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Synthesis, Reactivity and Biological Activity of Benzimidazoles

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Abstract Benzimidazole is a biologically important scaffold which displays important biological activities. Recent progress in the synthesis and bioactivity of benzimidazoles is reviewed. New synthetic procedures, including microwave-assisted synthesis, solid phase synthesis, natural product synthesis, and synthesis of bisbenzimidazoles are briefly described. Functionalization and cyclization reactions of benzimidazoles lead to a wide variety of novel benzimidazole structures. Selected bioactivity, such as anti-infective, anti-inflammatory, antitumor and receptor agonist/antagonist activities are presented.

Keywords Benzimidazole · Bioactivity · Bisbenzimidazole · Chemical reactivity · Microwave synthesis

Abbreviations

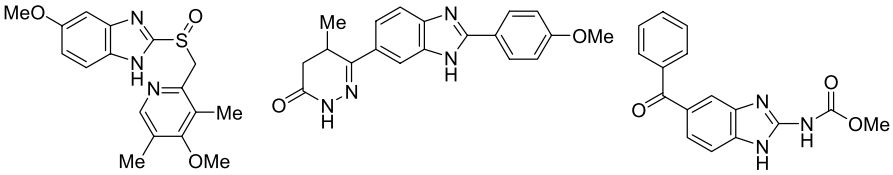
AIDS	Acquired Immunodeficiency Syndrome
CCl_4	carbon tetrachloride
CNS	central nervous system
DEAD	diethyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethyl ether
DMF	*N*,*N*-dimethylformamide
DNA	deoxyribonucleic acid
EtOAc	ethyl acetate
HIV	Human Immunodeficiency Virus
IC_{50}	half-maximal inhibitory concentration
MeOH	methanol
MIC	minimum inhibitory concentration
MW	microwave
NBS	*N*-bromosuccinimide
NMDA	*N*-methyl-D-aspartic acid
PEG	polyethylene glycol
PPA	polyphosphoric acid
PPh_3	triphenylphosphine
TBDMS	*tert*-butyldimethylsilyl

1 Introduction

Benzimidazole is a fused aromatic imidazole ring system where a benzene ring is fused to the 4 and 5 positions of an imidazole ring. Benzimidazoles are also known as benziminazoles and 1,3-benzodiazoles [1, 2]. They possess both acidic and basic characteristics. The NH group present in benzimidazoles is relatively strongly acidic and also weakly basic. Another characteristic of benzimidazoles is that they have the capacity to form salts. Benzimidazoles with unsubstituted NH groups exhibit fast prototropic tautomerism, which leads to equilibrium mixtures of asymmetrically substituted compounds [1].

The benzimidazole scaffold is a useful structural motif for the development of molecules of pharmaceutical or biological interest. Appropriately substituted benzimidazole derivatives have found diverse therapeutic applications such as in antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics [3]. The optimization of benzimidazole-based structures has resulted in various drugs that are currently on the market, such as omeprazole **1** (proton pump inhibitor), pimobendan **2** (ionodilator), and mebendazole **3** (anthelmintic) (Fig. 1). The spectrum of pharmacological activity exhibited by benzimidazoles has been reviewed by several authors [3–6].

Since the publications of these reviews, a number of new methods for the synthesis of benzimidazoles have been discovered and reported; such work



Omeprazole **1** Pimobendan **2** Mebendazole **3**

Fig. 1 Pharmacologically active benzimidazole drugs

continues due to their wide range of pharmacological activities and their industrial and synthetic applications. The present review focuses on the synthetic methodologies and biological activities of the benzimidazoles reported from 2000 to early 2007.

2
General Synthetic Methodologies for Benzimidazoles

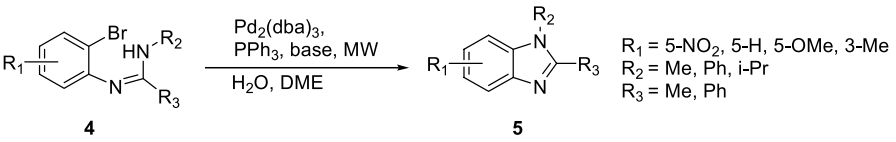
Traditionally, benzimidazoles have most commonly been prepared from the reaction of 1,2-diaminobenzenes with carboxylic acids under harsh dehydrating reaction conditions, utilizing strong acids such as polyphosphoric acid, hydrochloric acid, boric acid, or *p*-toluenesulfonic acid [7]. However, the use of milder reagents, particularly Lewis acids [8], inorganic clays [9], or mineral acids [6], has improved both the yield and purity of this reaction [10]. On the other hand, the synthesis of benzimidazoles via the condensation of 1,2-diaminobenzenes with aldehydes requires an oxidative reagent to generate the benzimidazole nucleus. Various oxidative reagents, such as nitrobenzene, benzoquinone, sodium metabisulfite, mercuric oxide, lead tetraacetate, iodine, copper(II) acetate, indium perfluorooctane sulfonates, ytterbium perfluorooctane sulfonates, and even air, have been employed for this purpose [11]. Moreover, a variety of benzimidazoles could also be produced via coupling of 1,2-diaminobenzenes with carboxylic acid derivatives such as nitriles, imidates, orthoesters, anhydrides or lactones [12].

Alternatively, benzimidazoles have also been prepared from 2-nitroanilides, in a two-step process. In the first step, the nitro group is reduced using one of many possible reagents (such as zinc, iron, tin(II) chloride, hydrogen, or Raney nickel). The second step involves the ring closure of the 2-aminoanilide derivative with either a carboxylic acid or an aldehyde [2, 10, 13]. However, this procedure sometimes requires multistep reactions to prepare the starting anilides, resulting in compromised yields and purity. In recent years, some innovative and improved pathways for the synthesis of benzimidazoles have been developed and these are discussed in the following sections.

2.1 Benzimidazole Ring Closure

Various substituted benzimidazoles have been synthesized in very good yields in solvent-free conditions from 1,2-diaminobenzene and aldehydes in the presence of titanium(IV) chloride as a catalyst. The method is applicable to most aromatic, unsaturated and aliphatic aldehydes and to substituted 1,2-diaminobenzenes without significant differences [14]. Several other catalysts, namely iodine [15], hydrogen peroxide [16], zirconyl(IV) chloride [17], boron trifluoride diethyl etherate [18], ytterbium perfluorooctane sulfonates [19, 20], zeolite [11, 21], and L-proline [22], have been effectively used for the synthesis of benzimidazole derivatives.

A palladium-catalyzed *N*-arylation reaction provided a novel synthesis of benzimidazoles **5** from (*o*-bromophenyl)amidine precursors **4** under microwave irradiation. The route was found to be flexible with respect to various substituents and allows for the preparation of highly substituted benzimidazoles, including *N*-substituted examples (Scheme 1) [23]. The method was later improved and optimized to achieve the rapid formation of benzimidazoles in high yield [24]. It has been found that 50% aqueous dimethyl ether (DME) is an optimal solvent for the reaction and that catalyst loading of palladium can be reduced to 1 mol %.



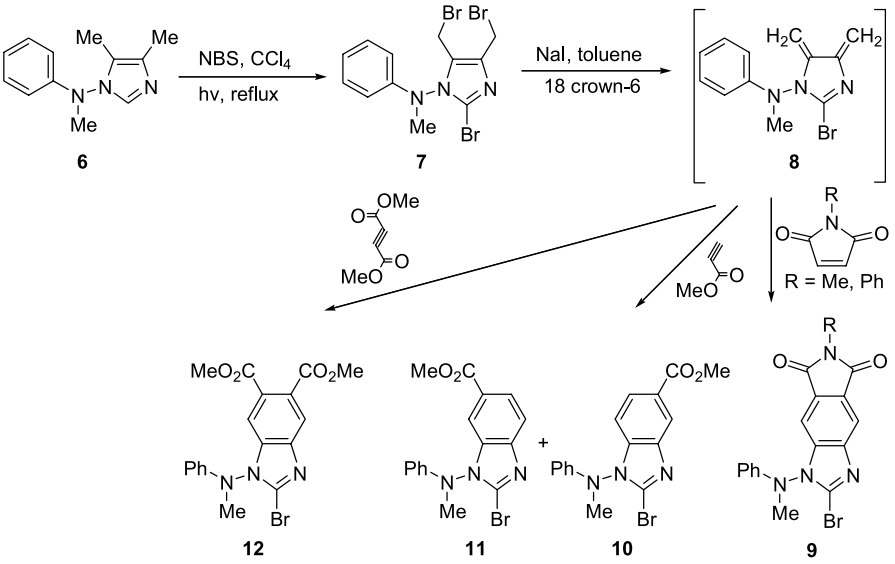
4 **5**

Scheme 1 Palladium-catalyzed synthesis of *N*-arylbenzimidazole

Imidazole *o*-quinodimethane intermediate **8**, synthesized from 2-bromo-4,5-bis(bromomethyl)imidazole derivative **7** via *N*-bromosuccinimide-mediated bromination of imidazole **6** undergoes a Diels–Alder reaction with several symmetrically and asymmetrically substituted dienophiles to yield the benzimidazole derivatives **9–12** in moderate yields [25]. The annulations of the aromatic systems depicted in Scheme 2 illustrate the ability of this reaction to give a variety of benzimidazoles.

