International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Study on Benzimidazole: A Comprehensive Review

Jiyaul Hak[1], Amit Aggarwal[2], Sandeep Kumar[3], Arvinder Pal Singh[4], Anshi Kumari[5]

[1]Assistant professor, IIMT University
[2,3,4,5]Students, Maharaja Agrasen School of Pharmacy, Maharaja Agrasen University, Baddi-174103, Distt.Solan, Himachal Pradesh, India.

Abstract
The chemical compound known as benzimidazole has been assigned to the category of heterocyclic aromatic in one of the potential classifications for it. This structure has a notable pharmacophore position in the scientific discipline of medicinal chemistry and enjoys a privilegedstatus within that discipline. As a result of the fact that it possesses a wide range of beneficial therapeutic effects, such as those of antiulcerants, antihypertensives, analgesics, medicines, antivirals, antifungals, anticancer, and antihistamines, it serves a very important purpose. This is due to the fact that it has a very important purpose. The literature review reveals that benzimidazolederivatives are effective chemicals, and a wide range of reviews that are currently available on themarket for organic chemistry and medical specialist studies have confirmed that the molecules ofthese compounds are helpful against a variety of different microorganisms. The importance of themethodology used in its synthesis has piqued the curiosity of synthetic organic chemists, who haveshown an interest in the processes involved. As a direct result of this, we have made an effort in our evaluation of the gift to assemble information on the chemistry that lies behind a wide varietyof substituted benzimidazole byproducts and the many medicinal applications of these substances.

Keywords: Benzimidazole, Heterocyclic aromatic, Synthesis, Anti-bacterial

INTRODUCTION

Benzimidazole derivatives are particularly important compounds due to the wide variety of biological activities and therapeutic applications they have, as well as their powerful restricting action and excellent property magnitude relation. Benzimidazole derivatives also have an excellentproperty magnitude relation.[1] In light of the significance of benzimidazole, it was decided to deviseand produce a variety of novel benzimidazole derivatives, each of which would consist of an oxadiazole moiety. The possible biological activity of these chemicals would next be investigatedin order to determine whether or not they had any of that potential. In the field of study pertainingto pharmaceuticals, the benzimidazole ring is an important part of the heterocyclic pharmacophore.[2] Compounds with a variety of substituents in the benzimidazole structure have been linked to a wide range of biological effects, including antibacterial, anticancer, antiviral, antioxidant, antifungal, helminthicidal, histamine-blocking, anticoagulant, and antihypertensive effects. These effects have been attributed to the compounds. The benzimidazole ring is generally recognised as a key pharmacophore at this point in time within the context of modern day drug

development. When it comes to health-related research, the synthesis of new benzimidazole derivatives is still regarded as an important area of focus for academic inquiry.[3]

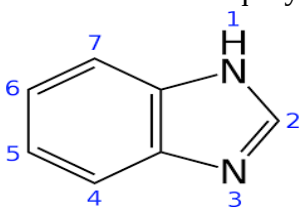


Fig. 1: Structure of Benzimidazoles

PHYSICAL PROPERTIES OF BENZIMIDAZOLES

It would seem, on the basis of the melting points of several benzimidazoles, that exchanging the 1-position results in a lower melting point the vast majority of the time.[4] Polar solvents have a greater capacity than organic solvents for the dissolution of benzimidazoles containing imide nitrogen. The solubility of the molecule might potentially be improved in liquids that are non-polarif additional non-polar substituents are inserted at different other places on the benzimidazole ring.In contrast, the presence of polar groups inside the molecule causes an increase in its solubility inpolar liquids. This effect may be seen in both aqueous and aqueous solutions. In general, benzimidazoles are soluble in mild acids and have a moderate basicity, which means that they are somewhat less basic than imidazole. This is because benzimidazoles have a benzene ring structureinstead of an imidazole ring structure. This is due to the fact that benzimidazoles are a kind of derivative derived from imidazole. Benzimidazoles are generally soluble in alkaline solutions, despite the fact that their high level of acidity renders them prone to the production of N-metallic compounds when they are dissolved in water. Similar to the situation with imidazole, it would seem that resonance-based ion stabilisation is to blame for the acidic characteristics of benzimidazoles. The dissolution of the more acidic benzimidazoles may be possible with a solutionthat is less basic, such as one that includes potassium carbonate. This is because there is a possibility that such a solution will contain potassium carbonate.[5]

CHEMICAL PROPERTIES OF BENZIMIDAZOLE

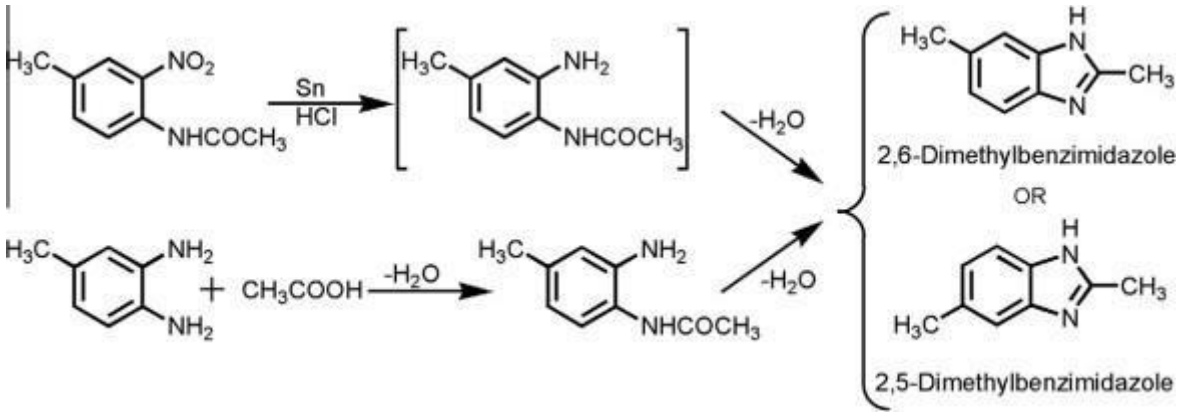
Reactions of the benzimidazole ring:

The benzimidazole ring is distinguished by a high level of stability as a defining characteristic. It makes no difference whether the benzo(a)imidazole is subjected to alkalis, hot hydrochloric acid,or intense sulfuric acid; its characteristics do not alter in any way.[6] Oxidation is a process that maybreak the benzene ring of benzimidazole, but only under very specific conditions. The benzimidazole ring is only able to tolerate decrease in its structure under certain circumstances.[7]

CHEMISTRY

There have been occasional attempts made to develop libraries of these molecules due to the extensive variety of bioactivities shown by benzimidazoles and the derivatives of these compounds. There are many different synthetic processes that have been developed and perfectedin order to make commodities with the amount, purity, and quality that have been specified by thecustomer. The first benzimidazole was either 2,5-dimethylbenzimidazole or 2,6- dimethylbenzimidazole, and it was created in 1872 by Hoebrecker by

the reduction of 2-nitro-4- methyl acetanilide. This discovery came about as a result of one of the first investigations into thechemical makeup of benzimidazole (Scheme 1).[8] Later on, Ladenburg ultimately succeeded in synthesising a chemical with equivalent qualities by refluxing 3,4-diamino toluene with acetic acid. His method was described as "refluxing" (Scheme 1). The early scientific literature referredto these substances as "Anhydro bases" since the creation of these compounds resulted in the lossof water throughout the process. Before settling on "benzimidazole" as their permanent appellation, benzimidazoles passed througha few different nomenclature periods that are easily distinguishable from one another. The o- phenylenediamine derivatives such as methyl-o-phenylenediamine were used in the production of benzimidazole (1); ethenyl-o-phenylenediamine was utilised in the production of 2- methyl benzimidazole (2); and so on.[9] Derivatives of the groups that make up the imidazole component of the ring have also been used to refer to these compounds. For example, o-phenylene formamidine is another word for benzimidazole. These derivatives have been used to refer to thesecompounds. 2(3H)-benzimidazoles (3) and benzimidazole-2 (3H) -thione was once known by thenames o-phenyl urea and o-phenylene thiourea, although o-phenyl urea was the more widespreadterm. o-phenylene thiourea is no longer in use (4). Isomerization happens as a consequence of thequick tautomerization of the hydrogen that is attached to the N-1 atom in the compounds that are produced as a result.[10] When discussing tautomeric compounds, it is common practise to provide not one but two sets of numbers to designate the location of the substituent group(s), with the second set of numbers being enclosed in parentheses to keep it distinct from the first set of numbers. For instance, the compounds on the list above are often referred to by their chemical name, which is 5(or 6)-methyl benzimidazole.[11]



