

**A SELECTIVE SEARCH FOR BIOLOGICALLY ACTIVE BIPARTATE  
NUCLEOSIDE PRODRUGS: I**

**BİYOLOJİK AKTİVİTESİ OLAN İKİ KISIMLI NÜKLEOSİT PRODRUG'LARI  
İÇİN SEÇİCİ BİR TARAMA: I**

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**ABSTRACT**

*The primary goal of prodrug is to provide an effective and desired concentration of a parent drug at the target organ. This goal is usually achieved by improved absorption, but ideally this must occur without accompanying toxicity. For this aim, various alkyl and amino acid esters of nucleosides have been synthesized to inhibit metabolism and improve oral bioavailability. In this review, it was described important examples of prodrugs such as ddl, ara-A and AZT which are already in the market for treatment of HIV (Human Immunodeficiency Virus) and some other biologically active prodrugs that were synthesized recently.*

*Key words: Prodrugs, Bipartate approaches, Activity*

**ÖZET**

*Ön ilaç yapmadaki temel amaç, ana ilacın hedef organa istenen ve etkili bir konsantrasyonda ulaşmasını sağlamaktır. Bu hedef genellikle absorpsiyonun artırılması ile başarılmıştır, fakat ideal olarak toksisitenin eşlik etmediği şekilde olmalıdır. Bu amaçla, çeşitli nükleosit alkil ve amino asit esterleri, metabolizmanın inhibe edilmesi ve oral biyoyararlanımlarının artırılması için sentezlenmişlerdir. Bu derlemede, ddl, ara-A, AZT gibi halihazırda HIV (İnsan İmmün Yetmezlik Virüsü) 'nün tedavisi için ilaç piyasasında olan önemli ön ilaç örnekleri ve son zamanlarda sentezlenen diğer bazı aktif ön ilaçlar tanımlanmaktadır.*

*Anahtar kelimeler: Ön ilaç, Bipartat yaklaşım, Aktivite*

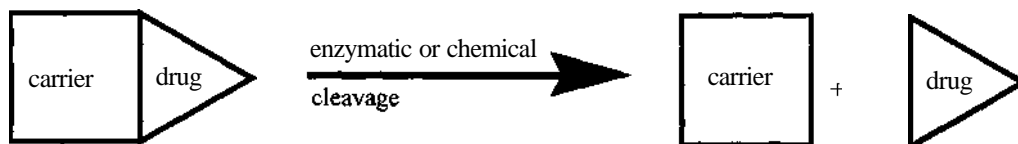
**INTRODUCTION**

The development of nucleoside prodrugs capable of undergoing intracellular activation to corresponding nucleotide has become an area of intense interest.

A Prodrug was defined by Albert (1) as being an agent, which undergoes chemical or enzymatic transformations *in vivo* to yield the active parent drug. Albert suggested that the

prodrug approach could be used to optimize the physicochemical properties, thereby improving the pharmacological and toxicological profiles of a given drug. He envisioned the possibility of site specific delivery or targeting of drugs to their specific site of action. However, most prodrugs that are used as therapeutic agents are unable to achieve site-specific delivery due to an incomplete understanding of physicochemical properties of the parent drug and physiological properties of the site of action. There are two types of prodrug approaches: bipartate and tripartate (2-5). The bipartate prodrug approach consists of a carrier or specifier moiety linked to a pharmacologically active compound.

The carrier targets the drug to the active site by making it a specific substrate for an enzyme that converts the prodrug to the parent drug. Additionally, the carrier may enhance the physicochemical properties of the drug entity. *In vivo* the carrier is cleaved from the prodrug by enzymatic hydrolysis of the bond linking carrier and drug, thus releasing the active drug in the body (Figure 1).



**Figure 1.** Bipartate Prodrug

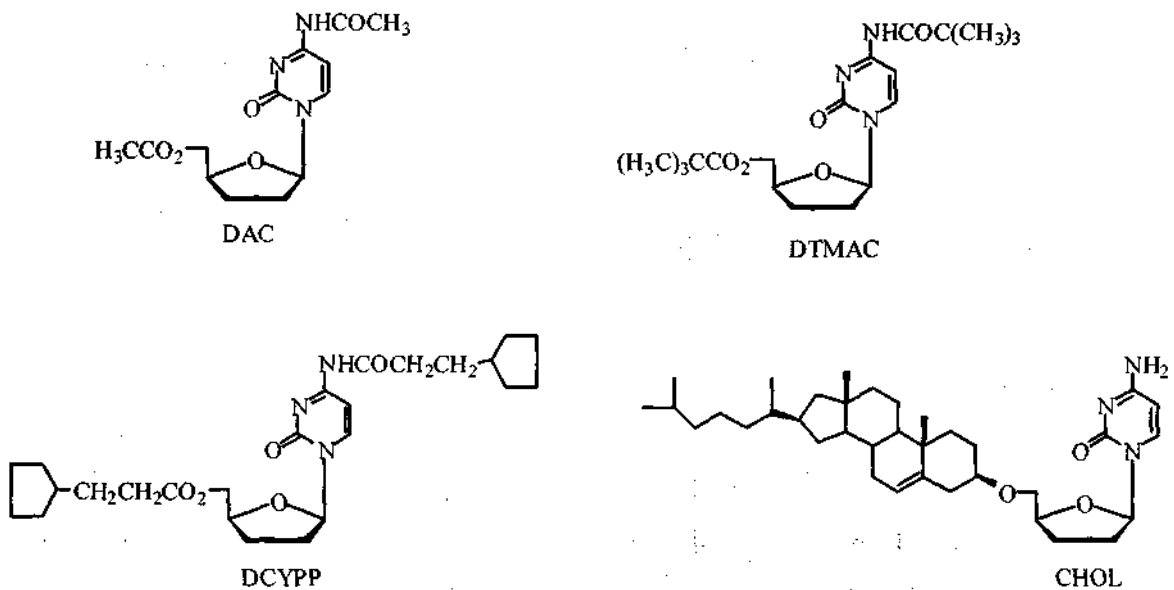
### **Bipartate Approach Applied to Nucleosides**

Many investigators have synthesized various derivatives of antiviral and anticancer agents as a method of improving their chemotherapeutic properties *via* prevention of enzymatic degradation, sustained release of parent compound, and increased bioavailability or site-specific targeting (6). These prodrugs are substrates of esterases or amidases that cleave the bond between carrier and nucleoside analogues. Subsequently, it is critical that the prodrug be a suitable substrate for the target enzyme. The rate of biotransformation of the prodrug to form the drug depends upon the clinical need for acute or sustained release of the parent compound.

