design of prodrugs

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Design of prodrugs

Preface

During the last decade it has become more obvious that the commonly used processes of delivering therapeutic agents to the sites of their action within the body are generally inefficient and unreliable. Optimization of drug delivery and, consequently, improvement in drug efficacy implies an efficient and selective delivery and transport of a drug substance to its site of action. Recognition of the importance of drug delivery for the therapeutic indices of many types of drugs has been followed by a large increase in research activities in this area, and much attention has been focussed on approaches which aim at enhancing the efficacy and reducing the toxicity and unwanted effects of drugs by controlling their absorption, blood levels, metabolism, distribution and cellular uptake.

Prodrug design comprises an area of drug research that is concerned with the optimization of drug delivery. A prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule.

A molecule with optimal structural configuration and physicochemical properties for eliciting the desired therapeutic response at its target site does not necessarily possess the best molecular form and properties for its delivery to its point of ultimate action. Usually, only a minor fraction of doses administered reaches the target area and, since most agents interact with non-target sites as well, an inefficient delivery may result in undesirable side effects. This fact of differences in transport and in situ effect characteristics for many drug molecules is the basic reason why bioreversible chemical derivatization of drugs, i.e., prodrug formation, is a means by which a substantial improvement in the overall efficacy of drugs can often be achieved.

Prodrug research matured as a branch of pharmaceutical research during the 1970s. Over the past decade this chemical approach to optimization of drug delivery has undergone considerable expansion, largely as a result of an increased awareness and understanding of the physicochemical factors that affect the efficacy of drug delivery and action. Several drugs are now used clinically in the form of prodrugs, and as the prodrug approach is becoming an integral part of the new drug design

process one may expect that the new drugs in many cases will appear as prodrugs.

The purpose of the present book is to provide a comprehensive and basic source of information on the recent developments within the prodrug area and on the rational basis for prodrug design. Admittedly, there are numerous review articles and a few texts devoted to one or more topics in the prodrug area, but a current and comprehensive treatment appears to be lacking.

The book is divided into eleven chapters, each written by active scientists in the field. The first chapter provides a review and classification of bioreversible derivatives for various functional groups and chemical entities occurring in drug substances. For most examples discussed due attention is given to the potential therapeutic benefits achievable by the derivatization, e.g., improved absorption. In chapter 2 the design of prodrugs through consideration of enzyme-substrate specificities is discussed. Various enzyme classes are considered and their usefulness as prodrug reconversion sites is discussed in detail.

The ideal site and rate for drug release from a prodrug depend upon the specific delivery problems which are meant to be overcome by the prodrug design. Therefore, the pharmacokinetic aspects are of great importance in prodrug design. Chapter 3 is devoted to these aspects and it provides surveys of the theory accompanying each goal achievable with a prodrug, methods for evaluating the success of the prodrugs and the practical limitations as evidenced by several examples, their successes and failures. Chapter 4 describes the use of the prodrug approach for the development of agents with prolonged duration of activity, including a discussion of polymeric prodrug sustained release delivery systems.

Chapter 5 deals with the very important area of providing site-specific delivery or targeting of drugs to their site of action by the prodrug approach. Several examples of site-specific delivery based on site-specific transport or prodrug cleavage are given, and the importance of the physicochemical properties of the parent drug to the site-specific delivery of drugs via prodrugs is stressed. The use of the prodrug approach to increase the therapeutic index of a drug is considered further in Chapter 6. An extensive review is given, with most examples being taken from amongst steroidal and non-steroidal anti-inflammatory agents, β-stimulants and anticancer agents.

The prodrug approach has been used frequently to solve pharmaceutical formulation problems, such as stability and solubilization. Chapter 7 treats this area of prodrug application in a physicochemical manner, with illustrative examples. In recent years the application of prodrugs to enhance the percutaneous absorption of drugs has received much interest, and this theme is treated in chapter 8. Besides reviewing the previous studies in the field, the chapter provides a rational basis for the design of prodrugs aiming at improving the delivery of drugs to the skin.

