity of compounds **118b** and **126**, which also displayed significant growth inhibitory concentrations of 2.10 and 2.23 μM, respectively.[63] The colon cancer cell line HCC-2998 was discovered to be extremely sensitive to derivative **126** among these tumor-sensitive cell lines, exhibiting a negative growth percentage value (lethal impact). The cancer cell line from the

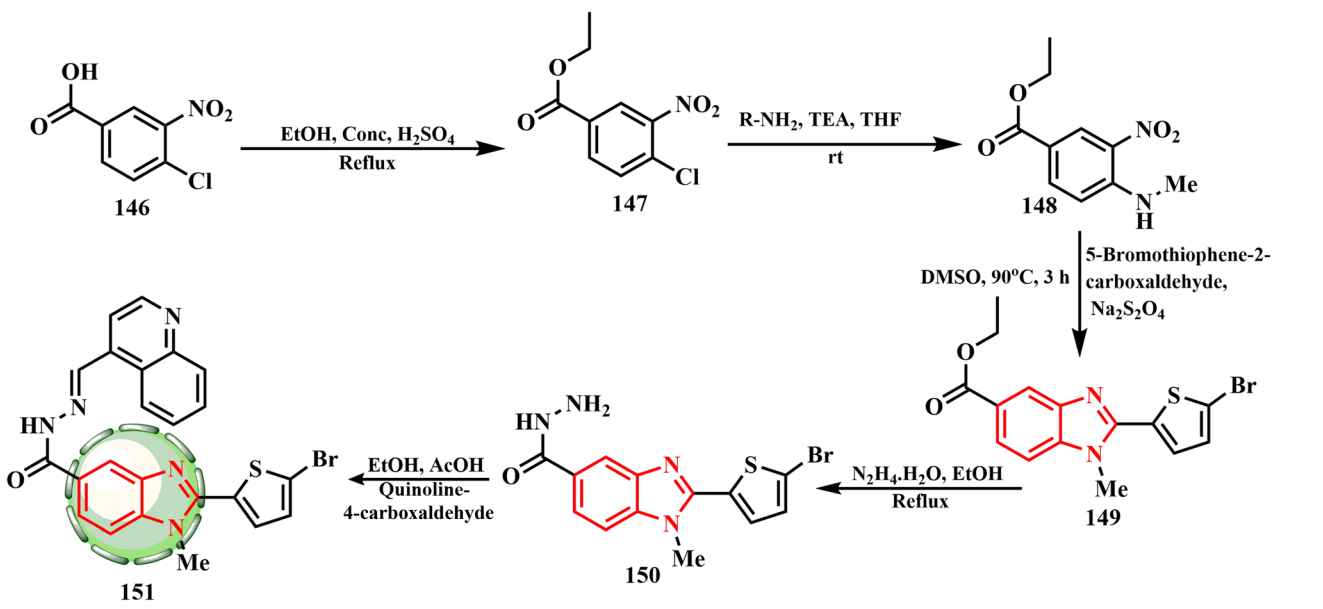
central nervous system (SF-539) was found to be highly susceptible to derivative **118b**. Ct-DNA intercalates with imidazo [1,2-*a*]pyrazine-benzimidazoles **118a** and bisbenzimidazole **126**,[64] exhibiting superior activity than bisbenzimidazole, as a key interaction for basic physiologically noteworthy effects. With cytostatic effects on the cell line, mono benzimidazole derivative **118a** was superior to bisbenzimidazole **126**; nevertheless, compound **126** subsequently revealed a cytotoxic influence on various cancer cell lines.

Scheme 28 shows the synthesis of benzimidazole-tethered pyrazole **132**. Arylhydrazine and suitable aralkyl ketone **128** are first condensed in glacial acetic acid to produce pyrazole-based carbaldehyde **131**. Hydrazone intermediate **129** is then cyclized utilizing Vilsmeier–Haack reaction. Compound **132** had the least toxicity and most promising effects, with IC_{50} values of 30.9, 32.8, and 80 μM against MRC5 cells, AsPC1, and SW1990.[65] Additionally, SAR investigations showed that a 4-fluorophenyl moiety increased its efficacy against all the evaluated cell lines.

1.1.4. *o*-Nitro arylamines or *o*-dinitro arenes. In their study aimed at selectively targeting cancer cells, Wu *et al.*[66] established a novel category of chemicals called benzimidazoles. Scheme 29 shows how various amines reacted with commercial substance **133** to produce amine-substituted nitrobenzene intermediates **134**. The corresponding anilines **135** and **138** were obtained by reducing the nitro groups in **134**. Subsequently, the final products **140a–g** were obtained by coupling with 2-(4-(ethylsulfonyl)phenyl)acetic acid (Scheme 29). The SAR revealed that the ethyl sulfone fragment was necessary for the high activity, while trifluoromethyl at the C-6 position of the benzimidazole moiety and fluoro on the phenyl ring were crucial for the activity. Moreover, hybrids **140a** and **b** showed encouraging efficacy against the AR-positive LNCaP, 22Rv1, and C4–2B prostate cancer cell lines (IC_{50}: 6.3–8.3 μM and 4.6–8.1 μM, respectively). When the size was increased to isopropyl formamide (**140c**), the activity was reduced by almost nine-fold. These findings showed that the best methyl group substituent for RORγ transcriptional activity was located at the R_1 position. Potency losses of 73 and 3.7 times were seen in comparable compounds **140d** and **140e** when the methyl or methoxy group at the R_1 position was fused to the R_2 position, respectively. However, the resultant compound **140f** had somewhat increased efficacy when the isopropyl formamide moiety at the R_1 position was fused to the R_2 location.

Methyl(5-(4-(methyl(oxetan-3-yl)amino)benzoyl)-1*H*-benzo[*d*] imidazol-2-yl)carbamate (**145**) was obtained *via* the microwave[67] condensation cyclization of 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea and intermediate **143** (Scheme 30). Compound **145** with oxetanyl substitution demonstrated significant cytotoxic activity against prostate (PC-3 and PC3MLN4 cell lines), lung (A549 cell lines), and ovarian cancers with considerable activity toward profoundly aggressive carcinogenic cell lines (IC_{50} = 0.9–3.8 μM).[68] The growth of existing tumors was greatly suppressed by compound **145** (30 mg kg^{-1}) without causing any detectable toxicity (T/C: 0.36). Additionally, as seen in compound **145**, SAR studies showed that the addition of the *para* to ketone group in mebendazole and the oxetane group in the phenyl ring on the left side of the compound increased the anticancer activity. A methyl carbamate moiety on the right side of the 1*H*-benzimidazole ring also increased the cytotoxic activity of the compound.

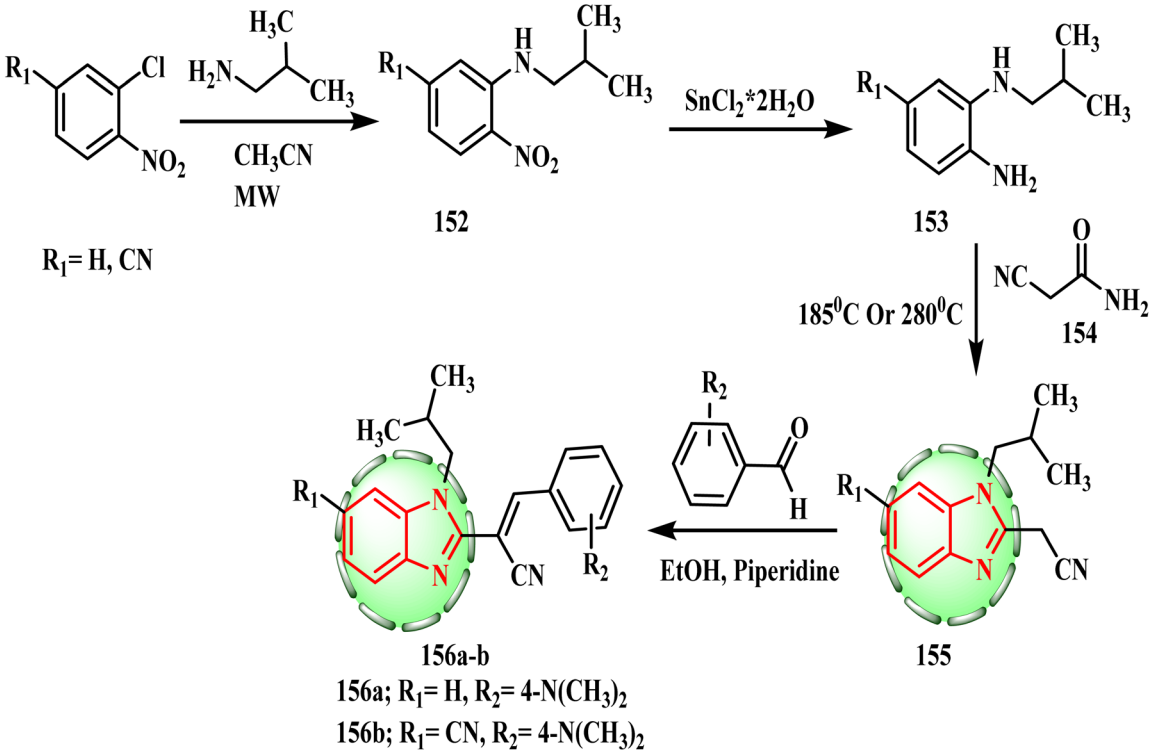
The synthetic route for benzimidazole–quinoline[69] hybrid **151** is presented in Scheme 31. Firstly, key intermediate **150**,[70] obtained initially from core nucleus benzimidazole-5-carboxylate **149**, was effectively produced by a 'one pot' nitro reductive cyclization process between ethyl 3-nitro-4-(substituted amino)benzoate **148** and 5-bromothiophene-2-carbaldehyde using $Na_2S_2O_4$ in DMSO.[71] When tested against



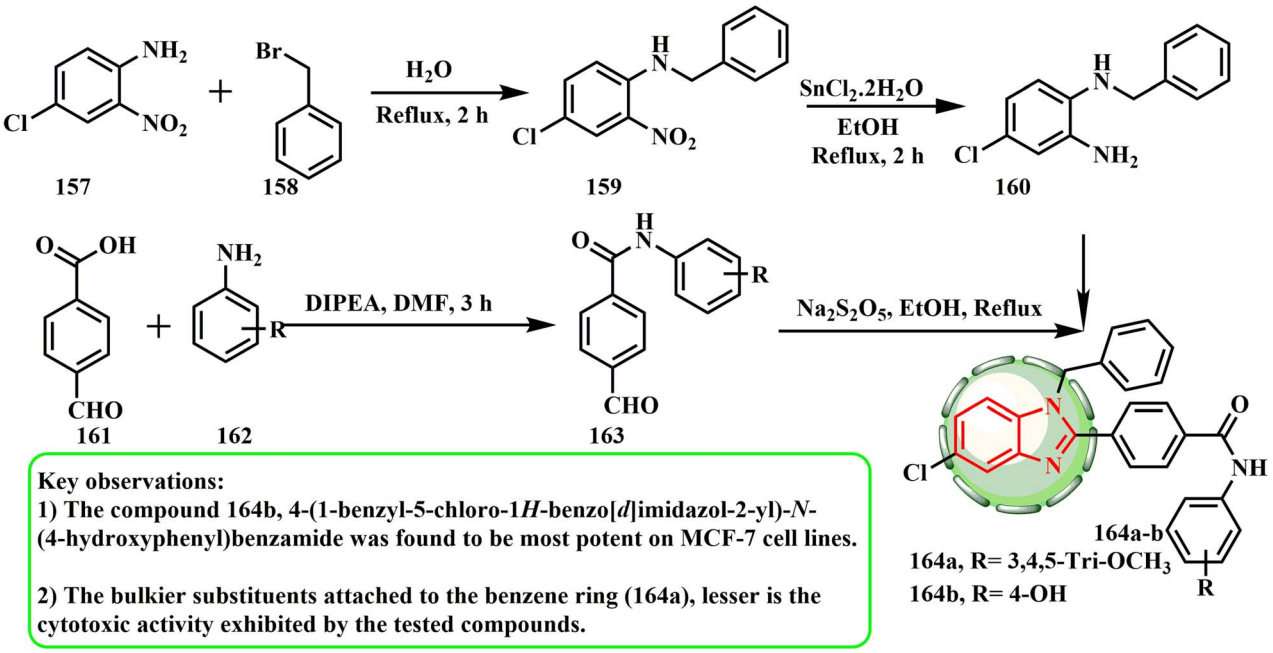
Scheme 31 Synthetic route for benzimidazole–quinoline hydride **151**.

two distinct cell lines, all other drugs showed moderate to good anticancer efficacy. Using cisplatin as a reference medication, compound **151** demonstrated activity against the A37 (IC_{50} = 34.7 ± 0.9 μg mL^{-1}) and MDA-MB-231 (IC_{50} = 20.4 ± 1.1 μg mL^{-1}) cell lines using the MTT test. However, the other substances did not show preference for these specific cell lines. Chemical substance **151** also showed cytotoxic properties. The IC_{50} value of compound **151** (A375) was 34.7 ± 0.9 μg mL^{-1}.[42] Compound **151** presented the highest % inhibition and lowest IC_{50} value of 604.8 μg mL^{-1}.

1.1.5. *o*-Substituted-*N*-substituted. The production and cytotoxic potential of *N*-substituted benzimidazole acrylonitrile hybrids were examined by Perin *et al.* Unsubstituted or cyano substituted *N*-isobutyl **152** was produced by uncatalyzed microwave-assisted amination beginning with the corresponding *o*-chloronitrobenzenes. Then, compounds **152** were reduced with $SnCl_2 \times 2H_2O$ in MeOH, which served as the primary precursor for the production of target molecules **156a** and **b**. The cyclocondensation reaction of amino derivative **153** with 2-cyanoacetamide (**154**) at elevated temperatures produced *N*-substituted-2-cyanomethylbenzimidazoles **155**. The condensation reaction of systems **155** with a chosen aromatic aldehyde in pure ethanol, followed by the addition of a few drops of piperidine as a weak base yielded the equivalent *N*-substituted-2-benzimidazolyl acrylonitrile **156a** and **b**, as demonstrated in Scheme 32. As lead compounds, *N*-substituted benzimidazole acrylonitrile, which has *N*-isobutyl and cyano substituents on the benzimidazole nuclei (**156a** and **b**), demonstrated potent antiproliferative action, while being noticeably less hazardous than the reference systems staurosporine and docetaxel.[72] According to SAR investigations, the affinity of the phenyl moiety significantly increased when an electron-donating *para*-substituted NMe_2 group was added. This tendency for access to optimum binding with Cys241 was reduced by substituting the electron-withdrawing cyano group (**156b**). The chance of favorable positioning was increased by the inclusion of the significant *N*-isobutyl group.



Scheme 32 Synthesis of *N*-substituted-2-benzimidazolyl acrylonitrile derivatives **156a** and **b**.

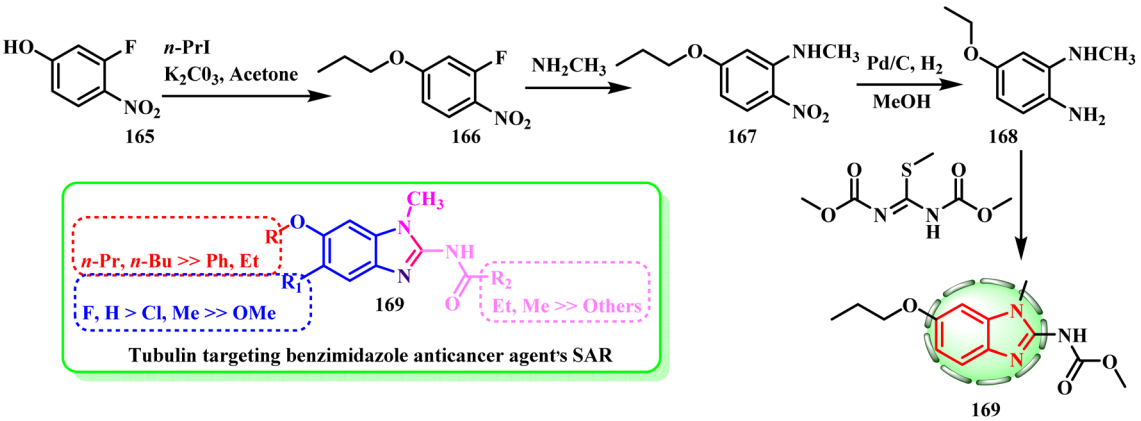


Scheme 33 Synthesis of various 1-benzyl-1*H*-benzimidazole analogues **164a** and **b**.

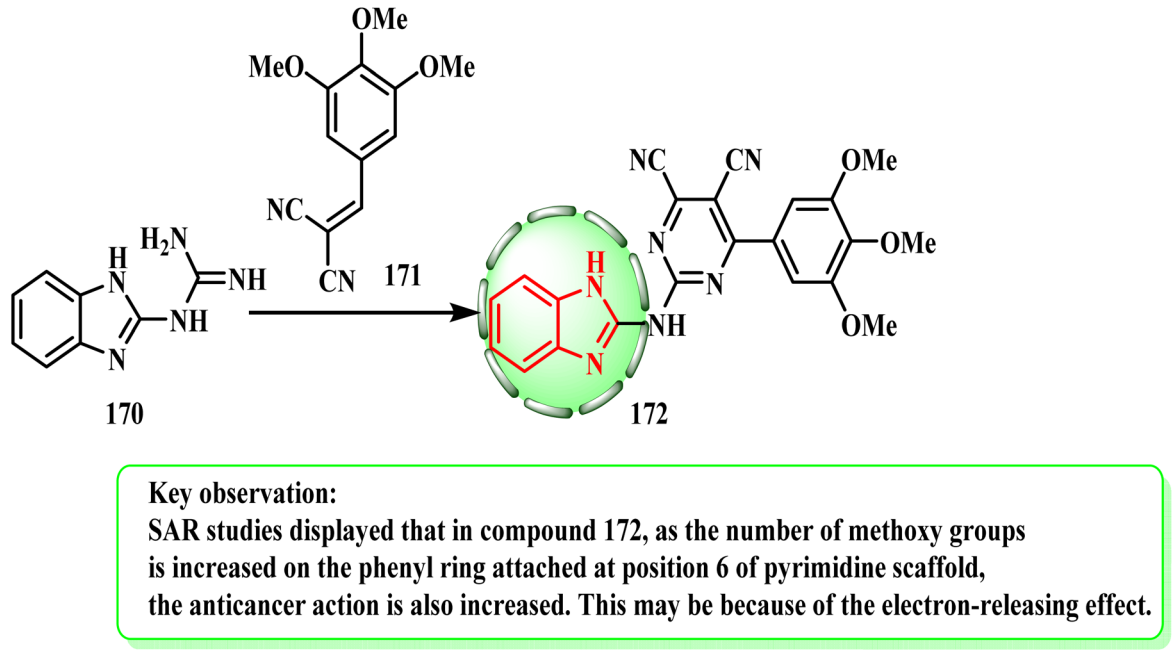
Kommi *et al.* investigated the production and cytotoxic potential of benzimidazole derivatives. Scheme 33 depicts the synthetic method utilized to prepare 1-benzyl-1*H*-benzimidazole analogues **164a** and **b**. 4-Formyl-*N*-phenylbenzamide **163** was utilized to condense N^1-benzyl-4-chlorobenzene-1,2-diamine (**160**). Using benzyl bromide (**158**) and the nitro group of compound **159**, the commercially available 4-chloro-2-nitro aniline (**157**) was first converted to *N*-benzyl-4-chloro-2-nitroaniline (**159**). Then, it was further reduced to an amino functional group using stannous chloride dihydrate, which produced N^1-benzyl-4-chlorobenzene-1,2-diamine (160).[73] Alternatively, the commercially existing 4-formyl benzoic acid (**161**) and aniline derivative (**162**) were used to create 4-formyl-*N*-phenylbenzamide (163).[74] Lastly, 4-formyl-*N*-phenylbenzamide (**163**) and N^1-benzyl-4-chloro orthophenylene diamine (**160**) were refluxed in ethanol in the presence of $Na_2S_2O_5$, yielding target compounds **164a** and **b**.[75] Among the compounds, with an IC_{50} value of 7.01 ± 0.20 μM, **164b** (4-(1-benzyl-5-chloro-1*H*-benzo[*d*]imidazol-2-yl)-*N*-(4-hydroxyphenyl)benzamide) demonstrated the highest efficacy and stopped the MCF-7 cell cycle in the G2/M phase and S-phase.[76] The SAR investigations revealed that larger substituents linked to the benzene ring (**164a**) reduced the cytotoxic activity of the examined compounds.