### **Bipartate Approach involving ester, ether and amide linkages between nucleosides and carriers**

Lipophilic prodrugs of 2',3'-dideoxycytidine (ddC) such as *N*<sup>4</sup>,5'-diacetyl-ddC (DAC), *N*<sup>4</sup>,5'-ditrimethylacetyl-ddC (DTMAC), *N*<sup>4</sup>,5'-dicyclopentylpropionyl-ddC (DCYPP) and 5'-cholesteryl-ddC (CHOL) were designed to target the brain (Figure 2) (7). The partition

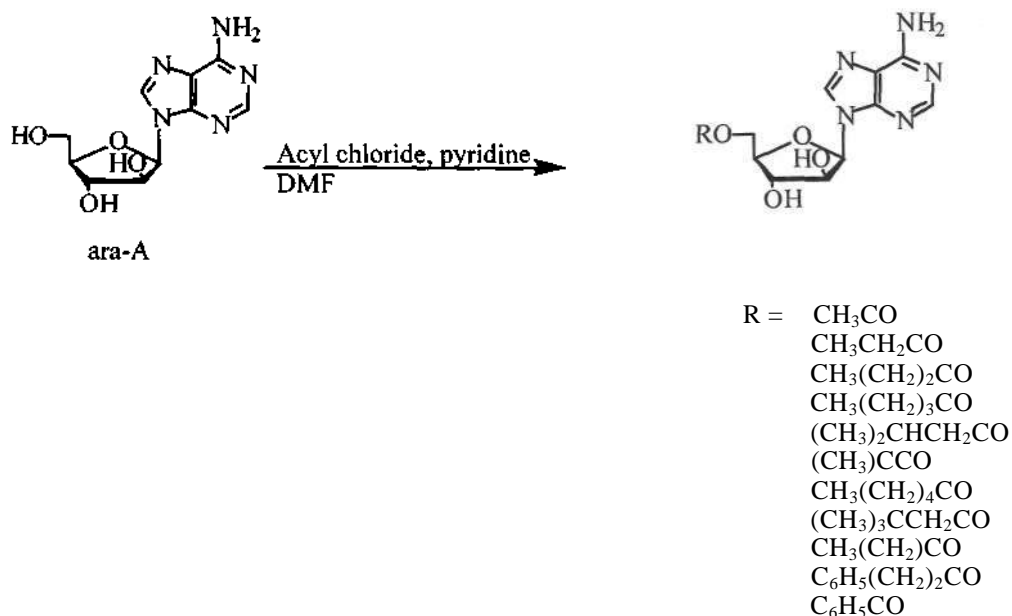
coefficient values for the compounds increased from 0.03 for ddC to 0.37, 28, 63 and 483 for DAC, DTMAC, DCYPP and CHOL, respectively. *In vitro* stability studies in phosphate buffered saline solution, pH 7.4 (PBS), human serum, mouse serum, mouse brain homogenate and liver homogenate showed that CHOL was the most stable in all media while DAC, DTMAC and DCYPP were stable only in PBS. Therefore, the latter three prodrugs were suitable substrates for enzymatic hydrolysis. The half-lives for DCYPP in mouse serum, liver and brain homogenates were 0.04, 0.35 and 0.34 h, respectively. The half-life for DAC in PBS was longer than that of DTMAC (0.82 vs. 0.38 h). In mouse brain homogenate, the half-life for DTMAC was 3.9 h while DAC had a half-life of 1.6 h. Nevertheless, both of these prodrugs were rapidly metabolized in mouse liver homogenate with half-lives of 0.36 h and 0.23 h for DAC and DTMAC, respectively. *In vivo* studies in mice, however, showed that the relative brain exposure (brain/serum concentrations ratio) was not improved by administering DAC and DTMAC prodrugs. DTMAC yielded a relative brain exposure value of 0.023, which was similar to that of ddC (0.028). No ddC was detected in the brain after DAC administration. Thus, although highly lipophilic, these prodrugs were not able to produce the desired result, which was to increase ddC brain delivery.



**Figure 2.** Lipophilic prodrugs of ddC

Baker *et al.* (8) synthesized 5'-*O*-acyl derivatives 9-(3-D-arabinofuranosyladenine (ara-A, vidarabine) in an effort to improve its pharmacokinetic properties (Scheme 1). Vidarabine has been useful in the treatment of fatal herpes encephalitis (9) and has demonstrated possible use as a topical agent for ocular herpes keratitis (10).

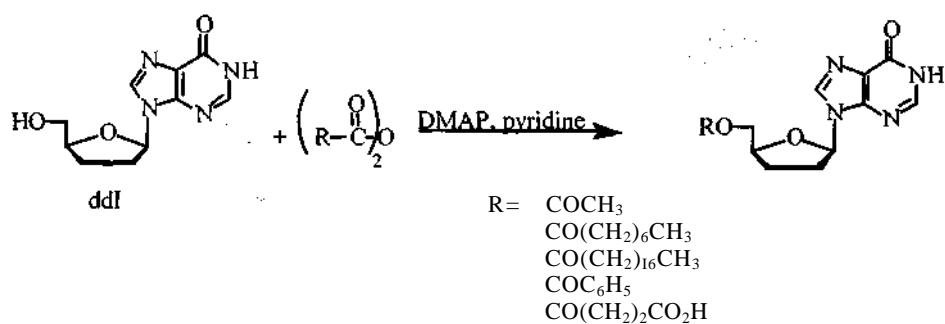
Unfortunately, its therapeutical use is limited by low aqueous solubility, short half-life due to deamination by adenosine deaminase and low lipophilicity, which hinders its use as a topical antiviral agent. The objective of the prodrug was to increase resistance to deamination and to increase lipophilicity. Among the prodrugs synthesized, the 5'-*O*-valeryl derivative was found to be the most promising because of its aqueous solubility (15-fold more soluble than ara-A), lipophilicity and anti-HSV activity.



