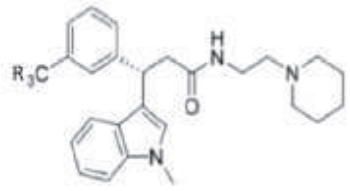
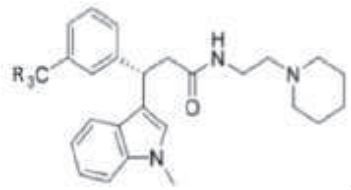
mitoketoscins that function as radiosensitizers and photosensitizers. The term “mitoketoscin” broadly refers to non-carcinogenic compounds that bind to at least one of ACAT1/2 and OXCT1/2 and inhibit mitochondrial ATP production. These compounds therefore are designed to target the mitochondrial enzymes responsible for ketone re-utilization and that have anti-cancer and antibiotic properties. These compounds bind to either or both active catalytic sites of OXCT1/2 and ACAT1/2 to inhibit mitochondrial function. The present disclosure further relates to methods of identifying mitoketoscins, methods of making such mitoketoscins, and methods of using mitoketoscins for therapeutic purposes.

[0005a] In one aspect, the present disclosure refers to a method of identifying a mitoketoscin using virtual high-throughput screening and phenotypic drug screening, the method comprising; identifying a mitoketoscin that targets a mitochondrial ketone re-utilization enzyme using virtual high-throughput screening; synthesizing the mitoketoscin; and testing the mitoketoscin for mitochondrial inhibition activity.

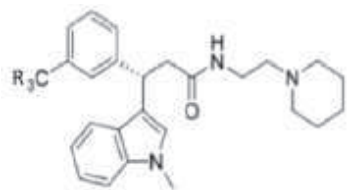
[0005b] In another aspect, the present disclosure refers to the use of a mitoketoscin in the manufacture of a medicament for treating cancer, wherein the mitoketoscin comprises the general formula: 

, wherein R may be selected from the group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides,

amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and wherein the medicament further comprises a pharmaceutically acceptable carrier.

[0005c] In yet another aspect, the present disclosure refers to the use of a mitoketoscin in the manufacture of a medicament for treating a microbial infection, wherein the mitoketoscin comprises general formula: 

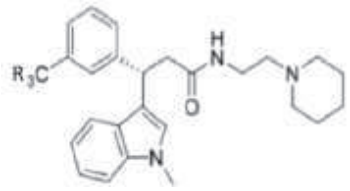
, wherein R may be selected from the group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides, amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and wherein the medicament further comprises a pharmaceutically acceptable carrier.

[0005d] In another aspect, the present disclosure refers to the use of a mitoketoscin in the manufacture of a medicament for treating an age- related condition, wherein the mitoketoscin comprises the general formula: 

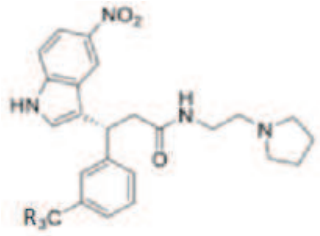
, wherein R may be selected from the

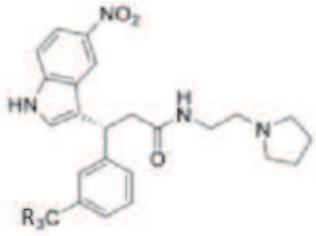
group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides, amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and wherein the medicament further comprises a pharmaceutically acceptable carrier.

[0005e] In another aspect, the present disclosure refers to a pharmaceutical composition comprising, as an active ingredient, a mitoketoscin comprising the general formula:



, wherein R may be selected from the group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides, amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and a pharmaceutically acceptable carrier.

[0005f] In another aspect, the present disclosure refers to the use of a mitoketoscin in the manufacture of a medicament for treating cancer, wherein the mitoketoscin comprises the general formula: , wherein R may be selected from the group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides, amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and wherein the medicament further comprises a pharmaceutically acceptable carrier.

[0005g] In another aspect, the present disclosure refers to a pharmaceutical composition comprising, as an active ingredient, a mitoketoscin comprising the general formula: , wherein R may be selected from the group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based

derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides, amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and a pharmaceutically acceptable carrier.

[0006] Given their mitochondrial inhibition properties, mitoketoscins may similarly be used to target bacteria and pathogenic yeast, provide anti-aging benefits, function as radiosensitizers and/or photo-sensitizers, sensitize bulk cancer cells and cancer stem cells to chemotherapeutic agents, pharmaceuticals, and/or other natural substances.

[0007] Mitoketoscins may be identified through a convergent approach of virtual high-throughput in silico screening followed by in vitro validation for mitochondrial inhibition. Mitoketoscins may be rapidly developed by combining in silico drug design with phenotypic drug screening.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] FIG. 1 shows a schematic diagram outlining a drug discovery strategy according to embodiments of the present approach.

[0009] FIG. 2 illustrates the chemical structures of eight candidate mitoketoscin compounds 1-8 identified following phenotypic drug screening.

CLAIMS

What is claimed is:

1. A method of identifying a mitoketoscin using virtual high-throughput screening and phenotypic drug screening, the method comprising;

identifying a mitoketoscin that targets a mitochondrial ketone re-utilization enzyme using virtual high-throughput screening;

synthesizing the mitoketoscin; and

testing the mitoketoscin for mitochondrial inhibition activity.

