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Research Paper

A Systemic Review on Benzimidazole Study

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ABSTRACT
One of the possible classifications for the chemical molecule known as benzimidazole has heterocyclic aromatic as its subcategory. The scientific field of medicinal chemistry accords this structure a prominent pharmacophore position and grants it special status. It plays a very significant function since it has a wide variety of positive therapeutic effects, including those of antiulcerants, antihypertensives, analgesics, medications, antivirals, antifungals, anticancer, and antihistamines. This is because it serves a very significant 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 of these 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*

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I. INTRODUCTION

The vast range of biological activities, medicinal uses, potent restricting action, and excellent property magnitude relation make benzimidazole derivatives extremely significant substances. Derivatives of the benzimidazole ring also exhibit excellent property magnitude relationships[1]. It was determined to create and construct a variety of unique benzimidazole derivatives, each of which would consist of an oxadiazole moiety, in light of the relevance of benzimidazole. The potential biological activity of these substances would next be examined in order to ascertain whether or not it existed. The benzimidazole ring is a crucial component of the heterocyclic pharmacophore in the study of medicines[2]. A wide range of pharmacological activities, including antibacterial, anticancer, antiviral, antioxidant, antifungal, helminthicidal, histamine-blocking, anticoagulant, and antihypertensive effects, have been associated with compounds with various substituents in the benzimidazole structure. The chemicals are blamed for these outcomes. The benzimidazole ring is currently acknowledged as a significant pharmacophore in the context of contemporary medication research. The creation of novel benzimidazole derivatives is still recognised as a crucial area of concentration for academic study in the field of health.[3]

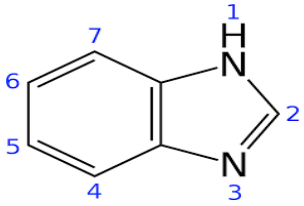


Fig. 1: Structure of BenzimidazolesCHARACTERISTICS OF BENZIMIDAZOLES

According to the melting points of many benzimidazoles, it appears that altering the 1-position almost always causes a lower melting point.[4] In comparison to organic solvents, polar solvents are better able to dissolve benzimidazoles that contain imide nitrogen. If additional non-polar substituents are introduced at various other

locations on the benzimidazole ring, the solubility of the molecule may be enhanced in non-polar liquids. In contrast, the molecule becomes more soluble in polar liquids when it contains polar groups. Both aqueous and aqueous solutions can exhibit this effect. In general, benzimidazoles are soluble in mild acids and have a moderate basicity, which means that they aresomewhat less basic than imidazole. This is because benzimidazoles have a benzene ring structureinstead of an imidazole ring structure.

This is because one type of derivative formed from imidazole is benzimidazoles. Despite their tendency to form N-metallic compounds when dissolved in water due to their high level of acidity, benzimidazoles are typically soluble in alkaline solutions. The acidic properties of benzimidazoles appear to be caused via resonance-based ion stabilisation, as was the case with imidazole. A less basic solution, such as one containing potassium carbonate, may be able to dissolve the more acidic benzimidazoles. The reason for this is that such a solution may contain potassium carbonate.[5]

BENZIMIDAZOLE'S CHEMICAL CHARACTERISTICS

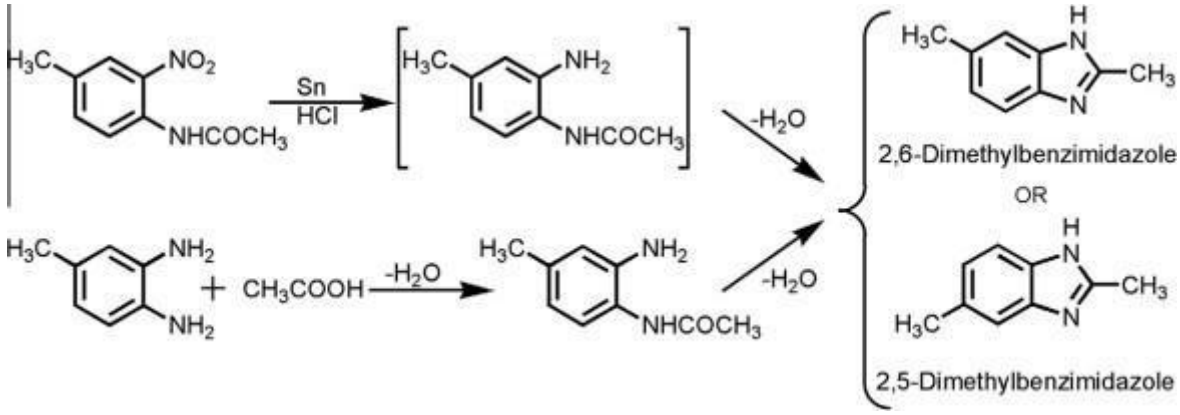
Reactions of the benzimidazole ring:

High stability is one of the distinguishing features of the benzimidazole ring. No matter if the benzo(a)imidazole is exposed to alkalis, warm hydrochloric acid, or corrosive sulfuric acid, its properties remain unchanged.[6] The benzene ring of benzimidazole may be broken by oxidation, but only under very particular circumstances. Under specific conditions, the benzimidazole ring can survive a reduction in structure.[7]

CHEMISTRY

Due to the wide range of bioactivities displayed by benzimidazoles and their derivatives, initiatives to construct libraries of these molecules have occasionally been made. To produce goods with the quantity, purity, and quality that the consumer has specified, numerous different synthetic methods have been created and improved. Hoebrecker produced the first benzimidazole in 1872 by reducing 2-nitro-4-methyl acetanilide, which was either 2,5-dimethylbenzimidazole or 2,6-dimethylbenzimidazole. 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 ofbenzimidazole (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 chemicals have been referred to as these derivatives. O-phenyl urea and o-phenylene thiourea were two old names for 2(3H)-benzimidazoles (3) and benzimidazole-2 (3H) -thione, though o-phenyl urea was the more common name. There is no longer a need for o-phenylene thiourea (4). The hydrogen that is bonded to the N-1 atom in the compounds that are created as a result of this rapid tautomerization undergoes isomerization.10 It is customary to give not one but two sets of numbers to indicate the location of the substituent group(s) when discussing tautomeric compounds, with the second set of numbers enclosed in brackets to distinguish it from the first set. 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

Derivative and synthesis of benzimidazoles

It took until the middle of the 20th century for the first benzimidazole nucleosides to be chemically synthesised. However, developments in genetic engineering techniques for creating nucleic metabolism-related enzymes have only been possible in the last 20 years.

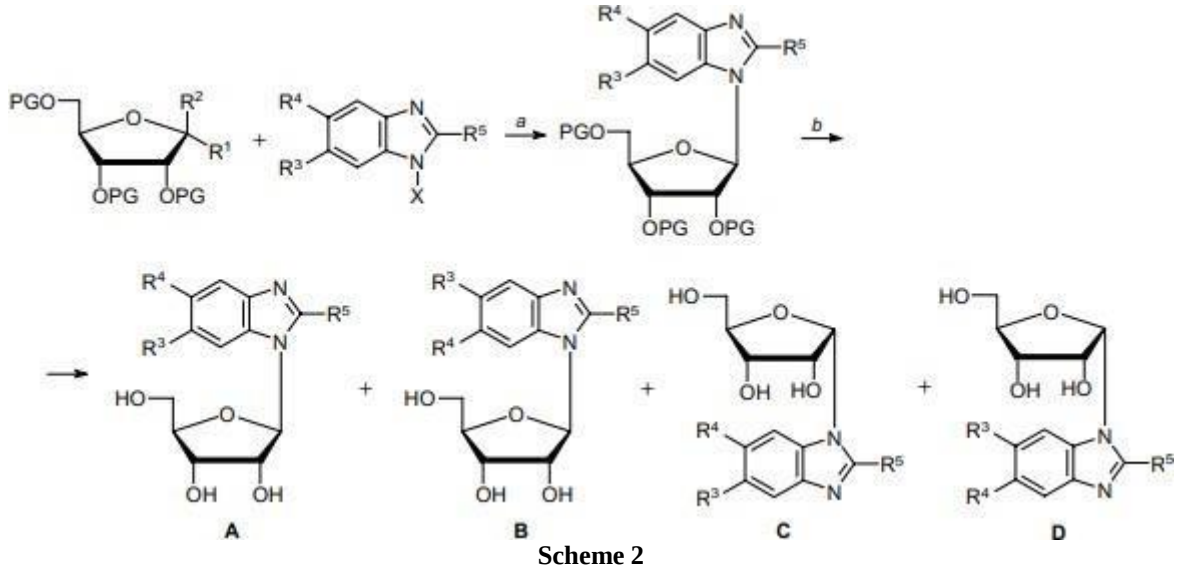
current investigation into chemo-enzymatic methods for producing these chemicals. Only the development of gene editing technologies has made these developments feasible. These discoveries were made possible by the application of genetic engineering in the synthesis of nucleic metabolism enzymes, which led directly to these breakthroughs.