2.2 Microwave-Assisted Synthesis of Benzimidazoles

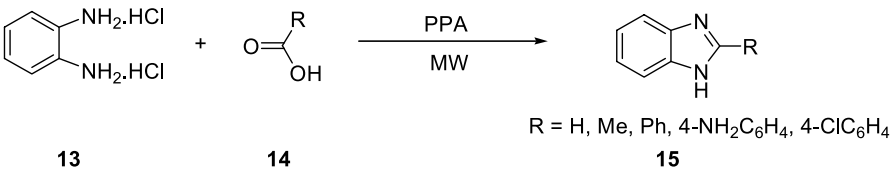
The use of microwave irradiation as a source of heat in synthetic chemistry has been heralded as a promising method of increasing productivity and quality and reducing reaction time since its first use by Gedye et al. in 1986 [26]. It has become a focal point in chemical synthesis in recent years in



Scheme 2 Synthesis of benzimidazoles by Diels–Alder reaction

terms of sustainable and green chemistry for improved resource management and the need to develop environmentally benign processes. Of particular importance is the reduction in the amounts of solvents and hazardous chemicals required to perform chemical reactions enabled by this approach, and its more efficient use of energy [27]. Since 1995, various substituted benzimidazole derivatives have been synthesized through microwave heating [28]. In this section, selected literature on the synthesis of benzimidazole by microwave technology is discussed.

Recently, 2-alkyl- and 2-aryl-substituted benzimidazole derivatives **15** have been synthesized from 1,2-diaminobenzene dihydrochloride **13** and its corresponding acids **14** in the presence of polyphosphoric acid using microwave-assisted methods (Scheme 3). The reaction time required for the synthesis of benzimidazole derivatives **15** was reduced to minutes by this method compared to conventional synthesis, which required up to four hours of heating to complete the reaction. Furthermore, it was found that the application of microwave irradiation increased yields by 10–50% (Table 1). It has been



Scheme 3 Synthesis of alkyl and aryl benzimidazoles under microwave conditions

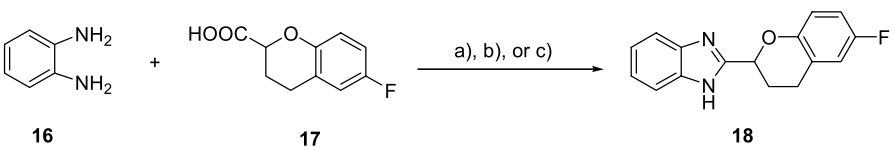
Table 1 Yield and reaction time for benzimidazole synthesis using microwave irradiation [29]

15 R =	RT	Yield (%)	MW	Yield (%)
H	2 h	80	1 min 20 s	92
Me	45 min	48	1 min 20 s	89
Ph	4 h	34	4 min 30 s	84
4-$NH_2C_6H_4$	4 h	57	5 min	95
4-ClC_6H_4	4 h	43	4 min 30 s	89

proposed that microwave heating easily provides the energy of activation required for the chemical reaction [29]. A similar one-pot high-yield procedure for the generation of 2-substituted benzimidazoles from the esters using ethane-1,2-diol as a solvent has been described [7]. Moreover, the single-step synthesis of benzimidazoles from a range of other diamines and carboxylic acids under microwave irradiation conditions has been developed, which provided a practical and efficient method for the high-throughput synthesis of 2-substituted benzimidazoles [12].

In addition, benzimidazoles containing furyl and aryl substituents at the C-2 position have been synthesized from 1,2-diaminobenzene and the corresponding carboxylic acids under microwave irradiation in the presence of artificial zeolites and catalytic amounts of DMF, used as the catalyst and energy transfer medium respectively. With this microwave technique, the reaction time was greatly shortened and the products were obtained in higher yields with easier workup than conventional heating methods [21].

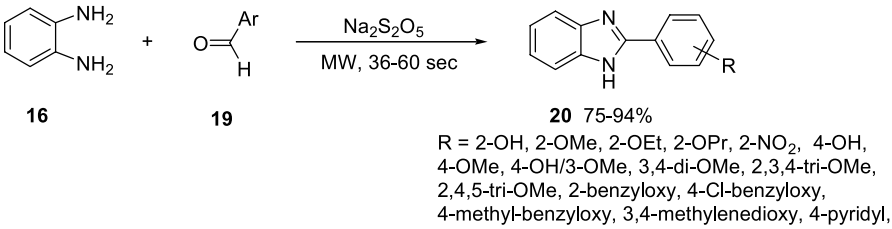
Conventional condensation of 1,2-diaminobenzene **16** with 6-fluoro-3,4-dihydro-2H-chroman-2-carboxylic acid **17** under Phillips' conditions or using Eaton's reagent (1 : 10 mixture of phosphorus pentoxide/methanesulfonic acid) yielded 2-(6-fluorochroman-2-yl)-1*H*-benzimidazole **18** (Scheme 4) [30]. However, irradiating the reaction mixture containing polyphosphoric acid as a catalyst with microwaves afforded the compound **18** in comparable yields in a matter of three minutes [30].



16 17 18

Scheme 4 Reagents and conditions: **a** 4 N HCl, reflux, 6 h, 85%; **b** MW, PPA, 100 W, 170 °C, 3 min, 85%; or **c** Eaton's reagent, 100 °C, 5 h, 80%

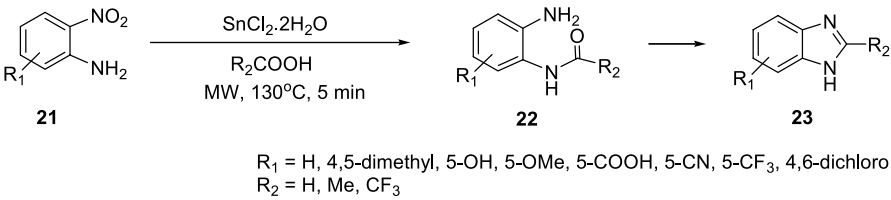
Recently, microwave-assisted synthesis of eighteen 2-(alkyloxyaryl)-1H-benzimidazole derivatives **20** related to the natural stilbenoid family has been



Scheme 5 Synthesis of 2-(alkyloxyaryl)-benzimidazole

reported (Scheme 5) [31]. These bioisosteric benzimidazole analogs **20** have been synthesized in high yields through a rapid three-component reaction starting from commercially available aldehydes **19** and 1,2-diaminobenzene **16**, and sodium metabisulfite in the absence of solvent. The in vitro spasmolytic activity of these compounds on the spontaneous contractions of the rat ileum suggests that bioactivity of these compounds depends upon the presence of oxygenated groups attached at C-2 and/or C-4 of the phenyl ring respectively [31].

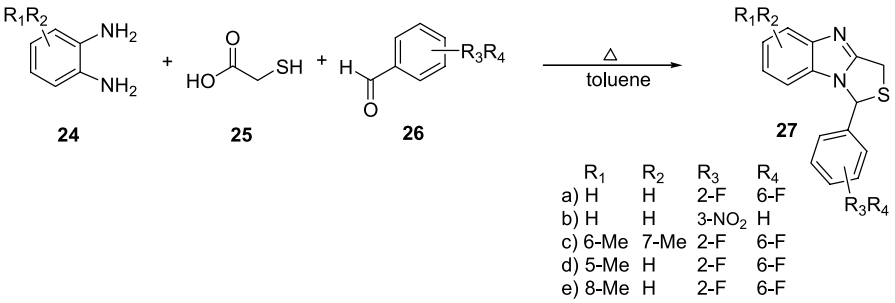
Recently, a facile, rapid one-pot procedure for the generation of 2-substituted benzimidazoles **23** directly from 2-nitroanilines **21** using a microwave procedure has been demonstrated (Scheme 6). An advantage of this approach is that the intermediate N-acyl derivatives **22** need not be isolated prior to cyclization [10].



Scheme 6 Synthesis of 2-substituted benzimidazoles from 2-nitroanilines

Classical condensation-cyclization reactions using 1,2-diaminobenzenes **24**, 2-mercaptoacetic acid **25** and appropriately substituted aromatic aldehydes **26** in dry benzene under reflux required a long reaction time to afford the thiazobenzimidazoles **27**, which are potent anti-HIV agents, by Scheme 7. On the other hand, the microwave-assisted synthesis of 1*H*,3*H*-thiazolo[3,4-a]benzimidazoles **27** was completed in toluene within 12 minutes [32].

Furthermore, a versatile and efficient microwave-promoted combinatorial library synthesis of two long alkyl chain benzimidazoles from *o*-substituted amines and fatty acids employing either bentonite, alumina or silica gel as solid supports has been developed [33]. Bismuth chloride [34], montmorillonite clay K-10 [35] and silica impregnated with sulfuric acid [36] have also



Scheme 7 Synthesis of thiazobenzimidazoles

been reported to act as inorganic catalysts for the benzimidazole ring closure reaction under microwave irradiation conditions.

2.3 Synthesis of Bisbenzimidazoles

Bisbenzimidazole derivatives such as Hoechst 33258 (also known as Pibenzimol) **28** (Fig. 2) is a A/T base pair selective compound that binds in the minor groove of DNA [37]. To investigate its full potential, a number of benzimidazole Hoechst motifs have been synthesized and evaluated for various biological activities [38–40].

