damage to ECs and leukocytes, release of cytokines and of inflammatory mediators, alteration in cell-cell and cell-matrix adhesion and in cytoskeleton function.

During the course of antiviral and antibacterial infections, patients can develop vascular leak that is induced as result of the initial infection. There is now a long felt need for a method of preventing vascular leak due to viral or bacterial infection, and therefore provide a method of increasing the survival of humans or other mammals infected with one or more pathogens. In addition, there is a long felt need for a method of preventing vascular leakage due to certain anticancer drugs or other anticancer therapies such that the administration of anticancer drugs or anticancer therapies can be given to humans or other mammals for a longer course of treatment or therapy.

SUMMARY

Disclosed herein are compounds that inhibit the intracellular catalytic site of human protein tyrosine phosphatase beta (~~PTP-β~~ HPTP-β) molecule. ~~PTP-β~~ HPTP-β is known only to be expressed in vascular endothelial cells. Inhibition of ~~PTP-β~~ HPTP-β reduces the rate of dephosphorylation of the Tie-2 receptor tyrosine kinase. This inhibition results in amplification of the Angiopoietin 1 (Ang-1) signal through Tie-2, and effectively counters the inhibitory effects of Angiopoietin 2 (Ang-2) on Tie-2. Because Tie-2 is critical to maintaining vascular endothelial integrity, the disclosed ~~PTP-β~~ HPTP-β inhibitors provide a method for providing vascular stabilization in humans and mammals. As such, the disclosed ~~PTP-β~~ HPTP-β inhibitors provide Tie-2 signal amplification. One important manifestation of vascular de-stabilization is vascular leak syndrome (VLS) which has many causes, for example, infection of a human or mammal by a pathogen. Another common cause of vascular leak syndrome is the use of certain chemotherapeutic agents, *inter alia*, IL-2 which is used in treating certain forms of cancer.

Disclosed herein are methods for stabilizing human and mammalian vasculature. The stabilization of vasculature in patients compromised with an infection due to the presence of pathogens, *inter alia*, bacteria, viruses, yeasts, and fungi, provide a method for preventing complications due to infection such as sepsis, pulmonary edema, and the like. Subjects suffering from or diagnosed with certain cancers are given chemotherapeutic agents that result in vascular leak syndrome as a primary side effect causing cessation of treatment before the desired full course has been achieved. For weakened humans and mammals, the onset of vascular leak syndrome due to one or more compromising events can be avoided by the disclosed methods for

monitoring the level of Ang-2 and administering the appropriate amount of ~~PTP-β~~ HPTP-β inhibitor, either alone, or as part of a prophylactic combination therapy.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts the effect of 4-{(*S*)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenyl-propanamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid ammonium salt (inhibitor) on murine blood pressure during IL-2 induced VLS at low and high IL-2 dosing. As depicted, High IL-2 dosing in the absence of a Tie-2 signal amplifier resulted in death. A depicts the control sample; B depicts mice treated with 180,000 IU of IL-2 for 5 days; C depicts mice treated with 180,000 IU of IL-2 for 5 days and 40 mg/kg of D91 for the first 2 days, then at 20 mg/kg for 3 days; D depicts mice treated with 400,000 IU of IL-2 for 5 days; E depicts mice treated with 400,000 IU of IL-2 for 5 days and 40 mg/kg of D91 for the first 2 days, then at 20 mg/kg for 3 days.

Figure 2 depicts the effect of 4-{(*S*)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenyl-propanamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid ammonium salt, a Tie-2 signal amplifier, on IL-2 induced shock in mice. A depicts the control sample; B depicts mice treated with 180,000 IU of IL-2 for 5 days; C depicts mice treated with 180,000 IU of IL-2 for 5 days and 40 mg/kg of D91 for the first 2 days, then at 20 mg/kg for 3 days; D depicts mice treated with 400,000 IU of IL-2 for 5 days; E depicts mice treated with 400,000 IU of IL-2 for 5 days and 40 mg/kg of D91 for the first 2 days, then at 20 mg/kg for 3 days.

