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MONOGRAPH

COBICISTAT

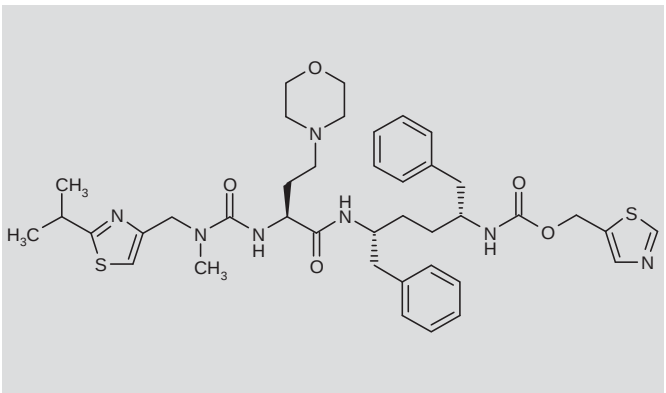
Rec INN; USAN

Cytochrome P450 CYP3A Inhibitor
Anti-HIV Agent

GS-9350

N-[1(*R*)-Benzyl-4(*R*)-[2(*S*)-[3-(2-isopropylthiazol-4-ylmethyl)-3-methyl]ureido]-4-(4-morpholinyl)butyramido]-5-phenylpentyl]carbamic acid thiazol-5-ylmethyl ester

InChI: 1S/C40H53N7O5S2/c1-29(2)38-43-34(27-53-38)25-46(3)39(49)45-36(16-17-47-18-20-51-21-19-47)37(48)42-32(22-30-10-6-4-7-11-30)14-15-33(23-31-12-8-5-9-13-31)44-40(50)52-26-35-24-41-28-54-35/h4-13,24,27-29,32-33,36H,14-23,25-26H2,1-3H3,(H,42,48)(H,44,50)(H,45,49)/t32-,33-,36+/m1/s1



$C_{40}H_{53}N_7O_5S_2$
Mol wt: 776.023
CAS: 414910-30-8
CAS: 1004316-88-4
EN: 644627

SUMMARY

Highly active antiretroviral therapy (HAART) has converted HIV-AIDS from one of history's worst pandemics to a chronic disease. HAART is the combination of different families of drugs that inhibit various stages of the HIV life cycle. Among these drug families, the protease inhibitors have a low systemic exposure and short half-life after oral administration due to their rapid metabolism by cytochrome P450 3A (CYP3A) enzymes, which can be circumvented by the concomitant administration of ritonavir, a mechanism-based inhibitor of CYP3A enzymes. Cobicistat (GS-9350) is a novel pharmacoenhancer with no anti-HIV activity, which produces mechanism-based CYP3A inhibition similar to that of ritonavir, with better physicochemical properties that allow coformulation with antiretrovirals, reduced off-target drug interactions and improved tolerability. Phase II and III trials are currently assessing the safety and efficacy of cobicistat-boosted protease inhibitors or integrase inhibitors as fixed-dose combinations in a single tablet.

Key words: Cobicistat – GS-9350 – CYP3A – Pharmacoenhancer – HIV-AIDS – HAART

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SYNTHESIS*

Cobicistat can be prepared by several different ways:

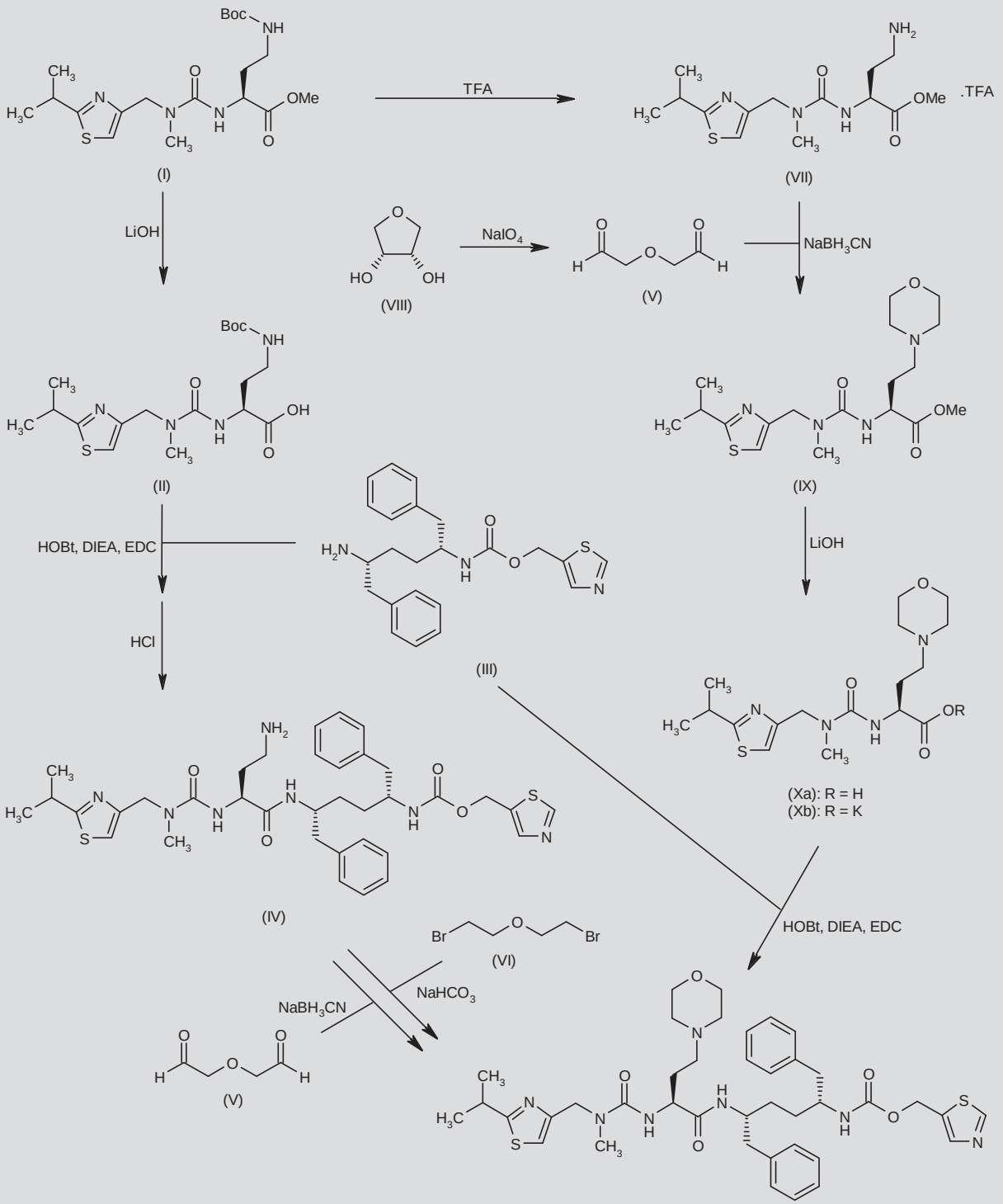
Hydrolysis of methyl 2(*S*)-ureido-4-aminobutyrate (I) by means of LiOH in THF/H_2O provides carboxylic acid (II), which is then condensed with (*R*,*R*)-*N*-[(4-amino-1,4-dibenzyl)butyl]carbamate (III) in the presence of EDC, HOBt and DIEA in THF, followed by *N*-Boc deprotection by means of HCl to yield the 2,4-diaminobutyric acid derivative (IV). Finally, construction of a morpholine ring onto the primary amine of compound (IV) is then performed by either double reductive alkylation with 2,2'-oxybis(acetaldehyde) (V) in the presence of $NaBH_3CN$ in $CH_3CN/CHCl_3/H_2O$ or by alkylation with bis(2-bromoethyl) ether (VI) in the presence of $NaHCO_3$ in DMF (1, 2).