SCHEME 1

Synthesis of benzimidazoles and the derivatives

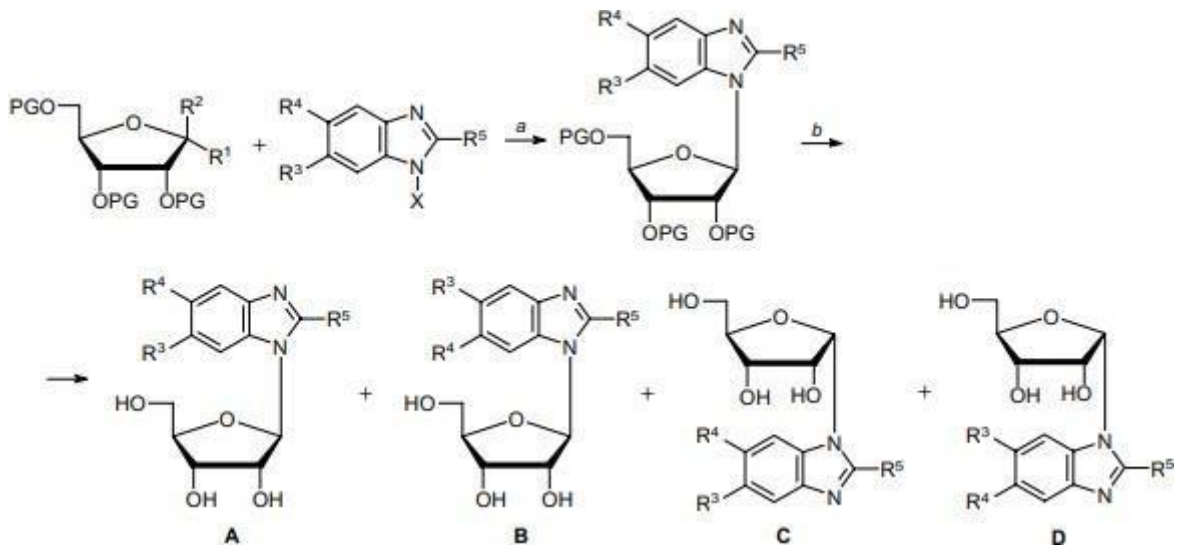
The first chemical synthesis of benzimidazole nucleosides did not take place until the middle of the twentieth century. However, it has only been within the last 20 years that advancements in genetic engineering methods for producing enzymes of nucleic metabolism have enabled for the active research of chemo-enzymatic approaches to the manufacture of these compounds. These advancements have only been possible because of the advent of gene editing technology. These breakthroughs came about as a direct consequence of the use of genetic engineering in the production of enzymes of nucleic metabolism, which made it feasible for these developments to take place.

There are two different chemical routes that may be used to create benzimidazole nucleosides. Oneof the

possible approaches is the tried-and-true Vorbruggen reaction, which involves the condensation of benzimidazole with a protected carbohydrate residue. When the protective groups at the end of this synthesis are removed, a combination of nucleosides (- and -epimers) in varied ratios is often generated. This makes purification difficult since the ratios vary. Using this procedure, it is feasible to synthesise a particular regio- and/or stereoisomer by adjusting various factors, such as silyl protection, selective catalysts, solvents, and temperature settings. This may be done to produce the desired isomer.[12].
One other technique involves changing the base or sugar residue of the nucleoside that was generated. The availability of the starting ingredients is a crucial factor in determining whether ornot this procedure is feasible. [13]

Glycosylation-mediated synthesis of benzimidazole β-D-ribosides

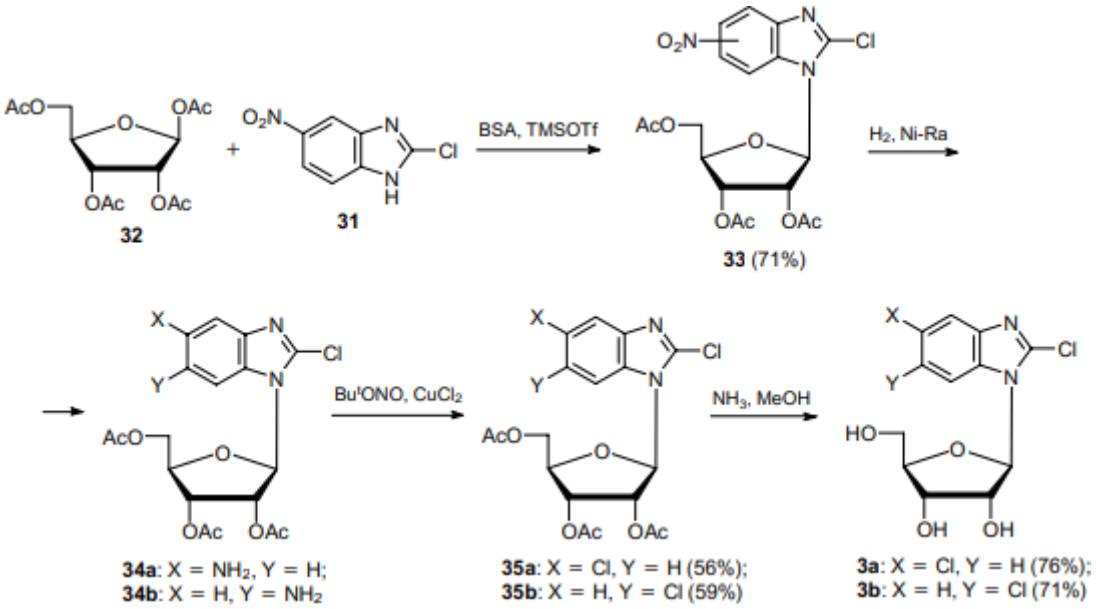
The synthesis of nucleosides is detailed in Scheme 2, which walks the reader through the Vorbruggen reaction (where, PG is a protecting group). By using this method, it is feasible to produce the -N(1)- (A), -N(3)- (B), -N(1)- (C), and -N(3)- (D) isomers. [14].



Scheme 2

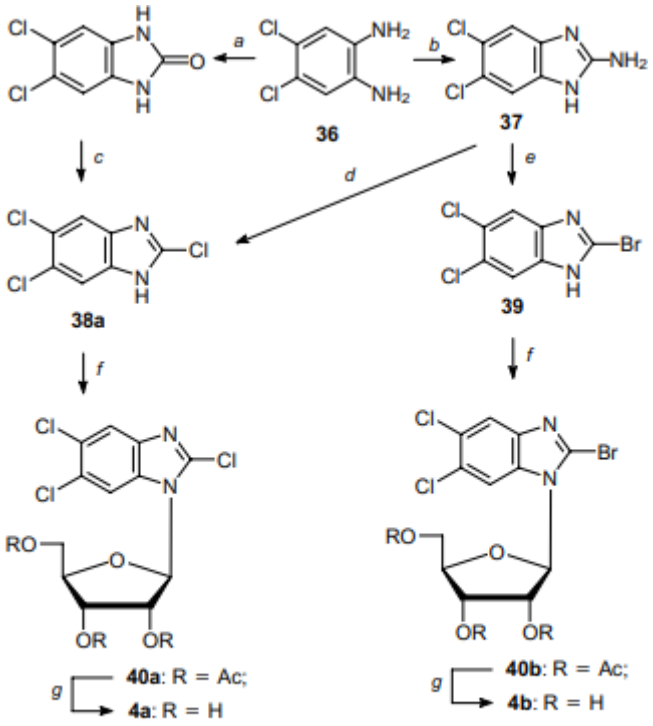
This approach is helpful for the synthesis of nucleosides that have the identical substituents at positions R3 and R4 on the benzimidazole ring. Glycosylation results in a mixture of N(1)- and N(3)- Regio isomers being produced if the substituents that are used are different, which makes ita difficult process to separate one from the other. The synthetic route to 2,5(6)-dichloro-1-(-D- ribofuranosyl) benzimidazoles is outlined in Scheme 3, which may be accessed here. When 2- chloro-5(6)-nitro benzimidazole (31) is combined with 1,2,3,5-tetra-O-acetyl—D-ribofuranose, the reaction results in the formation of two isomers: 2-chloro-5-nitro and 2-chloro-6-nitro-1-(2,3,5-tri-O-acetyl—D-ribofuranosyl) benzimidazoles. These isomers are (32, TAR). To separate these isomers, which are produced when hydrogen is passed over Raney nickel (Ni-Ra), resulting in theamino derivatives 34a and 34b, silica gel column chromatography is utilised. These isomers may then be analysed separately. The benzimidazole ring must then have an atom of chlorine added toit in the appropriate location for the following step to take place. In order to produce pure 5-chloroderivative 35a, one must first diazotize 5-amino isomer 34a with tert-butyl nitrite in acetonitrile while simultaneously being exposed to copper chloride. Through the process of simultaneous

diazotization, 6-amino isomer 34b may be transformed into 6-chloro derivative 35b. The removalof acetyl protecting groups by treatment with ammonia in methanol results in the production of 2,5- and 2,6-dichloro-1-(-D-ribofuranosyl) benzimidazoles, respectively (3a) and (3b), respectively (3b) [15].



