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Review Article

BENZIMIDAZOLE-2-CARBAMIC ACID AS A PRIVILEGED SCAFFOLD FOR ANTIFUNGAL, ANTHELMINTIC AND ANTITUMOR ACTIVITY A REVIEW

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ABSTRACT

Benzimidazole, a simple heterocycle continues to hold promise to medicinal chemists. A vast number of compounds contain this scaffold and many of these have become blockbusters such as omeprazole, astemizole, candesartan to name a few. Benzimidazoles are unique in that they have been reported to show activity against fungal, mammalian and helminthes cells via binding to microtubules. They are the only class of broad spectrum anthelmintic drugs available in the market till date. The introduction of thiabendazole in 1961 opened up research on 2-substituted benzimidazole and among these benzimidazole-2-carbamic acids and their esters have shown promise. Substituted benzimidazole-2-carbamic acids and their alkyl esters have been investigated first as antifungal agents and later their effectiveness was established against nematode pathogens. Further work led to establishing anticancer properties in mammalian cells. The major problem that still needs to be resolved includes the poor aqueous solubility and the drug resistance exhibited by commercially available compounds. This review, therefore, focuses on the benzimidazole-2-carbamic acid class of compounds and their use as antifungal, anthelmintic and anticancer compounds and reports the investigations and the research findings done till date so as to gain further insights and provide new leads for developing novel compounds from this class of compounds.

Keywords: Thiabendazole, Tubulin, Fungicidal, Anthelmintic, Antitumor.

INTRODUCTION

1H-Benzimidazole is a well known moiety and a privileged scaffold in Medicinal Chemistry. It is a white to beige solid having a melting point of 172°C. It is a bicyclic heterocyclic compound with the imidazole ring fused to a benzene ring. It forms the backbone of several drugs such as antiulcerants (omeprazole, a proton pump inhibitor), anthelmintic (mebendazole, a nematode tubulin polymerization inhibitor), antifungal (carbendazim, fungal tubulin polymerization inhibitor), cardiovascular (candesartan, an angiotensin II receptor antagonist), antihistamines (astemizole, H1-receptor antagonist) to list a few. The use of benzimidazole motif is not only restricted to pharmaceutical field but is also used in agrochemical field. Several thousands of compounds bearing different substituent have been synthesized so far and reported to possess therapeutic activity. The 2-substituent is most favored for therapeutic activity. The synthesis of such compounds can be achieved readily by cyclisation with different reagents. Of these, the 2-substituted benzimidazole containing the thiazolyl substituent, thiabendazole (figure 1) discovered in 1961 by Merck is used widely as an anthelmintic drug and is reported to possess antifungal activity as well. This marked the beginning of a major advancement in anthelmintic drug research [1-4].

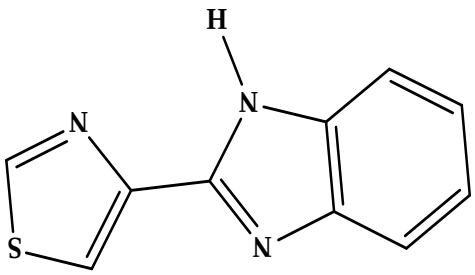


Fig. 1: It shows structure of 2-(4'-thiazolyl) -1H-benzimidazole (Thiabendazole) [5]

Another 2-substituted benzimidazole derivative, fuberidazole (figure 2) has been reported to possess only antifungal activity and no anthelmintic activity.

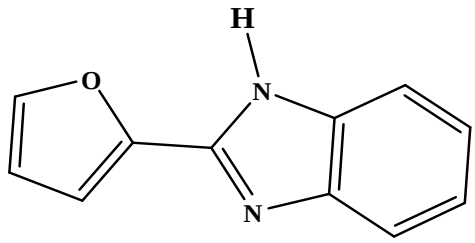


Fig. 2: It shows structure of 2-(furan-2-yl)-1H-1, 3-benzimidazole (Fuberidazole) [6]

2-substituted carbamic acid derivatives of benzimidazole having a 5(6) substituent on the benzene ring have been reported to possess antifungal, anthelmintic and anticancer properties. One example is that of nocodazole (figure 3).

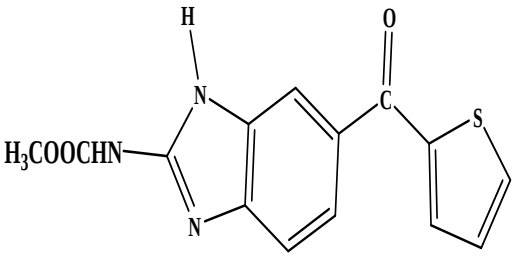


Fig. 3: It shows structure of methyl [5-(2-thienylcarbonyl)-1H-benzimidazol-2-yl] carbamate (Nocodazole) [7]

Benzimidazole Carbamates are compounds with high melting points and practically insoluble in water. This article therefore reviews the research work from the year 1960 till date on the benzimidazole-2-carbamic acid class of compounds and their ester derivatives those of which have been translated in to clinic or put in to commercial use, their synthetic methodologies and the scope of further research in this area with an aim to discover novel, biologically active

molecules against a particular target or to serve as lead compounds which can then be optimized.

General structure of benzimidazole-2-carbamic acid class of compounds

Figure 4 outlines the general structure of benzimidazole-2-carbamic acid class of compounds where R_2=NHCOOR (R=methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec butyl, n-pentyl, n-hexyl etc.), R_1=H, alkyl, acyl, alkenyl, aralkyl and R_3=H, phenoxy, alkoxy, alkyl, halo, amino, alkyl amino or heterocyclic. The scope of these substituent vary from limited to broad such as the R_2 substituent has limited scope i.e. as a fungicidal, the R_1 substituent if present has a broad scope in pharmaceutical and veterinary use and the R_3 substituent has a broad scope in anthelmintic and antitumor use.

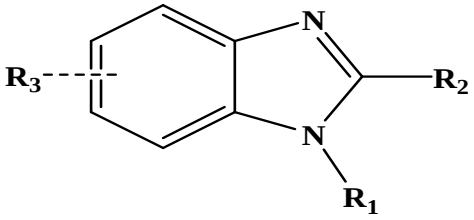


Fig. 4: It shows general structure of benzimidazole-2-carbamic acid derivatives [8].

