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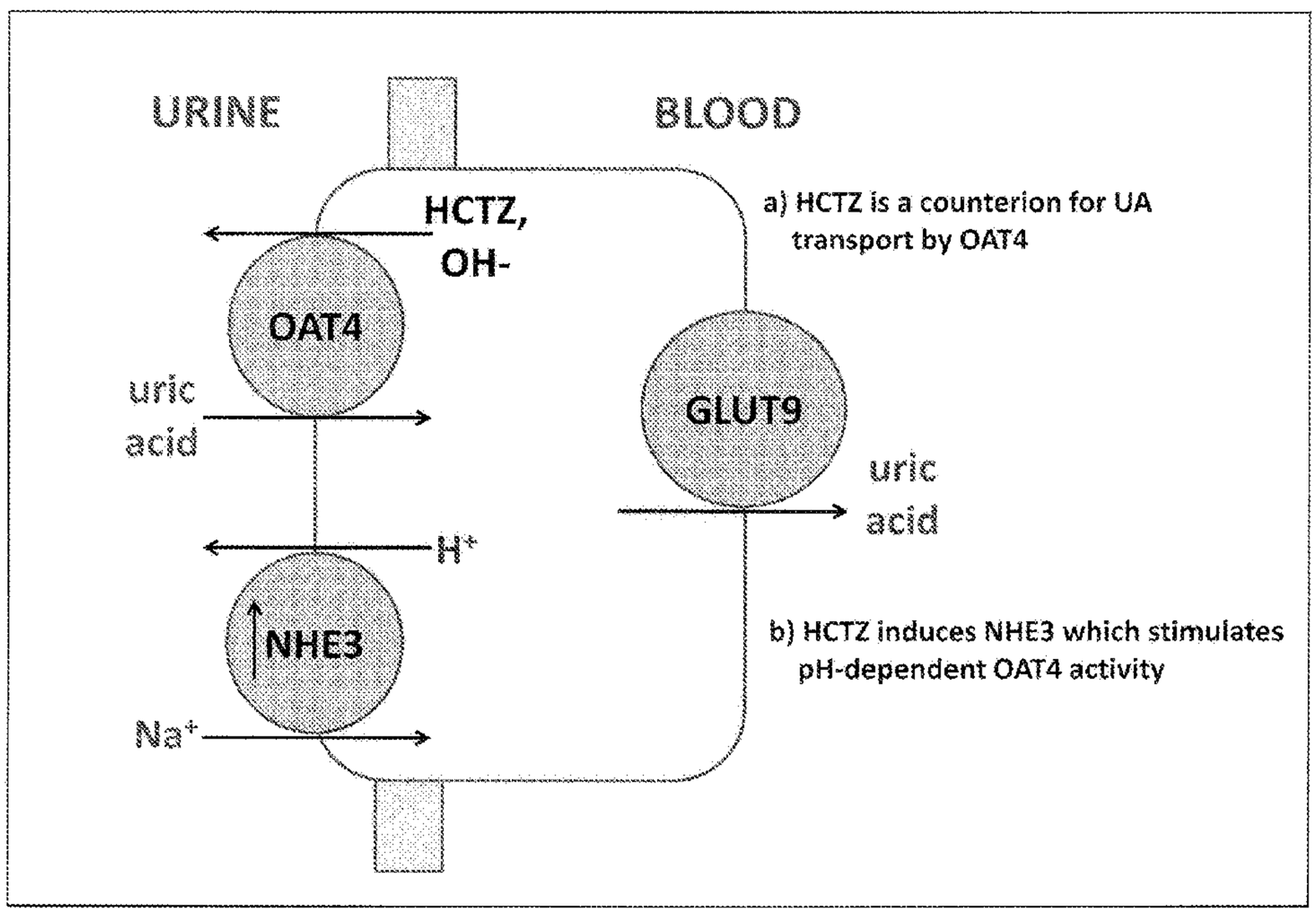
(54) Titre : HYPERTENSION ET HYPERURICEMIE
(54) Title: HYPERTENSION AND HYPERURICEMIA

FIG. 1



(57) Abrégé/Abstract:
A method for treating hypertension in a subject in need thereof (e.g., wherein said treatment does not result in an increase in serum uric acid levels, abnormally elevated serum uric acid levels, hyperuricemia, serum uric acid levels of above 6 mg/dL, or in the development of gout in the subject), the method comprising administering to the subject: a. a thiazide diuretic; and b. an organic anion transporter 4 (OAT4) inhibitor. The thiazide diuretic is selected from hydrochlorothiazide, bendroflumethiazide, benzothiadiazine, hydroflumethiazide, clorothiazide, methyclothiazide, polythiazide, chlorthalidone, metolazone, indapamide, bumetanide, ethacrynic acid, furosemide or torsemide. The OAT4 inhibitor is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)- 4H-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.

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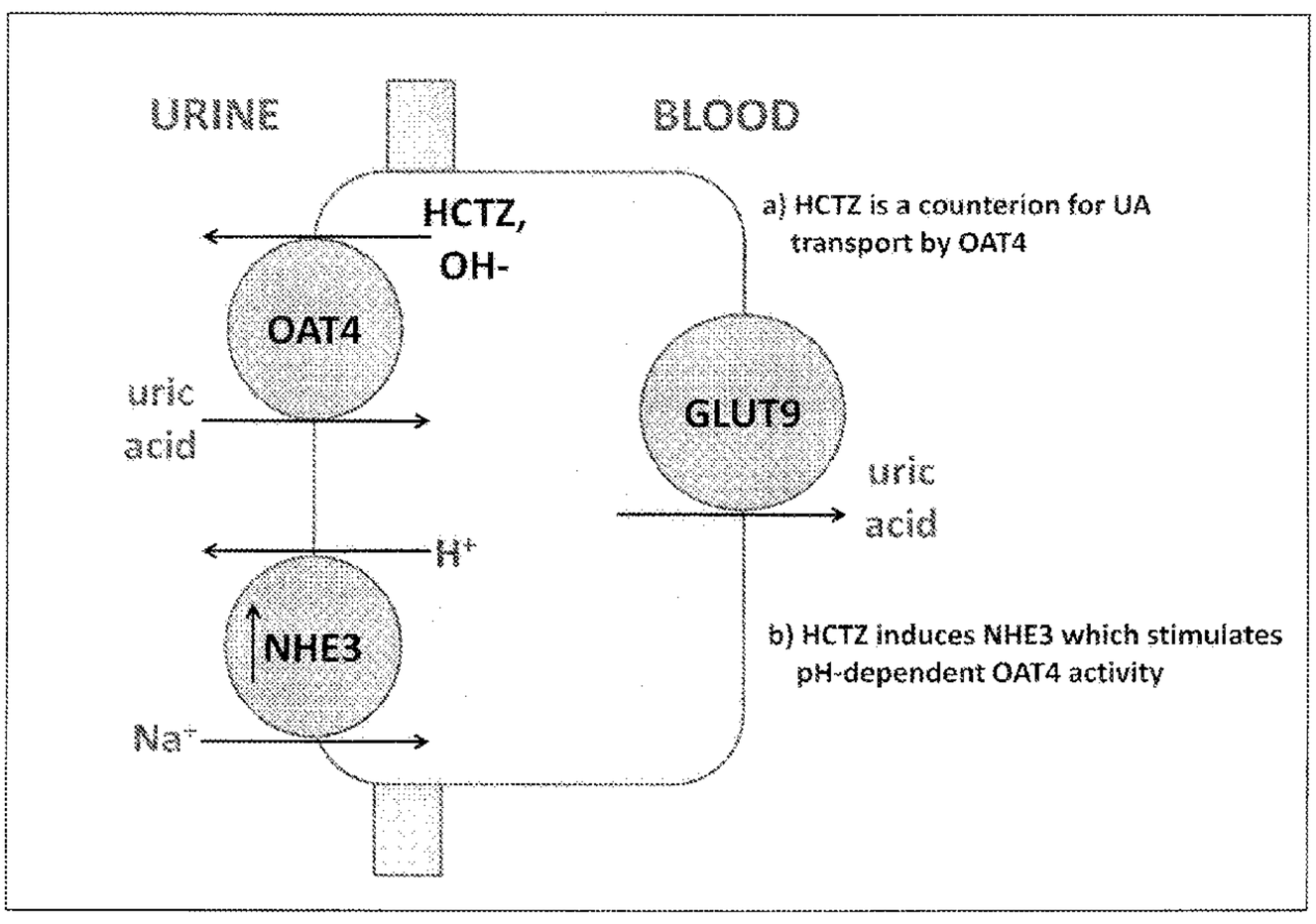
(54) Title: HYPERTENSION AND HYPERURICEMIA

FIG. 1



(57) Abstract: A method for treating hypertension in a subject in need thereof (e.g., wherein said treatment does not result in an increase in serum uric acid levels, abnormally elevated serum uric acid levels, hyperuricemia, serum uric acid levels of above 6 mg/dL, or in the development of gout in the subject), the method comprising administering to the subject: a. a thiazide diuretic; and b. an organic anion transporter 4 (OAT4) inhibitor. The thiazide diuretic is selected from hydrochlorothiazide, bendroflumethiazide, benzothiadiazine, hydroflumethiazide, clorothiazide, methyclothiazide, polythiazide, chlorthalidone, metolazone, indapamide, bumetanide, ethacrynic acid, furosemide or torsemide. The OAT4 inhibitor is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)- 4H-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.

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HYPERTENSION AND HYPERURICEMIA

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 61/489,597, filed May 24, 2011, which application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Hypertension is treated with anti-hypertensive agents such as thiazide diuretics, which may elevate serum uric acid levels.

SUMMARY OF THE INVENTION

[0003] Provided in certain embodiments herein is a method for treating hypertension in a subject in need thereof (e.g., wherein said treatment does not result in an increase in serum uric acid levels, does not result in abnormally elevated serum uric acid levels, does not result in hyperuricemia, does not result in serum uric acid levels of above 6 mg/dL, or does not result in the development of gout in the subject), the method comprising administering to the subject:

a. a thiazide diuretic; and
b. an organic anion transporter 4 (OAT4) inhibitor.

[0004] In some embodiments, the thiazide diuretic is selected from hydrochlorothiazide, bendroflumethiazide, benzothiadiazine, hydroflumethiazide, clorothiazide, methyclothiazide, polythiazide, chlorthalidone, metolazone, indapamide, bumetanide, ethacrynic acid, furosemide or torsemide.

[0005] In certain embodiments, the OAT4 inhibitor is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.

[0006] In some embodiments, any method described herein further comprises administering a URAT1 inhibitor to the subject. In specific embodiments, the OAT4 inhibitor and the URAT1 inhibitor are the same drug.

