Pharmaceutical Compositions and their Uses

The present invention relates to pharmaceutical compositions, such as topical compositions, comprising certain imidazo[1,2-b]pyridazine compounds and the pharmaceutically acceptable salts and/or solvates of such compounds. The invention also relates to the processes for the preparation of the pharmaceutical compositions, and the uses of such compositions in treating diseases or conditions associated with tropomyosin-related kinase (Trk) activity. More specifically the invention relates to topical pharmaceutical compositions comprising compounds of Formula (I) or a pharmaceutically acceptable salts and/or solvates thereof, which are useful in inhibiting Trk.

Tropomyosin-related kinases (Trks) are a family of receptor tyrosine kinases activated by neurotrophins, a group of soluble growth factors including Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF) and Neurotrophin-3 (NT-3) and Neurotrophin-4/5 (NT-4/5). The Trk receptors include three family members TrkA, TrkB and TrkC that bind to and mediate the signal transduction derived from the Neurotrophins. NGF activates TrkA, BDNF and NT-4/5 activate TrkB and NT3 activates TrkC.

Tropomyosin-related kinases have been implicated in the following diseases: atopic dermatitis, psoriasis, eczema and prurigo nodularis, acute and chronic itch, pruritus, inflammation, cancer, restenosis, atherosclerosis, thrombosis, pruritus, lower urinary tract disorder, inflammatory lung diseases such as asthma, allergic rhinitis, lung cancer, psoriatic arthritis, rheumatoid arthritis, inflammatory bowel diseases such as ulcerative colitis, Crohn's disease, fibrosis, neurodegenerative disease, diseases disorders and conditions related to dysmyelination or demyelination, certain infectious diseases such as *Trypanosoma cruzi* infection, (Chagas disease), cancer related pain, chronic pain, neuroblastoma, ovarian cancer, colorectal cancer, melanoma, head and neck cancer, gastric carcimoma, lung carcinoma, breast cancer, glioblastoma, medulloblastoma, secratory breast cancer, salivary gland cancer, papillary thyroid carcinoma, adult myeloid leukaemia, tumour growth and metastasis and interstitial cystitis. (C. Potenzieri and B. J. Undem, Clinical & Experimental Allergy, 2012 (42) 8-19; Yamaguchi J, Aihara M, Kobayashi Y, Kambara T, Ikezawa Z, J Dermatol Sci. 2009;53:48-54; Dou YC, Hagstromer L, Emtestam L, Johansson O., Arch Dermatol Res. 2006;298:31-37; Johansson O, Liang Y, Emtestam L., Arch Dermatol Res. 2002;293:614-619; Grewe M, Vogelsang K, Ruzicka T, Stege H, Krutmann J., J Invest Dermatol. 2000;114:1108-1112;

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Problems with existing pharmaceutical compositions may be that they are unable to be formulated as ointments, aqueous gels, non-aqueous gels, and/or creams depending upon the specific application. They may also suffer from low chemical stability of the active pharmaceutical ingredient, and/or low physical stability of the composition. Further, they may deliver an active pharmaceutical composition via an oral or i.v. route, and therefore may not be suitable for topical dosing. Topical dosing may be preferably for treatment of certain diseases or conditions such as dermatitis.

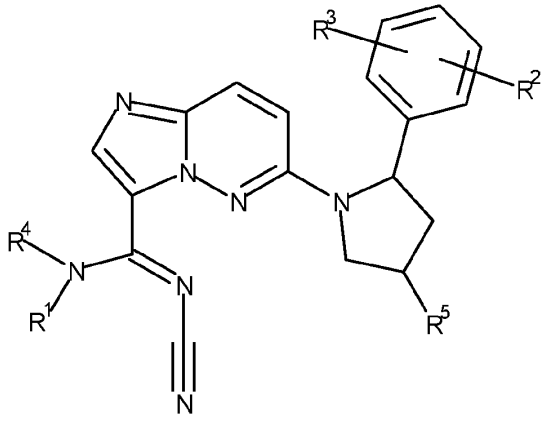
There is therefore a need for new topical pharmaceutical compositions comprising a Trk inhibitor that can be formulated as various types of topical formulations, that are stable when stored for long periods of time in terms of chemical and physical stability, do not irritate the skin when applied to a subject in need thereof, and which can deliver

therapeutic amounts of API to the dermis and epidermis. Other advantages of the claimed pharmaceutical compositions will also be apparent.

In a first aspect, the invention provides a topical pharmaceutical composition comprising (a) a compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof; and

(b) an excipient system,

wherein the compound of formula (I) is



(I)

wherein:

R^1 is selected from H, $-XR^7$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, and a C-linked 4-6 membered heterocycloalkyl containing 1 to 2 heteroatoms selected from N, O and S;

X is selected from $–CH_2–$;

R^2 is selected from H and $–SR^6$;

R^3 is selected from H and halo;

R^4 is selected from H and $(C_1\text{-}C_3)$alkyl

R^5 is selected from H and halo;

R^6 is methyl;

R^7 is phenyl substituted by hydroxy wherein the hydroxyphenyl is optionally further substituted by halo;

provided that if R^2 is H then R^1 is XR^7.

The compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate may be referred to herein as an “active pharmaceutical ingredient” (API). The topical pharmaceutical composition may be referred to as a “topical composition”, or for brevity as a “composition”.

The topical pharmaceutical composition of the present invention is a dosage form that is intended for topical application to deliver an API to a subject in need thereof, such as a human or other mammal. The topical composition may be applied to the skin or mucosa (e.g. the skin, the surface of the eye, or used nasally, vaginally, or rectally). The topical composition may be used for local and/or systemic pharmaceutical effects, however, it is preferred that the topical composition of the present invention is used for local effects.

The compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof may be present in the topical composition in an amount of from about 0.008% to about 30% by weight of the composition. The excipient system may be present in the topical composition in an amount of less than about 99.99 % by weight of the composition.

As used herein, the terms "about" means +/- 10%, preferably +/- 5%, more preferably +/- 2%, most preferably +/- 1%, of the associated value.

The amount of the compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof in the topical composition may depend on the amount required to be delivered to a subject to effectively treat or prevent a specific disease or condition. The amount of the compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof in the topical composition is preferably from about 0.01% to about 20%, more preferably from about 0.05% to about 5%, by weight of the composition. This may deliver to a subject a suitable amount of the compound of Formula (I) that is required to treat or prevent most diseases or conditions.

The topical pharmaceutical composition may take any suitable form, such as an ointment, aqueous gel, non-aqueous gel, cream, solution (such as aqueous solution), suspension, emulsion (such as microemulsion), dusting powder, dressing, foam, film, skin patch, wafer, implant, fibre, bandage, sprayable formulation e.g. for delivery by aerosol or the like. The exact form may be dependent upon the intended use. The components that make up the excipient system will dictate the form of the topical composition. The excipient system comprises one or more pharmaceutically acceptable excipients. The types of components that lead to the formation of each of the types of topical composition are well known to those skilled in the art. It is preferable that the topical pharmaceutical composition of the invention is an ointment, aqueous gel, non-aqueous gel, or cream, more preferably it is an ointment, non-aqueous gel, or cream.

The excipient system may comprise one or more carriers suitable for transdermal delivery of the compound of Formula (I) including absorbable pharmacologically acceptable solvents (such as those defined below) to assist delivery to therapeutically relevant compartments of the skin, such as the epidermis and dermis. For example, the topical pharmaceutical composition may be part of a transdermal devices in the form of a bandage comprising a backing member, a reservoir containing the topical pharmaceutical composition, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

A feature of the first aspect of the invention is that the excipient system comprises polyethylene glycol (PEG). It is preferable that the PEG selected from PEG 100 to PEG 900, and more preferably PEG 400. The inclusion of PEG as part of the excipient system may help to increase API loading in the composition. PEG may also increase chemical stability of the API in the composition, and physical stability of the composition, compared to other composition bases, particularly when a high purity grade of PEG 400 is used, such as super-refined PEG 400, such as that supplied by Croda. BHT or ascorbic acid, (preferably BHT) may also be included in the topical composition to further increase stability of the composition, particularly the stability of the API.

The PEG may be present in any suitable amount, such as from about 1% to about 60%, more preferably from about 5% to about 50%, most preferably from about 15% to about 50%, by weight of the composition.

The excipient system may comprise glycol, dialkyl glycol monoalkyl ether or a combination thereof. It is preferably that the glycol, dialkyl glycol monoalkyl ether or a combination thereof is present in an amount of from about 10% to about 70%, more preferably about 20% to about 55%, by weight of the composition.

As used herein, "glycol" means a chemical compound that comprise two hydroxyl groups. Such compounds include, but are not limited to, ethylene glycol, propylene glycol (propane-1,2-diol), and propane-1,3-diol, butylene glycol (such as 1,2-butanediol, 1,3-butanediol, 1,4-butanediol, 2,3-butanediol, 2-methyl-1,2-propanediol and 2-methyl-1,3-propanediol). It is preferred that the glycol is propylene glycol, i.e. propane-1,2-diol.

As used herein, "dialkyl glycol monoalkyl ether" includes, but is not limited to, diethylene glycol monoethyl ether (Transcutol P).

Without wishing to be bound by theory, is it believed that the combination of PEG (preferably PEG 400), Transcutol P and propylene glycol (propane-1,2-diol) in the excipient system leads to topical compositions that may benefit from a higher loading of API before they become saturated. For instance, such compositions may comprise the compound of Formula (I) in amounts in excess of at least about 0.2% by weight, preferably at least 1% by weight, more preferably at least 1.5% by weight, even more preferably 1.5% by weight, of the composition without crystallisation of API. This has the advantage of providing topical compositions that are able to deliver higher dosages of API to a subject in need thereof.

In view of the above, a particular feature of the first aspect of the invention is that the excipient system comprises

(A) PEG selected from PEG 100 to PEG 900, preferably PEG 400, and preferably wherein the PEG is present in an amount of from about 1% to about 60%, more preferably from about 5% to about 50%, most preferably from about 15% to about 50%, by weight of the composition;

(B) glycol in an amount of from about 1% to about 30%, preferably from about 5% to about 25%, more preferably from about 10% to about 20%, by weight of the composition, preferably the glycol is propylene glycol; and/or

(C) dialkyl glycol monoalkyl ether in an amount of from about 1% to about 40%, preferably from about 10% to about 35%, more preferably from about 15% to about 30%, by weight of the composition, preferably the dialkyl glycol monoalkyl ether is diethyl glycol monoethyl ether.

A particularly high loading of a compound of Formula (I) may be dissolved in these topical compositions before said compound crystallises.

As mentioned, the topical composition of the present invention may be an ointment, aqueous gel, non-aqueous gel, or cream dependent upon the components that form the excipient system, and that the skilled person will know the types of excipients to add to form each of those formulations. Notwithstanding this, particularly beneficial ointment-based topical compositions may comprise, as part of the excipient system, an oleaginous base, such as petroleum jelly, PEG selected from PEG 1000 to PEG 10000, yellow wax (such as that purified from the honeycomb of bees), and/or white wax (i.e. purified from yellow wax). The oleaginous base may be present in an amount of from about 15% to

about 30% by weight of the composition. In this regard, it is preferable that PEG is included and that it is PEG 3350 and/or PEG 4000.

Particularly beneficial non-aqueous gel-based topical compositions may comprise, as part of the excipient system, a gelling agent and a polyol. The gelling agent may be present in an amount of from about 0.5% to about 5%, preferably from about 1% to about 3%, by weight of the composition. Any suitable getting agent may be used, such as hydroxypropylcellulose MF (HPC MF) and/or hydroxypropylcellulose (HPC GF).

As used herein, "polyol" means a chemical compound that contains three or more hydroxyl groups. Such compounds include, but are not limited to, glycerol, butanetriol, pentanetirol, and polyethylene triols, in particular containing from 4 to 8 ethylene oxide units, and their mixtures. The polyol may be present in an amount of from about 1% to about 25% by weight of the composition. The preferred polyol is glycerol.

If an aqueous gel-based topical composition is required then, in addition to the gelling agent, water in an amount of from about 10% to about 30% by weight of the composition may be added. In such cases it is optional, and preferable, that a preservative, such as benzyl alcohol, is added to the excipient system. The preservative may be present in any suitable amount, however, an amount of from about 0.1% to about 5% by weight of the composition is typical.

Particularly beneficial cream-based topical compositions may comprise, as part of the excipient system, water, oil phase, emollient, emulsifier, and optionally a preservative. Preferably, the water may be present in an amount of from about 20% to about 30% by weight of the composition, the oil phase preferably in an amount of from about 0.5% to about 25% by weight of the composition, the emollient preferably in an amount of from about 5% to about 15% by weight of the composition, the emulsifier preferably in an amount of from about 2% to about 10% by weight of the composition. When present, the preservative may be present in an amount of from about 0.1% to about 5% by weight of the composition.

Particularly suitable emollients are cetostearyl alcohol and/or Span 60. A particularly suitable emulsifier is Tween, such as Tween 80. A particularly suitable preservative is benzyl alcohol or phenoxyethanol, preferably phenoxyethanol.

The skilled person will understand the breadth of compounds that may form the oil phase. Typical oil phases useful in the compositions of the invention are those that comprise one or more triglycerides, such as crodamol GTCC; liquid paraffin, or a combination thereof.

The topical compositions of the invention may have increased stability (both chemical and physical stability), compared to those of the prior art. Ointments and non-aqueous gels may exhibit further enhanced stability. Therefore, a particular feature of the first aspect of the invention is that the topical composition comprises an excipient system that comprises

(a) an oleaginous base, such as petroleum jelly, and/or PEG selected from PEG 1000 to PEG 10000 in an amount of from about 15% to 30% by weight of the composition, preferably the PEG is PEG 3350 or PEG 4000; or

(b) (i) a gelling agent in an amount of from about 0.5% to about 5%, preferably about 1% to about 3%, by weight of the composition, preferably the gelling agent is HPC MF or HPC GF; and

(ii) polyol, preferably glycerol, in an amount of from about 1% to about 25% by weight of the composition.

The excipient system, particular that of non-aqueous gel-based compositions, may comprise low molecular weight alcohol, i.e. C_1 to C_5 alcohol, such as methanol, ethanol, propanol, butanol, pentanol or a combination thereof. It is preferable that the low molecular weight alcohol is ethanol. When present, the low molecular weight alcohol may be in the excipient system in an amount of from about 2% to about 13% by weight of the composition.

The excipient system may comprise an antioxidant, preferably BHT or ascorbic acid. This may be present in any suitable amount, such as from about 0.01% to about 0.5%, preferably from about 0.05% to about 0.2%, by weight of the composition. The antioxidant may further increase stability of the topical composition, particularly the chemical stability of the composition.

The excipient system may comprise a UV filter. Any suitable UV filter may be used, such as octisalate. The UV filter may be present in any suitable amounts, such as from about 4% to about 8% by weight of the composition.

A specific ointment-based topical composition of the present invention comprises

(A) the compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof present in an amount of from about 1% to about 3% by weight of the composition;

(B) the excipient system which comprises

(i) PEG 400 in an amount of from about 35% to about 50% by weight of the composition;

(ii) propylene glycol in an amount of from about 5% to about 15% by weight of the composition;

(iii) diethyl glycol monoethyl ether in an amount of from about 15% to about 35% by weight of the composition;

(iv) PEG selected from PEG 1000 to PEG 10000 in an amount of from about 15% to 25% by weight of the composition, preferably the PEG is PEG 3350 or PEG 4000; and

(v) an antioxidant, preferably BHT, in an amount of from about 0.05% to about 0.5% by weight of the composition.

A specific non-aqueous gel-based topical composition of the present invention comprises

(A) the compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof present in an amount of from about 1% to about 3% by weight of the composition;

(B) the excipient system which comprises

(i) PEG 400, preferably SR PEG 400, in an amount of from about 25% to about 45% by weight of the composition;

(ii) glycerol in an amount of from about 1% to about 25% by weight of the composition;

(iii) propylene glycol in an amount of from about 5% to about 25% by weight of the composition;

(iv) diethyl glycol monoethyl ether in an amount of from about 22% to about 28% by weight of the composition; and

(v) low molecular weight alcohol, preferably ethanol, in an amount of from about 2% to about 13% by weight of the composition;

(vi) a gelling agent in an amount of from about 1% to about 3%, by weight of the composition, preferably the gelling agent is HPC MF or HPC GF; and

(vii) optionally an antioxidant, preferably BHT, in an amount of from about 0.05% to about 0.5% by weight of the composition.

A specific cream-based topical composition of the present invention comprises

(A) the compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof present in an amount of from about 0.05% to about 2% by weight of the composition;

(B) the excipient system which comprises

(i) PEG 400, preferably SR PEG 400, in an amount of from about 20% to about 28% by weight of the composition;

(ii) propylene glycol in an amount of from about 7% to about 17% by weight of the composition;

(iii) diethyl glycol monoethyl ether in an amount of from about 12% to about 18% by weight of the composition;

(iv) water in an amount of from about 17% to about 28% by weight of the composition;

(v) Tween 80 in an amount of from about 2% to about 10% by weight of the composition;

(vi) an oil phase comprising one or more triglycerides, such as crodamol GTCC; liquid paraffin, or a combination thereof in an amount of from about 0.5% to about 25%, preferably from about 3% to about 9%, by weight of the composition;

(vii) cetostearyl alcohol in an amount of from about 5% to about 15% by weight of the composition;

(viii) Span 60 in an amount of from about 0.2% to about 1.5% by weight of the composition;

(ix) optionally an antioxidant, preferably BHT or ascorbic acid, in an amount of from about 0.05% to about 0.5% by weight of the composition;

(x) optionally benzyl alcohol in an amount of from about 0.1% to about 5% by weight of the composition;

(xi) optionally a preservative, such as phenoxyethanol, in an amount of from about 0.1% to about 3% by weight of the composition; and

(xii) optionally a UV filter, such as octisalate.