Chapter 9 is concerned with anticancer prodrugs. The emphasis is put on prodrugs which improve the pharmacokinetic properties of anticancer agents, and in particular prodrugs which are activated selectively in tumour cells to the active drug.

The design and utility of macromolecular prodrugs is a relatively new area which certainly is going to be the focus of intense research in the near future. In chapter 10 the use of albumin as a transport group or carrier for drugs and, in particular, enzymes is specifically discussed. The promising properties of such conjugates for drug targeting are discussed, as are the many pitfalls and possible disadvantages that any given system might have.

The final chapter (Ch. 11) on prodrugs versus soft drugs has been included in the book in order to clarify some common confusion about these two rather different terms. Whereas a prodrug is an inactive derivative which is activated predictably in vivo to the active drug, a soft drug is an active species like any other drug, but it is designed in such a way that it will undergo a predictable transformation or metabolism to an inactive metabolite. Thus, the common feature of prodrugs and soft drugs is only that a transformation in vivo is involved, it being either an activation (prodrugs) or an inactivation (soft drugs). By definition, the two terms are just opposite to each other. Several examples are given to illustrate the difference between prodrugs and soft drugs, but examples of prodrugs of soft drugs are also included.

This book presents the basic principles of prodrug design and illustrates these principles with many examples. In addition, it provides a comprehensive review of the most recent literature concerning the design and application of prodrugs. Hopefully, the book will be useful to all those concerned with drug delivery and drug design in universities or industry and will initiate new research for increased practical utilization of the prodrug concept.

Hans Bundgaard

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Design of Prodrugs (Bundgaard, H., ed.)

CHAPTER 1

Design of prodrugs: Bioreversible derivatives for various functional groups and chemical entities

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1. Introduction

A basal requisite for the prodrug approach to be useful in solving drug delivery problems is the ready availability of chemical derivative types satisfying the prodrug requirements, the most prominent of these being reconversion of the prodrug to the parent drug in vivo. This prodrug – drug conversion may take place before absorption (e.g., in the gastrointestinal tract), during absorption, after absorption or at the specific site of drug action in the body, all dependent upon the specific goal for which the prodrug is designed. Ideally, the prodrug should be converted to the drug as soon as the goal is achieved. The prodrug per se is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug. For example, prodrugs designed to overcome solubility problems in formulating intravenous injection solutions should preferably be converted immediately to drug following injection so that the concentration of circulating prodrug would rapidly become insignificant in relation to that of the active drug. Conversely, if the objective of the prodrug is to produce a sustained drug action through rate-limiting prodrug conversion the rate of the conversion should not be too high.

The necessary conversion or activation of prodrugs to the parent drug molecules in the body can take place by a variety of reactions. The most common prodrugs are those requiring a hydrolytic cleavage mediated by enzymic catalysis. Active drug species containing hydroxyl or carboxyl groups can often be converted to prodrug esters from which the active forms are regenerated by esterases within the body, e.g., in the blood. In other cases, active drug substances are regenerated from their prodrugs by biochemical reductive or oxidative processes. Sulindac, for example, is active only when reduced to its thioether form [1,2] and a prodrug of the pyridinium

quaternary compound, 2-PAM, is converted to the parent drug through an enzymatic oxidation process in the body [3 – 5]. Besides usage of the various enzyme systems of the body to carry out the necessary activation of prodrugs, the buffered and relatively constant value of the physiological pH (7.4) may be useful in triggering the release of a drug from a prodrug. In these cases, the prodrugs are characterized by a high degree of chemical lability at pH 7.4 while preferably exhibiting a higher stability at, for example, pH 3 – 4. As will be discussed below, examples of such prodrugs include *N*-Mannich bases and various ring-opened derivatives of cyclic drugs. A serious drawback of prodrugs requiring chemical (non-enzymic) release of the active drug is the inherent lability of the compounds, raising some stability-formulation problems, at least in cases of solution preparations. As will be shown later, such problems have, in particular cases, been overcome by using a more sophisticated approach involving pro-prodrugs or cascade latentiation, where use is made of an enzymatic release mechanism prior to the spontaneous reaction.