[0007] Provided in some embodiments herein is a method for treating hypertension in a subject in need thereof, wherein said treatment does not result in an increase in serum uric acid levels, comprising administering to the subject:

a. hydrochlorothiazide; and
b. 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof

[0008] Provided in some embodiments herein is a method of reducing serum uric acid, treating gout, or reducing the incidences of elevated serum uric acid or gout in a subject suffering from hypertension, the method comprising administering an OAT4 inhibitor, such as an OAT4 inhibitor described herein. In specific embodiments, the elevated serum uric acid or gout is induced by the administration of a thiazide. In certain embodiments, provided herein is a method of treating an OAT4 mediated disorder in a subject by administering to the subject 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid, a pharmaceutically acceptable salt thereof, or an anlalog thereof. In specific embodiments, the OAT4 mediated disorder is OAT4 mediated hyperuricemia or OAT4 mediated gout.

[0009] In some embodiments, provided herein is a method for reducing the incidences of or likelihood of or reversing the diagnosis of hyperuricemia or gout in a patient receiving thiazide treatment, comprising administering an OAT4 inhibitor to the patient.

[0010] In certain embodiments, provided herein is a method for reducing serum uric acid levels in a patient suffering from hypertension, comprising administering to the subject an effective amount of an OAT-4 inhibitor, wherein the patient is receiving a thiazide diuretic, and wherein (absent the administration of the OAT-4 inhibitor) administration of the thiazide diuretic results in elevated serum uric acid levels.

[0011] In some embodiments, provided herein is a composition comprising:

a. a thiazide diuretic;
b. an OAT-4 inhibitor; and
c. a pharmaceutically acceptable excipient or carrier.

[0012] In specific embodiments, provided herein is a composition comprising:

a. hydrochlorothiazide;
b. 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof; and
c. a pharmaceutically acceptable excipient or carrier.

INCORPORATION BY REFERENCE

[0013] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0015] FIGURE 1 represents a pictorial representation of two mechanisms for Hydrochlorothiazide (HCTZ)-induced hyperuricemia; a) Direct - HCTZ enhancement of Uric acid uptake by OAT4; and b) Indirect - HCTZ enhances an OAT4 stimulatory protein (NHE3).

[0016] FIGURE 2 represents OAT4 transport activity of 6-carboxyfluorescein (CF) substrate incubated with 50μM Lesinurad (black) or vehicle (light grey) in HEK293T cells transiently transfected with either (a) control plasmid lacking OAT4 (pCMV) or (b) OAT4.

[0017] FIGURE 3 represents HEK293T cells transiently transfected with OAT4 (grey) or control plasmid lacking OAT4 (pCMV, black) incubated with 6-carboxyfluorescein (CF) substrate with various amounts (0, 0.5, 1, 2nM) cold uric acid illustrating urate acts as a competitive substrate for OAT4 of CF (EC_{50} ~900μM).

[0018] FIGURE 4 represents the amount of OAT4 urate transport (cpm) in the presence of varying amounts of Lesinurad (■) and benzbromarone (▲). The OAT4 IC_{50} of Lesinurad =5μM; and Benzbromarone = 10μM.

[0019] FIGURE 5 represents the percent inhibition of UA transport in 293T cells expressing URAT1 and/or OAT4 by Lesinurad at varying concentrations, indicating Lesinurad inhibits URAT1 and OAT4 with similar potency.

[0020] FIGURE 6 represents percent ^{3}H-Estrone sulphate (ES) transport in 293T cells stably expressing OAT4, in the presence (——) or absence (- - - -) of 1mM Hydrochlorothiazide (HCTZ), and varying concentrations of Lesinurad, indicating HCTZ has no effect on Lesinurad-mediated inhibition of OAT4 transporter activity.

[0021] FIGURE 7 represents the OAT4 transport activity of (a) 6-carboxyfluorescein (CF - 5μM) and (b) ^{14}C-uric acid (UA – 100μM) substrates in the presence of vehicle, Lesinurad, oxypurinol, or allopurinol (100μM – 5 min incubation) in OAT4-expressing HEK293 cells indicating oxypurinol and allopurinol do not inhibit OAT4 transport activity.

[0022] FIGURE 8 represents percent uptake of ^{3}H-Estrone sulfate (ES) in OAT4-expressing oocytes injected with various concentrations of Lesinurad (25, 50, 100μM – outside; 22, 44, 444μM – inside) or vehicle, indicating Lesinurad inhibits OAT4 primarily from the extracellular (apical) side.

[0023] FIGURE 9 represents the amount of ^{14}C-labeled Lesinurad (measured by scintillation counting) inside and outside OAT4-expressing oocytes after being injected with Lesinurad (50nL) and incubated for 30 mins, indicating Lesinurad remains inside injected oocytes for the duration of the experiment.

[0024] FIGURE 10A represents a schematic of a clinical phase 2 study design.

[0025] FIGURE 10B represents the proportion of patients with serum uric acid (sUA) levels below 6mg/dL, separated into those taking diuretics (black) and those not taking diuretic (light grey) for the various doses of Lesinurad, and indicating patients receiving diuretics had responded well to Lesinurad.

DETAILED DESCRIPTION OF THE INVENTION

[0026] While certain embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments described herein are, in some circumstances, employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[0027] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, without limitation, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

Diuretics and Hyperuricemia

[0028] Hypertension is prevalent in gout patients and they are often treated with anti-hypertensive agents, such as thiazide diuretics, which have been known since the 1950's to elevate serum uric acid levels (Healey *et. al.*, *NEJM*, **1959**, *261*, 1358). For example, one study revealed use of thiazide diuretics in doses of 25 mg/day or higher is associated with a significantly increased risk for initiation of anti-gout therapy (Gurwitz *et. al.*, *J Clin. Epidemiol.* 1997, *50(8)*, 953).

[0029] Meanwhile, urate-lowering therapies are generally believed to work less efficiently in patients taking diuretics concomitantly (Reyes, *Cardiovasc. Drugs Ther.,* 2003, *17*(5-6), 397). This effect is thought to be mediated by enhanced uric acid reabsorption due to activation of

OAT4 by two different mechanisms (see Figure 1); either direct thiazide enhancement of uric acid uptake by OAT4 (Hagos *et al*, *J. Am. Soc. Nephrol.,* 2007, *18*, 430), or indirect via thiazide enhancement of an OAT4 stimulatory protein (Sodium/hydrogen exchanger 3; NHE3) (Nijenhuis *et. al.*, *J. Clin. Invest*. 2005, *115*, 1651).

[0030] In addition to URAT1, organic anion transporter 4 (OAT4) is considered an important regulator of urate excretion. Organic anion transporter 4 (OAT4) is a urate transporter, also involved in renal secretion of anti-hypertensive drugs such as thiazide diuretics. In some instances, OAT4 exchanges these drugs against urate, thereby enhancing uric acid reabsorption resulting in their hyperuricemic effect. It has been postulated that OAT4 may be responsible for the hyperuricemia associated with some diuretics.

[0031] In some instances, diuretic use is linked to increase risk of gout and increased serum uric acid levels. (*Arch. Intern. Med.* 2005; 165: 742–8.) Indeed, all loop diuretics, and many thiazide-type diuretics elevate serum urate, with the exception of tienilic acid, (which is uricosuric and reduces serum urate). Sodium channel blockers (such as amiloride and triamterene) and aldosterone receptor blockers (such as spironolactone and eplerenone) also elevate serum urate levels, though the mechanisms are probably different for each drug class. Fractional excretion of urate is reduced in diuretic treated subjects (*J. Am. Soc. Nephrol.* 18:3101, 2007). In some instances, mechanisms that may explain these observations include possible volume effects of diuretics, inhibition of urate secretion transporters in proximal tubule (NPT), and direct or indirect activation of OAT4 (SLC22A11) and URAT1. (Reyes, *Cardiovascular Drugs and Serum Uric Acid*, Cardiovascular Drugs and Therapy 17:397, 2004.)

[0032] In some instances, diuretics function as counterion substrates, secreted into the urine by OAT4, which promotes reabsorption of uric acid. For examples, Hydrochlorothiazide (*J. Am. Soc. Nephrol.* 18:430, 2007) and torasemide (*J. Am. Soc. Nephrol.* 18:3101, 2007) increase OAT4 uric acid transport activity.

[0033] Genetic evidence supports the role of OAT4 and URAT1 in gout, hyperuricemia and OAT4 diuretic induced hyperuricemia, whereby two association studies show OAT4 independent associations (*Circ. Cardiovasc. Genet.* 2010; 3; 523-530 and Kolz et al, 2009. Vol 5:6), and another study shows OAT4 association with diuretic-induced hyperuricemia (McAdams presentation ACR Arthritis & Rheumatism, Volume 63, November 2011 Abstract Supplement).

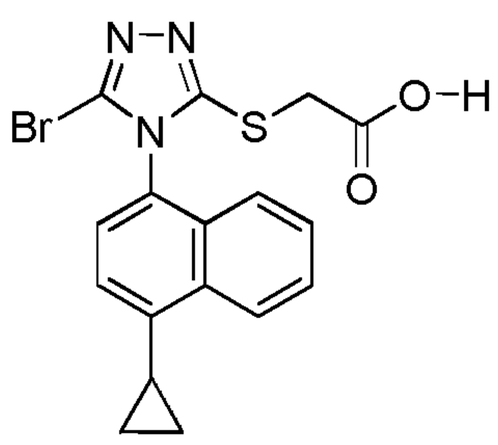
[0034] In some instances, fluid volume alterations are a dominant effect of diuretics through blockade of sodium transporters, and urate absorption parallels NaCl absorption by the proximal tubule. Iron urate and serum uric acid levels correlate well with volume status. Hyperuricemia is abrogated by salt loading the diuretic treated patients, consistent with volume status playing an

important role. (2 mg/dl decrease in SUA between hypertensive patients on ~20 mequ/day salt restriction versus 250 mEqu/day salt loading, with hyperuricemia in the salt-deprived patients.) In some instances, diuretics cause decreased fractional excretion of urate where the volume effects on sUA could be due to alterations in sodium and proton balance in proximal tubule cells leading to activation of URAT1 and OAT4. (*Am. J. Physiol.* 1996 Nov; 271(5 Pt 2):F1093-9 , Nijenhuis *et al, J. Clin. Invest.* 115:1651, 2005; *J. Am. Soc. Nephrol.* 18: 3101–3109, 2007).

