from the visual cycle (step 3b in Figure 1), a metabolic pathway in the back of the eye. The visual cycle (i) converts vitamin A from an alcohol (retinol) to a photoreactive aldehyde (11-*cis*-retinaldehyde) for use in phototransduction by opsin proteins in photoreceptor cell outer segments, and (ii) converts RAL to retinol after photo-transduction. As RAL escapes the visual cycle, A2E precursors form reversibly in photoreceptor outer segments, which are ingested by neighboring RPE cells after diurnal shedding. The final and irreversible step in the biosynthesis of A2E takes place in the acidic environment of RPE cell lysosomes.

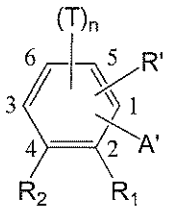
As A2E accumulates in RPE cells, it gradually poisons them by multiple mechanisms including lysosomal failure and oxidative stress. Lysosomal failure leads to the accumulation of undigested cellular debris called lipofuscin, which contains A2E and can be detected clinically by FAF imaging. Oxidative stress leads to RPE cell death by apoptotic mechanisms in GA, and triggers VEGF signaling by RPE cells which causes the choroidal neovascular growth that is the hallmark of wet AMD. Complement cascades are activated by oxidized A2E in drusen and cause further pathology by inflammatory pathways. As RPE cells deteriorate, they lose their ability to participate in the visual cycle and are unable to provide photoreceptors with the metabolic support required for normal visual function. As this metabolic support is withdrawn, photoreceptors fail to renew their shed outer segments and visual function is progressively lost. By reducing the formation of A2E pharmacologically, RPE cells can recover from A2E toxicities and resume their normal metabolic support of photoreceptor cells.

The PCT publication WO 2006/127945 discloses compounds and compositions that have been shown to reduce the formation of A2E. Those compounds are designed to inhibit A2E biosynthesis by reducing the amount of free RAL available for reaction with PE in photoreceptor outer segments. However, there still exists a need for compounds with desirable properties, such as improved potency and/or pharmacological half-life. The present application addresses that need.

## SUMMARY ~~OF THE INVENTION~~

The ~~invention~~ present disclosure relates to compounds, pharmaceutical compositions and methods for treating, reducing a symptom of or reducing the risk of developing a retinal disease or disorder in which the accumulation of A2E and/or lipofuscin in retinal tissue or VEGF signaling by RPE cells in response to oxidative stress is involved.

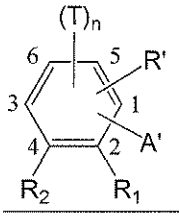
The present disclosure ~~invention~~ relates to a compound of formula (A):



(A),

or a pharmaceutically acceptable salt thereof, wherein each of R', A', $R_1$, $R_2$, T, and n are defined herein below.

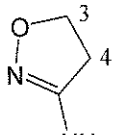
In one aspect of the present disclosure, there is provided a compound of formula (A):



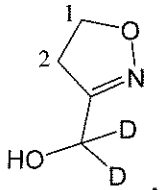
(A),

or a pharmaceutically acceptable salt thereof, wherein:

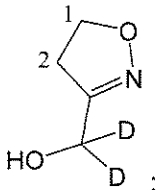
A' and R', together with the two adjacent carbon atoms to which they are attached, form a five-membered heteroaryl ring containing one nitrogen atom and one oxygen atom, wherein the heteroaryl ring is substituted with X', wherein "1", "2", "3", "4", "5", and "6" denote the points of attachment of the heteroaryl ring to the phenyl ring, provided that when

the heteroaryl ring is 

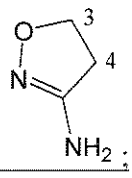
, then $R_1$ is $C(D)_2OH$, $R_2$ is absent, and X' is absent, and that

when the heteroaryl ring is 

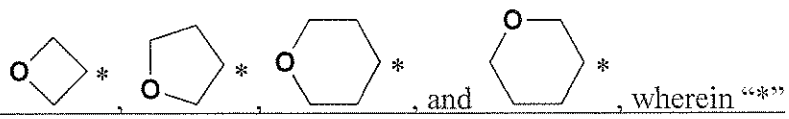
, then $R_1$ is absent, $R_2$ is $NH_2$, and X' is absent;

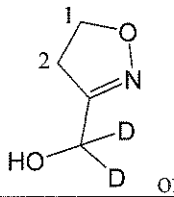
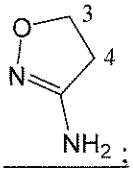
$R_1$ is $C(D)_2OH$, or $R_1$ is absent when A' and R', together with the two adjacent carbon atoms to which they are attached, form 

;

$R_2$ is $NH_2$, or $R_2$ is absent when A' and R', together with the two adjacent carbon atoms to which they are attached, form 

;

each D is independently $C_1$-$C_6$ alkyl or $C_3$-$C_6$ cycloalkyl, or two D, together with the carbon atom to which they are attached, form a $C_3$-$C_6$ carbocyclic ring or a saturated heterocycle selected from , wherein "*" denotes the position of the carbon atom to which the two D are attached;