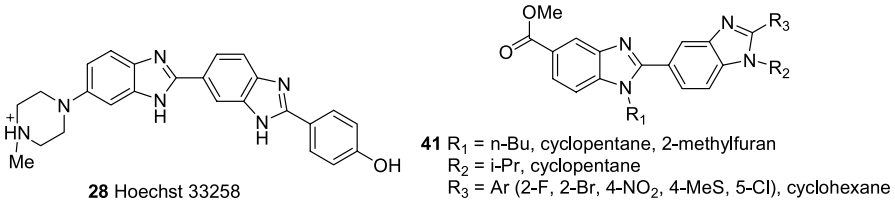
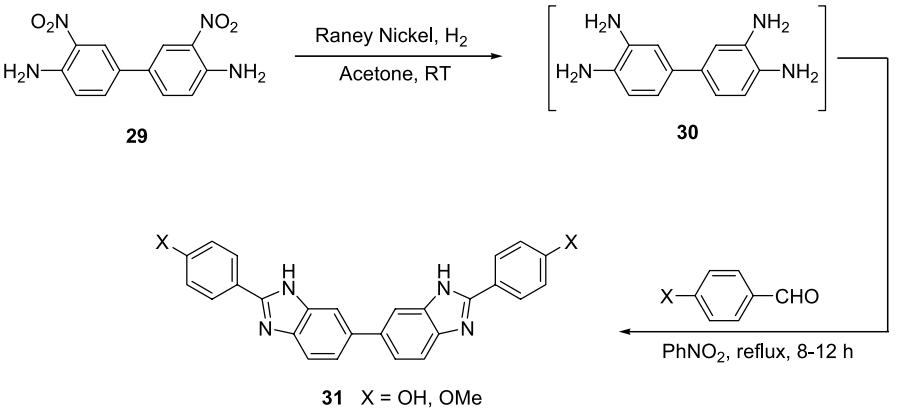


Fig. 2 Examples of some bisbenzimidazoles

Mann and coworkers have synthesized a new class of head-to-head bisbenzimidazoles **31** as DNA minor groove binding agents [41]. This new class of 6,6′-bisbenzimidazoles **31** was synthesized in moderate yields by the condensation of 3,3′,4,4′-tetraaminobiphenyl **30** with requisite aromatic aldehyde in nitrobenzene under reflux for 8–12 hours (Scheme 8).

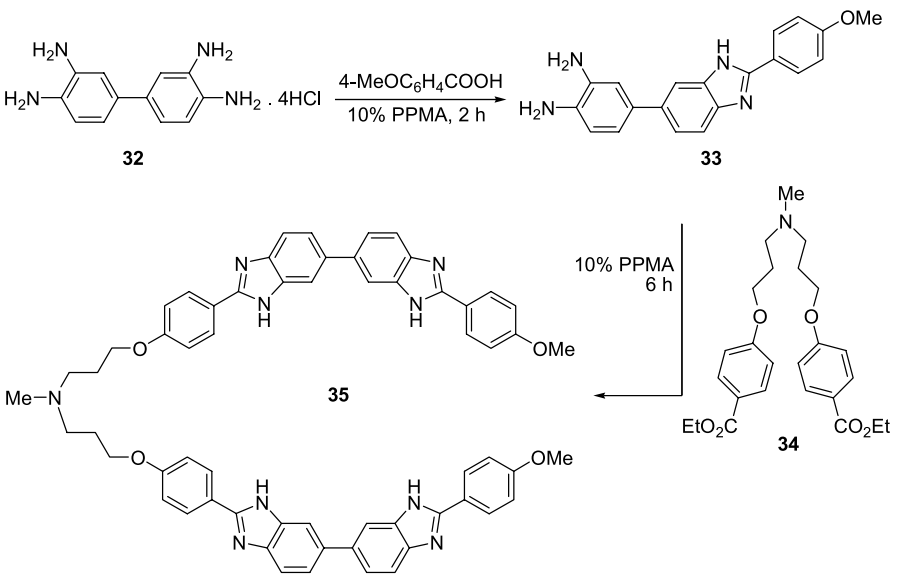
In order to target the minor groove of a longer sequence in the A/T rich region, the previous group also synthesized a novel dimeric bisbenzimidazole **35** where the two bisbenzimidazole rings are linked together via an appropriate linker [42]. The benzimidazole **33** was first obtained by condensation between 4-methoxybenzoic acid and 3,3′-diaminobenzidine tetrahydrochlo-



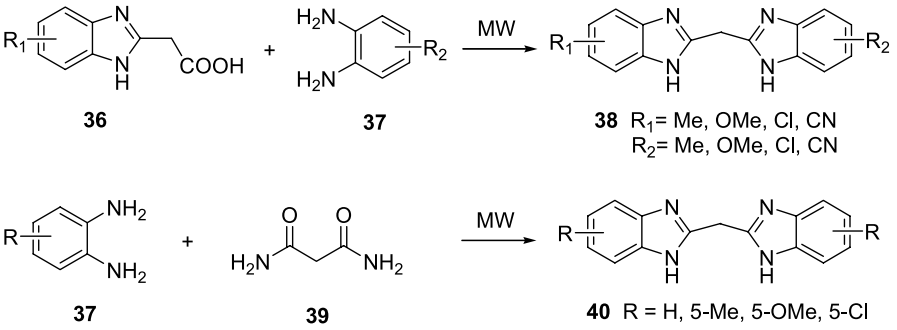
Scheme 8 Synthesis of head-to-head bisbenzimidazole

ride **32** (Scheme 9). The compound **33** was then condensed with the diester **34** to provide the desired dimeric bisbenzimidazole **35.**

The microwave-enhanced synthesis of symmetrical and asymmetrical bis(benzimidazol-2-yl)methanes **38** from appropriately substituted benzimidazole 2-acetic acid **36** and substituted-1,2-diaminobenzene **37** under solvent-free conditions without any catalyst has been performed in good yields (Scheme 10) [43]. The symmetrical bis(benzimidazol-2-yl)methanes **40** have similarly been prepared by one-step condensations of malon-



Scheme 9 Synthesis of a dimeric bisbenzimidazole **35**



Scheme 10 Synthesis of 2,2′-bisbenzimidazolylmethanes

amide **39** with appropriately substituted-1,2-diaminobenzene [44]. A similar microwave-assisted method for the synthesis of 2,2′-bisbenzimidazoles using 1,2-diaminobenzene **16** and oxalic acid or malonic acid in polyphosphoric acid has also been reported [45].

Combinatorial parallel synthesis of head-to-tail bisbenzimidazoles **41** has been performed using polymer-immobilized 1,2-diaminobenzenes (Fig. 2). The PEG-bound diamines were *N*-acylated at the primary aromatic amino group with 4-fluoro-3-nitrobenzoic acid. The substituted amides were cyclized to benzimidazoles under acidic conditions. Successive reduction and cyclization with various aldehydes yielded 5-(benzimidazol-2-yl)benzimidazoles. Finally, the desired products **41** were released from the polymer support to afford the bisbenzimidazoles in good yields and with high purity [46].

3 Benzimidazole Natural Products

Benzimidazole-derived alkaloids are rare in nature, and only a few examples of these natural products can be found in the literature. On the other hand, the occurrence of the imidazole skeleton in various natural sources is quite common [47–49]. The benzimidazole alkaloid kealiiquinone (Fig. 3) has been isolated from a yellow button-like Micronesian sponge species of *Leucetta* [49].

Recently, Nakamura et al. successfully synthesized a regioisomer of kealiiquinone (Scheme 11) [50]. 1-Methyl-2-phenylthio-1*H*-imidazole **44** was first converted into the 5-substituted imidazole **45**, then the benzylic hydroxyl group in **45** was protected by a *tert*-butyldimethylsilyl (TBDMS) group, and bromination with *N*-bromosuccinimide gave the bromide **46**. Lithiation by *tert*-butyllithium at the 4-position of **46** followed by trapping with 3,4-dimethoxy-2-(methoxymethoxy)benzaldehyde gave the tetrasubstituted imidazole **47** as a diastereomeric mixture. Acetylation of the hydroxy group of **47**

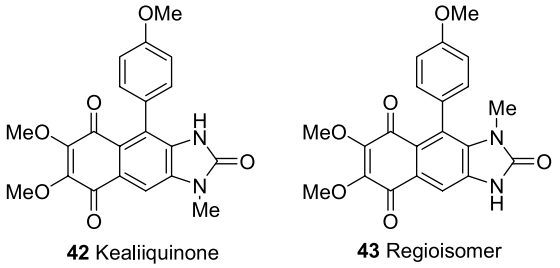
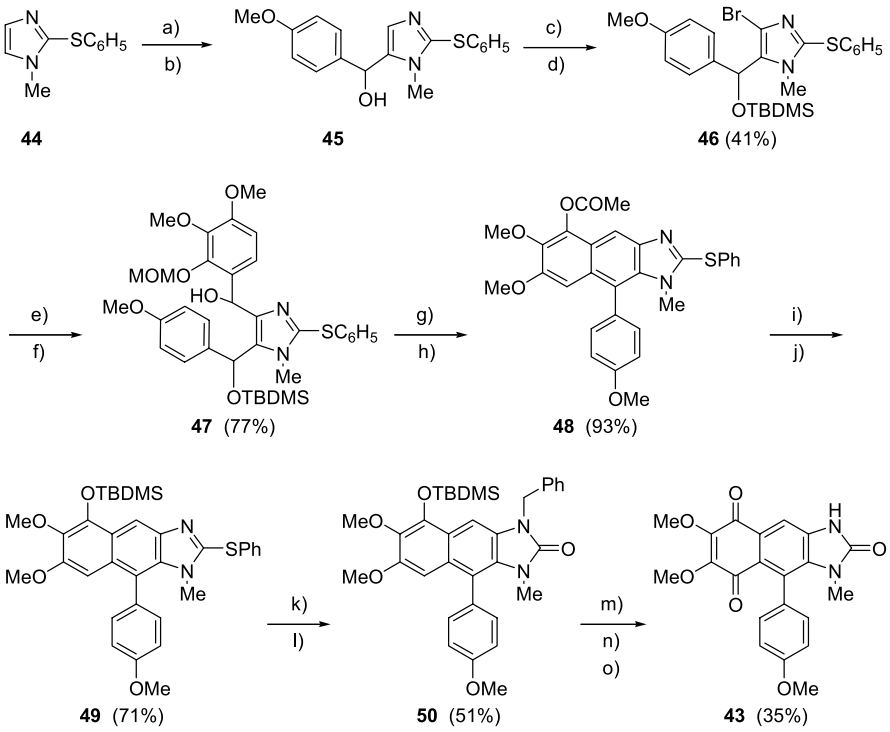


