

TOPICAL PHARMACEUTICAL COMPOSITIONS COMPRISING IMIDAZO[1,2-B]PYRIDAZINE COMPOUNDS

The present invention relates to pharmaceutical compositions, such as topical pharmaceutical 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, secretory 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; Urashima R, Mihara M .Virchows Arch. 1998;432:363-370; Kinkelin I, Motzing S,

- Koltzenburg M, Brocker EB., *Cell Tissue Res.* 2000;302:31-37; Tong Liu & Ru-Rong Ji, *Pflugers Arch - Eur J Physiol*, DOI 10.1007/s00424-013-1284-2, published online 1 May 2013.); International Patent Application publication numbers WO2012/158413, WO2013/088256, WO2013/088257 and WO2013/161919, (Brodeur, G. M., *Nat. Rev. Cancer* 2003, 3, 203-216), (Davidson. B. , et al. , *Clin. Cancer Res.* 2003, 9, 2248-2259), (Bardelli, A , *Science* 2003, 300, 949), (Truzzi, F. , et al. , *Dermato-Endocrinology* 2008, 3 (I), pp. 32-36), Yilmaz,T. , et al. , *Cancer Biology and Therapy* 2010, 10 (6), pp. 644-653), (Du, J. et al. , *World Journal of Gastroenterology* 2003, 9 (7), pp. 1431-1434), (Ricci A, et al., *American Journal of Respiratory Cell and Molecular Biology* 25 (4), pp. 439-446), (Jin, W. , et al. , *Carcinogenesis* 2010, 31 (11), pp. 1939-1947), (Wadhwa, S. , et al., *Journal of Biosciences* 2003, 28 (2), pp. 181-188), (Gruber-Olipitz, M. , et al. , *Journal of Proteome Research* 2008, 7 (5), pp. 1932-1944), (Euthus, D. M. et al. , *Cancer Cell* 2002, 2 (5), pp. 347-348), (Li, Y. -G. , et al., *Chinese Journal of Cancer Prevention and Treatment* 2009, 16 (6), pp. 428-430), (Greco, A , et al. , *Molecular and Cellular Endocrinology* 2010, 321 (I), pp. 44-49), (Eguchi, M., et al., *Blood* 1999, 93 (4), pp. 1355-1363), (Nakagawara, A (2001) *Cancer Letters* 169: 107-114; Meyer, J. et al. (2007) *Leukemia*, 1-10; Pierottia, M. A and Greco A, (2006) *Cancer Letters* 232:90- 98; Eric Adriaenssens, E., et al. *Cancer Res* (2008) 68:(2) 346-351), (FreundMichel, V; Frossard, N. *Pharmacology ck Therapeutics* (2008) 117(1), 52-76), (Hu Vivian Y; et. al. *The Journal of Urology* (2005), 173(3), 1016-21), (Di Mola, F. F, et. al. *Gut* (2000) 46(5), 670-678) (Dou, Y. -C. ,et. al. *Archives of Dermatological Research* (2006) 298(1), 31-37), (Raychaudhuri, S. P. , et al. , *J. Investigative Dermatology* (2004) 122(3), 812-819) and (de Melo-Jorge, M. et al. , *Cell Host ck Microbe* (2007) 1 (4), 251-261).
- 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

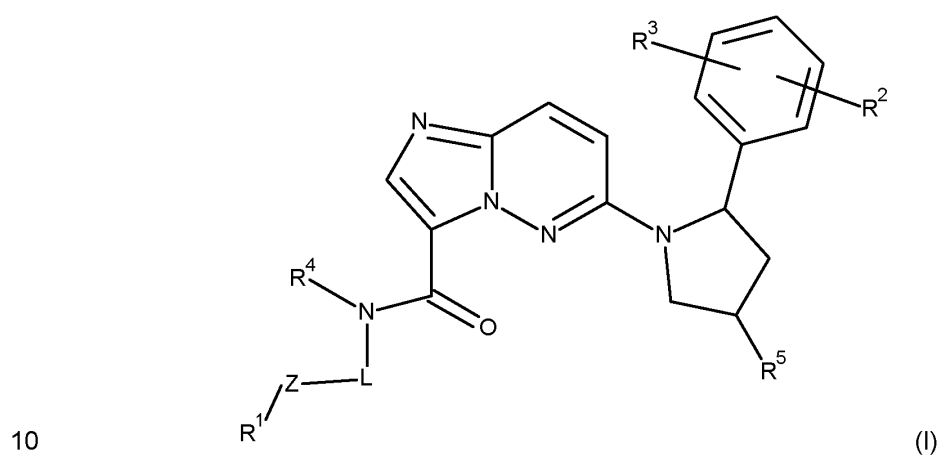
therapeutic amounts of API to the dermis and epidermis. Other advantages of the claimed pharmaceutical compositions will also be apparent.

In a first aspect, the invention provides a topical pharmaceutical composition comprising

5 (a) a compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof; and

(b) an excipient system,

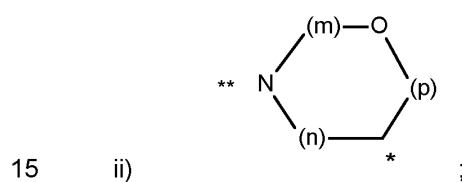
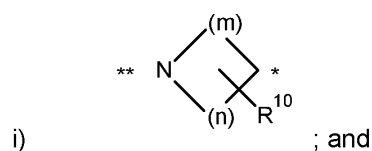
wherein the compound of formula (I) is



wherein:

L is $(CR^6R^7)_r$;

Z is absent or selected from:



wherein * denotes the point of attachment to L and ** denotes the point of attachment to R^1 ;

m is 1 or 2;

n is 1 or 2;

20 p is 0 or 1;

- provided that the sum of m, n and p is in the range of 2 to 4;
 r is 0 or 1;
 R^1 is $-XR^9$;
 X is selected from $-CH_2-$, $-C(O)-$, and $-S(O_2)-$;
- 5 R^2 is selected from H and $-SR^8$;
 R^3 is selected from H and halo;
 R^4 is selected from H and (C_1-C_3) alkyl;
 R^5 is selected from H, hydroxyl and halo;
 R^6 and R^7 are each independently selected from H and (C_1-C_3) alkyl;
- 10 R^8 is methyl;
 R^9 is phenyl substituted by a group selected from hydroxy, $-OC(O)(C_1-C_6)$ alkyl, $C(O)OH$ and $-C(O)O(C_1-C_6)$ alkyl, wherein the phenyl ring is optionally further substituted by halo;
 R^{10} is selected from H and (C_1-C_3) alkoxy.
- 15 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".
- 20 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
- 25 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
- 30 topical composition in an amount of less than about 99.99 % by weight of the composition.
- As used herein, the terms "about" means $\pm 10\%$, preferably $\pm 5\%$, more preferably $\pm 2\%$, most preferably $\pm 1\%$, of the associated value.
- 35 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
5 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),
10 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
15 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.

20 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
25 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.

30 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,
35 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%,
5 more preferably from about 5% to about 50%, by weight of the composition.

The excipient system may comprise glycol, polyol, dialkyl glycol monoalkyl ether or a combination thereof. It is preferably that the glycol, polyol, dialkyl glycol monoalkyl ether or a combination thereof is present in an amount of from about 10% to about 70%, more
10 preferably about 20% to about 60%, 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,
15 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, "polyol" means a chemical compound that contains three or more hydroxyl groups. Such compounds include, but are not limited to, glycerol, butanetriol,
20 pentanetriol, and polyethylene triols, in particular containing from 4 to 8 ethylene oxide units, and their mixtures.

As used herein, "dialkyl glycol monoalkyl ether" includes, but is not limited to, diethylene glycol monoethyl ether (Transcutol P).
25

Without wishing to be bound by theory, it is 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
30 compound of Formula (I) in amounts in excess of 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
35 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%, by weight of the composition;
- (B) glycol in an amount of from about 1% to about 30%, preferably from about 5% to about 25%, 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 30%, preferably from about 5% to about 25%, by weight of the composition, preferably the dialkyl glycol monoalkyl ether is diethyl glycol monoethyl ether.

10

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

A further feature is that the excipient system may optionally comprise, in addition to components (A) and (C), the additional component

15

- (D) polyol in an amount of from about 1% to about 30%, preferably from about 5% to about 25%, by weight of the composition.

When present, it is preferable that the polyol is glycerol.

20

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 20% 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.

25

Particularly beneficial non-aqueous gel-based topical compositions may comprise, as part of the excipient system, a gelling agent 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). 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

35

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.

5

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 35% 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.

15

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.

20 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.

25 The topical compositions of the invention may have increased stability (both chemical and physical stability), compared to those of the prior art. Ointments, aqueous gels 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

- 30 (a) an oleaginous base, such as petroleum jelly, and/or PEG selected from PEG 1000 to PEG 10000 in an amount of from about 20% to about 30% by weight of the composition, preferably the PEG is PEG 3350 or PEG 4000; or
- (b) a gelling agent in an amount of from about 0.5% to about 5%, preferably from about 1% to about 3%, by weight of the composition, preferably the gelling agent is HPC MF or HPC GF, and optionally wherein the excipient system
- 35 further comprises

- (i) water in an amount of from about 10% to about 30% by weight of the composition; and
- (ii) benzyl alcohol in an amount of from about 0.1% to about 5% by weight of the composition.

5

The excipient system, particular that of non-aqueous gel-based compositions, may comprise low molecular weight alcohol, i.e. C₁ to C₅ 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
10 alcohol may be in the excipient system in an amount of from about 2% to about 8% 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
15 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,
20 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
25 solvate thereof present in an amount of from about 1% to about 5% by weight of the composition;
- (B) the excipient system which comprises
 - (i) PEG 400 in an amount of from about 15% to about 35% by weight of the composition;
 - 30 (ii) glycerol in an amount of from about 12% to about 22% by weight of the composition;
 - (iii) propylene glycol in an amount of from about 5% to about 15% by weight of the composition;
 - (iv) diethyl glycol monoethyl ether in an amount of from about 5% to about
35 25% by weight of the composition;

- (v) PEG selected from PEG 1000 to PEG 10000 in an amount of from about 20% to 30% by weight of the composition, preferably the PEG is PEG 3350 or PEG 4000; and
- (vi) an antioxidant, preferably BHT, in an amount of from about 0.05% to about 0.5% by weight of the composition.

A specific aqueous gel and non-aqueous gel-based topical compositions 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 0.5% to about 4% 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 17% to about 23% by weight of the composition;
 - (iii) propylene glycol in an amount of from about 17% to about 23% by weight of the composition;
 - (iv) diethyl glycol monoethyl ether in an amount of from about 7% to about 13% by weight of the composition; and
 - (v) either
 - (a) low molecular weight alcohol, preferably ethanol, in an amount of from about 2% to about 8% by weight of the composition; or
 - (b) water in an amount of from about 10% to about 30% by weight of the composition; and
 - benzyl alcohol in an amount of from about 0.1% to about 5% 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 and/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 0.3% to about 1.5% by weight of the composition;
- (B) the excipient system which comprises
- 5 (i) PEG 400, preferably SR PEG 400, in an amount of from about 5% to about 15% by weight of the composition;
- (ii) glycerol in an amount of from about 5% to about 15% by weight of the composition;
- 10 (iii) propylene glycol in an amount of from about 7% to about 13% by weight of the composition;
- (iv) diethyl glycol monoethyl ether in an amount of from about 12% to about 17% by weight of the composition;
- (v) water in an amount of from about 20% to about 35% by weight of the composition;
- 15 (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; and
- 20 (viii) Span 60 in an amount of from about 0.2% to about 1% by weight of the composition; and
- (ix) optionally Tween 80 in an amount of from about 2% to about 10% by weight of the composition;
- 25 (x) 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;
- (xi) optionally benzyl alcohol in an amount of from about 0.1% to about 5% by weight of the composition; and
- 30 (xii) optionally a UV filter, such as octisalate, preferably in an amount of from about 4% to about 8% by weight of the composition.

The skilled person will understand the processes that may be used to form the topical pharmaceutical compositions of the invention. The topical compositions may

35 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
5 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,
10 propylene glycol, glycerol, 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
15 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).

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

In one embodiment of the invention as defined anywhere above, R^1 is $-\text{CH}_2\text{R}^9$.

25 In another embodiment of the invention as defined anywhere above, R^2 is $-\text{SR}^8$.

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.

30 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^5 is H.

35 In another embodiment of the invention as defined anywhere above, R^6 is H.

In another embodiment of the invention as defined anywhere above, R⁹ is phenyl substituted by hydroxy wherein the hydroxyphenyl is optionally further substituted by fluoro.

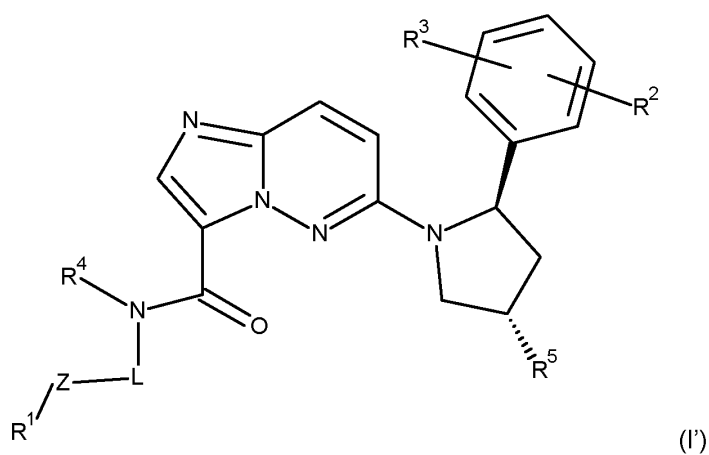
5 In another embodiment of the invention as defined anywhere above, R¹⁰ is H.

In another embodiment of the invention as defined anywhere above, r is 0.

In another embodiment of the invention as defined anywhere above, Z is absent.

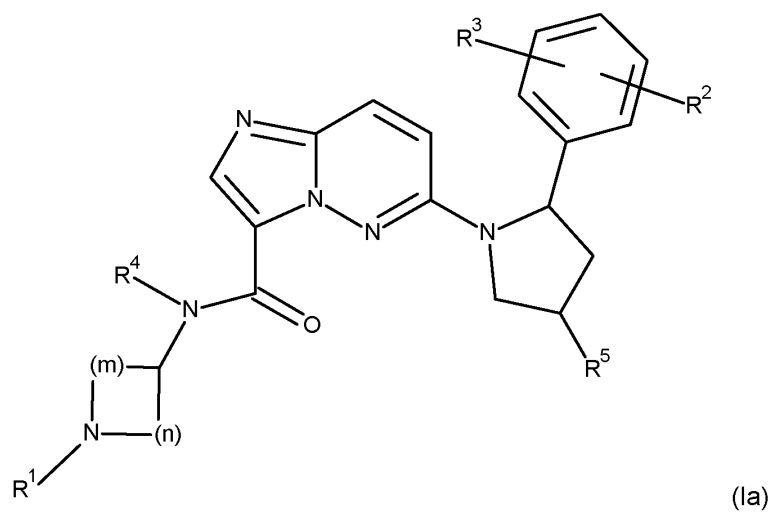
10

In another embodiment, the compound of Formula (I) is a compound of Formula (I')



15 or a pharmaceutically acceptable salt and/or solvate thereof wherein R¹, R², R³, R⁴, R⁵, L and Z, are as defined anywhere hereinabove in respect of a compound of Formula (I).

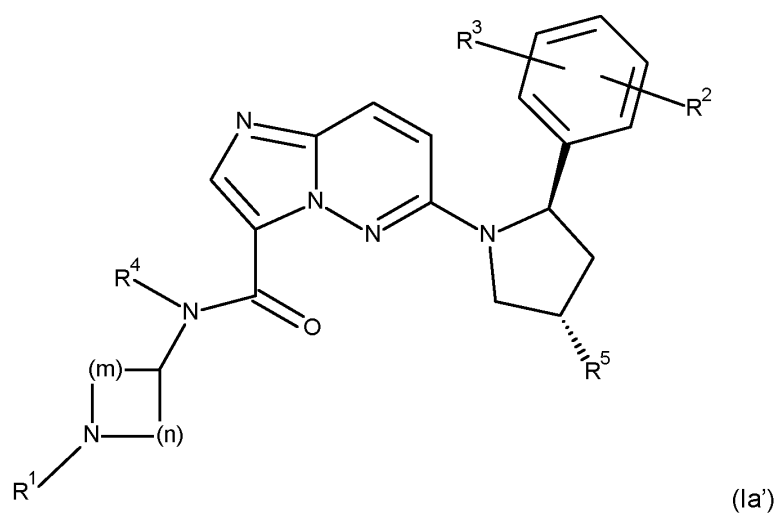
In another embodiment, the compound of Formula (I) is a compound of Formula (Ia)



or a pharmaceutically acceptable salt and/or solvate thereof wherein R¹, R², R³, R⁴, R⁵, m and n, are as defined anywhere hereinabove in respect of a compound of Formula (I).

5

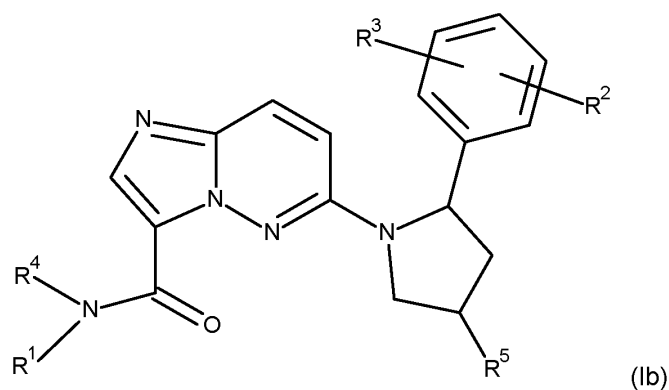
In a further embodiment, the compound of Formula (I) is a compound of Formula (Ia')



10 or a pharmaceutically acceptable salt and/or solvate thereof wherein R¹, R², R³, R⁴, R⁵, m and n, are as defined anywhere hereinabove in respect of a compound of Formula (I).

In an alternative embodiment, the compound of Formula (I) is a compound of Formula (Ib)

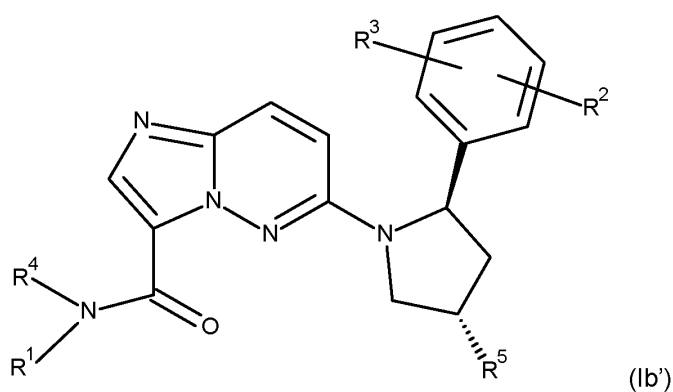
15



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

5

In a further embodiment, the compound of Formula (I) is a compound of Formula (Ib')



10 or a pharmaceutically acceptable salt or solvate thereof wherein R^1 , R^2 , R^3 , R^4 , R^5 , m and n , 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.

15

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 to 31 or a pharmaceutically acceptable salt and/or solvate thereof.

20

In another embodiment of the invention, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) which is selected from:

- 6-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 5 6-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 10 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 15 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 3-{[3-{6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}phenyl pentanoate;
- 20 Methyl 3-{[3-{6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}benzoate;
- 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 25 Butyl 3-{[3-{6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}benzoate;
- Ethyl 3-{[3-{6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}benzoate;
- 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(4-fluoro-3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 30 N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]-6-[2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- Methyl 3-{[3-{6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}benzoate;
- 35 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;

- 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
 5 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
 10 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]-4-methoxypyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[4-[(4-fluoro-3-hydroxyphenyl)methyl]-1,4-oxazepan-6-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
 15 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(4-fluoro-3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-(3-hydroxybenzoyl)pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
 3-[[3-{6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]phenyl acetate;
 20 3-[[3-{6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoic acid;
 Butyl 3-[[3-{6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate;
 25 5-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}pyrazolo[1,5-a]pyrimidine-3-carboxamide;
 or a pharmaceutically acceptable salt and/or solvate thereof.

- In another embodiment of the invention, there is provided a topical pharmaceutical
 30 composition comprising a compound of Formula (I) which is selected from:
 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
 35 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;

- 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 5 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide};
- 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 10 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]phenyl pentanoate;
- Methyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]benzoate];
- 15 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- Butyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]benzoate];
- Ethyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]benzoate];
- 20 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(4-fluoro-3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide;
- N-[(3S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]-6-[(2R)-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 25 Methyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]benzoate];
- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 30 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 35 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;

- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S,4S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]-4-methoxypyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-
 5 carboxamide;
 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(6S)-4-[(4-fluoro-3-hydroxyphenyl)methyl]-1,4-oxazepan-6-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(6R)-4-[(4-fluoro-3-hydroxyphenyl)methyl]-1,4-oxazepan-6-yl]imidazo[1,2-b]pyridazine-3-
 10 carboxamide;
 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(4-fluoro-3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-(3-hydroxybenzoyl)pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
 15 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]phenyl acetate;
 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]benzoic acid;
 20 Butyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]benzoate;
 5-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}pyrazolo[1,5-a]pyrimidine-3-carboxamide;
 or a pharmaceutically acceptable salt or solvate thereof.

25

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.

30

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
 35 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.

10

"C₁-C₃ alkyl", "C₁-C₆ alkyl", "C₁-C₈ 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.

"C₃-C₈-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.

30

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 preferably about 1-4 carbons.

35

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
 5 organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlorthephylionate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate,
 10 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.

15 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
 20 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.

25 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.

30

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, choline, diethanolamine, diethylamine, lysine, meglumine,
 35 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, isobutyrate,
5 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,
10 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
15 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
20 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
25 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.

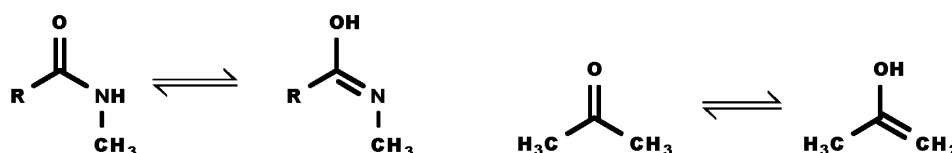
Compounds of the invention that contain groups capable of acting as donors and/or
30 acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures 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.
35 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
5 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.

