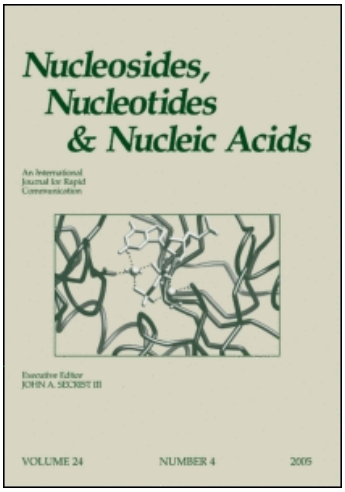

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STUDIES DESIGNED TO INCREASE THE STABILITY AND ANTIVIRAL ACTIVITY (HCMV) OF THE ACTIVE BENZIMIDAZOLE NUCLEOSIDE, TCRB

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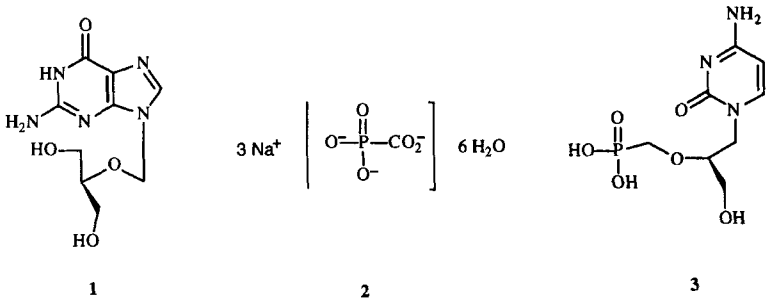
ABSTRACT: The potent activity of 2,5,6-trichloro-1-(ß-D-ribofuranosyl)benzimidazole (TCRB) against Human Cytomegalovirus with the concomitant low cellular toxicity at concentrations that inhibit viral growth prompted considerable interest in this research area. This interest was moderated by the pharmacokinetic studies of TCRB in rats and monkeys that revealed the instability of TCRB *in vivo*. These studies suggested that the instability was due to a cleavage of the glycosidic bond *in vivo* which released the heterocycle (2,5,6-trichlorobenzimidazole) into the bloodstream. This prompted us to initiate synthetic studies designed to increase the stability of the glycosidic bond of TCRB and BDCRB. Several synthetic approaches to address this and other problems are presented.

INTRODUCTION

Human cytomegalovirus (HCMV) is one of eight human herpes viruses. By adulthood, more than half of all Americans will have been infected with HCMV.[1] Although HCMV infections in immunocompetent individuals are usually asymptomatic, in immunocompromised patients, HCMV infections are often lifethreatening. Transplant recipients[2] and individuals with acquired immunodeficiency syndrome (AIDS)[3] are particularly vulnerable to HCMV. HCMV is also a leading cause of birth defects as a consequence of fetal infection *in utero*.[4] Currently, there are three FDA-approved drugs available (FIGURE 1) for the treatment of HCMV infections: ganciclovir (**1**)[5], foscarnet (**2**)[6] and cidofovir (**3**).[7] Unfortunately, all three drugs can produce some significant side effects and have limited oral bioavailability. Moreover, virus strains resistant to each of

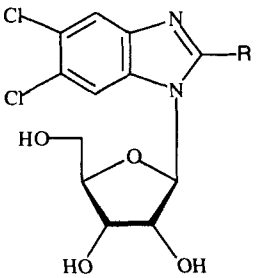


1 2 3

FIGURE 1. Structures of ganciclovir (**1**), foscarnet (**2**), cidofovir (**3**).

these drugs are emerging.[8] Consequently, there is still the need for a more potent and selective antiviral drug to treat HCMV infections.

As part of our research for new anti-cancer[9] and antiviral drugs,[10-11] a number of benzimidazole nucleosides were synthesized. Certain compounds, including 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB, **4**) and 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole (BDCRB, **5**) (FIGURE 2), have shown potent activity against HCMV with low cellular toxicity at concentrations which inhibit viral growth. Biological evaluation of TCRB has established that its antiviral activity does not involve inhibition of DNA, RNA or protein synthesis.[12] TCRB appears to act by a unique mechanism, which involves inhibition of viral DNA processing and virus assembly. However, pharmacokinetc studies of **4** in rats and monkeys[14] revealed that **4** disappeared