Benzimidazole nucleosides can be made by two separate chemical processes. The tried-and-true Vorbruggen reaction, which entails the condensation of benzimidazole with a protected carbohydrate residue, is one of the potential strategies. It is common to produce a mixture of nucleosides (- and -epimers) in a variety of ratios when the protecting groups at the conclusion of this synthesis are removed. The varying ratios make purification challenging. It is possible to synthesise a specific regio- and/or stereoisomer using this method by altering a number of variables, including silyl protection, selective catalysts, solvents, and temperature settings. To create the desired isomer, this could be done.[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]

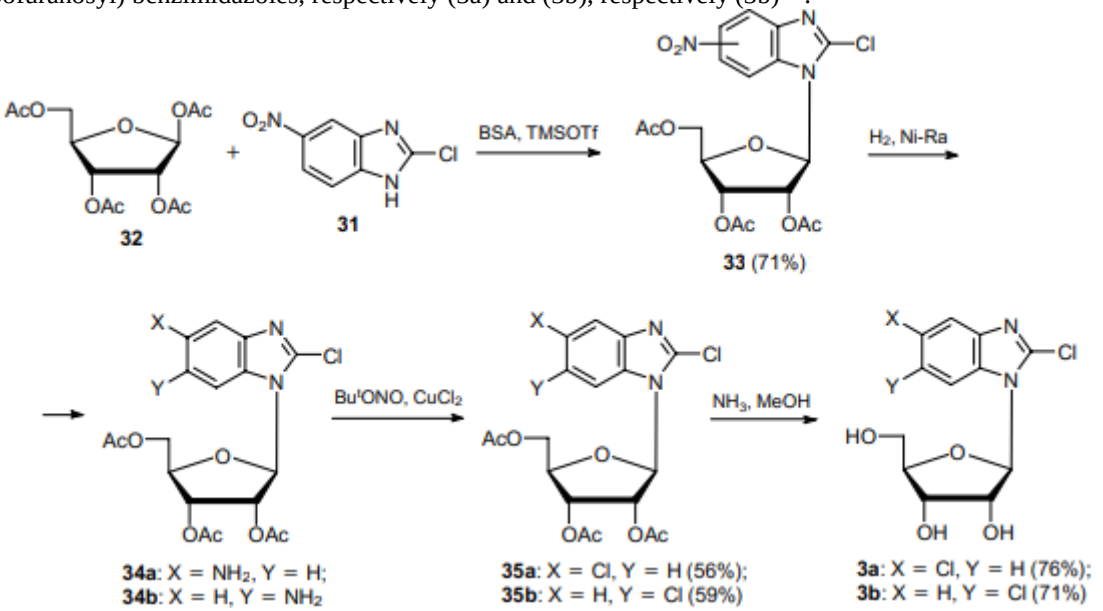
Synthesis of benzimidazole -D-ribosides via glycosylation- mediated

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

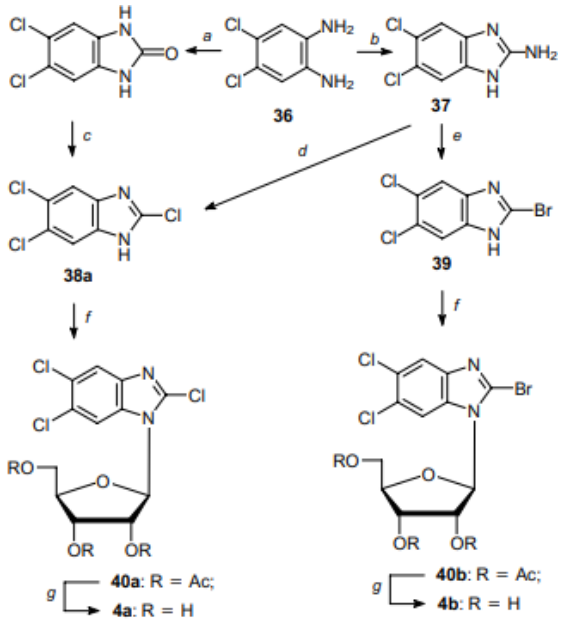
This approach is helpful for the synthesis of nucleosides that have the identical substituents at positions R3 and R4 on the benzimidazole ring. Glycosylation results in a mixture of N(1)- and N(3)- Regio isomers being produced if the substituents that are used are different, which makes ita difficult 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 removal of 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

