Intestinal Metabolism Promotes Regional Differences in Apical Uptake of Indinavir: Coupled Effect of P-Glycoprotein and Cytochrome P450 3A on Indinavir Membrane Permeability in Rat

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ABSTRACT

The purpose of this study was to investigate transport and metabolism contributions to low indinavir permeability in rat ileum and enhanced drug permeability in the jejunum. Permeability models utilized included single pass in situ rat intestinal perfusion and rat intestinal tissue mounted in Ussing chambers. Intestinal metabolism was measured by fractional appearance of metabolite (Fmet), determined as the percentage of the predominant metabolite M6 over luminal loss of indinavir in the perfusion model. Among the results, indinavir exhibited bidirectional transport across rat ileum. Verapamil and cyclosporin A inhibited net flux by 37 and 38%, respectively. Intestinal metabolism of indinavir was most significant in upper jejunum (Fmet = 65.78 ± 19.02%), decreasing in midjejunum (Fmet = 31.58 ± 5.63%). M6 was not detectable in ileum or colon. Western blot analysis of rat intestinal mucosal tissue samples confirmed that the axial expression of CYP3A was consistent with the regional pattern of formation of M6. Intestinal metabolism was saturable and could be inhibited by the CYP3A inhibitor, ketoconazole. A low luminal concentration of indinavir (1 μM) was associated with high Fmet (87.90 ± 14.30%), whereas a high luminal concentration of indinavir (50 μM) was associated with low Fmet (35.84 ± 11.59%). In the presence of ketoconazole, both Fmet and permeability of indinavir were reduced in the jejunum. These results suggest that 1) intracellular metabolism of indinavir enhances apical uptake of indinavir in the rat jejunum as a function of the increased concentration gradient generated across the epithelial cell membrane and 2) the efflux transporter P-glycoprotein limits apical uptake of indinavir in the ileum, resulting in low apparent permeability.

Indinavir (Crixivan; Merck & Co., Inc., Whitehouse Station, NJ; Fig. 1A) is a peptidomimetic HIV protease inhibitor approved by the Food and Drug Administration for treatment of acquired immunodeficiency syndrome. The metabolism of indinavir in several species has been reported (Balani et al., 1995; Lin et al., 1996). Seven prominent metabolites (M1–M7) have been identified in human urine and characterized (Balani et al., 1995). Except for a direct N-glucuronidation product (M1) that is specific to higher primates (Balani et al., 1995), in vitro studies in both human and rat liver microsomes indicate that all the other metabolites (M2–M6) are products of oxidative metabolic pathways mediated by cytochrome P450 isozyme IIIA (CYP3A) (Chiba et al., 1996, 1997). In vivo pharmacokinetic studies revealed that oxidative metabolism is the major route of elimination for indinavir in rat and human and the contribution of conjugation to elimination is minimal (<0.5% of dose) (Lin et al., 1995, 1996). In addition, all oxidative metabolites observed in vivo were also formed in NADPH-fortified liver and intestinal microsomes, with the N-dealkylated metabolite, M6 (Fig. 1B), being the predominant metabolite (Chiba et al., 1997).

Since CYP3A represents about 30 and 70% of total cytochrome P450 activity in liver and intestine, respectively (Watkins et al., 1987; de Waziers et al., 1990; Paine et al., 1997), first-pass metabolism is projected to play a significant role in poor and variable bioavailability of some drugs that are substrates for CYP3A (Back and Rogers, 1987; Schwenk, 1988). Intestinal first-pass metabolism mediated by CYP3A has been shown to be clinically relevant for several drugs such as cyclosporin A (Hebert et al., 1992; Wu et al., 1995),

ABBREVIATIONS: HIV, human immunodeficiency virus; P-gp, P-glycoprotein; LC/MS, liquid chromatography/mass spectrometry; ECL, enhanced chemiluminescence; MES, 4-morpholineethanesulfonic acid; DEX, dexamethasone.
CYP3A metabolism are functionally linked components of a xenobiotic detoxification system that limits the bioavailability of several drugs (Benet et al., 1999; Wacher et al., 2001). There is substantial overlap in substrate specificity between CYP3A and P-gp (Wacher et al., 1995; Kim et al., 1999), and several modulators/substrates of P-gp and CYP3A have been shown to coordinately up-regulate the expression of these proteins in vitro (Schuetz et al., 1996) as well as in vivo (Huang et al., 2001). Altered levels of these proteins could affect the oral absorption and pharmacokinetics of some drugs.

