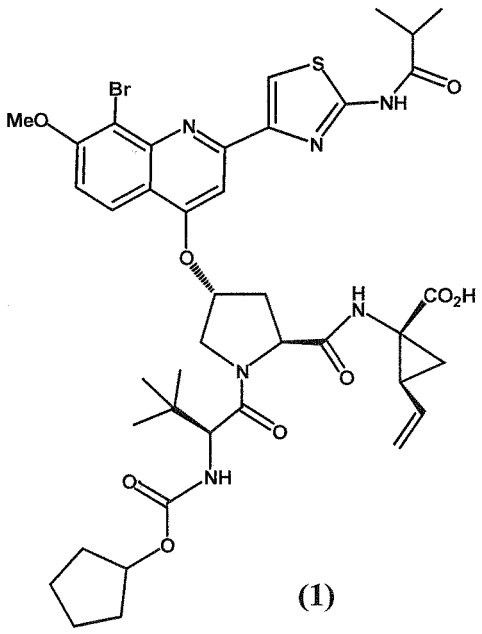
BRIEF SUMMARY ~~OF THE INVENTION~~

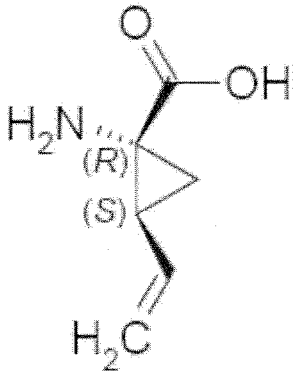
The present application is directed to various methods for controlling the level of the degradation product Compound X in liquid pharmacueutical compositions comprising Compound (1), or a pharmaceutically acceptable salt thereof, and to the resulting stabilized pharmacueutical compositions.

In a first aspect, there is provided a liquid pharmaceutical composition comprising a compound of formula (1):



(1)

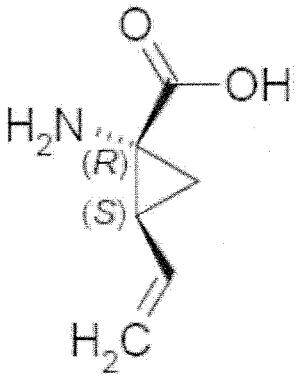
or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, wherein the amount of degradation product Compound X:



X

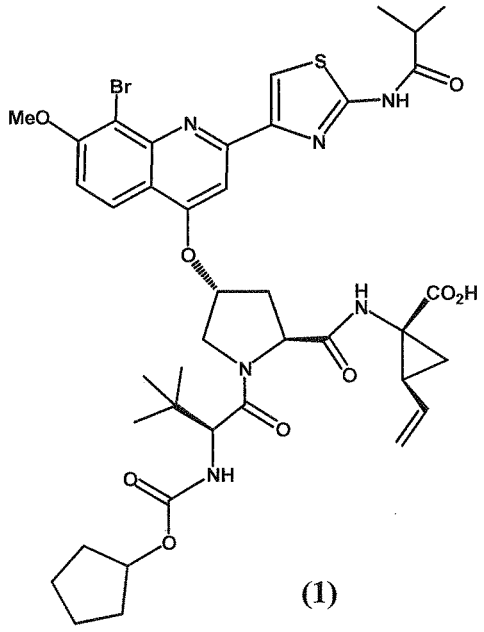
in the composition is below a level of about 400 µg when the composition contains a full daily dose of Compound (1) or pharmaceutically acceptable salt thereof in either single or multiple dosage units

In a ~~general embodiment~~second aspect, the present ~~invention~~ 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.

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

salt thereof in either single or multiple dosage units. And in a more specific embodiment, the composition has one or more of the following properties:

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

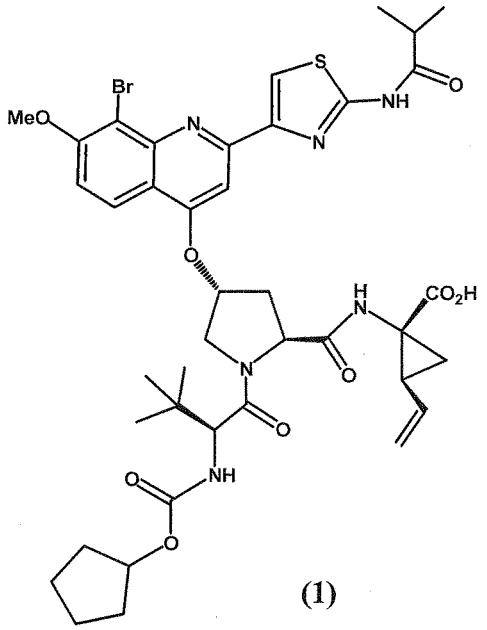
(b) an internal temperature of between about 2 and 8 degrees Celsius; or

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

Additional embodiments are directed to the above methods and compositions wherein the total resulting amount of degradation product in the composition is below a level of about 1.5 μg when the composition contains a full daily dose of Compound (1), or pharmaceutically acceptable salt thereof, in either single or multiple dosage units.

In a third aspect, there is provided 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

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the Compound X formation and stability over a 24 month period under different temperature conditions for a batch of 120 mg capsules of Compound (1) NA.

Figure 2 depicts the Compound X formation and stability over a 24 month period at room temperature for 120 mg capsules of Compound (1) NA having different levels of fill water content.

Figure 3 shows the combined effect of storage temperature and fill water content for 120 mg capsules of Compound (1) NA on Compound X formation and stability over a 12 month period.

Figure 4A is a graphic representation of a blister packaging system incorporating a desiccant in the product packaging, and the affect on water transmission.

Figure 4B shows a more detailed depiction of a capsule in an exemplary polymer blister packaging system and the water transmission in such system