SCHEME 3

A process for the synthesis of 1-(-d-Ribofuranosyl)-2,5,6-trichlorobenzimidazole (TCRB) (4a) and 2-Bromo-5,6-dichloro-1—d-ribofuranosyl benzimidazole (BDCRB) is given in Scheme 4, whichalso gives more information on the procedure (4b). After the ring closure of commercially available 4,5-dichloro-1,2-phenylenediamine (36) with cyanogen bromide, the 2,5,6- trichlorobenzimidazole (38a) was created by the diazotization of an amino derivative. This was done in order to synthesise the compound (37). This cyclization method of 4,5-dichloro-1,2- phenylenediamine (36) with cyanogen bromide in methanol may be used to produce a wide varietyof various 2-aminobenzimidazoles. After a number of transformations, the 2-amino-5,6- dichlorobenzimidazole (37) was produced in yields of 98 percent, which is a significant improvement over the 22 percent yield that was previously reported. Compound 37 was used in the subsequent step, which consisted of preparing 2,5,6-trichlorobenzimidazole (38a) and 2- bromo-5,6-dichlorobenzimidazole (39), respectively. This led to the synthesis of TCRB and BDCRB.[16]

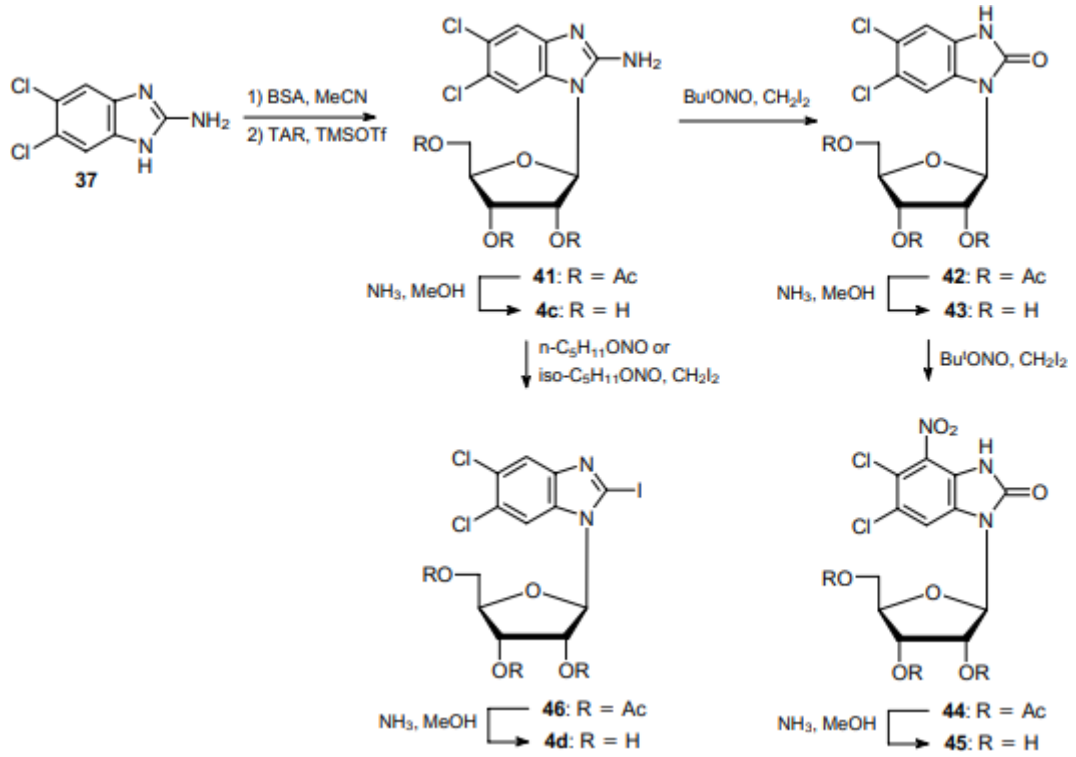


(*a*) $(NH_2)_2CO$, n-$C_5H_{11}OH$; (*b*) CNBr, MeOH; (*c*) $POCl_3$, HCl; (*d*) HCl, NaONO, $CuCl_2$; (*e*) HBr, NaONO, CuBr; (*f*) 1) BSA, MeCN; 2) TAR, TMSOTf; (*g*) NH_3, MeOH

SCHEME 4

The synthesis of the desired ribofuranoside continued with the second step, which consisted of thesilylation of 2,5,6-trichlorobenzimidazole (38a) using N,O-bis(trimethylsilyl)acetamide (BSA). The ribosylation of TAR (32) then occurred in the presence of trimethylsilyl trifluoromethanesulfonate after this step was completed (TMSOTf). Using this approach, 2,5,6- trichloro-1-(2,3,5-tri-O-acetyl—D-ribofuranosyl) benzimidazole (40a) was synthesised, along with a minuscule quantity of the -anomer. During the extraction procedure, a yield of 74% was attained after the target TCRB (4a) was treated with ammonia in methanol to remove the acetyl group. The synthesis of BDCRB (4b) proceeded according to the same technique as before (Scheme 4). In aqueous HBr, sodium nitrite was used to catalyse the diazotization of 2-amino-5,6-dichlorobenzimidazole (37). After being decomposed in the presence of copper bromide, the diazonium salt was silylated with BSA to produce 2-bromo-5,6-dichlorobenzimidazole (39). TAR ribosylation in the presence of TMSOTf led to the synthesis of 2-bromo-5,6-dichloro-2,3,5-tri-O-acetyl—D-ribofuranosyl) benzimidazole (40b). After the acetyl protecting groups were removed from BDCRB (4b), the compound was recovered with a 37 percent yield [17].

The synthesis of 5,6-dichloro-2-iodobenzimidazole through the Sandmeyer reaction seems to be difficult; hence, an alternative method using l-(-D-ribofuranosyl) benzimidazole was suggested asa solution to this problem. Because of the difficulties that have transpired, we decided to take thisaction (4d, IDCRB). This initial step was necessary because it allowed for the determination of theselectivity of the diazotization of 2-amino-5,6-disubstituted benzimidazole ribosides by tertiary alkynyl nitrites in a solution that did not include water. As a byproduct of the synthesis, the substance known as 2-amino-5,6-dichloro-1-(2,3,5-tri-O-acetyl—D-ribofuranose) was produced (Scheme 5) [18]



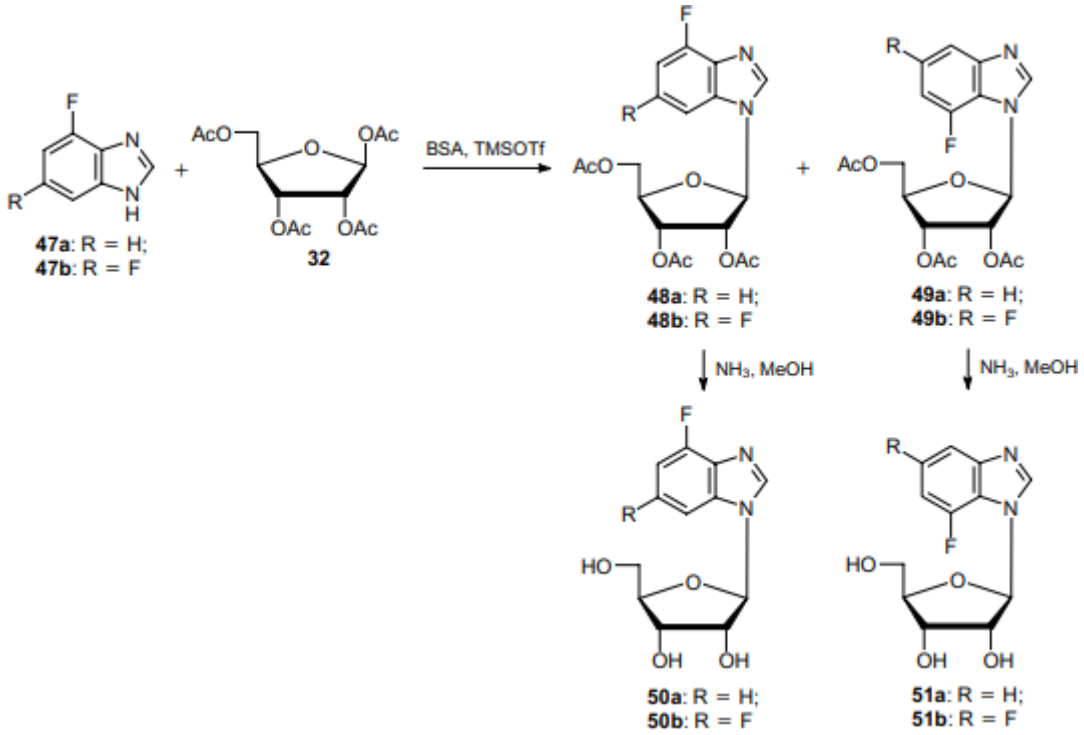
SCHEME 5

We were able to get protected ribofuranoside 41 with a yield of 51% by silylating 2-amino-5,6-dichlorobenzimidazole (37), followed by ribosylating it with TAR. (32). After being exposed to diiodomethane containing ten times the normal amount of tert-butyl nitrite, the second product experienced a transformation that was not anticipated. Instead of having an iodine group attachedto the benzene ring, the end product had a nitro group bonded to it. Isolating the crucial intermediate, 5,6-dichloro-l-(2,3,5-tri-O-acetyl—D-ribofuranosyl) benzimidazol-2-one, allowed for the determination of the mechanism underlying this peculiar reaction (42). Both intermediate 42 and its unprotected counterpart 43 were successfully synthesised on their own, which served asindependent confirmation of the structure of the intermediate. Specifically, ribosylation was carried out on 5,6-dichlorobenzimidazol-2-one (see Scheme 4) after it had been produced by completing the ring formation of 4,5-dichloro-1,2-phenylenediamine (36) in the presence of urea 19. After being treated with tert-butyl nitrite (10 equiv.) in diiodomethane at a temperature of 100 °Cfor two hours, compound 42 was completely converted into 5,6-dichloro-4-nitro-1-(2,3,5-tri-O- acetyl—D- ribofuranosyl) benzimidazol-2-one (44), and no byproducts were produced during thistransformation. Crystallization and separation of compound 44 was successful, resulting in an 86 percent purity rate. It is necessary to first de-protect the 5,6-dichloro-4-nitrobenzimidazol-2-one in order to get the ribosylated version of the compound (45).[20]