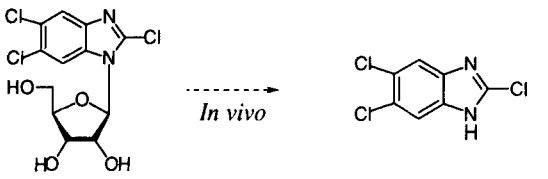


4 R = Cl, TCRB
5 R = Br, BDCRB

FIGURE 2. TCRB AND BDCRB

rapidly from the bloodstream following either intravenous or oral dosage. The disappearance of **4** was correlated with an increased blood concentration of 2,5,6-trichlorobenzimidazole (**6**) and suggested that the glycosidic bond in **4** (aminal linkage) was unstable *in vivo* (FIGURE 3). This instability of the glycosidic bond prompted us to initiate studies on the synthesis of more stable analogs

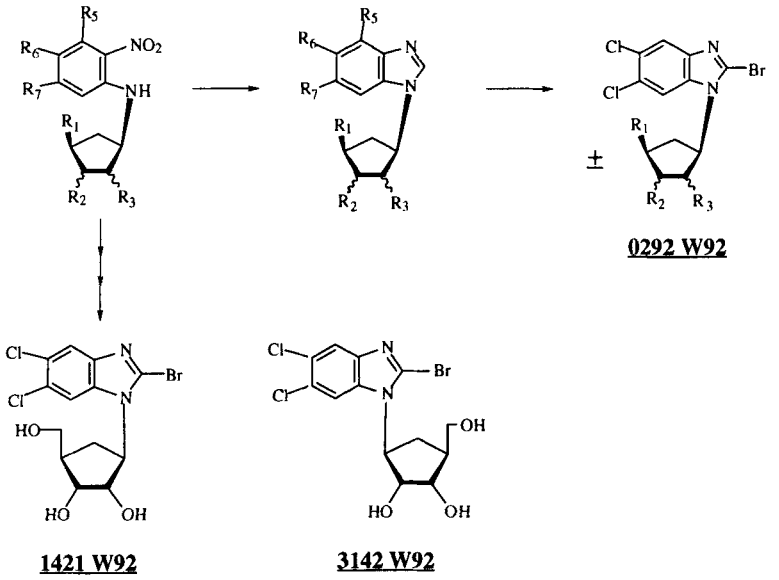
of **4**. In fact, we had already initiated research in several diverse areas structurally related to TCRB and BDCRB with the potential of a more stable glycosidic bond.



4 **6**

FIGURE 3. TCRB (**4**) is metabolically unstable in vivo and the glycosidic bond is cleaved to give the aglycon **6**.

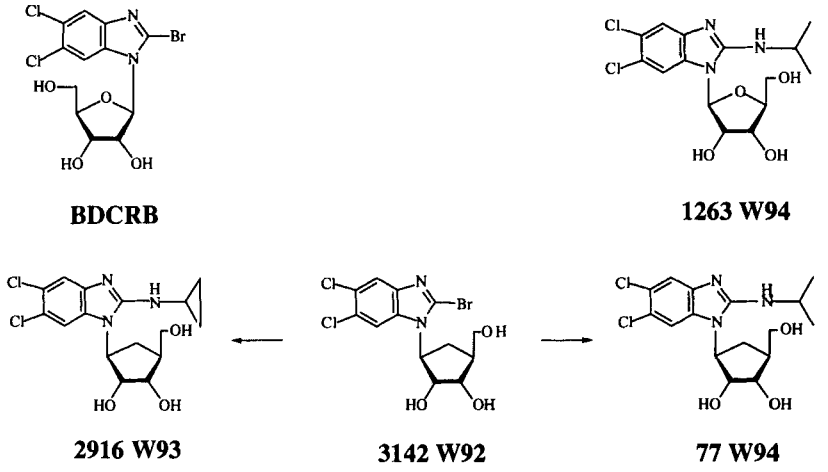
A collaboration was initiated in July 1991 to synthesize the carbocyclic analogs of TCRB and BDCRB. The initial phase of this collaboration produced[15] a mixture of the BDCRB analog (**±029W92**) (SCHEME 1). This was followed by a resolution of the



SCHEME 1. The "D" and "L" carbocyclic analogs of BDCRB.

