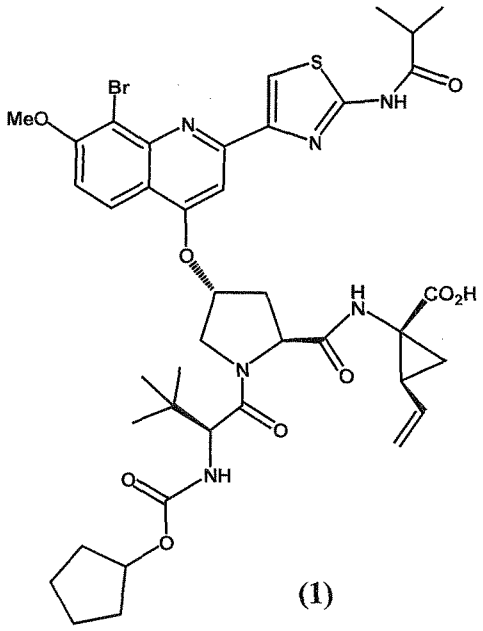
BRIEF SUMMARY

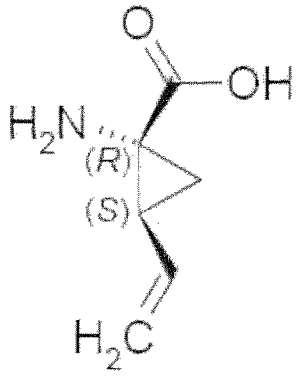
The present application is directed to various methods for controlling the level of the degradation product Compound X in liquid pharmacueutical compositions comprising Compound (1), or a pharmaceutically acceptable salt thereof, and to the resulting stabilized pharmacueutical compositions.

In a first aspect, there is provided a liquid pharmaceutical composition having an internal apparent pH of greater than 7 comprising a compound of formula (1):



(1)

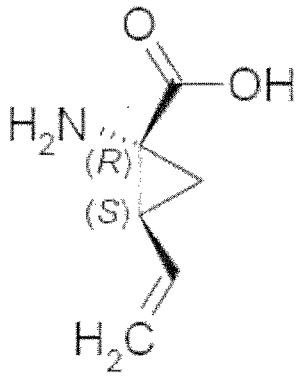
or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, wherein the amount of degradation product Compound X:



X

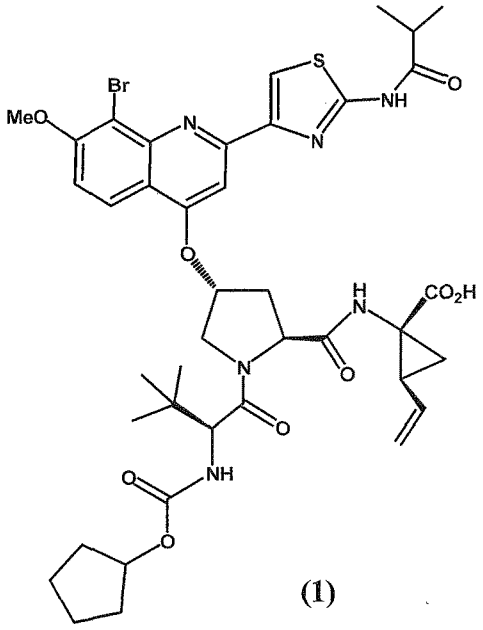
in the composition is below a level of ~~about~~ 400 μg. ~~when the composition contains a full daily dose of Compound (1) or pharmaceutically acceptable salt thereof in either single or multiple dosage units~~

The ~~In a second aspect, the~~ present application is directed to a method for controlling the level of degradation product Compound X:



X

in a liquid pharmaceutical composition comprising a Compound (1),



(1)

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, said method comprising one or more of the following:

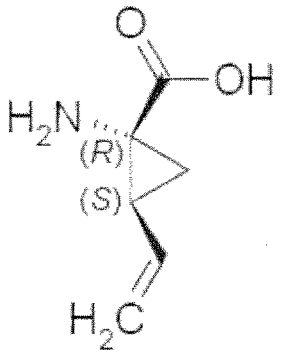
(a) drying said composition such that it has a water content of less than about 3.0 % w/w and storing the composition under conditions sufficient to maintain a water content of less than about 3.0 % w/w;

