

sents lower alkyl, OH, NH₂, NHR⁴, or NR⁵R⁶ wherein R⁴, R⁵ and R⁶ independently are lower alkyl or cycloalkyl and n is an integer of from 2 to 4, with the provision that when X is CH₂, Y is OH or NH-(CH₂)_n-OH, and pharmacologically acceptable salts thereof. Said compounds are said to be useful for preventing and/or treating autoimmune diseases.

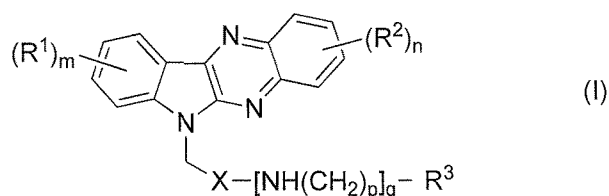
- 5 Some indoloquinoxalines also have been described for use as antiviral substances. Thus, in WO87/04436 the antiviral effect of a number of indoloquinoxalines, e.g. 2,3-dimethyl-6-(N,N-dimethylaminoethyl)-6H-indolo(2,3-b)quinoxaline (B-220), against herpes simplex virus of both type 1 and 2 is shown.

- 10 WO 2012/110631 discloses a pharmaceutical composition for topical administration comprising B-220 or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable carrier. The composition is useful for the treatment of herpes virus infections of the skin or mucous membranes in a mammal subject.

There however still remains a need for effective drugs and methods of treatment for primary as well as recurrent herpes infections.

15 SUMMARY

According to a first ~~aspect~~embodiment, a compound is provided according to formula (I)



wherein

m is an integer of from 0 to 4;

- 20 n is an integer of from 0 to 4;

p is an integer of from 1 to 4;

q is 0 or 1;

X is C=O, C=S or CH₂;

each R¹ is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

each R² is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

10 R³ is OH, NH₂, NHR⁴, NR⁴R⁵, or (NR⁴R⁵R⁶)⁺Y⁻;

R⁴ is selected from C1-C6 alkyl;

R⁵ is selected from C1-C6 alkyl;

R⁶ is selected from C1-C6 alkyl, optionally substituted with a halogen or OH; C2-C6 alkenyl; and C2-C6 alkynyl;

15 Y is a pharmaceutically acceptable anion;

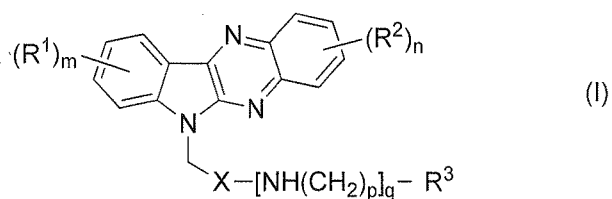
and pharmaceutically acceptable salts thereof;

with the proviso that if X is CH₂ and q is 0, R³ is OH or (NR³R⁴R⁵)⁺Y⁻,

for use in the treatment of a herpes viral infection.

20 In one particular embodiment, a compound of formula (I) is provided for topical administration to a mammal subject suffering from a primary or recurrent herpes virus infection, especially of oral-facial type.

According to a further ~~aspect~~embodiment, the use of a compound as defined herein is provided, for the manufacture of a medicament for use in the treatment of a herpes viral infection. In an aspect, there is provided the use of a compound of formula (I)



wherein

m is an integer of from 0 to 4;

n is an integer of from 1 to 4;

5 p is an integer of from 1 to 4;

q is 1;

X is C=O or C=S;

10 each R¹ is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

15 each R² is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

R³ is NH₂, NHR⁴, or NR⁴R⁵;

R⁴ is selected from C1-C6 alkyl;

R⁵ is selected from C1-C6 alkyl;

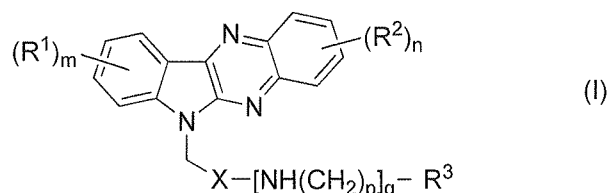
or a pharmaceutically acceptable salt thereof;

20 in the manufacturing of a medicament for the treatment of a herpes viral infection

In one embodiment, if X is CH₂ and q is 0, then R³ is (NR³R⁴R⁵)⁺Y⁻.