The skilled person will understand the processes that may be used to form the topical pharmaceutical compositions of the invention. The topical compositions may be formed by any suitable method, such as bringing the ingredients together in a mixer and mixing them until a homogeneous composition is formed. One preferred method of forming a topical pharmaceutical composition of the invention involves combining the compound of Formula (I) with one or more of the components of the excipient system to dissolve said compound, and then adding the remaining components of the excipient system in a mixer. It may be preferable to mix the compound of Formula (I) with a mixture comprising PEG selected from PEG 100 to PEG 900, such as PEG 400, to dissolve said compound prior to the addition of the remaining components of the excipient system. In a more preferred method, the compound of Formula (I) may be mixed with a mixture comprising PEG 400, propylene glycol and dialkyl glycol monoalkyl ether, to dissolve said compound prior to mixing with the remaining components of the excipient system. Certain excipients, such as PEG 3350, may require heating (for instance to 65 °C) to liquefy the excipient so that it may be combined with the other components. The exact method of forming the topical pharmaceutical composition will be easily ascertained by the skilled person.

The topical pharmaceutical composition of the invention may comprise a further therapeutic agent in addition to the compound of Formula (I).

It is preferable that the topical pharmaceutical compositions of the invention have a pH that means that they are suitable for application to the skin or mucosa of a subject. The compositions may have a pH of from about 4.0 to about 10.0, preferably from about 4.5 to about 9.0, more preferable from about 5.0 to about 7.8.

The following are particular embodiments of the compound of Formula (I).

In one embodiment of the invention as defined anywhere above, R^1 is selected from $-XR^7$, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and a C-linked 4-6 membered heterocycloalkyl containing 1 to 2 heteroatoms selected from N, O and S.

In a further embodiment of the invention as defined anywhere above, R^1 is selected from (C_1-C_6)alkyl and (C_3-C_8)cycloalkyl

In an alternative further embodiment of the invention as defined anywhere above, R^1 is selected from $-XR^7$ and a C-linked 4-6 membered heterocycloalkyl containing 1 to 2 heteroatoms selected from N, O and S.

In a yet further embodiment of the invention as defined anywhere above, R^1 is (C_1-C_6)alkyl

In a yet further embodiment of the invention as defined anywhere above, R^1 is selected from $-XR^7$ and a C-linked 4-6 membered heterocycloalkyl containing 1 to 2 heteroatoms selected from N and O.

In another embodiment of the invention as defined anywhere above, R^2 is $-SR^6$.

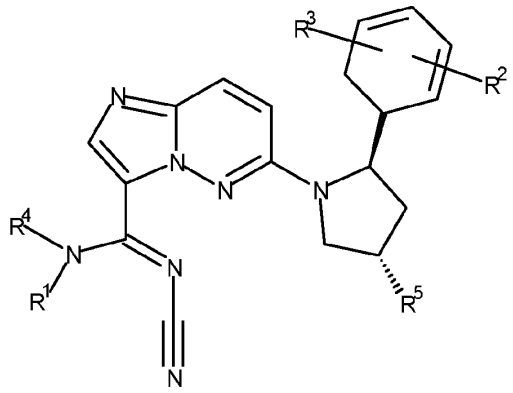
In another embodiment of the invention as defined anywhere above, R^3 is H or fluoro.

In another embodiment of the invention as defined anywhere above, R^4 is H.

In another embodiment of the invention as defined anywhere above, R^5 is H or fluoro.

In another embodiment of the invention as defined anywhere above, R^7 is phenyl substituted by hydroxy wherein the hydroxyphenyl is optionally further substituted by fluoro.

In a yet further embodiment, the compound of Formula (I) is a compound of Formula (Ia)



(Ia)

or a pharmaceutically acceptable salt and/or solvate thereof wherein R^1, R^2, R^3, $R^4$and R^5 are as defined anywhere hereinabove in respect of a compound of Formula (I).

In another embodiment, individual compounds of Formula (I) are those listed in the Examples section below.

In another embodiment of the invention, there is provided a topical pharmaceutical composition according to the invention which comprises a compound of Formula (I) selected from Examples 1, 2, 3, 4, 5, 6 and 7 or a pharmaceutically acceptable salt and/or solvate thereof.

In another embodiment of the invention, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) which is selected from:
N'-cyano-6-[2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3R)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
N'-cyano-6-[2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
N'-cyano-N-ethyl-6-[4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
N'-cyano-N-ethyl-6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
N-butyl-N'-cyano-6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
N'-cyano-N-cyclohexyl-6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide; and

N'-cyano-6-[2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboximidamide;
or a pharmaceutically acceptable salt and/or solvate thereof.

In another embodiment of the invention, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) which is selected from:
(Z)-N'-cyano-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3R)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
(Z)-N'-cyano-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
(Z)-N'-cyano-N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
(Z)-N'-cyano-N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
(Z)-N-butyl-N'-cyano-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
(Z)-N'-cyano-N-cyclohexyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide; and
(Z)-N'-cyano-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboximidamide;
or a pharmaceutically acceptable salt and/or solvate thereof.

In the embodiments mentioned herein, where only certain variables are defined, it is intended that the remainder of the variables are as defined in any embodiment herein. Thus, the invention provides for the combination of limited or optional definitions of variables.

The following terms as used herein are intended to have the following meanings:

"Optionally substituted" as used herein means the group referred to can be unsubstituted, or substituted at one or two or three positions by any one or any combination of the substituents listed thereafter.

As used herein, the term “halogen” or “halo” refers to fluoro, chloro, bromo, and iodo.

As used herein, the term “alkyl” refers to a fully saturated branched or unbranched hydrocarbon moiety having up to 20 carbon atoms. Unless otherwise provided, alkyl

refers to hydrocarbon moieties having 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 7 carbon atoms, or 1 to 4 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2- dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

"C_1-C_3 alkyl", "C_1-C_6 alkyl", "C_1-C_8 alkyl" and the like, as used herein, denotes an alkyl group that contains one to three, six or eight (or the relevant number) carbon atoms.

As used herein, the term "cycloalkyl" refers to saturated or unsaturated non-aromatic monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-12 carbon atoms. Unless otherwise provided, cycloalkyl refers to cyclic hydrocarbon groups having between 3 and 9 ring carbon atoms or between 3 and 7 ring carbon atoms. Exemplary monocyclic hydrocarbon groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl and the like. Exemplary bicyclic hydrocarbon groups include bornyl, indyl, hexahydroindyl, tetrahydronaphthyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl and the like.

"C_3-C_8-cycloalkyl" denotes a cycloalkyl group having 3 to 8 ring carbon atoms, for example a monocyclic group such as a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, or a bicyclic group such as bicycloheptyl or bicyclooctyl. Different numbers of carbon atoms may be specified, with the definition being amended accordingly.

As used herein, the term "alkoxy" refers to alkyl-O-, wherein alkyl is defined herein above. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, hexyloxy, cyclopropyloxy-, cyclohexyloxy- and the like. Typically, alkoxy groups have about 1-7, more suitably about 1-4 carbons.

As used herein, the term "heterocycloalkyl" refers to a saturated or unsaturated non-aromatic ring or ring system, *e.g.*, which is a 4-, 5-, 6-, or 7-membered monocyclic, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or 10-, 11-, 12-, 13-, 14- or 15-membered tricyclic ring system and contains at least one heteroatom selected from O, S and N, where the N and S can also optionally be oxidized to various oxidation states. The heterocyclic group

can be attached at a heteroatom or a carbon atom. A C-linked heterocyclic group can be attached at a carbon atom. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1, 4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, homomorpholine, and the like.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word “comprise”, or variations such as “comprises” or “comprising”, should be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The topical pharmaceutical compositions of the invention include compounds of Formula (I), and salts thereof as hereinafter defined, polymorphs, isomers and solvates thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labelled compounds of Formula (I).

The invention includes also pharmaceutically acceptable salts of a compound of Formula (I). A "pharmaceutically acceptable salt" is intended to mean a salt of a free acid or base of a compound represented by Formula (I),that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to a subject. See, generally, G.S. Paulekuhn, *et al.*, "Trends in Active Pharmaceutical Ingredient Salt Selection based on Analysis of the Orange Book Database", *J. Med. Chem.*, 2007, 50:6665-72, S.M. Berge, *et al.*, "Pharmaceutical Salts", *J Pharm Sci.*, 1977, 66:1 -19, and *Handbook of Pharmaceutical Salts, Properties, Selection, and Use*, Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, 2002.

Examples of pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for contact with the tissues of subjects without undue toxicity, irritation, or allergic response. A compound of Formula (I), may possess a sufficiently acidic group, a sufficiently basic group, or both types of functional groups, and accordingly react with a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride,

chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, , hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate , trifluoroacetate and trifluoromethylsulfonate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, trifluoromethylsulfonic acid, sulfosalicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

Examples of pharmaceutically acceptable salts particularly include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen- phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1 ,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates,

methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1 -sulfonates, naphthalene-2-sulfonates, and mandelates.

Additionally, any formula given herein is intended to refer also to hydrates, solvates, and polymorphs of such compounds, and mixtures thereof, even if such forms are not listed explicitly. A compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I) may be obtained as a solvate. Solvates include those formed from the interaction or complexation of compounds of the invention with one or more solvents, either in solution or as a solid or crystalline form. In some embodiments, the solvent is water and then the solvates are hydrates. In addition, certain crystalline forms of a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), may be obtained as co-crystals. In certain embodiments of the invention, a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I), may be obtained in a crystalline form. In other embodiments, a compound of Formula (I), may be obtained in one of several polymorphic forms, as a mixture of crystalline forms, as a polymorphic form, or as an amorphous form. In other embodiments, a compound of Formula (I), may convert in solution between one or more crystalline forms and/or polymorphic forms.

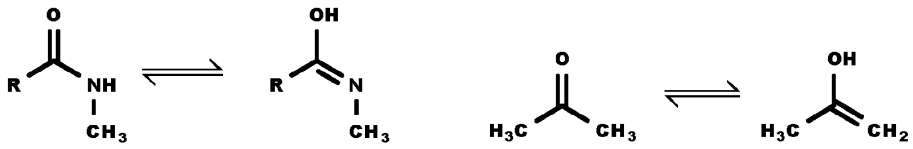
Compounds of the invention that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I).

Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of any formula given herein may have asymmetric centres and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof, are considered within the scope of the formula. Thus, any formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms,

and mixtures thereof. Furthermore, certain structures may exist as geometric isomers (i.e., *cis* and *trans* isomers), as tautomers, or as atropisomers.

Included within the scope of the claimed compounds of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of Formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base addition salts wherein the counter ion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Where a compound of Formula (I) contains for example, a keto or guanidine group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single compound may exhibit more than one type of isomerism. Examples of types of potential tautomerisms shown by the compounds of the invention include; amide ⇔ hydroxyl-imine and keto ⇔ enol tautomersims:



Cis/*trans* isomers may be separated by conventional techniques well known to those skilled in the art, for example, by chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or other derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on a resin with an asymmetric stationary phase and with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% ethanol, typically from 2 to 20%. Concentration of the eluate affords the enriched mixture.

Mixtures of stereoisomers may be separated by conventional techniques known to those skilled in the art (see, for example, "*Stereochemistry of Organic Compounds*" by E L Eliel (Wiley, New York, 1994)).

As used herein, the term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included. Tautomers are one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another. Examples of tautomers include but are not limited to those compounds defined in the claims.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 %

enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Since the compounds are intended for use in topical pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1 %, more suitably at least 5% and preferably from 10 to 59% of a compound of Formula (I).

When both a basic group and an acid group are present in the same molecule, the compounds of the present invention may also form internal salts, e.g., zwitterionic molecules.

Pharmaceutically acceptable prodrugs of a compound of Formula (I) may also be used in the topical compositions and be used in treatment methods employing such pharmaceutically acceptable prodrugs. The term "prodrug" means a precursor of a designated compound that, following administration to a subject, yields the compound *in vivo* via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to the compound of Formula (I)). A "pharmaceutically acceptable prodrug" is a prodrug that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to the subject. Illustrative procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "*Design of Prodrugs*", ed. H. Bundgaard, Elsevier, 1985.

A prodrug is an active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis, metabolism and the like, into a compound of Formula (I) following administration of the prodrug to a subject. The compounds of the present invention may themselves be active and/or act as prodrugs which convert *in vivo* to active compounds. The suitability and techniques involved in making and using pro-drugs are well known by those skilled in the art. Prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. See *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). Generally, bioprecursor prodrugs are compounds, which are inactive or have low activity compared to the corresponding active drug compound, that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity. Carrier prodrugs are drug compounds that contain a transport moiety, *e.g.*, that improve uptake and/or localized delivery to a site(s) of action.

Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, and any released transport moiety is acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, *e.g.*, certain polymers or other moieties, such as cyclodextrins. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement

in drug formulation (*e.g.*, stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of (a) hydroxyl groups with lipophilic carboxylic acids (e.g., a carboxylic acid having at least one lipophilic moiety), or (b) carboxylic acid groups with lipophilic alcohols (e.g., an alcohol having at least one lipophilic moiety, for example aliphatic alcohols).

Exemplary prodrugs are, *e.g.*, esters of free carboxylic acids and *S*-acyl derivatives of thiols and *O*-acyl derivatives of alcohols or phenols, wherein acyl has a meaning as defined herein. Suitable prodrugs are often pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, *e.g.*, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the ω(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester and the like conventionally used in the art. In addition, amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by -esterases *in vivo* releasing the free drug and formaldehyde (Bundgaard, *J. Med. Chem.* 2503 (1989)). Moreover, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard, *Design of Prodrugs*, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

The present invention also relates to pharmaceutically active metabolites of a compound of Formula (I), which may also be used in the methods of the invention. A "pharmaceutically active metabolite" means a pharmacologically active product of metabolism in the body of a compound of Formula (I), or salt thereof. Prodrugs and active metabolites of a compound may be determined using routine techniques known or available in the art. See, e.g., Bertolini, *et al.*, *J Med Chem.* 1997, 40, 201 1 -2016; Shan, *et al.*, *J Pharm Sci.* 1997, 86 (7), 765-767; Bagshawe, *Drug Dev Res.* 1995, 34, 220-230; Bodor, *Adv Drug Res.* 1984, 13, 224-331 ; Bundgaard, Design of Prodrugs (Elsevier Press, 1985); and Larsen, *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen, *et al.*, eds., Harwood Academic Publishers, 1991).

Any formula given herein is also intended to represent unlabelled forms as well as isotopically labelled forms of the compounds. Isotopically labelled compounds have structures depicted by the formulas given herein except that one or more atoms are

replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, and fluorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, respectively. Such isotopically labelled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques (such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)) including drug or substrate tissue distribution assays, or in radioactive treatment of subjects. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in PET studies for examining substrate receptor occupancy. In particular, an ^{18}F or ^{11}C labelled compound may be particularly preferred for PET studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. Certain isotopically-labelled compounds of formula (I) for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Isotopically labelled compounds of Formula (I) and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the Formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000

(90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Exemplary compounds useful in the topical composition of the invention, and the related methods will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Unless otherwise specified, the variables are as defined above in reference to Formula (I). Reactions may be performed between the melting point and the reflux temperature of the solvent, and preferably between 0 °C and the reflux temperature of the solvent. Reactions may be heated employing conventional heating or microwave heating. Reactions may also be conducted in sealed pressure vessels above the normal reflux temperature of the solvent.

All of the derivatives of Formula (**I**) can be prepared by the procedures described in the general methods presented below or by routine modifications thereof. The present invention also encompasses any one or more of these processes for preparing the derivatives of Formula (**I**), in addition to any novel intermediates used therein.

The routes below, including those mentioned in the Examples and Preparations, illustrate methods of synthesising the compound of Formula (I). The skilled person will appreciate that the compound of the invention, and intermediates thereto, could be made by methods other than those specifically described herein, for example by adaptation of the methods described herein, for example by methods known in the art. Suitable guides to synthesis, functional group interconversions, use of protecting groups, etc., are for example: "*Comprehensive Organic Transformations*" by RC Larock, VCH Publishers Inc. (1989); "*Advanced Organic Chemistry*" by J. March, Wiley Interscience (1985); "*Designing Organic Synthesis*" by S Warren, Wiley Interscience (1978); "*Organic*

Synthesis – The Disconnection Approach" by S Warren, Wiley Interscience (1982); "*Guidebook to Organic Synthesis*" by RK Mackie and DM Smith, Longman (1982); "*Protective Groups in Organic Synthesis*" by TW Greene and PGM Wuts, Fifth Ed, John Wiley and Sons, Inc. (2014); and "*Protecting Groups*" by PJ, Kocienski, Georg Thieme Verlag (1994); and any updated versions of these standard works.

In addition, the skilled person will appreciate that it may be necessary or desirable at any stage in the synthesis of compounds of the invention to protect one or more sensitive groups, so as to prevent undesirable side reactions. In particular, it may be necessary or desirable to protect phenol or carboxylic acid groups. The protecting groups used in the preparation of the compounds of the invention may be used in a conventional manner. See, for example, those described in *'Greene's Protective Groups in Organic Synthesis*' by Theodora W Greene and Peter G M Wuts, fifth edition, (John Wiley and Sons, 2014), in particular Chapter 3 ("*Protection for Phenols*") and Chapter 5 ("*Protection for the Carboxyl group")*, incorporated herein by reference, which also describes methods for the removal of such groups.

In the general synthetic methods below, unless otherwise specified, the substituents are as defined above with reference to the compound of Formula (I), above.

Where ratios of solvents are given, the ratios are by volume.

The skilled person will appreciate that the experimental conditions set forth in the schemes that follow are illustrative of suitable conditions for effecting the transformations shown, and that it may be necessary or desirable to vary the precise conditions employed for the preparation of the compound of Formula (I). It will be further appreciated that it may be necessary or desirable to carry out the transformations in a different order from that described in the schemes, or to modify one or more of the transformations, to provide the desired compound of the invention.

