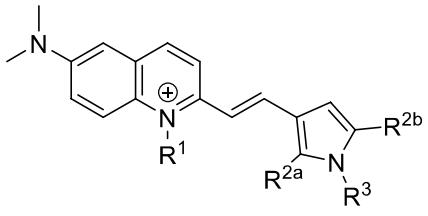
SUMMARY

In an aspect, there is provided a method for reprogramming a pre-cancerous mucosa to a non-cancerous state, the method comprising:

identifying a pre-cancerous mucosa comprising a metaplastic cell or a dysplastic cell; and

contacting the metaplastic cell or the dysplastic cell with a compound of formula (I), or a salt thereof:


(I),

wherein:

R^1 is C_{1-6}alkyl;

R^{2a} and R^{2b} are each independently C_{1-6}alkyl; and

R^3 is C_{6-12}aryl, wherein R^3 is optionally substituted with 1–5 R^X

R^X, at each occurrence, is independently C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, $–N(R^{Xa})_2$,

$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, $–SO_2R^{Xa}$, $–L^2\text{-}Y^2$, $–O\text{-}L^X\text{-}Y^X$, $–S\text{-}L^X\text{-}Y^X$, or $–N(R^{Xa})\text{-}L^X\text{-}Y^X$;

L^X, at each occurrence, is independently C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene;

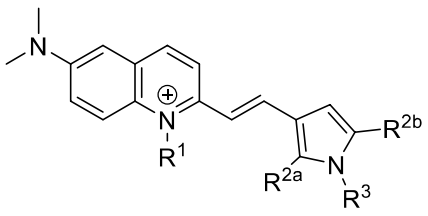
Y^X, at each occurrence, is independently hydrogen, cyano, halogen, haloalkyl, –OH, $–N(R^{Xa})_2$,

$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, or $–SO_2R^{Xa}$;

R^{Xa}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, or $–C(O)C_{1-4}$alkyl; and

R^{Xb}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, C_{1-2}haloalkyl, or $–C(O)C_{1-4}$alkyl.

In another aspect, there is provided Use of a compound of formula (I), or a salt thereof:


(I),

in the manufacture of a medicament for reducing the risk of cancer development in a living organism containing a metaplastic cell or a dysplastic cell

wherein:

R^1 is C_{1-6}alkyl;

R^{2a} and R^{2b} are each independently C_{1-6}alkyl; and

R^3 is C_{6-12}aryl, wherein R^3 is optionally substituted with 1–5 R^X

R^X, at each occurrence, is independently C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, $–N(R^{Xa})_2$,

$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, $–SO_2R^{Xa}$, $–L^2\text{-}Y^2$, $–O\text{-}L^X\text{-}Y^X$,

$–S\text{-}L^X\text{-}Y^X$, or $–N(R^{Xa})\text{-}L^X\text{-}Y^X$;

L^X, at each occurrence, is independently C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene;

Y^X, at each occurrence, is independently hydrogen, cyano, halogen, haloalkyl, –OH, $–N(R^{Xa})_2$,

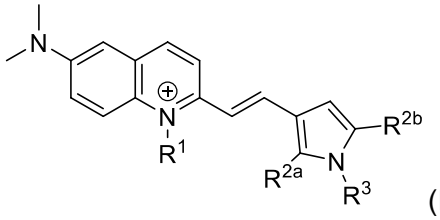
$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, or $–SO_2R^{Xa}$;

R^{Xa}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, or $–C(O)C_{1-4}$alkyl; and

R^{Xb}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, C_{1-2}haloalkyl, or $–C(O)C_{1-4}$alkyl.

In another aspect, there is provided the use of pyrvinium or a salt thereof in the manufacture of a medicament for reprograming a pre-cancerous mucosa to a non-cancerous state or reducing the risk of cancer development.