[0035] One study (Arthritis & Rheumatism, Volume 63, November 2011 Abstract Supplement, Abstracts of the Am Coll of Rheumatology/Assoc of Rheumatology Health Professionals Annual Scientific Meeting) concluded that the increased risk of gout related to diuretic use in hypertensive subjects was only observed among those with a higher genetic risk score for elevated serum urate levels, suggesting a urate gene-by-diuretic interaction, delineating an important interaction of genetic traits influencing urate metabolism and handling with diuretic use in hypertensive subjects.

Lesinurad

[0036] Lesinurad is the generic name for 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio)acetic acid, whose chemical structure is:



[0037] In some instances, the term Lesinurad also includes the sodium salt of Lesinurad, i.e. sodium 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)- 4H-1,2,4-triazol-3-ylthio)acetate.

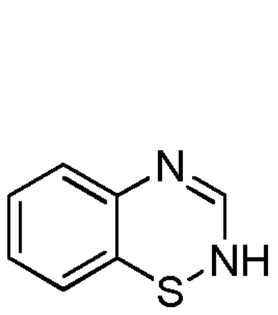
[0038] Lesinurad is a urate lowering therapy in clinical development for the treatment of gout. In some instances, Lesinurad blocks reabsorption of urate (UA) within the kidney proximal tubule by inhibiting the URAT1 transporter.

Thiazides / thiazide diuretics

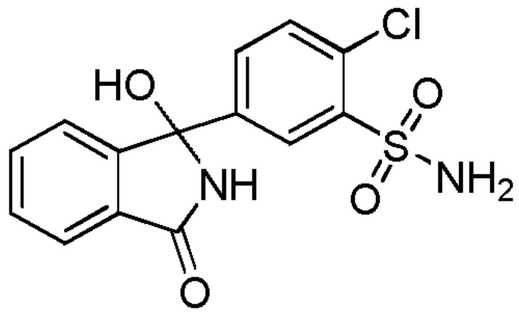
[0039] Thiazides or thiazide diuretics are used to treat hypertension (high blood pressure) and edema (such as that caused by heart, liver, or kidney disease), reducing the risk of death, stroke, heart attack and heart failure due to hypertension. Thiazides are the most commonly used diuretic as the recommended first-line treatment in the US and a recommended treatment in the Europe.

Thiazides are generally understood to work by inhibiting reabsorption of sodium and chloride ions from the distal convoluted tubules in the kidneys, by blocking the thiazide-sensitive Na^+-Cl^- symporter, resulting in increased sodium excretion and thereby increased water excretion, i.e. increasing urination. In some instances, decreasing the amount of water in the body may result in a lower blood volume, thereby reducing and cardiac output, and ultimately leading to a fall in arterial pressure.

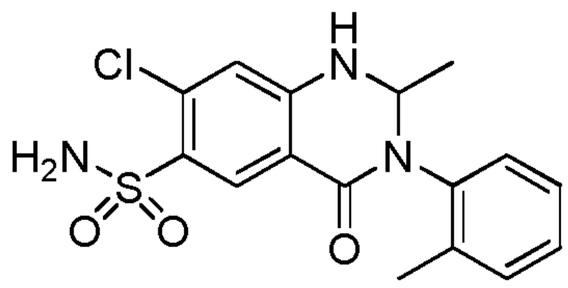
[0040] The term "thiazide" refers to a drug acting at a "thiazide receptor", and includes "thiazide-like diuretics" which act similarly to thiazides but do not contain the benzothiadiazine molecular structure. Examples of "thiazide-like diuretics" include, but are not limited to, bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, polythiazide, quinethazone, trichlormethiazide, chlortalidone and metolazone.



Benzothiadiazine



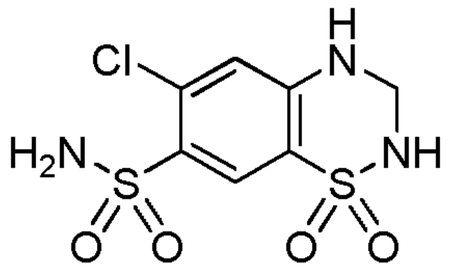
Chlortalidone



Metolazone

Hydrochlorothiazide

[0041] Hydrochlorothiazide, 6-Chloro-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide (HCTZ, HCT or HZT) is frequently prescribed for treatment of hypertension and congestive heart failure.



[0042] Hydrochlorothiazide is generally understood to act on the kidneys to reduce sodium reabsorption and inhibiting the kidneys' ability to retain water, thereby reducing blood volume, decreasing blood return to the heart and thus cardiac output. Hydrochlorothiazide competes for the chloride site on a Na^+/Cl^- co-transporter, thereby impairing sodium transport. One study observed that use of hydrochlorothiazide resulted in a 2.6-fold increase of OAT4-mediated uric acid uptake.

Organic Anion Transporter-4 (OAT4)

[0043] Human organic anion transporter 4 (hOAT4) is expressed in the kidney and, in some instances, encodes a 550 amino acid residue protein. In some instances, hOAT4 is involved in renal secretion and reabsorption of endogenous substances as well as many drugs and xenobiotics. Generally, OAT4 may be present at the luminal side membrane of the proximal renal tubule and mediates the transport of organic anions such as esteron sulfate (ES), dehydroepiandrosterone (DHEA) sulfate, and ochratoxin A, ρ-aminohippurate (PAH).

[0044] Benzbromarone and 6-hydroxybenzbromarone are inhibitors of OAT4, (which thereby promote uric acid excretion). Benzbromarone inhibits OAT4 uptake of ^{3}H-estrone sulfate with an IC50 of 5.4 μmol/L, and 6-hydroxybenzbromarone inhibits OAT4 uptake of ^{3}H-estrone sulfate with an IC50 of 3.2 μmol/L.

Examples

[0045] The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations.

[0046] The urate transporter OAT4 was stably expressed in cultured cells and oocytes.

[0047] For cultured cells, HEK293 cells stably expressing the transporters were produced through transfection of DNA constructs carrying the transporters, antibiotic selection, and clonal selection of clones with high transporter activity. Alternatively, cells transiently expressing the transporters were produced by reverse transfection of HEK293T cells. Transfectants were plated at high density onto poly-L-lysine coated multiwell plates and assayed 1-2 days later. Results were similar for stable and transient expressing cells.

[0048] Oocytes were injected with cRNA for OAT4 expression and assayed 3-4 days later.

[0049] Activity assays were performed by incubating the cells with transporter substrates in assay buffer containing 125 mM sodium gluconate, 4.8 mM potassium gluconate, 1.2 mM monobasic sodium phosphate, 1.2 mM magnesium sulfate, 1.3 mM calcium gluconate, 5.6 mM glucose, and 25 mM HEPES pH 7.1. test drugs were added to the cells prior to addition of substrate for the indicated times. Substrates used were 6-carboxyfluorescein (CF) at 5 μM, 3H-estrone sulfate (ES) at 50 nM, and 14C-uric acid (UA) at 100 μM. For transfected cells, substrates were incubated for 2 minutes and then removed by aspiration and the cells washed three times in a wash buffer containing 125 mM sodium gluconate and 25 mM HEPES pH 7.1. Cells were then lysed in 1 M sodium hydroxide prior to fluorescence measurement for CF

transport and liquid scintillation counting for ES and UA. Oocyte assays were performed similarly, except that test drugs were injected and then transport was measured after 30 minutes (ES) or 60 minutes (UA). The results of these assays are summarized in the figures as listed below.

[0050] FIGURE 1 represents a pictorial representation of two mechanisms for Hydrochlorothiazide (HCTZ)-induced hyperuricemia; a) Direct - HCTZ enhancement of Uric acid uptake by OAT4; and b) Indirect - HCTZ enhances an OAT4 stimulatory protein (NHE3).

[0051] FIGURE 2 represents OAT4 transport activity of 6-carboxyfluorescein (CF) substrate incubated with 50μM Lesinurad (black) or vehicle (light grey) in HEK293T cells transiently transfected with either (a) control plasmid lacking OAT4 (pCMV) or (b) OAT4.

[0052] FIGURE 3 represents HEK293T cells transiently transfected with OAT4 (grey) or control plasmid lacking OAT4 (pCMV, black) incubated with 6-carboxyfluorescein (CF) substrate with various amounts (0, 0.5, 1, 2nM) cold uric acid illustrating urate acts as a competitive substrate for OAT4 of CF (EC_{50} ~900μM).

[0053] FIGURE 4 represents the amount of OAT4 urate transport (cpm) in the presence of varying amounts of Lesinurad (■) and benzbromarone (▲). The OAT4 IC_{50} of Lesinurad =5μM; and Benzbromarone = 10μM.

[0054] FIGURE 5 represents the percent inhibition of UA transport in 293T cells expressing URAT1 and/or OAT4 by Lesinurad at varying concentrations, indicating Lesinurad inhibits URAT1 and OAT4 with similar potency.

[0055] FIGURE 6 represents percent ^{3}H-Estrone sulphate (ES) transport in 293T cells stably expressing OAT4, in the presence (——) or absence (- - - -) of 1mM Hydrochlorothiazide (HCTZ), and varying concentrations of Lesinurad, indicating HCTZ has no effect on Lesinurad-mediated inhibition of OAT4 transporter activity.

[0056] FIGURE 7 represents the OAT4 transport activity of (a) 6-carboxyfluorescein (CF - 5μM) and (b) ^{14}C-uric acid (UA – 100μM) substrates in the presence of vehicle, Lesinurad, oxypurinol, or allopurinol (100μM – 5 min incubation) in OAT4-expressing HEK293 cells indicating oxypurinol and allopurinol do not inhibit OAT4 transport activity.

[0057] FIGURE 8 represents percent uptake of ^{3}H-Estrone sulfate (ES) in OAT4-expressing oocytes injected with various concentrations of Lesinurad (25, 50, 100μM – outside; 22, 44, 444μM – inside) or vehicle, indicating Lesinurad inhibits OAT4 primarily from the extracellular (apical) side.

[0058] FIGURE 9 represents the amount of ^{14}C-labeled Lesinurad (measured by scintillation counting) inside and outside OAT4-expressing oocytes after being injected with Lesinurad

(50nL) and incubated for 30 mins, indicating Lesinurad remains inside injected oocytes for the duration of the experiment.

[0059] FIGURE 10A represents a schematic of a clinical phase 2 study design. The study was a 4-week, double-blind, placebo-controlled clinical trial in 208 gout patients who were not adequately responding to allopurinol with serum urate (sUA) $\geq$ 6 mg/dL while receiving a stable dose of allopurinol for at least 6 weeks. One of three doses of Lesinurad or matching placebo was added to the patients allopurinol regimen. The primary endpoint of the study was mean reduction in sUA at Week 4, with the key secondary endpoint the proportion of subjects with sUA < 6.0 mg/dL at Week 4. A small number of patients in this trial received a thiazide diuretic during the treatment period; their response rates were compared to those patients not receiving concomitant thiazide diuretics and the results presented in **FIGURE 10B.** This figure represents the proportion of patients with serum uric acid (sUA) levels below 6mg/dL, separated into those taking diuretics (black) and those not taking diuretic (light grey) for the various doses of Lesinurad, and indicating patients receiving diuretics had responded well to Lesinurad.