1.1.6. Imines. Oxibendazole with *O*-*n*-propyl was chosen for further investigation. In this phenotypic screening assay, *O*-*n*-propyl was determined to be the ideal size for hydrophobic interaction with tubulin binding, while O-ethyl and *O*-*n*-butyl derivatives were less active than oxibendazole. Thus, as a default benzimidazole C6 tail, oxibendazole with *O*-*n*-propyl was used (Scheme 34).[77]

1.1.7. Amidines. Target compound 2-(2-pyrimidinylamino) benzimidazole **172** (ref. 78) was produced, as indicated in



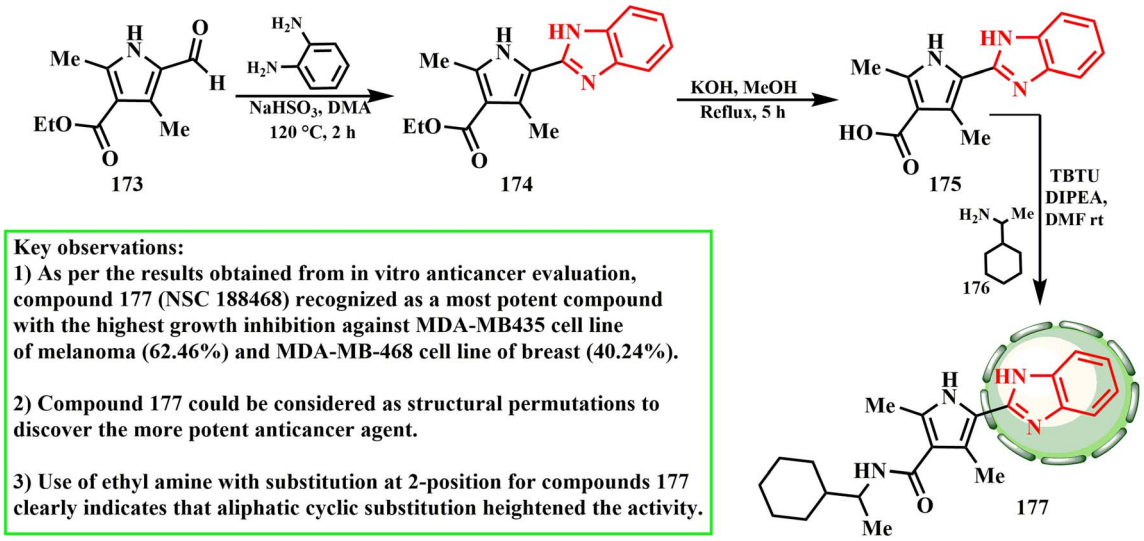
Scheme 34 General synthesis of compound **169**.



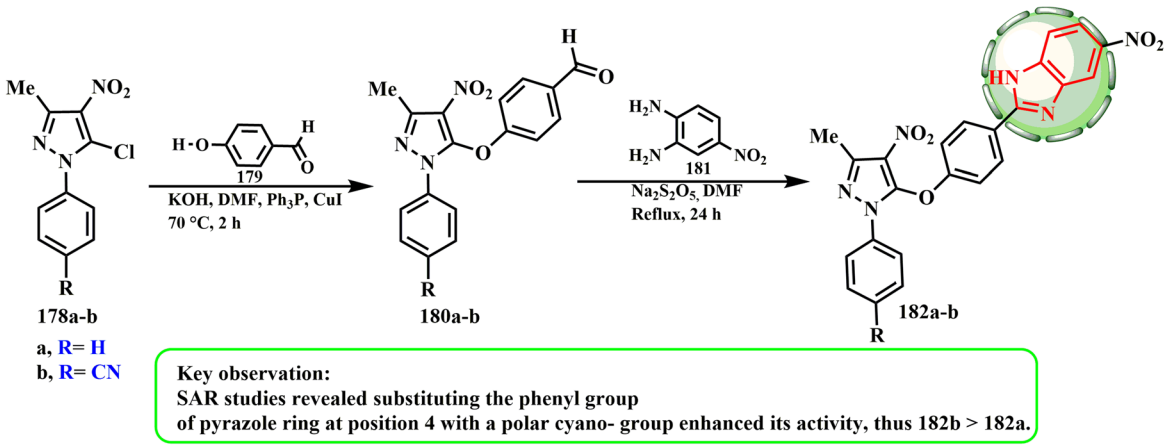
Scheme 35 Synthesis of 2-(2-pyrimidinylamino)benzimidazole **172**.

Scheme 35, where initially, 2-guanidinobenzimidazole (**170**)[79] was combined with olefinic derivatives arylidenes (**171**) under general mild reaction conditions. The amino group at position C2 of olefinic molecule **170** was attacked nucleophilically, and then an oxidative cyclization process took place. Compound (**172**) was obtained by the reaction[80] of compound **170** with arylidene malononitrile (**171**) in ethanol under reflux using piperidine as a catalyst. Ismail *et al.*[81] produced unique 2-amino(substituted pyrimidin-2-yl)benzimidazole hybrid **172** and tested it against a range of human cancer cell lines *in vitro* to determine its anti-cancer properties. Five-dose testing revealed that compound **172** had the most potential anti-cancer activity. SAR studies revealed that the more methoxy groups on the phenyl ring attached at position 6 of the pyrimidine scaffold, the stronger the anticancer activity of compound **172**. This can be ascribed to the electron-releasing effect.

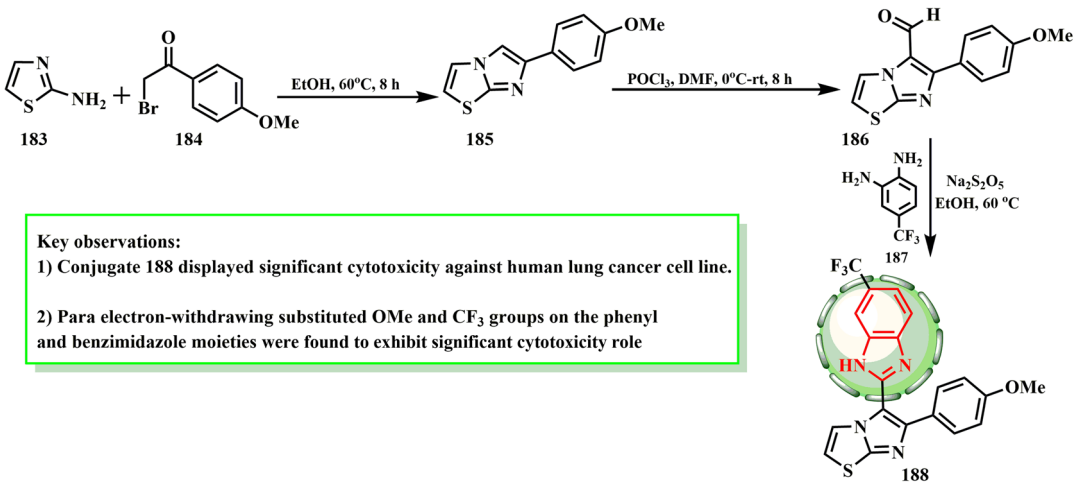
1.1.8. Heterocyclic scaffolds. Ethyl-5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**173**) was synthesized from the commercially available *tert*-butyl acetoacetate by adopting a previously reported literature procedure[82] and route outlined in Scheme 36. Target compound **175** was prepared *via* the hydrolysis of compound **174** using KOH as a base in a water–methanol mixture under reflux conditions. Subsequently, amide derivative **177** was synthesized by coupling acid **175** with



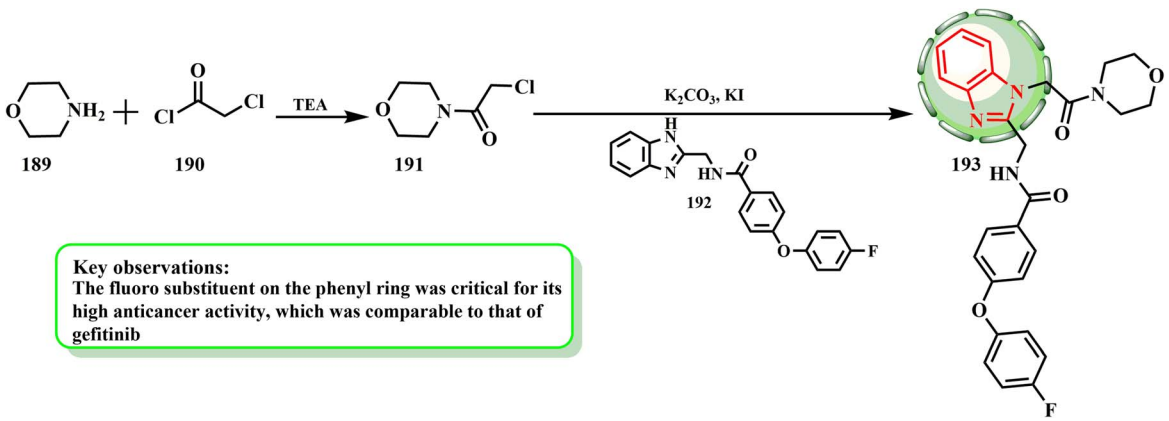
Scheme 36 Synthetic scheme for target compound **177**.



Scheme 37 Synthetic route from pyrazoles **178a** and **b** to pyrazole–benzimidazole conjugates **182a** and **b**, respectively.

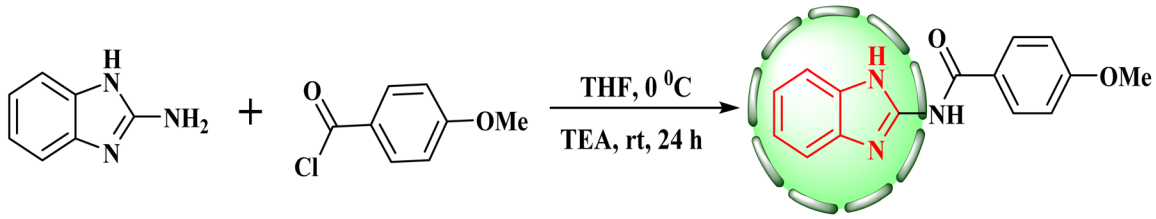


Scheme 38 Synthesis of imidazo[2,1-*b*]thiazole-benzimidazole conjugate **188**.



Scheme 39 Synthesis of designed compound **193**.

various amines **176** using the TBTU coupling reagent at ambient temperature in DMF solvent. Rasal *et al.*[83] produced a unique array of 2,4-dimethyl-1*H*-pyrrole-3-carboxamide hybrids with a 1*H*-benzimidazole moiety using the molecular hybridization approach. At a dose of 10 μM, they were tested for their anticancer activity against a variety of human cancer cell lines. Even at low concentrations, some of them demonstrated strong antiproliferative effects by functioning as VGEF inhibitors,

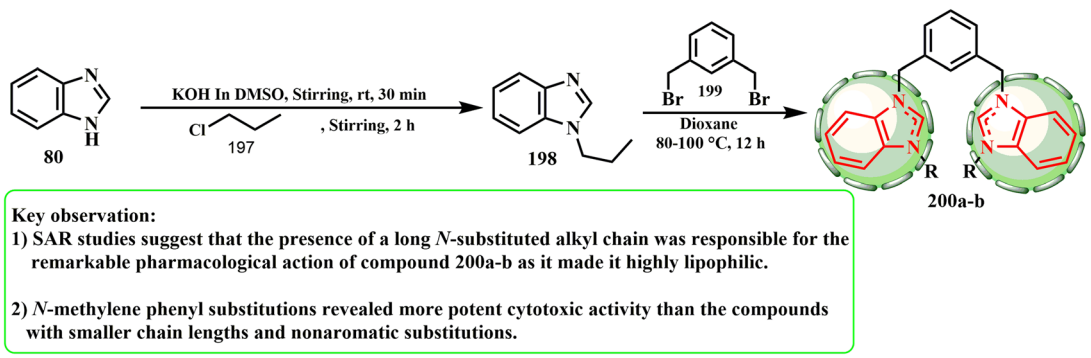


Scheme 40 Reaction of substituted benzoyl chloride with 2-aminobenzimidazole.

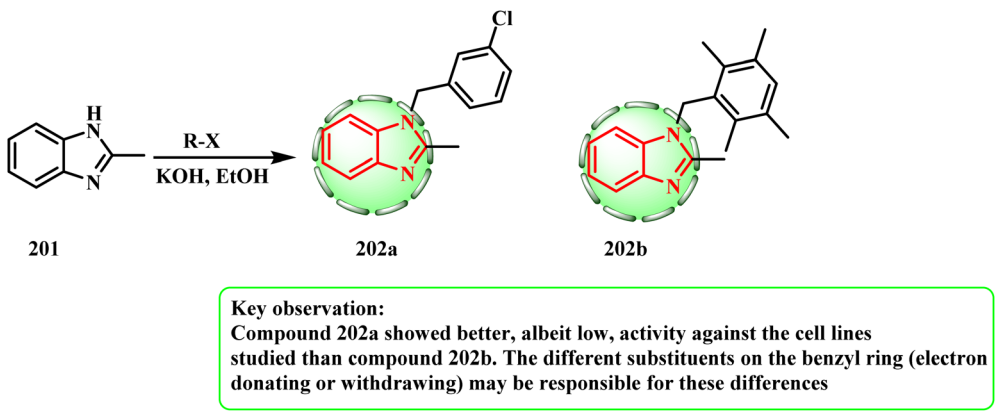
whereas compound **177**, or 5-(1*H*-benzo[*d*]imidazol-2-yl)-*N*-(1-cyclohexylethyl)-2,4-dimethyl-1*H*pyrrole-3-carboxamide, showed notable anticancer activity. According to SAR evaluations, the amide linkage had an impact on the anticancer efficacy of the compounds.

4-(5-(4-Formylphenoxy)-3-methyl-4-nitro-1*H*-pyrazol-1-yl) benzonitrile (**180b**) was obtained by reacting 4-(5-chloro-3-methyl-4-nitro-1*H*-pyrazol-1-yl)benzonitrile (**178b**) with 4-hydroxybenzaldehyde (**179**) in the presence of potassium hydroxide, DMF, and a catalytic amount of copper(I)iodide and triphenylphosphine, respectively. 4-(3-Methyl-4-nitro-5-(4-(5-nitro-1*H*-benzo[*d*]imidazol-2-yl)phenoxy)-1*H*-pyrazol-1-yl) benzonitrile (**182b**) was produced by the cyclocondensation reaction of compound **180a** and **b** with 4-nitro-1,2-phenylenediamine (**181**) in the presence of sodium thiosulphate and DMF (Scheme 37). Combining compound (**182b**) with doxorubicin was shown to greatly boost the anticancer effect of the drug and limit MCF-7 cell cycle growth.[84] According to SAR investigations, the anticancer activity of the 1*H*-benzimidazole moiety decreased when carboxylic or nitro groups were present at position 5, but it increased when a polar cyano-group was substituted for the phenyl group in the pyrazole ring at position 4.

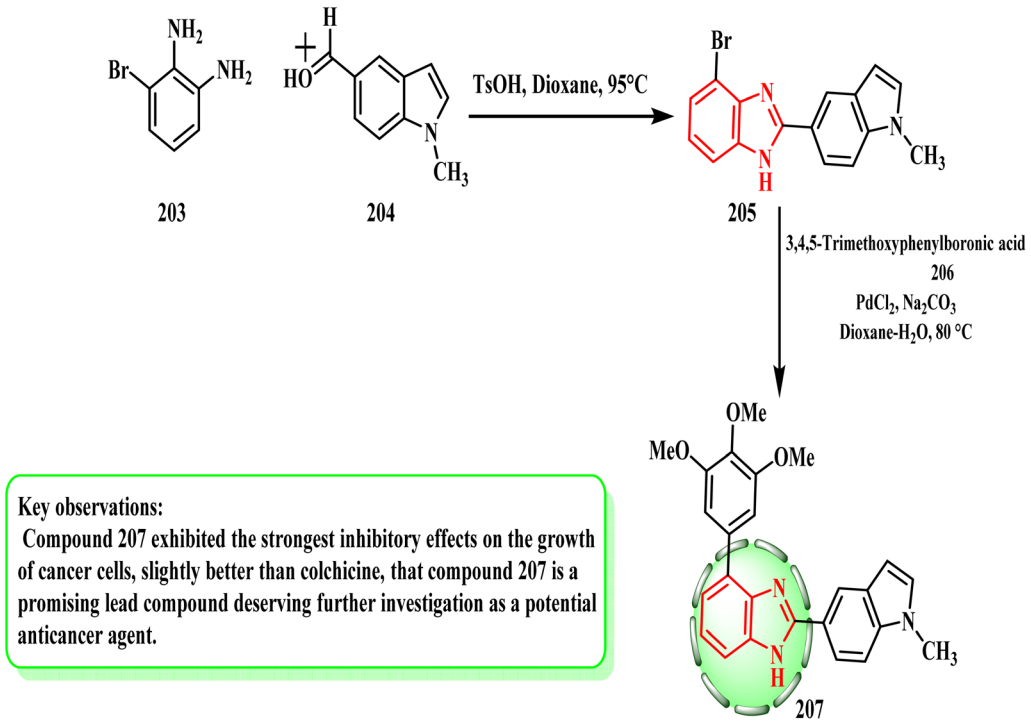
The synthesis and cytotoxic potential of imidazo[2,1-*b*] thiazole-benzimidazole conjugate **188** were examined by Baig *et al.* As illustrated in Scheme 38, imidazothiazole–



Scheme 41 Reaction representation of 1*H*-benzimidazole with propyl chloride.