One example described herein is a method for reprogramming a pre-cancerous mucosa to a non-cancerous state, the method comprising identifying a pre-cancerous mucosa comprising a metaplastic cell or a dysplastic cell; and contacting the metaplastic cell or the dysplastic cell with a compound of formula (I), or a salt thereof:



(I),

wherein:

R^1 is C_{1-6}alkyl;

R^{2a} and R^{2b} are each independently C_{1-6}alkyl; and

R^3 is C_{6-12}aryl, wherein R^3 is optionally substituted with 1–5 R^X

R^X, at each occurrence, is independently C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, $–N(R^{Xa})_2$,

$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, $–SO_2R^{Xa}$, $–L^2\text{-}Y^2$, $–O\text{-}L^X\text{-}Y^X$, $–S\text{-}L^X\text{-}Y^X$, or $–N(R^{Xa})\text{-}L^X\text{-}Y^X$;

L^X, at each occurrence, is independently C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene;

Y^X, at each occurrence, is independently hydrogen, cyano, halogen, haloalkyl, –OH, $–N(R^{Xa})_2$,

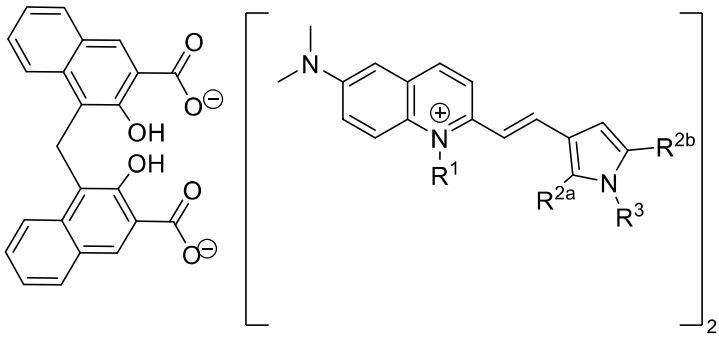
$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, or $–SO_2R^{Xa}$;

R^{Xa}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, or $–C(O)C_{1-4}$alkyl; and

R^{Xb}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, C_{1-2}haloalkyl, or $–C(O)C_{1-4}$alkyl.

In one example, the metaplastic cell or the dysplastic cell is contacted with a salt of the compound of formula (I).

In another example, the salt of the compound of formula (I) is a salt of formula (I-A),



(I-A).

In another example, R^1 is methyl.

In another example, R^{2a} and R^{2b} are each methyl.

In another example, R^3 is unsubstituted phenyl.

In another example, the compound of formula (I) is pyrvinium.

In another example, the metaplastic cell or the dysplastic cell is located within a living organism.

In another example, the pre-cancerous mucosa comprises a dysplastic cell.

In another example, the method comprises killing the dysplastic cell.

In another example, the dysplastic cell is positive for CD133 expression, CD166 expression, and/or Trop2 expression.

In another example, the dysplastic cell is a dysplastic gastric cell, a dysplastic esophageal cell, a dysplastic pancreatic cell, a dysplastic colon cell, or a dysplastic ovarian cell.

In another example, the dysplastic gastric cell is part of an organoid.

In another example, the pre-cancerous mucosa comprises a metaplastic cell.

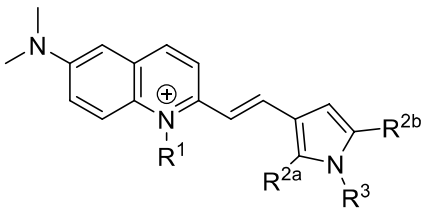
In another example, the metaplastic gastric cell is positive for CD133, CD166, and/or Trop2 expression.

In another example, the metaplastic cell is a metaplastic gastric cell, a metaplastic esophageal cell, a metaplastic pancreatic cell, a metaplastic colon cell, or a metaplastic ovarian cell.

In another example, the metaplastic gastric cell is part of an organoid.

Another example described herein is a method for reducing the risk of cancer development in a living organism containing a metaplastic cell or a dysplastic cell, the method comprising:

administering to the living organism a compound of formula (I), or a salt thereof:



(I),

wherein:

R^1 is $C_{1–6}$alkyl;

R^{2a} and R^{2b} are each independently $C_{1–6}$alkyl; and

R^3 is $C_{6–12}$aryl, wherein R^3 is optionally substituted with 1–5 R^X

R^X, at each occurrence, is independently C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, $–N(R^{Xa})_2$,

$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, $–SO_2R^{Xa}$, $–L^2$-Y^2, $–O$-L^X-Y^X, $–S$-L^X-Y^X, or $–N(R^{Xa})$-L^X-Y^X;

L^X, at each occurrence, is independently C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene;

Y^X, at each occurrence, is independently hydrogen, cyano, halogen, haloalkyl, –OH, $–N(R^{Xa})_2$,