Several types of bioreversible derivatives have been exploited for utilization in designing prodrugs. The purpose of the present chapter is to discuss various chemical approaches to obtain prodrug forms, with due attention to the potential therapeutic benefits achievable by the prodrug approach and with emphasis on recently developed types of bioreversible derivatives. In the past, esters mostly have been considered as prodrug types, and the best known prodrugs are in fact esters of drugs containing hydroxyl or carboxyl groups. Various reviews [6, 7] have dealt

TABLE 1
Examples of Ester Derivatives Developed as Prodrugs for Drugs Containing a Carboxyl Group

Drug	Ester	Reference
Prostaglandins	Phenyl esters	39, 40
γ-Aminobutyric acid	Aliphatic and steroid esters	41, 42, 43
Acetylsalicylic acid	Methylsulphinylmethyl ester	44,45
	Triglycerides	46, 47
L-Dopa	Methyl ester	48
Niflumic acid	β-Morpholinoethyl ester	49
Non-steroidal anti-inflammatory drugs	Methyl esters	50
Amino acids	Glycolic and lactic acid esters	51
Carbenicillin	Aliphatic and aromatic esters	52
Ibuprofen	Guiacol ester	53
Indomethacin	Triglycerides	54, 55
	Phenyl esters	56
	Glycolic acid ester	57
Glutathione	Ethyl ester	57a
Nicotinic acid	Tetrapentaerythritol ester	58, 58a

with esters as prodrug types, and therefore this important class will only be briefly treated herein.

Some other reviews have, more or less specifically, dealt with various prodrug types [8 – 13] and/or paid much attention to enzyme systems available in the organism and their utilization for performing the necessary conversion of prodrugs [14 – 17]. Furthermore, much information on the subject can be gathered from reviews dealing with several other aspects of prodrugs [18 – 24]; see also other chapters in this book.

2. Esters as prodrugs for compounds containing carboxyl and hydroxyl groups

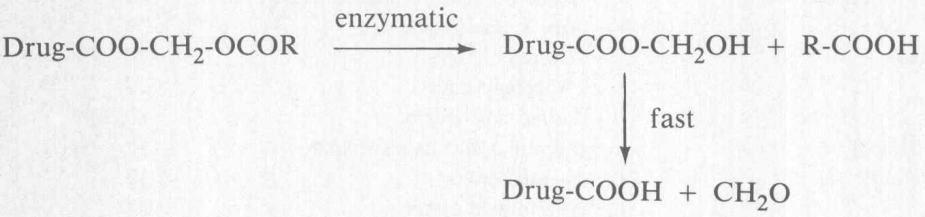
The popularity of using esters as a prodrug type for drugs containing carboxyl or hydroxyl functions (or thiol groups) stems primarily from the fact that the organism

TABLE 2
Examples of Ester Derivatives Developed as Prodrugs for Drugs Containing a Hydroxyl Group

Drug	Ester	Reference
Salicylic acid	Carboxylate and carbonate esters	59, 60
Paracetamol	Carbonate esters	61, 62
	Phosphate ester	63
Trichloroethanol	Carbonate esters	64, 65
	Phosphate ester	66
Cymarol	Diacetylester	67
Vidarabine	Mono- and diesters	68, 69
	Phosphate ester	70
Thymidine	Pivaloate	71
Oxazepam, lorazepam	Aliphatic and aromatic esters	72 – 74
	Amino acid esters	75
Metronidazole	Aromatic esters	76 – 78
	Phosphate ester	79
	Amino acid esters	80, 81
Chloramphenicol	Palmitate and hemisuccinate	82
Various steroids	Various esters	19
Phenols	Amino acid esters	83
Lincomycin	Dialkylcarbonate esters	84
Epinephrine	Dipivaloate	85
Etilefrine	Aliphatic and aromatic esters	86
2-Amino-6,7-dihydroxytetrahydronaphthalene (6,7-ADTN)	Various diesters	87
Terbutaline	Mono- and diesters	88
Isoproterenol	Ditoluyl and dipivaloyl esters	89
Cytarabine	Various mono- and diesters	90
Digitoxigenin	Amino acid esters	91
Acyclovir	Amino acid and hemisuccinate esters	92

