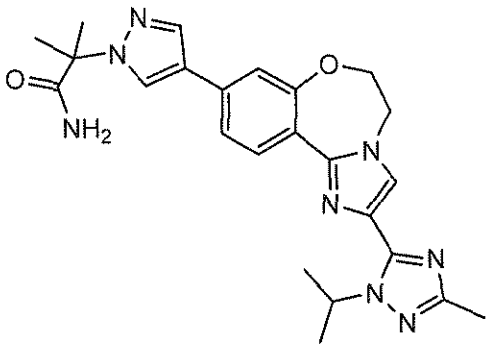
modulating or inhibitory agents would be expected to inhibit proliferation, reverse the repression of apoptosis and surmount resistance to cytotoxic agents in cancer cells (Folkes et al (2008) J. Med. Chem. 51:5522-5532; Yaguchi et al (2006) Jour. of the Nat. Cancer Inst. 98(8):545-556). The PI3K-PTEN-AKT signaling pathway is deregulated in a wide variety of cancers (Samuels Y, Wang Z, Bardellil A et al. High frequency of mutations of the PIK3CA gene in human cancers. (2004) Science; 304 (5670):554; Carpten J, Faber AL, Horn C. "A transforming mutation in the pleckstrin homology domain of AKT1 in cancer" (2007) Nature; 448:439–444).

GDC-0032, also known as 2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide, has potent PI3K activity (WO 2011/036280; US 8242104) and is being studied in patients with locally advanced or metastatic solid tumors.

SUMMARY ~~OF THE INVENTION~~

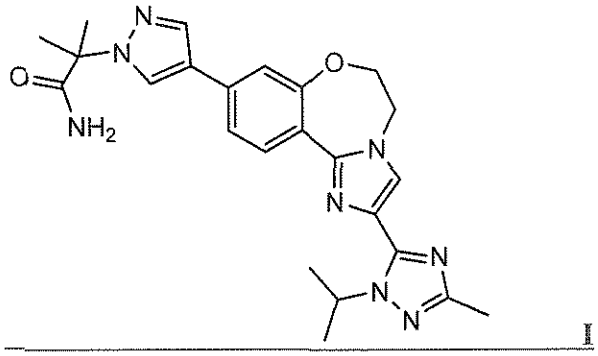
The ~~invention~~ disclosure relates to methods of making the PI3K inhibitor **I** (GDC-0032), named as 2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide, having the structure:



I (GDC-0032)

and stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof.

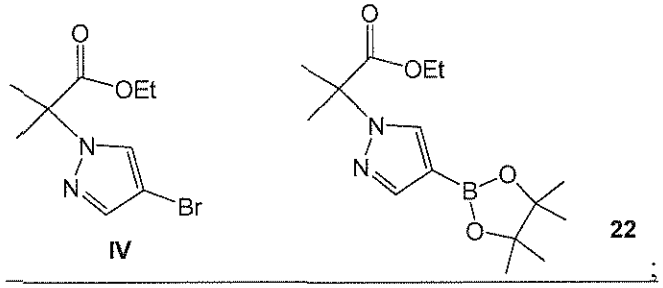
In one aspect, there is provided a process for preparing (2-(4-(2-(1-isopropyl-3-methyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)-1H-pyrazol-1-yl)-2-methylpropanamide **I**, having the structure:



I

and stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof, comprising:

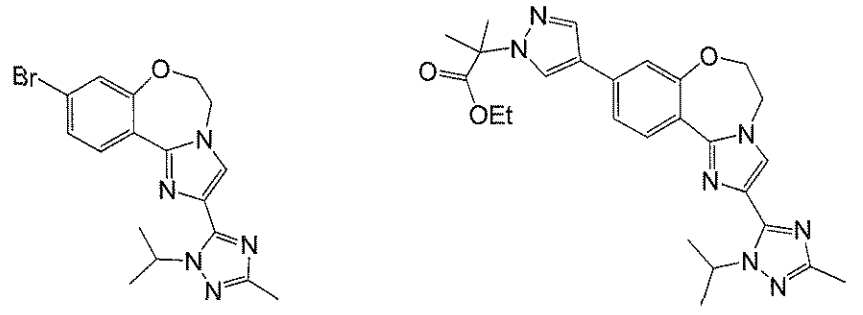
(a) reacting **IV** and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) to form **22**



IV **22**

;

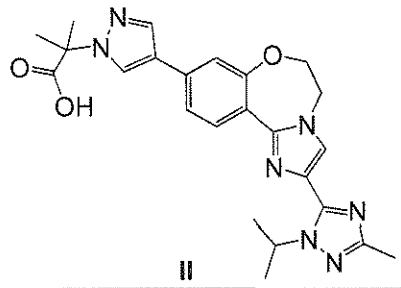
(b) reacting **22**, a palladium catalyst, and **III** to form **23**



III **23**

;

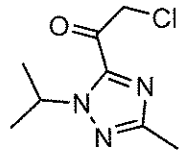
(c) reacting **23** with an aqueous basic reagent to form **II**



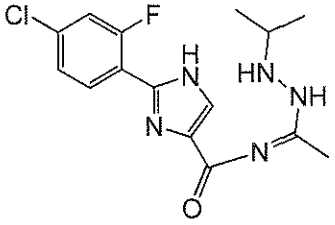
II ; and

(d) reacting **II** with an acyl activating reagent, followed by ammonia to give **I**.

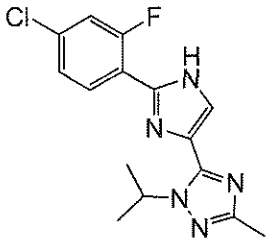
~~Another aspect of t~~The ~~invention~~ disclosure also includes novel intermediates useful for preparing GDC-0032 ~~and~~ having the structures:



13,



43, and



44 .

Hence, in another aspect, there is provided a compound selected from the structures 13, 26, 27, 30, 31, 33, 34, 36, 43 and 44 shown above.

DEFINITIONS

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the