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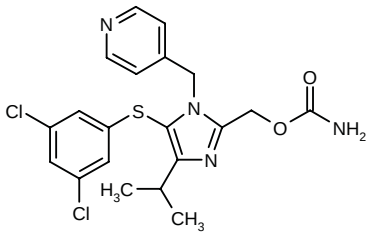
Capravirine

Prop INN

Anti-HIV Agent
Reverse Transcriptase Inhibitor

AG-1549
S-1153

Carbamic acid 5-(3,5-dichlorophenylsulfanyl)-4-isopropyl-1-(4-pyridylmethyl)imidazol-2-ylmethyl ester



$C_{20}H_{20}Cl_2N_4O_2S$

Mol wt: 451.376

CAS: 178979-85-6

EN: 256200

Abstract

Introduction of highly active antiretroviral therapy (HAART) including reverse transcriptase (RT) inhibitors has been effective in reducing HIV-1- and AIDS-related deaths. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) in particular are highly specific for RT and are not associated with nucleoside toxicity. However, first-generation NNRTIs are susceptible to the effects of single point mutations within RT conferring resistance, and significant cross-resistance of a single mutation to several NNRTIs is common. Capravirine (S-1153, AG-1549) is a second-generation NNRTI that is one of the most promising anti-HIV-1 agents to emerge. Capravirine has exhibited potent anti-HIV activity *in vitro* against both laboratory strains and clinical isolates and *in vivo* in a mouse model of HIV infection. The agent was shown to be active against many drug-resistant mutants and requires at least 2 mutations for RT to become resistant. Capravirine has an excellent safety profile and has shown efficacy in NNRTI-naïve and -experienced HIV-1-infected patients. Capravirine is undergoing phase III development as a treatment for HIV-1 infection.

Synthesis

Capravirine can be synthesized by several related ways:

1) Cyclization of 2,2-dichloroisobutyraldehyde (I) – obtained by reaction of isovaleraldehyde (II) with chlorine in DMF – with 2-benzyloxyacetaldehyde (III) – produced by reaction of 2-butene-1,4-diol (IV) with benzyl chloride by means of NaOH in water, followed by ozonolysis in MeOH and finally reduction with triphenylphosphine in ethyl acetate – and aqueous NH_4OH in methanol gives the imidazole derivative (VI), which is iodinated with I_2 and NaOH in dichloromethane to yield the 5-iodoimidazole derivative (VII). Condensation of compound (VII) with bis(3,5-dichlorophenyl)disulfide (VIII) by means of LiH in DMSO affords the dichlorophenylsulfanyl imidazole (IX), which is alkylated with 4-(chloromethyl)pyridine (X) and K_2CO_3 in DMF to provide the fully substituted imidazole (XI). Debenzylation of compound (XI) with conc. HCl in refluxing ethanol gives the carbinol (XII), which is finally treated with trichloroacetyl isocyanate and triethylamine in methanol/water (1, 2). Scheme 1.

2) The debenzylation of 2-(benzyloxymethyl)-5-(3,5-dichlorophenylsulfanyl)-4-isopropyl-1*H*-imidazole (IX) with hot aqueous HCl gives 5-(3,5-dichlorophenylsulfanyl)-4-isopropyl-1*H*-imidazole-2-methanol (XIII), which is condensed with chlorosulfonyl isocyanate in acetonitrile to yield carbamic acid 5-(3,5-dichlorophenylsulfanyl)-4-isopropyl-1*H*-imidazol-2-ylmethyl ester (XIV). Finally, this compound is alkylated with 4-(chloromethyl)pyridine (X) – obtained by reaction of 4-(hydroxymethyl)pyridine (XV) and $SOCl_2$ in acetonitrile – by means of $NaHCO_3$ in ethyl acetate/water (3). Scheme 2.

3) Alkylation of 2-(benzyloxymethyl)-4-isopropyl-1*H*-imidazole (VI) with 4-(chloromethyl)pyridine (X) by means of NaOH in toluene gives 2-(benzyloxymethyl)-4-isopropyl-1-(4-pyridylmethyl)-1*H*-imidazole (XVI), which is then condensed with 3,5-dichlorophenylsulfanyl chloride