2. The method of claim 1, wherein the mitoketoscin binds to OXCT1.

3. The method of claim1, wherein the mitoketoscin binds ACAT1.

4. The method of claim 1, wherein the phenotypic drug screening is in vitro drug screening.

5. The method of claim 1, wherein the phenotypic drug screening comprises an ATP-depletion assay.

6. The method of claim 1, wherein the phenotypic drug screening comprises an extracellular acidification rate assay.

7. The method of claim 1, wherein the phenotypic drug screening comprises an oxygen consumption rate assay.

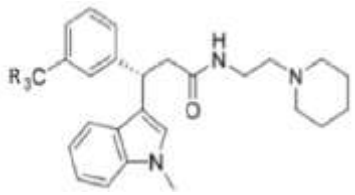
8. The method of claim 1, further comprising testing the mitoketoscin for anti-cancer activity.

9. The method of claim 8, wherein the anti-cancer activity tested is mammosphere formation.

10. The method of claim 8, wherein the anti-cancer activity tested is cell migration.

11. The method of claim 8 further comprising testing the mitoketoscin for anti-microbial activity.

12. Use of a mitoketoscin in the manufacture of a medicament for treating cancer, wherein the mitoketoscin comprises the general formula:

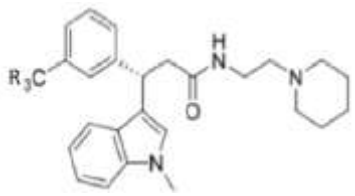


, wherein R may be selected from the group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides, amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and

wherein the medicament further comprises a pharmaceutically acceptable carrier.

13. The use of claim 12, wherein R comprises fluorine.

14. Use of a mitoketoscin in the manufacture of a medicament for treating a microbial infection, wherein the mitoketoscin comprises general formula:



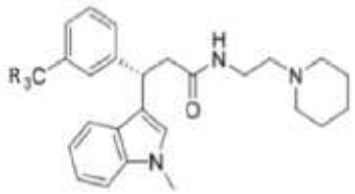
, wherein R may be selected from the group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic

alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides, amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and

wherein the medicament further comprises a pharmaceutically acceptable carrier.

15. The use of claim 14, wherein R comprises fluorine.

16. Use of a mitoketoscin in the manufacture of a medicament for treating an age-related condition, wherein the mitoketoscin comprises the general formula:

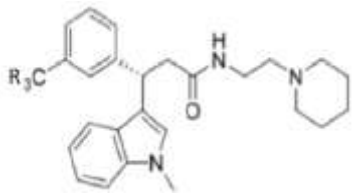


, wherein R may be selected from the group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides, amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and

wherein the medicament further comprises a pharmaceutically acceptable carrier.

17. The use of claim 16, wherein R comprises fluorine.

18. A pharmaceutical composition comprising, as an active ingredient, a mitoketoscin comprising the general formula:

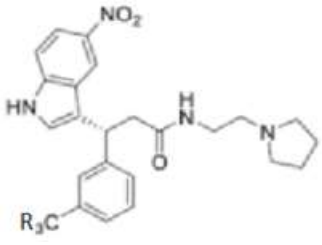


, wherein R may be selected from the group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides, amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and

a pharmaceutically acceptable carrier.

19. The pharmaceutical composition of claim 18, wherein R comprises fluorine.

20. Use of a mitoketoscin in the manufacture of a medicament for treating cancer, wherein the mitoketoscin comprises the general formula:



, wherein R may be selected from the group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic

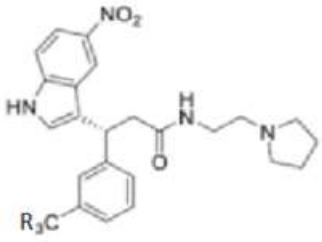
alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides, amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and

wherein the medicament further comprises a pharmaceutically acceptable carrier.

21. The use of claim 20, wherein R comprises fluorine.

22. The use of claim 20, wherein the medicament further comprises a mitochondrial support substrate comprising at least one of glucose, pyruvate, lactate, fatty acids and acetyl-carnitine.

23. A pharmaceutical composition comprising, as an active ingredient, a mitoketoscin comprising the general formula:



, wherein R may be selected from the group consisting of hydrogen, carbon, nitrogen, sulfur, oxygen, fluorine, chlorine, bromine, iodine, carboxyl, alkanes, cyclic alkanes, alkane-based derivatives, alkenes, cyclic alkenes, alkene-based derivatives, alkynes, alkyne-based derivative, ketones, ketone-based derivatives, aldehydes, aldehyde-based derivatives, carboxylic acids, carboxylic acid-based derivatives, ethers, ether-based derivatives, esters and ester-based derivatives, amines, amino-based derivatives, amides, amide-based derivatives, monocyclic or polycyclic arene, heteroarenes, arene-based derivatives, heteroarene-

based derivatives, phenols, phenol-based derivatives, benzoic acid, and benzoic acid-based derivatives; and

a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23, wherein R comprises fluorine.