



Review

The therapeutic journey of benzimidazoles: A review

Yogita Bansal, Om Silakari*

Molecular Modelling Lab (MML), Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, Punjab 147002, India

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ABSTRACT

Presence of benzimidazole nucleus in numerous categories of therapeutic agents such as antimicrobials, antivirals, antiparasites, anticancer, anti-inflammatory, antioxidants, proton pump inhibitors, antihypertensives, anticoagulants, immunomodulators, hormone modulators, CNS stimulants as well as depressants, lipid level modulators, antidiabetics, etc. has made it an indispensable anchor for development of new therapeutic agents. Varied substituents around the benzimidazole nucleus have provided a wide spectrum of biological activities. Importance of this nucleus in some activities like, Angiotensin I (AT₁) receptor antagonism and proton-pump inhibition is reviewed separately in literature. Even some very short reviews on biological importance of this nucleus are also known in literature. However, owing to fast development of new drugs possessing benzimidazole nucleus many research reports are generated in short span of time. So, there is a need to couple the latest information with the earlier information to understand the current status of benzimidazole nucleus in medicinal chemistry research. In the present review, various derivatives of benzimidazole with different pharmacological activities are described on the basis of substitution pattern around the nucleus with an aim to help medicinal chemists for developing an SAR on benzimidazole derived compounds for each activity. This discussion will further help in the development of novel benzimidazole compounds.

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1. Introduction

The therapeutic potential of benzimidazole nucleus can be traced back to 1944, when Woolley¹ speculated that benzimidazole

* Corresponding author. Tel.: +91 17582238211; fax: +91 1752283075.

E-mail address: omsilakari@rediffmail.com (O. Silakari).

can act similar to purines to elicit some biological responses. Five years later, Brink^{2,3} identified 5,6-dimethylbenzimidazole as degradation product of vitamin B₁₂ and subsequently found some of its derivatives having vitamin B₁₂ like activity. These initial reports sparked active research to explore the nucleus for varied activities. Over the years of active research, benzimidazole has evolved as an important heterocyclic system due to its presence in a wide range of bioactive compounds like antiparasitics, anticonvulsants, analgesics, antihistaminics, antiulcers, antihypertensives, antiviral, anticancers, antifungals, anti-inflammatory agents, proton pump inhibitors and anticoagulants.^{4–10} Optimization of substituents around the benzimidazole nucleus has resulted in many drugs like albendazole, mebendazole, thiabendazole as anthelmintics; omeprazole, lansoprazole, pantoprazole as proton pump inhibitors; astemizole as antihistaminic; envirodine as antiviral; candesartan cilexetil and telmisartan as antihypertensives and many lead compounds in a wide range of other therapeutic areas. The research in development of bioactive molecules from benzimidazole was accelerated during last 10 years. Some reviews on involvement of benzimidazole nucleus in anthelmintic activity^{4,6,8} and antiulcer activity⁷ are available in literature. Some compilations of reports on all activities associated with benzimidazole nucleus are also reported. Boiani and González have reviewed the imidazole and benzimidazole derived molecules and their N-oxides with reference to their antitumoral, antiparasitic, antiviral and antimicrobial activities.⁹ Recently, a review on therapeutic potential of benzimidazole nucleus appeared with a meager 50 references for all activities¹⁰ but no comprehensive report on varied activities of benzimidazole based compounds is available in literature till date. Hence, the present review presents a systematic compilation of more than 280 research and review articles to give a comprehensive insight into the current applications of benzimidazole nucleus in varied therapeutic fields. In addition to various therapeutic uses benzimidazoles have been found as important intermediates in many organic reactions.

2. Chemistry

Owing to immense synthetic importance and varied bioactivities exhibited by benzimidazoles and their derivatives efforts have been made from time to time to generate libraries of these compounds. Many synthetic methods have been developed and modified to get products of high yield, purity and of desired quality. An early review on chemistry of benzimidazole revealed that the very first benzimidazole (2,5 or 2,6-dimethylbenzimidazole) was prepared in 1872 by Hoebrecker through reduction of 2-nitro-4-methylacetanilide (Scheme 1). Several years later Ladenburg obtained the same com-

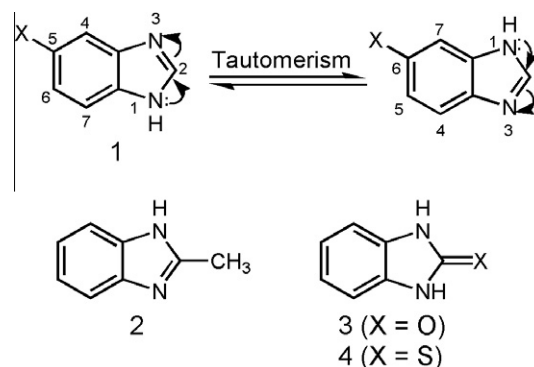
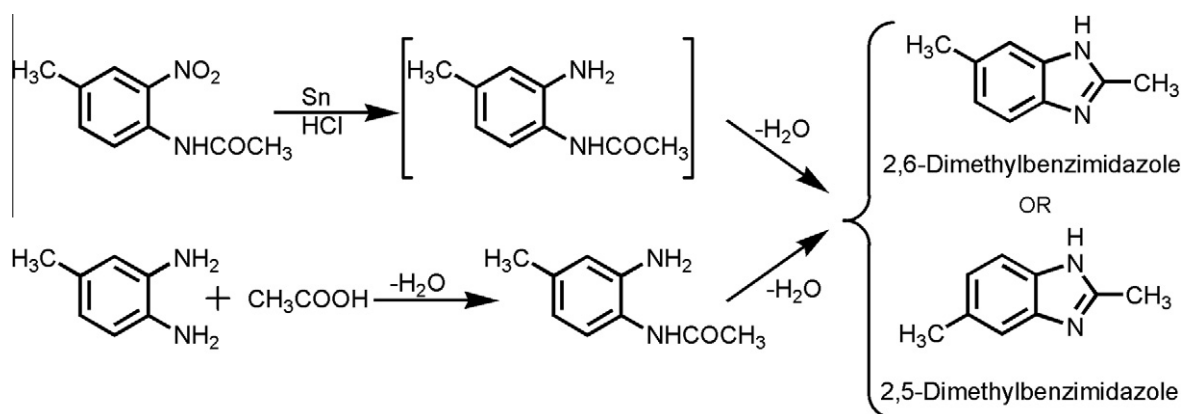


Figure 1. Tautomerism in benzimidazole.

pound by refluxing 3,4-diamino toluene with acetic acid (Scheme 1). Loss of water during formation of this type of compounds coined the term ‘Anhydrobase’ in the very early literature. Benzimidazoles were also known as benziminazoles and benzoglyoxalines. These were also named as derivatives of *o*-phenylenediamine, for example, benzimidazole (1) was called methenyl-*o*-phenylenediamine and 2-methylbenzimidazole (2) was called as ethenyl-*o*-phenylenediamine and so on. They were also named as derivatives of groups composing imidazole portion of ring, for example, benzimidazole has also been called as *o*-phenyleneformamidine. 2(3H)-benzimidazolone (3) and 2(3H)-benzimidazolethione (4) has been known as *o*-phenylurea and *o*-phenylenethiourea, respectively.¹¹ Hydrogen atom attached to N-1 of the nucleus readily tautomerises (Fig. 1) which is responsible for isomerisation in the derived compounds. In designating such tautomeric compounds, two numbers or sets of numbers are usually given to designate the position of the substituent group (or groups), the second number or groups of numbers being placed in parenthesis. According to this convention above compounds are named as 5(or 6)-methylbenzimidazole.¹¹

3. Biological activities

Benzimidazole nucleus can be termed ‘Master Key’ as it is an important core in many compounds acting at different targets to elicit varied pharmacological properties (Fig. 2). Though all seven positions in the benzimidazole nucleus can be substituted with a variety of chemical entities, but most of the biologically active benzimidazole based compounds bear functional groups at 1, 2 and/or 5(or 6) positions. Accordingly, the compounds may be mono-, di- or tri-substituted derivatives of the nucleus. In the present review, the various benzimidazole based compounds designed,



Scheme 1.

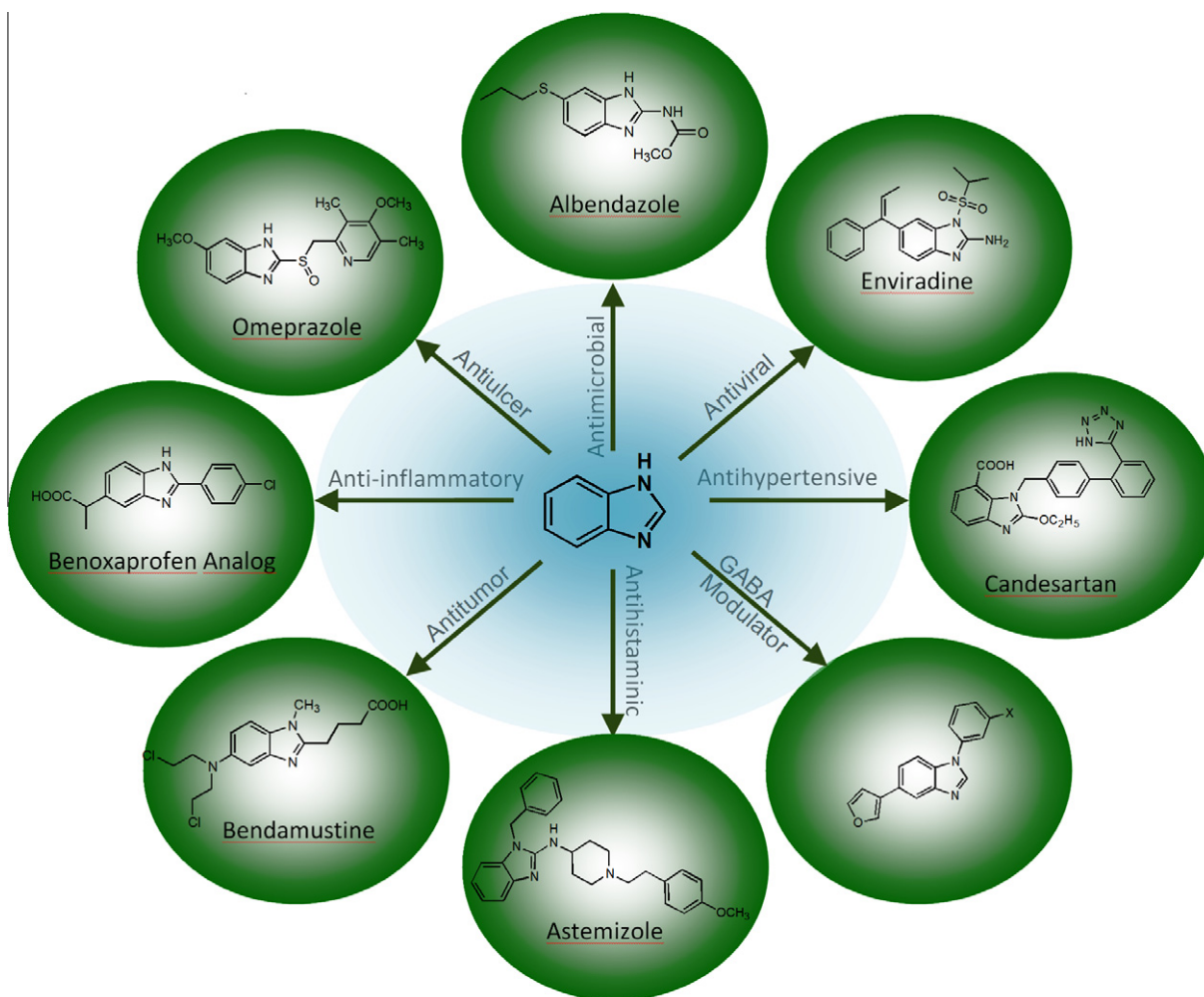


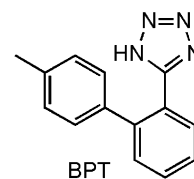
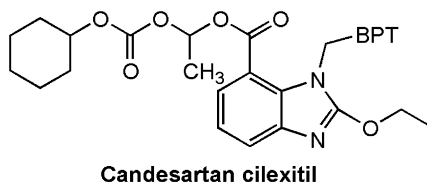
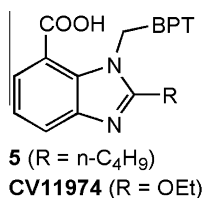
Figure 2. Benzimidazole, a multifunctional nucleus.

synthesized and evaluated have been categorized on the basis of their biological activities. The major activities include antihypertensive, anti-inflammatory, antibacterial, antifungal, anthelmintic, antiviral, antioxidant, antitumor, psychoactivity, etc.

3.1. Antihypertensive

Benzimidazole nucleus has been explored well for development of antihypertensive drugs. Many benzimidazole based compounds act as antihypertensives by intercepting with Renin–Angiotensin System (RAS). Angiotensin II (Ang II) is an octapeptide which is ac-

resulting in vasoconstriction, Na^+ retention and aldosterone release to cause hypertensive action. The various strategies to control these actions of Ang II include blocking production of Ang II through use of Renin and ACE inhibitors or blocking binding of Ang II to AT_1 receptors. Inhibition at the receptor level has proved maximally safe, specific and effective. Hence, much of the research and development activities on producing antihypertensives have been targeted towards development of AT_1 receptor blockers.¹² One of the first reports discloses 2-butyl-benzimidazole-7-carboxylic acid derivative (**5**) as a potent AT_1 receptor antagonist.¹³

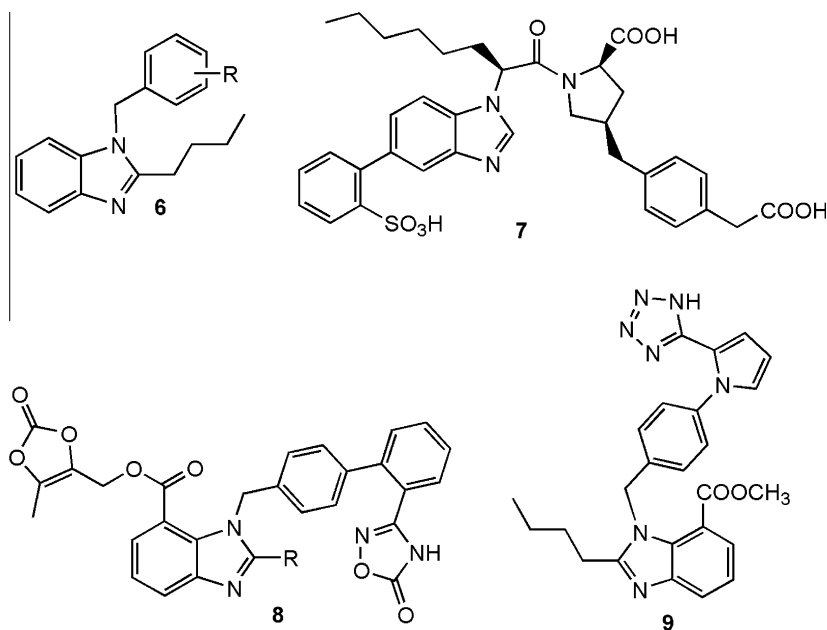


tive pressor produced by RAS cascade. Angiotensinogen, a polypeptide, is cleaved by rennin to produce a decapeptide, Ang I, which is further acted upon by Angiotensin converting enzyme (ACE) to generate Ang II. The latter acts on angiotensin receptor 1 (AT_1)

Optimization of the functional groups around the nucleus has produced CV-11974 which reduces blood pressure in dose-dependent manner by blocking AT_1 receptors in a non-competitive manner due to slow dissociation from AT_1 receptors.^{14–16} It is

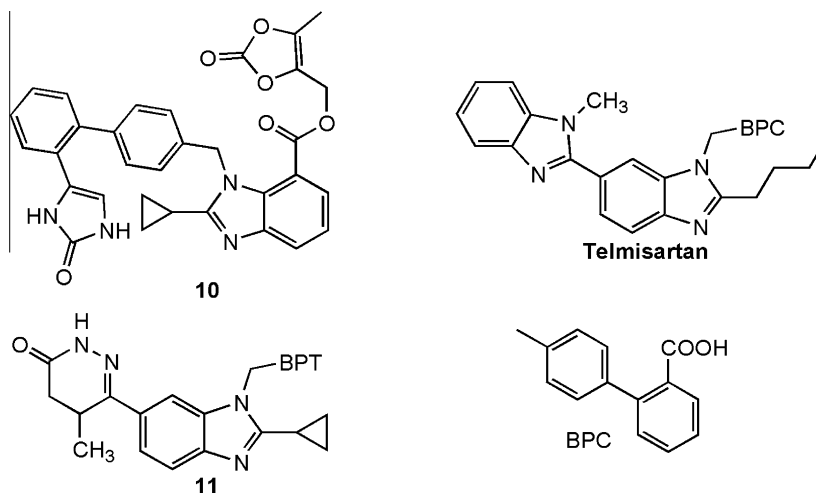
significantly more active than losartan and EXP3174.¹⁷ Esterification of 7-carboxyl group has culminated in discovery of orally active and long acting AT₁ receptor blocker, candesartan cilexetil^{18–22} which is now commercially available. It has triggered a spurt in research activities to explore all seven positions of the benzimidazole nucleus by various research groups to develop more potent compounds. In general, it has been found that the position 4 must remain unsubstituted for favorable interaction of N-3 of the nucleus with H-bond donor site in AT₁ receptor while positions 1 is reserved for biphenyl moiety. Replacement of biphenyl moiety with other moieties in the compounds (**6–9**) has produced the compounds with varied potencies.^{23–27}

compounds with varied activity.^{28–30} However, none of the compounds is found as potent and bioavailable as the one containing tetrazole. Incorporation of or substitution of tetrazole with a carboxyl group in the molecule has produced insurmountable and orally active antagonists.³¹ A –COOH group at 7-position provides potent compounds. Further esterification of this acidic function improves the oral bioavailability as indicated by clinical use of candesartan cilexetil. Recently, Kuroita et al. have disclosed 5-methyl-2-oxo-1,3-dioxol-4-yl methyl esters analogs (**10**) as potent orally active antagonists of Ang II.^{32–34} **Telmisartan** is an orally active, potent and insurmountable AT₁ selective antagonist that is formed by a bulky lipoph-