WHAT IS CLAIMED IS:

1. A compound for use in treating gout in a patient on concomitant thiazide diuretics, wherein the patient is not adequately responding to a non-lesinurad urate lowering therapy, wherein the compound is lesinurad.

2. The compound for use of claim **1**, wherein a dose of lesinurad is 200 mg.

3. The compound for use of claim **1**, wherein a dose of lesinurad is 400 mg.

4. The compound for use of claim **1**, wherein the non-lesinurad urate lowering therapy is allopurinol.

5. A compound for use in reducing the incidences of or likelihood of or reversing hyperuricemia or gout in a patient receiving thiazide treatment, wherein the compound is an OAT4 inhibitor.

6. The compound for use of claim **5**, wherein the OAT4 inhibitor is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.

7. The compound for use of claim **5**, wherein the thiazide treatment is treatment with hydrochlorothiazide, bendroflumethiazide, benzothiadiazine, hydroflumethiazide, chlorothiazide, methyclothiazide, polythiazide, chlorthalidone, metolazone, indapamide, bumetanide, ethacrynic acid, furosemide or torsemide.

8. A compound for use in reducing or reversing hyperuricemia or gout in a patient receiving hydrochlorothiazide, wherein the compound is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.

9. A compound for use in reducing serum uric acid levels in a patient suffering from hypertension, wherein the compound is an OAT-4 inhibitor,

   wherein the patient is receiving a thiazide diuretic, and

   wherein administration of the thiazide diuretic results in elevated serum uric acid levels.

10. The compound for use of claim **9**, wherein the OAT4 inhibitor is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.

11. A composition comprising:

(i) a thiazide diuretic;

(ii) an OAT-4 inhibitor; and

(iii) a pharmaceutically acceptable excipient or carrier.

12. A composition comprising:

(i) a thiazide diuretic;

(ii) 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable excipient or carrier.

13. A composition comprising:

(i) hydrochlorothiazide;

(ii) 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable excipient or carrier.

14. Use of a compound for treating gout in a patient on concomitant thiazide diuretics, wherein the patient is not adequately responding to a non-lesinurad urate lowering therapy, wherein the compound is lesinurad.

15. Use of a compound in the manufacture of a medicament for treating gout in a patient on concomitant thiazide diuretics, wherein the patient is not adequately responding to a non-lesinurad urate lowering therapy, wherein the compound is lesinurad.

16. The use of claim **14** or **15**, wherein a dose of lesinurad is 200 mg.

17. The use of claim **14** or **15**, wherein a dose of lesinurad is 400 mg.

18. The use of claim **14** or **15**, wherein the non-lesinurad urate lowering therapy is allopurinol.

19. Use of a compound for reducing the incidences of or likelihood of or reversing hyperuricemia or gout in a patient receiving thiazide treatment, wherein the compound is an OAT4 inhibitor.

20. Use of a compound in the manufacture of a medicament for reducing the incidences of or likelihood of or reversing hyperuricemia or gout in a patient receiving thiazide treatment, wherein the compound is an OAT4 inhibitor.

21. The use of claim **19** or **20**, wherein the OAT4 inhibitor is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.

22. The use of claim **19** or **20**, wherein the thiazide treatment is treatment with hydrochlorothiazide, bendroflumethiazide, benzothiadiazine, hydroflumethiazide, chlorothiazide, methyclothiazide, polythiazide, chlorthalidone, metolazone, indapamide, bumetanide, ethacrynic acid, furosemide or torsemide.

23. Use of a compound for reducing or reversing hyperuricemia or gout in a patient receiving hydrochlorothiazide, wherein the compound is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.

24. Use of a compound in the manufacture of a medicament for reducing or reversing hyperuricemia or gout in a patient receiving hydrochlorothiazide, wherein the compound is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.

25. Use of a compound for reducing serum uric acid levels in a patient suffering from hypertension, wherein the compound is an OAT-4 inhibitor,

wherein the patient is receiving a thiazide diuretic, and

wherein administration of the thiazide diuretic results in elevated serum uric acid levels.

26. Use of a compound in the manufacture of a medicament for reducing serum uric acid levels in a patient suffering from hypertension, wherein the compound is an OAT-4 inhibitor,

wherein the patient is receiving a thiazide diuretic, and

wherein administration of the thiazide diuretic results in elevated serum uric acid levels.

27. The use of claim **25** or **26**, wherein the OAT4 inhibitor is 2-(5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid or a pharmaceutically acceptable salt thereof.

FIG. 1

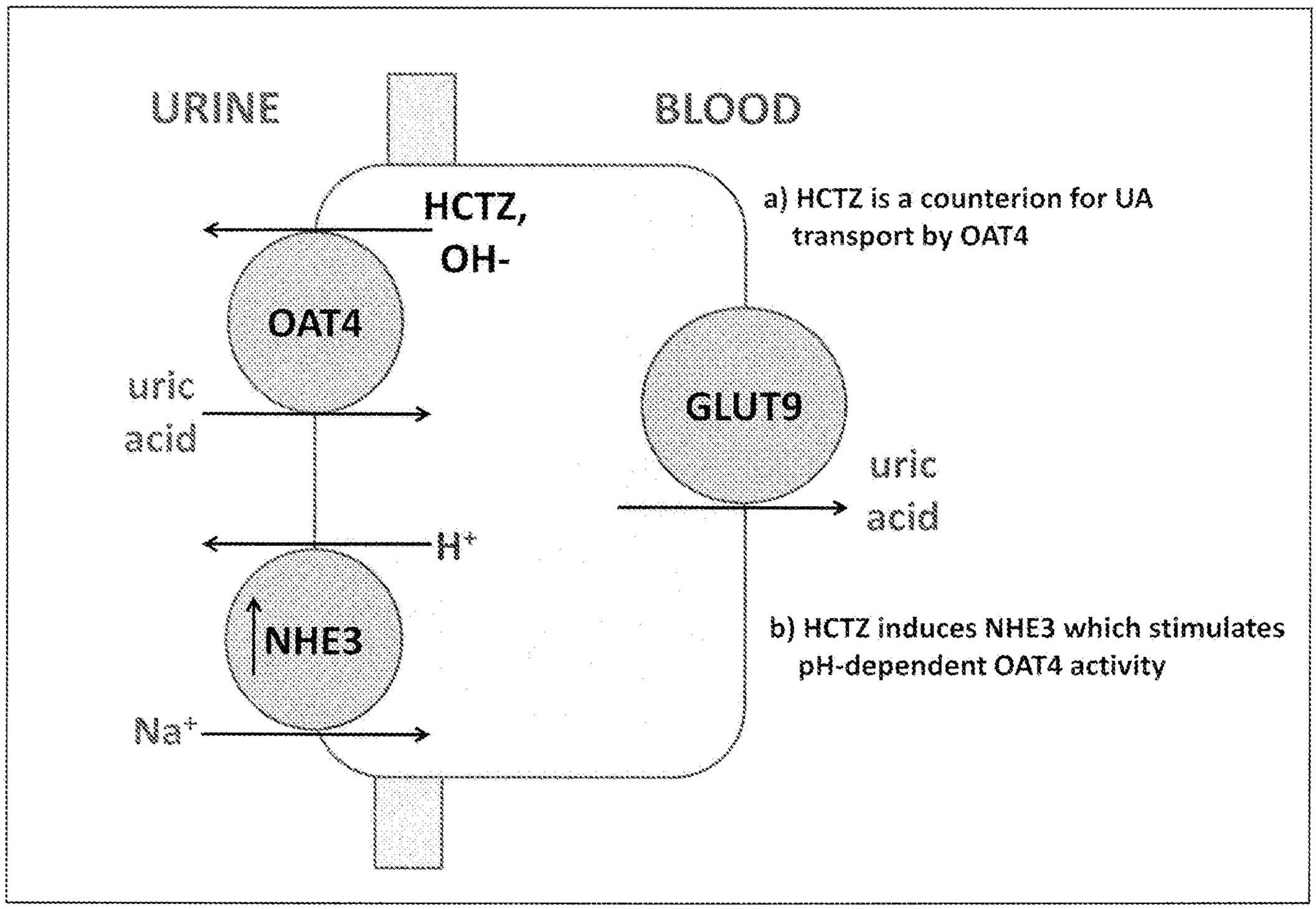

URINE
BLOOD
HCTZ,
OH-
OAT4
uric
acid
GLUT9
uric
acid
H+
NHE3
Na+
a) HCTZ is a counterion for UA transport by OAT4
b) HCTZ induces NHE3 which stimulates pH-dependent OAT4 activity