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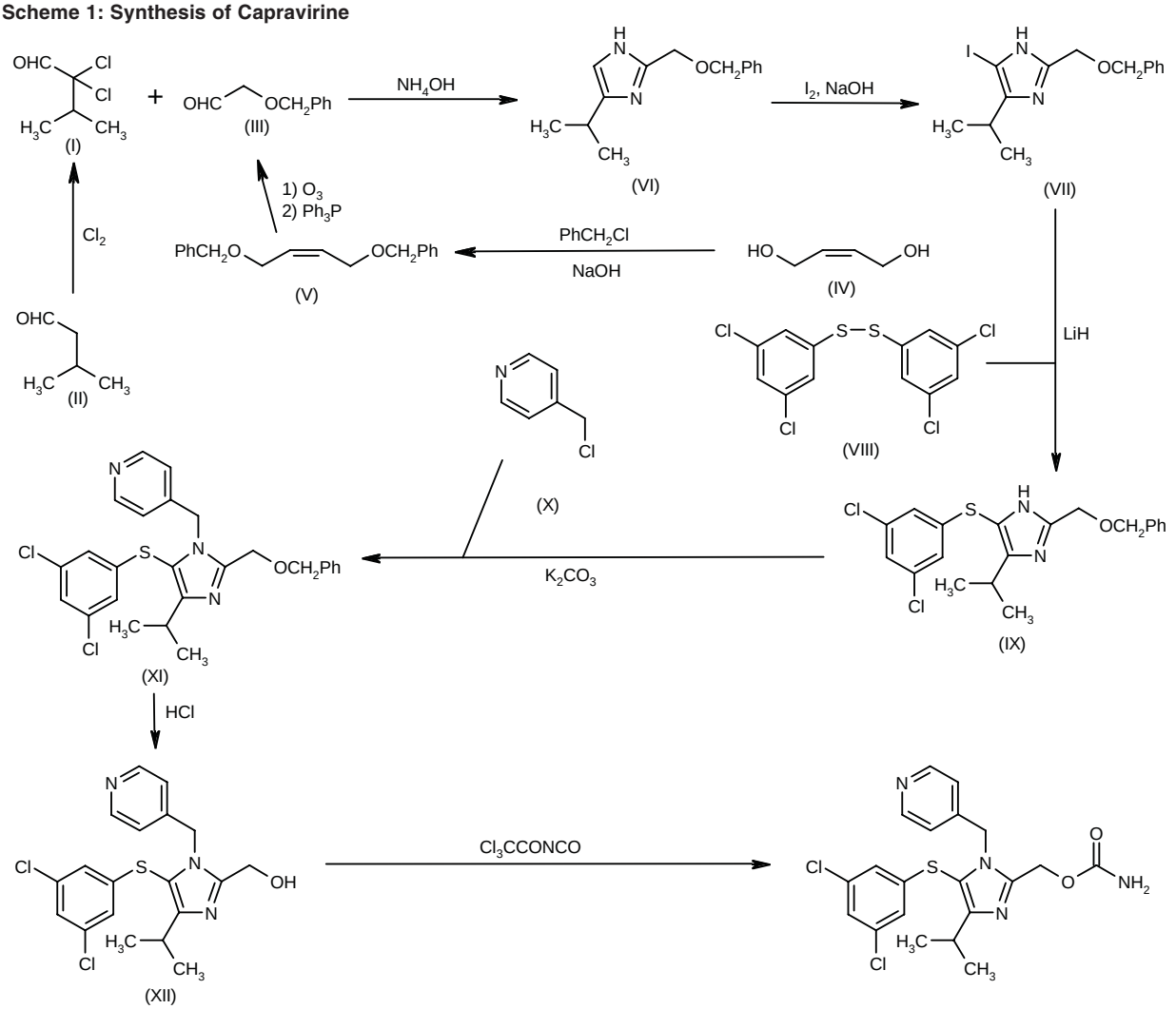
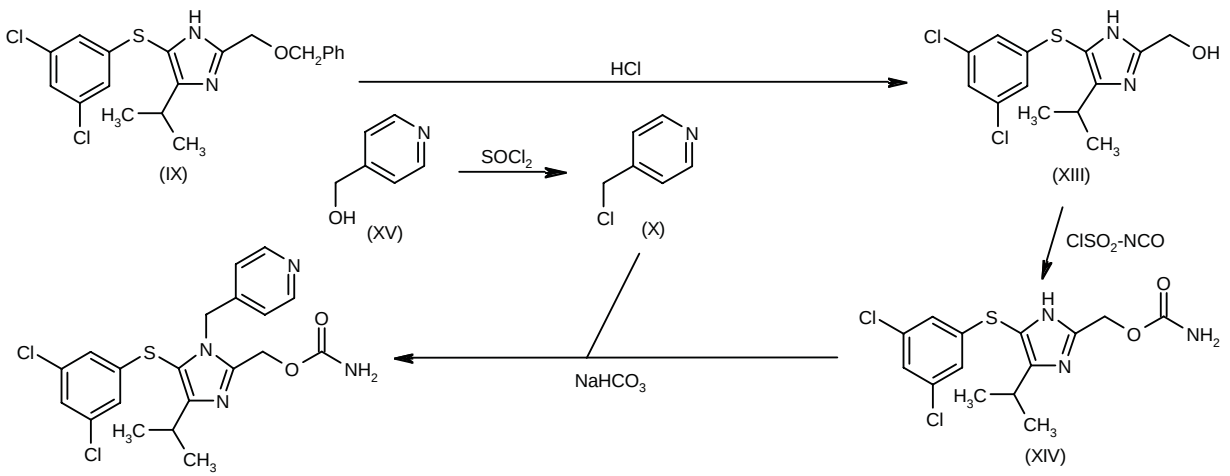
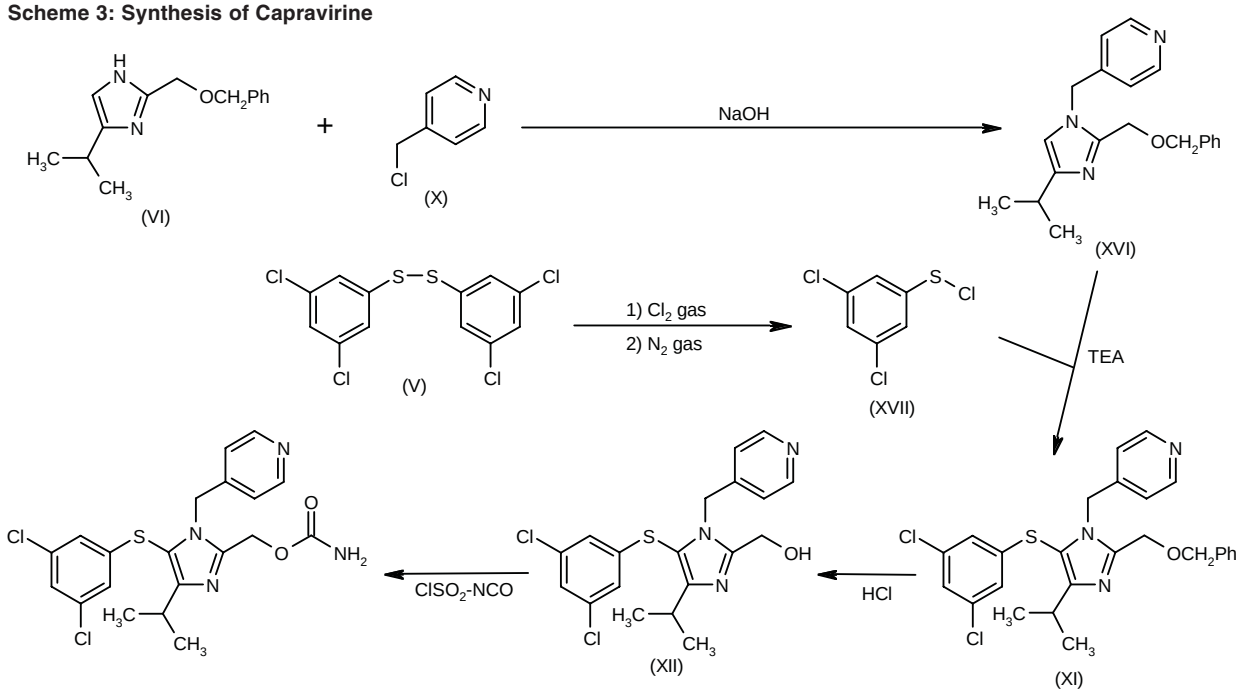
Scheme 1: Synthesis of Capravirine