Replacement of tetrazole moiety with varied acidic heterocycles like oxathiadiazole, oxatriazole, oxadiazolone, oxadiazolidindione, thiazolone, oxathiadiazolone, etc. has produced the

illic group at 6-position.^{35,36} Substitution with pyridazinone moiety also produces a potent benzimidazole derived compound (**11**).³⁷



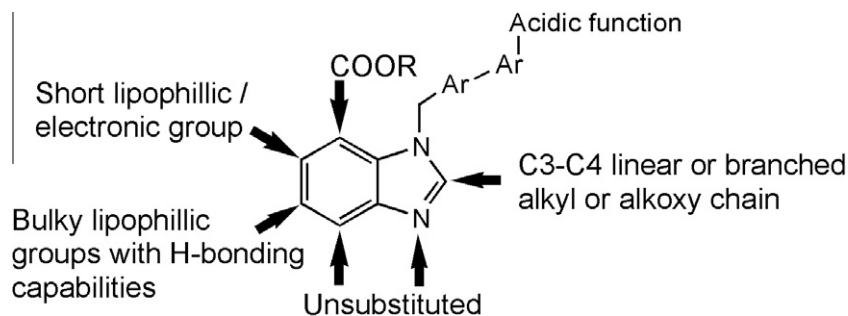
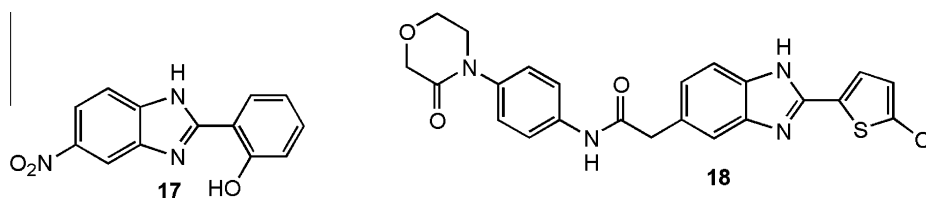


Figure 3. Structural features of a typical AT₁ receptor antagonist.

The position 5 is explored well by using varied substituents like nitro, amino, alkylcarboxamido, alkyl/arylsulfonamido (**12**) and it is established that a group of optimum size and hydrophilicity increases the activity significantly.^{38–40} Recently, Sharma et al. have synthesized a vast series of sartans by placing varied substituents at 2, 5 and 6-positions in tetrazolylbiphenyl or carboxylbi-

The compound **17** has been identified as the most potent compound of the series, showing IC₅₀ of 0.95 (with endothelium) and 2.01 μ M (without endothelium). 2,5-Disubstituted benzimidazole derivatives represented by compound **18** have been reported as inhibitors of factor Xa and hence useful in thromboembolic disorders.⁵⁰

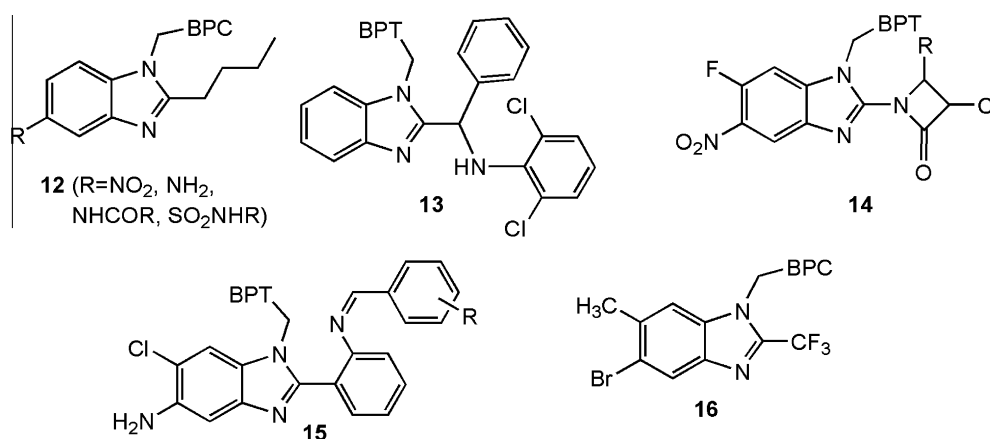


phenyl substituted benzimidazole.^{41–48} The compounds are evaluated using invasive and non-invasive Ang II induced hypertension models and in vitro model for determination of vasodilator activity. The compounds (**13–16**) are found to reduce the mean arterial blood pressure equivalent to losartan. Estrada-Soto et al. have synthesized a series of benzimidazole derivatives bearing substituted phenyl ring at 2-position and varied substituents ($-H$, $-CH_3$, $-NO_2$, $-CF_3$) at 5- and 6-positions and tested in vitro for vasorelaxant activity using rat aorta ring test.⁴⁹

Based on the available literature the varied structural features of benzimidazole derived AT₁ receptor antagonists can be summarised as in Figure 3.

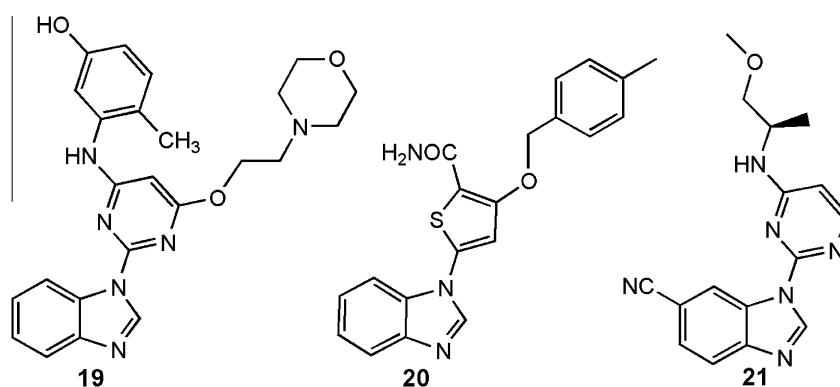
3.2. Anti-inflammatory

Control of inflammation has become of prime importance due to its association with numerous diseased states like Alzheimer's



disease, asthma, atherosclerosis, Crohn's disease, gout, multiple sclerosis, osteoarthritis, psoriasis, rheumatoid arthritis, diabetes mellitus, carcinoma, bacterial or viral infections, etc. which results in chronic inflammation.^{51,52} The most common and widely explored points for control of inflammation include inflammatory mediators like plasma proteases, prostaglandins, leukotrienes, histamine, serotonin, nitric oxide, interleukins 1–16 (IL-1 to IL-16), tumor necrosis factor- α (TNF- α), chemokines (CXC, CC and C subsets) and colony stimulating factors (CSF).^{53–55} These mediators are produced through various processes involving cyclooxygenases, caspases and kinases like cyclin dependent kinases (CDK1 and CDK5), mitogen activated protein kinase 38 (MAP38), c-Jun N-terminal kinase (JNK), serine threonine kinases (IKK1 and IKK2), interleukin receptor associated kinase 4 (IRAK-4), Janus kinases (JAK1- JAK3

pyrimidin-2-yl)benzimidazoles of which compound **19** has elicited anti-inflammatory effect by blocking activity of Lck.⁵⁹ Another similar compound (**20**) in which pyrimidine is replaced by thiophene has been identified as moderately potent inhibitor of IKK-3 kinase with pIC₅₀ of 5.4.⁶⁰ Based on extensive SAR studies, it has been found that replacement of the amide moiety in **20** by the nitrile group increases inhibitory effect on IKK-3. Further, substitution at 6-position in the benzimidazole has resulted in compound **21** as potent inhibitor of JAK3 which is expressed in high levels in natural killer cells, platelets, thymocytes, mast cells and inducible T and B cells.⁶¹ Buckley et al. have brought another similar 1,6-disubstituted compound as highly potent IRAK4 inhibitor having good TNF- α inhibition.⁶²

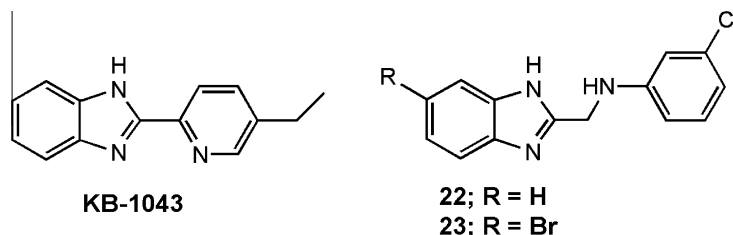


and Tyk2), kinase insert domain receptor (KDR), lymphocyte specific kinase (Lck), spleen tyrosin kinase (Syk) and TNF- α kinase (TNFK).^{56,57}

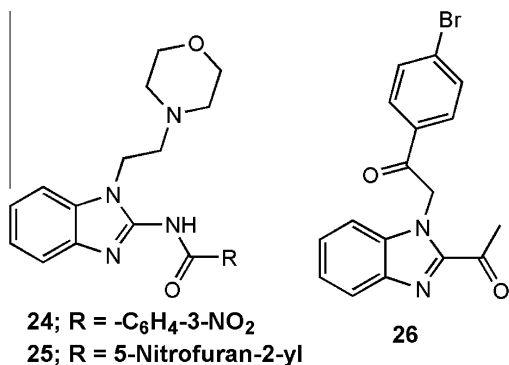
A large number of chemical entities derived from diverse group of heterocyclic nuclei are reported to inhibit or block the inflammatory process at one or the other stage. The search for anti-inflammatory compounds derived from benzimidazole nucleus is as old as the age of modern medical chemistry. Though a good number of research groups have reported various benzimidazole derivatives having well to excellent anti-inflammatory activity but no such molecule has made its way to the clinics so far. A number of compounds targeting the kinases are currently undergoing clinical trials related to inflammation and autoimmunity.⁵⁸

Benzimidazole nucleus substituted at 1-position with varied heterocycles has produced potent anti-inflammatory compounds. Sabat et al. have synthesized a series of 1-(substituted

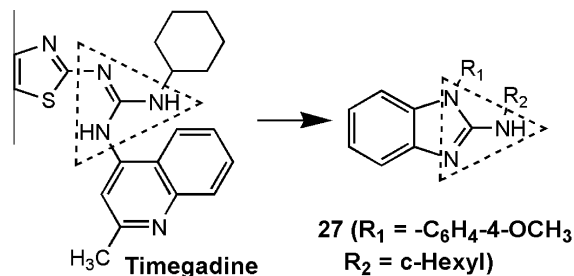
Based on the moderate anti-inflammatory and analgesic activities of thiabendazole (a well known anthelmintic), the Pharmaceutical Research Centre at Kanebo Ltd. (Japan) have developed a series of 2-(2-pyridinyl)benzimidazoles by isosteric replacement of thiazole ring in the lead.^{63–65} From a series of 55 compounds, 2-(5-ethyl-2-pyridinyl)benzimidazole (**KB-1043**) is found to have anti-inflammatory, analgesic and antipyretic activities better than phenylbutazone and tiaramide. Moreover, it has gastrointestinal irritation slightly less and therapeutic index 2–3 times better than the reference compounds. Recently, Achar et al. have synthesized novel 2-(substituted phenyl)aminomethyl benzimidazoles and evaluated using carrageenan-induced paw edema model. The compound **22** has emerged as potent compound (81% protection) and the activity is further improved (89% inhibition) by placement of bromo group at 6-position (**23**).⁶⁶



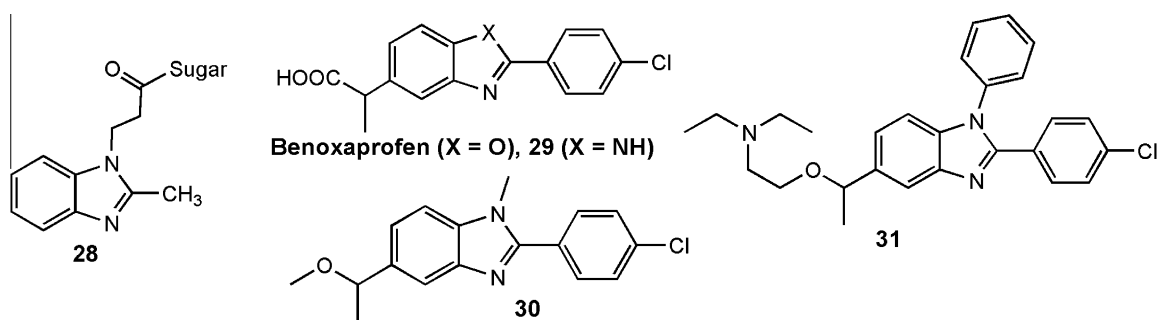
A high throughput screening (HTS) of small molecules followed by SAR studies at Amgen Inc. has identified **24** as potent inhibitor of IRAK4.⁶⁷ A recent patent also discloses similar *N*-acyl 2-aminobenzimidazole derivatives with varied aroyl and heteroaryl substituents at 2-position exemplified by compound **25** as potent IRAK4 inhibitor.⁶⁸ Another HTS at Abbott Corporate has identified a new series of 1,2-disubstituted benzimidazole derivatives through binding studies of CXCL10 to CHO cell membranes.⁶⁹ The compound **26** proved maximally active. Further, substitution with methoxy group at 4-position of benzimidazole nucleus retained the activity but the activity is decreased with substitution at 5- and 6-positions.



the importance of guanidine moiety for anti-inflammatory activity.

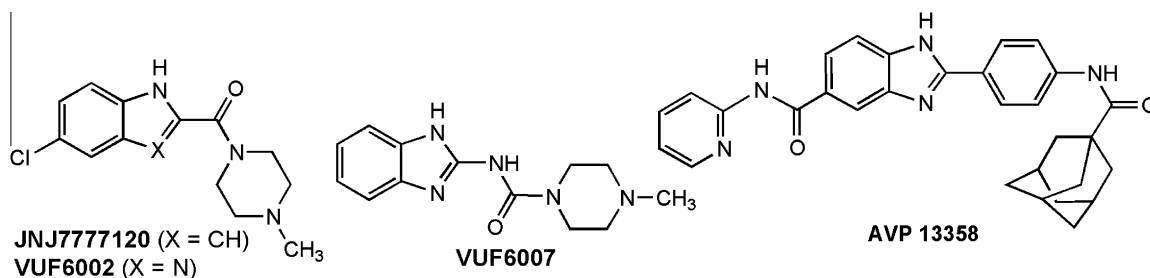


A structure based design of 2-methyl-*N*-substituted benzimidazole bearing varied sugar moieties (**28**) have been reported to have significant anti-inflammatory activity dependent on the kind and the linked-position of the sugar conjugated to the nucleus.⁷¹ Simultaneous substitutions at 2- and 5-positions of benzimidazole nucleus have fancied many research groups to develop novel anti-inflammatory drugs. Taking benoxaprofen as lead, Dunwel et al.⁷² have synthesized **29** by bioisosteric replacement of benzoxazole nucleus with benzimidazole. However, it did not reduce the inflammation in rat paw edema model probably due to lower solubility or altered drug-receptor interactions. Subsequently, Evans et al. from the same laboratory synthesized an exhaustive series of 72 benzimidazole derivatives and tested on rat adjuvant arthritis screen.⁷³ Only two compounds (**30** and **31**) have been found to exhibit activity comparable to indomethacin.



