Prodrugs of Antiinfective Agents: A Review

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ABSTRACT - Purpose. Prodrugs are the pharmacologically inactive derivatives of active drugs typically intended to optimize the exposure of active drug at target site, through manipulation of its physicochemical, biopharmaceutical or pharmacokinetic properties. This approach has a number of advantages over conventional drug administration. Antiinfective agents are associated with number of limitations, responsible for their reduced bioavailability. Various antiinfective prodrugs have been synthesized with reduced side effects and improved pharmacological properties. The present paper illustrates different vistas of prodrug approach of antiinfective agents describing brief classification, synthetic approaches, pharmacological aspects and recent patents. It is a very productive area of research and its prologue in human therapy has given triumphant outcomes in improving the clinical and therapeutic effectiveness of drugs.

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INTRODUCTION

Infection is the sequential event that starts from the invasion of pathogens in body tissues of host, followed by their multiplication, response of host tissues to these pathogens along with toxin produced by them (1). Scientific literature and medical experience indicate that microbial infection is one of the prime dangers to human life and World Health Organization considered it as leading cause of human death worldwide (2,3). As per available reports, infections caused by pathogenic viruses, bacteria, fungi and parasites account for millions of deaths per year (4,5).

The use of anti-infective agents are credited with saving more human lives than any other area of medicinal therapy discovered to date (6,7). Though antiinfective agents are being used for treatment of infectious disorders for last several decades, these are associated with some undesirable properties such as poor bioavailability, high first pass metabolism, toxicity, local irritation, incomplete absorption, poor aqueous solubility, lipophilicity, *etc*. as represented in Figure 1 (8-12).

Therefore, there is great emphasis on research to find out methods aimed at improving their desired characteristics [13-15]. The term "prodrug" or "proagent" was introduced by Albert to describe active pharmaceutical agents that undergoes biotransformation prior to elicit their pharmacological effects (16). Prodrug strategies consist of a transient modification of the physicochemical properties of a given compound through chemical derivatization. Such reversible

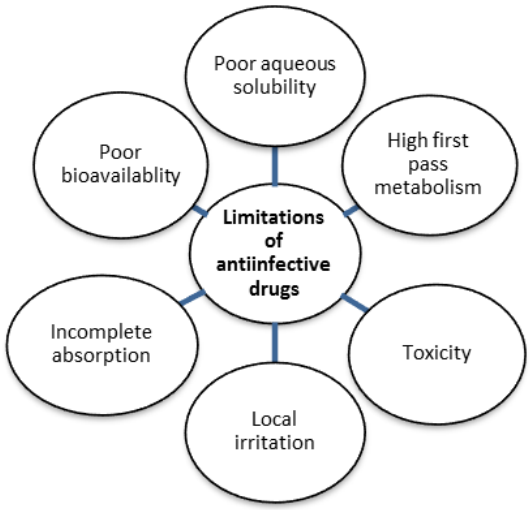

Figure 1. Various limitations of available antiinfective drugs.

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chemical modification is designed to augment chemical stability, alter aqueous solubility, or improve bioavailability while the intrinsic pharmacological properties of the parent drug remain intact (17-21). A very good indication of the success of prodrug approach can be observed by examining the prevalence of prodrugs in the market. A few marketed antiinfective prodrugs are given in Table 1 (15,17,22-25**)**.

Prodrugs are classified into carrier linked and bioprecursors on the basis of the way they release the active drug. Classification of prodrugs has been represented in Figure 2 (26-29).

Table 1. Marketed antiinfective prodrugs

Category	Prodrug	Parent drug	Trade name
Antiviral	Valacyclovir	Acyclovir	Valtrex
Antiviral	Famciclovir	Penciclovir	Famvir
Antibacterial	Tedizolid phosphate	Tedizolid	Sivextro
Antiherpes simplex B virus	Adefovir dipivoxil	Adefovir	Preveon
Antibacterial	Bacampicillin	Ampicillin	Bacacil
Antiretroviral	Tenofovir disoproxil	Tenofovir	Viread
Antiretroviral	Fosamprenavir	Amprenavir	Lexiva
Antiviral	Fludarabine phosphate	Fludarabine	Fludara
Antifungal	Fosfluconazole	Fluconazole	Procif
Antiviral	Oseltamivir	Oseltamivir carboxylate	Tamiflu

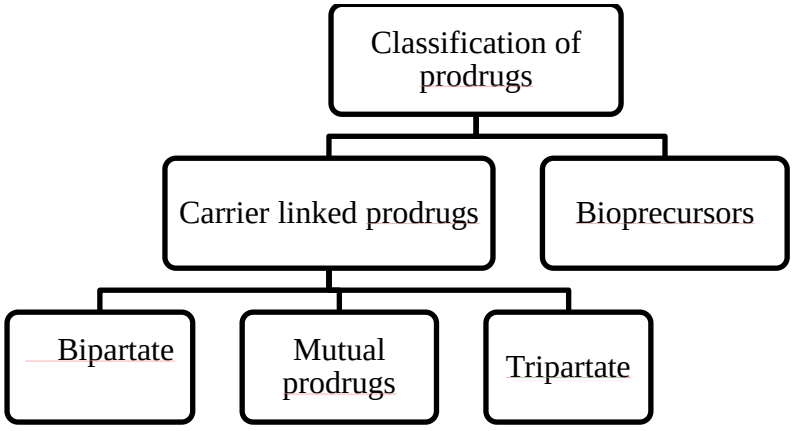


Figure 2. Classification of prodrugs

Limitations associated with various antiinfective agents and successful implementation of prodrug approach for a variety of medicinally active agents has encouraged the researchers to synthesize prodrugs of antiinfective agents. A number of scientific papers have been published in last 3-4 decades. In this article, we have attempted to review the prodrugs of antiinfecive agents and summarize the triumph of prodrugs in achieving their improved pharmacokinetic parameters. This paper also discusses briefly general aspects of prodrug design and some recent patents of antiinfective prodrugs.

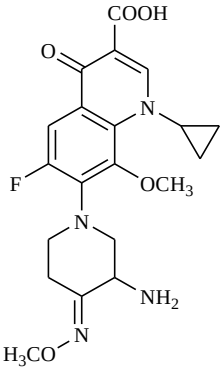
ANTIINFECTIVE ACTIVITY PROFILE OF VARIOUS PRODRUGS

Herein we describe some important synthesized prodrugs with antiinfective activities reported in literature of last few decades.

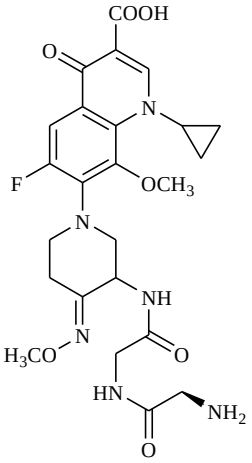
Prodrugs of Antibacterial Agents

Antibiotics are low molecular weight compounds produced by microorganisms and are active against pathogenic microorganisms (30). Treatment of infectious disorders depends upon several factors such as interactions among pathogens, facts related to host, physicochemical features of antimicrobial agents, its pharmacokinetics and pharmaco-dynamics. Infectious disorders caused by bacteria are the prime cause of mortality, affecting millions of people. Keeping in view the severity of these types of infections, continuous efforts for search of novel antibacterial agents are undertaken. In addition to search of novel antimicrobial agents, modification of existing drugs is a field of current and growing interest (31,32). Several attempts have been made to synthesize novel prodrugs of antibacterial agents.

Prodrug approach has been adopted for synthesis and evaluation of a series of amino acid and dipeptide prodrugs of IMB-070593, **1** by Zhang *et al*. Due to greater water solubility, compounds **2** and **3** were found to exhibit 1.19-1.50 fold high antibacterial activity against methicillin-sensitive *S. aureus* and *S. pneumonia* than the parent drug (28).



IMB-070593, **1**



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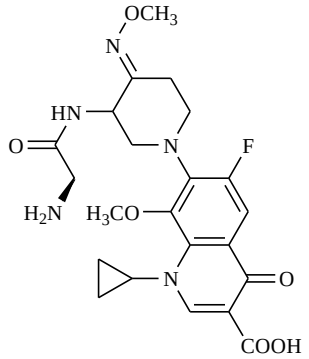
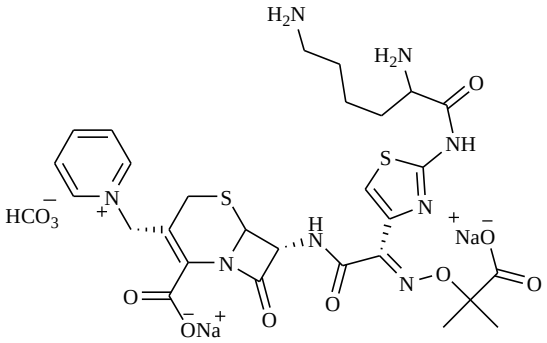


3

New derivatives of ceftazidime as possible prodrug were synthesized by Alwan *et al*. The compounds **4** and **5** showed reasonable antibacterial activities against G (+) *Streptococcus species* in comparison with ceftazidime, having no activity against these types of microorganisms (33).



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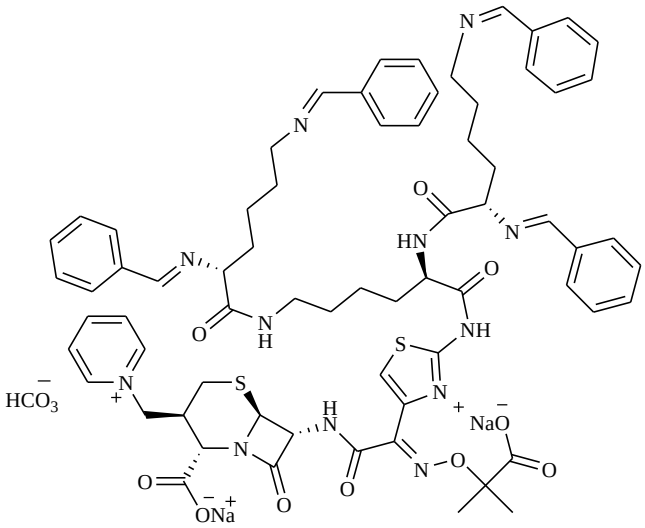
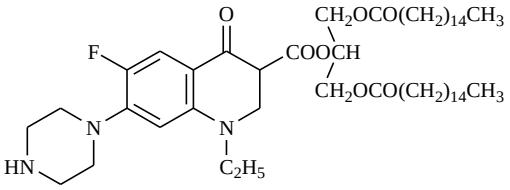


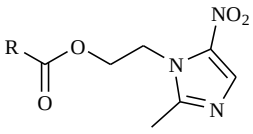
5

Prodrug approach was adopted using diglyceride as a promoiety to improve bioavailability of poorly absorbed drug, norfloxacin; a second generation fluoroquinolone antibacterial by Dhaneshwar *et al*. The prodrug **6** has been synthesized by standard procedures using dipalmitine as a carrier and found to exhibit improved pharmacological profile than the parent compound at equimolar dose that indirectly indicated improved bioavailability (9).



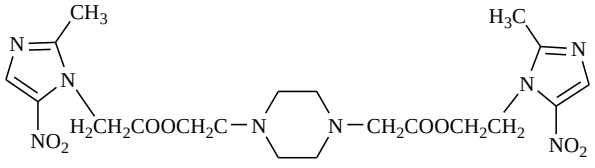
6

Dubey *et al* have synthesized and evaluated various novel aromatic and aliphatic esters of metronidazole to improve the physicochemical properties (Rm values, lipophilicity) using prodrug approach. The synthesized compounds **7** and **8** were found to be more potent in terms of MIC (μg/mL) against *C. Perfringens* in comparison to metronidazole due to enhanced lipophilicity (10).



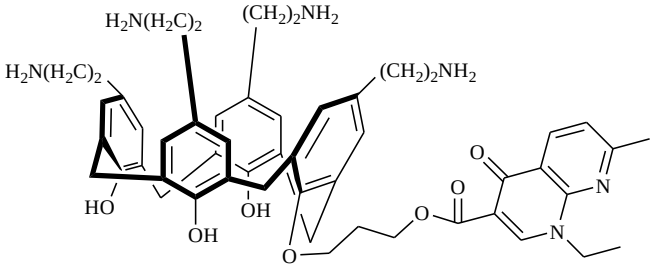
7: R = $-CH_2CH_2CH_2CH_2CH_3$
8: R = $-C_6H_6$

Abdul-Kadir *et al* prepared cyclic amine derivatives of metronidazole using acetate spacer. These derivatives showed better physicochemical and biological properties. As per studies, the compound **9** can be utilized on its own as effective mutual prodrug without requirement of any drug in connection (34).



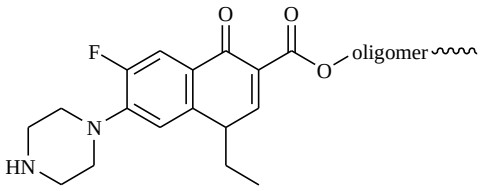
9

Dibama *et al* carried out drug release studies and investigated antibacterial behavior of a water-soluble nalidixic acid/calix[4]arene ester adduct **10**. *In vitro* antibacterial evaluation showed that the title compound was efficient on one Gram-negative (*E. coli*) and two Gram-positive (*S. aureus*) reference strains, with a clear gain of activity when compared to its two hydrolysis by-products (11).