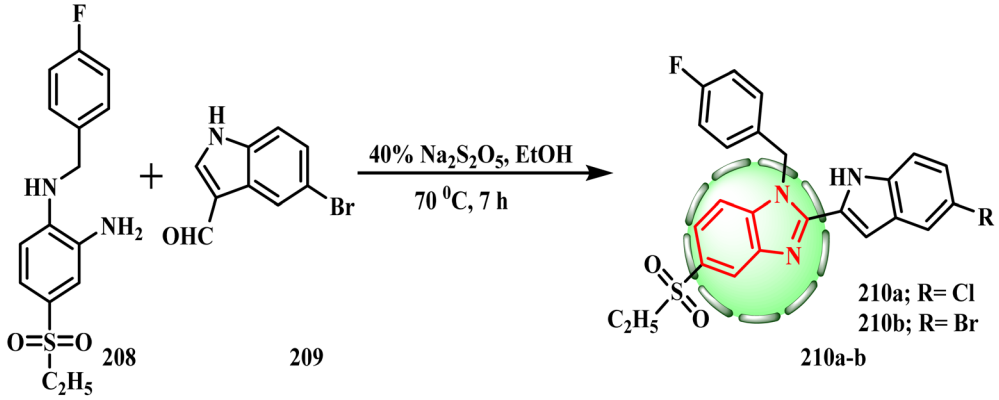


Scheme 42 Reaction of 2-methyl-1*H*-benzo[*d*]imidazole with alkyl halide.

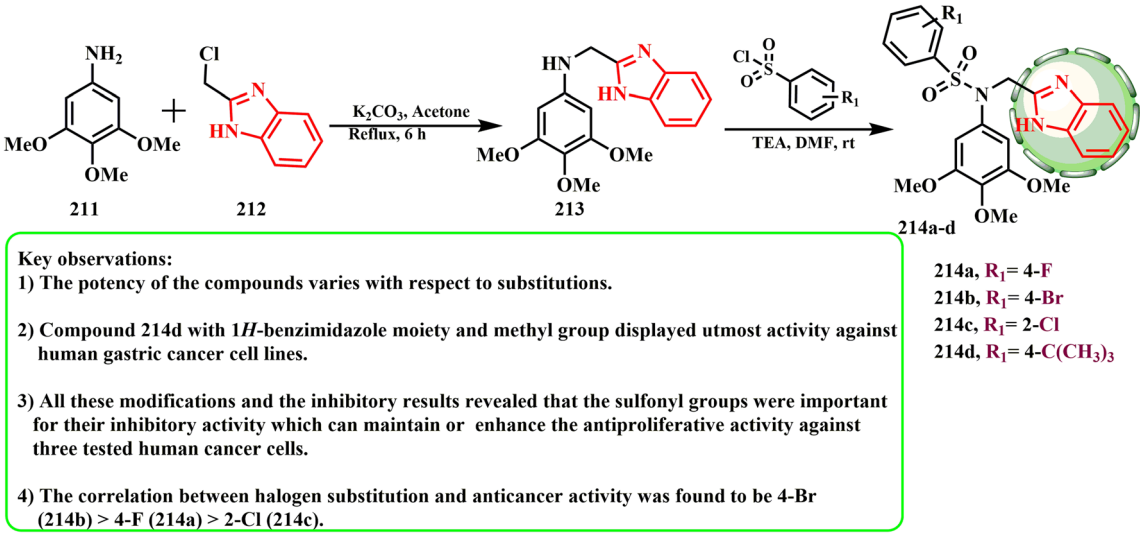


Scheme 43 Synthesis of benzimidazole derivatives 205 and 207.

benzimidazole conjugate **188** was produced by oxidatively cyclizing imidazo[2,1-*b*]thiazole-5-carbaldehyde (**186**) and substituting *o*-phenylenediamine (**187**) with sodium meta-bisulphite in ethanol. By using the Vilsmeier–Haack reaction with the equivalent imidazo[2,1-*b*]thiazole (**185**), which was derived from suitable 2-bromo-1-arylethanone **184** and 2-aminothiazole (**183**), imidazo[2,1-*b*]thiazole-5-carbaldehyde (**186**) was produced. Compound **188** (IC_{50} = 1.08 μM) showed significant cytotoxicity against the A549 cell line.[85] The cytotoxicity of conjugates containing electron-withdrawing groups as substituents, such as *p*-trifluoromethyl and *p*-methoxy



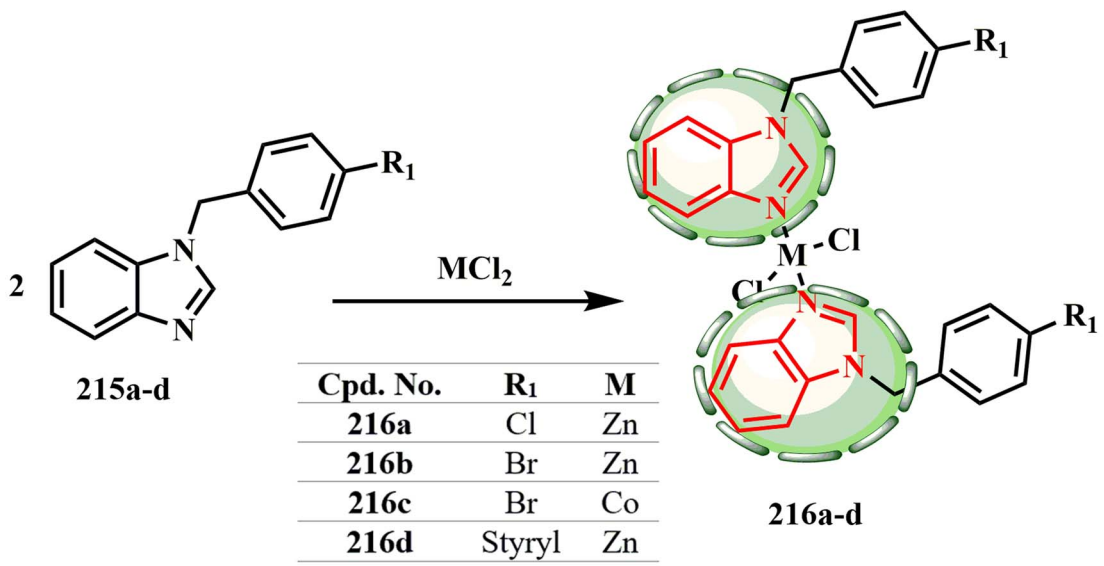
Scheme 44 Synthetic route for the preparation of benzimidazoles 210a and b.



Scheme 45 Synthesis of tertiary sulfonamide derivatives containing a benzimidazole moiety **214a–d**.

substituents, against A549 cells was demonstrated by SAR evaluations.

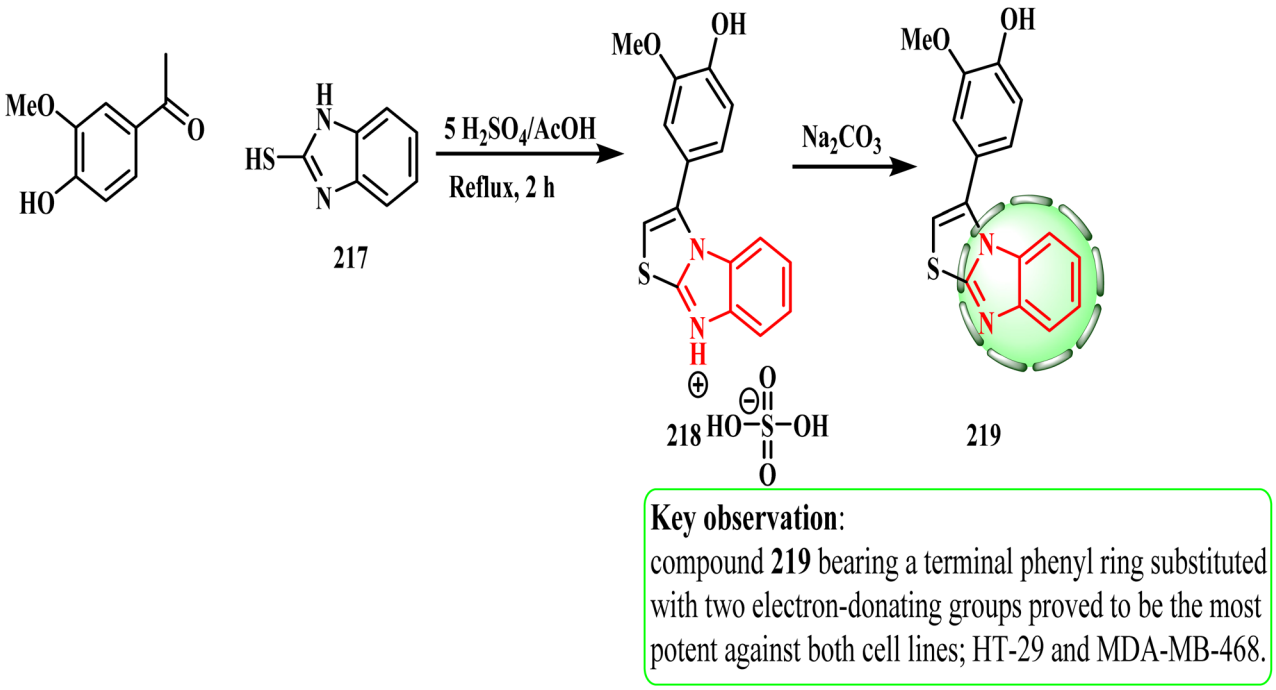
The synthesis and cytotoxic potential of 2-(aminomethyl) benzimidazole derivatives were examined by Al-Sultan *et al.* Scheme 39 states that all synthesized compounds began with amine derivative **189** and an equivalent quantity of TEA (primary amines did not use TEA). After being dissolved in 25 mL of diethyl ether and allowed to cool to 5 °C, chloroacetyl chloride (**190**) was gradually added to the mixture until the fumes stopped.[86] The antiproliferative features of the developed compounds on human breast cancer (T47D) and human alveolar cell carcinoma (A549) cells were evaluated *in vitro* using



Cpd. No.	R_1	M
216a	Cl	Zn
216b	Br	Zn
216c	Br	Co
216d	Styryl	Zn

Key observations:
1) Complex **216(a-b)** showed better anticancer activity than the standard drug docetaxel at a concentration of 0.1 μM against the A-2780 cell line.
2) The well-known zinc metal structural were found to be favorable than cobalt metal ligand with the benzimidazole skeleton for the activity against A-2780 cell line.

Scheme 46 Synthesis of benzimidazole metal complexes **216a–d**.

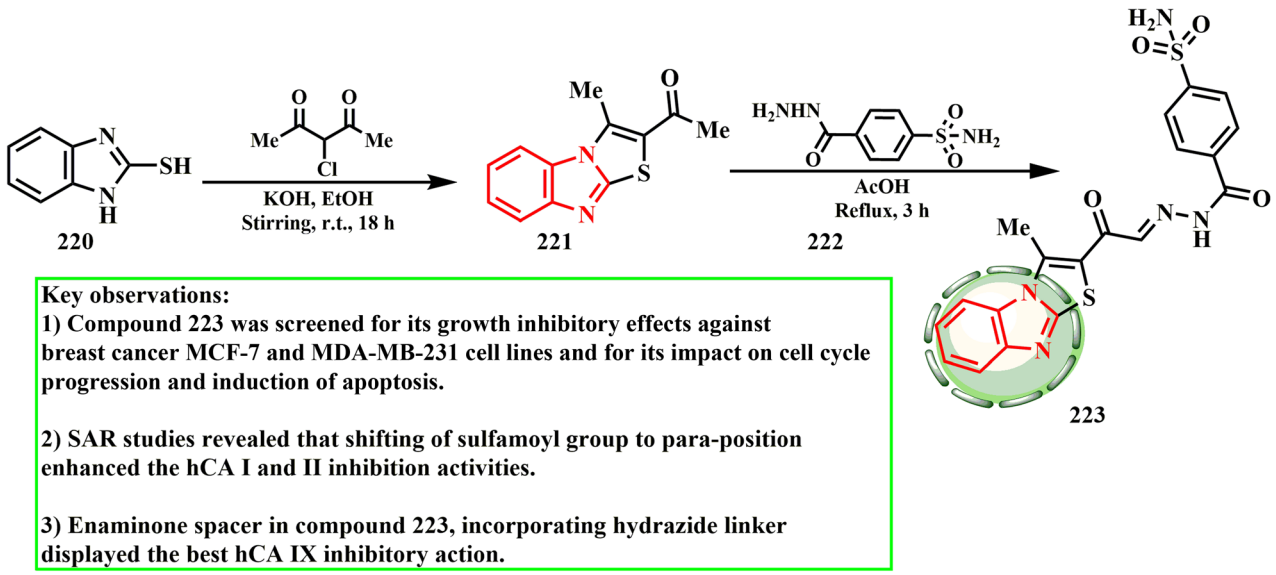


Scheme 47 Synthesis of compound phenylthiazolo[3,2-*a*]benzimidazole **219**.

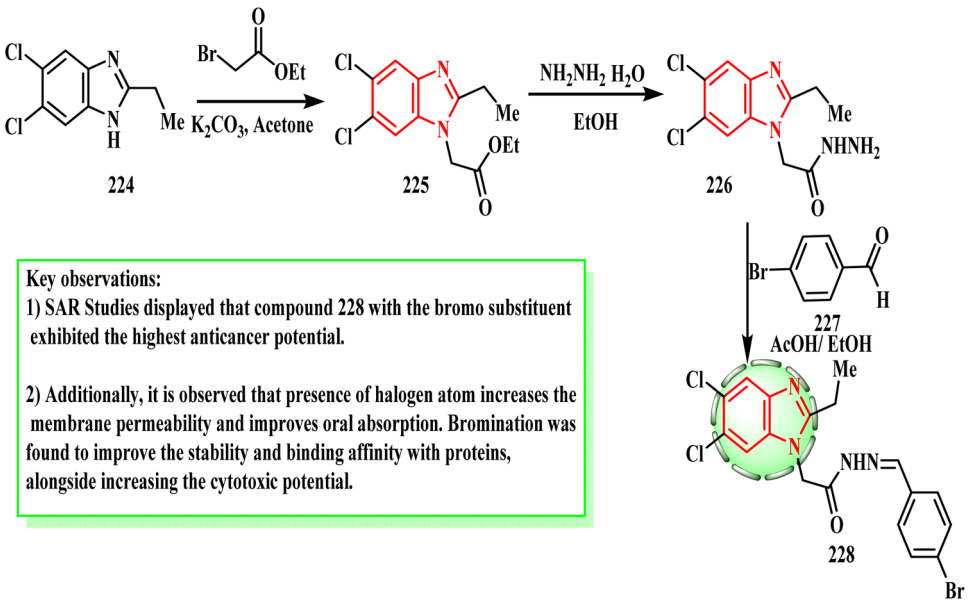
Vero cells (from the kidney of an African green monkey) as a standard control. The morphology of T47D with an inhibitory concentration of the cytotoxic chemicals, gefitinib, and the control was explained by additional research to confirm the antiproliferative effects of the extremely toxic substances (**193**) on T47D. Lastly, compounds **193** displayed IC_{50} values that were nearly identical to that of the positive control.

In THF and TEA, we used a normal reaction between substituted benzoyl chloride **195** (1.1 mmol) and 2-amino-benzimidazole (**194**) (1 mmol) (Scheme 40). *N*-(Benzimidazol-2-yl)-2-substituted benzamide structures **196** were synthesized efficiently in a single step. Interestingly, compound **196** showed the strongest anti-proliferative action against MCF-7 cancer cells ($IC_{50} = 3.84 \pm 0.62$ μM).[87]

A series of 3,3′-(1,3-phenylene(methylene))(1-alkyl-benzimidazolium)salts (**200**) was produced and characterized using the stated approach (Scheme 41).[88] We previously employed propyl chloride (**197**) as the electrophile for 1,2-(bromomethylene)benzene.[89] The method adopted for the synthesis of the title compounds was selective for the 1-position



Scheme 48 Synthesis of 3-methylthiazolo[3,2-*a*]benzimidazole-benzene sulfonamide conjugate **223**.

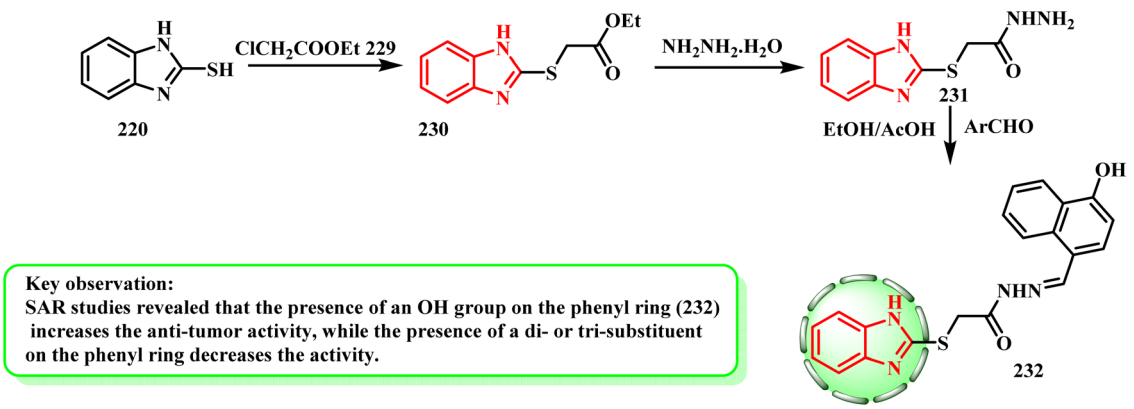


Scheme 49 Synthesis of benzimidazole derivative **228**.