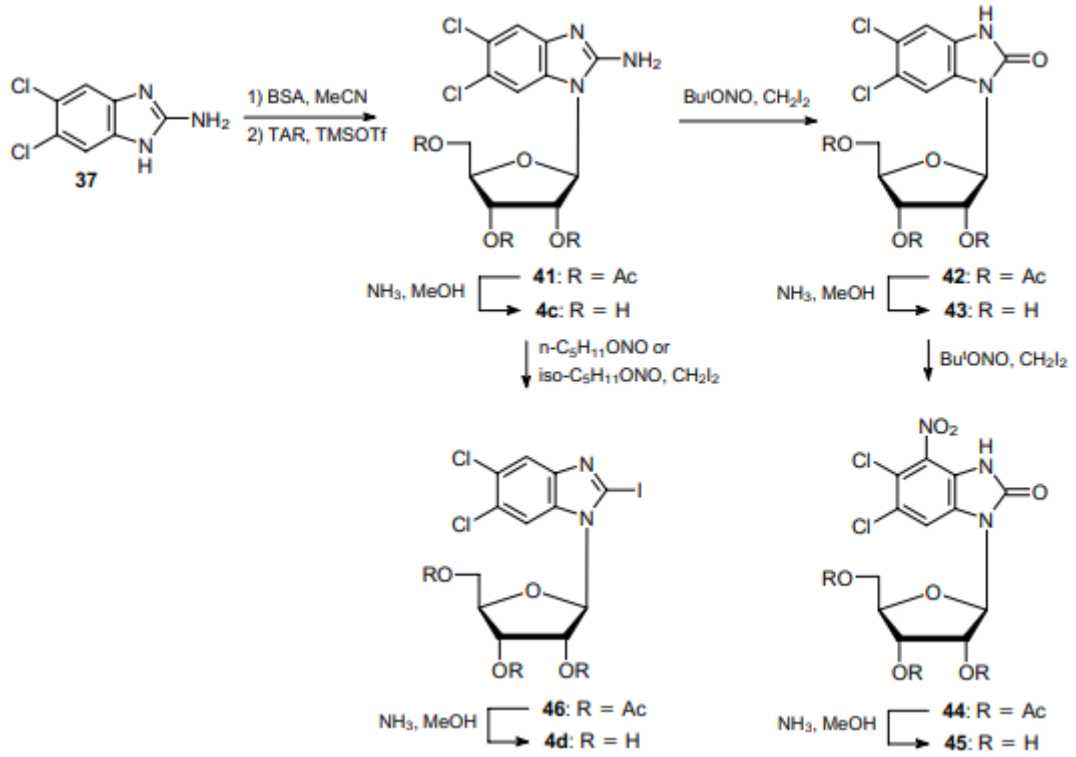
information on the procedure (4b). After the ring closure of commercially available 4,5-dichloro-1,2-phenylenediamine (36) with cyanogen bromide, the 2,5,6- trichlorobenzimidazole (38a) was created by the diazotization of an amino derivative. This was done in order to synthesise the compound (37). This cyclization method of 4,5-dichloro-1,2- phenylenediamine (36) with cyanogen bromide in methanol may be used to produce a wide variety of 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]



SCHEME 4

The second step of the synthesis of the required ribofuranoside involved silylating 2,5,6-trichlorobenzimidazole (38a) with N,O-bis(trimethylsilyl)acetamide (BSA). Following this step, TAR (32) was ribosylated in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf). This method led to the synthesis of 2,5,6-trichloro-1-(2,3,5-tri-O-acetyl—D-ribofuranosyl) benzimidazole (40a) and a minute amount of the -anomer. After treating the target TCRB (4a) with ammonia in methanol to remove the acetyl group, an extraction yield of 74% was achieved. The identical method as before (Scheme 4) was used for the synthesis of BDCRB (4b). 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). TARribosylation 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].

Since it appears to be difficult to synthesise 5,6-dichloro-2-iodobenzimidazole using the Sandmeyer reaction, a different approach involving l-(-D-ribofuranosyl) benzimidazole was proposed as a solution to this issue. We made the decision to take this action (4d, IDCRB) in light of the issues that have arisen. This first step was essential because it enabled the assessment of the selectivity of tertiary alkynyl nitrite-mediated diazotization of 2-amino-5,6-disubstituted benzimidazole ribosides in an aqueous solution. The molecule known as 2-amino-5,6-dichloro-1-(2,3,5-tri-O-acetyl—D-ribofuranose) was created as a byproduct of the synthesis (Scheme 5). [18]