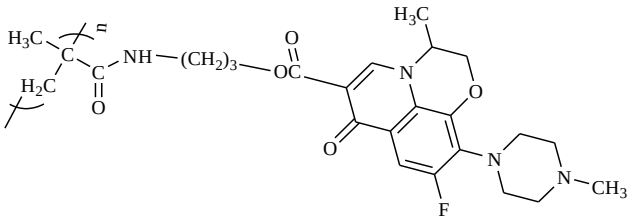
10

Sobczak *et al* developed and carried out structural analysis of polyester prodrugs of norfloxacin. The two, three and four arm star shaped poly(ε-caprolactone) and poly(D,L-lactide) homopolymers and copolymers of ε-caprolactone with D, L lactide were used for synthesis of norfloxacin polyester prodrugs. The synthesized polyester prodrugs, **11** were proved to be good potential candidates to be used as drug delivery carriers (35).



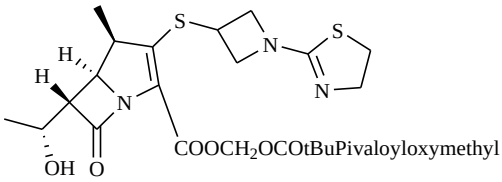
11

Yar *et al* synthesized macromolecule conjugate of hydroxypropyl methacrylamide–ofloxacin, **12**. They found that covalent linkage of ofloxacin to a biocompatible polymer, poly (hydroxypropyl methacrylamide), via the ester group leads to a delivery system which is capable of releasing the drug in a sustained manner over the gastrointestinal tract and ultimately increased $t_{1/2}$ of the drug (36).



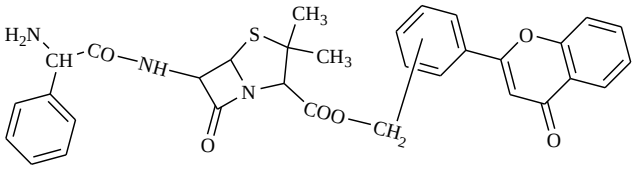
12

Isoda *et al* synthesized various prodrug esters and carried out their pharmacokinetic studies. Oral carbapenem antibiotic L-084, **13** was found to exhibit high bioavailability and C_{max} in humans. Compound **13** showed a strong antimicrobial activity against Gram-positive and Gram-negative bacteria and exhibited the highest intestinal absorption among synthesized prodrugs of (1*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-1-methyl-2-[1-(1,3-thiazolin-2-yl) azetidin-3-yl] thio-1-carbapen-2-em-3-carboxylic acid (37).



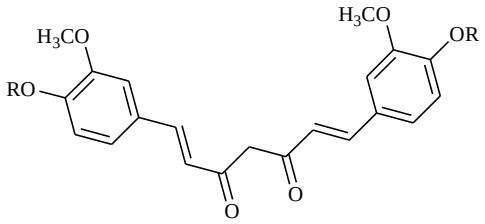
13

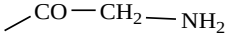
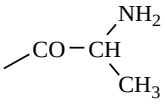
A novel series of flavonyl pro-drug esters of ampicillin was synthesized and evaluated for antimicrobial properties by ÜnlÜsoy *et al*. The synthesized compounds were tested for their antifungal and antibacterial activities *in vitro* and compound **14** was reported to have high activity against *S. aureus* (33 mm) comparable with ampicillin (38).

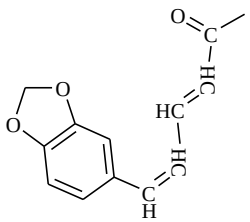


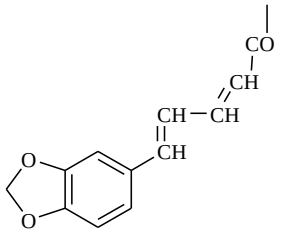
14

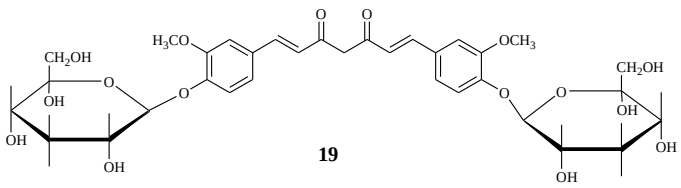
Mishra *et al* synthesized different curcumin bioconjugates viz. 4,4'-di-*O*-glycinoyl-curcumin **15**, 4,4'-di-*O*-(glycinoyl-di-N-piperoyl)-curcumin **16**, 4,4'-di-*O*-D-alaninoylcurcumin **17**, 4,4'-di-*O*-piperoyl curcumin **18**, curcumin-4,4'-di-*O*-β-D-glucopyranoside **19**, 4,4'-di-*O*-acetyl-curcumin **20** along with piperoyl glycine. The compound **16** and **20** were found to be more effective as compared to cefepime, an antibacterial drug existing in market, at the equivalent concentration. The compound **16** and **18** had antifungal activity *in vitro* almost comparable with fluconazole, the most accepted antifungal drug. The escalated activity of these bioconjugates compared to the parent molecule, curcumin may be due to improved cellular uptake or reduced metabolism of these bioconjugates resulting in building up of enough concentration inside the infected cells (39).



15: R=  **17**: R= 

16: R= 

18: R = 



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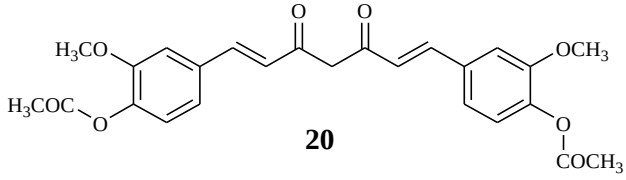
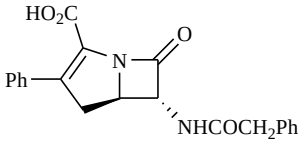


20

Hakimelahi designed, synthesized and evaluated two novel carbapenems *trans*-3-hydroxycarbonyl- 6-(phenylacetamido)carbapenem (±) **21** and *trans*-3- phosphono-6-(phenylacetamido) carbapenem (±) **22** for biological activity. Carbapenem **21** was found to possess antibacterial activity, comparable with imipenem (+)-**23**, against *S. aureus* FDA 209P, *E. coli* ATCC 39188, *K. pneumonia* NCTC 418, *P. aeruginosa* 1101-75 as well as the β-lactamase producing organism *P. aeruginosa* 18S-H and methicillin resistant organism *S. aureus* 95. On combining *trans* carbapenem 2**1** with *cis* carbapenem, compound **24** as well as clavulanic acid, **25** with *cis* carbapenem compound **26** via a tetrachloroethane linker exhibited remarkable activity against β-lactamase producing microorganisms *in vitro* (40).



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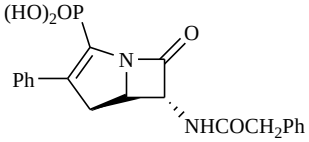

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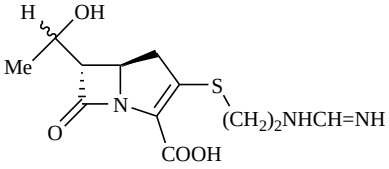

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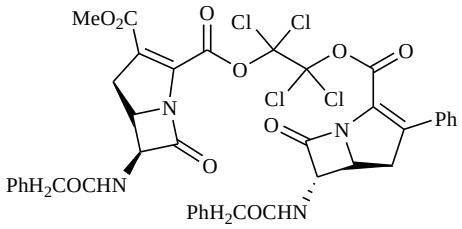

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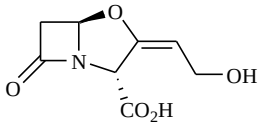

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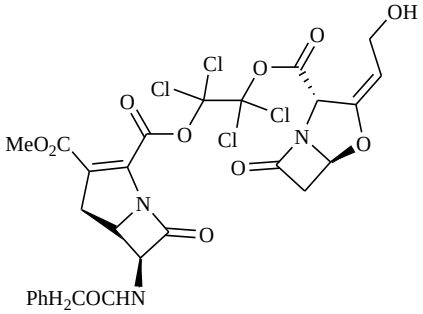
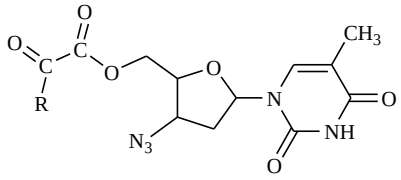


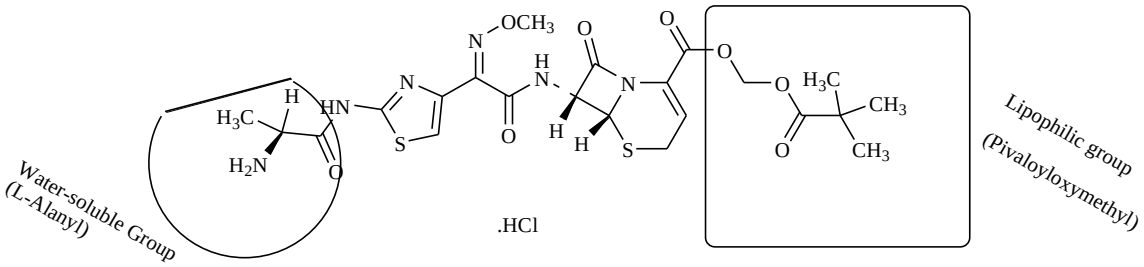
26

Four potential prodrugs of 3'-azido-3'-deoxythymidine (AZT), **27-30** with improved lipophilicity were synthesized and evaluated by Moroni *et al.* The 5'-OH group of 3'-azido-3'-deoxythymidine was functionalized with oxalyl chloride obtaining an acyl chloride derivative, which by further transformation with leucine, isoleucine and valine amino acids led to the corresponding AZT analogs, namely AZT-Leu, AZT-iLeu and AZT-Val. The most effective antibacterial drug AZT-Leu, (M.I.C.= 0.125 μgmL^{-1}) was found to be sixteen times more active than AZT (AZT, M.I.C.= 2 $\mu g\ mL^{-1}$) against *K. pneumoniae* ATCC 10031. The activity order for the studied compounds against the most sensitive strain (*K. pneumoniae* ATCC 10031) was found to be AZT-Leu > AZT-iLeu > AZT-Val > AZT-Ac > AZT (41).



Chemical structure of zidovudine analogs **(27-30)**

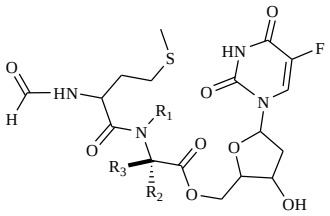
Compounds	**R**
AZT-Leu,**27**	$NHCH(COOH)CH_2CH(CH_3)_2$
AZT-iLeu,**28**	$NHCH(COOH)CH(CH_3)CH_2CH_3$
AZT-Val,**29**	$NHCH(COOH)CH(CH_3)_2$
AZT-Ac,**30**	OH



31

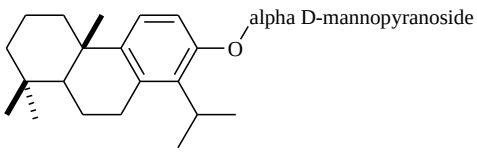
Mori *et al* designed and developed a novel prodrug **31**, AS-924, by esterifying ceftizoxime with a lipophilic pivaloyloxymethyl (POM) group and introducing a water soluble L-alanyl group. As AS-924 was found to have a good balance of lipophilicity and water solubility, it could be clinically expected that the synthesized prodrug, when administered orally, would be absorbed well and consequently show good clinical efficacy (42).

Wei *et al* synthesized 5'-dipeptidyl derivatives of 5-fluorodeoxyuridine (FdU), **32-35**. These prodrugs were found to be biologically inactive but could be activated by peptide deformylase. Because the deformylase is ubiquitous among bacteria but absent in mammalian cells, these prodrug compounds provided a novel class of potential antibacterial agents (43).



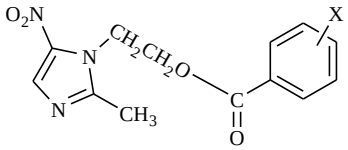
32: R_1, $R_2 = CH_2CH_2CH_2$, $R_3 = H$
33: R_1, $R_3 = CH_2CH_2CH_2$, $R_2 = H$
34: $R_1 = CH_3$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = H$
35: $R_1 = H$, $R_2 = R_3 = CH_3$

In order to illuminate the minimum structural requirements for antibacterial activity and in search of compounds with good bioavailability Evans *et al* synthesized totarol derivatives and evaluated their antibacterial activity. Amongst the synthesized pro-drugs, totaryl α-D-mannopyranoside **36** proved the most active *in vitro* (MIC 18 mM) against three Gram positive bacteria: β-lactamase positive and high level gentamycin resistant *E. faecalis*, penicillin resistant *S. pneumoniae* and methicillin resistant *S. aureus* (44).