Scheme 1. Synthesis of 5'-*O*-esters of Ara-A

Kawaguchi *et al.* (11) synthesized ester prodrugs to improve the bioavailability of 2',3'-dideoxyinosine (ddI) (Scheme 2), a drug approved for the treatment of HIV infection (12). Like other dideoxynucleoside analogues, the active form of ddI is the triphosphate metabolite, responsible for eliciting viral suppression by chain termination or competitive inhibition of reverse transcriptase (13). In comparison with AZT, ddI is less toxic towards human hematopoietic progenitor cells (14). Nevertheless, ddI has a major drawback in that it is very

labile to hydrolysis of the C'-N bond under acidic conditions (15). Lipophilic esters of ddl were therefore designed and synthesized to slow acidic hydrolysis down, thus increasing bioavailability. Among these prodrugs, the succinate (suc-ddl) was the only one that possessed a low partition coefficient (-1.5) and ample aqueous solubility (0.1g/ml) making it a promising prodrug candidate. Surprisingly, all of the prodrugs failed to increase the stability of ddl under acidic conditions. Susceptibility studies of prodrugs in rat plasma, liver and duodenum homogenates resulted in quantitative release of the parent drug, ddl. The octanoyl derivative C8-ddI was the most susceptible to enzymatic hydrolysis while suc-ddl was the least. These results were consistent with those reported for other nucleoside esters of 2', 3'-dideohydro-3'-deoxythymidine (d4T) (16,17) and AZT (18,19). C8-ddI, Bz-ddl (the benzoate) and suc-ddl prodrugs had relative bioavailabilities of 32%, 31% and 11.5%, respectively after oral administration. The oral bioavailability of the parent compound ddl was 15.2% in rats. The increase in bioavailability of C8-ddI and Bz-ddl may be attributed to low water solubility, which slows down chemical decomposition. Even though it displayed susceptibility to enzymatic hydrolysis, the stearic ester C18-ddI did not generate ddl after oral administration mainly due to its very low aqueous solubility. At the other extreme, hydrophilic esters suc-ddl (11.5%) and C2-ddI (4.5%) showed poor bioavailability, indicating a relationship between the degree of hydrophilicity and the bioavailability of ester prodrugs, as well as their enzymatic susceptibility.