10

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
15 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
20 compound may exhibit more than one type of isomerism. Examples of types of potential tautomerisms shown by the compounds of the invention include; amide $\rightleftharpoons$ hydroxyl-imine and keto $\rightleftharpoons$ enol tautomerisms:



25 *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
30 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%.

- 5 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)).

10

- 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
- 15 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
- 20 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
- 25 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
- 30 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
- 35 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 topical 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).

5

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.

- 10 Pharmaceutically acceptable prodrugs of a compound of Formula (I) may also be used in the topical composition 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
- 15 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.
- 20 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
- 25 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 prodrugs 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,
- 30 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
- 35 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 alkoxy carbonyl)-lower alkyl esters, the α -(lower alkanoyloxy, lower alkoxy carbonyl 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*
5 *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
10 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 ^2H , ^3H , ^{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 ^2H or
15 ^3H), 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
20 may be particularly preferred for PET studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) 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
25 studies. The radioactive isotopes tritium, i.e. ^3H , 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
30 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., ^2H or D) may
35 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.* D₂O, d₆-acetone, d₆-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*") Chapter 5 ("*Protection for the Carboxyl group*"), and Chapter 7 ("*Protection for the Amino 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

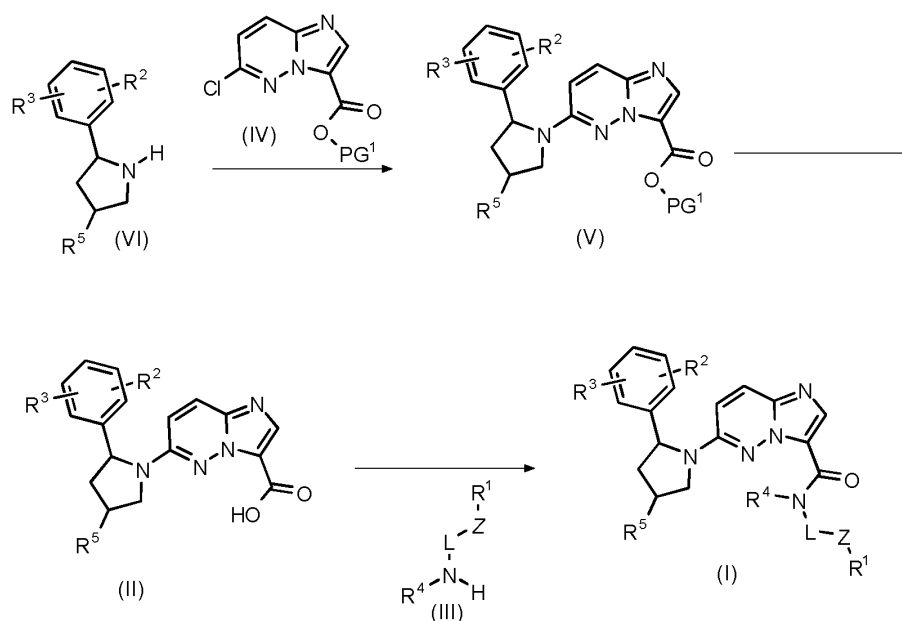
different order from that described in the schemes, or to modify one or more of the transformations, to provide the desired compound of the invention.

Compounds prepared according to the schemes described above may be obtained as
5 single enantiomers, diastereomers, or regioisomers, by enantio-, diastereo-, 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
10 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.

15
The compounds of Formula (I) 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
20 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
25 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 Formula (I).

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



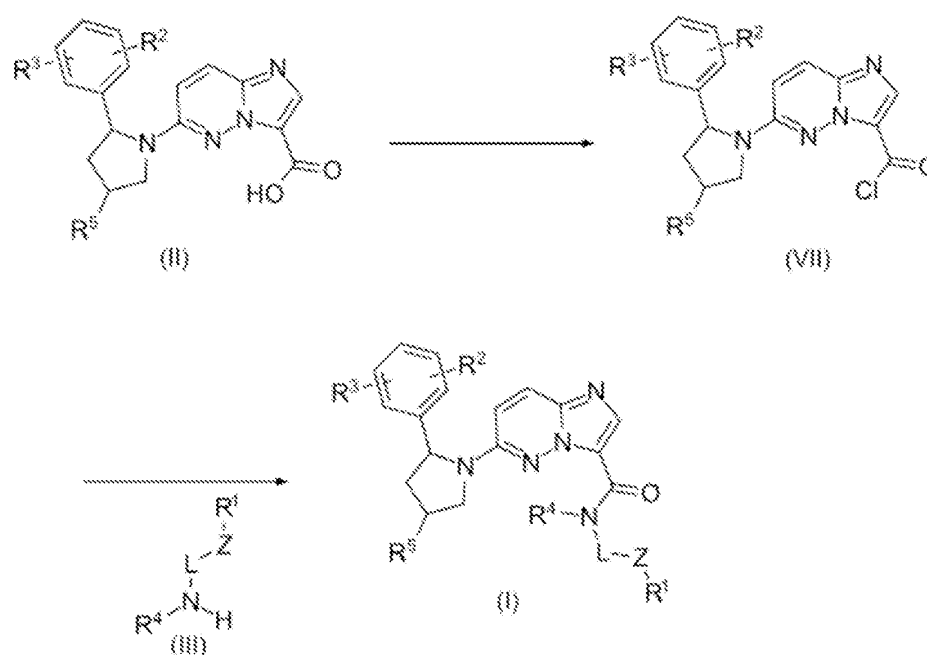
Scheme 1

PG¹ is C1-C4 alkyl, preferably Me or Et. The amine of Formula (III) is commercially available or may be prepared by analogy to methods known in the literature or as illustrated in **Scheme 6**. The chloride of Formula (IV) is commercially available or may be prepared by analogy to methods known in the literature. Compounds of Formula (VI) 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 (VI) may be prepared by analogy with the methods described by Huihui et. al. (*J.A.C.S.*, 2016, **138**, 5016-5019). The compound of Formula (V) may be prepared by treatment of the amine of Formula (VI) with the chloride of Formula (IV), in the presence of an inorganic base in a polar aprotic solvent at elevated temperature. Preferred conditions comprise treatment of the compound of Formula (IV) with the amine of Formula (VI) 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 compound of Formula (V) under suitable acidic or basic conditions in a suitable aqueous solvent. Preferred conditions comprise the treatment of the ester of Formula (V) with KOH in aqueous EtOH at room temperature. The compound of Formula (I) 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 or TPTU, in the presence of a suitable organic base,

typically DIPEA in a suitable solvent, such as DMF at room temperature. When R⁹ is a hydroxyl substituted phenyl group an appropriate phenol protecting group strategy, as selected by a person skilled in the art, may be employed, such as for example a silyl protecting group.

5

Alternatively, a compound of Formula (I) may be prepared from the compounds of Formulae (II), (III) and (VII) as illustrated by **Scheme 2**.



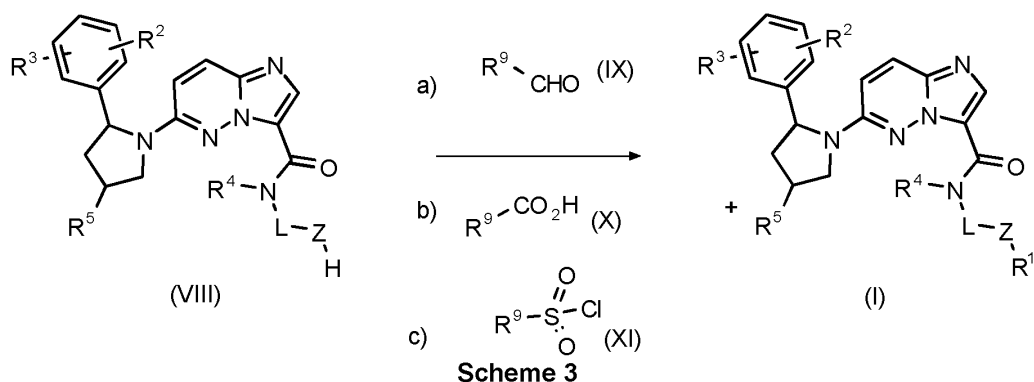
10

Scheme 2

The amine of Formula (I) may be prepared by formation of the acid chloride of Formula (VII) from the acid of Formula (II), typically using oxalyl chloride and DMF in DCM at room temperature and the subsequent amide bond formation of the acid chloride of Formula (VII) and the amine of Formula (III) in the presence of a suitable organic base, typically triethylamine at 0°C.

Alternatively, compounds of Formula (I), wherein Z is present may be prepared from compounds of Formulae (VIII), (IX), (X) and (XI) using either a reductive amination (a), amidation (b) or sulphonamide formation reaction as illustrated in **Scheme 3**.

20



Scheme 3

When Z is present and X is $-CH_2-$, the compound of Formula (I) may be prepared by the

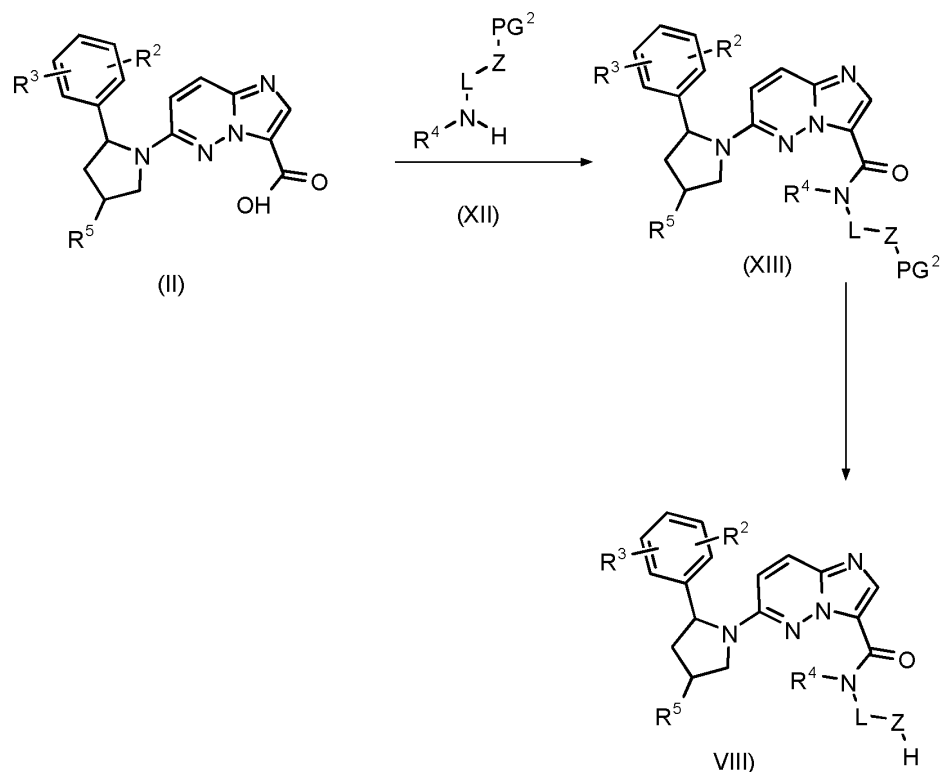
5 reductive amination (alternatively known as reductive alkylation) of an amine of Formula (VIII) with an aldehyde of Formula (IX) using a suitable reducing agent such as sodium triacetoxyborohydride in a suitable solvent such as DCM at an appropriate temperature such as room temperature. When Z is present and X is $-C(O)-$, the amide of Formula (I)

10 may be prepared by an amide bond formation of the acid of Formula (X) and the amine of Formula (VIII) 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 (X) with the amine of Formula (X) in the presence of HATU, in the presence of a suitable organic base, typically DIPEA in DMF at room temperature. When Z is present

15 and X is $-S(O)_2-$, the sulfonamide of Formula (I) may be prepared by reaction of the amine of Formula (VIII) with a sulfonyl chloride of Formula (XI) in the presence of an organic base, such as Et_3N or DIPEA, in a suitable solvent such as DCM at room temperature. Where R^9 is a hydroxy substituted phenyl group an appropriate phenol protecting group strategy, as selected by a skilled person, may be employed. Where R^9 is a carboxyl substituted phenyl group an appropriate acid protecting group strategy, as

20 selected by a skilled person, may be employed. Preferably, the protecting group is an alkyl ester, such as methyl.

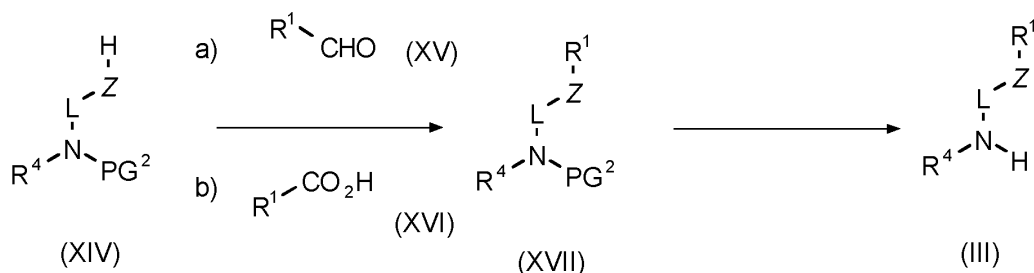
Compounds of Formula (VIII), may be prepared from compounds of Formulae (II), (XII), and (XIII), as illustrated in **Scheme 4**.



Scheme 4

PG² is a N protecting group, typically a carbamate and preferably Boc. The amine of
 5 Formula (XII) is commercially available or may be prepared by analogy to methods
 known in the literature or as illustrated in Scheme 6. The amide of Formula (XIII) may be
 prepared by an amide bond formation of the acid of Formula (II) and the amine of
 Formula (XII) 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
 10 Formula (II) with the amine of Formula (XII) in the presence of HATU, in the presence of
 a suitable organic base, typically DIPEA in DMF at room temperature. The amine of
 Formula (VIII) may be prepared by a suitable deprotection reaction typically involving
 treatment of the compound of Formula (XIII) with an acid such as HCl or TFA in a
 suitable aprotic solvent such as DCM or dioxane at an appropriate temperature such as
 15 0°C to reflux temperature, preferably at room temperature.

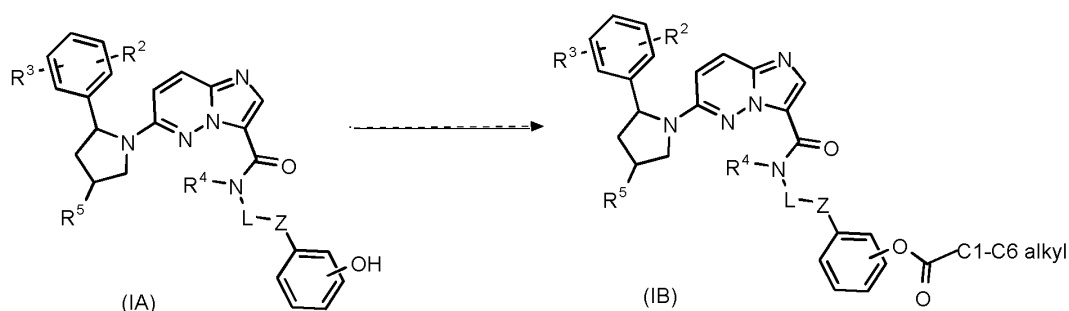
Compounds of Formula (III), may be prepared from compounds of Formulae (XIV), (XV),
 (XVI) and (XVII) as illustrated in **Scheme 5**.



Scheme 5

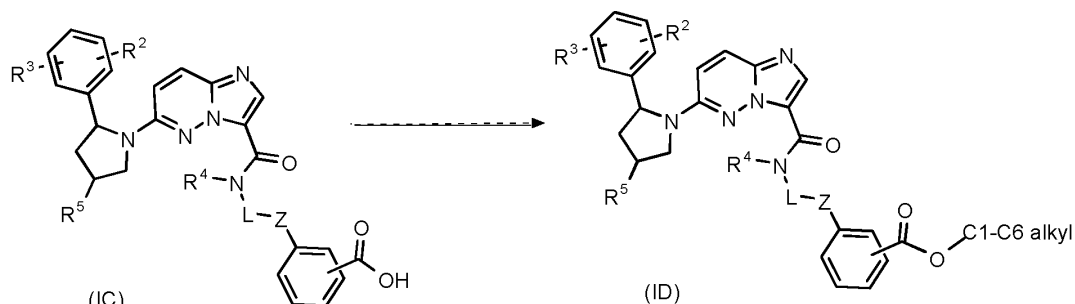
PG² is a suitable amine protecting group, typically a carbamate and preferably Boc. The compounds of Formulae (XIV), (XV) and (XVI) are commercially available or may be prepared by analogy to methods known in the literature. The amine of Formula (XVII) may be prepared using either a reductive amination (a) or amidation (b) procedure of compounds of Formula (XV) and (XVI) as previously described in **Scheme 3**. The amine of Formula (III) may be prepared by a suitable amine deprotection reaction as previously described in **Scheme 4**.

In a further embodiment, compounds of Formula (I) may be converted to alternative compounds of Formula (I) using standard chemical transformations as illustrated in **Scheme 6** and **Scheme 7**. Compounds of Formula (IB), wherein R⁹ is phenyl substituted by -OC-(O)(C₁-C₆)alkyl, may be prepared from compounds of Formula (IA), wherein R⁹ is phenyl substituted by OH, by treatment with a suitable (C₁-C₆)COCl or anhydride in the presence of an organic base, such as pyridine at room temperature.



Scheme 6

Compounds of Formula (ID), wherein R⁹ is phenyl substituted by -C-(O)O(C₁-C₆)alkyl, may be prepared from compounds of Formula (IC), wherein R⁹ is phenyl substituted by -C(O)₂H, by treatment with a suitable (C₁-C₆)OH in the presence of a suitable coupling agent such as DMAP and EDC.HCl at room temperature as illustrated in **Scheme 7**.



Scheme 7

5 The above general schemes may be used to prepare compounds of Formula (I). 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
10 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
15 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
20 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
25 removed readily (i.e. without the occurrence of undesired secondary reactions) for
30

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
5 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,
10 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
15 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
20 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
25 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
30 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
35 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
5 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
10 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 °C to about 190 °C, including, for
example, from approximately -80 °C to approximately 150 °C, for example at from -80 to
-60 °C, at room temperature, at from -20 to 40 °C or at reflux temperature, under
15 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
20 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,
25 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
30 *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
35 chromatography or partitioning.

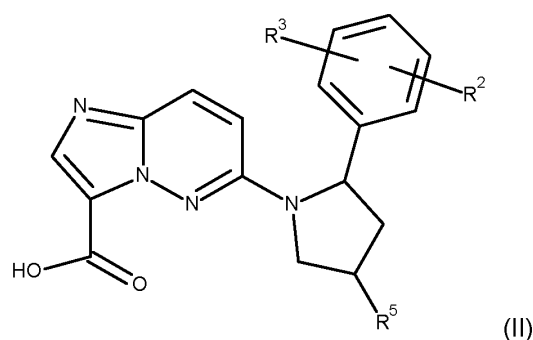
The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

- 5 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
10 invention is produced under the process conditions and processed further in situ.

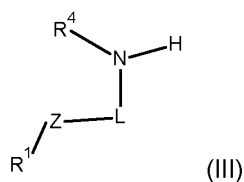
All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known
15 to one of ordinary skill in the art (Houben-Weyl 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
20 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:
25 amide bond formation via acid-amine coupling of the acid of Formula (II)

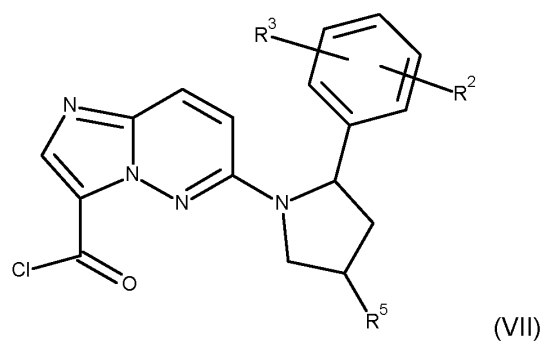


and the amine of Formula (III)

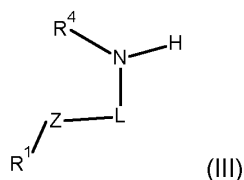


in the presence of a suitable coupling agent and organic base in a suitable polar aprotic solvent., wherein R^1 , R^2 , R^3 , R^4 and R^5 , L and Z are as defined anywhere hereinabove in
 5 respect of a compound of Formula (I).

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, comprising the step of:
 10 amide bond formation of the acid chloride of Formula (VII)

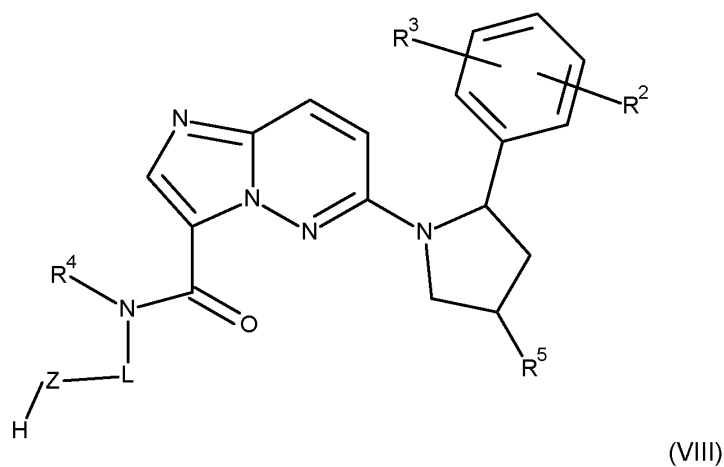


and the amine of Formula (III)



15 in the presence of a suitable coupling agent and organic base in a suitable polar aprotic solvent., wherein R^1 , R^2 , R^3 , R^4 and R^5 , L and Z 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
 20 compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, which is to be included in the claimed topical composition, wherein Z is present and X is $-\text{CH}_2-$, comprising the step of:
 reductive amination of an amine of Formula (VIII)



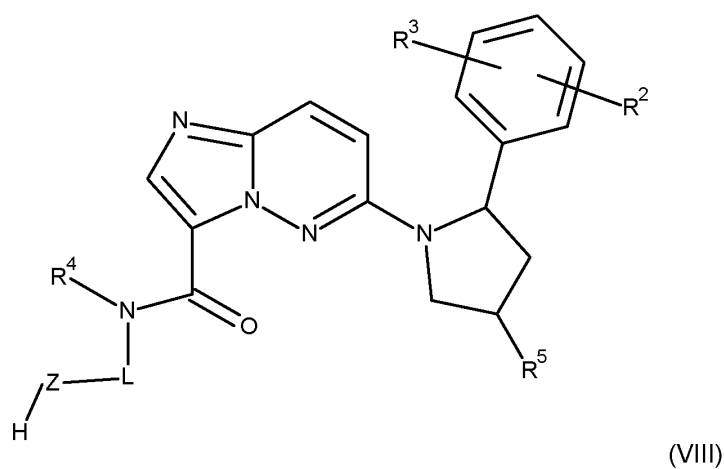
with an aldehyde of Formula (IX)



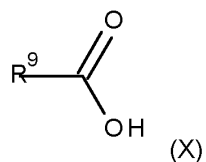
in the presence of a suitable reducing agent in a suitable solvent such as DCM at an appropriate temperature such as room temperature, wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^9 , L and Z are as defined anywhere hereinabove in respect of a compound of Formula (I).