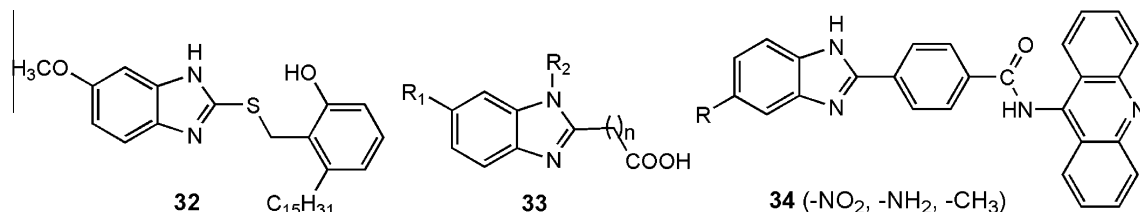
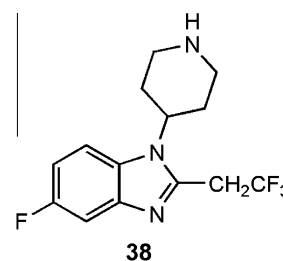
Based on importance of guanidine moiety in timegadinine, an anti-inflammatory drug, Taniguchi et al. have synthesized various 2-aminobenzimidazole derivatives bearing varied moieties at 1-position.⁷⁰ The compound **27** has been found to be more active than the reference drugs in inhibiting carrageenan induced inflammation and acetic acid induced writhing. However, replacements of amino with methylene at 2-position causes complete loss of activities supporting

VUF6002 is another 2,5-disubstituted benzimidazole compound designed by taking JNJ777120 as lead.⁷⁴ It exhibits good anti-inflammatory and antinociceptive effects in paw edema and hyperalgesia models. However, contrary to the importance of amino group at 2-position of the nucleus, another related benzimidazole derivative VUF6007 does not show any such activity.⁷⁵ Avanir Pharmaceuticals have developed AVP 13358 having an amide linker as a potent anti-IgE which is useful in various inflammatory conditions.⁷⁶



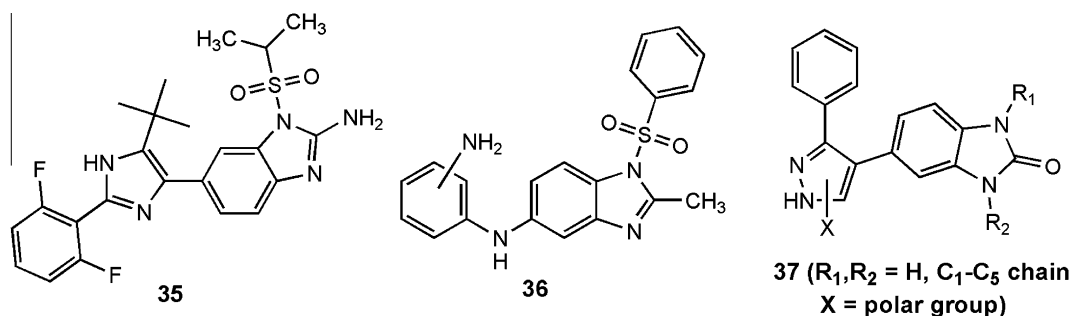
Some semisynthetic derivatives of anacardic acid (**32**) bearing long alkyl chain (C_{15}) is found to have inhibitory activity about 400 times greater at COX-2 than at COX-1.⁷⁷ Thakurdesai et al.⁷⁸ have reported a series of 2,6-disubstituted benzimidazole derivatives **33** wherein varied carboxylic acid groups are placed at 2-position while 6-position is substituted with electron-releasing or electron-withdrawing substituents. Activity is found largely dependent on substituents at 6-position in the order of $\text{Cl} > \text{OCH}_3 > \text{H} > \text{OCH}_2\text{CH}_3 > \text{NO}_2$. The activity decreases with increasing distance of the carboxyl group from C-2 of benzimidazole. Substitution with benzyl group at 1-position further increases the activity. All test compounds exhibit good acute anti-inflammatory activity at 100 mg/kg and higher doses and are found safe up to 2000 mg/kg, dose. A series of N-acridin-9-yl-4-benzimidazo-2-ylbenzamides (**34**) have been evaluated for anti-inflammatory and CDK inhibitory activities wherein importance of 5-position of the nucleus is indicated by pronounced activity of the compound bearing nitro group at 5-position against CDK1 and CDK5 while the activity is almost lost in compounds bearing amino or methyl group.⁷⁹ Recently, Makovec et al. have invented varied heterocyclic amidines out of which 2-phenyl-5-amidinobenzimidazoles actively inhibit production of IL-1 β .⁸⁰

Anderskewitz et al. at Boehringer Ingelheim International GmbH have reported compound **38** as CCR3 receptor blocker ($K_i = 100 \text{ nM}$).⁸⁵ Substitution at piperidinyl nitrogen with 3(4-fluorophenylthio)propyl group increases the activity significantly ($K_i = 9 \text{ nM}$) suggesting the importance of a bulky group at 1-position of benzimidazole, which is also supported by chemotactic activity of a series of similar compounds at Astra Zeneca.⁸⁶



Many polysubstituted benzimidazole derivatives have also been reported to exhibit moderate to potent anti-inflammatory activity. Based on the selective p38 α MAP kinase inhibitory activity of 2-aminobenzimidazole derivatives,⁸¹ Mader et al.⁸² have developed 2-amino-1-isopropylsulfonyl 6-substituted benzimidazole (**35**) as potent inhibitor of TNF- α and p38 α MAP kinase. Recently, Gaba et al.⁸³ have reported a similar series of 5-amino-1-phenylsulfonyl-2-methyl benzimidazoles (**36**) substituted with varied groups at amino nitrogen. The aniliny substituted analogs have exhibited potent anti-inflammatory and analgesic activities as compared to the alkyl and nitrophenyl substituted ones. A series of more than 550 compounds based on benzimidazol-2-one having general formula (**37**) has been synthesized and found to be potent inhibitors of p38 MAP kinase.⁸⁴

The activity exhibited by compounds derived from varied substituents all around the benzimidazole nucleus has prompted many research groups to synthesize fused benzimidazole compounds. Toja et al. have synthesized for the first time fused imidazole derivatives (benzbenzimidazoles or naphthimidazoles) substituted at 1 and 2 positions as non-acidic anti-inflammatory agents.⁸⁷ SAR studies on about 50 compounds revealed that an electron rich group such as $-\text{OCH}_3$, $-\text{OC}_2\text{H}_5$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$ on *para* position in phenyl ring at 2-position of the nucleus increases the activity. Compounds with substituent at 1-position exhibit a stronger anti-inflammatory potency. In addition to good anti-inflammatory, analgesic and antipyretic activities, all active compounds also lack ulcerogenic properties. The compounds **39** and **40** have emerged as the most potent compounds. Sondhi



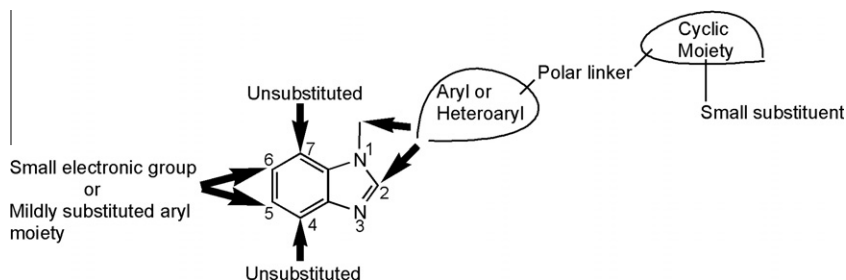
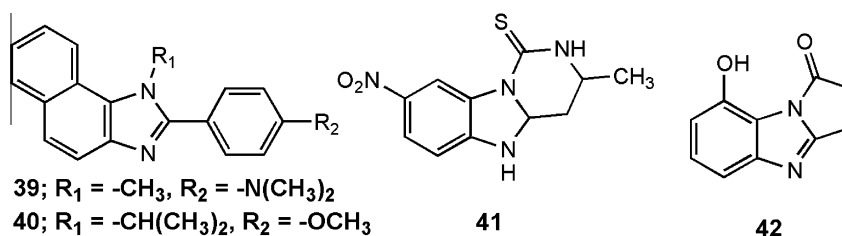


Figure 4. Structural requirements around benzimidazole nucleus anti-inflammatory activity.

et al. have synthesized and screened some tricyclic benzimidazole derivatives and revealed that pyrimido[1,6-*a*]benzimidazole derivative (**41**) control the inflammation and pain no better than ibuprofen but pyrazolo[1,2-*a*]benzimidazole (**42**) analogs exhibit the activity equivalent to ibuprofen.^{88,89} A similar pyrimido[1,2-*a*]benzimidazole derivative has also been found to have very weak anti-inflammatory and analgesic activities.⁹⁰

bear a bulky, lipophilic aryl/heteroaryl moiety appropriately substituted with alkyl, electronic or heterocyclic groups while the tolerable substituents at 5 or 6-position of the nucleus ranges from small electronic groups like halogens, nitro, amino, methyl or lower alkoxy to mildly substituted or unsubstituted aryl or aralkyl groups.

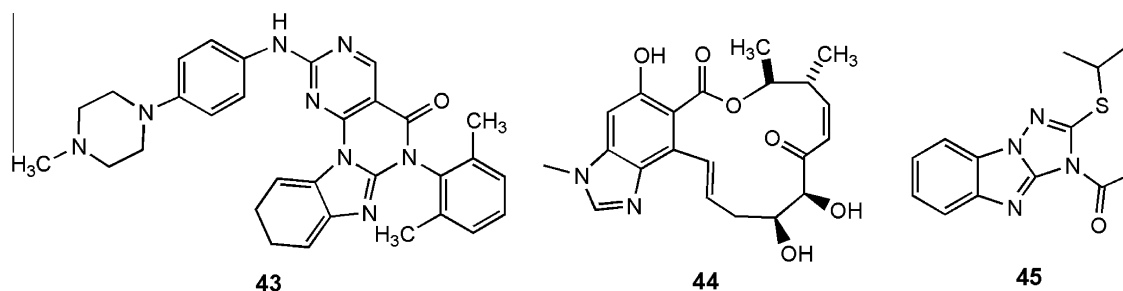


Further exploration of pyrimidobenzimidazoles has led to a series of pyrimido[5',4':5,6]pyrimido[1,2-*a*]benzimidazol-5-ones as potent orally active specific inhibitors of Lck. SAR studies have revealed the compound **43** as the most potent compound.⁹¹ Very recently, Shen et al. have discovered a novel compound (**44**) by fusion of an imidazole nucleus with phenyl ring of an active metabolite isolated from fermentation broth of fungus *Curvularia verruculosa* having strong inhibitory activity against TNF α transcription.⁹² A series of 1-acyl-2-alkylthio-1,2,4-triazolo[3,2-*a*]benzimidazole derivatives is reported from which the compound **45** exhibits the most potent anti-inflammatory and analgesic activities reiterating the importance of amino group at 2-position of benzimidazole nucleus.⁹³ It has also exhibited a superior GI safety profile compared to indomethacin.

3.3. Antimicrobial

Antimicrobial agents constitute a diverse group of chemical entities acting against varied kinds of microbes including bacteria, protozoa, helminths (worms), fungi and viruses. Various research groups have evaluated antibacterial, antiprotozoal, anthelmintic and/or antifungal activities concomitantly while evaluation of antiviral compounds remains solitary. Hence, in the present review compounds having antibacterial, antiprotozoal, anthelmintic and antifungal activities are discussed collectively under the heading of antimicrobials while antiviral compounds are discussed independently.

Most of the research activities on development of antimicrobials from benzimidazole nucleus have been taken up after the year 2000. Iwahi and Satoh have reported 2-(substituted pyridyl meth-

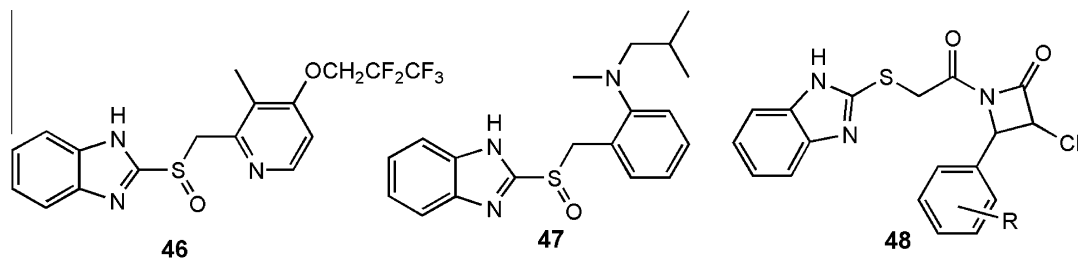


The salient structural features of a typical benzimidazole based anti-inflammatory compound as suggested by critical analysis of chemical structures of various such compounds are given Figure 4. Either of the 1 and 2 positions of the nucleus should

ylsulfinyl)benzimidazole (**46**) as antibacterial against *Campylobacter pylori*.⁹⁴ Modifications in **46** lead to similar compound (**47**) having antibacterial against *C. pylori* equivalent to omeprazole.⁹⁵ Coupling of 2-alkylthiobenzimidazole with β -lactam ring has

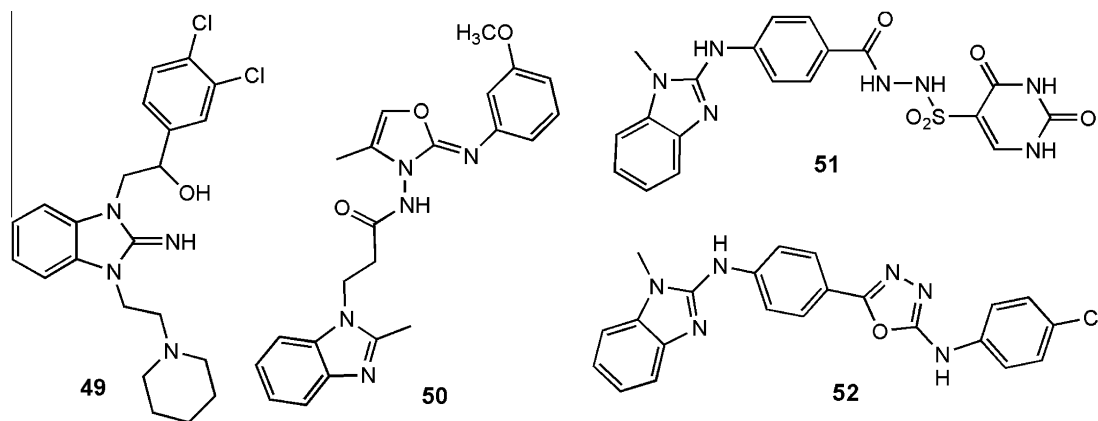
produced compound **48** wherein antibacterial and antifungal activities found dependent upon nature of R group.⁹⁶

Fusion of 5- or 6-membered heterocycle at N¹-C bond of benzimidazole nucleus has produced tricyclic derivatives of



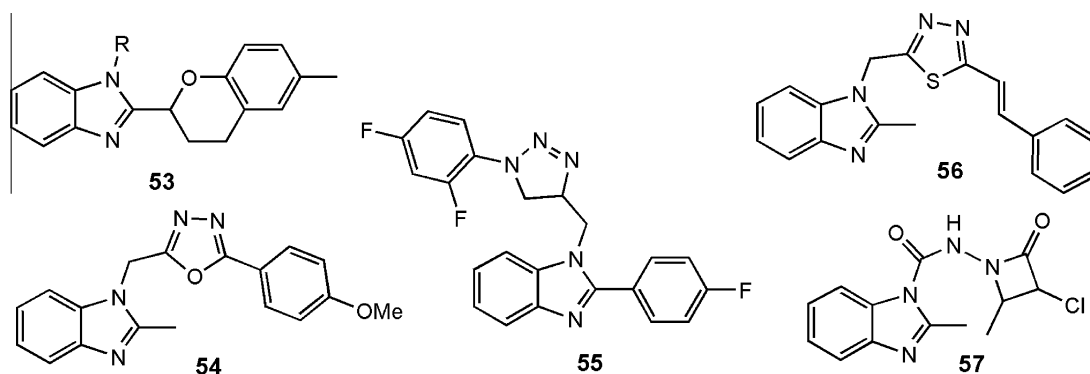
Holloway et al. have discovered 2-iminobenzimidazoles (**49**) as antibacterial acting through inhibition of Trypanothione reductase (a bacterial enzyme).⁹⁷ 1-Substituted benzimidazole compounds have been found to exhibit poor antimicrobial properties.⁹⁸ However, substitution at both 1- and 2-positions of benzimidazole has produced potent antimicrobials. Semicarbazide, thiosemicarbazide and carbamate substituent at 1-position along with a methyl group at 2-position has yielded compounds **50–52** as potent bactericidal.^{99–101}

