The Synthesis and Chemistry of Certain Anthelmintic Benzimidazoles

L.B. Townsend and D.S. Wise

A basis for interest in the benzimidazole ring system as a nucleus from which to develop potential chemotherapeutic agents was established in the 1950s when it was found that 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole (I) was an integral part of the structure of vitamin B₁₂. As a result of these interests and extensive studies, one health-related arena that has benefited greatly has been the treatment of parasitic diseases. The discovery of thiabendazole in 1961 further spurred chemists around the world to design and synthesize several thousand benzimidazoles for screening for anthelmintic activity but less than twenty of them have reached commercial use. Much of this work has been done by pharmaceutical companies and is only reported in the patent literature. In this paper, Leroy Townsend and Dean Wise review the development of some of the synthetic methods that have been critical to the preparation of the benzimidazoles of anthelmintic importance. Only a few molecules that demonstrate the processes are discussed here, but numerous reviews of the synthesis and chemistry of other benzimidazoles are available.

Box I. Tautomerism and isomerism

The systematic numbering of the benzimidazole ring system is shown in structure I. Although benzimidazole is depicted in I as possessing the proton at N₁, there actually exists a rapid exchange between the -NH- and =N- nitrogen atoms, and two tautomers, I and II, may be drawn for the benzimidazole molecule. Tautomerism occurs through either an intermolecular process involving two or more benzimidazole molecules or through interactions with a protic solvent such as water. It renders the 5- and 6- positions, and any group at that position in the ring system, chemically equivalent. In N-substituted benzimidazoles, tautomerism is no longer possible and two distinct non-equivalent molecules or isomers may be isolated and characterized. For example, the two dimethylated benzimidazoles shown are an isomeric pair of non-equivalent molecules, while the mono-methylated molecules are tautomers and equivalent.

Benzimidazole, as the name implies, is a bicyclic ring system in which benzene has been fused to the 4- and 5-position of the heterocycle (imidazole; Box 1). Benzimidazole compounds in general, and benzimidazole carbamates in particular, are crystalline materials, with fairly high melting points and are relatively insoluble in water. Compounds that are unsubstituted on either of the imidazole nitrogen atoms possess both acidic and basic characteristics.

Modifications of the benzimidazole ring system that have been made during the search for anthelmintic activity are summarized in Box 2. Combinations of the modifications at positions 2- and 5- of the molecule has provided the most active drugs. The synthetic pathways to the various benzimidazoles usually proceed through two steps, first the construction of a benzene ring containing the desired substituents and a 1,2-diamine grouping, followed by the ring closure of the 1,2-diaminobenzene (α-phenylenediamine) derivative to construct the imidazole ring. In many cases, this ring closure is the final step in the synthesis of the desired benzimidazole. However, in other instances this ring closure is followed by extensive derivatization of the ring system or of the existing exocyclic substituents (Box 3).

The discovery in 1961 that 2-(4'-thiazolyl)benzimidazole (thiabendazole) possessed a very potent broad spectrum of activity against gastrointestinal parasites was the breakthrough that opened up a new era in the treatment of parasitic diseases. In the initial studies, a group of researchers at Merck prepared thiabendazole by a condensation of α-phenylenediamine with thiazole-4-carboxamide in the presence of the dehydrating agent, polyphosphoric acid. This reaction was found to be quite general in nature and several hundred derivatives, including the 2-(2'-furyl)-, 2-phenyl-, 2-(2'-naphthyl)-, and 2-(5'-thiazolyl)-congeners, were also prepared to determine the best candidate for commercial development. Both the 2-phenyl- derivative and thiabendazole were very active drugs, and were...
Box 2. Chemical Structures of Some Benzimidazole Anthelmintics

Benzimidazoles

- **Benzimidazole Carbamates**
  - **Mebendazole**<sup>15</sup>
    - crystals, mp 288°C
    - insoluble in water
  - **Flubendazole**<sup>10</sup>
    - crystals, mp 260°C
    - insoluble in water
  - **Ciclobendazole**<sup>10</sup>
    - crystals, mp 250°C
  - **Albendazole**<sup>10</sup>
    - crystals, mp 208°C
  - **Oxibendazole**<sup>12</sup>
    - crystals, mp 230°C
    - practically insoluble in water
  - **Fenbendazole**<sup>13</sup>
    - powder, mp 233°C
    - insoluble in water
  - **Oxfendazole**<sup>14</sup>
    - crystals, mp 253°C
  - **Parbendazole**<sup>2</sup>
    - crystals, mp 225°C
    - insoluble in water

Chemical Structures:

- **Thiabendazole**
  - crystals, mp 304°C
  - insoluble in water, slightly soluble in alcohol
- **Mebendazole**
  - crystals, mp 288°C
  - insoluble in water
- **Flubendazole**
  - crystals, mp 260°C
  - insoluble in water
- **Ciclobendazole**
  - crystals, mp 250°C
- **Albendazole**
  - crystals, mp 208°C
- **Oxibendazole**
  - crystals, mp 230°C
  - practically insoluble in water
- **Fenbendazole**
  - powder, mp 233°C
  - insoluble in water
- **Oxfendazole**
  - crystals, mp 253°C
- **Parbendazole**
  - crystals, mp 225°C
  - insoluble in water