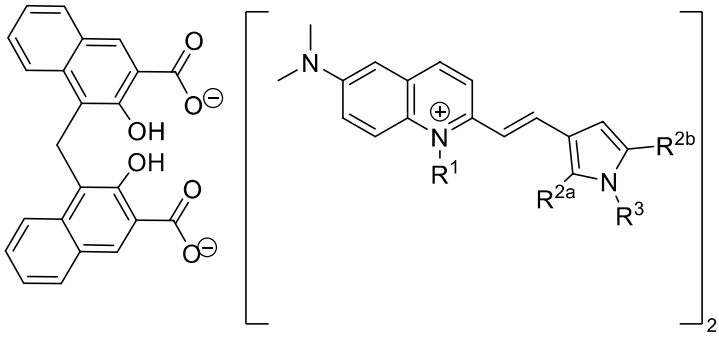
$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, or $–SO_2R^{Xa}$;

R^{Xa}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, or $–C(O)C_{1-4}$alkyl; and

R^{Xb}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, C_{1-2}haloalkyl, or $–C(O)C_{1-4}$alkyl.

In another example, a salt of the compound of formula (I) is administered to the living organism.

In another example, wherein the salt of the compound of formula (I) is a salt of formula (I-A),



(I-A).

In another example, the compound of formula (I) is pyrvinium.

In another example, the method inhibits STAT3 and MEK/ERK signaling pathways in the metaplastic cell or the dysplastic cell.

In another example, the living organism is a non-human animal.

In another example, the living organism is a human.

In another example, the human is at risk for developing cancer.

In another example, the method further comprises administering a second agent to the living organism.

In another example, the second agent comprises a kinase inhibitor.

In another example, the kinase inhibitor comprises a MEK inhibitor.

In another example, the MEK inhibitor comprises trametinib, binimetinib, cobimetinib, and/or selumetinib.

Another example described herein is the use of pyrvinium or a salt thereof in the manufacture of a medicament for reprograming a pre-cancerous mucosa to a non-cancerous state or reducing the risk of cancer development.

DESCRIPTION OF THE DRAWINGS

FIG. 1A–1H show that pyrvinium induces cell death in mouse dysplastic organoids. FIG. 1A shows phase-contrast, Hematoxylin & Eosin (H&E) images, and co-immunostaining for CD44v9, Aqp5, and Trop2 in Meta3 and Meta4 organoids. FIG. 1B–1C show H&E and phase-contrast images of Meta3 (FIG. 1B) and 3 different Meta4 organoids (FIG. 1C) treated with DMSO vehicle, 1 μM of trametinib (Tra), 100 nM of pyrvinium (Pyr) and their combinations for 3 days. FIG. 1D–1E show quantitation of organoid diameters before and after treatment. (FIG. 1F) Phase-contrast images and live/dead (Calcein AM/EthD-1) cell staining with the percentages of live and dead cells in Meta4 organoid after treatment. FIG. 1G–1H show phase-contrast images (FIG. 1G) and quantitation of diameters (FIG. 1H) of Meta4 organoids before and after treatment with 0, 0.2, 0.5, and 1 μM of SSTC3, a specific Casein Kinase 1α activator. Mean ± standard deviation. One-way ANOVA with Tukey's multiple comparisons. **P < 0.01, ****P < 0.0001. Scale bar = 500 μM.

FIG. 2A–2D show that a phospho-antibody array identifies downregulation of MAPK and STAT signaling pathways by pyrvinium. FIG. 2A is a heat map showing pathway enrichment analysis of differentially phosphorylated proteins after pyrvinium (Pyr) treatment for 3 days in Meta3 and Meta4 organoids using the Molecular Signatures Database (MSigDB) hallmark gene set collection. Shading scale represents standardized log2(FDR) values. FIG. 2B shows log2 fold change bar graphs of signaling pathways in Meta3 and Meta4 organoids after treatment. FIG. 2C is a heat map showing the upregulated or downregulated phospho-proteins in Meta4 organoids compared to Meta3 after treatment. FIG. 2D graphically shows changes in phosphorylation of STAT3Y705 and ERKT202/T204 between Meta3 and Meta4 organoids (upper panel) or between DMSO and Pyr treatment in Meta4 organoid (lower panel). Each square represents the signal ratio of the antibody against the unphosphorylated form of the site. FIG. 2E schematically illustrates how the STAT3 and DPPs in RAS/MAPK pathway is affected by Pyr treatment in precancerous organoids.