Fungicidal benzimidazole-2-carbamates

Fungi are responsible for a number of plant and crop diseases and cause a great reduction in the yield and quality of crops. Fungal infections are either deep-seated or superficial. Fungal infections are seldom life-threatening in normal individuals but the systemic fungal infections caused by *Aspergillus fumigatus* can be life-threatening. The *in vitro* antifungal activity of benzimidazole was first observed by Woolley in 1944. A spurt in research activities led to the synthesis of benzimidazole derivatives which have been reported in a number of patent literatures to possess fungicidal activity. Benzimidazole derivatives which have been exploited for commercial use as agricultural pesticides are carbendazim, benomyl, chlorfenazole, cypendazole, mecarbinzid, debacarb, fuberidazole, and rabenzazole. Of these, carbendazim, benomyl, cypendazole, debacarb and mecarbinzid are benzimidazole-2-carbamates. The development of benzimidazol-2-yl carbamate as systemic fungicides represents the selectivity of these compounds to fungal plant pathogens. They have a single-site (specific) mode of action. In addition to the benzimidazole pharmacophore, the 2-$NHCOOCH_3$ might assist in the formation of a complex between these compounds and a subunit of microtubule. It has been postulated that this group might be involved in interacting with the amino acid alanine at position 165 in beta tubulin. Hence it determines the binding properties between the toxicant and the protein. The net result is the inhibition of the spindle formation accounting for the anti-mitotic activity in the fungal cells and also resembling the anti-mitotic activity of colchicine and related compounds in mammalian cell cultures. The role of a 2-substituent is to reduce the basicity and increase the affinity to microtubule. Both thiabendazole and fuberidazole which do not contain the 2-carbamate group are less active than carbendazim although the spectrum of activity is similar. Table 1 shows the structures of these compounds. Carbendazim, benomyl, cypendazole and mecarbinzid are methyl esters of benzimidazole-2-carbamic acid. Benomyl has a butyl amino carbonyl substituent at 1-position. Benomyl is one of the most successful fungicides of this class because of its advantages like broad spectrum of activity and crop safety. It undergoes metabolism to methyl-2-benzimidazole carbamate (carbendazim) and n-butyl isocyanate. Cypendazole and Mecarbinzid also have substituted carbamoyl functionality at position 1 on nitrogen atom. This shows that the hydrogen at 1-position is not really required for antifungal activity and that it can be replaced with substituent which will not decrease the antifungal properties. The N-1 substituted active compounds show a different fungicidal profile. Thus the N-1 substituent might be important in altering the spectrum of activity and varying the physical and chemical properties like solubility. Debacarb is a long chain alkyl ester of Benzimidazole-2-carbamic acid. None of these compounds which are in use bear any substituent on the benzene ring which shows that the 5-substituent is not a prerequisite for anti-fungal activity.

Due to the widespread use of these fungicidal agents and their specific action, resistance is common in many fungal species. Several target site mutations in the β-tubulin gene, mostly ϵ198A/G/k, F200Y have been reported. Strains of *Botrytis* which cause gray mold in ornamental crops are now largely resistant to methyl benzimidazole carbamate fungicides. Solubility problems of these compounds have contributed to their low bioavailability which has restricted their use in the treatment of fungal diseases in plants and have now lost effectiveness for many important diseases. Moreover some of these compounds like benomyl and carbendazim have been banned from use. While it is essential to control fungal plant diseases, no benzimidazole-2-carbamates have been developed for human use. The reasons that can probably be cited here are the poor solubility and/or toxicity of these agents in humans.

Apart from the 2-substituted monoesters of benzimidazole-2-carbamic acids, various 1, 2-disubstituted esters and the trialkyl esters having the formula as shown in figure 5 and 6 have been synthesized and reported to possess outstanding fungicidal activity. But none of these have been optimized further for systemic use to control fungal diseases [9].

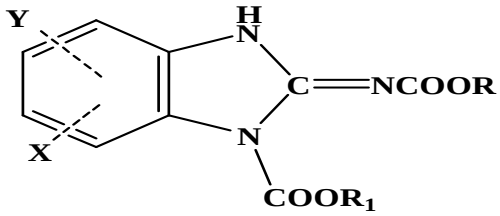


Fig. 5: It shows general structure of 1, 2-disubstituted esters of benzimidazol-2-yl carbamic acid [X=H, halogen, nitro, alkyl, alkoxy groups, Y=H, Cl, CH_3 and C_2H_5, R and R_1 may be same or different such as aliphatic hydrocarbons of less than 7 carbon atoms] [9].

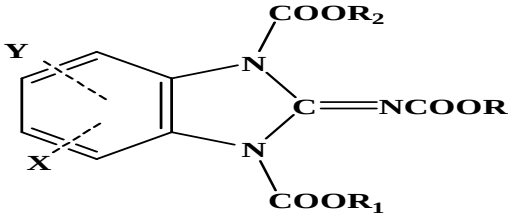


Fig. 6: It shows general structure of trialkyl esters of benzimidazol-2-yl carbamic acid [X=H, halogen, alkyl, alkoxy groups of less than 7 carbon atoms, Y=H, Cl, NO_2, CH_3 and C_2H_5, R and R_1 may be same or different such as aliphatic hydrocarbons of less than 7 carbon atoms] [9].

