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Benzimidazole(s): synthons, bioactive lead structures, total synthesis, and the profiling of major bioactive categories†

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Benzimidazole, a fused bicyclic compound with benzene and pentacyclic 1,3-diazole moieties, has a simple aromatic heterocyclic structure. The moiety has become an indispensable anchor for the development of new pharmacologically active products, and has yielded several therapeutic agents with anticancer, antihypertensive, antimicrobial, antifungal and antiulcer effects. Benzimidazoles, as synthetically feasible and pharmacophoric synthons, have been relentlessly pursued for the preparation of new analogues and derivatives, and they have successfully developed into some of the most sought-after and vital pharmacophores for drug discovery. The use of varied substituents and differing patterns around the benzimidazole nucleus has provided a wide spectrum of biological activities. In addition, the benzimidazole moiety constitutes a building block for the production of several drugs, drug candidates, new chemical entities, and lead molecules. The importance of this nucleus for bioactivity, e.g., antibacterial, antitubercular, antidiabetic, anticancer, antifungal, anti-inflammatory, analgesic, antioxidant, antihistaminic, and antimalarial activity, has led us to take note and provide an overview of the synthetic development approaches for various benzimidazole derivatives together with their biological actions. This review is projected to further assist in the design and development of new benzimidazole-based compounds for new and optimized pharmacologically active products towards new drug-development strategies.

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1. An introduction to benzimidazole: a saga of chemistry and pharmacology

Extensive research work on vitamin B12 highlighted the structure and importance of the benzimidazole nucleus. The 1,3-positions of a diazole ring were fused with the 4,5-positions of an aromatic benzene ring. This structure constitutes the basic benzimidazole ring.¹ Other benzo-substituted diazoles, with 1,2- and 2,3-substitutions of the five-membered aromatic diazole ring, keeping the fused benzene as an unsubstituted

heterocyclic ring, have been categorized as indazole and benzopyrazole, respectively. The IUPAC name for benzimidazole is 1*H*-1,3-benzimidazole. However, several other names have also been used, including azaindole; benzimidazole; benzoglyoxaline; benzimidazole; BZI; 1,3-diazaindene; and 3-azaindole. The molecular formula is C₇H₆N₂ with a molecular weight of 118.1359. The IUPAC standard InChI key is 1S/C7H6N2/c1-2-4-7-6(3-1)8-5-9-7/h1-5H,(H,8,9). The preliminary synthesis of benzimidazole has been reported from the condensation of phenylenediamine with formic acid, or its equivalent, trimethyl orthoformate. The benzimidazole nucleus has been found to be stable for the further build-up of extended new molecules incorporating the central benzimidazole ring; these played a pivotal role in finding new leads and developing new drugs and new drug templates. These provided diverse and impactful bioactivities; some examples are under pharmacological development and some have found clinical use as referral standards and drugs.

Progressive work involving the benzimidazole nucleus led to the development of several synthetic strategies to prepare benzimidazole-based, structurally diverse compounds with multiple bioactivities. From the standpoint of synthesis, different approaches utilizing various synthons and starting

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materials belonging to acid-, ester-, *ortho*-ester-, nitrile-, acid-chloride-, and orthoformate-based molecular frameworks have been used.² A plethora of compounds containing the benzimidazole bicyclic ring structure in their molecular framework have displayed prominent biological activity profiles with high therapeutic potentials in almost all fields of pharmacology and therapeutics.³ Benzimidazoles, as structural isosteres of nucleotides, have plentiful structures that can feasibly interact with polymers of biological origins, culminating in a broad spectrum of pharmacologically active compounds with lowered toxicity and better therapeutic outcomes.⁴

Over the past decades, numerous studies describing syntheses of chemical systems incorporating the benzimidazole nucleus as part of their synthetic strategies have been prepared, modified, and reported. Notwithstanding advances in synthetic strategies and protocols, direct and traditional patterns of convergent and cumulative synthesis, disconnection and retrosynthetic tactics, divergent and ligation-like approaches for synthesis/semi-synthesis, and bulk-scale preparation have also been used. A wide and diverse range of biological activity evaluations of benzimidazole-based structures, molecular templates, new chemical entities, and desired metal complexes has been reported.⁵ Studies reporting several classes of bioactivities, including antimicrobial,^{6–11} anthelmintic,^{12–14} antithrombotic,^{15,16} antiplatelet,^{17–19} anticoagulant,^{20–23} anti-inflammatory,^{24–28} antiulcer,^{29,30} antifungal,^{31–33} acetylcholinesterase^{34–37} antiprotozoal,^{4,38,39} antitubercular,^{40–43} antileishmanial,^{44–46} antimycobacterial,^{47,48} antiviral,^{49,50} anti-HIV,^{51,52} and antitumor^{53,54} activities, are abundantly available. Additionally, benzimidazole targets have been described as inhibitors of hepatitis C^{55–57} and as an indoleamine-2,3-dioxygenase-1 (IDO1) inhibitor, predicted from *in silico* SAR (structure–activity relationship) approaches through structure-based virtual screening. This culminated in obtaining *in vivo* biological activity profiles of several compounds.⁵⁸ Benzimidazole-structure-templated compounds have also been known to be antihypertensive in action,^{59,60} in addition to acting as a Zika virus inhibitor,⁶¹ an *in vitro* α -glucosidase inhibitor,^{62,63} a NOX2 antagonist,⁶⁴ and as antiglycation,⁶⁵ antioxidant,^{66–68} antileukemic,^{69–72} and antitubercular^{73–77} agents. Recently, the benzimidazole molecular template has also been reported to be a potent anticancer entity.^{78–83} More recently, the benzimidazole structural motif has been observed to be antihypertensive,^{84,85} a non-nucleoside reverse transcriptase inhibitor,^{86–89} an anticonvulsant,^{90–93} ulcerogenic,^{94–97} a non-peptide angiotensin-II receptor antagonist,^{98–100} an AMP-activated protein kinase activator,^{101–103} and an antileukemic activity agent^{69,101–103} in terms of its biological activity profiles.

The simple and complex structural moieties derived from the benzimidazole structural template, which are present in various compounds as sub-structural entities, have exponentially increased in number, showing vastly different biological properties.¹⁰⁴ The benzimidazole core template has proven to be an exceptional chemical structure that has manifested diverse ranges and types of biological and therapeutic activities.¹⁰⁵ In the past, many works reporting the importance of chemical systems incorporating a benzimidazole nucleus have broadly

been elaborated on. The diverse biological activities of benzimidazoles, and their derived structures have culminated in the development of several drugs which have been introduced to the market, *e.g.*, albendazole (antimicrobial); omeprazole (antiulcer); bendamustine, nocodazole, and abemaciclib (anti-tumor); envirodine (antiviral); candesartan (antihypertensive); and benoxaprofen analogues (anti-inflammatory),^{106,107} to name a few.

2. Biological activity profiles of benzimidazole-based compounds: the current status

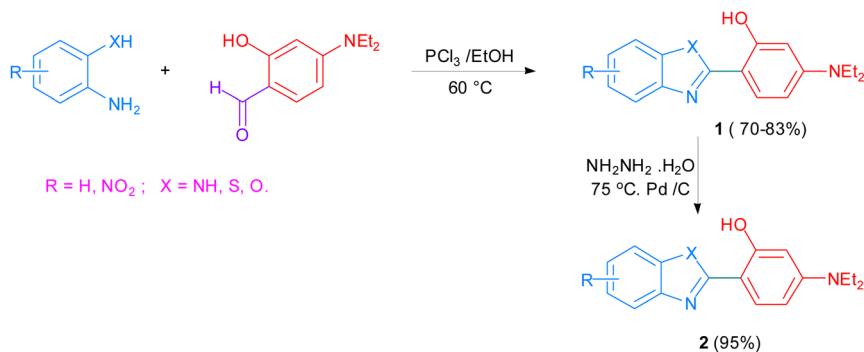
2.1 Antimicrobial activity

The gradual but continuous emergence of a number of drug-resistant microbial strains over the last several decades has pushed researchers towards searching for and developing new antimicrobial agents that are capable of combating this situation.^{108,109} The benzimidazole pharmacophore as a core structure has contributed to the molecular template of several leads which, together with benzimidazole derivatives, have served as part of several active substances showing significant antimicrobial activity.¹¹⁰ Recently, the elegant synthesis of 2-substituted benzimidazole, benzoxazole, and benzothiazole derivatives was achieved from the reaction of *p*-*N,N*-diethylamino-salicylaldehyde **1** with *o*-phenylenediamine, *o*-aminophenol, and *o*-amino-thiophenol, respectively, with PCl₃ in ethanol as the reaction medium. The 95% yield of product **2** and its derivatives provided ample material for bioactivity evaluations (Scheme 1). This established the potential of the benzimidazole structural unit as an antibacterial and antifungal template for developing new chemical entities exhibiting antimicrobial activity against several bacteria. These benzoxazole and benzothiazole derivatives displayed good antimicrobial activity against *E. coli* and *S. aureus*, while the developed benzothiazole derivatives showed remarkable antifungal activity potential against *Candida albicans* and *Aspergillus niger*.¹¹¹

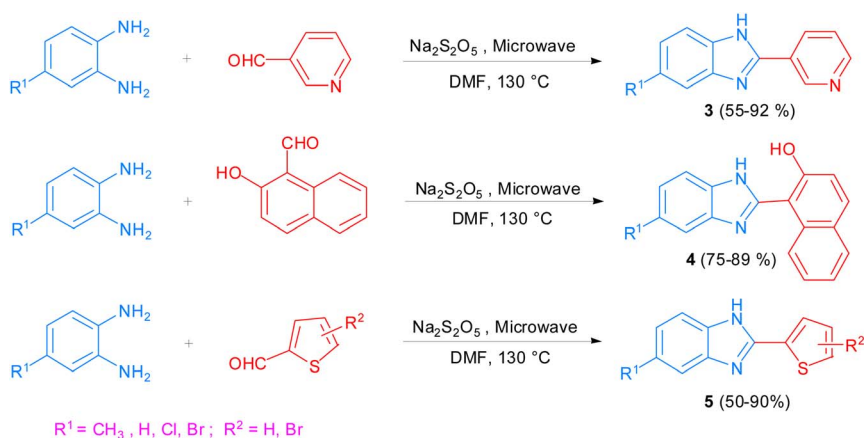
The development of 2,5-disubstituted benzimidazole derivatives as products **3**, **4** and **5**, obtained from substituted *o*-phenylenediamine and appropriately substituted aldehydes, was realized under microwave-assisted synthesis conditions in the presence of Na₂S₂O₅. Moderate-to-high yields in the range of ~90% were enough for bioactivity testing of the synthesized benzimidazoles, which exhibited antifungal and antibacterial activity against *E. coli* ATCC 25922, *S. aureus* ATCC 25923 and ATCC 3933, and *S. epidermidis* ATCC 12228. The MICs of 2-(3-bromothiophen-2-yl)-5-chloro-1*H*-benzimidazole and 5-bromo-2-(3-bromothiophen-2-yl)-1*H*-benzimidazole were found to be <4 $\mu\text{g mL}^{-1}$, while the lowest activity level was 2 $\mu\text{g mL}^{-1}$ (Scheme 2).¹¹²

The synthesis of the benzimidazole bidental ligand **6** was achieved from the condensation of 2-(4-aminophenyl)benzimidazole with a 5-bromosalicylaldehyde derivative. Metal complexation of ligand **6** yielded the dimeric *meta*-complex **7** (80% yields). The (*E*)-2-((4-(1*H*-benzo[*d*]imidazol-2-yl)phenylimino)-methyl)-4-bromophenol ligand **6** and





Scheme 1 The synthesis of 2-substituted benzimidazole templates, benzoxazole 2, and benzothiazole derivatives.

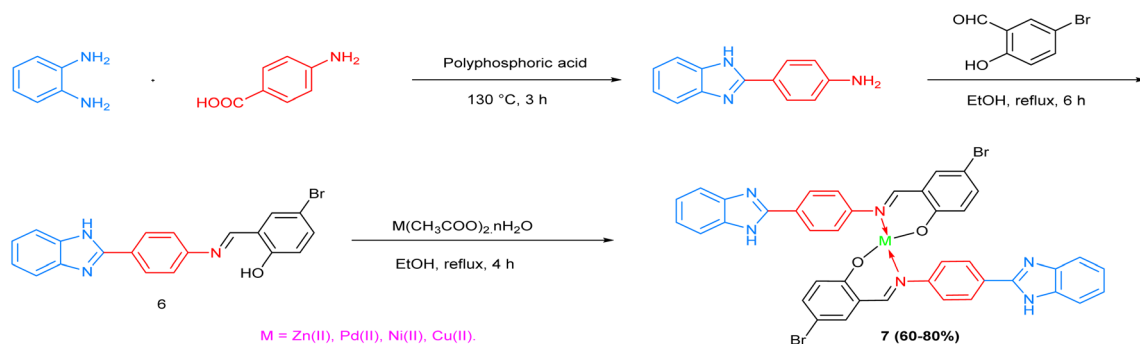


Scheme 2 The synthesis of the 2,5-disubstituted benzimidazoles 3, 4 and 5.

corresponding Zn(II), Ni(II), and Cu(II) complexes, 7, exhibited antibacterial activity against Gram-positive *Micrococcus luteus* and Gram-negative *Escherichia coli* and *Enterobacter aerogenes*. Evaluations of the antibacterial activities of Ni(II), Zn(II), and Cu(II) complexes demonstrated their moderate-to-excellent levels of activity (Scheme 3),¹¹³ therefore providing evidence for the antimicrobial potential of benzimidazole as a core component.

In a series of mono- and di-substituted benzimidazole derivatives reported by Ajani *et al.*, the 2-(2-aminophenyl)- and

2-(benzyl-*N*-phenylsulfonyl)-benzimidazole derivatives 8 and 9 were synthesized from the NH_4Cl -catalyzed condensation of *o*-phenylene-diamine with the corresponding carboxylic acid to produce the desired product. The synthesized compounds were tested against four bacterial strains, namely, *Staphylococcus aureus*, *Bacillus licheniformis*, *Proteus vulgaris*, and *Pseudomonas aeruginosa*. 2-(1*H*-Benzimidazol-2-yl)-aniline 8 and 2-benzyl-1-(phenylsulfonyl)-1*H*-benzimidazole 9 showed high antibacterial activities with an MIC value of 15.63 mg mL⁻¹ for both compounds (Scheme S-1, ESI file†).¹¹⁴



Scheme 3 The synthesis of the benzimidazole ligand 6 and its Zn(II), Pd(II), Ni(II) and Cu(II) metallic complexes 7.



The synthesis of the potent antibacterial 2-substituted benzimidazoles, *N*-5-aryl(1,3,5-triazinane-4-thione), and oxadiazinane-4-thione derivatives, were achieved from the iodine-catalysed condensation reaction of thiourea with the 2-benzimidazolyl-ethenone **10**, leading the formation of corresponding derivative, 2-aminothiazol-5-benzimidazolyl, product **11**. This latter was reacted with aryl isothiocyanate leading to the urea-based product **12**, which underwent a series of reactions of formol, and the mixture of methylamine/formol to produce the benzimidazolyl oxadiazinane, and the benzimidazolyl triazinane derivatives **13** and **14**, respectively. The microbial growth inhibition efficacy of the synthesized benzimidazole derivatives **13** and **14** was evaluated after screening six different types of bacterial strains, *i.e.*, *Bacillus subtilis* MTCC 441, *Bacillus cereus* ATCC 9372, *Staphylococcus aureus* ATCC 96, *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* MTCC 109, and *Salmonella typhi* ATCC 4420. These tested compounds possessed notable antimicrobial activities (Scheme S-2, ESI file†).¹¹⁵

The syntheses of 2-substituted benzimidazolyl isoxazole-5-one, compound **16**, pyrazol-3-one, compound **17**, and pyrimidin-4-one, compound **18**, were realized through cycloaddition reactions of hydrazono-ethyl acetoacetate **15** with NH₂OH·HCl, hydrazine, urea, and thiourea entities. These differently substituted benzimidazole end-product compounds exhibited interesting antimicrobial activities (Scheme S-3, ESI file†).¹¹⁶

The synthesis of methylene-*N*-aryl **19**, pyrazolo-3-one **20**, and the (4-fluorophenyl)-piperazin-2-substituted benzimidazole derivative **21** were achieved *via* the nucleophilic substitution of 2-chloromethylene benzimidazole. These products showed weak antimicrobial and cytotoxic activities (Scheme S-4, ESI file†).¹¹⁷ On the other hand, several azo-substituted benzimidazole derivatives, namely benzoxazole and benzothiazole, **22** and **23**, were prepared from electrophilic substitution reactions of diaza-sulfonyl-benzimidazole salt with the corresponding aromatic derivatives to yield the desired products. These polyheterocyclic compounds exhibited significant antimicrobial, antibacterial, and antitubercular activities (Scheme S-5, ESI file†).⁷ As another set of compounds based on a new triaryl benzimidazole scaffold, the derivatives 4-iodo- and 5-bromophenyl-*N*-aryl-azidine were prepared *via* electrophilic *tri*-aza-aromatic substitutions. The synthesized products, **23** and **24**, demonstrated high levels of bioactivity against MRSA and VRE bacteria (Scheme S-6, ESI file†).¹¹⁸

The synthesis of a polyaromatic bis(benzimidazolyl) carbamide derivative, **26**, spaced with a bi-aryl-pyridin-phenyl derivative was accomplished through a multi-step series of reactions. The prepared derivative, **26**, manifested strong bioactivity towards the tested bacteria (Scheme S-7, ESI file†).¹¹⁹ Contextually, a series of *N*-sulfoxyamide benzimidazole derivatives was prepared from the reaction of benzimidazole derivatives with chlorosulfonyl aromatic derivatives at moderate temperature, which exhibited strong antibacterial activity towards the tested bacteria (Scheme S-8, ESI file†).¹²⁰ Also, antibacterial agents from a new series of non-symmetrically substituted *p*-nitro-benzyl-containing benzimidazole *N*-

heterocyclic carbene-silver(i) complexes, **34** and **35**, were prepared through silver oxide metalation from *N*-(*p*-nitrobenzyl)-*N*-(alkyl)benzimidazolium hexafluorophosphate under mild conditions (Scheme S-9, ESI file†).¹²¹ The synthesis of the benzimidazole compound **36** was followed by reactions with hydrazine and carbon disulphide, with cyclisation as the final step (Scheme S-10, ESI file†).¹²² The antibacterially active benzimidazole-cored compound 4-amino-5-[2-(1*H*-benzimidazol-2-yl)-3-(4-chloroanilino)propyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione, **37**, was synthesized in four steps.

The polyaromatic heterocyclic benzimidazole derivatives **39**, were obtained from the reaction of different 2-, 3- and 4-substituted benzimidazole moieties (obtained from Michael cycloaddition with 1-naphthalic carbazide as a starting material) with the substituted benzimidazole-2-enone derivatives **38**. The *p*-nitro- and *p*-chloro-substituted products showed the highest antibacterial activity levels (Scheme S11, ESI file†).¹²³ Moreover, the synthesis of 2-(3-fluorobenzyl)-1*H*-benzimidazole derivatives, containing various substituted functional groups and heterocyclic ring moieties, was carried out *via* the *N*-nucleophilic substitution reaction of the starting material 2-(4-fluorobenzyl) benzimidazole **40** with various electrophilic functional groups and heterocycles in several steps. The reaction scheme shows the synthetic route and the prepared products, **41–44**, which were obtained in high yields (~80%). These products have been reported to show high antibacterial efficacy (Scheme 4).¹²⁴

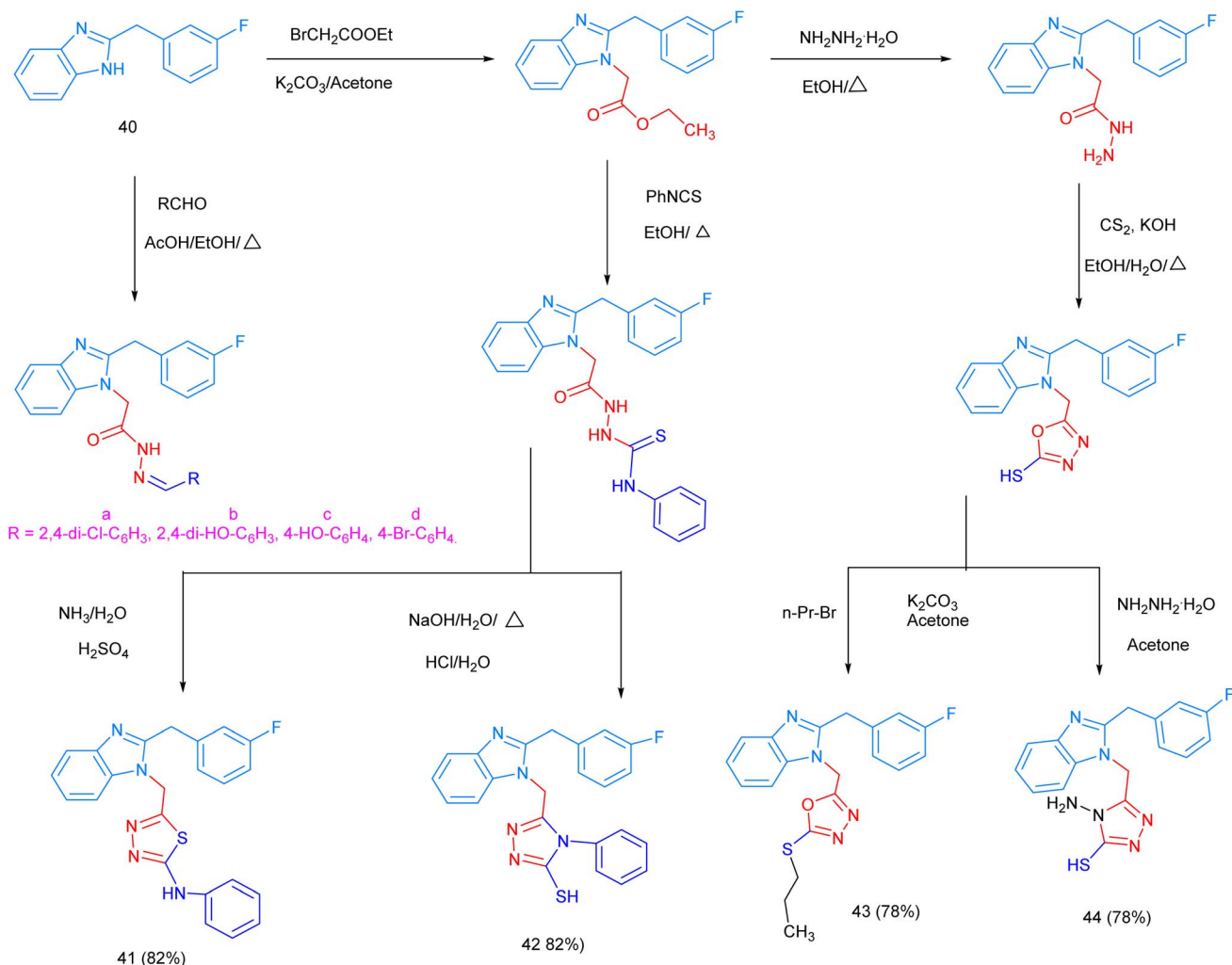
In a nutshell, the 2,5-disubstituted benzimidazole derivatives showed high levels of bioaction at doses as low as 2 μg mL⁻¹.