X' is $C_1$-$C_{10}$ alkyl, $C_1$-$C_{10}$ alkyl substituted with $C_3$-$C_6$ cycloalkyl, $C_3$-$C_6$ cycloalkyl, aryl, aryl substituted with $C_1$-$C_6$ alkyl, or $C_1$-$C_6$ alkoxy, or X' is absent when A' and R', together with the two adjacent carbon atoms to which they are attached, form  or ;

n is 0, 1, or 2, provided that when X' is phenyl, n is not 0; and

each T is independently halogen, $C_1$-$C_{10}$ alkyl, $C_1$-$C_{10}$ alkyl substituted with $C_3$-$C_6$ cycloalkyl, $C_3$-$C_6$ cycloalkyl, or cyano.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in treating, reducing a symptom of or reducing the risk of developing a retinal disease or disorder in which accumulation of A2E and/or lipofuscin in retinal tissue or VEGF signaling by RPE cells in response to oxidative stress is involved.

In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in treating, reducing a symptom of or reducing the risk of developing a retinal disease or disorder associated with accumulation of A2E and/or lipofuscin in retinal tissue or VEGF signaling by RPE cells in response to oxidative stress.

In yet another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating, reducing a symptom of or reducing the risk of developing a retinal

disease or disorder in which accumulation of A2E and/or lipofuscin in retinal tissue or VEGF signaling by RPE cells in response to oxidative stress is involved.

In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating, reducing a symptom of or reducing the risk of developing a retinal disease or disorder associated with accumulation of A2E and/or lipofuscin in retinal tissue or VEGF signaling by RPE cells in response to oxidative stress.

The present disclosure ~~invention~~ also relates to a pharmaceutical composition comprising a compound of each of the formulae described herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

The present disclosure ~~invention~~ also relates to a method of treating, reducing a symptom of or reducing the risk of developing a retinal disease or disorder in which accumulation of A2E and/or lipofuscin in retinal tissue or VEGF signaling by RPE cells in response to oxidative stress is involved.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this present disclosure ~~invention~~ belongs. In the case of conflict, the present specification, including definitions, will control. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present ~~invention~~disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the present disclosure~~invention~~. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

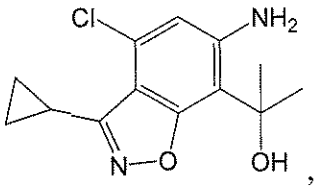
Other features and advantages of the present disclosure ~~invention~~ will be apparent from the following detailed description and claims.

## BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a scheme showing the visual cycle.

## DETAILED DESCRIPTION OF THE INVENTION

The invention provides heteroaryl compounds of the formulae described herein. These compounds possess desirable properties, such as improved potency (*e.g.*, more




or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

27. A compound of claims 1 to 23, or a pharmaceutically acceptable salt thereof, for use in ~~A method of~~ treating, reducing a symptom of or reducing the risk of developing a retinal disease or disorder in which accumulation of A2E and/or lipofuscin in retinal tissue or VEGF signaling by RPE cells in response to oxidative stress is involved ~~in a subject in need thereof, comprising administering a pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof to the subject~~.

28. A compound of claims 1 to 23, or a pharmaceutically acceptable salt thereof, for use in treating, reducing a symptom of or reducing the risk of developing a retinal disease or disorder associated with accumulation of A2E and/or lipofuscin in retinal tissue or VEGF signaling by RPE cells in response to oxidative stress.

~~28~~29. The compound ~~method~~ of any one of claims 27 or 28, wherein the retinal disease or disorder is macular degeneration.

30. The compound of any one of claims 27 or 28, wherein the retinal disease or disorder is wet age-related macular degeneration (wet AMD), dry age-related macular degeneration (dry AMD), GA secondary to dry AMD, or Stargardt's disease.

~~29. A composition for use in a method for treating, reducing a symptom of or reducing the risk of developing a retinal disease or disorder in which accumulation of A2E and/or lipofuscin in retinal tissue or VEGF signaling by RPE cells in response to oxidative stress is involved in a subject in need thereof, wherein the composition comprises a compound of claim 1 or a pharmaceutically acceptable salt thereof.~~

~~30. The composition of claim 29, wherein the retinal disease or disorder is macular degeneration.~~

31. Use of a compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating, reducing a symptom of or reducing the risk of developing a retinal disease or disorder in which accumulation of A2E and/or lipofuscin in retinal tissue or VEGF signaling by RPE cells in response to oxidative stress is involved ~~in a subject in need thereof~~.

32. Use of a compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating, reducing a symptom of or reducing the risk of developing a retinal disease or disorder associated with accumulation of A2E and/or lipofuscin in retinal tissue or VEGF signaling by RPE cells in response to oxidative stress.

~~32~~33. The use of any one of claims 31 or 32, wherein the retinal disease or disorder is macular degeneration.

34. The use of any one of claims 31 or 32, wherein the retinal disease or disorder is wet age-related macular degeneration (wet AMD), dry age-related macular degeneration (dry AMD), GA secondary to dry AMD, or Stargardt's disease.