- 10 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 Z is present and X is ---C(O)--- , comprising the step of:
- amide bond formation via acid-amine coupling of the amine of Formula (VIII)

15



and the acid of Formula (X)



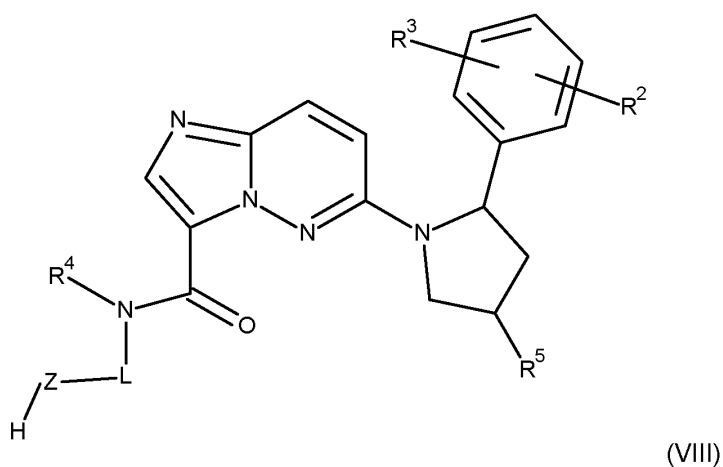
5

in the presence of a suitable coupling agent and organic base in a suitable polar aprotic solvent, wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^9 , L and Z are as defined anywhere hereinabove in respect of a compound of Formula (I).

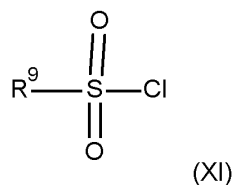
- 10 According to a further aspect of the invention there is provided a process of preparing a compound of Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, which is to be included in the claimed topical composition, wherein Z is present and X is $-S(O)_2-$, comprising the step of:

sulphonamide bond formation of the amine of Formula (VIII)

15



and the sulfonyl chloride of Formula (XI)



20

in the presence of a suitable coupling agent and organic base in a suitable polar aprotic solvent., wherein R¹, R², R³, R⁴, R⁵ and R⁹, L and Z are as defined anywhere hereinabove in respect of a compound of Formula (I).

5

The most preferred compound of Formula (I) is that of example 7.

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
10 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
15 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.

20 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),
25 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
30 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 Formula (I) 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
35 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).

- 5 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 ;
 10 dermatitis, atopic; eczema ;dermatitis, contact ; dermatitis, allergic contact ; dermatitis, irritant ; dermatitis, photoallergic ; dermatitis, phototoxic ; psoriasis ; pruritus; pruritus ani; pruritus, hereditary localized; Sjogrens syndrome associated pruritus; idiopathic pruritus; sclerosis multiplex pruritus; prurigo nodularis; brachioradial pruritus; acute itch; chronic itch; diabetes pruritus; iron deficiency anaemia pruritus; polycythemia vera pruritus; graft-
 15 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;
 20 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
 25 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;
 30 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 ;
 35 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 ;

5 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; erythemosquamous dermatosis; poikiloderma with neutropenia; erythema multiforme; angiolymphoid hyperplasia with eosinophilia; keratosis palmoplantaris striata 3; acne

10 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

15 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

20 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.

25

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

Therefore, according to a further aspect, the invention provides a topical pharmaceutical composition 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,

30 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

35 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
5 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,
10 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
15 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
20 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
25 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
30 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
35 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.

5

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.

15

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.

20

The topical pharmaceutical compositions of the invention may comprise one or more additional 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 compositions of the invention may be administered either simultaneously with, or before or after, one or more other therapeutic agent. The topical pharmaceutical compositions 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.

- 5 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
10 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
15 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
20 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
25 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
30 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
35 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.

5

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
10 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
15 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.

20

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
25 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
30 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
35 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.

5 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
10 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
15 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;
20 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.

25

In vitro assays

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

30

To determine the IC₅₀ 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.

35 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 (1 μ M). 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 Eu³⁺-cryptate (1:200 dilutions) and Streptavidin-XL665 (250nM). Assay plates were incubated
- 5 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
- 10 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. IC₅₀ was determined by plotting compound inhibition at respective dose in Graphpad prism5 using four parameter logistic curve fit.
- 15 Using the assay described above, the compounds of Formula (I) all exhibit of Trk inhibition activity, expressed as an IC₅₀ value, of less than 1 μ M. Preferred examples have IC₅₀ values of less than 200nM and particularly preferred examples have IC₅₀ values of less than 50nM. IC₅₀ values for the compounds of Examples 1 to 31 are given below in Table 1.

20

Example Number	TrkA Enz (nM)	TrkB Enz (nM)	TrkC Enz (nM)
1	1.77	2.06	2.81
2	1.78	3.33	3.36
3	0.92	0.79	1.19
4	1.75	1.05	1.93
5	1.90	1.19	2.11
6	1.47	0.81	1.56
7	0.90	0.49	1.25
8	0.79	1.51	1.64
9	3.81	8.76	8.43
10	1.18	2.15	2.12
11	1.57	2.27	2.46
12	3.82	10.3	10.9

13	1.70	2.53	2.01
14	0.95	0.57	1.47
15	4.86	9.15	8.30
16	1.73	4.54	3.28
17	2.41	5.04	4.62
18	2.87	7.82	5.19
19	2.46	3.04	2.99
20	2.69	3.76	3.72
21	1.48	1.50	1.97
22	1.40	2.01	2.13
23	2.37	10.3	6.85
24	6.90	23.6	17.3
25	6.10	11.4	8.72
26	1.87	1.85	2.97
27	1.34	1.01	1.87
28	4.63	5.67	4.88
29	5.84	5.34	3.98
30	22.4	14.9	22.4
31	1.38	0.86	1.38

EXAMPLES

- 5 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.

10 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.

- 15 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.
- 10 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 ₂ CO ₃	Cesium carbonate
Cy	cyclohexane
δ	chemical shift
d	doublet
dd	double doublet
ddd	Doublet of doublets of doublets
DCM	dichloromethane
DIPEA	N-ethyldiisopropylamine or N,N-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d ₆	hexadeuterodimethyl sulfoxide
Et	ethyl
Et ₃ N	triethylamine
EtOH	ethanol

EtOAc	ethyl acetate
g	gram
HCl	hydrochloric acid
HATU	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)
H ₂ O	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
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 <i>tert</i> -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 ₄ Cl	ammonium chloride
Na ₂ SO 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.

¹H 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 ¹H-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: CDCl₃, deuteriochloroform; DMSO-d₆, hexadeuterodimethyl sulfoxide; and MeOD-d₄, deuterio-methanol. Where appropriate, tautomers may be recorded within the NMR data; and some exchangeable protons may not be visible.

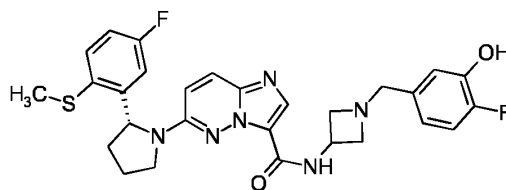
Mass spectra, MS (m/z), were recorded using either electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI). Where relevant and unless otherwise stated the m/z data provided are for isotopes ¹⁹F, ³⁵Cl, ⁷⁹Br and ¹²⁷I.

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

6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide



A suspension of N-(azetidin-3-yl)-6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 17, 100 mg, 0.23 mmol), 4-fluoro-3-hydroxybenzaldehyde (36 mg, 0.26 mmol) and sodium triacetoxyborohydride (36 mg, 0.32 mmol) in DCM (4 ml) was stirred at rt overnight. The reaction was quenched using sat NaHCO₃ and extracted with DCM, the combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude material was purified by reverse phase

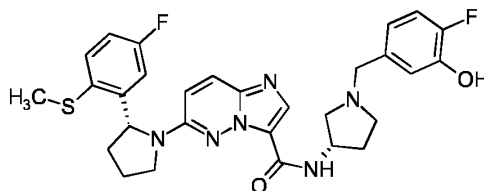
chromatography 5-50% MeCN/H₂O (0.1% NH₃ modifier), followed by normal phase chromatography 0-10% DCM/MeOH. The solid was triturated 9:1 Et₂O/EtOAc to afford the title compound as a colourless solid (22 mg, 17%).

LCMS m/z = 551.2 [M+H]⁺; 549.2 [M-H]⁺

- 5 ¹H NMR (CDCl₃, 400 MHz): δ : 9.10 (br s, 1H), 8.19 (s, 1H), 7.70 (d, 1H), 7.29 (m, 1H), 7.0 (m, 3H), 6.76 (m, 2H), 6.42 (br s, 1H), 5.24 (d, 1H), 4.57 (br m, 2H), 3.84 (m, 8H), 2.62 (s, 3H), 2.53 (m, 1H), 2.06 ppm (m, 3H).

Example 2

- 10 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide



The following compound was prepared (30 mg, 23%) from 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-

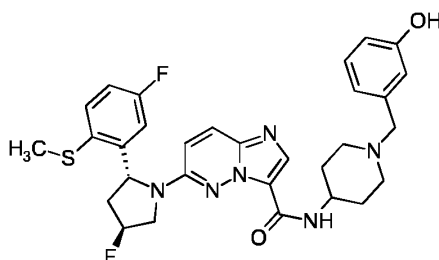
- 15 carboxamide (Preparation 18) and 4-fluoro-3-hydroxybenzaldehyde according to the procedure described in Example 1.

LCMS m/z = 565.4 [M+H]⁺

- ¹H NMR (DMSO-d₆, 400 MHz): δ : 9.70 (s, 1H), 9.14 (br s, 1H), 7.92 (s, 1H), 7.87 (d, 1H), 7.39-7.38 (m, 1H), 7.14 (m, 1H), 7.00 (m, 1H), 6.95-6.84 (m, 1H), 6.73-6.65 (m, 1H),
20 6.35-6.08 (m, 1H), 5.20 (m, 1H), 4.54-4.33 (m, 1H), 4.02-3.86 (m, 1H), 3.66-3.50 (m, 1H), 3.47-3.34 (m, 2H), 2.84-2.43 (m, 7H), 2.36-2.14 (m, 2H), 1.94-1.74 (m, 3H), 1.72-1.52 (m, 1H).

Example 3

- 25 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide



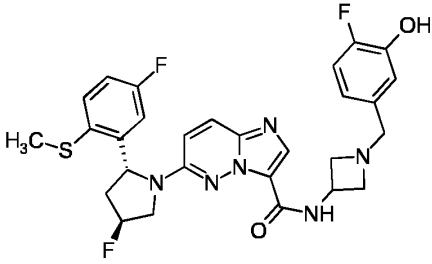
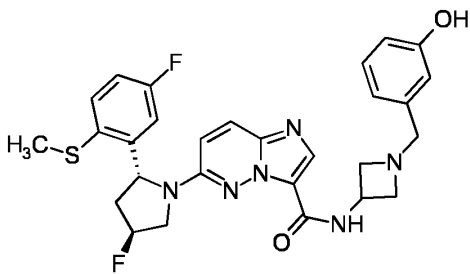
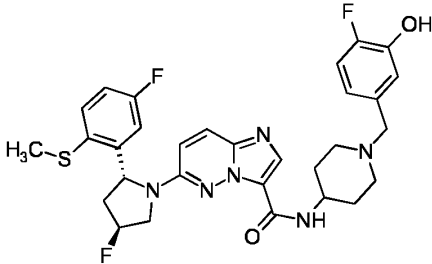
3-((4-Aminopiperidin-1-yl)methyl)phenol hydrochloride (Preparation 50, 2.86 g, 10.25 mmol) was added to a stirred solution of 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 28, 2.00 g, 5.12 mmol), TPTU (1.83 g, 6.15 mmol), and DIPEA (4.46 ml, 25.61 mmol) in dry DCM (36 ml) at rt under N₂. The solution was allowed to stir for 5 h, then diluted with DCM (50 ml) and the resulting solution was washed with distilled water (40 ml), saturated aqueous NaHCO₃ (3 x 40 ml), saturated aqueous NH₄Cl (3 x 40 ml) and distilled water (40 ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo* to afford an orange oil (3.5 g) which was loaded on a 120 g KP-Sil column and purified by Biotage® with 1 CV EtOAc and then 0-15 % MeOH in EtOAc over 12 CVs. The relevant fractions were combined and then concentrated *in vacuo* to afford 1.95 of a white solid (1.95 g). The solid was kept under house vacuum at 35°C over for 65 hours to afford the title compound as white solid (1.70 g, 57%).

LCMS m/z = 579 [M+H]⁺

¹H NMR (MeOD-d₄; 396 MHz): δ : 8.05 (s, 1H), 7.74 (m, 1H), 7.42 (m, 1H), 7.14-7.18 (m, 1H), 7.00-7.09 (m, 2H), 6.81-6.83 (m, 2H), 6.70-6.73 (m, 1H), 6.56 (m, 1H), 5.43-5.60 (m, 2H), 4.16-4.28 (m, 2H), 3.94-4.00 (m, 1H), 3.52 (s, 2H), 2.97-3.06 (m, 3H), 2.57 (s, 3H), 2.19-2.31 (m, 3H), 2.07 (s, 2H), 1.67-1.80 (m, 2H).

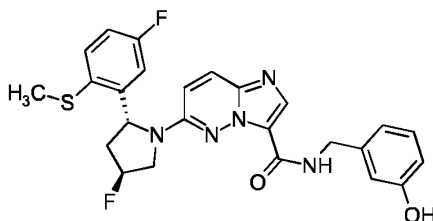
The following compounds were prepared from 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 28) and the appropriate amine according to the procedure described in Example 3.

Example No	Structure and Name	Starting material, Yield and Data
------------	--------------------	-----------------------------------

4	 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide	Amine: Preparation 51 15 mg, 26%, colourless solid. LCMS m/z = 569.1 $[M+H]^+$ 1H NMR (MeOD-d_4, 396 MHz): δ: 8.06 (br s, 1H), 7.76 (d, 1H), 7.42 (m, 1H), 7.10-7.00 (m, 3H), 6.96-6.92 (m, 1H), 6.79-6.76 (m, 1H), 6.61 (d, 1H), 5.62-5.44 (m, 2H), 4.64-4.58 (m, 1H), 4.30-4.19 (m, 2H), 3.78-3.63 (m, 4H), 3.41-3.34 (m, 2H), 3.07-2.97 (m, 1H), 2.57 (s, 3H), 2.32-2.16 (m, 1H).
5	 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide	Amine: Preparation 52 21.5 mg, 30%, colourless oil. LCMS m/z = 551.1 $[M+H]^+$ 1H NMR (MeOD-d_4, 396 MHz): δ: 8.03 (s, 1H), 7.74 (m, 1H), 7.39 (m, 1H), 7.14 (m, 1H), 7.03 (m, 2H), 6.79-6.76 (m, 2H), 6.71-6.68 (m, 1H), 6.59 (m, 1H), 5.59-5.41 (m, 2H), 4.62-4.56 (m, 1H), 4.27-4.16 (m, 2H), 3.77-3.65 (m, 4H), 3.40-3.34 (m, 2H), 3.04-2.94 (m, 1H), 2.54 (s, 3H), 2.29-2.12 (m, 1H).
6	 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide	Amine: Preparation 53 20 m, 26%, colourless solid. LCMS m/z = 597.2 $[M+H]^+$ 1H NMR (MeOD-d_4, 396 MHz): δ: 8.03 (s, 1H), 7.72 (m, 1H), 7.40 (m, 1H), 7.07-6.96 (m, 4H), 6.81 (m, 1H), 6.54 (m, 1H), 5.58-5.40 (m, 2H), 4.27-4.10 (m, 2H), 4.02-3.95 (m, 1H), 3.64 (s, 2H), 3.10-2.93 (m, 3H), 2.56 (s, 3H), 2.43-2.37 (m, 2H), 2.30-2.11 (m, 3H), 1.84-1.75 (m, 2H).

Example 7

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



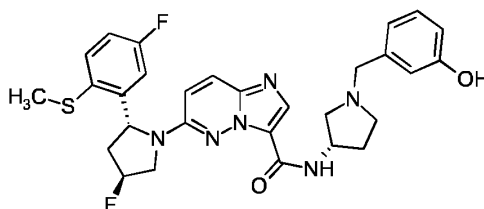
To a solution of 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 28, 40 mg, 0.102 mmol) in dry DCM (0.73 ml) at rt were added TPTU (365 mg, 0.122 mmol), 3-hydroxybenzylamine (138 mg, 0.122 mmol) and DIPEA (0.035 ml, 0.204 mmol) and the reaction mixture stirred at rt for 2 h. The reaction was diluted with DCM (15ml), washed with saturated NaHCO₃ solution (10 ml), saturated NH₄Cl solution (10 ml) and saturated brine solution (10 ml). The organic phase was dried over MgSO₄, concentrated *in vacuo* and purified by column chromatography (1-6 % MeOH in DCM) to afford the title compound as a colourless solid (281 mg, 55 %).

LCMS m/z = 496 [M+H]⁺

¹H NMR (MeOD-d₄, 396 MHz): δ : 8.95 (s, 1H), 8.73 (d, 1H), 8.06 (m, 2H), 7.82-7.77 (m, 3H), 7.63-7.56 (m, 3H), 6.38-6.17 (m, 2H), 5.47-5.37 (m, 2H), 4.95-4.82 (m, 2H), 3.94-3.85 (m, 1H), 3.31 (s, 3H), 3.09-2.89 (m, 1H).

Example 8

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



To a suspension of 3-[(3S)-3-aminopyrrolidin-1-yl]methylphenol hydrochloride (Preparation 54, 1.02 g, 3.86 mmol) in DCM (40 ml) was added triethylamine (1.79 ml, 12.87 mmol) and the mixture was cooled to 3°C in ice/water bath. 6-[(2S,4S)-4-fluoro-2-

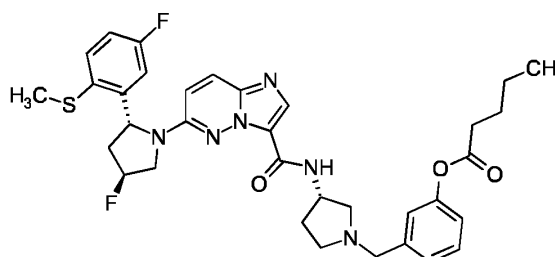
[5-fluoro-2-(methylsulfanyl)phenyl]cyclopentyl]imidazo[1,2-b]pyridazine-3-carbonyl chloride (Preparation 43, 1.05 g, 2.57 mmol) in DCM (40 ml) was added dropwise over 10 min. The reaction was left to stir in ice/water bath for 30 min and then left to stir for 3 h at rt. The reaction was quenched by addition of saturated NaHCO₃ solution (50 ml). The aqueous layer was separated and the organic layer washed with NH₄Cl (50 ml) and brine (2 x 50 ml). The organic layer was filtered through a phase separator and reduced to dryness to give the title compound as a pale yellow foam (1.37 g, 95%).

LCMS m/z = 565.3 [M+H]⁺ and 563.2 [M-H]⁻

¹H NMR (MeOD-d₄, 396 MHz): δ : 8.05 (m, 1H), 7.72 (m, 1H), 7.42 (m, 1H), 6.98-7.15 (m, 3H), 6.82-6.85 (m, 2H), 6.67-6.69 (m, 1H), 6.51 (m, 1H), 5.57 (m, 1H), 5.29-5.42 (m, 1H), 4.63 (s, 1H), 4.07-4.19 (m, 2H), 3.52-3.71 (m, 2H), 2.75-3.03 (m, 4H), 2.58 (m, 3H), 2.42-2.51 (m, 2H), 2.12-2.29 (m, 1H), 1.84-1.90 (m, 1H).

Example 9

3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl}phenyl]pentanoate



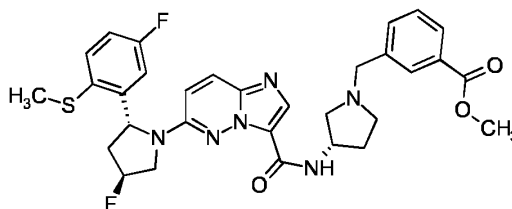
To a solution of 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Example 8, 65 mg, 0.117 mmol) in pyridine (3.0 ml) was added valeroyl chloride (30 mg, 0.246 mmol) at 0°C and the reaction was stirred at for 2h. A further portion of valeroyl chloride (21 mg, 0.175 mmol) was added to the reaction and stirred at 0°C for 2 h. The reaction was diluted with EtOAc (30 ml) and washed with saturated NaHCO₃ solution (3 X 50 ml) and brine (30 ml), dried (Mg₂SO₄) and concentrated *in vacuo*. The crude material was purified by normal phase chromatography 1-3% DCM/MeOH followed by reverse phase purification 40-100% acetonitrile/water. The material was re-purified by reverse phase chromatography (5-60%) to afford the title compound as a white solid (5.0 mg, 6.6%).

LCMS m/z = 649 $[M+H]^+$

1H NMR (MeOD- d_4 , 396 MHz): δ : 8.05 (s, 1H), 7.35 (m, 1H), 7.43 (m, 1H), 7.35 (m, 1H), 7.25 (m, 1H), 7.19-7.16 (m, 1H), 7.07 (m, 1H), 7.02-6.95 (m, 2H), 6.51 (m, 1H), 5.56 (m, 1H), 5.33 (m, 1H), 4.69-4.57 (m, 1H), 4.25-4.05 (m, 2H), 3.78 (m, 1H), 3.72 (m, 1H),
5 3.10-2.86 (m, 3H), 2.72 (m, 1H), 2.56 (s, 3H), 2.53-2.40 (m, 4H), 2.28-2.09 (m, 1H), 1.94-1.83 (m, 1H), 1.61-1.52 (m, 2H), 1.41-1.27 (m, 2H), 0.89 (m, 3H).

