[0005] Relapse rate post surgical intervention is high with >50% patients requiring further surgery within 10 years, many within 12 months. Consequently, patients suffer progressive loss of GI function and repeated resections can lead to major health complications such as short bowel syndrome.

[0006] Preclinical data has shown that Compound A exhibits strong anti-fibrotic therapeutic effects in multiple animal models of inflammatory bowel disease.

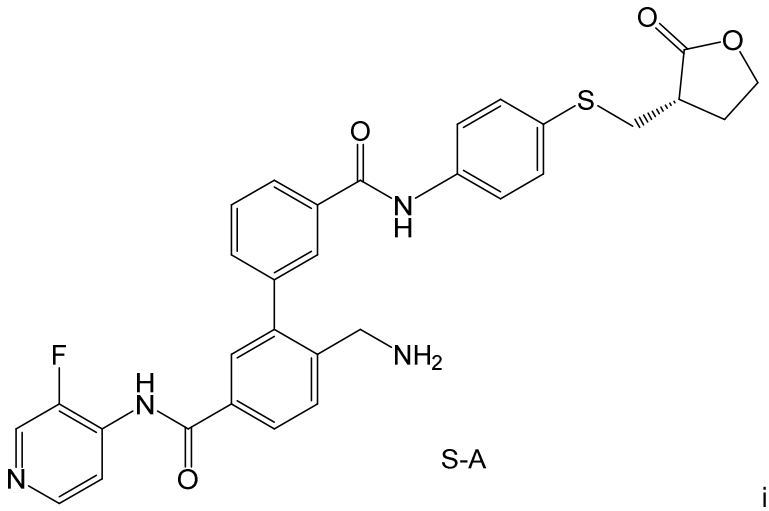
[0007] The freebase of Compound A has low stability.

[0008] It is an aim of certain embodiments of this invention to provide a stable crystalline form of Compound A. It is an aim of certain embodiments of this invention to provide a crystalline form of Compound A that is more stable than other crystalline forms.

[0009] Certain embodiments of this invention satisfy some or all of the above aims.

BRIEF SUMMARY OF THE DISCLOSURE

[0010] In a first aspect of the disclosure is provided the S-enantiomer (S-A) of compound A:



S-A

in substantially enantiopure form, or a pharmaceutically acceptable salt thereof. The S-enantiomer of compound A may be in the form of a freebase. The S-enantiomer of compound A may be in the form of a pharmaceutically acceptable salt. Said salt may be a crystalline salt form.

[0011] The inventors have found that the S-enantiomer of compound A exhibits lower inhibition of a wide-variety of alternative targets than the R-enantiomer. In particular, the S-enantiomer of compound A exhibits lower inhibition of a wide-variety of kinases other than ROCK than the R-enantiomer. This is particularly surprising as to date the inventors have

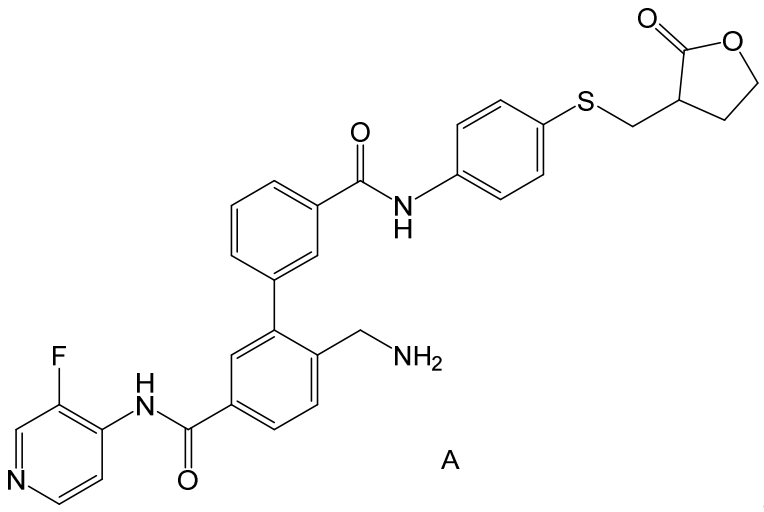
detected no statistically meaningful difference between the activities of the *S*-enantiomer and the *R*-enantiomer of compound **A** against kinases ROCK1 or ROCK2.

[0012] In addition, the S-enantiomer is less active than the R-enantiomer in a significant number of assays that are used to identify undesirable off target activity that may cause adverse effects in humans.

[0013] Where the disclosure relates to a pharmaceutically acceptable salt of Compound A, the salt will typically be an acid addition salt. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 1,5-naphthalenedisulfonate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

[0014] The salt may be selected from a hydrochloride salt and a succinate salt. The inventors have found that succinate and hydrochloride salts of compound A form crystals that are more stable than the freebase. The salt may be a succinate salt. The salt may be a hydrochloride salt. The inventors have found that crystalline forms of the hydrochloride salt of Compound A are particularly stable.

[0015] In a second aspect of the disclosure is provided a crystalline salt form of compound A:



A

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[0016] The freebase of Compound A has low chemical stability, particularly with respect to ester hydrolysis. The inventors have found that salt forms of Compound A exhibit improved stability relative to the freebase.

[0017] The disclosure relates to a pharmaceutically acceptable salt of Compound A. The salt will typically be an acid addition salt.

[0018] Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 1,5-naphthalenedisulfonate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

[0019] The salt may be selected from a hydrochloride salt and a succinate salt. The inventors have found that succinate and hydrochloride salts of compound A form crystals that are more stable than the freebase. The salt may be a succinate salt. The salt may be a hydrochloride salt. The inventors have found that crystalline forms of the hydrochloride salt of Compound A are particularly stable.