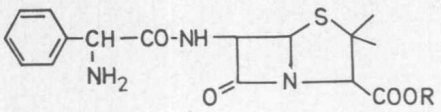
is rich in enzymes capable of hydrolyzing esters. The distribution of esterases is ubiquitous, and several types can be found in the blood, liver and other organs or tissues. In addition, by appropriate esterification of molecules containing a hydroxyl or carboxyl group it is feasible to obtain derivatives with almost any desirable hydrophilicity or lipophilicity as well as in vivo lability, the latter being dictated by electronic and steric factors. Accordingly, a great number of alcoholic or carboxylic acid drugs have been modified for a multitude of reasons using the ester prodrug approach. Several examples can be found in various reviews [6, 7, 14, 18 – 20] and in Tables 1 and 2.

Sometimes, simple aliphatic or aromatic esters may not be sufficiently labile in vivo to ensure a sufficiently high rate and extent of prodrug conversion. This is the case with penicillin esters. Although various simple alkyl and aryl esters of the thiazolidine carboxyl group are hydrolyzed rapidly to the free penicillin acid in animals, such as rodents, they proved to be far too stable in man to have any therapeutic potential [25]. This illustrates also – as do many other examples – the occurrence of marked species differences in the in vivo hydrolysis of ester prodrugs. A solution to the problem was found in 1965 by Jansen and Russell [26], who showed that a special double ester type (acyloxymethyl ester) of benzylpenicillin was hydrolyzed rapidly in the blood and tissues of several species, including man. The first step in the hydrolysis of such an ester is enzymatic cleavage of the terminal ester bond with formation of a highly unstable hydroxymethyl ester which rapidly dissociates to the parent penicillin and formaldehyde (Scheme 1). A reason for the different enzymatic stabilities of the acyloxymethyl ester and simple alkyl esters of penicillins is certainly that the penicillin carboxyl group is highly sterically hindered. The terminal ester in the acyloxymethyl derivative is less hindered, and thus should be more accessible to enzymatic attack.



Scheme 1

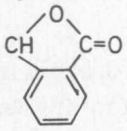
The principle has been used successfully to improve the oral bioavailability of ampicillin (1), and no fewer than three ampicillin prodrug forms are now on the market, namely, the pivaloyloxymethyl ester (2) (pivampicillin) [27], the phthalidyl ester (3) (talampicillin) [28, 29] and the ethoxycarbonyloxyethyl ester (4) (bacampicillin) [30], the latter containing a terminal carbonate ester moiety. The properties of these prodrugs as well as of other similar acyloxyalkyl esters of β-lactam an-



1 R = H

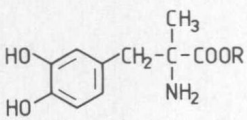
2 R = CH_2-OOC-C(CH_3)$_3$

3 R = CH(CH_3)-O-C(=O)-O-C_2H_5

4 R = 

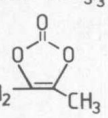
tibiotics, such as mecillinam and cephalosporins, have been reviewed extensively [24].

In more recent years the applicability of this double ester concept in prodrug design has been expanded further. Thus, similar esters have been prepared from indomethacin and other non-steroidal anti-inflammatory agents [31] as well as from cromoglycic acid [32], and found to be useful as prodrugs for enhancement of the dermal delivery of these acidic drugs. Other carboxylic acid agents where acyloxyalkyl esters have been developed as prodrugs include isoguvacine [33], methyldopa [34 – 36] and tyrosine [37]. Whereas methyldopa (5) is variably and incompletely absorbed its pivaloyloxyethyl ester (6) is almost completely and more uniformly absorbed in man following oral administration and is hydrolyzed rapidly on the first pass to the parent drug [35, 36]. A different ester type of methyldopa, a (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl derivative (7), was recently reported to be another potentially useful prodrug for improving the oral bioavailability [38]. A similar ester type of ampicillin has been described recently and shown to be an orally well absorbed prodrug [38a].