FIG. 3A–3M show that pyrvinium suppresses mouse dysplastic organoids through double blockade of ERK and STAT3 signaling pathways. FIG. 3A–3B show the Western blot analysis for

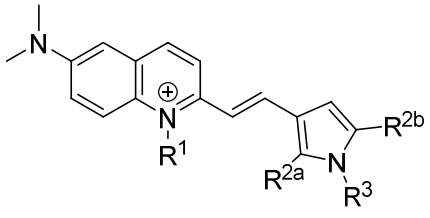
CLAIMS

What is claimed:

1. A method for reprogramming a pre-cancerous mucosa to a non-cancerous state, the method comprising:

identifying a pre-cancerous mucosa comprising a metaplastic cell or a dysplastic cell; and

contacting the metaplastic cell or the dysplastic cell with a compound of formula (I), or a salt thereof:



(I),

wherein:

R^1 is $C_{1–6}$alkyl;

R^{2a} and R^{2b} are each independently $C_{1–6}$alkyl; and

R^3 is $C_{6–12}$aryl, wherein R^3 is optionally substituted with 1–5 R^X

R^X, at each occurrence, is independently C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, $–N(R^{Xa})_2$,

$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, $–SO_2R^{Xa}$, $–L^2\text{-}Y^2$, $–O\text{-}L^X\text{-}Y^X$, $–S\text{-}L^X\text{-}Y^X$, or $–N(R^{Xa})\text{-}L^X\text{-}Y^X$;

L^X, at each occurrence, is independently C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene;

Y^X, at each occurrence, is independently hydrogen, cyano, halogen, haloalkyl, –OH, $–N(R^{Xa})_2$,

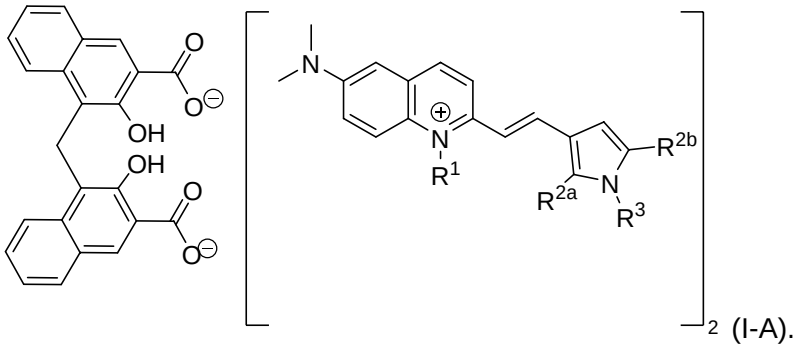
$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, or $–SO_2R^{Xa}$;

R^{Xa}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, or $–C(O)C_{1-4}$alkyl; and

R^{Xb}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, C_{1-2}haloalkyl, or $–C(O)C_{1-4}$alkyl.

2. The method of claim 1, wherein the metaplastic cell or the dysplastic cell is contacted with a salt of the compound of formula (I).

3. The method of claim 2, wherein the salt of the compound of formula (I) is a salt of formula (I-A),



(I-A).

4. The method of claim 1, wherein R^1 is methyl.

5. The method of claim 1, wherein R^{2a} and R^{2b} are each methyl.

6. The method of claim 1, wherein R^3 is unsubstituted phenyl.

7. The method of claim 1, wherein the compound of formula (I) is pyrvinium.

8. The method of claim 1, wherein the metaplastic cell or the dysplastic cell is located within a living organism.

9. The method of claim 1, wherein the pre-cancerous mucosa comprises a dysplastic cell.

10. The method of claim 9, wherein the method comprises killing the dysplastic cell.

11. The method of claim 9, wherein the dysplastic cell is positive for CD133 expression, CD166 expression, and/or Trop2 expression.

12. The method of claim 9, wherein the dysplastic cell is a dysplastic gastric cell, a dysplastic esophageal cell, a dysplastic pancreatic cell, a dysplastic colon cell, or a dysplastic ovarian cell.

13. The method of claim 12, wherein the dysplastic gastric cell is part of an organoid.

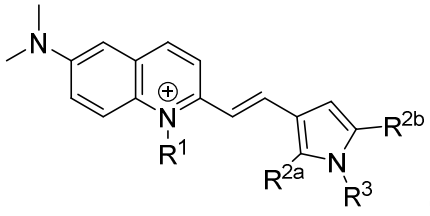
14. The method of claim 1, wherein the pre-cancerous mucosa comprises a metaplastic cell.