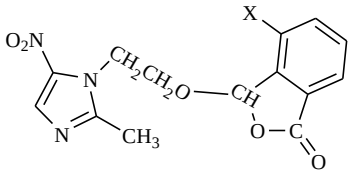


36

Bowden *et al* designed and synthesized a series of chain and cyclic acylbenzoate esters of metronidazole. The esters were designed to be both lipophilic and reactive in their hydrolysis reactions. The first series was composed of acylbenzoate esters of metronidazole **37-43,** and the second series was composed of the cyclic (pseudo) 2-formylbenzoate esters **44,45** *i.e.* 3-alkoxyphthalides. The antibacterial activity of these esters was found to be comparable to that of metronidazole (45).



37: X=H,
38. X=2-CHO,
39: X=4-CHO,
40: X=2-C(O)C(O)Ph
41. X = 2-C(O)CH_3
42: X=2-C(O)CF_3
43: X=2,6$(CHO)_2$



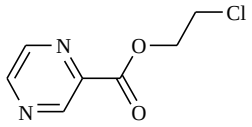
44: X=H,
45: X=CHO

Prodrugs of Antitubercular Agents

Tuberculosis is one of the major public health concerns globally, caused by *Mycobacterium tuberculosis* (46). It has been reported by WHO that 9 million people suffered illness and 1.5 million died due to tuberculosis in year 2013 alone (47).

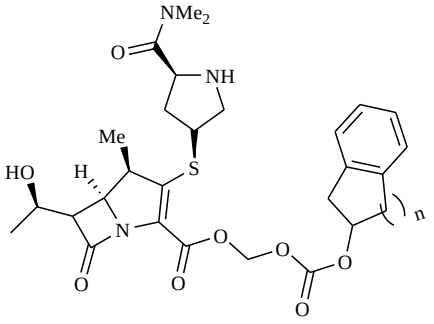
In recent years, tuberculosis is on the increase principally due to HIV infection, immigration, increased trade and globalization (48). Therefore, it is an urgent task to develop new derivatives or formulations of antitubercular drugs acting on novel drug targets to enhance stability, half life as well as oral bioavailability.

Fernandes *et al* synthesized pyrazinoic acid prodrug, 2-chloroethyl pyrazinoate, **46** and evaluated it for its activity in *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC27294) in minimal inhibitory concentration (MIC) assay using the microplate Alamar blue assay technique. The obtained MIC of the synthesized prodrug was found to be 3.96 g/mL, proved better than pyrazinamide (reported MIC 50–100 g/mL) (49).



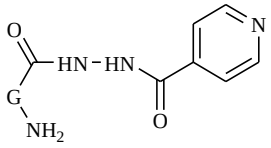
46

Several alkyloxycarbonyloxyalkyl ester prodrugs of meropenem were synthesized and evaluated in an effort to improve the lipophilicity as well as oral absorption of the parent carbapenem by Teitelbaum *et al*. Their stability in physiological aqueous solutions and guinea pig as well as human plasma was evaluated. The prodrugs containing the 2-benzosuberyl, 2-tetralyl, and 2-indanyl-oxycarbonyloxymethyl promoieties, **47-49** respectively were found to be significantly more stable at physiological pH 7.4 and intestinal pH 6.0. In simulated gastric fluid (pH 1.2), these compounds degraded to form the ring-opened prodrug metabolite (50).



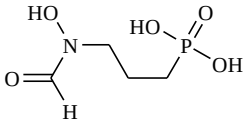
47: n=1
48: n=2
49: n=3

Cassano *et al* synthesized, characterized and carried out *in vitro* antitubercular activity of isoniazid-gelatin conjugate, **50**. Spectrophotometric analysis revealed that the protein derivative was an excellent isoniazid prodrug since there was a 40% reduction in release of toxic metabolites (isonicotinic acid) by the prodrug and the compound **50** showed significant antitubercular activity (12).

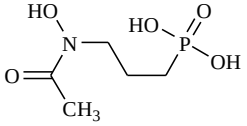


50: where G= gelatin

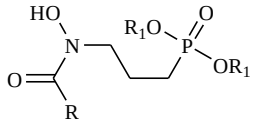
Uh *et al* synthesized a series of lipophilic, prodrug analogs of fosmidomycin, **51** and FR900098, **52**, inhibitors of the nonmevalonate pathway enzyme, 1-deoxy-D-xylulose-5-phosphate reductoisomerase. Several of these compounds **53-56** were found to show improved antibacterial activity against a panel of organisms relative to the parent compound, including better activity of compounds **57,58** as compared to **54-56** against *Mycobacterium tuberculosis* (51).



51



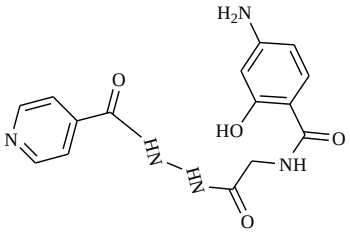
52



Lipophilic ester of 51 & 52

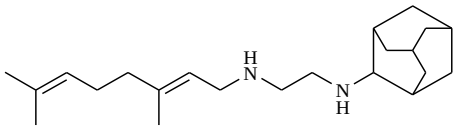
Compounds	R	R_1
53	CH_3	$-CH(CH_3)OCOOC(CH_3)_3$
54	H	Et
55	CH_3	Et
56	CH_3	*i*Pr
57	CH_3	$-CH_2OCOC(CH_3)_3$
58	CH_3	$-CH_2OCOC_6H_5$

Qasir *et al* designed and developed mutual prodrug (PAS-Gly-INH), **59** of p-amino salicylic acid (PAS) and isoniazid (INH), with improved physicochemical properties. The synthesized compound showed better partition coefficient and hence expected for better absorption compared with the original apromoiety (PAS, INH) (52).

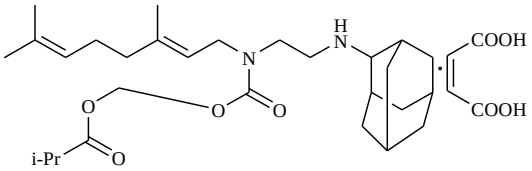


59

Meng *et al* reported a novel series of prodrugs of SQ109, **60**. The parent drug, **60** released from the synthesized prodrug, **61** after oral administration exhibited preferential tissue distribution into lung and spleen, the target organs of tubercular infection and replication (53).

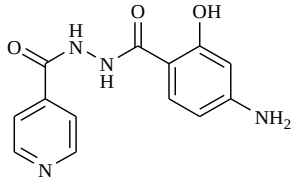


60

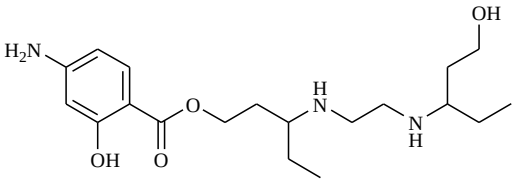


61

Mutual prodrugs of isoniazid, *p*-amino salicylic acid and ethambutol were synthesized and evaluated by Rawat *et al*. The results revealed that mutual prodrugs PI (isoniazid with p-amino salicylic acid), **62** and PE (ethambutol with p-amino salicylic acid), **63** significantly eliminate the problem of fast metabolism, toxicity and local irritation and reduction of therapeutic doses (54).

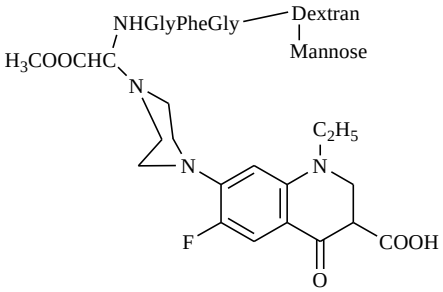


62



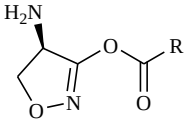
63

Roseeuw *et al* carried out synthesis, degradation and studied antimicrobial properties of targeted macromolecular prodrugs of norfloxacin. In Gly-Phe-Gly-Gly (α-norfloxacin)-OMe, **64** norfloxacin was linked to the carrier through an alpha bond. They demonstrated that targeting by using mannose as a homing device was required to achieve antimycobacterial activity *in vivo* (55).



64

Cycloserine (seromycin, 4(*R*)-amino-3-isoxazolidinone), a well-known drug used for the treatment of tuberculosis and certain genitourinary infections, especially when caused by *Enterobacteria* or *E. coli*. Systemic side effects check the usage of cycloserine and topical application or local delivery has restricted value because cycloserine is a highly water-soluble compound and inadequately permeable through lipophilic membranes such as the skin. Thorsteinsson *et al* synthesized various 4,5-dihydroisoxazol-3-yl fatty acid ester derivatives of cycloserine, **65-68** to improve skin permeation of cycloserine. The ester derivatives were synthesized using the *tert*-butoxycarbonyl (*t*-Boc) protection strategy. The skin permeation of cycloserine across the hairless mouse skin was reported to increase up to 20-fold by the fatty acid esters (56).

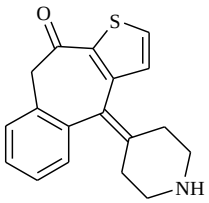


65: R = CH_3
66: R = $(CH_2)_6CH_3$
67: R = $(CH_2)_7CH{=}CH(CH_2)_7CH_3$
68: R = $(CH_2)_7CH{=}CH(CH_2)_7CH_3$

Prodrugs of Anitmalarial Agents

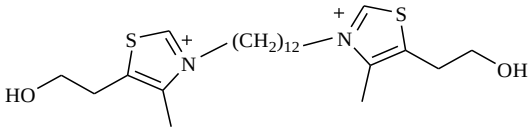
Malaria is a potentially lethal tropical disorder, spread by mosquitoes and its causative agent is protozoan parasites of the genus *Plasmodium*. According to latest estimates, approximately 198 million cases of malaria and 5,84000 deaths due to this diseases were observed globally in 2013 (57,58). New antimalarial compounds, particularly those based on compounds structurally unrelated to existing antimalarial drugs with new mechanisms of action or prodrugs of existing compounds with modified physicochemical characteristics/ pharmacokinetic parameters are urgently needed. Davanço *et al* prepared and evaluated the antimalarial activity along with toxicological profile of a novel dipeptide primaquine prodrug (Phe-Ala-PQ) using *in vitro* and *in vivo* assay. The prodrug was found to be more soluble in water, effective against sporogenic cycle and less toxic in a monkey kidney cell line (BGM) and human hepatoma cell line (HepG2) than the parent drug primaquine (59).

Milner *et al* synthesized few metabolites of ketotifen and evaluated their antimalarial activity and pharmacokinetics in mice. Norketotifen (WR621341), **69** the de-methylated metabolite of ketotifen, was found to be 15 and 8 fold more potent against Pf D6 and Pf W2, respectively, which are the two most susceptible strains of *Plasmodium falciparum*. They observed no toxicity with the metabolite WR621341, **69** even when dosed as high as 320 mg/kg for 3 days (60).

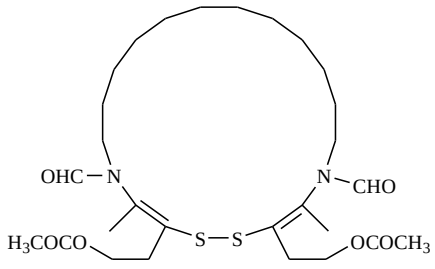


69

Caldarelli *et al* reported the design, synthesis, and biological screening of a series of 15 disulfide prodrugs as precursors of albitiazolium bromide (T3/SAR97276), **70,** a choline analogue which is currently being evaluated in clinical trials (phase II) for severe malaria. After oral administration, the cyclic disulfide prodrug **71,** showed the best improvement of oral efficacy in comparison to the parent drug (61).



70

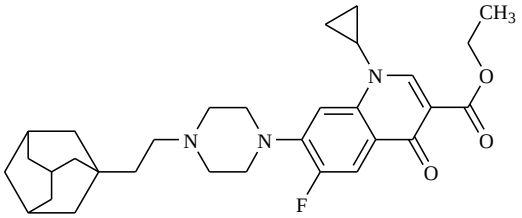


71

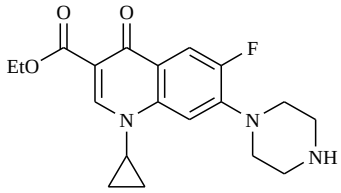
Dubar *et al* carried out the synthesis, antiparasitic evaluation and docking studies of ester prodrugs of ciprofloxacin as DNA-gyrase inhibitors. The synthesized compound **72** was found

to be more active as compared to ciprofloxacin, its ethyl ester prodrug, **73** and the dual mettallocenic/prodrug, ferrocenyl derivative of ciprofloxacin, **74** against *P. falciparum* as well as *T. gondii* (62).

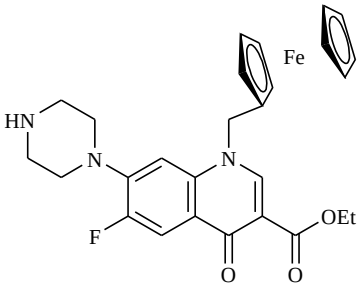
Dubar *et al* in their previous studies reported the enhancement of the antimalarial activity of ciprofloxacin using a double prodrug/ bioorganometallic approach. Two new achiral compounds **73** and **74** were found to be 10 to 100 fold more active than ciprofloxacin against *Plasmodium falciparum* chloroquine susceptible and chloroquine-resistant strains (63).