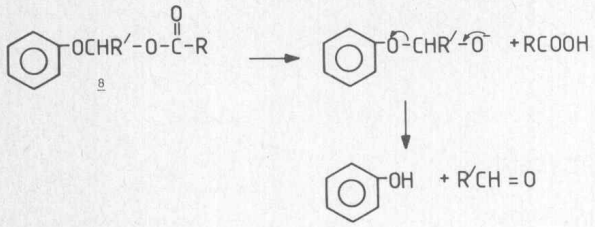


5 R=-H

6 R=-CH(CH_3)-OOC-C(CH_3)$_3$

7 R= -CH_2- 

The applicability of acyloxyalkyl esters as biologically reversible transport forms has been extended to include phenolic drugs, the derivatives being acyloxyalkyl ethers (8). Bodor and co-workers [93, 94] have recently prepared such acyloxyalkyl ethers of various phenols (e.g., β-estradiol and phenylephrine), thiophenol and catechols (e.g., dopamine and epinephrine). The derivatives are hydrolyzed by a sequential reaction involving the formation of an unstable hemiacetal intermediate (Scheme 2) and they are as susceptible as normal phenol esters to undergo enzymatic hydrolysis by, e.g., human plasma enzymes. However, the acyloxyalkyl ethers ap-

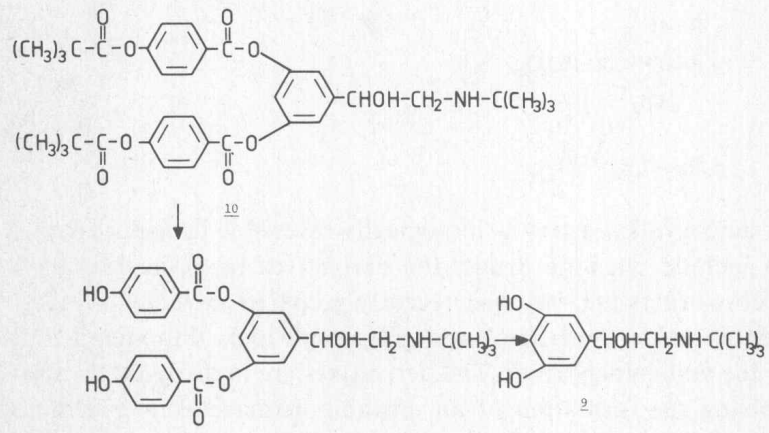


Scheme 2

pear to be more stable against chemical (hydroxide ion-catalyzed) hydrolysis than phenolate esters, and this may make them more favourable in prodrug design [93].

According to their cleavage mechanism, acyloxyalkyl esters and ethers can be considered as double prodrugs (pro-prodrugs). An interesting variant of the double ester prodrug concept is provided in the work by Olsson and co-workers [95, 96] on terbutaline (9). In order to achieve increased absorption, reduced first-pass metabolism and prolonged duration of action, a *p*-pivaloyloxybenzoate double ester prodrug (10) was made. Since the pivaloyl ester group is the most susceptible to undergo enzymatic hydrolysis, it was expected that the prodrug would undergo first-pass hydrolysis preferentially at the *p*-pivaloyloxy bond, followed by conjugation reactions with sulphuric and glucuronic acid at the resulting *p*-hydroxybenzoyl moiety (Scheme 3). In this way the active resorcinol moiety in terbutaline would be protected during first-pass and free terbutaline may be generated from hydrolysis of the conjugated or free *p*-hydroxybenzoate during and after the distribution phase. Experimental support for the cascade ester to function in this way was obtained and prolonged terbutaline plasma profiles were observed in dogs with this prodrug [96].