Example 10

Methyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfonyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate



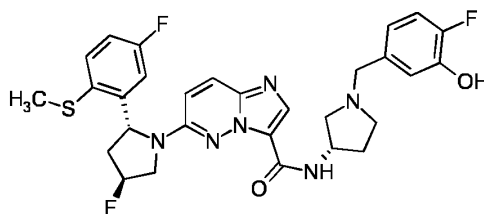
6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfonyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 36, 0.20 g, 0.436 mmol) and methyl 3-formylbenzoate (0.0787 g, 0.479 mmol) in dry DCM (2.73 ml) were stirred for 30
15 min at rt under N_2 . Sodium triacetoxyborohydride (0.277 g, 1.31 mmol) was added in one portion followed by acetic acid (0.0249 ml, 0.436 mmol) and the mixture was left to stir for 3 h at rt. The reaction was quenched by dropwise addition of saturated aqueous $NaHCO_3$ (5 ml). A further 15 ml of DCM was added. The layers were separated, the aqueous layer was extracted with DCM (2 x 15 ml). The combined organic layers were
20 dried and concentrated *in vacuo* to afford a colourless oil. The crude residue was purified by column chromatography (Biotage® Zip KP Sil 120 g cartridge 1-10 % MeOH in DCM for 10 CV) to give the title compound as a colourless solid (0.219 g, 83 %).

LCMS m/z = 607.1 $[M+H]^+$

1H NMR (MeOD- d_4 , 396 MHz): δ : 8.07 (s, 1H), 8.03 (s, 1H), 7.89 (d, 1H), 7.73-7.70 (m, 1H), 7.60 (m, 1H), 7.45-7.38 (m, 2H), 7.04 (m, 1H), 6.96 (m, 1H), 6.50 (m, 1H), 5.58-5.29 (m, 2H), 4.62-4.61 (m, 1H), 4.27-4.17 (m, 2H), 3.78-3.76 (m, 5H), 3.06-2.83 (m, 3H), 2.72 (m, 1H), 2.55 (s, 3H), 2.51-2.44 (m, 2H), 2.27-2.11 (m, 1H), 1.91-1.87 (m, 1H).

Example 11

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



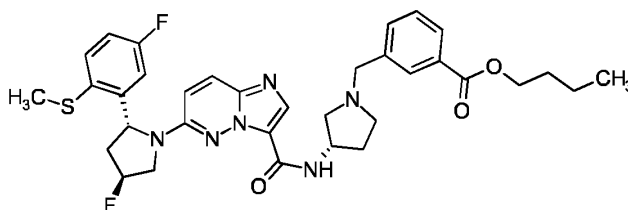
- 5 The following compound was prepared in 57% yield from 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfonyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 36) and 4-fluoro-3-hydroxybenzaldehyde according to the procedure described in Example 10.

LCMS m/z = 583.2 $[M+H]^+$

- 10 ^1H NMR (MeOD- d_4 , 396 MHz): δ : 8.05 (s, 1H), 7.74 (m, 1H), 7.42 (m, 1H), 7.08-6.97 (m, 4H), 6.82 (m, 1H), 6.56 (m, 1H), 5.57 (m, 1H), 5.40 (d, 1H), 4.60 (m, 1H), 4.22 (s, 1H), 4.14 (s, 1H), 3.77-3.66 (m, 2H), 3.10-2.89 (m, 4H), 2.57 (s, 3H), 2.50 (m, 2H), 2.29-2.13 (m, 1H), 1.95 (m, 1H).

15 Example 12

Butyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfonyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate



- A solution of 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfonyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoic acid (Preparation 44, 78 mg, 0.132 mmol), DMAP (4.8 mg, 0.039 mmol) and EDC.HCl (50 mg, 0.264 mmol) in n-butanol (0.66 ml) was stirred for 16 h at rt. The reaction mixture was partitioned between water (5 ml) and EtOAc (15 ml), the organic layer washed with brine (3 x 10 ml), dried with Na₂SO₄, filtered and the solvent

removed under reduced pressure. The crude material was purified by using NP chromatography (1- 5 % MeOH in DCM) to afford the title compound as a colourless solid (404 mg, 47%).

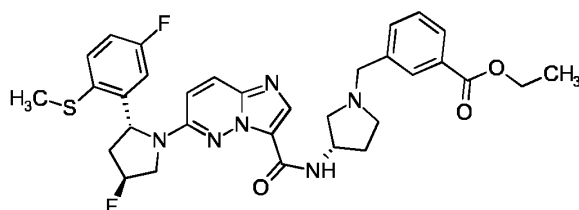
LCMS m/z = 649 [M+H]⁺

- 5 ¹H NMR (MeOD-d₄, 396 MHz): δ : 8.08 (s, 1H), 8.03 (s, 1H), 7.89 (m, 1H), 7.71 (m, 1H), 7.59 (m, 1H), 7.45-7.38 (m, 2H), 7.06-6.94 (m, 2H), 6.50 (m, 1H), 5.57-5.27 (m, 2H), 4.62 (s, 1H), 4.24-4.13 (m, 4H), 3.80 (s, 2H), 3.09-3.06 (m, 1H), 2.99-2.86 (m, 2H), 2.72 (m, 1H), 2.54 (s, 3H), 2.51-2.44 (m, 2H), 2.26-2.11 (m, 1H), 1.92-1.90 (m, 1H), 1.66-1.58 (m, 2H), 1.42-1.33 (m, 2H), 0.94-0.86 (m, 3H).

10

Example 13

Ethyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}benzoate



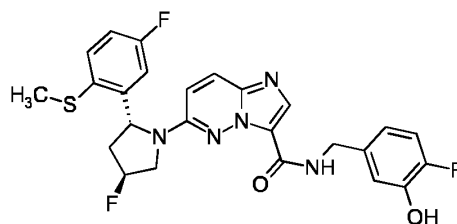
- 15 The following compound was prepared in 61% yield from 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}benzoic acid (Preparation 44) and EtOH according to the procedure described in Example 12.

LCMS m/z = 621.1 [M+H]⁺

- 20 ¹H NMR (MeOD-d₄, 396 MHz): δ : 8.07 (s, 1H), 8.03 (s, 1H), 7.89 (m, 1H), 7.71 (m, 1H), 7.59 (m, 1H), 7.38-7.44 (m, 2H), 6.94-7.06 (m, 2H), 6.50 (m, 1H), 5.29-5.57 (m, 2H), 4.62 (s, 1H), 4.17-4.28 (m, 4H), 3.75-3.82 (m, 2H), 2.69-3.10 (m, 4H), 2.55 (s, 3H), 2.42-2.50 (m, 2H), 2.12-2.27 (m, 1H), 1.87-1.91 (m, 1H), 1.24-1.28 (m, 3H).

25 Example 14

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



TPTU (18.26 g, 61.5 mmol) was added to a stirred suspension of 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 28, 20 g, 51.2 mmol), 5-(aminomethyl)-2-fluorophenol (14.46 g, 102.5 mmol), and DIEA (33.1 g, 256 mmol) in DMSO (200 ml). The reaction mixture was stirred at RT for 1.5 h. The reaction mixture was poured into EtOAc (600 ml) and water (600 ml) and the layers were separated. The organic layer was washed with distilled water (4 x 400 ml) and brine (400 ml). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo* to afford an oil. The crude material was purified by column chromatography (20 % MeOH in DCM) to give an oil. This was purified further on the Biotage® by reverse phase chromatography (0.1 % NH₃ in H₂O/0.1 % NH₃ in MeCN, 5 to 95) to give the bis-coupled product (7 g) and the title compound as an off white solid (5.60 g, 21 %).

LCMS m/z = 514 [M+H]⁺ and 512 [M-H]⁻

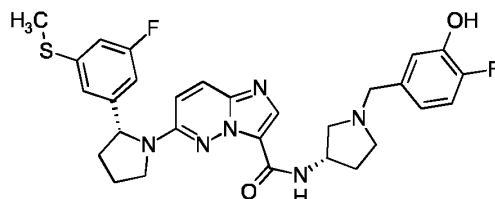
The bis-coupled product (7 g) was dissolved in EtOH (15 ml) at rt and sodium hydroxide (1.58 g, 7.9 mmol) was added which was previously dissolved in water (10 ml). The mixture was stirred for 1 h. The EtOH was removed *in vacuo*, diluted with water (50 ml) and then pH was adjusted with 2M HCl to ca. pH 4 to 5. The mixture was then extracted with DCM (2 x 15 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford an off-white solid (3.99 g). This was purified further by silica column chromatography (5 % MeOH in EtOAc) to give the title compound as an off-white solid (1.84 g, 3.58 mmol, 45 %).

LCMS m/z = 514 [M+H]⁺ and 512 [M-H]⁻

¹H NMR (MeOD-d₄, 396 MHz): δ: 8.03 (s, 1H), 7.82 (m, 1H), 7.13 (m, 1H), 6.99 (m, 1H), 6.92 (m, 3H), 6.89 (m, 1H), 6.79 (m, 1H), 5.51-5.25 (m, 2H), 4.47 (s, 2H), 4.01-3.87 (m, 2H), 3.12-2.94 (m, 1H), 2.41 (s, 3H), 2.07 (m, 1H).

Example 15

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



To a solution of 6-[(2R)-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 19, 70 mg, 0.16 mmol) in DCM (2 ml) were added 4-fluoro-3-hydroxybenzaldehyde (25 mg, 0.18 mmol) and sodium triacetoxyborohydride (144 mg, 0.66 mmol). The reaction mixture was stirred at rt for 1h and quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄ and reduced to dryness. The obtained residue was purified by normal phase chromatography (eluting with 2 to 10% MeOH in DCM) and reverse phase chromatography (eluting with 0.1 NH₃ in H₂O/0.1 NH₃ in MeCN 2 to 80% over 10 CVs) to afford the title compound as a white solid (20 mg, 22%).

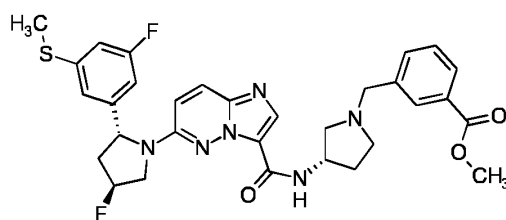
LCMS m/z = 565.1 [M+H]⁺

¹H NMR (DMSO-d₆, 396 MHz): δ : 9.74 (s, 1H), 9.11 (s, 1H), 7.93 (m, 2H), 7.06-6.92 (m, 4H), 6.81-6.54 (m, 2H), 5.16 (m, 1H), 4.45 (m, 1H), 3.95-3.90 (m, 1H), 3.75-3.43 (m, 4H), 2.73-2.40 (m, 4H), 2.45 (s, 3H), 2.32-2.19 (m, 2H), 1.91 (m, 4H).

15

Example 16

Methyl 3-[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}benzoate



To a solution of 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 37, 386 mg, 0.842 mmol) in DCM (15 ml) was added methyl 3-formylbenzoate (276 mg, 1.68 mmol) followed by acetic acid (0.096 ml, 1.68 mmol) and the reaction stirred at rt under N₂ for 30 min. Sodium triacetoxyborohydride (357 mg, 1.68 mmol) was added and the mixture left to stir at rt for 18 h. After this time the reaction was quenched by the addition of

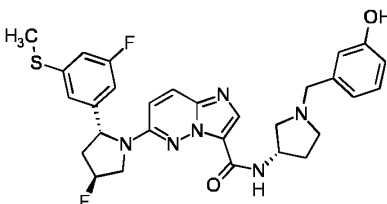
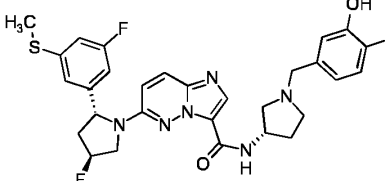
25

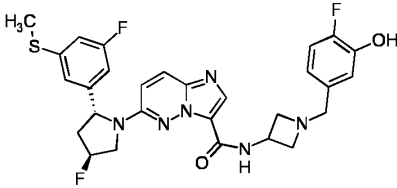
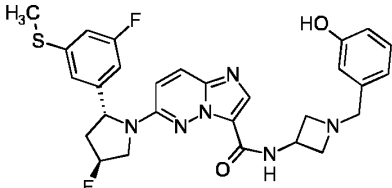
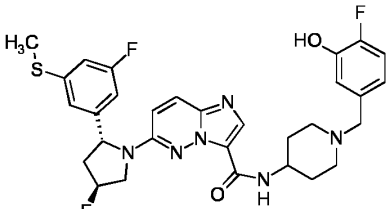
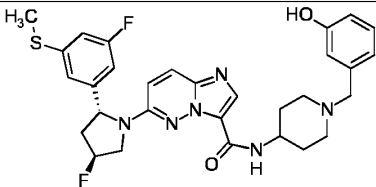
saturated aqueous NaHCO₃ (20 ml) and extracted with EtOAc (15 ml x 3). The combined organic layers were washed with brine (30 ml), dried (Na₂SO₄), filtered, and evaporated to dryness to give a light brown residue. The residue was loaded onto a Biotage® SNAP KP-Sil 100 g cartridge eluting with a gradient of MeOH in EtOAc (1 to 4%, 3CV; 4 to 6%, 5 1C; 20%, 1CV) followed by 5% MeOH in DCM. The correct fractions were combined to give the title compound as colourless solid (304 mg, 66%).

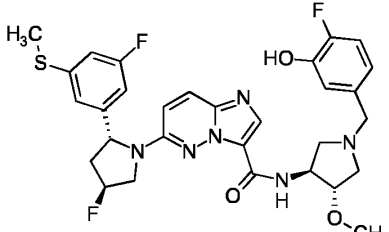
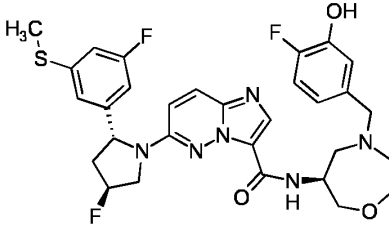
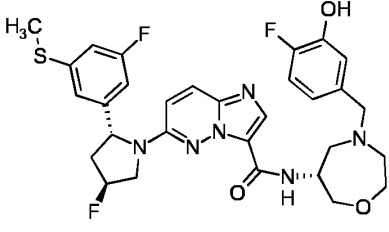
LCMS m/z = 607.1 [M+H]⁺

¹H NMR (DMSO-d₆, 396 MHz): δ : 8.90 (s, 1H), 7.98-7.93 (m, 3H), 7.86 (d, 1H), 7.63 (d, 1H), 7.49 (m, 1H), 7.12 (s, 1H), 6.96 (m, 2H), 6.74 (d, 1H), 5.44 (d, 1H), 5.27 (m, 1H), 10 4.49 (s, 1H), 4.27-4.06 (m, 2H), 3.85-3.65 (m, 2H), 3.78 (s, 3H), 3.4-3.3 (m, 2H), 2.93-2.63 (m, 3H), 2.50 (s, 3H), 2.33-2.09 (m, 2H), 1.66 (m, 1H).

The following compounds were prepared from the corresponding amine and aldehydes according to the procedure described in Example 16.

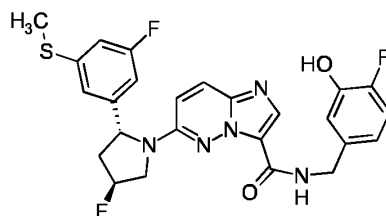
Example No	Structure and Name	Starting materials, Yield and Data
17	 <u>6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(3hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide</u>	Amine: Preparation 37 62%. LCMS m/z = 565 [M+H]⁺ ¹H NMR (MeOD-d₄, 396 MHz): δ: 8.04 (s, 1H), 7.76 (m, 1H), 7.15 (m, 1H), 7.05 (s, 1H), 6.90 (m, 1H), 6.88-6.76 (m, 4H), 6.70 (m, 1H), 5.45-5.21 (m, 2H), 4.67-4.54 (m, 1H), 4.26-4.00 (m, 2H), 3.73 (m, 1H), 3.65 (m, 1H), 3.15-3.01 (m, 1H), 3.00-2.77 (m, 3H), 2.59-2.37 (m, 5H), 2.20 (m, 1H), 1.88-1.69 (m, 1H).
18	 <u>6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide</u>	Amine: Preparation 37 33%. LCMS m/z = 583.2 [M+H]⁺ ¹H NMR (MeOD-d₄, 396 MHz): δ: 8.03 (s, 1H) 7.75 (d, 1H) 7.00 (s, 1H) 7.01-6.95 (m, 2H) 6.91-6.88 (m, 1H) 6.82-6.80 (m, 3H) 5.43-5.23 (m, 2H) 4.64-4.56 (m, 1H) 4.18-4.11 (m, 2H) 3.67 (d, 1H) 3.58 (d, 1H) 3.00-2.91 (m, 2H) 2.81-2.79 (m, 2H) 2.45-2.41 (m, 5H) 2.26-2.16 (m, 1H) 1.83-1.71 (m, 1H).

19	 <u>6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[4-fluoro-3-hydroxyphenyl]methyl}azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide</u>	Amine: Preparation 38 33.1 mg, 31%. LCMS m/z = 569.1 [M+H]⁺ ¹H NMR (MeOD-d₄, 396 MHz): δ: 8.04 (s, 1H) 7.79 (d, 1H) 7.06 (s, 1H) 7.05-7.00 (m, 1H) 6.95-6.79 (m, 5H) 5.53-5.27 (m, 2H) 4.58-4.56 (m, 1H) 4.26-4.19 (m, 2H) 3.81-3.74 (m, 4H) 3.51-3.39 (m, 2H) 3.01-2.91 (m, 1H) 2.45 (s, 3H) 2.30-2.15 (m, 1H).
20	 <u>6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[3-hydroxyphenyl]methyl}azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide</u>	Amine: Preparation 38 13%. LCMS m/z = 551.1 [M+H]⁺ ¹H NMR (MeOD-d₄, 396 MHz): δ: 8.04 (s, 1H) 7.77 (d, 1H) 7.16 (m, 1H) 7.06 (s, 1H) 6.91-6.79 (m, 5H) 6.72-6.70 (m, 1H) 5.53-5.26 (m, 2H) 4.60-4.57 (m, 1H) 4.26-4.29 (m, 2H) 3.76-3.69 (m, 4H) 3.36-3.31 (m, 2H) 3.01-2.91 (m, 1H) 2.45 (s, 3H) 2.31-2.14 (m, 1H).
21	 <u>6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[4-fluoro-3-hydroxyphenyl]methyl}piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide</u>	Amine: Preparation 39 19 mg, 38%. LCMS m/z = 597.2 [M+H]⁺ ¹H NMR (MeOD-d₄, 396 MHz): δ: 8.10-7.91 (m, 1H), 7.79-7.58 (m, 1H), 7.11-6.61 (m, 7H), 5.58-5.14 (m, 2H), 4.28-4.00 (m, 2H), 4.00-3.83 (m, 1H), 3.69-3.47 (m, 2H), 3.11-2.80 (m, 3H), 2.50-1.85 (m, 8H), 1.78-1.57 (m, 2H).
22	 <u>6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[3-hydroxyphenyl]methyl}piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide</u>	Amine: Preparation 39 70%. LCMS m/z = 579.2 [M+H]⁺ ¹H NMR (MeOD-d₄, 396 MHz): δ: 8.05 (s, 1H), 7.77 (d, 1H), 7.16 (m, 1H), 7.07 (m, 1H), 6.91 (m, 1H), 6.84-6.81 (m, 4H), 6.72 (d, 1H), 5.46 (d, 1H), 5.27 (m, 1H), 4.21-4.20-4.14 (m, 2H),

	<u>hydroxyphenyl)methyl]piperidin-4-yl]imidazo[1,2-b]pyridazine-3-carboxamide</u>	3.97-3.90 (m, 1H), 3.52 (m, 2H), 3.01-2.91 (m, 3H), 2.43 (s, 3H), 2.32-2.15 (m, 3H), 2.15-2.00 (m, 2H) 1.76-1.64 (m, 2H).
23	 <u>6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S,4S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]-4-methoxypyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide</u>	Amine: Preparation 40 42.5 mg, 48%. LCMS m/z = 613.3 [M+H]⁺ ¹H NMR (DMSO-d₆, 396 MHz): δ: 8.05 (s, 1H) 7.79-7.37 (m, 1H) 7.05-6.93 (m, 4H) 6.85-6.76 (m, 3H) 5.41-5.27 (m, 2H) 4.49-4.42 (m, 1H) 4.25-3.99 (m, 2H) 3.91-3.55 (m, 3H) 3.44-3.38 (s, 3H) 3.27-3.21 (m, 1H) 2.92-2.86 (m, 2H) 2.80-2.72 (m, 1H) 2.46-2.37 (m, 4H), 2.28-2.10 (m, 1H).
24	 <u>6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(6S)-4-[4-fluoro-3-hydroxyphenyl)methyl]-1,4-oxazepan-6-yl]imidazo[1,2-b]pyridazine-3-carboxamide*</u>	Amine: Preparation 41 26 mg, 46%. LCMS m/z = 613.2 [M+H]⁺ ¹H NMR (DMSO-d₆, 396 MHz): δ: 9.57 (d, 1H), 9.20 (s, 1H), 8.08-7.93 (m, 2H), 7.16-7.11 (m, 1H), 7.03-6.83 (m, 2H), 6.78-6.64 (m, 3H), 5.53 (m, 1H), 5.30 (m, 1H), 4.44-4.12 (m, 3H), 3.96 (m, 1H), 3.84-3.63 (m, 4H), 3.55-3.47 (m, 1H), 2.94-2.67 (m, 5H), 2.49 (m, 4H), 2.34-2.14 (m, 1H). *Stereochemistry arbitrarily assigned.
25	 <u>6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(6R)-4-[4-fluoro-3-hydroxyphenyl)methyl]-1,4-oxazepan-6-yl]imidazo[1,2-b]pyridazine-3-carboxamide*</u>	Amine: Preparation 42 27%. LCMS m/z = 613.2 [M+H]⁺ ¹H NMR (MeOD-d₄, 396 MHz): δ: 8.05 (s, 1H), 7.84 (m, 1H), 7.13 (m, 1H), 6.98-6.84 (m, 5H), 6.74 (m, 1H), 5.52-5.39 (m, 1H), 5.28 (m, 1H), 4.24-4.16 (m, 2H), 4.00-3.97 (m, 1H), 3.78-3.73 (m, 2H), 3.62-3.43 (m, 4H), 2.90-2.70 (m, 3H), 2.47-2.45 (m, 3H), 2.28-2.15 (m, 2H), 1.98 (m, 1H). *Stereochemistry arbitrarily assigned.