FIG. 2

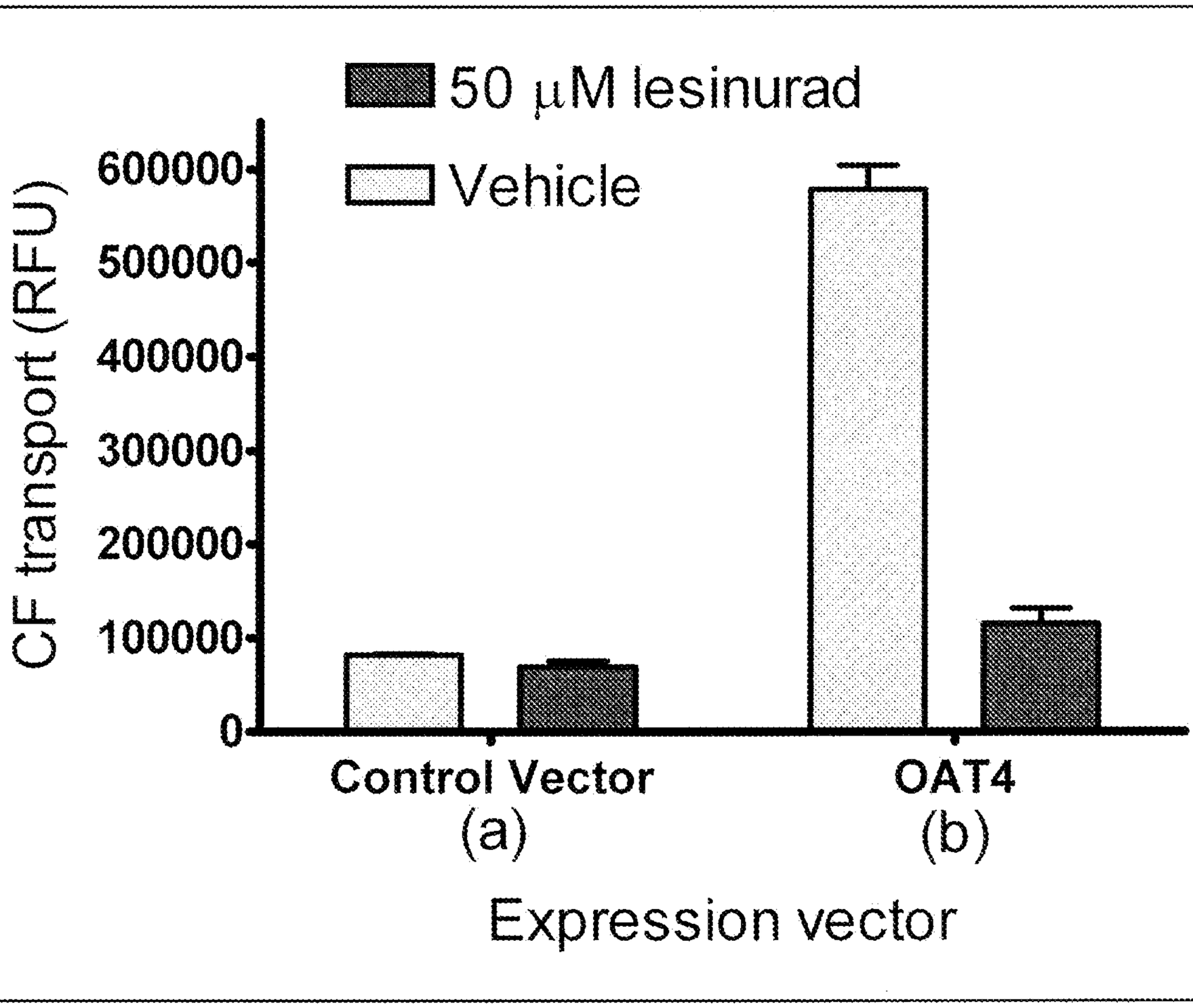

50 μM lesinurad
Vehicle
CF transport (RFU)
600000
500000
400000
300000
200000
100000
0
Control Vector
OAT4
(a)
(b)
Expression vector

FIG. 3

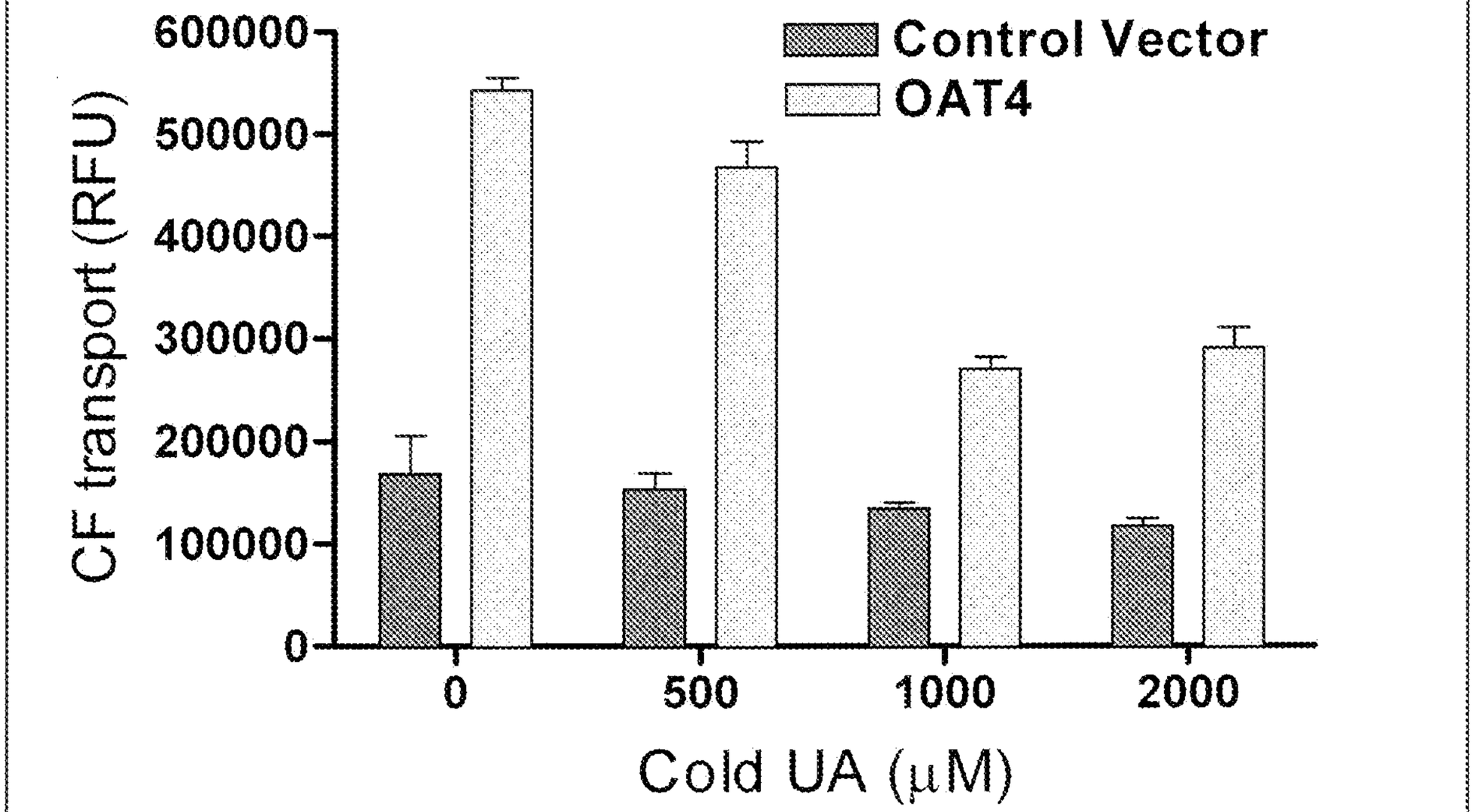

600000
500000
400000
300000
200000
100000
0
CF transport (RFU)
Control Vector
OAT4
0
500
1000
2000
Cold UA (μM)

FIG. 4

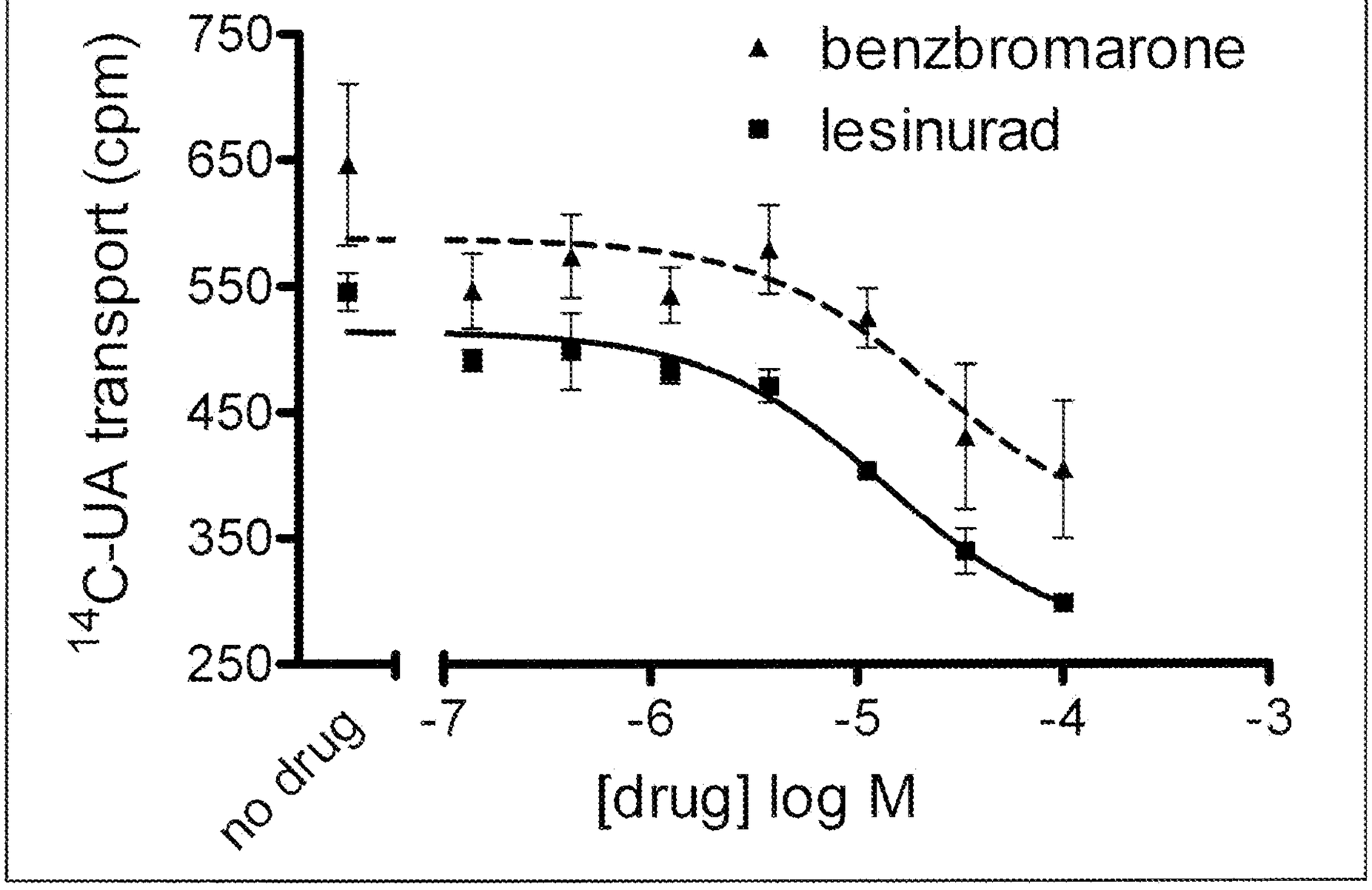

benzbromarone
lesinurad
^{14}C-UA transport (cpm)
750
650
550
450
350
250
no drug
-7
-6
-5
-4
-3
[drug] log M