mixture to provide the pure compounds **1421W92** and **3142W92**. Although the mixture (±) **0292W92** had shown some good activity (2.0 μM) against HCMV, evaluation of the

resolved BDCRB analogs **1421W92("D")** and **3142W92("L")** against HCMV in a plaque assay furnished some interesting results. It was determined that **3142W92("L")** was over 20 times more effective than **1421W92("D")** (0.57 μM vs. >12.0 μM) and essentially as effective as BDCRB but possessing the potential for an increase in the stability of the glycosidic bond. This prompted the synthesis of several new compounds that were structurally related to **3142W92**. These studies (SCHEME 2) included a number of chemical changes on the benzene moiety as well as changes at the two position of the benzimidazole ring including the very interesting 2-cyclopropylamino- (**2916W93**) and the 2-isopropylamino-(**77W94**) analogs which exhibited very good activity against

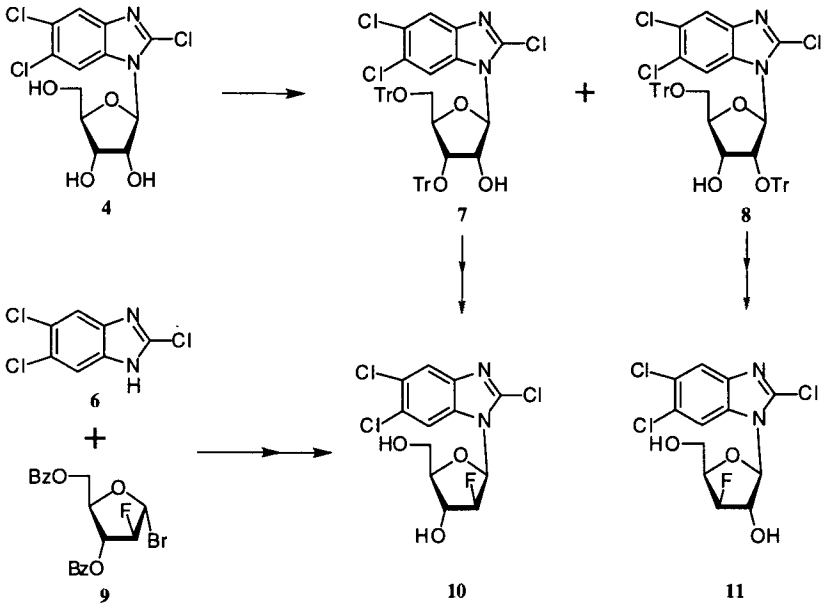


SCHEME 2. Synthesis of the carbocyclic analog of **1263 W94**.

HCMV. It is interesting to note the very close structural similarity between **77W94** and **1263W94** since **1263W94** is currently in clinical trials[17]. Additional studies are underway in this specific research area.

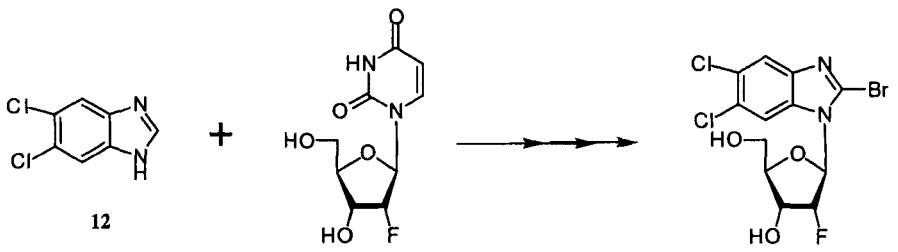
Another approach designed to increase the stability of the glycosidic bond, involved the synthesis of TCRB and BDCRB analogs with a fluoro group on the carbohydrate moiety. Synthesis of these analogs was first approached through chemical conversions of a suitably protected derivative of TCRB. Treatment of the protected[18] TCRB analogs **7** and **8** with DAST[19] was followed by deprotection to furnish 2,5,6-trichloro-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)benzimidazole (**10**) and 2,5,6-trichloro-1-(3-deoxy-3-fluoro-β-D-xylofuranosyl)benzimidazole (**11**) (SCHEME 3). However, the very low yield of the arabino analog **10** prompted us to explore an alternative procedure. The condensation of

2,5,6-trichlorobenzimidazole (**6**) with 1-bromo-3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranose[20] (**9**) using conditions similar to those described in the literature[21] gave an



SCHEME 3. Synthesis of the deoxy-fluoro arabino and xylo analogs of TCRB.