Fig. 3 Benzimidazole alkaloid kealiiquinone **42** and its regioisomer **43**



Scheme 11 Reagents and conditions: (**a**) LTMP, DME-THF; (**b**) *p*-anisaldehyde; (**c**) TBDMSCl, DMF, 12 h, 60 °C; (**d**) NBS, THF, 7 h, 0 °C; (**e**) *tert*-BuLi, *n*-pentane, Et_2O, 1 h, –78 °C; (**f**) 3,4-dimethoxy-2-(methoxymethoxy)benzaldehyde, Et_2O, 3 h, –78 °C; (**g**) Ac_2O, Et_3N, $CHCl_3$, 3 h, 0 °C; (**h**) PPA, Ac_2O, 12 h, 0 °C; (**i**) K_2CO_3, MeOH-H_2O, 3 H, r.t.; (**j**) TBDMSCl, DMF, 6 h, 60 °C; (**k**) benzyl bromide, EtOAc, 6 h, reflux; (**l**) aq. K_2CO_3, 1 h, 80 °C; (**m**) $Pd(OH)_2/C$, H_2 (4.2 kg/cm^{-2}), 48 h, r.t.; (**n**) TBAF, THF, 5 min, r.t.; (**o**) O_2, salcomin, 1 h, r.t.

and cyclization with polyphosphoric acid in the presence of acetic anhydride gave the tricyclic compound **48**. Alkaline hydrolysis of the ester group of **48** followed by conversion of the phenolic hydroxy group into a TBDMS group

afforded the silyl ether **49**. Quaternization of **49** with benzyl bromide followed by heating in aqueous potassium carbonate successfully afforded the 2-oxo compound **50**. The benzyl group and the TBDMS group of **50** were removed by Pd/C-catalyzed hydrogenation followed by treatment with TBAF, and the product was auto-oxidized in the presence of salcomin in THF to give the desired regioisomer of kealiiquinone compound **43** [50]. The kealiiquinone **42** and its synthetic regioisomer **43** both have relatively weak activities against a panel of 39 human cancer cell lines but are considered to have a unique mechanism of action [50].

Makaluvamines (pyrroloiminoquinones) **51** (Fig. 4) isolated from a Fijian sponge in the early 1990s display in vitro cytotoxicity against human colon tumor cell lines and also inhibit human topoisomerase II in vitro. The benzimidazole analog of this indole-based marine natural product, imidazoquinoxalinone **52**, has been synthesized starting from *p*-methoxydiacetanilide (Scheme 12) [51]. Treatment of the dinitration product **54** of *p*-methoxy-

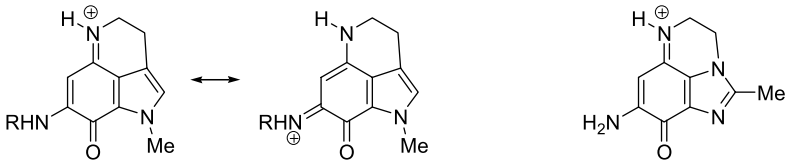
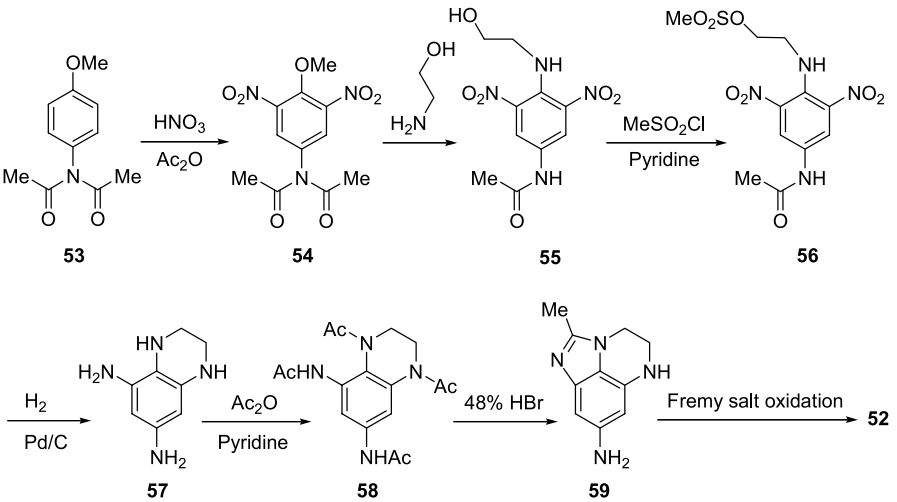
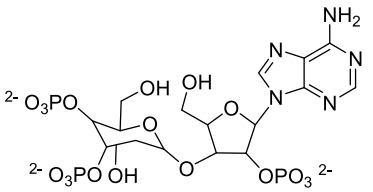


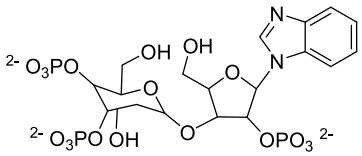
Fig. 4 Makaluvamine and its benzimidazole analog



Scheme 12 Synthesis of imidazoquinoxalinone



60 Adenophostin



61 Benzimidazole analog

Fig. 5 Adenophostin and its benzimidazole analog

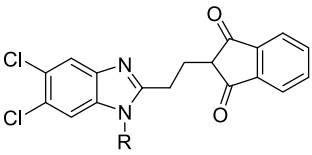
diacetanilide **53** with ethanolamine resulted in the formation of aminoethanol compound **55**. Conversion of the alcohol **55** to mesylate **56** followed by catalytic reduction of the nitro group afforded the tetrahydroquinoxoline **57**. Peracetylation of quinoxoline **57** afforded a stable amide **58**, which upon acid-catalyzed cyclization yielded the precursor benzimidazole **59**. Finally, Fremy salt oxidation of benzimidazole **59** afforded the iminoquinone **52**.

In comparison with the natural inositol 1,4,5-triphosphate, the adenophostins **60** (Fig. 5) exhibit higher receptor binding activity and Ca^{2+} mobilizing potencies and thus have significant biological importance. A total synthesis of a benzimidazole analog of adenophostin A **61** has been described by Shuto et al. [52].

4
Functionalization of the Benzimidazole Molecule

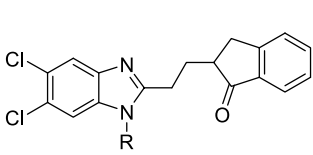
4.1
Substitution at the N-1 Position

N-substituted benzimidazoles **62** and **63** (Fig. 6) have been reported to show anti-hepatitis B virus activity, and thus several derivatives of novel benzimidazoles **62** and **63** have been prepared by Li et al. [53]. The precursor benzimidazoles readily undergo *N*-substitution reactions with sulfonyl chlorides in dichloromethane using DMAP as a base, whereas methylation can



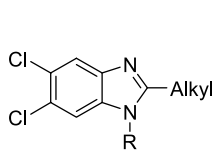
R = $MeSO_2$, Ts, Me, 4-Me-benzyl

62



R = $MeSO_2$, Ts, Me, 4-Me-benzyl

63



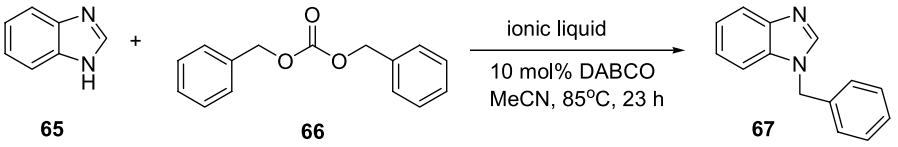
R = Me, Et

64

Fig. 6 *N*-substituted benzimidazoles

be achieved by potassium carbonate in DMF or sodium hydroxide in acetonitrile. Several N-alkyl benzimidazole derivatives **64** behave as selective androgen receptor antagonists [54].

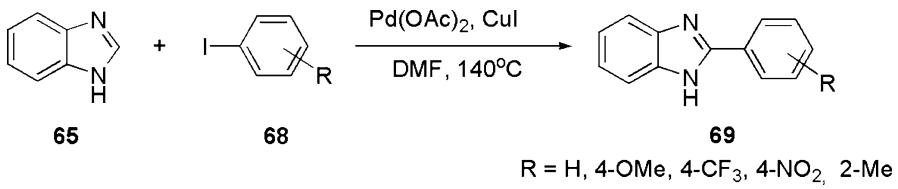
Ionic liquids have been reported to accelerate slow *N*-benzylation reactions of benzimidazole **65** utilizing dibenzyl carbonate **66** as an alkylating reagent (Scheme 13) [55]. An additional rate enhancement was observed when microwave irradiation was applied in this reaction to afford the *N*-benzylbenzimidazole **67**.



Scheme 13 *N*-benzylation reaction via dibenzyl carbonate

4.2 Direct Coupling at the C-2 Position

Functionalization of C – H bonds of heterocycles to C-arylation is an important synthetic reaction that is used to build important bioactive structures. Recently palladium and copper-mediated C-2 arylations of benzimidazole with aryl iodides under ligandless and base-free conditions have been described (Scheme 14) [56]. These reactions show complete selectivity under these conditions and allow for the use of substrates containing base-sensitive groups without their prior protection, such the NH group of benzimidazoles [56, 57]. The aryl-substituted benzimidazole compounds were obtained in high purities and yields within 48 hours, and the scheme was also applicable to other azoles.