Indinavir is known to be a substrate of both CYP3A and P-gp. The purpose of this study was to detail the intestinal metabolism of indinavir in vivo and to study the effect of CYP3A and P-gp on the intestinal transport of indinavir in an animal model.

**Experimental Procedures**

**Materials.** Indinavir capsules were purchased from the University of Michigan Hospital Pharmacy. Authentic indinavir used in HPLC and LC/MS assay development and validation was a gift from Merck & Co. Dexamethasone (DEX)-treated rat liver microsomes were purchased from Human Biology International (Scottsdale, AZ). Ketamine-HCl was obtained from Fort Dodge Laboratories (Fort Dodge, IA), and Rompun (xylazine) from Bayer Corp. (Shawnee Mission, KS). The rat cytochrome P450 IIIA ECL Western blotting kit was purchased from Amersham Biosciences UK Ltd. (Little Chalfont, Buckinghamshire, UK). Radiolabeled compounds included [3H]indinavir (3.2 Ci/mmol) and [3H]vinblastine sulfate (9.1 Ci/mmol) from Moravek Biochemicals (Brea, CA), [14C]midazolam (Paine et al., 1996), and possibly other CYP3A substrates, including the HIV protease inhibitor, saquinavir (Fitzsimmons and Collins, 1997). Chiba et al. (1997) showed that small intestinal microsomes are capable of metabolizing indinavir, but their calculations indicated only a minor contribution whereas the liver plays a much greater role in the first-pass metabolism of indinavir in both rat and human. Although microsomes provide in vitro metabolic profiles, an in vivo system including natural transport barriers and intact epithelial cells may be more representative of oral delivery limitations.

P-glycoprotein (P-gp), encoded by the human MDR1 and rodent mdr1a/1b genes, is constitutively expressed in the brush-border membrane of intestinal enterocytes and the canalicular membrane of hepatocytes and transports structurally and functionally diverse compounds (Ambudkar et al., 1999). Several lines of evidence indicate that P-gp plays a significant role in the oral absorption and excretion of some hydrophobic xenobiotics. P-gp limits the oral bioavailability of drugs such as paclitaxel (Taxol), talinolol, and digoxin, and it has been shown to excrete paclitaxel directly across the intestinal wall (Sparreboom et al., 1997; van Asperen et al., 1997). In humans, individual differences in P-gp expression in duodenal enterocytes are correlated with area under plasma concentration-time curves for digoxin (Hoffmeyer et al., 2000).

It has been postulated that mucosal transport by P-gp and
All animals, perfusion solutions, and the pumps were enclosed in a Plexiglas thermostatically controlled chamber set at 30°C. Intestinal effluent samples were collected in preweighed polypropylene vials every 10 min for up to 120 min. Each effluent fraction was reweighed after collection. Steady-state water and solute transport rates were established within 30 min after initiation of perfusion at the flow rate studied. Water transport was corrected by the gravimetric method. Relative drug loss from the perfusate was measured by HPLC or LC/MS.

The perfusion buffer contained 10 mM MES, 135 mM NaCl, 5 mM KCl, 1.1 mM CaCl₂, 5 mM glucose, and 5 mM mannitol. The pH was adjusted to 6.5 with NaOH. Mannitol, traced with radiolabeled man- nitol, served as a permeability marker. When inhibitors were added to the perfusion buffer, pH was readjusted when necessary, and the amount of NaCl was accordingly reduced to maintain iso-osmotic solutions. All perfusion solutions were isotonic.

The effective permeability (Pₑₒₚₜ) measured by intestinal perfusion was based on the loss of drug from the perfusate:

\[ P_{\text{eff}} = \left( -\frac{Q}{2L} \right) \ln \left( \frac{C_{\text{out}}}{C_{\text{in}}} \right) \]

where \( Q \) is the perfusate flow rate through the segment (0.14 ml/min), \( r \) is the radius of the segment (0.2 cm), \( L \) is the length of the perfused segment (10 cm), and \( C_{\text{in}} \) is the drug concentration of the perfusate entering the intestinal segment. \( C_{\text{out}} \) is the drug concentration in the exiting perfusate, \( C_{\text{out}} \) corrected for water transport according to the gravimetric method:

\[ C'_{\text{out}} = C_{\text{out}} \frac{V}{(Q \cdot \Delta t)} \]

where \( V \) is the volume of effluent and \( \Delta t \) is the collection interval.