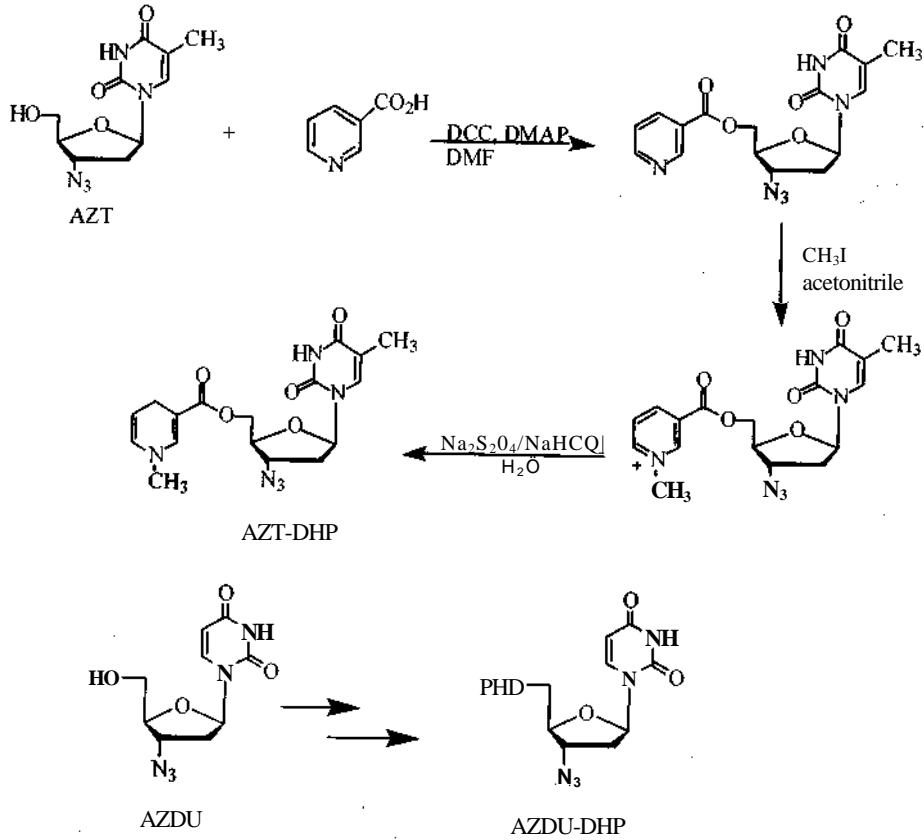


Scheme 2. Synthesis of esters of ddl

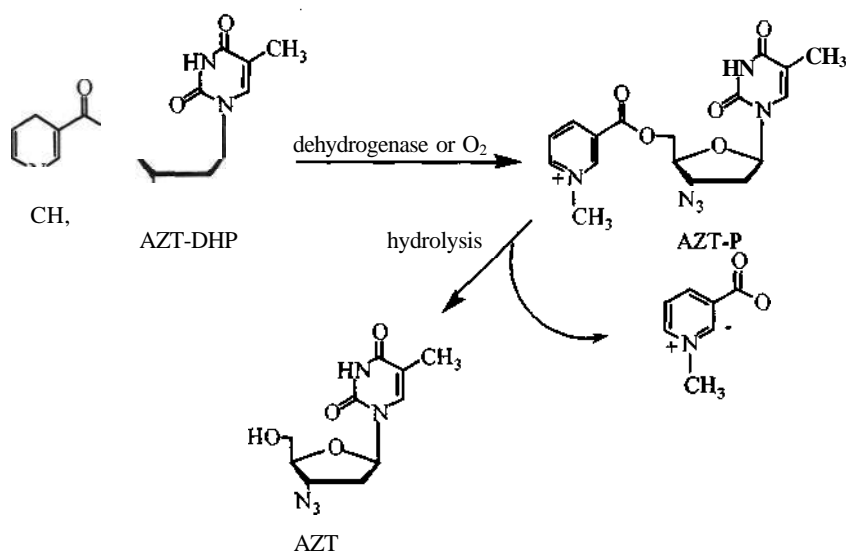
The expected advantages of the AZT prodrugs can be multiple = synergic drug interactions (20,21), enhancement of AZT intracellular uptake (22), increase of AZT brain delivery (23) and bypass of the first AZT phosphorylation step into the cells (24,25).

Torrence *et al.* (26) synthesized a dihydropyridine ester of 3'-azido-3'-deoxythymidine (AZT-DHP) in an attempt to increase the brain concentration of AZT by means of a redox delivery system (Scheme 3). The 1,4-dihydropyridine-pyridinium approach is based on the capability of the neutral lipophilic 1,4-dihydropyridine adduct to penetrate the blood-brain barrier. Once in the brain, dehydrogenases convert the dihydropyridine to pyridinium-form, which is potentially trapped in the brain due to its positive charge. The pyridinium adduct (AZT-P) is then hydrolyzed, releasing the parent compound (Figure 3). AZT-P was found to be more potent than AZT against murine sarcoma virus (MSV)-induced transformation of murine embryo C3H fibroblasts.

Chu *et al.* (27) also synthesized a dihydropyridine (DHP) derivative of 3'-azido-2',3'-dideoxy-5'-*O*-uridine (AZDU) as a prodrug to improve brain delivery of the parent compound (Scheme 3). *In vitro*, AZDU-DHP exhibited half-lives of 4.33, 0.56, 0.17 h in human serum, mouse serum, and mouse brain homogenate respectively, whereas AZT-DHP had half-lives of 7.70, 1.40 and 0.18 h. *In vivo*, these prodrugs displayed areas under the serum concentration-time curves (AUC) in mice similar to those of the parent compounds. Nevertheless, the brain AUCs for both AZDU (11.43  $\mu\text{g h/mL}$ ) and AZT (11.28  $\mu\text{g h/mL}$ ) after the administration of prodrugs were greater than that of parent compounds AZDU (2.09  $\mu\text{g h/mL}$ ) and AZT (1.21  $\mu\text{g h/mL}$ ). This indicates a substantial increase in exposure to the anti-HIV agents with relative exposures of 5.47 and 9.32 for AZDU and AZT, respectively. Other dihydropyridine derivatives of nucleosides, such as the bis-DHP derivative of 2',3'-dideoxycytidine (ddC), failed to produce enhanced brain delivery *in vitro* and *in vivo* studies, most likely due to their instabilities (28). 2',3'-Dideoxy-2',3'-didehydro-5'-*O*-[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]thymidine (d4T-DHP) showed an increased concentration of the parent compound in the brain of mice (29,30).



Scheme 3. Synthesis of AZT-DHP

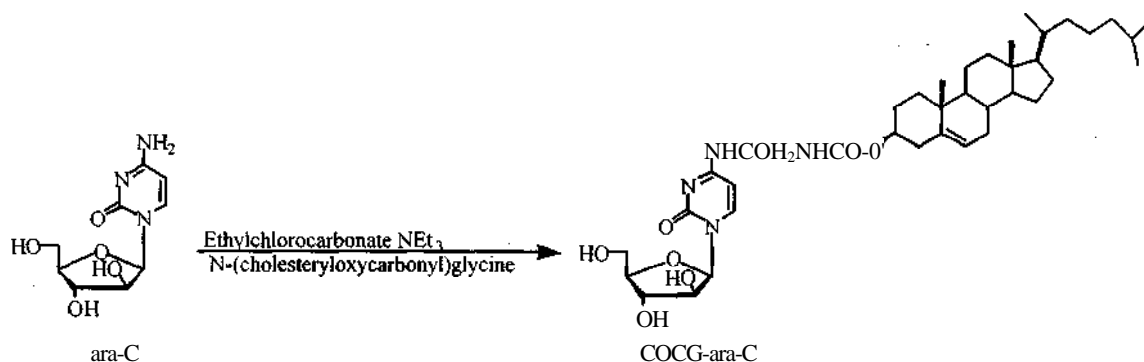


**Figure 3.** Proposed metabolism of AZT-DHP

Ara-C is a well-known drug used in the treatment of human acute myeloblastic and lymphoblastic leukemia (31,32). It has also been reported to be effective in combination against solid tumor (33). However, the clinical activity of ara-C has been limited by cytidine deaminase catalyzed deamination resulting in a short half-life of the compound (34). *N*<sup>4</sup>-[*N*-Cholesteryloxycarbonyl]glycyl]-ara-C (COCG-ara-C) was designed as a prodrug to provide sustained release delivery following intravenous administration, therefore allowing an increased half-life for ara-C (35).