2.2 Antiviral activity

Benzimidazole-based templated core compounds represent one of the major target molecules for manifesting high levels of antiviral activity.¹²⁵ A series of 2-substituted benzimidazole-*N*-carbamates was prepared through the conversion of trichloro-carbon-functionalized 2-trichlorocarbon benzimidazole, *i.e.*, compound **45**, to obtain amide or ester groups, yielding the products **46**, and **47**, which was further followed by *N*-acylation with different electrophilic reagents to produce the benzimidazole derivatives **48–56**. These products displayed antiviral activity, and compound **48** was among the most active compared with other compounds of the collection, while compound **57** presented moderate levels of antiviral activity, in contrast to compound **47**, which was inactive (Scheme S-12, ESI file†).¹²⁶

Another series of benzimidazoles compounds with tetracyclic fused structures, **60–66**, homologues to steroids in the structural patterning of the tetracyclic set-up, was successfully synthesized. The last step of the four stages resulted in the formation of 2-substituted benzimidazole templated core products through the condensation of 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea with the *o*-phenylene diamine derivatives **58** and **59** in an acidic environment. The biological activity results indicated that these compounds possessed antiviral activity against human cytomegalovirus (CMV) and varicella-zoster virus (VZV) (Scheme S-13, ESI file†).¹²⁷





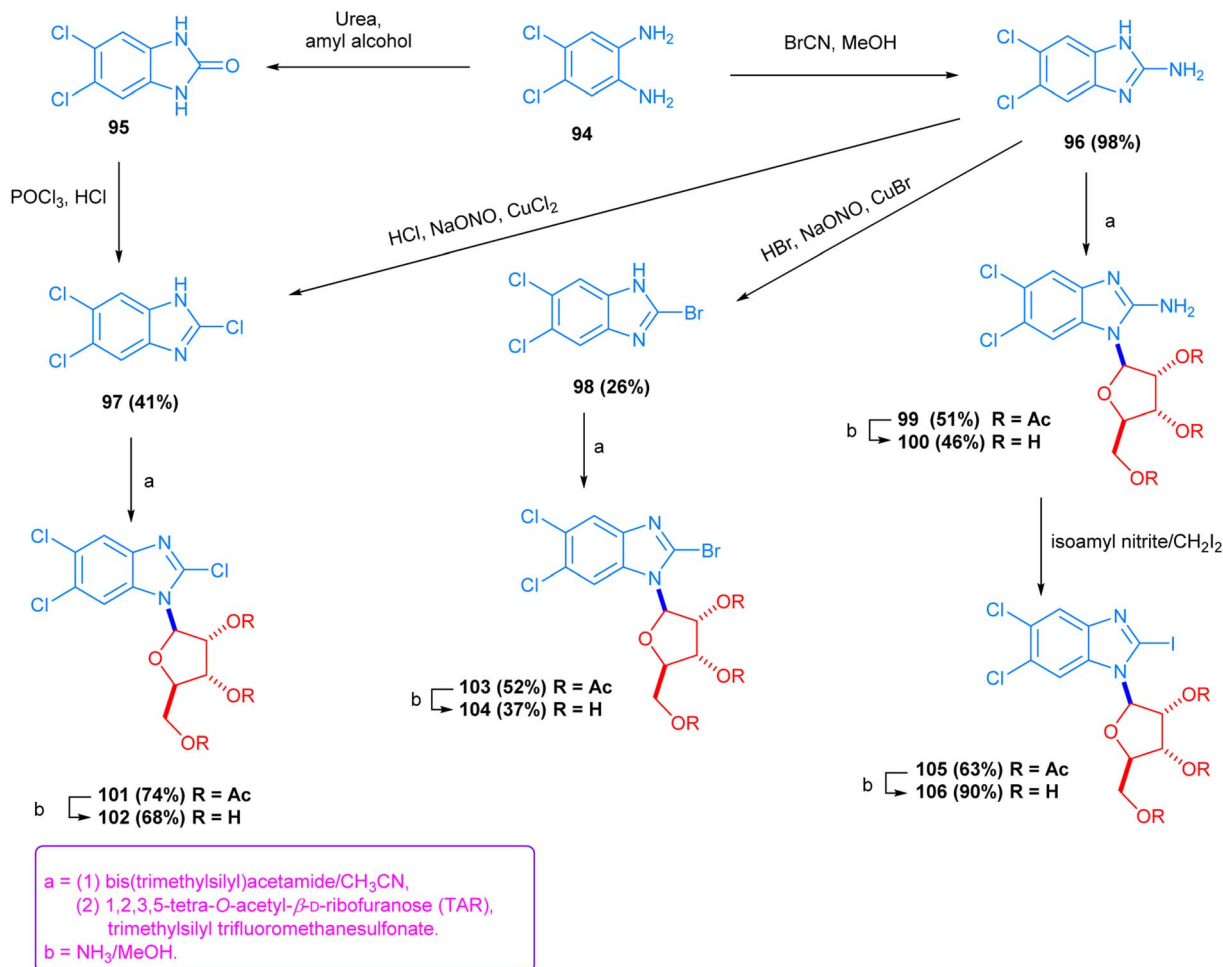
Scheme 4 The synthesis of 2-(3-fluorobenzyl)-1H-benzimidazole derivatives with various functional groups and heterocyclic moieties.

The condensation of 2,3-diaminobenzoic acid with different aldehydes, followed by amidation, provided a new class of benzimidazole derivatives, which were designated as 2-pyridyl-1H-benzimidazole-4-carboxamide derivatives, **67–84**. The compounds showed noticeable antiviral activity. Compounds **78** and **79** displayed strong and selective antiviral activity against coxsackievirus B3 in Vero cells under *in vitro* conditions (Scheme S-14, ESI file†).¹²⁸ Further structural expansion of the selected heterocyclic rings, *via* the condensation of 2,3-diaminobenzamides with heterocyclic 4-imidazol-, 4-pyrrol- and 4-pyridine-carboxaldehydes in absolute ethanol, yielded the corresponding imidazole, pyrrole, and pyridine benzimidazole structures **85–93**. Biological activity studies showed that the compounds containing pyridine rings, compounds **91–93**, displayed strong antiviral activity against RNA-replicating enteroviruses, whilst compound **88** manifested activity against all four types of tested viruses (Scheme S-15, ESI file†).¹²⁹ Newer derivatives, 2-chloro-, 2-bromo- and 2-iodo-5,6-dichlorobenzimidazole ribonucleosides, **101–106**, obtained in moderate-to-high yields (68–90%), were prepared by substituting the nitrogen atom of 5,6-dichlorobenzimidazole-2-

amines with bis(trimethylsilyl)acetamide, followed by reaction with 1,2,3,5-*tetra-O*-acetyl-β-D-ribofuranose (TAR). The compounds, **101–106**, showed interesting antiviral activity against two types of viruses. The brominated compound exhibited four times more antiviral activity than the compound containing the chlorine atom (Scheme 5).¹³⁰

The anomeric carbon atom of *tetra*-acetate ribose assisted the synthesis of a new set of benzimidazole *N*-riboses, 5-chloro-2-methoxy, 2-thioalcoxy, and 2-thiones **110–121**, through the *N*-acetylation of the 2-chloro-5-nitrobenzimidazole compound **107**. The synthesized products elicited higher levels of antiviral activity against different types of viruses, except compounds **114** and **117**, which were weakly active against the HCM virus and possessed no cytotoxicity within their antiviral dose range (Scheme S-16, ESI file†).¹³¹ Another set of reactions involving ribose anomeric acetate was used to produce 5'-modified 2,5,6-trichlorobenzimidazole ribonucleoside compounds, **123–127**, *via* the *N*-condensation of the 2,4,5-trichlorobenzimidazole substrate **122**. The methanol group of the ribonucleoside was converted to azidomethyl and chloromethyl groups, yielding compound **128**. The newly synthesized products also showed





Scheme 5 The synthesis of 2-chloro-, bromo-, and iodo-5,6-dichlorobenzimidazole ribonucleoside derivatives.

antiviral activity against certain other viruses, especially against HCM (Scheme S-17, ESI file†).¹³²

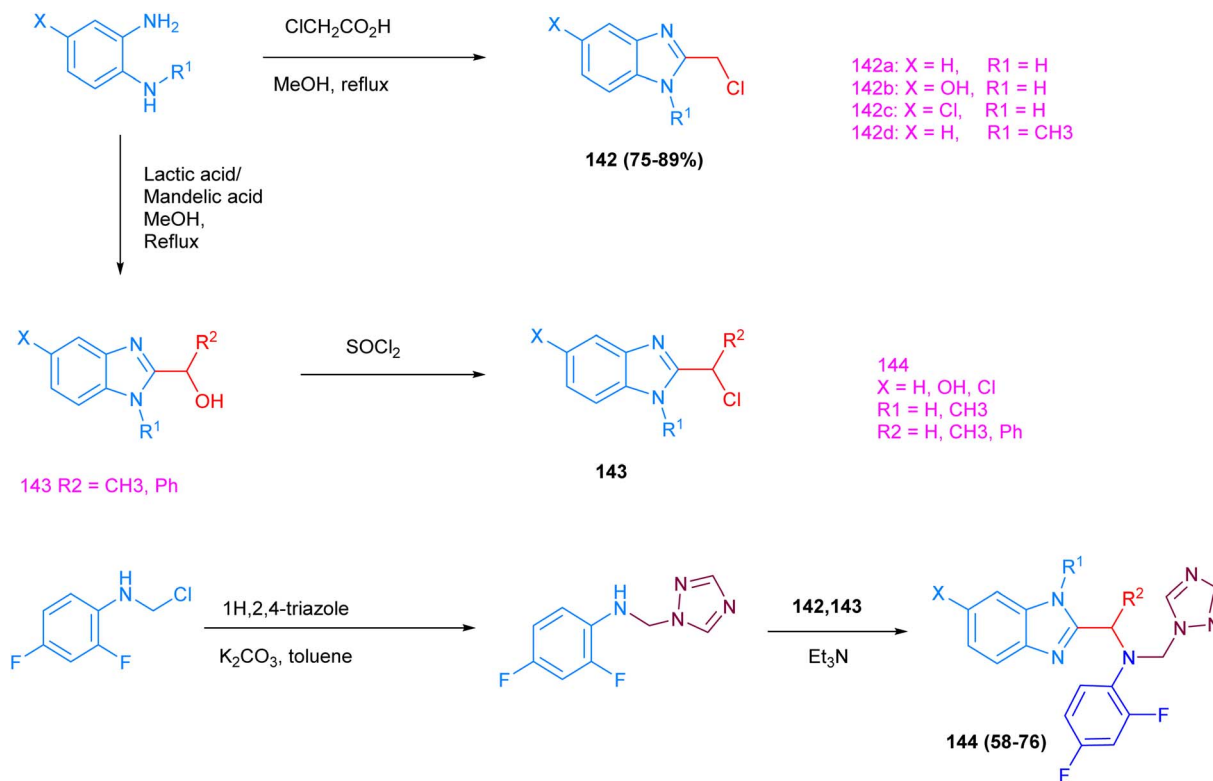
The introduction of sulpho-coumarins to the benzimidazole nucleus led to the synthesis of two series of 2-sulfurmethylenecoumarin- and 2-sulfurmethylenecoumarin-*N*-(2,3,5-triacetatoxy-pyran-4-yl)-benzimidazole 5,6-disubstituted derivatives, **131a–k**, and **134a–e**, which were synthesized from the double condensation of the benzimidazole-2-thione products **129a–f** with the 3,4,5,6-tetracetoxypyran and 3-chloromethylchromen-2-one compounds **130a–c**. The obtained products showed high activity against HCV, especially the compound 2-[(6-bromocoumarin-3-yl)methylene-thio]-5-fluorobenzimidazole, **131i**, and its derivative, 1-[(2,3,4,6-tetra-*o*-acetyl)glucopyranos-1-yl]-2-[(6-bromocoumarin-3-yl)methylenethio]benzimidazole, **134c** (Scheme S-18, ESI file†).¹³³ Additionally, in a single step, the 1-alkoxy-2-alkylbenzimidazole compounds **146–150** were produced *via* reacting the synthon 2-methyl-6-nitro-phenylamine, **145**, with primary iodo-alkanes in the presence of NaH as a strong base. The products **146–150** exhibited antiviral activity against certain viruses. Antiviral testing indicated that compound **148** was the most effective anti-HIV-1 product in the series (Scheme S-19, ESI file†).¹³⁴

Thus, a number of benzimidazole-based products, especially ribofuranose-containing and brominated products, and imidazole, pyrrole, and pyridine benzimidazole structures showed significant antiviral activity.

2.3 Antifungal compounds

The versatility of the benzimidazole molecular framework has been confirmed based on the strong antifungal activities^{135,136} of the prepared derivatives. New analogues containing tertiary amine, substituted benzimidazole, and triazole moieties have been synthesized, and screened against *Candida albicans* spores with significant levels of bioaction. Among the *N*-methyl- and *N*-phenyl-substituted benzimidazole derivatives, **144a–i**, containing an asymmetric carbon atom bound to C2, hydrogen, chlorine, or the hydroxyl group present on C5, the tertiary amine and 1,2,4-triazole substructures were synthesized in moderate yields through the reaction of difluoro-phenyl amino methyl triazole with the 2-chloromethylene benzimidazole derivatives **142** and **143**. The products manifested strong antifungal activity (Scheme 6).¹³⁷ However, the inherent toxicity of this series of compounds and the anti-bacterial resistance pushed the discovery of newer derivatives with improved antifungal activity.





Scheme 6 The synthesis of asymmetric-carbon-containing **144a–i**, where a benzimidazole moiety is C2-bonded with an *N*-methylene 1,2,4-triazole-*N*-(2,4-difluorophenyl) derivative.

Compound **147**, a 4-amino-5-phenyl-2,4-dihydro-[1,2,4] triazol-3-one benzimidazole derivative, was successfully prepared through the substitution of 5-chloro-2-(1-chlorobenzyl)-1*H*-benzimidazole **145** with amino-triazolone, compound **146**. Compound **147** was evaluated for its antifungal properties against *Candida glabrata*. The compound possessed a polar side chain and OH and SH groups, which culminated in it exhibiting higher potential for antifungal action (Scheme S-20, ESI file†).¹³⁸

Another interesting new series of benzimidazole-based Schiff base derivatives, **150**, was synthesized *via* the condensation of 1,6-disubstituted benzimidazole-2-carbaldehydes, **148**, and phenyl hydrazine derivative compounds, **149**. The antifungal activities of the final compounds were tested. The bioassay results indicated that noticeable inhibitory activity against *R. solani* and *M. oryzae* was shown by most of the synthesized compounds. The highest *in vitro* inhibition activities, which exceeded the reference drug's EC₅₀ value at 1.20 μg mL⁻¹ and 1.85 μg mL⁻¹, respectively, were shown by the compounds bearing 2,4-difluoro groups in their structures (Scheme S-21, ESI file†).¹³⁹

Moreover, recently, 10 new 2-aryl benzimidazole derivatives, **151a–g**, were also synthesized through the cycloaddition of substituted phenyl carbaldehydes and 4-substituted 1,2-phenylenediamine, catalysed in the presence of H₂SO₄/SiO₂ and reacted under microwave heating. The antifungal activities were evaluated against several filamentous fungi, *i.e.*, *Candida albicans*, *C. dubliniensis*, *C. parapsilosis*, *C. krusei*, *C. tropicalis*,

Cryptococcus neoformanse, *Aspergillus flavus*, *Aspergillus clavatus*, *Alternaria alternate*, *Microsporum canis*, and *Trichophyton mentagrophytes*. Among the synthesized derivatives, the compound containing fluorine at the *para*-position of the benzene ring exhibited the highest antifungal activity at a dose of 8.64 μg mL⁻¹ (Scheme S-22, ESI file†).¹⁴⁰

Thus, the pharmacophoric value of the benzimidazole molecular template was also demonstrated in terms of antifungal potency. Nonetheless, another benzimidazole derivative, a benzimidazole triazole, **156**, was obtained through a sequence of five steps. The benzimidazole compound, **152**, obtained through the condensation of 4-methyl-*o*-phenylenediamine with *p*-formyl methyl benzoate, after undergoing a reaction with hydrazine, produced the hydrazide **153**. The hydrazide **153** further underwent a reaction with isothiocyanate to yield the corresponding thiosemicarbazide **154**. Cyclization in a basic medium produced the corresponding 4-substituted-5-[4-(5-methyl-1*H*-benzimidazol-2-yl)-phenyl]-4*H*-[1,2,4]triazole-3-thiol compound **155**, which, finally, upon reacting with 2-bromo-1-phenylethanone yielded the final product **156**. All the new compounds in the synthetic sequence were evaluated for their antifungal activity against *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, and *Candida albicans*. According to biological evaluation assays, the majority of the derivatives showed moderate to strong antifungal activity against all the tested fungal strains. Compounds possessing 3,4-dihydroxy phenyl groups manifested the highest inhibitory activities against the fungal strains, with MIC₅₀ values ranging from 0.78



to 1.56 $\mu\text{g mL}^{-1}$. The products were also non-toxic at their bio-effective concentrations (Scheme S-23, ESI file†).¹⁴¹

Furthermore, various benzimidazolium *N*-phenyl methylthioformates, **158** and **159**, spirano-benzimidazolium, **160**, methyl dithioformic esters, **161** and **162**, and a 2-ethane nitrile 1,3-disubstituted benzimidazole compound, **163**, were synthesized. Synthesis was achieved by reacting the 3,1'-disubstituted-1,3'-diphenylethyl-2,2'-[2,2']bibenzoimidazolylidene compound **157** with isothiocyanate, isocyanate, carbon disulphide, and acetonitrile, which produced a number of products, **158–163**, of which compound **160** was the most active compound as an antifungal product (Scheme S-24, ESI file†).¹⁴² Another synthetic scheme involving the use of a benzimidazole molecular template produced 1,2-bis-(2-mercapto-benzoimidazol-1-yl)-ethane-1,2-dione, compound **165**, via the double condensation of the mercapto-benzimidazole synthon derivative **164** upon reacting with diethyl carbonate. Reaction with copper(II) and nickel(II) metal complexes of bis(ethane diamine) yielded the corresponding diiminic bis-(2-thiol benzimidazole) complexes **166**. The Cu(II) complex was far more active against fungi than the Ni(II) analogue due to the effects of the metal ion on the cells (Scheme S-25, ESI file†).¹⁴³ Another interesting benzimidazole-oxadiazole framework-based derivative, **170**, was produced as an antifungal agent. The corresponding carbonyl compound **168** was transformed, in the first step, via condensation with *p*-formyl methyl benzoate and 4-substituted *o*-phenylene-diamine, followed by the reaction of hydrazine hydrate with the corresponding benzimidazole phenyl ester **167**. Cyclization with carbon disulphide led to the mercapto-oxadiazole product **169**, which, when reacted with various derivatives of phenacyl bromides, produced multiple components. The compounds **186h** and **186p** were found to be promising candidates for further development towards the treatment of fungal infections (Scheme S-26, ESI file†).¹⁴⁴ Additionally, a series of fused thiazolo-benzimidazole benzoxazole products, **173**, was also synthesized in three consecutive steps. The first step involved the reaction of 5-substituted 2-mercapto-benzimidazole with benzofuran-2-yl-ethanone in an acidic medium, leading to the corresponding sulfanyl ketone **171**. Compound **171** was later converted through an intramolecular cycloaddition reaction, catalysed in the presence of PPA (polyphosphoric acid), to the corresponding 3-benzofuran-2-yl-benzo[4,5]imidazo[2,1-*b*]thiazole compound **172**. Further, through a one-pot three-component reaction, the latter compound reacted with a secondary amine and formaldehyde to yield the fused benzimidazole-thiazole analogue **173**. Biological activity testing results showed that the dibromo-substituted compounds were the most active products against the tested fungi, compared to the mono-bromo-substituted compounds (Scheme S-27, ESI file†).¹⁴⁵ A synthetically interesting agricultural fungicide, a benzo-[4,5]-imidazo[1,2-*d*][1,2,4] triazine derivative, was also synthesized through the condensation of 2-chloroacetic acid or 2-bromopropionic acid with *o*-phenylene-diamine to form the corresponding benzimidazole product **174**, which, when reacted with substituted phenylhydrazine, produced the corresponding hydrazino-benzimidazole compound **176**. Compound **176**, when treated

with an excess of a mixture of chloroformate and triethylamine, was converted to yield a 1,2,4-triazol-3-one fused benzimidazole through an intramolecular cyclization reaction. The product exhibited fungicidal activity at 50 $\mu\text{g mL}^{-1}$ (Scheme S-28, ESI file†).¹⁴⁶

