severe inflammation or show moderate/low efficacy (Kose O. et al., J. Dermatol. Treatment 2008, 19, 159-163). Similarly, liquid nitrogen cryotherapy or electrocautery and curettage may be used. The risks associated with cryotherapy include transient pain, edema, and blistering. Hypopigmentation and alopecia are also common and may be permanent, so treatment of hair-bearing areas and in darkly pigmented individuals is generally not recommended.

Cutaneous lymphomas are indolent but treatable (not curable) and usually not life-threatening.

Cutaneous T-cell lymphoma (CTCL) has variable limited skin involvement and may be accompanied by tumor formation, ulceration, and exfoliation, complicated by itching and infections. Cutaneous B-cell lymphomas (CBCL) are a less common version of cutaneous lymphomas, making up about 20-25% of all cutaneous lymphomas.

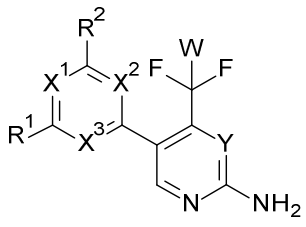
There are multiple treatments for cutaneous lymphoma (topical or systemic): Topical: Corticosteroids, Bexarotene (Targretin), Mechlorethamine (Mustargen and Valchlor), Carmustin (BCNU), Phototherapy, Local and total skin electron beam conventional radiotherapy. Systemic: Various targeted biological immuno-therapies, HDAC inhibitors and chemotherapies

In conclusion, there is an ongoing need for improved therapies for skin lesions.

SUMMARY

It has now surprisingly been found that the compounds of formula (I) are selective and specific inhibitors of mTOR and/or dual inhibitors of PI3K/mTOR and are highly effective in regressing skin lesions, in particular cutaneous squamous cell carcinoma (cSCC) and actinic keratosis (AK).

Thus, in a first aspect of the invention, there is provided a compound of formula (I),



(I)

wherein X^1, X^2 and X^3 are, independently of each other, N or CH; with the proviso that at

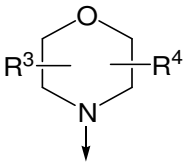
least two of X^1, X^2 and X^3 are N;

Y is N or CH;

W is H or F; with the proviso that when W is F, then X^1, X^2 and X^3 are N;

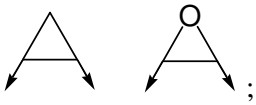
R^1 and R^2 are independently of each other

(i) a morpholinyl of formula (II)



(II)

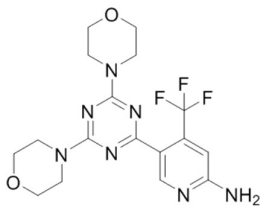
wherein the arrow denotes the bond in formula (I); and wherein R^3 and R^4 are independently of each other H, C_1-C_3alkyl optionally substituted with one or two OH, C_1-C_2fluoroalkyl, C_1-C_2alkoxy, C_1-C_2alkoxyC_1-C_3alkyl, CN, or C(O)O-C_1-C_2alkyl; or R^3 and R^4 form together a bivalent residue $–R^5R^6–$ selected from C_1-C_3alkylene optionally substituted with 1 to 4 F, -CH_2-O-CH_2-, -CH_2-NH-CH_2-, or any of the structures



;

wherein the arrows denote the bonds in formula (II); or (ii) a saturated 6-membered heterocyclic ring **Z** selected from thiomorpholinyl and piperazinyl, optionally substituted by 1 to 3 R^7; wherein R^7 is independently at each occurrence C_1-C_3alkyl optionally substituted with one or two OH, C_1-C_2fluoroalkyl, C_1-C_2alkoxyC_1-C_3alkyl, C_3-C_6cycloalkyl; or two R^7 substituents form together a bivalent residue $–R^8R^9–$ selected from C_1-C_3alkylene optionally substituted with 1 to 4 F, -CH_2-O-CH_2- or -O-CH_2CH_2-O-; with the proviso that at least one of R^1 and R^2 is a morpholinyl of formula II; and prodrugs, metabolites, tautomers, solvates and pharmaceutically acceptable salts thereof, for use in the prevention or treatment of a skin lesion in a subject.

In another aspect, the present disclosure refers to use of a compound



5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine

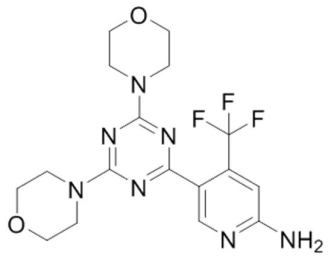
and tautomers, solvates and pharmaceutically acceptable salts thereof, in the manufacture of a medicament for preventing or treating of a skin lesion in a subject, wherein said skin lesion is a non-melanoma skin cancer (NMSC), and wherein said NMSC is selected from cutaneous squamous cell carcinoma (cSCC), cutaneous squamous cell carcinoma *in situ* (cSCCis), and actinic keratosis (AK).

DESCRIPTION OF FIGURES

K14-Fyn-Y528F mice were treated with a topical application of a gel containing Compound 1* (10 mg of Compound 1*) or nothing (control) were dissolved in 75 ul of DMSO and then propyleneglycol was added to 1000 mg (final concentration is 1% (w/w) (Fig. 1A, B and C). The Compound 1* treated cohort contained 6 mice with 20 cSCC lesions

CLAIMS

1. Use of a compound



5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine

and tautomers, solvates and pharmaceutically acceptable salts thereof,
in the manufacture of a medicament for preventing or treating of a skin lesion in a subject, wherein said skin lesion is a non-melanoma skin cancer (NMSC), and wherein said NMSC is selected from cutaneous squamous cell carcinoma (cSCC), cutaneous squamous cell carcinoma *in situ* (cSCCis), and actinic keratosis (AK).

2. The use according to claim 1, wherein said non-melanoma skin cancer is a cutaneous squamous cell carcinoma (cSCC).

3. The use according to claim 1, wherein said non-melanoma skin cancer (NMSC) is actinic keratosis (AK).

4. The use according to claim 1, wherein said non-melanoma skin cancer (NMSC) is cSCC in situ (cSCCis).