The fraction of metabolite measured in the jejunum was calculated as the concentration ratio of metabolite M6 over total loss of parent drug from the lumen:

\[ F_{\text{met}} = \left( \frac{[\text{M6}]_{\text{out}}}{[\text{indinavir}]_{\text{out}} - [\text{indinavir}]_{\text{in}}} \right) \]

**Intestinal Ussing Chamber Studies.** Procedures for the intestinal Ussing chamber studies were the same as previously reported (Jezzyk et al., 1999). Briefly, small sections of excised rat intestine, 2.5 to 3 cm in length, were opened along the mesenteric border. Assembled diffusion chambers were placed in a 37°C heating block, connected to a 95% O₂/5% CO₂ airtight, and filled with 5 ml of 37°C buffer, pH 7.4. The diffusion chambers and the airtight/heating block assembly were purchased from Precision Instrument Design (Lake Tahoe, CA) and Costar (Cambridge, MA), respectively.

After a 15-min equilibration period, the original buffer was replaced with warm fresh apical or basolateral buffer solutions. The transport studies were initiated by the addition of labeled and unlabeled drug to either the apical or basolateral chamber to give a final concentration of approximately 0.1 μCi/ml in the donor compartment. In inhibition studies, an unlabeled inhibitor was added to both chambers prior to addition of the drug. A 20-μl sample was taken from donor chamber at time 0 and also at the end of the transport study, respectively. Samples of 500 μl were taken from the receiver chamber every 30 min for up to 120 min and replaced with fresh warm buffer of the same pH. Sample activity was measured by liquid scintillation counting (Beckman LS 5000; Beckman Coulter, Inc., Fullerton, CA) using a dual label or single label program, as appropriate, and an external standardization quench method.

The buffer added to the basolateral chamber contained 112 mM NaCl, 5 mM KCl, 1.2 mM CaCl₂, 1.2 mM MgCl₂, 25 mM NaHCO₃, 1.6 mM Na₂HPO₄, 0.4 mM NaH₂PO₄, 5 mM d-glucose, and 5 mM mannitol. This basolateral buffer had a pH of 7.4 when bubbled with 95% O₂/5% CO₂ and maintained at 37°C. The buffer added to the apical chamber contained an additional 5 mM MES, and the pH was adjusted to 6.5 with HCl. Osomolalities for both buffers were 290 ± 15 mOsmol/kg (Wescor Vaporpressure Osmometer; Wescor Co., Logan, UT).

The steady state flux (Jₑₒₜ) and effective permeability (Pₑₒₚₜ) were based on the appearance of drug in the receiver chamber under sink conditions:

\[ P_{\text{eff}} = \frac{J_{\text{eff}}}{C_{\text{D}}} = \left( \frac{dC_{\text{eff}} \cdot V_{\text{R}}}{dt \cdot A} \right) \left( \frac{1}{C_{\text{D}}} \right) \]

where \( dC_{\text{eff}}/dt \) is the change in drug concentration in the receiver chamber at steady-state, \( V_{\text{R}} \) is the volume of receiver buffer (5 ml), \( A \) is the cross-sectional area of the exposed tissue (1.13 cm²), and \( C_{\text{D}} \) is the drug concentration in the donor chamber. The efflux ratio is calculated as the ratio of apical to basolateral permeability over basolateral to apical permeability at equal donor concentrations.

**Microscopic Incubations.** The oxidative metabolism of indinavir was confirmed in incubation preparations consisting of NADPH and DEX-treated rat liver microsomes. The incubation mixture (final volume of 0.5 ml in 50 mM phosphate buffer, pH 7.4) consisted of 1 mM NADPH, 0.5 mg/ml DEX-treated rat liver microsomes, and various concentrations of indinavir (1–10 μM). After a 3-min preincubation at 37°C, the reaction was initiated by the addition of 25 μl of 20 mM NADPH stock solution. A zero time point sample of 100 μl was taken immediately after initiation of the reaction. The mixture was then incubated for 10 or 20 min. The reaction was terminated, and the zero time point sample was treated with twice the volume of ice-cold acetonitrile and centrifuged at 14,000 rpm for 5 min. Supernatant was transferred to a clean tube and dried under nitrogen. The residue was reconstituted with 100 or 200 μl of acetonitrile/1% formic acid (50:50) and centrifuged again at 14,000 rpm for 15 min before the supernatant was stored for LC/MS analysis.