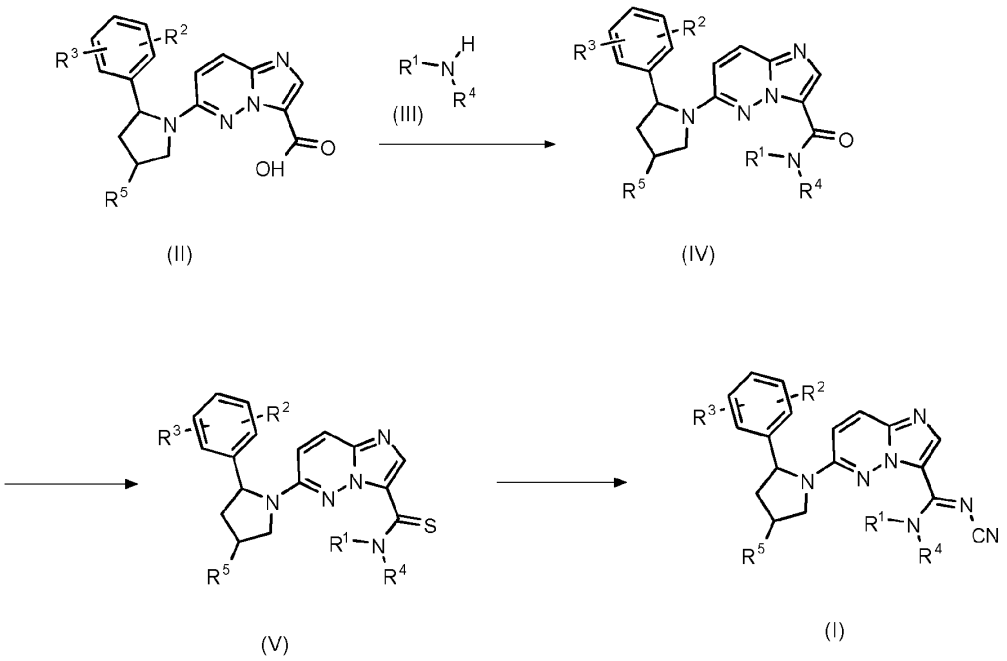
Compounds prepared according to the schemes described above may be obtained as single enantiomers, diastereomers, or regioisomers, by enantio- , diastero-, or regiospecific synthesis, or by resolution. Compounds prepared according to the schemes above may alternately be obtained as racemic (1:1) or non-racemic (not 1:1) mixtures or as mixtures of diastereomers or regioisomers. Where racemic and non-racemic mixtures of enantiomers are obtained, single enantiomers may be isolated using conventional separation methods known to one skilled in the art, such as chiral chromatography,

recrystallization, diastereomeric salt formation, derivatization into diastereomeric adducts, biotransformation, or enzymatic transformation. Where regioisomeric or diastereomeric mixtures are obtained, single isomers may be separated using conventional methods such as chromatography or crystallization.

The compounds of the invention may be prepared by any method known in the art for the preparation of compounds of analogous structure. In particular, the compound of the invention can be prepared by the procedures described by reference to the Schemes that follow, or by the specific methods described in the Examples, or by similar processes to either.

The skilled person will appreciate that the experimental conditions set forth in the schemes that follow are illustrative of suitable conditions for effecting the transformations shown, and that it may be necessary or desirable to vary the precise conditions employed for the preparation of the compound of Formula (I). It will be further appreciated that it may be necessary or desirable to carry out the transformations in a different order from that described in the schemes, or to modify one or more of the transformations, to provide the desired compound of the invention

A compound of Formula (I) may be prepared from compounds of Formulae (II), (III), (IV) and (V) as illustrated by **Scheme 1**.



Scheme 1

The amine of Formula (III) is commercially available or may be prepared by analogy to methods known in the literature.

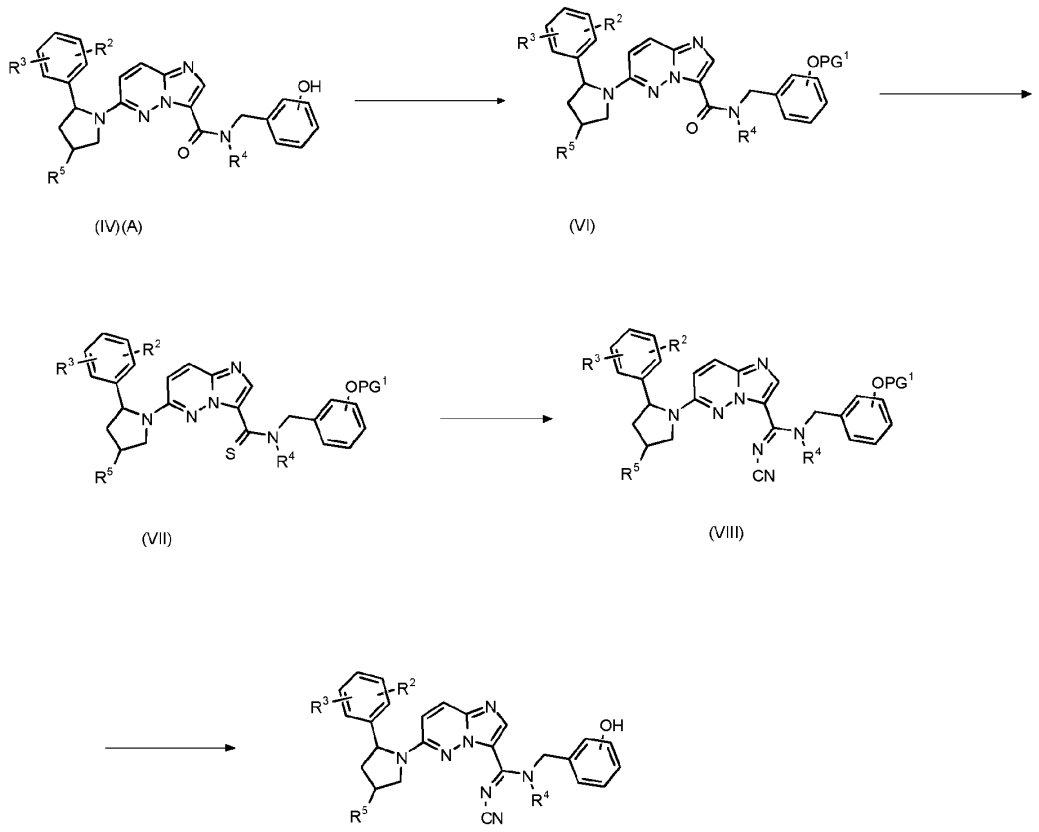
The compound of Formula (IV) may be prepared by an amide bond formation of the acid of Formula (II) and the amine of Formula (III) in the presence of a suitable coupling agent and organic base in a suitable polar aprotic solvent. Preferred conditions, comprise the reaction of the acid of Formula (II) with the amine of Formula (III) in the presence of HATU, in the presence of a suitable organic base, typically DIPEA in a suitable solvent, such as DMF at room temperature.

The compound of Formula (V) may be prepared by the thionation of the amide of Formula (IV) using a suitable thionating agent, such as phosphorous pentasulfide or Lawesson's reagent in a suitable solvent. Preferred conditions comprise treatment of the amide of Formula (IV) with Lawesson's reagent in a suitable solvent such as toluene at elevated temperature, such as 100°C.

The compound of Formula (I) may be prepared by treatment of the thioamide of Formula (V) with cyanamide in the presence of a suitable metal catalyst, optionally in the presence of an organic base such as Et_3N or DIPEA in a suitable solvent. Preferred

conditions comprise, treatment with cyanamide, in the presence of mercury (II) chloride with Et_3N in a solvent such as DMF at room temperature. Alternatively, this transformation may be achieved by treatment of the thioamide of Formula (V) with cyanamide in the presence of a suitable silver catalyst, such as AgOAc in a solvent such as MeOH at room temperature.

Compounds of Formula (I)(A), wherein R^1 is XR^7, may be prepared from compounds of Formulae (IV)(A), (VI), (VII) and (VIII) as illustrated in **Scheme 2.**



Scheme 2

PG^1 is a suitable phenol protecting group, typically a silyl ether group and preferably TBDMS.

The compound of Formula (VI) may be prepared by the protection of the compound of Formula (IV)(A), using a suitable silyl protecting group in a suitable solvent. Preferred

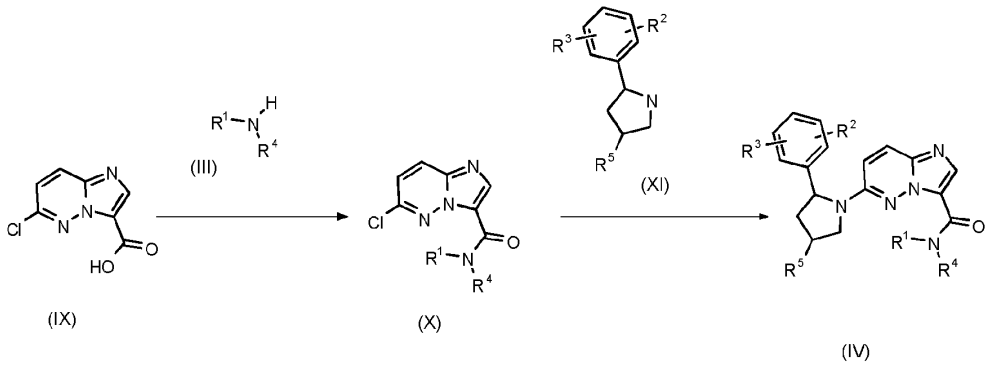
conditions comprise treatment of the compound of Formula (IV)(A) with TBDMSCl, in the presence of excess imidazole in DMF at room temperature.

The compound of Formula (VII) may be prepared by the thionation of the compound of Formula (VI) as described in Scheme 1, for the preparation of the compound of Formula (V).

The compound of Formula (VIII) may be prepared by the treatment of the compound of Formula (VII) with cyanamide as described in Scheme 1, for the preparation of the compound of Formula (I).

The compound of Formula (I)(A) may be prepared by the deprotection of the compound of Formula (VIII) under acidic conditions, or in the presence of a tetra-alkylammonium fluoride salt in a suitable solvent. Preferred conditions, comprise treatment of the compound of Formula (VIII) with TEAF in MeCN at elevated temperatures, such as 50°C.

A compound of Formula (IV) may be prepared from the compounds of Formulae (III), (IX), (X) and (XI) as illustrated by **Scheme 3**.



Scheme 3

A compound of Formula (IV)(A)(a compound of Formula (IV) wherein R^1 is XR^7) may also be prepared as illustrated by **Scheme 3**.

The compound of Formula (IX) is commercially available.

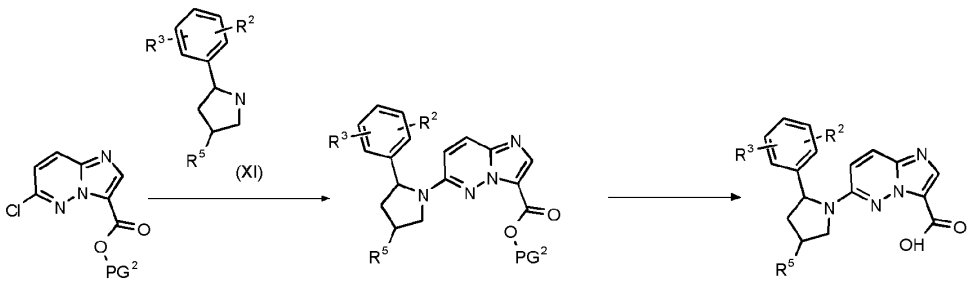
Compounds of Formula (XI) are commercially available or may be prepared in chiral form by analogy with the methods described by Brinner et. al. (*Org. Biomol. Chem.*, 2005,3, 2109-2113) or Fan et.al. (WO2012 034091). Alternatively, compounds of Formula (VIII)

may be prepared by analogy with the methods described by Huihui et. al. (J. Am. Chem. Soc., 2016, 138, 5016-5019). Alternatively they may be prepared as described in **Scheme 5** below.

The amide of Formula (X) may be prepared by an amide bond formation of the acid of Formula (IX) and the amine of Formula (III) in the presence of a suitable coupling agent and organic base, as previously described in Scheme 1. Preferred conditions comprise reaction of the acid of Formula (IX) with the amine of Formula (III) in the presence of HATU, in the presence of a suitable organic base, typically DIPEA, in DMF at room temperature.

The compound of Formula (IV) may be prepared by treatment of the compound of Formula (X) with the amine of Formula (XI), in the presence of an inorganic base in a polar aprotic solvent at elevated temperature. Preferred conditions comprise treatment of the compound of Formula (X) with the amine of Formula (XI) in the presence of KF in a solvent such as DMSO at elevated temperature, typically 130°C.

A compound of Formula (**II**) may be prepared from compounds of Formulae (XI), (XII), and (XIII) as illustrated by **Scheme 4**.



(XII) (XIII) (II)

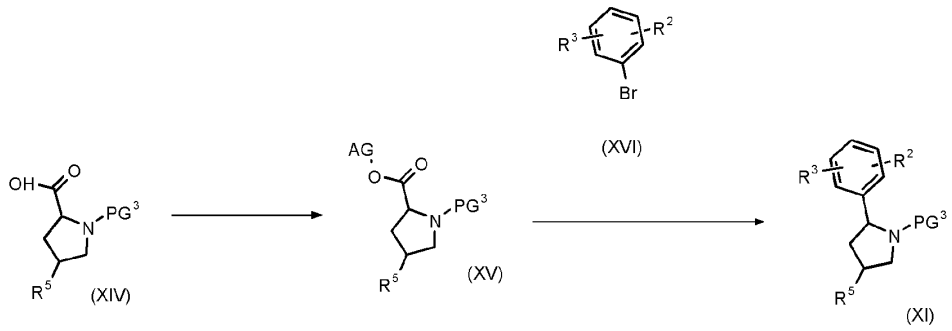
Scheme 4

PG^2 is a carboxyl protecting group, typically a C_1-C_3 alkyl, preferably, ethyl.

The compound of Formula (XII) is commercially available or may be prepared by analogy with the methods described by Fan et.al. (WO2012 034091). The compound of Formula (XIII) may be prepared by treatment of the chloride of Formula (XII) with the amine of Formula (XI), in the presence of an inorganic base in a polar aprotic solvent at elevated

temperature. Preferred conditions comprise treatment of the chloride of Formula (XII) with the amine of Formula (XI) in the presence of KF in a solvent such as DMSO at elevated temperature, typically 130°C. The compound of Formula (II) may be prepared by the hydrolysis of the ester of Formula (XIII) under suitable acidic or basic conditions in a suitable aqueous solvent. Preferred conditions comprise the treatment of the ester of Formula (XIII) with excess NaOH or KOH in aqueous EtOH at room temperature.

A compound of Formula (XI) may be prepared from compounds of Formulae (XIV) (XV) and (XVI) as illustrated by **Scheme 5**



Scheme 5

PG^3 is an N-protecting group, typically a carbamate or benzyl group, preferably Boc.

AG is an activating group, typically a phthalimide, benzotriazole or 7-azabenzotriazole and preferably a phthlimide group. The compound of Formula (XIV) is commercially available or may be prepared by analogy with known literature methods. The compound of Formula (XVI) is commercially available or may be prepared by analogy with known literature methods. The compound of Formula (XV) may be prepared by a coupling reaction of the acid of Formula (XIV) with AG-OH in the presence of a suitable coupling agent. Preferred conditions comprise reaction of the acid of Formula (XIV) with AG-OH in the presence of DCC in EtOAc at room temperature. The compound of Formula (XI) may be prepared in a two-step Fe or Ni catalysed cross coupling reaction from the bromide of Formula (XVI), via the formation of an intermediate Grignard reagent then treatment with the compound of Formula (XV), following the methods of Toriyama et al (J. Am. Chem. Soc. 2016, 138, 11132-35). Preferred conditions comprise treatment of the bromide of Formula (XVI) with Mg turnings in the presence of DIBAL-H and LiCl in THF at between 0°C and room temperature to prepare the intermediate Grignard reagent. Treatment with the compound of Formula (XV) with a suitable Fe catalyst such as $Fe(acac)_3$ or $Ni(Br)_2$ in a suitable polar aprotic solvent(s) such as THF and DMPU at low temperature, typically 0°C.

The above general schemes may be used to prepare compounds of the present invention. The desired specific compounds can be prepared by selecting the appropriate starting materials, reactants and reaction conditions.

The starting materials and reagents in the above scheme are all either available commercially or can be prepared following literature precedents.

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as *'Greene's Protective Groups in Organic Synthesis*' by Theodora W Greene and Peter G M Wuts, fifth edition, (John Wiley and Sons, 2014), in particular Chapter 3 ("*Protection for Phenols*") and Chapter 5 ("*Protection for the Carboxyl group")*, incorporated herein by reference, which also describes methods for the removal of such groups , in J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of Organic Chemistry), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (Amino acids, Peptides, Proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of Carbohydrates: Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (i.e. without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (*e.g.* by enzymatic cleavage).

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known to those skilled in the art. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, *e.g.* the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate

or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, *e.g.* by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, *e.g.* a free carboxy group and a free amino group, may be formed, *e.g.* by the neutralisation of salts, such as acid addition salts, to the isoelectric point, *e.g.* with weak bases, or by treatment with ion exchangers. Salts can be converted into the free compounds in accordance with methods known to those skilled in the art. Metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known to those skilled in the art into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by *e.g.* medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, *e.g.* using chromatographic methods, distribution methods, (re-) crystallization, and the like.

The following applies in general to all processes mentioned herein before and hereinafter.