Figure 3 depicts the effect of 4-{(*S*)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenyl-propanamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid ammonium salt, a Tie-2 signal amplifier, on IL-2 induced murine mortality. A depicts the control sample; B depicts mice treated with 180,000 IU of IL-2 for 5 days; C depicts mice treated with 180,000 IU of IL-2 for 5 days and 40 mg/kg of D91 for the first 2 days, then at 20 mg/kg for 3 days; D depicts mice treated with 400,000 IU of IL-2 for 5 days; E depicts mice treated with 400,000 IU of IL-2 for 5 days and 40 mg/kg of D91 for the first 2 days, then at 20 mg/kg for 3 days.

Figure 4 depicts the status of the animals of each group after treatment with High IL-2 dosing with and without the Tie-2 signal amplifier, 4-{(*S*)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenyl-propanamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid ammonium salt. A depicts the control sample; B depicts the status of mice treated with 400,000 IU of IL-2

typically in relation to some standard or expected value, in other words it is relative, but that it is not always necessary for the standard or relative value to be referred to.

By "prevent" or other forms of the word, such as "preventing" or "prevention," is meant to stop a particular event or characteristic, to stabilize or delay the development or progression of a particular event or characteristic, or to minimize the chances that a particular event or characteristic will occur. Prevent does not require comparison to a control as it is typically more absolute than, for example, reduce. As used herein, something could be reduced but not prevented, but something that is reduced could also be prevented. Likewise, something could be prevented but not reduced, but something that is prevented could also be reduced. It is understood that where reduce or prevent are used, unless specifically indicated otherwise, the use of the other word is also expressly disclosed.

By "treat" or other forms of the word, such as "treated" or "treatment," is meant to administer a composition or to perform a method in order to reduce, prevent, inhibit, break-down, or eliminate a particular characteristic or event (*e.g.*, vascular leakge). The disclosed compounds affect vascular leakage by inhibiting ~~PTP-β~~ HPTP-β (and the rodent equivalent, VE-PTP) which enhances or amplifies Tie-2 signaling.

By "chemotherapeutic agent" is meant any drug, pharmaceutical or otherwise, that can be given to a subject as part of a combination therapy. Non-limiting examples of chemotherapeutic agents include anticancer drugs, for example, IL-2, taxol, and the like, antimicrobials, anti-virals, anti-fungicides, and the like.

Throughout the description and claims of this specification the word "comprise" and other forms of the word, such as "comprising" and "comprises," means including but not limited to, and is not intended to exclude, for example, other additives, components, integers, or steps.

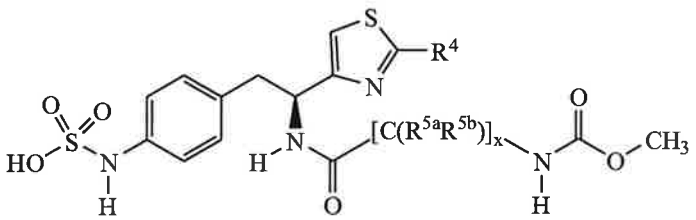
As used in the description and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a composition" includes mixtures of two or more such compositions, reference to "a phenylsulfamic acid" includes mixtures of two or more such phenylsulfamic acids, reference to "the compound" includes mixtures of two or more such compounds, and the like.

"Optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

2.31 mmol), 1-hydroxybenzotriazole (0.118 g, 0.79 mmol) and (*S*)-(2-*tert*-butoxycarbonyl-amino)-3-phenylpropionic acid (0.212 g, 0.80 mmol). The mixture is stirred at 0 °C for 30 minutes then at room temperature overnight. The reaction mixture is diluted with water and extracted with EtOAc. The combined organic phase is washed with 1 N aqueous HCl, 5 % aqueous $NaHCO_3$, water and brine, and dried over Na_2SO_4. The solvent is removed *in vacuo* to afford 0.395 g (90 % yield) of the desired product which is used without further purification. LC/MS ESI+ 573 (M+1).

