

METHODS OF TREATING INTRAOCULAR PRESSURE WITH ACTIVATORS OF TIE-2

CROSS REFERENCE

[0001] This Application claims the benefit of United States Provisional Application No. 62/222,481 filed September 23, 2015, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Intraocular pressure is a significant pathology associated with glaucomas, such as primary open angle glaucoma. The intraocular pressure is generated through damage to the trabecular meshwork of the eye, which results in optic nerve damage and loss of vision. Ocular hypertension occurs when the pressure in the eye surpasses the normal range with no detectable changes in vision or damage to the structure of your eyes. People with ocular hypertension have an increased risk of glaucoma.

INCORPORATION BY REFERENCE

[0003] Each patent, publication, and non-patent literature cited in the application is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

SUMMARY OF THE INVENTION

[0004] In some embodiments, the invention provides a method for reducing intraocular pressure in a subject in need thereof, the method comprising administering to the subject a therapeutically-effective amount of a Tie-2 activator, wherein the administration reduces the intraocular pressure by about 0.1 mmHg to about 9 mmHg compared to absence of administration.

[0005] In some embodiments, the invention provides a method for treating glaucoma in a subject in need thereof, the method comprising administering to the subject a therapeutically-effective amount of a Tie-2 activator, wherein the administration reduces intraocular pressure by about 0.1 mmHg to about 9 mmHg compared to absence of administration.

[0005a] In some embodiments, the invention provides a use of a therapeutically-effective amount of a Tie-2 activator in the manufacture of a medicament for reducing intraocular pressure in a subject in need thereof, wherein the medicament is to be administered to the subject, and wherein the administration reduces the intraocular pressure by about 0.1 mmHg to about 9 mmHg compared to absence of administration.

[0005b] In some embodiment, the invention provides a use of a therapeutically-effective amount of a Tie-2 activator in the manufacture of a medicament for treating glaucoma in a subject in need thereof, wherein the medicament is to be administered to the subject, and wherein the

administration reduces intraocular pressure by about 0.1 mmHg to about 9 mmHg compared to absence of administration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] FIGURE 1 illustrates changes in intraocular pressure from baseline. A: study eye; B: fellow eye.

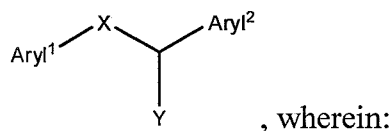
[0007] FIGURE 2 illustrates changes in intraocular pressure from baseline. A: **Compound 1** + Sham; B: **Compound 1** + RBZ; C: Placebo + RBA; D: All **Compound 1**.

[0008] FIGURE 3 illustrates changes in average plasma concentration of **Compound 1** after topical ocular administration in male New Zealand White rabbits.

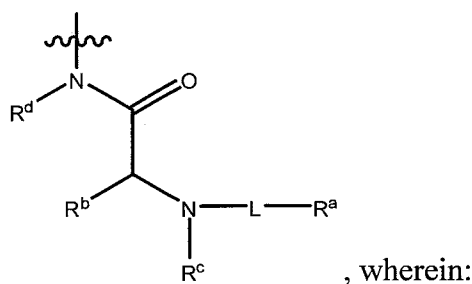
CLAIMS

WHAT IS CLAIMED IS:

1. Use of a therapeutically-effective amount of a Tie-2 activator in the manufacture of a medicament for reducing intraocular pressure in a subject in need thereof, wherein the medicament is to be administered to the subject, and wherein the administration reduces the intraocular pressure by about 0.1 mmHg to about 9 mmHg compared to absence of administration.
2. The use of claim 1, wherein the Tie-2 activator binds a phosphatase.
3. The use of claim 1, wherein the Tie-2 activator inhibits a phosphatase.
4. The use of claim 1, wherein the Tie-2 activator binds HPTP- β .
5. The use of claim 1, wherein the Tie-2 activator inhibits HPTP- β .
6. The use of claim 1, wherein the Tie-2 activator is a phosphate mimetic.
7. The use of claim 1, wherein the Tie-2 activator is a compound of the formula:



Aryl¹ is an aryl group which is substituted or unsubstituted; Aryl² is an aryl group which is substituted or unsubstituted; X is alkylene, alkenylene, alkynylene, an ether linkage, an amine linkage, an amide linkage, an ester linkage, a thioether linkage, a carbamate linkage, a carbonate linkage, a sulfone linkage, any of which is substituted or unsubstituted, or a chemical bond; and Y is H, aryl, heteroaryl, NH(aryl), NH(heteroaryl), NHSO₂R^g, or NHCOR^g, any of which is substituted or unsubstituted, or