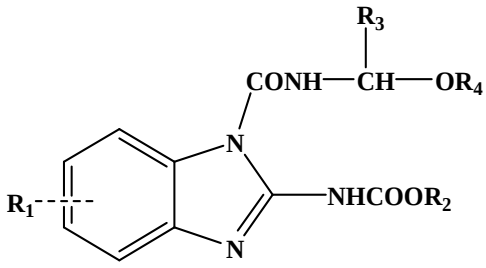
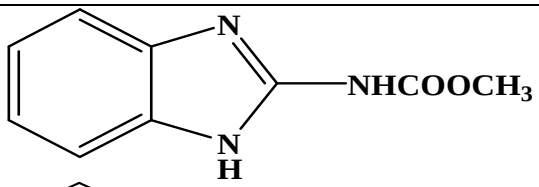
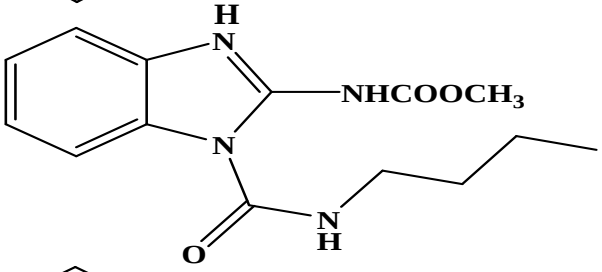
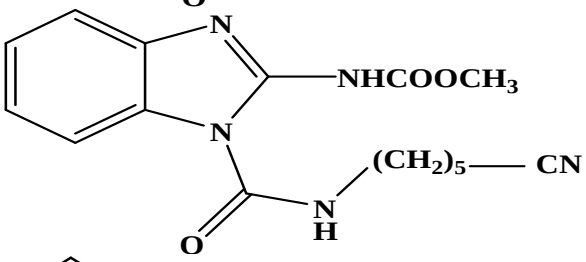
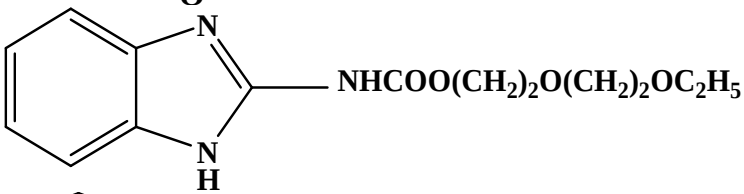
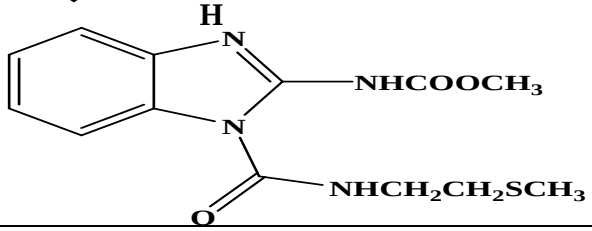


Fig. 7: It shows general formula of 3-(Halo alkoxy alkyl)-carbamoyl benzimidazole carbamate [15].

Table 1: It shows fungicidal benzimidazole-2-carbamates [10-14].

Compound name	Structure	IUPAC name
Carbendazim		1H-Benzimidazole-2-carbamic acid, methyl ester.
Benomyl		Methyl [1[(butyl amino)carbonyl]-1H-benzimidazol-2-yl-carbamate
Cypendazole		Methy1 1-(5-cyanopentyl carbamoyl) benzimidazol-2-yl carbamate
Debacarb		2-(2-ethoxy ethoxy) ethyl benzimidazol-2-yl carbamate
Mecarbinzid		Methyl 1-(2-methyl thioethyl carbamoyl) benzimidazol-2-yl carbamate

Benzimidazole carbamate having a haloalkoxy alkyl carbamoyl substituent at 3-position have been shown to possess fungicidal, antisporulant and acaricidal activity [15]. The general formula of such compounds is represented in figure 7 where R_1=H, NO_2 or X atom, alkyl or alkoxy group containing 1-4 carbon atoms, R_2=alkyl having 1-4 carbon atoms. R_3=H, alkyl or halo alkyl group with 1-4 carbon atoms and R_4 = alkyl, halo alkyl, aryl alkyl or aryl halo alkyl group with 1-12 carbon atoms.

Anthelmintic benzimidazol-2-yl carbamates

Helminthes infection in humans and animals are not life-threatening but contribute to economic burden in developing countries as well as developed countries. The discovery of the anthelmintic activity of thiabendazole in 1961 prompted the search for a series of 5(6) benzene ring substituted esters of benzimidazole-2-carbamic acid class of anthelmintic drugs. Since then several compounds have been synthesized and screened for anthelmintic activity [16-20]. The 2-(4-thiazolyl) substituent was modified with a number of substituent from which the 2-methyl carbamate stood out having great efficacy. A good number of them are in use to control helminthes infection in humans and in animals and these are listed in table 2 and table 3. The use of thiabendazole is now restricted largely to veterinary use. It has the potential to cause hepatotoxicity. Other agents available now are quite effective and less toxic compared to thiabendazole. Both mebendazole and albendazole are broad spectrum anthelmintic effective against a variety of nematodes.

The anthelmintic activity of benzimidazole carbamate has been attributed to their anti-mitotic activity as these agents bind selectively and preferentially to helmintic tubulin over mammalian tubulin. All the above compounds have an H atom at 1- position and a methyl carbamate at 2-position with a 5(6) substituent for anthelmintic activity. The methyl esters have increased activity over ethyl and other alkyl esters. The alkyl and benzoyl substituent at 5(6) position enhance the activity in these compounds. The 5(6) ethers, thioethers and thiazolyl heterocyclic ring too have been investigated for activity against intestinal nematodes and have been found to confer enhanced activity. Other substituent which have been investigated for anthelmintic activity and/or antifungal activity include the pyridinoyl, thiazolyl, pyridylhydroxymethyl, thiazylhydroxymethyl, pyridylmethyl, pyridylethyl or pyrrolidinyl carbonyl, piperidino carbonyl, piperazinyl carbonyl or morpholino carbonyl [21, 22]. The selectivity of these agents to bind to helminthes tubulin contributes to minimal toxicity to the host. Another mechanism to account for the action of these compounds is the inhibition of the enzyme fumarate reductase involved in oxidative phosphorylation and important in production of ATP [23].