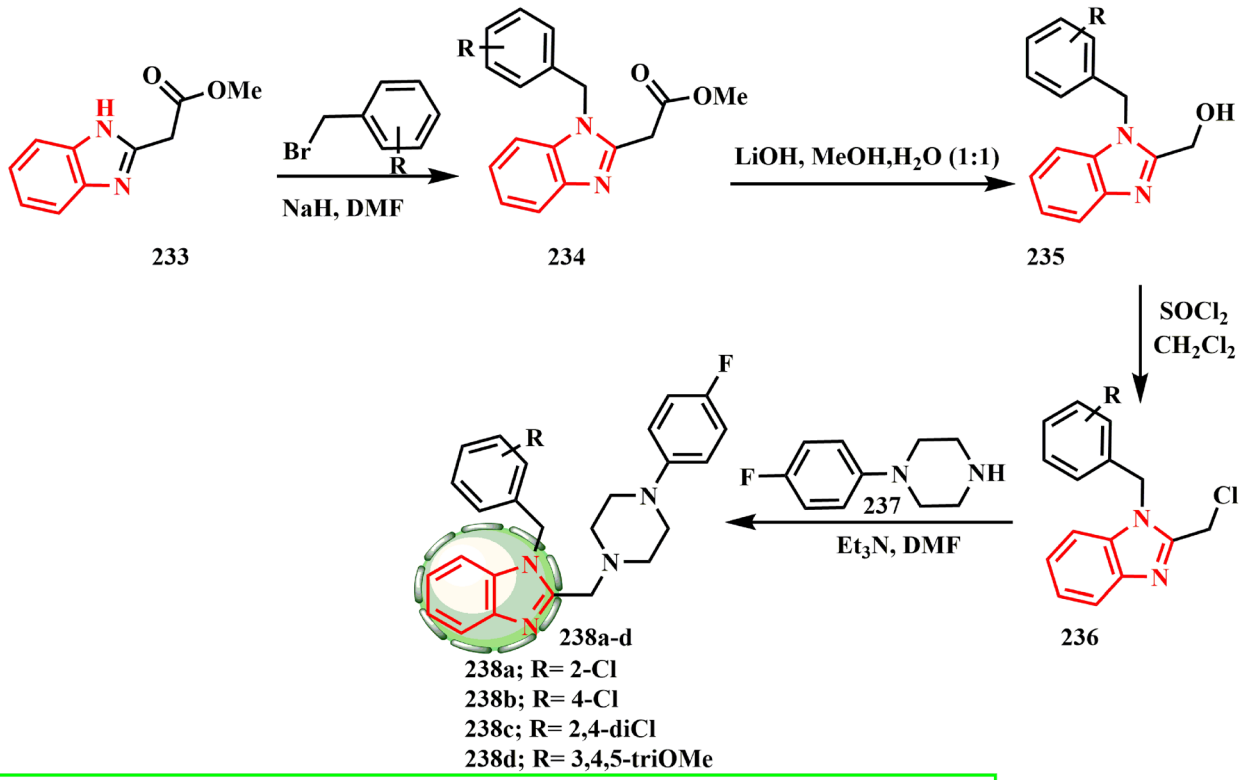
heterocycle. Indeed, upon treating alkyl benzimidazole **198** with *m*-xylyl dibromide (1,3-(bromomethylene)benzene) (**199**), the respective bisbenzimidazolium salt was observed to give **200**. ul Huda *et al.*[90] developed and produced unique 1,10-(1,3-phenylenebis(methylene))bis(3-alkyl/aryl-1*H*-benzimidazol-3-ium) salt hybrids, and using the SRB assay, evaluated their anticancer potential against the MCF-7 and HCT-116 (CRC) human breast cancer cell lines. Compound **200b** was shown to be the most effective anticancer drug overall, inhibiting the growth of HCT-116 cells with an IC_{50} of 0.1 μg mL^{-1}. According to the SAR evaluations, the notable pharmacological effect of compound **200** was caused by its lengthy *N*-substituted alkyl chain, which presented it as extremely lipophilic. Compounds with shorter chain lengths, such as isopropyl chain (**200a**) and nonaromatic replacements, exhibited less cytotoxic action than *N*-methylene phenyl (**200b**) substitutions.

The compounds were prepared in accordance with the literature[91,92] (Scheme 42). Because of its efficiency in supplying high quantities of hydroxide ions, KOH is a characteristically strong base utilized in a range of laboratory and chemical synthesis applications. For 12 h, the reaction was carried out at 80 °C. According to the results, **202a** had relatively antiproliferative efficacy against the A549, DLD-1, and L929 cell lines compared to cisplatin; however, **202b** was essentially effective against the A549 cell line. Compound **202b** has substituents with the methyl group at the 2-, 3-, 5-, and 6-positions, whereas compound **202a** has a chloro group on the benzyl ring at the 3-position. Compared to compound **202b**, compound **202a** had more advanced, albeit weaker, activity against the cell lines under investigation. The various substituents on the benzyl ring, which may either donate or withdraw electrons, could be the cause of these variations.[93]

Ren *et al.* researched the production of benzimidazole derivatives and their potential for cytotoxicity. Scheme 43 shows the preparation of compound **207**. Benzimidazole intermediates **205** were produced by cyclizing 3-bromo-1,2-



Scheme 50 Synthesis of benzimidazole derivative **232**.



Key observations:
1) Among the synthesized molecules, compound 238b showed the most balanced cytotoxic effect against lung (A-549) and breast (MCF-7) cancer cells with IC_{50} values of 4.6 and 11.0 μM, respectively.

2) A chlorine is preferred either at para position of the *N*-benzyl ring along with para fluoro in the piperazine-phenyl part (i.e. 238b), affording potent antiproliferative activity in tested tumor cells in the low micromolar range.

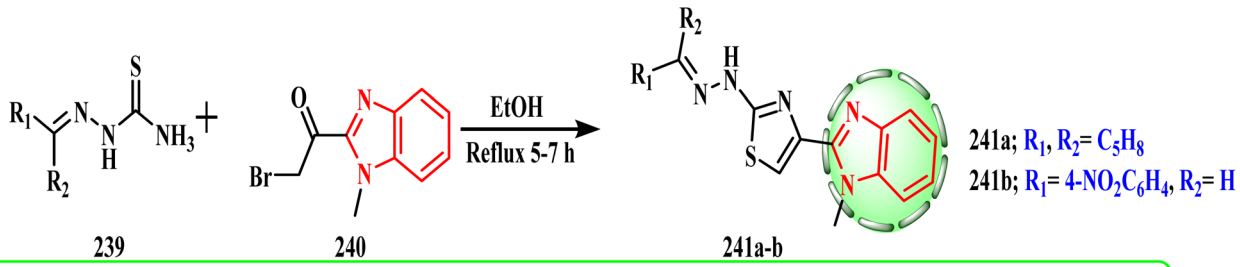
3) Additionally, the presence of bulky groups like 2,4-dichloro (238c) and 3,4,5-trimethoxy on the *N*-benzyl ring (238d) decreased the activity.

Scheme 51 Synthesis of benzimidazole derivatives 238a–d.

benzenediamine (**203**) with various aldehydes **204**. Subsequently, compound **207** was produced by the Suzuki reaction between compound **205** and 3,4,5-trimethoxyphenylboronic acid (**206**). Compound **207**, which is slightly more potent than colchicine, showed the strongest inhibitory effects on the growth of cancer cells (IC_{50} = 50 nM).[94] In melanoma tumors, compound **207** showed a 78.70% inhibition rate. Stronger hydrogen bonds and hydrophobic interactions may be the cause of the significant activity of **207**, according to the SAR evaluations.

Until the starting materials were exhausted (as determined by TLC), a combination of the proper *o*-phenylenediamine (1 mmol) (**208**), related indole derivative (1 mmol) (**209**), and $Na_2S_2O_5$ (40%) (2 mL) in EtOH (4 mL) was refluxed[95,96] (Scheme 44). Especially compound **210a** and **b** could alter the ER target gene expression, and an integrated stress response was induced in a dose-related manner.[97] The MCF-7 transcriptome was shown to be significantly influenced by compounds **210a** and **b**, which resulted in the upregulation and downregulation of an appropriate number of genes. According to the SAR investigations, the presence of an electron-withdrawing group at the indole ring and 4-fluorobenzyl at the 1*H*-benzimidazole ring demonstrated comparatively stronger anticancer effects. Furthermore, the lipophilic characteristic of the indole moiety was improved by the presence of –Br, which facilitated effective binding.

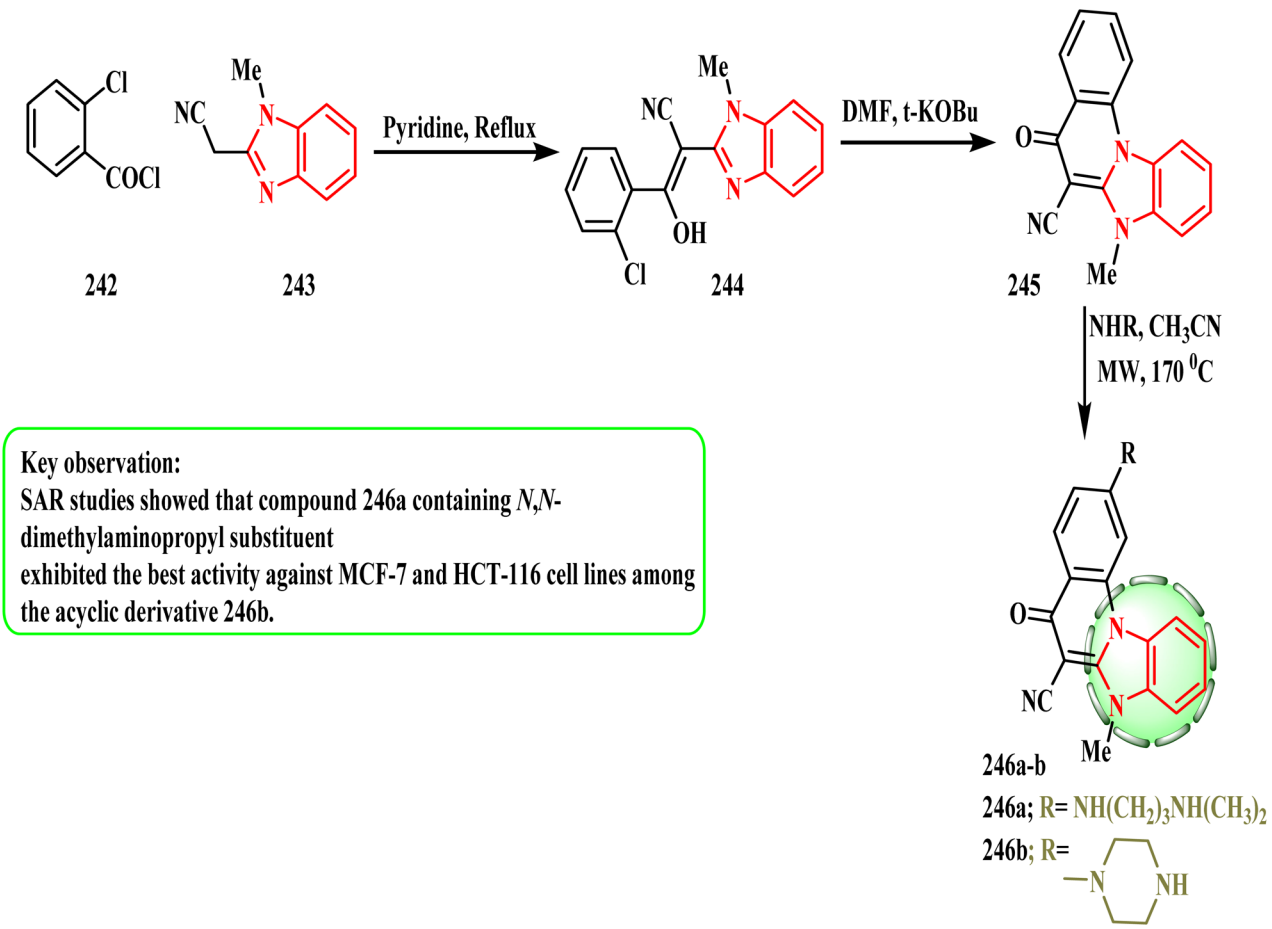
The synthesis and cytotoxic potential of tertiary sulfonamide derivatives with a benzimidazole moiety were examined by Gao *et al.* Benzyl chloride **212** and 3,4,5-trimethoxyaniline (**211**) interacted in the presence of K_2CO_3 in acetone to give secondary amine **213**, which reacted with different benzene sulfonyl chloride derivatives **37** to obtain tertiary sulfonamide



Key observations:
1)Furthermore, the cyclopentyl 241a derivative was less likely to inhibit the viability of the cancer cells than erlotinib.

2) SAR studies suggested that when 4-nitrophenyl 241b was replaced with cyclopentyl (as in compound 241a) there was a significant reduction in the potency. It was also observed that reduction in the polarity of molecules and increase in the bulkiness of the substituent decreased the effectiveness of the tested compound i.e.241a>241b.

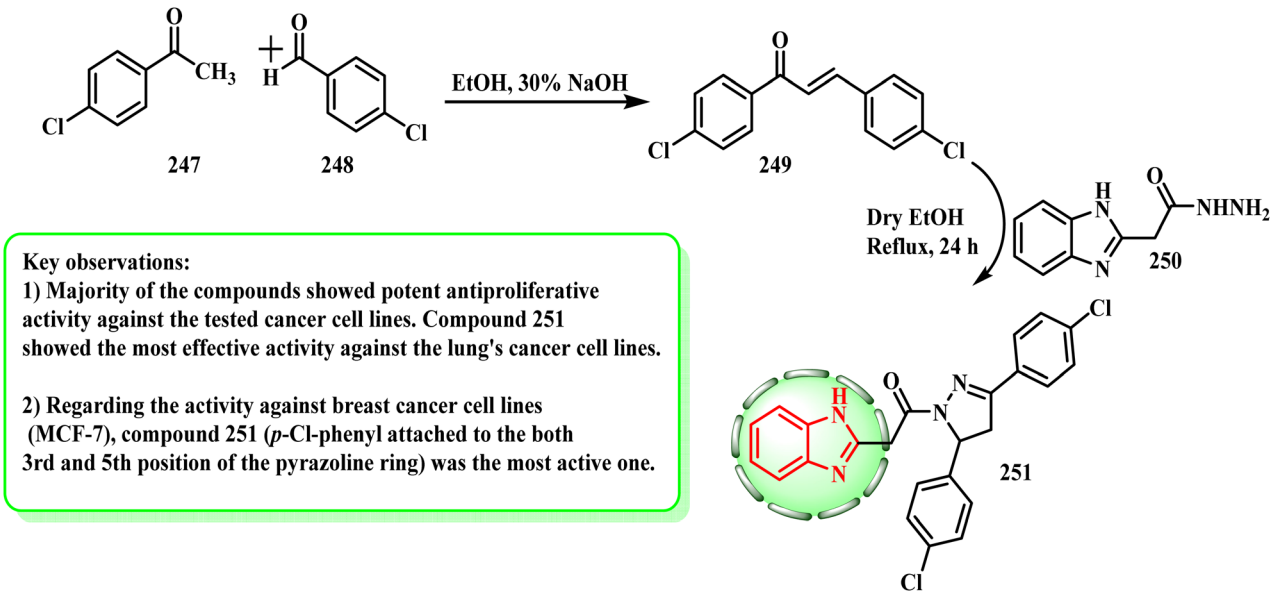
Scheme 52 Route for constructing the target thiazolo–benzimidazole hybrids **241a** and **b**.



Key observation:
SAR studies showed that compound 246a containing *N,N*-dimethylaminopropyl substituent
exhibited the best activity against MCF-7 and HCT-116 cell lines among the acyclic derivative 246b.

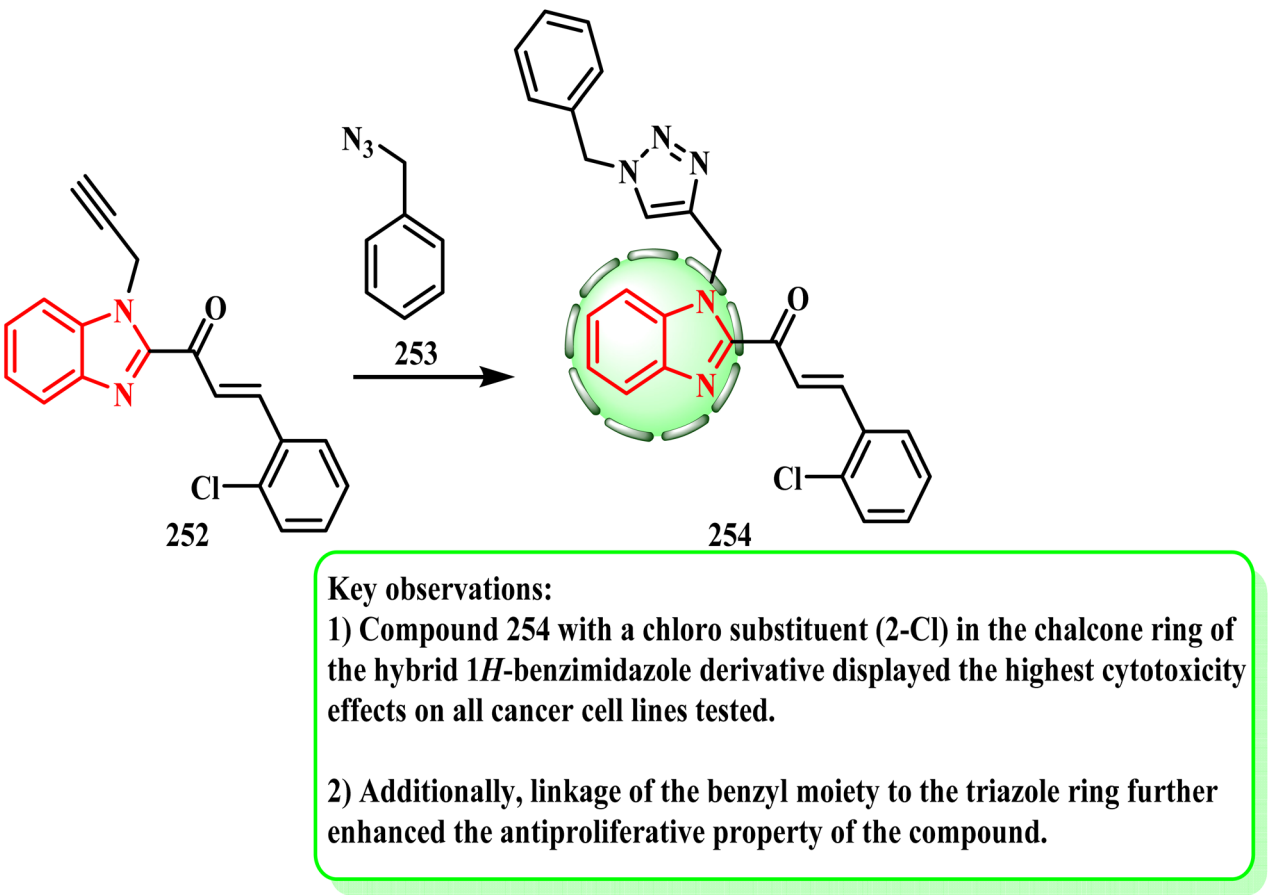
Scheme 53 Synthesis of new fused benzimidazole analogues **246a** and **b**.

derivatives **214a–d** (Scheme 45). MGC-803 cells were more sensitive to compounds **214a–d** than PC-3 and MCF-7 cells. Among the compounds that had notable antiproliferative activity, compound **214b** demonstrated the strongest anticancer activity against MGC-803 cells (IC_{50} = 2.19 μM).[98] The presence of a 3,4,5-trimethoxy group at the phenyl ring was crucial for the anticancer actions according to the SAR evaluations. The most effective compound against human stomach cancer cell lines