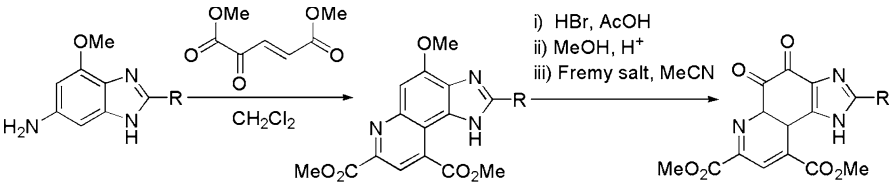
Scheme 14 Palladium-catalyzed direct C-2 coupling

A similar general method for the rhodium-catalyzed direct coupling of benzimidazoles with aryl bromides or iodides has also been developed under microwave-assisted conditions, and it has shown to provide rapid access to medicinally relevant compounds. Both electron-rich and electron-poor aryl iodides were observed to couple with tricyclohexylphosphine. The desired

arylated products were obtained in good yields by conventionally heating the reaction mixtures in sealed tubes. N-Heterocyclic carbene/rhodium complexes were considered to be intermediates during C – C bond formation [58].

4.3
Doebner–Von Miller Reaction at the C-7 Position

Imidazoquinolines **71** have been synthesized in good yield by coupling benzimidazole **70** with dimethyl *trans*-2-ketoglutaconate under Doebner–Von Miller reaction conditions in dichloromethane (Scheme 15). The compound **71** was demethylated using hydrobromic acid in glacial acetic acid, re-esterifed with methanolic hydrochloric acid, and oxidized to afford benzimidazole quinone **72** [59].



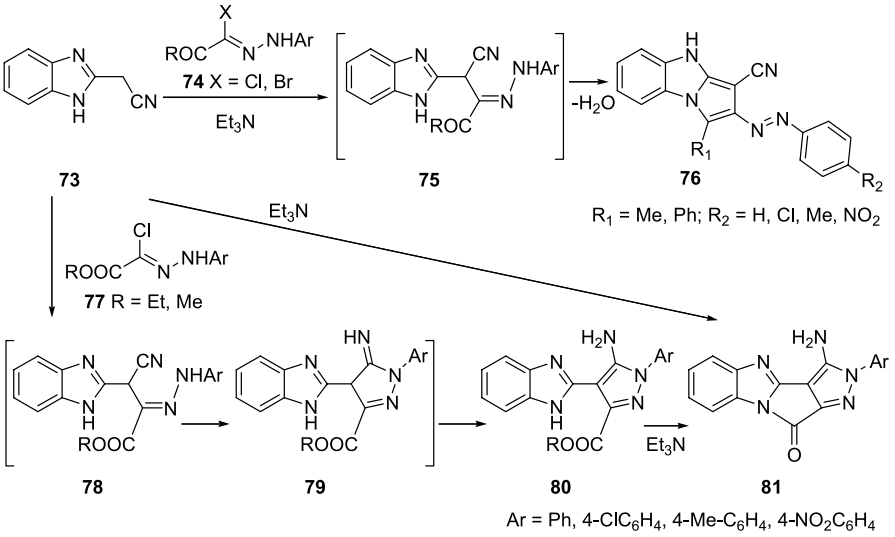
70 **71** R = H, Me **72** R = H, Me

Scheme 15 Doebner–Von Miller reaction at C-7 position

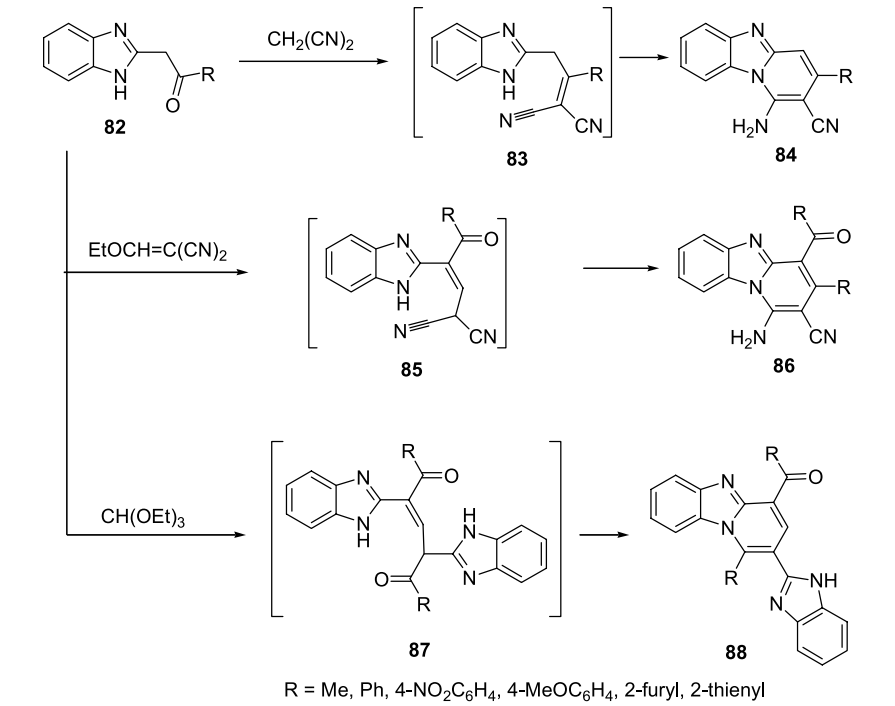
4.4
Cyclization Between the N-1 and C-2 Positions

Various benzimidazole derivatives can be fused between the C-2 and N-1 positions in order to build novel heterocyclic ring systems. For example, the reaction of 2-cyanomethylbenzimidazole **73** with hydrazonoyl halides **74** in the presence of triethylamine led to the formation of pyrrolo[1,2-a]benzimidazoles **76** (Scheme 16) [60]. It has been suggested that the reaction starts with the nucleophilic substitution of the halogen by the benzimidazole carbanion to give intermediate **75**, which upon cyclization via elimination of water gives the desired cyclic pyrrolobenzimidazoles **76.** On the other hand, the reaction of hydrazonoyl chlorides **77** with 2-cyanomethylbenzimidazole **73** in sodium ethoxide afforded pyrazole-3-carboxylate **80**, which upon treatment under triethylamine yielded the pyrazolopyrrolobenzimidazole **81**. The product was also obtained by the direct reaction of 2-cyanomethylbenzimidazole **73** with hydrazonoyl chlorides **77** in the presence of triethylamine.

Dzvinchuk has synthesized several pyrido[1,2-*a*]benzimidazoles (**84**, **86** and **88**) via reactions of 2-acylmethylbenzimidazole **82** (Scheme 17). Treatment of **82** with malononitrile led to the formation of the dicyanomethylene-



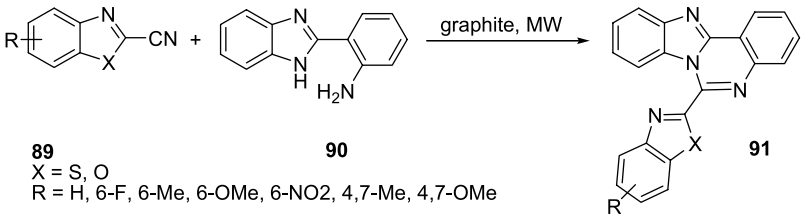
Scheme 16 Synthesis of pyrrolobenzimidazoles



Scheme 17 Synthesis of pyrido[1,2-*a*]benzimidazoles

substituted compounds **83**, which by intramolecular addition of the benzimidazole imino group to the nitrile gave the pyridobenzimidazoles **84**. The similar reaction of 2-acylmethylbenzimidazole **82** with ethoxymethylenemalononitrile yielded the pyridobenzimidazoles **86** by the cyclization of the intermediate compound **85**. On the other hand, attachment of the 2-acylmethylbenzimidazole **82** to triethylorthoformate joins two benzimidazole molecules of the starting keto compound at the active methylene group to give the intermediate **87**, which then undergoes cyclocondensation of a benzimidazole imino group at the keto group to give the substituted pyridobenzimidazoles **88** [61].

Polyheterocyclic structures such as benzimidazoquinazolines **91** made up of two fused heterocyclic rings often possess potent biological activity, like antiproliferative and DNA-intercalator activity [62], antifertility activity [63], anticonvulsant activity, and myorelaxant activity [64]. These benzimidazoquinazoline compounds **91** have been obtained by the condensation of 2-cyanobenzothiazoles **89** or benzoxazoles **89** with 2-(2-aminophenyl)benzimidazole **90** under microwave conditions in the presence of graphite as a catalyst [65].

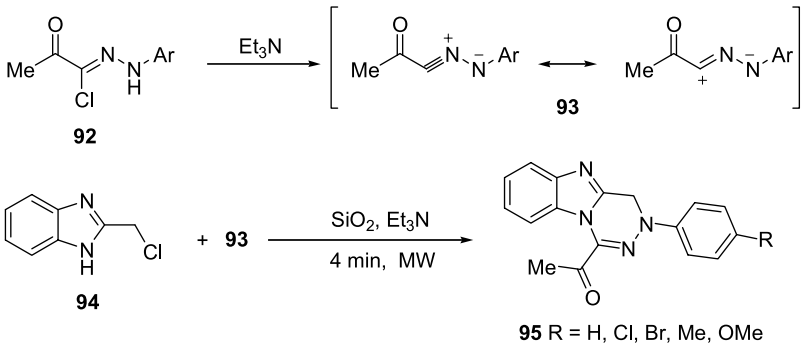


Scheme 18 Synthesis of polyheterocyclic benzimidazoquinazolines

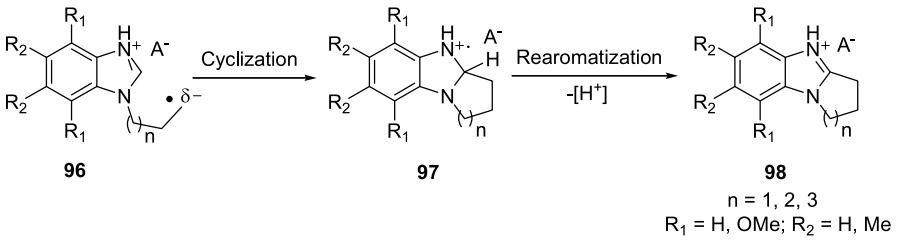
The intermediate 1,3-dipolar nitrile imines **93**, generated in situ from hydrazonyl chloride **92**, have been reacted with 2-chloromethylbenzimidazole **94** in the presence of triethylamine and silica gel under microwave irradiation for four minutes to afford the synthesis of the novel tricyclic benzimidazole system **95** [66].