Preparation of ~~4-{(*S*)-2-(*S*)-2-(*tert*-butoxycarbonyl)-3-phenylpropaneamido-2-(2-phenylthiazole-4-yl)}phenylsulfamic acid~~ (4-((*S*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-phenylpropaneamido)-2-(2-phenylthiazol-4-yl)ethyl)phenyl)sulfamic acid (9): *tert*-butyl (*S*)-1-(*S*)-2-(4-nitrophenyl)-1-(2-phenylthiazole-4-yl)ethylamino-1-oxo-3-phenylpropan-2-ylcarbamate, 8, (0.360 g) is dissolved in MeOH (4 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 12 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (12 mL) and treated with SO_3-pyridine (0.296 g). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH (10 mL) is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.050 g of the desired product as the ammonium salt. ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.20 (d, J = 8.1 Hz, 1H), 7.96-7.99 (m, 2H), 7.48-7.52 (m, 3H), 7.00-7.23(m, 7H), 6.89 (s, 1H), 5.28 (q, J = 7.5 Hz, 1H), 4.33 (t, J = 6.6 Hz, 1H), 3.09-3.26 (m, 2H), 3.34 (dd, J = 13.2 and 8.4 Hz, 1H), 2.82 (dd, J = 13.2 and 8.4 Hz, 1H), 1.38 (s, 9H).

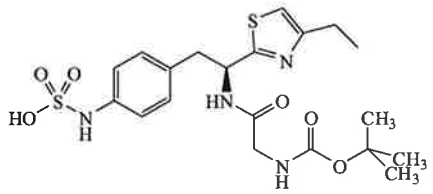
The first aspect of Category II of the present disclosure relates to compounds wherein R is a substituted or unsubstituted thiazol-4-yl unit having the formula:



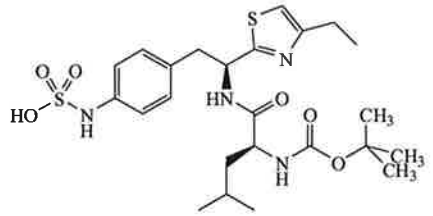
one embodiment of which relates to inhibitors having the formula:

Preparation of 4-{(*S*)-2-[(*S*)-2-(*tert*-butoxycarbonylamino)-3-methylbutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid (17): *tert*-Butyl (*S*)-1-[(*S*)-(4-ethylthiazol-2-yl)-2-(4-nitrophenyl)ethylamino]-3-methyl-1-oxobutan-2-ylcarbamate, 16, (0.219 g) is dissolved in MeOH (4 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 2 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (5 mL) and treated with SO_3-pyridine (0.146 g). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH (30 mL) is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.148 g of the desired product as the ammonium salt. ^{1}H NMR (CD_3OD): δ 7.08 (s, 4H), 7.02 (s, 1H), 5.43 (s, 1H), 3.85 (s, 1H), 3.28-2.77 (m, 4H), 1.94 (s, 1H), 1.46 (s, 9H), 1.29 (s, 3H, *J*=7.3 Hz), 0.83 (s, 6H).

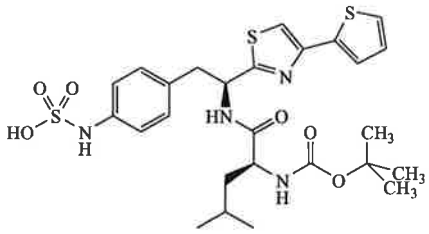
The following are further non-limiting examples of the second aspect of Category IV of the present disclosure.



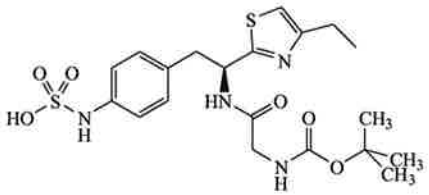
~~(*S*)-4-{2-[2-(*tert*-Butoxycarbonyl)acetamide]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid~~ (*S*)-4-{2-[2-(*tert*-Butoxycarbonyl)amino]acetamido-2-(4-ethylthiazol-2-yl)ethyl}-phenylsulfamic acid: ^{1}H NMR (CD_3OD): δ 7.09-6.91 (m, 5H), 5.30 (t, 1H, *J*=8.4 Hz), 3.60-2.64 (m, 6H), 1.34 (s, 9H), 1.16 (t, 3H, *J*=7.5 Hz).



