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# Fosamprenavir

Prop INN

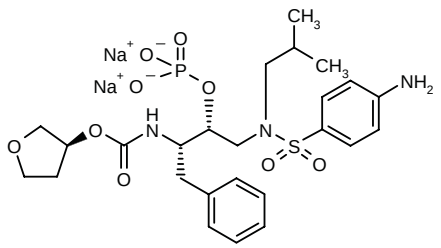
*Anti-HIV*
*HIV Protease Inhibitor*

GW-433908
VX-175

### Fosamprenavir Sodium

GW-433908A

*N*-[3-[*N*-(4-Aminophenylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-(phosphonooxy)propyl]carbamic acid tetrahydrofuran-3(*S*)-yl ester disodium salt



$C_{25}H_{34}N_3Na_2O_9PS$ Mol wt: 629.5756

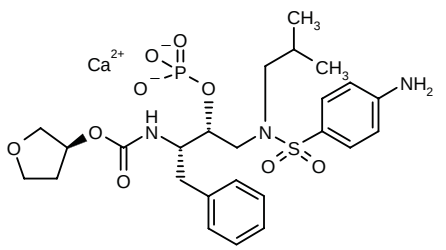
CAS: 226700-80-7
CAS: 226700-79-4 (as free acid)

EN: 278740

### Fosamprenavir Calcium

GW-433908G

*N*-[3-[*N*-(4-Aminophenylsulfonyl)-*N*-isobutylamino]-1(*S*)-benzyl-2(*R*)-(phosphonooxy)propyl]carbamic acid tetrahydrofuran-3(*S*)-yl ester calcium salt



$C_{25}H_{34}CaN_3O_9PS$ Mol wt: 623.6736

CAS: 226700-81-8

EN: 285394

### Synthesis

Fosamprenavir is obtained by several related methods involving two different ways of obtaining the key intermediate (1*S*,2*R*)-1-benzyl-2-hydroxy-3-[*N*-(4-nitrophenylsulfonyl)-*N*-ispropylamino]propylcarbamic acid (3*S*)-tetrahydro-3-furanyl ester (XIII):

1) The reaction of the chiral epoxide (I) with isobutylamine (II) in refluxing ethanol gives the secondary amine (III), which is protected with benzyl chloroformate (IV) and TEA, yielding dicarbamate (V). Selective deprotection of (V) with dry HCl in ethyl acetate affords the primary amine (VI), which is treated with 3(*S*)-tetrahydrofuryl *N*-succinimidinyl carbonate (VII) – obtained by reaction of tetrahydrofuran-3(*S*)-ol (VIII) first with phosgene and then with *N*-hydroxysuccinimide (IX) – and DIEA in acetonitrile to provide the corresponding carbamate (X). Deprotection of (X) by hydrogenation with $H_2$ over Pd/C in ethanol gives the secondary amine (XI), which is condensed with 4-nitrophenylsulfonyl chloride (XII) by means of $NaHCO_3$ in dichloromethane/water to yield the sulfonamide intermediate (XIII) (1, 2). Scheme 1.

2) The reaction of the chiral epoxide (I) with isobutylamine (II) in refluxing ethanol gives the secondary amine (III), which is condensed with 4-nitrophenylsulfonyl chloride (XII) and TEA in hot toluene, yielding sulfonamide (XIV). Deprotection of (XIV) with HCl in hot toluene/ water affords the primary amine (XV), which is condensed with imidazole-1-carboxylic acid 3(*S*)-tetrahydrofuryl ester (XVI) – prepared by reaction of tetrahydrofuran-3(*S*)-ol (VIII) with carbonyldiimidazole (CDI) in ethyl acetate – to provide intermediate (XIII) (3). Scheme 2.

Esterification of the OH group of compound (XIII) with $PO_3H_3$ by means of DCC in hot pyridine gives the corresponding phosphite (XVII), which is oxidized with bis(trimethylsilyl)peroxide in bis(trimethylsilyl)azane to yield the expected phosphate (XVIII) (4-7). Reduction of the nitro group of (XVIII) with $H_2$ over Pd/C in ethyl acetate affords fosamprenavir (XIX) (4-8). Finally, fosamprenavir (XIX) is treated with aqueous $NaHCO_3$ (4-7) or with calcium acetate in water (8, 9) to provide the corresponding salts. Scheme 3.

