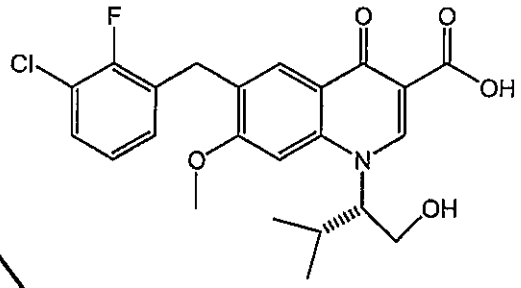
Claims

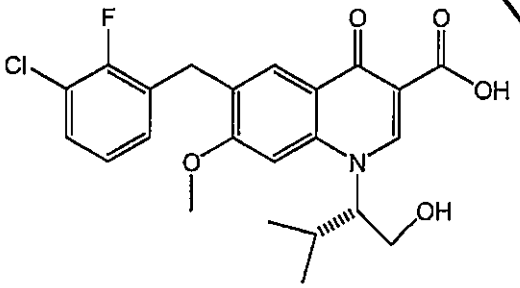
1. The use of ritonavir or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for administration with an integrase inhibitor of formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

for the treatment of an integrase responsive condition, wherein ritonavir is administered orally once a day in a dose between 20 mg to 200 mg and the compound of formula Ia is administered orally once a day in a dose of 20 mg to 500 mg.

2. The use of ritonavir or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for improving the pharmacokinetics of an HIV integrase inhibitor or a pharmaceutically acceptable salt thereof in a patient, wherein the integrase inhibitor is a compound of formula Ia or a pharmaceutically acceptable salt thereof:

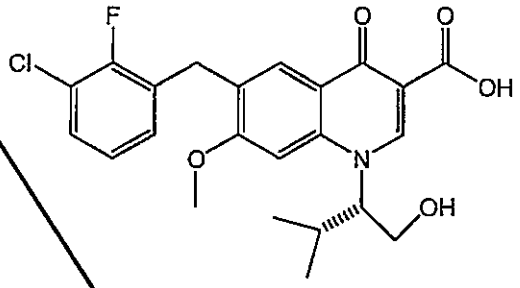


(Ia)

wherein ritonavir is administered orally once a day in a dose between 20 mg to 200 mg and the compound of formula Ia is administered orally once a day in a dose of 20 mg to 500 mg.

3. The use of any one of claims 1 or 2 wherein the blood level of the integrase inhibitor or the pharmaceutically acceptable salt thereof is increased.

4. The use of ritonavir or a pharmaceutically acceptable salt thereof, and a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

for the manufacture of a medicament for inhibiting HIV integrase in a patient, wherein ritonavir is administered orally once a day in a dose between 20 mg to 200 mg and the compound of formula Ia is administered orally once a day in a dose of 20 mg to 500 mg.

5. The use of any one of claims 1-4, wherein the compound or its pharmaceutically acceptable salt and ritonavir or its pharmaceutically acceptable salt are administered to the patient as a single composition to the patient.

6. The use of any one of claims 1-5 wherein the patient is also receiving one or more agents selected the group consisting of stavudine, emtricitabine, tenofovir, emtricitabine, abacavir, lamivudine, zidovudine, didanosine, zalcitabine, phosphazide, efavirenz, nevirapine, delavirdine, tipranavir, saquinavir, indinavir, atazanavir, nelfinavir, amprenavir, samprenavir, ,

fosamprenavir, lopinavir, ritonavir, enfuvirtide, Fozivudine tidoxil, Alovudine, Dexelvucitabine, Apricitabine, Amdoxovir, Elvucitabine (ACH126443), Racivir (racemic FTC, PSI-5004), MIV-210, KP-1461, fosalvudine tidoxil (HDP 99.0003), AVX756, Dioxolane Thymine (DOT), TMC-254072, INK-20, 4'-Ed4T, TMC-125 (etravirine), Capravirine, TMC-278 (rilpivirine), GW-695634, Calanolide A, BILR 355 BS, and VRX 840773, and pharmaceutically acceptable salts thereof.