4-{(*S*)-2-[(*S*)-2-(*tert*-Butoxycarbonylamino)-4-methylpentanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid: ^{1}H NMR (CD3OD) δ 7.19-7.00 (m, 4H), 5.50-5.40 (m, 1H), 4.13-4.06 (m, 1H), 3.32 (1H, A of ABX, J = 7.5, 18Hz), 3.12 (1H, B of ABX, J = 8.1, 13.8Hz), 2.79 (q, 2H, J = 7.8, 14.7Hz), 1.70-1.55 (m, 1H), 1.46 (s, 9H), 1.33 (t, 3H, J = 2.7Hz), 0.92 (q, 6H, J = 6, 10.8Hz).

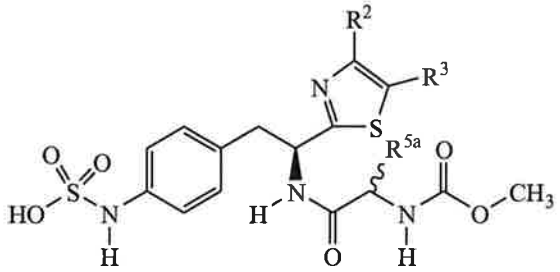


4-{(*S*)-2-[(*S*)-2-(*tert*-Butoxycarbonylamino)-4-methylpentanamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid: ^{1}H NMR (CD3OD) δ 8.06 (d, 1H, J = 8.4Hz), 7.61-7.58 (m, 1H), 7.57 (s, 1H), 7.15 (t, 1H, J = 0.6Hz), 7.09-6.98 (m, 6H), 5.30-5.20 (m, 1H), 4.10-4.00 (m, 1H), 3.19-3.13 (m, 2H), 1.63-1.55 (m, 2H), 1.48-1.33 (m, 10H), 0.95-0.89 (m, 6H).



~~(*S*)-4-{2-[2-(*tert*-Butoxycarbonyl)acetamide]-2-(4-ethylthiazol-2-yl)ethyl}-phenylsulfamic acid~~ (*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(methoxycarbonylamino)acetamido]ethyl}-phenylsulfamic acid: ^{1}H NMR (CD_3OD): δ 7.09-6.91 (m, 5H), 5.30 (t, 1H, *J*=8.4 Hz), 3.60-2.64 (m, 6H), 1.34 (s, 9H), 1.16 (t, 3H, *J*=7.5 Hz).

A further embodiment of Category IV relates to inhibitors having the formula:

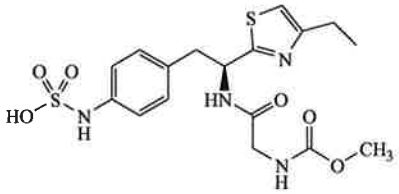


wherein R units and R^{5a} units further described in Table VII.

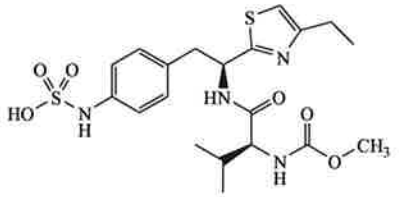
TABLE VII

No.	R	R^{5a}
G151	thiazol-2-yl	hydrogen
G152	4-methylthiazol-2-yl	hydrogen
G153	4-ethylthiazol-2-yl	hydrogen
G154	4-propylthiazol-2-yl	hydrogen
G155	4-*iso*-propylthiazol-2-yl	hydrogen
G156	4-cyclopropylthiazol-2-yl	hydrogen

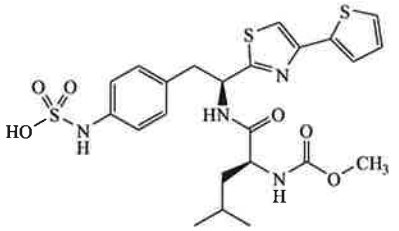
~~4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonyl)-4-methylpentan-amido]ethyl}phenylsulfamic acid~~ 4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonylamino)-4-methylpentan-amido]ethyl}phenylsulfamic acid: ^{1}H NMR (CD3OD) δ 7.12-7.03 (m, 5H), 6.84 (d, 1H, J = 8.4Hz), 5.40 (t, 1H, J = 5.7Hz), 4.16 (t, 1H, J = 6.3Hz), 3.69 (s, 3H), 3.61-3.55 (m, 1H), 3.29-3.27 (m, 1H), 3.14-3.07 (m, 1H), 2.81 (q, 2H, J = 3.9, 11.2Hz), 1.66-1.59 (m, 1H), 1.48-1.43 (m, 2H), 1.31 (t, 3H, J = 4.5Hz), 0.96-0.90 (m, 6H).