72

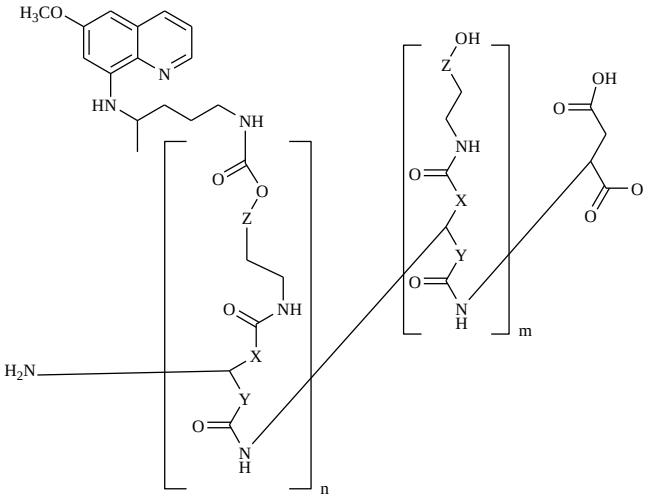


73



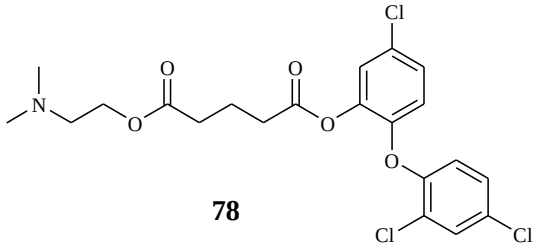
74

New primaquine conjugates with glucosamine and two polymers of polyaspartamide type, poly [α, β-(*N*-2-hydroxyethyl-DL-aspartamide)] (PHEA) and poly[α,β-(*N*-3-hydroxypropyl-DL-aspartamide)] (PHPA), were synthesized, characterized and screened for their antimalarial activity by Rajić *et al*. They found that polymeric conjugates, **75-77** showed better antimalarial activity than the glucosamine conjugate (64).



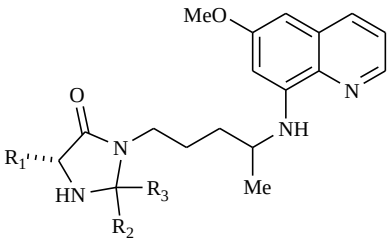
75: (PHEA-PQ) Z = 0
76: (PHEA-PQ) Z = 0
77: (PHPA-PQ) Z = CH2
α unit X = CH_2, Y = 0, β unit X = 0, Y = CH_2

Various triclosan-conjugated analogs bearing biodegradable ester linkage were synthesized, characterized and evaluated for their antimalarial and antibacterial activities by Mishra *et al*. Dimethylaminoethyl-glutaryl esters of triclosan, **78** showed four-fold enhanced activities against *P. falciparum* and *E. coli* cultures than triclosan itself (65).

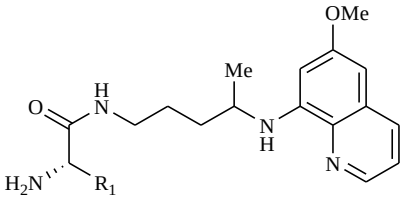


78

Chambel *et al* synthesized the imidazolidin-4-ones, **79-89** as potential pro-prodrugs of the antimalarial primaquine. These compounds were designed with the aim of reducing the metabolic inactivation pathway of primaquine that involves oxidative deamination at the primary amino group. It also diminishes the blood toxicity induced by primaquine particularly its ability to provoke oxidation of oxyhemoglobin to methemoglobin. These compounds were found to be convincingly stable compounds, hydrolyzing to the consequent amino acid derivatives, **90** in pH 7.4 buffer at 37°C with half-lives ranging from 9 to 30 days (66).

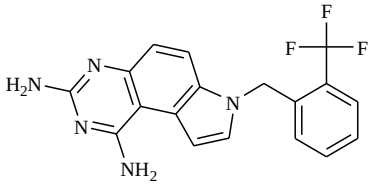


	R_1	R_2	R_3
79:	H	Me	Me
80:	CH_2Ph	Me	Me
81:	$CHMe_2$	Me	Me
82:	H	$(CH_2)_4$	
83:	CH_2Ph	$(CH_2)_4$	
84:	$CHMe_2$	$(CH_2)_4$	
85:	H	$(CH_2)_5$	
86:	Me	$(CH_2)_5$	
87:	CH_2Ph	$(CH_2)_5$	
88:	$CHMe_2$	$(CH_2)_5$	
89:	H	$(CH_2)_6$	

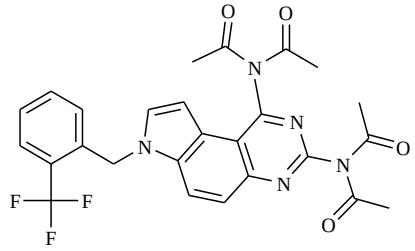


90

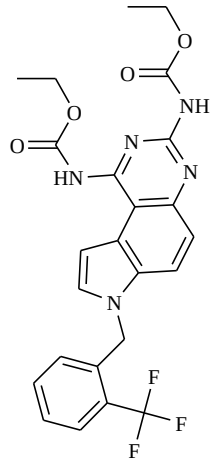
Xie *et al* carried out therapeutic index evaluation and investigated pyrroloquinazoline-diamine (PQD), **91,** its prodrugs tetra-acetamide pyrroloquinazolinediamine (PQD-A4), **92** and bis-ethylcarbamyl pyrroloquinazolinediamine (PQD-BE), **93** for antimalarial activity. PQD-A4, PQD-BE, and PQD administered orally were found to be 20.0, 8.0, and 2.5 times safer than intravenously given artesunate (67).



91

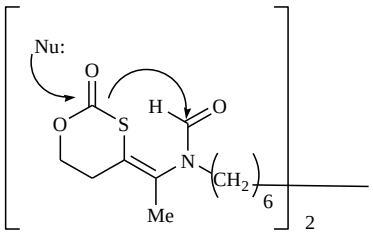


92



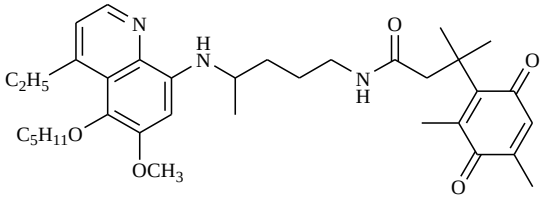
93

Vial *et al* synthesized neutral antimalarial prodrugs that deliver bisthiazolium compounds with antimalarial activity in the nanomolar range. These compounds were found to be suitable for both parenteral as well as oral use and plasma promotes rapid conversion of the prodrug into the parent drug. Oral administration of the TE3 prodrug, **94** was found to entirely cure *Plasmodium cynomolgi* infection in rhesus monkeys (68).



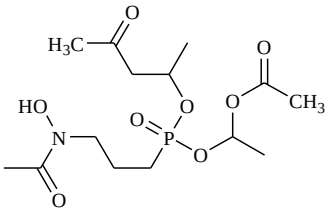
94

Vangapandu *et al* reported antimalarial activities of N^8-(4-amino-1-methylbutyl)-5-alkoxy-4-ethyl-6-methoxy-8-quinolinamines and their pro prodrug analogues synthesized by covalently connecting them to the redox-sensitive and esterase-sensitive linkers via the amide linkage. Synthesized analogues were evaluated for *in vivo* blood-schizontocidal activity as potential pro prodrug models for the primary amino group containing 8-quinolinamines.The most effective pro prodrug analogue, **95** displayed potential activities against drug-sensitive and drug-resistant strains of *Plasmodia in vivo* (69).



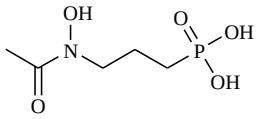
95

Ortmann *et al* developed acyloxyalkyl ester prodrugs of FR900098 with improved *in vivo* antimalarial activity. The most successful compound **96** demonstrated 2-fold increased activity in mice infected with the rodent malaria parasite *Plasmodium vinckei* (70).

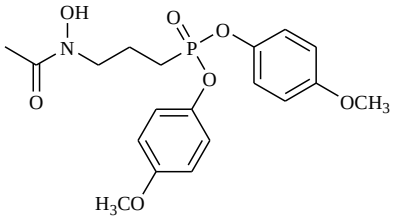


96

Reichenberg *et al* reported the synthesis of diaryl ester prodrugs of FR900098, **97** with improved *in vivo* antimalarial activity. The bis-(4-methoxy phenyl) ester **98**, was proved not only much efficient than FR900098 but proved to be equivalent to FR900098 administered by ip route (71).

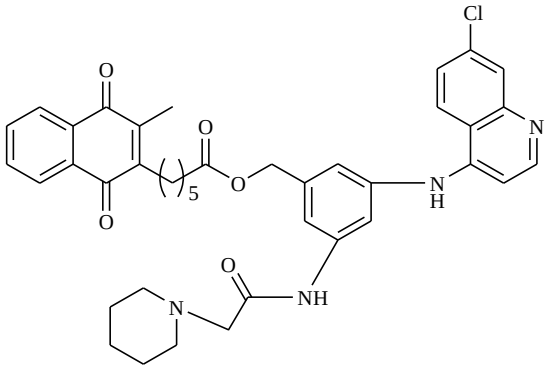


97, FR900098



98

Prodrug form of a *Plasmodium falciparum* glutathione reductase inhibitor conjugated with a 4-anilinoquinoline was identified by Davioud Charvet *et al*. They found that amino ester **99**, was proved to be most active compound and equally effective against chloroquine sensitive and chloroquine resistant strains of *Plasmodium falciparum* (72).

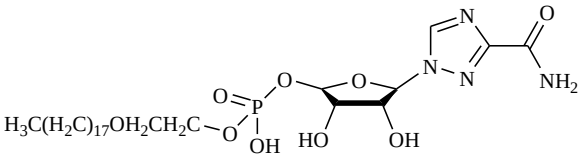


99

Kinyanjui *et al* studied the reversal of activity against *Plasmodium falciparum* of WR99210 (4,6-diamino-1,2-dihydro-2,2-dimethyl-1-[(2,4,5-trichlorophenoxy)propyloxy]-1,3,5-triazine), a triazine antimalarial drug, and of the pro-drug PS-15 by folic acid (FA) and folinic acid (FNA). They suggested that the action of PS-15 against *P. falciparum* was primarily due to a non-folate mechanism. PS-15, (N-(3-(2,4,5-trichlorophenoxy)propyloxy)-N'-(1-methylethyl)-imidocarbo-nimidodiamide hydrochloride), a close analog of proguanil, and a prodrug of WR99210 were developed to overcome the low bioavailability and gastrointestinal intolerance resulted from oral dosages of WR99210 in humans (73).

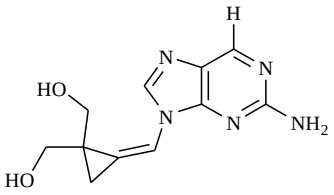
Prodrugs of Antiviral Agents

Viral infections are considered one of the principle threats to human life and health worldwide (74). Dong *et al* reported a new alkoxyalkylphosphodiester prodrug of ribavirin, designed to release the active ribavirin-monophosphate species selectively in nucleated cells while limiting its exposure in anucleated red blood cells (RBCs). Prodrug **100** was found to display enhanced *in vitro* antiviral activity against the hepatitis C virus replicon and influenza virus. These results indicated that synthesized prodrug was found to have the potential for safer, lower, less common and consistent administration than ribavirin (75).



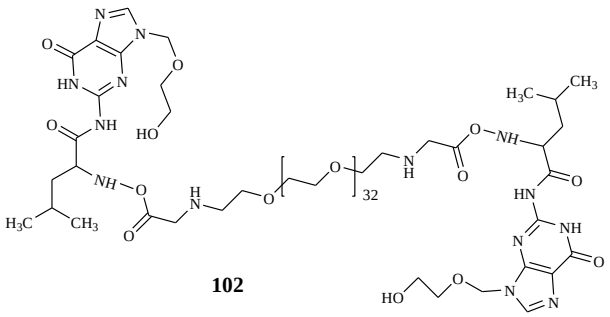
100

Li *et al* described the synthesis of 6-deoxycyclopropavir **101,** a prodrug of cyclopropavir along with its *in vitro* and *in vivo* antiviral activity. It was found to exhibit little antiviral activity in culture but effective against murine cytomegalovirus infections in mice and against human cytomegalovirus infections in severe combined immunodeficient mice (76).