Radical cyclizations of nucleophilic N-alkyl radicals **96** onto the benzimidazole 2-position, mediated by tributyltin hydride and activated by quaternizing the pyridine-like N-3 of imidazole with camphorsulfonic acid, have recently been reported (Scheme 20) [67]. These new five-, six- and seven-membered homolytic aromatic substitutions of nucleophilic N-alkyl radicals onto the benzimidazole-2-position occurred upon the use of large excesses of the azo-initiator, 1,1′-azobis(cyclohexanecarbonitrile), to supplement the non-chain reaction. The intermediate **97** aromatizes in high yields to the cyclized benzimidazoles **98**.

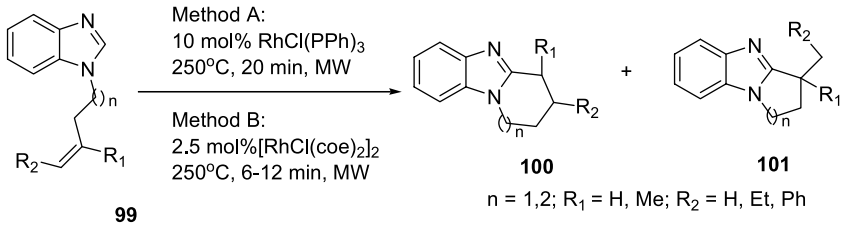
Microwave irradiation has been shown to strongly accelerate the rhodium-catalyzed intramolecular C – H bond coupling of benzimidazole alkenes **99** to



Scheme 19 Synthesis of novel tricyclic benzimidazole



Scheme 20 Intramolecular homolytic aromatic substitution mechanism



Scheme 21 Microwave-assisted intramolecular coupling reaction

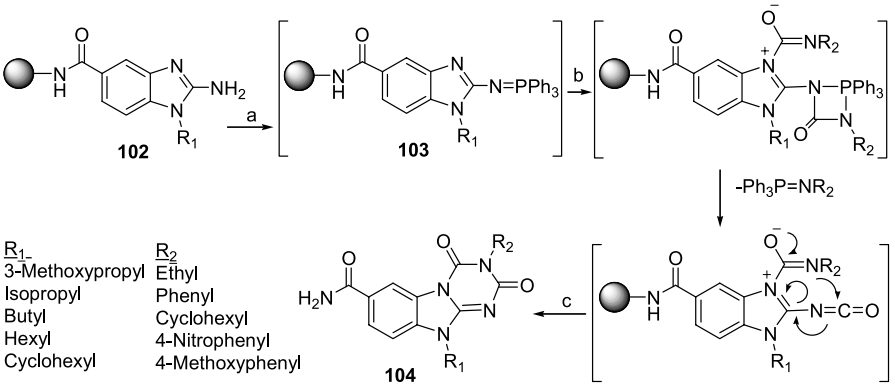
cyclic benzimidazoles **100** and **101**. These products were formed in moderate to excellent yields with reaction times of less than 20 minutes. Additionally, the use of microwave irradiation allowed the reactions to be performed without any solvent and purification and with minimal precautions to exclude air [68].

4.5 Solid Phase Synthesis

The use of solid phase synthesis has been directed towards high-speed synthesis and biological screening of diverse libraries as part of the drug dis-

covery process. The widespread use of solid phase synthesis is due to its advantages of inexpensive apparatus, easy workup and filtration. Thus, it has become an increasingly popular tool for combinatorial synthesis as well as green chemistry in recent years [69, 70]. From a combinatorial chemistry perspective, the benzimidazole scaffold allows the stepwise incorporation of diverse functionality with control over regiochemistry, making it a suitable target for library synthesis using solid and solution phase approaches as well as parallel polymer-assisted synthesis [10, 71–75].

Resin-bound iminophosphoranes **103** derived from the reaction of resin-bound 2-aminobenzimidazole **102** with triphenylphosphine oxide were reacted with aryl isocyanates in an abnormal aza-Wittig reaction with a chemoselectivity that depends on the reaction temperature and the nature of the aryl isocyanate (Scheme 22). The mechanism considered for the solid phase synthesis reaction involves the loss of triphenylphosphinimide instead of triphenylphosphine oxide, resulting in the formation of isocyanates instead of carbodiimides as intermediates. Optimization studies revealed that employing electron-poor aryl isocyanates at high temperature leads to 95% of the abnormal aza-Wittig products 3-aryl 2,4-dioxo-1,3,5,-triazino[1,2-*a*]benzimidazoles **104** [76].



Scheme 22 Solid phase synthesis of triazinobenzimidazoles (reagents and conditions: (**a**) PPh_3, DEAD, THF, 25 °C, 3 days; (**b**) R_2NO_2, toluene, 25 °C, 2 days; (**c**) HF, anisole, 0 °C, 1.5 hour)

Using polymer-immobilized liquid phase synthesis and controlled microwave irradiation, trisubstituted bisbenzimidazoles have been prepared and released with good yield and purity [77]. Furthermore, a wide range of benzimidazole derivatives have been synthesized with excellent yields and purities by simple washing and filtration using liquid phase synthesis on a soluble polymer support [78].

4.6
Benzimidazole-Derived Metal Complexes

Recently, neutral dimeric zinc(II) complexes have been constructed from phenolic benzimidazole derivatives containing N and O donor atoms. These complexes exhibited a trigonal-bypyramidal geometry [79]. Pal recently reported a benzimidazole N-donor dinuclear palladacycle complex **105** [80] (Fig. 7). The X-ray crystal structure revealed that the two bisbenzimidazole ligands assembled through complexation to two palladium (II) ions to give a compressed rectangular metallamacrocycle. The complex effectively catalyzed Suzuki cross-coupling reactions in methanol at room temperature [80]. Moreover, a series of nickel(II) complexes **106** and **107** ligated by 2-(2-benzimidazole)-pyridine derivatives and nickel dichloride hexahydrate have been prepared [81]. Interestingly, benzimidazole-derived copper(II) and nickel(II) complexes have revealed antibacterial, antifungal and DNA intercalator activities [82], whereas lanthanide(III) complexes exhibited seed germination inhibition activity [83].

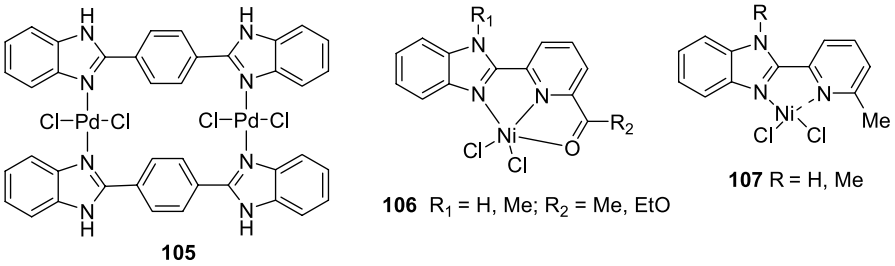


Fig. 7 Some benzimidazole–metal complexes

5
Biological Activities of the Benzimidazole Analogs

5.1
Anti-infective Agents

5.1.1
Antibacterial and Antifungal Agents

The search for compounds with antibacterial activity has gained increasing importance in recent times, due to growing worldwide concern over the alarming increase in the rate of infection by antibiotic-resistant microorganisms [84]. Owing to the current importance of developing novel antimicrobials and the varied bioactivities exhibited by benzimidazoles, sev-

eral reseachers have investigated the antimicrobial activities of benzimidazole derivatives.

2-Mercaptobenzimidazole derivatives are known to possess varied biological activities [85]. Recently, an efficient and rapid synthesis of novel benzimidazole azetidin-2-ones **108** has been established [86], and antibacterial screening revealed that all newly synthesized azetidin-2-ones **108** exhibited potent antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli*. In general, compounds **108a**, **108i** and **108j** exhibited more pronounced antibacterial activity than compounds **108b–h**, with better activity against both Gram-positive and Gram-negative bacteria (Fig. 8). Among all of the compounds investigated, **108i** and **108j** exhibited the greatest antibacterial activity against Gram-negative *E. coli* as compared to the antibiotic streptomycin [86]. Benzimidazole benzyl ethers **109** have exhibited good antibacterial activity against *S. aureus* and antifungal activity against *Candida albicans* and *Candida krusei*. In general the dichlorophenyl-substituted benzimidazoles **109e**, **109f**, and **109h** showed the best antibacterial (MIC 3.12 μg/mL) and antifungal (MIC 12.5 μg/mL) activity [87]. In addition, 5-fluoro benzimidazole carboxamide derivatives **110** [88] and benzimidazole isoxazolines **111** [89] have been reported to show antibacterial and antifungal activities. N-alkylated or acylated derivatives of benzimidazole **18** also exhibited good antibacterial activities [30]. Numerous other reports of benzimidazole derivatives with antimicrobial activities have been published [90–99].