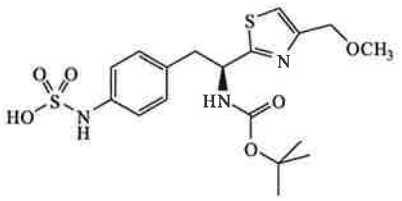
(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(methoxycarbonyl)acetamido]ethyl}-phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.12-7.07 (m, 4H), 7.03 (s, 1H), 5.42 (t, 1H, *J*=5.7 Hz), 3.83-3.68 (q, 2H, *J*=11.4 Hz), 3.68 (s, 3H), 3.34-3.04 (m, 2H), 2.83-2.76 (q, 2H, *J*=7.8 Hz), 1.31 (t, 3H, *J*=7.5 Hz).



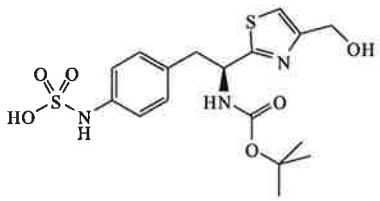
~~4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonyl)-3-methylbutanamido]-ethyl}phenylsulfamic acid~~ 4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonylamino)-3-methylbutanamido]-ethyl}phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 8.56 (d, 1H, J = 7.8Hz), 7.09 (s, 4H), 7.03 (s, 1H), 5.26-5.20 (m, 1H), 3.90 (d, 1H, J = 7.8Hz), 3.70 (s, 3H), 3.30 (1H, A of ABX, obscured by solvent), 3.08 (1H, B of ABX, J = 9.9, 9Hz), 2.79 (q, 2H, J = 11.1, 7.2Hz), 2.05-1.97 (m, 1H), 1.31 (t, 3H, J = 7.5Hz), 0.88 (s, 3H), 0.85 (s, 3H), 0.79-0.75 (m, 1H).



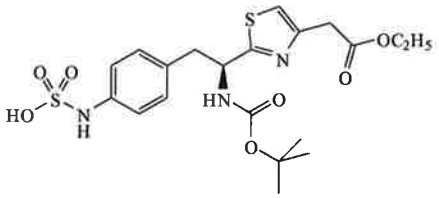
~~4-{(*S*)-2-[(*S*)-2-(Methoxycarbonyl)-4-methylpentanamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid~~ 4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-4-methylpentanamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid: ^{1}H NMR(CD_3OD) δ 8.22 (d, 1H, J = 9Hz), 7.62-7.57 (m, H), 7.15 (t, 1H, J = 0.6Hz), 7.10-6.97 (m, 4H), 5.30-5.20 (m, 1H), 4.16-4.11 (m, 1H), 3.67 (s, 2H), 3.22 (1H, A of ABX, J = 6.9, 13.5Hz), 3.11 (1H, B of ABX, J = 7.8, 13.6Hz), 1.65-1.58 (m, 1H), 1.50-1.45 (m, 2H), 0.95-0.88 (m, 6H).



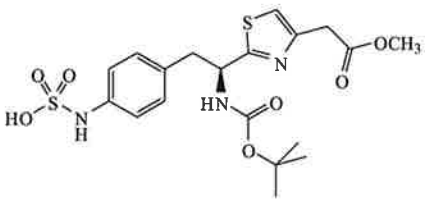
(S)-4-(2-(*tert*-Butoxycarbonylamino)-2-(4-(methoxymethyl)thiazol-2-yl)ethyl)-phenyl sulfamic acid: ^{1}H NMR (300 MHz, CD_3OD): δ 7.36 (s, 1H), 7.14-7.05 (m, 4H), 5.06 (dd, *J*=9.0, 5.1 Hz, 1H), 4.55 (s, 2H), 3.42 (s, 3H), 3.31-3.24 (m, 1H), 2.97 (dd, *J*=13.8, 9.9 Hz, 1H), 1.47-1.31 (m, 9H).