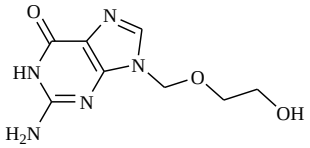
101

Hiramath *et al* synthesized and carried out *in vitro* and bioavailability studies of acyclovir prodrug. The macromolecular prodrug of acyclovir was synthesized by coupling the drug to PEG which was then polymerized to get polymeric prodrug, **102**. The delayed release of free drug from the conjugate resulted in longer retention time in plasma and was found to have higher bioavailability of acyclovir from the PEG conjugate (77).

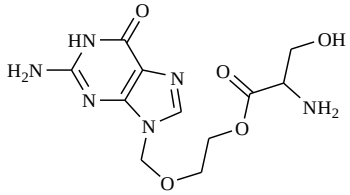


102

The affinity and permeability patterns of the amino acid ester prodrugs of acyclovir (ACV), **103** L-alanine-ACV, L-serine-ACV, L-serine-succinate-ACV and L-cysteine-ACV were characterized by Katragadda *et al* on rabbit primary corneal epithelial cell culture as well as on rabbit cornea. In comparison to ACV, L-serine-ACV, **104** exhibited superior permeability across cornea along with excellent antiviral activity against herpes simplex virus and varicella-zoster virus (78).

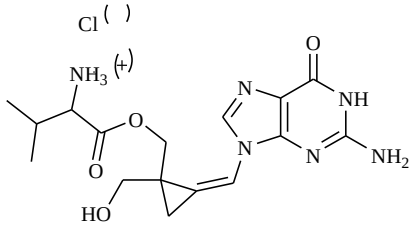


103

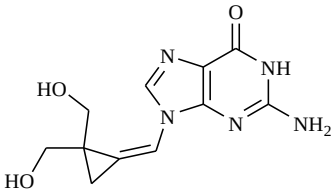


104

Wu *et al* reported the synthesis of L-valine ester of cyclopropavir (valcyclopropavir) following the example of L-valine prodrugs of antiviral nucleosides analogues. Valcyclopropavir, **105** inhibited replication of human cytomegalovirus (HCMV, Towne and AD 169 strains) to approximately the same extent as the parent drug cyclopropavir, **106** and pharmacokinetic studies in mice indicated that the oral bioavailability of this prodrug was found to be 95% (79).



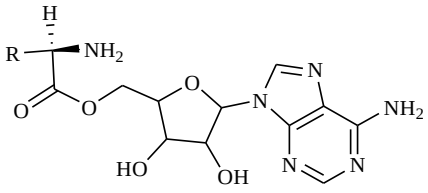
105



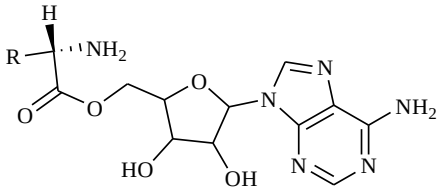
106

Shen *et al* synthesized 5'-*O*-D- and L-amino acid derivatives, **107-115** and 5′-*O*-(D- and L-amino acid methyl ester phosphoramidate), **116-117,** derivatives of vidarabine (ara-A). A number of

compounds were found to be equi- or more potent *in vitro* against two pox viruses. These compounds exhibited improved uptake by cultured cells compared to the parent drug, **118** (80).



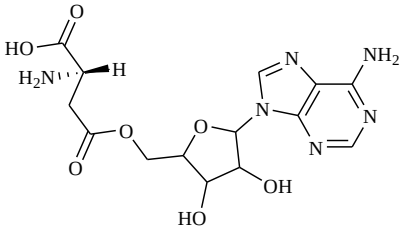
D-amino acid ester (a-g)



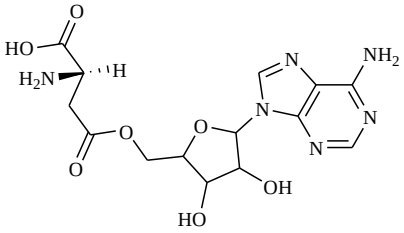
L-amino acid ester (i-o)

R:

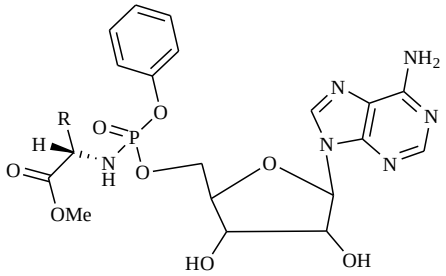
107: a, i valine **108:** b, j leucine
109: c, k isoleucine **110:** d,i phenylalanine
111: e,m lysine **112:** f, n serine
113: g, o aspartic acid



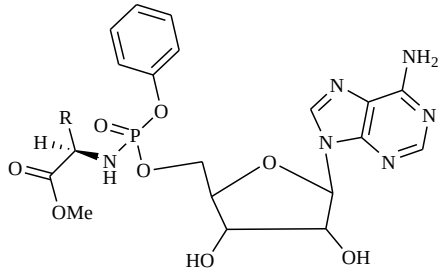
114



115



116



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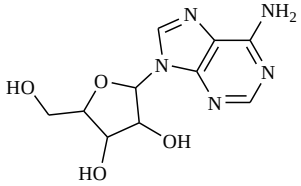
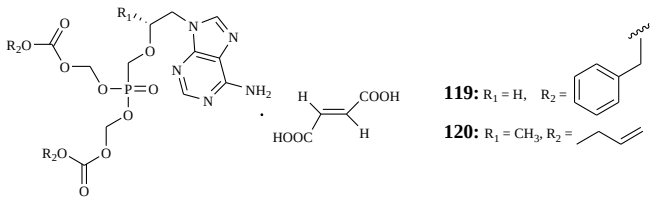


118

Tang *et al* synthesized a series of ester analogues of acyclic nucleotide adefovir and tenofovir as potent antiviral agents. The antiviral evaluation results indicated that bis benzyl ester prodrug of adefovir, **119** and bis allyl ester prodrug of tenofovir, **120** exhibited potent antiviral activities (81).

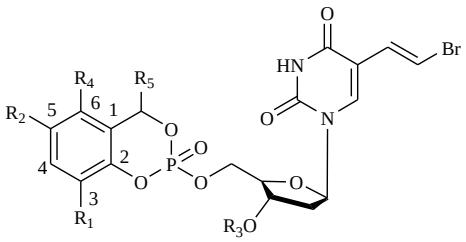


119: $R_1 = H$, $R_2 =$

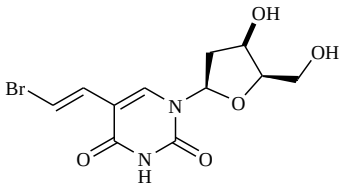
120: $R_1 = CH_3$, $R_2 =$

Meerbach *et al* presented a series of 42 lipophilic bromovinyldeoxyuridine monophosphates (BVDUMP) as potential prodrugs of the antiviral agent (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU). They applied 5'-*cyclo*Sal-

masking group technique to this cyclic nucleoside analogue to accomplish delivery of the monophosphate of BVDU within the target cells. The triesters 3-methyl-*cyclo*Sal-3'-OH-BVDUMP **121**, 5-H-*cyclo*Sal-3'-OH-BVDUMP **122**, 5-*O*-methyl-*cyclo*Sal-3'-OH-BVDUMP **123**, 3,5-dimethyl-*cyclo*Sal-3'-OH-BVDUMP **124** and 6-chloro-7-ethoxycarbonylmethyl*cyclo*Sal-3'-OH-BVDUMP **125** showed pronounced anti-Epstein Barr Virus effectiveness, which was found to be comparable with or even higher than that of acyclovir **103**. Two derivatives 5-H-*cyclo*Sal-3'-*O*-acetyl- BVDUMP **126** and compound **124** had a slightly higher anti-varicella zoster virus activity than the parent compound BVDU **127** (82).

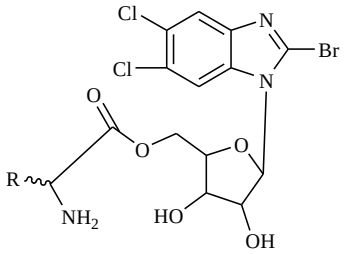


	R_1	R_2	R_3	R_4	R_5
121	CH_3	H	H	H	H
122	H	H	H	H	H
123	H	OCH_3	H	H	H
124	CH_3	CH_3	H	H	H
125	H	H	H	Cl	Ethoxycarbonyl methyl
126	H	H	$COCH_3$	H	H



127

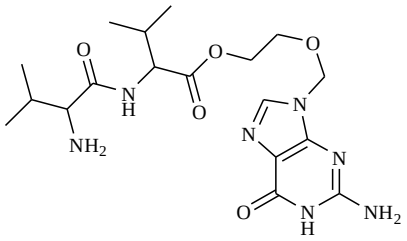
Song *et al* described the synthesis of amino acid ester prodrugs of the antiviral agent 2-bromo, 5-6 dichloro-1-(β-D-ribofuranosyl) benzimidazole and carried out evaluation of these compounds to check their efficiency as potential substrates of hPEPT1 transporter. These ester prodrugs, **128-139**, were found to have 2-4 fold higher affinity for hPEPT1 compared to 2-bromo,5-6 dichloro-1-(β-D-ribofuranosyl) benzimidazole (83).



Where R =

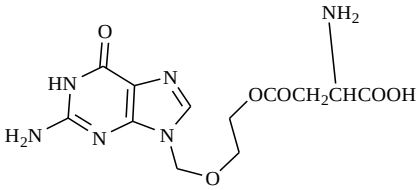
128: $_L$-Val-BDCRB
129: $_D$- Val-BDCRB
130: p-chloro-L-Phe-BDCRB
131: p-metoxy- L-Phe-BDCRB
132: $_L$- Pro-BDCRB
133: $_L$- Lys-BDCRB
134: $_L$-Ile-BDCRB
135: $_L$-Phe-BDCRB
136: $_D$- Phe-BDCRB
137: p-ethoxy- L-Phe-BDCRB
138: $_L$-Asp-BDCRB
139: $_D$- Asp-BDCRB

A dipeptide prodrug of the antiviral nucleoside acyclovir (ACV), val-val-ACV (VVACV), was developed and evaluated *in vivo* as a potential drug candidate for improving antiviral efficacy against herpetic epithelial and stromal keratitis by Anand *et al*. VVACV, the dipeptide prodrug of ACV, **103** was found to be highly soluble, stable in water, significantly less cytotoxic than parent drug and allowed formulation into 1% to 3% eye drops. *In vivo*, VVACV **140** exhibited excellent antiviral activity against epithelial and stromal keratitis in the rabbit eye model (84).



140

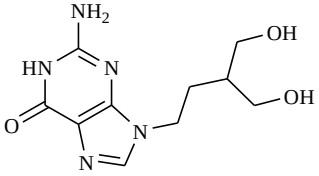
Yang *et al* carried out chemical stability, enzymatic hydrolysis and nasal uptake studies of amino acid ester prodrugs of acyclovir. They found that the $_L$-aspartate β-ester prodrug, **141** could be absorbed nasally and was proved to be least labile to enzymatic hydrolysis in the nasal mucosa (85).



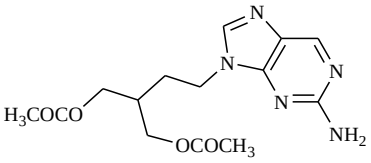
141

Potential oral prodrugs of the antiherpesvirus acyclonucleoside 9-[4-hydroxy-3-(hydroxymethyl)-but1-yl]guanine (BRL 39123, **142**) have been synthesized and evaluated for bioavailability in the blood of mice by Harnden *et al*. Oral bioavailability studies in healthy human subjects confirmed compound **143** as an effective prodrug (86).

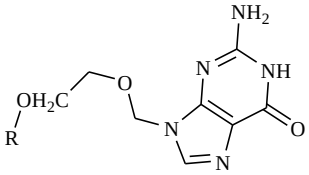
Colla *et al* reported several water-soluble ester derivatives of acyclovir [9-[(2-hydroxyethoxy)methyl]guanine], i.e., the 2'-*O*-glycyl-, 2'-*O*-α-alanyl-, 2'-*O*-β-alanyl- and 2'-*O*-3-carboxypropionyl esters for their antiviral activity in cell culture. These four acyclovir esters **144-147** were proved to be almost as active as acyclovir, **103** and got readily hydrolyzed to release the parent compound (87).



142, BRL 39123



143

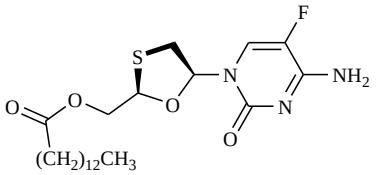


144: R= $COCH_2NH_2.HCl$
145: R= $COCH(CH_3)NH_2.HCl$
146: R= $COCH_2CH_2NH_2.HCl$
147: R= $COCH_2CH_2COONa$

Acquired immunodeficiency syndrome (AIDS) is a degenerative disorder of the immune and central nervous system which is caused by human immunodeficiency virus (HIV). The HIV virus enters the CNS early in the course of the systemic infection, and any blockade in its progression leads to AIDS dementia and other neurological manifestations of HIV infection [88]. According to the statistical facts on the AIDS, outbreak of epidemic provided in 2013 by WHO, there were suspected cases of about 35 million people having HIV infection and 1.5 million deaths due to this disorder [89,90]. HIV acquires resistance to all presently accessible drugs, resulting in swiftly decreased drug effectiveness. There is incredible potential for improving anti-HIV therapy not only by increasing the potency of antiviral drugs, but also by reducing the burden of the dosing regimen. This can be achieved by modifying the physicochemical, biopharmaceutical and pharmacokinetic properties of drug through the development of prodrugs (91).