**Immunoblotting.** Rat small intestinal enterocytes were scraped off immediately following completion of perfusion experiments. Samples were prepared and stored for protein analysis according to the previously published method (Lown et al., 1997).

Small intestinal CYP3A in these rats was detected using a primary rabbit anti-rat cytochrome P450 IIIA antibody and secondary anti-rabbit IgG-biotinylated species-specific whole antibody (included in the rat cytochrome P450 IIIA ECL Western blotting kit; Amersham Biosciences). Blots were incubated with streptavidin-horseradish peroxidase conjugate before being visualized with ECL detection reagents (Amersham Biosciences).

P-glycoprotein was detected with the C-219 monoclonal antibody (Signet Laboratories, Dedham, MA). Villin was detected with a mouse monoclonal antibody raised against chick villin that cross-reacts with rat villin (Chemicon International, Inc., Temecula, CA). The secondary antibodies used were peroxidase-conjugated rabbit anti-mouse IgG (Sigma-Aldrich). Immunoblot protein concentrations were determined by computer-aided densitometry with ScionImage (Scion Corp., Frederick, MD). P-glycoprotein immunoblots were repeated four times. Variation of enterocyte content was corrected by using villin as an internal control as previously described by Lown et al. (1994).

**Analytical Method.** The HPLC system consisted of a Shimadzu GT-104 degasser, FCV-10AL low-pressure gradient flow control valve, and LC-10AT serial dual plunger pump (all from Shimadzu, Kyoto, Japan), a Waters (Milford, MA) 712 WISP autosampler, an Applied Biosystems (Foster City, CA) 783 UV detector, a Hewlett-Packard ChemStation Software.

HPLC analysis of indinavir was based on a previously published method (Carver et al., 1999) with the following modifications: analytical column, Zorbax Rx-C8 column (150 × 4.6 mm, 5 μm particle size; Agilent Technologies, Palo Alto, CA) with a 2 μm frit (0.062 × 0.062 × 0.250 in.) before the column (Upchurch Scientific Inc., Oak Harbor, WA); mobile phase acetonitrile/water (25:75, v/v), with an aqueous phase of 50 mM phosphate buffer with the pH adjusted to
2.5 with triethylamine; wavelength, 260 or 210 nm, depending on sensitivity requirements; flow rate, 1.5 ml/min; injection volume, 50 μl; and ambient temperature.

LC/MS analyses of indinavir and M6 were performed on a Quattro II mass spectrometer (Micromass, Beverly, MA) equipped with electrospray and operated in positive ion mode. Data were acquired by single ion monitoring mode. Mass spectrometer operating conditions were optimized, including cone voltage, collision energy, collision gas pressure, source temperature, drying, and nebulizing gas flow rates. The HPLC system consisted of Hewlett Packard HP1100 series binary pump and HP1100 autosampler (Hewlett Packard). Chromatographic separation was accomplished on a Kromasil (Eka Chemicals, Bohus, Sweden) C-8 reverse phase column (5 μm, 2.1 × 15 cm). The mobile phase consists of a 50:50 mixture of Milli-Q water containing 0.5% formic acid and acetonitrile at a flow rate of 0.2 ml/min.

Statistics. Treatment differences were determined using Student's t test. Significant treatment differences were specified in accordance with a p value of 0.05. Paired two-tailed test was used only when regional permeability values were determined in the same animal in the same experimental run. Error bars in all graphs represent the standard error of the mean.