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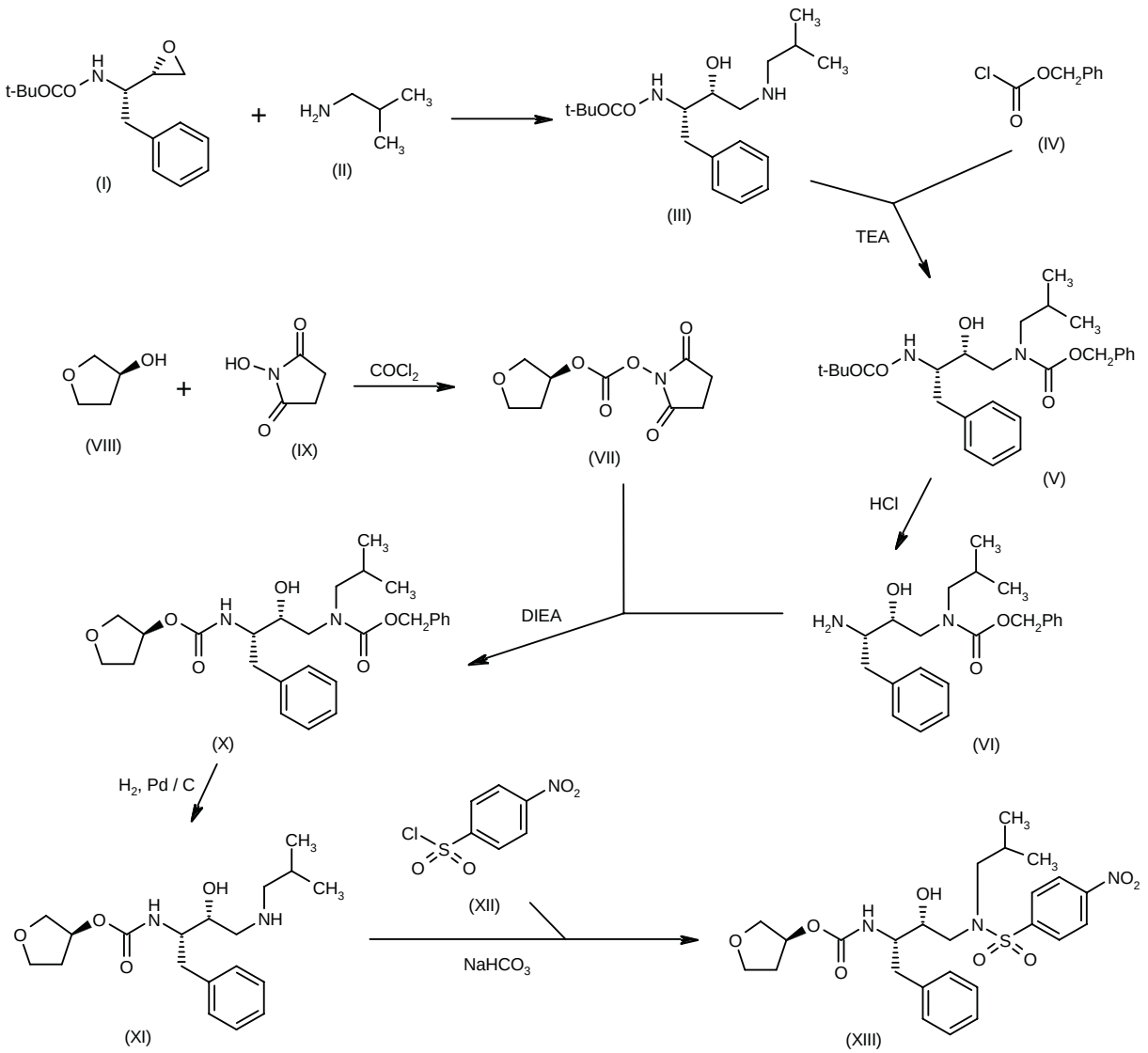
**Scheme 1: Synthesis of Intermediate (XIII) of Fosamprenavir**