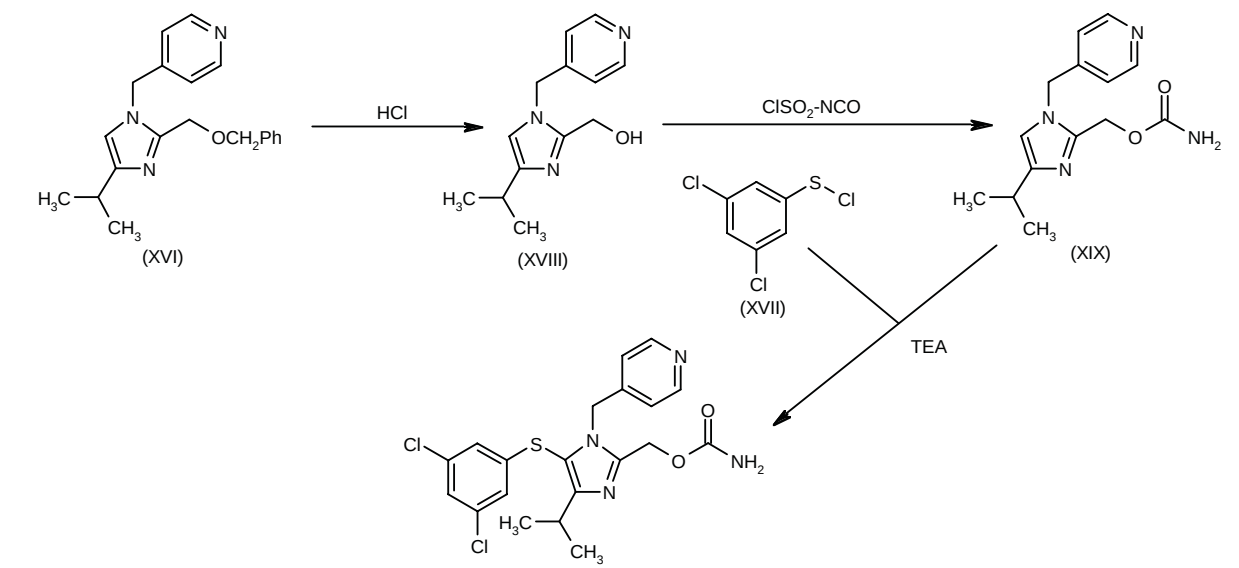
Scheme 2: Synthesis of Capravirine



Scheme 3: Synthesis of Capravirine



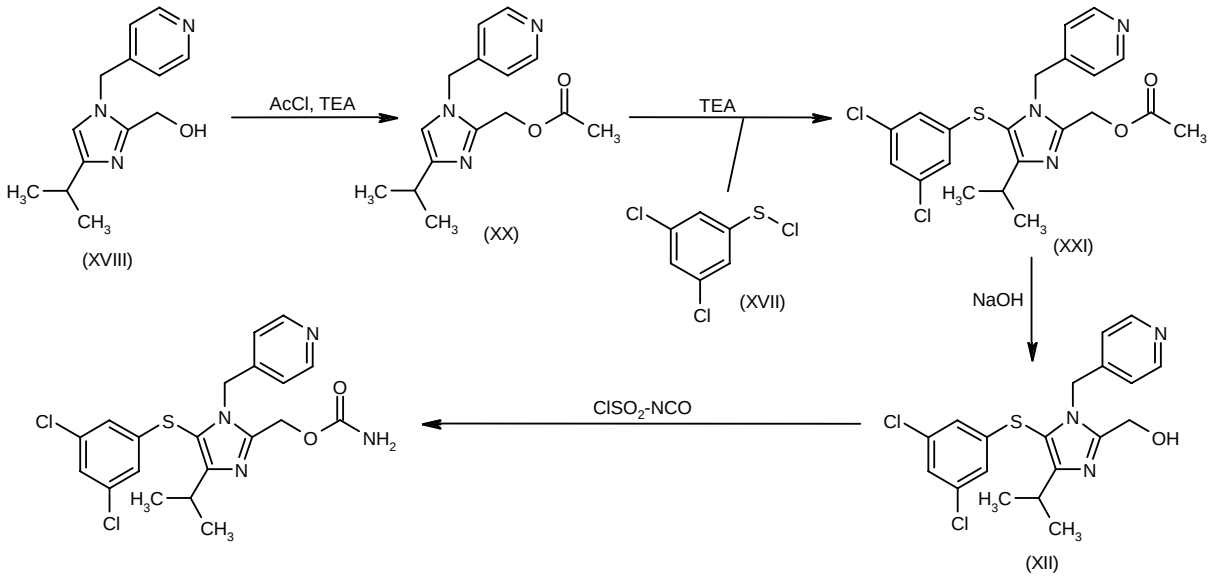
Scheme 4: Synthesis of Capravirine



(XVII) – obtained by reaction of bis(3,5-dichlorophenyl)-disulfide (VIII) first with chlorine gas in CCl_4 or toluene and then dried nitrogen gas – by means of triethylamine in toluene/water to afford 2-(benzyloxymethyl)-5-(3,5-dichlorophenylsulfanyl)-4-isopropyl-1-(4-pyridylmethyl)-1*H*-imidazole (XI). Debenzylation of compound (XI) by means of hot aqueous HCl provides the hydroxymethyl derivative (XII), which is finally esterified with chlorosulfonyl isocyanate in ethyl acetate (4). Scheme 3.

4) Debenzylation of 2-(benzyloxymethyl)-4-isopropyl-1-(4-pyridylmethyl)-1*H*-imidazole (XVI) with hot aqueous HCl gives the hydroxymethyl derivative (XVIII), which is condensed with chlorosulfonyl isocyanate in ethyl acetate to yield carbamic acid 1-(4-pyridylmethyl)-4-isopropyl-1*H*-imidazol-2-ylmethyl ester (XIX). Finally, this compound is condensed with 3,5-dichlorophenylsulfanyl chloride (XVII) by means of triethylamine in DMF/toluene (4). Scheme 4.

Scheme 5: Synthesis of Capravirine



5) Esterification of 4-isopropyl-1-(4-pyridylmethyl)-1*H*-imidazol-2-ylmethanol (XVIII) by means of acetyl chloride and triethylamine in dichloromethane gives the acetate ester (XX), which is condensed with 3,5-dichlorophenylsulfanyl chloride (XVII) by means of triethylamine in toluene/acetonitrile to yield the thioether (XXI). Hydrolysis of the acetate group of compound (XXI) by means of NaOH in ethanol affords the hydroxymethyl compound (XII), which is finally condensed with chlorosulfonyl isocyanate in acetonitrile (4). Scheme 5.

Introduction

The introduction of highly active antiretroviral therapy (HAART) using combinations of agents has resulted in considerable reductions in death rates from human immunodeficiency virus type 1 (HIV-1) and AIDS. However, HIV-1 infection remains a major global health problem, with an estimated 16,000 new cases diagnosed each day. This is due to the emergence of drug-resistant strains in the presence of suboptimal treatment regimens that do not fully inhibit virus replication. Thus, new therapeutics are needed for the long-term management of HIV infection and for acute HIV-1 infection by drug-resistant strains (5-7).