In an alternative route, deprotection of compound (I) via cleavage of the Boc group by means of TFA in CH_2Cl_2 gives the free amine (VII), which by double reductive alkylation with 2,2'-oxybis(acetaldehyde) (V) [prepared by oxidative ring cleavage of *cis*-tetrahydrofuran-3,4-diol (VIII) with $NaIO_4$ in H_2O] in the presence of $NaBH_3CN$ in $CH_3CN/H_2O/CHCl_3$ produces the morpholine derivative (IX). Hydrolysis of the methyl ester (IX) with LiOH in THF yields the corresponding free acid (Xa), which is finally [or alternatively its potassium (Xb)] condensed with the amine (III) in the presence EDC, HOBt and DIEA in (1-3). Scheme 1.

Synthesis of amine intermediate (III):

Condensation of L-phenylalaninol (XI) with dimethylsulfamoyl chloride (XII) using DIEA in CH_2Cl_2 gives the sulfamide-sulfamate (XIII). Cyclization of compound (XIII) with NaH in 2-MeTHF yields 2(*S*)-benzyl-*N*,*N*-dimethylaziridine-1-sulfonamide (XIV), which can also

Scheme 1. Synthesis of Cobicistat



be obtained by condensation of 2(*S*)-benzylaziridine (XV) with dimethylsulfamoyl chloride (XII) in the presence of DIEA in CH_2Cl_2. Then, dimerization of the sulfamoyl aziridine (XIV) by means of LiTMP in THF/heptanes provides the hexene-bis(sulfamide) derivative (XVI). Deprotection of compound (XVI) by heating in 1,3-diaminopropane at 110 °C leads to 1,6-diphenyl-3-hexene-2(*S*),5(*S*)-diamine (XVII), which is then hydrogenated over Pd/C in MeOH, producing the saturated alkanediamine (XVIII). Finally, amine (XVIII) is condensed with 4-nitrophenyl 5-thiazolylmethyl carbonate (XIX) [prepared by treatment of bis(4-nitrophenyl) carbonate (XX) with 5-thiazolylmethanol (XXI) and Et_3N in CH_2Cl_2 (1, 2)] by means of Et_3N in CH_2Cl_2 (3). Scheme 2.

Synthesis of alkanediamine intermediate (XVIII):

Deprotonation of *N*-Boc-aminosulfone (XXII) with BuLi in THF at –78 °C, followed by condensation of the resulting dianion with *N*-protected-phenylalaninal (XXIII) in the presence of DIBAL-OMe (generated in situ from DIBAL-H and MeOH) in THF at –78 °C, yields the hydroxy sulfone (XXIV) as a diastereomeric mixture. After acetylation of hydroxy sulfone (XXIV) with Ac_2O and pyridine in CH_2Cl_2, reductive elimination by means of Na(Hg) and NaH_2PO_4 in MeOH provides alkene (XXV). *N*-Debenzylation of compound (XXV) using Na in liquid NH_3/THF produces alkene (XXVI), which by double bond hydrogenation by means of Pd/C in MeOH, followed by Boc group cleavage with TFA in CH_2Cl_2, yields 1,6-diphenylhexane-2(*R*),5(*R*)-diamine (XVIII) (1, 2). Scheme 3.

In an alternative way, alkenediamine (XVIII) is prepared by ring closure of diol (XXVII) with CSDI in THF at 65 °C to produce the 2-thioxo-1,3-dioxolane derivative (XXVIII), which by reductive elimination in $P(OEt)_3$ at 160 °C provides the protected diaminoalkene (XXIX). Finally, alkene (XXIX) is submitted to double bond saturation and simultaneous *N*-deprotection with H_2 in the presence of Pd/C in *i*-PrOH/EtOAc (1, 2). Scheme 3.

Synthesis of intermediate (Xa):

Hydrolysis of 2(*S*)-ureido lactone (XXX) with NaOH in EtOH results in the hydroxy acid (XXXI). Subsequent esterification of acid (XXXI) with benzyl bromide in DMF provides the benzyl ester (XXXII), which by Swern oxidation of its alcohol group by means of DMSO and $Pyr{\cdot}SO_3$ in the presence of Et_3N gives the aldehyde (XXXIII). Reductive amination of aldehyde (XXXIII) with morpholine (XXXIV) using $NaBH(OAc)_3$ in AcOH/CH_3CN provides 4-(4-morpholinyl)butyrate derivative (XXXV), which is finally saponified with NaOH in EtOH (1, 2). Scheme 4.

Alternatively, ring opening of lactone (XXX) with TMSI and EtOH in CH_2Cl_2 produces the 4-iodobutyrate derivative (XXXVI), which, without isolation, is condensed with morpholine (XXXIV), and then treated with oxalic acid in acetone to yield the *N*-substituted morpholine derivative (XXXVII). After liberation of the free base of (XXXVII) with $KHCO_3$ in H_2O/CH_2Cl_2, hydrolysis of the ethyl ester group with KOH in H_2O yields the corresponding potassium carboxylate (Xb) (3). Scheme 4.

Synthesis of intermediate (I):

Condensation of (2-isopropyl-4-thiazolyl)methylamine dihydrochloride (XXXVIII) with CDI by means of Et_3N in THF gives *N*-(2-isopropyl-4-thiazolylmethyl)imidazole-1-carboxamide (XXXIX), which, without isolation, is alkylated with MeI and *t*-BuOK in THF to yield the *N*-methylcarboxamide (XL) (3). Alternatively, reaction of *N*-(2-isopropyl-4-thiazolylmethyl)-*N*-methylamine (XLI) with CDI in the presence of DIEA in CH_2Cl_2 produces imidazolide (XL). Finally, compound (XL) is condensed with the N^6-Boc-2(*S*),4-diaminobutyric acid methyl ester (XLII) in CH_2Cl_2 (1, 2). Scheme 5.