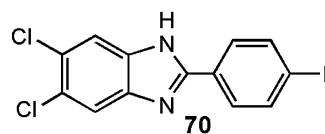
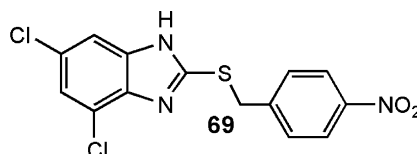
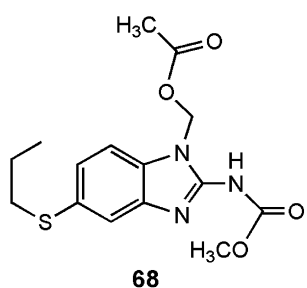
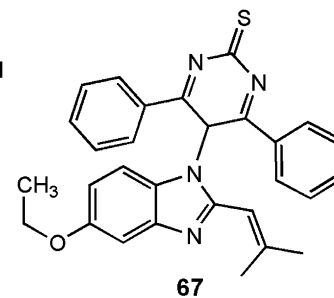
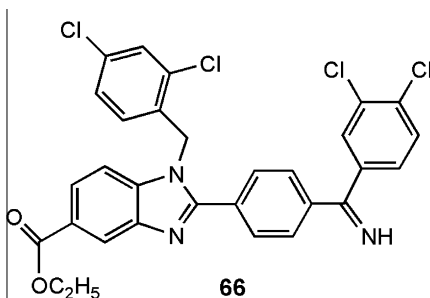
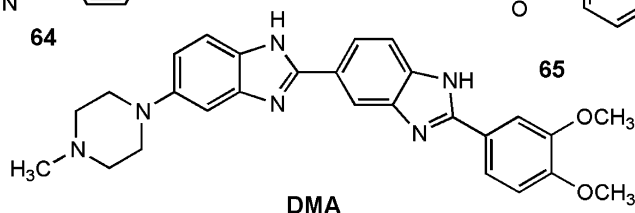
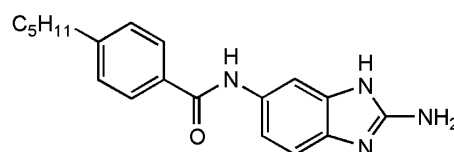
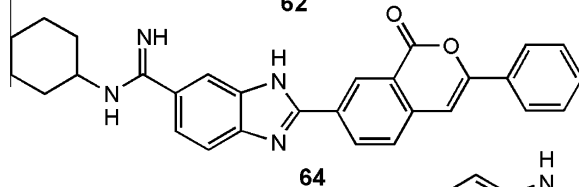
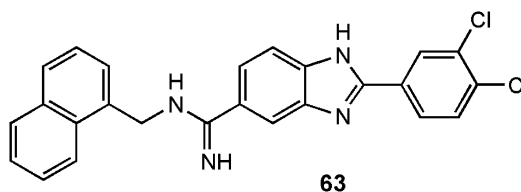
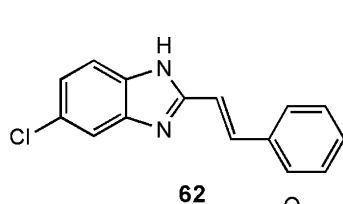
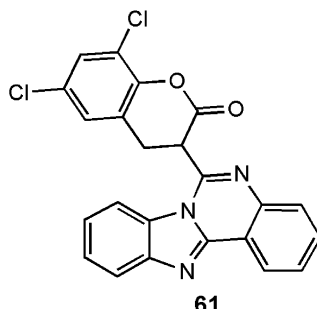
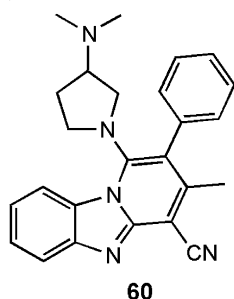
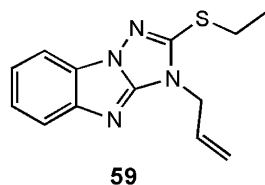
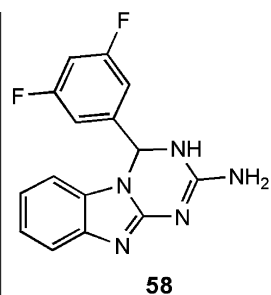
benzimidazole like triazino[1,2-*a*]benzimidazole (**58**) bearing fluorophenyl group as moderately antibacterial,¹⁰⁷ 1,2,4-triazolo[2,3-*a*]benzimidazole bearing short alkyl and alkenyl groups (**59**) as potent antimycobacterial¹⁰⁸ and pyridobenzimidazole derivatives (**60**) as antifungal.^{109,110} Recently, Kuarm et al. have reported benzimidazo[1,2-*c*]quinazolin-5-yl chromene derivative (**61**) as antibacterial agent.¹¹¹ Replacement of chloro groups with bromo groups converted the molecule to antifungal. Varied 2,5- and 2,6-disubstituted



Attachment of other heterocycles like chromane, β -lactam, thiazole and oxadiazole to benzimidazole nucleus resulted in hybrid compounds (**53–57**) having potent antibacterial and/or antifungal properties.^{102–106}

benzimidazole derivatives have also been explored for antimicrobial activities.





The compounds **62** and **63** are 2,5-substituted derivatives exhibiting moderate to good antibacterial activities against gram +ve and gram -ve bacteria as well as methicillin resistant *Staphylococcus aureus* (MRSA).^{112,113} Bansal et al. have found another such derivative (**DMA**) to inhibit bacterial topoisomerase I.¹¹⁴ The 2,6-substituted derivatives include **64** and **65** having excellent activity against MRSA, methicillin resistant *Staphylococcus epidermidis* (MRSE) and *Candida albicans*.^{115,116}

Various 1,2,5-trisubstituted benzimidazoles have also been explored for antimicrobial and antifungal activities. The compounds **66** and **67** have evolved as potential antimicrobial against MRSA and MRSE^{117,118} whereas compounds **68** and **69** are found to have neomocidal and antimycobacterial activities, respectively.^{119,120} The compound **70** is 2,5,6-trihalo-gen analog exhibiting potent antibacterial activity against MRSA.¹²¹

Bis-benzimidazole derivatives have emerged as potent antimicrobial and antiviral agents. The compound **71** is found as potent antiprotozoal. Any change in length of the linker methylene chain lowers the activity¹²² whereas substitution of methoxy group in benzimidazole nucleus increases the activity significantly.¹²³ A

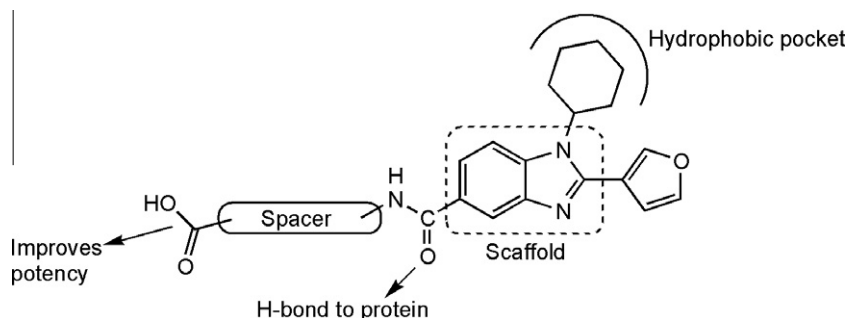
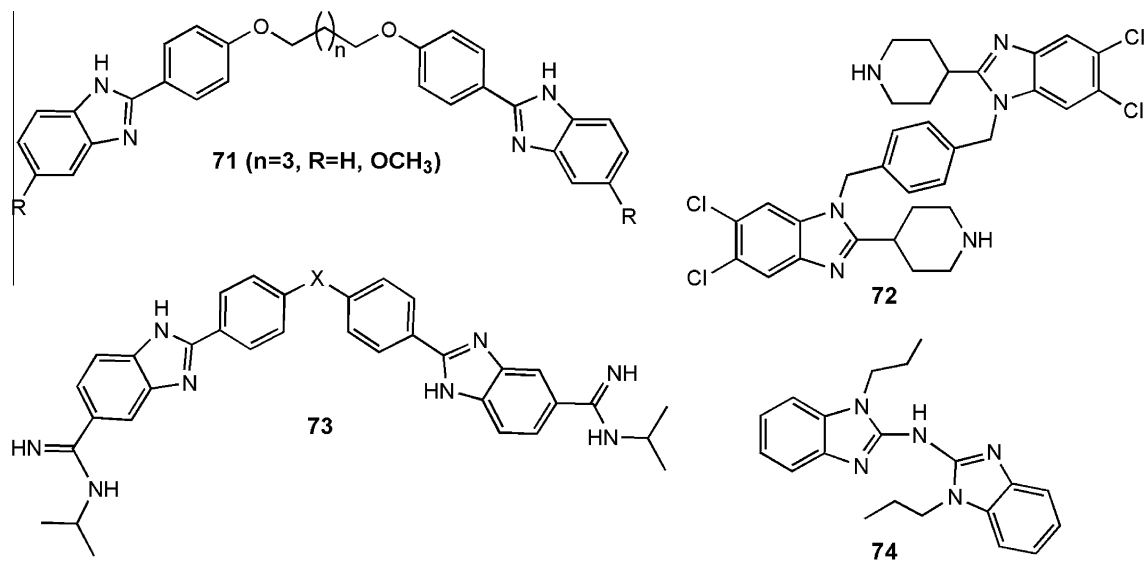


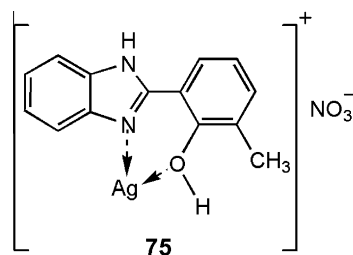
Figure 5. Hypothetical receptor model for Hepatitis C viral inhibition.

polysubstituted bis-benzimidazole compound (**72**) has been synthesized and tested as potent broad spectrum antibacterial equipotent to paromomycin.¹²⁴ Hu et al. have developed a series of compounds (**73**) and found the ethereal linker ($-O-$) to exhibit antimicrobial activity better than Penicillin-G.^{125–127} Linking two benzimidazole nuclei at 2-positions with an amino group has produced a novel bis-benzimidazole (**74**) having antifungal activity better than albendazole.¹²⁸

zimidazol-2-yl)ethanone thiosemicarbazone,¹³³ gold complexes of 1,3-di-isopropylbenzimidazolinium bromide,¹³⁴ cadmium complexes of 1,1'-(1,3-propanediyl)bis-1*H*-benzimidazole,¹³⁵ transition metal complexes of bis(benzimidazole-2'-yl methyl)amine,¹³⁶ zinc complexes of 2-(5-substituted benzimidazol-2-yl)-phenols¹³⁷ and silver complexes of 1-(2,4,6-trimethylbenzyl)-3-methoxyethyl)benzimidazolidine.¹³⁸



Complexation of benzimidazole compounds with varied metal ions like Fe^{3+} , Cu^{2+} , Zn^{2+} , Ag^+ , Co^{2+} is reported to increase antimicrobial activities of the compounds. Tavman et al. have complexed 2-(2-hydroxyphenyl)benzimidazole analogs with various transition metals^{129,130} and found an Ag^+ complex (**75**) as a potent antibacterial agent. Zn^{2+} and Pd^{2+} complexes of different bis-benzimidazoles are also reported as potent antimicrobial compounds.¹³¹ The other complexes of benzimidazole derivatives exhibiting antimicrobial activities include cobalt complexes of 2-aminobenzimidazole¹³² and 1-(1*H*-ben-

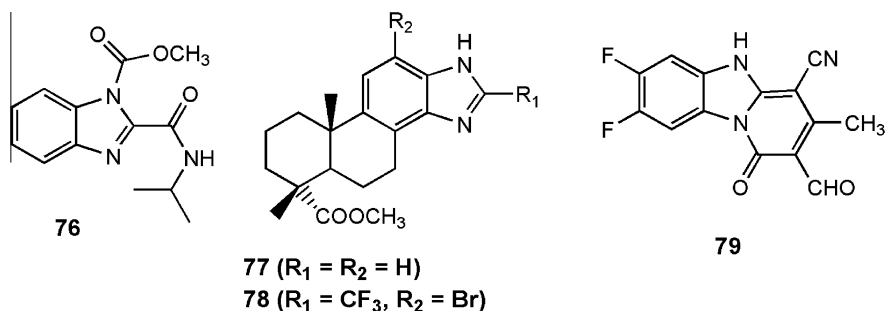


A critical analyses of these variedly substituted derivatives has revealed that either of the 1 and 2 positions of benzimidazole nucleus should bear a bulky electronic and lipophilic group while the other should have a small alkyl substituent for the optimum antimicrobial activity. Further, a small lipophilic group containing a heteroatom at 5/6-position incurs additional activity.

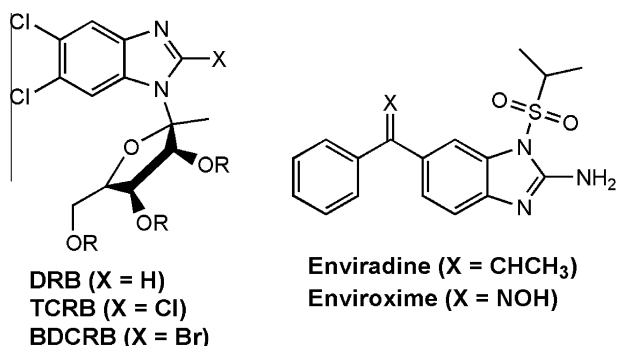
3.4. Antiviral activity

Antiviral properties of various benzimidazole derivatives have been evaluated using different virus strains, such as human cyto-

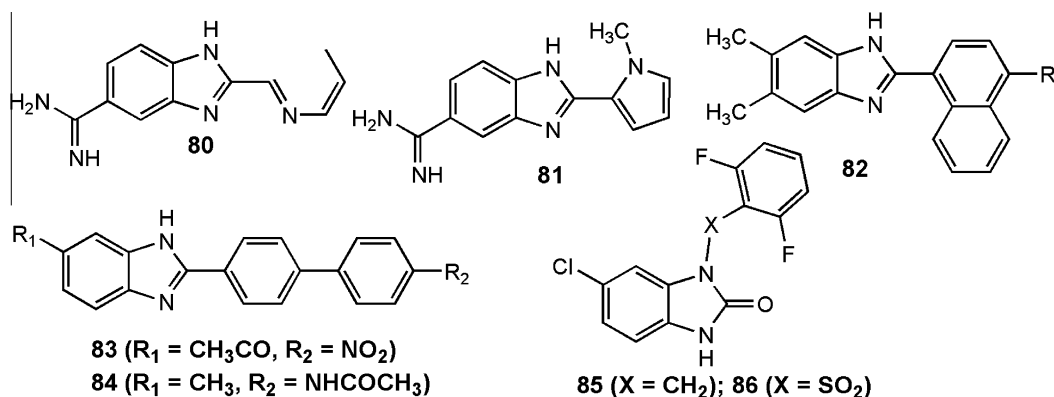
Garuti et al. have reported some 2-substituted benzimidazole-*N*-carbamates as potent antiviral compounds amongst which isopropylcarboxamide group at 2-position (**76**) led to the best activity.¹⁴³ Dehydroabiatic acid derivatives of benzimidazoles exemplified by **77** and **78** inhibit both varicella-zoster virus (VZV) and cytomegalovirus (CMV) replication at concentrations much lower than their cytotoxic concentrations.¹⁴⁴ Various fluorinated pyrido[1,2-*a*]benzimidazoles have exhibited no antiviral properties except compound **79** which inhibited the growth of variolovaccine and monkeypox viruses.¹⁴⁵



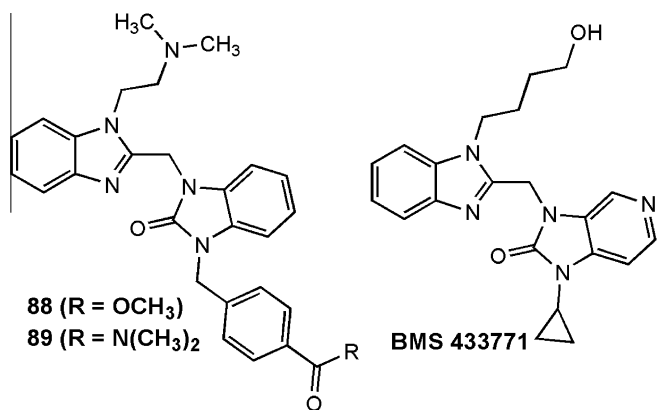
megalovirus (HCMV), human herpes simplex virus (HSV-1), human immunodeficiency virus (HIV), and hepatitis B and C virus (HBV and HCV). Numerous nucleoside analogs of benzimidazole derivatives have been synthesized during 1950–1990s as selective inhibitors of HCMV amongst which 5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (**DRB**) is the most explored nucleus. It inhibits viral RNA synthesis by blocking RNA polymerase II.^{139,140} Incorporation of chloro and bromo group at 2-position of **DRB** provided **TCRB** and **BDCRB**, respectively having dramatically improved therapeutic index. A ribosyl moiety at 1-position proved to be very important for the activity.¹⁴¹ The non-nucleoside derivatives of DRB prepared by replacing β-D-ribofuranosyl with a benzyl and phenethyl group were found inferior in activity against HCMV but active against HIV-1.¹⁴² **Enviroxime** and **enviroxime** are the other non-nucleoside analogs which came in to clinical use in the early 1980s as potent broad spectrum inhibitors of RNA viruses.