- L^2 is alkylene, alkenylene, or alkynylene, any of which is substituted or unsubstituted, or together with the nitrogen atom to which L^2 is bound forms an amide linkage, a carbamate linkage, or a sulfonamide linkage, or a chemical bond, or together with any of R^a , R^b , R^c , and R^d forms a ring that is substituted or unsubstituted;
- R^a is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or together with any of L^2 , R^b , R^c , and R^d forms a ring that is substituted or unsubstituted;
- R^b is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or together with any of L^2 , R^a , R^c , and R^d forms a ring that is substituted or unsubstituted;
- R^c is H or alkyl which is substituted or unsubstituted, or together with any of L^2 , R^a , R^b , and R^d forms a ring that is substituted or unsubstituted;
- R^d is H or alkyl which is substituted or unsubstituted, or together with any of L^2 , R^a , R^b , and R^c forms a ring that is substituted or unsubstituted; and
- R^g is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or a pharmaceutically-acceptable salt, tautomer, or zwitterion thereof.

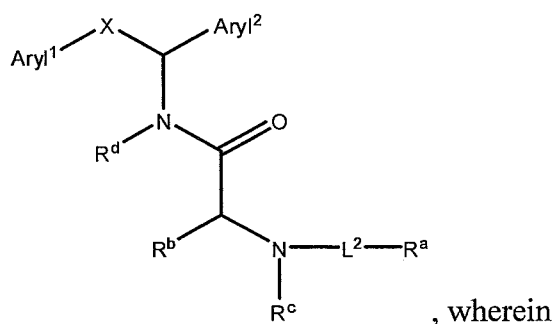
8. The use of claim 7, wherein:

- Aryl¹ is substituted or unsubstituted phenyl;
- Aryl² is substituted or unsubstituted heteroaryl; and
- X is alkylene.

9. The use of claim 8, wherein:

- Aryl¹ is substituted phenyl;
- Aryl² is substituted heteroaryl; and
- X is methylene.

10. The use of claim 9, wherein the compound that activates Tie-2 is a compound of the formula:

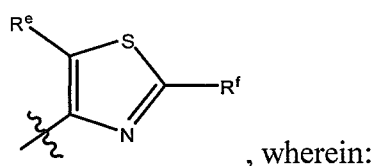


- Aryl¹ is para-substituted phenyl;
- Aryl² is substituted heteroaryl;
- X is methylene;
- L² is alkylene, alkenylene, or alkynylene, any of which is substituted or unsubstituted, or together with the nitrogen atom to which L² is bound forms an amide linkage, a carbamate linkage, or a sulfonamide linkage, or a chemical bond;
- R^a is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted;
- R^b is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted;
- R^c is H or alkyl which is substituted or unsubstituted; and
- R^d is H or alkyl which is substituted or unsubstituted.

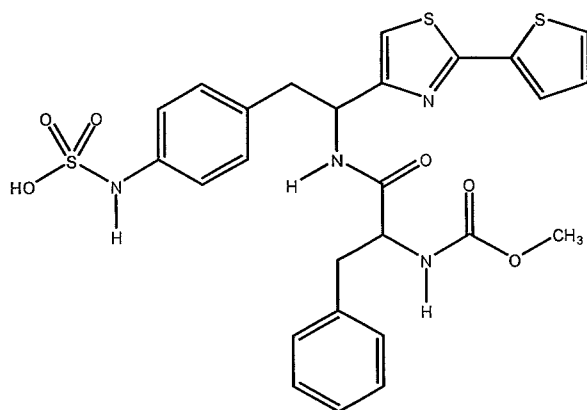
11. The use of claim 10, wherein:

- Aryl¹ is para-substituted phenyl;
- Aryl² is a substituted thiazole moiety;
- X is methylene;
- L² together with the nitrogen atom to which L² is bound forms a carbamate linkage;
- R^a is alkyl, which is substituted or unsubstituted;
- R^b is arylalkyl, which is substituted or unsubstituted;
- R^c is H; and
- R^d is H.