All the above-mentioned process steps can be carried out under reaction conditions that are known to those skilled in the art, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, *e.g.* in the H+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for

example in a temperature range of from about -100 ºC to about 190 ºC, including, for example, from approximately -80 ºC to approximately 150 ºC, for example at from -80 to -60 ºC, at room temperature, at from -20 to 40 ºC or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described under "Additional process steps".

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or *N*-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, methycyclohexane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

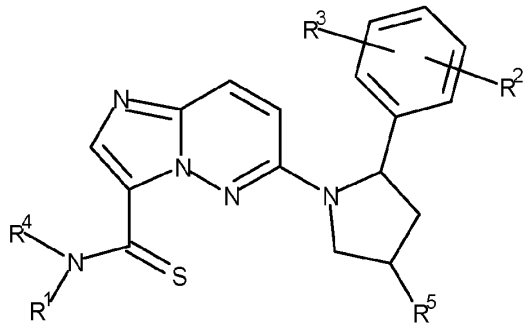
The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21).

As a further aspect of the present invention, there is also provided a process for the preparation of compounds of Formula I or a pharmaceutically acceptable salt and/or solvate thereof.

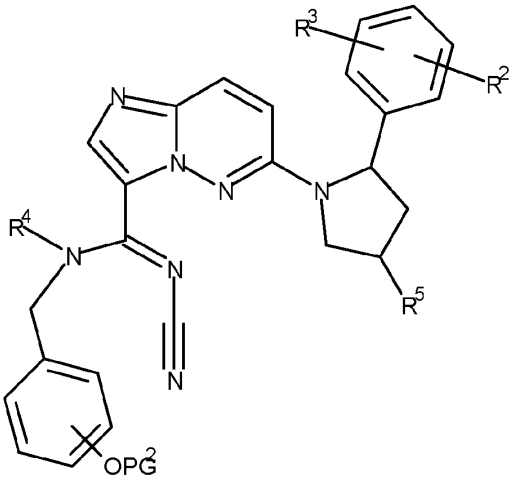
According to a further aspect of the invention there is provided a process of preparing a compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, which is to be included in the claimed topical composition, comprising the step of:
treatment of a thioamide of Formula (V)



(V)

with cyanamide in the presence of a suitable metal catalyst, optionally in the presence of an organic base such as Et_3N or DIPEA in a suitable solvent, wherein R^1, R^2, R^3, R^4 and R^5 are as defined anywhere hereinabove in respect of a compound of Formula I.

According to a further aspect of the invention there is provided a process of preparing a compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, which is to be included in the claimed topical composition, wherein R^1 is XR^7 comprising the step of:
deprotection of the compound of Formula (XIII)



(XIII)

under acidic conditions, or in the presence of an tetraalkylammonium fluoride salt in a suitable solvent, wherein R^2, R^3, R^4 and R^5 are as defined anywhere hereinabove in respect of a compound of Formula I and PG^2 is a protecting group.

The most preferred compound of Formula (I) is that of example 3.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of Formula (I) and intermediates can also be converted into each other according to methods generally known to those skilled in the art.

According to a further aspect, the present invention provides novel intermediate compounds described herein, which may be useful in the claimed topical compositions.

The compounds of Formula (I) exhibit valuable pharmacological properties, e.g. Trk modulating properties, e.g. as indicated in in vitro and in vivo tests as provided in the next sections and are therefore indicated for therapy.

Having regard to their ability to inhibit Trk activity, the compounds of Formula (I), hereinafter alternately referred to as "agents", are useful in the treatment or prevention of a condition or disorder which is mediated by Trk.

In particular, the compounds of Formula (I), and therefore the claimed topical compositions, are useful for the treatment of disorders or conditions mediated by the high affinity neurotrophin receptors TrkA, TrkB and TrkC, and the actions of their cognate neurotrophin ligands - NGF, BDNF/NT-4/5, NT-3 - on these receptor tyrosine kinases. Particularly the compounds are useful for treating or preventing conditions of skin (dermal) inflammation and itch (pruritus) that are mediated by the high affinity neurotrophin receptors TrkA, TrkB and TrkC, and associated with inflammation and nerve hypersensitivity, in particular atopic dermatitis.

Infiltration and activation of immune cells in the skin (including T-cell, mast cells, eosinophils) play a key role in inflammatory skin pathologies (Ilkovitch D. J Leukoc Biol. 2011, 89(1):41-9; Kim et al, Int J Mol Sci. 2016,17(8)). Trk A, B, and C and their cognate endogenous neurotrophin ligands have been demonstrated to play a role in the immunological and neurogenic mechanisms associated with skin pathologies (Botchkarev et al, J Invest Dermatol. 2006, 126(8):1719-27.; Truzzi et al, Dermatoendocrinol. 2011, 3(1):32-6; Minnone et al, Int J Mol Sci. 2017, 11;18(5)), and mediate inflammatory functions of skin resident immune cells, particularly those involved in atopic dermatitis pathology (Raap et al, Clin Immunol. 2005, (5):419-24), including T-cells (Sekimoto et al, Immunol Lett. 2003, 88(3):221-6; Matsumura et al, J Dermatol Sci. 2015,78(3):215-23), mast cells (Quarcoo et al, J Occup Med Toxicol. 2009, Apr 22;4:8.), and eosinophils (Raap et al, J Allergy Clin Immunol. 2005, 115:1268-75; Raap et al, Clin Exp Allergy.2008, 38(9):1493-8).

NGF, BDNF, NT-3 and NT-4/5 levels are higher in the lesional skin cells and plasma of atopic dermatitis patients compared to normal subjects and levels correlate with disease severity (Yamaguchi et al, J Dermatol Sci. 2009, 53(1):48-54; Toyoda et al, Br J Dermatol 2002, 147:71–79; Raap et al, J Allergy Clin Immunol. 2005, 115:1268-75; Raap et al, Allergy. 2006, 61(12):1416-8). Trk levels are also upregulated in atopic dermatitis lesional skin cells (Dou et al, Arch Dermatol Res. 2006, (1):31-7; Raap et al, Clin Exp Allergy. 2008, 38(9):1493-8). In addition, the high affinity neurotrophin receptors and their endogenous ligands, in particular Trk A/NGF have been shown to sensitize primary afferent nerves and mediate dermal hyperinnervation, thereby contributing to peripheral itch sensitization and pruritus in particular in atopic dermatitis (Tominaga et al, J Dermatol. 2014, 41(3):205-12; Roggenkamp D et al, J Invest Dermatol 2012, 132: 1892–1900; Grewe et al, J Invest Dermatol 2000, 114:1108–1112). In preclinical mouse models of atopic dermatitis, inhibition of Trk signalling with small molecule compounds

that have Trk inhibitory activity, reduced dermatitis and scratching behaviour, with concomitant decreases in nerve fibres in the epidermis (Takano et al, Br J Dermatol. 2007, 156(2):241-6; Narayanan et al, PLoS One. 2013, 26;8(12)).

The compounds of Formula (I), and therefore the claimed topical compositions, may be used for the treatment or prevention of skin pathologies or conditions including diseases of dermatitis such as atopic dermatitis (eczema), contact dermatitis, allergic dermatitis; diseases of pruritus such as urticaria (Rössing et al, Clin Exp Allergy. 2011, 41(10):1392-9), Cutaneous T-cell lymphoma (CTCL) -associated pruritus including Sezary syndrome (Suga et al, Acta Derm Venereol. 2013, 93(2):144-9; Saulite et al, Biomed Res Int. 2016 doi: 10.1155/2016/9717530); Psoriasis (Raychaudhuri et al, Prog Brain Res. 2004, 146:433-7); diseases of skin pain and neuropathy (Hirose et al, Pain Pract. 2016, 16(2):175-82; Wang et al, J Neurosci. 2009, 29(17):5508-15).

In particular, conditions or disorders which are mediated by Trk, in particular Trk A, B, and C, include, but are not limited to: diseases of pruritus and itch; autoimmune diseases of the skin; diseases of skin pain and neuropathy; and diseases of dermatitis.

Diseases of pruritus and itch include, but are not limited to: skin diseases, eczematous ; dermatitis, atopic; eczema ;dermatitis, contact ; dermatitis, allergic contact ; dermatitis, irritant ; dermatitis, photoallergic ; dermatitis, phototoxic ; psoriasis ; pruritus; pruritus ani; pruritus, hereditary localized; Sjogrens syndrome associated pruritis; idiopathic pruritus; sclerosis multiplex pruritus; prurigo nodularis; brachioradial pruritus; acute itch; chronic itch; diabetes pruritus; iron deficiency anaemia pruritus; polycythemia vera pruritus; graft-versus-host-disease ; uraemic pruritus; cholestatic pruritus; pruritic urticarial papules and plaques of pregnancy; pemphigoid gestationis; senile pruritus; HIV associated pruritus; shingles; herpes zoster oticus; larva migrans; tinea corporis; tungiasis; exanthema; Fox-Fordyce disease; skin diseases, parasitic; skin diseases, bacterial; cutaneous T-cell; lymphoma-associated pruritus; Sezary syndrome; mycosis fungoides; colorectal cancer; melanoma; head and neck cancer; drug eruption pruritus (iatrogenic); drug reactions; urticarial; vibratory urticarial; physical urticarial; familial cold urticarial; allergic urticarial; dermatographia; dermatitis herpetiformis; Grover disease.

Autoimmune diseases of the skin include, but are not limited to: autoimmune disease of skin and connective tissue; autoimmune disease with skin involvement; autoimmune bullous skin disease; pemphigoid, bullous.

Diseases of skin pain and neuropathy include but are not limited to: diabetic neuropathies ; neuralgia; painful neuropathy ; nerve compression syndromes ; neuritis; sensory peripheral neuropathy ; alcoholic neuropathy ; radiculopathy ; complex regional pain syndromes ; polyneuropathy due to drug; plantar nerve lesion; polyradiculopathy; sciatic neuropathy;trigeminal neuralgia.

Diseases of dermatitis include, but are not limited to: skin diseases, eczematous ; dermatitis, atopic ; eczema ; dermatitis, contact; dermatitis, allergic contact ; dermatitis, irritant ; dermatitis, photoallergic ; dermatitis, phototoxic; chronic irritative hand dermatitis; dermatitis, occupational ; fiberglass dermatitis ; dermatitis, toxicodendron ; eczema, dyshidrotic; eczematous dermatitis of eyelid; allergic contact dermatitis of eyelid; hand and foot dermatitis; digital dermatitis; dermatitis, exfoliative; radiodermatitis; dermatitis herpetiformis ; juvenile dermatitis herpetiformis ; autoimmune progesterone dermatitis ; dermatitis, seborrheic; pityriasis lichenoides; blepharitis; nummular dermatitis ; Seborrhea-Like Dermatitis with Psoriasiform Elements; infective dermatitis associated with HTLV-1; psoriasis; generalized pustular psoriasis; skin diseases, papulosquamous; parapsoriasis; keratosis; hyperkeratosis, epidermolytic; skin sarcoidosis; skin atrophy; erythematosquamous dermatosis; poikiloderma with neutropenia; erythema multiforme; angiolymphoid hyperplasia with eosinophilia; keratosis palmoplantaris striata 3; acne vulgaris; lamellar ichthyosis; lichen disease; lichen planus; actinic lichen planus; lichen planus, oral ; lichen planus follicularis ; lichen sclerosus et atrophicus ; lichen nitidus; lichen sclerosus; lichen simplex chronicus; scleroderma, limited; keratosis linearis with ichthyosis congenita and sclerosing keratoderma; erythrokeratoderma, reticular; keratosis palmoplantaris papulose; skin diseases, genetic; autosomal recessive congenital ichthyosis; autosomal recessive congenital ichthyosis 1; autosomal recessive congenital ichthyosis 2; autosomal recessive congenital ichthyosis 3 ;autosomal recessive congenital ichthyosis 4A; autosomal recessive congenital ichthyosis 5; autosomal recessive congenital ichthyosis 6; autosomal recessive congenital ichthyosis 7; autosomal recessive congenital ichthyosis 8 autosomal recessive congenital ichthyosis 9; autosomal recessive congenital ichthyosis 10; autosomal recessive congenital ichthyosis 11.

More particularly, the condition or disorder which is mediated by Trk, in particular Trk A, B, and C, may be atopic dermatitis.

Treatment in accordance with the invention may be symptomatic or prophylactic.

Therefore according to a further aspect, the invention provides a topical pharmaceutical composition of the invention for treating or preventing a condition or disorder which is mediated by Trk, in particular Trk A, B, and C. It is preferable that the condition or disorder is dermatitis, preferably atopic dermatitis.

According to a further aspect, the invention provides the use of a compound of Formula (I) in the manufacture of a medicament for the prevention or treatment of a condition or disorder which is mediated by Trk, in particular Trk A, B, and C, wherein the medicament comprises the topical pharmaceutical composition of the invention. It is preferable that the condition or disorder is dermatitis, preferably atopic dermatitis.

According to a further aspect, the invention provides a method for preventing or treating a condition or disorder which is mediated by Trk, in particular Trk A, B, and C, which comprises administering to a subject (i.e. human) in need thereof a therapeutically effective amount of the topical pharmaceutical composition of the invention. It is preferable that the condition or disorder is dermatitis, preferably atopic dermatitis.

As referred to herein a "disorder" or a "disease" refers to an underlying pathological disturbance in a symptomatic or asymptomatic organism relative to a normal organism, which may result, for example, from infection or an acquired or congenital genetic imperfection.

A "condition" refers to a state of the mind or body of an organism which has not occurred through disease, e.g. the presence of a moiety in the body such as a toxin, drug or pollutant.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat”, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, “treat”, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

"Prevention" of a condition or disorder refers to delaying or preventing the onset of a condition or disorder or reducing its severity, as assessed by the appearance or extent of one or more symptoms of said condition or disorder.

As used herein, the term "subject" refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. It is preferable that the subject is a primate or human, and more preferably the subject is a human.

As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

The term "a therapeutically effective amount" of the topical pharmaceutical composition refers to an amount of the composition that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the topical pharmaceutical composition of the invention that, when administered to a subject, is effective to at least partially alleviating, inhibiting, preventing and/or ameliorating a condition or disorder which is mediated by TrK, in particular Trk A, B, and C. In another non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the topical pharmaceutical composition of the invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially inhibiting Trk activity, in particular Trk A, B, and C.

In one embodiment of the present invention, the condition or disorder which is mediated by Trk, in particular Trk A, B, and C, is selected from diseases of pruritus and itch; autoimmune diseases of the skin; diseases of skin pain and neuropathy; and diseases of dermatitis.

In a particularly preferred embodiment, the condition or disorder which is mediated by Trk, in particular Trk A, B, and C, is atopic dermatitis.

As described above, the agents, which inhibit Trk, in particular Trk A, B, and C, have various clinical applications and thus a further aspect of the invention provides pharmaceutical compositions containing agents of the invention. The use of the topical

pharmaceutical composition comprising these agents as a medicament forms a further aspect of the invention.

Topical pharmaceutical compositions as claimed herein for use as a medicament, in particular for use in treating or preventing disorders or conditions mediated by Trk, in particular Trk A, B, and C, such as the conditions described herein, and methods of treatment or prophylaxis using such compositions and use of said agents for the preparation of a medicament for treating or preventing such disorders or conditions, form further aspects of the invention.

"Pharmaceutically acceptable" as referred to herein refers to ingredients that are compatible with other ingredients of the compositions as well as physiologically acceptable to the recipient.

Pharmaceutically acceptable excipients refer to a substance that are non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of an agent and that is compatible therewith. In addition to the excipients in the excipient system as defined above, examples of additional excipients that may be included in the topical pharmaceutical composition of the invention include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

Notwithstanding the above, topical pharmaceutical compositions according to the invention may be formulated in conventional manner using readily available ingredients. Thus, the pharmaceutically active ingredient may be incorporated, optionally together with other active substances.

The topical pharmaceutical compositions of the invention may comprise one or more agents that reduce the rate by which the compound of the present invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc. These are in addition to those mentioned above.

The topical pharmaceutical composition of the invention may be administered either simultaneously with, or before or after, one or more other therapeutic agent. The topical pharmaceutical composition of the invention may be administered separately, by the same or different route of administration, or together in the same topical pharmaceutical composition as the other agents.

In one embodiment, the invention provides the topical pharmaceutical composition of the invention and at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a condition or disorder which is mediated by Trk, in particular Trk A, B, and C. Products provided as a combined preparation include the topical composition of the invention and the other therapeutic agent(s) together in the same composition, or the topical pharmaceutical composition of the invention and the other therapeutic agent(s) in separate form, *e.g.* in the form of a kit.

In one embodiment, the invention provides the topical pharmaceutical composition of the invention and another therapeutic agent(s).

In one embodiment, the invention provides a kit comprising two or more separate pharmaceutical compositions, at least one of which is the topical pharmaceutical composition of the invention. In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet.

The kit of the invention may be used for administering different dosage forms, for example, oral and topical, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the invention typically comprises directions for administration.

In the combination therapies of the invention, i.e. those that comprise the administration of the topical pharmaceutical composition and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the topical pharmaceutical composition of the invention and the other therapeutic may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.* in the case of a kit comprising the topical pharmaceutical composition of the invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in

the patient themselves, *e.g.* during sequential administration of the topical pharmaceutical composition of the invention and the other therapeutic agent.

Accordingly, the invention provides the use of a topical pharmaceutical composition of the invention for treating a condition or disorder which is mediated by Trk, in particular Trk A, B, and C, wherein the medicament is prepared for administration with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a condition or disorder which is mediated by Trk, in particular Trk A, B, and C, wherein the medicament is administered with the topical pharmaceutical composition of the invention.

The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency or effectiveness of an active agent according to the invention), decrease one or more side effects, or decrease the required dose of the active agent according to the invention.