FIG. 5

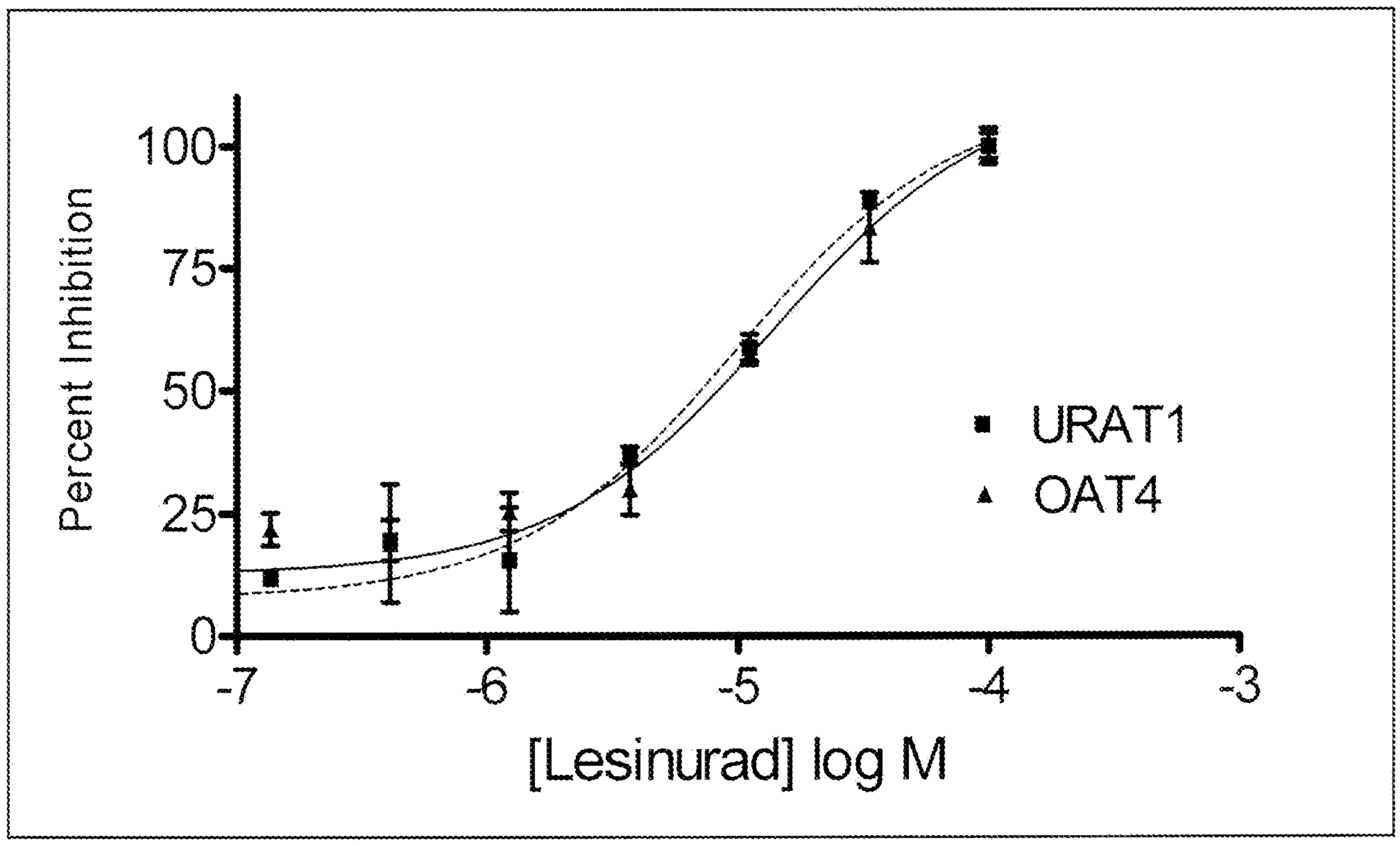

Percent Inhibition
100
75
50
25
0
-7
-6
-5
-4
-3
URAT1
OAT4
[Lesinurad] log M

FIG. 6

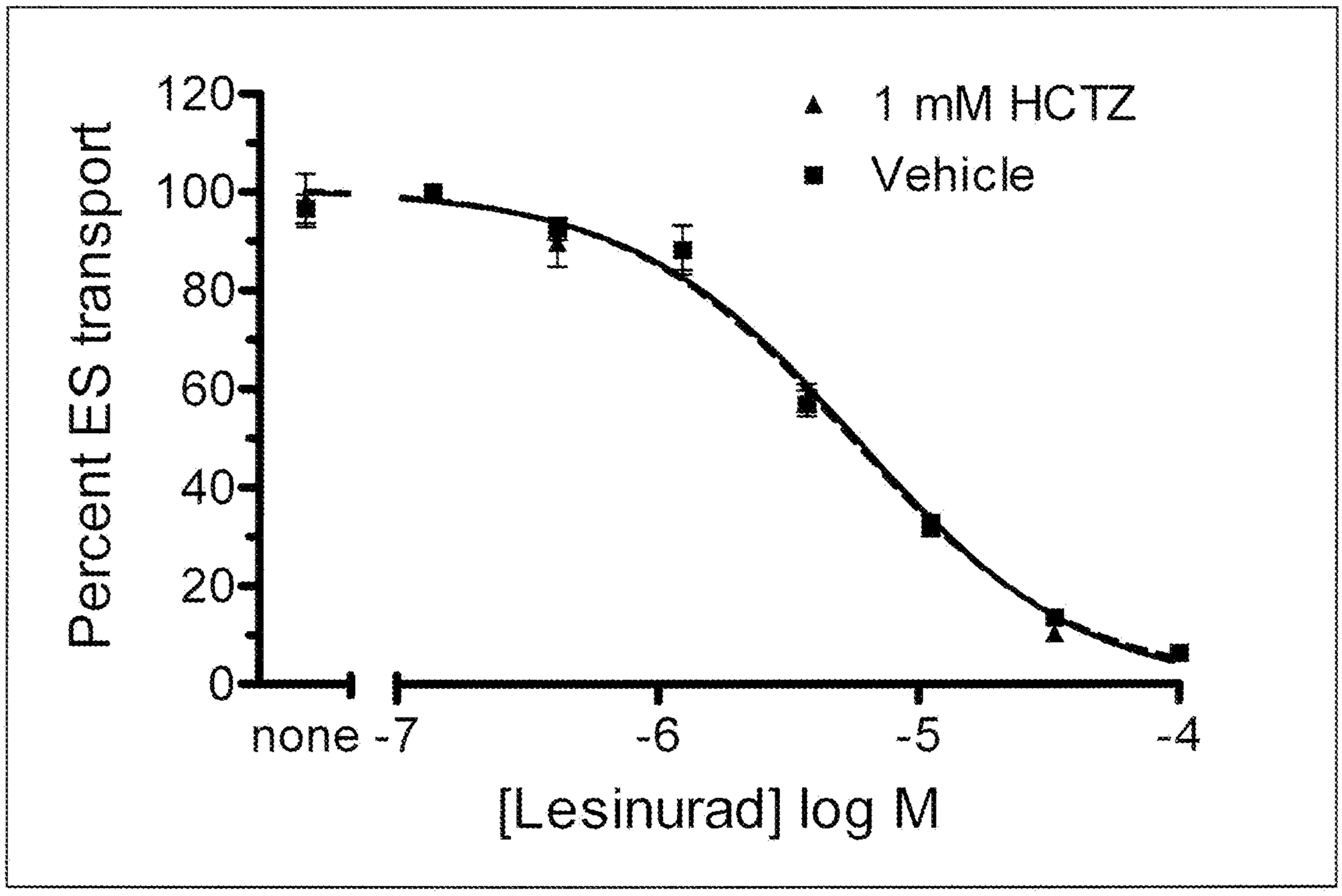
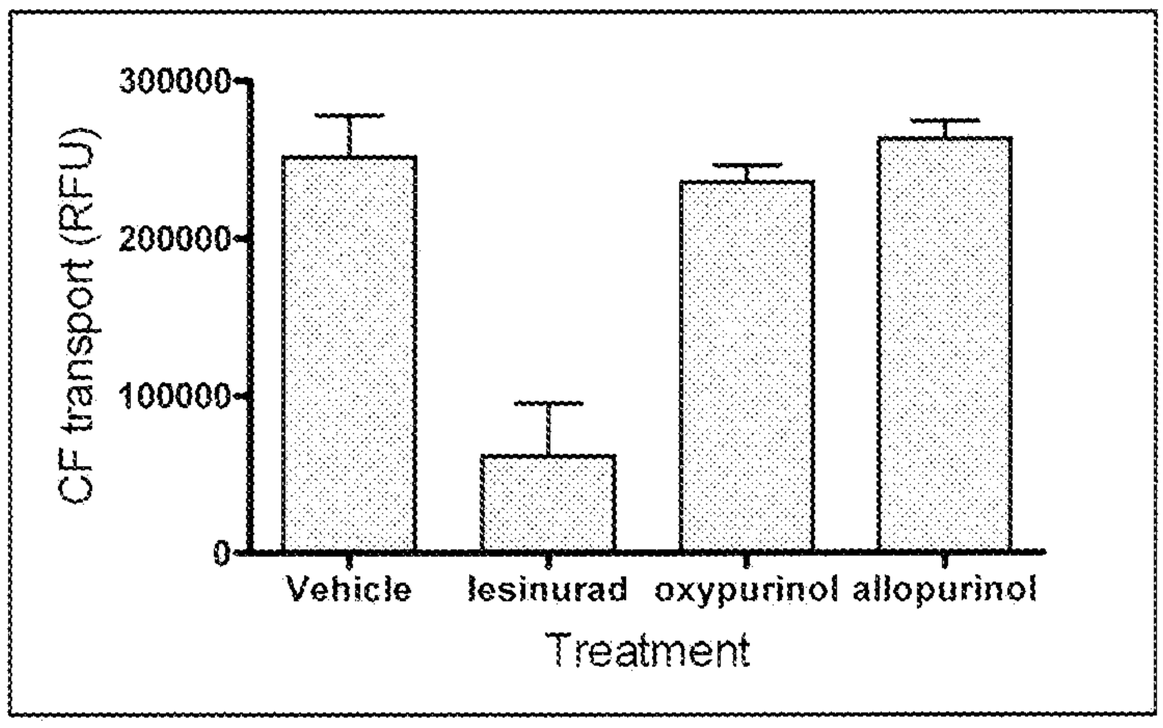
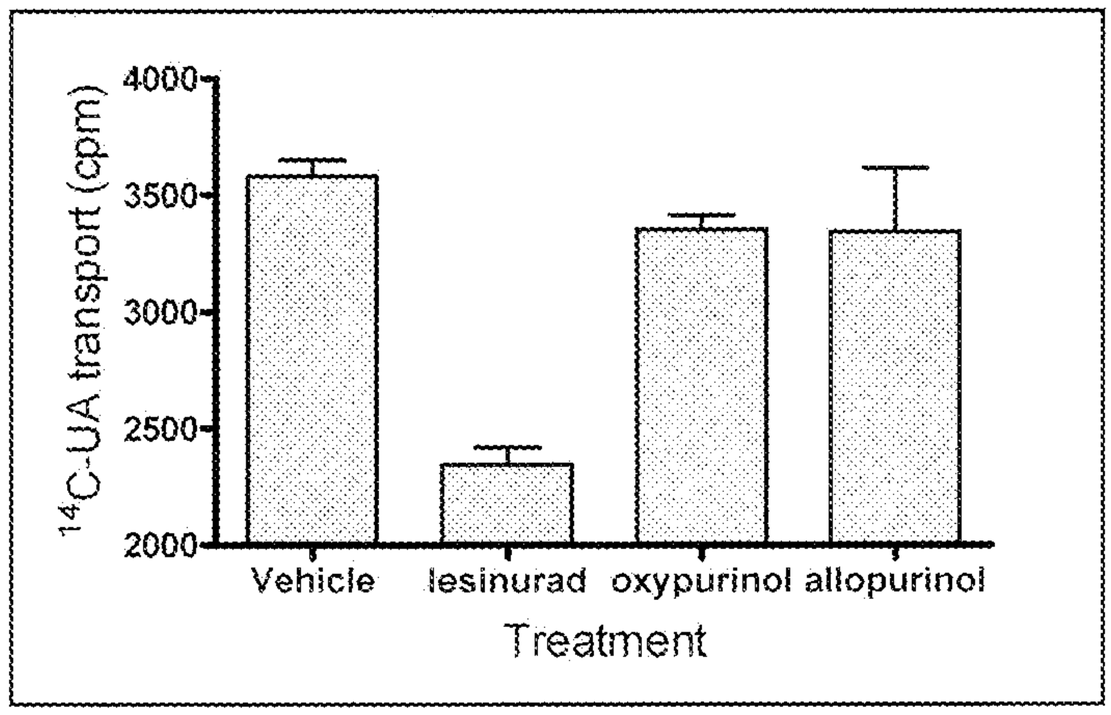