Amongst a series of benzimidazole derivatives bearing amidino group at 5-position and varied heteronucleic such as pyridine, *N*-methyl-pyrrole or imidazole, the compounds with pyridine ring at 2-position (**80**) showed distinct and selective antiviral activity toward RNA replicating enteroviruses. In contrast to it, pyrrole substituted compound (**81**) showed prominent activity against other types of viruses especially adenovirus.¹⁴⁶ SAR study on 2-naphthyl benzimidazoles with varied substituents at 5,6-positions of benzimidazole ring and 4-position of naphthyl ring (**82**) suggests that electron releasing groups on benzimidazole enhances the activity. An amino group on naphthalene ring yields a potent antiviral compound. Replacement of amino with nitro and acetyl groups decreases the activity significantly.¹⁴⁷ Taking this 2-aryl benzimidazole as a lead, 2-biphenyl derivatives of benzimidazoles are developed but most of the compounds except **83** and **84** showed no activities against all viruses tested.¹⁴⁸ 1*H*-Benzimidazole-4-carboxamide derivatives bearing furyl at 2-position and aryl moiety at carboxamide nitrogen possess good inhibitory activity.^{149,150} Barreca et al. reported 1-benzyl-1,3-dihydro-2*H*-benzimidazol-2-ones as potential non-nucleoside reverse transcriptase inhibitors (NNRTIs) active against HIV-1.¹⁵¹ A 6-chloro-1-(2,6-difluorobenzyl)-substituted derivative (**85**) was found to possess significant activity against HIV-1. Subsequently molecular modeling studies on **85** led to the rational discovery of *N*¹-arylsulfonyl-1,3-dihydro-2*H*-benzimidazol-2-one (**86**) as a novel template for design of new NNRTIs active against wild-type and mutant strains of HIV-1.¹⁵²

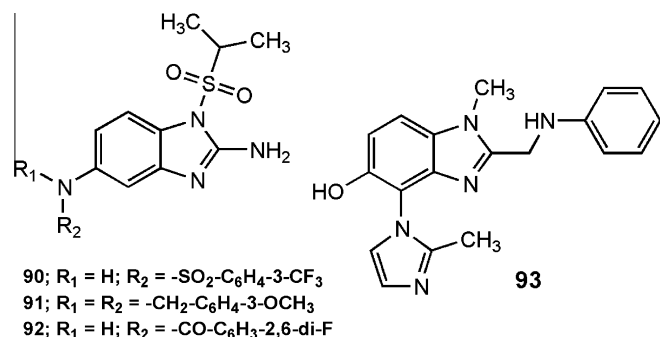


Respiratory syncytial virus (RSV) is identified as the most common viral cause of death in children below 5 years of age. Identification of potent and selective inhibitors of RSV has thus attracted considerable attention. A research group from The Bristol-Myers Squibb Pharmaceutical Research Institute initiated the development of RSV inhibitors with a series of benzotriazole-substituted benzimidazoles (**87**).¹⁵³ Replacement of benzotriazole with benzimidazol-2-one yielded better RSV inhibitors with a broader tolerance for substituent size at 1-position.¹⁵⁴ Further, structural modifications to improve solubility properties for in vivo evaluation produced compounds **88** and **89** exhibiting good efficacy following oral administration. However, these compounds suffered from severe metabolic degradation.¹⁵⁵ The continual efforts of the group led to 6-aza benzimidazolone derivative (**BMS-433771**) demonstrating good oral bioavailability and antiviral activity.¹⁵⁶ Attempts to further increase the activity culminated in 5-amino-methyl analog exhibiting potent antiviral activity towards wild-type RSV and excellent inhibitory activity towards a BMS-433771 resistant viral strain.¹⁵⁷ Replacement of the benzimidazol-2-one moiety with benzoxazole, oxindole, quinoline-2-one, quinazolin-2,4-dione and benzothiazine revealed that intrinsic potency of 6,6-fused ring systems is generally less than that of 5,6-fused heterocycles.¹⁵⁸

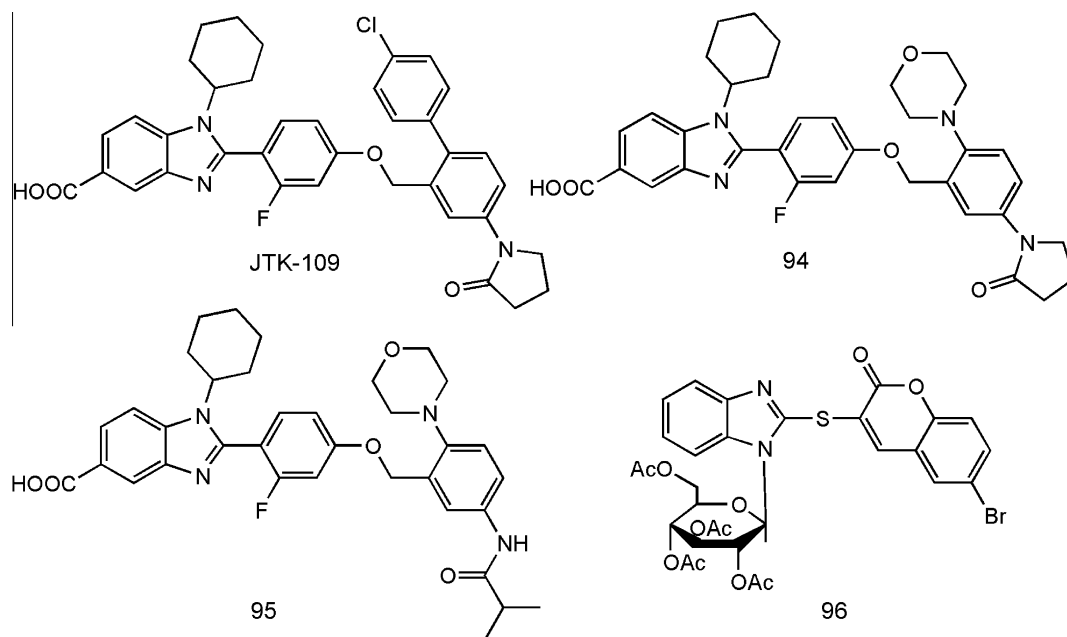


HBV infection is the world's ninth leading cause of death, and responsible for both acute and chronic hepatitis. Only a few agents have been approved for the clinical

treatment of HBV infections including interferon and nucleoside analogs. However, population based efficacy of Interferon- α and drug resistance associated with long-term use of nucleoside analogs triggered an urgent need for development of novel classes of anti-HBV agents. Li et al. have identified *N*-(2-Amino-1-(isopropylsulfonyl)-1*H*-benzo[d]imidazol-6-yl)-3-(trifluoromethyl) benzenesulfonamide (**90**) as a lead potent inhibitor of HBV.¹⁵⁹ Modification at 5- and 6-positions of the benzimidazole core produced **91** and **92** as the most promising compounds from this series. Recently, a new series of 1-methyl-1*H*-benzimidazol-5-ol is reported to inhibit HBV DNA replication with potency more than lamivudine. The compound **93** is found to be most potent with an IC₅₀ value of 7.8 mM.¹⁶⁰

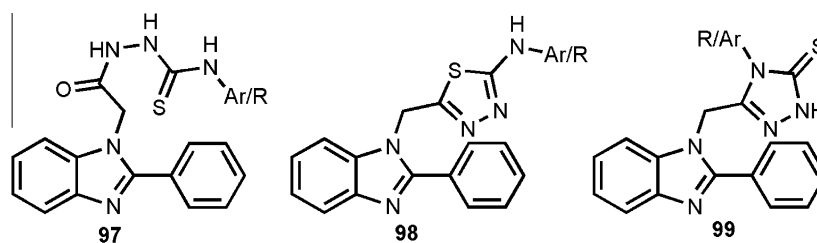


HCV is reported to be another common pathogen in various hepatic disorders. Hirashima et al. have reported **JTK-109** as a potent inhibitor of HCV NS5B RNA-dependent RNA polymerase.¹⁶¹ Replacing the biphenyl moiety with a 2-morpholinophenyl and pyrrolidone group yielded potent compounds **94** and **95**.¹⁶² SAR studies on a series of hybrid molecules containing benzimidazole and coumarin with a methylenethio linker and the corresponding *N*-glucosides has revealed **96** as lead anti HCV compound.¹⁶³ Beaulieu et al. have developed some benzimidazole-based allosteric inhibitors of HCV NS5B that bind to Thumb Pocket I of the HCV NS5B polymerase.¹⁶⁴ These inhibitors are referred as 'finger-loop inhibitors'.



The SAR around three benzimidazole sub-series of NS5B inhibitors containing a 5-carboxybenzimidazole scaffold suggests a common binding mode of these molecules to the enzyme allosteric site. A hypothetical pharmacophore model (Fig. 5) and further optimisation of these molecules led to development of potent diamide derivative.¹⁶⁵

possess weak antioxidant activity.¹⁷¹ In continuation on their work on imidazobenzimidazole, hydroxyl group in aroyl moiety (**104**) are reported to possess high antioxidant activity.¹⁷² However, 2,2,2-trichloro-1-hydroxyethyl group at 3-position (**105**) weaken the antioxidant potential which complies with their earlier reports.¹⁷³ A halogenophenyl group at 2-position incurs moderate antioxidant



3.5. Antioxidant activity

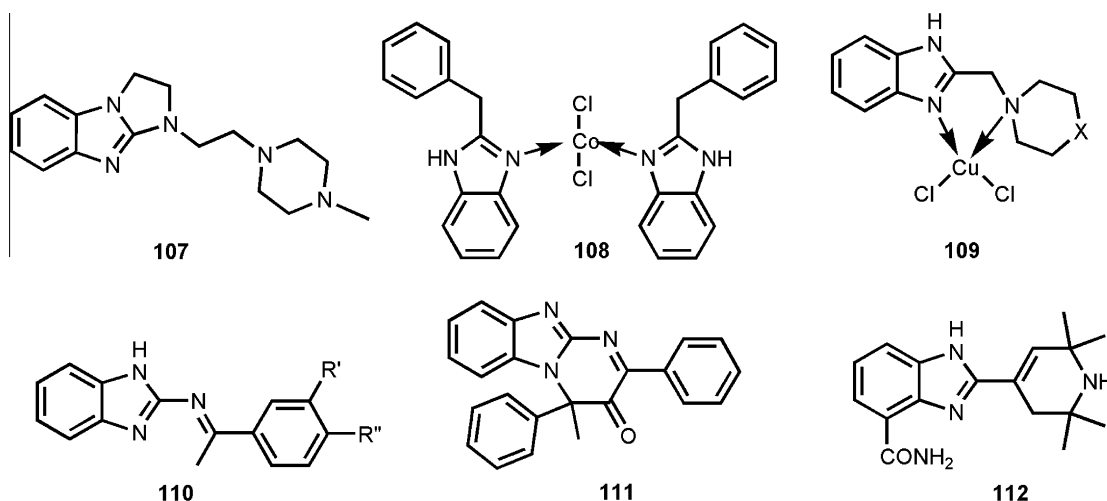
The drugs possessing antioxidant and free radical scavenging activity have been implicated in treatment of various diseases like cancer which are directly related to lack of antioxidant capacity of organism. Cole et al. in 1974 reported 5-hydroxybenzimidazole and 5-hydroxy-2-methylbenzimidazole as effective antioxidants.¹⁶⁶ Incorporation of thiadiazoles, triazoles and their open chain counterparts, that is, thiosemicarbazides at 1-position of benzimidazole incurs antioxidant activity. Further placement of varied aryl and alkyl substituents on these heteronuclei at 1-position has also yielded potent antioxidants (**97–99**). Amongst these, semicarbazide derivatives produced stronger inhibitory effects on lipid peroxidation levels as well as DPPH model.^{167,168}

Fused thiazolo[3,2-*a*]benzimidazoles substituted at 3-position by aminomethyl group (**100**) inhibited the oxidation of adrenaline to adrenochrome by preventing the formation of superoxide radical.¹⁶⁹ Anisimova et al. reported a series of 2-(heteroaryl)imidazo[1,2-*a*]benzimidazoles possessing 1-methylbenzimidazol-2-yl (**101**) and 5-bromo-2-thienyl (**102**) at R_2 with varied dialkylaminoalkyl substituents at R_1 as antioxidants in in vitro model of ascorbate dependent lipid peroxidation model.¹⁷⁰ Subsequently, the same research group disclosed *N*-acetylmethyl derivatives of 9*H*-2,3-dihydroimidazo (**103**) and 10*H*-2,3,4,10-tetrahydropyrimido[1,2-*a*]benzimidazole with varied substituents at 1-position to

activity with fluorine producing the maximally active compound (**106**) from the series.¹⁷⁴

	R_1	R_2	R_3
101	$-\text{CH}_2\text{CH}_2\text{NEt}_2$		H
102	$-\text{CH}_2\text{CH}_2\text{NEt}_2$		H
103	$-\text{CH}_2\text{COR}$	H	H
104	$-\text{CH}_2\text{CH}(\text{OH})\text{Ar}$	H	H
105	$-\text{CH}_2\text{CH}_2\text{NR}_2$	R/Ar	$-\text{CH}(\text{OH})\text{CCl}_3$
106	$-\text{CH}_2\text{CH}_2\text{NR}_2$		H

Recently, cyclization of dialkylaminoethyl at 1-position to 4-substituted piperazines and piperidines (**107**) have been investigated for antioxidant activity.¹⁷⁵ Monodentate and bidentate ligands derived from Cu^{2+} and Co^{2+} coordination compounds with 2-substituted benzimidazole compounds have also been evaluated for NO scavenging and superoxide dismutase activity from which compounds **108** and **109** show significant NO scavenging (IC_{50} 65 $\mu\text{g}/\text{ml}$) and potent dismutase (IC_{50} 0.26 μM) activities, respectively.¹⁷⁶ Recently, Schiff's bases of benzimidazole (**110**) have been found to exhibit high lipid peroxidation inhibitory activity which increases with lipophilicity. The compound **111** is found as the most potent antioxidant amongst the series.¹⁷⁷ A 4-carboxamidobenzimidazole analog **112** is identified to possess potent hydroxyl radical scavenging property through poly (ADP-Ribose)polymerase (PARP) inhibition.¹⁷⁸



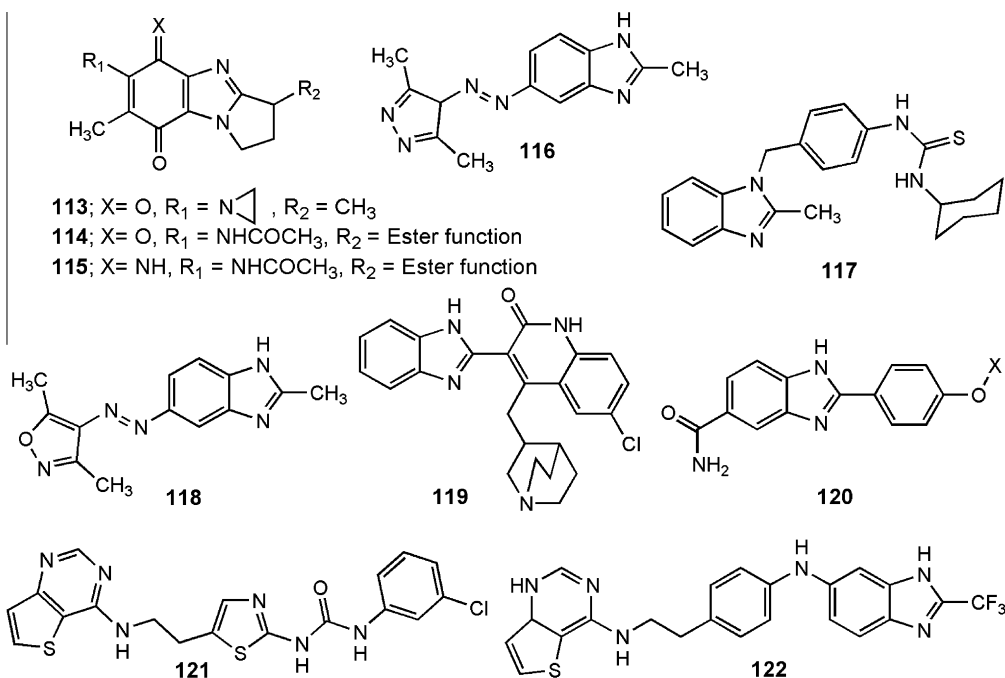
3.6. Antitumor activity

Cancer is one of the leading health hazards which are affecting a wide majority of world population. Various anticancer agents (also referred as antitumor, antiproliferative and antineoplastics) reported for treatment of varied kinds of cancers act through different mechanisms. However, the major side effect associated with

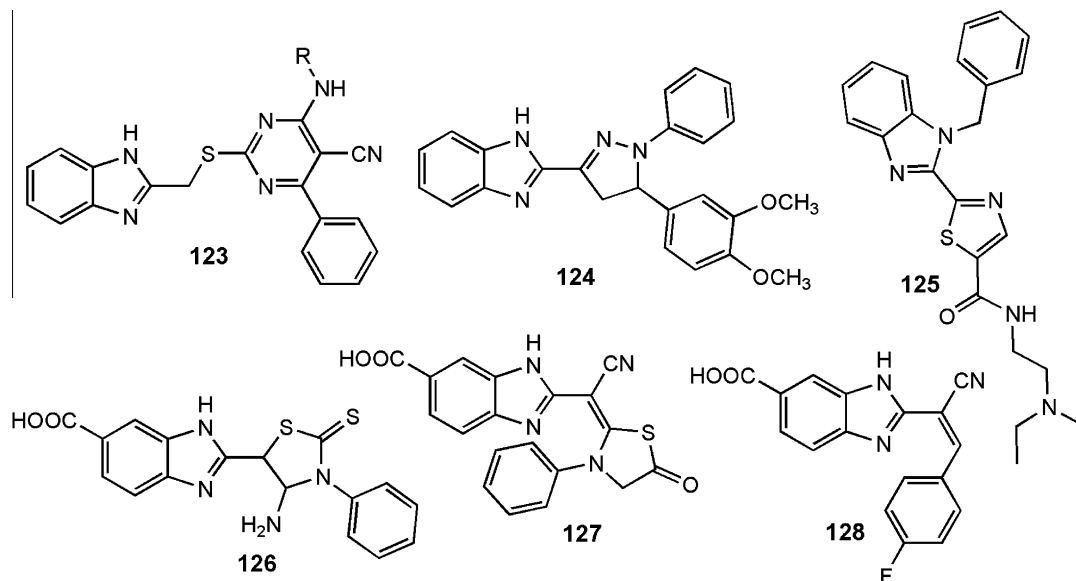
these agents is cytotoxicity towards normal cells due to lack of selectivity for the abnormal cells. Therefore search on anticancer agent has been in continuum since many years. Benzimidazole being an isostere of purine based nucleic acid and an important scaffold in various biologically active molecules is widely explored for development of anticancer agents.