Example 26

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



- 5 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 29, 109 mg, 0.28 mmol), 1-{3-[(tert-butyl)dimethylsilyl]oxy}-4-fluorophenylmethanamine (Preparation 57, 79 mg, 0.31 mmol) and HATU (130 mg, 0.34 mmol) were dissolved in DMF (4.5 ml) under N₂ and DIPEA (108 mg, 0.84 mmol) was added. The reaction was stirred overnight at rt. Water (10 ml)
- 10 and EtOAc (10 ml) were added and the layers were partitioned. The organic layer was washed with water (3 x 10 ml) and with brine (10 ml). After drying over MgSO₄ the solvent was removed under vacuum. The crude was used in the next step without further purification.

LCMS m/z = 628.4 [M+H]⁺

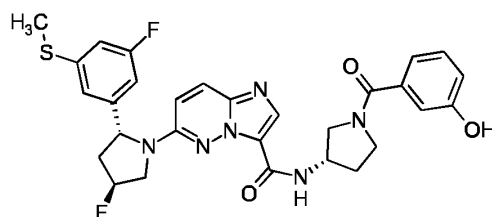
- 15 The crude was dissolved in MeCN (2 ml) and TEAF.H₂O (117 mg, 0.7 mmol) was added. The reaction was heated at 50 °C. After 2 h the reaction mixture was cooled down to rt and the solvent was removed under vacuum. The crude was purified by reverse phase chromatography eluting with H₂O (0.1% NH₃):MeCN (0.1% NH₃) – 2 to 70% over 15 CV. The product was obtained as white solid after freeze-drying (73 mg, 51%).

- 20 LCMS m/z = 514.3 [M+H]⁺

¹H NMR (DMSO-d₆, 396 MHz): δ: 9.73 (s, 1H); 8.53 (br s, 1H); 7.98 (d, 1H); 7.93 (s, 1H); 7.06-7.00 (m, 2H); 6.84-6.81 (m, 4H); 6.65 (br s, 1H); 5.38 (d, 1H); 5.13 (m, 1H); 4.45 (m, 1H); 4.23-3.90 (m, 3H); 2.83-2.73 (m, 1H); 2.35 (s, 3H); 2.11-1.94 (m, 1H).

Example 27

- 25 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-(3-hydroxybenzoyl)pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide



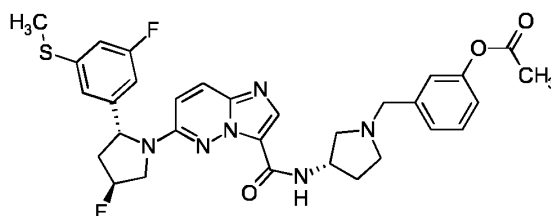
To 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide (Preparation 37, 70 mg, 0.152 mmol) in DMF (2 ml) were added 3-hydroxybenzoic acid (23 mg, 0.167 mmol) and HATU (64 mg, 0.167 mmol, 1.1 equiv.). The mixture was stirred at rt for 5 min, N-ethyl- N-isopropylpropan-2-amine (0.053 ml, 0.30 mmol) added and the reaction mixture stirred at rt for a further 16 h before diluting with EtOAc (15 ml). This was then washed with water (15 ml), saturated brine solution (15 ml), dried over Na₂SO₄, concentrated *in vacuo* and purified by Biotage® ZIP KP-SIL 45g cartridge (EtOAc:MeOH, 100:0 to 90:10) to afford a solid which was loaded onto a Biotage® C18 cartridge and eluted with a gradient (2to95 in 10CV) of ACN in water (both phases containing 0.1% ammonium hydroxide). The combined fractions were evaporated, redissolved in EtOAc, washed with water, dried (Na₂SO₄), filtered and evaporated to give the title compound as a colourless solid (36 mg, 40%).

LCMS m/z = 579.1 [M+H]⁺

¹H NMR (DMSO-d₆, 396 MHz): δ : 9.61 (d, 1H), 8.73-8.62 (br m, 1H), 7.90-7.97 (m, 2H), 7.19 (m, 1H), 7.11 (s, 1H), 6.69-6.96 (m, 6H), 5.25-5.54 (m, 2H), 4.83-4.39 (m, 1H), 3.95-4.22 (m, 2H), 3.37-3.84 (m, 3H), 2.77-2.91 (m, 1H), 2.46-2.45 (m, 4H), 1.86-2.29 (m, 3H).

Example 28

3-[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}phenyl acetate



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

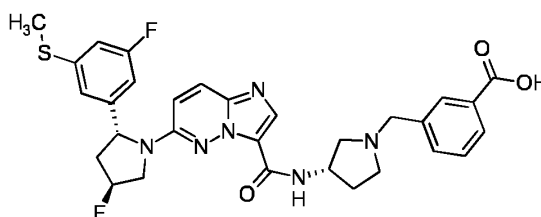
(Example 17, 60.7 mg, 0.107 mmol) was dissolved in pyridine (1.07 ml), acetic anhydride (20 μ L, 0.215 mmol) was added and the mixture was stirred at rt for 1 hour. The pyridine was removed under reduced pressure and the crude material was dissolved in water (5 ml) and extracted with EtOAc (3 x 5 ml). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and the solvent removed under reduced pressure. The crude material was purified by Biotage® chromatography (gradient 1-10 % MeOH in DCM) to give the title compound as a colourless solid (54.6 mg, 84%).

LCMS m/z = 607.2 $[\text{M}+\text{H}]^+$

^1H NMR (MeOD-d_4 , 396 MHz): δ : 8.04 (s, 1H) 7.76 (d, 1H) 7.35 (m, 1H) 7.25 (d, 1H) 7.16 (s, 1H) 7.04 (s, 1H) 7.00-6.98 (m, 1H) 6.92-6.89 (m, 1H) 6.82-6.79 (m, 2H), 5.38-5.25 (m, 2H) 4.66-4.57 (m, 1H) 4.16-4.07 (m, 2H) 3.77 (d, 1H) 3.69 (d, 1H) 3.02-2.75 (m, 4H) 2.46-2.39 (m, 5H) 2.25-2.16 (m, 4H) 1.82-1.72 (m, 1H).

Example 29

3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl}benzoic acid



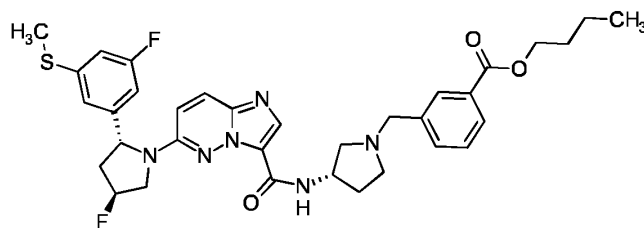
To a solution of methyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl} benzoate (Example 16, 234 mg, 0.386 mmol) in MeOH (2.0 ml) was added dropwise a solution of NaOH (77 mg, 1.93 mmol, 5.0 eq), dissolved in water (0.5 ml). The reaction mixture was stirred at rt for 30 min. After this time the reaction was adjusted to pH 4 by addition of 2.0 M HCl, the volatiles removed under reduced pressure and the aqueous extracted with DCM (10 ml). The organic phase was dried (Na_2SO_4), filtered and reduced to dryness to give the title compound as brown solid (100 mg) which was used without further purification. The aqueous layer was reduced to dryness, the residue was loaded onto a SNAP KP-SIL Biotage® cartridge and purified eluting with a gradient of MeOH in EtOAc (1 to 4% in 3CV, 4 to 6% in 1CV, 20% for 1CV) then 20% MeOH in DCM. The correct fractions were collected and reduced to dryness to give a second batch of the title compound as colourless solid (101 mg, 87% overall).

LCMS m/z = 593.1[M+H]⁺

¹H NMR (DMSO-d₆, 396 MHz): δ : 8.84 (br s, 1H), 7.91-7.72 (m, 4H), 7.34-7.22 (m, 2H), 7.09 (s, 1H), 6.94 (m, 2H), 6.67 (d, 1H), 5.38 (d, 1H), 5.20 (m, 1H), 4.52-4.36 (m, 1H), 4.19-3.98 (m, 2H), 3.73-3.55 (m, 2H), 2.87-2.58 (m, 4H), 2.44-2.41 (m, 3H), 2.36-2.09 (m, 2H), 1.84 (s, 1H), 1.65-1.49 (m, 1H).

Example 30

Butyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]benzoate



10

3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]benzoic acid (Example 29, 100 mg, 0.168 mmol), 4-dimethylamino pyridine (4.1 mg, 0.032 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (64 mg, 0.337 mmol) and n-butanol (0.077 ml, 0.843 mmol) were dissolved in DMF (0.84 ml) under N₂. The reaction was stirred at rt for 16 h. After this time 4-dimethylamino pyridine (4.1 mg, 0.032 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (64 mg, 0.337 mmol) and n-butanol (0.077 ml, 0.843 mmol) were added. The reaction was heated to 40°C and stirred for 18 h. The reaction was quenched by addition of water and extracted with EtOAc (15 ml). The organic layer was washed with brine (3 x 10 ml), dried with Na₂SO₄, filtered and the solvent removed under reduced pressure. The crude material was purified by chromatography (5 % MeOH in DCM for 10 CV). The resulting solid was further purified by reverse phase column chromatography (acetonitrile/water) to give the title compound as colourless solid (104 mg, 10%).

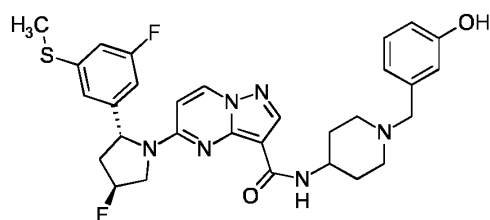
25 LCMS m/z = 649.4 [M+H]⁺

¹H NMR (MeOD-d₄, 396 MHz): δ : 8.02-8.07 (m, 2H), 7.89 (d, 1H), 7.72-7.76 (m, 1H), 7.59 (d, 1H), 7.43 (m, 1H), 7.02 (s, 1H), 6.88 (m, 1H), 6.75-6.80 (m, 2H), 5.21-5.38 (m, 2H), 4.61-4.62 (m, 1H), 4.13-4.25 (m, 4H), 3.78 (s, 2H), 2.70-3.10 (m, 4H), 2.41-2.48 (m,

5H), 2.11-2.28 (m, 1H), 1.73-1.78 (m, 1H), 1.60-1.68 (m, 2H), 1.36-1.43 (m, 2H), 0.86-0.92 (m, 3H).

Example 31

- 5 5-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}pyrazolo[1,5-a]pyrimidine-3-carboxamide



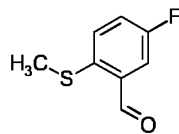
To a solution of 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 29, 100 mg, 0.256 mmol) in DCM (5.0 ml) at rt, TPTU (91 mg, 0.307 mmol) was added and the reaction was stirred for 10 min. Then 3-((4-aminopiperidin-1-yl)methyl)phenol hydrochloride (Preparation 50, 68 mg, 0.282 mmol) was added, followed by DIPEA (148 mg, 1.28 mmol, 5.0 equiv) and the reaction was allowed to stir for 2 h. The reaction was quenched with a saturated solution of NH₄Cl (30 ml) and extracted with DCM (3 x 50 ml). The combined organic layers were washed with brine, dried and evaporated. The crude was then loaded on NP Biotage® (75-100%EtOAc), but some of the title compound remained on silica. The rest was flushed through (50%THF/DCM) and the cleaner crude purified by RP Biotage®. The crude was loaded on RP biotage and columned under basic conditions to yield 972-102-1 as a white solid (10.4 mg, 7%).

- 20 LCMS m/z = 579 [M+H]⁺

¹H NMR (DMSO-d₆, 396 MHz, 80°C): δ: 8.96 (s, 1H), 8.62 (m, 1H), 8.09 (s, 1H), 7.57-7.30 (m, 1H), 7.07 (m, 2H), 6.94 (m, 1H), 6.86 (d, 1H), 6.75-6.69 (m, 2H), 6.62 (m, 2H), 6.42-6.20 (m, 1H), 5.47 (d, 1H), 5.37-5.28 (m, 1H), 4.30-4.09 (m, 2H), 3.80-3.67 (b, 1H), 3.38 (s, 2H), 2.97-5.69 (m, 3H), 2.42 (s, 3H), 2.18-2.07 (m, 3H), 1.91-1.82 (m, 1H), 1.55-1.38 (m, 2H).

Preparation 1

5-Fluoro-2-(methylsulfanyl)benzaldehyde

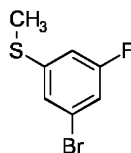


n-BuLi in hexane (2.5 M, 0.4 ml, 1 mmol) was added dropwise to a solution of 2-bromo-4-fluoro-1-(methylsulfanyl)benzene (221.0 mg, 1 mmol) in dry THF (10 ml) at -78°C under N₂ atmosphere, so the temperature was maintained below -70°C. DMF (80.0 mg, 1.1 mmol) was added and the reaction stirred at -78°C for a further 30 mins. The resulting mixture was quenched by the addition of ice-cold sat. aq. NH₄Cl solution (10 ml), warmed to rt and extracted with EtOAc (10 ml). The organic extracts were washed with saturated brine (10 ml), dried (MgSO₄), 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%).

¹H NMR (CDCl₃, 400MHz): δ: 10.35 (s, 1H); 7.52-7.56 (m, 1H); 7.35-7.39 (m, 1H), 7.25-7.30 (m, 1H); 2.51 (s, 3H).

Preparation 2

15 1-Bromo-3-fluoro-5-(methylsulfanyl)benzene

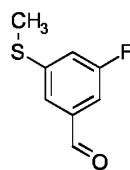


To 1-bromo-3,5-difluorobenzene (50.0 g, 259.08 mmol) in DMF (120 ml) was added sodium methanethiolate (18.16 g, 259.08 mmol). The mixture was heated to 150°C for 30 min, then cooled to rt, poured into a saturated solution of NH₄Cl (250 ml) and extracted with MTBE (2 x 150 ml). The combined organic layers were washed with water (150 ml) and brine (150 ml), dried (MgSO₄), filtered and evaporated to afford the desired compound as a yellow oil (25g, containing solvent residues, quantitative).

¹H NMR (CDCl₃, 400MHz): δ: 7.13 (s, 1H); 6.98-7.01 (m, 1H), 6.85-6.88 (m, 1H); 2.43 (s, 3H).

25

Preparation 3

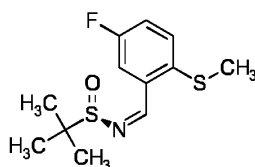
3-Fluoro-5-(methylthio)benzaldehyde

n-BuLi (1.6 M solution in hexanes, 2.82 ml, 4.52 mmol) was added dropwise *via* a syringe to a solution of 1-bromo-3-fluoro-5-(methylsulfanyl)benzene (Preparation 2, 1.0 g, 4.52 mmol) in anhydrous THF (20 ml) under N₂ at -78°C. The mixture was stirred for 15 min before anhydrous DMF (0.42 ml, 5.43 mmol) was added dropwise and the mixture stirred at -78°C for a further 30 min. The mixture was quenched by addition of 20 ml of saturated aqueous solution of NH₄Cl. The two layers were partitioned and the water phase was extracted with EtOAc (10 ml). The organic layers were combined, dried (Na₂SO₄), filtered and evaporated to afford the product as brown oil (0.73 g, 95%).

¹H NMR (CDCl₃, 400MHz): δ: 9.95 (s, 1H); 7.50-7.55 (m, 1H); 7.32-7.35 (m, 1H), 7.15-7.20 (m, 1H); 2.48 (s, 3H).

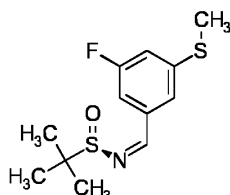
Preparation 4

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



Cs₂CO₃ (300.0 mg, 0.92 mmol) was added to a solution of 5-fluoro-2-(methylsulfanyl)benzaldehyde (Preparation 1, 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 h. Water (15 ml) was carefully added and the layers separated. The organic layer was dried (MgSO₄) 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]⁺

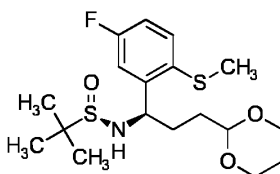
Preparation 5(R)-N-[(1Z)-[3-fluoro-5-(methylsulfanyl)phenyl]methylidene]-2-methylpropane-2-sulfinamide

- 5 To 3-fluoro-5-(methylthio)benzaldehyde (Preparation 3, 7.85 g, 46.12 mmol), (R)-2-methylpropane-2-sulfinamide (6.71 g, 55.3 mmol) in anhydrous DCM (150 ml) was added cesium carbonate (15.0 g, 46.1 mmol) under N₂ and the mixture was stirred at rt for 16h. The mixture was diluted with water (200 ml) and the organic layer separated, dried (Na₂SO₄), filtered and evaporated. The crude oil was diluted with DCM (5 ml),
- 10 loaded onto a Zip KP-SIL 120g biotage cartridge and eluted with 10 to 50% EtOAc in heptane to afford the title product as an orange oil (7.54g, 60%).

LCMS m/z = 274.0 [M+H]⁺

Preparation 6

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



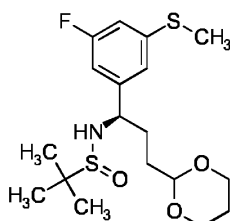
- A solution (0.5 ml) of 2-(2-bromoethyl)-1,3-dioxolane (1.81 g, 10 mmol) in dry THF (5 ml) was added to a suspension of activated Mg turnings (729.0 mg, 30.0 mmol) under N₂ (g) in dry THF (10 ml) and the reaction warmed until Grignard formation had initiated. The remaining 2-(2-bromoethyl)-1,3-dioxolane 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 h, then re-cooled to -50°C. A solution of (R)-N-[(1Z)-[5-fluoro-2-(methylsulfanyl)phenyl]methylidene]-2-methylpropane-2-sulfinamide
- 25 (Preparation 4, 270.0 mg, 1 mmol) in dry THF (5 ml) was added dropwise, the reaction stirred at -50°C for 1 h and then allowed to warm to rt. Saturated aq. NH₄Cl solution (20

ml) was added to quench the reaction and the mixture partitioned between EtOAc (30 ml) and water (30 ml). The aqueous layer was further extracted with EtOAc (30 ml) and the combined organic layers washed with brine (60 ml), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting
 5 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 7

10 (R)-N-((R)-3-(1,3-dioxan-2-yl)-1-(3-fluoro-5-(methylthio)phenyl)propyl)-2-methylpropane-2-sulfinamide



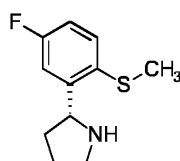
Mg turnings (2.67 g, 109.82 mmol) were stirred under N₂ at rt for 16 h. Anhydrous THF was added (20 ml) followed by iodine (15 mg, 59 μmol), and the mixture heated up until
 15 iodine started to sublime. The mixture was allowed to cool to rt before 2ml of a solution (2 ml) of 2-(2-bromoethyl)-1,3-dioxolane (7.14 g, 36.6 mmol) in dry THF (25 ml) was added to the magnesium turning suspension. The mixture was gently warmed-up until the Grignard formation initiated and the remaining solution of 2-(2-bromoethyl)-1,3-dioxolane were added slowly while maintaining the temperature below 50°C. The
 20 Grignard solution was allowed to cool down to rt over 30 min and stirred for a further 1 h at rt. The mixture was cooled to -70°C and a solution of (R)-N-[(1Z)-[3-fluoro-5-(methylsulfanyl)phenyl]methylidene]-2-methylpropane-2-sulfinamide (Preparation 5, 1.0 g, 3.66 mmol) in dry THF (18 ml) was added, stirred at -50°C for 1 h and warmed up to rt for a further 1 h. The reaction mixture was quenched at 0°C with an aqueous solution of
 25 NH₄Cl (40 ml). The reaction mixture was partitioned between EtOAc and water (1:1, 200 ml). The layers were separated and the aqueous was extracted with EtOAc (100 ml). The combined organic layers were washed with brine (100 ml), dried over Na₂SO₄ and reduced to dryness. The crude yellow oil was dissolved in EtOAc (5 ml), loaded onto a Biotage® ZIP KP-SIL 120 g column eluting with 50 to 100% EtOAc in heptane. The

desired fractions were evaporated yielding the title compound as light yellow oil (1.41g, 99%).

LCMS m/z = 388.1 $[M-H]^+$

5 Preparation 8

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

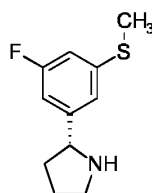


A solution of (R)-N-[(1R)-3-(1,3-dioxan-2-yl)-1-[5-fluoro-2-(methylsulfanyl)phenyl]propyl]-2-methylpropane-2-sulfinamide (Preparation 6, 390.0 mg, 1 mmol) in TFA:water (10 ml, 20:1) was stirred at rt for 30 min. Et₃SiH (1.16 g, 10 mmol) was added and the reaction stirred vigorously at rt for 16 h. The 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:NH₄OH, 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 9

(2R)-2-(3-Fluoro-5-(methylthio)phenyl)pyrrolidine



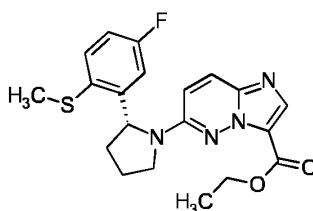
To a solution of (R)-N-((R)-3-(1,3-dioxan-2-yl)-1-(3-fluoro-5-(methylthio)phenyl)propyl)-2-methylpropane-2-sulfinamide (Preparation 7, 1.41 g, 3.62 mmol) in water (2 ml) was added TFA (36 ml). The resulting solution was stirred at rt for 30 min. Et₃SiH (4.21 g, 36.2 mmol) was then added and the biphasic solution was stirred vigorously at rt over 48h. The reaction mixture was concentrated *in vacuo*. The resulting crude was loaded onto a SCX cartridge in MeOH, the cartridge rinsed with 40 ml of MeOH and eluted with

7N NH₄OH in MeOH (50 ml). The collected fractions were evaporated affording the title compound as brown oil (0.65 g, 85%).

