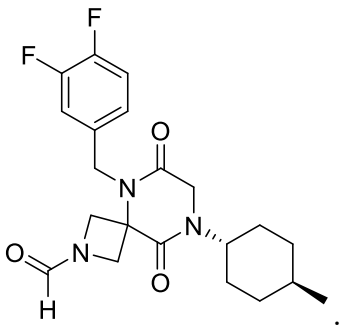
leads to recognized adverse effects that limit their use. These adverse effects include cell damage caused by an increased rate of energy expenditure, exacerbation of relaxation abnormalities, and potential arrhythmogenic side effects that may result from increased cytosolic Ca^{2+} and cyclic AMP concentrations in the inotropically stimulated myocardium. Given the limitations of current agents, new approaches are needed to improve cardiac function in HCM and HFpEF.

[0006] There remains a great need for agents that exploit new mechanisms of action and which may have better outcomes in terms of relief of symptoms, safety, and patient mortality, both short-term and long-term. New agents with an improved therapeutic index over current agents will provide a means to achieve these clinical outcomes. The selectivity of agents directed at the cardiac sarcomere (for example, by targeting cardiac myosin) has been identified as an important means to achieve this improved therapeutic index. 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde (compound 1) is a selective allosteric inhibitor of cardiac myosin that have little to no effect on smooth muscle myosin. Benefits of this compound include a wider therapeutic index, less impact on cardiac relaxation, better pharmacokinetics, and better safety and therefore it provides a potential treatment for cardiac diseases and conditions.

[0007] To move a drug candidate such as compound 1 to a viable pharmaceutical product, it is important to understand whether the drug candidate has polymorph forms, as well as the relative stability and interconversions of these forms under conditions likely to be encountered upon large-scale production, transportation, storage and pre-usage preparation. The ability to control and produce a stable polymorph with a robust manufacturing process can be key for regulatory approval and marketing. Large scale production processes to prepare compound 1 with high purity can be improved by using particular crystalline forms. Accordingly, there is a need for new crystalline forms of compound 1 with desirable chemical and physical stabilities, and formulations and uses of the same.

BRIEF SUMMARY

[0008] In one example, provided herein are polymorphs of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde (compound 1). In one aspect, the present disclosure refers to a crystalline form of the compound of Formula 1: .

[0009] In another example, provided herein are methods of preparing polymorphs of compound 1. In one aspect, the present disclosure refers to a method of preparing the crystalline form as disclosed herein, comprising (1) forming a mixture of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde and a solvent selected from the group consisting of an alcohol, water and mixtures thereof, and (2) cooling the mixture of step (1). In another aspect, the present disclosure refers to a method of preparing the crystalline form as disclosed herein, comprising (1) forming a mixture of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde and a first solvent; (2) heating the mixture of step (1) to a first temperature between 75 °C and 95 °C; (3) adding a second solvent to the mixture of step (2); (4) cooling the mixture of step (3) to a second temperature between 10 °C and 30 °C; and (5) filtering the mixture of step (4) to obtain the crystalline form.

[0010] In another example, provided herein are compositions containing the polymorphs of compound 1 as described herein. In one aspect, the present disclosure refers to a pharmaceutical composition comprising the crystalline form as disclosed herein, and a pharmaceutically acceptable excipient.

[0011] In another example, provided herein are methods of treating a heart disease in a subject in need thereof using polymorphs of compound 1. In one aspect, the present disclosure refers to use of the crystalline form as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of heart disease in a subject in need thereof. In another aspect, the present disclosure refers to use of the crystalline form as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of a disease or condition associated with hypertrophic cardiomyopathy, secondary left ventricular wall thickening, small left ventricular cavity and cavity obliteration, hyperdynamic left ventricular contraction, myocardial ischemia, or cardiac fibrosis, or a disease or condition selected from muscular dystrophies and glycogen storage diseases in a subject in need thereof. In yet another aspect, the present disclosure refers to use of the crystalline form as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the inhibition of cardiac sarcomere.

DESCRIPTION OF THE DRAWINGS

[0012] FIG. 1A shows an experimental X-ray powder diffraction (XRPD) pattern of crystalline Form I of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde.

[0013] FIG. 1B shows differential scanning calorimetry (DSC) and thermographic analysis (TGA) graphs of crystalline Form I of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde.

[0014] FIG. 1C shows a Gravimetric Vapor Sorption (GVS) graph of crystalline Form I of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde.

[0015] FIG. 1D shows an overlay of XRPD patterns of crystalline Form I of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde before and after storage for 7 days at 40°C/75% RH and 25°C/97% RH (from top to bottom: Form I after being stored for 7 days at 40°C/75% RH, Form I after being stored for 7 days at 25°C/97% RH, Form I before being stored for 7 days at 40°C/75% RH and 25°C/97% RH).

[0016] FIG. 1E shows XRPD patterns of crystalline Form I of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde before and after GVS measurement (top: after GVS; bottom: before GVS).

[0017] FIG. 2A shows an experimental XRPD pattern of crystalline Form II of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde.

[0018] FIG. 2B shows DSC and TGA graphs of crystalline Form II of 5-(3,4-difluorobenzyl)-8-((1r,4r)-4-methylcyclohexyl)-6,9-dioxo-2,5,8-triazaspiro[3.5]nonane-2-carbaldehyde.