Synthesis of intermediate (XXX):

Quaternization of acyl imidazolide (XL) with MeI provides the 3-methylimidazolium derivative (XLIII), which, without isolation, is condensed with L-homoserine lactone (XLIV) in the presence of DIEA in THF (3). Scheme 5.

Alternative route to (XXX):

In an alternative way, cyclization of L-methionine (XLV) by means of $BrCH_2CO_2H$ in refluxing H_2O/*i*-PrOH/AcOH, and subsequent treatment with HCl in dioxane at 60 °C leads to (*S*)-α-aminobutyrolactone hydrobromide (XLVI), which is finally condensed with CDI by means of DIEA in dioxane at 60 °C, followed by reaction with *N*-(2-isopropyl-4-thiazolylmethyl)-*N*-methylamine (XLI) in CH_2Cl_2 (3). Scheme 5.

BACKGROUND

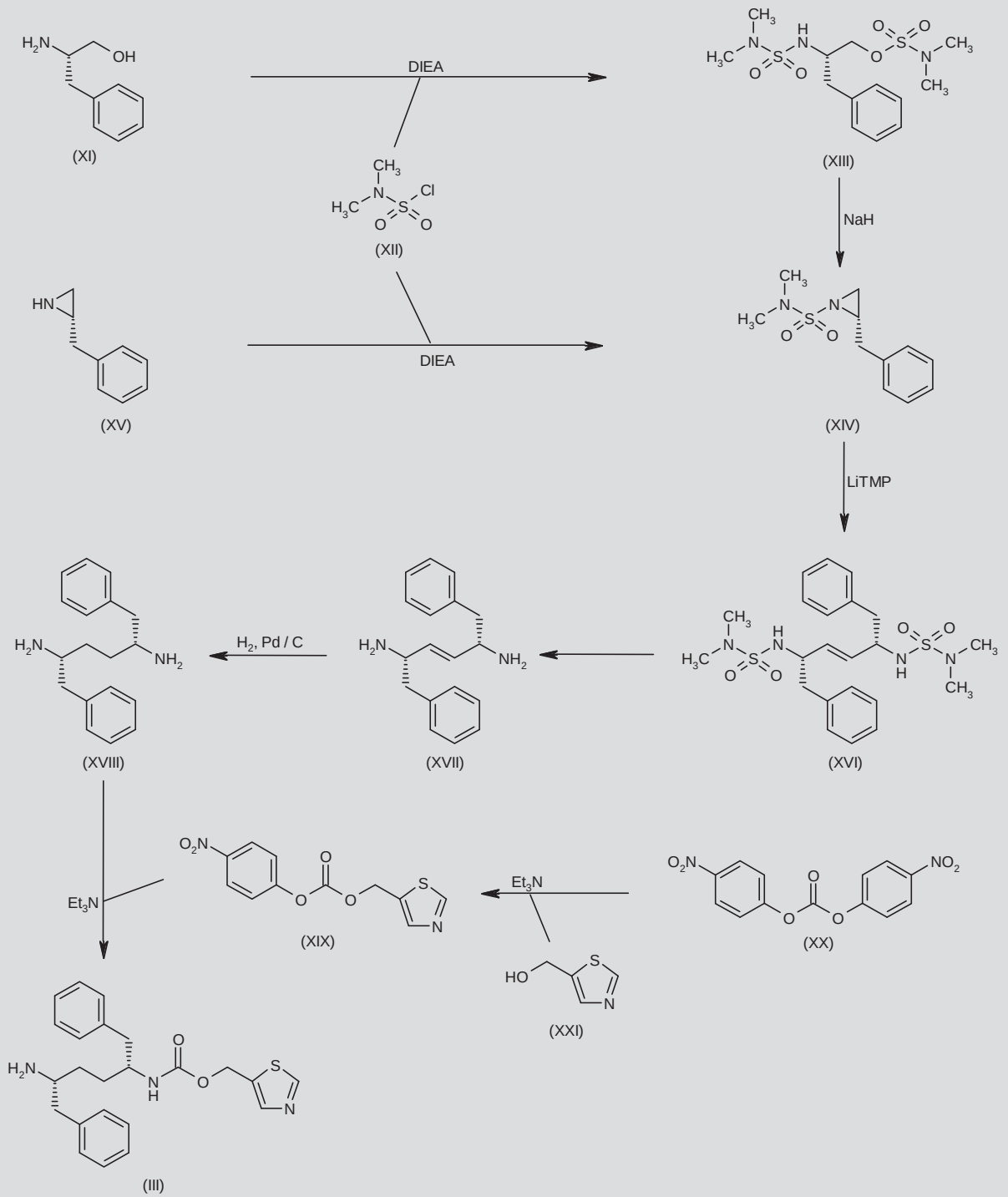
HIV-AIDS has been defined as one of history's worst pandemics (4). The facts are gruesome enough: it has resulted in 60 million infections, 25 million deaths and more than 33 million persons are currently living with HIV infection or AIDS (5). In the early years of the HIV-AIDS epidemic, the median survival after AIDS diagnosis was measured in weeks to months (6). Nowadays, however, antiretroviral therapy can warrant a life expectancy close to normal; hence, HIV-AIDS has acquired the characteristics of a chronic rather than a lethal disease (7). Furthermore, antiretroviral therapy decreases the replication of HIV-1, and according to some ecological studies, it reduces the incidence of new cases of HIV-1 infection (8).

However, antiretroviral therapy requires adherence, because poor compliance increases the risk of incomplete viral suppression and the emergence of drug resistance. Adherence can be improved by low pill burden, convenient dosing schedule and a good safety profile (9).