Some of the drawbacks with the use of these agents to treat gastrointestinal helmintic diseases include long treatment and high dosage regimen. This is due to the poor solubility and erratic absorption *in vivo* although poor absorption may pose an advantage since these agents are used to treat helminthes infection in the intestine. The agents also show crossed resistance which may diminish

their therapeutic potential in future. Several analogues of mebendazole and albendazole have been synthesized and such compounds have been reported to inhibit the growth of protozoa *in vitro* further extending the anti parasitic profile of these compounds [24]. In some compounds the 2-methyl carbamate group has been replaced by the 2-trifluoromethyl group to improve their water solubility. Another approach that has been utilized is the development of prodrugs that are suitably substituted benzene derivatives and can undergo cyclisation to the active benzimidazole carbamate enzymatically after being absorbed by the host. Examples of such prodrugs are thiophanate (methyl), febantel and netobimin (figure 8). An advantage of netobimin is that has good water solubility.

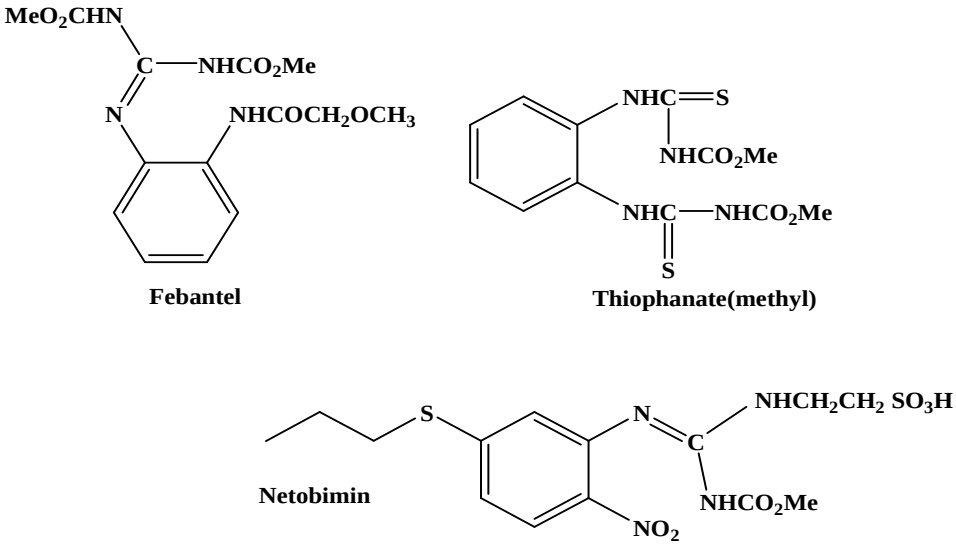


Fig. 8: It shows prodrugs of benzimidazole-2-carbamates [1, 25].

Table 2: It shows Anthelmintic 5(6)-substituted Benzimidazol-2-yl Carbamates [1, 25].

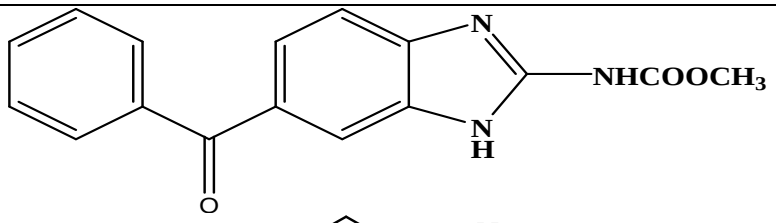
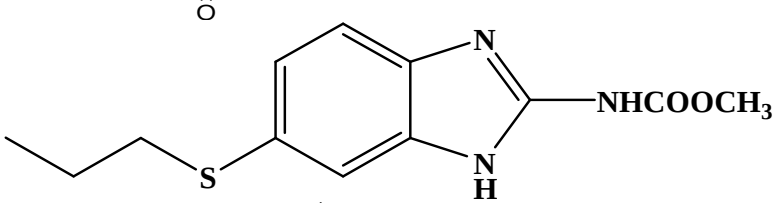
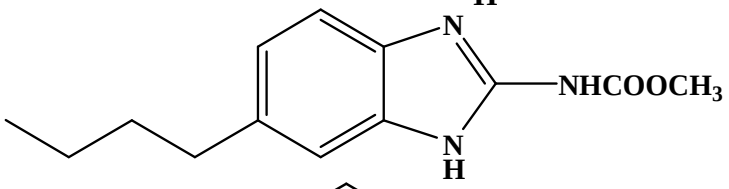
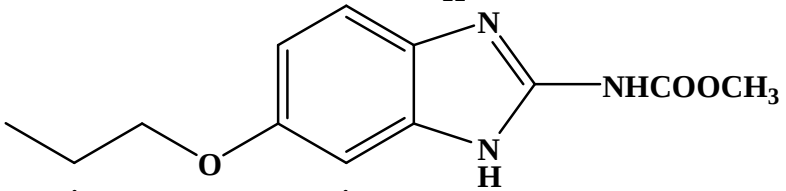
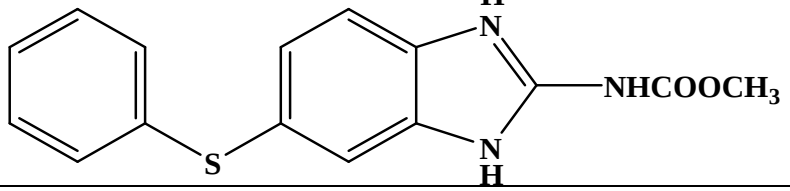
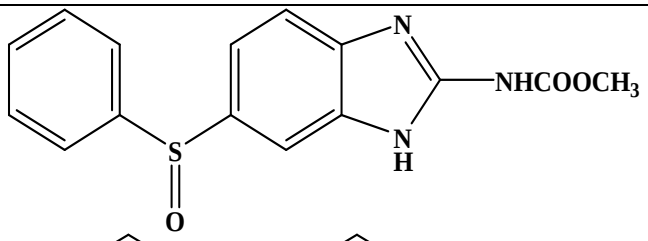
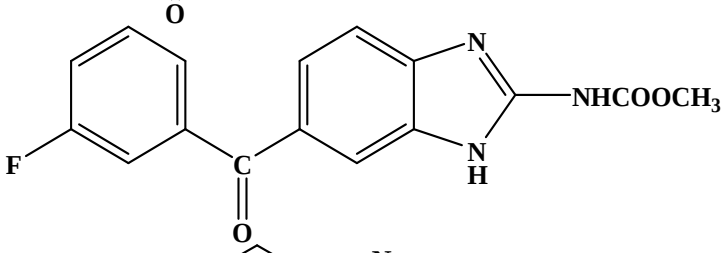
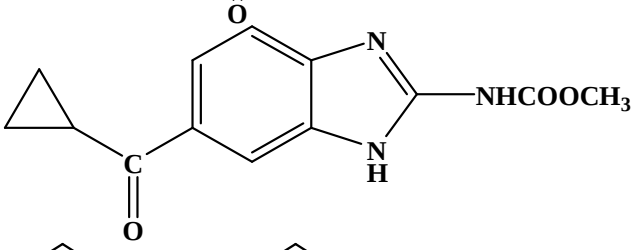
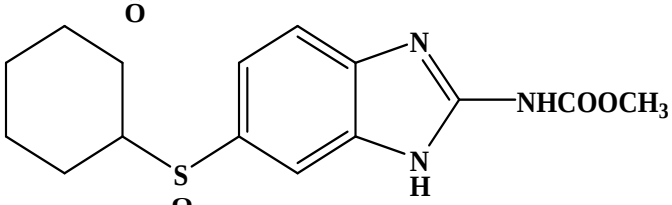
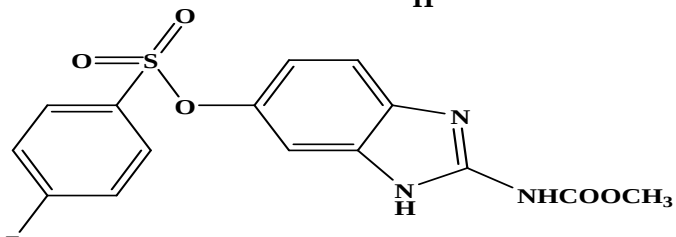
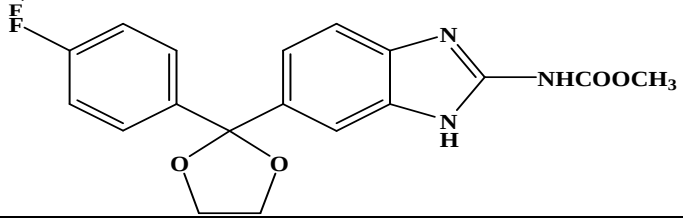
Compound name	Structure	IUPAC name
Mebendazole		Methyl-5-benzoyl-benzimidazol-2-yl carbamate
Albendazole		Methy1 [5-(propyl thio)-1H-benzimidazol-2-yl carbamate
Parbendazole		Methyl -5-n-butyl-benzimidazol-2-yl carbamate
Oxibendazole		Methyl-N-(6-propoxy-1H-benzimidazol-2-yl) carbamate
Fenbendazole		Methyl 1-N-(6-phenyl sulfanyl-1H- benzimidazol-2-yl) carbamate