SCHEME 5

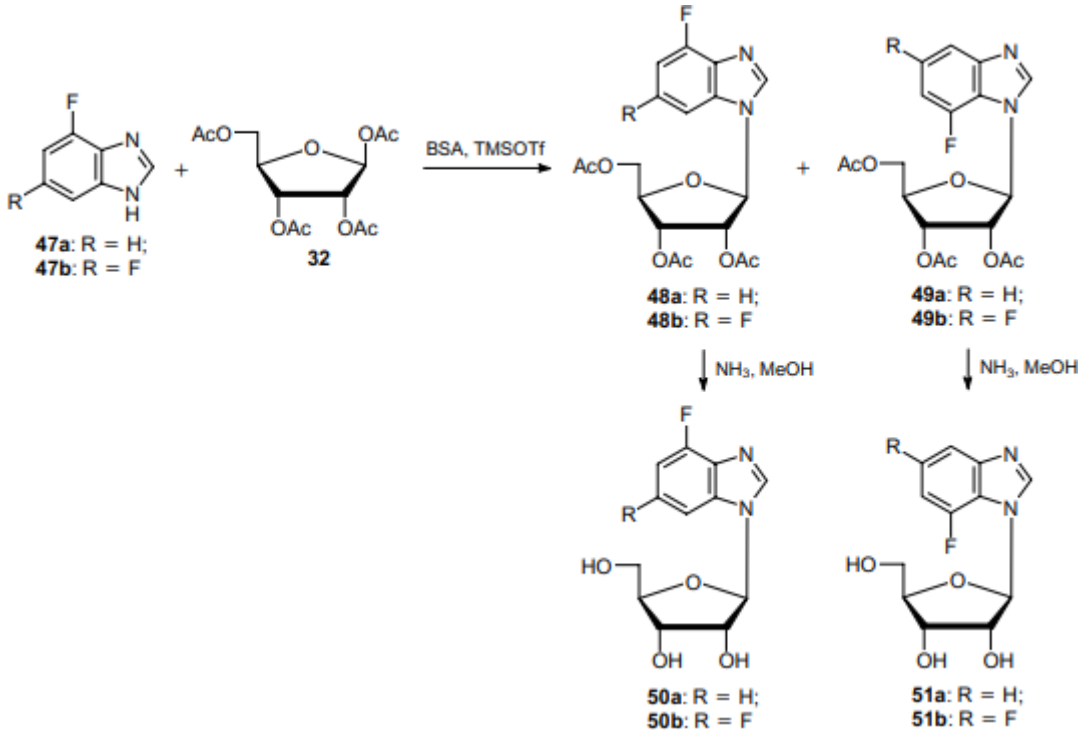
By silylating 2-amino-5,6- dichlorobenzimidazole (37), then ribosylating it with TAR, we were able to obtain protected ribofuranoside 41 with a yield of 51%. The second product underwent an unexpected transition after being exposed to diiodomethane having ten times the usual amount of tert-butyl nitrite. The final product had a nitro group linked to the benzene ring rather than an iodine group. 5,6-dichloro-l-(2,3,5-tri-O-acetyl—D-ribofuranosyl)benzimidazol-2-one, a key intermediate, was isolated.

for figuring out the mechanism underlying this odd behaviour (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 this transformation. 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]

The diazotization of primary alkynyl nitrite is a crucial step that results in a useful reagent in the production of the 2-iodo derivative (46; Scheme 5). It was found that the same circumstances that produced the undesired product 44 also produced compound 41 when it was treated with amyl or isoamyl nitrite. The inquiry led to the result that was reached. This led to the production of the identical compound, 5,6-dichloro-2-iodo-l-(2,3,5-tri-O-acetyl—D-ribofuranosyl) benzimidazole (46), with either a 55% or 63% yield. After removing the protecting groups with ammonia in methanol, the necessary 5,6- dichloro-2-iodo-l-(- D-ribofuranosyl) benzimidazole (4d) was produced (yield: 90%) for figuring out the mechanism underlying this odd behaviour (42).[21]

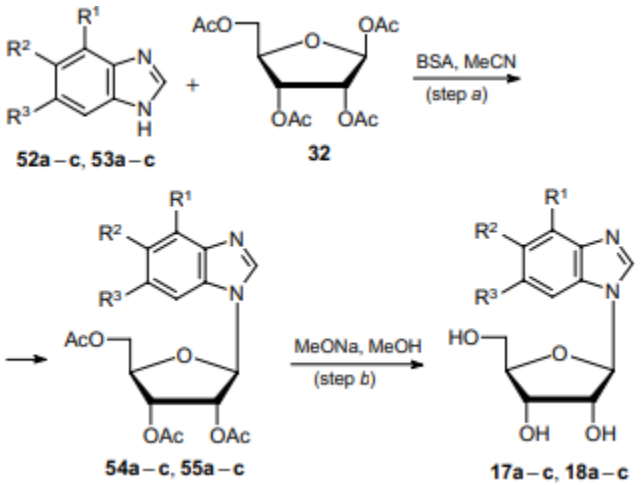
Producing fluorinated benzimidazole ribosides required the assistance of the Vorbruggen reaction (Scheme 6). After heating 4-fluoro-1H-benzimidazole (47) with BSA in the presence of reflux, thebase was trans-silylated with TAR (32) in the presence of TMSOTf, which led to the production of 4-fluoro-1-(2,3,5-tri-O-acetyl—D-ribofuranosyl) 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