LCMS m/z = 212.0 [M+H]⁺

5 Preparation 10

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

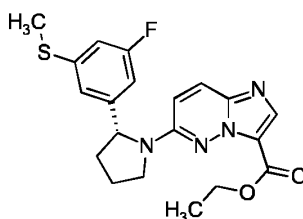


A solution of (2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidine (Preparation 8, 640 mg, 3.03 mmol) in 4M HCl in dioxane (20 ml) was stirred at rt for 30 min, then concentrated *in vacuo*. Ethyl 6-chloroimidazo[1,2-b]pyridazine-3-carboxylate (0.59 g, 2.52 mmol) in DMSO (20 ml) was added and the reaction heated at 130°C for 16 h. 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 (MgSO₄) 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 11

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

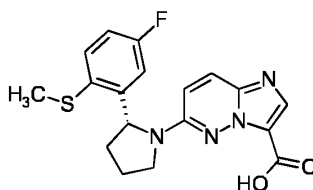


To (2R)-2-(3-fluoro-5-(methylthio)phenyl)pyrrolidine (Preparation 9, 0.30mmol, 1.2 equiv.), ethyl 6-chloroimidazo[1,2-b]pyridazine-3-carboxylate (0.25mmol) and KF (2.8mmol, 11 equiv.) was added DMSO (2ml) and the reaction was heated at 130°C. After overnight reaction the reaction mixture was cooled to rt. Water (10ml) and EtOAc (10 ml) were added and the layers partitioned. The organic layer was washed three times with brine (10ml), dried over Na₂SO₄ and the solvent was removed under vacuum. The crude material containing the title compound was used without further purification.

LCMS m/z = 401.1 [M+H]⁺

10 Preparation 12

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

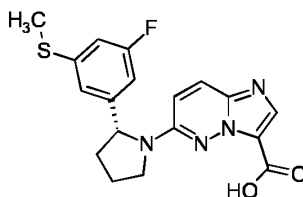


KOH (0.71 g, 12.6 mmol) was added portionwise to a solution of ethyl 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylate (Preparation 10, 1.0 g, 2.52 mmol) in EtOH:water (12 ml, 6:1) and the reaction stirred at rt for 1.5 h. The mixture was concentrated *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 layers were dried (MgSO₄) and concentrated *in vacuo* to give the title compound as a beige solid (999 mg, 99%).

LCMS m/z = 373.2 [M+H]⁺

Preparation 13

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

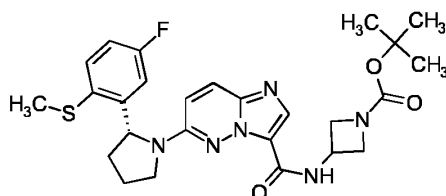


Water (0.15ml) and KOH (1.25mmol) were added to ethyl 6-[(2R)-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylate (Preparation 11, 0.25mmol) in EtOH (1ml) under N₂. The reaction was stirred at rt. After 1 hour water (10ml) and DCM (10ml) were added to the reaction mixture and the pH was adjusted to 4. The layers were partitioned and the aqueous layer was extracted three times with 2-MeTHF (10ml). The combined organic layers were dried over Na₂SO₄ and the solvent was removed under vacuum to afford the title compound as a brown solid (98%, 91mg).

10 LCMS m/z = 373.1 [M+H]⁺

Preparation 14

tert-Butyl 3-{6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}azetidine-1-carboxylate



15

To a solution of 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 12, 150 mg, 0.4 mmol), HATU (183 mg, 0.48 mmol) and *tert*-butyl 3-aminoazetidine-1-carboxylate (76 mg, 0.44 mmol) in DMF (5 ml) was added DIPEA (0.14 ml, 0.81 mmol) and the reaction was stirred at rt for 72 h. The reaction was quenched with H₂O and diluted with MTBE the phases were separated and the aqueous extracted with MTBE, the combined organic layers were washed with H₂O (3 x 10 ml) and brine, dried (MgSO₄) and concentrated *in vacuo* to afford the title compound as a brown oil used without further purification (216 mg).

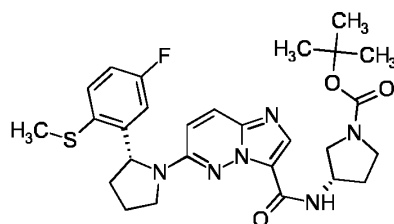
¹H NMR (CDCl₃, 396 MHz): δ : 8.22 (s, 1H), 7.70 (d, 1H), 7.22-7.31 (m, 1H *under CDCl₃), 6.99-7.07 (m, 1H), 6.77 (m, 1H), 6.36 (d, 1H), 5.29 (d, 1H), 4.88 (m, 1H), 4.36

25

(m, 2H), 3.88-3.98 (m, 2H), 3.70-3.79 (m, 2H), 2.58 (s, 3H), 2.46-2.54 (m, 1H), 2.04-2.20 (m, 3H), 1.46 (d, 9H).

Preparation 15

- 5 *tert*-Butyl (3S)-3-{6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidine-1-carboxylate

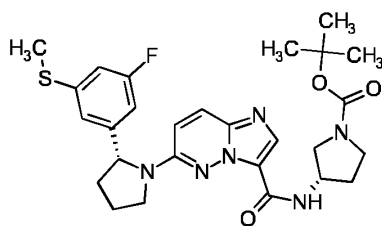


The title compound was prepared (216 mg, crude) from 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 12) and *tert*-butyl (S)-3-aminopyrrolidine-1-carboxylate following the procedure described in Preparation 14.

LCMS m/z = 541.2 $[M+H]^+$

Preparation 16

- 15 *tert*-Butyl (3S)-3-{6-[(2R)-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidine-1-carboxylate



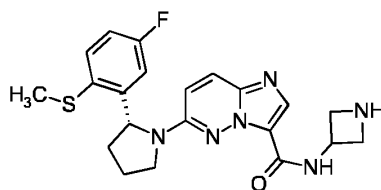
6-[(2R)-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 13, 91 mg, 0.24 mmol) and HATU (111 mg, 0.29 mmol) were dissolved in DMF (3 ml). *tert*-butyl (S)-3-aminopyrrolidine-1-carboxylate (51 mg, 0.27 mmol) was added followed by DIPEA (85 μ L, 0.49 mmol). The reaction mixture was stirred for 3.5 h under N_2 and partitioned between water and MTBE. The aqueous phase was extracted with MTBE. The combined organic layers were washed with water, brine,

dried over Na₂SO₄, and reduced to dryness under vacuum to afford the title compound which was used without further purification (117 mg, 90%).

LCMS m/z = 541.1[M+H]⁺

5 Preparation 17

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

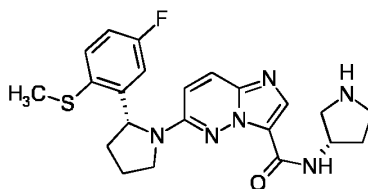


To a solution of *tert*-butyl 3-{6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}azetidine-1-carboxylate (Preparation 14, 216 mg, 0.4 mmol) in DCM (2 ml) was added TFA (1 ml) and the reaction was stirred at rt for 30 min. The reaction was concentrated and azeotroped with DCM. The crude material was purified by SCX-ion exchange resin followed by normal phase chromatography 2-30 DCM/MeOH to afford the title compound (169 mg, 59%).

LCMS m/z = 427 [M+H]⁺

Preparation 18

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



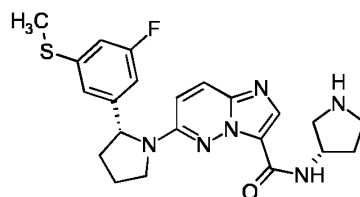
20

The following compound was prepared from *tert*-butyl (3S)-3-{6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidine-1-carboxylate (Preparation 15) following the procedure described in Preparation 17, (140mg, 64%).

LCMS $m/z = 441.3 [M+H]^+$

Preparation 19

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



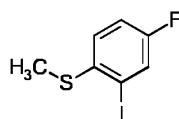
tert-Butyl (3S)-3-{6-[(2R)-2-[3-fluoro-5-(methylsulfonyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidine-1-carboxylate (Preparation 16, 117 mg, 0.22 mmol) was dissolved in DCM (1 ml) and TFA (2 ml) was added dropwise while stirring the mixture at
 10 rt. The reaction mixture was stirred at same temperature overnight. After removal of the solvent the residue was co-evaporated with DCM. The crude material was loaded on the SCX column and eluted first using MeOH and then ammonia 7.0 N in MeOH. The solvent was evaporated to give the title compound (70 mg, 72%).

LCMS $m/z = 441.1[M+H]^+$

15

Preparation 20

4-Fluoro-2-iodo-1-(methylsulfonyl)benzene



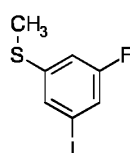
20 2-Bromo-4-fluoro-1-(methylsulfonyl)benzene (0.5 g, 2.26 mmol) was added dropwise to a suspension of activated Mg turnings (1.92 g, 79 mmol) under N_2 in dry THF (80 ml) and the reaction warmed until Grignard formation had initiated. The remaining 2-bromo-4-fluoro-1-(methylsulfonyl)benzene (17 g, 76.89 mmol) was added dropwise, so as to maintain the temperature below $50^\circ C$ and after complete addition, the reaction was
 25 allowed to cool to rt and stirred for 16 h. 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 $10^\circ C$. The reaction was stirred at $0^\circ C$ for 1 h, at rt for 1 h, 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. $\text{Na}_2\text{S}_2\text{O}_3$ solution, dried (Na_2SO_4), and concentrated *in vacuo* to afford the title compound as a brown oil (21.5 g, 83%).

- 5 ^1H NMR (CDCl_3 , 396 MHz): δ : 7.55 (m, 1H), 7.08-7.11 (m, 2H), 2.45 (s, 3H).

Preparation 21

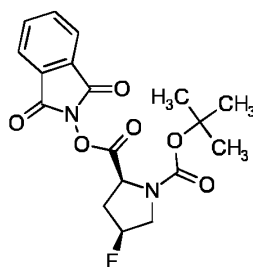
1-Fluoro-3-iodo-5-(methylsulfanyl)benzene



- 10 To a stirred solution of 1,3-difluoro-5-iodobenzene (50.0 g, 208.3 mmol) in DMF (250 ml) was added portionwise MeSNa (14.6 g, 208.3 mmol). The reaction was heated at 150°C for 1 h. Further MeSNa (1.5 g, 21 mmol) was added and the reaction was stirred at 150°C for a further 30 min. The reaction mixture was allowed to cool to rt before being diluted with distilled water (250 ml) and then extracted five times with MTBE (5 x 150 ml).
- 15 The combined organic layers were then washed three times with brine (3 x 150 ml). The organic layer was dried (MgSO_4), filtered and concentrated *in vacuo* to afford a yellow oil (61 g). This oil was combined with 54 g batch from another synthesis to give a combined total of 115 g (429 mmol). This was purified by silica column chromatography (n-heptane) to afford a colourless oil (84.18 g, 76 %).
- 20 ^1H NMR (CDCl_3 ; 400 MHz): δ : 7.31 (s, 1H), 7.18 (m, 1H), 6.88 (m, 1H), 2.45 (s, 3H).

Preparation 22

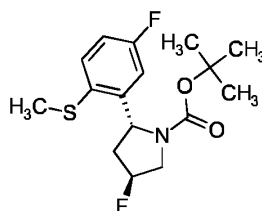
1-*tert*-Butyl 2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl) (2S,4S)-4-fluoropyrrolidine-1,2-dicarboxylate



- 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 N₂(g) and the reaction stirred at rt for 4 h. 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. NaHCO₃ (4 x 30 ml) and the organic layer dried (MgSO₄), 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-Boc]⁺

Preparation 23

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



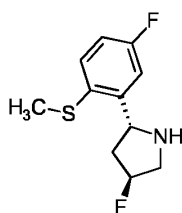
- Dry N,N-dimethylacetamide (4 ml) was added to nickel dibromide glyme complex (0.09 g, 0.291 mmol) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.08 g, 0.298 mmol) under N₂. The mixture was stirred for 15 min, then 4-fluoro-2-iodo-1-(methylsulfanyl)benzene (Preparation 20, 0.51 g, 1.49 mmol), 1-*tert*-butyl 2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl) (2S,4S)-4-fluoropyrrolidine-1,2-dicarboxylate (Preparation 22, 0.62 g, 1.64 mmol) and zinc dust (0.251 g, 3.84 mmol) were added and the reaction mixture was stirred at 28°C for 17 h. The mixture was filtered through a plug of silica and washed with diethyl ether (75 ml). The collected solution was extracted with brine (4 x 75 ml), the organic layers were combined, dried (MgSO₄), 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-Boc]⁺

5 Preparation 24

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

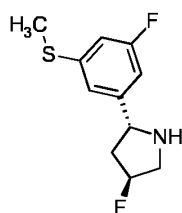


To a solution of *tert*-butyl (2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidine-1-carboxylate (Preparation 23, 1.21 g, 3.67 mmol) in MeOH (15 ml) was added HCl (4M solution in dioxane, 10 ml) and the mixture was stirred at rt for 2 h. The mixture was concentrated *in vacuo* to afford a dark brown oil which was taken up in MeOH (2 ml) and loaded onto an SCX cartridge and flushed with 7N ammonium hydroxide in MeOH. The combined solution was concentrated *in vacuo* to afford the title compound as a dark orange oil (0.4 g, 53%).

15 LCMS m/z = 230.0 [M+H]⁺

Preparation 25

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



20 NiBr₂(glyme) (14.33 g, 46.43 mmol, 15 mol %) was added to 4,4'-di-*tert*-butyl-2,2'-bipyridine (12.46 g, 46.43 mmol, 15 mol %). N₂ was flushed through the flask for 15 min before the addition of dry N,N-dimethylacetamide (325 ml). The mixture was stirred under N₂ for 15 min. 1-Fluoro-3-iodo-5-(methylsulfanyl)benzene (Preparation 21, 82.98 g, 309.5 mmol), 1-*tert*-butyl 2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl) (2S,4S)-4-

fluoropyrrolidine-1,2-dicarboxylate (Preparation 22, 175.67 g, 464.3 mmol) and zinc dust (40.47 g, 619.1 mmol) were added. The temperature was controlled to maintain the internal temperature below 40 °C. The reaction mixture was stirred at 28°C for 17 h. The reaction mixture was filtered through a plug of silica and washed three times with MTBE (3 x 200 ml). The filtrate was washed with brine (2 x 500 ml), then with 2 M KOH (5 x 300 ml) and then finally with distilled water (500 ml). The organic layer was collected, dried (MgSO₄), filtered and concentrated *in vacuo* to afford a dark orange/brown residue (132 g). This residue was purified by silica column chromatography (on 900 g of silica) eluting from neat n-heptane to 30 % MTBE in n-heptane to afford tert-butyl (2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidine-1-carboxylate (42.40 g, 70 % purity by ¹H NMR) as a light yellow oil, which is contaminated with with tert-butyl (S)-3-fluoropyrrolidine-1-carboxylate (30 % by ¹H NMR).

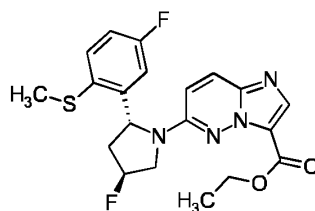
The light yellow oil was dissolved in MeOH (64 ml) at rt under N₂. To this at 0°C was added portionwise 4 M HCl in 1,4-dioxane (130 ml, 510 mmol). After 1 h the reaction mixture was concentrated *in vacuo* and taken up in distilled water (400 ml). This aqueous mixture (pH 2) was extracted twice with MTBE (2 x 250 ml) before being adjusted to pH 10 with solid NaOH. The basic aqueous layer (pH 10) was extracted four times with DCM (4 x 250 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the title compound as a reddish/brown oil (20.49 g, 89.4 mmol).

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

The title compound (20.49 g, 89.4 mmol, 1 eq.) was dissolved in dry 1,4-dioxane (45 ml) under N₂ and cooled to 0 °C. To this stirred solution was added portionwise 4 M HCl in 1,4-dioxane (33.5 ml, 134 mmol, 1.5 eq.) and the mixture was stirred at this temperature for 15 min before being concentrated *in vacuo* to afford the title compound as hydrochloride salt which was used without further purification (23.75 g, 29 % overall).

Preparation 26

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

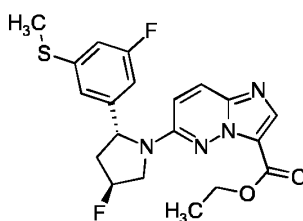


- Ethyl 6-chloroimidazo[1,2-b]pyridazine-3-carboxylate (89 mg, 0.40 mmol), KF (253 mg, 4.36 mmol) and (2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidine (Preparation 24, 100 mg, 0.38 mmol) were suspended in dry degassed DMSO (5 ml).
- 5 The reaction was heated at 130°C for 20 h. The mixture was diluted with EtOAc (20 ml), washed with water (15 ml) and brine (2 x 15 ml), dried (Na₂SO₄), filtered and evaporated to dryness to afford the title compound as a light yellow solid (174 mg, 85%).

LCMS m/z = 419.0 [M+H]⁺

10 Preparation 27

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

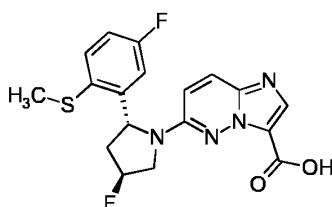


- (2R,4S)-4-Fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidine hydrochloride (Preparation 25, 23.75 g, 89.4 mmol), KF (46.73 g, 804.3 mmol), ethyl 6-chloroimidazo[1,2-b]pyridazine-3-carboxylate (19.76 g, 87.6 mmol) were suspended in DMSO (350 ml). The reaction was heated at 130°C for 82 h. The reaction mixture was allowed to cool to rt before being poured into distilled water (750 ml), which precipitated a beige solid. The liquid was decanted and the solid was washed with distilled water three
- 15 times (3 x 250 ml). The beige solid was taken up in MTBE (500 ml) and partitioned between sat. aq. NH₄Cl (500 ml) and then finally brine (500 ml). The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford a dark reddish residue which
- 20 was used without further purification (30.52 g, 82 %).

LCMS m/z = 419 [M+H]⁺

Preparation 28

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



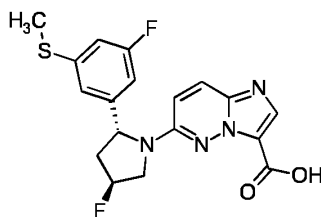
5

To a solution of ethyl 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylate (Preparation 26, 174 mg, 0.42 mmol) in EtOH (897 μ L) and water (143 μ L) was added KOH (117 mg, 2.08 mmol). The reaction was stirred at rt for 15 min, then diluted with water (20 ml) and washed with EtOAc (2 x 20 ml). The water was acidified to pH 4, then extracted with EtOAc (3 x 20 ml) and concentrated *in vacuo* to afford the title compound as a light yellow vitreous solid (94 mg, 50%).

LCMS m/z = 391 [M+H]⁺

15 Preparation 29

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



Ethyl 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylate (Preparation 27, 30.52 g, 72.9 mmol) was dissolved in EtOH (159 ml) at rt. To this stirred mixture was added portionwise a solution of NaOH (14.59 g, 364.7 mmol) in water (26 ml) at rt. After 3 h, EtOH was removed *in vacuo* and the resulting residue was dissolved in distilled water (500 ml). This was extracted with MTBE (2 x 250 ml). The basic aqueous solution was acidified to pH 5 by the dropwise addition

20

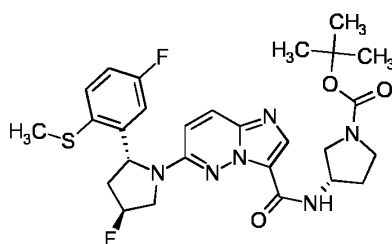
of conc. HCl and then was extracted with EtOAc (5 x 250 ml). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to give a beige solid (24.65 g, 87%).

LCMS m/z = 391 [M+H]⁺

5

Preparation 30

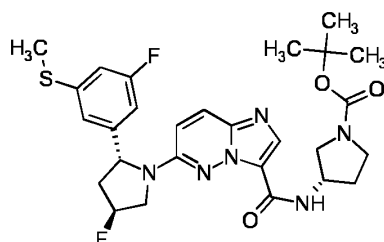
tert-Butyl (3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidine-1-carboxylate



- 10 6-[(2R,4S)-4-Fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 28, 0.30 g, 0.768 mmol) was dissolved in anhydrous DCM (5.49 ml) followed by TPTU (0.273 g, 0.922 mmol) and left to stir under N₂ for 10 min. (S)-(-)-1-Boc-3-aminopyrrolidine (0.157 g, 0.845 mmol) was added and left to stir for a further 20 min at rt before DIPEA (0.267 ml, 1.54 mmol) was added. The
- 15 resulting solution was stirred at rt under N₂ for 1 hour. The reaction was diluted with DCM (20 ml) and water (15 ml), the organic layer was further washed with sat. NH₄Cl (3 x 15 ml) and with brine (15 ml). The organic layer was dried with MgSO₄ filtered and the solvent removed under reduced pressure to afford the title compound as a pale yellow solid which was used in the next step without further purification (0.463 g, >99 %).
- 20 LCMS m/z = 559.1 [M+H]⁺

Preparation 31

tert-Butyl (3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidine-1-carboxylate

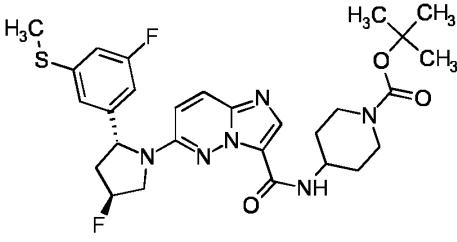
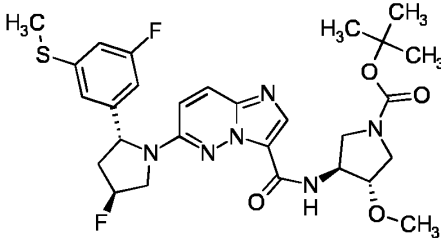
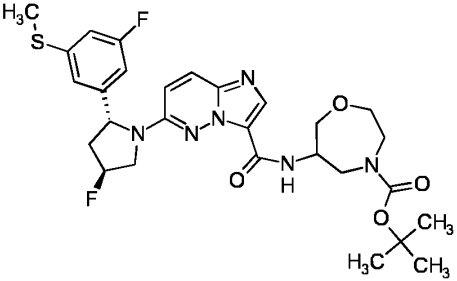


6-[(2R,4S)-4-Fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 29, 600 mg, 1.54 mmol) was dissolved in DMF (15.84 ml) and stirred at rt under N₂. HATU (0.699 g, 1.84 mmol) was added in one
 5 portion and the solution was stirred for 10 min at rt. *tert*-Butyl (S)-3-aminopyrrolidine-1-carboxylate (0.314 g, 1.69 mmol) was added and the solution stirred for 20 min before DIPEA (0.53 ml, 3.09 mmol) was added. The mixture was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc (50 ml) and washed with brine (3 x 30 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo* to give
 10 the title compound as a yellow oil which was used without further purification (1.42 g).