Table 3: It shows Anthelmintic 5(6)-substituted Benzimidazol-2-yl Carbamates [1, 25].

Compound name	Structure	IUPAC name
Oxfendazole		Methyl N-[6-(benzene sulfinyl)-1H-1,3-benzimidazol-2-yl] carbamate
Flubendazole		Methyl –N[6-(4-fluorobenzoyl)-1H-benzimidazol-2-yl] carbamate
Ciclobendazole		Methyl N-[6-cyclopropane carbonyl)-1H-benzimidazol-2-yl] carbamate
Dribendazole		Methyl (5-cyclohexylthio)-1H-benzimidazol-2-yl] carbamate
Luxabendazole		Methyl 5-hydroxy-2-benzimidazole carbamate p-fluoro benzenesulfonate
Etibendazole		Methyl [5-[2-(4-fluoro phenyl)-1,3-dioxolan-2-yl] 1H-benzimidazol-2-yl carbamate

Antitumor benzimidazolyl carbamates

The anthelmintic benzimidazole carbamate, albendazole has been investigated for its cytotoxic effect against some cancer cell lines and has been found to have great potential in the treatment of cancer. But the aqueous solubility of this drug is the factor which limits its clinical application. Therefore, certain albendazole derivatives have been synthesized and reported to show cytotoxic effects against human colorectal cancer cell line (Ht-29) and human prostate cancer cell line (PC-3). Figure 9 outlines the structure of one such derivative. MEABZ has been reported to be 10 times more cytotoxic than benzimidazole. However the albendazole derivatives such as N1-(2-methoxy ethoxy carbonyl)-2-amino-5-propylthio benzimidazole, N1-(2-methoxy ethoxy carbonyl)-2-amino-6-propylthio benzimidazole and (2-hydroxy ethyl)-5-propylthio-1H-benzimidazol-2-yl carbamate do not show any cytotoxic effects. Recently it has been reported that the solubility of MEABZ derivative of albendazole can be increased by encapsulating it with cucurbit[n] uril [26].

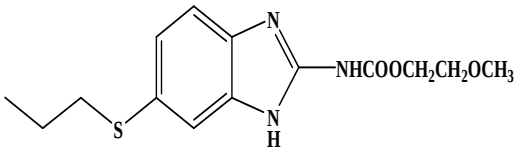


Fig. 9: It shows (2-methoxy ethyl) 5-propylthio-1H-benzimidazol-2-yl-carbamate (MEABZ) [26].