(b) storing said composition at a temperature of between about 2 and 8 degrees Celsius;

(c) adding a basifier to said composition to achieve an internal apparent pH of greater than about 7; or

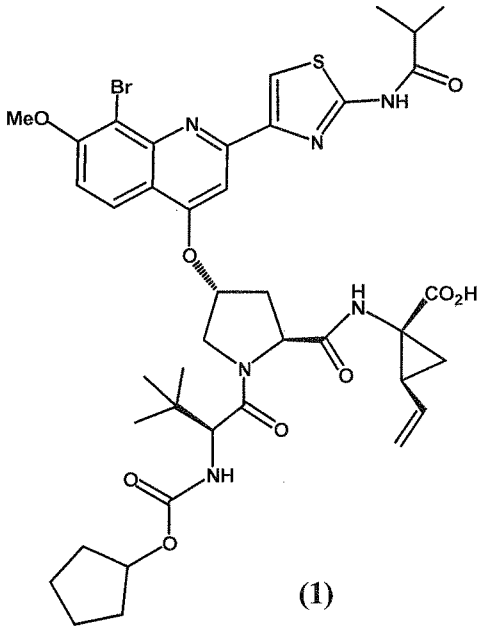
(d) if the liquid pharmaceutical composition is to contain water as an excipient material, preparing a first formulation pre-mixture comprising only Compound (1), or pharmaceutically acceptable salt thereof, and non-aqueous based excipients and a second formulation pre-mixture comprising water as an excipient, and then mixing the first and second formulation pre-mixtures to prepare the final formulation just prior to patient use.

In a second aspect, there is provided a method for controlling the level of degradation product Compound X:



X

in a liquid pharmaceutical composition comprising a compound of formula (1):



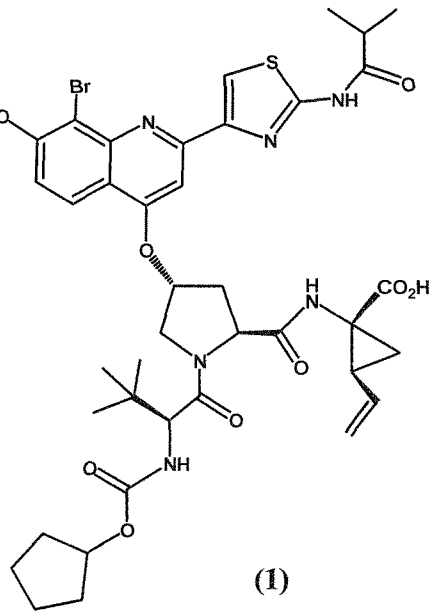
(1)

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, said method comprising adding a basifier to said composition to achieve an internal apparent pH of greater than 7.

Additional embodiments are directed to liquid pharmaceutical composition comprising a Compound (1), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, wherein the amount of degradation product Compound X in the composition is below a level of about 400 μg, or below a level of about 200 μg, or below a level of about 60 μg, or below a level of about 20 μg, when the composition contains a full daily dose of Compound (1) or pharmaceutically acceptable

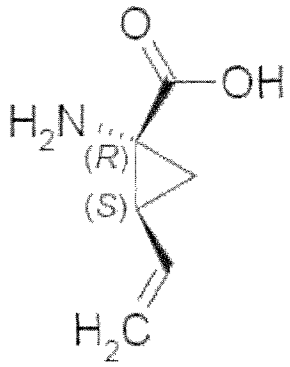
CLAIMS

1. A liquid pharmaceutical composition having an internal apparent pH of greater than 7 comprising a compound of formula (1):



(1)

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, wherein the amount of degradation product Compound X:



X

in the composition is below a level of ~~about~~ 400 µg ~~when the composition contains a full daily dose of Compound (1) or pharmaceutically acceptable salt thereof in either single or multiple dosage units~~.

2. A liquid pharmaceutical composition according to claim 1, wherein the composition has one or more of the following properties:

(a) a water content of less than ~~about~~ 3.0 % w/w;

(b) an internal temperature of between ~~about~~ 2 and 8 degrees Celsius~~;~~

~~(c) a internal apparent pH of greater than about 7~~.

