MONOHYDRATE OF (1-{9-[4S,2R,3R,5R)-3,4-DIHYDROXY-5-(HYDROXYMETHYL) OXOLAN-2-YL]-6-AMINOPURIN-2-YL} PYRAZOL-4-YL)-N-METHYLCARBOXAMIDE

This application is a continuation of U.S. patent application Ser. No. 12/765,623, filed Apr. 22, 2010, now U.S. Pat. No. 8,106,183, issued on Jan. 31, 2012, which is a continuation of U.S. patent application Ser. No. 11/701,699, filed Feb. 2, 2007, now U.S. Pat. No. 7,732,595, issued on Jun. 8, 2010, which claims priority to U.S. Provisional Patent Application Ser. No. 60/801,857, filed May 18, 2006, and to U.S. Provisional Patent Application Ser. No. 60/765,114, filed Feb. 3, 2006, which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to a process for the large scale preparation of an A_{2A}-adenosine receptor agonist, and also relates to polymorphs of that compound, and to methods of isolating a specific polymorph.

BACKGROUND

Adenosine is a naturally occurring nucleoside, which exerts its biological effects by interacting with a family of adenosine receptors known as A_1, A_{2A}, A_{2B}, and A_3, all of which modulate important physiological processes. One of the biological effects of adenosine is to act as a coronary vasodilator; this result being produced by interaction with the A_{2A} adenosine receptor. This effect of adenosine has been found to be useful as an aid to imaging of the heart, where coronary arteries are dilated prior to administration of an imaging agent (for example thallium 201), and thus, by observation of the images thus produced, the presence or absence of coronary artery disease can be determined. The advantage of such a technique is that it avoids the more traditional method of inducing coronary vasodilation by exercise on a treadmill, which is clearly undesirable for a patient that has a coronary disease.

However, administration of adenosine has several disadvantages. Adenosine has a very short half life in humans (less than 10 seconds), and also has all of the effects associated with A_1, A_{2A}, A_{2B}, and A_3 receptor agonism. Thus the use of a selective A_{2A} adenosine receptor agonist would provide a superior method of producing coronary vasodilation, particularly one with a longer half life and few or no side effects.

A class of compounds possessing these desirable properties was disclosed in U.S. Pat. No. 6,403,567, the complete disclosure of which is hereby incorporated by reference. In particular, one compound disclosed in this patent, (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide, has been shown to be a highly selective A_{2A}-adenosine receptor agonist, and is presently undergoing clinical trials as a coronary vasodilator useful in cardiac imaging.

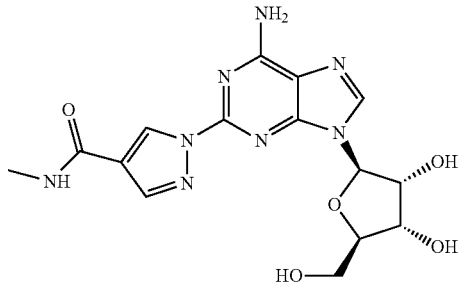
Given the heightened interest in this and similar compounds, it has become desirable to find new methods of synthesis that provide a convenient method for making large quantities of the material in good yield and high purity. The patent that discloses the compound of interest (U.S. Pat. No. 6,403,567) provides several methods for preparing the compound. However, although these methods are suited to small scale syntheses, all synthetic methods disclosed in the patent utilize protecting groups, which is undesirable for large scale syntheses.

Additionally, it was discovered that the desired product (that is (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide) is capable of existing in at least three different crystalline forms, the most stable of which is a monohydrate. This polymorph is stable under relative humidity stress conditions, up to its melting point. Accordingly, it is desirable that the final product produced in the new syntheses is obtained as the stable monohydrate.

SUMMARY OF THE INVENTION

Thus, it is an object of this invention to provide convenient syntheses for the large scale preparation of (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide, and polymorphs thereof, preferably as its monohydrate. Accordingly, in a first aspect, the invention relates to the preparation of a compound of the Formula I:

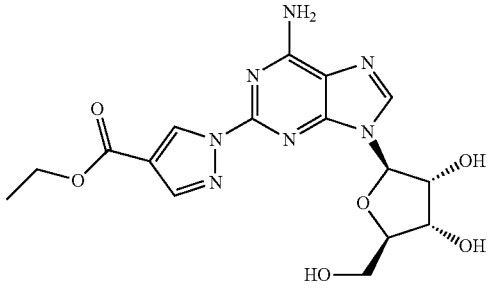
Formula I



comprising:

contacting a compound of the formula (3):

(3)



with methylamine.

In one embodiment the reaction is conducted in an aqueous solution of methylamine, initially at a temperature of about 0-5° C., followed by warming to about 50-70° C. Alternatively, the reaction is conducted as above but in a sealed pressure reactor.

In a second embodiment, the product is isolated as the pure monohydrate by dissolving the product in a solvent, for example dimethylsulfoxide, addition of purified water, filtering the slurry thus formed, washing the contents of the filter with water followed by ethanol, and drying the solid that remains under vacuum at a temperature that does not exceed 40° C.

In a second aspect, the invention relates to the preparation of a compound of the formula (3):