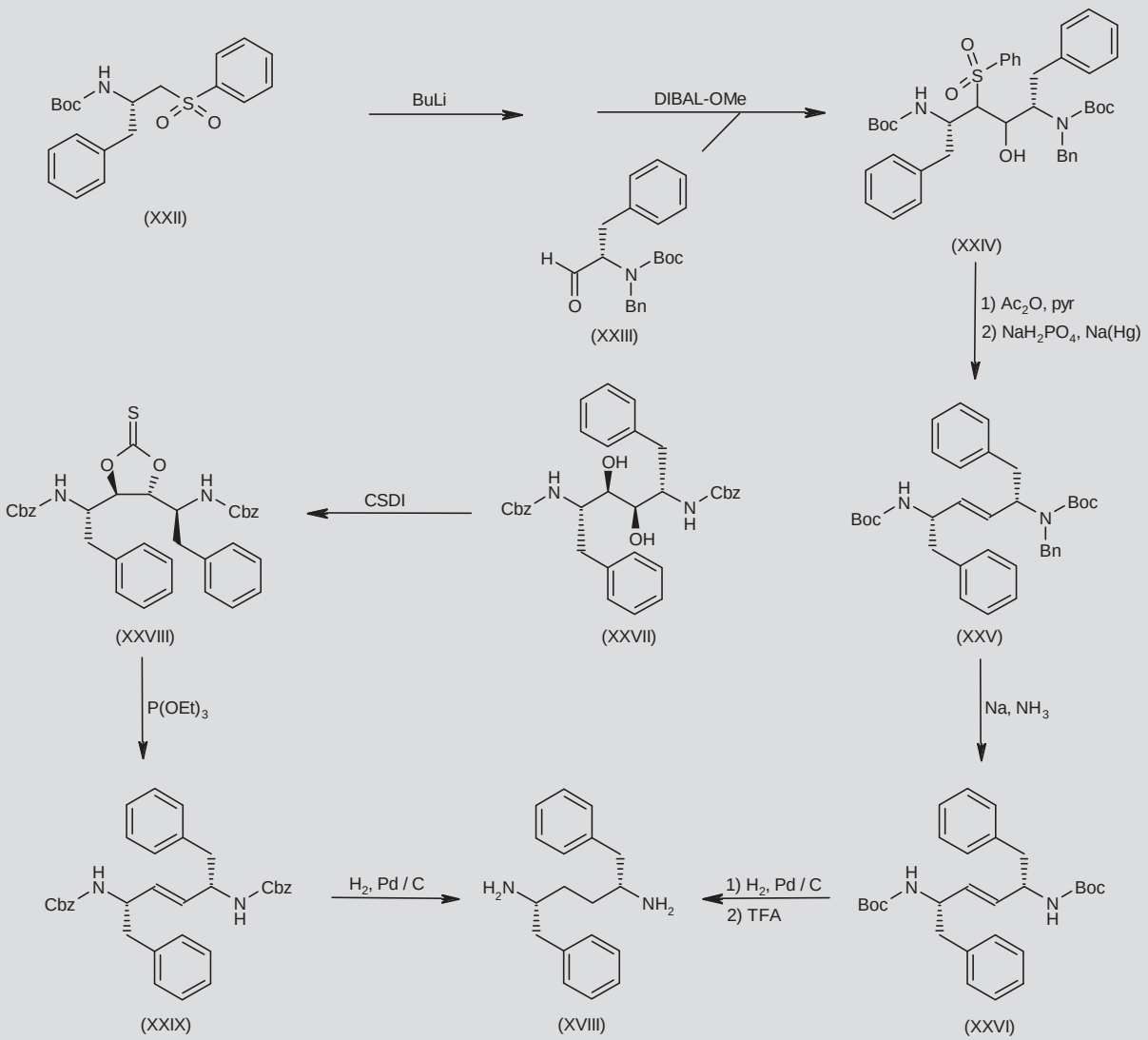
Highly active antiretroviral therapy (HAART) is the combination of drugs that inhibit different stages of the HIV life cycle, generally including a backbone of two nucleoside or nucleotide analogue reverse transcriptase inhibitors and a potent third agent from one of the following classes: non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase strand transfer inhibitors or chemokine CCR5 receptor antagonists (10).

Protease inhibitors have a low systemic exposure and short half-life after oral administration due to their rapid metabolism by cytochrome P450 3A (CYP3A) enzymes in the intestine and liver (11). In the early use of protease inhibitors, the mechanism-based inhibition of CYP3A enzymes by subtherapeutic doses of ritonavir was discovered by serendipity (12, 13). In fact, the concomitant administration of ritonavir enhances plasma levels of other protease inhibitors that are metabolized by CYP3A enzymes, allowing reduced pill burden and dosing frequency (14). Apart from protease inhibitors, other important antiviral drugs that are CYP3A substrates can be com-

Scheme 2. Synthesis of Amine Intermediate (III)



Scheme 3. Synthesis of Intermediate (XVIII)



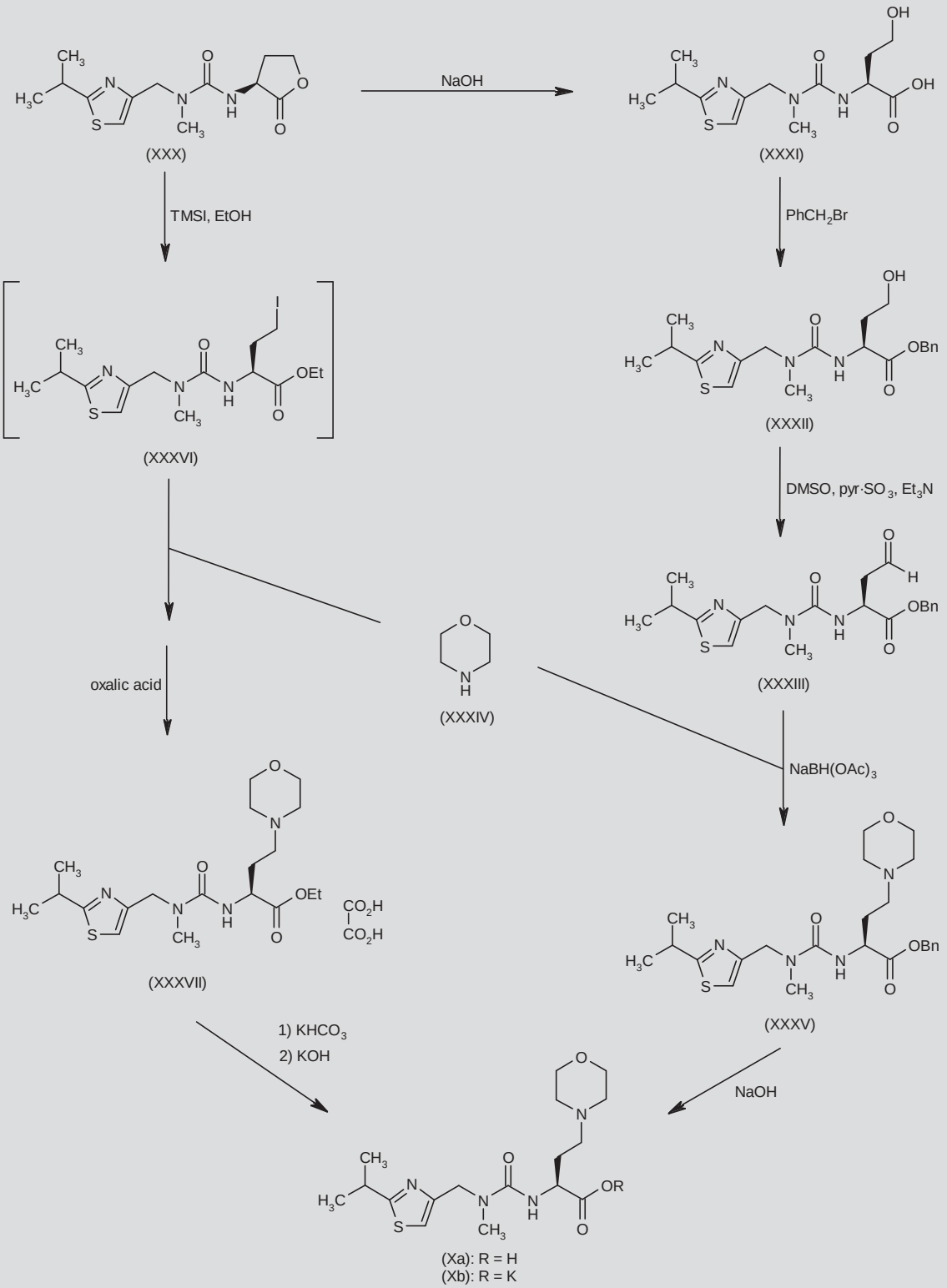
bined with ritonavir, such as the integrase inhibitor elvitegravir (15), the chemokine CCR5 receptor antagonist maraviroc (16) and the hepatitis C virus protease inhibitor narlaprevir (17).