A series of 2-chloromethyl-1*H*-benzimidazole derivatives was achieved through multistep reactions. The initial step consisted of the condensation of 2-chloroacetic acid with *o*-phenylenediamine derivatives in acidic media, leading to 2-chloromethylbenzimidazole structures. These intermediates were later reacted with acyl-chloride and methyl sulphate to produce *N*-methylated benzimidazole and *N*-acylated benzimidazole products, **178** and **181**. Benzimidazole derivatives also reacted with 2-chloro-*N*-methyl-*N*-(2-methylamino-phenyl)-acetamide, **179**, and *o*-phenylenediamine, thereby yielding the corresponding targeted benzimidazole derivatives **180a–q** and **183a–n**. Several of these alkoxy-methyl-1*H*-benzimidazole products were effective against a number of agricultural fungi (Scheme S-29, ESI file†).¹⁴⁷ An extension of substituted *o*-phenylenediamine and substituted phenyl acrylic acids also produced compounds as a series of novel 5-(nitro/bromo)-substituted 2-styryl benzimidazole derivatives. In this context, compound **184** was synthesized in ethylene glycol, which showed that bromo-containing compounds were more biologically active than nitro-containing compounds against fungi for this specific molecular framework (Scheme S-30, ESI file†).¹⁴⁸

Furthermore, a library of 2-benzimidazolylimino-5-arylidene-4-thiazolidinones, compounds **188a–k**, was also synthesized. The approach started with the condensation of chloro-acetyl chloride to 2-aminobenzimidazole, yielding the corresponding chloro-acetamide, compound **185**, which underwent intramolecular cyclization to produce the fused tricyclic compound 1*H*-1,3*a*,8-triaza-cyclopenta[*a*]inden-2-one, **186**. Compound **185** was also reacted with ammonium thiocyanate to yield 2-(1*H*-benzoimidazol-2-ylamino)-thiazol-4-one, compound **187**, which, when treated with substituted benzaldehydes, produced the targeted pharmacophores **188a–k**. These compounds were tested for their potential antifungal effects and showed positive activity against agricultural fungi, especially against the phytopathogens *B. elliptica*, *Fusarium graminearum*, *P. nicotianae*, and *R. solani* (Scheme S-31, ESI file†).¹⁴⁹ A simple and effective approach towards the synthesis of the benzimidazole derivative **189** was established using *o*-phenylene-diamine and a substituted aldehyde, which were reacted in the presence of a mild catalyst, nano-SnCl₄/SiO₂. The compound was active in bioactivity testing against various yeasts and filamentous fungi, based on the broth microdilution method of testing (Scheme S-32, ESI file†).¹⁴⁹

2.4 Anti-protzoal activities

Strong levels of antiprotzoal activity are reportedly shown by benzimidazole-derived compounds.^{150,151} A series of benzimidazole pentamidine compounds was synthesized in which the peripheral amidine groups of the pentamidine moiety were transformed into substituted benzimidazole groups, which led to better antiprotzoal activity being shown by the products,

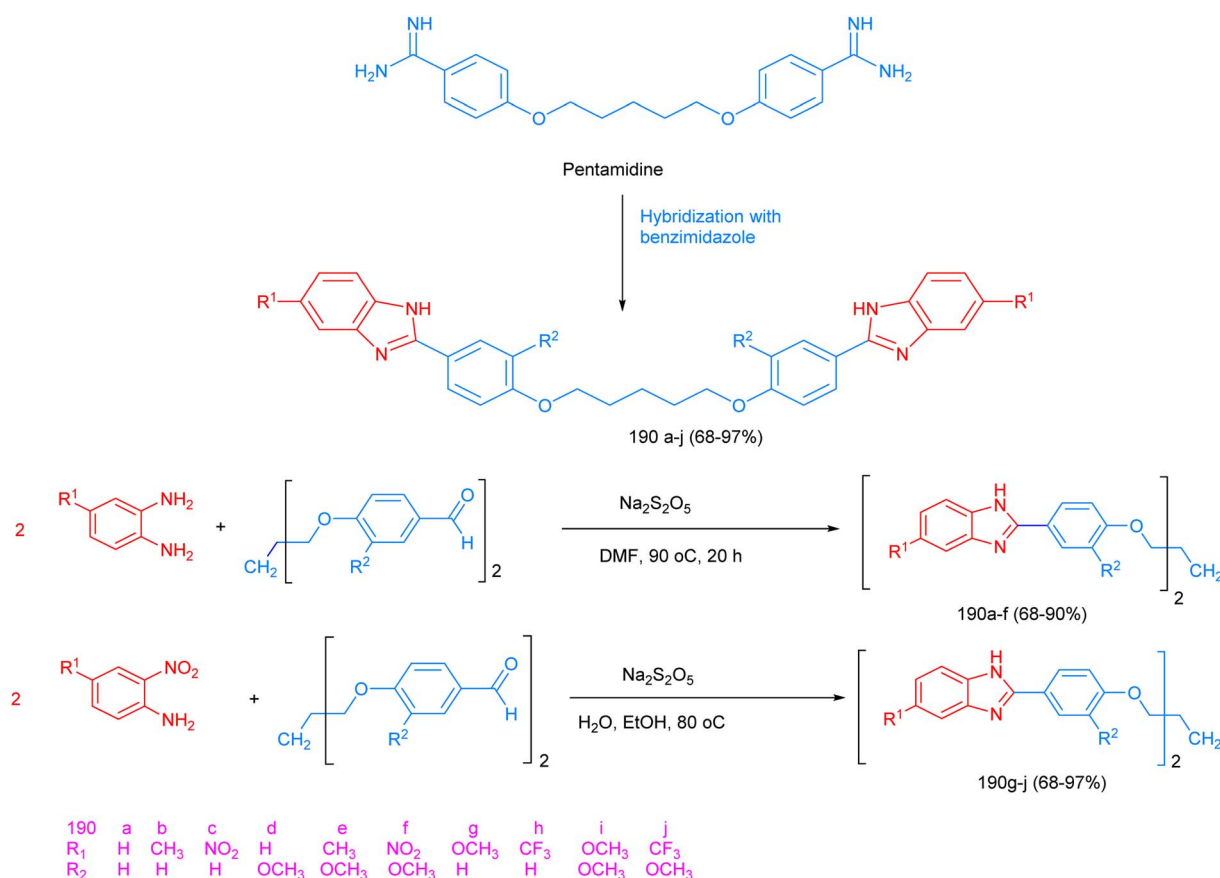


especially compound **190**. Another concurrent approach produced compounds **190a–j** in 68–90% yields, with diversified substitutions; these also exhibited desired levels of antiprotozoal activity (Scheme 7).¹⁵²

2-(2-Amino-4(5)-nitro-1*H*-benzimidazol-1-yl)-*N*-arylaceta-mides were also synthesized as antiprotozoal compounds. First, bromo-cyanogen was reacted with activated 4-nitro-*o*-phenylenediamine to produce the corresponding product 2-amino-5-nitrobenzimidazole. The intermediate was then condensed with 2-chloro-*N*-aryl-acetamide to afford a mixture of regio-isomeric products, 4- and 5-nitrobenzimidazole-*N*-aryl-acetamides, as the compounds **191** and **192**. These compounds were found to be antiprotozoal products (Scheme S-33, ESI file†).¹⁵³ In another attempt, a synthetic strategy for biphenyl benzimidazole diamidines was developed, which primarily consisted of the synthesis of 5-cyano-2-(cyanoaryl) benzimidazoles, **194a–i**, through the condensation of a substituted 3'-formyl-biphenyl-carbonitrile, **3a**, with 3,4-phenylene-diamines, yielding the desired active products. The two cyano groups of compounds **194a–i**, when treated with hydrochloric hydroxylamine, were transformed into the corresponding *N*-hydroxy amidines (compounds **195a–i**). These intermediates were later reduced into the corresponding amidine groups (compounds **196a–i**). These compounds displayed remarkable biological activities, and compounds **196c**, **196d**,

196f, **196h**, and **196i** were good antiprotozoal products. Also, there were three compounds, **196f**, **196h**, and **196i**, which showed significant improvements in bioactivity compared to the furamidines **IIa** and **III** (Scheme S-34, ESI file†).¹⁵⁴

Among other antiprotozoal products, the synthetic approach to 2-[[2-(1*H*-imidazol-1-yl)ethyl]sulfanyl]-1*H*-benzimidazole has been outlined in detail. The compound 2-mercapto-1,5,6-trisubstituted-1*H*-benzimidazole, **197**, which was obtained from the condensation of carbon disulphide with the corresponding 1,2-diaminobenzene, showed bioactivity. Compound **197** reacted with 1-(2-chloro-ethyl)-1*H*-imidazole to yield the corresponding thioether **198**. The developed series of compounds, **198d–g**, was treated with methyl iodide to produce the corresponding benzimidazolium salts. These benzimidazole derivatives manifested higher biological activities than the reference standard compound. Compounds **198p–s** were the most active of all in the series and showed strong antiprotozoal activities (Scheme S-35, ESI file†).¹⁵⁵ Contextually, sulphur heterocycles containing a series of benzimidazole derivatives of thieno[2,3-*d*]pyrimidin-4-ones, prepared through the condensation of substituted benzimidazole, 2-mercaptobenzimidazole, and 2-mercaptomethylbenzimidazole with 2-(2-chloro-ethyl)-5,6-disubstituted-3*H*-thieno[2,3-*d*]pyrimidin-4-one, showed considerable levels of antiprotozoal activity (Scheme S-36, ESI file†).¹⁵⁶



Scheme 7 The synthesis of the spaced bis(2-arylbenzimidazoles) **190a–j**.



The synthetic route to *N*-methylated benzimidazole esters and amides, **205–208**, involved the synthesis of an intermediate, 5,6-disubstituted-1-methylbenzimidazole-2-carbaldehyde, compound **204**, which was prepared in two steps from *o*-phenylenediamine and 2-hydroxyacetic acid; it was easily converted to the corresponding ester and amide derivatives. Bioactivity testing exhibited moderate antiprotozoal activity, thereby indicating that the ester analogue compounds were more active than others in the series (Scheme S-37, ESI file†).¹⁵⁷ Another series of new benzimidazole–benzothiazole entities connected with an amide moiety, obtained from *N*-methyl-2-nitrobenzoate, was synthesized through saponification in the first step, followed by condensation with 2-amino-5-nitrothiazole, yielding the product. The study also mentioned that the compounds **211** and **212** were strongly active as antiprotozoal agents (Scheme S-38, ESI file†).¹⁵⁸

Moreover, the condensation of *o*-phenylenediamine with both 3-trifluoromethyl cinnamic acid and iso-nicotinic acid yielded the corresponding 2-substituted-benzimidazole intermediates **213** and **214**, which were further reacted with aminopyridines under microwave conditions, in the presence of formaldehyde, yielding the corresponding 2,3-disubstituted benzimidazoles, **215** and **216**, which possessed high antiprotozoal activity (Scheme S-39, ESI file†).⁴⁰

2.5 Antimalarial compounds

Several benzimidazole derivatives were proposed, synthesized, and investigated for their bioactivity as antimalarial agents against several malaria-causing pathogenic *Plasmodium* species,¹⁵⁹ e.g., *P. falciparum*, *P. ovale*, *P. malariae*, *P. vivax*, and *P. knowlesi*.¹⁶⁹ For the synthesis of antimalarial agents, 6-*O*-, and *N*-substituted diamino pyridine derivatives, **217**, were condensed with cyanogen bromide to yield the 2-aminobenzimidazole analogue compounds **218**, which were later reacted with phenacyl bromide to produce the 6-substituted 2-amino-3-benzoylbenzimidazole compounds **219**. Upon reduction, they yielded the corresponding alcohols, **220**. Many 2-amino-pyridin-benzimidazole derivative products were also produced, which displayed antimalarial activity. These newly synthesized products were quick to kill pathogens, and showed an absence of cross-resistance, together with a low

frequency of pathogenic resistance re-emergence. The products also showed excellent oral bioavailability (Scheme 8).¹⁶⁰ These products had the distinction of being active and non-cross-resistant against the studied pathogens.

Recently, a new antimalarial compound, identified as the fused pyrido[1,2-*a*] benzimidazole **223**, was synthesized under microwave conditions through the nucleophilic substitution of the chlorine atom of the tetracyclic compound **222**, obtained from 3,4-disubstituted aniline **221**. The bioactivity was tested under *in vivo* and *in vitro* conditions (Scheme S-40, ESI file†).¹⁶¹

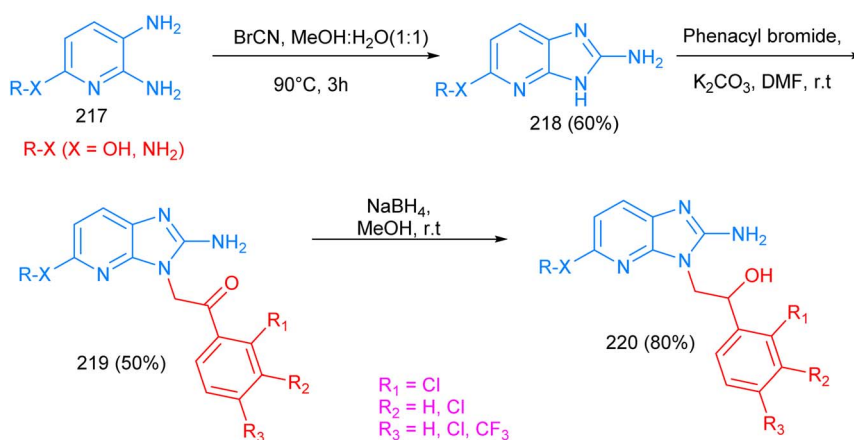
2.6 Antitubercular compounds

New benzimidazole derivatives containing nitrogen heterocycles are conspicuously present in the antitubercular drug domain.¹⁶² Heterocycles containing *N*-atom(s) have been pursued in search of new chemical entities and new drug lead(s) for developing newer anti-tubercular agents.¹⁶³ In this context, a library of 5-methyl-carboxylate-substituted benzimidazole derivatives, **225**, was prepared *via* the condensation of *N*-alkyl diaminobenzoate with sodium phenyl methane sulfonate with DMF as the solvent at 90 °C, with high yields (75–84%). The antitubercular activities of derivative compounds with the base structure **225** were evaluated against mycobacteria. The results demonstrated that the most effective compound contained a trifluoromethyl group in its structure (Scheme 9).¹⁶⁴

Moreover, a novel series of compounds, 2-styryl-benzoyl-1*H*-benzimidazoles, was synthesized from the base compound **30** by the condensation of 3,4-diaminobenzophenone with malonic acid (method 1) or acetic acid to produce the corresponding 2-methyl benzimidazole derivatives, which were later reacted with aromatic aldehydes (method 2). 5-Nitro homologous structures based on template **31** were prepared. Antitubercular activity screening of the products showed better bioactivity with electron-donating-group substitution, *i.e.*, Cl, O, and S, in the structural frameworks (Scheme S-41, ESI file†).¹⁶⁵

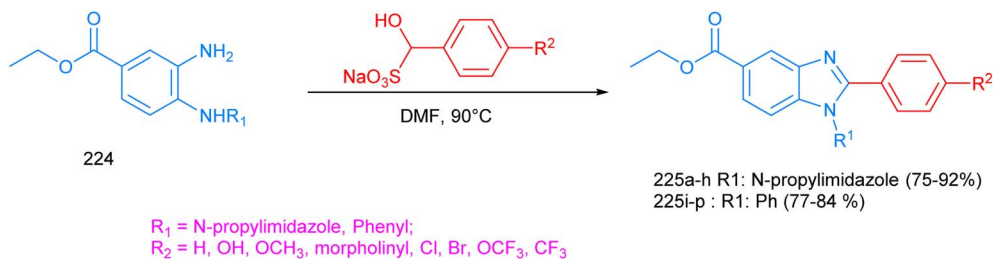
2.7 Anti-inflammatory and analgesic compounds

Benzimidazole-core-derived compounds have also been shown to possess anti-inflammatory activity in parallel to nonsteroidal



Scheme 8 The synthesis of 3-*N*-trisubstituted phenylethanol-3*H*-imidazopyridin-2-amines in three steps from substituted diamino-pyridines.



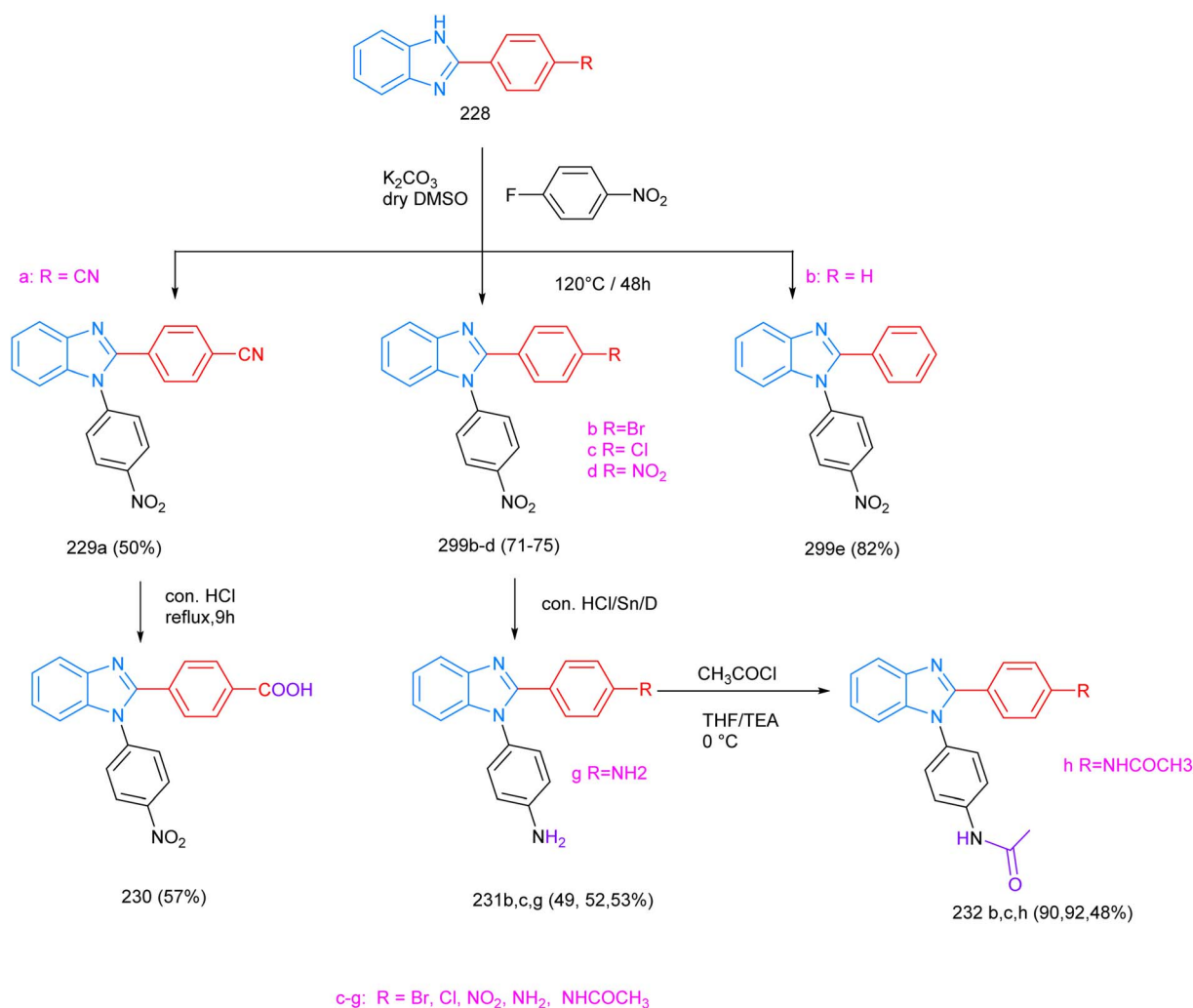


Scheme 9 The synthesis of 5-methyl-carboxylate 2,3-disubstituted benzimidazoles 225.

anti-inflammatory drugs (NSAIDs). The compound *N*-(4-(2-phenyl-1*H*-benzo[*d*]imidazol-1-yl) phenyl)acetamide, **232**, was synthesized according to Scheme 10.¹⁶⁶ The 2-*p*-substituted-aryl benzimidazoles **228** were reacted with *p*-nitro-fluorobenzene to produce the corresponding 3-*p*-nitrophenyl-2-*p*-substituted-aryl benzimidazole compounds **229a–g**. When treated with concentrated HCl, the cyano group of compound **229a** was transformed into the carboxylic acid derivative **230**. In the presence of HCl and Sn, compounds **229c–g** underwent the reduction of the nitro group into an amine. This functional

group was then transformed into the corresponding acetamide by simple treatment with acetyl chloride to produce the target compound **232**. During bioactivity testing, 1,2-diphenyl benzimidazoles (DPBIs) with *para*-nitro and *para*-bromo substitutions at N1-Ph and C2-Ph (**232**, R = *p*-NO₂, R = *p*-Br), obtained in relatively low yields (48–57%), exhibited high anti-inflammatory activities under *in vitro* and *in vivo* conditions.