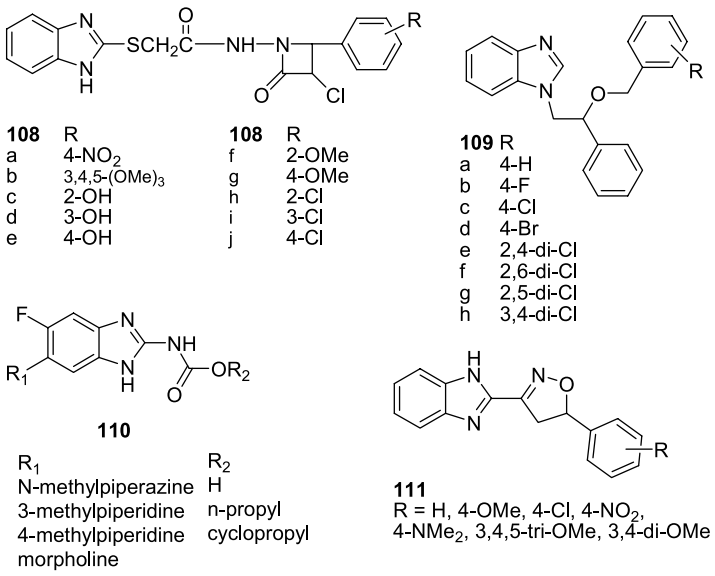


Fig. 8 Some antimicrobial benzimidazole derivatives

5.1.2 Anthelmintic Agents

Anthelmintic resistance is almost cosmopolitan in distribution and it has been reported in almost all species of domestic animals and even in some parasites of human beings. All of the major groups of anthelmintics have encountered variable degrees of resistance from different species of gastrointestinal nematodes [100]. Bearing in mind previous benzimidazole anthelmintics (e.g., albendazole, mebendazole), the search for new anthelmintic drugs is being actively pursued. Synthetic benzimidazole piperazine derivatives exhibited 50% anthelmintic activity in mice infected with *Syphacia obvelata* [101]. Furthermore, piperazine derivatives of 5(6)-substituted-(1*H*-benzimidazol-2-ylthio) acetic acids **112–114** [102] and benzimidazolyl crotonic acid anilide **115** have shown good anthelmintic activity [103] (Fig. 9).

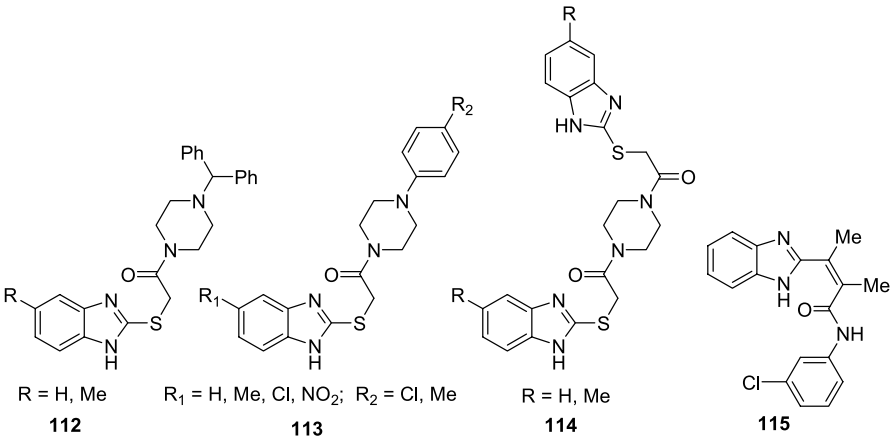


Fig. 9 Benzimidazole anthelmintic agents

5.1.3 Antiretroviral Agents

Reverse transcriptase is a key enzyme which plays an essential and multifunctional role in the replication of HIV-1 and thus constitutes an attractive target for the development of new drugs that could be used in AIDS therapy. A combination of reverse transcriptase and protease inhibitors is an effective approach to the treatment of AIDS [32]. However, side effects and the clinical emergence of resistant mutants suggests an increasing need for novel antiviral drugs.

Thiazolobenzimidazoles **27** proved to be a highly potent inhibitor of HIV-1-induced cytopathic effects. Structure–activity relationship studies showed

that the C-1 substituents in benzimidazole greatly influence the interaction of the active compound with the receptor. Substitution on the benzene-fused ring influences the inhibitory potency depending on the nature and position of the substituent; the presence of a methyl group at C-3 is favorable to the pharmacological profile [104].

5.2 Anti-inflammatory and Antiulcer Agents

Structure–activity relationship studies of the 5,6-dialkoxy-2-thiobenzimidazole derivatives **116** have revealed that compounds **116a–116k** possess pronounced anti-inflammatory properties [105] (Fig. 10). Using the carrageenan model, the most significant anti-inflammatory effects were observed for com-

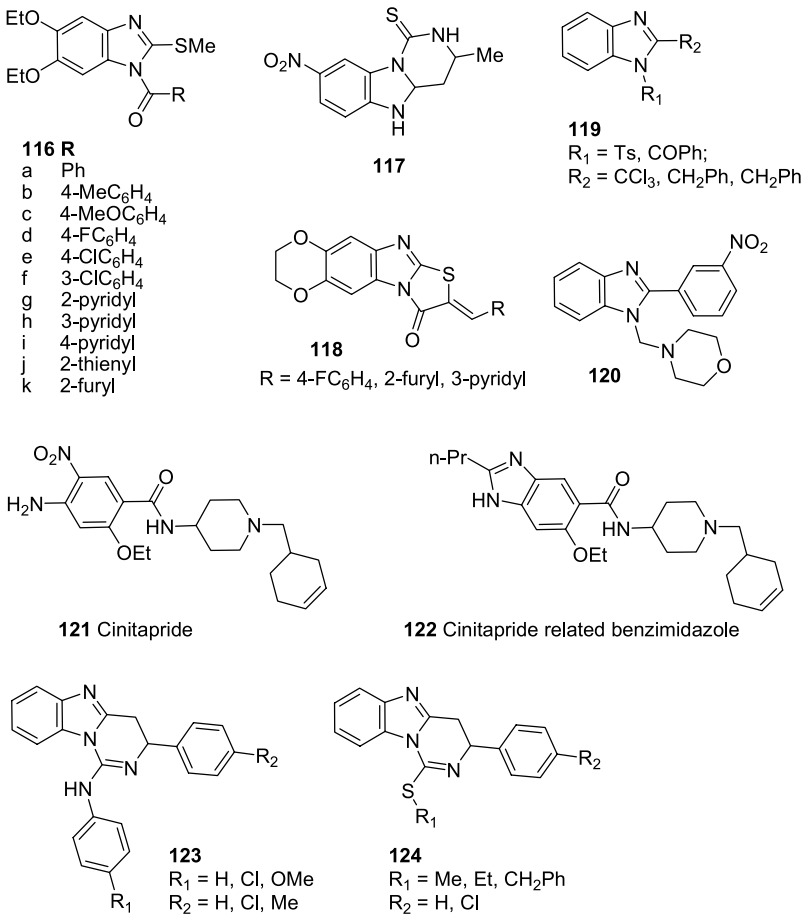


Fig. 10 Anti-inflammatory benzimidazole derivatives

pounds **116a**, **116d**, **116h**, **116i**, and **116j**. While using the bentonite model, the maximum activities were observed for compounds **116e** and **116h**. These results indicated that benzimidazoles are promising leads for the development of new anti-inflammatory agents.

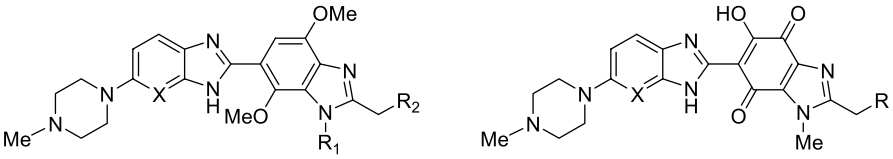
Pyrimidobenzimidazole **117** [106] and dioxinobenzimidazothiazol-9-ones **118** [107] exhibited anti-inflammatory and analgesic activity, as evaluated by carrageenan-induced rat paw edema and phenylquinone-induced writhing tests. In addition, N-benzoyl and N-tosyl benzimidazole compounds **119** showed significant anti-inflammatory activity, as indicated by ear swelling induced by xylene in mice, and their ulcer indices were all lower than those of aspirin [108]. Furthermore, N-morpholinomethylbenzimidazole **120** and its derivatives have been recently reported to show significant anti-inflammatory activity [99].

Despite the success of several commercial benzimidazole proton pump inhibitors for the treatment of ulcer disease, work is still in progress to discover new benzimidazole-derived antiulcer drugs. Cinitapride (**121**)-related benzimidazole derivatives **122** have been prepared and studied for their antiulcerative activity [109]. In addition, 1,3-disubstituted 3,4-dihydropyrimido[1,6-a]benzimidazoles and 3-substituted 3,4-dihydropyrimido[1,6-a]benzimidazol-1(2*H*)-thiones exhibited good gastric antisecretory activity (> 50% inhibition) [110].