Pyrrolo[1,2-*a*]benzimidazoles (**113–115**) is one of the early classes of anticancer agents acting through cleavages of G and A bases and reductive alkylation of DNA.^{179–183} The variedly substituted benzimidazole derivatives (**116–118**) are reported cytotoxic against lung and breast cancers.^{184,185} Ni et al. have developed some 2-(substituted quinolinon-3-yl)benzimidazoles as serine/threonine checkpoint kinase (CHK-1) inhibitors for treatment of cancer.¹⁸⁶ The compound **119** has emerged as potent compound

with subnanomolar IC_{50} value. Neff et al. have reported another series (**120**) of CHK-1 inhibitors but all compounds are found to have inhibitory activity significantly less than that of **119**.¹⁸⁷ Taking SNS-314 (**121**) as lead which is in clinical trials for anticancer use, 2-aminobenzimidazole derivatives have been designed and compound **122** is found as potent Aurora kinase inhibitor.¹⁸⁸

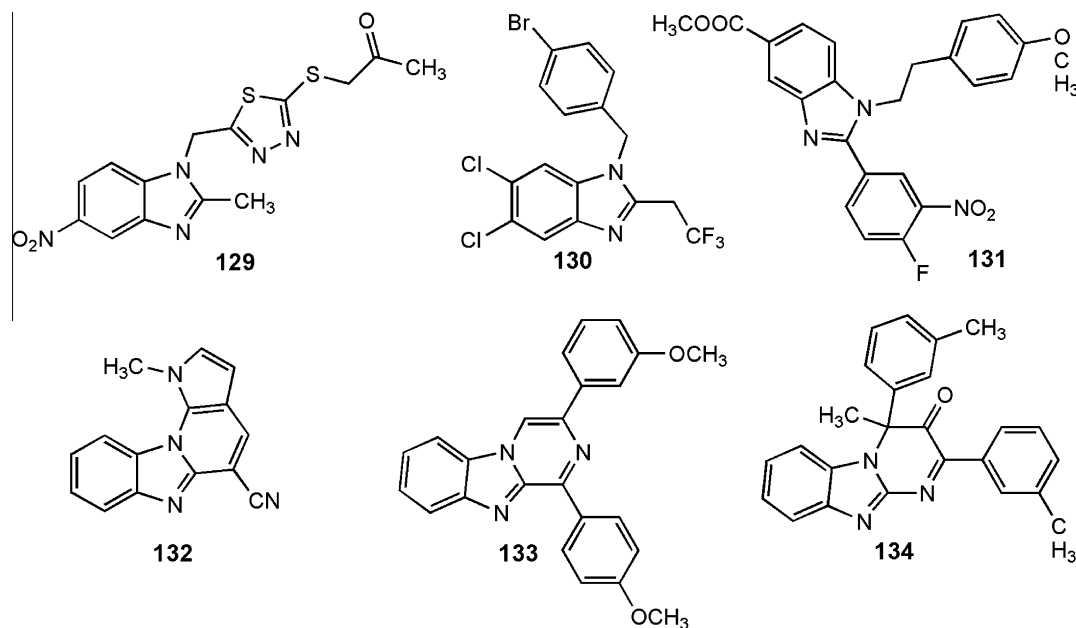


Recent developments on 2-substituted benzimidazoles have revealed varied heterocycles at 2-position to yield potent anticancer agents at various carcinoma cell lines. These include pyrimidine derivatives (**123**),¹⁸⁹ pyrazoline derivatives (**124**),¹⁹⁰ and thiazole derivatives (**125**).¹⁹¹ Further, 2-substituted benzimidazoles with chloro or carboxy group at 5-position having 4-amino-thioxothiazole (**126**), 4-oxothiazolidine (**127**), 4-fluorobenzylidene (**128**) and cycloalkylidene are reported as potent antitumour agents.¹⁹²



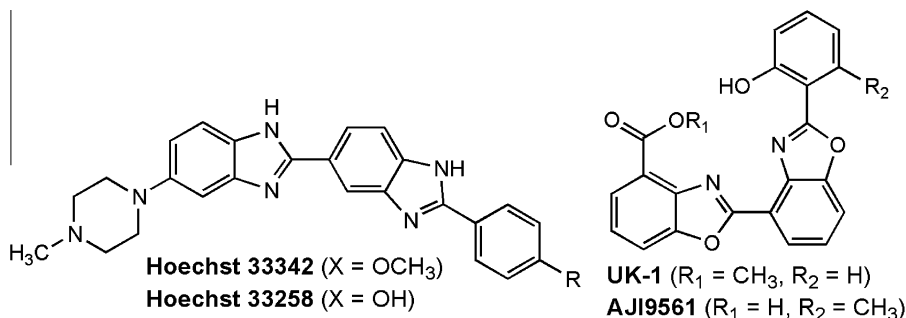
Evaluation of 2-methyl-5-nitro benzimidazoles substituted at 1-position with varied heterocycles revealed that thiadiazole ring linked through a methylene group at 1-position (**129**) incurs the

potent cytotoxicity. The exemplaries include **133** (pyrimido[1,2-*a*]benzimidazole-3(4*H*)-one)¹⁹⁷ and **134** (1,3-diarylpyrazino[1,2-*a*]benzimidazole).¹⁹⁸



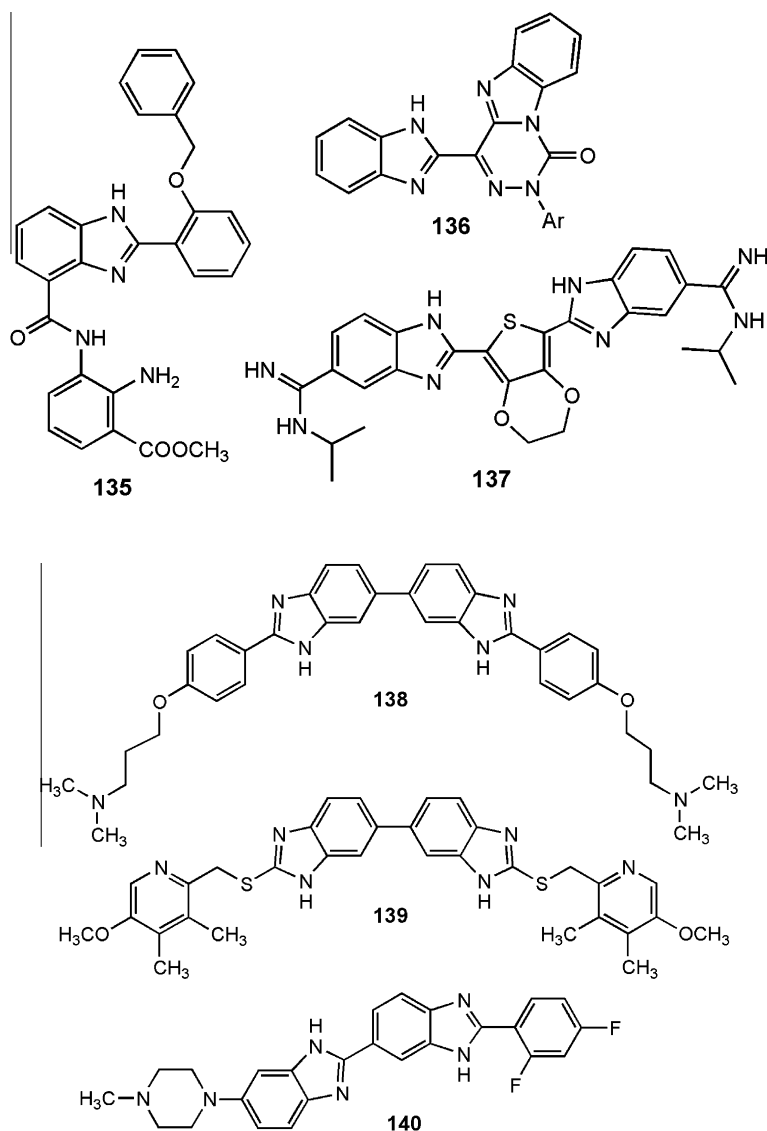
maximum antitumor activity. It is also revealed that nitro group at 5-position of benzimidazole is critical for the activity.¹⁹³ Ng et al. have explored some 2,5,6-trihalo-benzimidazoles as androgen receptor antagonists for their use in prostate cancer.¹⁹⁴ The SAR studies have led to a 1-(4-bromobenzyl) derivative (**130**) as the most potent androgen receptor antagonist. Benzimidazole-5-carboxylic acid analogs have been evaluated as anti-

leukemic agents wherein compound **131** is found to activate apoptosis.¹⁹⁵ Planar fused benzimidazole analogs have the potential to get inserted into the space between the base pairs of DNA resulting in DNA cleavage. Based on this mechanism, a benzimidazo[1,2-*a*]quinoline derivative (**132**) has exerted potent activity on all cell lines tested with IC₅₀ of 0.8–30 μM.¹⁹⁶ Recently, more fused planar benzimidazole derivatives have been reported to exhibit



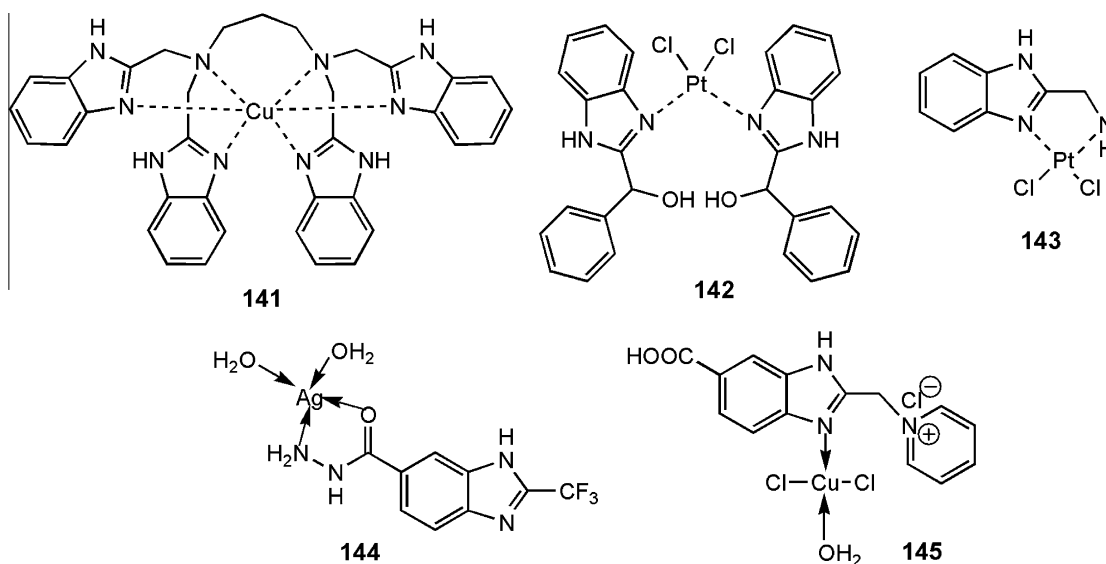
Huang et al. have synthesized their benzimidazole isosteres amongst which **135** is found as the most potent anticancer synthetic precursor of bis(benzimidazoles) against human A-549, BFTC-905, RD, MES-SA, and HeLa carcinoma cell lines.²⁰⁸ Benzimidazolyl-1,2,4-triazino[4,5-*a*]benzimidazol-1-one (**136**) is another bis(benzimidazole) analog having significant activity against multidrug-resistant P-glycoprotein expressing cell lines.²⁰⁹ Two benzimidazole nuclei linked through a thiophene ring have displayed moderate to strong antiproliferative effect toward a panel of eight carcinoma cell lines. The most active compound (**137**) of the series is reported to enter into live HeLa cells within 30 min, but did not accumulate in nuclei even after 2.5 h.²¹⁰

Taking Hoechst-33258 (a head-to-tail bis-benzimidazole wherein benzo ring a benzimidazole nucleus is connected to the imidazole ring of the other nucleus through a bond) and a head-to-head bis-benzimidazole (**138**), wherein two benzimidazole nuclei are connected at either their benzo or imidazole rings through a bond as leads, Yang et al. have designed and synthesized another series of symmetrical head-to-head bis-benzimidazoles and found **139** to possess good antitumour activity.²¹¹ Very recently, Singh and Tandon have modified Hoechst-33258 to synthesize another series of head-to-tail bis-benzimidazole bearing aryl group at 2-position.²¹² The derivatives bearing electron withdrawing groups like F (**140**) and Cl on the aryl ring exhibited potent anticancer activity over the compounds bearing electron releasing groups.



Complexes of benzimidazoles (ligand) with transition metal ions possess antitumor activity. Cu^{2+} complex of benzimidazolyl-methyl-1,3-diaminopropane (**141**) has the ability to intercalate into the double helix of DNA.²¹³ *N*-Trimethylsilylpropylbenzimidazole metal complexes exhibit cytotoxic activity on four mono-layer tumor cell lines.²¹⁴ Assessment of Pt^{2+} complexes (**142**, **143**) for antiproliferative properties showed potent activity against human MCF-7 breast cancer cell line and HeLa cervix cancer cell lines.^{215–220} Among the metal (copper, silver, iron, manganese) complexes of 2-methyl benzimidazol-5-carboxylic acid hydrazides, the silver complex (**144**) is found to display cytotoxicity (IC_{50} 2 μM) against two human cell lines.²²¹ A Cu^{2+} complex of 2-pyridinylbenzimidazole-5-carboxylic acid (**145**) has been found to exert potent topoisomerase II inhibitory activity.²²²

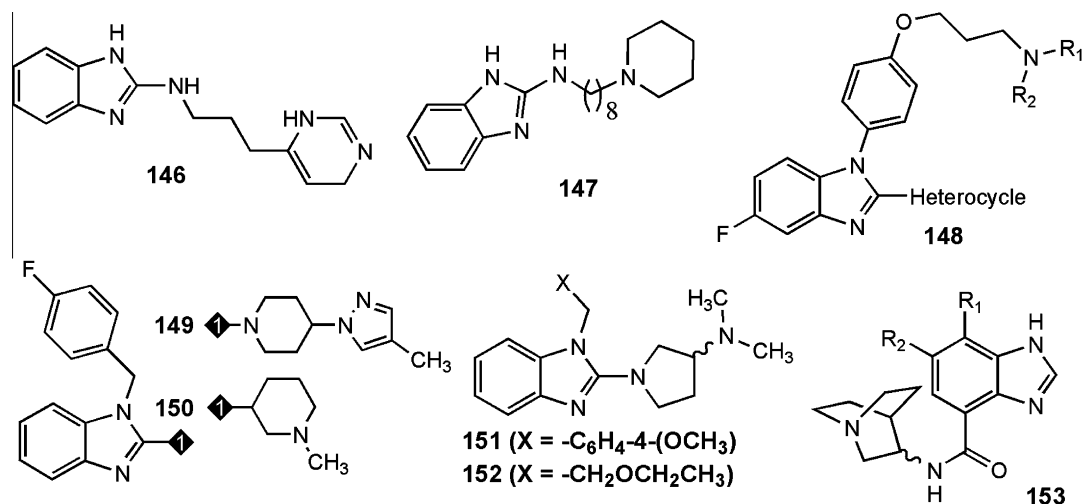
spacer to a 2-aminobenzimidazole moiety was designed and synthesized. Its QSAR and quantitative structure-property relationship (QSPR) analysis suggested a three carbon atoms chain length (**146**) optimum for the antagonistic activity.²²³ Replacement of imidazole ring with piperidine and chlorophenoxy substituents retained the affinity for H_3 receptor inferring the importance of 2-aminobenzimidazole in receptor interactions. The piperidine analog (**147**) showed good affinity for H_3 -receptor.²²⁴ 1,2-Disubstituted-5-fluorobenzimidazole derivatives with aza-heterocycles (**148**) are evaluated to have potent H_3 antagonist activity.²²⁵ 2-Aminobenzimidazole scaffold has also been selected for development of H_1 -antihistaminic agents therapeutically used for insomnia. The varied compounds evolved starting from a series of 2-aminobenzimidazoles in-