(*S*)-4-(2-*tert*-Butoxycarbonylamino)-2-(4-(2-hydroxymethyl)thiazol-2-yl)ethyl)phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.22-7.25 (m, 1H), 7.09-7.15 (m, 4H), 5.00-5.09 (m, 1H), 4.32-4.35 (m, 1H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.23-3.29 (m, 1H), 3.09-3.18 (m, 1H), 2.98 (t, *J* = 6.6 Hz, 2H), 1.41 (s, 9H).



~~(*S*)-4-(2-*tert*-Butoxycarbonylamino)-2-(4-(2-ethoxy-2-oxoethyl)-thiazole-2-yl)-ethyl)phenylsulfamic acid~~ (*S*)-(4-(2-*tert*-Butoxycarbonylamino)-2-(4-(2-ethoxy-2-oxoethyl)-thiazole-2-yl)-ethyl)phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.29 (s, 1H), 7.09-7.16 (m, 4H), 5.04-5.09 (m, 1H), 4.20 (q, *J* = 6.9 Hz, 2H), 3.84 (s, 2H), 3.30 (dd, *J* = 4.8 and 14.1 HZ, 1H), 2.97 (dd, *J* = 9.6 Hz and 13.8 Hz, 1H), 1.41 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H).



(*S*)-4-(2-(*tert*-Butoxycarbonylamino)-2-(4-(2-methoxy-2-oxoethyl)thiazol-2-yl)ethyl)phenylsulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.31 (s, 1H), 7.01-7.16 (m, 4H), 5.04-5.09 (m, 1H), 4.01 (s, 2H), 3.78 (s, 2H), 3.74 (s, 3H), 3.29 (dd, *J* = 5.1 and 13.8 Hz, 1H), 2.99 (dd, *J* = 9.3 and 13.8 Hz, 1H), 1.41 (s, 9H).

EXAMPLE 9

4-((*S*)-2-(2-(3-chlorophenyl)acetamido)-2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl)phenylsulfamic acid (23)

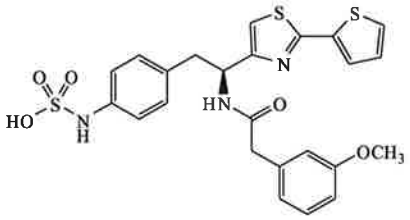
Preparation of (*S*)-2-(4-nitrophenyl)-1-[(thiophen-2-yl)thiazol-4-yl]ethanamine hydrobromide salt (22): A mixture of (*S*)-tert-butyl 4-bromo-1-(4-nitrophenyl)-3-oxobutan-2-ylcarbamate, 7, (7.74g, 20mmol), and thiophen-2-carbothioic acid amide (3.14g, 22mmol) in CH_3CN (200 mL) is refluxed for 5 hours. The reaction mixture is cooled to room temperature and diethyl ether (50 mL) is added to the solution. The precipitate which forms is collected by filtration. The solid is dried under vacuum to afford 7.14 g (87 % yield) of the desired product. ESI+ MS 332 (M+1).

Preparation of 2-(3-chlorophenyl)-*N*-{(*S*)-2-(4-nitrophenyl)-1-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}acetamide (23): To a solution of 2-(4-nitrophenyl)-1-(2-thiophene2-ylthiazol-4-yl)ethylamine, 22, (0.41 g, 1mmol) 3-chlorophenylacetic acid (0.170g, 1mmol) and 1-hydroxybenzotriazole (HOBt) (0.070g, 0.50mmol) in DMF (5 mL) at 0 °C, is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (0.190g, 1mmol) followed by triethylamine (0.42mL, 3mmol). The mixture is stirred at 0 °C for 30 minutes then at room temperature overnight. The reaction mixture is diluted with water and extracted with EtOAc. The combined organic phase is washed with 1 N aqueous HCl, 5 % aqueous $NaHCO_3$, water and brine, and dried over Na_2SO_4. The solvent is removed *in vacuo* to afford 0.290 g (60 % yield) of the desired product which is used without further purification. ESI- MS 482 (M-1).