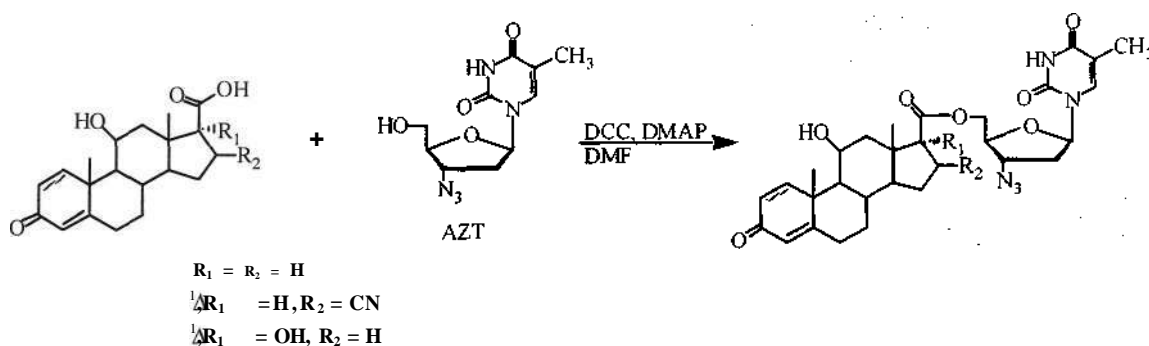
In the synthesis of COCG-ara-C, (cholesteryloxycarbonyl)glycine was condensed with *N*-(cholesteryl-oxycarbonyl)glycine (36) in the presence of ethylchlorocarbonate and triethylamine (Scheme 4). COCG-ara-C was found labile to chemical as well as enzymatic hydrolysis (rat, mouse and human plasma). *In vitro* studies showed that this prodrug possessed only one-fifth of the antitumor activity of ara-C against P 388 leukemia cells. In contrast, COCG-ara-C bearing liposomes were found to be superior to ara-C against L 1210 leukemia in mice. Prodrug bearing liposomes displayed antitumor activity against human lung adenocarcinoma A549 xenograft implanted in kidney capsules of mice.





**Scheme 4.** Synthesis of COCG-ara-C

Sharma *et al.* (37) also designed and synthesized steroidal esters of AZT to improve its pharmacokinetic profile and to reduce dose-related bone marrow toxicities such as severe anemia and leukemia by influencing its half-life (Scheme 5). 5'-*O*-gluronidation is the major metabolic process that results in a rapid elimination of AZT. Therefore, 5'-hydroxyl protection can inhibit this metabolic pathway, which may improve uptake by target tissues. The coupling of AZT with a steroidal moiety was conceptualized as being the ideal approach for increasing the half-life and intracellular delivery of AZT. Preliminary *in vitro* studies showed that the activity of the prodrug was comparable to that of AZT against HIV infected CEM cells.

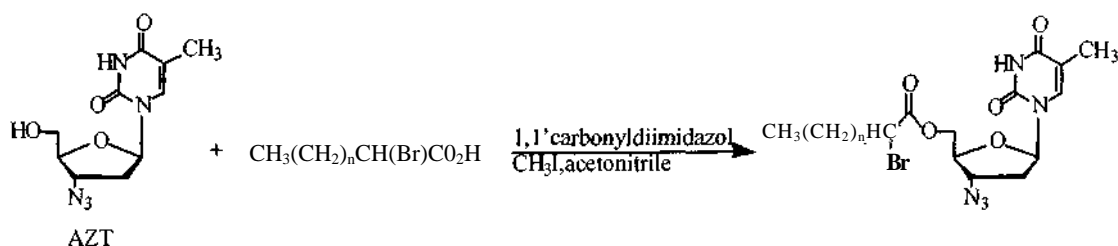


**Scheme 5.** Synthesis of steroidal derivatives of AZT

Parang *et al.* (38) synthesized a dually active prodrug, 3'-azido-2',3'-dideoxy-5'-*O*-(2-bromomyristoyl)thymidine by using 1,1'-carbonyldiimidazole in the presence of methyl iodide to couple AZT with 2-bromomyristic acid to yield the ester prodrug (Scheme 6).

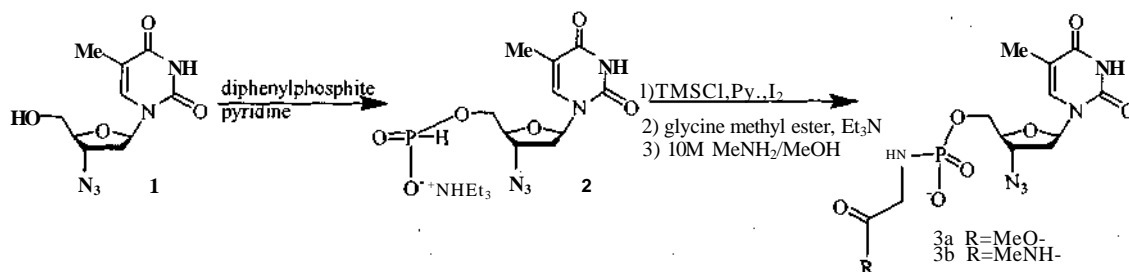
Bromomyristic acid, along with other 2-halotetradecanoic acids, is an inhibitor of *Cryptococcus neoformans*, which attacks the CNS of late-stage HIV patient (39). Therefore, the 2-bromomyristic acid portion of the prodrug could serve as a lipophilic carrier and an anti-fungal agent.

This dual acting prodrug was found to have a distribution half-life of 4.2 min in comparison with 4.4 min for AZT. The short distribution of the lipophilic prodrug may be associated with sequestration by lipoidal tissues. The elimination half-life (428.5 min) was substantially greater than that of AZT (112.5 min). Surprisingly, the prodrug was detected in mouse blood throughout the experiment, which indicates that metabolic stability of the prodrug may play a major part in the persistence of this nucleoside ester in the blood along with possible redistribution from peripheral tissues to blood. *In vivo* studies confirmed that high concentrations of prodrug are distributed in the liver. AZT concentrations within the brain were not significantly changed, but the concentration of AZT increased from 10 to 25 nmol/g one minute after administration of the prodrug. The relative brain exposure (AUC for AZT in the brain after prodrug administration divided by AUC for AZT after parent drug administration) was 2.07 which indicates favorable delivery.