Additionally, 2-methylthiobenzimidazole compounds with different combinations of aromatic and heterocyclic substituents were synthesized in multiple steps. This approach started

Scheme 10 The synthetic approach to 3-*p*-acetamide phenyl-2-*p*-substituted-aryl benzimidazoles 232.

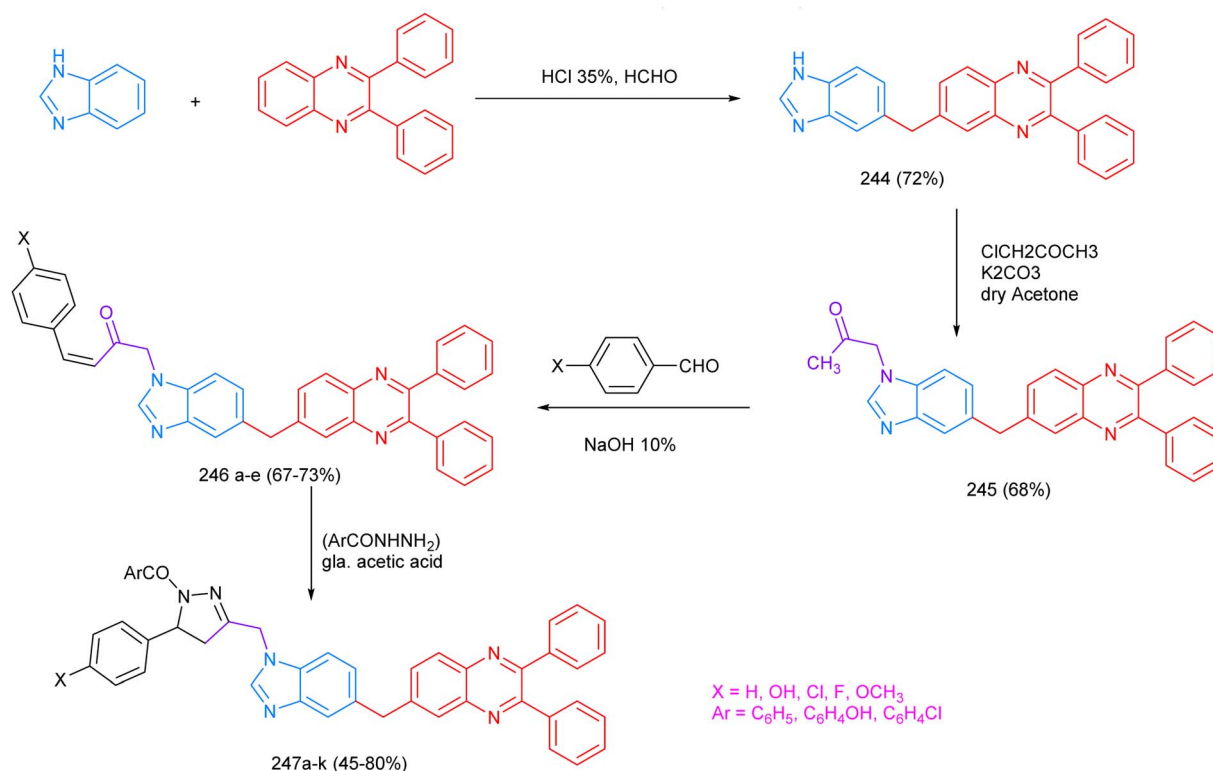
with the synthesis of 4-(2-methylthiobenzimidazol-1-yl)-thiazol-2-ylamine **233**, which was obtained from the treatment of 2-methylthio-1*H*-benzimidazole with chloro-acetyl chloride, thiourea and hydroxylamine. The heterocyclic nitrogen atom of substrate **233** acted as a nucleophile to yield the iminic salt **234**. In certain other reactions, the primary amine functional group of the same substrate reacted as a nucleophilic species with halogen derivatives to generate the corresponding amino-ketones **235a–b** and the amide **236**. In particular, compound **234** underwent intramolecular cycloaddition upon refluxing in (2 N) HCl solution and then washing with aq. NH₄OH to yield the fused heterobicyclic imidazo[2,1-*b*]thiazole benzimidazole product **237**. In turn, compound **235b** underwent a reaction with phenyl thiosemicarbazide to produce the corresponding product **238**, which was reacted with *p*-substituted and unsubstituted phenacyl bromide and methyl bromo acetate to afford the target products **239** and **240**, thereby incorporating a second thiazole ring (Scheme S-42, ESI file†).¹⁶⁷ *In vitro* screening showed that benzimidazole–thiazole hybrids linked to the acetyl moiety, phenyl thiosemicarbazone, 1,3-thiazolines, 4-thiazolidinedione, and 1,3-thiazoline substituted with *p*-chlorophenyl moieties were the highest inhibitors of the COX-2 enzyme. The benzimidazole-thiazole derivative possessing a 4-thiazolidinedione substructure exhibited the highest inhibition under *in vivo* assay conditions.

Furthermore, a novel compound, the 2-methylaminobenzimidazole derivative **241**, was also synthesized *via* the *N*-alkylation of 2-chloromethylbenzimidazole and *p*-substituted aniline. The analgesic and *in vivo* anti-inflammatory

biological activities were tested. Most of the new compounds showed potent analgesic and anti-inflammatory activity compared to the corresponding reference drugs (Scheme S-43, ESI file†).¹⁶⁸ Moreover, a number of substituted 2-(2-hydroxynaphthyl)-3-alkyl benzimidazole derivatives, **241**, were synthesized *via* the condensation of substituted *o*-phenylenediamines with 2-hydroxynaphthaldehyde. The appropriately obtained benzimidazole derivative **242** was later reacted with an alkyl iodide. The target compound **243** possessed analgesic activity (Scheme S-44, ESI file†).¹⁶⁹ The products **241** and **243** and benzimidazole–thiazole extended products were active at higher levels as analgesic and anti-inflammatory compounds. The thiazole derivative was the highest level COX-2 inhibitor.

2.8 Antihistamine compounds

Another set of benzimidazole-derived multiple-ring expanded phenyl-pyrazole conjugated benzimidazole-quinoxaline derivatives was synthesized. The products showed considerable levels of antihistaminic activity. The synthetic processes utilized the condensation of benzimidazole, 2,3-diphenylquinoxaline, and formaldehyde to yield the corresponding methylene-spaced hybrid benzimidazole-quinoxaline derivative **244**. The obtained product was reacted with chloroacetone to introduce a methyl ketone group, forming molecule **245**, which was further condensed with *p*-substituted benzaldehyde(s), leading to the corresponding aromatic enone-derivative-based products **247** in 45–80% yields. The compounds were later reacted with aryl carbazide to afford the corresponding *N*-substituted 4,5-



Scheme 11 The synthetic route to *N*-substituted 4,5-dihydropyrazolic benzimidazole-quinoxaline derivatives **247**.



dihydropyrazolic benzimidazole-quinoxaline derivatives **247** (Scheme 11).¹⁷⁰

Another series of extended-ring benzimidazole derivatives, 2-(3-aminopiperidin)-benzimidazoles, was proposed as a H1-antihistamine for insomnia therapy. One of these new derivatives exhibited activity equivalent to the currently used H1-antihistamine. The synthetic route was implemented through the condensation of *o*-phenylenediamine with piperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester, yielding the corresponding 2-substituted benzimidazole derivative **248**, which underwent two successive alkylation reactions with halogen derivatives to yield the expected target product **250** (Scheme S-45, ESI file†).¹⁷¹ The 2-(3-aminopiperidin)-benzimidazole was very active as a H1-antihistamine, and it holds promise for the future.

2.9 Antihypertensive activity

A set of 5-nitro benzimidazoles bearing 1,4-disubstituted and 1,5-disubstituted indole components was prepared through the *N*-acylation of 4-nitro-*o*-phenylenediamine, yielding the amidic compound **251**, which underwent an intramolecular cyclization reaction to produce the corresponding benzimidazole product **252**. Condensation with (4-(bromomethyl)-1*H*-indol-1-yl)(phenyl)methanone **253** yielded the corresponding product 1-(1*H*-indol-4-ylmethyl)-5-nitro-2-alkyl-1*H*-benzimidazole **254**. The nitrogen atom of the indole moiety was reacted with 2-fluorobenzonitrile, which led to the corresponding benzimidazole-indole-benzonitrile, product **255**. Product **255** was refluxed under basic conditions to transform it into a carboxylic acid, the final target product **256** (Scheme S-46, ESI file†).¹⁷² The results of bioactivity studies showed antihypertensive activity. The compound 11,2-(4-((2-butyl-5-nitro-1*H*-benzo[*d*]imidazole-1-yl) methyl)-1*H*-indol-1-yl)benzoic acid, **256c**, was the most active product.

Additionally, another series of 6-substituted benzimidazole-indole derivatives was prepared from 1,4-disubstituted or 1,5-disubstituted indole and benzoic acid moieties. According to Scheme S-47,† the 2-(2-substituted-7-methyl-3*H*-benzimidazol-5-yl)-4,6-disubstituted benzoxazole **257** reacted with the 4- or 5-bromomethyl-1-(2-methylcarboxylate) indoles **258a–b** to yield the corresponding *N*-alkylated indole carboxylate derivatives **259** and **260**, which, when converted by refluxing in basic media, produced the targeted benzimidazole-oxazole-indole carboxylic acid derivatives **261** and **262**. The bioactivity results indicated that compounds **261b** and **262b** effectively reduced blood pressure, and they were considered effective against hypertension (Scheme S-47, ESI file†).¹⁷³ Another di-substituted benzimidazole product, 2,5-disubstituted benzimidazole **263**, was produced by condensing 4-substituted *o*-phenylenediamine with salicylaldehyde and *p*-anisaldehyde under microwave irradiation conditions. The expected target products manifested antihypertensive activity. The reaction was extended to differently substituted compounds. Among the prepared products, compounds **263c–f** were the most active of the series (Scheme S-48, ESI file†).¹⁷⁴ Other structurally extended benzimidazole compounds, bis-benzimidazole-indole-benzoic acid derivatives **266**, were reported in terms of their synthesis and

biological activity. The 2-(4-bromomethyl-indol-1-yl)-benzimidazole **264** was reacted with 2'-substituted-1,7'-dimethyl-1*H*,3'*H*-[2,5']bis-benzimidazolyl, which yielded the corresponding product **265**; after hydrolysis in a basic medium, this yielded the expected target product, **266**. Among these benzimidazole derivatives, compound **266c** was an effective antihypertensive product (Scheme S-49, ESI file†).¹⁷⁵

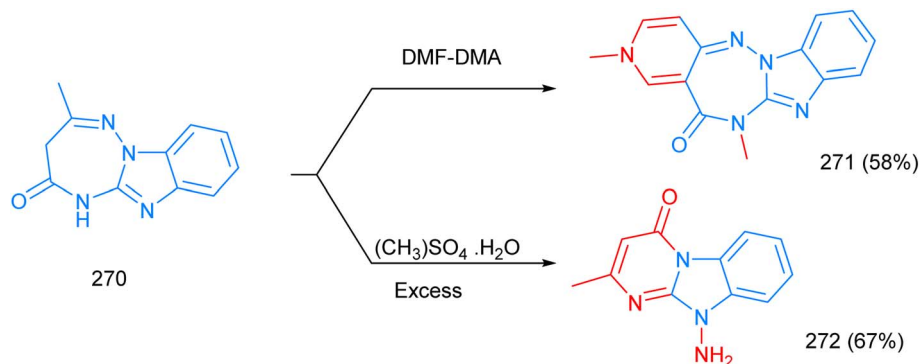
Another series of benzimidazole analogues, 4'-2-butyl-5-sulfamoylbenzimidazolmethyl-biphenyl-2-carboxylic acids **269**, was prepared when an amine was mixed with 5-chlorosulfonyl benzimidazole **268**, which was obtained by treating 4-(2-butyl-benzimidazol-1-ylmethyl)-biphenyl-2-carboxylic acid **267** with chlorosulfonic acid. Among the series of 5-alkylsulfamoyl benzimidazole derivatives, compounds **269g** and **269h** showed significant antihypertensive activity (Scheme S-50, ESI file†).¹⁷⁶ The compounds in the series **266** and **269** exhibited promising anti-hypertensive activity.

2.10 Antidiabetic compounds

A benzimidazole core template has also been utilized as a bioactive pharmacophore for developing antidiabetic compounds. Hyperglycaemia is widespread in the global population and is almost endemic to a large extent. Several drug candidates and lead compounds have been developed to maintain glucose levels below a recommended control value and within prescribed limits. Benzimidazole derivatives demonstrated high levels of antidiabetic activity.¹⁷⁷ Two new compounds, namely 3,6-dimethyl-5-oxo-pyrido[3,4-*f*][1,2,4]triazepino[2,3-*a*]benzimidazole **271** and 10-amino-2-methyl-4-oxo-pyrimido[1,2-*a*]benzimidazole **272**, were synthesized. When reacted with DMF-DMA, 6-methyl-7*H*,9*H*-4*b*,5,9,10-tetra-aza-benzo[*a*]azulen-8-one, compound **270**, containing a benzimidazole moiety, transformed into the fused tetra-heterocyclic product **271** in 58% yield. After treatment with an excess of methyl sulphate in an aqueous medium, the same substrate underwent an intramolecular rearrangement, yielding the fused tricyclic amino product **272** in 67% yield. Compound **271** exhibited high biological activity against both α -amylase and α -glucosidase enzymes, while the latter derivative, compound **272**, showed comparatively lower levels of bioactivity against both enzymes (Scheme 12).¹⁷⁸

2-Mercapto-benzimidazole, a sulfurized benzimidazole derivative, was utilized for producing another set of antidiabetic compounds; it was reacted with ethyl 2-chloroacetate through a nucleophilic reaction to yield the thio-ester **273**. When treated with hydrazine hydrate, the thio-ester functional group was transformed into the corresponding thio-semicarbazide-benzimidazole, intermediate **274**, which later underwent a reaction with various carboxylic acid derivatives in the presence of POCl₃, forming the corresponding 1,3,4-oxadiazole-based structure **275**. However, when compound **274** was reacted with an aldehyde followed by a reaction with 2-thioacetic acid, this yielded the amidic thiazolidin-4-one benzimidazole product **277**. The thiazolidinone **275** and oxadiazole **277** products, possessing a 2-mercapto benzimidazole nucleus, were tested *in vivo* for their antidiabetic activity using the oral glucose tolerance





Scheme 12 The synthesis of 3,6-dimethyl-5-oxo-pyrido[3,4-f][1,2,4]triazepino[2,3-a]benzimidazole **271** and 10-amino-2-methyl-4-oxo-pyrimido[1,2-a]benzimidazole **272**, which are described to be antidiabetic agents.

test (OGTT), and superior antidiabetic activity was shown by the compounds with NO₂, OH, and Cl substituents (Scheme S-51, ESI file†).¹⁷⁹

Based on predictive studies, the compound (5*Z*)-5-[3(4)-(1*H*-benzimidazol-2-yl-methoxy)benzylidene]-1,3-thiazolidine-2,4-dione **279** was synthesized when 2-chloromethylbenzimidazole reacted with phenols to form the equivalent benzimidazole intermediate coupled with a phenoxy group, **278**. This compound underwent an electrophilic substitution at the *meta*-position with a thiazolidine-2,4-dione moiety. The three newly synthesized benzimidazole-pharmacophore-possessing compounds showed antihyperglycemic activity related to insulin sensitization (Scheme S-52, ESI file†).¹⁸⁰

Another novel antidiabetic product, *N*-substituted-2-[4-(2-substituted-benzimidazol-1-ylmethyl)-[1,2,3] triazol-1-yl]-acetamide **280**, was synthesized. The condensation of 2-substituted benzimidazole with propargyl bromide yielded the corresponding *N*-propargylated benzimidazole intermediate. The intermediates were later reacted with a mixture of sodium azide and 2-bromo-ketone, in the presence of copper(i) as a catalyst, through a click chemistry approach to yield the 1,4-disubstituted 1,2,3-triazole product **280**. The new analogues of product **280** were screened for their antidiabetic activity. All the compounds manifested significant activity toward the α -amylase and α -glucosidase enzymes in antidiabetic testing (Scheme S-53, ESI file†).¹⁸¹ 26 new derivatives resulting from the structural diversification of fused benzimidazoles and oxadiazoles were synthesized. The synthetic approach involved the condensation of 3-methyl-*o*-phenylenediamine and 4-formylmethylbenzoate, leading to the corresponding 4-(7-methyl-1*H*-benzimidazol-2-yl)-methyl benzoate product **281**, which was transformed into the hydrazide intermediate **282**, which, when treated with hydrazine hydrate and different aryl carbaldehydes, produced the hydrazone derivative **283**. The hydrazine compound underwent intramolecular cyclisation and, catalysed by PhI(AcO)₂, was transformed into the 2-substituted-[1,3,4] oxadiazole product **284**. The product and its several derivatives displayed strong enzymatic inhibition activity against α -glucosidase. The compound activities were also validated through molecular docking studies (Scheme S-54, ESI file†).¹⁸²

Recently, a library of benzimidazole–triazolothiadiazole derivatives was prepared. The compound 4,5-dimethyl-*o*-phenylenediamine was reacted with 4-carboxybenzaldehyde to produce the corresponding compound 4,5-dimethylbenzimidazole-benzoic acid **285**. When treated with thiosemicarbazide, the obtained compound was converted into 4-amino-4*H*-benzimidazole-[1,2,4]triazole-3-thiol **286**, which was then reacted with carboxylic acid in the presence of POCl₃ to produce the fused bicyclic 6-substituted-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazole benzimidazole derivative **287**. The product **287** and its derivatives were evaluated as β -glucuronidase inhibiting agents, and they manifested higher antidiabetic activity compared to the reference standard agent *D*-saccharic acid 1,4-lactone (Scheme S-55 ESI file†).¹⁸³

Another new benzimidazole-based derivative, benzoyl aryl benzimidazole **289**, was synthesized using ammonium chloride or a mixture of ammonium chloride and sodium metabisulfite as a catalyst. The compound 3,4-diamino benzophenone **288** and appropriately substituted aryl aldehydes were reacted. *In vitro* antidiabetic assays of product **289** and its derivatives/ analogues showed good-to-exceptionally-high antidiabetic activity against α -amylase and β -glucosidase. The target benzimidazole, an analogue of product **289**, having a hydroxyl group at the *p*-position of the phenyl part of the structure of the product **289**, demonstrated significant inhibitory activity against α -amylase (IC₅₀ = 12.09 ± 0.38 M) and β -glucosidase (IC₅₀ = 11.02 ± 0.04 M) in comparison to the reference standard acarbose (Scheme S-56, ESI file†).¹⁸⁴

Another series of newer benzimidazole derivatives, combining sulphur and hydrazide functionalities, which had shown good antidiabetic activity, was proposed and synthesized. The compound 2-thioester hydrazide **290** was reacted with carboxylic acid in the presence of POCl₃ to yield the 1,3,4-oxadiazole intermediate **291**. When treated with aldehydes, the compound yielded the benzimidazole hydrazine product **292**. The compound **292** and its derivatives were reacted with mercaptoacetic acid in DMF in a reducing medium to yield the corresponding benzimidazol-2-ylthio-*N*-2-methyl-4-oxothiazolidin-3-yl-acetamide product **293**. The set of benzimidazole derivatives showed remarkable antidiabetic activity. The bioactivity test results favoured the four compounds



291c, **291d**, **291h** and **291i**, which were highly active (Scheme S-57, ESI file†).¹⁸⁵

Another set of benzimidazole analogues, derived from 7-methyl-3*H*-imidazo[4,5-*b*]pyridine **295**, were prepared through the condensation of 4-methyl-pyridine-*o*-diamine **294** with aromatic aldehydes under microwave heating conditions. The compound **295** was oxidized using $\text{KMnO}_4/\text{NaOH}$ to yield the corresponding carboxylic acid derivative **296**, which was reacted with a 4-substituted pyridinic primary amine to allow the production of the secondary amide target **297**. The final products, imidazopyridine analogues of benzimidazole, were thus prepared, and their antidiabetic activity was tested. The products displayed strong effects in terms of reducing blood glucose levels in experimental models (Scheme S-58, ESI file†).¹⁸⁶

Another series of antidiabetic products, starting from the condensation of 5-nitrophenylenediamine with [4-(4-formyl-phenyl)-cyclohexyl]-ethyl ethanoate **298**, produced the desired compound 5-amino-3-substituted benzimidazole **299**, which acted as a nucleophile with different electrophilic species to produce the corresponding *N*-alkylated-benzimidazole phenyl cyclohexyl ethyl ethanoate compound series **300a–p** from the appropriately derived intermediates **298** and **299**. The compound **300k** exhibited distinctive antidiabetic activity (Scheme S-59, ESI file†).¹⁸⁷

N-Benzyl, *N*-benzoyl, and *N*-diphenyl benzimidazole derivatives, compounds **302**, **303** and **304**, were synthesized through reactions involving the fused tri-heterocyclic benzimidazole structure **301**, providing a range of functionalized bromide derivatives as the products. Among the synthesized benzimidazole derivatives, compounds **302-2b** and **302-3b** displayed the highest antidiabetic activity during biotesting (Scheme S-60, ESI file†).¹⁸⁸

Another type of benzimidazole-derived products, metal-complexed compounds, was prepared with the aim of finding better antidiabetic agents. The compound 1-(2-methyl-benzimidazol-1-ylmethyl)-1*H*-benzotriazole was complexed with Cu(II) chloride, Cu(II) nitrate, and Zn(II) chloride to yield the corresponding bidentate metal complexed species **305**, **306** and **307**, respectively. The compounds $[\text{Cu}(\text{mbmb})_2\text{Cl}_2]$ (**305**) $[\text{Cu}(\text{mbmb})_2(\text{NO}_3)_2]$ (**306**), and $[\text{Zn}(\text{mbmb})_2\text{Cl}_2]$ (**307**), which structurally contained 1-[(2-methyl-1*H*-benzimidazol-1-yl)methyl]-1*H*-benzotriazole as part of the final metal-complexed