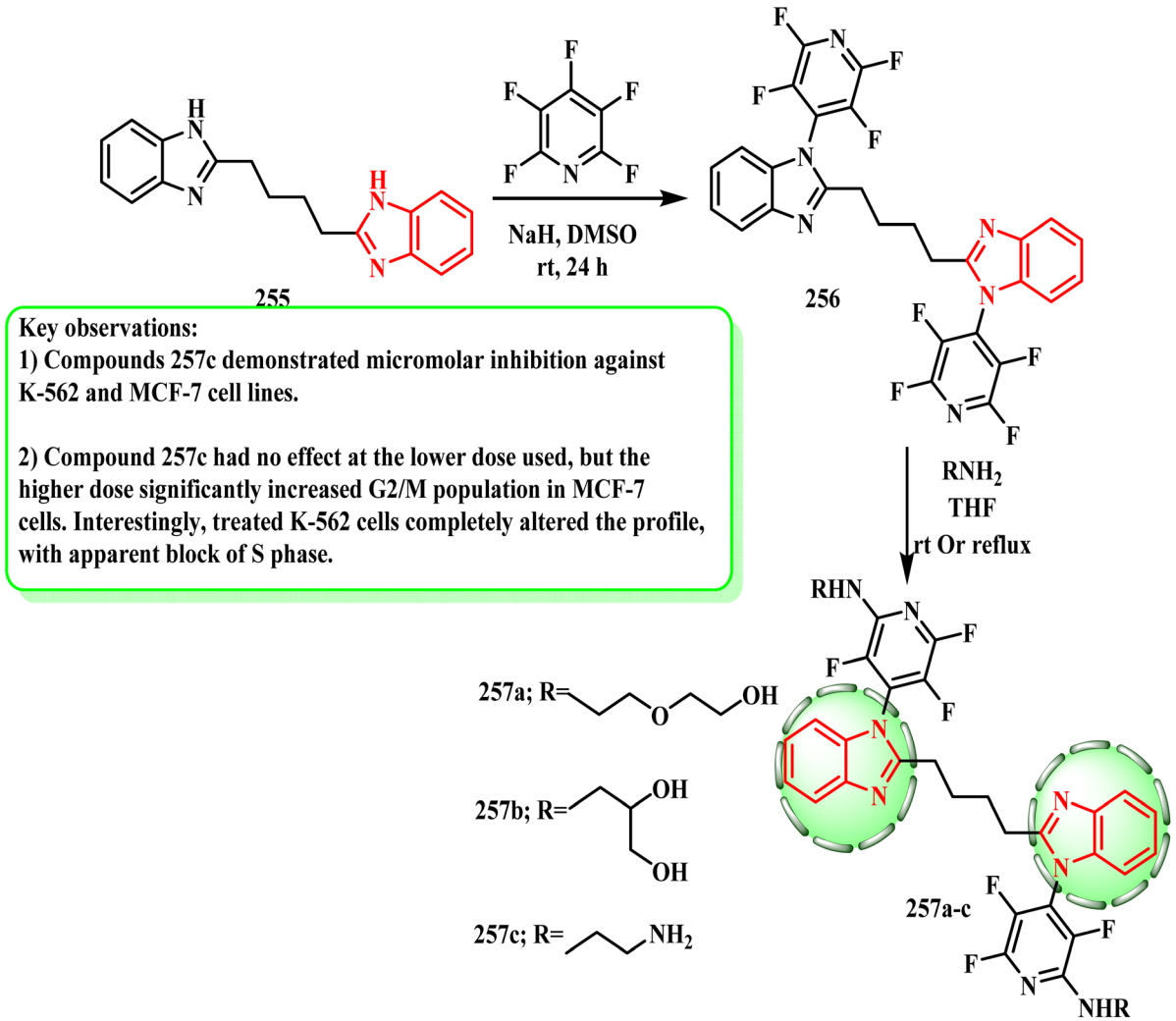


Scheme 54 Synthesis of benzimidazole–bearing pyrazole derivative **251**.

was compound **214d**, which had a methyl group and a 1*H*-benzimidazole moiety. 4-Br (**214b**) > 4-F (**214a**) > 2-Cl (**214c**) was the association between halogen substitution and anticancer efficacy. The sulfonyl groups were crucial for their inhibitory effect, which can maintain or improve the antiproliferative activity against the three tested human cancer cells, according to all the reported changes and inhibitory findings.



Scheme 55 Reaction between the azide derivative **253** and propargyl molecule **252**.

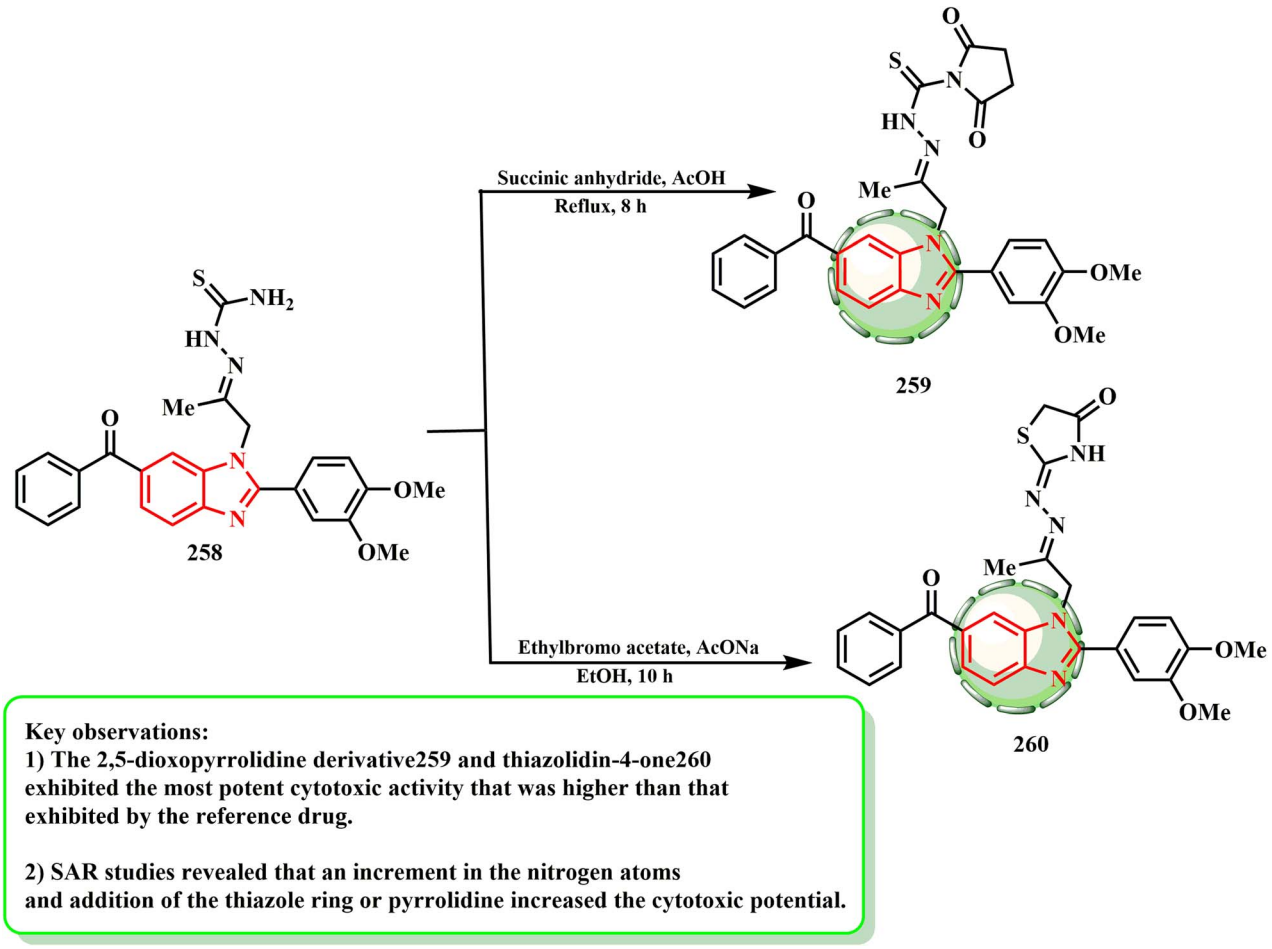


Scheme 56 Synthesis of different fluoroaryl benzimidazole derivatives **257a–c**.

The production and cytotoxic potential of new benzimidazole ligands and their cobalt(II) and zinc(II) complexes were examined by Yılmaz *et al.* $ZnCl_2 \cdot 6H_2O$ or $CoCl_2$ in EtOH was used to produce benzimidazole complexes **216a–d** from benzimidazole ligands (**215a**, **215b**, and **215c**). Ligands of benzimidazoles **215a** (ref. 99) and **215b** (ref. 100) were produced using the methods outlined in the literature. In this work, the Mizoroki–Heck reaction was used to synthesize benzimidazole ligand **215d** for the first time, similar to the literature technique[101,102] (Scheme 46). Compounds **216a–d** ($\log IC_{50} = -0.97$, -1.30, 1.13, and -0.73 μM, respectively) were identified to have higher anticancer potency than the standard docetaxel medication ($\log IC_{50} = -0.81$ μM) against the A-2780 cell line at 0.1 μM concentration.[99]

Scheme 47 shows the route for the preparation of target compound **219** in this work. Acetophenone and 2-mercaptobenzimidazole **217** reacted in refluxing acetic acid with five equivalents of sulphuric acid to produce sulphate salt **218** in a one-pot, two-component heterocyclization process. Phenylthiazolo[3,2-*a*]benzimidazole **219** was obtained by neutralizing sulphate salt **218** by stirring with an aqueous solution of sodium bicarbonate. HT-29 (colon) and MDA-MB-468 (breast) cancer cell lines were used to investigate the cytotoxic potential of synthetic compound **219**. CD133 inhibition in cancer stem cells and the cytotoxicity of specific 3-phenylthiazolo[3,2-*a*]benzimidazoles including their design, direct synthesis, and *in vitro* biology were investigated.[103] Compound **219** decreased the surface expression of CD133 on cells by 50% and showed strong anticancer activity against both cancer cell lines with IC_{50} values of 9 and 12 μM, respectively. According to the SAR investigation, the electron-donating group in the phenyl ring of **219** enhanced the suppression of tumor cells.

However, employing 3-chloro-2,4-pentanedione, the acetyl thiazolo[3,2-*a*]benzimidazole derivative (**221**) was constructed as previously described for the mercaptan alternative **220**. The target **223** was obtained, as shown in Scheme 48, by condensing the acetylthiazolo[3,2-*a*]benzimidazole derivative (**221**) with 4-(hydrazinecarbonyl)benzene sulfonamide (**222**) in acetic acid. Compound **223** was found to induce cell cycle arrest and death and exhibit prospective proliferation inhibition against the MCF-7 and MDA-MB231 breast cancer cell lines.[104] According to the SAR investigations, the hCA I and II inhibitory activities



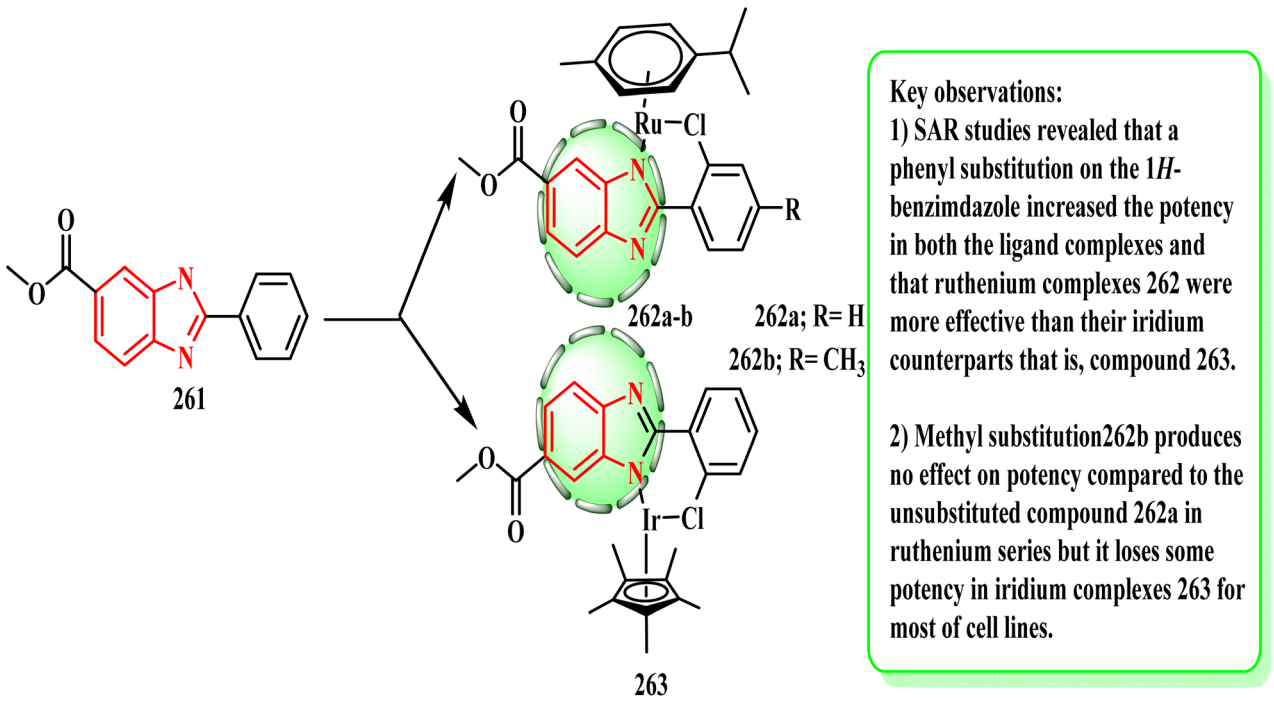
Scheme 57 Reaction representative of benzimidazole with different reagents.

were improved by moving the sulfamoyl group to the *para*-position. Compound **223**, which has a hydrazide linker and an enaminone spacer, exhibited the highest hCA IX inhibitory activity.

The synthesis and cytotoxic potential of benzimidazole derivatives were examined by Atmaca *et al.* By first reacting the amino group of **224** with ethylbromo acetate to produce ethyl [5,6-dichloro-2-ethyl-1*H*-benzimidazol-1-yl]acetate (**225**), the intended powerful derivative **228** was synthesized. Subsequently, compound **226** was produced by reacting acetate derivative **225** with hydrazine hydrate in ethanol. Finally, the desired hybrid molecule **228** was produced by the successful condensation of the nucleophilic nitrogen with the substituted aromatic aldehyde **227** (Scheme 49). Compound **228** was found to exhibit a potential cytotoxic effect against the MCF-7 (IC_{50} = 17.8 ± 0.24 μg mL^{-1}), DU-145 (IC_{50} = 10.2 ± 1.4 μg mL^{-1}), and H69AR (IC_{50} = 49.9 ± 0.22 μg mL^{-1}) cancer cell lines.[105] Compound **228** with a bromo substituent showed the strongest anticancer potential and may be a promising anticancer treatment drug according to the SAR investigations. Furthermore, it was noted that the presence of halogen atoms enhanced its oral absorption and increased its membrane permeability. It was discovered that bromination increased the cytotoxic potential, while also improving the stability and protein binding affinity.

The synthesis of benzimidazole derivatives was reported by Yadav *et al.*[106] By first esterifying mercaptan derivative **220** with ethyl chloroacetate (**229**) to produce acetate **230**, the desired derivative **232** was synthesized. After that, **230** was subjected to hydrazinolysis reaction with hydrazine hydrate to yield **231**. Lastly, the Schiff base reactionof acetohydrazide **231** with aromatic aldehyde gave **232** (Scheme 50). Yadav *et al.*[106] established a novel series of 1*H*-benzimidazole compounds and tested their anti-proliferative properties *in vitro*. When tested against the MCF-7 cell line, compound **232** (IC_{50} = 0.0013 μM) was found to be a more effective anti-cancer therapeutic candidate than 5-fluorouracil. According to the SAR investigations, the anti-tumor activity increased when an OH group was present on the phenyl ring and decreased when a di- or tri-substituent was present.

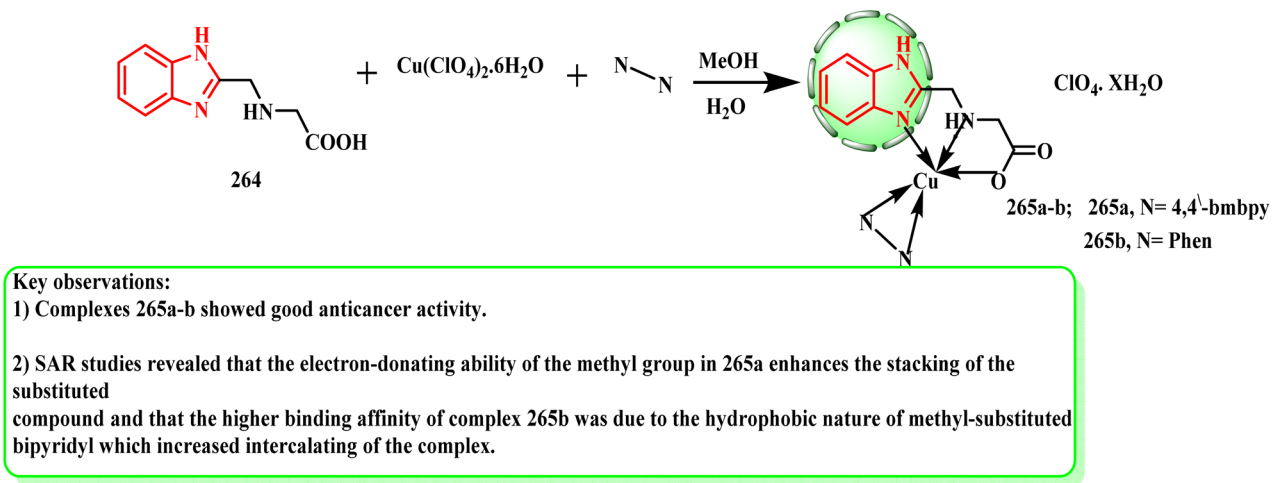
Using the well-known general techniques, compounds **238a–d** were produced in accordance with the reaction sequence shown in Scheme 51. Thus, using established techniques, 2-acetyloxymethylbenzimidazole (**233**), which was produced by acetylating 2-hydroxymethylbenzimidazole,[107] was converted into *N*-benzylated derivatives **234** by treating it with substituted benzyl halides in the presence of a base. *N*-Benzyl-2-hydroxymethylbenzmidazoles **235** were produced by hydrolyzing intermediates **234** in aqueous alkali, and they then



Scheme 58 Generalized process to synthesize benzimidazole complex **262a** and **b** and **263**.

reacted with thionyl chloride to form alkyl chlorides **236**. To obtain the target compounds **238a–d**, intermediate alkyl chlorides **236** were finally treated with the relevant phenylpiperazine derivatives **237**. Özdemir *et al.*[108] developed and produced a unique range of 1*H*-benzimidazole-piperazine hybrids, and then tested them against two human cancer cell lines (MCF-7 and A549) to determine whether they have antiproliferative properties. Compound **238b** demonstrated the most potent cytotoxicity (IC_{50} = 11.0 μM against MCF-7 cells and 4.6 μM against A549 cells). A mono-chloro substituent on the *N*-benzyl ring at the *ortho*- (**238a**) or *para*-positions (**238b**) increased the potency against the A549 cell line, according to the SAR evaluations. Furthermore, the activity was reduced when large groups such as 3,4,5-trimethoxy and 2,4-dichloro (**238c**) were present on the *N*-benzyl ring (**238d**).