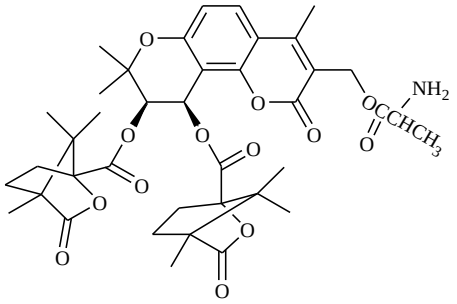
Agarwal HK *et al* synthesized three fatty acyl conjugates of emtricitabine as nucleoside prodrugs and evaluated these prodrugs against various strains of HIV-1. Due to improved lipophilicity and better cellular uptake the compound myristoylated conjugate of emtricitabine, **148** was proved to be a more effective analogue with a better resistance profile compared to its parent compound (92).

Guo *et al* designed and synthesized a series of ester prodrugs of 3-Hydroxymethyl-4-methyl- 3', 4'-di-*O*-(S)-camphanoyl-(+)-*cis*-khellactone to explore the new drug candidates as non-nucleoside reverse transcriptase inhibitor. The $_L$-alanine ester prodrug



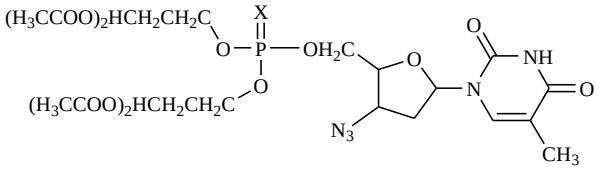
148

149 exhibited desirable pharmacokinetic properties *in vitro* and *in vivo* and showed improved oral bioavailability of 26% in rat, and would be a potential clinical candidate as a new anti-AIDS drug (93).

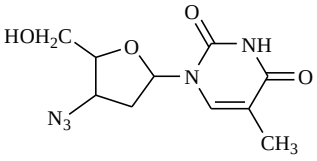


149

Phosphate and thiophosphate prodrugs **150,151** of anti-HIV agent azidothymidine were synthesized, and their anti-HIV activities as well as cytotoxicities were investigated *in vitro by* Qing-bin *et al*. The therapeutic index of **150** was found to be significantly higher than that of its parent drug azidothymidine, **152** and its thiophosphate counterpart **151** due to enhanced lipophilicity (94).

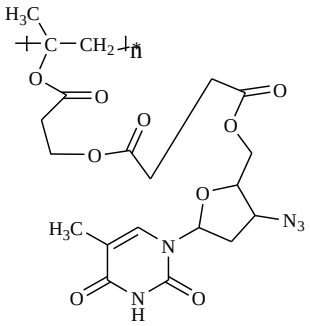


150: X=O,
151: X=S

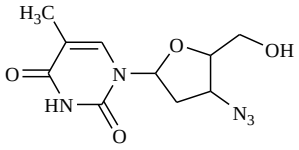


152

Agrawal *et al* designed and evaluated prodrug of zidovudine by coupling it to 2-hydroxymethyl methacrylate through a succinic spacer to get a monomeric drug conjugate which was polymerized to obtain the polymeric prodrug. Poly (HEMA-zidovudine) conjugate, **153** was found to exhibit improved pharmacokinetics as compared to parent drug zidovudine, **154** by increasing its short life and bioavailability resulting in less frequent administration and decreased toxicity (95).

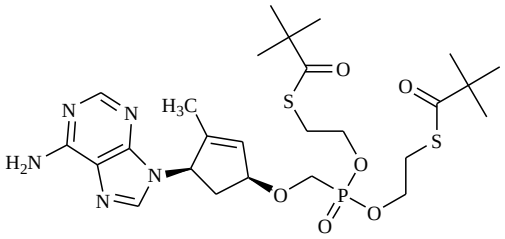


153



154

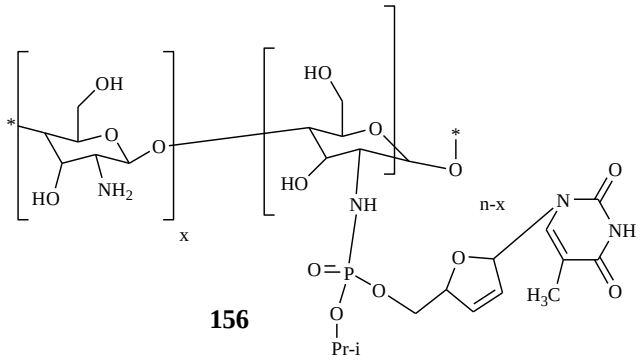
Li *et al* described the synthesis of S-acyl-2-thioethyl (SATE) prodrug of 2' modified 5' noncarbocyclic adenine analogue and tested these prodrugs for antiviral activity. As the ionic character of a phosphonic acid presented an obstacle for cellular permeability, S-acyl-2-thioethyl masked these charges with neutral groups to form more lipophilic derivatives capable of crossing the gastrointestinal wall and reverted back to the parent nucleoside phosphonic acid. SATE prodrug, **155** was found to exhibit 4 fold higher anti-HIV activity compared to parent compound (96).



155

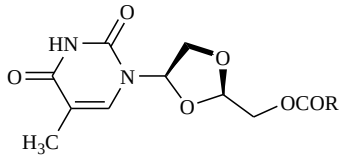
Yang *et al* synthesized a novel water-soluble chitosan-*O*-isopropyl-5'-*O*-stavudine monophosphate conjugate, **156**. This resulting polymeric conjugate were evaluated in MT4 cell line and they were found to exhibit remarkable anti-HIV effect and rather low cytotoxicity relative to parent nucleoside analogue owing to the effect of bypassing the rate-limiting step of monophosphorylation mediated by thymidine kinase.

Nanoparticles of compound **156** were prepared by the process of ionotropic gelation using tripolyphosphate to augment the delivery to viral reservoirs of HIV. On comparing the data of chitosan-*O*-isopropyl-5'-*O*-stavudine monophosphate conjugate and stavudine-loaded nanoparticles, *in vitro* drug release studies revealed that the crosslinked conjugate nanoparticles can prevent the coupled drug from leaking out of the nanoparticles in blood circulation and provide a mild sustained release of stavudine 5'-(*O*-isopropyl) monophosphate without the burst release (97).



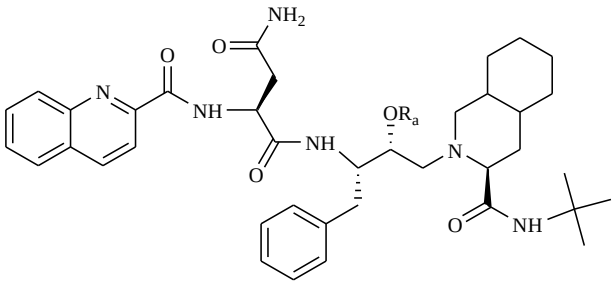
156

Liang *et al* synthesized a series of (-)-β-$_D$-(2R,4R)-dioxolane-thymine-5'-*O*-aliphatic acid esters as well as amino acid esters as prodrugs of (-)-β-$_D$-(2R,4R)-dioxolane-thymine. These synthesized compounds were evaluated for anti-HIV activity against HIV-1_{LAI} in human peripheral blood mononuclear (PBM) cells and for their cytotoxicity in PBM, T-lymphoblastoid cell line obtained from American Type Culture Collection as well as African green monkey kidney cells. On comparing with the parent drug, the compounds **157–159**, (5'-*O*-aliphatic acid esters) were found to be chemically stable and exhibited improved anti-HIV potency *in vitro* without increase in cytotoxicity (98).

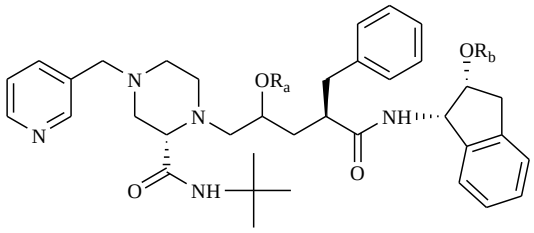


157: **R** = C_4H_9
158: **R** = C_7H_{15}
159: **R** = $C_{11}H_{23}$

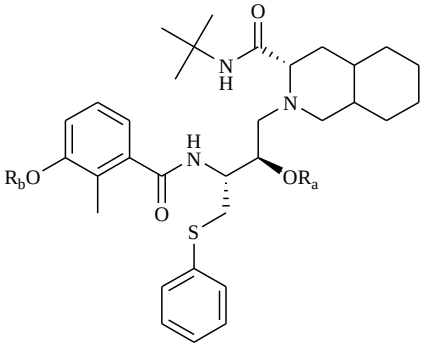
To improve the pharmacological properties as well as pharmacokinetic profiles of the current protease inhibitors (PIs) and consequently therapeutic potential, Roche *et al* reported the synthesis of PI-spacer-valine prodrugs (PI-saquinavir, indinavir and nelfinavir). They evaluated these synthesized prodrugs for *in vitro* stability with respect to hydrolysis, anti-HIV activity, cytotoxicity and permeation through a monolayer of Caco-2 cells as compared with their parent PIs and first generation of valine-PIs. They found that PI-spacer-valine prodrugs, **160-164** proved to be chemically more stable than the first generation PI-Val prodrugs with respect to hydrolysis (99).



160:Saq-C(O)C5NVal, R_a=ValNH$(CH_2)_5$C(O),

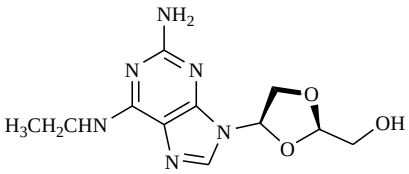


161: Ind(8)-C(O)C5NVal, R_a=H,
R_b= ValNH$(CH_2)_5$CO
162: Ind [C(O)C5NVal)]2, R_a=R_b= ValNH$(CH_2)_5$CO

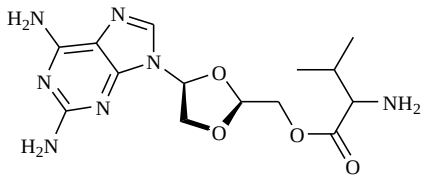


163: Nelf(1)-(C)OC5NVal, R_a= H, R_b= ValNH$(CH_2)_5$CO
164: Nelf-[C(O)C5NVal]2(2TFA), R_a=R_b= ValNH$(CH_2)_5$CO

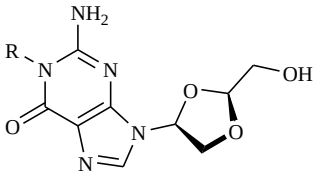
Prodrugs of (−)-β-$_D$-(2*R*,4*R*)-1,3-dioxolane-2,6-diamino purine (DAPD), amdoxovir, organic salts of DAPD, 5'-$_L$-valyl DAPD and *N*−1 substituted (−)-β-$_D$-(2*R*,4*R*)-1,3-dioxolane guanosine (DXG) have been synthesized and evaluated for anti-HIV activity against HIV-1_{LAI} in primary human lymphocytes by Narayanasamy *et al*. (−)-β-$_D$-(2*R*,4*R*)-1,3-dioxolane-2-amino-6-aminoethyl purine, **165** was found to be 17 times more potent than that of DAPD. 5'-$_L$-Valyl DAPD, **166** and organic acid salts, **167**–**170** also indicated enhanced anti-HIV activity in comparison to DAPD due to improved water solubility, while DXG prodrugs exhibited lower potency than that of DXG or DAPD (100).



165

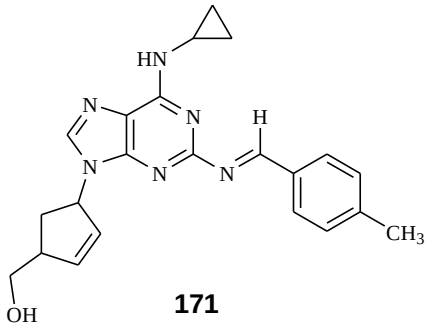


166



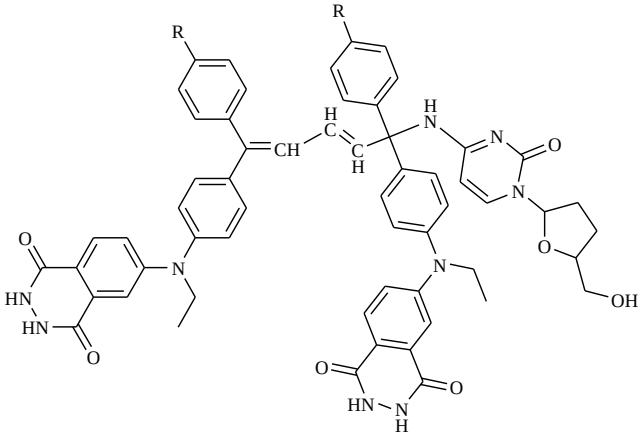
167: DAPD maleate mono salt
169: DAPD citrate hemi salt
168: DAPD tartarate hemi salt
170: DAPD fumarate hemi salt

Sriram *et al* described the synthesis of a new series of abacavir prodrugs with improved lipophilicity. The *in vitro* anti-HIV activities indicated that compound (3-(2-(4-methylamino-benzylideneamino)-6-(cyclopropylamino)-9H-purin-9-yl) cyclopentyl)methanol **171,** proved to be most potent compound with EC_{50} (effective concentration of compound (lM) achieving 50% protection in MT-4 cell lines against the cytopathic effect of HIV-1) of 0.05 µM and CC_{50} (cytotoxic concentration of compound (lM) required to reduce the viability of mock infected American Type Culture Collection cells by 50%), of >100 µM with selectivity index of >2000 (101).