Scientists at Gilead Sciences succeeded in improving ritonavir and discovered cobicistat (GS-9350), a pharmacoenhancer with no anti-HIV activity, which produces mechanism-based CYP3A inhibition similar to that of ritonavir, with better physicochemical properties that allow coformulation with antiretrovirals, reduced off-target drug interactions and improved tolerability (18-20).

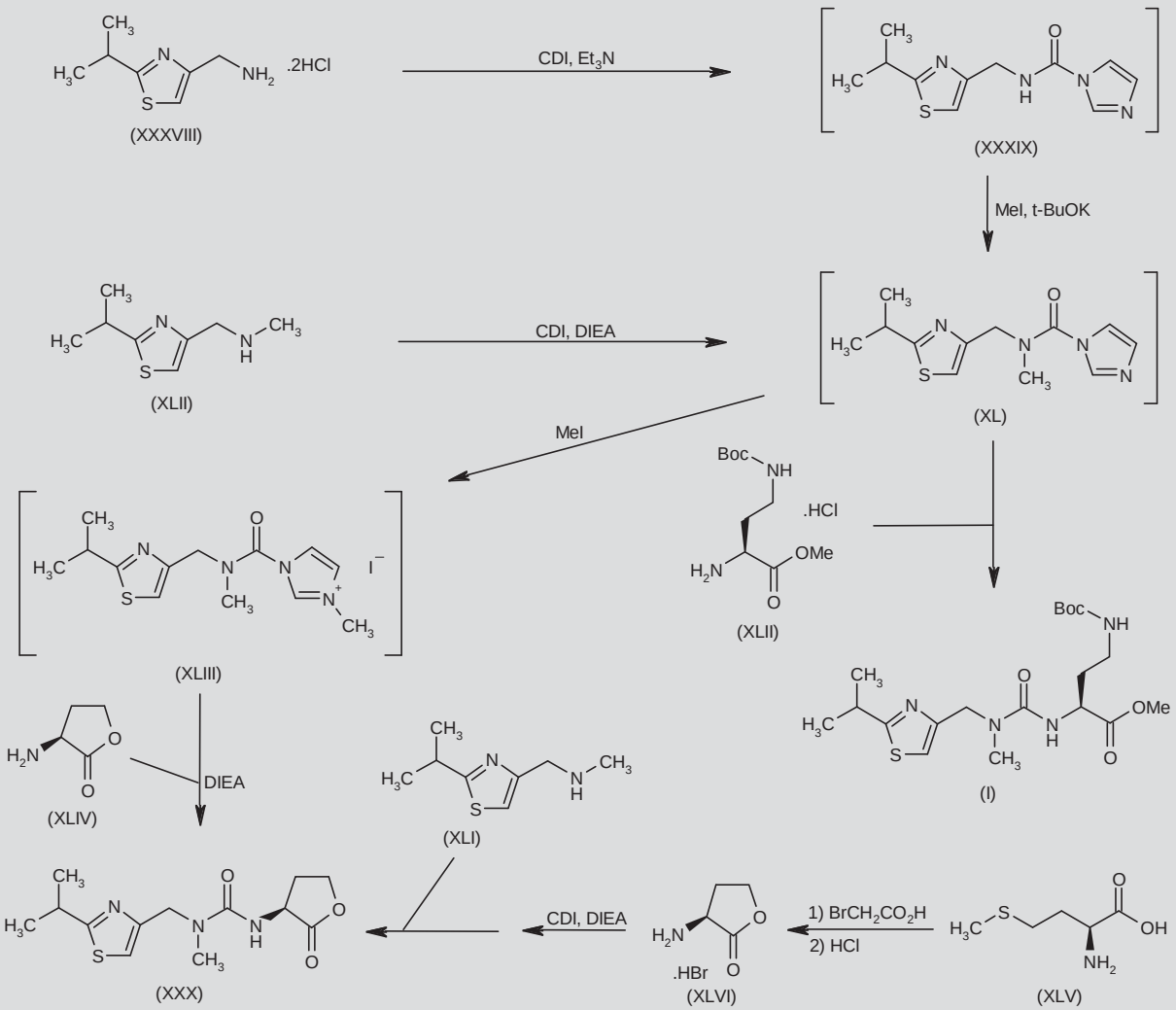
PRECLINICAL PHARMACOLOGY

In enzymatic studies, cobicistat inactivated human hepatic microsomal CYP3A activity by mechanism-based inhibition with kinetic parameters comparable to those of ritonavir, suggesting that it inhibits CYP3A via the same mechanism of action as ritonavir (18, 20, 21). However, in contrast to ritonavir, cobicistat is a specific CYP3A inhibitor. Indeed, it does not inhibit CYP1A2, CYP2C8, CYP2C9 or CYP2C19 (IC_{50} > 25 μM) and only weakly inhibits CYP2B6 (IC_{50} = 2.8 μM) and CYP2D6 (IC_{50} = 9.2 μM) (20, 22).

Scheme 4. Synthesis of Intermediate (Xa)



Scheme 5. Synthesis of Intermediate (I) and (XXX)



Cobicistat was inactive against HIV-1 protease when tested in an enzymatic assay (IC_{50} > 30 μM) and did not inhibit HIV replication (IC_{50} > 30 μM), thereby avoiding the potential risk of viral resistance (18-22).

PHARMACOKINETICS AND METABOLISM

Cobicistat is soluble in water (6.5 mg/mL at pH 2.2) and can be formulated as a single-agent tablet or coformulated with antiretroviral agents (18-21).

In preclinical in vitro studies, cobicistat showed poor concentration-dependent metabolic stability. At high concentrations, it can inhibit its own metabolism. Therefore, in preclinical pharmacokinetic studies, cobicistat showed a high clearance at low doses. In dogs, the oral absorption of cobicistat is above 50% (20).