Scheme 52 showed the synthesis methods used for constructing the target thiazol–benzimidazole hybrids **241a** and **b**. Thiosemicarbazone **239** (ref. 109–113) with 2-bromo-1-(1-methyl-1*H*-benzo[*d*]imidazo-2-yl)ethan-1-one (**240**) in refluxing ethanol[114,115] afforded the corresponding targeted 2-(2-(substituted)hydrazinyl)-4-(1-methyl-1*H*-benzo [*d*]imidazol-2-yl) thiazole derivative[116] **241a** and **b**. Compound **241a** revealed strong cytotoxic activity by EGFR TK inhibition[117] (IC_{50} = 109.71 nM)[109] as well as an anti-breast cancer agent.[118,119] SAR evaluations of this study revealed a notable decrease in potency when 4-nitrophenyl **241b** was substituted with cyclopentyl (as in



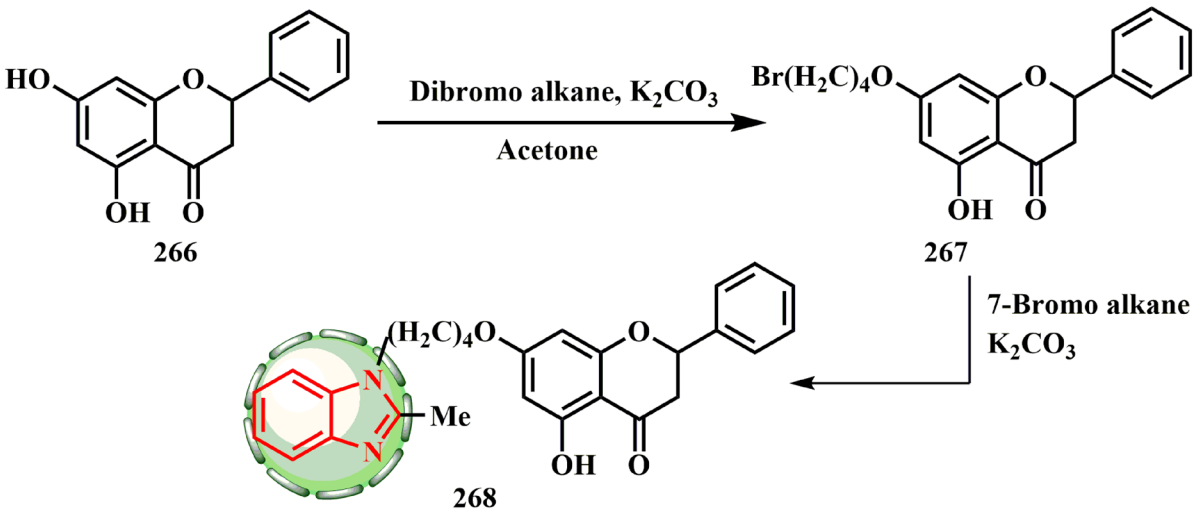
Scheme 59 Reaction representative of benzimidazole with BIGH ligand.

compound **241a**). Additionally, it was found that the efficacy of the tested drug was reduced when the polarity of the molecules decreased and the bulkiness of the substituent increased.

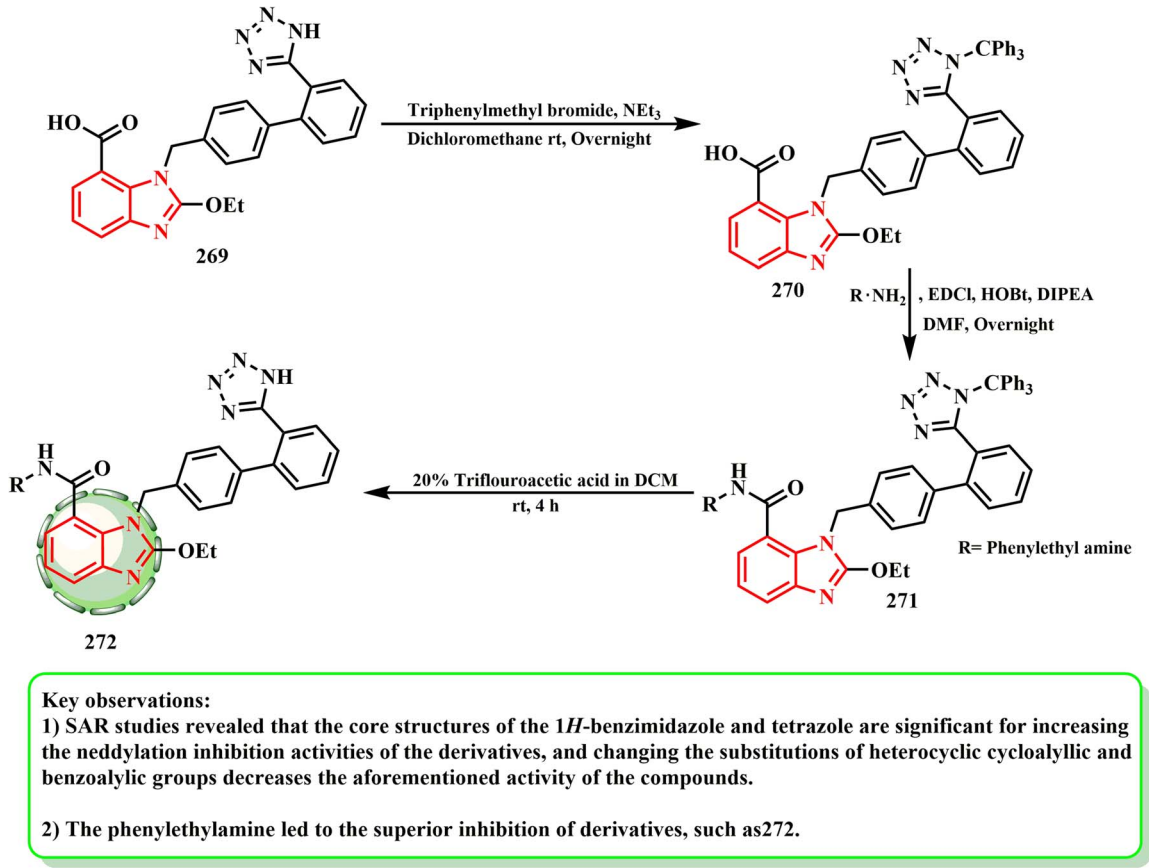
Subsequently, compound **245** was converted into the intended 2-amino-substituted analogues **246a** and **b** in the reaction with an excess of the appropriate amine microwave irradiation utilizing the previously disclosed optimized reaction conditions[120,121] (Scheme 53). Perin *et al.*[122] produced amino-substituted *N*-methylated-benzimidazo[1,2-*a*]quinolines and tested them against human cancer cell lines *in vitro* to determine if they had any anti-proliferative properties. Two of the strongest substances, **246a** and **246b**, were specifically active against the HCT-116 cancer cell line, causing cell death and a reduction in the proportion of cells in the S phase (IC_{50} values of 0.2 and 0.4 μM, respectively). Between the acyclic derivatives, compound **246a** with the *N*,*N*-dimethylaminopropyl substituent demonstrated stronger efficacy against the MCF-7 and HCT-116 cell lines, according to the SAR evaluations.

Scheme 54 lists the synthetic pathways for the synthesis of **251**. Substituted benzaldehyde **248** and acetophenone **247** were chosen and stirred in a pure form in 30% NaOH to produce chalcone **249**. Intermediate compound **250** with compound **249** under reflux in absolute ethanol could be readily converted into the final compound **251**.[123] By causing cell cycle arrest in the G2/M phase and apoptosis by binding to active pockets of EGFR (IC_{50} = 0.97 μM), compound **251** demonstrated encouraging growth inhibition on the A549 cell line (IC_{50} = 2.2 μM).[124] Additional research revealed that the effectiveness of compound **251** is attributed to its chloro atom at the 4-position of the phenyl substituent connected to C3 and C5 of the pyrazoline ring.

Therefore, the reaction between the pre-synthesized azide derivative **253** and propargyl molecule **252** (ref. 125 and 126) produced a structural alternative of 1,2,3-triazole–benzimidazole–chalcone hybrid **254** (Scheme 55) by using dichloromethane/water (1 : 1) as the solvent solution, catalyzed by $CuSO_4 \cdot 5H_2O$ and sodium ascorbate at room temperature. On all the chosen cancer cell lines, hybrid **254** with the chloro-substituent (2-Cl) demonstrated the strongest cytotoxic effect.[127] Compared to doxorubicin, the most active compound, **254**, was almost fourfold less active in MDA-MB-231 cells, forty-eight times less active in T47-D cells, and fifteen-fold less active in PC-3 cells. The documented chloro-substituted benzimidazole–triazole hybrids were already demonstrated to have good cytotoxic effects against mouse embryonic fibroblast cell lines NIH/3T3 (IC_{50} 1.63 μM) according to their structure–activity-relationship (SAR).[128] Additionally, the SAR showed that the inclusion of chloro-substituents in the chalcone ring increased the cytotoxic effect of the hybrid 1*H*-benzimidazole derivative against the PC-3, MDA-MB-231, and T47-D cell lines. Furthermore, the antiproliferative properties of the compound were



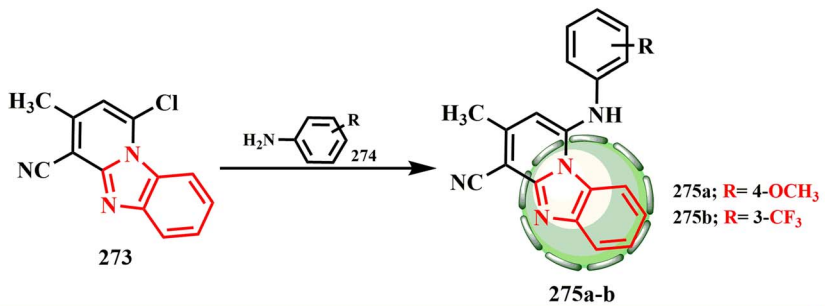
Scheme 60 General synthesis of compound **268**.



Key observations:
1) SAR studies revealed that the core structures of the 1*H*-benzimidazole and tetrazole are significant for increasing the neddylation inhibition activities of the derivatives, and changing the substitutions of heterocyclic cycloalyllic and benzoalylic groups decreases the aforementioned activity of the compounds.

2) The phenylethylamine led to the superior inhibition of derivatives, such as272.

Scheme 61 Preparation of derivative 272.



Key observations:
1) Compound 275b exhibits potent cytotoxic activity against the UACC-62 and breast cancer BT-549 cancer cells lines due to the impact of the lipophilic trifluoromethyl substitution on the biological activity profile. .

2) The well-known 4-methoxy structural setting on the pyrido[1,2-*a*]benzimidazole skeleton 275a was found to be showed different cytotoxic profiles.

Scheme 62 Synthesis of pyrido benzimidazole derivatives 275a and b.

further strengthened by the attachment of a benzyl moiety to the triazole ring.

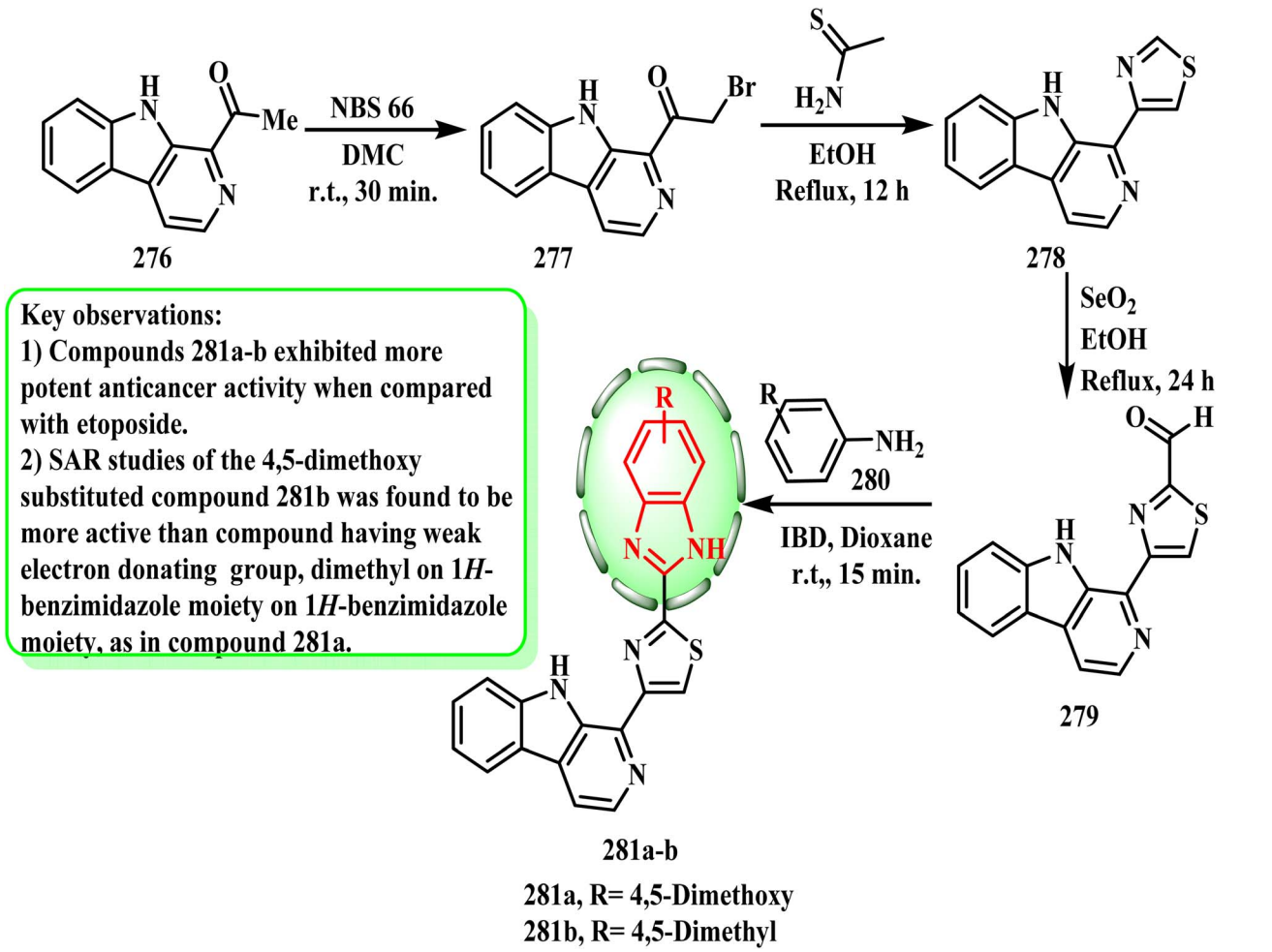
In the tetrafluoropyridine rings (**256**), the amines all reacted at the next most electrophilic site, adding to C-2 to create aminopyridine derivatives **257a–c** (ref. 129) (Scheme 56), adding to C-2, forming aminopyridine derivatives **257a–c** (Scheme 56). Bhambra *et al.*[45] established a library of fluoroaryl benzimidazole derivatives **257a–c**, which showed micromolar inhibition against the K-562 and MCF-7 cell lines. The product obtained by adding ethylenediamine **257c** was considerably less active against G361 and HOS, but exhibited good activity against two other cell lines. According to reports, compounds **257a** and **257c**

activate caspases, which are crucial for the death of cancer-causing cells.

An effective intermediary for the subsequent synthesis of various benzimidazole-heterocyclic compounds was thiosemicarbazone analogue **258**. Thus, 2,5-dioxopyrrolidine derivative **259** was formed by the condensation of **258** with various acid anhydrides, such as succinic anhydride in acetic acid. Additionally, thiazolidinone derivative **260** was produced by cyclizing **258** with a haloketone, such as ethyl bromoacetate (Scheme 57). Abd El-Meguid *et al.*[130] established a novel series of 1*H*-benzimidazole compounds, which were evaluated against the HeLa cell line using doxorubicin as the standard medication. The compounds with the strongest anti-cancer activity against the HeLa cell line were **259** (1.62 ± 0.16 μM) and **260** (1.44 ± 0.06 μM). According to the SAR evaluations, the cytotoxic potential was enhanced by an increase in nitrogen atoms and presence of pyrrolidine or thiazole rings.

The generalized process illustrated in Scheme 58 was used to synthesize each of the ruthenium compounds. The analogue of ruthenium metal complex **262a** was obtained by treating benzimidazole ligand **261** with *para*-cymene ruthenium(II) [(*p*-cymene)$RuCl_2]_2$ and sodium acetate in dichloromethane for 24 h at room temperature. Pentamethylcyclopentadienyl chlorido iridium(III) was the starting point for the preparation of half-sandwich iridium(III) complexes **263**. Yellol *et al.*[131] established a variety of novel iridium(III) **263** and ruthenium(II) **262a** and **b** *C*,*N*-cyclometalated benzimidazole complexes. The A2780 (ovary), 5637 (bladder), SISO (uterine cervical), and HT29 (rectal) human cancer cell lines were used to investigate their cytotoxicity. In the active hy926 (umbilical vein endothelial) human cell line, certain complexes were anti-angiogenic and triggered apoptosis by enhancing caspase-3 at a concentration of 0.5 μM. In contrast to their respective ligands, the metal complexes exhibited noticeably higher cell growth inhibitory rates. According to the SAR evaluations, ruthenium complex **262a** was more potent than its iridium counterpart, compound **263**, where a phenyl substitution on the 1*H*-benzimdazole enhanced the potency in both ligand complexes.

The ligand BIGH was produced using a well-known process[132] (Scheme 59). By using DOX according to the MTT assay, the produced complexes were tested for their pro-apoptotic and anticancer effectiveness against the normal HEK293 (embryonic kidney), HeLa (cervical), MCF-7 (breast), and A549 human cancer cell lines.[133] The produced complexes exhibited a moderate level of activity against the A549, HeLa and MCF-7 cancer cell lines. All the evaluated cancer cell lines were successfully inhibited by



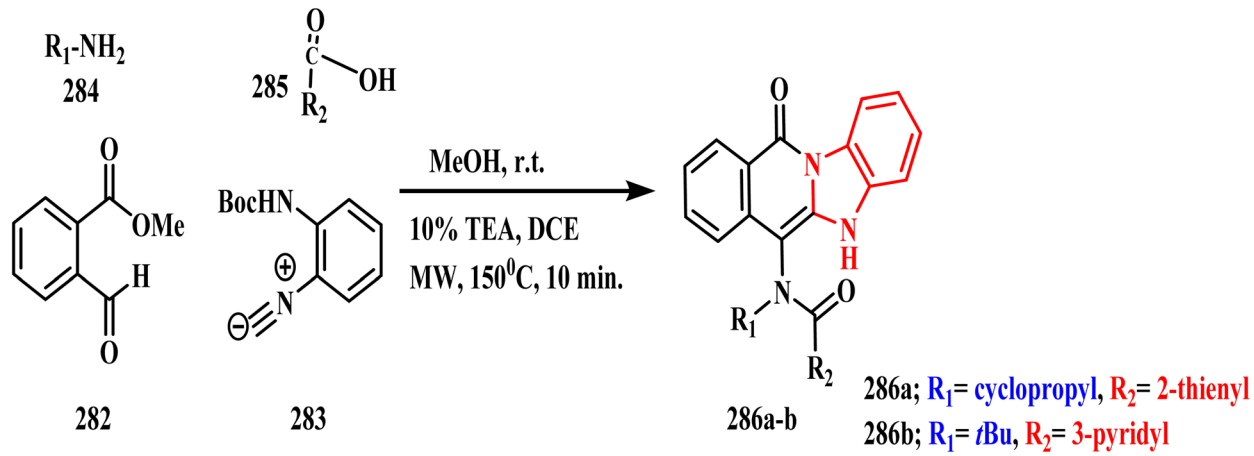
Scheme 63 Synthesis of benzimidazole analogous **281a** and **b**.

complexes **265a** (IC_{50} HeLa = 36.70 ± 0.073 μM; IC_{50} MCF-7 = 43.20 ± 0.048 μM; and IC_{50} A-549 = 51.30 ± 0.018 μM) and **265b** (IC_{50} HeLA = 45.85 ± 0.031 μM; IC_{50} MCF-7 = 51.30 ± 0.083 μM; and IC_{50} A549 = 32.30 ± 0.052 μM), respectively. The SAR studies indicate that the hydrophobic nature of the methyl-substituted bipyridyl contributed to the higher binding affinity of complex **265b** by increasing its intercalation, whereas the electron-donating capacity of the methyl group in complex **265a** enhanced the stacking of the substituted molecule.