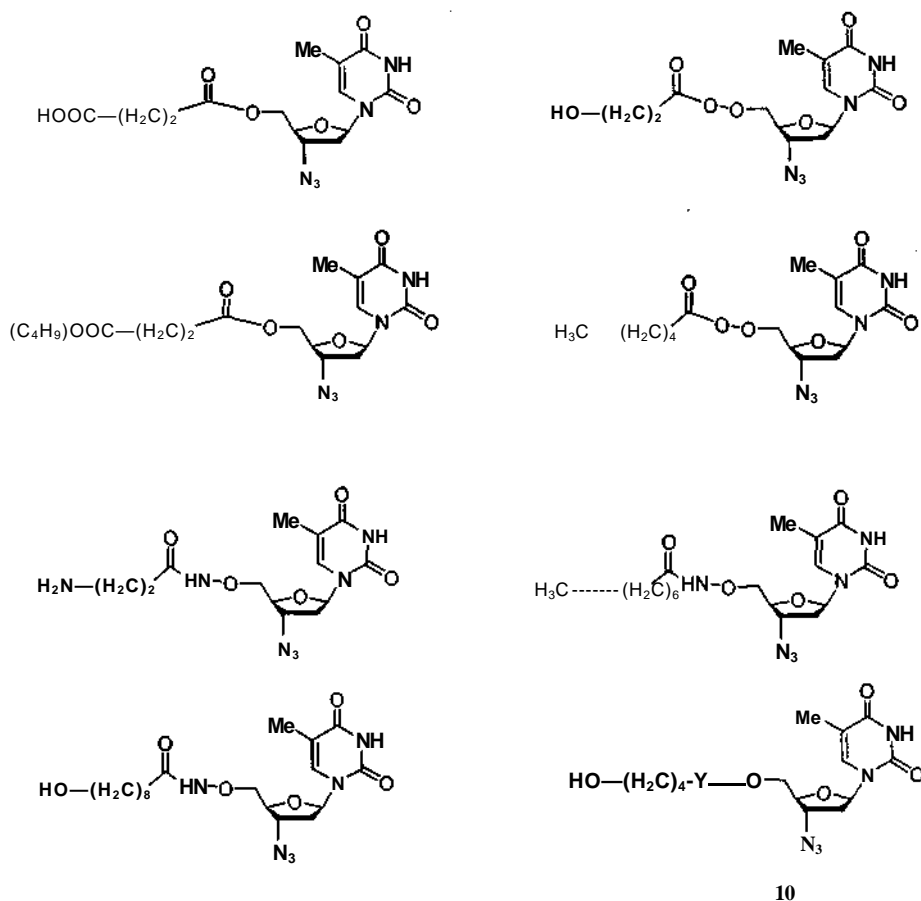
**Scheme 6.** Synthesis of the bromomyristoyl ester of AZT

Besides the evaluation of thymidine kinase (TK) activity in AIDS patients treated with AZT pronucleotides, anti-breast cancer activity of AZT phosphoramidate monoesters were investigated (Scheme 7) (40). Alkyl amide phosphoramidate monoesters of 3'-azido-3'-deoxythymidine **3a,b** were synthesized and evaluated for *in vitro* cytotoxicity toward the human pleural effusion breast adenocarcinoma cell line, MCF-7. The methyl amide of the AZT-(L)-glycyl phosphoramidate **3b** exhibited greater cytotoxicity relative to the methyl ester **3a**. In addition, the *in vivo* potency of these compounds may exceed that of AZT, since they exhibit significantly longer half-lives and larger volumes of distribution in rats than the parent nucleoside.



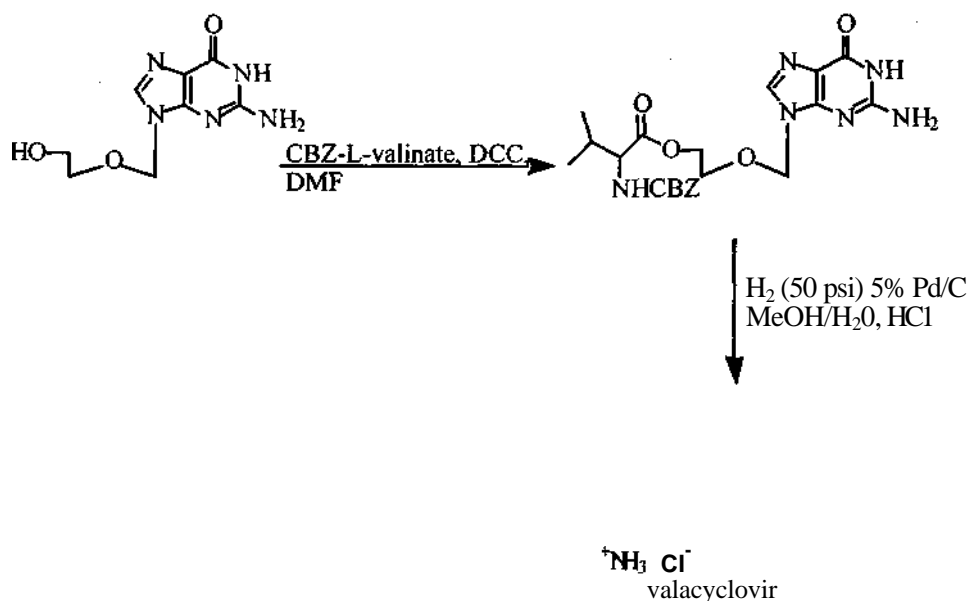
Scheme 7. Synthesis alkyl Amide Phosphoramidate Monoesters of 3'-Azido-3'-deoxythymidine

3'-Azido-3'-deoxythymidine-5'-yl *O*-(co-hydroxyalkyl) carbonate prodrugs of zidovudine (AZT) have been synthesized in an effort to enhance its uptake by HIV-1 infected cells and its anti-HIV activity (41). The prodrug moieties include 5'-*O*-Carbonate, 5'-*O*-Carbamate, and 5'-*O* ester (Figure 4). Analogues of the 3'-azido-3'-deoxy thymidin-5'-yl *O*-((co-hydroxyalkyl) carbonate series were particularly interesting since they were rearranged through an intramolecular cyclic process during their enzymatic hydrolysis. Evidence of this prodrug rearrangement was confirmed by comparison of the serum half-lives of 5'-*O*-carbonate prodrugs with their corresponding 5'-*O*-ester- and 5'-*O*-carbamate-AZT prodrugs. Our results suggest that the specific intramolecular rearrangement associated with the 3'-azido-3'-deoxythymidine-5'-yl *O*-(co-hydroxyalkyl) carbonate prodrugs could explain the remarkable anti-HIV activity of this series of AZT prodrugs. Prodrug 10 may therefore have better clinical potential than AZT for the treatment of AIDS.