The synthesis of nocodazole (R17934, NSC 238159) provided a major breakthrough in the search for novel antitumor agents from the class of benzimidazole-2-carbamic acid [27]. It has the 2-$NHCOOCH_3$ group and the 5(6) thienyl carbonyl substituent. This compound possesses antifungal, anthelmintic and antitumor activity. The antitumor activity of this compound was found to be against a range of experimental tumor systems like L1210 leukemia, MO_4 Sarcoma, B16 melanoma, Lewis lung carcinoma, P388 and

LSTRA leukemia. The mechanism of action of this compound is via interference with microtubule assembly, accumulation of cells in mitosis and hence subsequent effect on their survival. The anti-micro tubular activity of thiabendazole, mebendazole, oxfendazole, oxibendazole, cambendazole and parbendazole to develop potential anti-tumor agents has been investigated in mammalian cells after it was found out that nocodazole has antineoplastic activity. Studies on the role of 5(6) substituent to understand the interaction of benzimidazole carbamate with tubulin for investigating the pharmacological specificity of 5(6)-substituted benzimidazole-2-carbamates as antifungal, anthelmintic or antitumor agents have been carried out. The study suggests hydrophobic substituents are better inhibitors of tubulin polymerization [28]. In another separate study it was also established that there is no absolute correlation between the effectiveness of benzimidazole carbamate as anthelmintic with their anti-micro tubular activity [29]. A conclusion on the findings was thus drawn that there may be present some distinct differences in the mammalian and helminthes tubulin.

Although nocodazole as a compound had advantages like ease of synthesis and showed great promise, its poor aqueous solubility led to formulation problems. Using it as a lead structure, further modifications were made to obtain nocodazole derivatives in order to improve its anti-tumor activity and to improve solubility [30]. Thus, a series of such analogues were synthesized and it led to compounds with improved activity. However there was not much success in improving solubility.

In another study carried out, 5(6)-substituted benzimidazole-2-carbamates have been reported to selectively damage the newly formed vascular endothelium while having no effect on the normal mature vascular endothelium. Such compounds have been referred to as vascular damaging agents [31].

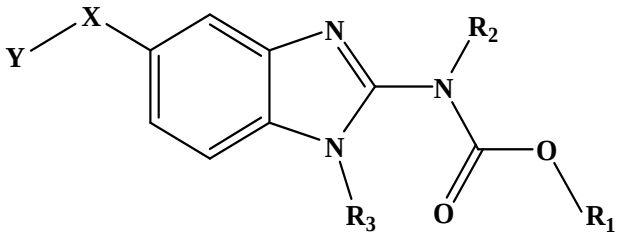


Fig. 10: It shows general structure of 5(6)-substituted benzimidazole-2-carbamates reported to possess vascular damaging properties [30].

Therefore, it has been reported that these compounds can be used in the treatment of diseases involving neo-vascularization such as solid tumors [32]. The general structure of these compounds is outlined in the figure 10 where R_1=alkyl group, X= heteroatom (O, N, S, SO), R_2 = H, alkoxy carbonyl, cyano methyl, cyano ethyl, alkoxy methyl or acetoxy methyl or alkyl or cycloalkyl group R_3=H, alkyl amino carbonyl or alkoxy carbonyl, and Y= substituted aromatic, heteroaromatic or heterocycloalkyl group. In the search for an anticancer agent, databases of existing molecules have been screened and in that carbendazim (Methyl-2-benzimidazole carbamate), an antifungal agent has been recently reported to possess potent antitumor activity *in vitro* against both the murine B16 melanoma and human HT-29 colon carcinoma cell lines. The compound is currently being evaluated in Phase 1 clinical trials of adult patients with advanced malignancies [33].

6-substituted imidazo [1, 2-a] pyridine-2-carbamates and imidazo [1, 2-b] pyridazine-2-carbamates

An interesting finding of the ongoing research activity in the development of new benzimidazole carbamate in areas of anthelmintic and antitumor research and which deserves a mention here has been in the replacement of the benzimidazole core nucleus with other heterocyclic isosteres. Some of these compounds such as the 6-substituted imidazo [1, 2-a] pyridine-2-carbamates (figure 11) have been shown to be potent in activity against nematodes [34]. Another compound coded as 1069C, an imidazo [1, 2-b] pyridazine-2-carbamate is devoid of anthelmintic activity but reported to be a very potent inhibitor of microtubule function in P388 tumor cells (figure 12). This compound has been reported to be very useful in the treatment of lymphocytic leukemia [35, 36]. Both the classes of compounds showed great promise initially during the development phase but some problems although not reported in the literature quite clearly still remains as further developments in these areas have not been reported till date.

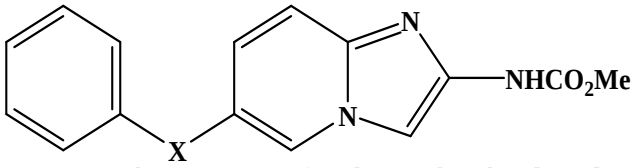


Fig. 11: It shows structure of 6-substituted imidazo [1, 2-a] pyridine-2-carbamate [34].

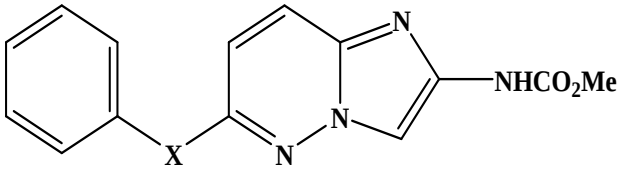


Fig. 12: It shows structure of 6-substituted imidazo [1, 2-b] pyridazine-2-carbamate [35].

General scheme for synthesis of benzimidazole-2-carbamates

Various routes for synthesis have been described in the literature. A few such viable routes are discussed. A convenient and inexpensive method for the preparation of anthelmintic benzimidazole-2-carbamic acid esters is described in the literature [37]. This involves the reaction of ring substituted or unsubstituted 2-amino benzimidazole with an alkyl chloroformate according to the reaction pathway in figure 13.

A further improvement in yields of 2-alkoxy carbonyl amino benzimidazole is mentioned wherein, the use of carbonic acid esters in place of chloroformic acid esters results in substitution taking place directly at the 2-amino group in the benzimidazole [38]. No by-products are obtained by this reaction which results in improvement in the overall yield of the desirable product as shown in figure 14.

