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PREPARATION OF FUNCTIONALIZED DERIVATIVES OF BENZIMIDAZOLE: ALBENDAZOLE AND ITS SULFOXIDE AND SULFONE

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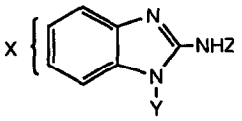
Abstract. A series of substituted benzimidazoles, especially albendazole and its oxidized derivatives, have been prepared with pendant carboxylic acid functional groups attached to three different positions of the benzimidazole ring. The acids were converted to reactive esters with 3-hydroxysuccinimide and DCC and coupled to proteins.

Introduction

Methyl 2-benzimidazole carbamate, **1**, is the parent of an important class of anthelmintics used in livestock.[1,2] Albendazole **2**, as well as its sulfoxide and sulfone metabolites, are among the most potent members of this class.[3] We are developing an immunoassay to screen food products for adulterant levels of these drugs. Since antibodies are required for the immunoassay, benzimidazole, albendazole and its oxidized metabolites must



	X	Y	Z
1.	H	H	CO_2CH_3
2.	C_3H_7S	H	CO_2CH_3
3.	H	H	H
4.	C_3H_7S	H	H
	Functionalization of the Benzimidazole Nitrogen		
5.	H	CH_2CO_2H	CO_2CH_3
6.	C_3H_7S	CH_2CO_2H	CO_2CH_3
	Functionalization of the 2-Amino Group		
7.	H	H	$CO(CH_2)_2CO_2H$
8.	C_3H_7S	H	$CO(CH_2)_2CO_2H$
9.	$C_3H_7S(O)$	H	$CO(CH_2)_2CO_2H$
10.	$C_3H_7S(O)_2$	H	$CO(CH_2)_2CO_2H$
	Functionalization of the 5(6) Position through Sulfur		
11.	HS	H	CO_2CH_3
12.	$HO_2C(CH_2)_2S$	H	CO_2CH_3
13.	$HO_2C(CH_2)_2S(O)$	H	CO_2CH_3
14.	$HO_2C(CH_2)_2S(O)_2$	H	CO_2CH_3

be made antigenic by preparing derivatives with a pendant arm containing a reactive functional group and coupling this group to a protein. The unique feature of this biologically active, heterocyclic system is that its parent, 1*H*-benzimidazol-2-ylamine, **3**, can be derivatized at three different locations: at the benzimidazole ring nitrogen, at the 2-amino group and, for the albendazole analog, **4**, at the 5(6) position (depending on the site of ring protonation) of the aromatic ring system through sulfur. By substituting at each of these sites, variable protein conjugates can be formed. These carboxylic acid derivatives were coupled to proteins (horseshoe crab hemocyanin, horseradish peroxidase and BSA) *via* their N-hydroxysuccinimidyl esters in DMSO because they are insoluble in other solvents. This is the first time that DMSO was used as a solvent in the coupling reaction.

Functionalization of the Benzimidazole Ring Nitrogen

Methyl 2-Benzimidazole carbamate, **1**, and albendazole, **2**,were alkylated with $BrCH_2CO_2CH_3$ using K_2CO_3 in DMF and hydrolyzed with NaOH in a mixed solvent system consisting of dioxane, THF, ethanol and water. The salts were acidified to pH 3 and isolated as the free acids, **5** and **6**.

Functionalization of the 2-Amino Group

Replacement of the entire carbamate group by a succinamic acid group was chosen as an alternative method of forming functionalized derivatives of **1**. The 2-amino derivative, **3**, and its albendazole analog, **4** were prepared by the method of Ram[4]. The amines, **3** and **4**, were treated with succinic anhydride to give the succinamic acids, **7** and **8**. Since the oxidation products of albendazole are metabolites, the carbamate groups of albendazole sulfoxide and albendazole sulfone were cleaved with potassium hydroxide in methanol to give 5-(propylsulfinyl)-1*H*-benzimidazol-2-yl amine and 5-(propylsulfonyl)-1*H*-benzimidazol-2-yl amine, respectively. The amines were acylated with succinic anhydride to give the succinamic acids, **9** and **10**.

Functionalization of the 5(6) Position of the Aromatic Ring

Derivatives of **2** in which the terminal position of the thiopropyl group is functionalized were prepared by cleaving the propyl group from the sulfur atom of albendazole with Na in $NH_{3(liq)}$[5,6] to give the aromatic thiol, **11**. The benzimidazole and carbamate moieties were unaffected by this treatment. **11** was treated with ethyl 4-bromobutanoate to give the thioether with a terminal ester (methyl 5-((3-carboxyethyl)propylthio)-1*H*-benzimidazol-2-yl carbamate) which was saponified to give **12.** As an alternative route to haptens of the oxidation products of albendazole, **12** was oxidized to the sulfoxide, **13**, with $(C_4H_8)_4N^+$ IO_4^- and to the sulfone, **14**, with *meta*-chloroperbenzoic acid. A mixed solvent system of CF_3CO_2H in DMF was used in the oxidation since **12** and its derivatives are very insoluble in other solvent systems.

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