In another embodiment, if ~~if~~ X is CH₂ and q is 0, then R³ is OH.

Some of the compounds of formula (I) are novel and therefore, in one ~~aspect~~ embodiment there is provided a compound of formula (I)



5 wherein

m is an integer of from 0 to 4;

n is an integer of from 0 to 4;

p is an integer of from 1 to 4;

q is 0 or 1;

10 X is C=O, C=S or CH₂;

each R¹ is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

15 each R² is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

R³ is OH, NH₂, NHR⁴, NR⁴R⁵, or (NR⁴R⁵R⁶)⁺Y⁻;

20 R⁴ is selected from C1-C6 alkyl;

R⁵ is selected from C1-C6 alkyl;

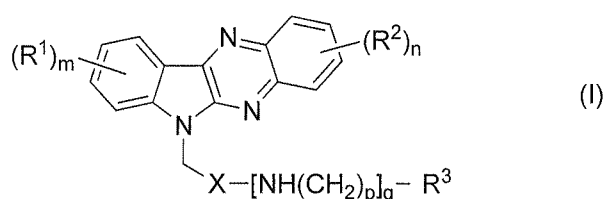
R^6 is selected from C1-C6 alkyl, optionally substituted with a halogen or OH; C2-C6 alkenyl; and C2-C6 alkynyl;

Y is a pharmaceutically acceptable anion;

and pharmaceutically acceptable salts thereof;

5 with the proviso if R^3 is different from $(NR^3R^4R^5)^+Y^-$, X is C=S.

In another aspect, there is provided a compound of formula (I)



wherein

m is an integer of from 0 to 4;

10 n is an integer of from 1 to 4;

p is an integer of from 1 to 4;

q is 1;

X is C=S;

15 each R^1 is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

20 each R^2 is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

R³ is NH₂, NHR⁴, or NR⁴R⁵;

R⁴ is selected from C1-C6 alkyl;

R⁵ is selected from C1-C6 alkyl;

or a pharmaceutically acceptable salt thereof.

5 According to a still further ~~aspect embodiment~~, a pharmaceutical composition is provided comprising a compound according to formula (I) as defined herein above, with the proviso if R³ is different from (NR³R⁴R⁵)⁺Y⁻, X is C=S, in association with at least one pharmaceutical-
ly acceptable excipient. In a still further aspect, there is provided a pharmaceutical composi-
10 tion comprising a compound as defined herein above and at least one pharmaceutically ac-
ceptable excipient.

In another ~~aspect embodiment~~, there is provided a compound according to formula (I) as defined herein above, with the proviso if R³ is different from (NR³R⁴R⁵)⁺Y⁻, X is C=S, for use in therapy.

15 In another aspect, there is provided a patch, stick, spray dispenser, tube, or pen containing a pharmaceutical composition ~~comprising a compound according to formula (I) as defined herein above, with the proviso if R³ is different from (NR³R⁴R⁵)⁺Y⁻, X is C=S.~~

In one embodiment, the pharmaceutical composition is an antiviral composition suitable for the treatment of a viral infection, e.g. a herpes viral infection.

20 In one particular embodiment, the composition of the disclosure is useful for topical administration to a mammal subject suffering from a primary or recurrent herpes virus infection, especially of oral-facial type.

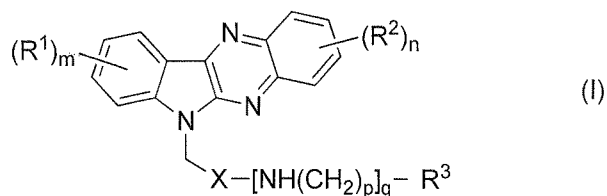
In one embodiment, the pharmaceutical composition of the disclosure additionally comprises at least one additional therapeutically active ingredient suitable for topical administration.