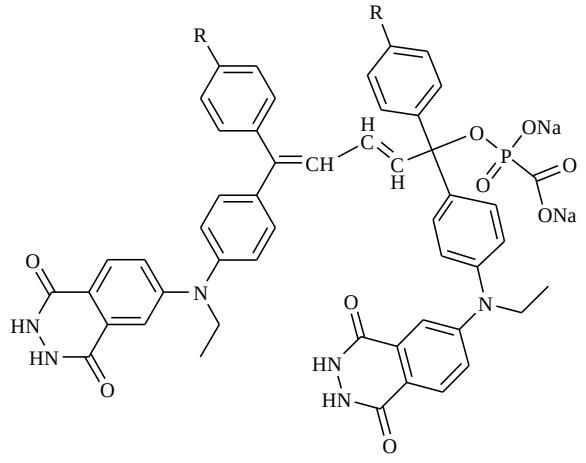


171

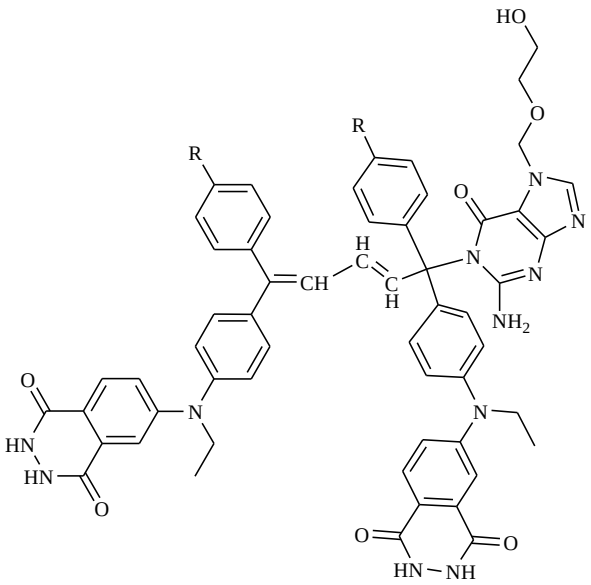
Mills *et al* synthesized and evaluated novel prodrugs of foscarnet and dideoxycytidine, **172-176** with a universal carrier compound comprising a chemiluminescent and a photochromic conjugate to enhance their cellular uptake. An increase of about 5 times in the activity of prodrugs of foscarnet as well as dideoxycytidine was observed in cultured macrophages infected with HIV and in mice infected with the retrovirus Friend leukemia virus than the parent drug (101).



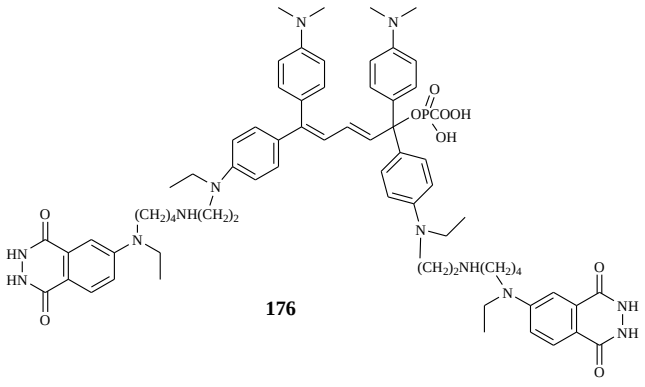
172: R = $N(CH_3)_2$
173: R = H



174: R = $N(CH_3)_2$

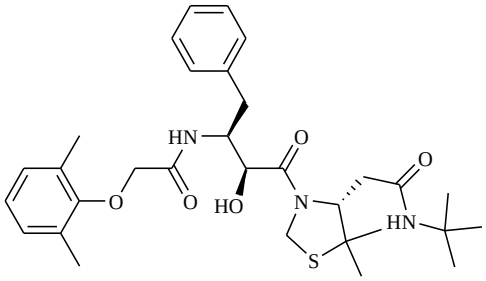


175: R = $N(CH_3)_2$



176

Hamada *et al* designed and synthesized water-soluble prodrugs of KNI-727, **177** a potent small-sized dipeptide-type HIV-1 protease inhibitor consisting of an Apns-Dmt core (Apns; allophenylnorstatine, Dmt; (R)- 5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid) as inhibitory machinery and carried out its kinetic studies. The synthetic prodrug, **178** was found to exhibit improved water-solubility (13mg/mL) more than 8000-fold in comparison with the parent compound, **177** resulted in improved oral absorption and bioavailability (102).



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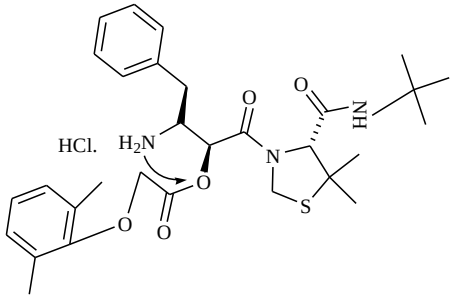
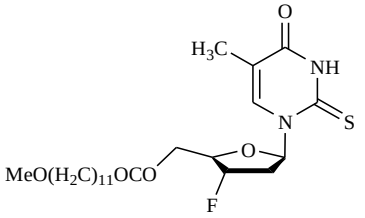
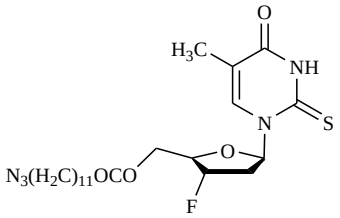


178

Miazga *et al* presented the novel synthesis of 2',3'-dideoxy-3' fluoro-2-thiothymidine (S^2FLT) based on transformation of appropriately protected 1-β-D-threo-ribofuranosylthymine. **179** and **180** were found to be most potent inhibitors of HIV-1 and exhibited ten times higher anti-HIV-1 activity and higher therapeutic index than their mother nucleoside S^2FLT (103).

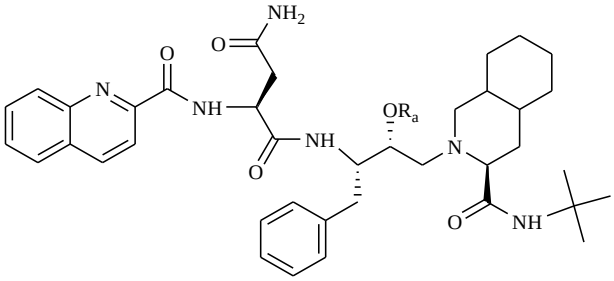


179



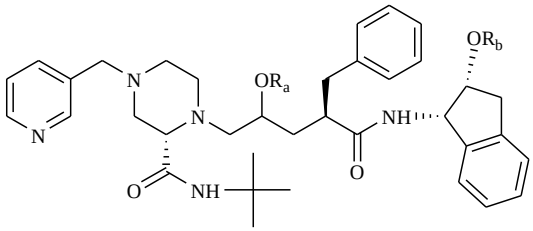
180

To modify the transport of the HIV protease inhibitors across the intestinal and blood brain barriers and their penetration into the central nervous system, the development of different acyl and carbamatoyl glucose-containing prodrugs derived from saquinavir, indinavir and nelfinavir have been carried out by Rouquayrol *et al.* They also evaluated these compounds for *in vitro* stability with respect to hydrolysis and anti-HIV activity. These glucose-linked ester and carbamate prodrugs **181-189** were found to display a promising therapeutic potential (104).



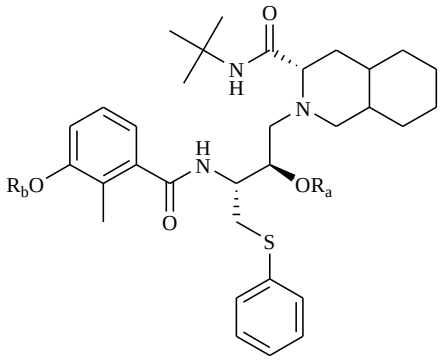
Saquinavir (R_a = H)

181: R_a = $C(O)(CH_2)_2C(O)$-Glc
182: R_a = $C(O)CH_2$-Glc
183: R_a = $C(O)(CH_2)_4$Glc
184: R_a = $C(O)NH(CH_2)_4$-Glc



Indinavir (R_a = R_b = H)

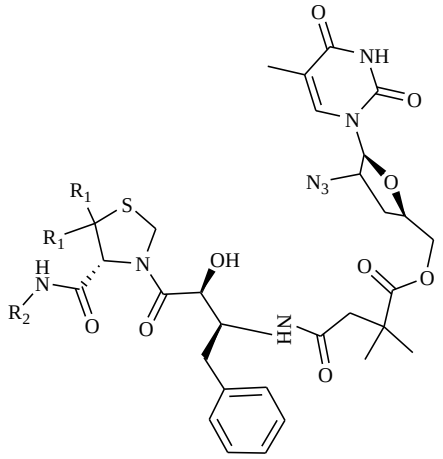
185: R_a = H, R_b = $C(O)(CH_2)_2C(O)$-Glc
186: R_a = H, R_b = $C(O)(CH_2)_4$-Glc
187: R_a = $C(O)NH(CH_2)_4$-Glc, R_b = H



Nelfinavir (R_a = R_b = H)

188: R_a = H, R_b = $C(O)(CH_2)_2C(O)$-Glc
189: R_a = $C(O)NH(CH_2)_4$-Glc, R_b = H

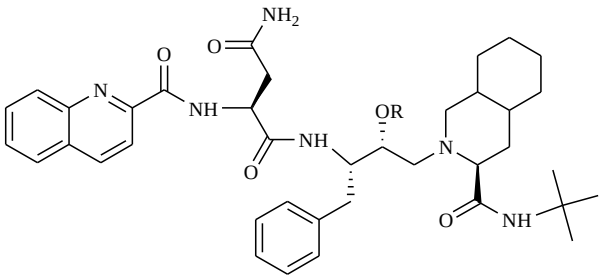
Matsumoto *et al* designed and synthesized conjugates of HIV protease inhibitors with nucleoside reverse transcriptase inhibitors based on the prodrug concept as well as the combination of two classes of anti HIV agents. The low antiviral activities of these inhibitors were probably due to their inadequate cell membrane permeability caused by the presence of free carboxylic acid in the inhibitors. Direct esterification of carboxyl group of the HIV protease inhibitors with 5'-hydroxyl group of the nucleoside reverse transcriptase inhibitor provided remarkably potent anti-HIV agents. **190** and **191** conjugates exhibited excellent antiviral activity compared with that of individual inhibitors (105).



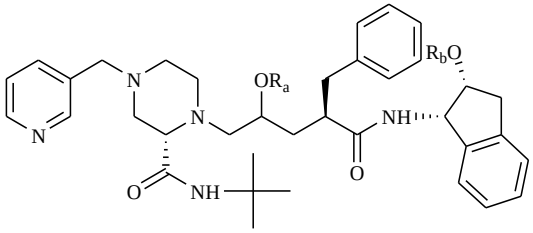
190: (R_1= Me, R_2= tert-butyl)
191: (R_1= Me, R_2= 2-methylbenzyl)

Farèse-Di Giorgio *et al* synthesized and investigated anti HIV activity as well as

cytotoxicity of prodrugs derived from saquinavir and indinavir, **192-199**. Ind-Oleyl, **196** displayed both a high inhibitory level and high chemical stability. No cytotoxicity was detected for these synthesized prodrugs for concentration as high as 10 or even 100 µM (106).



192: **Saq-Oleyl,** R=$CO(CH_2)_7CH=CH(CH_2)_7CH_3$
193: **Saq-Myr,** R= $CO(CH_2)_{12}CH_3$
194: **Saq PEG350,** R= $COC_2H_4CO(OC_2H_4)_7OCH_3$
195: **Saq PEG2000,** R= $COC_2H_4CO(OC_2H_4)_{44}H_3$



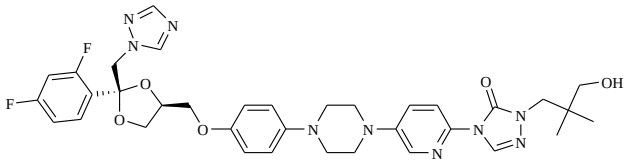
196: **Ind-Oleyl,** R_a= H, R_b=$CO(CH_2)_7CH=CH(CH_2)_7CH_3$
197: **Ind-Myr,** R_a= H, R_b= $CO(CH_2)_{12}CH_3$
198: **Ind-PEG350,** R_a=R_b= $COC_2H_4CO(OC_2H_4)_7OCH_3$
199: **Ind-PEG2000,** R_a= H, R_b=$COC_2H_4CO(OC_2H_4)_{44}OCH_3$

Machado *et al* studied antiviral activity and resistance profile of phosphazid, a novel prodrug of zidovudine. This prodrug was found to have a higher selective index than the parent drug (107).