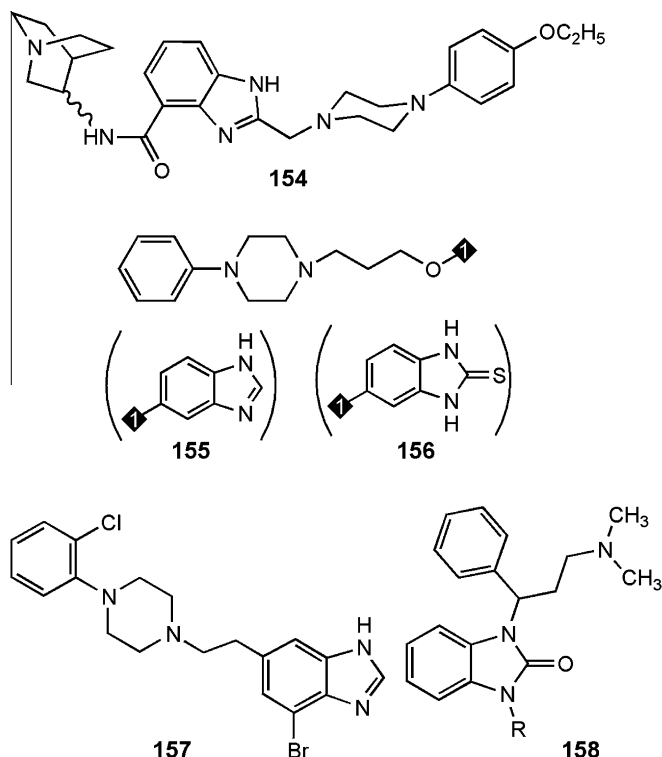
3.7. Benzimidazoles as psychoactive agents

The H_3 receptors in CNS are associated with central disorders such as impaired cognitive functions. A series of H_3 -antagonists composed of an imidazole ring connected through an alkyl

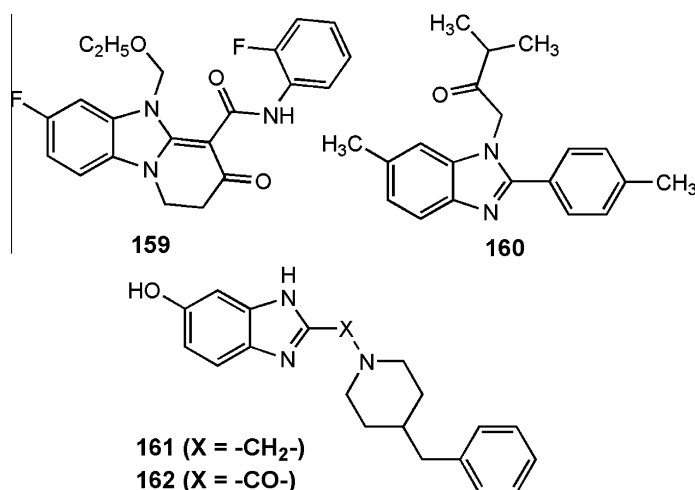
cludes **149–152**.^{226,227} Involvement of specific subtypes of 5-HT receptors is well established in psychiatric disorders such as anxiety, depression and memory loss. Azabicyclic benzimidazole derivatives (**153**) are characterized as potent and selective 5-HT_{3R} antagonists.



Incorporation of additional pharmacophoric moiety in this molecule led to benzimidazole-arylpiperazine derivatives (**154**) with mixed affinity for serotonergic 5-HT_{1A} and 5-HT₃ receptors and selectivity over α 1-adrenergic and dopamine D₂ receptors.²²⁸ Substituted arylpiperazines with 3-propoxy-benzimidazole or 3-propoxy-benzimidazole-2-thione groups are reported as atypical neuroleptics exhibiting good 5-HT_{2A/D2} pK_i binding ratios. Compounds **155** and **156** exhibited a non-cataleptic action in rats and antagonized amphetamine-induced hyperlocomotion in mice, suggesting their possible atypical antipsychotic potency.²²⁹ Andric et al. have found 4-halo-6-[2-(4-arylpiperazin-1-yl)ethyl]-1H-benzimidazoles to have affinity towards both D₂-like and 5-HT_{1A} receptors higher than their nonhalogenated analogs.²³⁰ Further, bromo derivatives showed a higher affinity than their chloro counterparts. Compound **157** is reported as a good candidate for antipsychotic activity. 1- or 3-(3-amino-1-phenyl propyl)-1,3-dihydro-2H-benzimidazol-2-ones are reported to be active in psychiatric disorders due to their selective norepinephrine reuptake inhibitory activity. Compounds substituted with methyl or cyclohexyl at N-1 (**158**) are found the most active from this class.²³¹



Another important category of the psychoactive drug comprises of the agents possessing GABAergic potential. The research group at Johnson and Johnson Pharmaceutical Research Institute has developed pyrido[1,2-*a*]benzimidazoles as potent GABA-A receptor agonists having potential anxiolytic activity.^{232,233} SAR studies have revealed that a polar group at N-1 of benzimidazole nucleus incurs maximum activity with ethoxymethyl group (**159**) found as the optimum substituent. N-substituted benzimidazoles (**160**) are reported as potent in vivo sedatives due to their interaction with benzodiazepine and α 1 receptors.²³⁴ The NR2B subunit containing NMDA receptors are thoroughly studied targets in a wide range of CNS pathologies. Varied number of benzimidazole derivatives identified with modest NR2B activity includes **161** and **162**.²³⁵

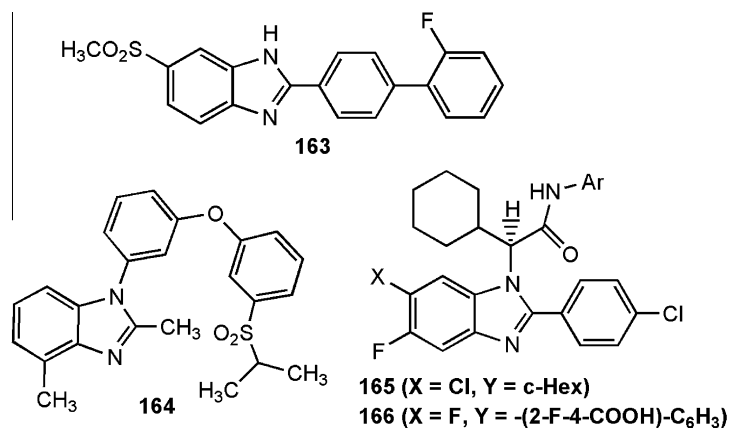


3.8. Lipid modulating activity

Lipids play an important role in pathophysiology of many metabolic diseases like diabetes, dyslipidemia, CVS related disorders, cancer, etc. Hence, regulation of lipid levels of lipids is an important strategy in treatment of varied diseases.^{236,237} Off the various targets that modulate lipid levels, HMG-CoA reductase is the most widely explored target and many drugs inhibiting this enzyme are clinically available. In addition to this, many new targets are identified which are being exploited for development of novel drugs for modulation of lipid levels.

Steroyl coenzyme-A desaturase (SCD) catalyzes monosaturation of fatty esters which are major components of triglycerides, cholesterol and phospholipids. Human SCD (*h*SCD) exists in two isoforms, that is, *h*SCD1 and *h*SCD5. The *h*SCD1 is expressed in adipose tissues and liver while *h*SCD5 is found in brain and pancreas. Compounds acting selectively on *h*SCD1 are implicated in control of lipid levels. In search of compounds having high *h*SCD5/*h*SCD1 selectivity, Powell et al. have identified 2-arylbenzimidazoles. The compound **163** is found to have *h*SCD5/*h*SCD1 selectivity value of about 1000.²³⁸

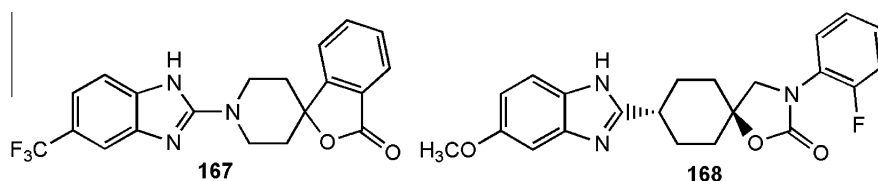
Liver X receptors (LXR) are the gene transcription factors which are responsible for cellular lipid efflux. In addition to this, the anti-inflammatory role of these receptors has implicated LXR agonists in prevention of atherosclerosis.²³⁹ Based on the rational design by taking leads from the existing literature,^{240–243} Travins et al. have designed and synthesized a series of benzimidazole derivatives and found compound **164** having IC₅₀ of 5 nM for LXR.²⁴⁴ Farnesoid X receptor (FXR) is another kind of nuclear hormone receptor which is expressed in liver, intestine, kidneys and adrenal glands and is responsible for conversion of cholesterol to bile acids and hence decreases intestinal absorption of dietary lipids. The receptor is also shown to have controlled glucose plasma levels and have insulin sensitizing activity. Therefore, FXR receptor agonists have the potential for treatment of dyslipidemia and diabetes. Recently, Richter et al. have developed a novel benzimidazole derivative (**165**) having potent and partial agonist activity for FXR but poor aqueous solubility.²⁴⁵ Incorporation of varied polar functions in **165** produced compound **166** having excellent FXR agonist activity as well as ADME properties.²⁴⁶



Neuropeptide Y (NPY) causes orexigenic effects by binding with NPY receptors. The receptor subtype 5 (NPY Y5) is responsible for centrally mediated NPY-induced feeding response.²⁴⁷ Hence, compounds able to antagonize the action of NPY at Y5 receptors may be useful in treatment of obesity. Ogino et al. have synthesized a long series of compounds based on spiro[isobenzofuran-piperidine]-1-yl benzimidazoles and found compound **167** as potent, brain-permeable and orally available Y5 selective antagonist.²⁴⁸ Pizzi et al. have designed another series of spiro derivatives of benzimidazole and then optimized the functional groups around the nucleus to improve the pharmacokinetic profiles.²⁴⁹ The compound **168** emerged as potent and selective Y5 antagonist.

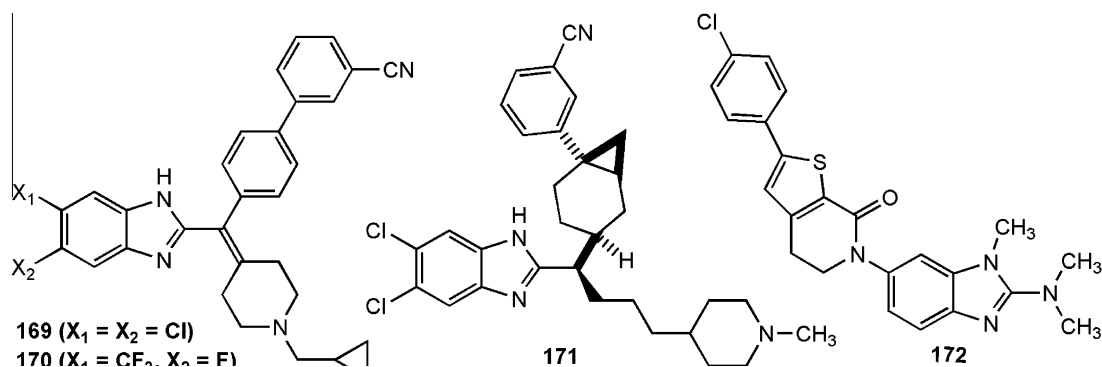
onists and its further modification has led to benzimidazole analog (**172**) having improved activity after oral administration in obese animals.²⁵³

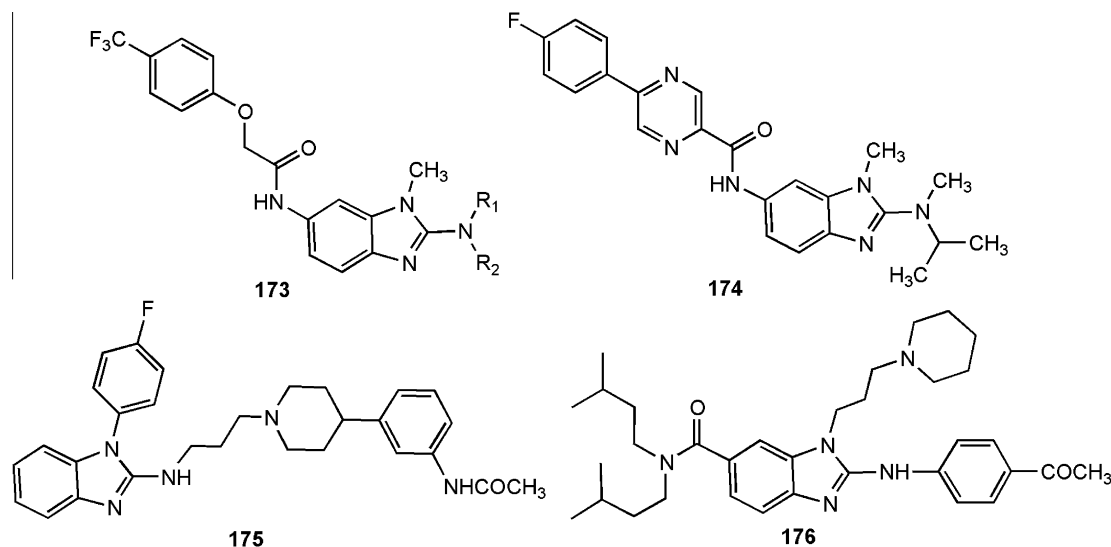
Arienzo et al. have modified their lead quinoline based MCH R1 antagonists to design benzimidazole analogs and found all compounds of the benzimidazole series (**173**) as potent and selective antagonists with good ADME profiles.²⁵⁴ Moriya et al. have also modified the same quinoline based MCH R1 antagonist by replacing the quinoline ring with more hydrophilic benzimidazole ring to arrive at compound **174** which showed good plasma and brain levels.²⁵⁵ Taking SNAP-7941, a quinazolinone based compound²⁵⁶ as



Melanin-concentrating hormone (MCH) interacts with MCH receptor 1 (MCH R1) to regulate eating behavior in mammals.²⁵⁰ Wu et al. have designed a series of benzimidazole derivatives in order to resolve the mutagenicity associated with a lead biaryl urea compound.²⁵¹ The compounds **169** and **170** have shown potent antagonism at MCH R1 with good pharmacokinetic properties and oral bioavailability. The research group from the same laboratory also developed another series of compounds amongst which **171** exhibited the most potent activity.²⁵² Thienopyrimidinone derivatives have been discovered as potent MCH R1 antag-

lead, Sasmal et al. at Dr. Reddy's laboratory have developed a pharmacophore model by studying key interactions between the receptor and a series of benzimidazole derived compounds.²⁵⁷ The compound **175** has been selected as prototypical member of the series. Contrary to biochemical role of MCH R1, inhibition of another MCH subtype (MCH R4) induces hunger and weight gain²⁵⁸ and hence useful in treatment of cachexia related syndromes.²⁵⁹ Poitout et al. have identified a novel series of benzimidazole analogs as potent and selective inhibitors of MCH R4. The compound **176** has been found to have IC₅₀ of 2 nM and able to cross BBB.²⁶⁰