Results

Regional permeability, calculated from the water-corrected decrease in outlet perfusate indinavir concentration compared with inlet perfusion concentration (eq. 1), was significantly higher in upper small intestine than in lower small intestine or colon (Fig. 2A). This comparison was made at a 10 μM indinavir inlet perfusion concentration, which is approximate to indinavir total solubility at perfusion pH 6.5. The perfusate assay showed a substantial second peak in the jejunum that was not observed in the other regions. This extra peak was suspected and later confirmed with LC/MS to be the dealkylation metabolite of indinavir, M6 (Fig. 1), the major metabolite formed in vivo via CYP3A (Balani et al., 1995). Appearance of M6 was region-specific and decreased along the gastrointestinal tract. Intestinal metabolism was most significant when indinavir solution was perfused in rat upper jejunum and the relative appearance of M6 decreased in the midjejunal region. M6 was not detectable in the ileum or colon (Fig. 2B).

This regional appearance pattern of M6 is consistent with the distribution of CYP3A in the intestinal mucosa of these same animals (Fig. 3). Perfusion of rat jejunum as a function of increasing indinavir concentration (high concentration of indinavir was achieved by slight acidification of the perfusing buffer by 0.2 pH units) led to decreases in the relative appearance of M6 that were accompanied by increasing indinavir apparent permeability (Table 1). At 10 μM indinavir concentrations, the relative appearance of M6 decreased in the presence of ketoconazole, a potent CYP3A inhibitor (Fig. 3).
The apparent jejunal permeability of indinavir also decreased in the presence of ketoconazole. Because indinavir is known to be both a CYP3A and P-gp substrate, concentration dependence and inhibition studies were performed in both the perfusion and Ussing chamber system to evaluate the potential contributions of indinavir metabolism and export to limiting drug absorption in the small intestine. The fact that luminal M6 appearance was not observed in the ileum allowed for an unambiguous assessment of indinavir export in rat lower small intestine. Ileal perfusion studies showed no uptake of indinavir at lower drug concentrations (data not shown), suggesting the involvement of an export process. Luminal concentration of indinavir around its solubility at perfusion pH 6.5 (10^(-6) M) resulted in an ileal permeability value of 8.97 ± 1.46 × 10^{-6} cm/s, comparable with that of mannitol (5.25 ± 0.49 × 10^{-6} cm/s), which served as a low-permeability marker in the perfusion experiment. Bidirectional transport of indinavir in ileal tissues was demonstrated in the Ussing chamber system and compared with other marker compounds (Fig. 5). Mannitol and diazepam, used as low- and high-permeability markers, respectively, had efflux ratios close to unity based on comparable effective permeabilities evaluated from drug flux in either direction. The presence of verapamil, a P-gp inhibitor, did not alter the permeability of mannitol or diazepam in either direction (data not shown). In the same ileal Ussing chamber study, indinavir, similar to vinblastine, showed an efflux ratio considerably greater than unity, suggesting that indinavir is a substrate for P-gp-mediated mucosal export (Fig. 5). This bidirectional transport of indinavir could not be eliminated with probenecid, or procainamide, or a combination of gly-sar, cephalixin, and enalapril (Fig. 6A); however, the net flux of indinavir was significantly reduced to 63 and 61% of control with verapamil and cyclosporin A, respectively. Finally, it was demonstrated that at high inhibitor-to-drug ratios (200 μM verapamil and 0.1 μM indinavir), bidirectional transport of indinavir was completely abolished (Fig. 6B), indicating that verapamil could completely inhibit indinavir export in rat ileum. Expression of P-gp in the rat ileal mucosa was also confirmed by Western blot analysis (data not shown).

### Discussion

The rat has been widely used as an animal model for projection of human intestinal permeability and to study the mechanism of intestinal transport of drugs with a spectrum of physicochemical and biochemical properties (Chiou and Barve, 1998). Human perfusion studies demonstrated an excellent correlation between intestinal permeabilities of the two species for a variety of compounds (Amidon et al., 1995). Although the oral bioavailability of indinavir is much lower in the rat than in humans (Lin et al., 1996; Yeh et al., 1998), this difference has been mainly attributed to differences in hepatic metabolism between the two species (Chiba et al.,...
In contrast to the ileum, indinavir permeability was significantly higher in the upper jejunum (Fig. 2). Further investigation revealed that this favorable jejunal permeability profile was the result of enhanced apical uptake of indinavir due to its intracellular intestinal metabolism. Based on recent results showing that the indinavir metabolite, M6, is also a P-gp substrate (Hochman et al., 2001), possible competition for P-gp export between indinavir parent drug and the M6 metabolite may also play a positive role in indinavir absorption in the upper small intestine.