7. The use of any one of claims 1-6 wherein the medicament is for administration to the patient with food.

8. The use of any one of claims 1-6 wherein the medicament is formulated as a unit dosage form tablet.

9. Use of the compound 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for increasing the bioavailability of the compound 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid in a patient when the medicament is administered with food, to be administered with ritonavir or a pharmaceutically acceptable salt thereof.

10. Use of the compound 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for increasing the absorption of the compound 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid in a patient when the medicament is administered with food, to be administered with ritonavir or a pharmaceutically acceptable salt thereof.

11. Use of the compound 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting activity of a retrovirus integrase in a patient when the medicament is administered with food, to be administered with ritonavir or a pharmaceutically acceptable salt thereof.

12. Use of the compound 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prophylaxis of a retrovirus infection in a patient when the medicament is administered with food, to be administered with ritonavir or a pharmaceutically acceptable salt thereof.

13. Use of the compound 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of an integrase responsive condition in a patient when the medicament is administered with food, to be administered with ritonavir or a pharmaceutically acceptable salt thereof.

14. The use of claim 1 or 13 wherein the integrase responsive condition is a retrovirus infection.

15. The use of claim 14 wherein the retrovirus infection is an HIV infection or AIDS.

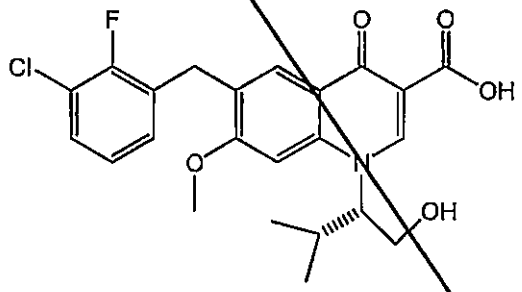
16. The use of any one of claims 9-15 wherein the compound or the pharmaceutically acceptable salt thereof is administered between about one hour prior to the consumption of food to about two hours after the consumption of food.

17. The use of claims 9-15 wherein the compound or the pharmaceutically acceptable salt thereof is administered substantially at the same time as the consumption of food.

18. The use of claims 9-15 wherein the compound or the pharmaceutically acceptable salt thereof is administered immediately after the consumption of food and up to about one hour after consumption of the food.

19. The use of any one of claims 9-15 wherein the compound is administered orally once a day in a dose of 20 mg to 500 mg and ritonavir is administered orally once a day in a dose between 20 mg and 200 mg.

20. Pharmaceutical composition comprising ritonavir or a pharmaceutically acceptable salt thereof for improving the pharmacokinetics of an HIV integrase inhibitor in a patient wherein the integrase inhibitor is a compound of formula Ia or a pharmaceutically acceptable salt thereof:



(Ia)

and wherein ritonavir is administered orally once a day in a dose between 20 mg to 200 mg and the compound of formula Ia is administered orally once a day in a dose of 20 mg to 500 mg.

21. The pharmaceutical composition of claim 20 to be administered with food.

22. A kit comprising: (1) a pharmaceutical composition comprising 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, or a pharmaceutically acceptable salt thereof; (2) prescribing information; and (3) a container; wherein the prescribing information includes advice regarding administering 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof with food and advice regarding administering 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof with ritonavir.

23. The kit of claim 22, wherein the prescribing information includes a description of improved pharmacokinetics of 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid when administered with ritonavir than without ritonavir.

24. The kit of claim 22, wherein the prescribing information includes a description of increased bioavailability of 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid when administered with food than without food.

25. The kit of claim 22, wherein the prescribing information includes advice regarding administering 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof between about one hour prior to the consumption of food to about two hours after the consumption of food.