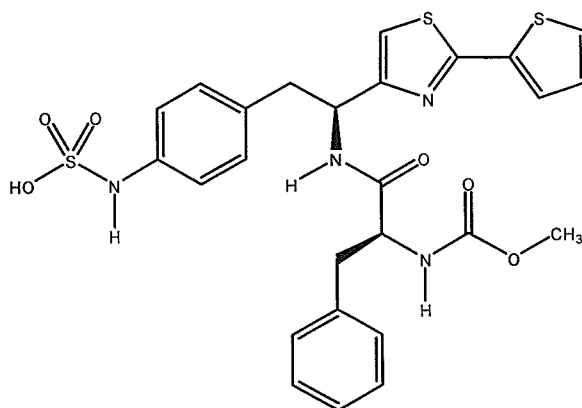
12. The use of claim 11, wherein Aryl² is:



- R^e is H, OH, F, Cl, Br, I, CN, alkyl, alkenyl, alkynyl, an alkoxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted; and
 - R^f is H, OH, F, Cl, Br, I, CN, alkyl, alkenyl, alkynyl, an alkoxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted.
13. The use of claim 12, wherein:
- R^e is H, OH, F, Cl, Br, I, alkyl, an alkoxy group, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted; and
 - R^f is H, OH, F, Cl, Br, I, alkyl, an alkoxy group, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted.
14. The use of claim 12, wherein:
- R^e is H, OH, F, Cl, Br, I, alkyl, or an alkoxy group, any of which is substituted or unsubstituted; and
 - R^f is alkyl, aryl, heterocyclyl, or heteroaryl, any of which is substituted or unsubstituted.
15. The use of claim 12, wherein:
- Aryl¹ is 4-phenylsulfamic acid;
 - R^a is alkyl, which is substituted or unsubstituted;
 - R^b is arylalkyl, which is substituted or unsubstituted;
 - R^e is H; and
 - R^f is heteroaryl.
16. The use of claim 7, wherein the compound is:



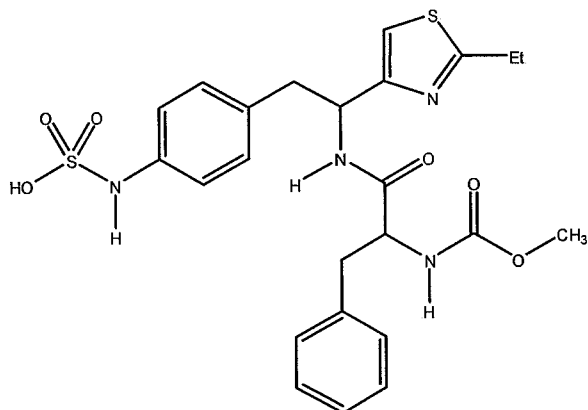
17. The use of claim 7, wherein the compound is:



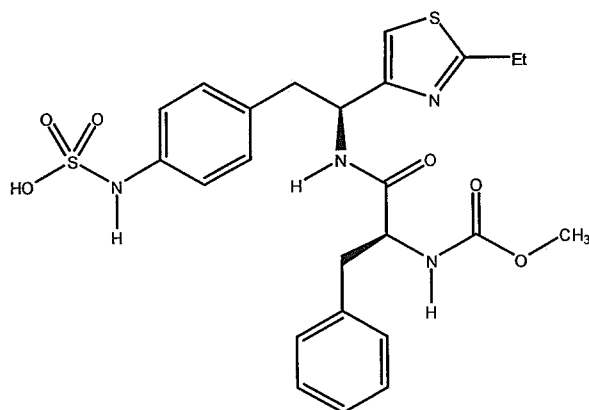
18. The use of claim 12, wherein:

- Aryl¹ is 4-phenylsulfamic acid;
- R^a is alkyl, which is substituted or unsubstituted;
- R^b is arylalkyl, which is substituted or unsubstituted;
- R^c is H; and
- R^f is alkyl.

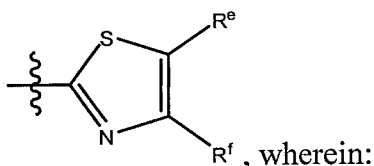
19. The use of claim 7, wherein the compound is:



20. The use of claim 7, wherein the compound is:



21. The use of claim 11, wherein Aryl² is:



- R^e is H, OH, F, Cl, Br, I, CN, alkyl, alkenyl, alkynyl, an alkoxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted; and
 - R^f is H, OH, F, Cl, Br, I, CN, alkyl, alkenyl, alkynyl, an alkoxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted.
22. The use of claim 21, wherein:
- R^e is H, OH, F, Cl, Br, I, alkyl, an alkoxy group, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted; and
 - R^f is H, OH, F, Cl, Br, I, alkyl, an alkoxy group, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted.