LCMS m/z = 559.2 [M+H]⁺

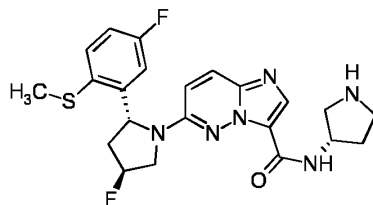
The following compounds were prepared from 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 29) and appropriate amines according to the procedure described in
 15 Preparation 31.

Preparation No	Name and Structure	Starting Material, Yield and Data
32	<i>tert</i>-butyl 3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}azetidine-1-carboxylate	Amine: <i>tert</i>-butyl 3-aminoazetidine-1-carboxylate 480 mg, 98%. LCMS m/z = 545 [M+H]⁺

33	 <i>tert</i>-butyl 4-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}piperidine-1-carboxylate	Amine: <i>tert</i>-butyl 4-aminopiperidine-1-carboxylate 167 mg, 78%. LCMS m/z = 571.2 [M-H]⁺
34	 <i>tert</i>-butyl (3S,4S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}-4-methoxypyrrolidine-1-carboxylate	Amine: <i>tert</i>-butyl (3S,4S)-3-amino-4-methoxypyrrolidine-1-carboxylate 94.6 mg, 78%. LCMS m/z = 589.2 [M+H]⁺
35	 <i>tert</i>-butyl 6-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}-1,4-oxazepane-4-carboxylate	Amine: <i>tert</i>-butyl 6-amino-1,4-oxazepane-4-carboxylate 230 mg, 73%. LCMS m/z = 589.3 [M+H]⁺

Preparation 36

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

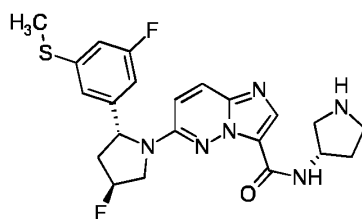


tert-Butyl (3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidine-1-carboxylate (Preparation 30, 0.429 g, 0.768 mmol) was dissolved in DCM (5.91 ml) at rt and TFA (1.69 ml, 14.86 mmol) was added dropwise. The mixture was allowed to stir at rt for 90 min. The mixture was concentrated *in vacuo*, then DCM (30 ml) was added before being concentrated *in vacuo* again. This was repeated (2 x 30 ml of DCM). The crude residue was loaded onto an SCX cartridge (10 g, pre-washed with 3 CVs MeOH), washed with 4 CVs MeOH and then finally eluted with 5 CVs of 2M NH₃ in MeOH. The relevant fractions were combined and concentrated *in vacuo* to afford the title compound as a yellow oil which was used without further purification (0.351 g, quantitative).

LCMS $m/z = 459.0$ [M+H]⁺

Preparation 37

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

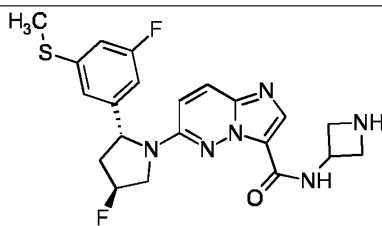
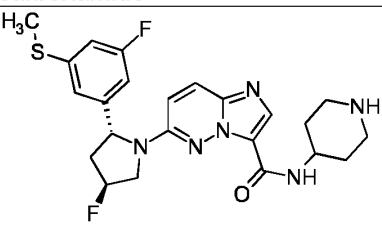
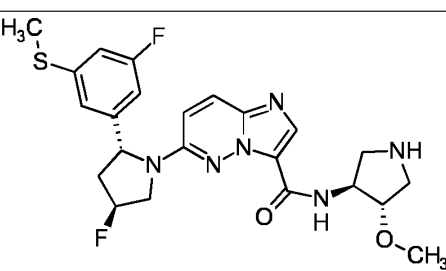


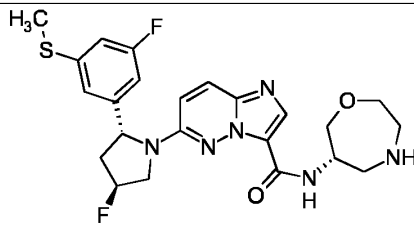
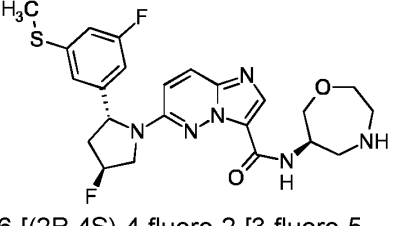
tert-Butyl (3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidine-1-carboxylate (Preparation 31, 0.858 g, 1.54 mmol) was dissolved in DCM (11.81 ml) at rt and TFA (2.27 ml, 29.7 mmol, 19.35 eq.) was added dropwise. The reaction was allowed to stir at rt for 90 min. The reaction was concentrated *in vacuo* and then co-evaporated with DCM (3 x 10 ml). The crude residue was loaded onto an SCX cartridge (5g, pre-washed with 3 CVs MeOH), washed with 4 CVs MeOH and then finally eluted with 5 CVs of 2M NH₃ in MeOH. The relevant

fractions were combined and concentrated *in vacuo* to afford the title compound as a yellow oil (0.722 g, quantitative).

LCMS $m/z = 459.2$ $[M+H]^+$

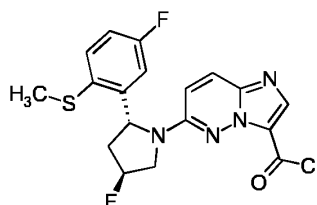
The following compounds were prepared from the appropriate protected amines
5 according to the procedure described in Preparation 37.

Preparation No	Structure and Name	Starting Material, Yield and Data
38	 N-(azetidin-3-yl)-6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide	Amine: Preparation 32 0.355g, 89 %. LCMS $m/z = 445.0$ $[M+H]^+$
39	 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-(piperidin-4-yl)imidazo[1,2-b]pyridazine-3-carboxamide	Amine: Preparation 33 87 mg, 79%. LCMS $m/z = 473.2$ $[M+H]^+$
40	 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S,4S)-4-methoxypyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide	Amine: Preparation 34 0.0712 g, 91%. LCMS $m/z = 489.2$ $[M+H]^+$

41*	 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(6S)-1,4-oxazepan-6-yl]imidazo[1,2-b]pyridazine-3-carboxamide*	Amine: Preparation 34 44 mg (41) and 17 mg (42), 37% overall. Isomer (41): LCMS m/z = 489.1 [M+H]⁺ Isomer (42): LCMS m/z = 489.1 [M+H]⁺ Boc deprotection was carried out using formic acid instead of trifluoroacetic acid in DCM. *Stereochemistry arbitrarily assigned.
42*	 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(6R)-1,4-oxazepan-6-yl]imidazo[1,2-b]pyridazine-3-carboxamide*	

Preparation 43

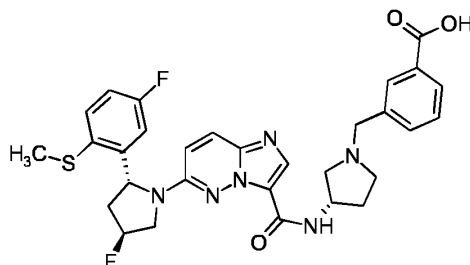
6-[(2S,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]cyclopentyl]imidazo[1,2-b]pyridazine-3-carbonyl chloride



To a suspension of 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxylic acid (Preparation 28, 1.0 g, 2.57 mmol) in DCM (50 ml) was added oxalyl chloride (390 mg, 0.264 ml, 3.08 mmol) followed by 1 drop of DMF. Gas evolution was observed and internal temperature increased from 20°C to 21°C. The reaction was left to stir at rt for 30 min and then reduced to dryness to yield the title compound as pale yellow foam which was used without further purification.

Preparation 44

3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]benzoic acid

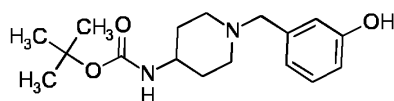


To a solution of methyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl)methyl]benzoate (Example 10, 190 mg, 0.313 mmol, 1 equiv.) in MeOH (0.69 ml) was added a solution of NaOH (62 mg, 1.57 mmol, 5.0 equiv.) in water (0.46 ml) at rt. The mixture was stirred for 1 hour, then a further solution of NaOH (5 equiv.) in water (0.46 ml) added and the reaction mixture stirred at rt for 16 h. The MeOH was removed *in vacuo*, the reaction mixture diluted with water (15 ml) and the pH adjusted with 2M HCl to pH 4. The mixture was extracted with EtOAc (2 x 20 ml). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the title compound as a white solid (166 mg, 89%).

LCMS m/z = 593 [M+H]⁺

Preparation 45

tert-Butyl N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}carbamate

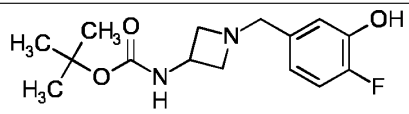
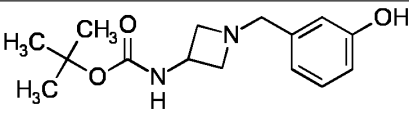
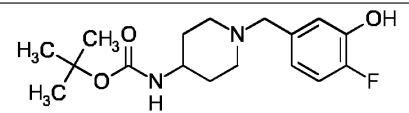


To *tert*-butyl N-(piperidin-4-yl)carbamate (8.19 g, 40.9 mmol) and 3-hydroxybenzaldehyde (5.00 g, 40.9 mmol) in DCM (100 ml) at rt was added acetic acid (3.79 ml, 49.1 mmol, 1.1 eq.) and the reaction mixture stirred for 15 min before adding sodium triacetoxymethylborohydride (17.35 g, 81.80 mmol) portionwise. The resulting mixture was stirred at rt for 18 h. The reaction mixture was diluted with DCM (250 ml) and the organic layer was washed with water (2 x 250 ml). The aqueous layer was basified to pH 5 by careful addition of sodium hydrogen carbonate. The aqueous was then extracted using MTBE/EtOAc (3 x 300 ml). The combined organic layers were dried (MgSO₄),

filtered and concentrated *in vacuo* to give the title compound as a colourless solid (9.0 g, 72%).

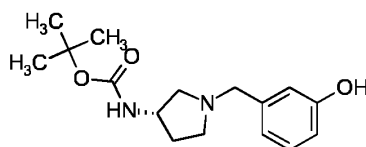
¹H NMR (CDCl₃; 400 MHz): δ : 7.18 (m, 1H); 7.08 (bs, 1H); 6.94-6.75 (m, 2H); 4.60 (m, 1H); 3.71 (s, 2H); 3.61-3.33 (m, 1H); 3.20-2.90 (m, 2H); 2.48-2.18 (m, 2H); 2.18-1.87 (m, 2H); 1.87-1.57 (m, 2H); 1.52-1.34 (m, 10H).

The following compounds were prepared from the appropriate amines and aldehydes according to the procedure described in Preparation 45.

Preparation No	Structure and Name	Starting Materials, Yield and Data
46	 tert-butyl N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}carbamate	tert-butyl N-(azetidine-4-yl)carbamate, 4-fluoro-3-hydroxybenzaldehyde. 329 mg, 97%, colourless solid. LCMS <i>m/z</i> = 241.0 [M-tBu] ⁺
47	 tert-butyl N-{1-[(3-hydroxyphenyl)methyl]azetidin-3-yl}carbamate	tert-butyl N-(azetidine-4-yl)carbamate; 3-hydroxybenzaldehyde. 311 mg, 96%, white solid. LCMS <i>m/z</i> = 223.1 [M-tBu] ⁺
48	 tert-butyl N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]piperidin-4-yl}carbamate	tert-butyl N-(piperidin-4-yl)carbamate, 4-fluoro-3-hydroxybenzaldehyde. 6.6 g, 76%. ¹ H-NMR (MeOD-d ₄ ; 396 MHz): δ : 6.95 (m, 1H), 6.88 (m, 1H), 6.75-6.67 (m, 1H), 3.39 (s, 2H), 2.82 (m, 2H), 2.07 (m, 2H), 1.81 (m, 2H), 1.51-1.36 (m, 12H).

Preparation 49

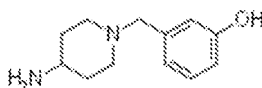
10 tert-butyl N-[(3S)-1-[(3-hydroxyphenyl)methyl]pyrrolidin-3-yl]carbamate



- To *tert*-butyl N-[(3S)-pyrrolidin-3-yl]carbamate (20.0 g, 107 mmol, 1 eq.) and 3-hydroxybenzaldehyde (13.1 g, 107 mmol, 1 eq.) in DCM (250 ml) at rt was added acetic acid (6.76 ml, 118 mmol, 1.1 eq.) and the reaction mixture stirred for 1 hour before adding portionwise sodium triacetoxyborohydride (45.5 g, 215 mmol, 2 eq.). The resulting mixture was stirred at room for 4 h. The reaction mixture was carefully poured into a beaker of sat. aq. NaHCO₃ at 0°C and stirred overnight. The layers were separated and the aqueous was extracted with further DCM (250 ml). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*, then azeotroped with TBME to give the title compound as a clear glass solid (33.60 g, quantitative).
- LCMS m/z = 293 [M+H]⁺

Preparation 50

3-((4-Aminopiperidin-1-yl)methyl)phenol hydrochloride

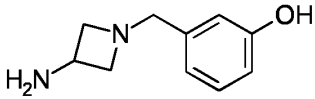
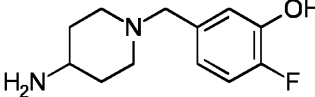


- To a solution of *tert*-butyl N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}carbamate (Preparation 45, 9.00 g, 29.40 mmol, 1 eq.) in MeOH (75 ml) was added 4 M HCl in 1,4-dioxane (37 ml, 146.9 mmol, 9 eq.) at rt under N₂ and the resulting mixture was stirred for 18 h. The reaction mixture was concentrated *in vacuo* and triturated with TBME to give the title compound as a white hydrochloride salt (7.00 g, quantitative). *Note*: this material is hygroscopic and should be stored under N₂.

¹H NMR (MeOD-d₄; 400MHz): δ: 7.34-7.19 (m, 1H); 7.02-6.93 (m, 2H); 6.92-6.79 (m, 1H); 4.23 (s, 2H); 3.69-3.36 (m, 3H); 3.15 (bs, 2H); 2.21 (bs, 2H); 1.99 (bs, 2H).

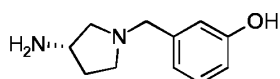
The following compounds were prepared from the appropriate protected amines according to the procedure described in Preparation 50.

Preparation No	Structure and Name	Starting material, Yield & Data
51	5-[(3-aminoazetidin-1-yl)methyl]-2-fluorophenol hydrochloride	Amine: Preparation 46 300 mg, 97%, yellow solid. ¹H-NMR (MeOD-d₄; 396 MHz) δ: 7.18-7.10 (m, 2H), 6.99-6.91 (m, 1H), 4.47-4.32 (m, 5H), 3.66 (s, 2H).

52	 3-[(3-aminoazetidin-1-yl)methyl]phenol hydrochloride	Amine: Preparation 47 267 mg, 99%, white solid. ¹H-NMR (MeOD-d₄; 396 MHz): δ: 7.29 (m, 1H), 6.96-6.88 (m, 3H), 4.45-4.35 (m, 7H).
53	 5-[(4-aminopiperidin-1-yl)methyl]-2-fluorophenol hydrochloride	Amine: Preparation 48 5.5 g, quantitative, off white solid. ¹H-NMR (MeOD-d₄; 396 MHz): δ: 7.19-7.08 (m, 2H), 7.01-6.92 (m, 1H), 4.22 (s, 2H), 3.55 (d, 3H), 3.12 (m, 2H), 2.23 (m, 2H), 1.98 (m, 2H).

Preparation 54

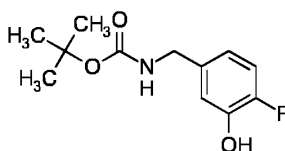
3-[(3S)-3-aminopyrrolidin-1-yl]methyl]phenol hydrochloride



- 5 To the title compound of Preparation 49 (33.60 g, 115 mmol) at rt under N₂ was added 4 M HCl in 1,4-dioxane (259 ml, 1.03 mol) and the resulting mixture was stirred for 2 h. The reaction mixture was concentrated *in vacuo* and azeotroped with TBME (2 x 100 ml) and DCM (100 ml) to give the title compound as a white solid (31.20 g, quantitative). *Note:* this material is hygroscopic and should be stored under N₂.
- 10 LCMS *m/z* = 193 [M+H]⁺

Preparation 55

tert-butyl N-[(4-fluoro-3-hydroxyphenyl)methyl]carbamate



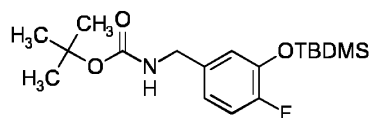
- 15 To 5-(aminomethyl)-2-fluorophenol (500 mg, 3.54 mmol) in THF (7 ml) at rt were added sodium hydrogen carbonate (893 mg, 10.63 mmol) in water (7 ml) and di-*tert*-butyl dicarbonate (850 mg, 3.90 mmol) and the resulting mixture was stirred at rt for 2 h. The reaction mixture was diluted with EtOAc (15 ml), washed with brine (2 x 15 ml), dried

(Na₂SO₄), filtered and then concentrated *in vacuo*. The residue was purified on the Biotage® with a ZIP KP-Sil 80 g column (10 % EtOAc in n-heptane for 1 CV and then 10-80 % EtOAc in n-heptane over 10 CVs) to afford the title compound as an amber oil (294 mg, 34 %).

5 LCMS m/z = 240.0 [M-H]⁺

Preparation 56

tert-Butyl N-({3-[(*tert*-butyldimethylsilyl)oxy]-4-fluorophenyl}methyl)carbamate

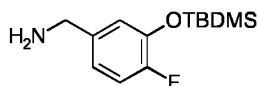


- 10 To a solution of *tert*-butyl N-[(4-fluoro-3-hydroxyphenyl)methyl]carbamate (Preparation 55, 294 mg, 1.22 mmol) in DMF was added at rt TBDMSCl (276 mg, 1.83 mmol) and imidazole (125 mg, 1.83 mmol). The reaction mixture was stirred for 2 h, then partitioned between water (20 ml) and EtOAc (20 ml). The organic layer was washed with water (3 x 20 ml), saturated brine solution (20 ml), dried over Na₂SO₄ and concentrated *in vacuo* to
- 15 afford the title compound as an amber oil (433 mg, quantitative).

LCMS m/z = 240 [M-TBDMS]⁺

Preparation 57

1-{3-[(*tert*-butyldimethylsilyl)oxy]-4-fluorophenyl}methanamine



20

- To a solution of *tert*-butyl N-({3-[(*tert*-butyldimethylsilyl)oxy]-4-fluorophenyl}methyl)carbamate (Preparation 56, 433 mg, 1.22 mmol) in DCM (2.4 ml), cooled to 0°C, was added TFA (2.4 ml) dropwise and the reaction mixture stirred at 0°C for 3 h before partitioning between DCM (20 ml) and water (20 ml). The pH was adjusted
- 25 with NaOH to ~pH 11, the layers separated and the aqueous layer extracted with 20 ml

DCM. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound as a brown oil (320 mg, quantitative).

¹H-NMR (CDCl₃; 396 MHz): 6.99 (m, 1H); 6.86 (m, 1H); 6.84-6.80 (m, 1H); 3.77 (s, 2H); 1.53 (br s, 2H); 1.00 (s, 9H); 0.19 (s, 3H); 0.18 (s, 3H).