anomeric mixture which was separated and deprotected to provide a good yield of the 2'-deoxy-2'-fluoro-β-D-arabino TCRB analog **10**. We elected to use an enzymatic procedure for the synthesis of the 2'-deoxy-2'-fluororibofuranosyl analogs. An enzymatic transfer of the carbohydrate moiety of **13**[22] to **6** was found to be unsuccessful. However, an enzymatic transfer of the carbohydrate moiety of **13** to 5,6-dichlorobenzimidazole (**12**) was successful (SCHEME 4) and after appropriate protection, introduction of bromine at the two position with NBS in dioxane and a facile deprotection with sodium carbonate, we obtained the BDCRB analog 2-bromo-5,6-dichloro-1-(2-deoxy-2-fluoro-β-D-ribofuranosyl)benzimidazole (**14**). The three target fluorinated benzimidazole nucleosides **10, 11,** and **14** were evaluated for their *in vitro* activity against herpes simplex virus type 1 (HSV-1) and human cytomegalovirus (HCMV) for cytotoxicity in human foreskin fibroblasts (HFF) and a human oral carcinoma cell line (KB cells). These studies revealed a definite decrease in the activity of **10, 11** and **14** against HCMV in comparison to the activity observed for the lead compounds TCRB and BDCRB. These observations[23] were not as surprising as the concomitant increase in cytotoxicity which effected a dramatic

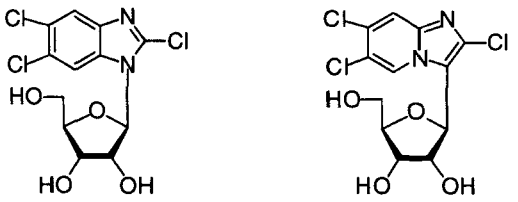


12 13 14

SCHEME 4. Synthesis of the deoxy-fluororibo analog of BDCRB.

decrease in the selectivity index. These data led to a decision that further studies involving the stability of the glycosidic bond of the nucleosides were not warranted.

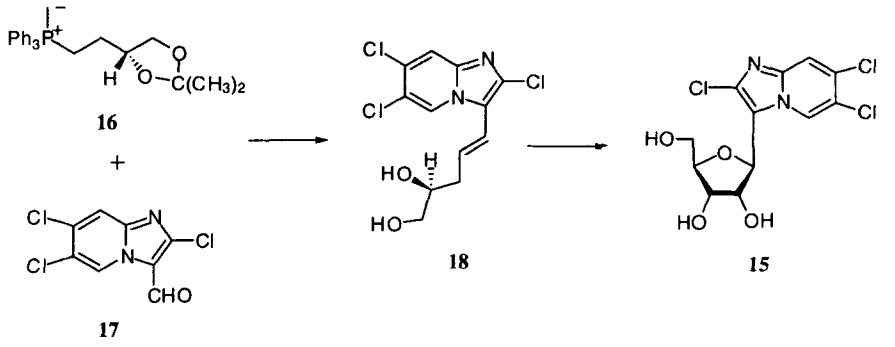
Another alternative approach which has been used successfully is to replace a C-N glycosidic bond with a C-C bond, while keeping most of the heterocyclic aglycone structurally intact and the exocyclic groups of the aglycone in approximately the same juxtaposition This prompted us to initiate studies designed to incorporate these specific features into a target compound. This target compound involved a simple transposition of the N-1 and C-7a atoms of TCRB, i.e., 2,6,7-trichloro-3-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyridine (**15**) (FIGURE 4). The Wittig olefination of 3-formyl-2,6,7-trichloroimidazo[1,2-*a*]pyridine[24] (**17**) with 3,4-(S)-O-isopropylidene-3,4-dihydroxybut-1-yl triphenylphosphonium iodide[25] (**16**) gave a good yield of 2,6,7-trichloro-3-(1,2(S)-dihydroxypent-4(E)en-5-yl)imidazo[1,2-*a*]pyridine (**18**). A



4 15

FIGURE 4. The imidazo[1,2-*a*]pyridine C-nucleoside **15** has a C-glycosidic bond that should be more stable in vivo.

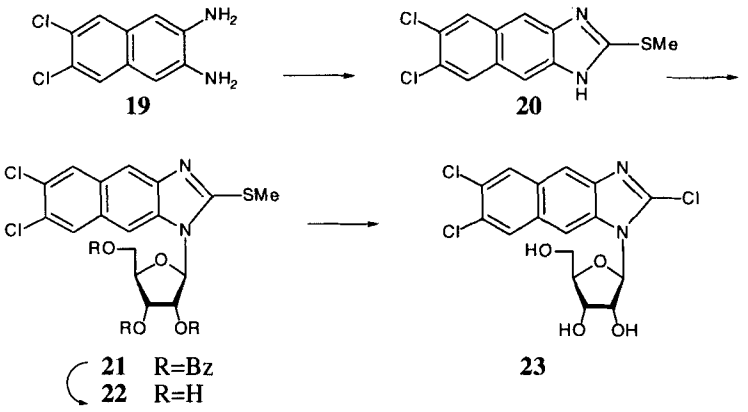
multi-step conversion using **18** as the starting material resulted in the formation of the target compound **15** (SCHEME 5). The biological evaluation of compound **15** against HCMV provided some very unexpected results. This simple transposition of the N-1