According to one embodiment, the disclosure relates to a compound of formula (I) as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of herpes virus infections of the skin or mucous membranes in a mammal subject by topical administration of a therapeutically effective dose thereof to the skin and/or mucous membrane of the mammal subject.

According to another embodiment, the disclosure relates to a method of prophylactic and/or curative treatment of herpes virus infections of the skin or mucous membranes in a mammal subject comprising topical administration of a therapeutically effective dose of a compound of formula (I) as defined herein or a pharmaceutically acceptable salt thereof.

CLAIMS

1. ~~A Use of~~ a compound of formula (I)



wherein

5 m is an integer of from 0 to 4;

n is an integer of from ~~0~~ 1 to 4;

p is an integer of from 1 to 4;

q is ~~0 or~~ 1;

X is C=O ~~or~~, C=S ~~or~~ CH₂;

10 each R¹ is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

each R² is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, 15 C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

R³ is ~~OH~~, NH₂, NHR⁴, or NR⁴R⁵, ~~or (NR⁴R⁵R⁶)⁺Y⁻~~;

R⁴ is selected from C1-C6 alkyl;

20 R⁵ is selected from C1-C6 alkyl;

R^6 is selected from C1-C6-alkyl, optionally substituted with a halogen or OH; C2-C6-alkenyl; and C2-C6-alkynyl;

Y is a pharmaceutically acceptable anion;

or a pharmaceutically acceptable salt thereof;

5 with the proviso that if X is CH_2 and q is 0, R^3 is OH or $(NR^4R^5)^+Y^-$,
in the manufacturing of a medicament for use in the treatment of a herpes viral infection.

2. The compound for use according to claim 1, wherein X is CH_2 .

3. The compound for use according to claim 1, wherein X is C=O or C=S.

4. The compound for use according to any one of the claims 1 to 3, wherein q is 0.

10 5. The compound for use according to any one of the claims 1 to 3, wherein q is 1.

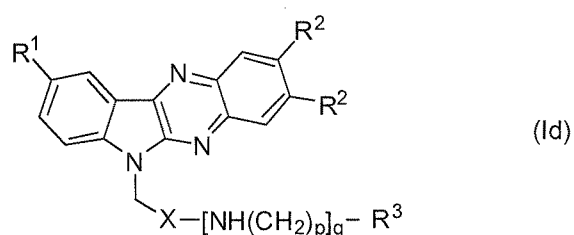
62. The compound for use according to any one of the claims 1 to 5 claim 1, wherein m is 0 or 1.

3. The use according to claim 1, wherein m is 1.

74. The compound use according to any one of the claims 1 to 63, wherein n is 2.

5. The use according to claim 1, wherein m is 1 and n is 2.

15 6. The use according to claim 1, wherein the compound is of formula (Id)



wherein R^1 , R^2 , R^3 , X, p and q are as defined in claim 1.

8. The compound for use according to any one of the claims 1 to 7, wherein R^3 is NH_2 , NHR^4 , NR^4R^5 , or $(NR^4R^5R^6)^+Y^-$.

~~97. A compound for~~The use according to claim 1, wherein the compound is selected from

~~2,3-Dimethyl-6-[2-(trimethylamino)ethyl]-6H-indolo[2,3-b]quinoxaline iodide,~~

9-chloro-*N*-[2-(dimethylamino)ethyl]-2,3-dimethyl-6*H*-Indolo[2,3-*b*]quinoxaline-6-acetamide, and

9-chloro-*N*-[2-(dimethylamino)ethyl]-2,3-dimethyl-6*H*-Indolo[2,3-*b*]quinoxaline-6-thioacetamide,

~~2,3-dimethyl-6-[2-(trimethylamino)ethyl]-6H-indolo[2,3-b]quinoxaline methyl sulfate, and~~

~~N-(2-(2,3-dimethyl-6H-indolo[2,3-b]quinoxalin-6-yl)ethyl)-N,N-dimethylprop-2-en-1-aminium bromide,~~

or a pharmaceutically acceptable salt thereof.