5 Example 32 – Topical pharmaceutical compositions

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

10 Ointment-based (O) topical pharmaceutical compositions

Formulation	O1	O2	O3	O4	O5
Example 7	5.00	4.38	4.14	4.14	4.14
SR PEG 400	32.67	32.96	23.62	23.62	20.79
Glycerol	18.67	18.83	18.90	18.90	15.97
Propylene Glycol	9.33	9.42	9.45	9.45	9.10
Transcutol P	9.33	9.42	18.90	18.90	18.90
Octisalate	-	-	-	-	6.10
BHT	0.10	0.10	0.10	0.10	0.10
PEG 3350	24.90	-	24.90	-	-
PEG 4000	-	24.90	-	24.90	24.90
Total	100	100	100	100	100

Aqueous gel (AG) and non-aqueous gel-based (NAG) topical pharmaceutical compositions

15

Formulation	AG1	AG2	NAG1	NAG2	NAG3
Example 7	2.60	2.60	2.70	2.70	2.70
SR PEG 400	29.30	29.30	40.20	40.20	34.10
Ethanol	-	-	5.00	5.00	5.00
Glycerol	20.00	20.00	20.00	20.00	20.00
Propylene Glycol	20.00	20.00	20.00	20.00	20.00
Transcutol P	10.00	10.00	10.00	10.00	10.00
Deionised water	14.00	14.00	-	-	-
Benzyl Alcohol	2.00	2.00	-	-	-

Octisalate	-	-	-	-	6.10
BHT	0.10	0.10	0.10	0.10	0.10
HPC MF	2.00	-	2.00	-	2.00
HPC GF	-	2.00	-	2.00	-
Total	100	100	100	100	100

Cream-based (CR) topical pharmaceutical compositions

Formulation	CR1	CR2	CR3	CR4	CR5
Example 7	0.80	0.80	1.10	1.10	1.10
SR PEG 400	10.65	9.57	9.33	9.27	9.27
Glycerol	7.90	7.90	12.90	12.90	12.90
Propylene Glycol	10.00	10.00	10.00	10.00	10.00
Transcutol P	15.55	15.63	15.57	15.63	15.63
Deionised water	30.00	30.00	25.00	25.00	25.00
Benzyl Alcohol	2.00	2.00	2.00	2.00	2.00
Tween 80	4.41	4.41	4.32	4.41	4.41
BHT	-	-	0.10	0.10	0.10
Ascorbic Acid	0.10	0.10	-	-	-
Cetostearyl Alcohol	12.00	12.00	12.00	12.00	12.00
Liquid paraffin	-	7.00	-	7.00	0.90
Span 60	0.59	0.59	0.68	0.59	0.59
Crodamol GTCC	6.00	-	7.00	-	-
Octisalate	-	-	-	-	6.10
Total	100	100	100	100	100

5 Examples 33 – 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

Formulation	t = 2 weeks		t = 4 weeks		t = 6 months	
	25 °C	40 °C	25 °C	40 °C	25 °C	40 °C
O1	94.51	94.02	92.17	94.49	96.09	90.43
O2	quant.	95.23	97.07	99.91	-	-
O3	97.64	97.07	96.37	95.14	-	-
O4	99.35	97.06	99.93	quant.	-	-
O5	quant.	97.87	quant.	quant.	quant.	quant.
AG1	96.00	98.83	102.91	101.96	-	-
AG2	quant.	99.81	104.22	101.22	-	-
NAG1	99.54	98.31	97.68	98.04	-	-
NAG2	99.02	98.27	98.82	98.34	-	-
NAG3	quant.	quant.	quant.	quant.	97.12	quant.
CR1	99.75	99.96	quant.	98.30	-	-
CR2	quant.	99.49	quant.	99.49	quant.	quant.
CR3	quant.	99.05	quant.	quant.	-	-
CR4	quant.	quant.	quant.	quant.	-	-
CR5	quant.	92.71	96.86	93.06	quant.	97.14

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

- 5 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.

5

Physical stability of topical pharmaceutical compositions

All of the ointment, aqueous gel and 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

10

Example 34 – 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, aqueous gels and non-aqueous gels have a particularly high API loading ability, with API loading being over 4% by weight of the composition. The ointments performed even better exhibiting 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.

15

20

Example 35 – RHE irritancy test (in vitro irritancy study using RHE cultures)

25

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 cm²) were equilibrated overnight in a humidified incubator at 37 °C and 5% CO₂. 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% CO₂ 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: $100 \times [\text{OD}(\text{sample})/\text{OD}(\text{neg control})]$. 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 $\pm$ standard deviation (n=3).

Formulation	Mean percent viability	Classification
O1	130.0	non-irritant
O5	53.9	non-irritant
NAG3	67.5	non-irritant
CR3	114.5	non-irritant
CR5	60.9	non-irritant
O1 PBO	121.4	non-irritant
O5 PBO	112.6	non-irritant
NAG3 PBO	120.0	non-irritant
CR3 PBO	128.5	non-irritant
CR5 PBO	146.9	non-irritant

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

5

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

Example 36 – Human skin penetration study

10

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.

15

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 $500 \pm 50 \mu\text{m}$ 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.

20

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 $10 \mu\text{Lmin}^{-1}$.

25

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.

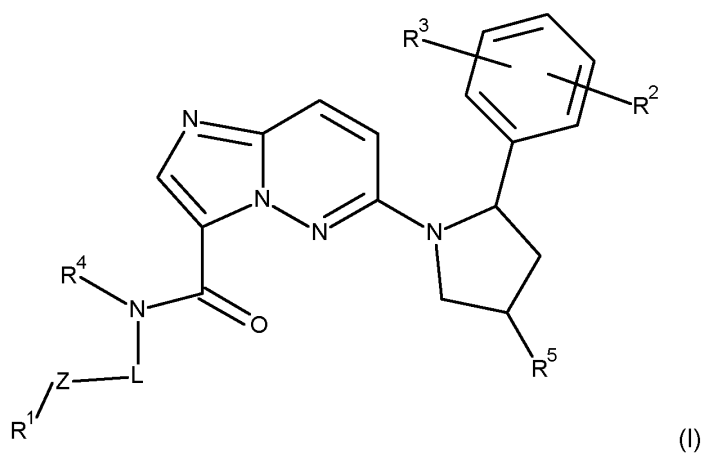
Mobile Phase A	0.01% Formic Acid in water			
Mobile Phase B	Methanol			
Purge solvent	0.01% Formic Acid in water			
Wash solvent	Methanol			
Injection Volume (µL)	5.0			
Multiplexing?	No			
Guard Column	Phenomenex SecurityGuard Ultra C18			
Column	Supelco Titan C18 2.1 x 20 mm, 1.9 µm			
Flow Rate (initial)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

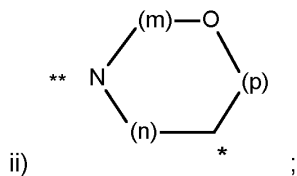
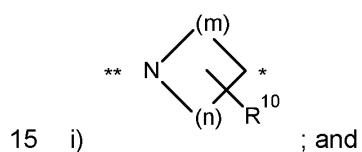
1. A topical pharmaceutical composition comprising
- (a) a compound of Formula (I) or a pharmaceutically acceptable salt and/or
- 5 solvate thereof in an amount of from about 0.008% to about 30%, preferably from about 0.01% to about 20%, more preferably from about 0.05% to about 5%, by weight of the composition; and
- (b) an excipient system in an amount of less than about 99.99 % by weight of the composition,
- 10 wherein the compound of Formula (I) is



and wherein

L is $(CR^6R^7)_r$;

Z is absent or selected from:



wherein * denotes the point of attachment to L and ** denotes the point of attachment to R¹;

m is 1 or 2;

20 n is 1 or 2;

- p is 0 or 1;
 provided that the sum of m, n and p is in the range of 2 to 4;
 r is 0 or 1;
 R¹ is -XR⁸;
- 5 X is selected from -CH₂-, -C(O)-, and -S(O₂)-;
 R² is selected from H and -SR⁸;
 R³ is selected from H and halo;
 R⁴ is selected from H and (C₁-C₃)alkyl;
 R⁵ is selected from H, hydroxyl and halo;
- 10 R⁶ and R⁷ are each independently selected from H and (C₁-C₃)alkyl;
 R⁸ is methyl;
 R⁹ is phenyl substituted by a group selected from hydroxy, -OC(O)(C₁-C₆)alkyl, C(O)OH
 and -C(O)O(C₁-C₆)alkyl, wherein the phenyl ring is optionally further substituted by halo;
 R¹⁰ is selected from H and (C₁-C₃)alkoxy.
- 15
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 50%, by weight of the
 20 composition.
3. The topical pharmaceutical composition according to claim 1 or claim 2,
 wherein the excipient system comprises glycol, polyol, dialkyl glycol monoalkyl ether
 or a combination thereof, preferably in an amount of from about 10% to about 70%,
 25 more preferably about 20% to about 60%, 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,
 30 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%, by weight of the composition;
- (B) glycol in an amount of from about 1% to about 30%, preferably from about 5%
 35 to about 25%, 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 30%, preferably about 5% to about 25%, by weight of the composition, preferably the dialkyl glycol monoalkyl ether is diethyl glycol monoethyl ether; and optionally
- 5 (D) polyol in an amount of from about 1% to about 30%, preferably from about 5% to about 25%, by weight of the composition, preferably the polyol is glycerol.
5. The topical pharmaceutical composition according to any preceding claim, wherein the excipient system comprises
- 10 (a) an oleaginous base, such as petroleum jelly, and/or PEG selected from PEG 1000 to PEG 10000 in an amount of from about 20% to 30% by weight of the composition, preferably the PEG is PEG 3350 and/or PEG 4000;
- (b) a gelling agent in an amount of from about 0.5% to about 5%, preferably from about 1% to about 3%, by weight of the composition, preferably the gelling agent is HPC MF or HPC GF, and optionally wherein the excipient system comprises
- 15 (i) water in an amount of from about 10% to 30% by weight of the composition; and
- (ii) optionally a preservative, such as benzyl alcohol, in an amount of from about 0.1% to about 5% by weight of the composition; or
- 20 (c) (i) water preferably in an amount of from about 20% to about 35% 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;
- 25 (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, preferably Tween, such as Tween 80, and preferably in an amount of from about 2% to about 10% by weight of the composition; and
- 30 (v) optionally a preservative, such as benzyl alcohol, in an amount of from about 0.1% to about 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 20% to about 30% by weight of the composition, preferably the PEG is PEG 3350 or PEG 4000; or
 - (b) a gelling agent in an amount of from about 0.5% to about 5%, preferably from about 1% to about 3%, by weight of the composition, preferably the gelling agent is HPC MF or HPC GF, and optionally wherein the excipient system further comprises
 - (i) water in an amount of from about 10% to about 30% by weight of the composition; and
 - (ii) benzyl alcohol in an amount of from about 0.1% to about 5% 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 or solvate thereof is present in an amount of from about 1% to about 5% by weight of the composition;
 - (B) the excipient system comprises
 - (i) PEG 400 in an amount of from about 15% to about 35% by weight of the composition;
 - (ii) glycerol in an amount of from about 12% to about 22% by weight of the composition;
 - (iii) propylene glycol in an amount of from about 5% to about 15% by weight of the composition;
 - (iv) diethyl glycol monoethyl ether in an amount of from about 5% to about 25% by weight of the composition;

- (v) PEG selected from PEG 1000 to PEG 10000 in an amount of from about 20% to 30% by weight of the composition, preferably the PEG is PEG 3350 or PEG 4000; and
 - (vi) an antioxidant, preferably BHT, in an amount of from about 0.05% to about 0.5% by weight of the composition.
- 5
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 0.5% to about 4% by weight of the composition;
- 10
- (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 17% to about 23% by weight of the composition;
 - (iii) propylene glycol in an amount of from about 17% to about 23% by weight of the composition;
 - (iv) diethyl glycol monoethyl ether in an amount of from about 7% to about 13% by weight of the composition; and
 - (v) either
 - (a) low molecular weight alcohol, preferably ethanol, in an amount of from about 2% to about 8% by weight of the composition; or
 - (b) water in an amount of from about 10% to about 30% by weight of the composition; and
- 15
- benzyl alcohol in an amount of from about 0.1% to about 5% 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 and/or HPC GF; and
- 20
- (vii) optionally an antioxidant, preferably BHT, in an amount of from about 0.05% to about 0.5% by weight of the composition.
- 25
- 30
11. The topical pharmaceutical composition according to claim 1, wherein

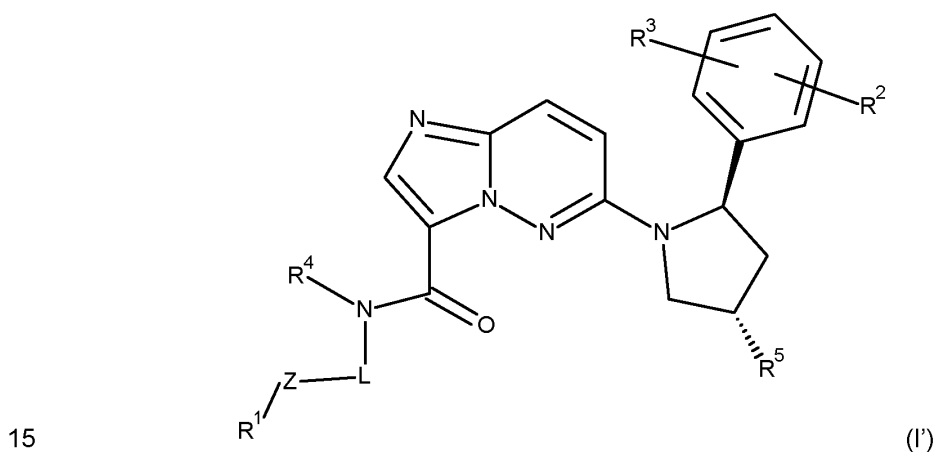
- (A) the compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof is present in an amount of from about 0.3% to about 1.5% by weight of the composition;
- (B) the excipient system comprises
 - 5 (i) PEG 400, preferably SR PEG 400, in an amount of from about 5% to about 15% by weight of the composition;
 - (ii) glycerol in an amount of from about 5% to about 15% by weight of the composition;
 - (iii) propylene glycol in an amount of from about 7% to about 13% by weight of the composition;
 - 10 (iv) diethyl glycol monoethyl ether in an amount of from about 12% to about 17% by weight of the composition;
 - (v) water in an amount of from about 20% to about 35% by weight of the composition;
 - 15 (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; and
 - 20 (viii) Span 60 in an amount of from about 0.2% to about 1% by weight of the composition; and
 - (ix) optionally Tween 80 in an amount of from about 2% to about 10% by weight of the composition;
 - 25 (x) 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;
 - (xi) optionally benzyl alcohol in an amount of from about 0.1% to about 5% by weight of the composition; and
 - 30 (xii) optionally a UV filter, such as octisalate, preferably in an amount of from about 4% to about 8% by weight of the composition.

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

35 R^1 is $-CH_2R^9$;

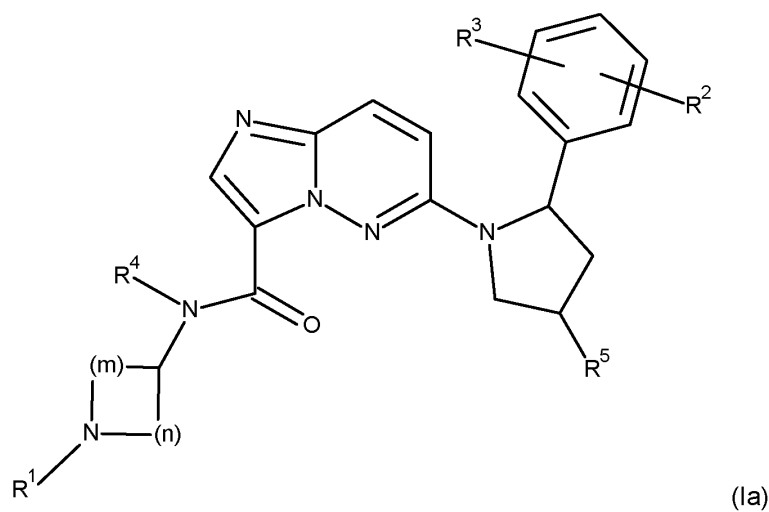
- R^2 is $-SR^8$;
 R^3 is H or fluoro;
 R^4 is H;
 R^5 is H or fluoro;
 5 R^6 is H;
 R^7 is H;
 R^9 is phenyl substituted by hydroxy wherein the hydroxyphenyl is optionally further substituted by fluoro;
 R^{10} is H;
 10 r is 0; and/or
 Z is absent.

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



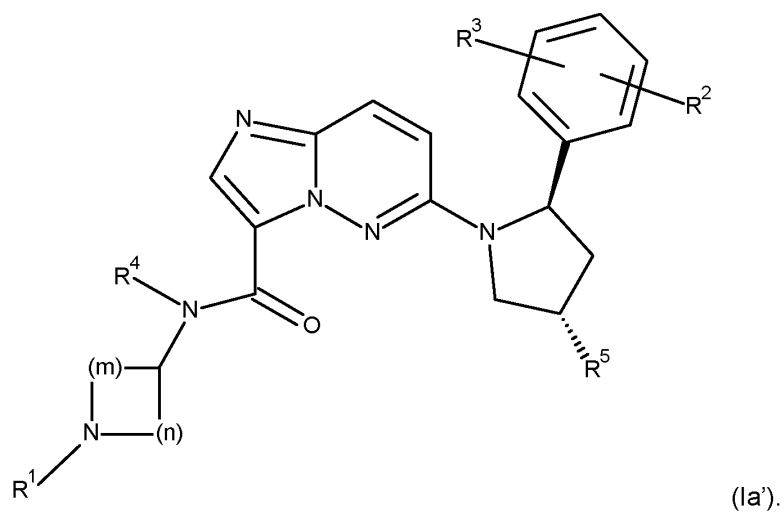
or a pharmaceutically acceptable salt and/or solvate thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , L and Z , are as defined in claim 1 or claim 12.

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

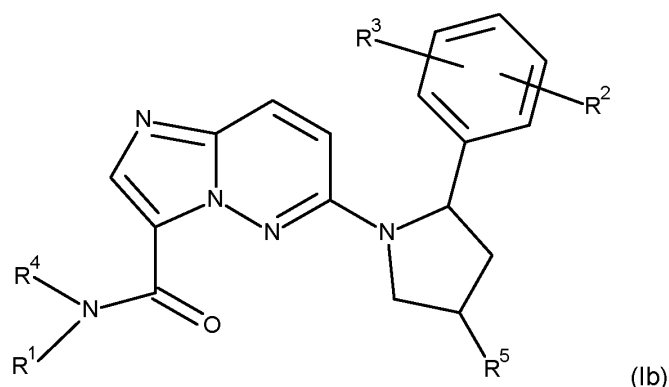


or a pharmaceutically acceptable salt and/or solvate thereof wherein R^1 , R^2 , R^3 , R^4 , R^5 , m and n , are as defined in any one of claims 1, 12 and 13,

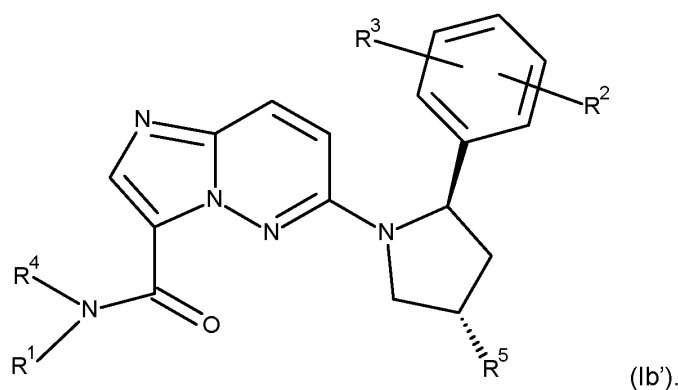
- 5 preferably wherein the compound of Formula (I) is a compound of Formula (Ia')



15. The topical pharmaceutical composition according to any one of claims 1 to 13, wherein the compound of formula (I) is a compound of formula (Ib)



or a pharmaceutically acceptable salt and/or solvate thereof, wherein R¹, R², R³, R⁴ and R⁵ are as defined in any one of claims 1, 12 and 13, preferably wherein the compound of Formula (I) is a compound of Formula (Ib')



5

16. The topical pharmaceutical composition according to any previous claim, wherein the compound of Formula (I) is selected from
- 6-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 10 6-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 15 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 20 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;

- 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 5 3-[[3-{6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]phenyl pentanoate;
- Methyl 3-[[3-{6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate;
- 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 10 Butyl 3-[[3-{6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate;
- Ethyl 3-[[3-{6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate;
- 15 6-[4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(4-fluoro-3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide;
- N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]-6-[2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- Methyl 3-[[3-{6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate;
- 20 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 25 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(3-hydroxyphenyl)methyl]azetidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]piperidin-4-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 30 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(3-hydroxyphenyl)methyl]piperidin-4-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-[(4-fluoro-3-hydroxyphenyl)methyl]-4-methoxypyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 35 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[4-[(4-fluoro-3-hydroxyphenyl)methyl]-1,4-oxazepan-6-yl]imidazo[1,2-b]pyridazine-3-carboxamide;

- 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(4-fluoro-3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[1-(3-hydroxybenzoyl)pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
 5 3-[[3-{6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}phenyl acetate;
 3-[[3-{6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoic acid;
 Butyl 3-[[3-{6-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-
 10 b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate;
 5-[4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}pyrazolo[1,5-a]pyrimidine-3-carboxamide;
 or a pharmaceutically acceptable salt and/or solvate thereof.
- 15 17. The topical pharmaceutical composition according to any previous claim, wherein the compound of Formula (I) is selected from
 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[(2R)-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(4-fluoro-3-
 20 hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
 25 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3-
 30 hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide;
 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
 3-[[3-(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}phenyl pentanoate;
 35 Methyl 3-[[3-(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate;

- 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- Butyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate;
- 5 Ethyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate;
- 6-[(2R,4S)-4-fluoro-2-[5-fluoro-2-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(4-fluoro-3-hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide;
- N-[(3S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]-6-[(2R)-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 10 Methyl 3-[[[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl]benzoate;
- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 15 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]azetidin-3-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 20 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(4-fluoro-3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}imidazo[1,2-b]pyridazine-3-carboxamide;
- 25 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S,4S)-1-[(4-fluoro-3-hydroxyphenyl)methyl]-4-methoxypyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(6S)-4-[(4-fluoro-3-hydroxyphenyl)methyl]-1,4-oxazepan-6-yl]imidazo[1,2-b]pyridazine-3-
- 30 carboxamide;
- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(6R)-4-[(4-fluoro-3-hydroxyphenyl)methyl]-1,4-oxazepan-6-yl]imidazo[1,2-b]pyridazine-3-
- carboxamide;
- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(4-fluoro-3-
- 35 hydroxyphenyl)methyl]imidazo[1,2-b]pyridazine-3-carboxamide;

- 6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-[(3S)-1-(3-hydroxybenzoyl)pyrrolidin-3-yl]imidazo[1,2-b]pyridazine-3-carboxamide;
 3-[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}phenyl acetate;
 5 3-[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}benzoic acid;
 Butyl 3-[(3S)-3-{6-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]imidazo[1,2-b]pyridazine-3-amido}pyrrolidin-1-yl]methyl}benzoate;
 5-[(2R,4S)-4-fluoro-2-[3-fluoro-5-(methylsulfanyl)phenyl]pyrrolidin-1-yl]-N-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}pyrazolo[1,5-a]pyrimidine-3-carboxamide;
 10 or a pharmaceutically acceptable salt or solvate thereof.

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

15

19. 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.

20. The topical pharmaceutical composition for use according to claim 19, wherein the condition or disorder is dermatitis, preferably atopic dermatitis.

21. 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 18, preferably wherein the condition or disorder is mediated by TrkA, TrkB, and TrkC.

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

30

23. Use of a compound of Formula (I) as defined in any one of claims 1, and 12 to 17, in the manufacture of a medicament for 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, wherein the medicament comprises the topical pharmaceutical composition as defined in any one of claims 1 to 11, and 18.

35

24. The use according to claim 23, wherein the condition or disorder is dermatitis, preferably atopic dermatitis.