Prodrugs

- **Netobimin**
  - crystals, water soluble
- **Thiophanate (methyl)**
  - crystals, soluble in alcohol
- **R = CH₃CH₂H₂O - Thiabendazole'**
  - crystals, mp 280°C
  - insoluble in water
- **R = (CH₂)₄CHOCONH - Cambendazole**
  - crystals, mp 238°C
  - insoluble in water, soluble in alcohol
- **R = H Thiabendazole**
  - crystals, mp 304°C
  - insoluble in water, slightly soluble in alcohol
- **R = (CH₂)₄CHOCONH - Cambendazole**
  - crystals, mp 238°C
  - insoluble in water, soluble in alcohol

Studied further. A new, efficient procedure for the conversion of N-aryl amides with hypochlorite and a base to form benzimidazoles was devised by the Merck group<sup>5</sup>, and this discovery made it economically practical to market the 2-phenyl derivative and thiabendazole. In this procedure it is unnecessary to prepare the o-phenylenediamine compound because aniline is used as a starting material. Thus, to prepare thiabendazole (4), aniline is reacted with 4-cyanothiazole (2) in the presence of aluminium trichloride (a Lewis acid), to give the intermediate N-arylamidine hydrochloride (3). The critical oxidative cyclization to give (4) is then carried out by treating (3) with sodium hypochlorite in the presence of a base. The latter reaction has been accomplished commercially in one step, but it may also be performed stepwise through the intermediate (5).

It was later found that both thiabendazole and 2-phenylbenzimidazole suffer from an enzymatic hydroxylation at the 5-position to give (6), which inactivates the drug and therefore limits its effectiveness. To overcome this problem, investigators began to prepare second generation benzimidazoles with structural modifications that might prevent metabolic inactivation. These studies led to an abundance of potential anthelmintic benzimidazoles, and many methods of preparation.

Since hydroxylation was occurring at the 5-position, analogs of thiabendazole with different groups at this position were developed. As a potential candidate, 5-aminothiabendazole (9) was prepared by a condensation of 4-nitrophenylenediamine (7) with (2) to furnish 5-nitrothiabendazole (8). The nitro group of compound (8) was then reduced to furnish 5-aminothiabendazole (9). Compound (9) was nearly (80%) as active as the parent thiabendazole. Acylation of the 5-amino functional portion of (9) with isopropyl chloroformate produced the 5-isoproxycarboxylimino derivative (10), which was marketed under the name cambendazole<sup>6</sup>. Later,
Cambendazole was prepared directly from thiabendazole by an electrophilic substitution of a nitrene or nitrene-like intermediate derived from isopropyl azidoformate, initiated by heat or UV light. Another unique synthesis of cambendazole involves a reduction of the 3-(4-thiazolyl)benzotriazine 1-oxide (I). Through a systematic study involving a modification of the thiazole ring at the 2-position of thiabendazole, workers at Smith Kline and French found that the thiocarbonate compound (I) possessed anthelmintic activity. This led to the preparation of 2-acylaminobenzimidazoles (I), 2-benzimidazolylcarbamates (Ic) and 2-benzimidazolylureas (Id). All of these compounds possessed anthelmintic activity, however, the 2-methylcarbamate derivative stood out as the most effective. Several compounds were prepared that possessed this group at the 2-position. One of these compounds, prepared by the reaction of 4-butyloxyphenylmethane (I) with carbomethoxy cyanamide (I) in boiling propanol, was methyl 5-butyldolbenzimidazolylcarbamate (I).

Following the introduction of this compound, additional drugs were produced by several pharmaceutical companies. Janssen Pharmaceutica produced mebendazole, flubendazole, and ciclobendazole among others; Smith Kline and French discovered albenza10, oxibendazole12, and fenbendazole13; and Syntex developed oxfendazole14. To prepare these benzimidazoles, several new ring closing reagents were employed or invented and these 2-carboxylicarboxylate synthons are shown in Table 1.

To prepare mebendazole, flubendazole, ciclobendazole, and a variety of benzimidazoles containing a group attached to the 5-position of the benzimidazole by a carbonyl (C=O) linkage, a general reaction scheme was developed by researchers at Janssen (see Box 3). In this synthetic sequence, the initial step is to append to ring A, the group which becomes the 5-carbonyl linked substituent. This is accomplished using a
Table I. Reagents used for the formation of methyl benzimidazole carbanilates