In the synthesis of 2-iodo derivative (46), the diazotization of primary alkynyl nitrite is an important step that yields a valuable reagent (Scheme 5). It was discovered that the same conditions that led to the development of the undesirable product 44 also worked for the treatment of compound 41 with amyl or isoamyl nitrite. This was the conclusion that was reached after the investigation. As a consequence of this, the same molecule, namely 5,6-dichloro-2-iodo-l-(2,3,5- tri-O-acetyl—D-ribofuranosyl) benzimidazole

(46), was generated with a yield of either 55% or 63%. The required 5,6- dichloro-2-iodo-l-(- D-ribofuranosyl) benzimidazole (4d) was generated after the removal of the protecting groups with ammonia in methanol (90 percent yield).[21]

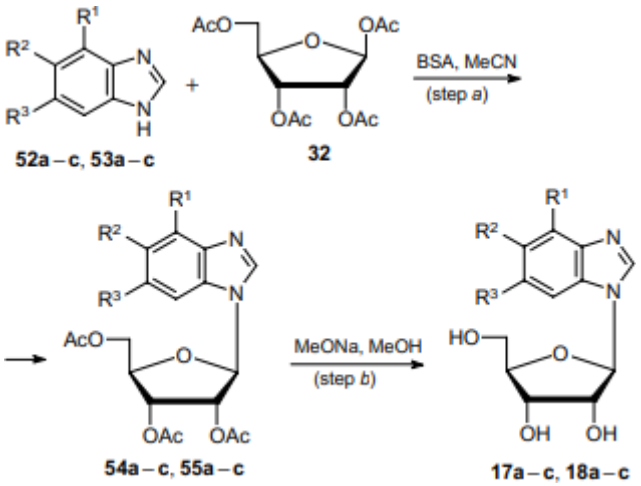
Producing fluorinated benzimidazole ribosides required the assistance of the Vorbruggen reaction(Scheme 6). After heating 4-fluoro-1H-benzimidazole (47) with BSA in the presence of reflux, thebase was trans-silylated with TAR (32) in the presence of TMSOTf, which led to the production of 4-fluoro-1-(2,3,5-tri-O-acetyl—D-ribofuranosyl) benzimidazole (48a) in a yield of 65 percent.This compound was named after its tri-O-acet N (3)-isomer (49a) was successfully separated by the use of chromatography as a byproduct, and the overall yield was 8%. [22]



SCHEME 6

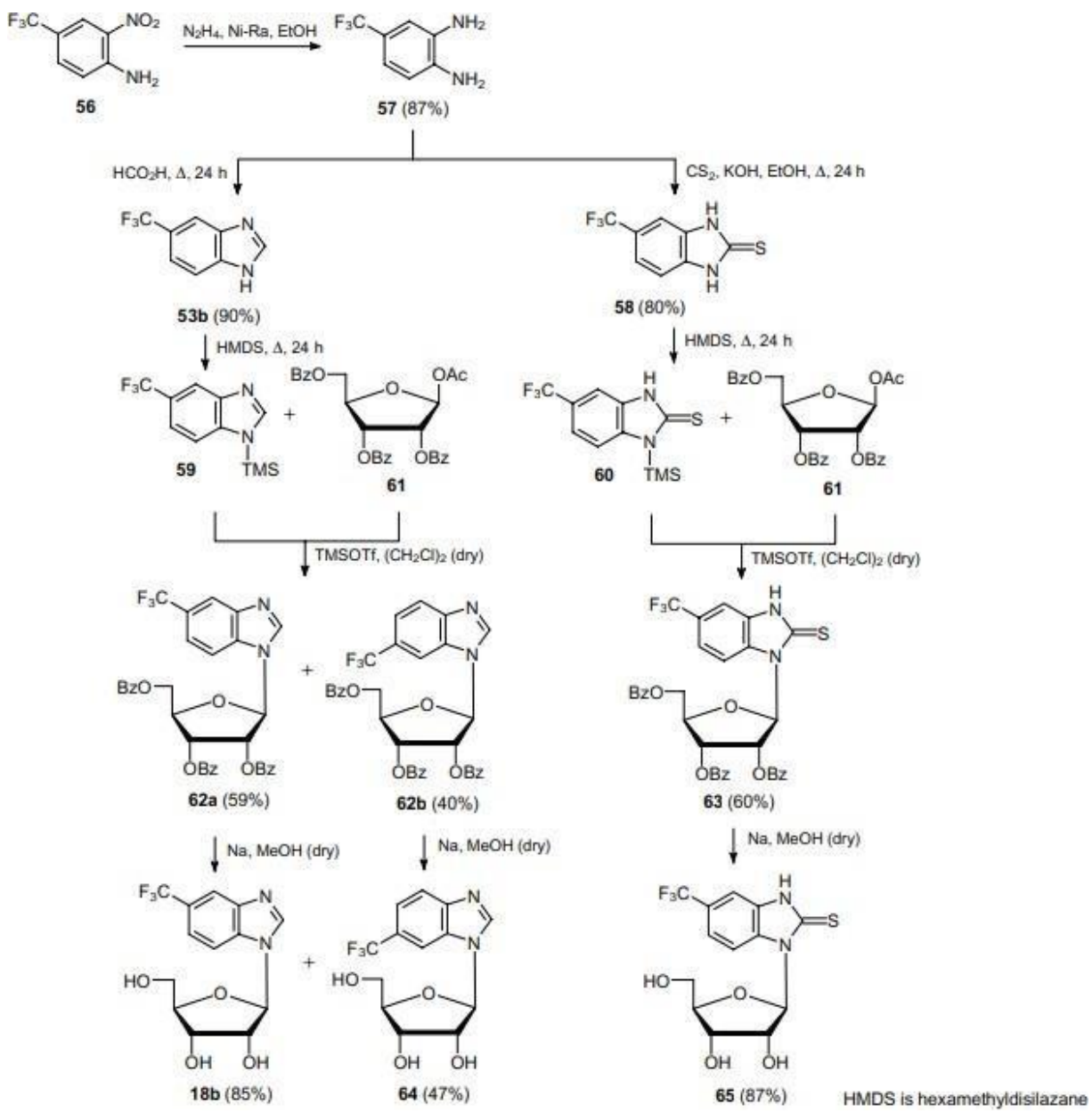
During the synthesis of 4,6-difluoro-1H-benzimidazole riboside (50b), the protected -D- ribofuranoside (48b) was obtained with a yield of 67 percent, as indicated in Scheme 6, while theN (3)-isomer (49b) was created with a yield of 11 percent. After that, methanolic ammonia was used in order to eliminate the acetyl protecting groups that were present on nucleosides 48 and 49.It was possible to effectively isolate both free nucleosides 50a and 50b, as well as their N (3)- regio-isomers 51a and 51b, which resulted in yields of 89 and 94 percent, respectively.[23]

Synthesis of the fluorinated benzimidazole ribosides 17a-c and 18a-c, respectively, was accomplished with the help of the related benzimidazoles 52a-c and 53a-c. Following treatment with sodium methoxide in methanol, the acetyl protecting groups that had been present on ribosides 54a-c and 55a-c have been successfully eliminated. (Scheme 7).[24]