The pharmacokinetics of cobicistat were studied in healthy volunteers (aged 18-45 years) who received single oral doses of 50, 100, 200, 300 or 400 mg, and daily repeated doses of 50, 100, 200 and 300 mg for up to 14 days. Cobicistat showed a plasma half-life of 1.4-

5.2 hours with single doses and 2.2-8.1 hours with repeated doses. Its rapid elimination reduces the potential for drug accumulation and for unwanted side effects. Plasma concentration–time profiles showed substantial increases in exposure after single-dose escalation (164-fold increase in AUC_{inf} with 50-400 mg cobicistat) and multiple-dose escalation (47-fold increase in AUC with 50-300 mg), as is expected for an inhibitor that inhibits its own clearance. Of note, cobicistat is potent enough to inhibit CYP3A after a single dose, based on a dose-apparent clearance curve (22).

The relative bioavailability and pharmacokinetics of a fixed-dose combination tablet containing cobicistat, the integrase inhibitor elvitegravir and the reverse transcriptase inhibitors emtricitabine and tenofovir disoproxil fumarate were assessed in 44 healthy subjects. They received fixed-dose combination tablets containing elvitegravir 150 mg, emtricitabine 200 mg, tenofovir 300 mg and cobicistat 150 mg; elvitegravir 150 mg boosted with ritonavir 100 mg; or capsules of emtricitabine 200 mg plus tablets of tenofovir disoproxil fumarate 300 mg. The main pharmacokinetic parameters obtained were AUC_{tau}, C_{max} and C_{tau}. Cobicistat 150 mg improved elvitegravir systemic exposure in a similar way as ritonavir 100 mg. Indeed, elvitegravir showed AUC_{tau} values of 27 and 22.5 µg·h/mL, respectively, C_{max} values of 2.66 and 2.50 µg/mL, respectively, and C_{tau} values of 490 and 410 ng/mL, respectively, when boosted with cobicistat or ritonavir. It deserves to be mentioned that the efficacy of elvitegravir is related to its high C_{tau}. In addition, the concomitant administration of cobicistat 150 mg slightly improved emtricitabine and tenofovir disoproxil fumarate exposures. For tenofovir, that can be explained by potential P-glycoprotein transporter inhibition by cobicistat in the intestine during absorption. In summary, the study demonstrated the ability of cobicistat to boost elvitegravir exposures to levels similar to those achieved by ritonavir (23).

SAFETY

Cobicistat showed low liability for enzymatic induction through the activation of the xenobiotic receptors, including the aryl hydrocarbon receptor, the pregnane X receptor and the constitutive androstane receptor (18-22). On the contrary, ritonavir, a potent pregnane X receptor agonist (EC_{50} = 1.9 µM) (19-22), induces the expression of CYP3A4, CYP2B6, CYP2C9, CYP2C19, UDP-glucuronosyltransferase 1-4 and P-glycoprotein, leading to clinically significant drug–drug interactions (24-27).

In vitro, cobicistat had minimal effects on lipid accumulation and insulin-stimulated glucose uptake in human and mouse adipocytes, respectively, whereas ritonavir inhibited lipid accumulation and glucose uptake (18-22), an effect consistent with the induction of metabolic syndrome caused by chronic treatment of HIV-infected patients (27). In addition, cobicistat showed minimal cytotoxicity (20).

The safety of cobicistat was assessed in 84 healthy subjects (aged 18-45 years) who received single oral doses of 50, 100, 200, 300 or 400 mg, and daily repeated doses of 50, 100, 200 or 300 mg for up to 14 days. The assessment of adverse events continued during dosing, with a follow-up visit 14 days after the last administration of the multiple-dosing period. Cobicistat was generally well tolerated, with mild-grade headache, somnolence and abnormal dreams the most frequently reported drug-related adverse events. No treatment-related laboratory abnormalities or corrected QT interval (QTcF) alterations were detected (22).

The safety of a tablet containing cobicistat at 100 or 150 mg coformulated with elvitegravir 150 mg, emtricitabine 200 mg and tenofovir 300 mg was studied in 44 healthy subjects who received the treatment for 10 days. Safety assessments were performed at different times during the study, and up to 14 days after the last administration. The treatments were well tolerated. All treatment-related adverse events were mild, except for two cases of asymptomatic acute hepatitis defined by alanine aminotransferase (ALT) elevations that occurred when receiving the tablet containing cobicistat 100 mg. Total bilirubin values remained unaffected, and the events resolved 14 and 22 days later. No subjects experienced moderate or severe elevations of liver function upon administration of the tablets containing cobicistat 150 mg (23).

A 48-week phase II trial compared the safety of a single Quad tablet (efavirenz/cobicistat/emtricitabine/tenofovir disoproxil fumarate) with that of Atripla® (single tablet containing efavirenz/emtricitabine/tenofovir disoproxil fumarate) in antiretroviral-naive HIV-1-infected adults. Quad tablets contain elvitegravir 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg/cobicistat 150 mg, and Atripla® tablets contain efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg. At weeks 24 and 48, Quad was associated with lower rates of study drug-related adverse events (35% and 46%, respectively) than Atripla® (57% in both time periods). At week 48, Quad led to a decrease in the estimated glomerular filtration rate (eGFR) of 20 mL/min, on the order of what was observed at week 24 (28, 29).

The safety of cobicistat versus ritonavir as a pharmacoenhancer for atazanavir coadministered with fixed-dose emtricitabine/tenofovir disoproxil fumarate was studied in a 48-week phase II trial in antiretroviral-naive HIV-1-infected adults. Adverse events and laboratory abnormalities were graded for severity, and were assessed throughout the study. A total of 50 patients received the treatment containing cobicistat 150 mg, atazanavir 300 mg and emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, whereas 29 patients received ritonavir 100 mg as a pharmacoenhancer. Adverse events caused the discontinuation of 4% and 3% of cobicistat- and ritonavir-treated patients, respectively. Through 48 weeks, 36% of cobicistat- and 48% of ritonavir-treated patients showed treatment-related adverse events, mostly assessed as mild or moderate in severity. Hyperbilirubinemia (at least grade 3) was observed in 63% and 45%, respectively, of the patients in the cobicistat and ritonavir groups. Hyperbilirubinemia is a side effect of atazanavir due to its inhibition of UDP-glucuronosyltransferase 1-1. Although cobicistat-treated participants showed slightly higher bilirubin levels than those receiving ritonavir, clinical sequelae in the two groups were similar. Indeed, ocular icterus was detected in 12% and 14%, respectively, of the patients receiving cobicistat and ritonavir. Estimated glomerular filtration ratio decreased at week 2 (108 mL/min with cobicistat vs. 117 mL/min with ritonavir; P = 0.02), reaching a nadir by week 24, and not progressing further through week 48, in both groups. In summary, the combination of cobicistat as a pharmacoenhancer for atazanavir with emtricitabine/tenofovir disoproxil fumarate showed a satisfactory safety profile in HIV-1-infected adults (12, 28, 29).