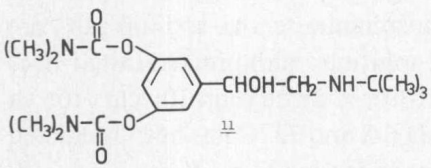
Carbamate esters may be promising prodrug candidates for phenolic drugs. The



Scheme 3

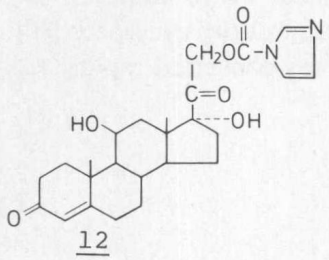
bis-*N,N*-dimethylcarbamate of terbutaline (11) was also examined in the work by Olsson and Svensson [96] referred to above. It showed a half-life of hydrolysis in human plasma of about 10 hours, and this relatively high stability was partly due to the fact that the compound inhibited its own hydrolysis by reversible binding to plasma esterases. As a result of the improved hydrolytic stability, the prodrug survived the first-pass hydrolysis in the dog to a substantial degree and produced sustained blood levels of the parent drug in the dog following a single oral dose.

The enzymatic hydrolytic behaviour of carbamate esters has been examined by Digenis and Swintosky [6]. *N*-Unsubstituted or -monosubstituted carbamates derived from phenols showed high lability and strong enzymatic catalysis whereas most *N*-disubstituted carbamates proved highly stable, as did carbamates of aliphatic hydroxy compounds. The kinetics and mechanism of the non-enzymatic hydrolysis of carbamates have been studied thoroughly [97 – 102].



11

Whereas carbamates of alcohols in general appear to be of no value in prodrug design due to their high stability, certain activated carbamates may be useful. Imidazole-1-carboxylic acid esters belong to this category and such derivatives of hydrocortisone (12) and testosterone (13) have been shown recently to undergo a relatively facile hydrolysis in aqueous buffer solutions [103]. At pH 7.4 and 37°C the half-life of hydrolysis of the hydrocortisone derivative was found to be 8 minutes and that for the testosterone derivative 65 hours, the different reactivity being ascribed to the different steric hindrance in the alcohol portions of the steroids. No enzymatic catalysis by human plasma was observed. Due to protonation of the imidazole group ($pK_a \approx 3.5$) the derivatives showed increased solubility in acidic aqueous solution relative to the parent steroids [103].



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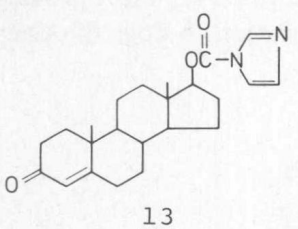
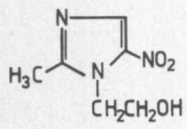


13

Ester formation has long been recognized as an effective means of increasing the aqueous solubility of drugs containing a hydroxyl group, with the aim of developing prodrug preparations suitable for parenteral administraton. Two physicochemical

strategies can be employed to increase aqueous solubility: (i) introduction of an ionic or ionizable group by the pro-moiety and (ii) derivatization in such a manner that the prodrug shows a decreased melting point [104].