120
100
80
60
40
20
0
Percent ES transport
1 mM HCTZ
Vehicle
none
-7
-6
-5
-4
[Lesinurad] log M

FIG. 7


300000
200000
100000
0
CF transport (RFU)
Vehicle
lesinurad
oxypurinol
allopurinol
Treatment

(a)


4000
3500
3000
2500
2000
^{14}C-UA transport (cpm)
Vehicle
lesinurad
oxypurinol
allopurinol
Treatment

(b)

FIG. 8

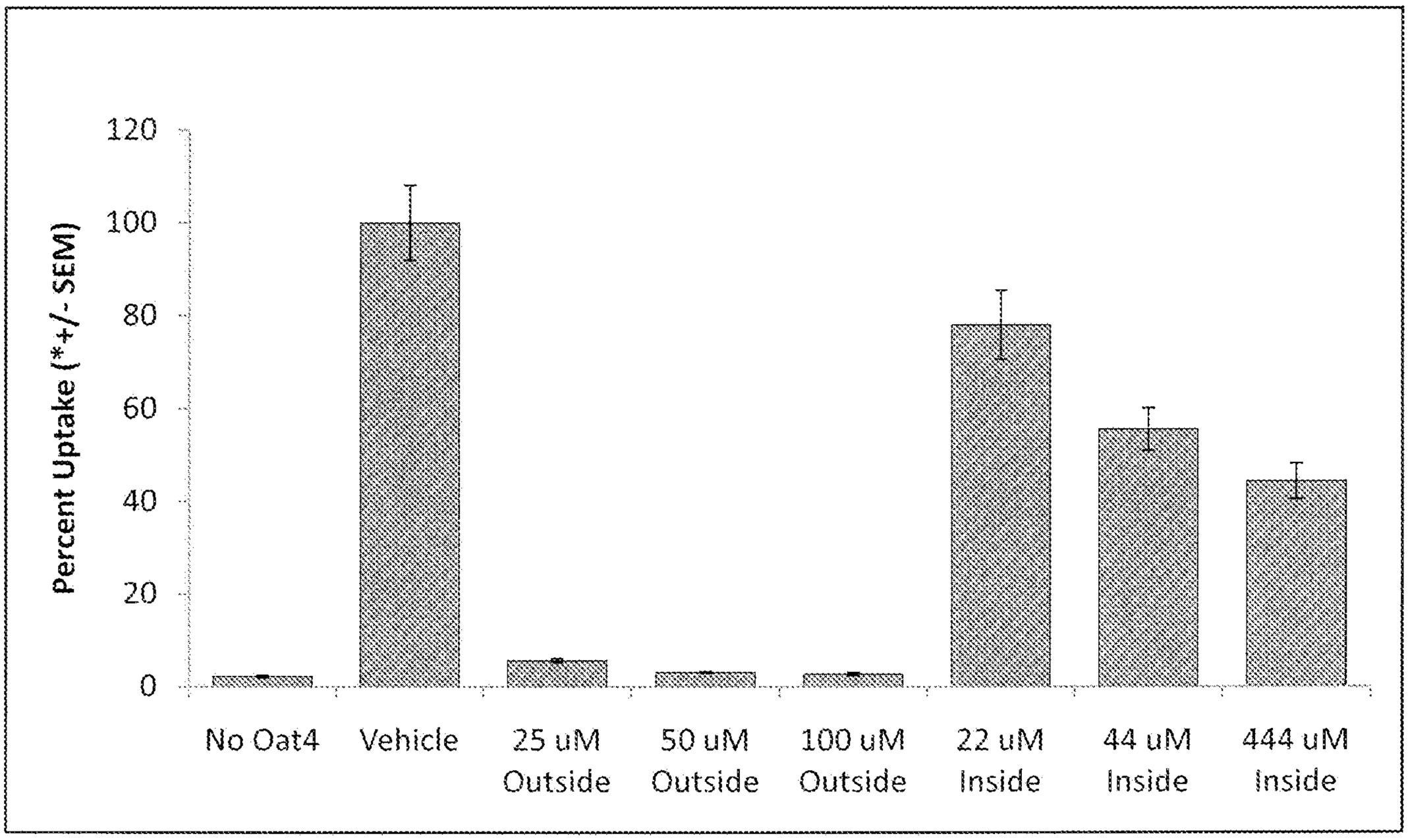

Percent Uptake (*+/- SEM)
120
100
80
60
40
20
0
No Oat4
Vehicle
25 uM Outside
50 uM Outside
100 uM Outside
22 uM Inside
44 uM Inside
444 uM Inside

FIG. 9

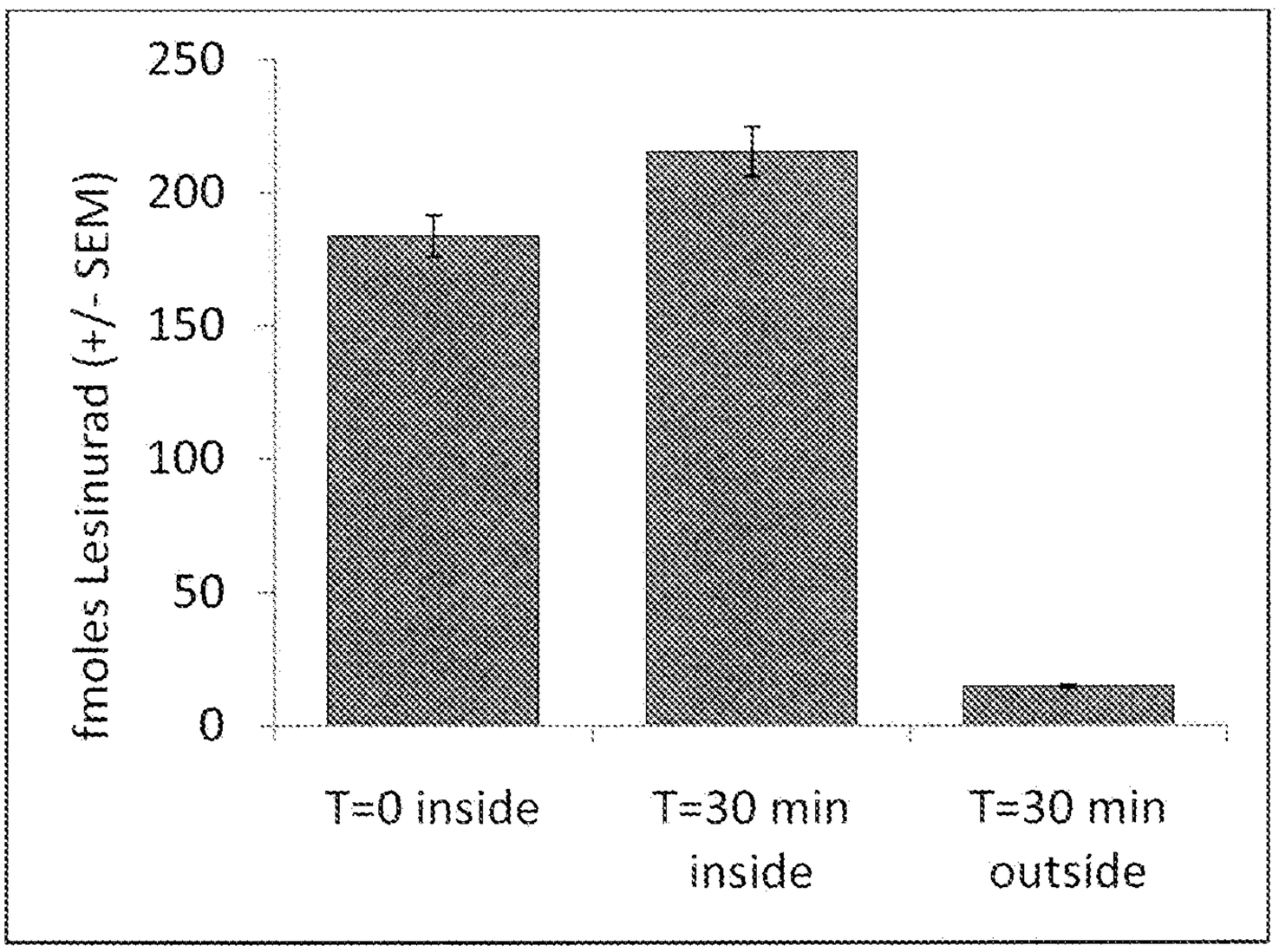

250
200
150
100
50
0
fmoles Lesinurad (+/- SEM)
T=0 inside
T=30 min inside
T=30 min outside