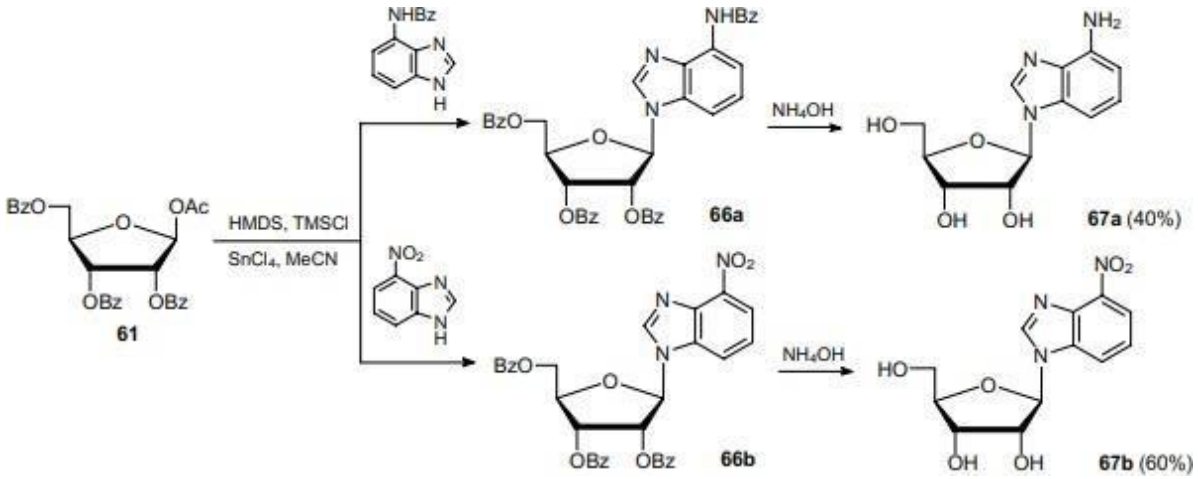
SCHEME 7

In 2016, both the riboside 5-trifluoromethylbenzimidazole (18b) and its thio equivalent were manufactured for the purpose of conducting cytotoxicity and antitumor effectiveness tests. In order to complete the synthesis of 18b, the intermediate known as 2-nitro-4-trifluoromethylaniline (56) was used. The synthesis was carried out in the manner shown in Scheme 8 by following the typical steps for the Vorbruggen glycosylation and Zemplen deprotection procedures. Benzimidazole (53b) was obtained in a reasonable yield from 4-trifluoromethylphenylene-1,2-diamine (57), which was treated with formic acid under reflux. On the other hand, 2-thioxo-5-trifluoromethyl- 1H-benzimidazole (58) was obtained in a high yield from diamine (57), which was treated with carbon disulfide under reflux. After completing the synthesis of silyl derivatives, the bases 59 and 60 were subjected to a reaction with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (ABR, 61) in the presence of TMSOTf in dry dichloroethane (61). The 62a and 62b isomers were separated from each other using column chromatography. In the end, trifluoromethyl benzimidazole nucleosides 18b and 64, in addition to their 2-thione analogue 65, were produced by deprotecting compounds 62a, 62b, and 63 with sodium methoxide in dry methanol. This allowed for the synthesis of these nucleosides [25].



SCHEME 8

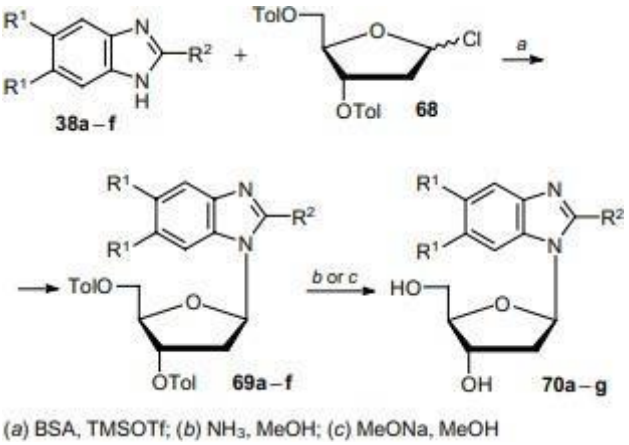
On silylated 4-(benzoylamino) benzimidazoles and 4-nitro benzimidazoles that were prepared bytreating the appropriate starting heterocyclic bases with hexamethyldisilazane (HMDS)trimethylsilyl chloride (TMSCl) mixture at room temperature using tin (IV) chloride as a catalystwithout intermediate isolation, Vorbruggen glycosylation was carried out with 1-O-acetyl-2,3,5 (Scheme 9). Ribosides containing 4-amino- (67a) and 4-nitro-benzimidazole (67b) were generatedby ammonolysis of the protecting groups of nucleosides 66a and 66b using an ammonia solution containing 25%. This process was carried out using nucleosides 66a and 66b (67b).[26]



SCHEME 9

To prepare 2-deoxyribonucleosides using substituted benzimidazoles

The majority of benzimidazole nucleosides that are synthetic are in the form of -D-ribosides. It was shown that C(2)-substituted 5,6-dichlorobenzimidazoles may be converted into 20 different -deoxy analogues of -D-ribosides. (Scheme 10) [27].

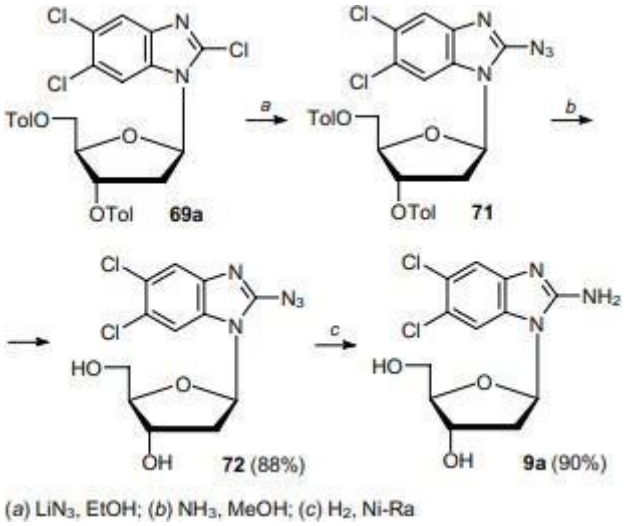


SCHEME 10

Synthesis of -anomers was accomplished by Zou et al. by the use of 2-deoxy-3,5-di-O-p-toluyl—D-erythro-pentofuranosyl chloride (68). This allowed for stereoselective glycosylation of the base2,5,6-trichlorobenzimidazole (38a). The 2,5,6-trichloro-l-(2-deoxy-3,5-di-O-p-toluyl-D-erythro-pentofuranosyl) benzimidazole (69a) was successfully synthesised in an environment free of nitrogen with a yield of 89 percent. This was accomplished in the synthesis of the compound. Following deprotection, a yield of 70a of 2,5,6-trichloro-l-(2-deoxy—D-erythro-pentofuranosyl) benzimidazole nucleoside was produced. The yield was 70%. Two more -D-2-deoxyribosides, numbers 69b-f and 70b-f, were synthesised by starting with benzimidazoles (38b-f) that had the

appropriate substituents. We were successful in producing 70 grammes of free 5,6-dichloro-1- (2-deoxy—D-erythro-pentofuranosyl)-2-methoxybenzimidazole by processing compound 69a with sodium methoxide in methanol. [28]

After treating nucleoside 69a with lithium azide and subsequently deprotecting azide 71 with methanolic ammonia, the 2-azido-5,6-dichloro-1-(2-deoxy—D-erythro- pentofuranosyl) benzimidazole (72) was produced (Scheme 11). After reducing the azido group ofnucleosides 72 with hydrogen on Raney nickel, the resulting compound, 2-Amino-5,6-dichloro-1-(2-deoxy—D-erythro-pentofuranosyl) benzimidazole (9a), could be obtained. [29]

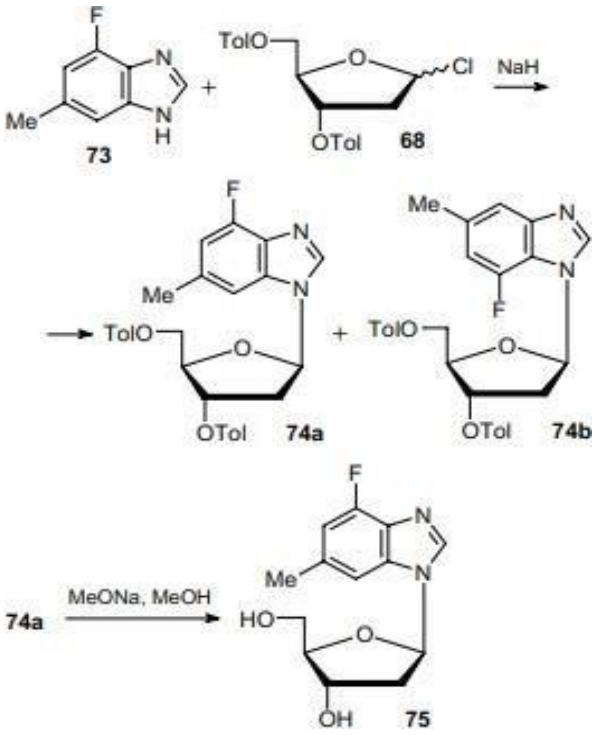


(*a*) LiN_3, EtOH; (*b*) NH_3, MeOH; (*c*) H_2, Ni-Ra

SCHEME 11

15 percent was the total yield of the synthesis of 2-fluoro-4-methylaniline to 4-fluoro-6-methyl benzimidazole (73), which included five separate steps. Following the completion of step 73's reaction with step 68's 2-deoxy-3,5-di-O-p-toluyl—D-erythro- pentofuranosyl chloride, the resulting base was neutralised using sodium hydride (Scheme 12).

