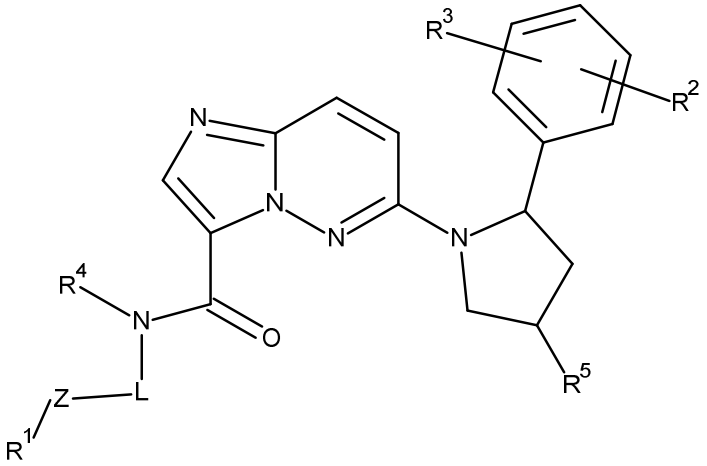
CLAIMS

1. A topical pharmaceutical composition comprising

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

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

wherein the compound of Formula (I) is

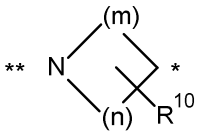


(I)

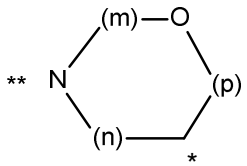
and wherein

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

Z is absent or selected from:



i) ; and



ii) ;

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;

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 $–S(O_2)$-;

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;

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.

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 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%, 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, 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% 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

(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

(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

(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

(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;

(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

(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.

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;

(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

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.

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

(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;

(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;

(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

(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;

(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

(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)

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;

R^6 is H;

R^7 is H;

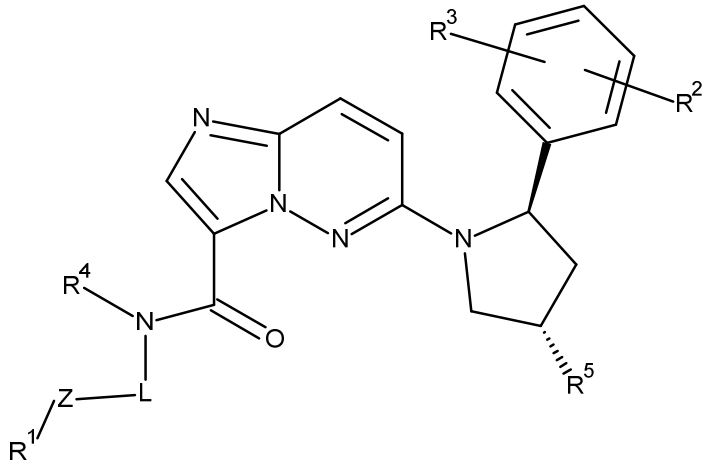
R^9 is phenyl substituted by hydroxy wherein the hydroxyphenyl is optionally further substituted by fluoro;

R^{10} is H;

r is 0; and/or

Z is absent.

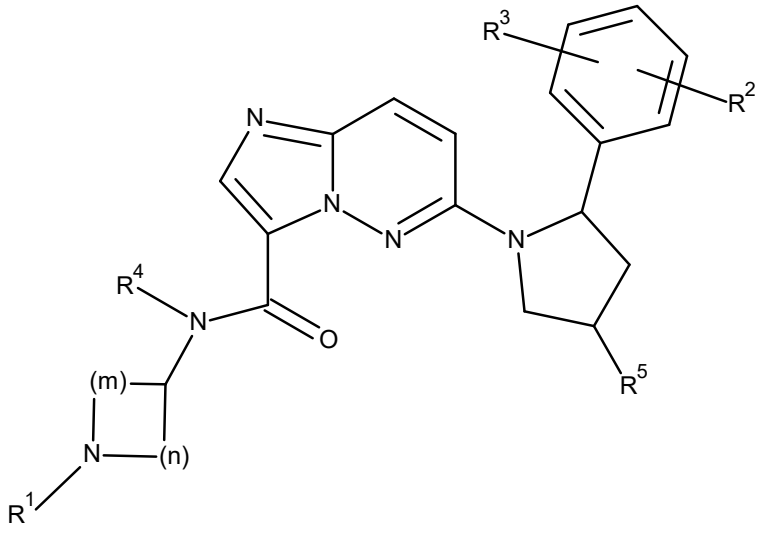
13. The topical pharmaceutical composition according to any preceding claim, wherein the compound of Formula (I) is a compound of Formula (I')