In phase I and II studies, cobicistat has decreased the eGFR, based on serum creatinine (12, 29). Therefore, its effects on renal function were studied in non-HIV-infected subjects by comparing the eGFR to

the actual glomerular filtration rate using iohexol, a probe almost exclusively excreted by glomerular filtration. Two cohorts, one with normal renal function (eGFR > 80 mL/min) and another with mild to moderate renal impairment (eGFR = 50-79 mL/min), were treated with cobicistat (150 mg/day for 7 days). Cobicistat did not modify the actual GFR in either cohort. However, when the eGFR was measured after 7 days of treatment, statistically significant decreases were observed in both experimental groups, which disappeared 7 days later. These effects on the eGFR are consistent with altered proximal tubular secretion of creatinine by a putative inhibition of transporters in the kidney tubules (30). In fact, an in vitro study has demonstrated that cobicistat inhibited some proximal renal tubular cell transporters, namely the organic cation 2 transporter (OCT2; IC_{50} = 14 μM) and the multidrug and toxin extrusion protein 1 (MATE-1; IC_{50} = 1.87 μM), which may explain the effects of cobicistat on the eGFR measured by the excretion of creatinine (31).

CLINICAL STUDIES

The anti-CYP3A activities of cobicistat and ritonavir were compared in a randomized, double-blind, double-dummy phase I study in 84 healthy subjects (aged 18-45 years). Midazolam maleate, which was used to assess the extent of CYP3A inhibition elicited by cobicistat and ritonavir, was administered at steady state of each inhibitor, i.e., after daily administration for 14 days. The doses of cobicistat tested were 50, 100 and 200 mg, while ritonavir was administered at 100 mg. The pharmacokinetic parameters of midazolam were assessed at baseline and when administered concomitantly with cobicistat or ritonavir. The midazolam C_{max}, C_{last}, AUC_{inf} and half-life dose-dependently increased extensively from baseline with cobicistat or when administered with ritonavir. Conversely, apparent clearance (CL/F) decreased, reaching a 95% reduction with both compounds. This is consistent with the agents' pharmacoenhancer role via CYP3A inhibition (22).

In a phase I pharmacokinetic study in healthy subjects, atazanavir was bioequivalent when administered concomitantly with cobicistat 150 mg or ritonavir 100 mg, demonstrating the pharmacoenhancing effects of cobicistat (32).

A prospective, double-blind, double-dummy, active-controlled, 48-week phase II study compared the Quad regimen to Atripla® in treatment-naive HIV-1-infected individuals. The viral suppression (expressed as the percentage of patients with HIV RNA levels below 50 copies/mL) was the same at 24 and 48 weeks: 90% with Quad and 83% with Atripla®. $CD4^+$ cell counts increased by 161 and 113 mean cells/mm^3, respectively, at week 24, and by 240 and 162 mean cells/mm^3, respectively, at week 48 with Quad and Atripla®. In conclusion, Quad showed a sustained high rate of virological suppression (90%), statistically noninferior to that of Atripla® (83%) (28, 29).

The efficacy of cobicistat versus ritonavir as a pharmacoenhancer for atazanavir, coadministered with fixed-dose emtricitabine/tenofovir disoproxil fumarate, was studied in a randomized, partially placebo-controlled, double-blind, multicenter, 48-week phase II trial in antiretroviral-naive HIV-1-infected adults. In the atazanavir/cobicistat arm, 50 patients received atazanavir 300 mg, cobicistat 150 mg and emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg. In the atazanavir/ritonavir arm, 29 patients received atazanavir 300 mg, ritonavir 100 mg and emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg. At week 24, viral suppression was 84% and 86%, respectively, for the cobicistat- and ritonavir-boosted arms. At week 48, these respective values were 82% and 86%. The increases in $CD4^+$ cell count were 203 and 199 mean cells/mm^3, respectively, at week 24, and 230 and 206 mean cells/mm^3, respectively, at week 48, for the cobicistat- and ritonavir-boosted arms. No virological failure was observed (12, 28, 29). Other protease inhibitors boosted with ritonavir and coadministered with emtricitabine/tenofovir disoproxil fumarate gave similar rates of virological suppression (83% with fosamprenavir once daily [33] and 78% with lopinavir twice daily [34]).

Several cobicistat clinical trials are ongoing. These phase II or III trials are assessing the safety and efficacy of regimens containing a cobicistat-boosted protease inhibitor or a cobicistat-boosted integrase inhibitor as fixed-dose combinations in single-tablet regimens (35).

CONCLUSIONS

Current antiretroviral therapy has converted HIV-AIDS into a chronic disease. HAART is the combination of various families of drugs that inhibit different stages of the HIV life cycle. Among these families, the protease inhibitors have a low systemic exposure and short half-life after oral administration due to their rapid metabolism by CYP3A enzymes. This can be circumvented by concomitant administration of ritonavir, a mechanism-based inhibitor of CYP3A enzymes.

Cobicistat is a novel, potent, selective, mechanism-based inhibitor of human CYP3A, which can be useful as a pharmacoenhancer administered concomitantly with protease inhibitors or other CYP3A substrates in antiretroviral regimens. Ongoing phase II and III trials are assessing the safety and efficacy of treatments containing a cobicistat-boosted protease inhibitor or integrase inhibitor as fixed-dose combinations in single tablets.

SOURCES

Gilead Sciences, Inc. (US); licensed in Japan to Japan Tobacco.

DISCLOSURES

The author states no conflicts of interest.

REFERENCES

1. Desai, M.C., Hong, A.Y., Liu, H., Xu, L., Vivian, R.W. (Gilead Sciences, Inc.). *Modulators of pharmacokinetic properties of therapeutics*. EP 2049506, JP 2009542696, US 2008108617, US 2009291952, US 7939553, WO 2008010921.
2. Desai, M.C., Hong, A.Y., Hui, H.C., Liu, H., Vivian, R.W., Xu, L. (Gilead Sciences, Inc.). *Modulators of pharmacokinetic properties of therapeutics*. EP 2118082, JP 2010519314, JP 2011231132, US 2008207620, US 2010189687, US 8148374, WO 2008103949.
3. Polniaszek, R., Pfeiffer, S., Yu, R. et al. (Gilead Sciences, Inc.). *Methods and intermediates for preparing pharmaceutical agents*. EP 2414325, KR 2012006035, US 2010256366, WO 2010115000.
4. De Cock, K.M., Jaffe, H.W., Curran, J.W. *Reflections on 30 years of AIDS*. Emerg Infect Dis 2011, 17(6): 1044-8.
5. Dieffenbach, C.W., Fauci, A.S. *Thirty years of HIV and AIDS: Future challenges and opportunities.* Ann Intern Med 2011, 154(11): 766-71.
6. Rothenberg, R., Woelfel, M., Stoneburner, R., Milberg, J., Parker, R., Truman, B. *Survival with the acquired immunodeficiency syndrome. Experi-*

ence with 5833 cases in New York City. N Engl J Med 1987, 317(21): 1297-302.