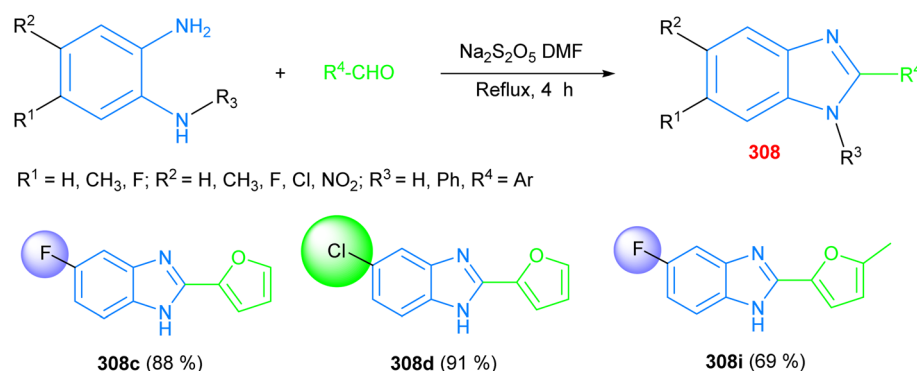
products, were tested against three enzymes, namely α -amylase, α -glucosidase, and β -galactosidase, for their antidiabetic efficacy. The compound **305** showed a higher level of activity as an antidiabetic product in α -amylase testing, while the compound **307** showed no significant level of antidiabetic activity (Scheme S-61, ESI file†).¹⁸⁹

Notwithstanding that benzimidazole-templated structures offer a wide spectrum of biological activity as potent antidiabetics, the development of benzimidazole-based antidiabetic products is still ongoing. A series of newer products was obtained from the condensation of differently substituted *o*-phenylenediamines with aryl aldehydes in the presence of sodium metabisulfite to yield the disubstituted aryl benzimidazole based structures **308**, with 88%, 91%, and 69% yields, respectively, of the products **308c**, **308d**, and **308i**, where the chloro-derivative **308d** was the highest-yield product. *In vitro* screening of these products manifested considerable levels of α -amylase inhibition, particularly the chloro- and fluoro-substituted products **308c**, **308d** and **308i**, all of which showed high IC_{50} values, ranging from 1.86 ± 0.08 M to 3.16 ± 0.31 M, compared to the standard acarbose ($\text{IC}_{50} = 1.46 \pm 0.26$ M) (Scheme 13).¹⁹⁰

The synthesis of the 2-aryl benzimidazole derivative **309** was achieved *via* the condensation of 4,5-disubstituted-1,2-aminobenzene under reflux in DMF using $\text{Na}_2\text{S}_2\text{O}_5$. The yields of the products **309a–k** varied from low to moderate to high levels. *In vitro* testing of the α -amylase inhibitory activity followed. All the products exhibited α -amylase inhibitory potential compared to the reference standard acarbose ($\text{IC}_{50} = 1.46 \pm 0.26$ M), with IC_{50} values ranging from 1.48 ± 0.38 M to 2.99 ± 0.14 M for the products (Scheme 14).¹⁹¹ A number of products, including the 2-aryl, Cu-metal-complexed, and benzoyl aryl benzimidazoles, showed anti-diabetic activity nearly on par with the reference standard compound used for antidiabetic activity.

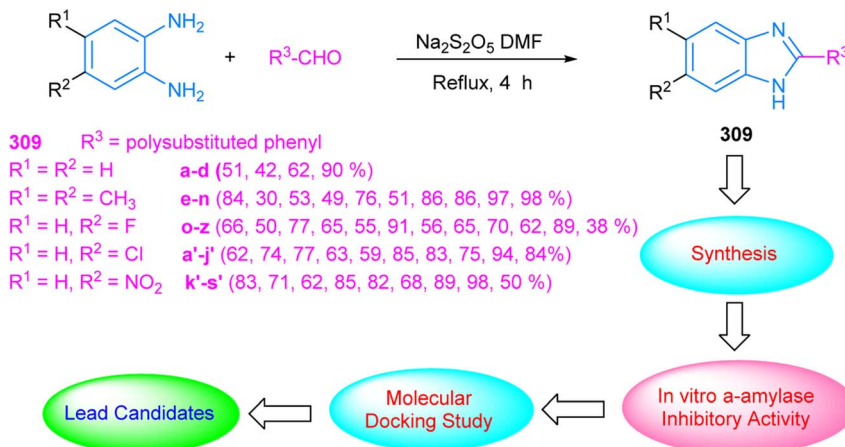
2.11 Anticancer compounds

Benzimidazole-templated compounds have also been found to be some of the most significant heterocyclic structures in terms of showing considerable levels of cytotoxic effects under *in vitro* and *in vivo* experimental conditions. The anticancer properties of benzimidazole products have been studied against several



Scheme 13 The synthesis of disubstituted aryl-benzimidazoles **308**, which can act as antidiabetic agents.





Scheme 14 The synthesis of the targeted 2-arylbenzimidazole derivatives **309**.

cancer cell lines.¹⁹² Among the developed compounds, a new series based on the ethyl-(1,2-disubstituted)-5-carboxylate benzimidazole derivative **310**, which was obtained from the condensation of 3,4-diamino ethyl benzoates (produced after three synthetic steps) with 4-substituted benzaldehydes in an aqueous medium and in the presence of sodium bisulphite solution in 76–90% yields, showed potent sirtuin inhibition activity (SIRT1/SIRT2). Among the new derivatives, ethyl-2-(4-(dimethylamino)-phenyl)-1-phenyl-1*H*-benzo[*d*]-imidazole-5-carboxylate displayed high SIRT2 inhibition, with an IC_{50} value of $26.85 \pm 1.92 \mu M$, with the product showing antitumor activity against three cancer cell lines, *i.e.*, colon (HCT-116), breast (MDA-MB-468), and leukaemia (CCRF-CEM) (Scheme 15).¹⁹³

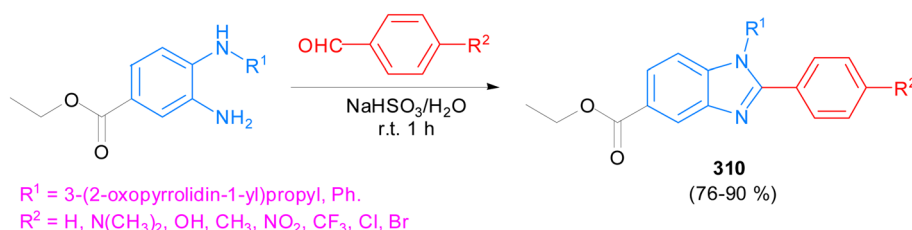
Another series of benzimidazole derivatives, compounds **311**, **312** and **314**, incorporating tetracyclic sub-structures, was synthesized through the one-step microwave-assisted condensation of substituted 1,2-diaminobenzene with cyclohexane, 1,2-cyclohex-4-ene carboxylic anhydride, and (1-carboxymethyl-cyclohexyl)-acetic acid. The anticancer activities of all the synthesized compounds were established against breast (T47D), lung (NCl H-522), colon (HCT-15), ovarian (PA-1) and liver (Hep G2) cancer cell lines. Some of the synthesized benzimidazole derivatives exhibited satisfactory anti-proliferative activity, with IC_{50} values ranging from $7.5 \pm 0.3 \mu M$ to $14.6 \pm 0.4 \mu M$ (Scheme S-62, ESI file†).¹⁹⁴ Also, several other variants of structurally diverse heterocyclic compounds containing benzimidazole and pyrazole substructures were synthesized by condensing 1,3-disubstituted pyrazole-4-carbaldehyde **314** with (1*H*-

benzimidazol-2-yl)-acetonitrile. The cyano-benzimidazole-pyrazole compound **315** was successful against the pancreatic cancer cell lines SW1990 and AsPCL, with IC_{50} values of $30.9 \pm 0.77 \mu M$ and $32.8 \pm 3.44 \mu M$, respectively, when compared with gemcitabine as a reference standard drug. The compound containing a *p*-fluorophenyl substituent was among the most active products (Scheme S-63, ESI file†).⁸¹

Recently, more structurally complex benzimidazoles based on a 2-((imidazole/benzimidazol-2-yl)thio)-aryl ethanone template, **316**, were obtained by neutralizing mercapto-keto-imidazolium sulphate salts, which were produced by the reaction of 2-mercapto-1*H*-imidazole and 3-oxo-3-aryl ethyl propionate. The anticancer activity was evaluated in cell-based assays against the human breast cancer cell lines T4-7D and MCF-7, and compared with the cell-free cyclin-dependent kinase 2 assay. The test results indicated that these products possessed good antiproliferative activity (Scheme S-64, ESI file†).¹⁹⁵

As a type of metallo-organic product, manganese-based hexacoordinated complexes were produced using 1-benzyl-1*H*-benzimidazoles as ligands and 2,2'-bipyridine as co-ligands, having the general formula, $Mn(CO)_5(bpy)L$. These complexes showed promising anticancer activity in preliminary testing (Scheme S-65, ESI file†).¹⁹⁶

Also, 2-amino-benzimidazole and 1-methyl-imidazole-2-carbaldehyde were reacted to lead to the corresponding Schiff base, compound **318**. The obtained product was used as a ligand to prepare copper(II)- and zinc(II)-complexed structures having the framework of compound **319**. The prepared



Scheme 15 The synthesis of 5-ethyl-carboxylate-2-(4-substituted phenyl)benzimidazoles **310**, which can act as anticancer agents.



Review

complexes showed anticancer effects. The copper complex was also active as an anti-breast-cancer complex (Scheme S-66, ESI file†).¹⁹⁷

Another newer series of benzimidazole compounds derived from {5-[4-(methyl-oxetan-3-yl-amino)-benzoyl]-1*H*-benzimidazol-2-yl}-methyl carbamate, **320**, was prepared by the condensation of 4-substituted-*o*-phenylenediamine with 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea in methanol under microwave irradiation. The benzimidazole-derived product, with water soluble characteristics, showed effects against lung and prostate cancers when administered orally (Scheme S-67, ESI file†).¹⁹⁸

Yet another benzimidazole derivative, **326**, was prepared in seven steps starting from salicylic acid. Upon treatment with acetic acid, compound **324** was converted to the corresponding benzimidazole intermediate, which was transformed into 2'-(2-hydroxyphenyl)-1*H*,1'*H*-[2,4']bibenzimidazolyl-4-methyl carboxylate, compound **326**, under hydrogenation using H₂/Pd-C. The benzimidazole-based compounds **324**, **325** and **326** manifested significant biological activities against the human lung cancer cell line A-549 and epithelial and HeLa cell lines (Scheme S-68, ESI file†).¹⁹⁹

In a similar manner, 2-hydroxynaphthalene imino-benzimidazole, compound **327**, was intuitively produced by condensing methyl-2-amino-1*H*-benzimidazol with 2-hydroxy naphthaldehyde in ethanol. The resulting product was employed as a ligand for coordination with zinc(II) (69%), cobalt(II) (74%), and copper(II) (82%) salts, showing effects against liver, skin, colon, breast, and cervical cancer cell lines; the compound containing Zn(II) was far more active than the compounds containing Cu(II) and Co(II) as part of the metal-complexed structure (Scheme S-69, ESI file†).²⁰⁰

A series of benzimidazole-biphenyl-pyrazolo-ethenones based on the structure template **332** was prepared. Benzimidazole-acetic hydrazide reacted with the chalcone **331** to produce the compounds. The target set of benzimidazole structures **332** showed interesting anticancer activities. The product **332a** proved its efficacy against lung cancer cell lines (Scheme S-70, ESI file†).²⁰¹

The 5-chloro- and carboxy-1*H* benzoimidazol-2-yl-acetonitriles **333a** and **b** were used as starting materials to synthesize diversely functionalized, heterocyclic acetonitrile products, including thiazolidin-4-one **334b**, 4-amino-3-substituted-3*H*-thiazole-2-thiones **335a₁** and **335a₂**, 3-substituted-5-oxo-thiazolidin-2-ylidenes **338a₁**, **338a₂**, **339a₁**, and **339a₂**, 3,4-disubstituted-3*H*-thiazol-2-ylidenes **340a₁**, **b₁**, and **b₂**, and 3-substituted-[1,3]thiazinan-2-ylidenes **341a** and **b**. After being evaluated under *in vitro* conditions against human cell lines expressing human colon carcinoma (HCT 116), human breast adenocarcinoma (MCF7), and human hepatocellular carcinoma (HEPG2), the produced compounds showed anticancer activity, with IC₅₀ values of less than 10 μg mL⁻¹ (Scheme S-71, ESI file†).²⁰²

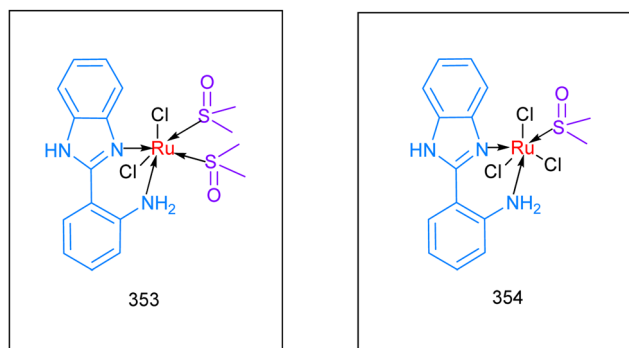
For another interesting series of anticancer compounds, the chalcone precursor **342** was obtained by reacting 2-acetyl benzimidazole with a substituted aromatic aldehyde to produce several derivative intermediates. These intermediates were then

cyclo-condensed using hydrazine hydrate and phenyl hydrazine in two different processes, producing the pyrazoline derivatives **343a-g** and **344a-g**, respectively. It was discovered that the 2-[5-(3,4-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-3-pyrazolyl] **344f** was the most active product in the series. After closely examining the substitutions, it was inferred that the electron-donating group (-OCH₃) on the phenyl ring at the fifth position of the pyrazoline moiety played a significant role in the anticancer activity (Scheme S-72, ESI file†).²⁰³

With the aim of synthesizing new thiazolidinedione compounds, both conventional and microwave-assisted approaches were used. The reaction of 3,4-diamino methyl benzoate with tetra-substituted benzaldehydes in the presence of Na₂S₂O₅ as a reducing agent produced the 2-phenyl-substituted benzimidazolyl methyl carboxylate products **345a-d**. The ester groups of these compounds were reduced to primary alcohols to yield the products **346a-d**, which underwent moderate oxidation reactions to lead to the corresponding aldehydes **347a-d**. The products **347a-d** were used as starting materials to undergo condensation with 2-(2,4-dioxo-thiazolidin-3-yl) derivatives to yield the 5-methylenebenzimidazole-3-substituted thiazolidine-2,4-dione structures **349a-t**, **350a-d**, **351a-d** and **352**. Interestingly, a panel of human cancer cell lines, including breast (MDAMB231), prostate (PC-3), cervical (HeLa), lung (A549), bone (HT1080), and kidney (HeK-293T), were utilised to assess the *in vitro* cytotoxic potentials of some of these newly synthesized compounds **349n**, **349p** and **349q**, and these products showed strong cytotoxic effects. Anticancer efficacy toward PC-3, HeLa, A549, and HT1080 cancer cells was exhibited, with IC₅₀ values ranging from 0.096 to 0.63 μM. In contrast to the tested cancer cell lines, the majority of the products was determined to be ineffective against normal HeK-293T kidney cells. The treatment of the cell lines with compounds **349p** and **349q** resulted in the desired morphological characteristics of apoptosis, *i.e.*, nuclear fragmentation and cell shrinkage. Additionally, the test products caused the assembly of F-actin proteins to be disrupted, which inhibited cell migration. As demonstrated by Hoechst and DCFH-DA staining and mitochondrial membrane and annexin binding tests, the growth of cancer cells was suppressed, inducing apoptosis in the A549 cell line (Scheme S-73, ESI file†).²⁰⁴

Furthermore, two novel ruthenium-DMSO-based metal complexes with 2-aminophenyl benzimidazole were also synthesized. The ruthenium-DMSO-based complexes **353** and **354** were synthesized by the complexation of 2-(2-aminophenyl)-benzimidazole with RuCl₃ salt in DMSO. In compound **353**, ruthenium is coordinated with the benzimidazole nitrogen atom, aniline nitrogen, two chlorides, and two DMSO molecules. In compound **354**, ruthenium is connected to the benzimidazole nitrogen atom, aniline nitrogen, three chlorides, and one DMSO species. The anticarcinogenic activity of these products was tested under *in vitro* and *in vivo* conditions. The *in vitro* screening was performed against the human breast cancer cell line MCF7, the human colorectal cancer cells Caco-2, and the normal human liver cell line THLE-2. The metal complex **353** displayed mild *in vitro* anticancer activity with lower toxicity towards normal cells, while the other complex **354** manifested high inhibition potential under *in vivo* conditions (Scheme 16).²⁰⁵





Scheme 16 The ruthenium–DMSO-based complexes 353 and 354.

Moreover, Schiff bases derived from 2-aminophenyl benzimidazoles were also synthesized as probable anticancer agents. The compounds 3-[[2-(1*H*-benzimidazol-2-yl)-phenylimino]-methyl]-phenyl-2-ol 355 and naphthalen-2-ol 356 (HL1 and HL2) were complexed with $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in the presence of 2-mercaptobenzothiazole or 2-aminobenzothiazole as a sulphur source, with sulphur being a contributor to cytotoxicity. The four obtained complexes, compounds 357–360, showed tetrahedral coordination. Based on *in vitro* anticancer activity testing against A-549, Caco-2, HT29 and RPE-1 cell lines, the best anticancer activity results were obtained with complex 358, which presented higher activities towards both the A-549 and Caco-2 cell lines, indicating good selectivity for the human lung cancer cell line A-549 and moderate selectivity for the colorectal cell line Caco-2 at doses of 10.9 and 15.7 μM , respectively (Scheme 17).⁸³ The importance of these metal complexes is well understood in the anticancer realm, especially as anti-lung-cancer agents. However, compound 358 needs to be evaluated under *in vivo* conditions. In general, the metal complex compounds discussed in this section are superior in terms of bioactivity during preliminary testing under *in vitro* conditions and seem promising for future development. Thus, in the anticancer area of pharmacological activity, benzimidazole-based metal-complexed compounds hold promise for the future.

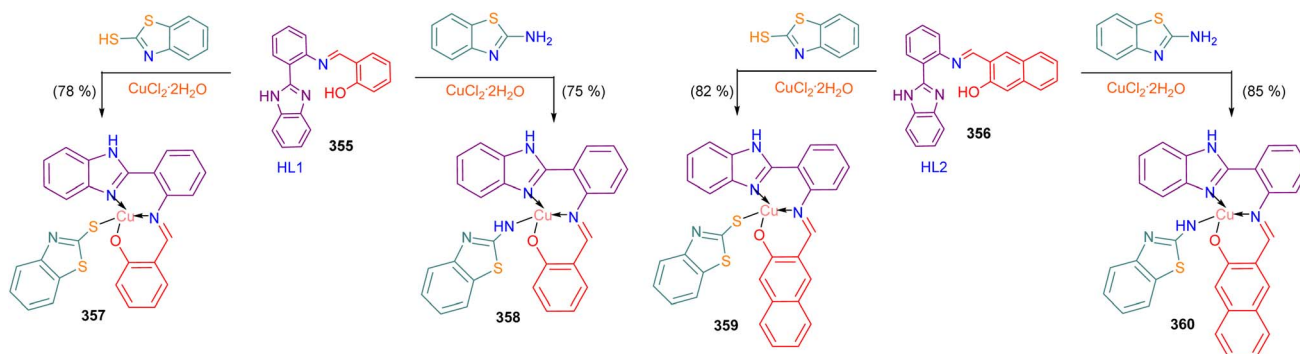
Additionally, other Schiff bases were produced from 2-aminomethylbenzimidazole and naphthaldehyde, compound 361. The intended complexes were synthesized by reacting one equivalent of an ethanolic solution of the ligand (H2L) with one

equivalent of a metal chloride salt (ZrCl_4 , $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, and $\text{CdCl}_2 \cdot 6\text{H}_2\text{O}$). Based on *in vitro* antitumor activity testing of the complexes, the cadmium complex 362 showed significant cytotoxicity against MCF-7, Hep G2 and HCT 116 cell lines. The iron complex product 363 also presented strong cytotoxicity towards the Hep G2 and HCT cell lines, together with moderate activity against the MCF-7 cell line (Scheme S-74, ESI file†).²⁰⁶

2.12 Antioxidant compounds

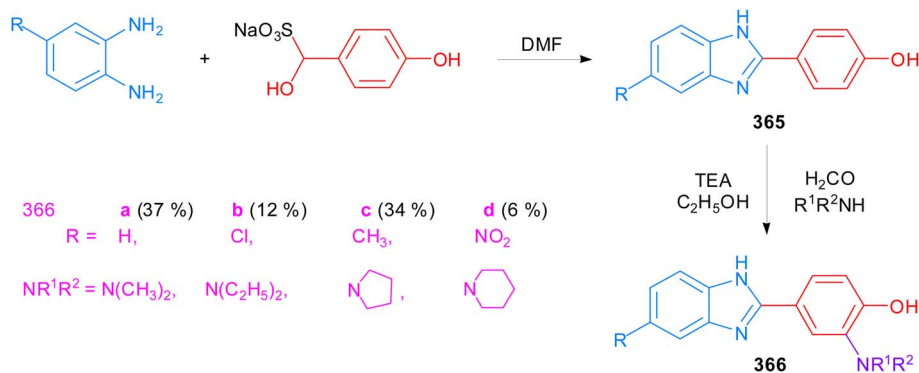
For the design and synthesis of several antioxidant compounds, benzimidazole-templated molecules were chosen. Detrimental reactive oxygen and nitrogen species (ROS and RNS) and other free radicals, considered as the progenitors of physiological malfunction and biological disorders in living beings, have been effectively neutralized by large numbers of chemical entities, including both naturally sourced and synthetic products.^{207–210} Certain amines possessing N–H bonds have also functioned as antioxidant molecules,^{211,212} and, against this backdrop, benzimidazole products were designed and synthesized as antioxidant agents. In one synthetic approach, sodium bisulphite was reacted with 4-hydroxybenzaldehyde to yield hydroxy methane sodium sulfonate, which reacted under *in situ* conditions with 4-substituted *o*-phenylenediamines to yield the 2,4-disubstituted benzimidazole derivatives of compound 365. Compound 365 underwent the Mannich reaction at the *ortho* position of the phenolic group with formaldehyde and a tertiary amine derivative to reach the target compound based on template 366, though in low yields. The benzimidazole derivatives worked well as potent antioxidants, and the Mannich-benzimidazole derivatives' phenolic function was experimentally validated, showing them to be strong antioxidant agents. The results showed that most of these derivatives (Scheme 18) can be referred to as free radical scavengers and potent antioxidants.²¹³

Moreover, combining *N*-methyl-*o*-phenylenediamine or 2-amino-phenol with aromatic aldehydes and aromatic acids, in the presence of polyphosphoric acid (PPA) as an effective catalyst and solvent, under an efficient synthetic protocol allowed the formation of novel 2-substituted benzimidazole and benzoxazole derivatives; these were confirmed to have the structure 367, and were potential antimicrobial and antioxidant agents.