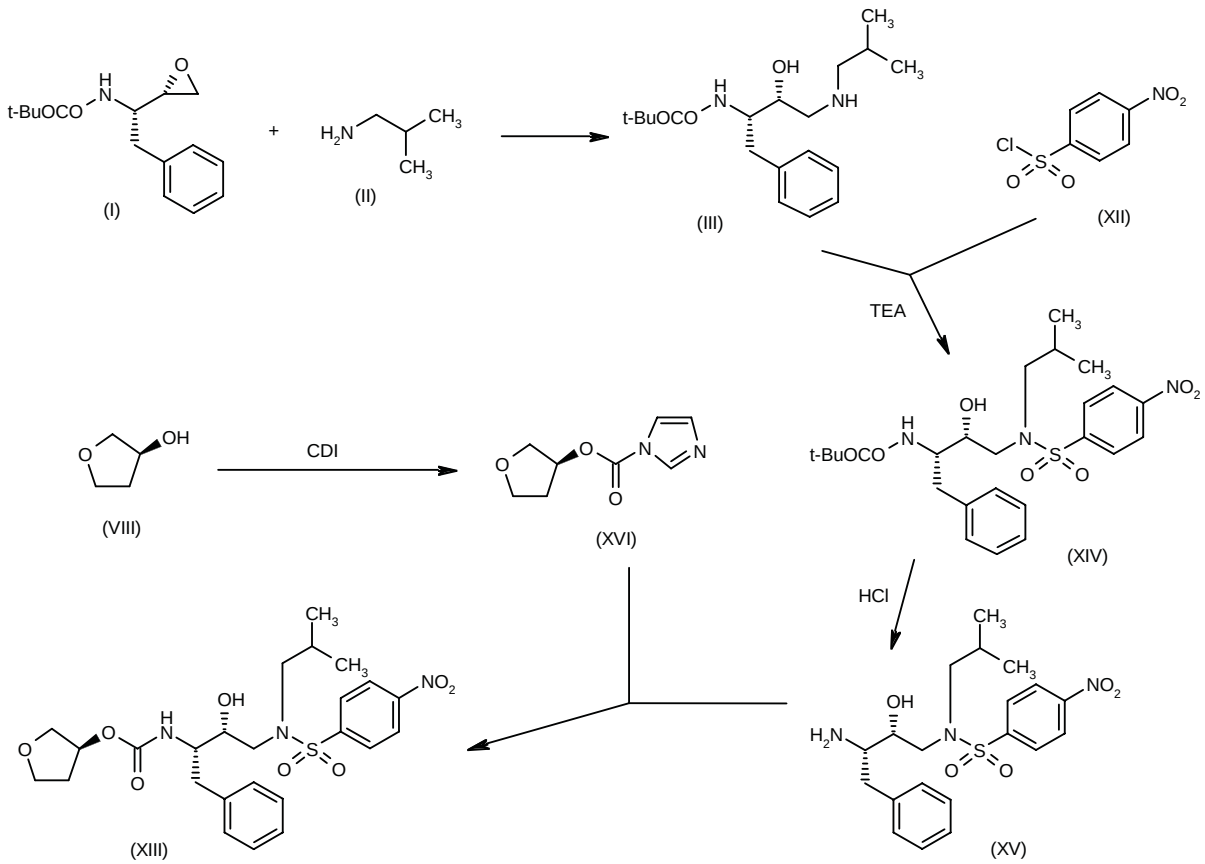

Alternatively, the phosphate (XIX) can be obtained directly by reaction of intermediate (XIII) with $POCl_3$ in pyridine, followed by hydrolysis with 2N HCl (4-8). Scheme 3.

## Introduction

The introduction of the protease inhibitors (PIs) as a potent class of antiretroviral agents in 1995 has strikingly altered therapy for the treatment of HIV infection and AIDs. Today, treatment is referred to as highly active antiretroviral therapy (HAART) and it usually includes a PI. Although other agents have been developed for the treatment of HIV infection and AIDs, PIs continue to play an imperative role in antiretroviral regimens. The addition of PIs to HAART has been demonstrated to cause marked viral suppression and delay in the progression of HIV-1-related disease and death (10-13).

