PRODRUGS OF PHOSPHONATE NUCLEOTIDE ANALOGUES

This non-provisional application is a continuation application of application Ser. No. 10/354,207, filed Jan. 28, 2003, now abandoned, which is a continuation application of application Ser. No. 09/909,560, filed Jul. 20, 2001, now abandoned, which is a regular utility application of provisional application 60/220,021, filed Jul. 21, 2000, now abandoned, all of which are incorporated herein by reference.

This application relates to prodrugs of methoxyphosphonate nucleotide analogues. In particular it relates to improved methods for making and identifying such prodrugs.

Many methoxyphosphonate nucleotide analogues are known. In general, such compounds have the structure $A\text{-}OCH_2P(O)(OR)_2$ where A is the residue of a nucleoside analogue and R independently is hydrogen or various protecting or prodrug functionalities. See U.S. Pat. Nos. 5,663,159, 5,977,061 and 5,798,340, Oliyai et al, "Pharmaceutical Research" 16(11):1687-1693 (1999), Stella et al., "J. Med. Chem." 23(12):1275-1282 (1980), Aarons, L., Boddy, A. and Petrak, K. (1989) *Novel Drug Delivery and Its Therapeutic Application* (Prescott, L. F. and Nimmo, W. S., ed.), pp. 121-126; Bundgaard, H. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 70-74 and 79-92; Banerjee, P. K. and Amidon, G. L. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 118-121; Notari, R. E. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 135-156; Stella, V. J. and Himmelstein, K. J. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 177-198; Jones, G. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 199-241; Connors, T. A. (1985) *Design of Prodrugs* (Bundgaard, H., ed.) pp. 291-316. All literature and patent citations herein are expressly incorporated by reference.

SUMMARY OF THE INVENTION

Prodrugs of methoxyphosphonate nucleotide analogues intended for antiviral or antitumor therapy, while known, traditionally have been selected for their systemic effect. For example, such prodrugs have been selected for enhanced bioavailability, i.e., ability to be absorbed from the gastrointestinal tract and converted rapidly to parent drug to ensure that the parent drug is available to all tissues. However, applicants now have found that it is possible to select prodrugs that become enriched at therapeutic sites, as illustrated by the studies described herein where the analogues are enriched at localized focal sites of HIV infection. The objective of this invention is, among other advantages, to produce less toxicity to bystander tissues and greater potency of the parental drug in tissues which are the targets of therapy with the parent methoxyphosphonate nucleotide analogue.

Accordingly, pursuant to these observations, a screening method is provided for identifying a methoxyphosphonate nucleotide analogue prodrug conferring enhanced activity in a target tissue comprising:

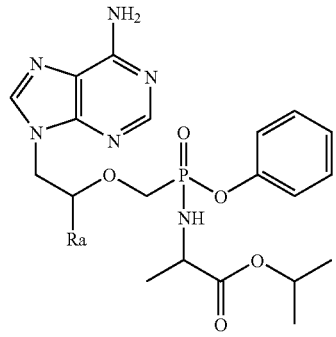
(a) providing at least one of said prodrugs;
(b) selecting at least one therapeutic target tissue and at least one non-target tissue;
(c) administering the prodrug to the target tissue and to said at least one non-target tissue; and
(d) determining the relative antiviral activity conferred by the prodrug in the tissues in step (c).

In preferred embodiments, the target tissue are sites where HIV is actively replicated and/or which serve as an HIV reservoir, and the non-target tissue is an intact animal. Unexpectedly, we found that selecting lymphoid tissue as the target

tissue for the practice of this method for HIV led to identification of prodrugs that enhance the delivery of active drug to such tissues.

A preferred compound of this invention, which has been identified by this method has the structure (1),

(1)

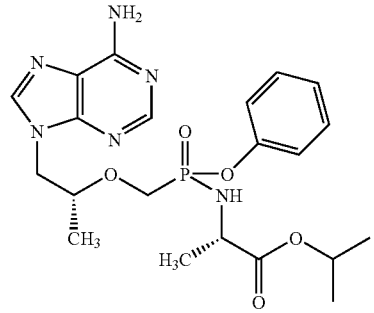


where Ra is H or methyl,

and chirally enriched compositions thereof, salts, their free base and solvates thereof.

A preferred compound of this invention has the structure (2)

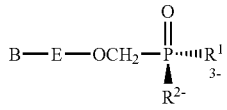
(2)



and its enriched diasteromers, salts, free base and solvates.

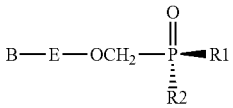
In addition, we unexpectedly found that the chirality of substituents on the phosphorous atom and/or the amidate substituent are influential in the enrichment observed in the practice of this invention. Thus, in another embodiment of this invention, we provide diastereomerically enriched compounds of this invention having the structure (3)

(3)



which are substantially free of the diastereomer (4)

(4)



wherein

R^1 is an oxyester which is hydrolyzable in vivo, or hydroxyl;

B is a heterocyclic base;

R^2 is hydroxyl, or the residue of an amino acid bonded to the P atom through an amino group of the amino acid and having each carboxy substituent of the amino acid optionally esterified, but not both of R^1 and R^2 are hydroxyl;