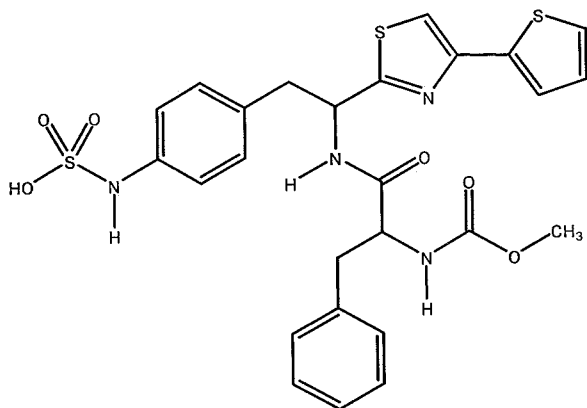
23. The use of claim 21, wherein:

- R^e is H, OH, F, Cl, Br, I, alkyl, or an alkoxy group, any of which is substituted or unsubstituted; and
- R^f is alkyl, aryl, heterocyclyl, or heteroaryl, any of which is substituted or unsubstituted.

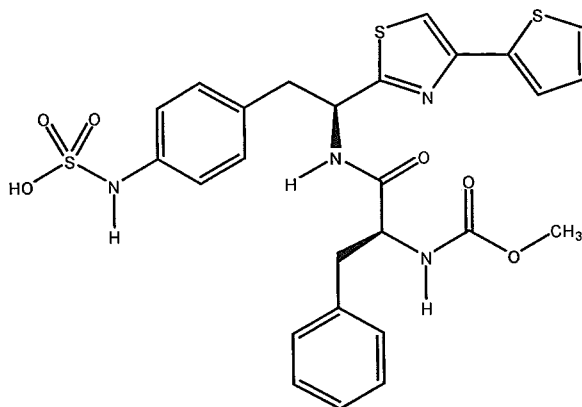
24. The use of claim 21, wherein:

- Aryl¹ is 4-phenylsulfamic acid;
- R^a is alkyl, which is substituted or unsubstituted;
- R^b is arylalkyl, which is substituted or unsubstituted;
- R^e is H; and
- R^f is heteroaryl.

25. The use of claim 7, wherein the compound is:



26. The use of claim 7, wherein the compound is:



27. The use of claim 1, wherein the therapeutically-effective amount is from about 1 mg to about 100 mg.

28. The use of claim 27, wherein the therapeutically-effective amount is from about 0.5 mg to about 30 mg.
29. The use of claim 28, wherein the therapeutically-effective amount is about 15 mg.
30. The use of claim 28, wherein the therapeutically-effective amount is about 22.5 mg.
31. The use of claim 1, wherein the therapeutically-effective amount is about 30 mg.
32. The use of claim 1, wherein the medicament is to be administered to an eye of the subject.
33. The use of claim 1, wherein the medicament is to be administered intravitreally.
34. The use of claim 1, wherein the medicament is to be administered subcutaneously.
35. The use of claim 1, wherein the medicament is to be administered topically.
36. The use of claim 1, wherein the medicament is to be administered topically to an eye of the subject.
37. The use of claim 1, wherein the Tie-2 activator, or a pharmaceutically-acceptable salt thereof, is formulated as a drop.
38. The use of claim 1, wherein the Tie-2 activator, or a pharmaceutically-acceptable salt thereof, is formulated as a drop, wherein the drop is to be administered to an eye of the subject.
39. The use of claim 1, wherein the subject is a human.
40. The use of claim 1, wherein the intraocular pressure is reduced by at least about 2 mmHg.
41. The use of claim 1, wherein the subject has glaucoma, wherein the intraocular pressure is associated with glaucoma.

42. The use of claim 1, wherein the intraocular pressure is ocular hypertension.
43. The use of claim 42, wherein the subject has glaucoma, wherein the ocular hypertension is associated with glaucoma.
44. Use of a therapeutically-effective amount of a Tie-2 activator in the manufacture of a medicament for treating glaucoma in a subject in need thereof, wherein the medicament is to be administered to the subject, and wherein the administration reduces intraocular pressure by about 0.1 mmHg to about 9 mmHg compared to absence of administration.