Reverse transcriptase (RT) is an essential viral enzyme responsible for retrotranscription of viral RNA into DNA, which is then integrated into the genome of host cells. Targeting of HIV RT is an extremely attractive approach for anti-HIV therapy since this enzyme is only found in retroviruses and has no known homologue in human cells. Reverse transcriptase activity can be inhibited in two ways. DNA chain termination can be achieved by the incorporation of a nucleoside analogue into DNA, making coupling to another nucleoside by RT impossible. The first RT inhibitors were nucleoside substrate analogues that bind to the active ATP-binding pocket, where they function as substrate decoys and chain terminators. Many selective nucleoside RT inhibitors (NRTIs), such as zidovudine (AZT) and didanosine (ddI), are currently available and in clinical use. However, these agents have considerable toxicity against cellular and mitochondrial DNA synthesis and have been shown to have limited efficacy in certain combinations because of the emergence of resistance mutations and their association with hematological toxicities (5, 8). Consequently, a second class of RT inhibitors was developed, the non-nucleoside RT inhibitors (NNRTIs). These agents are highly specific, binding to the allosteric site on the HIV-1 enzyme to inactivate it. Moreover, they are not associated with nucleoside toxicity. However, a major disadvantage of the first-generation NNRTIs, such as nevirapine and delavirdine, is their susceptibility to the effects of single point mutations within RT, conferring resistance and cross-resistance to other NNRTIs, even in the case of a single mutation (9, 10). Thus, the search continues for agents for which resistance can only occur with multiple mutations (5).