PIs act through inhibition of the HIV-1 protease. This aspartic protease is necessary for viral maturation, cleaving the gag and gag-pol precursor molecules of HIV into smaller proteins. These cleavages steps occur late in the viral life cycle when virions are released from infected cells. Malfunctioning of this enzyme can result in blockage of production of the virion core structural proteins (*i.e.*, p17, p24, p9 and p7) and viral enzymes (*e.g.*, reverse transcriptase, protease and integrase). The result

**Scheme 2: Synthesis of Intermediate (XIII) of Fosamprenavir**




is production of virions that are immature and, more importantly, noninfectious (14-16).

To date, the FDA has approved 6 PIs for the treatment of HIV infection. These agents are shown in Table I. Moreover, hundreds of ongoing trials continue to examine the efficacy of PIs as compared to other antiretroviral agents and are attempting to investigate modified or simplified PI dosing schedules. However, as HIV strains emerge that are resistant to the available PIs, the search for new PIs continues. Those PIs currently in clinical trials are shown in Table II.

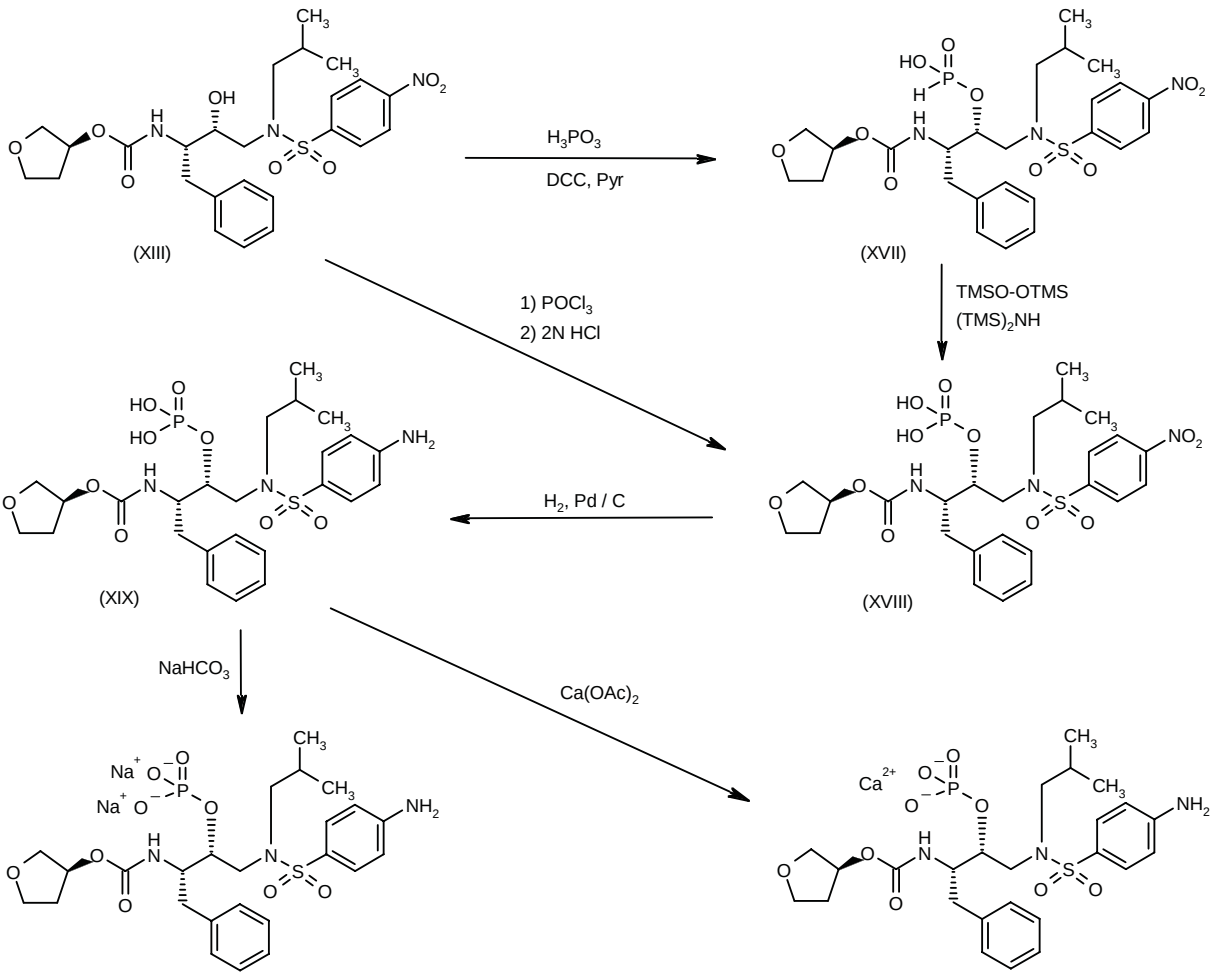
The launched compound amprenavir possesses excellent antiviral potency and good tolerability in addition to a superior half-life of 7-10 h. (17) However, the agent has a slow kinetic wetting profile and high lipophilicity (water solubility of approximately 0.04 mg/ml), thus limiting its total bioavailability when dosed as a crystalline solid. As a result, the formulation of the agent must include a high percentage of organic excipients to facilitate gastric dissolution. In response to these drawbacks, fosamprenavir (VX-175; GW-433908) was developed. Fosamprenavir is an inactive phosphate ester that is a highly water soluble prodrug of amprenavir. It allows more convenient dosing (*i.e.*, reduction in pill counts) as compared to amprenavir and it has been selected for further development (4).