The invention also provides the topical pharmaceutical composition of the invention for use in a method of treating a condition or disorder which is mediated by Trk, in particular Trk A, B, and C, wherein the topical pharmaceutical composition of the invention is prepared for administration with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a condition or disorder which is mediated by Trk, in particular Trk A, B, and C, wherein the other therapeutic agent is prepared for administration with the topical pharmaceutical composition of the invention. The invention also provides the topical pharmaceutical composition of the invention for use in a method of treating a condition or disorder which is mediated by Trk, in particular Trk A, B, and C, wherein the topical pharmaceutical composition of the invention is administered with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a condition or disorder which is mediated by Trk, in particular Trk A, B, and C, wherein the other therapeutic agent is administered with the topical pharmaceutical composition of the invention.

The invention also provides the use of the topical pharmaceutical composition of the invention for treating a condition or disorder which is mediated by Trk, in particular Trk A, B, and C, wherein the subject has previously (*e.g.* within 24 hours) been treated with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a condition or disorder which is mediated by Trk, in particular Trk A, B,

and C, wherein the subject has previously (*e.g.* within 24 hours) been treated with the topical pharmaceutical composition of the invention.

In one embodiment, a topical pharmaceutical composition of the invention is administered alongside one or more other therapeutically active agents. For example, the topical pharmaceutical composition of the invention may therefore be used in combination with one or more further agents for the treatment of atopic dermatitis, such as: one or more topical and/or oral corticosteroids; one or more antihistamines; one or more antibiotics; one or more topical calcineurin inhibitors such as tacrolimus and/or pimecrolimus; one or more systemic immunosuppressants such as cyclosporin, methotrexate, interferon gamma-1b, mycophenolate mofetil and/or azathioprine; one or more PDE4 inhibitors such as crisaborole; one or more monoclonal antibodies such as dupilumab.

A skilled person will appreciate that the topical pharmaceutical composition of the invention may be administered to a subject, particularly a human subject, wherein the subject is being treated with phototherapy for a condition or disorder which is mediated by Trk, in particular Trk A, B, and C, such as atopic dermatitis. A topical pharmaceutical composition of the invention may also be administered to a subject, particularly a human subject, wherein the subject has previously (*e.g.* within 24 hours) been treated with phototherapy for a condition or disorder in which is mediated by Trk, in particular Trk A, B, and C, such as atopic dermatitis. A subject, particularly a human subject may also be treated with phototherapy for a condition or disorder which is mediated by Trk, in particular Trk A, B, and C, such as atopic dermatitis wherein a topical pharmaceutical composition of the invention has previously (*e.g.* within 24 hours) been administered to a subject.

Accordingly, the invention includes as a further aspect a combination of the topical pharmaceutical composition of the invention with one or more further agents for the treatment of atopic dermatitis, such as: one or more topical and/or oral corticosteroids; one or more antihistamines; one or more antibiotics; one or more topical calcineurin inhibitors such as tacrolimus and/or pimecrolimus; one or more systemic immunosuppressants such as cyclosporin, methotrexate, interferon gamma-1b, mycophenolate mofetil and/or azathioprine; one or more PDE4 inhibitors such as crisaborole; one or more monoclonal antibodies such as dupilumab; and phototherapy.

In vitro assays

A suitable assay for determining the Trk inhibition activity of a compound of Formula (I) is detailed herein below.

To determine the IC_{50} of small molecule compounds for the Human TRK receptors, HTRF® KinEASE™ kinase kits from Cisbio were used. Assays were carried out in low volume, black 384-well plates.

Recombinant Human TRK enzymes (Invitrogen) were incubated in the presence or absence of the compound (11-point dose response with FAC as 10µM) for 30 minutes at 23°C. Kinase reaction was started by addition of ATP to a mixture containing the enzyme (NTRK1-4nM, NTRK2-1nM, NTRK3-10nM) and substrate (1µM). Kinase reaction was allowed to carry on for 10 to 45 minutes at 23°C after which it was stopped by addition of the detection mix (supplied by vendor) containing EDTA, TK-Ab- labelled with Eu^{3+}-cryptate (1:200 dilutions) and Streptavidin-XL665 (250nM). Assay plates were incubated in this detection mix for 60 minutes at 23°C. The resulting TR-FRET signal, calculated as the fluorescence ratio at 665/620 nm, was read on an Envision and was proportional to the level of phosphorylation of the peptide in the presence or absence of the compound. The uniformity of the plates were assured with Z' value [1-{3*(SDHPE+SDZPE)/ (ZPE-HPE)}]. The percent (%) effect i.e. Inhibition of compound was calculated in comparison to the signal in the positive (HPE) and negative control (ZPE) wells within each assay plate. The endpoint value % Inhibition for the Standard compound was evaluated in each experiment as a quality control measure. IC_{50} was determined by plotting compound inhibition at respective dose in Graphpad prism5 using four parameter logistic curve fit.

Using the assay described above, the compounds of Formula (I) all exhibit of Trk inhibition activity, expressed as an IC_{50} value, of less than 1 µM. Preferred examples have IC_{50} values of less than 200nM and particularly preferred examples have IC_{50} values of less than 50nM. IC_{50} values for the compounds of Examples 1, 2, 3, 4, 5, 6 and 7 are given below in Table 1.

Table 1: Trk inhibition activity, expressed as IC_{50} values

Example	**TrkA Enz (nM)**	**TrkB Enz (nM)**	**TrkC Enz (nM)**
1	0.95	0.88	1.60

2	1.04	0.83	1.78
3	1.17	0.37	1.53
4	0.97	0.23	1.00
5	1.10	0.41	1.61
6	1.52	0.70	1.91
7	1.44	1.55	3.16

EXAMPLES

Referring to the examples that follow, compounds of the preferred embodiments are synthesized using the methods described herein, or other methods, which are known in the art.

It should be understood that the organic compounds according to the preferred embodiments may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the preferred embodiments encompasses any tautomeric form of the drawn structure.

It is understood that the invention is not limited to the embodiments set forth herein for illustration, but embraces all such forms thereof as come within the scope of the above disclosure.

General Conditions:

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure. The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, *e.g.*, microanalysis and spectroscopic characteristics, *e.g.*, MS, IR, NMR. Abbreviations used are those conventional in the art. If not defined, the terms have their generally accepted meanings.

Abbreviations and acronyms used herein include the following:

Abbreviation/acronym	**Term**
AcOH	Acetic acid

AgOAc	Silver acetate
aq	aqueous
Bn	benzyl
br	broad
°C	degrees Celsius
$CDCl_3$	deutero-chloroform
Cs_2CO_3	Cesium carbonate
Cy	cyclohexane
δ	chemical shift
d	doublet
dd	double doublet
ddd	Doublet of doublets of doublets
DCC	N,N'-dicyclohexylcarbodiimide
DCM	dichloromethane
DIBAL-H	Diisobutylaluminium hydride
DIPEA	N-ethyldiisopropylamine or N,N-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMPU	N,N'-dimethylpropylene urea
DMSO	Dimethylsulfoxide
DMSO-d_6	hexadeuterodimethyl sulfoxide
Et	ethyl
Et_3N	triethylamine
EtOH	ethanol
EtOAc	ethyl acetate
$Fe(acac)_3$	Iron (III) acetylacetone
g	gram
HCl	hydrochloric acid
HATU	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)
H_2O	water
HPLC	high pressure liquid chromatography
Hr	hour
IPA	Isopropyl alcohol
KF	Potassium fluoride

KOH	Potassium hydroxide
L	litre
Lawesson's Reagent	2,4-Bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane
LCMS	liquid chromatography mass spectrometry
LiCl	Lithium chloride
m	multiplet
M	molar
mBar	millibar
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MeOD-d_4	deutero-methanol
2-MeTHF	2-methyltetrahydrofuran
mg	milligram
MHz	mega Hertz
mins	minutes
mL	millilitres
mmol	millimole
MS m/z	mass spectrum peak
MsCl	methanesulfonyl chloride
MTBE	Methyl *tert*-butyl ether
M/V	Mass volume ratio
N_2	nitrogen
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
NH_3	ammonia
NH_4Cl	ammonium chloride
Na_2SO_4	sodium sulfate
PtO_2	platinum (IV) oxide
q	quartet
rt	room temperature
RT	retention time
s	singlet
sat.	saturated

soln.	solution
t	triplet
TBDMS	tert-butyldimethylsilyl
TBDMSCl	tert-butyldimethylsilyl chloride
TEAF	tetraethylammonium fluoride
THF	tetrahydrofuran
TMS	trimethylsilyl
µL	micro litres
v/v	volume volume percent
w/w	Weight/weight percent

Referring to the examples that follow, compounds of the preferred embodiments were synthesized using the methods described herein, or other methods, which are known in the art.

The various starting materials, intermediates, and compounds of the preferred embodiments may be isolated and purified, where appropriate, using conventional techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Unless otherwise stated, all starting materials are obtained from commercial suppliers and used without further purification. Salts may be prepared from compounds by known salt-forming procedures.

It should be understood that the organic compounds according to the preferred embodiments may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the preferred embodiments encompasses any tautomeric form of the drawn structure.

^{1}H nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane (for ^{1}H-NMR) using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used for common solvents: $CDCl_3$, deuterochloroform; DMSO-d_6, hexadeuterodimethyl sulfoxide; and MeOD-d_4, deuteron-methanol. Where appropriate, tautomers may be recorded within the NMR data; and some exchangeable protons may not be visible.

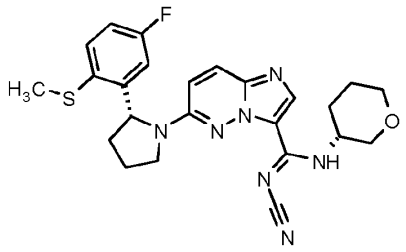
Mass spectra, MS (m/z), were recorded using either electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI). Where relevant and unless otherwise stated the m/z data provided are for isotopes ^{19}F, ^{35}Cl, ^{79}Br and ^{127}I.

Where preparative TLC or silica gel chromatography have been used, one skilled in the art may choose any combination of solvents to purify the desired compound.

Example compounds of Formula (I) useful in the topical pharmaceutical composition of the present invention include:

Example 1

(Z)-N'-cyano-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3R)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboximidamide

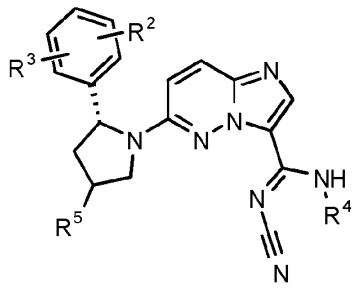


Mercury dichloride (144 mg, 0.530 mmol) was added in one portion, followed by cyanamide (62 mg, 1.48 mmol) to a solution of 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3R)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carbothioamide (Preparation 27, 100 mg, 0.212 mmol) in DMF (2 mL) under N_2 and the reaction stirred at rt for 16 hrs. The mixture was concentrated *in vacuo*, the residue re-suspended in DCM (10 mL), filtered through a pad of Dicalite®, rinsing through with 20% MeOH in DCM (20 mL). The filtrate was concentrated *in vacuo* and purified by column chromatography on silica gel eluting with heptanes:EtOAc:MeOH, (80:20:0 to 0:100:0 to 0:90:10). The product was triturated with MeOH to afford the title compound as a colourless solid, 30 mg, 30%.

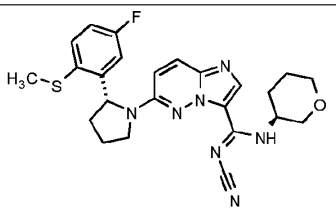
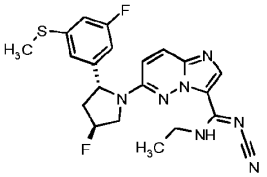
LCMS m/z = 480.2 $[M+H]^+$

^1H NMR (DMSO-d_6, 400MHz): δ 1.55-1.57 (m, 1H), 1.80-2.02 (m, 5H), 2.39-2.50 (m, 5H), 3.44-3.73 (m, 3H), 3.76-3.87 (m, 1H), 3.94-4.04 (m, 1H), 4.07-4.20 (m, 1H), 5.26 (d, 1H), 6.40 (br s, 1H), 6.92 (dd, 1H), 7.16 (dd, 1H), 7.41 (dd, 1H), 7.97 (d, 1H), 8.70 (s, 1H), 9.75 (br s, 1H).

Examples 2 to 3



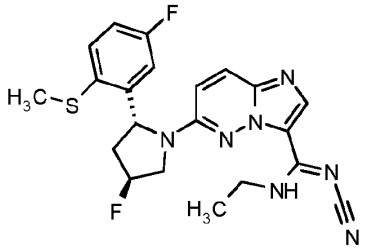
The compounds in the table below were prepared from the appropriate thioamide using the method described in Example 1.

Example	Structure and name	Starting Materials, Yield and Data
2	 (Z)-N'-cyano-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboximidamide	6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carbothioamide (Preparation 28) 13% as a colourless solid LCMS m/z = 480.3 $[M+H]^+$ ^{1}HNMR (MeOD-d_4, 400 MHz): δ 1.57-1.70 (m, 1H), 1.90-2.11 (m, 6H), 2.50-2.68 (m, 4H), 3.63-3.73 (m, 1H), 3.74-3.85 (m, 3H), 3.86-3.96 (m, 1H), 4.06-4.17 (m, 1H), 4.22-4.33 (m, 1H), 5.36-5.46 (m, 1H), 6.50-6.60 (m, 1H), 6.80-6.90 (m, 1H), 7.01-7.11 (m, 1H), 7.38-7.48 (m, 1H), 7.78 (d, 1H), 8.85-8.91 (m, 1H).
3	 (Z)-N'-cyano-N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-	N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carbothioamide (Preparation 31) 47% yield as a colourless solid LCMS m/z = 441.9 $[M+H]^+$

	yl]imidazo[1,2-b]pyridazine-3-carboximidamide	^{1}HNMR (DMSO-d_6, 400 MHz): δ 1.18 (t, 3H), 2.04-2.22 (m, 1H), 2.47 (s, 3H), 2.80-2.90 (m, 1H), 3.32-3.42 (m, 2H), 4.14-4.26 (m, 2H), 5.29 (t, 1H), 5.32, 5.57 (2x s, 1H), 6.93-7.00 (m, 3H), 7.14 (s, 1H), 8.05 (d, 1H), 8.53 (s, 1H), 9.11 (br s, 1H).

Example 4

(Z)-N'-cyano-N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide



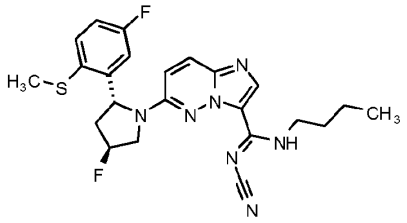
Silver acetate (33 mg, 0.18 mmol) was added to a stirred solution of N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carbothioamide (Preparation 30, 86 mg, 0.20 mmol), and cyanamide (42 mg, 0.99 mmol) in dry MeOH (2 mL) under N_2. The mixture was stirred for 2 hr at rt, additional silver acetate (33 mg, 0.18 mmol) added and the reaction flask protected from light by covering with aluminium foil. The reaction was stirred for a further 48 hrs, the resulting suspension filtered and the filtrate evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with DCM:MeOH (96:4) and then by reverse phase column chromatography eluting with MeCN:water (5:95 to 95:5)to afford the title compound as a colourless solid, 35 mg, 40%.

^{1}HNMR (MeOD-d_4, 400 MHz): δ 1.25 (t, 3H), 2.08-2.24 (m, 1H), 2.58 (s, 3H), 3.00-3.10 (m, 1H), 3.48-3.54 (m, 2H), 4.16-4.32 (m, 2H), 5.39-5.59 (m, 2H), 6.92-7.10 (m, 3H), 7.40 (dd, 1H), 7.86 (d, 1H), 8.72 (s, 1H)

LCMS m/z = 442.0 $[M+H]^+$

Example 5

(Z)-N-butyl-N'-cyano-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide



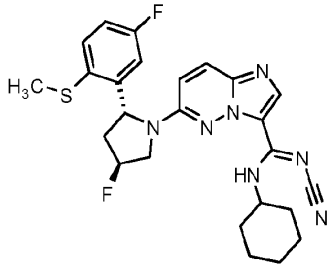
The title compound was obtained as a colourless solid in 43% yield, from of N-butyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carbothioamide (Preparation 32), following the method described in Example 4.

LCMS m/z = 470 $[M+H]^+$

^{1}H-NMR (MeOD-d_4, 396 MHz) : δ 1.01 (t, 3H), 1.40-1.50 (m, 2H), 1.54-1.71 (m, 2H), 2.10-2.27 (m, 1H), 2.57 (s, 3H), 3.02-3.12 (m, 1H), 3.48 (t, 2H), 4.18-4.30 (m, 2H), 5.39-5.58 (m, 2H), 6.89-7.09 (m, 3H), 7.41 (dd, 1H), 7.83 (d, 1H), 8.70 (s, 1H).

Example 6

(Z)-N'-cyano-N-cyclohexyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide



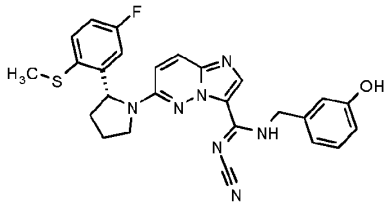
The title compound was obtained as a pale yellow solid in 4% yield, from N-cyclohexyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carbothioamide (Preparation 33), following the method described in Example 4.

LCMS m/z =496 $[M+H]^+$

^{1}HNMR (MeOD-d_4, 400 MHz): δ 1.24-1.57 (m, 5H), 1.67-1.81 (m, 1H), 1.82-1.96 (m, 2H), 2.08-2.34 (m, 3H), 2.58 (s, 3H), 2.88-3.20 (m, 1H), 3.95-4.26 (m, 3H), 5.39-5.66 (m, 2H), 6.64 (d, 1H), 6.96-7.16 (m, 2H), 7.44 (dd, 1H), 7.80 (d, 1H), 8.66 (s, 1H).