The imidazole derivative capravirine (S-1153, AG-1549) is a second-generation NNRTI that is one of the most promising anti-HIV-1 agents to emerge. Capravirine has exhibited potent *in vitro* anti-HIV activity against both laboratory strains and clinical isolates. The agent has been shown to maintain efficacy against many drug-resistant mutants and requires at least 2 mutations for RT to become resistant. Capravirine was thus chosen for further development as a treatment for HIV-1 infection (11).

Pharmacological Actions

Capravirine potently inhibited purified RT with an IC_{50} value of 0.45 μM. In comparison, the IC_{50} value for nevirapine was 6.51 μM. The K_m values for capravirine and dTTP were 1.63 and 2.62 μM, respectively (11).

The anti-HIV activity of capravirine against known NNRTI-resistant mutants was compared with other NNRTIs, NRTIs and protease inhibitors. Results from MTT assays examining inhibition of virus-induced cytopathic effects in MT-4 cells showed that capravirine was the most potent agent (EC_{50} = 1.4 ± 0.5 ng/ml), being more potent than nevirapine (EC_{50} = 18 ± 5 ng/ml), loviride (EC_{50} = 11 ± 4 ng/ml), delavirdine (EC_{50} = 11 ± 2 ng/ml), AZT (EC_{50} = 1.9 ± 0.6 ng/ml), ddI (EC_{50} = 550 ± 150 ng/ml), ddC (EC_{50} = 18 ± 3 ng/ml), lamivudine (EC_{50} = 39 ± 10 ng/ml), saquinavir (EC_{50} = 3.7 ± 0.6 ng/ml), indinavir (EC_{50} = 14 ± 6 ng/ml), ritonavir (EC_{50} = 26 ± 3 ng/ml) and nelfinavir (EC_{50} = 10 ± 2 ng/ml). The anti-HIV activity of capravirine was also more potent than AZT and nevirapine in MTT assays using MT-4, MT-2, M8166 cells or peripheral blood mononuclear cells (PBMCs) infected with different HIV-1 strains (IIIB, SF33, SF-2, NL432) or clinical isolates of HIV. The EC_{50} for capravirine against strains with single amino acid substitutions conferring NNRTI resistance, including the Y181C mutant, ranged from 0.3 to 7 ng/ml. The emergence of capravirine-resistant variants was markedly slower than for nevirapine (more than 31 vs. 7-10 days of culture). Genotypic analysis of the capravirine-resistant variants showed that at least 2 amino acid substitutions (*e.g.*, K103T + V106A + L234I; V106A + F227L) were required for capravirine resistance. The capravirine-resistant variants were still susceptible to the NRTIs AZT and lamivudine (11).

Capravirine has been shown to have potent antiviral activity against laboratory strains and clinical isolates of HIV. The EC_{50} values ranged from 0.7 (2.2 including RT-resistant strains) to 10.3 nM and the EC_{90} values ranged from 2.4 (6.0 including RT-resistant strains) to 21.5 nM. Activity was also demonstrated against a panel of recombinant HIV-1 NL4.3 strains containing RT amino acid substitutions that confer resistance to other NRTIs and NNRTIs. K103N, V106A and L100I substitutions were found to be fully sensitive to capravirine. Only those strains which contained 2 or more substitutions conferring resistance to NNRTIs had a significant reduction in susceptibility to capravirine (12, 13).

Further *in vitro* experiments examined the efficacy of capravirine in combination with the protease inhibitors nelfinavir, ritonavir, indinavir or saquinavir against acute HIV-1IIIB and HIV-1RF infections in MT-4 and CEM-SS cells, respectively. Results suggested that combination treatment resulted in strong synergistic antiviral effects (13).

The resistance and cross-resistance profile of capravirine was further examined using recombinant HIV-1 strains derived from plasma of antiretroviral therapy-experienced patients; the strains contained NNRTI and NRTI resistance-associated substitutions. Potent antiviral activity was reported for capravirine against isolates containing K103N, L100I + K103N or K103N + P225H, which are associated with cross-resistance to other NNRTIs (14).

The resilience of capravirine to RT mutations may be explained by the manner in which the compound interacts with HIV RT. Analysis of the crystal structure of capravirine complexed with HIV RT revealed that binding of the agent involves an extensive network of hydrogen bonds with main chain residues 101, 103 and 236 of the p66 RT subunit. Side-chain mutations in RT would be highly unlikely to disrupt this type of interaction (15).

The anti-HIV efficacy of capravirine has been demonstrated *in vivo* in a mouse/MT-4 cell model of HIV infection. Dose-dependent inhibition of HIV-1 replication was observed in BALB/c mice treated with oral capravirine or oral AZT alone immediately following injection of HIV-infected MT-4 cells into the peritoneal cavity. Capravirine was shown to accumulate in the lymph nodes. Moreover, synergistic inhibition of HIV replication was observed in animals treated with combination of capravirine and AZT (11).