~~108. The compound for~~use according to any one of the claims 1 to ~~97~~, wherein the herpes virus is herpes simplex 1.

~~119. The compound~~use according to any one of the claims 1 to ~~108~~, wherein the medicament comprises~~for use together with~~ at least one further therapeutically active agent, ~~in sequence or in combination.~~

~~1210. The compound for~~use according to claim ~~119~~, wherein the at least one further therapeutically active agent is selected from ~~from~~ antiviral agents, antibiotics, analgesics, anaesthetic agents, antiphlogistic agents and antiinflammatory agents.

~~1311. The compound for~~use according to claim ~~1210~~, wherein the at least one further therapeutically active agent is an antiphlogistic agent.

~~1412.~~ The compound ~~for use~~ according to claim ~~1210~~, wherein the at least one further therapeutically active agent is an antiinflammatory agent.

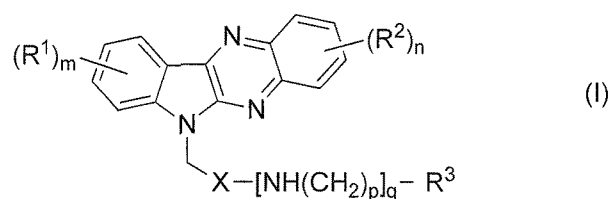
~~1513.~~ The compound ~~use~~ according to any one of the claims 1 to ~~1412~~, wherein the medicament is ~~for use by~~ topical administration.

~~1614.~~ The compound ~~use~~ according to claim ~~1513~~, wherein the medicament is ~~for use in~~ dermal or mucosal treatment.

~~1715.~~ The compound ~~use~~ according to claim ~~1513~~ or claim ~~1614~~, ~~for use in~~ wherein the medicament is ~~a formulation~~ in the form of a cream, liquid, lotion, gel, spray, foam or ointment.

~~1816.~~ The compound ~~use~~ according to claim ~~1513~~ or claim ~~1614~~, wherein the medicament is for administration by use of a patch, stick, spray dispenser, tube, or pen containing the compound and at least one pharmaceutically acceptable excipient.

~~1917.~~ A compound of formula (I)



wherein

m is an integer of from 0 to 4;

n is an integer of from 0 to 4;

p is an integer of from 1 to 4;

q is 0 or 1;

X is $\text{C}=\text{O}$, $\text{C}=\text{S}$ or CH_2 ;

each R^1 is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

each R^2 is independently selected from halogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, C1-C6 alkoxy, C2-C6 alkenyloxy, C2-C6 alkynyloxy, C3-C6 cycloalkyloxy, and OH, any alkyl, alkenyl, alkynyl or cycloalkyl optionally being substituted by at least one halogen;

R^3 is OH , NH_2 , NHR^4 , or NR^4R^5 , or $(\text{NR}^4\text{R}^5\text{R}^6)^+\text{Y}^-$;

R^4 is selected from C1-C6 alkyl;

R^5 is selected from C1-C6 alkyl;

R^6 is selected from C1-C6 alkyl, optionally substituted with a halogen or OH; C2-C6 alkenyl; and C2-C6 alkynyl;

Y is a pharmaceutically acceptable anion;

or a pharmaceutically acceptable salt thereof;

with the proviso if R^3 is different from $(\text{NR}^3\text{R}^4\text{R}^5)^+\text{Y}^-$, X is $\text{C}=\text{S}$.

20. The compound according to claim 19, wherein X is CH_2 .

21. The compound according to claim 19, wherein X is $\text{C}=\text{O}$ or $\text{C}=\text{S}$.

~~22. The compound according to any one of the claims 19 to 21, wherein q is 0.~~

~~23. The compound according to any one of the claims 19 to 21, wherein q is 1.~~

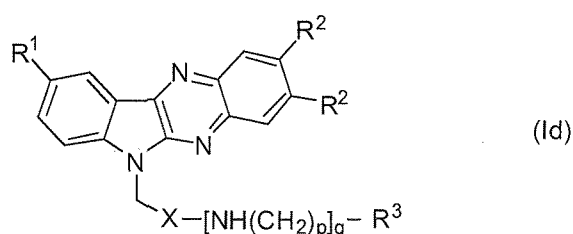
~~24~~18. The compound according to ~~any one of the claims 19 to 23~~17, wherein m is 0 or 1.