Example 7

(Z)-N'-cyano-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboximidamide



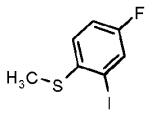
TEAF (73 mg, 0.49 mmol) was added in one portion to a solution of (Z)-N-({3-[(tert-butyldimethylsilyl)methyl]phenyl}methyl)-N'-cyano-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide (Preparation 34, 60 mg, 0.097 mmol) in MeCN (0.5 mL) and the reaction stirred at 50 °C for 4 hrs. The cooled mixture was evaporated *in vacuo*, the residue diluted with EtOAc (15 mL), washed with water (3 x 15 mL), the organic phase dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography on silica gel eluting with DCM:MeOH (99:1 to 92:8) and the product triturated with water to afford the title compound, as a colourless solid, 16 mg, 33%.

LCMS m/z = 502.0 $[M+H]^+$

^{1}H NMR (MeOD-d_4, 400MHz): δ 1.89-1.99 (m, 3H), 2.42-2.48 (m, 4H), 3.10-3.30 (m, 2H), 4.53-4.58 (m, 2H), 5.33 (d, 1H), 6.67-6.99 (m, 6H), 7.15-7.25 (m, 2H), 7.80-7.87 (m, 1H), 8.90 (s, 1H).

Preparation 1

4-fluoro-2-iodo-1-(methylsulfanyl)benzene

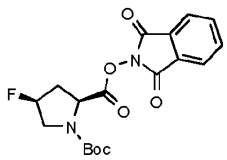


2-Bromo-4-fluoro-1-(methylsulfanyl)benzene (0.5 g, 2.26 mmol) was added dropwise to a suspension of activated Mg turnings (1.92 g, 79 mmol) under N_2(g) in dry THF (80 mL) and the reaction warmed until Grignard formation had initiated. The remaining 2-bromo-4-fluoro-1-(methylsulfanyl)benzene (17 g, 76.89 mmol) was added dropwise, so as to maintain the temperature below 50°C and after complete addition, the reaction was allowed to cool to rt and stirred for 16 hrs. The solution was added via cannula to an ice-cooled solution of iodine (24.11 g, 94.99 mmol) in dry THF (80 mL) maintaining the temperature below 10 °C. The reaction was stirred at 0 °C for 1 hr, at rt for 1 hr then poured into an ice-cold sat. NH_4Cl soln. (300 mL). The mixture was concentrated *in vacuo* to remove organic solvents then extracted with Et_2O (3 x 300 mL). The combined organic layers were washed with a sat. $Na_2S_2O_3$ soln., dried (Na_2SO_4), and concentrated *in vacuo* to afford the title compound as a brown oil, 21.5 g, 83 %.

^{1}H NMR ($CDCl_3$, 396 MHz): δ 2.45 (s, 3H), 7.08-7.11 (m, 2H), 7.55 (dd, 1H).

Preparation 2

1-*tert*-butyl 2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl) (2S,4S)-4-fluoropyrrolidine-1,2-dicarboxylate

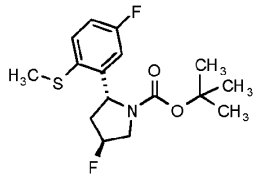


A solution of (2S,4S)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1.07 g, 4.6 mmol) in EtOAc (12.5 mL) was added to a stirred mixture of N-hydroxyphthalimide (0.75 g, 4.6 mmol) and N,N'-dicyclohexylcarbodiimide (0.95 g, 4.6 mmol) in EtOAc (12.5 mL) under N_2(g) and the reaction stirred at rt for 4 hrs. The mixture was filtered through a plug of silica, washed with EtOAc (50 mL) and the filtrate concentrated *in vacuo.* The resulting oil was re-dissolved in EtOAc (20 mL), washed with sat. aq. $NaHCO_3$ (4 x 30 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the title compound as a white solid, 1.55 g, 89 %.

LCMC m/z = 278.9 $[M\text{-}Boc]^+$

Preparation 3

tert-butyl (2R, 4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidine-1-carboxylate

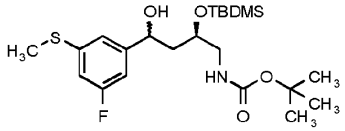


Nickel dibromide ethylene glycol dimethyl ether complex (0.09 g, 0.291 mmol) and 4,4'-di-tert-butyl-2,2'-bipyridine (0.08 g, 0.298 mmol) were flushed with N_2(g) and dry DMA (4 mL) added. The resulting blue-green mixture was stirred under N_2(g) for 15 mins then 4-fluoro-2-iodo-1-(methylsulfanyl)benzene (Preparation 1, 0.51 g, 1.49 mmol), 1-*tert*-butyl 2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl) (2S,4S)-4-fluoropyrrolidine-1,2-dicarboxylate (Preparation 2, 0.62 g, 1.64 mmol) and zinc dust (0.251 g, 3.84 mmol) were added and the reaction was stirred at 28 °C for 17 hr. The reaction mixture was filtered through a plug of silica and washed with Et_2O (75 mL). The filtrate was washed with brine (4 x 75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with heptanes:EtOAc (100:0 to 90:10) to afford the title compound as a yellow oil, 0.24 g, 36%.

LCMS m/z = 230.1 $[M\text{-}Boc]^+$

Preparation 4

tert-butyl N-[(2R)-2-[(tert-butyldimethylsilyl)oxy]-4-[3-fluoro-5-(methylsulfanyl)phenyl]-4-hydroxybutyl]carbamate

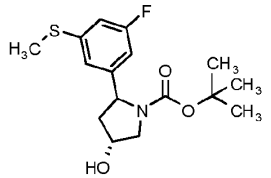


20 mL of a solution of 3-bromo-5-fluoro-1-(methylsulfanyl)benzene (38.0 g, 146 mmol) in dry THF (110 mL) was added dropwise to a stirred suspension of activated Mg turnings (10.7 g, 438 mmol) under N_2(g) in dry THF (110 mL) and the reaction warmed until Grignard formation had initiated. The remaining 3-bromo-5-fluoro-1-(methylsulfanyl)benzene solution was then added so as to maintain the temperature below 50°C. After complete addition, the reaction was allowed to cool to rt and stirred for a further hr. The solution was added via cannula to a -20 °C solution of tert-butyl (R)-4-(tert-butyldimethylsilyloxy)-2-oxopyrrolidine-1-carboxylate (US9701681, Example 6, 38.4 g, 122 mmol) in dry THF (220 mL) so as to maintain the temperature below -10 °C. The mixture was stirred at -50 °C for 1 hr, at 0 °C for 1 hr then re-cooled to -20 °C. MeOH (150 mL) was added dropwise, followed by $NaBH_4$ (6.91 g, 182 mmol) in 5 portions and the reaction stirred at -15 °C for 30 mins then for 3.5 hrs at rt. The mixture was poured into ice-cold sat. NH_4Cl soln. (150 mL), then concentrated *in vacuo* to remove organic solvents and extracted with EtOAc (3 x 150 mL). The combined organic phases were dried ($MgSO_4$), evaporated under reduced pressure and the crude product purified by column chromatography on silica gel eluting with heptanes:EtOAc, (95:5 to 60:40) to afford the title compound as a pale yellow oil, 35.8 g, 64 %.

LCMS m/z = 342.4 $[M\text{-Boc-}H_2O]^+$

Preparation 5

tert-butyl (4R)-2-[3-fluoro-5-(methylsulfanyl)phenyl]-4-hydroxypyrrolidine-1-carboxylate



Et_3N (33 mL, 237 mmol) followed by mesyl chloride (9.10 mL, 117 mmol) were added dropwise to an ice cooled solution of tert-butyl N-[(2R)-2-[(tert-butyldimethylsilyl)oxy]-4-[3-fluoro-5-(methylsulfanyl)phenyl]-4-hydroxybutyl]carbamate (Preparation 4, 35.8 g, 77.9 mmol) in anhydrous DCM (210 mL) and the reaction stirred for 2 hrs. The mixture was

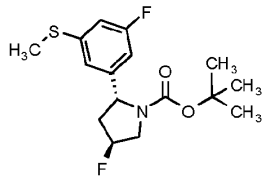
poured into ice-cold water (140 mL), extracted with DCM (3 x 70 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*.

The residue was dissolved in THF (140 mL), TBAF (1M in THF, 110 mL, 110 mmol) added and the reaction stirred at rt for 2 hrs. This was then poured into cold water (200 mL), concentrated *in vacuo* to remove organic solvents and extracted with EtOAc (3 x 150 mL). The combined organic phases were dried ($MgSO_4$), evaporated under reduced pressure and purified by column chromatography on silica gel eluting with heptanes:EtOAc (95:5 to 0:100) to afford the title compound as a light yellow oil, 23.7 g, 93 %.

LCMS m/z = 228 $[M\text{-Boc}]^+$

Preparation 6

tert-butyl (2R, 4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidine-1-carboxylate

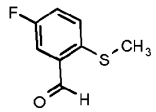


DAST (16.9 mL, 139 mmol) was added dropwise to a -5 °C solution of *tert*-butyl (4R)-2-[3-fluoro-5-(methylsulfanyl)phenyl]-4-hydroxypyrrolidine-1-carboxylate (Preparation 5, 22.74 g, 69.5 mmol) in dry DCM (290 mL) so as to maintain the internal temperature below 0 °C. The reaction mixture was stirred for 2.5 hrs at rt, then poured carefully into an ice-cold sat. aq. $NaHCO_3$ soln. (250 mL). This mixture was extracted with DCM (3 x 200 mL), the combined organic layers dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography on silica gel eluting with heptanes:TBME (100:0 to 70:30) to provide the title compound as a pale yellow oil, 4.2 g, 18%.

^1H NMR ($CDCl_3$, 400MHz): δ 1.25 (s, 6H), 1.46 (s, 3H), 2.20-2.36 (m, 1H), 2.45 (s, 3H), 2.48-2.67 (m, 1H), 3.76 (dd, 1H), 3.97 (dd, 1H), 4.81-5.08 (m, 1H), 5.20-5.26 (m, 1H), 6.70-6.76 (m, 1H), 6.76-6.80 (m, 1H), 6.87-6.90 (m, 1H).

Preparation 7

5-fluoro-2-(methylsulfanyl)benzaldehyde



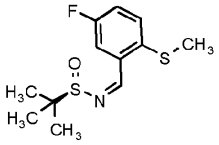
n-BuLi in hexane (2.5 M, 0.4 mL, 1 mmol) was added dropwise to a solution of 2-bromo-4-fluoro-1-(methylsulfanyl)benzene (221.0 mg, 1 mmol) in dry THF (10 mL) at -78 °C

under N_2(g), so the temperature was maintained below -70 °C. DMF (80.0 mg, 1.1 mmol) was added and the reaction stirred at -78°C for a further 30 mins. The resulting mixture was quenched by the addition of ice-cold sat. aq. NH_4Cl soln. (10 mL), warmed to rt and extracted with EtOAc (10 mL). The organic extracts were washed with saturated brine (10 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography on silica gel eluting with heptanes:EtOAc (95:5) to afford the title compound as colourless oil, 88 mg, 52%.

^{1}H NMR ($CDCl_3$, 400MHz): δ 2.51 (s, 3H), 7.25-7.30 (m, 1H), 7.35-7.39 (m, 1H), 7.52-7.56 (m, 1H), 10.35 (s, 1H).

Preparation 8

(R)-N-[(1Z)-[5-fluoro-2-(methylsulfanyl)phenyl]methylidene]-2-methylpropane-2-sulfinamide

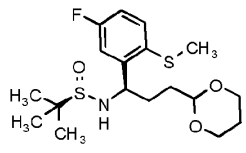


Cs_2CO_3 (300.0 mg, 0.92 mmol) was added to a solution of 5-fluoro-2-(methylthio)benzaldehyde (Preparation 7, 130.0 mg, 0.76 mmol) and (R)-2-methylpropane-2-sulfinamide (93.0 mg, 0.76 mmol) in DCM (15 mL) and the reaction stirred at rt for 18 hrs. Water (15 mL) was carefully added, the phases separated, the organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with heptanes:EtOAc (95:5 to 85:15) to afford the title compound as a yellow oil, 130 mg, 62%.

LCMS m/z = 274.1 $[M+H]^+$

Preparation 9

(R)-N-[(1R)-3-(1,3-dioxan-2-yl)-1-[5-fluoro-2-(methylsulfanyl)phenyl]propyl]-2-methylpropane-2-sulfinamide



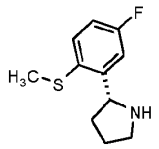
A solution (0.5 mL) of 2-(2-bromoethyl)-1,3-dioxolane (1.81 g, 10 mmol) in dry THF (5 mL) was added to a suspension of activated Mg turnings (729.0 mg, 30.0 mmol) under

N_2(g) in dry THF (10 mL) and the reaction warmed until Grignard formation had initiated. The remaining 2-(2-bromoethyl)-1,3-dioxolane solution (4.5 mL) was slowly added maintaining the temperature below 50°C. After complete addition, the reaction mixture was allowed to cool to rt, stirred for a further 1 hr then re-cooled to -50 °C. A solution of (R)-N-[(1Z)-[5-fluoro-2-(methylsulfanyl)phenyl]methylidene]-2-methylpropane-2-sulfinamide (Preparation 8, 270.0 mg, 1 mmol) in dry THF (5 mL) was added dropwise, the reaction stirred at -50°C for 1 hr and then allowed to warm to rt. Sat. aq. NH_4Cl soln. (20 mL) was added to quench the reaction and the mixture partitioned between EtOAc (30 mL) and water (30 mL). The aqueous phase was further extracted with EtOAc (30 mL) and the combined organics washed with brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel eluting with heptanes:EtOAc, (50:50 to 0:100) to afford the title compound as a colourless oil, 420 mg, 100%.

LCMS m/z = 390.0 $[M+H]^+$

Preparation 10

(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidine

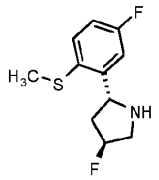


A solution of (R)-N-[(1R)-3-(1,3-dioxan-2-yl)-1-[5-fluoro-2-(methylsulfanyl)phenyl]propyl]-2-methylpropane-2-sulfinamide (Preparation 9, 390.0 mg, 1 mmol) in TFA:water (10 mL, 20:1) was stirred at rt for 30 mins. Et_3SiH (1.16 g, 10 mmol) was added and the reaction stirred vigorously at rt for 16 hrs. The mixture was diluted with toluene (30 mL), concentrated *in vacuo* then azeotroped with toluene (2 x 30 mL). The residual oil was purified by column chromatography on silica gel eluting with (DCM:MeOH:NH_4OH, 98:2:0.2 to 95:5:0.5) to afford the title compound product as an oil 125 mg, 59%.

LCMS m/z = 212.0 $[M+H]^+$

Preparation 11

(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidine

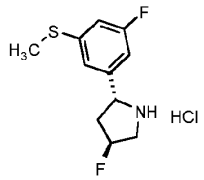


HCl (4M solution in dioxane, 10 mL) was added to a solution of tert-butyl (2R, 4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidine-1-carboxylate (Preparation 3, 1.21 g, 3.67 mmol) in MeOH (15 mL) and the reaction stirred at rt for 2 hrs. The mixture was concentrated *in vacuo* to afford a dark brown oil which was dissolved in MeOH (2 mL) and loaded onto an SCX ion exchange cartridge washing through with 7N NH_4OH in MeOH. The filtrate was evaporated under reduced pressure to afford the title compound as a dark orange oil, 0.4 g, 53%.

LCMS m/z = 230.0 $[M+H]^+$

Preparation 12

(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidine hydrochloride

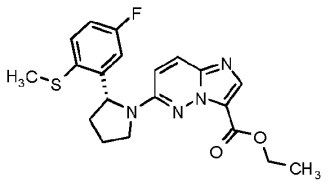


A solution of tert-butyl (2R,4S)-4-fluoro-2-[5-fluoro-3-(methylthio)phenyl]pyrrolidine-1-carboxylate (Preparation 6, 3.88 g, 11.79 mmol) in 4M HCl in dioxane (60 mL) was stirred at rt for 2 hrs. The solution was concentrated *in vacuo* to afford the title compound as a beige solid, 3.69 g, 99%.

LCMS m/z = 230 $[M+H]^+$

Preparation 13

Ethyl 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylate

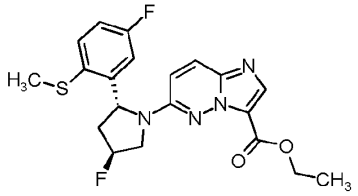


A solution of (2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidine (Preparation 10, 640 mg, 3.03 mmol) in 4M HCl in dioxane (20 mL) was stirred at rt for 30 mins then concentrated *in vacuo*. Ethyl 6-chloroimidazo[1,2-b]pyridazine-3-carboxylate (0.59 g, 2.52 mmol) in DMSO (20 mL) was added and the reaction heated at 130 °C for 16 hrs. The cooled mixture was partitioned between water (20 mL) and EtOAc (20 mL), and the layers separated. The organic phase was washed with brine (3 x 20mL), dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound as a brown oil, 1.13 g, 99%.

LCMS m/z = 401.2 $[M+H]^+$

Preparation 14

Ethyl 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylate

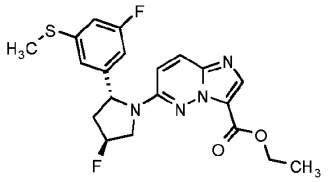


The title compound was obtained as a yellow solid in 85% yield from (2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidine (Preparation 11) following the procedure described in Preparation 13.

LCMS m/z = 419.0 $[M+H]^+$

Preparation 15

Ethyl 6-[(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylate

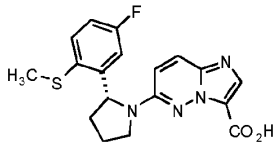


The title compound was obtained as a brown oil in 78% yield from (2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidine hydrochloride (Preparation 12) following the procedure described in Preparation 13.