Pharmacokinetics and Metabolism

A 3-way crossover study conducted in 42 healthy subjects compared the pharmacokinetics of single-dose capravirine (1400 mg p.o. x 3 separated by a 7-day washout period) administered under fasting conditions or with a high-fat (60% fat; about 1,000 calories) or low-fat (33% fat; about 730 calories) meal. Mean geometric t_{max}, C_{max} and AUC values under fasted conditions (2 h, 0.9 mg/l and 3.24 mg/l·h, respectively) were significantly different from those obtained in subjects fed a high-fat (4.5 h, 1.80 mg/l and 6.05 mg/l·h, respectively) or low-fat (4 h, 1.76 mg/l and 5.97 ml/l·h, respectively) meal; there were no differences in the pharmacokinetics obtained from subjects fed high-fat or low-fat meals. Results suggest that the bioavailability of capravirine increased 2-fold when administered with a meal as compared to under fasting conditions (16) (Table I).

A 3-period, 35-day, multiple-dose phase I trial in 42 subjects examined the effect of capravirine (200, 400 and 700 mg b.i.d.) on the pharmacokinetics of lopinavir/ritonavir (400/100 and 533/133 mg b.i.d.). Thirty-eight subjects completed the study. AUC values for lopinavir were dose-dependently reduced in subjects administered capravirine and the standard lopinavir/ritonavir dose (400/100 mg). However, this was not observed with the higher (533/133 mg) lopinavir/ritonavir dose. It was concluded that the effects of capravirine on lopinavir may be due to the induction of CYP3A4 and/or the membrane transporter P-glycoprotein (17) (Table I).

A 21-day, parallel-group study in 27 healthy subjects examined the pharmacokinetic drug–drug interactions between capravirine (days 2-21; group 1, 400 mg b.i.d.; group 2, 700 mg b.i.d.), lopinavir/ritonavir (days 10-21;

Table I: Pharmacokinetic interactions of capravirine with lopinavir/ritonavir (LPV/RTV) and tenofovir (TDF) in healthy subjects and effects of food (from Prous Science Integrity®).

Capravirine	Dose (mg) TDF	LPV/RTV	AUC (mg·h/l)	C_{max} (mg/l)	t_{max} (h)	C_{min} (mg/l)	$t_{1/2}$ (h)
200		400/100	5.98	1.20	3.00	0.15	3.50
200		533/133	5.29	1.16	2.50	0.13	3.59
400			1.46	0.59	3.00	–	1.15
400	300		1.23	0.55	3.00	–	1.09
400		400/100	15.8	3.12	3.50	0.41	3.19
400		533/133	14.7	2.81	3.00	0.39	3.13
400	300	400/100	20.0	3.19	2.50	0.75	4.53
700			4.56	1.54	3.00	–	1.95
700	300		4.37	1.34	3.00	0.01	2.15
700		400/100	30.2	5.43	4.00	0.92	3.44
700		533/133	32.0	5.81	3.00	0.95	3.18
700	300	533/133	38.4	6.11	4.00	0.74	4.43
Effect of food							
1400	*Fasted*		3.24*	0.90	2.00		
1400	*High-fat meal*		6.05*	1.80	4.50		
1400	*Low-fat meal*		5.97*	1.76	4.00		

AUC, area under concentration-time curve from 0 to 12 h; AUC(*) from 0 to infinity; C_{max}, peak plasma concentration; C_{min}, plasma concentration at 12 h; t_{max}, time to reach peak plasma concentration; $t_{1/2}$, elimination half-life. Capravirine was administered orally b.i.d., alone or in the presence of LPV/RTV b.i.d. for 10 days, TDF s.d., or both LPV/RTV b.i.d. and TDF o.d. for 12 days. Effect of food was studied after single oral doses of capravirine. (Data from references 16-18.)

group 1, 400/100 mg b.i.d.; group 2, 533/133 mg b.i.d.) and tenofovir (300 mg/day on days 1 and 9-21). AUC values for tenofovir increased at least 1.33-fold, while the half-life values were unchanged in the presence of capravirine and lopinavir/ritonavir. In addition, the AUC values for capravirine increased 13.6- and 8.34-fold in groups 1 and 2, respectively, and the half-life increased at least 2-fold. The increases in concentrations of both capravirine and tenofovir in the presence of lopinavir/ritonavir were suggested to be due to induction of CYP3A4 and/or the membrane transporter P-glycoprotein (18) (Table I).

The safety and pharmacokinetics of short-course capravirine monotherapy (700, 1400 or 2100 b.i.d. or 700 or 1400 mg t.i.d. p.o. for 10 days) were examined in a study in 36 HIV-infected, antiretroviral therapy-naïve patients. Pharmacokinetic analysis was performed on days 1, 5 and 10 and controls were treated with nelfinavir and AZT/lamivudine. Treatment was well tolerated, with no serious adverse events reported. The most common adverse events were nausea, vomiting and headache. The pharmacokinetics of capravirine were linear. C_{max}, C_{min} at steady state and half-life values obtained for the agent were 2.22-6.65 mg/l, 0.0475-0.417 mg/l and about 2 h, respectively. Mean reductions in viral load ranged from 1.23 $\log_{10}$ for 700 mg b.i.d. to 1.69 $\log_{10}$ for 2100 mg b.i.d.; the mean viral load reduction for the control group was 1.65 $\log_{10}$ (19).

The pharmacokinetics of capravirine (175-1800 mg b.i.d. for 28 days) in the presence of protease inhibitors were examined in a study in 40 HIV-infected patients on stable therapy including nelfinavir (or indinavir), AZT (or d4T) and 3TC (lamivudine). Capravirine was well tolerated. No serious adverse events were observed and the most common were diarrhea and nausea. Pharmacokinetic analysis revealed that capravirine had first-order elimination over the dose range examined. The plasma C_{min} and C_{max} values for capravirine were 0.128-3.24 μg/ml and 1.79-9.13 μg/ml, respectively. When compared to other trials in which capravirine was administered in the absence of protease inhibitors, it was concluded that nelfinavir increased the concentration of capravirine by about 2-fold (20).