26. The kit of claim 22, wherein the prescribing information includes advice regarding administering 6-(3-chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a

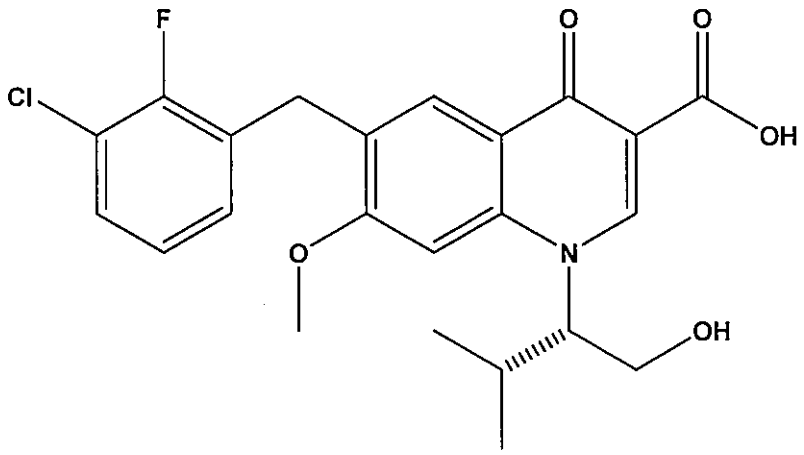
pharmaceutically acceptable salt thereof substantially at the same time as the consumption of food.

27. The kit of claim 22, wherein the prescribing information includes advice regarding administering 6-(3-chloro-2-fluorobenzyl)-1-[(*2S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof immediately after the consumption of food and up to about one hour after the consumption of food.

28. The kit of claim 22-27 wherein the pharmaceutical composition is in a unit dosage form of a tablet.

CLAIMS

1. The compound ((2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane) (ritonavir) or a pharmaceutically acceptable salt thereof, for use in the improvement of the pharmacokinetics of an HIV integrase inhibitor in a patient, the HIV integrase inhibitor being the compound of the formula (Ia):

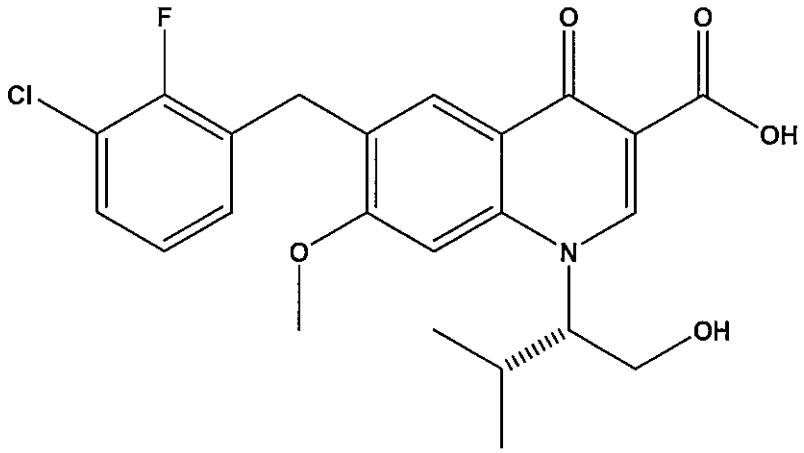


(Ia)

or a pharmaceutically acceptable salt thereof, the ritonavir being for an oral administration to the patient once a day in a dose between 20 mg to 200 mg, and the compound of formula (Ia) being for an oral administration to the patient once a day in a dose of 20 mg to 500 mg.

2. The compound ((2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane) (ritonavir) or a pharmaceutically acceptable salt thereof, for use in the inhibition of an HIV integrase in a patient with an integrase inhibitor, the integrase inhibitor being

the compound of the formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof, the ritonavir being for an oral administration to the patient once a day in a dose between 20 mg to 200 mg, and the compound of formula (Ia) being for an oral administration to the patient once a day in a dose of 20 mg to 500 mg.