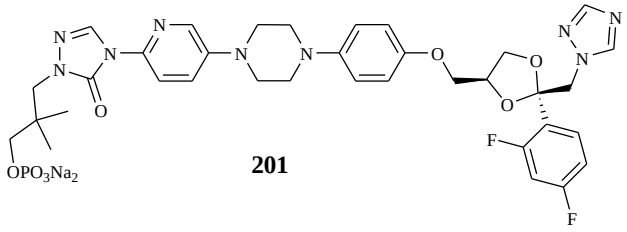
Prodrugs of Antifungal Agents

Fungal pathogens are a major public health threat with significant global effects which, surprisingly, are not being addressed as they should. These pathogens are widely distributed in soil, plant debris and other organic substrates (108). Fungal infections are caused by these microscopic organisms that can invade the epithelial tissue. Especially in the developed countries fungal infections have grown rapidly in last few decades and proved to be a significant cause of morbidity and mortality despite advances in medicinal chemistry. For the treatment of opportunistic fungal infections, the development of new potent or structural modification of the already available antifungal drugs is an important challenging task for modern medicine, with a potent, broad spectrum of antifungal activity, good pharmacokinetics and excellent bioavailability.

A number of prodrugs have been synthesized to combat the severity of fungal infections. Few of them are mentioned here. To improve the aqueous solubility of an itraconazole analogue YL-24, **200,** Liu *et al* synthesized a series of novel prodrugs and carried out its *in vivo* antifungal activity. The phosphate disodium salt compound **201**, among these prodrugs, exhibited excellent aqueous solubility (9.8 mg/mL) at near-neutral pH, adequate stability in buffer solutions, as well as complimentary pharmacokinetic profiles (107).

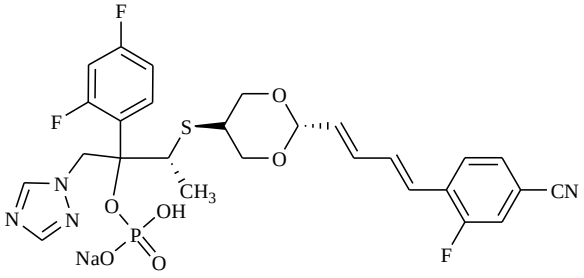


200



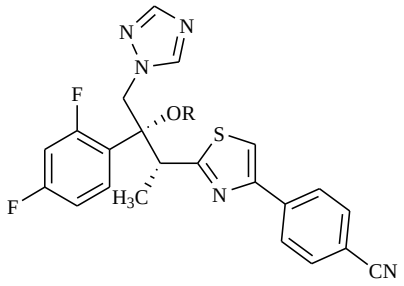
201

Kagoshima *et al* described the synthesis and evaluation of a number of novel water soluble ester prodrugs of antifungal triazole CS-758. Compound **202** was found to have good water solubility (>30 mg/mL), consequently proved to be a promising antifungal agent for parenteral use (108).



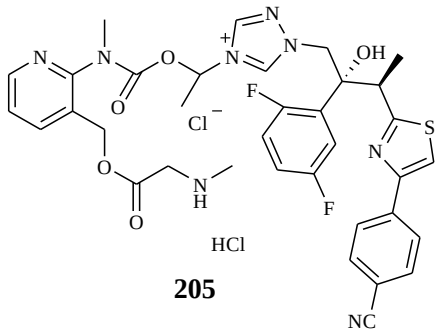
202

Synthesis of phosphonooxymethyl derivatives of ravuconazole, 2 (BMS-379224) and 3 (BMS-315801) and their biological evaluation as potential water-soluble prodrugs was described by Ueda *et al*. Both derivatives exhibited high solubility in water and transformed to the parent compound in presence of alkaline phosphatase, as well as *in vivo*. BMS-379224, **203** has proved to be one of the most promising prodrug and has now advanced to its clinical study as an intravenous formulation of parent compound, ravuconazole **204** (109).



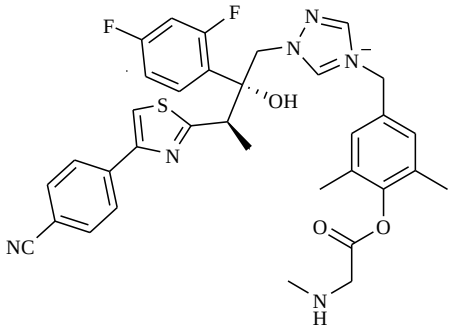
203: BMS 379224, R=-$CH_2OP(O)(OH)_2$
204: Ravuconazole, R=H,

Design, synthesis and antifungal activity of a novel water soluble prodrug, RO0098557, **205** of antifungal triazole was carried out by Ohwada *et al*. This synthesized prodrug was found to exhibit high chemical stability and water solubility along with strong antifungal activity against systemic candidiasis and aspergillosis (110).



205

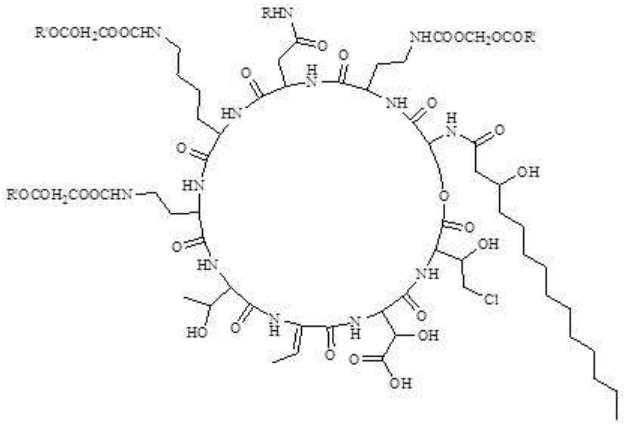
In previous study Ohwada *et al* synthesized water soluble N-benzyltriazolium or N-benzylimidazolium salt type prodrugs of many highly lipophilic triazole or imidazole antifungals. The prodrug **206** was found to have sufficient chemical stability as well as water solubility for parenteral use. It showed rapid and quantitative transformation to the active substance in human plasma (111).



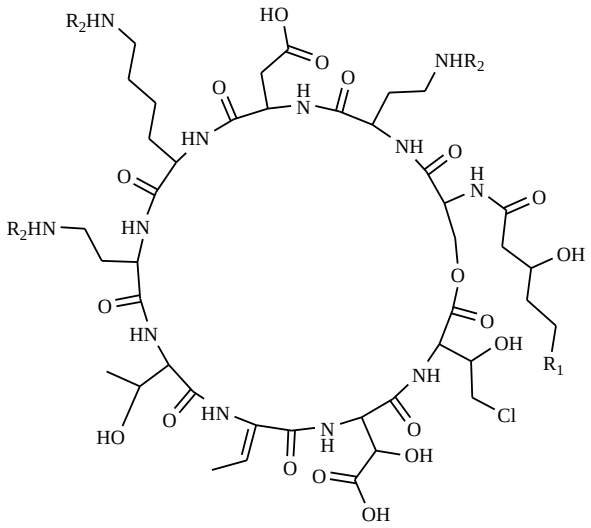
206

Sun *et al* carried out synthesis and evaluation of various N-acyloxymethylcarbamate linked prodrugs of 3-amido pseudomycin analogues. These synthesized combinations, **207-210** demonstrated improved toxicity profiles in comparison to their corresponding 3-amides as well as the parent pseudomycin B. They were found to exhibit good *in vivo* efficacy against murine candidiasis (112).

In another study Sun *et al* described the synthesis, bioconversion, antifungal activity, in addition to preliminary toxicology evaluation of a series of N-acyloxymethyl carbamate linked triprodrugs of pseudomycins. Two pseudomycin triprodrugs **211, 212** showed excellent *in vivo* efficacy against systemic candidiasis (113).

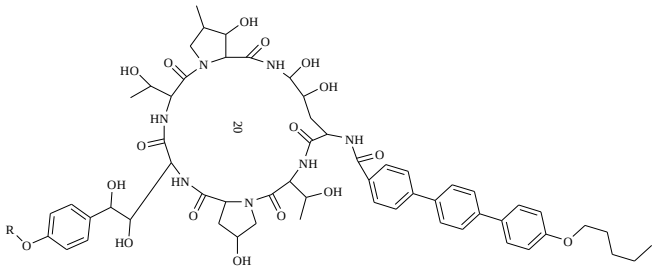


207: R=c-Pr, R'=i-Pr
208: R= $CH_2CH_2NMe_2$, R'=i-Pr
209: R=GlyOMe, R'=i-Pr
210: R=GlyOMe, R'=t-Bu



211: $R_1 = C_9H_{19-n}$, R_2 = -C(O)OCH$_2$OC(O)Bu-t
212: $R_1 = C_{11}H_{23-n}$, R_2 = -C(O)OCH$_2$OC(O)Bu-t

Rodriguez *et al* reported synthesis of phosphonate and phosphate esters prodrugs on the phenolic hydroxy of two echinocandin semisynthetic derivatives. Phosphate analogs have been developed in order to improve the water solubility properties of this important class of antifungal compounds. The phosphate prodrug, **213** possessed enhanced water solubility (> 12 mg/mL) relative to parent drug, **214** (< 0.1 mg/mL) (114).



213: R=P(O)(OH)$_2$
214: R=H

RECENT PATENTS

Over the past few decades, number of patents has been issued in the field of anti-infective agents encompassing a range of drugs having various activities. The patents described in Table 2 reveal information related to various features, salient approaches and advancements of antiinfective agents.

FUTURE PROSPECTS

Prodrugs of antiinfective agents can present an attractive option to improve undesirable properties of a wide variety of these drugs without losing the benefits of the parent drug molecule. Nonetheless, developing a prodrug of these available antimicrobial agents can still be more feasible, economical and faster strategy than searching for an entirely new therapeutically active agent with suitable ADME (absorption, distribution, metabolism and excretion) properties. Hence, antiinfective prodrugs are becoming an essential element of drug discovery paradigm, as illustrated by the increasing number of its approved prodrugs and patents. Moreover, the development of novel and highly efficacious antimicrobial prodrugs and their preface in clinical therapy would be much fruitful in forthcoming years.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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Table 2. List of patents related to antiinfective prodrugs

S. No.	Publication date	Patent number	Invention disclosed	Reference
1.	26/09/2013	US0253196A1	Salts of prodrugs of piperazine and substituted piperidine antiviral agents	(115)
2.	13/06/2013	WO084214A2	Pyrazinoic acid prodrugs activated by esterases of mycobacteria	(116)
3.	27/12/2012	WO177986A2	Conjugate-based antifungal and antibacterial prodrugs	(117)
4.	20/12/2012	WO174121A2	Decoquinate prodrugs	(118)
5.	15/12/2011	WO156674A2	Thioether prodrug compositions as anti-hiv and anti-retroviral agents	(119)
6.	25/10/2011	US 8044230 B2	Water soluble prodrugs of chloramphenicol, thiamphenicol, and analogs thereof	(120)
7.	06/09/2011	US8012987B2	Indolo[2,1-b] quinazole-6,12-dione antimalarial compounds and methods of treating malaria therewith	(121)
8.	29/04/2010	WO 047737 A2	Antimicrobial indoline compounds for treatment of bacterial infections	(122)
9.	25/03/2010	WO032165A2	Prodrugs of artemisinin	(123)
10.	30/01/2008	EP1881974A2	Phosphonated fluoroquinolones, antibacterial analogstherof, and methods for the prevention and treatment of bone and joint infections.	(124)
11.	16/01/2007	US007163923B2	Peptide deformylase activated prodrugs	(125)
12.	03/06/2004	WO 046153A1	Prodrug esters of ceftriaxone	(126)
13.	10/07/2003	US0130205A1	Novel pharmaceutical anti-infective agents containing carbohydrate moieties and methods of their preparation and use	(127)
14.	15/05/2003	US0092755 A1	Novel prodrugs for antimicrobial amidines	(128)
15.	26/11/2002	US6486200B1	Prodrugs for antimicrobial amidines	(129)
16.	22/05/2001	US6235728B1	Water soluble prodrugs of azole compounds	(130)
17.	12/12/2000	US6159706A	Application of enzyme prodrugs as anti-infective agents	(131)
18.	23/03/1996	WO015132A1	Improved antiviral prodrugs	(132)
19.	08/11/1989	EP 0340778A2	Prodrugs of 2',3' –Didehydro-2’,3’ Dideoxynucleosides	(133)
20.	22/01/1985	US4495180	Prodrugs of ARA-A an antiviral agent	(134)
21.	24/01/1984	US4427582	Antimicrobial disulfide prodrugs	(135)

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