The metabolism of capravirine was examined in an *in vitro* study using rat liver microsomes. Seven metabolites were identified, with the *S*-oxide, *N*-oxide and sulfone of capravirine being the major metabolites. Two minor metabolites found appeared to be formed by hydroxylation of the isopropyl moiety (21).

Clinical Studies

A phase I dose-escalation study conducted in 55 HIV-infected patients (CD4 cell count = 50-500 cells/ml) on concomitant, stable (for more than 4 weeks) antiretroviral therapy other than protease inhibitors or other NNRTIs, examined the safety, tolerability and efficacy of capravirine (1.7, 3.3, 5.0 or 6.7 mg/kg t.i.d. for 14 days, or 8.3 mg/kg t.i.d. or 12.5 mg/kg b.i.d. for 28 days). Capravirine was well tolerated. The most frequent capravirine-related adverse events reported were nausea, taste alteration and vomiting; other adverse events were mild or moderate. Measurable plasma

concentrations of capravirine were maintained at both 8 and 12 h postdosing. Of the 26 patients (baseline HIV-1 RNA > 10,000 copies/ml; of whom 21 had received more than 6 months of NRTIs, 6 had prior protease inhibitor experience and 11 were concomitantly taking protease inhibitors while on the study), 14 had a mean reduction in viral load of > 1.64 $\log_{10}$ over 15 days (22). The results of this and several other clinical studies described below or in the previous section are summarized in Table II.

An ongoing, double-blind, placebo-controlled phase II trial in 75 protease inhibitor-naïve patients infected with HIV (baseline HIV RNA > 2000 copies/ml) and failing

Table II: Clinical studies of capravirine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, Double-blind	Capravirine, 200 mg bid + Lopinavir, 400 mg bid + Ritonavir, 100 mg bid x 35 d Capravirine, 400 mg bid + Lopinavir, 400 mg bid + Ritonavir, 100 mg bid x 35 d Capravirine, 700 mg bid + Lopinavir, 400 mg bid + Ritonavir, 100 mg bid x 35 d Capravirine, 200 mg bid + Lopinavir, 533 mg bid + Ritonavir, 133 mg bid x 35 d Capravirine, 400 mg bid + Lopinavir, 533 mg bid + Ritonavir, 133 mg bid x 35 d Capravirine, 700 mg bid + Lopinavir, 533 mg bid + Ritonavir, 133 mg bid x 35 d	42	Capravirine combined with lopinavir and ritonavir showed a good safety profile when administered to healthy volunteers	17
Healthy volunteers	Randomized, Double-blind	Tenofovir, 300 mg od on d 1, 9 & 21 + Capravirine, 400 mg bid on d 2-21 + Lopinavir, 400 mg bid x 12 on d 10-21 + Ritonavir, 100 mg bid x 12 on d 10-2 Tenofovir, 300 mg od on d 1, 9 & 21 + Capravirine, 700 mg bid on d 2-21 + Lopinavir, 533 mg bid x 12 on d 10-21 + Ritonavir, 133 mg bid x 12 on d 10-21	14	A sequential combination of tenofovir, lopinavir, ritonavir and capravirine was well tolerated when administered to healthy volunteers for 21 days	18
HIV infection	Randomized, Double-blind	Capravirine, 700 mg po bid x 10 d (n=6) Capravirine, 1400 mg po bid x 10 d (n=6) Capravirine, 2100 mg po bid x 10 d (n=6) Capravirine, 700 mg po tid x 10 d (n=6) Capravirine, 1400 mg po tid x 10 d (n=6) Nelfinavir + Zidovudine + Lamivudine x 10 d (n=6)	36	Capravirine was well tolerated and was as effective as a combination of nelfinavir, zidovudine and lamivudine in reducing the viral load of antiretroviral-naïve patients with HIV-1 infection	19
HIV infection	Open	Capravirine, 175-800 mg bid + Background therapy (n=29)	40	Capravirine was well tolerated and was not associated with any serious adverse events when administered to HIV-infected patients receiving stable antiretroviral therapy	20
HIV infection		Capravirine, 1.7 mg/kg tid x 14 d Capravirine, 3.3 mg/kg tid x 14 d Capravirine, 5.0 mg/kg tid x 14 d Capravirine, 6.7 mg/kg tid x 14 d Capravirine, 8.3 mg/kg tid x 28 d Capravirine, 10.0 mg/kg bid x 28 d Capravirine, 12.5 mg/kg bid x 28 d	55	Capravirine b.i.d. or t.i.d. was well tolerated and showed strong antiviral activity in patients with HIV-1 infection	22
HIV infection	Randomized, Double-blind	Capravirine, 1400 mg bid x 12 wks Capravirine, 2100 mg bid x 12 wks Placebo	50	After 12 weeks of treatment, more than 50% of the patients treated with capravirine showed HIV RNA levels < 400 copies/ml	23
HIV infection	Randomized, Double-blind	Capravirine Placebo	71	Capravirine showed strong antiviral activity in patients with HIV infection previously treated with non-nucleoside reverse transcriptase inhibitors. A total of 50% of the viral isolates showed no significant reduction in their susceptibility to capravirine at the end of the study	24
HIV infection	Open	Capravirine	646	Treatment with capravirine resulted in similar rates of vasculitis and other adverse events in both patients with HIV and healthy volunteers	27