**Figure 4.** Structure of the three series of 5'-O-AZT prodrugs.

Valacyclovir (2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl-L-valinate) was synthesized as a prodrug of the antiviral agent acyclovir (Scheme 8) (42). Acyclovir was the first antiviral agent that possessed potent and selective viral inhibition (43). Nevertheless, acyclovir efficacy was limited due to poor oral bioavailability (44). In-patient, the approximate bioavailability was 20 to 25% after oral administration. Low bioavailability of acyclovir may be linked to its lack of sufficient aqueous solubility and possibly to the mechanism of absorption (39). Once in the circulatory system, acyclovir has a half-life of 2.5 h, with 67% eliminated in the urine *via* renal excretion (45). However, valacyclovir at a 1000 mg dose had an absolute bioavailability of 54% after oral administration to healthy patients (46). The absorption of 'valacyclovir appeared to involve the saturable dipeptide transporter system of the intestinal brush border.

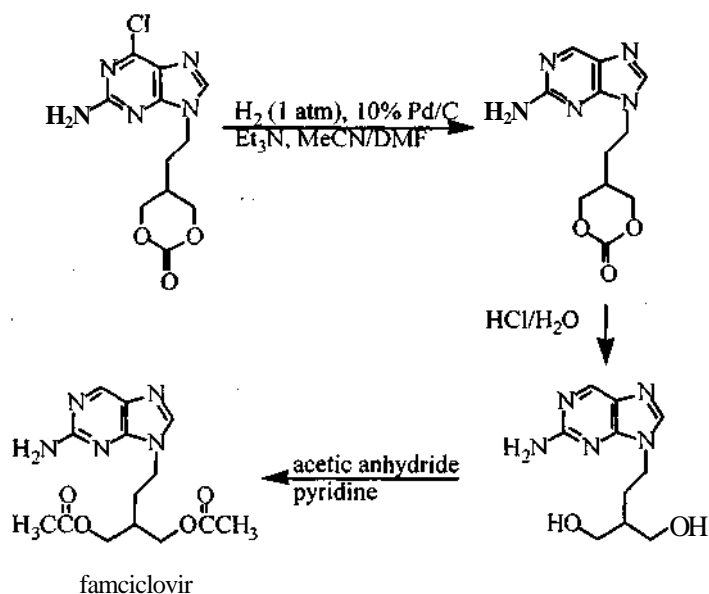


**Scheme 8.** Synthesis of valacyclovir

Penciclovir (9-(4-hydroxy-3-hydroxymethyl-but-1-yl)guanine), an acyclic nucleoside, is a broad inhibitor of herpes viruses, which include herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and hepatitis B virus (HBV) (47-49). As with acyclovir, its efficacy is limited by low oral bioavailability in rats and mice (50,51). As a prodrug, famciclovir (2-amino-9-(4-acetoxy-3-acetoxymethylbut-1-yl)purine) was designed to improve oral absorption (Scheme 9) (52,53). Famciclovir, the 6-deoxy diacetate ester of penciclovir, was found to increase the bioavailability of penciclovir to 77% (54). Bioconversion of famciclovir to penciclovir requires three metabolic steps: two deacetylations and oxidation of the heterocyclic ring (Figure 5) (55). Cytosolic enzyme aldehyde oxidase of the liver is responsible for the oxidation of the guanine ring. In-patient, between 50 and 67% of famciclovir is converted to penciclovir between 30 min to 1 h after oral administration (56). The remaining amount consisted mostly of the 6-deoxy mono-acetate. Approximately 21% of the oral dose was observed in feces, with 17% and 4% consisting of 6-deoxy-penciclovir and penciclovir, respectively. This observation suggests incomplete absorption of famciclovir and ultimately degradation to 6-deoxy-penciclovir and penciclovir in the digestive tract.

Kim *et al.* (57) synthesized racemic mixtures of alkylcarbonate derivatives of 2-amino-9-(3-hydroxymethyl-4-alkoxycarbonyloxybut-1-yl)purines as dual prodrugs of penciclovir. The prodrugs require enzyme-mediated oxidation and hydrolysis in order to generate the parent drug penciclovir as with famciclovir. These prodrugs showed no significant activity at concentrations up to 100  $\mu\text{M}$  against human cytomegalovirus (HCMV) in human embryonic lung fibroblast (HEL) 299 cells. Nevertheless, no cytotoxicity was exhibited at a maximum concentration of 100  $\mu\text{M}$  in HEL 299 cells.

In rats, the bioavailabilities of ganciclovir range from 29 to 45% after prodrug administration. The monoisobutyrate derivative showed the highest ganciclovir bioavailability (45%) which was 15 fold higher than that of ganciclovir.