FIG. 10A

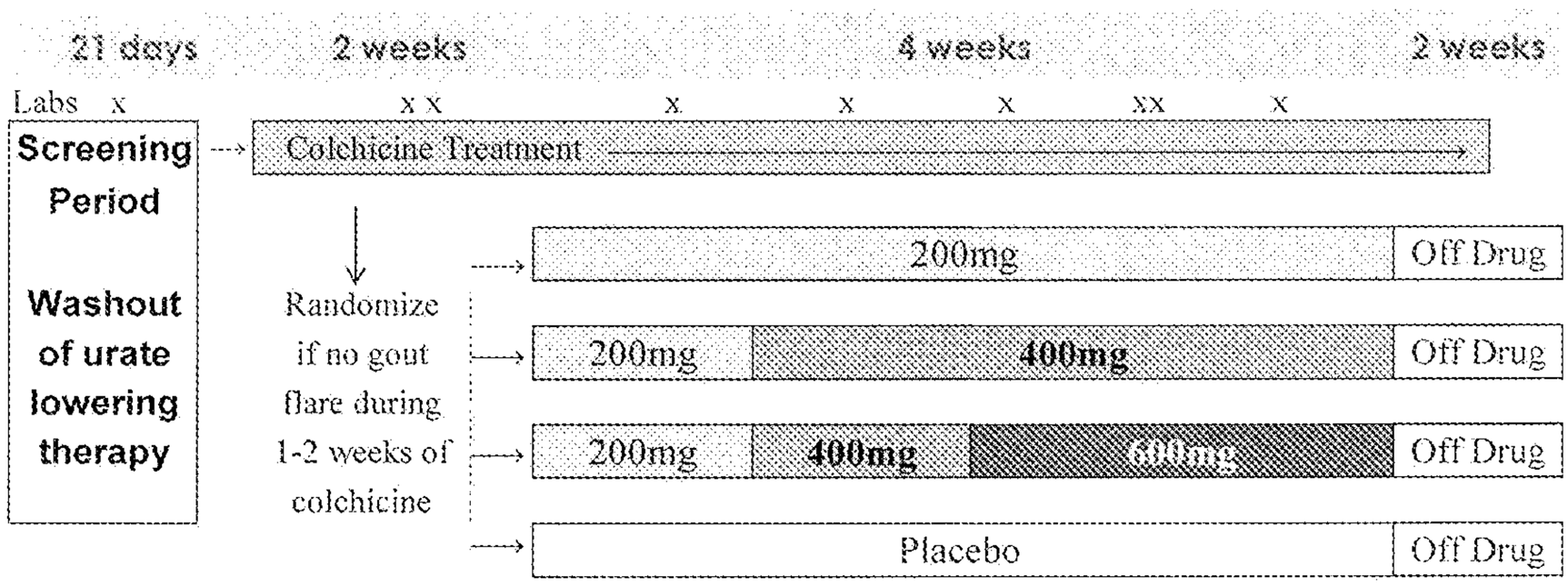


FIG. 10B

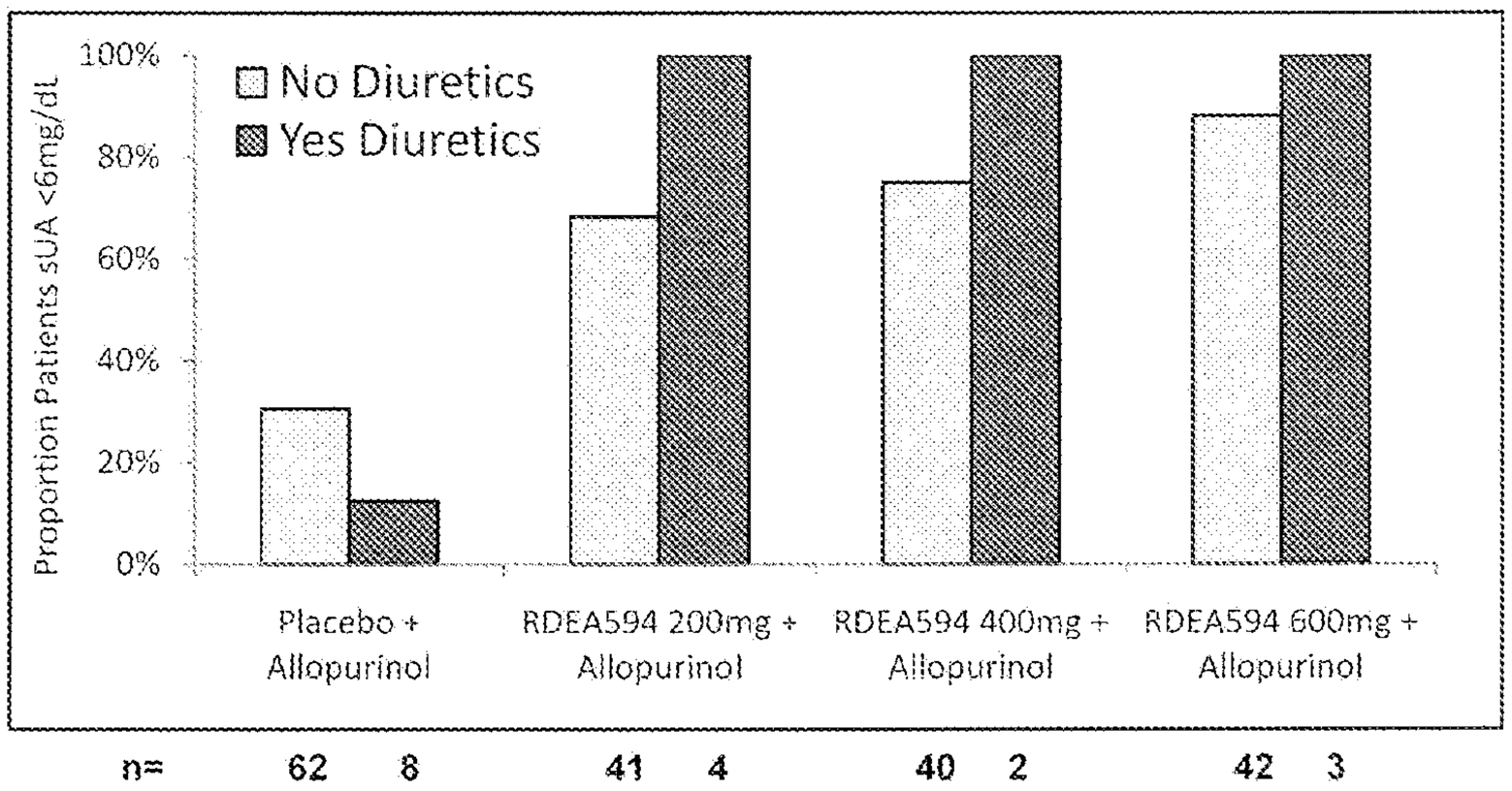
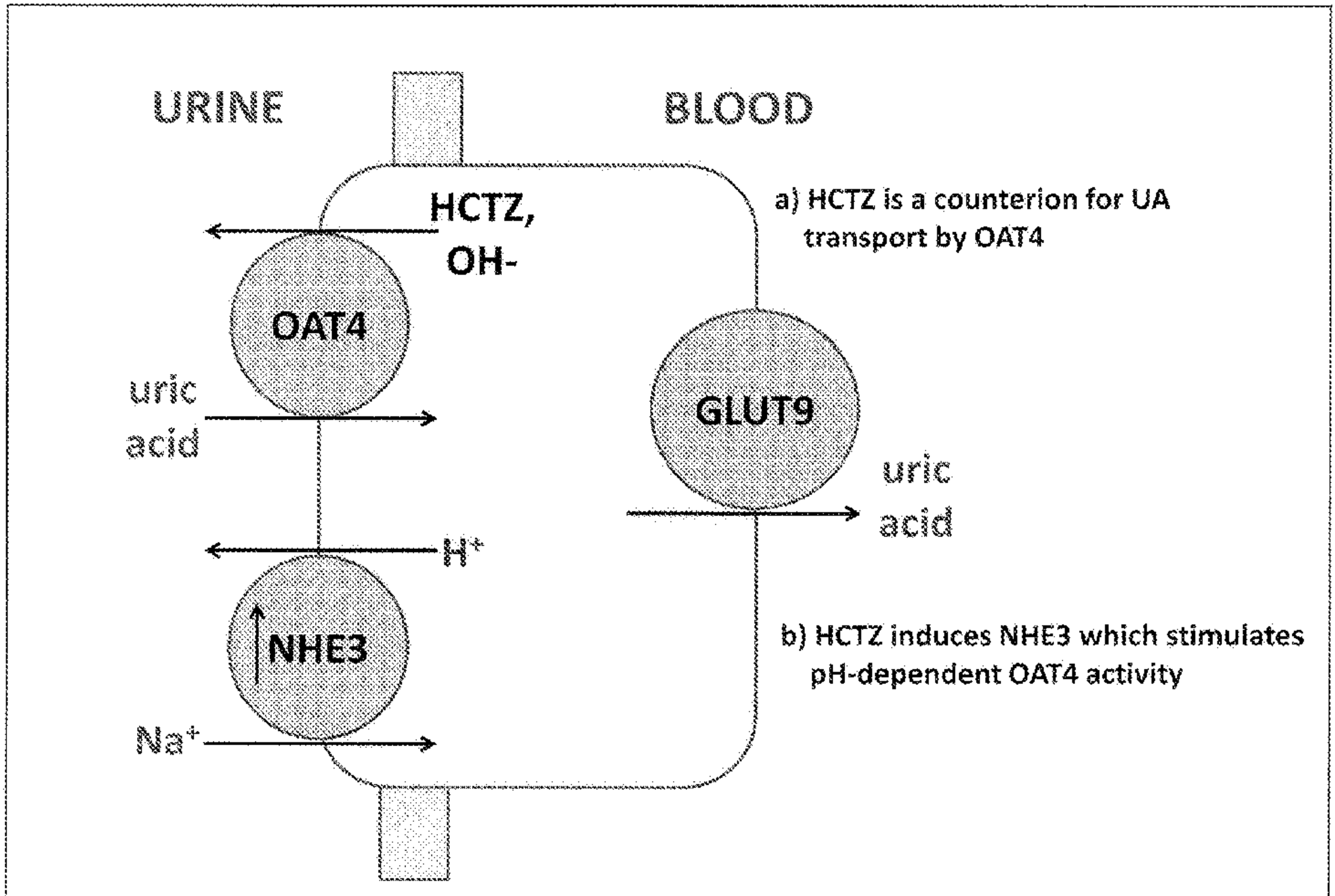


FIG. 1


URINE
BLOOD
HCTZ,
OH-
a) HCTZ is a counterion for UA transport by OAT4
OAT4
uric acid
GLUT9
uric acid
H+
NHE3
Na+
b) HCTZ induces NHE3 which stimulates pH-dependent OAT4 activity