~~3. A liquid pharmaceutical composition according to claim 2, wherein the composition has been stored for a period of at least 6 months under conditions sufficient to maintain one or more of the following properties:~~

~~(a) a water content of less than about 3.0 % w/w;~~

~~(b) an internal temperature of between about 2 and 8 degrees Celsius;~~

~~(c) a internal apparent pH of greater than about 7.~~

~~4. A liquid pharmaceutical composition according to any of claims 1 to 3, wherein the composition has a water content of less than about 3.0 % w/w.~~

~~5. A liquid pharmaceutical composition according to claim 4, wherein the composition is stored in moisture resistant packaging optionally further including a desiccant material.~~

~~6. A liquid pharmaceutical composition according to any of claims 1 to 3, wherein the composition has an internal temperature of between about 2 and 8 degrees Celsius~~

~~7. A liquid pharmaceutical composition according any of claims 1 to 3, wherein the liquid pharmaceutical composition is contained within a capsule and has one or both of the following properties: (a) a water content of less than about 3.0 % w/w; and (b) an internal temperature of between about 2 and 8 degrees Celsius.~~

~~8~~3. A liquid pharmaceutical composition according to claim ~~7~~1, wherein the liquid pharmaceutical composition is contained within a capsule shell material ~~is substantially~~ free of citric acid.

~~9~~4. A liquid pharmaceutical composition according to any of claims 1 to ~~8~~3, wherein the composition contains a fatty acid excipient.

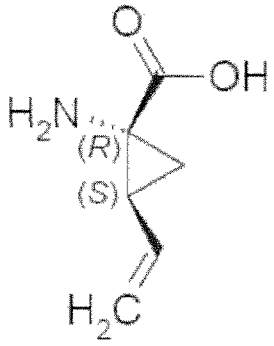
~~10. A liquid pharmaceutical composition according to claim 2, wherein the composition has an internal apparent pH of greater than about 7~~

~~11~~5. A liquid pharmaceutical composition according to claim ~~10~~2, wherein the composition is a water-containing solution ~~designed for oral administration and wherein the composition is optionally~~ stored at a temperature of between ~~about~~ 2 and 8 degrees Celsius.

~~12. A liquid pharmaceutical composition according to any of the preceding claims, wherein the composition is in the form one or more discrete dosage units contained within a packaging, wherein the packaging further comprises written instructions for use indicating that the composition should be stored at a temperature in the range of from 2 to 8 degrees Celsius~~

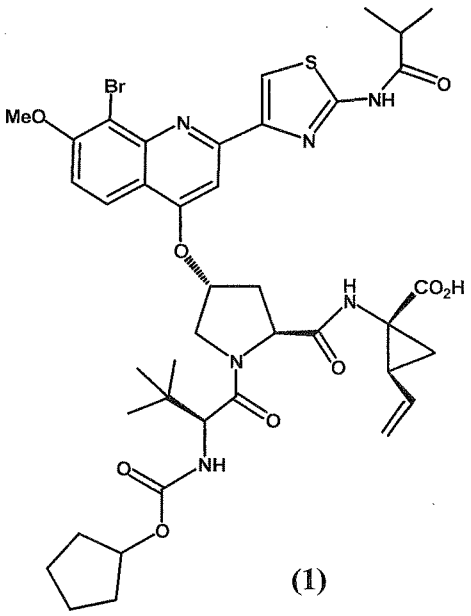
~~13. A liquid pharmaceutical composition according to claim 12, wherein the packaged dosage units are stored together with a temperature monitoring device to measure and record the environmental temperature during storage or shipment.~~

~~14~~6. A method for controlling the level of degradation product Compound X:



X

in a liquid pharmaceutical composition comprising a compound of formula (1):



(1)

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, said method comprising ~~one or more of the following:~~

~~(a) drying said composition such that it has a water content of less than about 3.0 % w/w and storing the composition under conditions sufficient to maintain a water content of less than about 3.0 % w/w;~~

~~(b) storing said composition at a temperature of between about 2 and 8 degrees Celsius;~~

~~(c)~~ adding a basifier to said composition to achieve an internal apparent pH of greater than ~~about~~ 7~~; or~~.