[0020] The crystalline salt form may be a solvate. The crystalline salt form may be a hydrate. The crystalline salt form may not be a solvate. The crystalline salt form may not be a hydrate.

[0021] Compound A contains a single chiral centre, at the point of attachment of the furanone ring to the rest of the molecule. In the crystal forms of the first aspect of the disclosure, Compound A may be a mixture of the two enantiomers. Compound A may be a racemic mixture of the two enantiomers. Compound A may be substantially in the form of a single enantiomer.

[0022] The single enantiomer may be the S-enantiomer (S-A):

at 2θ selected from 18.2± 0.2, 18.6± 0.2, 19.1± 0.2, 21.4± 0.2, 23.0± 0.2, 24.1± 0.2 and 25.8± 0.2 when measured using Cu radiation with a $K_{\alpha2}$ / $K_{\alpha1}$ ratio of 0.5. It may be that the salt is a succinate salt of a single enantiomer of compound A, characterised in that said crystalline salt form has an XRPD pattern with at least four peaks at 2θ selected from 18.2± 0.2, 18.6± 0.2, 19.1± 0.2, 21.4± 0.2, 23.0± 0.2, 24.1± 0.2 and 25.8± 0.2 when measured using Cu radiation with a $K_{\alpha2}$ / $K_{\alpha1}$ ratio of 0.5. It may be that the salt is a succinate salt of a single enantiomer of compound A, characterised in that said crystalline salt form has an XRPD pattern with peaks at 2θ selected from 18.2± 0.2, 18.6± 0.2, 19.1± 0.2, 21.4± 0.2, 23.0± 0.2, 24.1± 0.2 and 25.8± 0.2 when measured using Cu radiation with a $K_{\alpha2}$ / $K_{\alpha1}$ ratio of 0.5. It may be that said crystalline form has an XRPD pattern substantially as shown in Figure 2 when measured using Cu radiation with a $K_{\alpha2}$ / $K_{\alpha1}$ ratio of 0.5. This crystal form is known in this specification as Succinate Salt Form I. The single enantiomer may be the S enantiomer. The single enantiomer may be the R enantiomer.

[0029] HCl Salt Form I, HCl Salt Form II and Succinate Salt Form I are all chemically stable crystalline materials and are more stable than the freebase of compound A. HCl Salt Form I and HCl Salt Form II are more stable than Succinate Salt Form I. HCl Salt Form II is particularly beneficial as it is more crystalline than HCl Salt Form I and also more soluble at low pH.

[0030] Provided is a pharmaceutical formulation comprising the crystalline salt form of the first aspect or the compound A, or pharmaceutical salt thereof, of the second aspect. In a third aspect of the disclosure is provided a pharmaceutical composition comprising the compound A of the first aspect or of the crystalline salt form of the second aspect.

[0031] In one example is provided the crystalline salt form of the first aspect or the compound A, or pharmaceutical salt thereof, of the second aspect for use in medical treatment.

[0032] In one example is provided the crystalline salt form of the first aspect or the compound A, or pharmaceutical salt thereof, of the second aspect for use in treating a disease.

[0033] In one example is provided a method of treating a disease, the method comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline salt form of the first aspect or the compound A, or pharmaceutical salt thereof, of the second aspect.

[0034] In one example is provided the use of the crystalline salt form of the first aspect or the compound A, or pharmaceutical salt thereof, of the second aspect in the manufacture of a medicament for treating a disease.

[0035] The disease may be a fibrotic disease. In one aspect of the disclosure is provided the compound A of the first aspect or the crystalline form of the second aspect for treating a fibrotic disease.

[0036] The disease may be a disease of the gastrointestinal system.

[0037] The disease may be an inflammatory bowel disease.

[0038] The disease may be Crohn's disease, e.g.

fibrostenotic Crohn's disease

[0039] The disease may be a cancer, e.g. colorectal cancer.

[0040] The disease may be a skin disease, e.g. keloids or scleroderma.

[0041] The disease may be an ocular disease.

[0042] In yet another aspect of the disclosure is provided a method of making HCl crystalline salt form II of a single enantiomer of Compound A, the method comprising:

a) suspending a sample of HCl crystalline salt form I of a single enantiomer of Compound A in a solvent to form a suspension;

b) filtering the suspension to obtain HCl crystalline salt form II.

[0043] The solvent may be a mixture of solvents.

[0044] The solvent may be a polar aprotic organic solvent. The solvent may comprise a polar aprotic organic solvent. The solvent may be water. The solvent may comprise water. The solvent may be a polar protic organic solvent. The solvent may comprise a polar protic organic solvent.

[0045] The solvent may be a mixture of a polar aprotic organic solvent and a solvent selected from a polar protic organic solvent and water. The solvent may be a mixture of a polar aprotic organic solvent and water.

[0046] Suitable polar aprotic organic solvents include dimethylsulfoxide (DMSO), acetone, acetonitrile, ethers (e.g. THF, diglyme, ethylene glycol dimethyl ether, t-butyl-methyl ether), esters (e.g. ethyl acetate).

[0047] Suitable polar protic organic solvents include ethanol, methanol, isopropanol, ethylene glycol.

[0048] The solvent may comprise acetone. The solvent is preferably a mixture of acetone and water. The inventors have found that use of a mixture of acetone and water provides a cleaner product than other possible solvent systems.

[0049] The proportion of polar aprotic organic solvent (e.g. acetone) to water may be in the range 1:1 to 50:1 acetone:water by volume. The proportion of polar aprotic organic solvent (e.g. acetone) to water may be in the range 10:1 to 30:1 acetone:water by volume.