SCHEME 5. Synthesis of 2,6,7-trichloro-3-(β-D-ribofuranosyl)imidazo[1,2-*a*]pyridine

and C-7a atoms of TCRB resulted[26] in a complete lack of activity and cytotoxicity for compound **15**. Based on these results, further studies on the stability of the glycosidic bond of **15** were not warranted.

Another approach involved a study on the effect which a benzene spacer between the imidazole ring and the dichlorobenzene ring of TCRB would have on the stability of the glycosidic bond. The key intermediate for the synthesis of the requisite aglycon was the previously unknown 2,3-diamino-6,7-dichloronaphthalene (**19**) which was prepared from 1,2-**bis**(bromomethyl)-4,5-dichlorobenzene[27] via a multi-step synthesis (SCHEME 6). The diamino compound **19** was treated with (thiocarbonyl)diimidazole to effect a ring



SCHEME 6. Synthesis of a linear tricyclic nucleoside analog of TCRB.

annulation followed by methylation to afford the requisite aglycon **20**. Ribosylation of **20** furnished the nucleoside **21** which on deprotection furnished nucleoside **22** and chlorination of nucleoside **22** furnished[28] the target compound 2,6,7-trichloro-1-(β-D-

ribofuranosyl)naphtho[2,3-*d*]imidazole (**23**). The evaluation of nucleoside **23** against HCMV revealed that the linear tricyclic analog of TCRB retained essentially the same activity as TCRB but this activity was accompanied by a large increase in cytotoxicity to give essentially no selectivity. Additional studies on the use and evaluation of other "spacers" are currently in progress.

One of my colleagues (L.B.) has previously stated that *"Benzimidazoles will be a really BIG fishing hole"* and this was a very good prediction since studies in this specific research area have provided the following:

DNA Synthesis Inhibitor DNA Maturation Inhibitor RNA Processing Inhibitor ? ?

1263 W94 - Clinical Trials **275175X** - Clinical Trials **UM 2382 & UM 2389**

We are currently investigating ("fishing") (FIGURE 5) other chemical modifications related to the above examples of C-nucleosides and N-nucleosides at the University of Michigan as part of a National Cooperative Drug Discovery Group

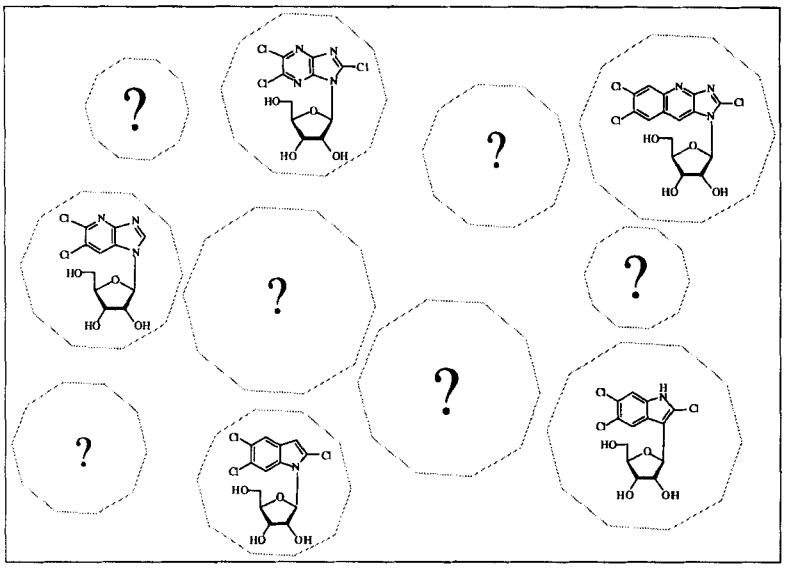


FIGURE 5. Current and Future Research

(U-19-AI-31718) (circles with structures) from the National Institute of Allergy and Infectious Diseases, N.I.H., as well as research by the University of Michigan and Glaxo Wellcome, Inc. as part of a research agreement (DRDA-94292) (circles with question marks) between the University of Michigan and Glaxo Wellcome, Inc.

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