Scheme 17 The synthesis of Schiff base complexes derived from 2-aminophenyl benzimidazoles.





Scheme 18 The synthesis of the Mannich-benzimidazole derivatives **366** possessing phenolic functionality, which were tested as antioxidant agents.

When compared to conventional medications, the newly synthesized benzoxazole and benzimidazole derivatives exhibited good to excellent antibacterial and antioxidant properties (Scheme S-75, ESI file†).²¹⁴

Another set of benzimidazole-component-based products was synthesized to act as strong antioxidants. The reaction of benzimidazole-based derivatives with thiazole analogues provided products **368**, based on alkyl-thiourea and 2-bromo-1-(1-methyl-1*H*-benzimidazol-2-yl)-ethanone, which exhibited exceptional antioxidant activity in comparison to the tested reference standard antioxidant molecule. *In vitro* antioxidant testing of the final products showed significantly stronger radical scavenging capacity than the widely recognized antioxidant standard BHA (Scheme S-76, ESI file†).²¹⁵

In another recently reported study, antioxidant compounds based on 5,6-dimethyl-2-phenyl-1*H*-benzimidazole derivatives were successfully synthesized. The compound 5,6-dimethyl-2-phenyl-1*H*-benzimidazole was reacted with 2-bromoethyl ethanoate, and the ester group was transformed into the corresponding hydrazide **369**, whereupon the intermediate **369** was used as the starting material for various extended reactions aimed towards the targeted preparations of antioxidant compounds. Upon reacting with benzaldehyde, isothiocyanate, and carbon disulphide, the hydrazide compound afforded the hydrazone **370**, thiosemicarbazide **371**, and 2-mercapto-[1,3,4]-oxadiazole **372**, respectively. The compounds **371** were hydrolysed under basic conditions to produce the [1,2,4]-triazole-3-thiol benzimidazole compounds **373**; then, in an acidic medium, the reaction yielded [5-(5,6-dimethyl-2-phenylbenzimidazol-1-ylmethyl)-[1,3,4]-thiadiazol-2-yl] alkyl amine compounds **374**. Most of the new compounds exhibited moderate levels of antioxidant activity. Higher levels of antioxidant activity were reported for the compounds possessing carbothioamide- and 1,2,4-triazole-derivative-based substructures (Scheme S-77, ESI file†).²¹⁶ Meanwhile, another class of antioxidant compounds that included indole-tethered benzimidazole-based 1,2,3-triazoles was also developed. Reactions of propargyl bromide with 1*H*-indole-3-carbaldehyde, followed by condensation with *o*-phenylenediamine, yielded the corresponding

2-(1-prop-2-ynyl-1*H*-indol-3-yl)-1*H*-

benzimidazole product **375**, which was again reacted with aromatic azides through a click chemistry reaction. It was catalysed by Cu(I) and led to the 2-[1-(1-aryl-1*H*-[1,2,3]-triazol-4-ylmethyl)-1*H*-indol-3-yl]-1*H*-benzimidazole compound **376** and its derivatives. The obtained derivatives showed antioxidant radical scavenging potential, with IC₅₀ values ranging from 8.50 to 10.05 μg mL⁻¹. It was observed that the presence of 4-methyl, 2-methoxy, and 4-methoxy substituents on the phenyl ring resulted in strong antioxidant activity (Scheme S-78, ESI file†).²¹⁷

Another series of compounds with strong antioxidant activity was synthesized incorporating the benzimidazole core as the principal pharmacophoric and molecular template. In the presence of the reducing reagent Na₂S₂O₅, arylaldehydes were condensed with 3,4-diamino-benzene, benzoic acid, benzonitrile, and sulfonic acid to produce the corresponding 2-aryl-5-(nitrile, carboxylic acid, and sulfonic acid) benzimidazole products **377a-d**. The three categories of aryl benzimidazole derivatives were evaluated for their antioxidant properties against various radicals using DPPH, FRAP, and ORAC assays, revealing varying levels of radical scavenging activity. The results indicated that the number and positions of hydroxy groups on the 2-aryl part, as well as the presence of a diethylamino or 2-styryl group, correlated well with the high antioxidant activity (Scheme S-79, ESI file†).²¹⁸

Two newer series, 2-(aryl)-6-morpholin-4-yl-benzimidazole derivatives **378** and 4-methylpiperazin-1-yl-benzimidazole derivatives **379**, were synthesized from 5-morpholin-4-yl- and 5-(4-methylpiperazin-1-yl)-2-nitroaniline using aryl aldehydes. The process was realized *via* a one-pot synthetic protocol through the reduction of the nitro group, followed by a cyclization step with sodium hydrosulphite as the reducing agent, adopting both conventional and microwave energy techniques for all the reactions carried out in this synthesis. The benzimidazole-based morpholines and piperazines possessed the potential to be used as a pharmaceutical source for antioxidant action, which was demonstrated by the reported results. A majority of the synthesized products showed high scavenging activity based on the CUPRAC, FRAP, DPPH, and ABTS methods of antioxidant activity testing. It was specifically the compounds containing morpholine and piperazine rings at the C-6 position



of the benzimidazole ring that were the most active products (Scheme S-80, ESI file†).²¹⁹

A new series of benzimidazoles, obtained using the aza-Michael reaction, in the form of 1,3-disubstituted benzimidazole-2-thiones was synthesized. Carbon disulphide was condensed with 4-substituted-*o*-phenylenediamine to produce the 5-substituted-1,3-dihydrobenzimidazole-2-thione. Under reflux in DMF with methyl acrylate, the precursor afforded the corresponding bis(*N*-methyl propanoate) products **380a–e**, which were further converted to their corresponding propanoic hydrazides **381a–d**. The biological test results revealed that 1,3-disubstituted benzimidazole-2-thione was an effective oxidative stress inhibitor that was found to work for liver regenerative treatment (Scheme S-81, ESI file†).²²⁰

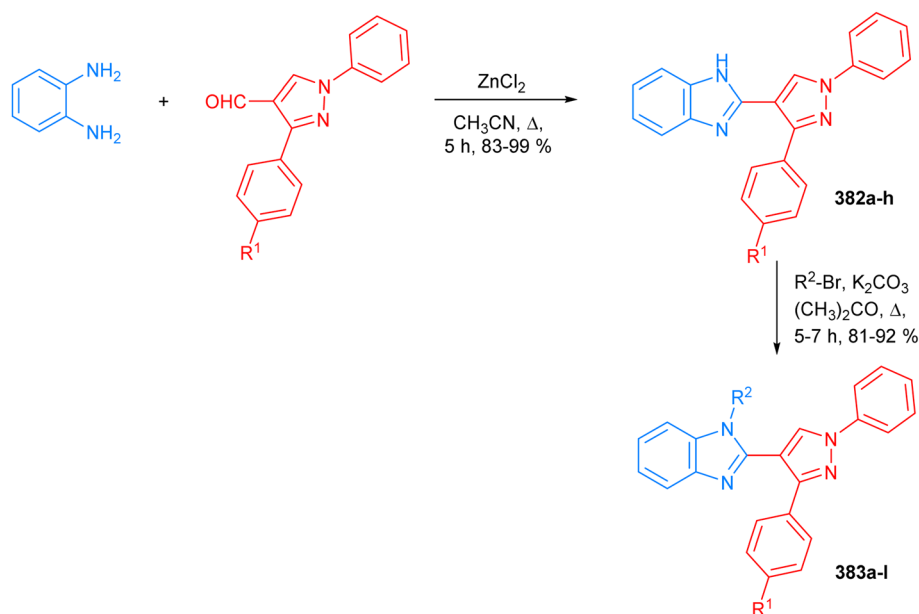
Pyrazolyl benzimidazole derivatives were also prepared in a two-step process. The synthesis of *N*-substituted pyrazolyl benzimidazoles was achieved through the condensation of *o*-phenylenediamine with 1-phenyl-3-(4-substituted-phenyl)-1*H*-pyrazole-4-carbaldehydes, in the presence of zinc chloride, which afforded the 2-[1,2-disubstituted-1*H*-pyrazol-4-yl]-1*H*-benzimidazole structures **382a–h** in very high yields, ranging from 85% to 92%. Later transformations of these compounds **382a–h** resulted in the corresponding *N*-alkylated products **383a–i**. These products were obtained upon reacting **382a–h** with a variety of alkyl bromide derivatives, in high yields (81% to 99%). These products also demonstrated strong antioxidant activity (Scheme 19 and Table 1).²²¹

Another set of 2-(4-substituted-phenyl)-5-methyl-1*H*-benzimidazoles derivatives **384a–e** was synthesized through the condensation of 4-methyl-*o*-phenylenediamine and 4-substituted benzaldehydes in the presence of sodium meta-bisulfite, with absolute ethanol as the solvent, at room temperature. The products were tested for their antioxidant activity employing the DPPH free radical scavenging assay.

These products demonstrated substantial antioxidant action, with IC₅₀ values of 1.054–19.05 μg mL⁻¹, when compared with the reference standard BHT (26.96 μg mL⁻¹) (Scheme S-82, ESI file†).²²² These products are prospective candidates for further development as antioxidants, which are key progenitors for managing a number of physiological disorders, including cancers, diabetes and neurological malfunctions.

The synthesis of another target compound, bis-(*N*-allyl-1*H*-benzimidazol-2-yl-methyl)-benzylamine, compound **386**, was achieved. It involved, firstly, the preparation of benzyl dicarbamic acid *via* the condensation of benzylamine in the presence of excess 2-chloroacetic acid. Secondly, the dicarbamic acid was reacted with *o*-phenylenediamine, leading to the bis(*N*-methyl-2-benzimidazolyl)-benzyl amine intermediate **385**. This compound **385** subsequently underwent double *N*-allylation with allyl bromide. The obtained product **386** was used as a ligand to produce Ni(II) complexes, which showed significant antioxidant activity compared with known natural antioxidants, *i.e.*, mannitol and vitamin C (Scheme S-83, ESI file†).²²³

Yet, another set of new benzimidazole carboxamide derivatives was also synthesized as antioxidant agents. In the presence of acetic acid, 4-(bromomethyl)-biphenyl-2-carboxylic acid, compound **387**, was reacted with tetraethyl orthocarbonate to produce the 1-[(2'-cyanobiphenyl-4-yl)-methyl]-5-carboxylate-2-ethoxybenzimidazole-derivative intermediate **388**. The hydrolysis of compound **388** in sodium hydroxide solution yielded compound **389**. The target **390** was effectively produced by reacting different substituted benzylamines with derivatives of compound **389** in the presence of TBTU and DPIA. The reagent 1,1-diphenyl-2-picrylhydrazyl (DPPH) was used to investigate the free radical scavenging capacity of the synthesized compounds **390a–j** in comparison with ascorbic acid as a standard antioxidant substrate. These results showed that five



Scheme 19 The synthesis of two series of new *N*-substituted pyrazole-containing benzimidazoles **382** and **383**.



Table 1 Data on the series of new *N*-substituted pyrazole-containing benzimidazoles **382** and **383**

Compound number	Substituents		Yield (%)	Compound number	Substituents		Yield (%)
	R ₁	R ₂			R ₁	R ₂	
382a	H	—	91	383a	H	<i>n</i> -C ₅ H ₁₁	89
382b	NO ₂	—	92	383b	H	—CH=CH ₂	94
382c	—OCH ₃	—	89	383c	H	Bn	98
382d	Cl	—	85	383d	NO ₂	<i>n</i> -C ₅ H ₁₁	83
382e	OH	—	90	383e	NO ₂	—CH=CH ₂	96
382f	NH ₂	—	92	383f	NO ₂	Bn	99
382g	CH ₃	—	87	383g	—OCH ₃	<i>n</i> -C ₅ H ₁₁	81
382h	Br	—	85	383h	OCH ₃	—CH=CH ₂	85
				383i	OCH ₃	Bn	90
				383j	Cl	<i>n</i> -C ₅ H ₁₁	81
				383k	Cl	—CH=CH ₂	87
				383l	Cl	Bn	92

compounds, *i.e.*, **390a**, **390c**, **390d**, **390f** and **390i**, had higher antioxidant activity (Scheme S-84, ESI file†).²²⁴

Two new metal-complexed compounds, the 2-(4'-thiazolyl) benzimidazole-based Cu(II)-dipeptide complexes [Cu(Gly-Gly)(TBZCl)]·4H₂O **391** and [Cu(Gly-L-Leu)(TBZCl) H₂O] **392**, were synthesized (Scheme S-85, ESI file†). The dipeptide glycylglycine reacted, in the presence of sodium hydroxide, with 2-thiazol-2-yl-1*H*-benzimidazole and copper(II) chloride, yielding the tetrahydrate and monohydrate complexes **391** and **392**. In these structures, copper metal chelated with the oxygen atom of the carboxylate and the nitrogen atom of the primary amine, and it bonded with the two nitrogen-atom-based imine (N=C) moieties of the 2-thiazol-2-yl-1*H*-benzimidazole compounds. The study mentioned the excellent antioxidant capabilities of these final products.²²⁵

3. Structure–activity relationships in benzimidazole derivatives

A survey of benzimidazole-based compounds, lead structures, and new chemical entities reflects the versatile nature of benzimidazole and its broadly diverse derivatives as essential pharmacophores in numerous biologically active heterocyclic compounds, with a diverse range of pharmacological activities. The NH group in benzimidazole exhibits the characteristics of being both significantly acidic and mildly basic in nature.^{226,227} The compound possessed the capacity to allow salt preparation. The notion that the benzimidazole moiety holds significant potential in the pharmaceutical domain for the advancement of innovative medicinal compounds with a range of pharmacological activities not only illustrates its significance as a near-universal and highly versatile pharmacophore but also poses challenges in terms of choice with regards to the best structural selections to complement the benzimidazole pharmacophore to obtain the intended bioactivity.

The structure–activity relationships (SARs) of some of the most potent benzimidazole compounds in terms of anticancer activity are presented. Even though there are many potential causes of cancer, the two most prevalent ones are thought to be

aberrant enzyme activity and genetic abnormalities. There are approximately 277 different types of cancers that have been identified, and lung cancer is the most common among men and the leading cause of cancer-related deaths. Colorectal and prostate cancers are the next most prevalent cancers in terms of incidence, while hepatocellular and stomach cancers are leading causes of mortality. Compared to males, females are more likely to die from breast, colorectal, lung and cervical cancers.²²⁸ According to Satija *et al.*,²²⁹ a number of potential targets exist for anticancer therapy, primarily involving topoisomerase-II, which mediates DNA cleavage and cell death; serine/threonine kinase inhibitors, which induce cell arrest; tyrosine kinase inhibitors, which prevent angiogenesis; tubulin polymerization inhibitors, which are known to produce mitotic arrest; COX inhibitors, which prevent tumor invasion; and PDGFs, which mediate apoptosis and proliferation.

Compounds with piperazine linked to benzimidazole-pyrimidine hybrids were prepared and tested for cytotoxicity by Sana *et al.*,²³⁰ and at concentrations ranging from 2.21 to 7.29 μM, the amine-linked benzimidazole-pyrimidine demonstrated the highest levels of cytotoxic activity against A549 human lung cancer cell lines. Compound **393** showed promising activity as an anticancer agent against A549 cell lines. Based on the results of structure–activity relationship (SAR) tests, products with an amine linkage showed superior anticancer activity. The cytotoxicity against A549 cell lines was increased by sterically hindering the trifluoromethyl substituent at the C2-position of the benzimidazole ring (Fig. 1).

The 1,2-diarylbenzimidazoles **394** showed anticancer activity, with an IC₅₀ value of 8.47 μM and GI₅₀ values ranging from 0.71 to 2.41 μM. Testing with HepG2 and HeLa cells confirmed that apoptosis halted tumor cells in the G2/M phase, and molecular docking studies confirmed the binding capacity to tubulin crystals. The *para*-substitution of the compounds improved their bioactivity compared to *ortho*- or *meta*-substitution. The presence of 3,4-(OCH₃)₂ resulted in the highest activity compared with other *ortho-para* di-substitutions, but the activity of *meta-para* di-substituted compounds was found to be much higher²³¹ (Fig. 2).



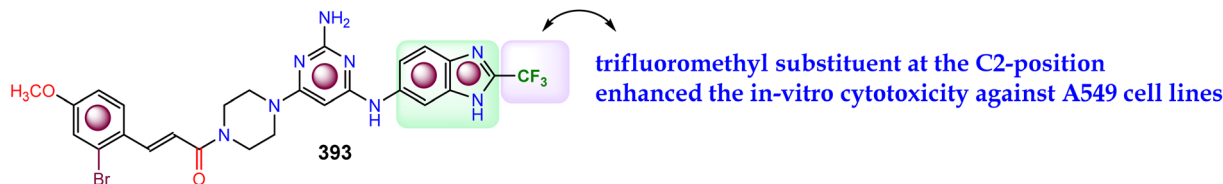


Fig. 1 Compound 393, which is an anticancer product with activity against A549 cell lines.

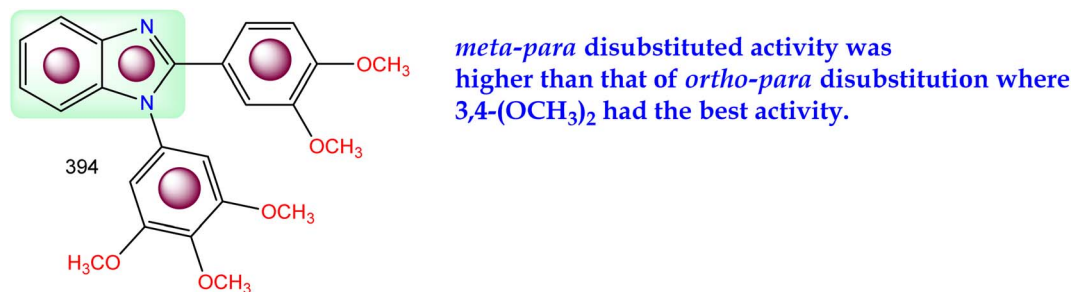


Fig. 2 Enhanced *in vitro* activity against HeLa and Hepg2 cell lines was shown owing to *meta-para*-disubstitutions.

A new set of CHK-2 enzyme inhibitors **395**, obtained by substituting pyrazole for an aryl moiety in 2-aryl-1*H*-benzimidazoles, was synthesized. Products showed anticancer efficacy, with a range of IC₅₀ values from 52.8 μM to 5.5 μM against the MCF-7 cell line. The anticancer activity was improved with substitution at the pyrazole ring by a polar group at position 4, while carboxylic or nitro groups at position 5 of the 1*H*-benzimidazole decreased the activity (Fig. 3).²³²

Novel 1*H*-benzimidazole-linked β-carbolines **396** were synthesized by Siresha *et al.* The compounds tested positive for anticancer activity against several cancer cell lines, including MCF-7 cell lines. The compounds were CLK binders with molecular interactions with kinase. A 5,6-dimethoxy substitution was found to introduce more activity than a molecule without substitution at the 1*H*-benzimidazole core. The presence of a weak electron-donating group (EDG) and the presence of a dimethyl group on the 1*H*-benzimidazole entity decreased the activity (Fig. 4).²³³

Diabetes mellitus resulting from metabolic abnormalities is characterized by elevated blood glucose levels, known as hyperglycemia. Severely diabetic individuals experience a variety of symptoms, including weight loss, refractory infections, recurrent vomiting, dermatological and ocular complications, as well as drug-resistant nausea.^{234,235} α-Amylase and α-glucosidase are involved in the digestion of carbohydrates. Concerning the antidiabetic structure–activity relationships of

benzimidazole derivatives, novel thiazole–benzimidazole **397** analogues have been reported²³⁶ as multipotent inhibitors of α-amylase and α-glucosidase. Recently discovered analogs also exhibited inhibition potential against α-amylase and α-glucosidase. SAR studies indicated that the inhibition efficiency is increased by smaller (F and Cl) groups or the presence of groups capable of forming hydrogen bonds (OH) with targeted enzymes. The potency of analogs with fluoro-substitution at the *meta*-position and homologs with a *para*-fluoro-substitution towards α-amylase was high, whereas analogs with large substituents, such as Br, or groups that do not form hydrogen bonds, like CH₃, showed poor activity (Fig. 5).