previous NNRTI-containing regimens examined the safety and efficacy of capravirine (1400 or 2100 mg b.i.d.). All patients received concomitant nelfinavir (1250 mg b.i.d.) and two new NRTIs. Four and 7 patients discontinued due to treatment failure and adverse events, respectively, and 50 were evaluable (median baseline HIV-1 RNA = 4.14 $\log_{10}$ copies/ml and CD4 cell count = 362/mm^3). The most common adverse events that were of at least moderate severity related to capravirine were diarrhea, nausea and vomiting; these events were more frequent in the group receiving 2100 mg b.i.d. Preliminary results at week 12 from the 50 evaluable patients showed that more than 50% of those who received capravirine were rescued (HIV RNA < 400 copies/ml) (23).

The antiviral activity of capravirine was determined according to antivirogram phenotype analysis of isolates from 71 patients who failed NNRTI-containing regimens (62%, 32% and 1% with prior nevirapine, efavirenz and emivirine experience, respectively) and who were treated in a double-blind, placebo-controlled trial examining the efficacy and safety of capravirine. Potent antiviral activity of capravirine was observed for 45 of 52 (86%) isolates examined (EC_{50} < 70 nM) and no significant reduction in susceptibility was observed for 26 of 52 isolates (50%). However, of 53 isolates tested, only 7 (13%), 9 (17%) and 20 (38%) were susceptible to nevirapine, efavirenz and delavirdine, respectively. The most frequent amino acid substitution observed was K103N, with or without up to 4 other NNRTI mutations, in 29 of 55 (53%) isolates genotypically analyzed. Of 28 K103N-containing isolates (alone or in combination with V108I or P225H), 18 (64%) retained full susceptibility to capravirine; however, only 5 (18%) remained susceptible to nevirapine, delavirdine or efavirenz (24).

A similar study determined the inhibitory quotient (IQ = ratio of the free trough concentrations of capravirine determined at week 4 of the study to the IC_{50} values) of capravirine in NNRTI-experienced patients participating in a phase II trial examining the safety and efficacy of capravirine (1400 mg) in combination with nelfinavir and 2 NRTIs. Of 45 isolates examined, 37 (84%) displayed over 10-fold resistance to at least 1 approved NNRTI and 34 (76%) exhibited < 10-fold resistance to capravirine. The median IC_{50} and free trough concentration for capravirine were 0.26 ng/ml and 11.4 ng/ml, respectively. A median IQ of 33 was estimated in 45 patients, with the highest IQs obtained in patients infected with wild-type HIV (16% of the patients) or with HIV variants containing K103N with or without other NNRTI resistance-related substitutions (58%). Those patients (27%) infected with NNRTI-resistant HIV variants that did not contain K103N had a median IQ of 2.5. Thus, potent antiviral activity was shown for capravirine in isolates from NNRTI-experienced patients (25).

The development of capravirine was stopped by the FDA in January 2001 due to the unexpected finding of vasculitis obtained in dogs administered a high dose of the agent in a 12-month toxicology study. However, development was reinitiated in November 2001 following analysis of results from a monitoring plan that evaluated patients involved in clinical trials and healthy volunteers exposed to capravirine (during treatment and at 6-month follow-up after discontinuation of treatment). A total of 1,009 subjects were eligible, of whom 646 underwent a current-status visit (432 exposed to active capravirine and 214 given placebo; 155 healthy subjects and 277 HIV-infected patients). The majority of healthy subjects had received less than 2100 mg/day, while the majority of HIV-infected patients had been administered 2800 mg/day. There was no significant difference between adverse event onset (including cutaneous vasculitis) in capravirine- and placebo-treated subjects. It was concluded that treatment with capravirine does not appear to increase the risk of development of vasculitis. Ongoing capravirine trials continue to prospectively monitor for the risk of development of vasculitis (26, 27).

Capravirine continues to undergo phase II and phase III development to determine the antiviral efficacy and tolerability in HIV-infected patients. A phase I trial is currently recruiting patients (between 4 months and 21 years of age; who have received less than 6 weeks of antiretroviral treatment, have not benefitted from antiretroviral therapy after 12 weeks of treatment or have discontinued antiretroviral therapy for adverse events) to examine the safety, tolerability and efficacy of capravirine (once daily for 6 days starting after a washout period) in children and adolescents infected with HIV. In addition, 2, randomized, double-blind, placebo-controlled, parallel-group phase II trials are recruiting HIV-infected patients who failed an initial NNRTI-containing regimen or who failed other antiviral regimens. The trials will examine the safety and efficacy of capravirine in combination with other antiretroviral agents. In one trial, patients who failed an initial NNRTI-containing regimen will receive capravirine in combination with nelfinavir and 2 NRTIs. The other 48-week multicenter trial will be conducted in patients who failed at least 1 protease inhibitor (not more than 3), at least 1 NNRTI and at least 2 NRTIs and who have had no previous experience with lopinavir/ritonavir, and will examine the safety and efficacy of a 4-drug combination regimen including capravirine, lopinavir/ritonavir and other nucleosides.

Sources

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