5.3 Cytotoxic and Antitumor Agents

In cancer chemotherapy there is currently much interest in the design of small molecules that bind to DNA with sequence selectivity and noncovalent interactions [37]. A possible lead for this new class of compounds is Hoechst 33258 **28** (Fig. 2), which recognizes A/T sequences in human DNA and is also an effective inhibitor of mammalian DNA topoisomerase [37]. Several structure–activity relationship studies have been performed on the Hoechst motif. The replacement of the terminal piperazine ring with an amidinium, an imidazoline or a tetrahydropyridinium group significantly reinforces the affinity of the drug for the A/T stretches [111]. The corresponding trisbenzimidazole derivative prepared by the addition of one more benzimidazole unit to the structure of Hoechst 33258 exhibits high A/T-base pair selectivity [112].

Novel bisbenzimidazoles with general formula **125–128** incorporating benzimidazole, pyridoimidazole, and imidazoquinone moieties as one of the units of bisbenzimidazole with a piperazinyl functional group have been synthesized (Fig. 11) [113]. The series of bisbenzimidazoles contains different leaving groups along with *p*-methoxy substituents. The latter may be expected to have some influence on the nitrogen lone pair and consequently on the binding characteristics of the ligand. These novel bisbenzimidazoles are found to be actively cytotoxic against many human cancer cell lines, with



125 X = N, R_1 = H
126 X = CH, R_1 = H
127 X = N, R_1 = Me
R_2 = OMe, OEt, OAc, OH

128 X = N, CH; R = OH, Cl

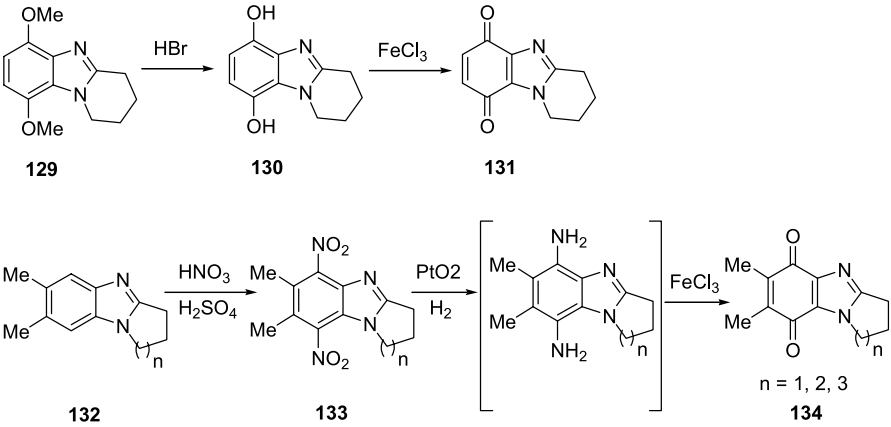
Fig. 11 Cytotoxic benzimidazole derivatives

GI_{50} values of between 0.01 and 100 μM, especially in the cases of renal cancer, CNS cancer, colon cancer, melanoma, and breast cancer cell lines. The pyridoimidazole compounds **125** and **127** are generally more potent. The derivative **128**, characterized by the presence of a *p*-quinone moiety, a characteristic feature found in the bioreductively activated alkylating agent mitomycin C, exhibits enhanced cytotoxic activity. This biological result suggests that the modification of the bisbenzimidazole structure by the incorporation of a quinone moiety might have significant potential for the development of bioreductive quinone-based drugs [37].

Furthermore, novel head-to-head bisbenzimidazole compound **31** binds with high affinity to the minor groove of double-stranded B-DNA with a strong preference for A/T-rich regions. The bisbenzimidazole **31** showed potent growth inhibition in human ovarian carcinoma cell lines (IC_{50} = 200–300 nM), with no significant cross-resistance in two acquired cisplatin-resistant cell lines and a low level of cross-resistance in the *p*-glycoprotein overexpressing doxorubicin-resistant cell line. In addition, compound **31** was found to have significant in vivo activity in the allowed fiber assay and tumor xenografts (CH1 cells) [37, 41, 114].

The bioactive benzimidazolequinone **131** has been synthesized by demethylation of the dimethoxybenzimidazole **129** followed by facile oxidation of the intermediate dihydroxy compound **130** by ferric chloride to yield the quinone **131** in excellent yield (Scheme 23). Synthesis of the related benzimidazolequinones **134** was achieved by dinitration of **132** followed by the reduction of **133** and oxidation as above. The benzimidazole-6,9-dione **134** has been found to be 300 times more cytotoxic towards the human skin fibroblast cell line in the MTT assay than the clinically used bioreductive drug, mitomycin C. Attaching methyl substituents onto the quinone moiety increased reductive potential and decreased cytotoxicity and selectivity towards hypoxia [67].

In addition, the alkyl-linked bisbenzimidazole **135** [115] and thiazolylbenzimidazole-4,7-diones **136** [116] exhibited cytotoxic activity against tumor cell lines (Fig. 12).



Scheme 23 Synthesis of benzimidazole diones

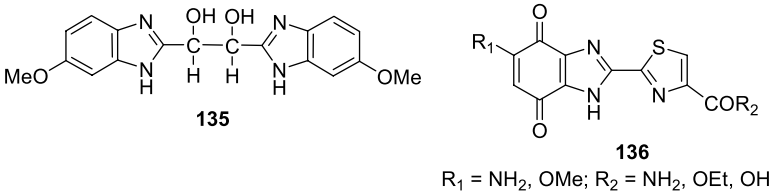


Fig. 12 Cytotoxic benzimidazole derivatives

5.4 Enzyme and Receptor Agonists/Antagonists

Several benzimidazole derivatives have been reported to act on various enzymes and receptors. Some examples of benzimidazoles acting as agonists or antagonists of various receptors and enzymes are listed in Table 2.

6 Conclusions

Conventional synthetic methods remain the mainstream routes for the synthesis of benzimidazoles. However, a few novel synthetic methodologies for the synthesis of benzimidazole have been reported in the time frame selected for this review. The popularity of microwave-assisted synthesis has been increasing rapidly since it enables the effective synthesis of benzimidazoles and its analogs. A wide variety of benzimidazole analogs have been synthesized, and several of these look promising for further drug discovery efforts.

Table 2 Benzimidazole derivatives that act on enzymes/receptors

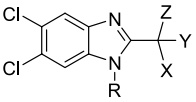
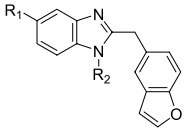
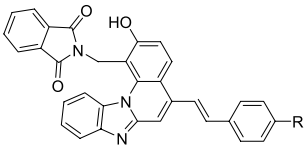
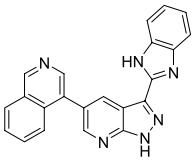
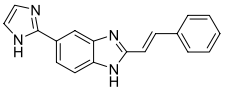
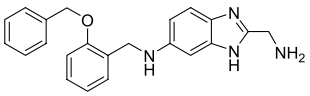
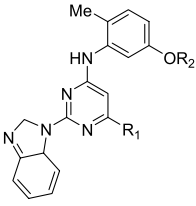
Compound	Enzyme/receptor	Activity	Refs.
 R = H, Me, Et X = H, OH Y = Me, Et, n-Pr Z = Me, Et	Androgen receptor	Antagonist	[54, 117, 118]
 R_1 = Et_2NCO, t-BuCONMe R_2 = CH_2Ph, CH_2CH_2Ph	Cannabinoid 2 (CB2) receptor	Agonist	[119]
 R = H, OH	Cholecystokinin B receptor	Antagonist	[120]
	Cyclin-dependent kinase 1 (CDK1)	Inhibitory	[121]
	Enkephalinase B (DPP III)	Antagonist	[122]
	Gelatinase B	Inhibitory	[75]
 R1 Cl NH_2 $NHCH_3$ OMe Etc R2 H Me	Lymphocyte specific kinase	Inhibitory	[123]

Table 2 (continued)

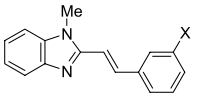
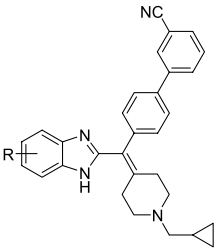
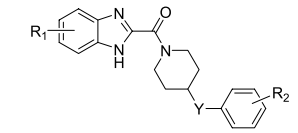
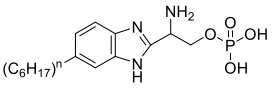
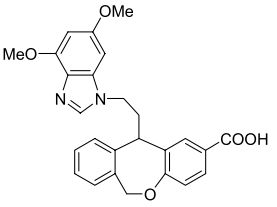
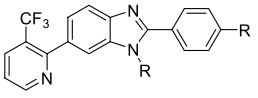
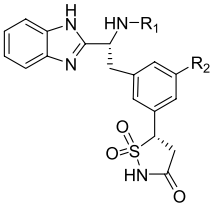
Compound	Enzyme/receptor	Activity	Refs.
 X = H, Cl, F	Monoamine oxidases B receptor	Antagonist	[124]
 R = 5-F, 6-CF_3, 5,6-Cl_2	Melanin-concentrating hormone receptor 1 (MCH R1)	Antagonist	[125]
 R_1 = 5(6)-OH, 4(7)-OH, 5(6)-NH_2 Y = O, CH_2 R_2 = H, 2-Me, 3-Me, 4-Me, 3-F, 4-F,4-Cl, 3-OMe	NMDA receptor	Antagonist	[126]
	Sphingosine-1-phosphate receptor	Agonist	[127]
	Thromboxane A_2 (TXA_2) receptor	Antagonist	[128]
 R = CF_3, *tert*-butyl, Me, F	Transient receptor potential vanilloid 1 (TPRV1)	Antagonist	[129]

Table 2 (continued)

Compound	Enzyme/receptor	Activity	Refs.
 R_1 = 2-(benzothiazolyl), 2-(phenylsulfonyl) R_2 = H, Me, Cl, F, Br	Tyrosine phosphatase 1B	Inhibitory	[53, 130]

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