The effectiveness of benzimidazole scaffolds in inhibiting α-amylase and α-glycosidase was evaluated relative to acarbose. Designed products with halogen groups at the *para*-position of the phenyl part hindered enzyme activity *via* direct interaction. Molecular docking experiments showed binding affinity with the HPA and HLAG active sites. Aroua *et al.* proposed a facile method for synthesizing diverse benzoyl-aryl-benzimidazoles **398**. This entailed the condensation of 3,4-diaminobenzophenone with an appropriately substituted aryl aldehyde utilizing derivatives, using ammonium chloride or a combination of ammonium chloride and sodium bisulfite as the catalyst (Fig. 6).¹⁸³

Benzimidazole derivatives of *N*-substituted benzimidazoles **399** prevented the growth of methicillin-resistant *Staphylococcus*

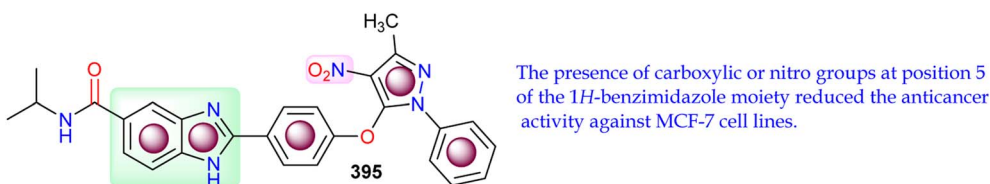


Fig. 3 The effects of the benzimidazole 5-position on the anticancer activity.



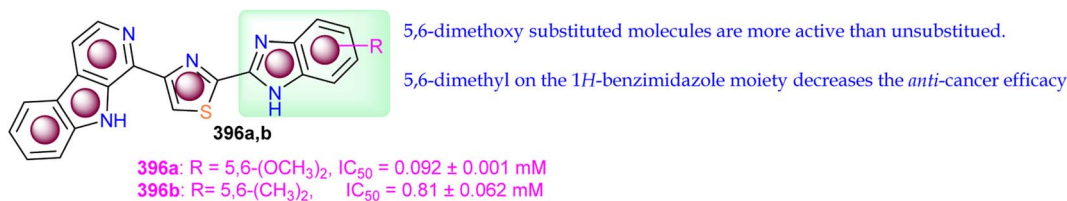


Fig. 4 Substitution at positions 5 and 6 favored higher anticancer activity.

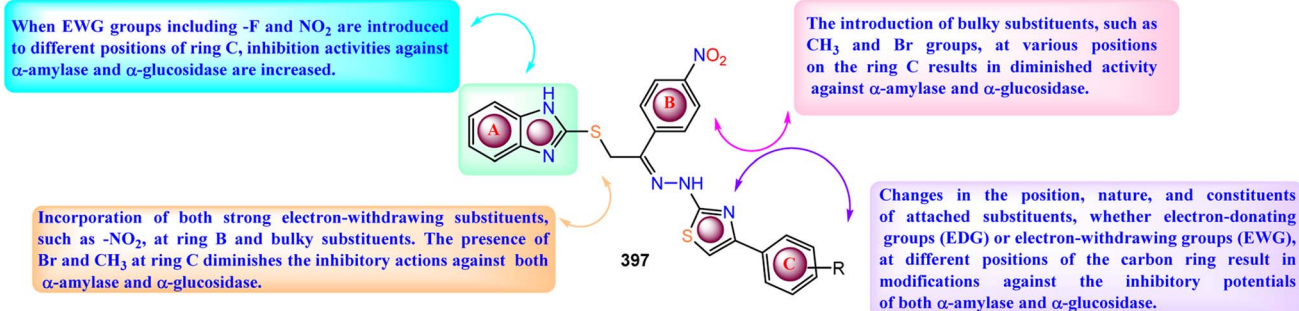
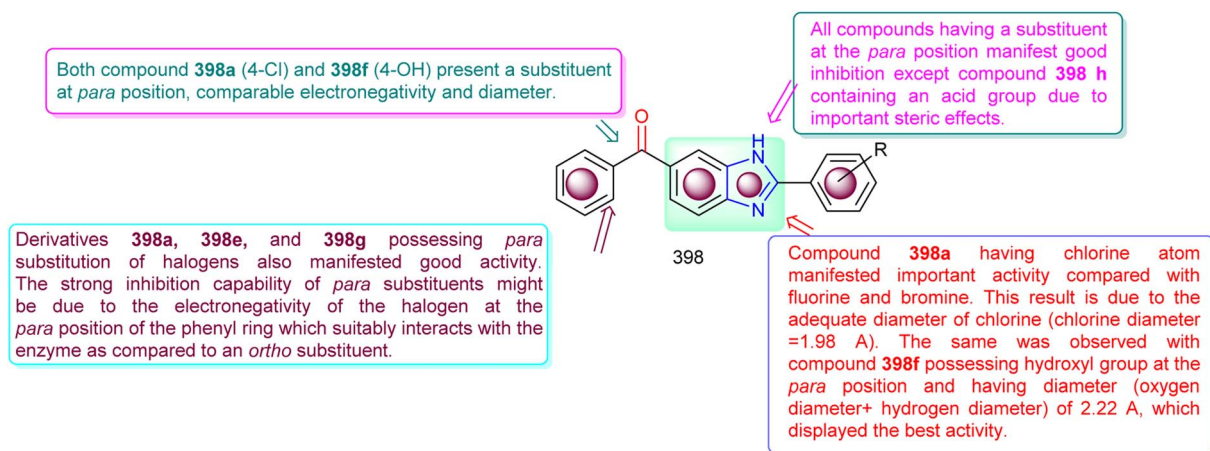
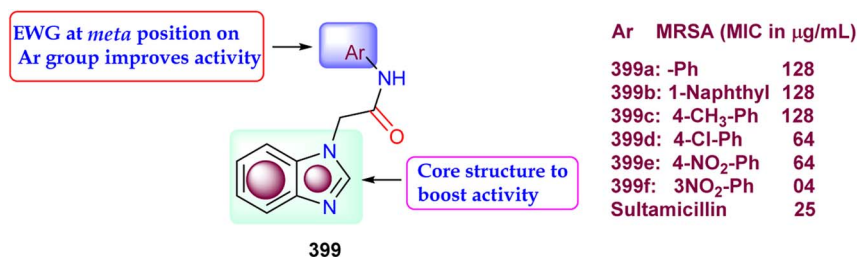


Fig. 5 Antidiabetic SAR considerations.

Fig. 6 The SAR for *para*-substituted halogens on the phenylic part of the benzimidazole.

aureus MRSA (ATCC4330) under *in vitro* conditions, presenting MICs of up to 4 μg mL⁻¹, which were better than sultamicillin (MIC = 25 μg mL⁻¹). Also, these compounds exhibited no toxicity toward mammalian Vero cell lines, demonstrating their safe

nature as antimicrobials, with IC₅₀ values of 298 μM. The presence of a strong electron-withdrawing group, *e.g.*, nitro, at the 3-position of the phenyl ring at the *N*-position of the benzimidazole was observed to facilitate efficacy against MRSA (Fig. 7).²³⁷

Fig. 7 *N*-Substitution as a facilitator of the antimicrobial activity of benzimidazole.

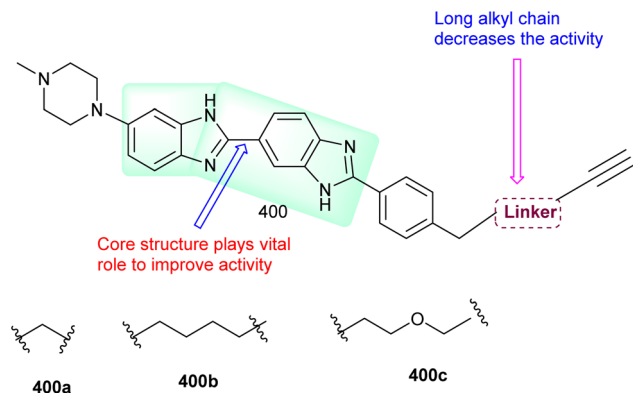


Fig. 8 Chain-length effects on bioactivity from SAR studies of benzimidazole derivatives.

Benzimidazole molecules **400** having a short chain alkyl group at the terminal end with mildly hydrophobic character enhanced the antimicrobial activity (Fig. 8).²³⁸

A small number of 2-phenylsubstituted benzimidazoles **401** were investigated for their ability to inhibit COX-1 and -2, and 5-lipoxygenase. Fig. 9 showed that the inhibition of COX-1 and -2, and 5-lipoxygenase was best achieved by products with no substitutions at the R², R³, and R⁴ positions, while the presence of an amine group at R¹ improved the inhibition of all three enzymes. Nonetheless, the inhibition of COX-1 was favored by the presence of a lipophilic group at R⁵, the inhibition of COX-2 was enhanced by the presence of a hydrophilic group, and the inhibition of 5-lipoxygenase was favored by methoxy substitution. Molecules with 2-aminopyridin-4-yl in the product structures enhanced the inhibition of 5-lipoxygenase (Fig. 9).²³⁹

4. Recent advances in synthesis and green approaches for benzimidazoles

The search for innovative synthetic procedures for the preparation of prospective lead structures has emerged as a prominent field, with the pursuit of effective and practical synthetic

methods for benzimidazole synthesis in continuous focus.²⁴⁰ Concurrently, researchers have sought to develop novel synthetic methodologies,²⁴¹ with a strong emphasis on green and eco-friendly methodologies.^{242,243} These green advancements have influenced reaction conditions, reagents, solvents, and a range of other parameters, including the utilization of neat,²⁴⁴ green,²⁴⁰ and ionic solvents;²⁴⁵ the use of material-conserving, cheap, eco-friendly,²⁴⁶ and recyclable solvents and catalysts;²⁴⁷ the incorporation of ionic liquids,^{248,249} the use of solid supports,^{250,251} combinatorial and parallel synthetic approaches; and the exploration of energy-efficient protocols, such as the use of microwave irradiation,²⁵² mechanochemical methods,²⁴⁵ and ultrasound energy.²⁴⁰ Shaikh *et al.*²⁴⁵ reported a novel green synthetic method for the synthesis of benzimidazole derivatives **402** utilizing a catalytic quantity of 1-ethyl-3-methylimidazolium tetrachloroaluminate ([EMIM]AlCl₄), the ionic liquid, as a catalyst, ethanol as an eco-friendly solvent, and mechanochemical energy (grinding in a mortar and pestle) at room temperature (Fig. 10).

In addition to its simplicity and the ease of catalyst recovery, the reaction provided good yields in short times. The utilization of catalysts has gained significant attention. The application of Lewis acids as effective catalysts in several transformations has demonstrated more eco-friendly methods for the synthesis of benzimidazole derivatives. In their work on the green synthesis of benzimidazole derivatives, Shaibuna *et al.*²⁴² employed deep eutectic solvents (DES) as green solvents. The DES consisted of a combination of ZrOCl₂·8H₂O and urea. After optimization, they determined the optimal ratio of ZrOCl₂·8H₂O to urea in the DES to be 1 : 5 (DES 1). To validate this method, the reaction was performed using 4-chloro-1,2-phenylenediamine and 3,4-diaminotoluene with variously substituted aldehydes (Fig. 11). Notably, the reaction exhibited total selectivity, yielding exclusively mono- or di-substituted benzimidazole derivatives **403** and **404**. The di-substituted derivatives were obtained only when thionyl chloride was used as the aldehyde source (Table 2).

Srinivasulu *et al.*²⁵³ achieved the synthesis of benzimidazole derivatives **405** under solvent-free conditions, employing a catalytic amount of the commercially available, inexpensive,

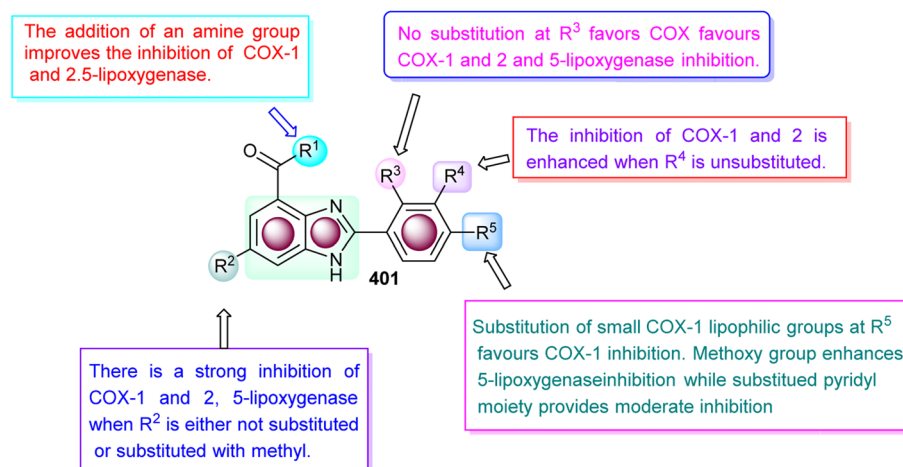


Fig. 9 The SAR of 2-phenyl-substituted benzimidazoles.



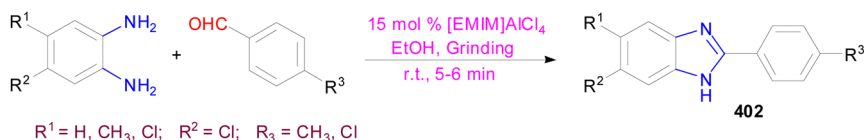
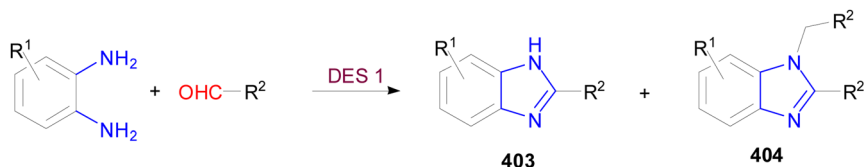
Fig. 10 The [EMIM]AlCl₄-catalysed synthesis of benzimidazole derivatives.

Fig. 11 The eco-friendly synthesis of benzimidazole derivatives.

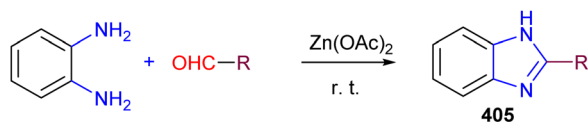
Table 2 Synthetic yields and preparation times of benzimidazole derivatives

Entry	R ¹	R ²	t (min)	Yield (%)	
				403	404
1	H	C ₆ H ₅	10	97	0
2		4-CH ₃ -O-C ₆ H ₄	15	97	0
3		1-Thienyl	10	0	47
4		3,4-(CH ₃ O) ₂ -C ₆ H ₃	25	94	0
5		1-Naphtyl	20	95	0
6		4-Cl-C ₆ H ₄	20	90	0
7		4-Br-C ₆ H ₄	25	92	0
8		3-NO ₂ -C ₆ H ₄	40	85	0
9		4-NO ₂ -C ₆ H ₄	35	90	0
10	4-Cl	1-Thienyl	15	0	45
11		1-Naphtyl	25	84	0
12	4-CH ₃	4-CH ₃ -O-C ₆ H ₄	15	98	0
13		1-Thienyl	10	0	49
14		4-Br-C ₆ H ₄	25	89	0

and eco-friendly catalyst zinc acetate at room temperature (Fig. 12). The reaction proceeded with high selectivity and excellent yields.

Zhang *et al.*²⁵⁴ achieved the synthesis of a set of benzimidazole derivatives **406** utilizing PhSiH₃ and CO₂, a greenhouse gas, as reagents. The reaction was carried out under convenient conditions using a B(C₆F₅)₃ catalyst, affording yields of up to 95% (Fig. 13).

Interestingly, nearly all of the low molecular weight (LMW), <500 amu, drug molecules contained at least 59% of nitrogen heterocycles in one form or another as part of their structural template. The benzimidazoles, owing to the availability of 1 to 5



$R = \text{Ph, 2-Cl-Ph, 3-Cl-Ph, 4-Cl-Ph, 2-CH}_3\text{-Ph, 4-CH}_3\text{-Ph, 2-OCH}_3\text{-Ph, 4-OCH}_3\text{-Ph, 3NO}_2\text{-Ph, Ph-CH}_2\text{-}$

Fig. 12 The synthesis of benzimidazole using an efficient green Zn(OAc)₂ catalyst.

substitution site positions, are second only to indoles in the drug design, discovery, and bioactivity fields; a diverse range of bioactivities and structural variations are available, and they show ease of synthesis, as multiple routes and starting materials are available to produce benzimidazole derivatives and structural variations. Moreover, due to the versatility of the benzimidazoles as potent pharmacophores for various medicinal domains, benzimidazole derivatives have been widely reported to exhibit diverse biological and pharmacological activities.²⁵⁵ One of the reasons for the widespread interest in their use to develop newer drugs is their propensity for relatively straightforward preparation with numerous synthetic routes available. The benzimidazole core also exhibits sufficient stability to undergo multiple successive reactions, enabling molecular modifications to achieve the desired target structure without ring cleavage. These properties make them a valuable scaffold for the development of a wide range of compounds with applications in numerous medicinal fields.

A recent search of the Scopus database for derivatives of benzo-fused five-membered heterocycles yielded almost 135 000 (134 662) publications. The results showed that indole is the most frequently reported moiety, accounting for 69.41% of publications (94 858). Benzimidazole follows this, with 20.84% (28 897 publications). Other moieties, such as benzothiazole (7.54%), benzotriazole (3.18%), benzoxazole, and benzopyrazole, were less frequently cited, each representing only 0.01% of publications (Chart 1); this confirmed the versatility, interest in, and usability of these categories of compounds and their vital roles in chemical development and from a pharmacological activity standpoint.

5. Limitations, challenges, and shortcomings related to the benzimidazole structure, preparation techniques, and toxicity

Benzimidazole derivatives have exhibited diverse biological activities, but their development has been accompanied by many constraints. Their pharmacological utility is diminished



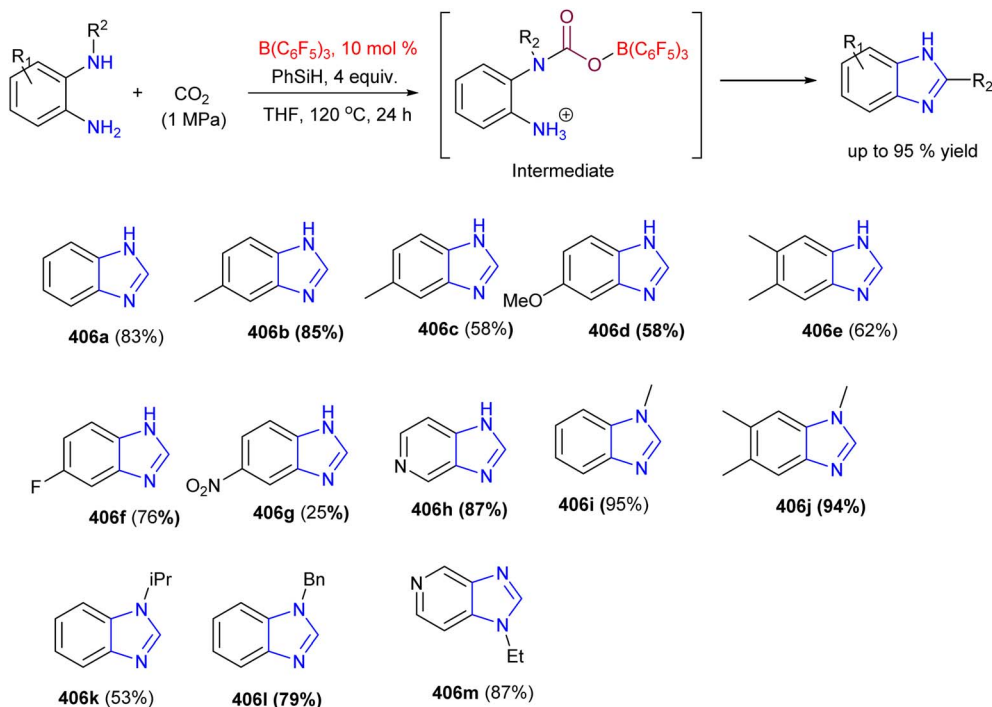


Fig. 13 The synthesis of benzimidazole derivatives obtained upon reacting CO₂, an atmospheric pollutant.