Through the use of silica gel chromatography, protected nucleoside 74a was successfully isolatedfrom the mixture of isomers 74a and 74b, with a yield of 46%. After deprotecting it with sodium methoxide in methanol, the required 4-fluoro-6-methylbenzimidazole 2-deoxy riboside (75) was then purified chromatographically to achieve a yield of 65%. This process was repeated three times.[30]



SCHEME 12

SCHEME 12

The synthesis of a wide range of 2,5,6-trisubstituted and 5,6-disubstituted deoxy ribosides was made possible by the manufacture of sodium salts of the parent compounds 76a-e (Scheme 13). After the protecting groups of the nucleosides 77a-e were removed, a high yield of product 1b as well as products 78a-d were produced from the nucleosides.[31]

SCHEME 13

BIOLOGICAL SIGNIFICANCE

Antimalarial activity

Malaria mostly affects infants and young children in sub-Saharan Africa who are under the age offive. The bulk of persons who are affected with the condition are found to be children and adolescents. Malaria is responsible for more than a thousand fatalities each year and is estimated to be the cause of between 350 million and 500 million clinical episodes each year. In terms of thenumber of deaths that occur all over the globe, infectious illnesses that are caused by protozoa come in at number five. According to findings from

recent studies, over 3.3 billion people in 109 countries are at risk of catching a protozoal infection while they are sleeping. These individuals are exposed to the chance of catching the illness while they are sleeping.[32] Infections brought on by protozoa have a significant and detrimental influence on the economies of nations in which theyare common. These infections also add to the vicious cycle of poverty that many nations are caughtup in. Beginning in the 1980s, an increase in parasite and vector resistance to antimalarial medicineand pesticides, the weakening of traditional protozoal infection management programmes, rapid decentralisation and integration into deteriorating primary health services, and the development of humanitarian crisis items all contributed to an increase in mortality and morbidity from protozoalinfections in several malaria-endemic areas. In addition, these factors all contributed to an increasein the number of protozoal infections. All of these variables led to an increase in the mortality andmorbidity rates that were caused by protozoal infections.[33] An increase in both mortality and morbidity was caused by the combination of all of these causes. Because of this exponential rise,
there is a compelling and urgent need for the development of new therapy targets, as well as novelprotozoal diseases, with mechanisms of action that are distinct from those that are now characterised.[34] Recent research has indicated that the antiparasitic medication chloroquine may be able to prevent the production of hemozoin inside the feeding cavity of the parasite. It is predicted that a significant number of quinoline anti-malarial medicines would target the same chemical mechanism.[35] Hemozoin is a crystalline form of ferriprotoporphyrin IX that exhibits cyclic variable resistance. It was formerly believed that hemozoin was created as a consequence of a chemical transition of hematin; however, this theory is no longer regarded to be correct. Instead, it is now believed that hemozoin was generated independently. It is a plausible and substantial prospective target for the development of novel anti-malarial drugs since the creation of hemozoin is a process that can only be carried out by sporozoans. This makes it an unique traitof sporozoans. It would be tremendously exciting to witness the development of new medicines that hit the same key target as antimalarial medications but are not defeated by the same resistancemechanism. [36]

5.1. Antifungal activity

Over the course of the last several decades, diseases that cannot be cured have developed into moremajor threats to the health of humans. In parallel with this development, a general decrease in sensitivity to antimicrobial drugs that are currently in use has been seen. Gram-positive bacteria and some tenacious parasites are examples of the kinds of microorganisms that are becoming moreresistant to the therapies that are available. This misperception has led to a significant misinterpretation of their role as inhibitors in the biosphere, which has resulted in their function being abused.[37] Fluconazole is the medicine of choice for the treatment of disorders caused by Candida albicans and Cryptococcus neoformans because of its potent activity, excellent safety profile, and favourable pharmacokinetic properties. Because of this, the World Health Organization considers it to be the anti-parasitic medicine of first-line treatment in the triazole class (WHO). This is due to the fact that fluconazole has an advantageous pharmacokinetic profile,which enables it to be effective. In particular, it is vital to emphasise the relevance of the fact thatfluconazole has built up a great track record as a choice for treating Candida. This is because fluconazole has been shown to be effective in treating Candida. It is not a drug that kills fungus and hence cannot be used to treat obtrusive aspergillosis effectively.[38] In addition, the extensive use of fluconazole in therapeutic settings has resulted in the identification of an increasing number of hitherto unknown spiro[indole-thiazolidinones]. These spiro[indole-thiazolidinones] are safe touse in combination with fluconazole, and their anti-infectious action against Rhizoctonia solani, Fusarium oxysporum, and Collectotrichum has been evaluated in vitro.[39]

5.2. Antiviral activity

According to some estimates, more than one-third of the people living in this planet have a persistent infection with the hepatitis C virus (HCV). Due to this fact, HCV is a substantial risk factor that may lead to the development of liver disease as well as cancer. The limitations of contemporary medical expertise include the need that patients get treatment for an average of 48 weeks, with only a five hundredth persistent medication response rate. This is because there is nopreventative vaccination now available. A significant new development in the field is the recoveryof genomic hepatitis C virus (HCV) ribonucleic acid (JFH1) from a patient with acute liver illness, followed by the transfection of human malignant hepatoma cells with this material. This representsan important step forward in the field. Due to the versatility of this model that is based on cell culture, researchers have the opportunity to analyse HCV at any stage of its life cycle.[40] In a varietyof investigations in which various viruses served as test subjects, it was shown that certain benzimidazole derivatives have antiviral capabilities. These qualities were demonstrated by the derivatives' ability to inhibit the growth of the viruses. These viruses include the human immunodeficiency virus (HIV), which is also known as the human herpes virus (HCMV), as wellas the hepatitis C virus. The molecule known as bis(5-amidino-2-benzimidazolyl) paraffin (BABIM) is an example of an amidino-substituted benzimidazole that has been shown to impede cell fusion in response to the metastatic syncytial virus. This was discovered via research that wasconducted (RS). Additionally, it has been shown that the addition of an amidino moiety to the benzimidazole ring provides a highly powerful antibacterial and anti-protozoal activity. This wasdiscovered by incorporating an amidino moiety into the benzimidazole ring.[41]

5.3. Antiproliferative activity

Two-aminobenzimidazole and modified aromatic aldehydes have the potential to be employed inthe creation of new Schiff bases, according to various sources. The reduction of the compounds by using NaBH4 led to the synthesis of 2-benzylaminobenzimidazoles as an intermediate product.When acylated with cinnamoyl chloride, these 2-benzyl aminobenzimidazoles produced 2-(o- bromobenzylamino)-1-cinnamoylbenzimidazole. This substance is a molecule that has been associated to the development of autoimmune disorders. The compounds were examined in vitro,and the results showed that they have anti-proliferative characteristics.[42]

5.4. Antitumor activity

There is some evidence to support the concept that a number of the newly found nitro benzimidazoles have cytotoxic qualities that may battle cancer. These nitro benzimidazoles were discovered recently. The research that has been believed to have been conducted suggests that theaction may also be displayed by chemicals such as thiadiazol, tetrazole, triazines, and imidazole.[43]

5.5. Anti-inflammatory activity

By adhering to this method, the scientists were able to successfully produce and identify a large variety of 2-methyl aminobenzimidazole derivatives. By watching the writhing of mice and the paw oedema of rats that had been generated by carrageenan, tests were conducted on the newly synthesised compounds to evaluate whether or not they had analgesic and anti-inflammatory characteristics. The results of these tests were seen. It is believed that when benzimidazole and iodole skeleton are used together, their anti-inflammatory effects are comparable to those of indomethacin.[44]

5.6. Antioxidant activity

It has been shown that many different compounds containing dihydrochlorides exhibit both antioxidant activity and a slight antiaggregant effect for platelets and erythrocytes. It has also beennoted that the

combination of a benzimidazole with a trimethyl group may have an antioxidative effect by reducing the activity of 5-lipoxygenase. This discovery was made after it was discoveredthat this combination may have an antioxidative benefit.[45]

5.7. Antiprotozoal activity

In addition to derivatives of benzimidazole that have thioalkyl or thioaryl replacements, there are other derivatives of this compound that contain 5,6-dinitro substitutions. These dynamic compounds are known for their effectiveness against Stenotrophomonas malthophilia due to theirantimicrobial properties. The antibacterial activities of these compounds are comparable to those of metronidazole, and they are effective against both gram-positive and gram-negative bacteria.[46]There have apparently been reports of the discovery of a number of distinct 2- trifluorobenzimidazoles that have a broad range of substitutions. It has been shown by researchers to be effective in the prevention of giardiasis. In another line of inquiry, a series of 2- (trifluoromethyl)-1H-benzimidazole derivatives are produced by cyclo-condensing a modified 1,2-phenylenediamine with trifluoroacetic acid. The Philips cyclocondensation reaction is the name given to this particular process. In vitro testing revealed that a few of the compounds had a nanomolar effect against the protozoan parasites that had been discussed before. These parasites included Giardia intestinalis, Entamoeba histolytica, Trichomenas vaginalis, and Leishmania mexicana. Tests were conducted in both vitro and in vivo to see whether or not the chemicals wereeffective in battling the Trichinella spiralis worm. The results of these experiments are shown below.[47]