One of the earliest method for preparation of esters of benzimidazole-2-carbamic acid as shown in the scheme involves the condensation of o-phenylene diamine or substituted o-phenylene diamine with the reaction product of S-methyl thiourea and alkyl chloroformate to construct the imidazole ring of the benzimidazole moiety. This method is quite convenient in that the alkyl S-methyl isothiourea carboxylate obtained need not be isolated and can be reacted in situ with an appropriately substituted o-phenylene diamine [39]. The 5(6) alkyl and aryl oxy derivatives and the 5(6) thioethers have been synthesized using 5-chloro-2-nitro aniline as the substituted o-phenylene diamine by replacement of the chloro group at 5-position by reacting with suitably substituted alcohols or thiols. The 5(6) acyl derivatives have been prepared using 3, 4-diamino benzoic acid. Several ring closing agents referred to as the 2-methoxy carbamate synthons can be used in this process. One such reagent mentioned is 1, 3-bis (alkoxy carbonyl)-S-methyl isothiourea which can be readily synthesized in the laboratory using thiourea, dimethyl sulfate and alkyl chloroformate. In general this reaction sequence consists of attaching a group in the benzene ring which then becomes the 5(6) substituent. The drawback of this method is the release of odoriferous mercaptans. Using this procedure various alkyl esters of N-[5(6)-acyl-2-benzimidazolyl] carbamic acid having anthelmintic activity have been prepared readily.

Figure 15 outlines the reaction sequence for preparation of such compounds.

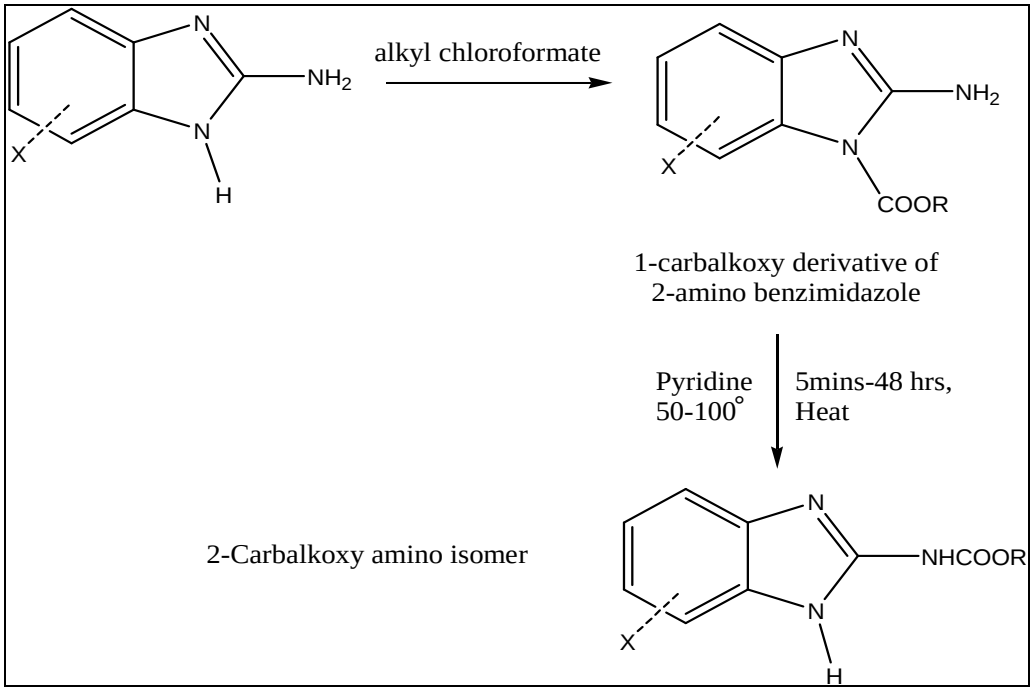


Fig. 13: It shows the scheme for synthesis of benzimidazole-2-carbamic acid esters using 2-amino benzimidazole and alkyl chloroformate [37].