The most commonly used esters for increasing aqueous solubility of alcoholic drugs are hemisuccinates, phosphates, dialkylaminoacetates and amino acid esters. However, their use is not without problems, considering the ideal properties of such prodrugs: they should possess adequate aqueous solubility, sufficient aqueous solution stability to allow long-term storage of its solution (i.e., 2 years at room temperature) and yet they should be converted rapidly in vivo to the active parent drug. For example, succinate esters are not good substrates for hydrolytic enzymes [15] and often show relatively slow and incomplete cleavage in vivo, as has been described for such esters of various corticosteroids [105, 106] and chloramphenicol [82, 107 – 109]. Besides, their solution stability is limited due to intramolecular reactions (e.g., catalysis of ester hydrolysis or *O*-acyl migration in corticosteroids) of the terminal succinate carboxyl group [110, 111]. Phosphate esters as sodium salts are freely water-soluble and are so stable in vitro that solutions with practical shelf-lives often can be formulated [112 – 115]. Thus, a shelf-life of more than 10 years for an aqueous solution of vidarabine-5′-phosphate at pH 6.8 and 25°C has been predicted [113]. They are also rapidly hydrolyzed enzymatically in vivo (e.g., Refs. 116 – 118, 122), although exceptions exist. Thus, the phosphate ester (15) of metronidazole (14) shows a rather slow rate of conversion in human serum, the hydrolysis exhibiting apparent zero-order kinetics [79]. For the third type of water-soluble ester derivatives, i.e., esters with an ionizable amino function in the acid portion, only sparse information is available on their enzymatic hydrolysis. Bundgaard et al. [80, 81] have prepared eight amino acid esters of metronidazole (14) and evaluated their potentiality as water-soluble parenteral delivery forms of the parent drug whose solubility in water is limited (≈ 1% w/v). Hydrochloride salts of all the esters exhibited a water solubility greater than 20% w/v but their susceptibility to undergo enzymatic hydrolysis varied widely, as seen from the data in Table 3. Due to its facile cleavage in plasma, excellent solubility properties (> 50% w/v in water) and ease of synthesis and purification, the hydrochloride salt of metronidazole *N,N*-dimethylglycinate (16) appeared to be the most promising prodrug candidate [80]. Following intravenous administration to dogs the ester was converted rapidly ($t_{1/2}$



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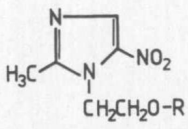

15 R = $-P(=O)-(OH)_2$

16 R = $-C(=O)-CH_2-N(CH_3)_2$

≈ 5 min) and completely to metronidazole [81]. It is of interest to compare the in vivo half-life in dogs (5 minutes) to that observed in vitro in dog plasma (25 minutes). A disadvantage of this prodrug is that it is not sufficiently stable for formulation as a ready-to-use solution [81] and must be used as a formulation to be reconstituted as a solution prior to use. Recently, some kinds of water-soluble amino acid 21-esters of corticosteroids possessing both a high in vitro stability and a high susceptibility of undergoing enzymatic hydrolysis have been developed by Anderson et al. [119–121].

TABLE 3
Half-lives for the Hydrolysis of Various Amino Acid Esters of Metronidazole in 80% Human Plasma (pH 7.4) and 0.05 M Phosphate Buffer (pH 7.40) at 37°C [a]

Ester	$t_{½}$ in human plasma (minutes)	$t_{½}$ in buffer (minutes)
N,N-Dimethylglycinate	12	250
Glycinate	41	115
N-Propylglycinate	8	90
3-Aminopropionate	207	315
3-Dimethylaminopropionate	46	52
3-Dimethylaminobutyrate	334	580
4-Morpholinoacetate	30	1880
4-Methyl-1-piperazinoacetate	523	1720

a. From Bundgaard et al. [80].

Sulphate esters of alcohols and phenols have long been considered as prodrug forms useful for obtaining injectable preparations [14]. However, recent studies indicate that such esters may be very resistant to undergoing hydrolysis in vivo and, accordingly, would not be suitable prodrugs. Thus, Miyabo et al. [122] found that dexamethasone-21-sulphate produced virtually no free dexamethasone in plasma and urine following intravenous injection in man, but was excreted largely unchanged in urine. Similarly, Williams et al. [123] have found that the sulphate esters of paracetamol and 3-hydroxymethyl-phenytoin do not generate the parent drugs when administered parenterally to mice or rats.

A high crystal lattice energy of solid compounds, as manifested in a high melting point, results in poor solubility (in all solvents). Therefore, an approach to reduce this energy may result in improved aqueous solubility. An example of the usefulness of this approach in prodrug design concerns vidarabine (17). It has a low water solubility (0.5 mg ml^{-1}), primarily due to the occurrence of intermolecular hydrogen bonding in the crystalline state, as reflected in its melting point of 260°C. By esterification of the 5′-hydroxyl group this bonding is reduced, and, further, by choosing an only slightly lipophilic acyl group such as formyl a vidarabine ester with