## Pharmacokinetics

The calcium salt of fosamprenavir is a crystalline solid whose solubility is pH-dependent, with a maximum solubility of equal to or more than 100 mg/ml at pH 3-4; the sodium salt is extremely hygroscopic and is an amorphous solid; its solubility is > 100 mg/ml at pH 7. A study exposing Caco-2 monolayers to fosamprenavir showed that the prodrug was only present on the apical side in contrast to amprenavir which was detected on the basal lateral side only. These results indicate that fosamprenavir was cleaved to amprenavir and absorbed but not significantly absorbed itself (18).

Studies administering the sodium salt by oral gavage (40 mg/kg amprenavir equivalents in a water suspension or disodium water solution) to rats reported high blood levels of amprenavir with an $AUC_{0\text{-}12}$ value for amprenavir of < 1 and 11.7 μg·h/ml, respectively, depending on

**Scheme 3: Synthesis of Fosamprenavir Sodium and Fosamprenavir Calcium**



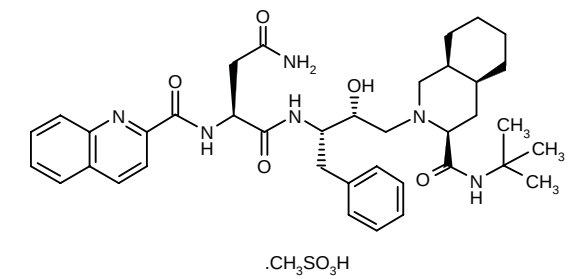

the formulation. Fosamprenavir was not detected in plasma, suggesting rapid and complete conversion to amprenavir across gastrointestinal epithelium. The $t_{1/2}$ value for amprenavir following fosamprenavir dosing was similar to that obtained with amprenavir although total exposure to amprenavir was sightly reduced; the relative bioavailability was 90% as compared to amprenavir (4, 19).

Pharmacokinetic studies in dogs showed that fosamprenavir sodium (20 mg/kg p.o.) administration resulted in exposure (AUC = 17.9 *vs.* 23.5 μg·h/ml) and $C_{max}$ (6.6 *vs.* 6.8 μg/ml) values that were 76 and 97%, respectively, of the values seen with amprenavir dosing. The exposure to fosamprenavir was 0.6% of the exposure to amprenavir. Examination of concentration of the agents in the portal vein following oral fosamprenavir calcium dosing (35 mg/kg) revealed that at 0.25 h postdosing, the concentration of the prodrug was at the most 2.2% of the concentration of amprenavir. These results indicate that the prodrug was cleaved to amprenavir at or in the gut epithelium (18).