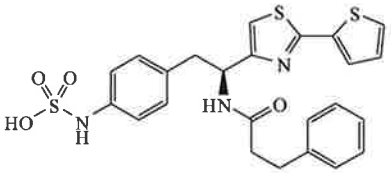
~~Preparation of {4-[2-(3-chlorophenyl)acetylamino]-2-(2-thiophen-2-ylthiazol-4-yl)ethyl]phenyl}sulfamic acid~~ (S)-(4-(2-(2-(3-chlorophenyl)acetylamino]-2-(2-(thiophen-2-ylthiazol-4-yl)ethyl]phenyl)sulfamic acid (24): 2-(3-chlorophenyl)-*N*-{(*S*)-2-(4-nitrophenyl)-1-[2-(thiophene2-yl)thiazol-4-yl]ethyl}acetamide, 23, (0.290 g) is dissolved in MeOH (4 mL). A catalytic amount of Pd/C (10% w/w) is added and the mixture is stirred under a hydrogen atmosphere 18 hours. The reaction mixture is filtered through a bed of CELITE™ and the solvent is removed under reduced pressure. The crude product is dissolved in pyridine (12 mL) and treated with SO_3-pyridine (0.157 g). The reaction is stirred at room temperature for 5 minutes after which a 7% solution of NH_4OH is added. The mixture is then concentrated and the resulting residue is purified by reverse phase chromatography to afford 0.078 g of the desired product as the ammonium salt. ^1H NMR (CD3OD) δ 7.61 (d, 1H, J =3.6Hz), 7.58 (d, 1H, J =

5.1Hz), 7.41-7.35 (m, 1H), 7.28-7.22 (m, 2H), 7.18-6.98 (m, 6H), 5.33 (t, 1H, J = 6.6Hz), 3.70 (d, 2H, J = 3.9Hz), 3.23 (1H, A of ABX, J = 6.6, 13.8Hz), 3.07 (1H, B of ABX, J = 8.1, 13.5Hz).

The following are non-limiting examples of compounds encompassed within the second aspect of Category V of the present disclosure.



~~4-((*S*)-2-(2-(3-Methoxyphenyl)acetamido)-2-(2-(thiophene2-yl)thiazol-4-yl)ethyl)-phenylsulfamic acid~~ 4-((*S*)-2-(2-(3-Methoxyphenyl)acetamido)-2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl)-phenylsulfamic acid: ^{1}H NMR (CD3OD) δ 8.35 (d, 1H, J = 8.7Hz), 7.61-7.57 (m, 2H), 7.25-7.20 (m, 2H), 7.25-7.20 (m, 2H), 7.09 (s, 1H), 7.05 (d, 2H, J = 4.2Hz), 6.99 (d, 1H, J = 8.7Hz), 6.81 (d, 1H, J = 7.8Hz), 6.77 (s, 1H), 5.30-5.28 (m, 1H), 3.76 (s, 3H), 3.51 (s, 2H), 3.20 (1H, A of ABX, J = 6.3, 13.6Hz), 3.06 (1H, B of ABX, J = 8.1, 13.8Hz).

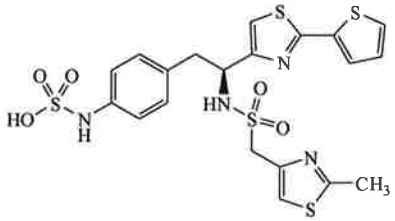


~~4-{(*S*)-2-(3-Phenylpropanamido)-2-[2-(thiophene2-yl)thiazol-4-yl]ethyl}-phenylsulfamic acid~~ 4-{(*S*)-2-(3-Phenylpropanamido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}-phenylsulfamic acid: ^{1}H NMR (CD3OD) δ 8.30 (d, 1H, J = 9Hz), 7.61-7.56 (m, 2H), 7.26-7.14 (m, 7H), 7.12 (d, 1H, J = 1.5Hz), 7.09 (d, 1H, J = 2.1Hz), 6.89 (s, 1H), 5.28-5.26 (m, 1H), 3.18 (1H, A of ABX, J = 6.2, 13.8Hz), 2.96 (1H, B of ABX, J = 8.4, 13.6Hz).