The synthesis and cytotoxic potential of chrysin-benzimidazole derivatives were examined by Wang *et al.*[134] By first reacting the hydroxy group of **266** with dibromo alkane to yield **267**, the most powerful derivatives were synthesized. The essential hybrid molecule **268** was later produced by reacting bromide derivative **267** with benzimidazole in acetone (Scheme 60). Wang *et al.*[134] established a novel variety of chrysin-1*H*-benzimidazole compounds and tested them against the MFC cell line to see if they may be used as anti-carcinogenic agents. Compound **268** was determined to be the most promising antiproliferative drug among the derivatives (IC_{50} = 25.72 ± 3.95 μM), causing MFC cells to undergo apoptosis and inhibiting the progression of the cell cycle in the G0/G1 phase in a dose-dependent manner. According to the SAR evaluations, the compounds with a methyl substituent at the 1*H*-benzimidazole ring 2-position had enhanced inhibitory efficacy compared to those with that at the 5- or 6-position of the ring. Additionally, investigations from the previous year revealed that when the OH group was at position 5 and the chrysin derivatives had higher polarity, they showed stronger anti-cancer effects.

Derivative **272** was prepared according to the route shown in Scheme 61. Trifluoroacetic acid was hydrolyzed to get derivatives **272**, and after candesartan and triphenylmethyl bromide reacted to form intermediate **270**, which was subsequently condensed with different substituted amines. Compared to candesartan cilexetic, the optimal benzimidazole-derived **272** demonstrated enhanced NAE inhibition, namely CDC (IC_{50} = 5.51 μM *vs.* 16.43 μM), together with effective target inhibitory action and selective death of cancerous cells according to research.[135] In an enzyme assay, the optimal benzimidazole-derived **272** showed better neddylation inhibition than CDC. It also showed promising target inhibitory action and cancer cell killing selectivity. The results of cellular mechanism investigations and tumor growth suppression in A549 human lung cancer cells *in vivo* suggest that **272** may be developed as a promising neddylation inhibitor for anticancer treatment. According to SAR investigations, the core structures of tetrazole and 1*H*-benzimidazole are significant for increasing the neddylation inhibitory activities of the derivatives, whereas changing the substitutions of the heterocyclic cycloalyllic and benzoalylic groups diminished the activity of the compounds.

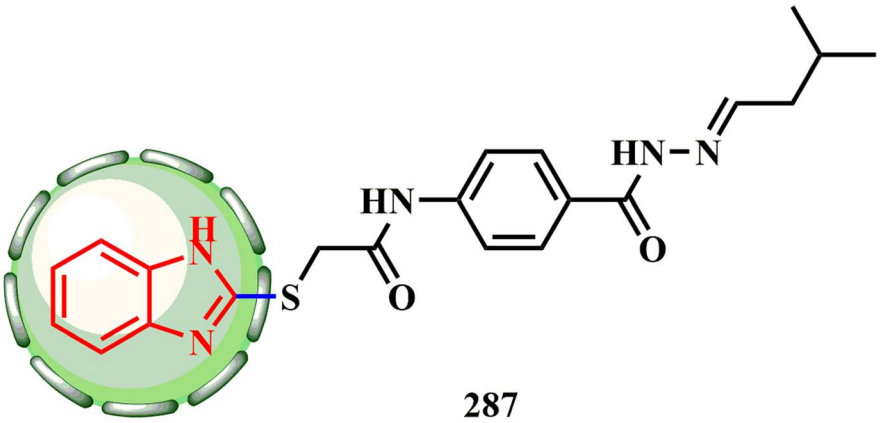
The production and cytotoxic potential of pyrido[1,2-*a*] benzimidazole hybrids were examined by Samia *et al.*[136] The initial reaction of chloro derivative **273** resulted in the development of the most effective derivative that was investigated,[136] and dioxane with appropriate arylamines **274** produced the intended hybrid molecules **275a** and **b** (Scheme 62). The anti-cancer activity results showed that compound **275b** had the most significant inhibition, as indicated by the growth percentage (*G*%), against the breast cancer BT-549 (19.39%) and



Key observations:
1) Of the compounds evaluated, 286b exhibited the most promising anticancer properties.

2) Presence of a *N*-substituted bulky group and a 5-membered ring at carbonyl group of amide side linkage (286a) suppressed the activity of the compound.

Scheme 64 Synthesis of fused benzimidazole–isoquinolinone scaffolds **286a** and **b**.



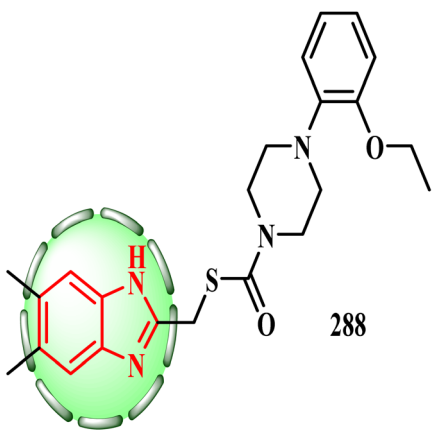
287

Key observation:
SAR studies revealed that substitution of a branched aliphatic aldehyde moiety increased the anticancer potential (compound **287**).

Fig. 1 2-Mercapto-1*H*-benzimidazole nucleus with anticancer activity.

melanoma UACC-62 (11.90%) cell lines. Among the compounds tested, compound **275b** was found to have promising anticancer activity. This might be because of how the biological activity profile is affected by the lipophilic trifluoromethyl substitution. Compound **275a** exhibits weak activity against the breast cancer BT-549 (87.45%) and melanoma UACC-62 (86.58%) cell lines.

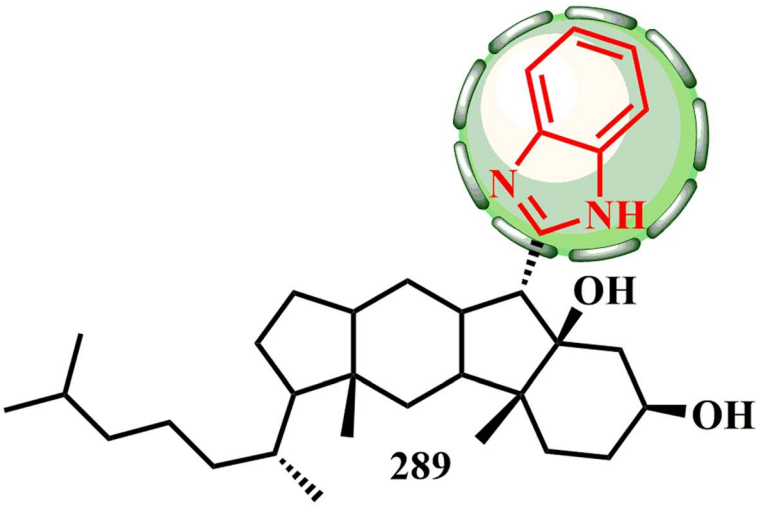
Scheme 63 describes the synthetic procedures used to establish logically constructed 1-(9*H*-pyrido[3,4-*b*]indol-1-yl) (**281a** and **b**) derivatives that are connected to benzimidazole and benzoxazole. Pure 2-bromo-1-(9*H*-pyrido[3,4-*b*]indol-1-yl) ethanone (**277**) was obtained by reacting the starting compound 1-(9*H*-pyrido[3,4-*b*]indol-1-yl)ethanone (**276**) with *N*-bromo succinimide (NBS) in dry dichloromethane (DCM) solvent and stirring the reaction mixture for approximately 30 min at room temperature. 1-(2-Methylthiazol-4-yl)-9*H*-pyrido [3,4-*b*]indole (**278**) was obtained by refluxing the resultant ethanone intermediate **277** with ethanethioamide in pure EtOH for approximately 12 h. The obtained thiazole **278** (ref. 137) was converted to pure 4-(9*H*-pyrido[3,4-*b*]indol-1-yl)thiazole-2-carbaldehyde (**279**) by oxidizing it with selenium dioxide in ethanol for 24 h at 100 °C. To produce their respective benzimidazoles/benzoxazoles as pure final compounds **281a** and **b**, aldehyde **279** was finally allowed to react with different substituted 1,2-diamine **280** in the presence of diacetoxyiodobenzene (IBD) in dry 1,4-dioxane by stirring at room temperature for around 15 min. In the study conducted by Sireesha *et al.*,[138] a novel type of 1*H*-benzimidazole-linked β-carboline was produced, and its anticancer activity against a range of human cancer cell lines was evaluated. Compounds **281a** (IC_{50} = 0.092 ± 0.001 μM) and **281b** (IC_{50} = 0.81 ± 0.062



288

Key observation:
The SAR study showed that a thiocarbamate linker was essential for activity.

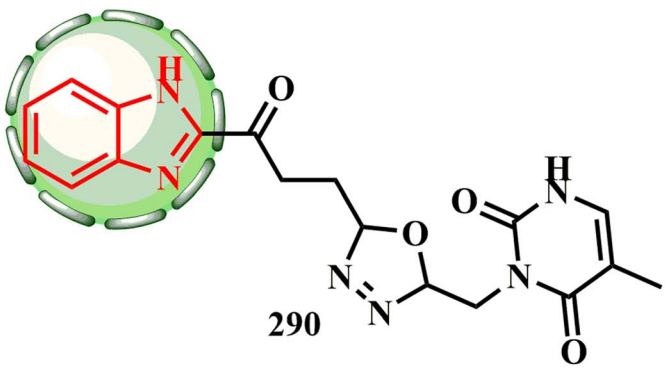
Fig. 2 Benzimidazole moiety with its antiproliferative activity.



Key observation:
The SAR study proved that the electron-donating group smoothed the insertion of the molecule **289** into DNA.

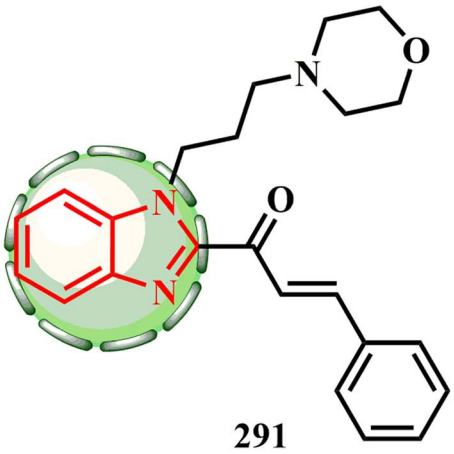
Fig. 3 1*H*-Benzimidazole scaffold with its *in vitro* studies.

μM) had the greatest anticarcinogenic properties against the MCF-7 cell line, according to the findings. According to the SAR evaluations, compound **281a** was more active than the reference standard due to the presence of 4,5-dimethoxy substitutions (MCF-7 = 0.092 ± 0.001 μM, A549 = 0.72 ± 0.042 μM, Colo-205 = 0.34 ± 0.071 μM, and A-2780 = 1.23 ± 0.55 μM). Alternatively, compound **281b** showed good action on four cancer cell lines despite having weak electron-donating 4,5-dimethyl substitutions on the benzimidazole moiety (A-2780 = 1.80 ± 0.59 μM, MCF-7 = 0.81 ± 0.062 μM, A549 = 1.90 ± 0.88 μM, and Colo-205 = 0.41 ± 0.12 μM).



Key observation:
SAR studies showed that benzimidazole derivatives containing a 1,3,4-oxadiazole ring (**290**) had greater anticancer activity than benzimidazoles with other heterocyclic rings.

Fig. 4 Hybrid **290** with its antiproliferative properties.

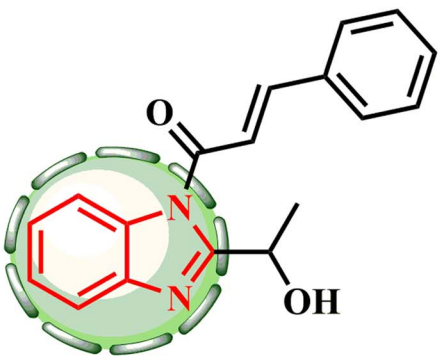


291

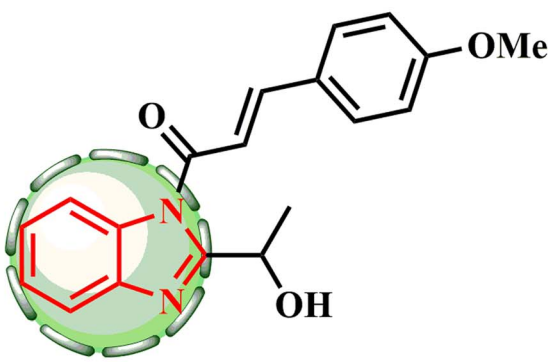
Key observation:
SAR studies showed that the *N*-substitution of benzimidazole with a hydrocarbon spacer linked to nitrogen (**291**) was essential for activities.

Fig. 5 Benzimidazole–chalcone hybrid **291** with its promising antiproliferative character.

1.1.9. Four components. Both the production and cytotoxic potential of fused benzimidazole–isoquinoline scaffolds were examined by He *et al.*[139] They used amine **284**, carboxylic acid **285**, methyl 2-formylbenzoate (**282**), and isonitrile **283** in methanol to perform a Ugi four-component reaction (U-4CR). This was followed by overnight stirring at normal room temperature and 15 min of microwave irradiation with 10% TFA/DCE at 150 °C (Scheme 64).[139] The findings indicated that **286b** exhibited the most promising cytotoxic activity among the compounds (GI_{50} = 23.78 μM [SW620] and GI_{50} = 24.13 μM [HT29]), suppressing growth and causing cell cycle arrest at the G2/M checkpoint because of the weakened signaling *via* CDK1 and cyclin B1 protein and increased p21 and p53 action.[139] SAR evaluations revealed that the activity of this compound was inhibited by the presence of a 5-membered ring and an *N*-



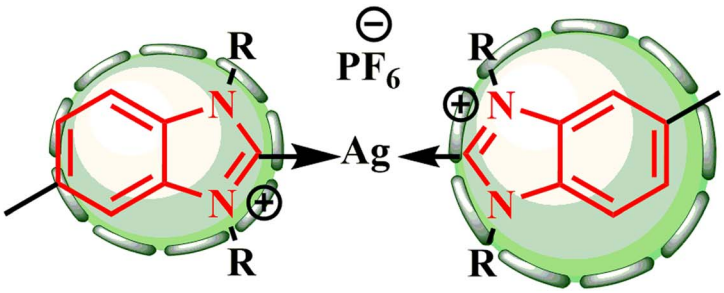
292a



292b

Key observation:
SAR studies have shown the importance of *p*-methoxy phenyl substituents and unsubstituted phenyl rings in chalcones for anticancer activity.

Fig. 6 Benzimidazole–chalcone hybrids **292a** and **b** with their SAR.



293a-c

R= Propyl, Butyl, Pentyl, respectively

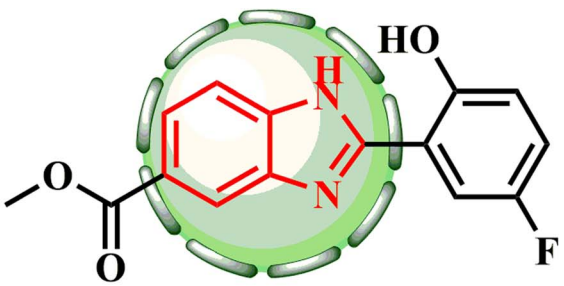
Key observation:
An SAR study showed that the activity of these complexes was enhanced by increasing the length of the side chain, which in turn increased the lipophilicity of the benzimidazole ring.

Fig. 7 Benzimidazole complexes **293a–c** with their SAR.

substituted bulky group at the carbonyl group of the amide side linkage (**286a**).

Tahlan *et al.*[140] employed ((1*H*-benzo[*d*]imidazol-2-ylthio) acetamido)benzo hydrazide to establish a novel azomethine of 2-mercapto-1*H*-benzimidazole. Using 5-fluorouracil as the standard medication, they were screened *in vitro* using the SRB assay against the HCT-116 (colorectal) human cancer cell line. Compound **287** was found to be the most potent of all the synthesized derivatives and have strong anticancer activity (IC_{50} = 30 μg mL^{-1}). According to the SAR study findings, the anticancer potential was enhanced by substituting a branched aliphatic aldehyde moiety (compound **287**) (Fig. 1).

However, compound **288** had strong antiproliferative activity against MCF-7 cells, with an IC_{50} of 5.58 μg mL^{-1}, which was similar to the IC_{50} of the common therapeutic doxorubicin, which has an IC_{50} of 4.1 μg mL^{-1}. The fundamental manner of



294

Key observation:
Methyl ester is substituted with a hydroxyl group at C-2, whereas a fluoro group at the C5 position in the aryl ring (**294**) inhibits microtubule and is very active against breast cancer cells

Fig. 8 1*H*-Benzimidazole-5-carboxylate **294** with its activity on MCF-7 cell line.

action of compound **288** was to induce cell cycle arrest and apoptosis at the G2/M phase. A thiocarbamate linker was necessary for action, according to the SAR investigation, as shown in Fig. 2.[141]

Compound **289** (ref. 142) B-norcholesteryl benzimidazole demonstrated activity when tested against the HeLa, MCF-7, T-47D, and SKOV3 cell lines, with an IC_{50} in the range of 7.90 μM to 20.10 μM.[143,144] The SAR[145] study demonstrated that the electron-donating group enhanced the insertion of this molecule into DNA[142] (Fig. 3).

Hybrid **290** (ref. 146) exhibited strong antiproliferative properties; its GI_{50} values against the SNB-75 and COLO 205 cell lines were 0.09 μM and 0.35 μM, respectively. Additionally, with a selectivity index of 3.66, it demonstrated moderate selectivity towards prostate cancer cell lines. According to SAR research, the benzimidazole derivatives with a 1,3,4-oxadiazole ring exhibited stronger anticancer properties than those with other heterocyclic rings[147,148] (Fig. 4).

Moreover, compound **291** (ref. 149 and 150) had IC_{50} values of 8.91 μM, 10.93 μM, and 10.67 μM against the MCF-7, HepG-2, and OVCAR-3 cell lines, respectively, indicating its promising antiproliferative action. Alternatively, cisplatin had IC_{50} values of 11.70 μM, 3.97 μM, and 16.04 μM, respectively.[151] According to the SAR investigations, the activities were attributed to the *N*-substitution of benzimidazole with a nitrogen-linked hydrocarbon spacer[149,152] (Fig. 5).