~~(d) if the liquid pharmaceutical composition is to contain water as an excipient material, first preparing a first formulation pre-mixture comprising only Compound (1), or pharmaceutically acceptable salt thereof, and non-aqueous based excipients and a second formulation pre-mixture comprising water as an excipient, and then mixing the first and second formulation pre-mixtures to prepare the final composition just prior to patient use.~~

7. A method according to claim 6, wherein the method further comprises one or more of the following:

(a) drying said composition such that it has a water content of less than 3.0 % w/w and storing the composition under conditions sufficient to maintain a water content of less than 3.0 % w/w;

(b) storing said composition at a temperature of between 2 and 8 degrees Celsius; or

(c) if the liquid pharmaceutical composition is to contain water as an excipient material, first preparing a first formulation pre-mixture comprising only Compound (1), or pharmaceutically acceptable salt thereof, and non-aqueous based excipients and a second formulation pre-mixture comprising water as an excipient, and then mixing the first and second formulation pre-mixtures to prepare the final composition just prior to patient use.

~~15. A method according to claim 14, wherein the resulting amount of degradation product Compound X in the composition is below a level of about 400 µg when the~~

~~composition contains a full daily dose of Compound (1) or pharmaceutically acceptable salt thereof in either single or multiple dosage units.~~

~~16. A method according to claim 15, wherein the composition, or in the case of (d) the first formulation pre-mixture, has been stored for a period of at least 6 months under conditions sufficient to maintain one or more of the following properties:~~

~~(a) a water content of less than about 3.0 % w/w;~~

~~(b) an internal temperature of between about 2 and 8 degrees Celsius;~~

~~(c) a internal apparent pH of greater than about 7.~~

~~17. A method according to any of claims 14 to 16, wherein said composition is dried such that it has a water content of less than about 3.0 % w/w and stored under conditions sufficient to maintain a water content of less than about 3.0 % w/w.~~

~~18. A method according to any of claims 14 to 17, wherein the composition is stored in moisture resistant packaging, optionally further including a desiccant material.~~

~~19. A method according to any of claims 14 to 18, wherein said composition is stored at a temperature of between about 2 and 8 degrees Celsius.~~

~~20~~8. A method according to ~~any of~~ claims ~~14 to 19~~7, wherein the liquid pharmaceutical composition is contained within a capsule and one or both of the following methods are applied to the capsule: (a) it is dried such that it has a water content of less than ~~about~~ 3.0 % w/w and stored under conditions sufficient to maintain a water content of less than ~~about~~ 3.0 % w/w; and/or (b) it is stored in at a temperature of between ~~about~~ 2 and 8 degrees Celsius.

~~21. A method according to claim 20, wherein the capsule shell material is substantially free of citric acid~~

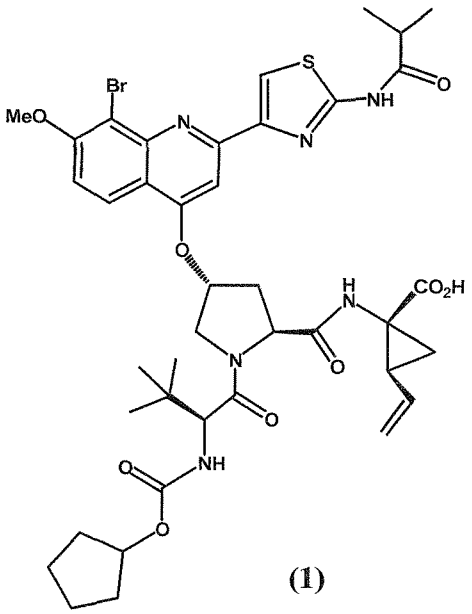
229. A method according to any of claims 14 6 to 218, wherein the composition contains a fatty acid excipient.

~~23. A method according to claim 14 comprising adding a basifier to said composition to achieve an internal apparent pH of greater than about 7.~~

~~24. A method according to claim 23, wherein the composition is a water-containing solution designed for oral administration and wherein the composition is optionally stored at a temperature of between about 2 and 8 degrees Celsius.~~

2510. A kit comprising:

(a) a first formulation pre-mixture comprising a compound of formula (1):



(1)

or a pharmaceutically acceptable salt thereof, and one or more non-aqueous based excipients; and

(b) a second formulation pre-mixture comprising water as an excipient, and optionally one or more additional excipients.