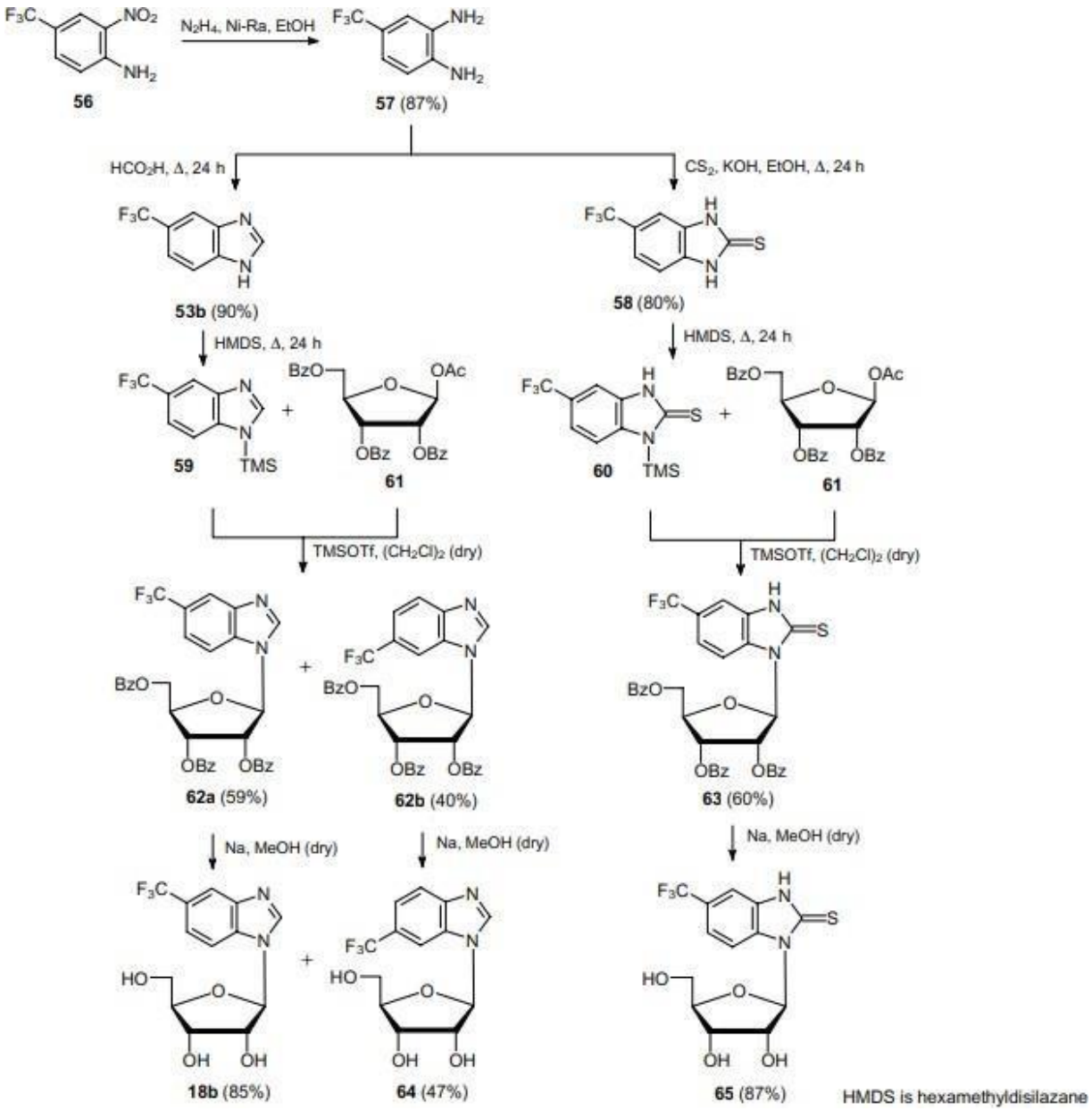
As shown in Scheme 6, the protected -D- ribofuranoside (48b) was produced during the synthesis of the 4,6-difluoro-1H-benzimidazole riboside (50b) with a yield of 67 percent, while the N (3)-isomer (49b) was produced with a yield of 11 percent. The acetyl protecting groups on nucleosides 48 and 49 were then removed with the help of methanolic ammonia. With yields of 89 and 94 percent, respectively, it was successful in isolating free nucleosides 50a and 50b as well as their N (3)- regio-isomers 51a and 51b.[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]