Previous in vivo human plasma data, as well as in vitro metabolism work in human intestinal and liver microsome systems, identified a dealkylation product, M6, as a predominant species of metabolite generated by CYP3A (Chiba et al., 1997). The validity of using rat as an intestinal metabolism model was confirmed with the identification of M6 as the major metabolite from rat hepatic microsomes as well as in situ rat jejunal perfusion. Studies in a CYP3A-induced Caco-2 cell culture model had demonstrated unidirectional transport of M6 to the apical side (Hochman et al., 2000), which is mediated by P-gp (Hochman et al., 2001). Based on this information, the parameter \( F_{\text{met}} \), fraction of metabolite (eq. 2), over luminal drug loss is utilized in this report as a measure of the extent of intestinal metabolism in rat jejunum. Intestinal metabolism was found to be region-dependent (Fig. 2B) and consistent with the decreasing expression levels of CYP3A protein along the gastrointestinal tract, demonstrated in this study (Fig. 3) as well as by other laboratories (Kolars et al., 1992).

The reduction in \( F_{\text{met}} \) with increasing luminal drug concentration projects a saturation of jejunal metabolism of indinavir (Table 1). The highest indinavir concentration tested (50 mM) was included, assuming that in vivo concentrations of indinavir could reach supersaturation in the intestinal lumen either as a result of bile-salt solubilization or variation in intestinal pH. As a low \( K_a \) weak base, indinavir total solubility is high at typical gastric pH and much lower at small intestinal pH. The permeability of indinavir was enhanced as the luminal concentration of indinavir increased, an opposite trend from that of \( F_{\text{met}} \). Given that permeability was calculated based on total drug loss from the intestinal lumen, the permeability trend may indicate that at high intracellular metabolite concentrations, M6 serves to minimize drug export via competition for P-gp. This is consistent with high passive permeability of the lipophilic drug and poor passive transport of the more polar metabolite (Sababi et al., 2001). Further studies performed at 10 \( \mu \)M indinavir showed that drug permeability followed the fractional metabolite formed (Fig. 4), i.e., inhibition of metabolism by the CYP3A inhibitor, ketoconazole, reduced the fractional metabolite as well as reducing drug permeability.

The regional dependence highlighted in this study suggests that indinavir is well absorbed in the upper small intestine but poorly absorbed in the lower small intestine. Despite high lipophilicity, ileal absorption is compromised by mucosal drug export. In the jejunum, intracellular metabolism will serve to promote mucosal uptake of indinavir by maintaining sink conditions inside the cell, thus enhancing the concentration driving force of the drug across the mucosal membrane. In addition, drug flux and absorption will be enhanced compared with the ileum since the generated metabolite will compete for drug export into the lumen.
The transport mechanism demonstrated in this study is in agreement with the pharmacokinetic profile of indinavir in rat and human. The early \( t_{\text{max}} \) of indinavir in both species, 0.5 h for rats (Lin et al., 1995) and 1 h for humans (Yeh et al., 1998), are consistent with a short elimination half-life and an early absorption window in the upper small intestine. The major excretory path for indinavir is through fecal elimination, and the majority of radioactivity found in feces is in the form of metabolites (Balani et al., 1996). In addition to biliary excretion, intestinal metabolism and export of metabolites into the lumen may also be responsible for the recovery of metabolite-associated radioactivity in feces. The fact that indinavir has an early narrow absorption window might also explain its negative food effect, reported both in healthy subjects (Yeh et al., 1998) and in HIV-infected patients (Carver et al., 1999). Under fasted state conditions, indinavir is highly soluble in the stomach and could reach supersaturated concentrations in the intestine. At this high concentration, intestinal metabolism is saturated and hepatic metabolism plays a dominant role in the overall first-pass clearance process, as previously predicted from in vitro microsomal studies (Chiba et al., 1997); however, under fed state or other conditions, which may decrease either the luminal concentration of indinavir or the rate of drug delivery to intestinal epithelia, the potential for saturating intestinal indinavir clearance might be reduced. Under these conditions, intestinal metabolism in the jejunum and export in the ileum may play a more significant role in limiting the oral absorption of indinavir. The pharmacokinetic ramifications related to differences in intestinal transport and metabolism of HIV protease inhibitors are the subject of a subsequent article.

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References


Effect of P-gp and CYP3A on Permeability of Indinavir


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