5.8. Androgen Receptor antagonist

There are also other compounds that are based on benzimidazole, such as those that are based on 5,6-dichloride. It has come to light that the addition of the trifluoromethyl group significantly boosted the prostrate antagonistic action. When treating androgen-dependent prostate cancer, the nonsteroidal antiandrogen bicalutamide is often recommended as an effective therapeutic option.[48]

5.9. Anti-cancer activity

Researchers were able to successfully synthesis 1,3-dialkylpyrazinobenzimidazole derivatives, and they then studied these chemicals to see whether or not they had any possible anticancer qualities. In order to accomplish this goal, 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles were generated by the reaction of 2-aryloylbenzimidazole derivatives with 2-bromoacetophenones in acetone. After mixing a byproduct with ammonium acetate in acetic acid, the resulting combination was then subjected to a reaction in order to make the chemical. The operation that was mentioned earlier was completed by means of irradiation with microwaves, which was definedas the way that was employed to carry out the operation.[49] An other method that has been disclosed involves the production of derivatives of 1-(4-methoxy phenethyl)-1H-benzimidazole-5- carboxylic acid and the subsequent assessment of these molecules. Treatment of leukemic cells with methyl 1-(4-methoxyphenethyl)-2-(4-fluoro-3-nitrophenyl)-1H-benzimidazole-5-carboxylate, which had an IC50 value of 3 microM, resulted in the greatest amount of cell death possible.[50]

5.10. Anti-convulsant Agents

In the early stages of the study and development of anticonvulsant medications, a variety of 1,2,5-trisubstituted benzimidazoles derivatives were among the substances used. [51] According to the findings of the QSAR analysis and the findings of the examination of a large number of physicochemical parameters, the optimal chain length at position two is the factor responsible forthe anticonvulsant action (R2). Quantitative structure-activity connection tests indicated that compounds that were developed with an electron-withdrawing group like nitro at position five hada greater anti-convulsant impact than other compounds (R3).[52]

CONCLUSION

Because it has been shown that benzimidazoles exhibit antibacterial, antiviral, anti-inflammatory,and anticancer properties, researchers have arrived at the conclusion that this family of heterocyclicchemicals has a significant amount of untapped potential. This page provides a synopsis of the chemical and biological characteristics shared by a number of different substituted benzimidazolederivatives. These characteristics have been analysed in light of their connections to one another. Medical professionals make use of a huge number of chemicals that are derived from benzimidazole in order to treat a wide range of illnesses. These molecules are called "benzimidazole derivatives." In spite of the extensive and concentrated research that has been carried out on a wide variety of chemicals that have the potential to act as anti-inflammatory agents,immunomodulators, lipid modulators, and other such things, not a single one of these molecules has yet made it to the market or the clinic. This may be the result of the absence of a single site that houses all of the research that has been carried out on a certain activity and that has the potential to shed light on the SAR of the compounds. Drug designers and medicinal chemists whoare looking for information that is both comprehensive and target-oriented for the purpose of producing compounds that are therapeutically viable have the opportunity to find what they are looking for thanks to this examination of a large number of sources, which provides them with theopportunity to find what they are looking for. This allows them to produce compounds that are therapeutically viable.

REFERENCES

1. Akhtar W, Khan MF, Verma G, Shaquiquzzaman M, Rizvi MA, Mehdi SH, Akhter M,Alam MM. Therapeutic evolution of benzimidazole derivatives in the last quinquennial period. European journal of medicinal chemistry. 2017 Jan 27;126:705-53.
2. Alzhrani ZM, Alam MM, Nazreen S. Recent advancements on benzimidazole: A versatilescaffold in medicinal chemistry. Mini Reviews in Medicinal Chemistry. 2022 Feb 1;22(2):365-86.
3. Singh A, Agarwal A, Chakraborty A, Bhardwaj R, Sutradhar S, Mittal AK, Rajput SK, Gupta M, Ray D, Mukherjee M. Click chemistry tailored benzimidazole functionalized triazole block-co-polymer for emergence of exotic chimaeric nano-crystalsomes.EuropeanPolymer Journal. 2022 Sep 5;178:111503.
4. Manna SK, Das T, Samanta S. Polycyclic benzimidazole: Synthesis and photophysical properties. ChemistrySelect. 2019 Aug 14;4(30):8781-90.
5. Ralkhal S, Shahrabi T, Ramezanzadeh B, Bahlakeh G. A combined electrochemical, molecular dynamics, quantum mechanics and XPS analysis of the mild steel surface protected by a complex film composed of neodymium (III) and benzimidazole. Applied Surface Science. 2019 Jan 15;464:178-94.
6. Keri RS, Hiremathad A, Budagumpi S, Nagaraja BM. Comprehensive review in current developments of benzimidazole-based medicinal chemistry. Chemical biology & drug design. 2015 Jul;86(1):19-65.
7. Abdulazeez I, Khaled M, Al-Saadi AA. Impact of electron-withdrawing and electron- donating substituents on the corrosion inhibitive properties of benzimidazole derivatives: a quantum chemical study. Journal of Molecular Structure. 2019 Nov 15;1196:348-55.
8. Vasava MS, Bhoi MN, Rathwa SK, Jethava DJ, Acharya PT, Patel DB, Patel HD. Benzimidazole: A milestone in the field of medicinal chemistry. Mini Reviews in Medicinal Chemistry. 2020 Apr 1;20(7):532-65.
9. Basuri P, Gonzalez LE, Morato NM, Pradeep T, Cooks RG. Accelerated microdroplet synthesis of benzimidazoles by nucleophilic addition to protonated carboxylic acids. Chemical science.

2020;11(47):12686-94.
10. Marinescu M, Cinteză LO, Marton GI, Chifiriuc MC, Popa M, Stănculescu I, Zălaru CM,Stavarache CE. Synthesis, density functional theory study and in vitro antimicrobial evaluation of new benzimidazole Mannich bases. BMC chemistry. 2020 Dec;14(1):1-6.
11. Asemanipoor N, Mohammadi-Khanaposhtani M, Moradi S, Vahidi M, Asadi M, Faramarzi MA, Mahdavi M, Biglar M, Larijani B, Hamedifar H, Hajimiri MH. Synthesis and biological evaluation of new benzimidazole-1, 2, 3-triazole hybrids as potential α- glucosidase inhibitors. Bioorganic chemistry. 2020 Jan 1;95:103482.
12. 12. Kharitonova MI, Konstantinova ID, Miroshnikov AI. Benzimidazole nucleosides: antiviral and antitumour activities and methods of synthesis. Russian Chemical Reviews. 2018 Nov 1;87(11):1111.
13. Ujvary I, Christie R, Evans-Brown M, Gallegos A, Jorge R, de Morais J, Sedefov R. DARKclassics in chemical neuroscience: etonitazene and related benzimidazoles. ACS ChemicalNeuroscience. 2021 Mar 24;12(7):1072-92.
14. Matyugina ES, Kochetkov SN, Khandazhinskaya AL. Synthesis and biological activity ofaza and deaza analogues of purine nucleosides. Russian Chemical Reviews. 2021 Nov 1;90(11):1454.
15. Maiuolo L, De Nino A. Synthesis of isoxazolidines by 1, 3-dipolar cycloaddition: recent advances. Targets Heterocycl. Syst. 2015;19:299-345.
16. Townsend LB, Gudmundsson KS, Daluge SM, Chen JJ, Zhu Z, Koszalka GW, Boyd L, Chamberlain SD, Freeman GA, Biron KK, Drach JC. Studies designed to increase the stability and antiviral activity (HCMV) of the active benzimidazole nucleoside, TCRB. Nucleosides, Nucleotides & Nucleic Acids. 1999 Apr 1;18(4-5):509-19.
17. Kharitonova MI, Fateev IV, Kayushin AL, Konstantinova ID, Kotovskaya SK, Andronova VL, Galegov GA, Charushin VN, Miroshnikov AI. Chemoenzymatic Synthesis and Antiherpes Activity of 5-Substituted 4, 6-Difluorobenzimidazoles Ribo- and 2′- Deoxyribonucleosides. Synthesis. 2016 Feb;48(03):394-406.
18. Townsend LB, Devivar RV, Turk SR, Nassiri MR, Drach JC. Design, synthesis, and antiviral activity of certain 2, 5, 6-Trihalo-1-(. beta.-D-ribofuranosyl) benzimidazoles. Journal of medicinal chemistry. 1995 Sep;38(20):4098-105.
19. Devivar RV. Design and synthesis of 2-substituted analogs of 2, 5, 6-trichloro-1-(beta-D-ribofuranosyl) benzimidazole and related imidazo (4, 5-b) pyridine nucleosides as potentialantiviral agents for the treatment of human cytomegalovirus infections. University of Michigan; 1992.
20. Yang XH, Ouyang XH, Wei WT, Song RJ, Li JH. Nitrative Spirocyclization Mediated byTEMPO: Synthesis of Nitrated Spirocycles from N-Arylpropiolamides, tert-Butyl Nitrite and Water. Advanced Synthesis & Catalysis. 2015 Apr 13;357(6):1161-6.
21. Sengupta S, Das P. Application of diazonium chemistry in purine modifications: Afocusedreview. Journal of Heterocyclic Chemistry. 2022 Jan;59(1):5-21.
22. Matyugina ES, Kochetkov SN, Khandazhinskaya AL. Synthesis and biological activity ofaza and deaza analogues of purine nucleosides. Russian Chemical Reviews. 2021 Nov 1;90(11):1454.
23. Kumar R, Kumar V, Mathur D, Kumar R, Kumar A, Prasad AK. Biocatalyst CAL-B catalyzed synthesis of modified nucleosides: An overview. Synthetic Communications. 2019 Jul 3;49(13):1659-78.
24. Konstantinova ID, Selezneva OM, Fateev IV, Balashova TA, Kotovskaya SK, Baskakova ZM, Charushin VN, Baranovsky AV, Miroshnikov AI, Balzarini J, Mikhailopulo IA. Chemo-enzymatic