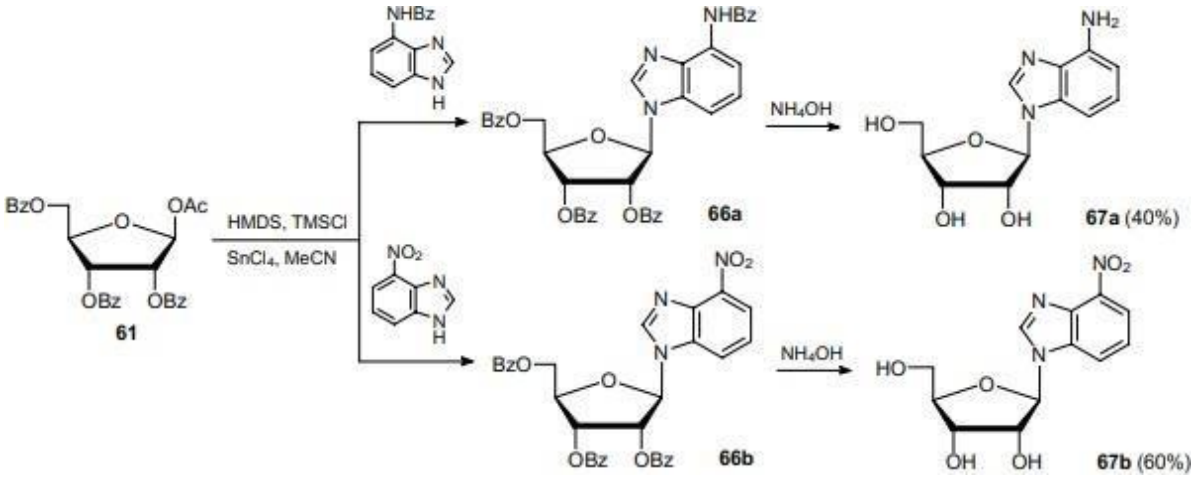
SCHEME 7

In order to conduct cytotoxicity and antitumor efficacy testing, the riboside 5-trifluoromethylbenzimidazole (18b) and its thio counterpart were both produced in 2016. The intermediate 2-nitro-4-trifluoromethylaniline (56) was employed to finish the synthesis of 18b. Following the standard processes for the Vorbruggen glycosylation and Zemplen deprotection procedures, the synthesis was carried out as depicted in Scheme 8. When formic acid was used to treat 4-trifluoromethylphenylene-1,2-diamine (57) under reflux, benzimidazole (53b) was produced in a respectable yield. On the other hand, diamine (57), which was treated with carbon disulfide while in reflux, allowed for the high yield synthesis of 2-thioxo-5-trifluoromethyl-1H-benzimidazole (58). The bases 59 and 60 were then used to react with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (ABR, 61) in the presence of TMSOTf in dry dichloroethane (61), following the completion of the synthesis of silyl derivatives. Using column chromatography, the 62a and 62b isomers were isolated from one another. In the end, by deprotecting molecules 62a, 62b, and 63 with sodium methoxide in dry methanol, trifluoromethyl benzimidazole nucleosides 18b and 64, as well as their 2-thione counterpart 65, were generated. This made it possible to create these nucleosides. [25].



SCHEME 8

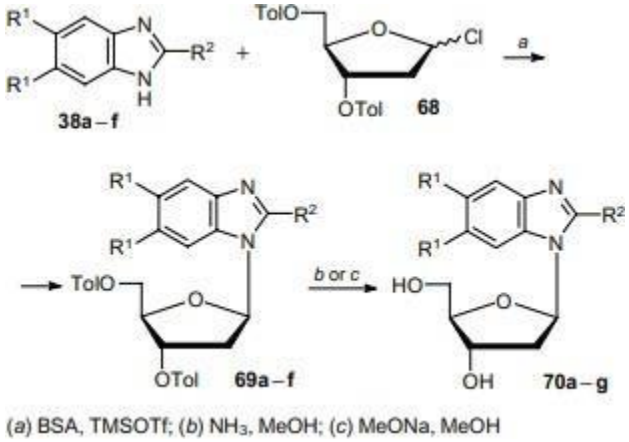
Using tin (IV) chloride as a catalyst, silylated 4-(benzoylamino) benzimidazoles and 4-nitro benzimidazoles were produced by treating the appropriate starting heterocyclic bases with a hexamethyldisilazane (HMDS) trimethylsilyl chloride (TMSCl) mixture at room temperature without intermediate isolation (Scheme 9). By ammonolyzing the protecting groups of nucleosides 66a and 66b with a 25% ammonia solution, ribosides 67a and 67b containing 4-amino- and 4-nitro-benzimidazole were produced. Nucleosides 66a and 66b (67b) were used in this procedure.[26]