The pharmacokinetics of fosamprenavir have also been examined in healthy humans. An open, randomized, single-dose, 5-way crossover phase I study conducted in 16 healthy male volunteers examined the safety and pharmacokinetics of the calcium and sodium salts of fosamprenavir and the effects of dosing with a high-fat meal. Volunteers orally received either the sodium or calcium salt of fosamprenavir (1200 mg amprenavir molecular weight equivalent [APV eq.]) while fasting, the calcium salt of fosamprenavir (1200 mg APV eq.) with a high-fat meal, the calcium salt of fosamprenavir (1800 mg APV eq.) while fasting or 1200 mg amprenavir (as 150 mg capsules) while fasting. Fosamprenavir exposure was < 0.17% of amprenavir exposure. While fosamprenavir calcium was bioequivalent to amprenavir ($C_{max}$ = 27% lower) showing dose-proportionality ($C_{max}$ = 14% lower at

*Table I: Protease inhibitors launched for the treatment of HIV infection (Prous Science Integrity database).*

| Drug Name | Company | Year Launched |
|---|---|---|
| 1. Saquinavir mesilate (*Invirase*; *Fortovase*) | Roche | 1995 |
| 2. Indinavir sulfate (*Crixivan*) | Merck & Co. | 1996 |
| 3. Ritonavir (*Norvir*) | Abbott/Dainippon | 1996 |
| 4. Nelfinavir mesilate (*Viracept*) | Agouron/Roche/Welfide/Japan Tobacco | 1997 |
| 5. Amprenavir (*Angerase*; *Prozei*) | GlaxoSmithKline/Vertex/Kissei | 1999 |
| 6. Lopinavir/Ritonavir (*Kaletra*) | Abbott | 2000 |

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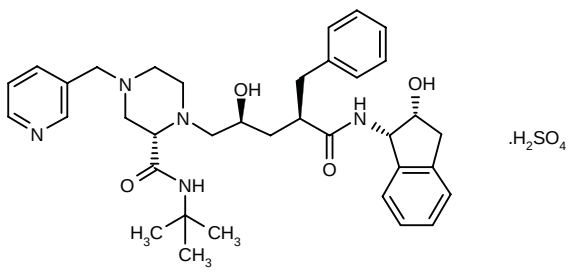


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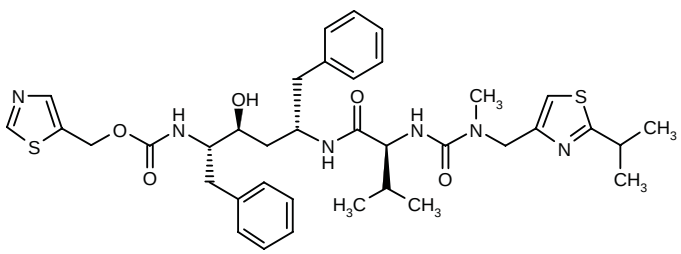

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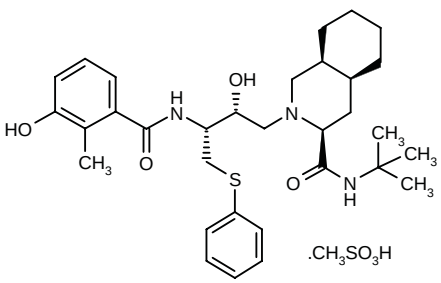


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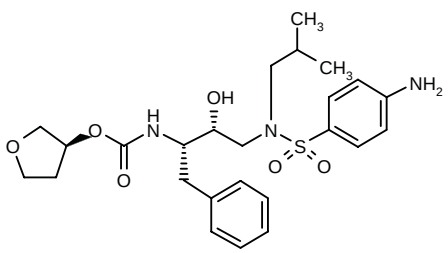

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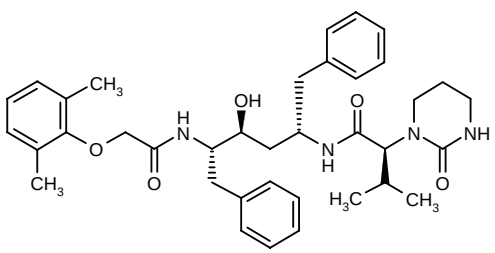