synthesis and biological evaluation of 5, 6-disubstituted benzimidazole ribo-and 2′-deoxyribonucleosides. Synthesis. 2013 Jan;45(02):272-80.
25. Kharitonova MI, Fateev IV, Kayushin AL, Konstantinova ID, Kotovskaya SK, Andronova VL, Galegov GA, Charushin VN, Miroshnikov AI. Chemoenzymatic Synthesis and Antiherpes Activity of 5-Substituted 4, 6-Difluorobenzimidazoles Ribo- and 2′- Deoxyribonucleosides. Synthesis. 2016 Feb;48(03):394-406.
26. Matyugina ES, Kochetkov SN, Khandazhinskaya AL. Synthesis and biological activity ofaza and deaza analogues of purine nucleosides. Russian Chemical Reviews. 2021 Nov 1;90(11):1454.
27. Shelkar R, Sarode S, Nagarkar J. Nano ceria catalyzed synthesis of substituted benzimidazole, benzothiazole, and benzoxazole in aqueous media. Tetrahedron Letters. 2013 Dec 18;54(51):6986-90.
28. Amer HH, Ali OM, El-Kafaween IK. Synthesis of some new nucleosides derived from 2-mercapto benzimidazole with expected biological activity. Orient. J. Chem. 2017 Oct 1;33:2303-10.
29. Break LM. Synthesis of Some of Fluorinated Benzimidazole Nucleosides. International Journal of Chemistry. 2016;8(1):188.
30. Wojtowicz-Rajchel H. Synthesis and applications of fluorinated nucleoside analogues. Journal of Fluorine Chemistry. 2012 Nov 1;143:11-48.
31. Hernández D, Boto A. Nucleoside analogues: synthesis and biological properties of azanucleoside derivatives. European Journal of Organic Chemistry. 2014 Apr;2014(11):2201-20.
32. Emadi A. Schiff Benzimidazole Derivatives: Synthesis, Properties and Antimicrobial Activity. Intl. J. Farm. Alli. Sci. 2020;9:72-82.
33. Chugh A, Kumar A, Verma A, Kumar S, Kumar P. A review of antimalarial activity of two or three nitrogen atoms containing heterocyclic compounds. Medicinal Chemistry Research. 2020 Oct;29(10):1723-50.
34. de Sousa AC, Combrinck JM, Maepa K, Egan TJ. Virtual screening as a tool to discover new β-haematin inhibitors with activity against malaria parasites. Scientific Reports. 2020Feb 25;10(1):1-0.
35. Baartzes N, Jordaan A, Warner DF, Combrinck J, Taylor D, Chibale K, Smith GS. Antimicrobial evaluation of neutral and cationic iridium (III) and rhodium (III) aminoquinoline-benzimidazole hybrid complexes. European Journal of Medicinal Chemistry. 2020 Nov 15;206:112694.
36. Mueller R, Reddy V, Nchinda AT, Mebrahtu F, Taylor D, Lawrence N, Tanner L, Barnabe M, Eyermann CJ, Zou B, Kondreddi RR. Lerisetron Analogues with Antimalarial Properties: Synthesis, Structure–Activity Relationship Studies, and Biological Assessment. ACS omega. 2020 Mar 17;5(12):6967-82.
37. Chung YC, Lee DH, Choi JW, Chun BC. Application of recycled polyol and benzimidazole to the enhancement of antifungal activity of polyurethane. Journal of Applied Polymer Science. 2018 Aug 20;135(32):46600.
38. Savanur HM, Pawashe GM, Kim KM, Kalkhambkar RG. Synthesis and Molecular Modeling Studies of Coumarin-and 1-Aza-Coumarin-Linked Miconazole Analogues and Their Antifungal Activity. ChemistrySelect. 2018 Sep 7;3(33):9648-53.
39. Desai NC, Pandya D, Vaja D. Synthesis and antimicrobial activity of some heterocyclic compounds bearing benzimidazole and pyrazoline motifs. Medicinal Chemistry Research.2018 Jan;27(1):52-60.
40. Shen YF, Liu L, Feng CZ, Hu Y, Chen C, Wang GX, Zhu B. Synthesis and antiviral activityof a new coumarin derivative against spring viraemia of carp virus. Fish & Shellfish Immunology. 2018 Oct

1;81:57-66.
41. Chernyshov VV, Yarovaya OI, Fadeev DS, Gatilov YV, Esaulkova YL, Muryleva AS, Sinegubova KO, Zarubaev VV, Salakhutdinov NF. Single-stage synthesis of heterocyclicalkaloid-like compounds from (+)-camphoric acid and their antiviral activity. Molecular diversity. 2020 Feb;24(1):61-7.
42. Eldehna WM, El Hassab MA, Abo-Ashour MF, Al-Warhi T, Elaasser MM, Safwat NA, Suliman H, Ahmed MF, Al-Rashood ST, Abdel-Aziz HA, El-Haggar R. Development of isatin-thiazolo [3, 2-a] benzimidazole hybrids as novel CDK2 inhibitors with potent in vitro apoptotic anti-proliferative activity: Synthesis, biological and molecular dynamics investigations. Bioorganic Chemistry. 2021 May 1;110:104748.
43. Koronkiewicz M, Kazimierczuk Z, Orzeszko A. Antitumor activity of the protein kinase inhibitor 1-(β-D-2′-deoxyribofuranosyl)-4, 5, 6, 7-tetrabromo-1H-benzimidazole in breastcancer cell lines. BMC cancer. 2022 Dec;22(1):1-2.
44. Rathore A, Sudhakar R, Ahsan MJ, Ali A, Subbarao N, Jadav SS, Umar S, Yar MS. In vivo anti-inflammatory activity and docking study of newly synthesized benzimidazole derivatives bearing oxadiazole and morpholine rings. Bioorganic chemistry. 2017 Feb 1;70:107-17.
45. Abdelgawad MA, Bakr RB, Ahmad W, Al-Sanea MM, Elshemy HA. New pyrimidine-benzoxazole/benzimidazole hybrids: Synthesis, antioxidant, cytotoxic activity, in vitro cyclooxygenase and phospholipase A2-V inhibition. Bioorganic chemistry. 2019 Nov 1;92:103218.
46. Patel VM, Patel NB, Chan-Bacab MJ, Rivera G. N-Mannich bases of benzimidazole as a potent antitubercular and antiprotozoal agents: Their synthesis and computational studies. Synthetic Communications. 2020 Mar 18;50(6):858-78.
47. Rocha-Garduño G, Hernández-Martínez NA, Colín-Lozano B, Estrada-Soto S, Hernández-Núñez E, Prieto-Martínez FD, Medina-Franco JL, Chale-Dzul JB, Moo-PucR, Navarrete- Vázquez G. Metronidazole and secnidazole carbamates: synthesis, antiprotozoal activity, and molecular dynamics studies. Molecules. 2020 Feb 12;25(4):793.
48. Latysheva AS, Zolottsev VA, Veselovsky AV, Scherbakov KA, Morozevich GE, Pokrovsky VS, Novikov RA, Timofeev VP, Tkachev YV, Misharin AY. New steroidal oxazolines, benzoxazoles and benzimidazoles related to abiraterone and galeterone. Steroids. 2020 Jan 1;153:108534.
49. Hosseinzadeh Z, Ramazani A, Razzaghi-Asl N. Anti-cancer nitrogen-containing heterocyclic compounds. Current Organic Chemistry. 2018 Oct 1;22(23):2256-79.
50. McGivern TJ, Afsharpour S, Marmion CJ. Copper complexes as artificial DNA metallonucleases: from Sigman's reagent to next generation anti-cancer agent?.Inorganica Chimica Acta. 2018 Mar 1;472:12-39.
51. Sahoo BM, Banik BK, Rao NS, Raju B. Microwave assisted green synthesis of benzimidazole derivatives and evaluation of their anticonvulsant activity. Current Microwave Chemistry. 2019 Jan 1;6(1):23-9.
52. Faraji L, Shahkarami S, Nadri H, Moradi A, Saeedi M, Foroumadi A, Ramazani A, Haririan I, Ganjali MR, Shafiee A, Khoobi M. Synthesis of novel benzimidazole and benzothiazole derivatives bearing a 1, 2, 3-triazole ring system and their acetylcholinesterase inhibitory activity. Journal of Chemical Research. 2017Jan;41(1):30-5.