SCHEME 9

To prepare 2-deoxyribonucleosides using substituted benzimidazoles

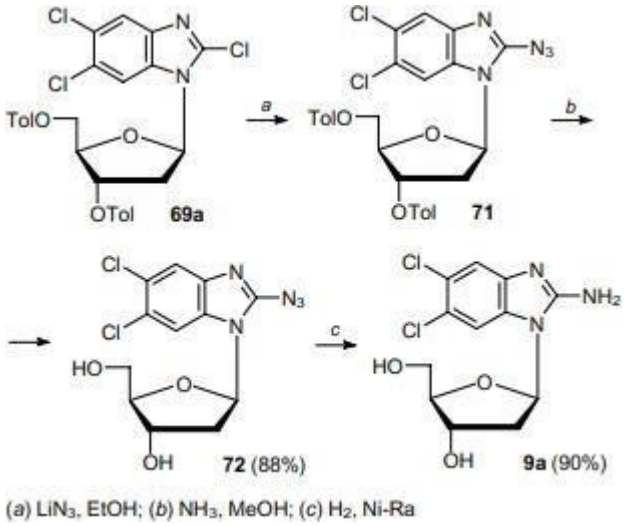
The majority of benzimidazole nucleosides that are synthetic are in the form of -D-ribosides. It was shown that C(2)-substituted 5,6-dichlorobenzimidazoles may be converted into 20 different -deoxy analogues of -D-ribosides. (Scheme 10) [27].



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 base 2,5,6-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]

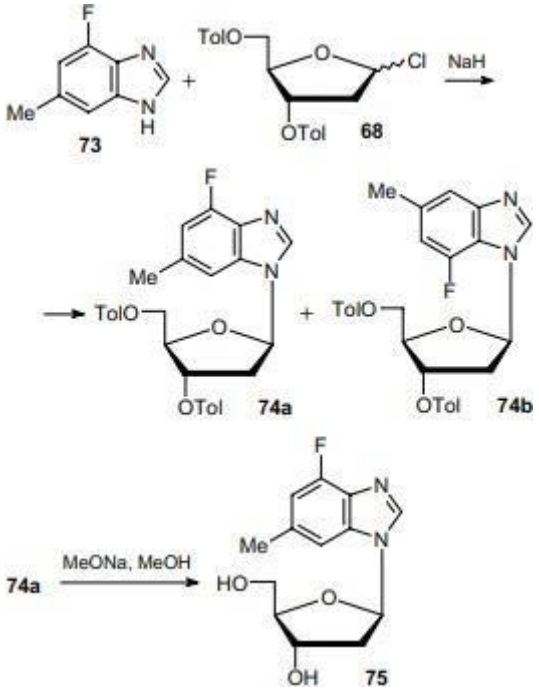
After treating nucleoside 69a with lithium azide and subsequently deprotecting azide 71 with methanolic ammonia, the 2-azido-5,6-dichloro-1-(2-deoxy—D-erythro-pentofuranosyl)benzimidazole (72) was produced (Scheme 11). After reducing the azido group ofnucleosides 72 with hydrogen on Raney nickel, the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



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

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 APPLICATION OF BENZIMIDAZOLES

Antimalarial activity

In sub-Saharan Africa, newborns and young children under the age of five are most commonly affected by malaria. Children and adolescents make up the majority of those impacted by the illness. Malaria is thought to be the cause of between 350 million and 500 million clinical episodes annually and more than a thousand fatalities. Infectious diseases brought on by protozoa rank fifth in terms of the total number of fatalities that occur worldwide. 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 medicine and pesticides, the weakening of traditional protozoal infection management programmes, rapid decentralisation and integration into deteriorating primary health services, and the development ofhumanitarian 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 novel protozoal 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 past few decades, incurable illnesses have grown more serious and pose a greater threat to human health. A general decline in sensitivity to currently prescribed antimicrobial medicines has been observed concurrently with this trend. Gram-positive bacteria and a few hardy parasites are two examples of the types of microorganisms that are evolving a greater resistance to the existing treatments. This misunderstanding has resulted in a serious misreading of their function as inhibitors in the biosphere, which has led to abuse of it.[37] Due to its potent activity, excellent safety profile, and advantageous pharmacokinetic properties, fluconazole is the drug of choice for treating conditions brought on by Candida albicans and Cryptococcus neoformans. 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, the hepatitis C virus (HCV) is a chronic infection that affects more than one-third of the world's population. As a result, HCV is a serious risk factor that can result in the development of cancer and liver disease. The requirement for patients to get treatment for an average of 48 weeks and the fact that only a fifth of chronic drug recipients respond to it are examples of the limitations of modern medical knowledge. This is because there is currently no approved prophylactic immunisation. The recovery of genomic hepatitis C virus (HCV) ribonucleic acid (JFH1) from a patient with acute liver disease, followed by the transfection of human malignant hepatoma cells with this material, represents a significant new discovery in the field. 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 their antimicrobial 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.

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