3. The compound of claims 1 or 2 wherein the use further involves the administration to the patient of one or more agents selected from the group consisting of stavudine, emtricitabine, tenofovir, emtricitabine, abacavir, lamivudine, zidovudine, didanosine, zalcitabine, phosphazide, efavirenz, nevirapine, delavirdine, tipranavir, saquinavir, amprenavir, samprenavir,, fosamprenavir, enfuvirtide, Fozivudine tidoxil, Alovudine, Dexelvucitabine, Apricitabine, Amdoxovir, Elvucitabine (ACH126443), Racivir (racemic FTC, PSI-5004), MIV-210, KP-1461, fosalvudine tidoxil (HOP 99.0003), AVX756, Dioxolane Thymine (DOT), TMC-254072, INK-20, 4'-Ed4T, TMC-125 (etravirine), Capravirine, TMC-278 (rilpivirine), GW-695634, Calanolide A, BILR 355 BS, and VRX 840773, and pharmaceutically acceptable salts thereof.

4. The compound of any one of claims 1 to 3, which is for an oral

administration to the patient once a day in a dose of 50 mg.

5. The compound of any one of claims 1 to 3, which is for an oral administration to the patient once a day in a dose of 100 mg.

6. The compound of any one of claims 1 to 3, which is for an oral administration to the patient once a day in a dose of 200 mg.

7. The compound of any one of claims 1 to 6, wherein the compound of formula (Ia) is for an oral administration to the patient once a day in a dose of 85 mg.

8. The compound of any one of claims 1 to 6, wherein the compound of formula (Ia) is for an oral administration to the patient once a day in a dose of 150 mg.

9. The compound of any one of claims 1 to 6, wherein the compound of formula (Ia) is for an oral administration to the patient once a day in a dose of 200 mg.

10. The compound 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof, for use in combination with ritonavir or a pharmaceutically acceptable salt thereof and food taken by a patient, in the increase of the bioavailability of the compound in the patient,

wherein said compound or a pharmaceutically acceptable salt thereof is for an administration to the patient

- when the patient has taken the food during a period between 1 hour prior to the administration of the compound to the patient and 2 hours after the administration of the compound to the patient; or

- during a period between 1 hour prior to the consumption of the food by the patient and 2 hours after the consumption of the food by the patient; and

wherein the administration of the compound is an oral administration once a day in a dose of 20 mg to 500 mg and the administration of the ritonavir is an oral administration once a day in a dose between 20 mg to 200 mg.

11. The compound 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof, for use in combination with ritonavir or a pharmaceutically acceptable salt thereof and food taken by a patient, in the increase of the absorption of the compound in the patient,

wherein said compound or a pharmaceutically acceptable salt thereof is for an administration to the patient

- when the patient has taken the food during a period between 1 hour prior to the administration of the compound to the patient and 2 hours after the administration of the compound to the patient; or

- is for an administration to the patient in a therapeutically effective amount during a period between 1 hour prior to the consumption of food by the patient and 2 hours after the consumption of the food by the patient; and

wherein the administration of the compound is an oral administration orally once a day in a dose of 20 mg to 500 mg, and the administration of the ritonavir is an oral administration once a day in a dose between 20 mg to 200 mg.

12. The compound 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a

pharmaceutically acceptable salt thereof, for use in combination with ritonavir or a pharmaceutically acceptable salt thereof and food taken by a patient for the inhibition of a retrovirus integrase in the patient,

wherein said compound or a pharmaceutically acceptable salt thereof is for an administration to the patient

- when the patient has taken the food during a period between 1 hour prior to the administration of compound to the patient and 2 hours after the administration of compound to the patient; or

- during a period between 1 hour prior to the consumption of the food by the patient and 2 hours after the consumption of the food by the patient; and

wherein the administration of the compound is an oral administration once a day in a dose of 20 mg to 500 mg, and the administration of the ritonavir is an oral administration once a day in a dose between 20 mg to 200 mg.