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>Refs</th>
</tr>
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<tbody>
<tr>
<td>CH₃C=NC≡N-CO₂CH₃</td>
<td>1-methoxycarbonyl-S-methylisothioure</td>
<td>10,16</td>
</tr>
<tr>
<td>CH₅C=NC≡N-CO₂CH₃</td>
<td>1,3-bis-(methoxycarbonyl)-S-methylisothioure</td>
<td>10,16,17,18</td>
</tr>
<tr>
<td>RS⁻⁻⁻C≡N-CO₂CH₃</td>
<td>methyl bis-alkyl or bis-arylthiomethyleneamino carboxylate</td>
<td>16,19</td>
</tr>
<tr>
<td>NC⁻⁻⁻NH⁻⁻⁻CO₂CH₃</td>
<td>carbomethoxycyanamide</td>
<td>16,20</td>
</tr>
<tr>
<td>Cl⁻⁻⁻C⁻⁻⁻C≡N</td>
<td>methyl bis-(chloro)methyleneamino carboxylate</td>
<td>21</td>
</tr>
<tr>
<td>S⁻⁻⁻C⁻⁻⁻N⁻⁻⁻CO₂CH₃</td>
<td>methoxycarbonyl isothiocyanate</td>
<td>15,22</td>
</tr>
</tbody>
</table>

Owing to the electron donating effects of the adjacent nitro group, the 4-methoxy or chloro group is readily converted to the 3-nitro-4-aniline derivative (18). Reduction of the nitro group by a variety of methods gives (19), which is ring closed to the desired benzimidazole using methoxycarbonyl-S-methylisothiourea.

To prepare oxfendazole, the necessary diamine (24) is prepared by a series of reactions including a nucleophilic substitution of the chloro moiety of 2-amino-4-chloronitrobenzene (20) with thiophenol (21) in the presence of potassium carbonate. This reaction affords 2-amino-4-phenylsulfurylnitrobenzene (22). Oxidation of (22) with one equivalent of peracetic acid gives the sulfoxide (23), which is selectively hydrogenated to give (24). Oxfendazole is obtained by an annulation of the diamine system of (24) with 1,3-bis-(methoxycarbonyl)-S-methylisothiourea.

The synthetic steps required to prepare albendazole further illustrate how the benzene ring may be modified before ring closure to the benzimidazole system. In this five step synthesis, 4-chloro-2-nitroaniline (25) is first acetylated with acetic anhydride to give 1-acetamido-4-chloro-2-nitrobenzene (26). Treatment of (26) with potassium thiocyanate furnishes the key intermediate 1-acetamido-2-nitro-4-thiocyanatobenzene (27). Conversion of the thiocyanato group of (27) into the required n-propylthiо- analog, with a simultaneous conversion of the acetamido group to the free amine, is effected by treating (27) with 1-bromopropane in the presence of a base. Reduction of the nitro group of (28) provides the diamine (29), which is subsequently ring closed to albendazole.

In an alternative synthesis, mebendazole has also been reported to be prepared in good yield from benz-2,1,4-thiadiazines. 2-Amino-4-benzoylnitrobenzene (30) was con-
densed with methoxycarbonyl isothiocyanate to give an o-nitr-
arylthiocarbamoylcarbamate (31). Reduction with sodium
dithionite gives the key intermediate benzo-2,1,4-thiadiazine
(32). Reaction of (32) with triphenylphosphine gives a yield of
99%.

Both mebendazole and flubendazole have been prepared in
an improved overall yield by a series of reactions shown
below. In this synthesis, the key step is a ring closure of the
appropriate diamine with methoxycarbonyl isothiocyanate, in
the presence of dicyclohexyl carbodiimide (DDC) in acetoni-
trile. The overall yields are 77% of mebendazole and 55% of
flubendazole, respectively.

Poor drug absorption and lack of water solubility are
problems that limit the use of most benzimidazole carbamates
against intestinal parasites. In addition, recently developed
resistance to the current commercially available drugs by
certain parasites is also of concern, and together these prob-
lems have prompted the development of new benzimidazole
carbamate types. Among these are heterocyclic isosteres,
compounds which contain a heterocyclic core other than
benzimidazole. Prodrugs are being developed that are appro-
priately substituted benzene molecules that are enzymatically
converted to an active benzimidazole carbamate after absorp-
tion by the animal under treatment.

A series of 6-substituted imidazo[1,2-a]pyridine-2-
carbamates have been prepared, and one of these (40) has
shown higher activity than any known benzimidazole against
certain parasites. To synthesize (40), the picoline (34) is pre-
pared by the addition of chlorine to 5-ethyl-2-methylpyrid-
ine (33) and is subsequently dehydrohalogenated with a strong
base to furnish the 5-trichloro substituted intermediate (35).
Four more synthetic steps (35–39) are necessary in order to
convert the 2-methyl group of (35) to the 2-amino derivative
(39). Ring cyclization of (39) with methyl (chloroacetyl) carba-
mate produced the target compound (40). This compound is
still under investigation.

Examples of prodrugs are thiofhanate (methyl) (41),
febantel (42), and netobimin (43), all of which are conver-
ted to benzimidazole carbamates by the host. For example,
accomplished by treatment of the 5-methylisothiourea derivative (45) with taurine. It should be noted that netobimin as a salt is freely soluble in water and, as such, has major advantages over the benzimidazoles per se. This is an area of research that has great promise.

We have attempted to show a few examples of benzimidazole syntheses that have shown great value to humankind. Does the synthesis of new benzimidazoles still have merit, and is research in this area still going on? The answer is yes. Resistance to the now commercially available benzimidazoles has developed and poor oral absorption remains a problem which have yet to be solved.

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References