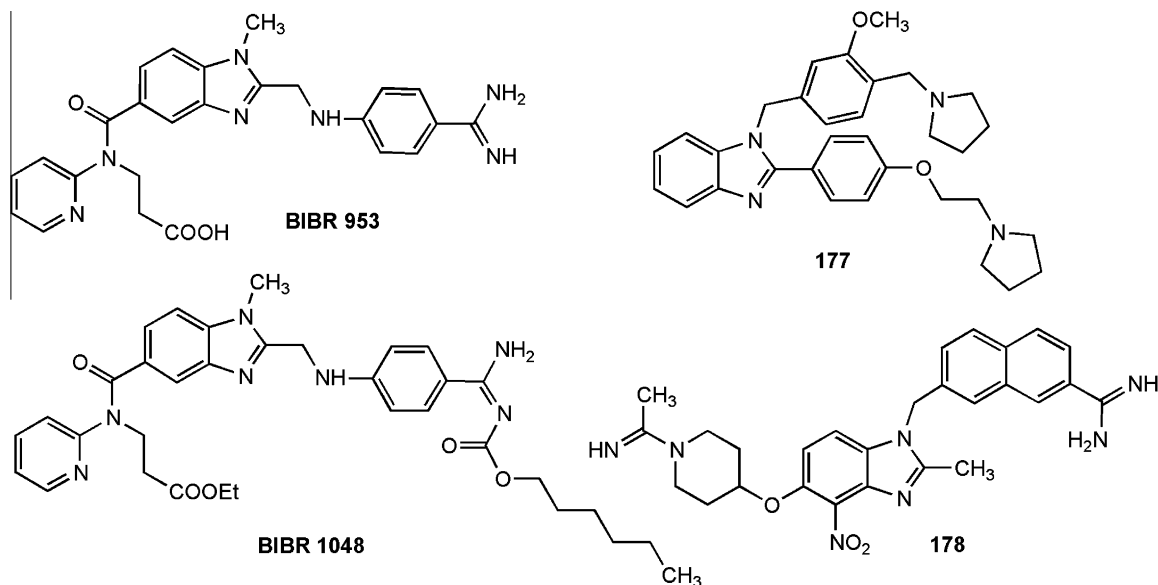




3.9. Anticoagulants

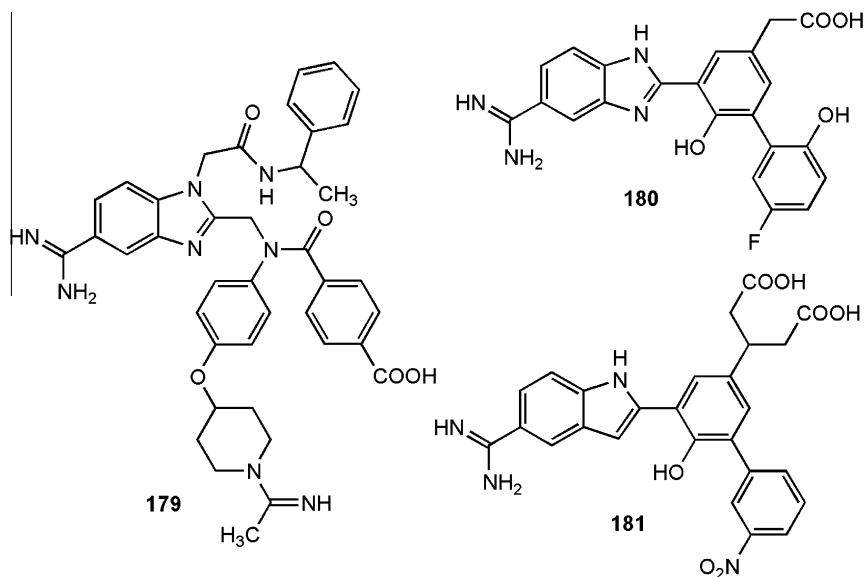
Thrombin causes proteolytic cleavage of fibrinogen, induces platelet activation and triggers a wide range of effects secondary to thrombosis, for example, vascular smooth muscle cell and fibroblast proliferation, monocyte chemotaxis, and neutrophil adhesion. Inhibition of thrombin is an important mechanism for inhibition of coagulation. Benzimidazole nucleus act as an appropriate template

template affords potent fXa inhibitors with excellent thrombin selectivity.²⁶³ Replacing the naphthylamide with differently substituted biphenylamides caused a disappointing change in *in vitro* profile. However, simplification of the naphthylamide group to yield a propenylbenzene group dramatically improved the potency and selectivity over the unsubstituted naphthalene analogs.²⁶⁴



to place the varied substituents required for interaction with thrombin. Huel et al. have designed a series of benzimidazole derivatives and arrived at Bibr 953 having excellent inhibitory potency and tolerability.²⁶¹ Its double prodrug Bibr 1048 has exhibited good pharmacokinetic properties and is in clinical evaluations. 1,2-Disubstituted benzimidazole derivatives (**177**) possessing basic amine moieties have been reported as active site directed thrombin inhibitors.²⁶² Berlex Biosciences have reported tetra-substituted benzimidazole with naphthylamide group at 1-position (**178**) as anticoagulant due to factor Xa (fXa) inhibition. The activity is found independent of the substituent at C-2 where as substitution of a nitro group at 4-position on the benzimidazole

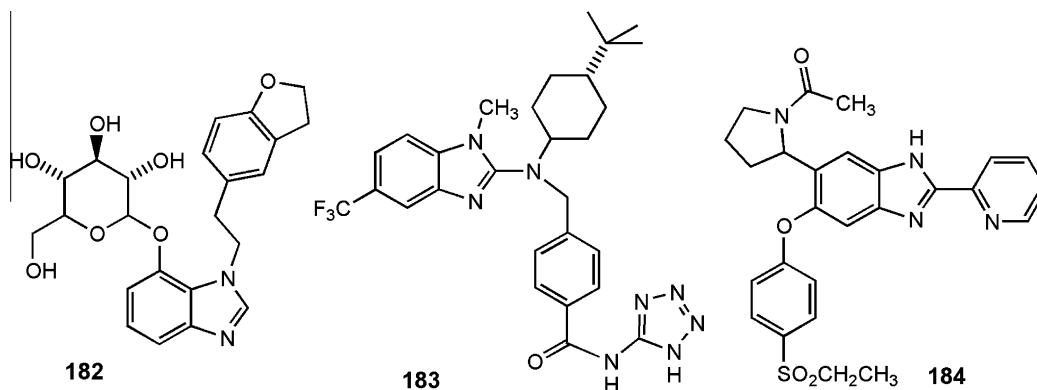
Ueno et al. have conducted a SAR studies leading to benzimidazole derivative (**179**) as potent and selective factor Xa inhibitors possessing excellent anticoagulant activity with no fatal acute toxicity.²⁶⁵ Inhibitor of factor VIIa/Tissue Factor (fVIIa/TF) complex is another class of compounds for treatment of thromboembolic diseases. The research group at Celera Genomics have designed and optimized a series of benzimidazole molecules derivatives wherein compound **180** has emerged as safe anticoagulant but having less residence time due to excessive glucuronidation.²⁶⁶ Further research into the compounds has led to development of selective dicarboxylic acid analog **181** with pharmacokinetic profile amenable to once daily subcutaneous dosing in humans.



3.10. Antidiabetic agents

Diabetic mellitus is a metabolic disorder that is characterized by high blood pressure due to insulin resistance and relative insulin deficiency. Non-insulin dependent diabetes mellitus (NIDDM) is the most prevalent type. The primary goal of treatment of NIDDM

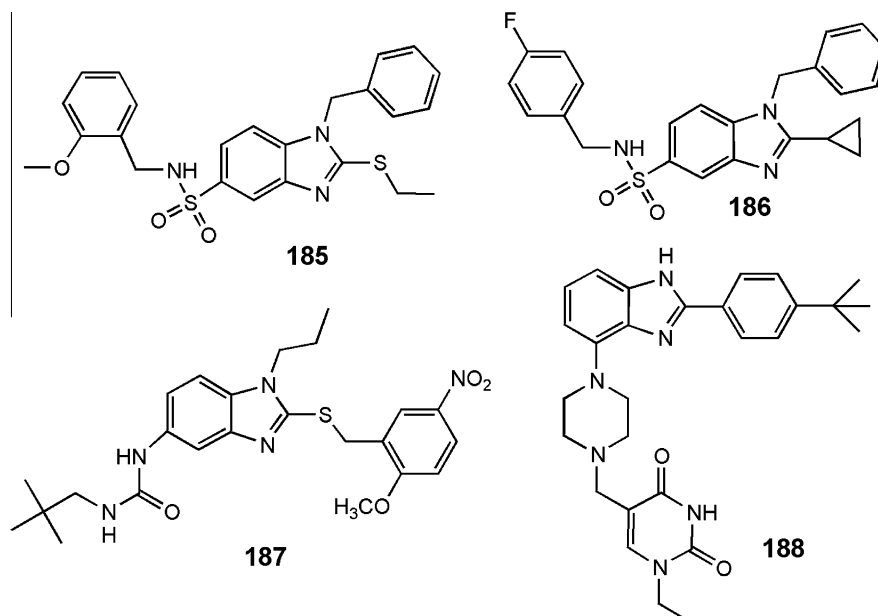
increase insulin secretion in beta cells and hence GK activators are expected to act as hypoglycemic agents. Systematic modification of novel 2-(pyridin-2-yl)-1H-benzimidazole identified from a HTS has led to discovery of a potent and metabolically stable GK activator **184** which demonstrated glucose lowering efficacy in a dose-dependent manner at 3 mg/kg.²⁶⁹



is controlling the levels of blood glucose. The sodium-glucose co-transporters (SGLTs) in the proximal tubules are responsible for glucose reabsorption in the intestine (SGLT1) and kidney (SGLT2) and hence, provide a novel target for treatment of NIDDM through inhibition of renal glucose reabsorption. Phlorizin is a natural SGLT2 inhibitor. Zhang et al. have synthesized structural analogs of phlorizin and found a benzimidazole analog (**182**) to exhibit potent SGLT2 inhibitory activity.²⁶⁷ Glucagon receptor (GCCR) involved in hepatic glucose production has also emerged as novel target for designing antidiabetics. GCCR antagonists inhibit glucagon-induced glucose production and decrease glucose levels. Kim et al. have designed and synthesized varied derivatives of aminobenzimidazole as GCCR antagonists and found compound **183** as orally efficacious inhibitor of glucagon-mediated glucose production in mice and rhesus monkeys at an oral dose of 3 mg/kg.²⁶⁸ Furthermore, its chronic oral administration to mice with high-fat diet-induced hyperglycemia caused significant reductions in blood glucose levels. GK (Glucose Kinase) activators catalyze reaction of glucose to glucose-6-phosphate and GK activation in liver increases hepatic glucose utilization. GK activity is also coupled to

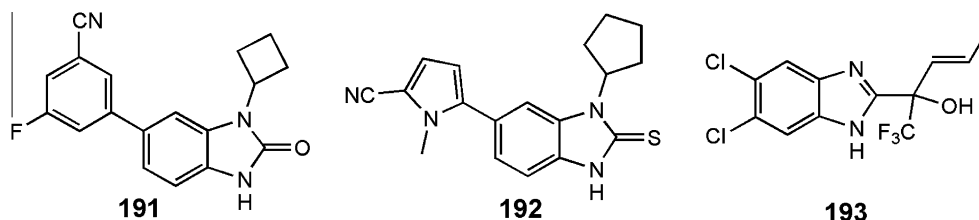
3.11. Miscellaneous activities

Bayer Yakuin reports varied benzimidazole derivatives as luteinizing hormone-releasing hormone (LHRH) or gonadotropin releasing hormone antagonists. Initially, 1-benzyl-2-ethylsulfanyl-1H-benzimidazole-5-sulfonamide **185** was identified as functional LHRH antagonist with potency in micromolar ranges.²⁷⁰ The other related series of compounds exemplified by **186** was developed yielding the potency in nanomolar doses.²⁷¹ Keeping the molecular core identical to that in the earlier series, a structure-activity relationship was developed which revealed that presence of phenyl group at 2-position, *t*-butylurea at 5-position and small alkyl groups at 1-position produce a potent LHRH antagonist (**187**).²⁷² Based on this substitution pattern, an alternative binding mode was also suggested. Pelletier et al.²⁷³ have reported 2-phenyl-4-piperazinylbenzimidazoles as GnRH antagonists with nanomolar potency (**188**, IC₅₀ 1.7 nM) in in vitro binding and functional assays as well as excellent bioavailability.



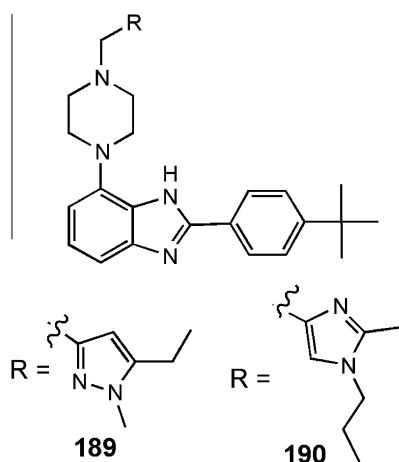
Amongst a series of compounds synthesized by appending small heterocycles to the 2-(4-*tert*-butylphenyl)-4-piperazinyl-benzimidazole template, two imidazole analogs, **189** and **190**, have shown to possess substantial *in vitro* potency at the target receptor

to exhibit its therapeutic utility towards hypogonadism, cachexia etc. Compound **193** is found as the most potent compound in this category.²⁷⁷

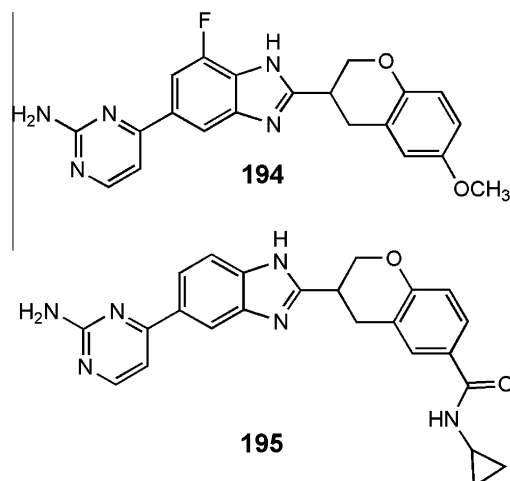


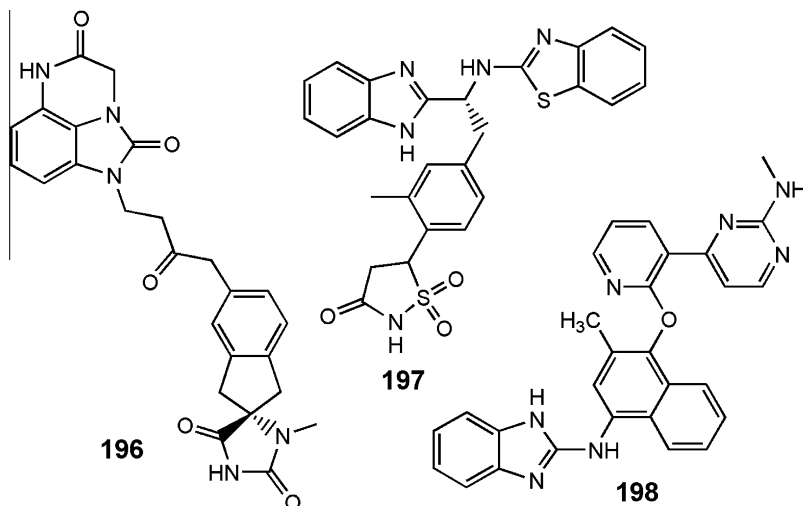
(hGnRH IC_{50} 7 and 18 nM, respectively) as well as aqueous solubility (55 and 100 μ g/mL at pH 7.4, respectively). Both are reported to have good oral bioavailability.²⁷⁴

Rho kinase, a serine/threonine kinase expressed in vascular tissues, plays an important role in essential signal transduction pathways and has potential utility in wide range of activities. In 2008, the benzimidazole derivatives (**194**) have been reported as excellent inhibitors of Rho kinase with $IC_{50} < 1$ nM.²⁷⁸ Later in 2010, varied positions of benzimidazole nucleus was explored by the same research group to optimise the structure for selectivity towards other protein kinases. Compound **195** developed with modification in the chromane ring showed Rho kinase inhibition in nanomolar doses where as affinity towards other protein kinases is in micromolar concentrations.²⁷⁹



Amongst a series of novel 6-phenyl benzimidazolones, compound **191** has been found to exhibit potent progesterone receptor (PR) antagonist activity in T47D cell alkaline phosphatase assay.²⁷⁵ Further replacement of phenyl at the 5(6)-position of benzimidazole by pyrrole has yielded potent progesterone antagonist **192** with less selectivity towards glucocorticoid and androgen receptors.²⁷⁶ A 2-(2,2,2)-trifluoroethyl-benzimidazole scaffold has been explored as tissue-selective androgen receptor modulators (SARMs) that are agonist in muscles and antagonists in prostate





Theberge et al.²⁸⁰ have identified compound **196** as inhibitor of neuropeptide calcitonin gene-related peptide (CGRP) inhibitor that plays a key role in migraine pathology. A few other benzimidazole derived compounds acting on specific receptors include benzimidazole-(S)-isothiazolidinone ((S)-IZD) derivatives **197** as protein tyrosine phosphatase 1B (PTP1B) inhibitor²⁸¹ and pyridyl-pyrimidine benzimidazole **198** as potent Tie-2 inhibitor.²⁸²

4. Concluding remarks

Numerous compounds derived from benzimidazole nucleus are used in the clinics for treatment of many diseases. However, despite the active, exhaustive and target based research on development of many compounds as anti-inflammatory, immunomodulatory, lipid modulators, etc. no molecule has made its way to the market and clinic. It can be probably due to lack of a comprehensive compilation of various research reports in each activity capable of giving an insight into the SAR of the compounds. The present review covering more than 280 references is expected to provide a low-height flying bird's eye view of the benzimidazole derived compounds to a drug designer and medicinal chemist for a comprehensive and target oriented information for development of clinically viable molecules.

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