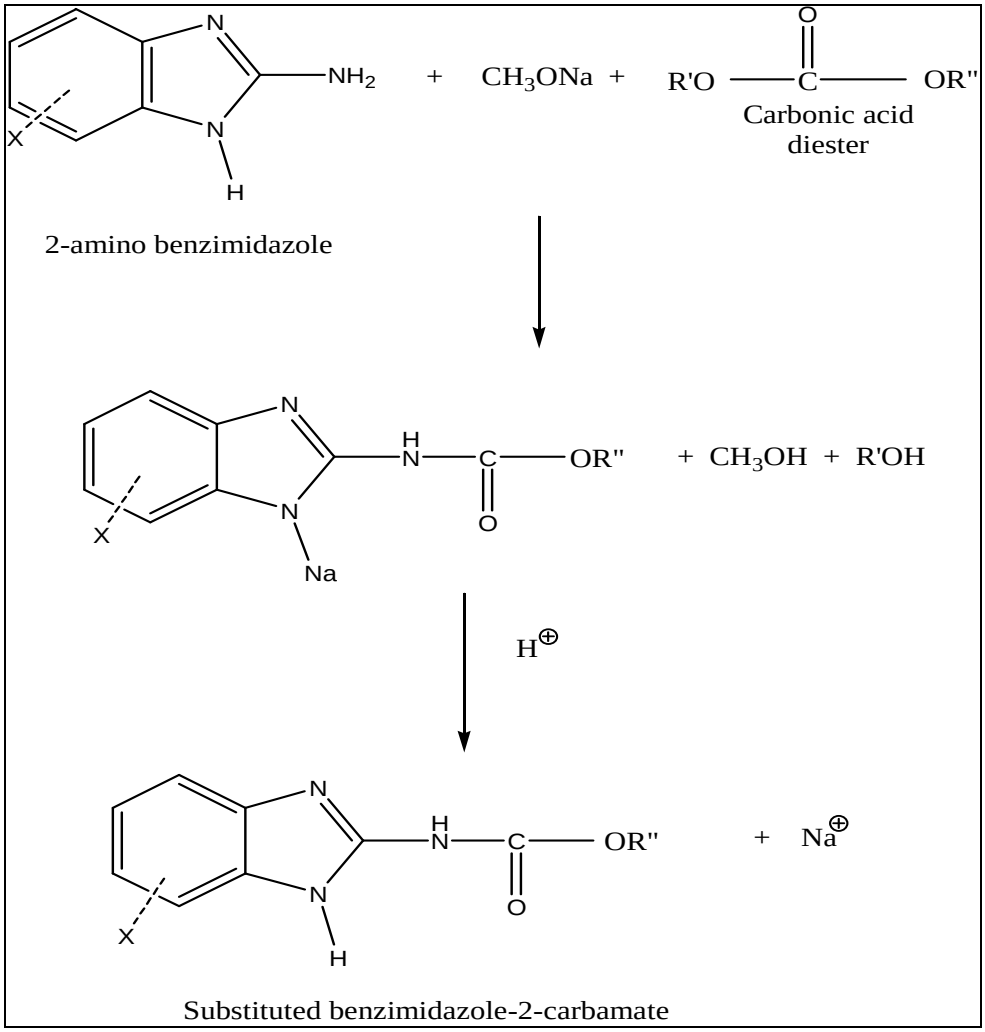


Fig. 14: It shows the synthesis of substituted benzimidazole-2 carbamate using carbonic acid esters [38].

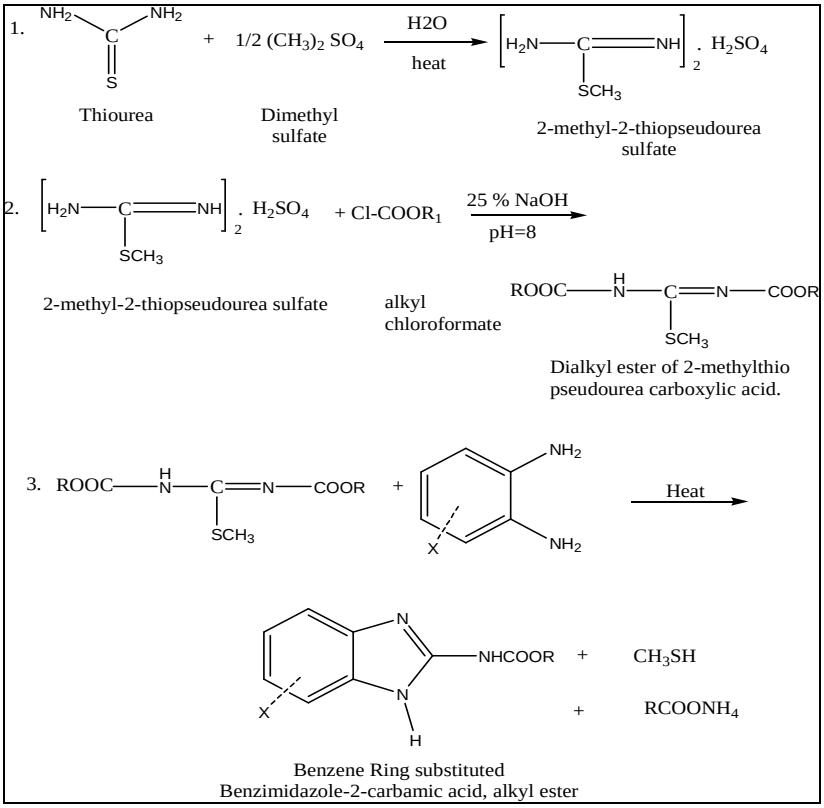


Fig. 15: It shows the synthesis of benzimidazole -2-carbamic acid esters using 2-methoxy carbamate synthon [39].

CONCLUSION

Have all the areas of research in this field been exhausted? The answer to this question is a big no. A vast number of benzimidazole-2-carbamates have been synthesized of which carbendazim although used initially as an antifungal agent is devoid of anthelmintic activity, but is now being investigated for its antitumor activity. Screening of other 5(6) substituted benzimidazole-2-carbamates led to oncodazole, a compound which is antifungal, anthelmintic and antitumor drug. These compounds are promising for developing newer benzimidazole-2-carbamates and optimizing their structural requirements due to their ease of synthesis (ready amenability to synthesis). It is also necessary to look for some synthetic derivatives which will be superior inhibitors of tubulin polymerization which can then become potential anti-tumor agents. Such compounds can be as an alternative to the naturally occurring and semi-synthetic agents such as colchicines, vinblastine, maytansine and their analogues. The presently available anti-tumor compounds possess disadvantages like toxicity to healthy cells and resistance to certain tumor types. So there will always be a need for new and improved anti-tumor agents. The synthesis of compounds in search for novel drugs is a critical part as these molecules should resemble biologically active molecules and should contain essential structural features required for binding to their targets. The potential drawbacks to their use however are their low solubility which can be overcome by introducing suitable functional groups to enhance their aqueous solubility. This once again can open up a new area of research. It can also generate interest in developing novel compounds with a benzimidazole backbone for anti-tumor activity and possessing good aqueous solubility. For compounds being developed as mammalian cell tubulin inhibitors, it is necessary to correlate the *in vitro* cytotoxicity (tubulin binding) with the *in vivo* antineoplastic activity.

Although the use of benzimidazole carbamate as a class of broad spectrum anthelmintic is well established in a series of patents, research into introduction of newer benzimidazole carbamate as anthelmintic drugs has slowed down considerably due to many reasons such as fewer molecular targets available for exploration and this area of research does not remain profitable anymore. As a result no new anthelmintic drug is being introduced. So there are only about a few safe and efficacious drugs for treating helminthes infection. Is it necessary to add newer agents to the already existing list of anthelmintic compounds? The answer is yes. The problems of resistance of the existing drugs and poor oral absorption still needs to be addressed.

The incidence of fungal infections has grown manifold. In humans fungal infections still remain a cause for mortality and morbidity particularly in a nosocomial setting. Amongst the systemic fungicides used for controlling fungal plant diseases, the emergence of resistance is an ever growing problem which needs to be effectively tackled. The data reviewed here can be used to propel further research in this area so as to develop suitable drug candidates having improved potency and lesser toxicity possessing antifungal, anthelmintic or antitumor activity. Of great benefit would be the drug design, synthesis and pharmacological evaluation of a compound possessing both antifungal and antineoplastic activity as infections caused by *Candida* species in patients being treated for leukemia and in immuno compromised patients is very common and still poses a big risk.

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