LCMS m/z = 419.0 $[M+H]^+$

Preparation 16

6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid



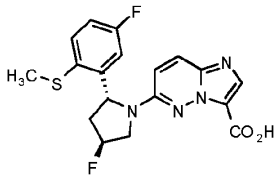
KOH (0.71 g, 12.6 mmol) was added portion wise to a solution of ethyl 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylate

(Preparation 13, 1.0 g, 2.52 mmol) in EtOH:water (12 mL, 6:1) and the reaction stirred at rt for 1.5 hrs. The mixture was concentrated *in vacuo*, the residue partitioned between water (20 mL) and DCM (20 mL) and the layers separated. The aqueous phase was adjusted to pH 4 with 2 M HCl solution, then extracted with DCM (3 x 20 mL). These combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a beige solid, 999 mg, 99%.

LCMS m/z = 373.2 $[M+H]^+$

Preparation 17

6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid

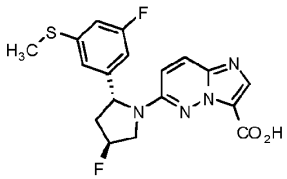


The title compound was obtained as a yellow solid in 50% yield from ethyl 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylate (Preparation 14) following the procedure described in Preparation 16.

LCMS m/z = 391 $[M+H]^+$

Preparation 18

6-[(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid

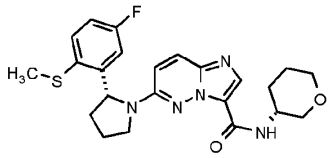


The title compound was obtained as a brown oil in 78% yield from ethyl 6-[(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylate (Preparation 15) following the procedure described in Preparation 16.

LCMS m/z = 391 $[M+H]^+$

Preparation 19

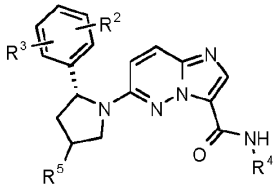
6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3R)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide



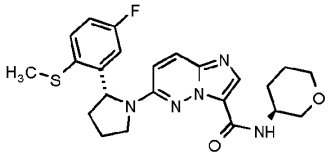
To a solution of 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 16, 150 mg, 0.407 mmol) in DMF (5 mL) was added (R)-tetrahydro-2H-pyran-3-amine hydrochloride (61 mg, 0.443 mmol) and HATU (168 mg, 0.443 mmol). The mixture was stirred at rt for 5 mins, DIPEA (0.140 mL, 0.805 mmol) added and the reaction stirred at rt for a further 16 hrs. The reaction was diluted with EtOAc (15 mL), washed with water (15 mL) and brine (15 mL), then dried (Na_2SO_4) and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel eluting with DCM:MeOH (99:1 to 92:8) and the product azeotroped with water to afford the title compound as a colourless solid, 133 mg, 72%.

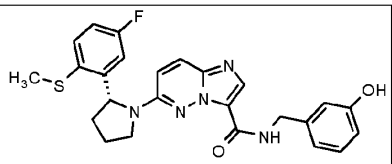
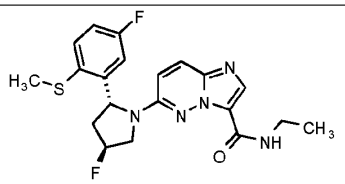
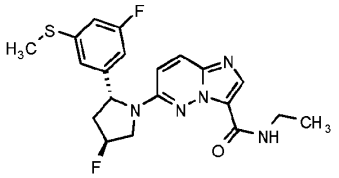
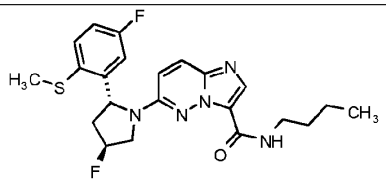
LCMS m/z = 456.2 $[M+H]^+$

Preparations 20 to 24



The following compounds were prepared from the appropriate carboxylic acid and amine, R^4NH_2, following the procedure described in Preparation 19.

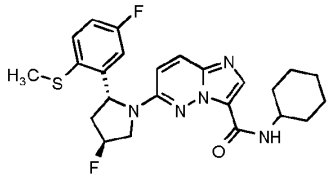
Preparation No	Structure and Name	Starting Materials	Yield, Data
20	 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide	6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 16) and (S)-tetrahydro-2H-pyran-3-amine hydrochloride	Brown solid, 77% LCMS m/z = 456 $[M+H]^+$

21	 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide	6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 16) and 3-hydroxybenzylamine hydrochloride	Colourless solid, 55% LCMS m/z = 478.1 $[M+H]^+$
22	 N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide	6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 17) and ethylamine	Colourless solid, 77% LCMS m/z = 418.0 $[M+H]^+$
23	 N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide	6-[(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 18) and ethylamine	Yellow oil, 97% LCMS m/z = 418.0 $[M+H]^+$
24	 N-butyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-	6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 17) and n-butylamine	Off-white solid, 92% LCMS m/z = 446 $[M+H]^+$

	(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide		

Preparation 25

N-cyclohexyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide

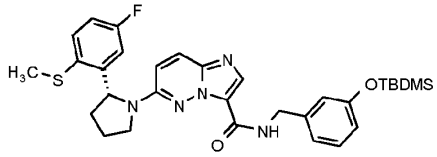


To a solution of 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 17, 150 mg, 0.380 mmol) in DCM (2 mL) was added cyclohexylamine (46 mg, 0.460 mmol), TBTU (136 mg, 0.460 mmol) and DIPEA (0.132 mL, 0.760 mmol) and the reaction stirred at rt for 1 hr. The mixture was diluted with DCM (10 mL) washed with saturated NH_4Cl soln. (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a yellow gum, 133 mg, 72%.

LCMS m/z = 472 $[M+H]^+$

Preparation 26

N-({3-[(tert-butyldimethylsilyl)oxy]phenyl}methyl)-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide

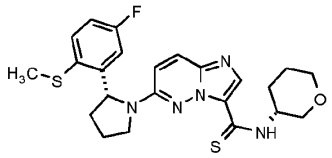


TBDMSCl (59 mg, 0.392 mmol) and 1H-imidazole (44 mg, 0.653 mmol) were added to a solution of 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 21, 156 mg, 0.327 mmol) in DMF (2 mL) and the reaction stirred at rt for 16 hrs. The mixture was partitioned between MTBE (50 mL) and water (50 mL) and the organic layer washed with saturated brine (3 x 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with DCM:MeOH, (99:1 to 92:8) to afford the title compound as a colourless gum, 166 mg, 86%.

LCMS m/z = 592.2 $[M+H]^+$

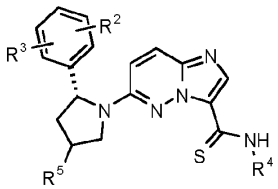
Preparation 27

6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3R)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carbothioamide

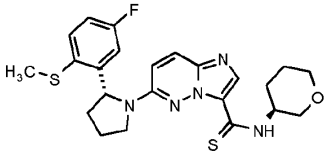


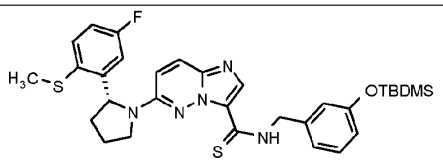
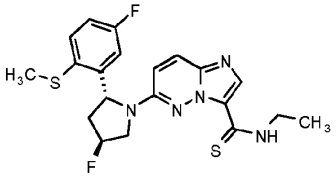
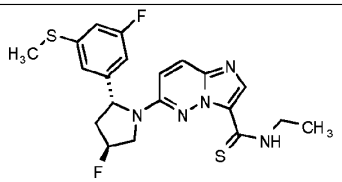
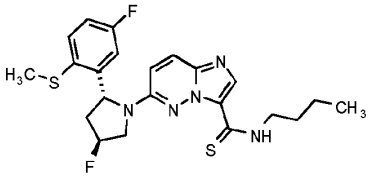
Lawesson's reagent (0.12 g, 0.297 mmol) was added to a solution of 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3R)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 19, 0.113 g, 0.248 mmol) in toluene (2 mL) and the reaction stirred at 100 °C for 16 hrs then cooled to rt. The mixture was concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with DCM:MeOH (99:1 to 92:8) to afford the title compound as a yellow solid, 106 mg, 90%.
LCMS m/z = 472 $[M+H]^+$

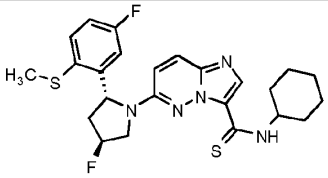
Preparations 28 to 33



The following compounds were prepared from the appropriate amide and Lawesson's reagent, following the procedure described in Preparation 27.

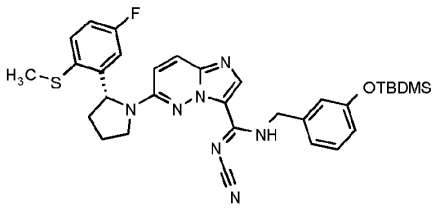
Preparation No	Structure and Name	Starting Material	Yield, Data
28	 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carbothioamide	6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 20)	Yellow solid, 67% LCMS m/z = 472 $[M+H]^+$

29	 N-({3-[(tert-butyldimethylsilyl)oxy]phenyl}methyl)-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carbothioamide	N-({3-[(tert-butyldimethylsilyl)oxy]phenyl}methyl)-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 26)	Yellow solid, 67% LCMS m/z = 608.2 $[M+H]^+$
30	 N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carbothioamide	N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 22)	Yellow solid, 65% LCMS m/z = 434.1 $[M+H]^+$
31	 N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carbothioamide	N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 23)	Orange oil, 77% yield. LCMS m/z = 434 $[M+H]^+$
32	 N-butyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-	N-butyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 24)	Yellow solid, 95% yield. LCMS m/z = 462 $[M+H]^+$

	carbothioamide		
33	 N-cyclohexyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carbothioamide	N-cyclohexyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 25)	Yellow solid, quantitative yield LCMS m/z = 488 $[M+H]^+$

Preparation 34

(Z)-N-({3-[(tert-butyldimethylsilyl)methyl]phenyl}methyl)-N'-cyano-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide



Mercury dichloride (111 mg, 0.411 mmol) followed by cyanamide (50 mg, 0.493 mmol) were added to a solution of N-({3-[(tert-butyldimethylsilyl)oxy]phenyl}methyl)-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carbothioamide (Preparation 29, 100 mg, 0.164 mmol) in DMF (2 mL) under N_2(g) and the reaction stirred at rt for 16 hrs. The mixture was concentrated *in vacuo*, re-suspended in DCM (10 mL), filtered through a pad of Dicalite®, rinsing through with 20% MeOH in DCM (20 mL). The filtrate was concentrated *in vacuo* and purified by column chromatography on silica gel eluting with heptanes:EtOAc:MeOH, (80:20:0 to 0:100:0 to 0:90:10) to afford the title compound as a colourless gum, 60 mg, 59%.

LCMS m/z = 616 $[M+H]^+$

Example 8 – Topical pharmaceutical compositions

The following examples are topical pharmaceutical compositions according to the invention.

Ointment-based (O) topical pharmaceutical compositions

Formulation	O1	O2	O3	O4	O5
Example 3	1.76	1.76	1.60	1.60	1.60
PEG 400	38.24	48.14	48.30	48.30	42.20
Propylene Glycol	10.00	10.00	10.00	10.00	10.00
Transcutol P	30.00	20.00	20.00	20.00	20.00
Octisalate	-	-	-	-	6.10
BHT	0.10	0.10	0.10	0.10	0.10
PEG 3350	19.90	-	20.00	-	-
PEG 4000	-	20.00	-	20.00	20.00
Total	**100**	**100**	**100**	**100**	**100**
pH	7.62	6.92	7.40	6.77	7.06

Non-aqueous gel-based (NAG) topical pharmaceutical compositions

Formulation	NA1	NA2	NA3	NA4	NA5
Example 3	1.97	1.97	1.95	1.95	1.58
PEG 400	46.93	46.93	20.95	40.85	46.32
Ethanol	10.00	10.00	10.00	10.00	5.00
Glycerol	4.00	4.00	20.00	4.00	10.00
Propylene Glycol	10.00	10.00	20.00	10.00	10.00
Transcutol P	25.00	25.00	25.00	25.00	25.00
Octisalate	-	-	-	6.10	-
BHT	0.10	0.10	0.10	0.10	0.10
HPC MF	2.00	-	-	-	-
HPC GF	-	2.00	2.00	2.00	2.00
Total	**100**	**100**	**100**	**100**	**100**
pH	6.37	6.37	7.58	6.39	7.57

Cream-based (CR) topical pharmaceutical compositions

Formulation	CR1	CR2	CR3	CR4	CR5
Example 3	0.22	0.22	0.34	0.34	0.34
SR PEG 400	24.68	23.68	23.56	23.56	23.56

Propylene Glycol	10.00	10.00	15.00	15.00	15.00
Transcutol P	15.00	15.00	15.00	15.00	15.00
Buffered deionised water pH 7 (citrate/phosphate)	25.00	25.00	20.00	20.00	20.00
Phenoxyethanol	1.00	1.00	1.00	1.00	1.00
Tween 80	5.05	5.04	4.94	5.04	5.04
BHT	0.10	0.10	0.10	0.10	0.10
Cetostearyl Alcohol	12.00	12.00	12.00	12.00	12.00
Liquid paraffin	0.00	7.00	0.00	7.00	0.90
Span 60	0.95	0.96	1.06	0.96	0.96
Crodamol GTCC	6.00	-	7.00	-	-
Octisalate	-	-	-	-	6.10
Total	**100**	**100**	**100**	**100**	**100**
pH	8.73	8.72	8.85	8.87	8.91

Examples 9 – Stability studies

Chemical stability of the API

Stability of the active pharmaceutical ingredient in the topical pharmaceutical compositions according to the invention was assessed. The compositions were stored at 25 °C and 40 °C for a period of two weeks, four weeks and six months (t = 2 weeks, t = 4 weeks, and t = 6 months).

	Mean percentage recovery (% w/w) of API					
	t = 2 weeks		t = 4 weeks		t = 6 months	
Formulation	**25 °C**	**40 °C**	**25 °C**	**40 °C**	**25 °C**	**40 °C**
O1	96.58	98.00	96.52	97.57	97.89	96.33
O2	quant.	quant.	99.95	quant.	-	-
O3	quant.	quant.	quant.	quant.	-	-
O4	quant.	quant.	99.84	quant.	-	-
O5	99.74	quant.	99.75	quant.	quant.	quant.
NAG1	quant.	quant.	quant.	98.64	-	-
NAG2	quant.	quant.	quant.	99.76	-	-
NAG3	99.54	quant.	99.18	99.29	quant.	quant.
NAG4	97.81	97.36	90.20	99.68	-	-
NAG5	quant.	99.28	94.01	quant.	-	-
CR1	98.81	99.34	94.49	98.50	-	-
CR2	quant.	99.94	94.01	quant.	99.44	98.87

CR3	quant.	98.45	94.73	99.65	quant.	98.66
CR4	quant.	99.23	98.46	99.45	-	-
CR5	99.98	99.96	100.11	98.67	-	-

In the table above, the term "quant." means that a quantitative amount of the API was measured.

The amount of active pharmaceutical ingredient was measured by HPLC using the following method.

Column	XBridge Shield RP18 3.5 µm, 4.6 x 150 mm		
Detection wavelength	254 nm		
Mobile phase A (Phase A)	0.1 % phosphoric acid in water		
Mobile phase B (Phase B)	0.1 % phosphoric acid in acetonitrile		
Gradient flow	Time (min)	% Phase A	% Phase B
	0	70	30
	2	70	30
	10	60	40
	18	48	52
	22	35	65
	25	35	65
	25.01	70	30
	28	70	30
Initial flow rate	1 mL/min		
Column temperature	30 °C		
Injection volume	10 µL		
Sample and standard diluent	100 % acetonitrile		
Seal wash and line storage	60:40 v/v methanol: water		
Needle wash	100 % acetonitrile		

All of the topical pharmaceutical compositions according to the invention showed increased chemical stability of the active pharmaceutical ingredient under both the ambient temperature (25 °C) and increased temperature (40 °C) stability studies.

Physical stability of topical pharmaceutical compositions

All of the ointment, non-aqueous gel and cream-based topical pharmaceutical compositions exhibit suitable physical stability of the formulation, with the ointment, aqueous gel and non-aqueous gel exhibiting the greatest physical stability

Example 10 – Drug loading

All of the topical pharmaceutical compositions of the present invention benefit from the ability to include the active pharmaceutical ingredient in a high amount (i.e. a high API loading). Of the claimed topical pharmaceutical compositions, the ointments non-aqueous gels have a particularly high API loading ability, with API loading being over 1.5% by weight of the composition. The ointments performed even better exhibiting 1.5% by weight of the composition API loading and with higher expected (see drug loadings in example 32). One advantage of topical pharmaceutical compositions with higher API loading is that a higher concentration of drug may be applied to an area of skin or mucosa.

Example 11 – RHE irritancy test (in vitro irritancy study using RHE cultures)

The following materials were used in this example.

Material	**Cat. Number**	**Supplier**
RHE	RHE-24	ZenSkin™
Triton-X 100	C34H62011	Fisher
HCl	SA49	Fisher
Reagent A-MTT	CT01-5	EMD Millipore
NaOH	SS267	Fisher
PBS	P4417	Fisher

RHE cultures (ZenSkin®) (surface area = 0.33 cm^2) were equilibrated overnight in a humidified incubator at 37 °C and 5% CO_2. The next day RHE were removed from the incubator and inspected for residual liquid on the apical surface. Excess moisture was removed with sterile cotton swab and 30 µL of a topical pharmaceutical composition was applied to triplicate cultures (n=3). Sterile water served as a negative control and 1% Triton X-100 served as positive control. Once treated, RHE cultures were returned to the incubator for 1 hour and then gently washed to remove test substance. The washed inserts were then transferred to new 12 well plates prefilled with fresh 0.5 mL media.