(6)*

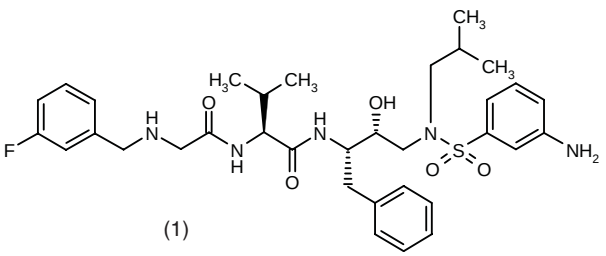
*Structure of lopinavir

the high dose), the sodium salt was more bioavailable than amprenavir ($C_{max}$ = 12% greater). The $AUC_{\infty}$ and $C_{max}$ values of amprenavir were decreased by 20 and 41%, respectively, when fosamprenavir was given with a high-fat meal. The $t_{1/2}$ values were comparable for all treatments. All regimens were well tolerated with no serious adverse events or clinically significant changes in laboratory parameters or vital signs observed (20).

The pharmacokinetics of fosamprenavir calcium and the effects of food intake on these parameters were further investigated in another open, randomized, single-dose, 6-way crossover study conducted in 24 healthy males. Subjects orally received fosamprenavir (1200 mg APV eq.) in tablet form while fasting or with a high- or low-fat meal, fosamprenavir (1200 mg APV eq.) in a suspension while fasting or amprenavir (1200 mg capsules) while fasting or with a low-fat meal. Both the tablet and suspension forms of the calcium salt of fosamprenavir were bioequivalent to amprenavir ($C_{max}$ = 41% lower). In this study, food intake did not significantly alter the pharmacokinetics of fosamprenavir; the $C_{max}$ value decreased by only 12% following a high-fat meal.

*Table II: Protease inhibitors in clinical trials for the treatment of HIV infection (Prous Science Integrity database).*

| Drug Name | Company | Status |
|---|---|---|
| 1. DPC-681 | DuPont Pharm. | Phase I |
| 2. DPC-684 | DuPont Pharm. | Phase I |
| 3. DMP-450 | Triangle Pharm. | Phase I/II |
| 4. KNI-272 | Japan Energy | Phase II |
| 5. Tipranavir | Pharmacia/Boehringer Ingelheim | Phase II |
| 6. BMS-232632 | Bristol-Myers Squibb | Phase III |
| 7. Fosamprenavir calcium | Vertex/GlaxoSmithKline | Phase III |



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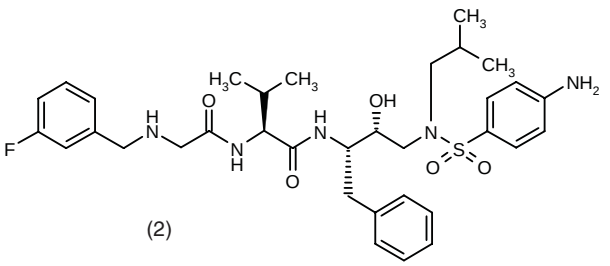

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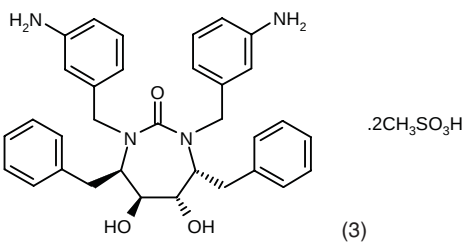
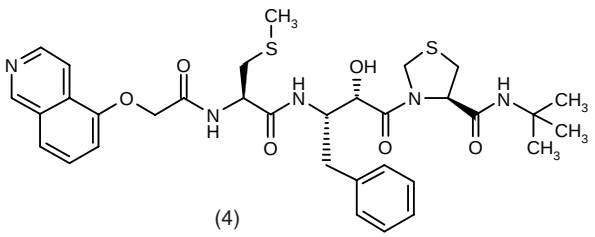