Scheme 9. Synthesis of famciclovir

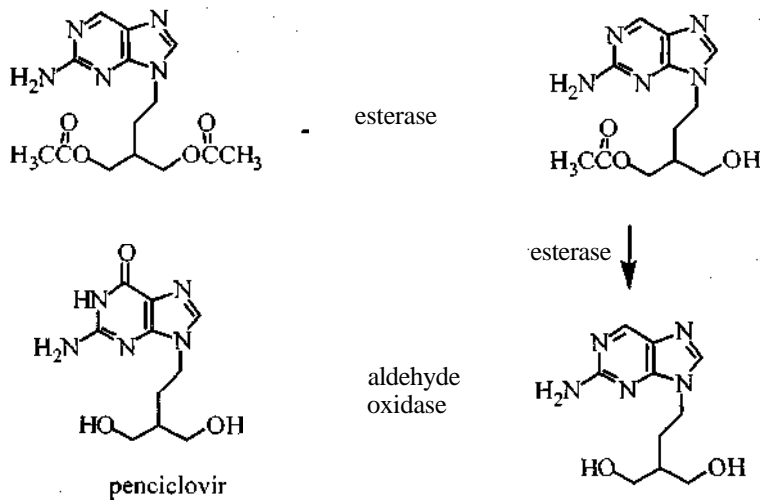
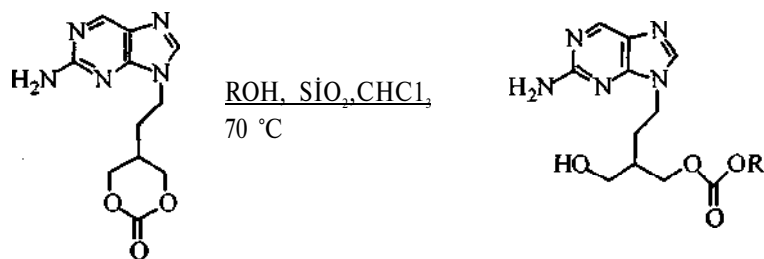


Figure 5. Major route of metabolism of famciclovir

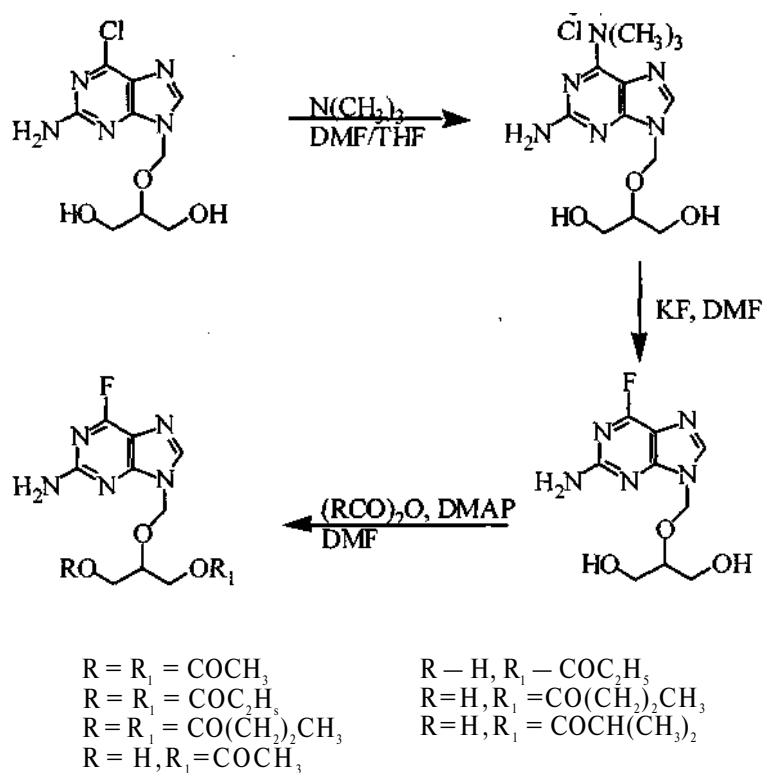
In the synthesis of monocarbonates of 2-amino-9-(3-hydroxymethyl-4-alkoxycarbonyloxybut-1-yl)purines, the diol prepared by condensation of *O*-benzyl-2-bromoethanol and diethyl malonate (58). The 2-amino-6-chloropurine analogue was subjected to hydrogenation in the presence of triethylamine to obtain the 6-deoxy cyclic carbonate. Ring opening reactions of the 6-deoxy-cyclic carbonate were performed with the appropriate alcohol in the presence of activated silica gel (Scheme 10).

Having reported that 2-amino-9-(1,3-dihydroxy-2-propoxymethyl-6-fluoropurine) undergoes bioconversion to ganciclovir in the presence of calf intestinal mucosal adenosine deaminase (59), Kim *et al.* (60) decided to prepare its mono and diesters as prodrugs of ganciclovir (GCV) (Scheme 11). Ganciclovir [9-(1,3-dihydroxy-2-propoxymethyl)guanine] is the drug of choice for the treatment of Cytomegalovirus (CMV) retinitis (61,62). Recently, oral administration of ganciclovir has been approved by the Food and Drug Administration (FDA) as an alternative to intravenous infusion for the maintenance therapy of CMV retinitis (63). However, the bioavailability of orally administered ganciclovir in humans ranges from 2 to 7%.



R = Me, Et, n-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *n*-pentyl, isopentyl

**Scheme 10.** Synthesis of carbonates of famciclovir



**Scheme 11.** Synthesis of mono and diesters of the 6-fluoro analogue of ganciclovir

Among the compounds synthesized and evaluated in rats as prodrugs of ganciclovir, the monoisobutyrate appeared to provide the highest ganciclovir bioavailability (45%) followed by the diisobutyrate (42%), the diacetate (41%), the monobutyrate (41%), the monopropionate (39%), the dipropionate (35%), the dibutyrate (35%) and the monoacetate (29%). The monoacetate, monopropionate, monobutyrate and monoisobutyrate prodrugs were very stable at pH 7.4 ( $t_{1/2} \geq 7$  days) but had relatively short half-lives at pH 1.2 ( $t_{1/2} = 60$ -83 min).



## Conclusions

The prodrug concept has been utilized to overcome specific problems associated with certain drugs. Investigators, through the knowledge of factors influencing drug absorption, distribution, metabolism and excretion, have designed and synthesized prodrugs to resolve some problems associated with the parent drugs. Chemical modification to increase lipid solubility to facilitate oral absorption, however, can be limited by the dissolution rate. Furthermore, a prodrug may apparently be poorly absorbed into systemic circulation as a result of first-pass gastrointestinal and liver metabolism during its initial passage through these organs.

The most important examples of prodrugs such as valaciclovir and famciclovir have shown that chemical manipulation of nucleosides can overcome the shortcomings of parent compounds.

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