The tissues were incubated for 24 hours, culture media was replaced with fresh media, and incubated for an additional 18 hours (42 hours total from time of treatment).

After 42-hour incubation, the tissue cultures were transferred to a new plate containing fresh MTT substrate in tissue media and placed in the incubator at 37 °C and 5% CO_2 for 2 hours. After incubation, the wells were rinsed three times with DPBS and transferred to clean 12 well plates. The tissues were submerged in lysis buffer (0.04N HCl/isopropanol) for at least 2 hours with shaking. Extraction solution (0.2 mL) was transferred to a 96 well plate. Optical density was measured at 570 nm without using a reference filter. A blank well (extraction buffer only) was subtracted from all wells as a background control.

Percent cell viability was calculated as follows: 100 x [OD(sample)/OD(neg control)]. RHE irritation assay was deemed acceptable as the positive control (1% triton X-100) showed <20% viability compared to the negative control tissue (water only). The test formulations were classified as irritant or non-irritant based on EU and GHS classification, according to which an irritant (R38/Category 2) is determined if the mean relative tissue viability of tissues exposed to test material is reduced below 50% of the negative control.

The results are shown in the table below and Figures 1 and 2. Entries with the suffix PBO (for placebo) relate to formulations without the active pharmaceutical compound. Data in Figures 1 and 2 are presented as the mean ± standard deviation (n=3).

Formulation	Mean percent viability	Classification
O1	119.7	non-irritant
O9	86.1	non-irritant
CR32	137.0	non-irritant
CR33	94.0	non-irritant
O1 PBO	119.6	non-irritant
O5 PBO	142.4	non-irritant
CR2 PBO	97.9	non-irritant
CR3 PBO	109.7	non-irritant

Figure 1 shows the mean percentage cell viability of RHE for compositions O1, O5, NAG3, CR3, and CR5.

Figure 2 shows the mean percentage cell viability of RHE for placebo compositions (compositions without API) O1, O5, NAG3, CR3, and CR5.

Example 12 – Human skin penetration study

An ex vivo skin permeation and penetration experiment using flow through diffusion cells (MedFlux-HT®) was performed.

Figure 3 contains a schematic of the MedFlux-HT process used in this study.

Human skin from cosmetic reduction surgery was used (from a single donor). The subcutaneous fat was removed mechanically and the skin was dermatomed to a thickness of 500 ± 50 µm using an Integra Life Sciences Model SB Slimline Dermatome. The skin was stored at -80 °C if not used immediately. If frozen, the skin was allowed to thaw at ambient temperature prior to placement into the diffusion cells.

The skin was placed between the donor and receptor compartments of the MedFlux-HT. Each formulation was individually applied to the top of the skin at a dosage of 2 mg per cm^2. A receiver fluid (PBS + 0.01% Brij-O20) continually flowed through the compartment under the skin sample as shown in Figure 3, for a period of 24 hours at a rate of 10 $\mu L min^{-1}$.

The skin was removed and the epidermis and dermis were heat-separated in an incubator at 60 °C for 2 mins. The epidermal and dermal layers were individually homogenised at 5000RPM for 3 x 30 sec at ambient temperature in an extraction solvent of 90:10 v/v ethanol : water. The homogenised epidermal and dermal layers were then shaken on an orbital shaker at 130 RPM at ambient temperature for 30 mins. The homogenate was transferred to 96-well plates and centrifuged at around 3200 g-force.

Analysis of the liquid samples was carried out by the following LC-MS/MS method using a Verapamil internal standard.

Mobile Phase A	0.01% Formic Acid in water
Mobile Phase B	Methanol
Purge solvent	0.01% Formic Acid in water
Wash solvent	Methanol
Injection Volume (µL)	5.0
Multiplexing?	No
Guard Column	Phenomenex SecurityGuard Ultra C18
Column	Supelco Titan C18 2.1 x 20 mm, 1.9 um
Flow Rate (initial) (mL/min)	0.4
%B (initial)	3

Run Time (min.)	2.8			
Column Temperature (°C)	50			
Autosampler Temperature (°C)	10			
Divert Valve	Start with flow going to waste, at 36 seconds flow diverted to LC and at 120 seconds, flow diverted back to waste			
LC time programme	**Time (min)**	**Flow rate**	**% B**	**Value**
	Initial	0.400	3.0	Initial
	0.20	0.400	3.0	6
	1.70	0.400	100	6
	1.75	0.600	100	6
	2.25	0.600	100	6
	2.30	0.400	3.0	6
	2.80	0.400	3.0	6

Figure 4 shows the mean concentration of active pharmaceutical ingredient (µg/g) recovered from epidermis (top graph) and dermis (bottom graph) 24 hours post-application to the apical surface of the skin of the topical pharmaceutical compositions. Each bar represents the mean (three skin donors; n=3 per donor), with error bars representing standard error of the mean. Blank is skin with no formulation applied.

As can be seen from the results, topical pharmaceutical compositions are able to deliver therapeutic amounts of the active pharmaceutical ingredient to the dermis and epidermis.

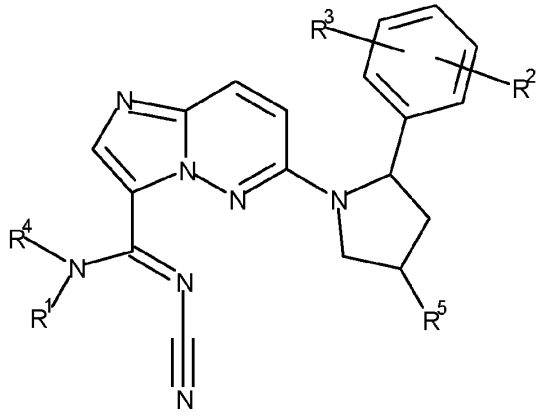
CLAIMS

1. A topical pharmaceutical composition comprising

(a) a compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof in an amount of from about 0.008% to about 30%, preferably from about 0.01% to about 20%, more preferably from about 0.05% to about 5%, by weight of the composition; and

(b) an excipient system in an amount of less than about 99.99 % by weight of the composition,

wherein the compound of Formula (I) is



(I)

wherein

R^1 is selected from H, $-XR^7$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, and a C-linked 4-6 membered heterocycloalkyl containing 1 to 2 heteroatoms selected from N, O and S;

X is selected from $–CH_2–$;

R^2 is selected from H and $–SR^6$;

R^3 is selected from H and halo;

R^4 is selected from H and $(C_1\text{-}C_3)$alkyl

R^5 is selected from H and halo;

R^6 is methyl;

R^7 is phenyl substituted by hydroxy wherein the hydroxyphenyl is optionally further substituted by halo;

provided that if R^2 is H then R^1 is XR^7.

2. The topical pharmaceutical composition according to claim 1, wherein the excipient system comprises PEG selected from PEG 100 to PEG 900, preferably PEG 400, and preferably wherein the PEG is present in an amount of from about 1% to about

60%, more preferably from about 5% to about 55%, most preferably from about 15% to about 50%, by weight of the composition.

3. The topical pharmaceutical composition according to claim 1 or claim 2, wherein the excipient system comprises glycol, dialkyl glycol monoalkyl ether or a combination thereof, preferably in an amount of from about 10% to about 70%, more preferably about 20% to about 55%, by weight of the composition, even more preferably wherein the excipient system comprises propylene glycol, and diethyl glycol monoethyl ether.

4. The topical pharmaceutical composition according to any preceding claim, wherein the excipient system comprises

(A) PEG selected from PEG 100 to PEG 900, preferably PEG 400, and preferably wherein the PEG is present in an amount of from about 1% to about 60%, more preferably from about 5% to about 50%, most preferably from about 15% to about 50%, by weight of the composition;

(B) glycol in an amount of from about 1% to about 30%, preferably from about 5% to about 25%, more preferably from about 10% to about 20%, by weight of the composition, preferably the glycol is propylene glycol; and/or

(C) dialkyl glycol monoalkyl ether in an amount of from about 1% to about 40%, preferably from about 10% to about 35%, more preferably from about 15% to about 30%, by weight of the composition, preferably the dialkyl glycol monoalkyl ether is diethyl glycol monoethyl ether.

5. The topical pharmaceutical composition according to any preceding claim, wherein the excipient system comprises

(a) an oleaginous base, such as petroleum jelly and/or PEG selected from PEG 1000 to PEG 10000 in an amount of from about 15% to 30% by weight of the composition, preferably the PEG is PEG 3350 and/or PEG 4000;or

(b) (i) a gelling agent in an amount of from about 0.5% to about 5%, preferably about 1% to about 3%, by weight of the composition, preferably the gelling agent is HPC MF or HPC GF; and

(ii) polyol, preferably glycerol, in an amount of from about 1% to about 25% by weight of the composition; or

(c) (i) water preferably in an amount of from about 10% to about 30% by weight of the composition;

(ii) an oil phase preferably in an amount of from about 0.5% to about 25% by weight of the composition;

(iii) an emollient, such as cetostearyl alcohol and/or Span 60, preferably in an amount of from about 5% to about 15% by weight of the composition;

(iv) an emulsifier, such as Tween, i.e. Tween 80, and preferably in an amount of from about 2% to about 10% by weight of the composition; and

(v) optionally a preservative, such as phenoxyethanol, in an amount of from about 0.1% to 5% by weight of the composition.

6. The topical pharmaceutical composition according to claim 5, wherein the oil phase comprises one or more triglycerides, such as crodamol GTCC, liquid paraffin, or a combination thereof.

7. The topical pharmaceutical composition according to any preceding claim, wherein the excipient system comprises

(a) an oleaginous base, such as petroleum jelly, and/or PEG selected from PEG 1000 to PEG 10000 in an amount of from about 15% to 30% by weight of the composition, preferably the PEG is PEG 3350 or PEG 4000; or

(b) (i) a gelling agent in an amount of from about 0.5% to about 5%, preferably about 1% to about 3%, by weight of the composition, preferably the gelling agent is HPC MF or HPC GF; and

(ii) polyol, preferably glycerol, in an amount of from about 1% to about 25% by weight of the composition.

8. The topical pharmaceutical composition according to any preceding claim, wherein the composition comprises an antioxidant, preferably BHT or ascorbic acid, in an amount of from about 0.01% to about 0.5%, preferably about 0.05% to about 0.2%, by weight of the composition, and optionally a UV filter, preferably octisalate, in an amount of from about 4% to about 8% by weight of the composition.

9. The topical pharmaceutical composition according to claim 1, wherein

(A) the compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof is present in an amount of from about 1% to about 3% by weight of the composition;

(B) the excipient system comprises

(i) PEG 400 in an amount of from about 35% to about 50% by weight of the composition;

(ii) propylene glycol in an amount of from about 5% to about 15% by weight of the composition;

(iii) diethyl glycol monoethyl ether in an amount of from about 15% to about 35% by weight of the composition;

(iv) PEG selected from PEG 1000 to PEG 10000 in an amount of from about 15% to 25% by weight of the composition, preferably the PEG is PEG 3350 or PEG 4000; and

(v) an antioxidant, preferably BHT, in an amount of from about 0.05% to about 0.5% by weight of the composition.

10. The topical pharmaceutical composition according to claim 1, wherein

(A) the compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof is present in an amount of from about 1% to about 3% by weight of the composition;

(B) the excipient system comprises

(i) PEG 400, preferably SR PEG 400, in an amount of from about 25% to about 45% by weight of the composition;

(ii) glycerol in an amount of from about 1% to about 25% by weight of the composition;

(iii) propylene glycol in an amount of from about 5% to about 25% by weight of the composition;

(iv) diethyl glycol monoethyl ether in an amount of from about 22% to about 28% by weight of the composition; and

(v) low molecular weight alcohol, preferably ethanol, in an amount of from about 2% to about 13% by weight of the composition;

(vi) a gelling agent in an amount of from about 1% to about 3%, by weight of the composition, preferably the gelling agent is HPC MF or HPC GF; and

(vii) optionally an antioxidant, preferably BHT, in an amount of from about 0.05% to about 0.5% by weight of the composition.

11. The topical pharmaceutical composition according to claim 1, wherein

(A) the compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof is present in an amount of from about 0.05% to about 2% by weight of the composition;

(B) the excipient system comprises

(i) PEG 400, preferably SR PEG 400, in an amount of from about 20% to about 28% by weight of the composition;

(ii) propylene glycol in an amount of from about 7% to about 17% by weight of the composition;

(iii) diethyl glycol monoethyl ether in an amount of from about 12% to about 18% by weight of the composition;

(iv) water in an amount of from about 17% to about 28% by weight of the composition;

(v) Tween 80 in an amount of from about 2% to about 10% by weight of the composition;

(vi) an oil phase comprising one or more triglycerides, such as crodamol GTCC; liquid paraffin, or a combination thereof in an amount of from about 0.5% to about 25%, preferably from about 3% to about 9%, by weight of the composition;

(vii) cetostearyl alcohol in an amount of from about 5% to about 15% by weight of the composition;

(viii) Span 60 in an amount of from about 0.2% to about 1.5% by weight of the composition;

(ix) optionally an antioxidant, preferably BHT or ascorbic acid, in an amount of from about 0.05% to about 0.5% by weight of the composition;

(x) optionally benzyl alcohol in an amount of from about 0.1% to about 5% by weight of the composition;

(xi) optionally a preservative, such as phenoxyethanol, in an amount of from about 0.1% to about 3% by weight of the composition; and

(xii) optionally a UV filter, such as octisalate.

12. The topical pharmaceutical composition according to any preceding claim, wherein in Formula (I)

R^1 is selected from -XR^7, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and a C-linked 4-6 membered heterocycloalkyl containing 1 to 2 heteroatoms selected from N, O and S, preferably R^1 is selected from

(a) (C_1-C_6)alkyl and (C_3-C_8)cycloalkyl, more preferably R^1 is (C_1-C_6)alkyl; or

(b) -XR^7 and a C-linked 4-6 membered heterocycloalkyl containing 1 to 2 heteroatoms selected from N, O and S, more preferably -XR^7 and a C-linked 4-6 membered heterocycloalkyl containing 1 to 2 heteroatoms selected from N and O;

R^2 is –SR^6;

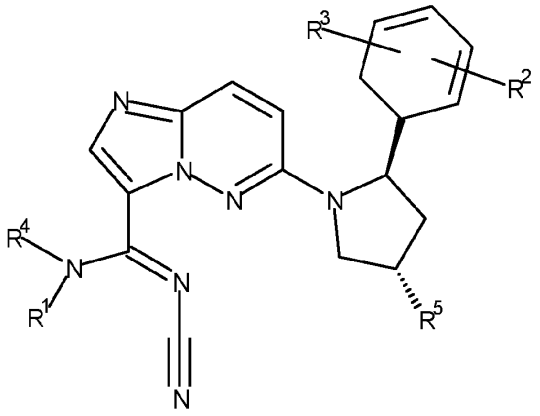
R^3 is H or fluoro;

R^4 is H;

R^5 is H or fluoro; and/or

R^7 is phenyl substituted by hydroxy wherein the hydroxyphenyl is optionally further substituted by fluoro.

13. The topical pharmaceutical composition according to any preceding claim, wherein the compound of Formula (I) is a compound of Formula (Ia)



(Ia)

or a pharmaceutically acceptable salt and/or solvate thereof, wherein R^1, R^2, R^3, R^4, and R^5 are as defined in claim 1 or claim 12.

14. The topical pharmaceutical composition according to any previous claim, wherein the compound of Formula (I) is selected from

N'-cyano-6-[2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3R)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;

N'-cyano-6-[2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;

N'-cyano-N-ethyl-6-[4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
N'-cyano-N-ethyl-6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
N-butyl-N'-cyano-6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
N'-cyano-N-cyclohexyl-6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide; and
N'-cyano-6-[2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboximidamide;
or a pharmaceutically acceptable salt and/or solvate thereof.

15. The topical pharmaceutical composition according to any previous claim, wherein the compound of Formula (I) is selected from
(Z)-N'-cyano-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3R)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboximidamide ;
(Z)-N'-cyano-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-oxan-3-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
(Z)-N'-cyano-N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-3-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
(Z)-N'-cyano-N-ethyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
(Z)-N-butyl-N'-cyano-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide;
(Z)-N'-cyano-N-cyclohexyl-6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboximidamide; and
(Z)-N'-cyano-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboximidamide;
or a pharmaceutically acceptable salt and/or solvate thereof.

16. The topical pharmaceutical composition according to any previous claim wherein the composition comprises a further therapeutic agent.

17. The topical pharmaceutical composition according to any previous claim for use in the treatment or prevention of a condition or disorder which is mediated by Trk, preferably the condition or disorder is mediated by TrkA, TrkB, and TrkC.

18. The topical pharmaceutical composition for use according to claim 17, wherein the condition or disorder is dermatitis, preferably atopic dermatitis.

19. A method for preventing or treating a condition or disorder which is mediated by Trk, which comprises administering to a subject a therapeutically effective amount of the topical pharmaceutical composition as defined in any one of claims 1 to 16, preferably wherein the condition or disorder is mediated by TrkA, TrkB, and TrkC.

20. The method according to claim 19, wherein the condition or disorder is dermatitis, preferably atopic dermatitis.

21. Use of a compound of Formula (I) as defined in any one of claims 1, and 12 to 15, in the manufacture of a medicament for the treatment of prevention of a condition or disorder which is mediated by Trk, preferably the condition or disorder is mediated by TrkA, TrkB, and TrkC, wherein the medicament comprises the topical pharmaceutical composition as defined in any one of claims 1 to 11, and 16.

22. The use according to claim 21, wherein the condition or disorder is dermatitis, preferably atopic dermatitis.