Compounds **292a** and **b** had IC_{50} values in the range of 6.83 μM to 18.16 μM. Both substances exhibited strong affinity for the tyrosine kinase receptor. *P*-Methoxy phenyl substituents and unsubstituted phenyl rings are crucial for the anticancer action of the chalcones, according to the SAR studies[153] (Fig. 6).

When tested against the MDA-MB-231 and HCT-116 cell lines, complexes **293a–c** demonstrated greater anticancer activity than their respective benzimidazole ligands, with IC_{50} values ranging from 4.22 μM to 10.3 μM. Additionally, their ligands showed reduced activity, with IC_{50} values between 25.51 μM and 34.21 μM, which were similar to that of the reference pharmaceuticals 5-FU (IC_{50} = 5.5 μM against HCT-116 cells) and tamoxifen (IC_{50} = 8.20 μM against MDA-MB-231 cells). Increasing the side chain length improved the activity of the complexes, according to a SAR investigation, in which it additionally contributed to making the benzimidazole ring more lipophilic[154] (Fig. 7).

Methyl 2-(5-fluoro-2-hydroxyphenyl)-1*H*-benzimidazole-5-carboxylate (MBIC)[155] (**294**) with a methyl ester is substituted with a hydroxyl group at C-2, whereas a fluoro group at the C5

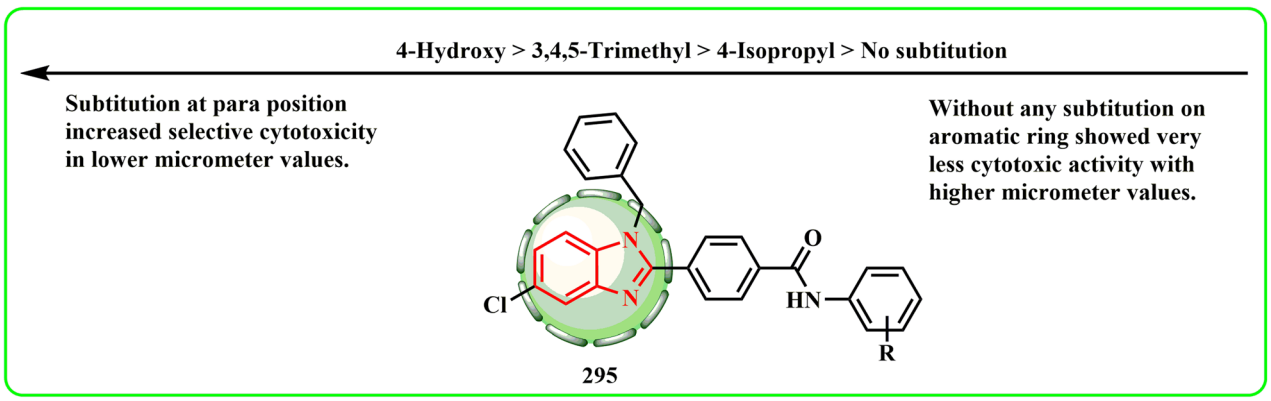


Fig. 9 Representative SAR studies of 1-benzyl-1*H*-benzimidazole analogues as anticancer agents.

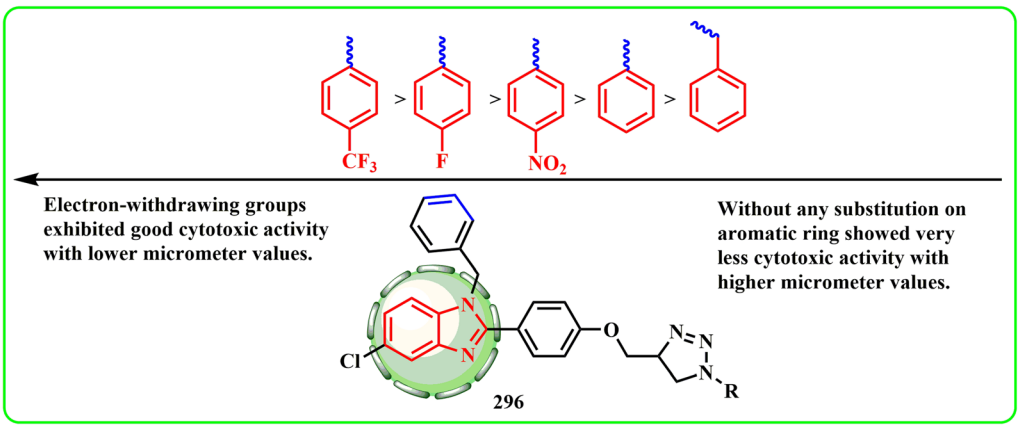


Fig. 10 Representative SAR studies of 1-benzyl-1*H*-benzimidazole-triazole analogues as anticancer agents.

position in the aryl ring inhibits microtubule[156] and is very active against breast cancer cells[157,158] (Fig. 8).

With an IC_{50} of 10.69 ± 0.14 μM, 13.89 ± 0.74 μM, 7.01 ± 0.20 μM, 14.04 ± 0.62 μM, and 12.91 ± 0.52 μM against the A-549, DU-145, MCF-7, MDA-MB-231, and HCT-116 cancer cell lines, the 4-hydroxy compound **295** showed a noticeable decrease in tumor cell proliferation (Fig. 9). The 4-hydroxy arylamide moiety **295** of the 1*H*-benzyl benzimidazole derivative had strong anticancer activity, according to the SAR analysis. MCF-7 development was significantly inhibited when aromatic or heterocyclic rings, such as pyrrole, 3-ethoxy-4-hydroxyphen, and 3,5-dimethoxy-4-hydroxyphen, were connected to benzyl benzimidazole scaffolds.[159]

Further investigation of the distinct 1-benzyl-1*H*-benzimidazole hybrids for selective gal-1 inhibition resulted in the development of a variety of novel 1-benzyl-1*H*-benzimidazole-triazole analogues due to the promoting results of 1-benzyl-1*H*-benzimidazole analogues as possible anticancer agents mediated by gal-1. The 1,3-dipolar cycloaddition of the benzimidazole intermediate with a terminal alkyne group to various benzyl and phenyl azides in the presence of a copper(I) catalyst produced 1-benzyl-1*H*-benzimidazole-triazole hybrids. 4-Triflourophenyl compound **296** showed no cytotoxicity against normal embryonic kidney cells, but it displayed cytotoxic function against MCF-7, NCI-H460, MDA-MB-231, A-549, and HaCaT cells with IC_{50} values of 1.3 ± 0.18 μM, 0.99 ± 0.01 μM, 0.94 ± 0.02 μM, 0.63 ± 0.21 μM, and 2.99 ± 0.09 μM, respectively. The SAR investigations demonstrated that in comparison to electron-donating groups and in the absence of any substitution on the aromatic ring, electron-withdrawing groups on the aromatic ring have remarkably greater cytotoxicity (Fig. 10).[160]

Hagar *et al.*[161] benzimidazole-1,3,4-oxadiazole–chalcone hybrids were established and synthesized (Fig. 11), and their ability to inhibit EGFR for cell destruction was studied. According to cell line tests, compound **297**, which has a para-methoxyphenyl group at the second position of the benzimidazole ring, demonstrated potential potency in inhibiting apoptosis and EGFR inhibition.

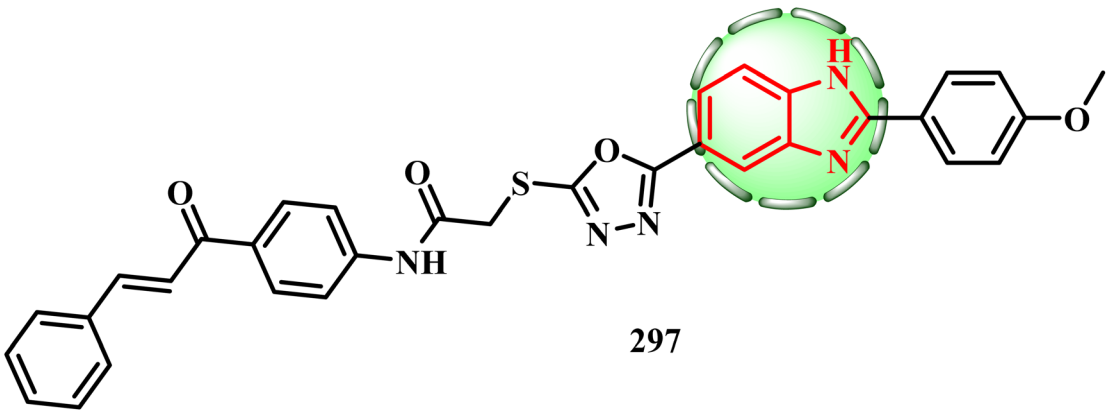


Fig. 11 Benzimidazole-containing moiety exhibiting anticancer activity.

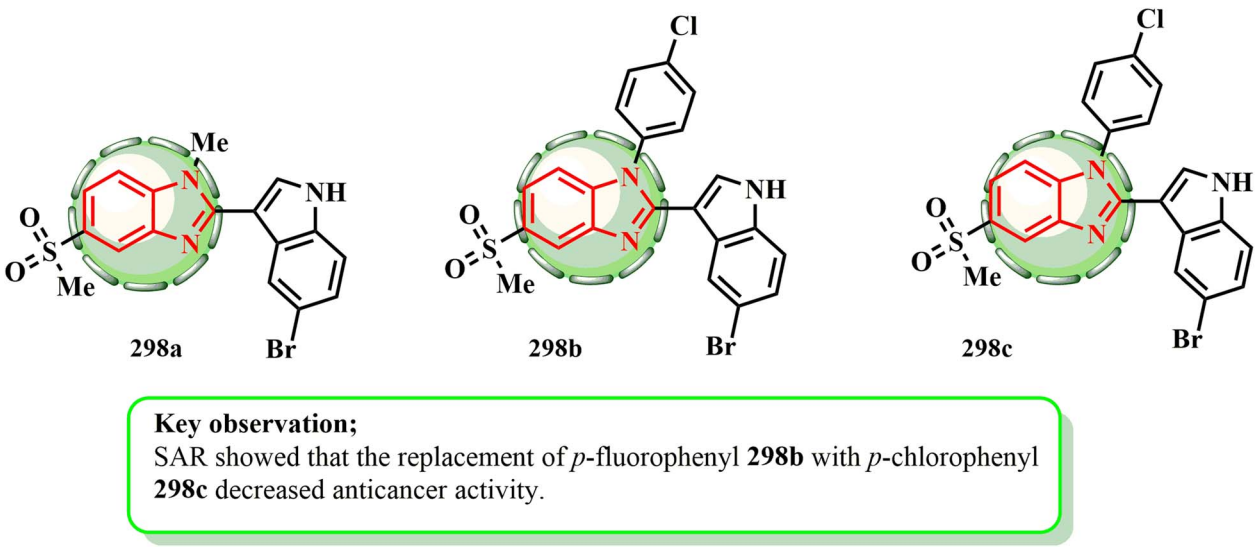


Fig. 12 Indole–benzimidazole derivatives with anticancer properties.

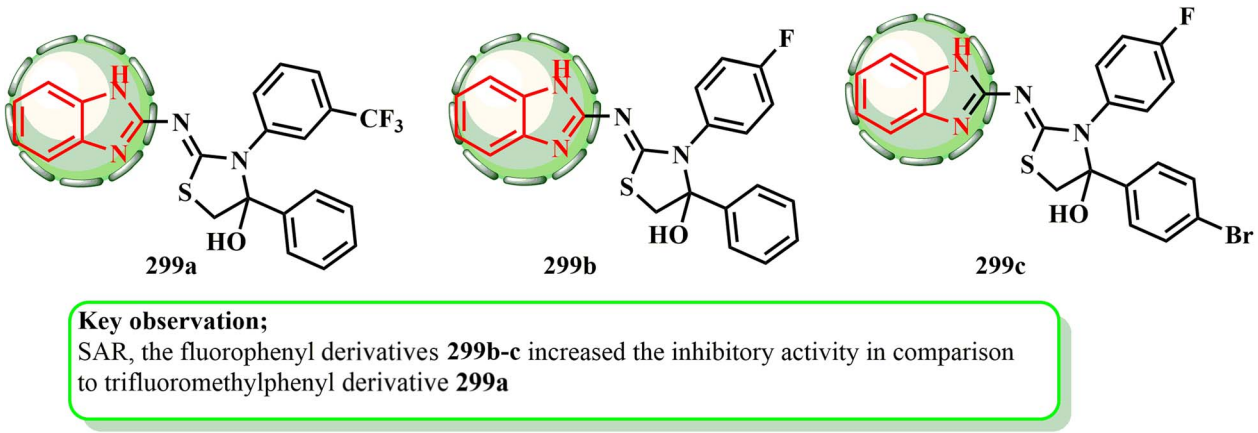


Fig. 13 Benzimidazoldiphenyl-2-imino-thiazolidine-4-ol **299a–c** derivatives with anticancer properties.

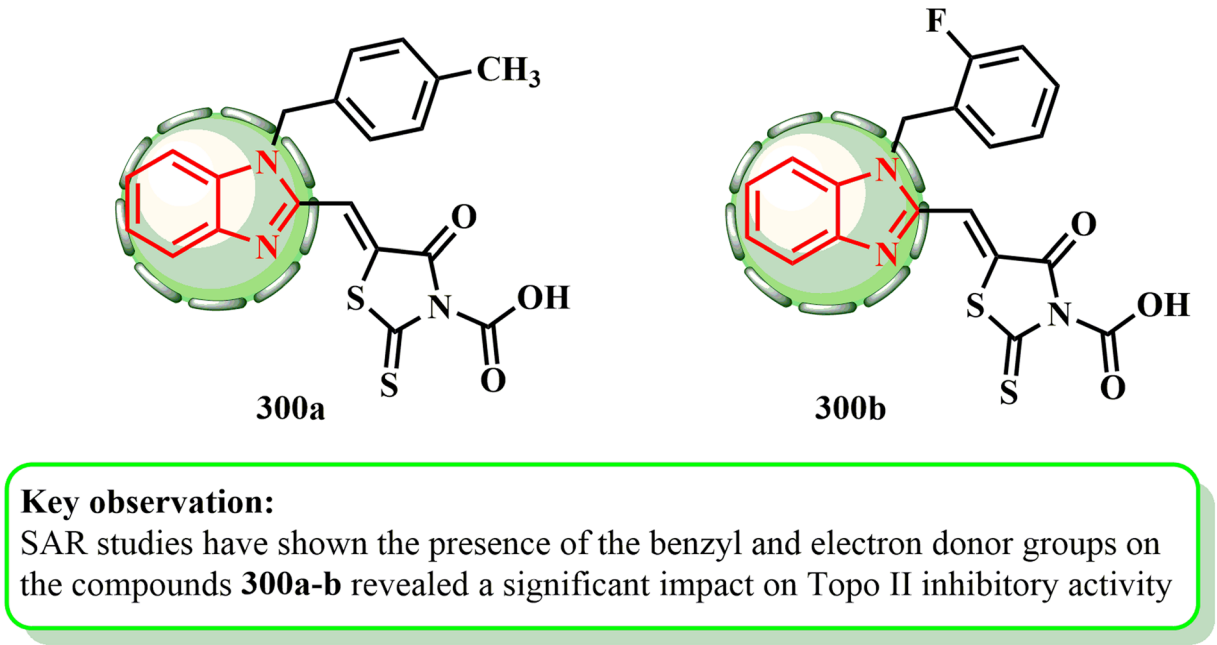


Fig. 14 Benzimidazole–rhodanine conjugates **300a** and **b** with anticancer properties.

The anticancer activities of indole–benzimidazole derivatives were reported.[162] Among the evaluated compounds, **298a** (ref. 163) (R_1 = methyl and R_2 = Br) had the highest activity, with an IC_{50} value of 28.73 μM. As a result, compound **298a** may have anticancer properties together with potential modulatory effects on estrogen and the corresponding receptors. The *p*-fluorophenyl scaffold molecule **298b** exhibited less productive anticancer properties, according to the structural activity relationship (SAR). At this point, the anticancer activity was reduced when *p*-chlorophenyl **298c** was substituted for *p*-fluorophenyl (Fig. 12).

Under efficient metal-free conditions, benzimidazoldiphenyl-2-imino-thiazolidine-4-ol derivatives **299a–c** were synthesized.[164–166] Doxorubicin was administered as a control for evaluating the targeted compounds against four distinct human cancer cell lines, including breast, colon, prostate, and lung panels. In comparison to doxorubicin (IC_{50} = 1.75 μM), compounds **299a** (IC_{50} = 3.89 μM), **299b** (IC_{50} = 2.80 μM), and **299c** (IC_{50} = 3.14 μM) had the strongest inhibitory activity against the lung cancer cell line among the published compounds characterized for anticancer activity. Additionally, compared to trifluoromethylphenyl functionalities **299a**, the inhibitory effect was enhanced by the fluorophenyl functions **299b–c** (Fig. 13).

In another study, Li *et al.*[167] showed that a panel of benzimidazole–rhodamine conjugates have potent antiproliferative properties against human cervical, breast, lung, and prostate cancer cells, as well as human lymphoma and acute leukemia. As non-intercalative Topo II inhibitors, compounds **300a** and **b** bind to the Topo II enzyme ATP-binding site to inhibit enzymatic activity. The Topo II inhibitory action was significantly

influenced by the benzyl and electron donor groups in the compounds (Fig. 14).

2 Conclusion

The structural analogy of benzimidazole to nucleosides presents it as a potentially effective anticancer agent. The metal complexes or benzimidazole hybrids with antiproliferative properties were presented in this review. The examples included in this overview demonstrated the variety of synthetic preparation techniques used to achieve benzimidazoles and their antiproliferative properties. Additionally, we focused our attention to the SAR of the various molecular templates based on BZ that have been established by researchers globally. To accomplish our objectives, we collected information from an extensive range of publications to provide researchers, medicinal chemists, and drug designers with an excellent foundation for the development of the next generation of safe and effective BZ-based therapy. This review may shed light on the wide range of cancers that benzimidazoles can target, such as MCF-7, HepG2, MGC-803, HeLa, HCT-116, A-549, PC-3, MDA-MB-231, HUVEC, NIH/3T3, RMS, C-26, HT1080, LNCaP, 22Rv1, C4-2B prostate, DU-145, HEK293, MCF12A, H69AR, A2780, SISO, HT29, HCC2998, SF-539, UACC-62, and breast cancers BT-549, SW620, K-562, A37, SNB-75, COLO 205, and OVCAR-3. Their ability to disrupt important cellular processes such as Topo II-mediated DNA, VGEF, hCA IX, cell cycle progression, and mitosis has been demonstrated by investigations. This can lead to novel possibilities for the development of precision medicine-based benzimidazole anticancer drugs. Furthermore, this is the route forward to develop new medicinal compounds and benzimidazole anticancer drugs.

Data availability

The article describes a study that did not utilize any data.

Author contributions

Basant Farag, Sobhi M. Gomha, and Doaa A. Elsayed contributed to the conceptualization, supervision, and writing – review and editing. Basant Farag and Doaa A. Elsayed performed formal analysis and data curation. Magdi Zaki and Doaa A. Elsayed were responsible for investigation, methodology, and validation. Basant Farag and Doaa A. Elsayed led the writing – original draft preparation. All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors declare that they have no known financial conflicts of interest or personal relationships that could have influenced the work presented in this study.

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