7. van Sighem, A.I., Gras, L.A., Reiss, P., Brinkman, K., de Wolf, F. *Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals.* AIDS 2010, 24(10): 1527-35.
8. Montaner, J.S., Lima, V.D., Barrios, R. et al. *Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: A population-based study.* Lancet 2010, 376(9740): 532-9.
9. Parienti, J.-J., Bangsberg, D.R., Verdon, R., Gardner, E.M. *Better adherence with once-daily antiretroviral regimens: A meta-analysis.* Clin Infect Dis 2009, 48(4): 484-8.
10. Thompson, M., Aberg, J.A., Cahn, P. et al. *Antiretroviral treatment of adult HIV infection. 2010 Recommendations of the International AIDS Society–USA Panel.* J Am Med Assoc 2010, 304(3): 321-33.
11. Gerber, J.G. *Using pharmacokinetics to optimize antiretroviral drug-drug interactions in the treatment of human immunodeficiency virus infection.* Clin Infect Dis 2000, 30(Suppl. 2): S123-9.
12. Elion, R., Cohen, C., Gathe, J. et al. *Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine/tenofovir df in the initial treatment of HIV infection.* AIDS 2011, 25(15): 1881-6.
13. Kempf, D.J., Marsh, K.C., Kumar, G. et al. *Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir.* Antimicrob Agents Chemother 1997, 41(3): 654-60.
14. Youle, M. *Overview of boosted protease inhibitors in treatment experienced HIV-infected patients.* J Antimicrob Chemother 2007, 60(6): 1195-205.
15. DeJesus, E., Berger, D., Markowitx, M. et al. *Antiviral activity, pharmacokinetics, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment-naïve and treatment-experienced patients.* J Acquir Immune Defic Syndr 2006, 43(1): 1-5.
16. Ramanathan, S., Abel, S., Tweedy, S., West, S., Hui, J., Kearney, B.P. *Pharmacokinetic interaction of ritonavir-boosted elvitegravir and maraviroc.* J Acquir Immune Defic Syndr 2010, 53(2): 209-14.
17. Vierling, J., Poordad, F., Lawitz, E. et al. *Once daily narlaprevir (SCH 900518) in combination with PEGINTRON™ (peginterferon alfa-2b)/ribavirin for treatment-naïve subjects with genotype-1 CHC: Interim results from NEXT-1, a phase 2a study.* 60th Annu Meet Am Assoc Study Liver Dis (AASLD) (Oct 30-Nov 3, Boston) 2009, Abst LB4.
18. Xu, L., Liu, H., Murray, B.P. et al. *Discovery of GS-9350: A novel pharmacoenhancer without anti-HIV activity.* 49th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, San Francisco) 2009, Abst H-934.
19. Xu, L. *GS-9350: A novel and selective pharmacoenhancer without anti-HIV activity.* 239th ACS Natl Meet (March 21-25, San Francisco) 2010, Abst MEDI 318.
20. Xu, L., Liu, H., Murray, B.P. et al. *Cobicistat (GS-9350): A potent and selective inhibitor of human CYP3A as a novel pharmacoenhancer.* ACS Med Chem Lett 2010, 1(5): 209-13.
21. Mathias, A., Lee, M., Callebaut, C., Xu, L. et al. *GS-9350: A pharmacoenhancer without anti-HIV activity.* 16th Conf Retroviruses Opportunistic Infect (CROI) (Feb 8-11, Montreal) 2009, Abst 40.
22. Mathias, A.A., German, P., Murray, B.P. et al. *Pharmacokinetics and pharmacodynamics of GS-9350: A novel pharmacokinetic enhancer without anti-HIV activity.* Clin Pharmacol Ther 2010, 87(3): 322-9.
23. German, P., Warren, D., West, S., Hui, J., Kearney, B.P. *Pharmacokinetics and bioavailability of an integrase and novel pharmacoenhancer-containing single-tablet fixed-dose combination regimen for the treatment of HIV.* J Acquir Immune Defic Syndr 2010, 55(3): 323-9.
24. Foisy, M.M., Yakiwchuk, E.M., Hughes, C.A. *Induction effects of ritonavir: Implications for drug interactions.* Ann Pharmacother 2008, 42(7): 1048-59.
25. Zastre, J.A, Chan, G.N.Y., Ronaldson, P.T. et al. *Up-regulation of P-glycoprotein by HIV protease inhibitors in a human brain microvessel endothelial cell line.* J Neurosci Res 2009, 87(4): 1023-36.
26. Kharasch, E.D., Mitchell, D., Coles, R., Blanco, R. *Rapid clinical induction of hepatic cytochrome P4502B6 activity by ritonavir.* Antimicrob Agents Chemother 2008, 52(4): 1663-9.
27. Carr, A., Samaras, K., Burton, S., Law, M., Freund, J., Chisholm, D.J., Cooper, D.A. *A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors.* AIDS 1998, 12(7): F51-8.
28. Cohen, C., Shamblaw, D., Ruane, P. et al. *The single-tablet, fixed-dose regimen of elvitegravir/GS-9350/emtricitabine/tenofovir DF (Quad) achieves a high rate of virologic suppression and GS-9350 is an effective booster.* 17th Conf Retroviruses Opportunistic Infect (CROI) (Feb 16-19, San Francisco) 2010, Abst 58LB.
29. Elion, R., Gathe, J., Rashbaum, B. et al. *The single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF; 'Quad') maintains a high rate of virologic suppression, and cobicistat (COBI) is an effective pharmacoenhancer through 48 weeks.* 50th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, Boston) 2010, Abst H-938B.
30. German, P., Liu, C., Warren, D., Hepner Harris, M., Andrews, J., Kearney, B., Mathias, A. *Effect of cobicistat on glomerular filtration rate (GFR) in subjects with normal and impaired renal function.* 51st Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 17-20, Chicago) 2011, Abst H2-804.
31. Lepist, E.I., Murray, B.P., Tong, L., Roy, A. Bannister, R., Ray, A.S. *Effect of cobicistat and ritonavir on proximal renal tubular cell uptake and efflux transporters.* 51th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 17-20, Chicago) 2011, Abst A1-1724.
32. Ramanathan, S., Warren, D., Wei, L., Kearney, B. *Pharmacokinetic boosting of atazanavir with the pharmacoenhancer GS-9350 versus ritonavir.* 49th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, San Francisco) 2009, Abst A1-1301.
33. Smith, K.Y., Weinberg, W.G., Dejesus, E. et al. *Fosamprenavir or atazanavir once daily boosted with ritonavir 100 mg, plus tenofovir/emtricitabine, for the initial treatment of HIV infection: 48-Week results of ALERT.* AIDS Res Ther 2008, 5: 5.
34. Molina, J.M., Andrade-Villanueva, J., Echevarria, J. et al. *Once daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48-Week efficacy and safety results of the CASTLE study.* Lancet 2008, 372(9639): 646-55.
35. ClinicalTrials.gov Web site, February 8, 2012.