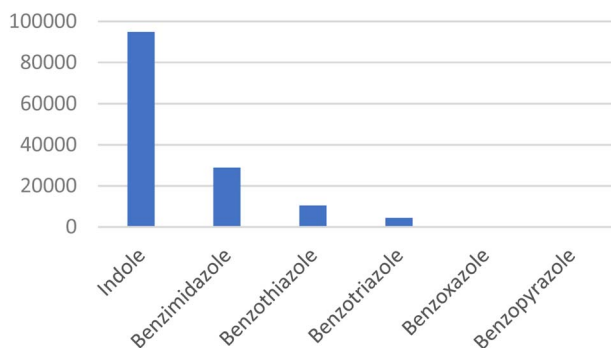


Chart 1 The number of publications on benzo-fused five-membered heterocyclic derivatives, according to the Scopus database.

due to the toxicity of some benzimidazole derivatives. Certain benzimidazoles and their metabolic byproducts cause liver and DNA damage, adverse reactions, and side effects.²⁵⁶ The resistance of parasitic nematodes to benzimidazole anthelmintics is well-documented and typically caused by mutations in the α -tubulin gene, and the situation is similar for certain other benzimidazole-based antiparasitic drugs.²⁵⁷ Also, during synthesis, the use of harsh conditions and toxic raw materials, catalysts and solvents plays a part in eliciting toxicity.²⁵⁸ Additionally, solubility issues connected with certain benzimidazoles have limited their bioavailability and, in turn, their therapeutic efficacy.²⁵⁹ Nonetheless, certain benzimidazoles are rapidly metabolized under *in vivo* conditions, leading to shorter half-lives and reduced therapeutic efficiency. This necessitates structural optimization during the development of benzimidazole-based drug candidates and related pro-drugs.²⁶⁰

6. Benzimidazole-based drugs and drug candidates under clinical trials

The benzimidazole core has gained importance as a pharmacophore and as part of extended pharmacophores in drug discovery exercises owing to its inherent wide-ranging pharmacological properties.²⁶¹ The rational synthesis of benzimidazole derivatives has become a focal point in medicinal chemistry, enabling the development of novel therapeutics with improved efficiency and reduced side effects and toxicity.²⁶²

Clinical uses of benzimidazoles include in the management of gastrointestinal disorders, such as gastric ulcers, and as proton pump inhibitors. The role of omeprazole and lansoprazole is one such example. Combating parasitic infections with albendazole and mebendazole and treating nausea and vomiting with droperidol are some common clinical applications now undertaken. Benzimidazole derivatives, such as astemizole and pimozone, are also available as antihistamine and neuroleptic drugs, respectively. The wide range of clinical and therapeutic uses of benzimidazole has shown how important this group of synthetic chemical entities is, in terms of both pharmacodynamics and pharmacokinetics. This has also driven researchers and pharmaceutical companies to design new benzimidazole templates as drug leads, with the aim of developing new drugs and enhancing the safety profile and bioavailability of existing benzimidazoles. Fig. 14 shows known and marketed benzimidazole drugs.

Table 3 provides a list of the trade and chemical names of benzimidazole-based drugs, their clinical applications as a pharmacological class, and their principal mode of action; all of which are available on the market.



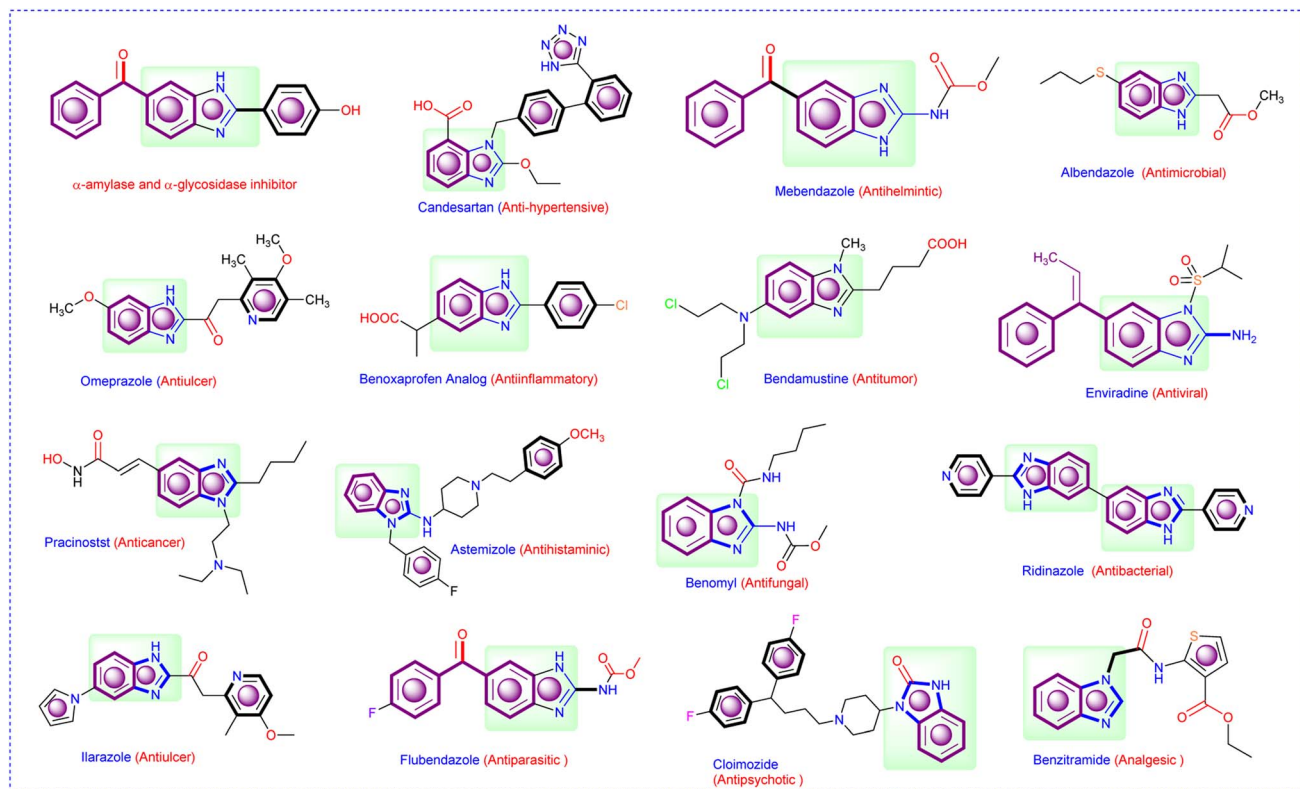


Fig. 14 Marketed benzimidazole drugs.

Also, at the same time, several benzimidazole-derived drug candidates are approaching the final stages of clinical trial and licensing, demonstrating the ongoing interest in this pharmacophore. Researchers are studying benzimidazoles for their potential efficacy in cancer treatment and as antiviral agents. Preliminary research has shown encouraging results, indicating the compound's capacity to suppress tumor proliferation and augment the effectiveness of currently available cancer chemotherapeutics. A list of benzimidazole-based compounds involved in clinical trials is provided in Table 4.

7. Specific areas of research or application that can be the most impactful for benzimidazole-based compounds in the next decade

The versatility of benzimidazole-based compounds has made them a hot topic of research in many different industries. Over the past few years, benzimidazole pharmacophores have found various applications in the pharmaceutical industry, including antibacterial,^{263–265} antifungal,^{266,267} antitubercular,^{268,269} anti-inflammatory,²⁷⁰ antidiabetic,^{271,272} and anticancer^{273–275} uses. Research indicates that benzimidazole materials are commonly used as insecticides and fungicides in agricultural settings.^{276,277} Polymer science^{278,279} and corrosion inhibition^{280,281} are two areas where the benzimidazole core has been shown to be effective in materials research.

Furthermore, environmental science represents a significant area of application. In this context, several research studies have been conducted, including the prediction of potential risks associated with tenazole and benzimidazole fungicides in relation to their aryl hydrocarbon receptor agonistic activity in aquatic ecosystems; the development of two coordination polymers based on rigid benzimidazole carboxylic acid ligands, focusing on electrode performance and dye adsorption;²⁸² the preparation of molecular-scale hybrid membranes utilizing benzimidazole-based monomers for high-performance hydrogen purification;²⁸³ the exploration of benzil-imidazole blue fluorophores and their application in blue/white light-emitting diodes,²⁸⁴ sensing, and anticounterfeiting; and the investigation of tetra-benzimidazoles flanking divinyl-phenothiazine as AIEgens acting as aza-Michael acceptors in concentration-tuned responses to biogenic amine vapors.²⁸⁵

A range of environmentally friendly synthesis methods for benzimidazoles includes the use of a dual-chain metallo-micellar catalyst for aerobic oxidative synthesis in water;²⁸⁶ a sustainable approach utilizing reusable CaAl_2O_4 nanophosphors as a catalyst for benzimidazole-based Schiff base synthesis, with a focus on metal(II) complexes and DNA interactions;²⁸⁷ an effective microwave-assisted copper-catalyzed aerobic oxidation strategy for quinazolinone and benzimidazole synthesis;²⁸⁸ and the green synthesis of benzimidazole scaffolds employing copper-substituted zinc aluminate *via* a sol-gel process.²⁸⁹ In addition, benzimidazole materials were utilized in battery technology to improve the safety and





Table 3 Benzimidazole-based drugs, their clinical applications, and mode of actions

Benzimidazole drug	Chemical name	Clinical applications	Mechanism of action
Albendazole	Methyl- <i>N</i> -(6-propylsulfanyl-1 <i>H</i> -benzimidazol-2-yl)carbamate	Anthelmintic	Interferes with tubulin polymerization
Mebendazole	Methyl- <i>N</i> -(6-benzoyl-1 <i>H</i> -benzimidazol-2-yl)carbamate	Anthelmintic	Inhibits microtubule production in parasite cells
Thiabendazole	4-(1 <i>H</i> -Benzimidazol-2-yl)-1,3-thiazole	Anthelmintic	Helminth-specific enzyme fumarate reductase inhibition
Omeprazole	6-Methoxy-2-[(<i>R</i>)-(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfanyl]-1 <i>H</i> -benzimidazole	Proton-pump inhibitor for gastric ulcers	Inhibits the parietal cell
Lansoprazole	2-[[3-Methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl]methylsulfanyl]-1 <i>H</i> -benzimidazole	Proton-pump inhibitor for gastric ulcers	H ⁺ /K ⁺ adenosine triphosphate pump
Rabeprazole	2-[[4-(3-Methoxypropoxy)-3-methyl pyridin-2-yl]methylsulfanyl]-1 <i>H</i> -benzimidazole	Proton-pump inhibitor for gastric ulcers	H ⁺ /K ⁺ adenosine triphosphate pump
Etodesnitazene	2-[2-[(4-Ethoxy phenyl) methyl] benzimidazol-1-yl]- <i>N,N</i> -diethylethylamine	Analgesic	Inhibits the parietal cell H ⁺ /K ⁺ adenosine triphosphate pump
Metodesnitazene	<i>N,N</i> -Diethyl-2-[(4-methoxyphenyl) methyl]-1 <i>H</i> -benzimidazole-1-ethanamine	Analgesic	Synthetic opioid
Etodesnitazene	2-[(4-Ethoxyphenyl)methyl]- <i>N,N</i> -diethyl-1 <i>H</i> -benzimidazole-1-ethanamine	Analgesic	Synthetic opioid
Bendamustine	4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid	Chemotherapy of chronic lymphocytic leukemia	Inhibits the parietal cell H ⁺ /K ⁺ adenosine triphosphate pump
Nocodazole	Methyl- <i>N</i> -[6-(thiophene-2-carbonyl)-1 <i>H</i> -benzimidazol-2-yl]carbamate	Chemotherapy	Synthetic opioid
Dovitinib	4-Amino-5-fluoro-3-[5-(4-methyl-1-piperazinyl)-1,3-dihydrobenzimidazol-2-ylidene]-2-quinolinone	Anticancer	Synthetic opioid
Binimetinib	6-(4-Bromo-2-fluoroanilino)-7-fluoro- <i>N</i> -(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide	Anticancer	Alkylating agent
Selumetinib	6-(4-Bromo-2-chloroanilino)-7-fluoro- <i>N</i> -(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide	Anticancer	Inhibits the self-assembly of tubulin
Velparib	2-[(2 <i>R</i>)-2-Methylpyrrolidin-2-yl]-1 <i>H</i> -benzimidazole-4-carboxamide	Anticancer	Multi-target FGFR kinase inhibitor
Pracinostat	(<i>E</i>)-3-[2-Butyl-1-[2-(diethylamino) ethyl]benzimidazol-5-yl]- <i>N</i> -hydroxyprop-2-enamide	Anticancer	Mitogen-activated protein kinase (MEK) inhibitor
Galeterone	(3 <i>S</i> ,8 <i>R</i> ,9 <i>S</i> ,10 <i>R</i> ,13 <i>S</i> ,14 <i>S</i>)-17-(Benzimidazol-1-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15-decahydro-1 <i>H</i> -cyclopenta[<i>g</i>]phenanthren-3-ol	Anticancer	MEK1 and MEK2 inhibitor
		Anticancer	PARP inhibitor preventing DNA repair in cancer cells
		Anticancer	Histone deacetylase (HDAC) inhibitor
		Anticancer	Androgen receptor modulator and CYP17 lyase inhibitor



Table 4 Benzimidazole-based compounds involved in clinical trials

Drug candidate	Chemical name	Clinical trial ID	Clinical trial area	Clinical application
Nazartinib	<i>N</i> -(7-chloro-1-[(3 <i>R</i>)-1-[(<i>E</i>)-4-(dimethylamino)but-2-en-1-yl]azepan-3-yl]benzimidazol-2-yl)-2-methylpyridine-4-carboxamide	NCT03529084	Third-generation, mutant-selective epidermal growth factor receptor (EGFR) inhibitor	Anticancer
Nazartinib	<i>N</i> -(7-chloro-1-[(3 <i>R</i>)-1-[(<i>E</i>)-4-(dimethylamino)but-2-en-1-yl]azepan-3-yl]benzimidazol-2-yl)-2-methylpyridine-4-carboxamide	NCT02335944	The combination of capmatinib and nazartinib for patients with EGFR-mutated non-small-cell lung cancer	Anticancer
Nazartinib	<i>N</i> -(7-chloro-1-[(3 <i>R</i>)-1-[(<i>E</i>)-4-(dimethylamino)but-2-en-1-yl]azepan-3-yl]benzimidazol-2-yl)-2-methylpyridine-4-carboxamide	NCT02108964	Safety and effectiveness of nazartinib (EGF816) in people with EGFR-mutant non-small-cell lung cancer	Anticancer
Binimetinib	6-(4-bromo-2-fluoroanilino)-7-fluoro- <i>N</i> -(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide	NCT04965818	Binimetinib tested in combination with fufibatatin in patients with advanced KRASmt tumors	Anticancer
Binimetinib	6-(4-bromo-2-fluoroanilino)-7-fluoro- <i>N</i> -(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide	NCT03170206 (https://clinicaltrials.gov/show/NCT03170206)	Combination of palbociclib and binimetinib for patients with advanced KRAS mutant non-small-cell lung cancer	Anticancer
Bendamustine	4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid	NCT04217317	Bendamustine tested in combination with CPI-613 in patients with relapsed/refractory T-cell non-Hodgkin lymphoma	Anticancer
Bendamustine	4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid	NCT04510636	Study of pembrolizumab with bendamustine against Hodgkin lymphoma	Anticancer
Selumetinib	6-(4-bromo-2-chloroanilino)-7-fluoro- <i>N</i> -(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide	NCT02768766	Combination of selumetinib and dacarbazine for patients with metastatic uveal melanomas	Anticancer
Abemaciclib	<i>N</i> -[5-[(4-ethylpiperazin-1-yl)methyl]pyridin-2-yl]-5-fluoro-4-(7-fluoro-2-methyl-3-propan-2-yl)benzimidazol-5-yl]pyrimidin-2-amine	NCT04003896 (https://clinicaltrials.gov/show/NCT04003896)	A trial to assess abemaciclib in late biliary tract carcinomas that failed prior first-line therapy	Anticancer
Abemaciclib	<i>N</i> -[5-[(4-ethylpiperazin-1-yl)methyl]pyridin-2-yl]-5-fluoro-4-(7-fluoro-2-methyl-3-propan-2-yl)benzimidazol-5-yl]pyrimidin-2-amine	NCT04040205	A trial to assess abemaciclib activity in the treatment of bone and soft-tissue sarcomas with cyclin-dependent kinase (CDK) pathway alteration	Anticancer
Veliparib	2-[[2 <i>R</i>]-2-Methylpyrrolidin-2-yl]-1 <i>H</i> -benzimidazole-4-carboxamide	NCT02723864	A combination of veliparib and cisplatin in patients with refractory solid tumors	Anticancer
Veliparib	2-[[2 <i>R</i>]-2-Methylpyrrolidin-2-yl]-1 <i>H</i> -benzimidazole-4-carboxamide	NCT01434316	The combination of veliparib and dinaciclib in treating patients with advanced solid tumors	Anticancer
Dovitinib	4-Amino-5-fluoro-3-[5-(4-methyl-1-piperazinyl)-1,3-dihydrobenzimidazol-2-ylidene]-2-quinolinone	NCT01635907	A trial conducted to assess the effect of dovitinib in managing cancer in people with certain kinds of neuroendocrine tumors. This research will also assess the safety of this medicine	Anticancer
Pracinostat	(<i>E</i>)-3-[2-Butyl-1-[2-(diethylamino)ethyl]benzimidazol-5-yl]- <i>N</i> -hydroxyprop-2-enamide	NCT03848754	The combination of pracinostat and gemtuzumab ozogamicin (PrAGO) in patients with relapsed/refractory acute myeloid leukemia	Anticancer
Galeterone	(3 <i>S</i> ,8 <i>R</i> ,9 <i>S</i> ,10 <i>R</i> ,13 <i>S</i> ,14 <i>S</i>)-17-(Benzimidazol-1-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15-decahydro-1 <i>H</i> -cyclopenta[<i>a</i>]phenanthren-3-ol	NCT04098081	A combination of galeterone with gemcitabine for patients with metastatic pancreatic adenocarcinomas	Anticancer

performance of lithium metal batteries; a thermally stable poly(aryl ether benzimidazole) separator with 2D-functionalized boron nitride was used for 3000 hours of lithium plating/stripping²⁹⁰ and multi-channeled halloysite nanotube-blended polybenzimidazole separators were used for enhancing lithium-ion battery performance.²⁹¹ A benzimidazole-linked polymer has also been identified for its application potential in membranes designed for efficient syngas (H₂/CO/CO₂) separation.²⁹²

8. Patent landscape

The patent landscape relating to benzimidazoles is diverse. Benzimidazoles and their derivatives have been patented for a range of uses and applications in diverse industries, including the pharmaceutical industry. A recent search revealed >100 000 entries in the Google Patents database; for the European patent office, an Espacenet search of benzimidazole-specific patents returned 10 000 entries [Espacenet – results view (https://worldwide.espacenet.com/searchResults?submitted=true&locale=en_EP&DB=EPODOC&ST=singleline&query=benzimidazole)]; the Japanese patent office showed 71 patents [Simple Search|J-PlatPat [JPP] (<https://www.j-platpat.inpit.go.jp/s0100>)]; the World Intellectual Property Organization (WIPO) through Patentscope® provided 1805 entries [WIPO – Search International and National Patent Collections (https://patentscope.wipo.int/search/en/result.jsf?_vid=P21-M607U9-54819)]; a United States Patents Office site search produced >95 000 entries [Patent Public Search Basic|USPTO (<https://ppubs.uspto.gov/pubwebapp/static/pages/ppubsbasic.html>)]; and Canadian patent entries related to benzimidazole were found to reach around 20 000 [Search Results – Canadian Patents Database (https://brevets-patents.ic.gc.ca/opic-cipo/cpd/eng/search/results.html?query=benzimidazole&start=1&num=10&type=basic_search&newSearch=0)]. The patent activity peaked between 2001 and 2013, with a majority of patents being filed during this period. Benzimidazole bioactivity patents peaked during the period 2016–2019 [bioactivity benzimidazole – Google Patents ([https://patents.google.com/?q=\(bioactivity+benzimidazole\)&oq=bioactivity+benzimidazole](https://patents.google.com/?q=(bioactivity+benzimidazole)&oq=bioactivity+benzimidazole))]. The Takeda, Merck, Pfizer, and Janssen pharmaceutical and chemical companies are worth mentioning. A review compilation of benzimidazole patents in the periods 2010–2012,²⁹³ 2013–2014,²⁹⁴ and 2021 (ref. 295) demonstrates over 10 years of progress in the area of benzimidazole patents. Compilations of marketed drugs and drugs under development, which are part of clinical trial registries, are provided above.

9. Conclusions

Based on a benzimidazole molecular template, a plethora of structurally diverse compounds has been derived through various functional-group and ring-system substitutions, together with substructure entanglements through the use of a vast spectrum of different synthons, starting materials, and intermediates; in addition, new and novel synthetic approaches have yielded compounds and significant leads that

have exhibited a range of different kinds of pharmacological activities. Several categories of biologically promising compounds with different activities, including antimicrobial, antiviral, antiparasitic, anticancer, anti-inflammatory, antioxidant, antihypertensive, and antidiabetic activity, have been overviewed and described in detail with their respective synthetic schemes, highlighting the synthetic protocols and how benzimidazole is the core pharmacophore responsible for the activity. Different structures that were developed based on a benzimidazole core have shown potential for further research to develop bioactive compounds in the form of new chemical entities, lead compounds and drugs, strengthening drug discovery. The benzimidazole molecular template, as a core part of active organo-medicinal products, possesses potential for the expedited development of new drug candidates with various types of bioactivity and pharmacological action. The various structural derivatives and benzimidazole-templated analogues have successfully opened new vistas, utilizing SAR- and QSAR-based drug discovery, with benzimidazole as a central molecular component. The vast number of structures and derivatives produced through benzimidazole intermediaries that are currently available also demonstrates the potential to further explore 3D-QSAR-based approaches in minute detail for intricate drug design and consequential drug discovery; this can be carried out in conjunction with activity prediction, structural mapping, and toxicity studies, using *in vivo*, *in vitro*, and *in silico* approaches. The current status of structural diversification and the range of notable bioactivities have also provided an opening for understanding the mechanisms of action of benzimidazole-derived drugs, both developed and in development, helping to understand the metabolomics and toxicokinetics, to suppress and remove the inherent toxicity, side effects, and biological cross-reactivity in developed products that are harming future drug development plans. The profound versatility of pharmacological activities, the structural diversity, and the utility of the retained benzimidazole pharmacophore are all beneficial; in addition, the biological potential of the would-be and already synthesized pools of diversely substituted benzimidazole structures, which may be produced through combinatorial and parallel synthesis, as well as their bioactivities, which have been confirmed through high-throughput screenings, offer new avenues and unexplored domains for chemical synthesis, drug design and development, and the introduction of new pharmacological activities while working with the benzimidazole template.

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

Conflicts of interest

There are no conflicts to declare.



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