15. The method of claim 14, wherein the metaplastic gastric cell is positive for CD133, CD166, and/or Trop2 expression.

16. The method of claim 14, wherein the metaplastic cell is a metaplastic gastric cell, a metaplastic esophageal cell, a metaplastic pancreatic cell, a metaplastic colon cell, or a metaplastic ovarian cell.

17. The method of claim 16, wherein the metaplastic gastric cell is part of an organoid.

18. Use of a compound of formula (I), or a salt thereof:



(I),

in the manufacture of a medicament for reducing the risk of cancer development in a living organism containing a metaplastic cell or a dysplastic cell

wherein:

R^1 is $C_{1–6}$alkyl;

R^{2a} and R^{2b} are each independently $C_{1–6}$alkyl; and

R^3 is $C_{6–12}$aryl, wherein R^3 is optionally substituted with 1–5 R^X

R^X, at each occurrence, is independently C_{1-6}alkyl, C_{1-4}haloalkyl, halogen, cyano, $–N(R^{Xa})_2$,

$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, $–SO_2R^{Xa}$, $–L^2\text{-}Y^2$, $–O\text{-}L^X\text{-}Y^X$, $–S\text{-}L^X\text{-}Y^X$, or $–N(R^{Xa})\text{-}L^X\text{-}Y^X$;

L^X, at each occurrence, is independently C_{1-6}alkylene, C_{2-6}alkenylene, or C_{2-6}alkynylene;

Y^X, at each occurrence, is independently hydrogen, cyano, halogen, haloalkyl, –OH, $–N(R^{Xa})_2$,

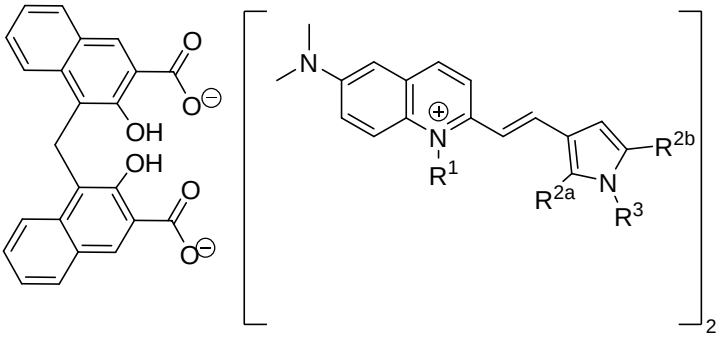
$–OR^{Xb}$, $–SR^{Xb}$, $–C(O)R^{Xb}$, $–CO_2R^{Xb}$, $–C(O)N(R^{Xa})_2$, or $–SO_2R^{Xa}$;

R^{Xa}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, or $–C(O)C_{1-4}$alkyl; and

R^{Xb}, at each occurrence, is independently hydrogen, C_{1-4}alkyl, C_{1-2}haloalkyl, or $–C(O)C_{1-4}$alkyl.

19. The use of claim 18, wherein a salt of the compound of formula (I) is to be administered to the living organism.

20. The use of claim 19, wherein the salt of the compound of formula (I) is a salt of formula (I-A),



(I-A).

21. The use of claim 18, wherein the compound of formula (I) is pyrvinium.

22. The use of claim 18, wherein the method inhibits STAT3 and MEK/ERK signaling pathways in the metaplastic cell or the dysplastic cell.

23. The use of claim 18, wherein the living organism is a non-human animal.

24. The use of claim 18, wherein the living organism is a human.

25. The use of claim 24, wherein human is at risk for developing cancer.

26. The use of claim 18, the method further comprising a second agent to be administered to the living organism.

27. The use of claim 26, wherein the second agent comprises a kinase inhibitor.

28. The use of claim 27, wherein the kinase inhibitor comprises a MEK inhibitor.

29. The use of claim 28, wherein the MEK inhibitor comprises trametinib, binimetinib, cobimetinib, and/or selumetinib.

30. Use of pyrvinium or a salt thereof in the manufacture of a medicament for reprograming a pre-cancerous mucosa to a non-cancerous state or reducing the risk of cancer development.