19. The compound according to claim 18, wherein m is 1.

5 ~~25~~20. The compound according to any one of the claims ~~19-17~~ to ~~24~~19, wherein n is 2.

21. The compound according to claim 17, wherein m is 1 and n is 2.

22. The compound according to claim 17, of formula (Id)



wherein R^1 , R^2 , R^3 , X, p and q are as defined in claim 17.

10 ~~26. The compound according to any one of the claims 19 to 25, wherein R^3 is NH_2 , NHR^4 , NR^4R^5 , or $(NR^4R^5R^6)^+Y^-$.~~

~~27~~23. A compound according to claim ~~19~~17, selected from which is

~~2,3-Dimethyl-6-[2-(trimethylamino)ethyl]-6H-indolo[2,3-b]quinoxaline iodide,~~

9-chloro-N-[2-(dimethylamino)ethyl]-2,3-dimethyl-6H-Indolo[2,3-b]quinoxaline-6-

15 thioacetamide,

~~2,3-dimethyl-6-[2-(trimethylamino)ethyl]-6H-indolo[2,3-b]quinoxaline methyl sulfate, and~~

~~N-(2-(2,3-dimethyl-6H-indolo[2,3-b]quinoxalin-6-yl)ethyl)-N,N-dimethylprop-2-en-1-aminium bromide,~~

or a pharmaceutically acceptable salt thereof.

20 ~~28. A compound according to any one of the claims 19 to 27, for use in therapy.~~

~~29. A compound according to any one of the claims 19 to 27, for use as an antiviral agent.~~

~~30~~24. A pharmaceutical composition comprising a compound according to any one of the claims ~~19-17~~ to ~~27~~23 and at least one pharmaceutically acceptable excipient.

~~31~~25. The pharmaceutical composition according to claim ~~30~~24, for topical administration.

~~32~~26. The pharmaceutical composition according to claim ~~30-24~~ or claim ~~31~~25, wherein the compound according to any one of the ~~compounds-claims 19-17~~ to ~~27-23~~ is present in an amount of 0.1-10% (w/w).

~~33~~27. The pharmaceutical composition according to any one of the claims ~~30-32~~24-26, comprising at least one additional therapeutically active ingredient.

~~34~~28. The pharmaceutical composition according to claim ~~33~~27, wherein the additional therapeutically active ingredient is selected from antiviral agents, antibiotics, analgesics, anaesthetic agents, antiphlogistic agents and antiinflammatory agents.

~~35~~29. The pharmaceutical composition according to claim ~~34~~28, wherein the additional therapeutically active ingredient is an antiphlogistic agent.

~~36~~30. The pharmaceutical composition according to claim ~~34~~28, wherein the additional therapeutically active ingredient is an antiinflammatory agent.

~~37~~31. The pharmaceutical composition according to any one of the claims ~~33-36~~27-30, wherein the additional therapeutically active agent is present in an amount of 0.005-5% (w/w).

5 | ~~38. The pharmaceutical composition according to any of claims 30-37, for use in the prophylaxis and/or treatment of a herpes virus infection in a mammal subject.~~

~~39~~32. The pharmaceutical composition according to any one of the claims ~~30-38~~24-31, for dermal or mucosal treatment.

10

~~40~~33. The pharmaceutical composition according to any one of the claims ~~30-39~~24-32, in the form of a cream, liquid, lotion, gel, spray, foam or ointment.

15

~~41~~34. A patch, stick, spray dispenser, tube, or pen containing a pharmaceutical composition according to any one of the claims ~~30-40~~24-33.

~~42. The use of a compound according to any one of the claims 1 to 9 or 19 to 27 in the manufacture of a medicament for treatment of a herpes virus infection.~~

20