13. The compound of claim 12, wherein the retrovirus integrase is HIV integrase.

14. The compound 6-(3-chloro-2-fluorobenzyl)-1-[(25')-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof, for use in combination with ritonavir or a pharmaceutically acceptable salt thereof and food taken by a patient, for the treatment or prophylaxis of a retrovirus infection in the patient,

wherein said compound or a pharmaceutically acceptable salt thereof is for an administration to the patient in a therapeutic effective amount

- when the patient has taken the food during a period between 1 hour prior to the administration of compound to the patient and 2 hours after the administration of the compound to the patient; or

- during a period between 1 hour prior to the consumption of the food by the patient and 2 hours after the consumption of the food by the patient; and

wherein the administration of the compound is an oral administration once a day in a dose of 20 mg to 500 mg, and the administration of the ritonavir is an oral administration once a day in a dose between 20 mg to 200 mg.

15. The compound of claim 14, wherein the retrovirus infection is an HIV infection.

16. The compound of any one of claims 10 to 15, wherein the administration of the ritonavir is an oral administration once a day in a dose of 50 mg.

17. The compound of any one of claims 10 to 15, wherein the administration of the ritonavir is an oral administration once a day in a dose of 100 mg.

18. The compound of any one of claims 10 to 15, wherein the administration of the ritonavir is an oral administration once a day in a dose of 200 mg.

19. The compound of any one of claims 10 to 18, wherein the administration of the compound is an oral administration once a day in a dose of 85 mg.

20. The compound of any one of claims 10 to 18, wherein the administration of the compound is an oral administration once a day in a dose of 150 mg.

21. The compound of any one of claims 10 to 18, wherein the administration of the compound is an oral administration once a day in a dose of 200 mg.

22. A kit comprising:

(1) a pharmaceutical composition in unit dosage form comprising 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4- dihydroquinoline-3-carboxylic acid, or a pharmaceutically acceptable

salt thereof in a dose between 20 mg to 500 mg, and a pharmaceutically acceptable carrier;

(2) ritonavir, or a pharmaceutically acceptable salt thereof in a dose between 20 mg to 200 mg;

(3) prescribing information; and

(4) a container; wherein the prescribing information includes advice regarding administering 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof with food.

23. The kit of claim 22, wherein the ritonavir is in a dose of 50 mg.

24. The kit of claim 22, wherein the ritonavir is in a dose of 100 mg.

25. The kit of claim 22, wherein the ritonavir is in a dose of 200 mg.

26. The kit of any one of claims 22 to 25, wherein the 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid is in a dose of 85 mg.

27. The kit of any one of claims 22 to 25, wherein the 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid is in a dose of 150 mg.

28. The kit of any one of claims 22 to 25, wherein the 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid is in a dose of 200 mg.

29. The compound 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a

pharmaceutically acceptable salt thereof, for use with food for increasing the bioavailability of the compound in a patient, the patient having taken the food during the period between 1 hour prior to the administration of the compound and 2 hours after the administration of the compound, wherein the compound is used in combination with ritonavir or a pharmaceutically acceptable salt thereof.

30. The compound 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof, for use with food for increasing the absorption of the compound in a patient, the patient having taken the food during the period between 1 hour prior to the administration of the compound and 2 hours after the administration of the compound, wherein the compound is used in combination with ritonavir or a pharmaceutically acceptable salt thereof.

31. The compound 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, for use with food for the inhibition of a retrovirus integrase in a patient, the patient having taken the food during the period between 1 hour prior to the administration of compound and 2 hours after the administration of the compound, wherein the compound is used in combination with ritonavir or a pharmaceutically acceptable salt thereof.

32. The compound of claim 31, wherein the retrovirus integrase is HIV integrase.

33. The compound 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount, for use with food for the treatment or prophylaxis of a retrovirus infection in a patient, the patient having taken the food during the period between 1 hour prior

to the administration of compound and 2 hours after the administration of the compound, wherein the compound is used in combination with ritonavir or a pharmaceutically acceptable salt thereof.

34. The compound of claim 33, wherein the retrovirus infection is an HIV infection.