(I')

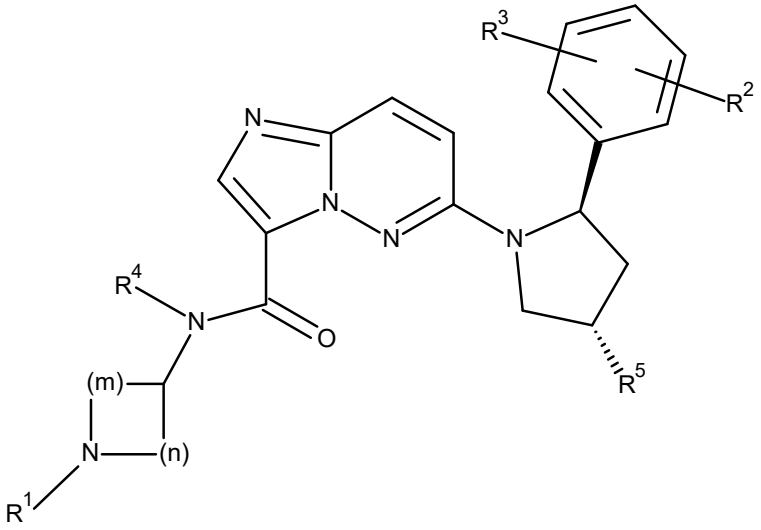
or a pharmaceutically acceptable salt and/or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, L and Z, are as defined in claim 1 or claim 12.

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



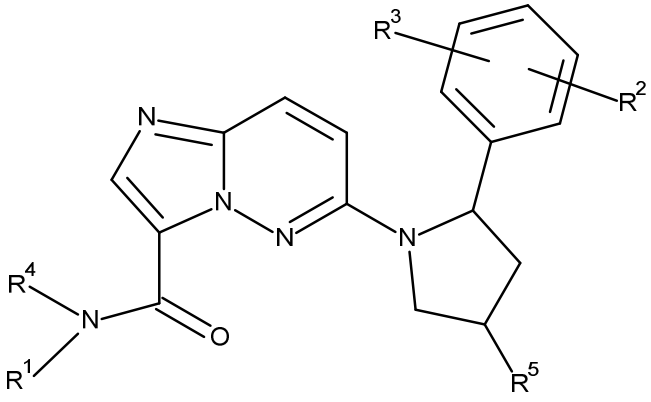
(Ia)

or a pharmaceutically acceptable salt and/or solvate thereof wherein R^1, R^2, R^3, R^4, R^5, m and n, are as defined in any one of claims 1, 12 and 13,
preferably wherein the compound of Formula (I) is a compound of Formula (Ia')



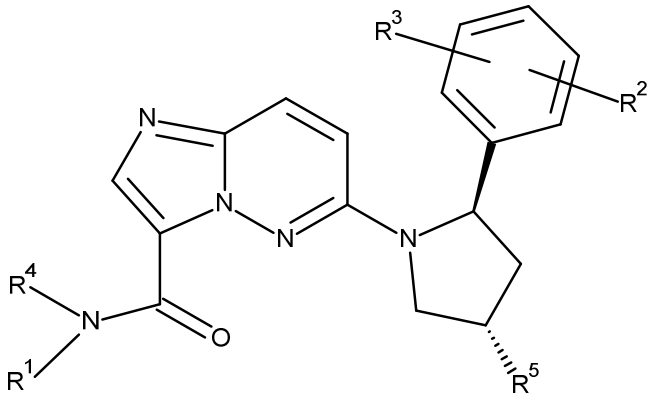
(Ia').

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)



(Ib)

or a pharmaceutically acceptable salt and/or solvate thereof, wherein R^1, R^2, R^3, R^4 and R^5 are as defined in any one of claims 1, 12 and 13,
preferably wherein the compound of Formula (I) is a compound of Formula (Ib')



(Ib').

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;
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;
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.

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-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;
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-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-{[(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;

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;

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;

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;

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;

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-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-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;

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;

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.

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

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. 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 of prevention of a condition or disorder which is mediated by Trk, preferably the condition or disorder is mediated by TrkA, TrkB, and TrkC, wherein the medicament comprises the topical pharmaceutical composition as defined in any one of claims 1 to 11, and 18.

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