.2$CH_3SO_3H$

(3)



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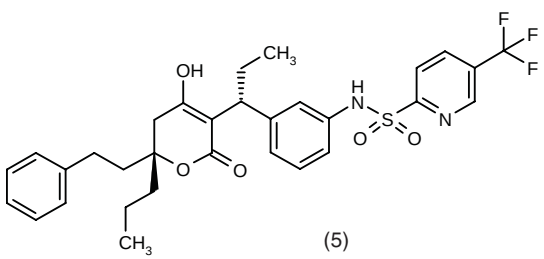

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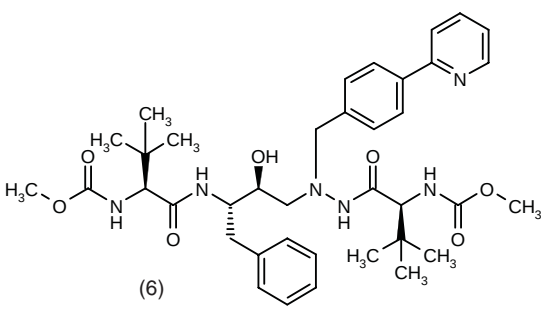

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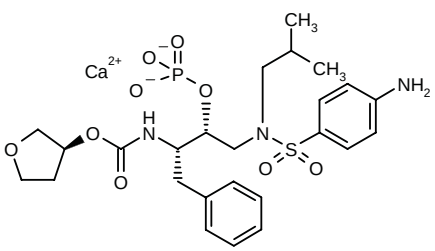

(7)

However, fosamprenavir was 23% more bioavailable as compared to amprenavir when administered with a low-fat meal and amprenavir was 23% less bioavailable when given in the fasted state ($C_{max}$ = 46% lower). All treatments were well tolerated with no serious adverse events or changes in laboratory parameters or vital signs noted (21).

The pharmacokinetics of fosamprenavir were reported from a randomized study involving 85 treatment-naive HIV infected adults also given abacavir (300 mg b.i.d.) and lamivudine (150 mg b.i.d.). For 28 days patients received either fosamprenavir as 1395 mg (3 tablets) b.i.d. or 1860 mg (4 tablets) b.i.d. or amprenavir (1200 mg b.i.d.); after 28 days, amprenavir-treated patients were

crossed over to one of the fosamprenavir doses and fosamprenavir-treated patients were crossed over to amprenavir until day 42. $C_{max}$ values for the 1395 and 1860 mg fosamprenavir and amprenavir dose groups differed (5.06, 4.69 and 6.62 mg/l, respectively), although overall drug exposure was similar for all treatment groups ($AUC_{0-12}$ = 16.88, 16.85 and 16.28 mg·h/l, respectively) (22).

## Clinical Studies

The safety and efficacy of fosamprenavir were also examined in the above mentioned randomized study involving 85 treatment-naive HIV infected adults. At baseline, HIV-1 RNA and $CD4^+$ counts were 4.52-4.75 $\log_{10}$ copies/ml and 177-348 cells/$mm^3$, respectively, for all treatment groups. The mean changes in HIV-1 RNA after 28 days of treatment with 1395 mg fosamprenavir, 1860 mg fosamprenavir and amprenavir were –9.7, –1.88 and –1.98, respectively, while the mean changes in CD4+ counts were 111, 106 and 92, respectively. Drug-related side effects were similar for all treatment groups although a lower incidence of moderate nausea (5 *vs.* 17%) and abdominal pain (2 *vs*. 17%) were observed in the fosamprenavir treatment groups. Moderate, transient headache (5 *vs.* 0%) and sleep disorders (7 *vs.* 0%) were more frequently noted in the fosamprenavir groups (22).

Fosamprenavir continues to undergo phase III testing. Two trials involving antiretroviral treatment-naive patients are currently under way. One of these trials is examining the efficacy of once-daily fosamprenavir in combination with ritonavir. Other phase III trials planned include a study conducted in treatment-experienced patients (23, 24).

## Manufacturer

Vertex Pharmaceuticals, Inc. (US); licensed to GlaxoSmithKline plc (GB).

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