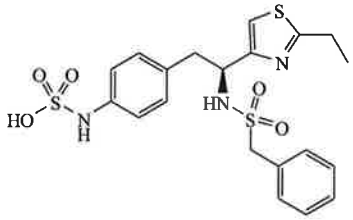
~~4-{(*S*)-2-(3-(3-Chlorophenyl)propanamido)-2-[2-(thiophene2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid~~ 4-{(*S*)-2-(3-(3-Chlorophenyl)propanamido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid: ^{1}H NMR (CD_3OD) δ 7.61-7.56 (m, 3H), 7.22-7.14 (m, 6H), 7.08 (d, 1H), 7.00 (d, 1H, J = 77.5Hz), 6.870 (s, 1H), 5.25 (t, 1H, J = 7.8Hz), 3.18 (1H, A of ABX, J = 6.6, 13.8Hz), 2.97 (1H, B of ABX, J = 7.8, 13.8Hz), 2.87 (t, 2H, J = 7.5Hz), 2.51 (t, 2H, J = 7.2Hz).

Preparation of (2-methylthiazol-4-yl)methanesulfonyl chloride (41): Sodium (2-methylthiazol-4-yl)methanesulfonate, 40, (357 mg, 1.66 mmol) is dissolved in phosphorous oxychloride (6 mL) and is treated with phosphorous pentachloride (345 mg, 1.66 mmol). The reaction mixture is stirred at 50 °C for 3 hours, then allowed to cool to room temperature. The solvent is removed under reduced pressure and the residue is re-dissolved in CH_2Cl_2 (40 mL) and is washed with sat. $NaHCO_3$ and brine. The organic layer is dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to afford 0.095 g of the desired product as a brown oil. LC/MS ESI+ 211 (M+1). Intermediates are obtained in sufficient purity to be carried forward according to Scheme IX without the need for further purification.

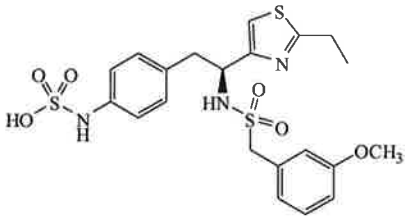


~~4-{(S)-2-[(2-methylthiazol-4-yl)methylsulfonamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid~~ (*S*)-(4-(2-((2-Methylthiazol-4-yl)methylsulfonamido)-2-(2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl)phenyl)sulfamic acid: ^{1}H NMR (CD_3OD): δ 7.71-7.66 (m, 2H), 7.27-7.10 (m, 7H), 4.87 (t, 1H, *J*=7.3 Hz), 4.30-4.16 (q, 2H, *J*=13.2 Hz), 3.34-3.13 (m, 2H), 2.70 (s, 3H).

The following are non-limiting examples of compounds encompassed within Category VIII of the present disclosure.

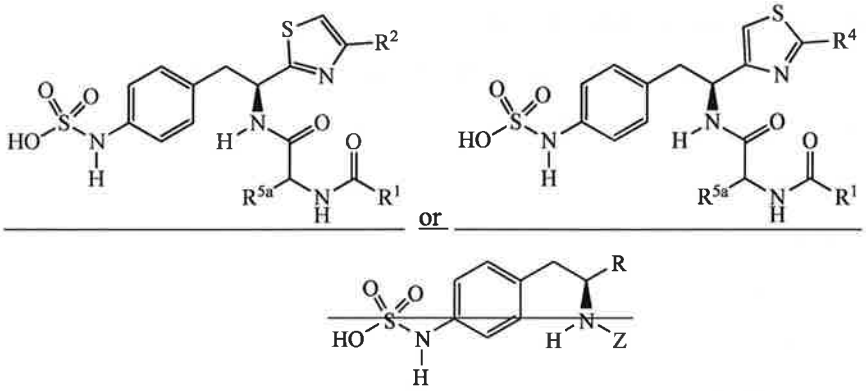


~~{4-(*S*)-[2-Phenylmethanesulfonylamino-2-(2-ethylthiazol-4-yl)ethyl]phenyl}-sulfamic acid~~ *S*)-(4-(2-(2-Ethylthiazol-4-yl)-2-((3-ethoxyphenyl)methylsulfonamido)ethyl)-phenyl)sulfamic acid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.27–7.32 (m, 3H), 7.16-7.20 (m, 3H), 7.05-7.6 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 4.70 (t, *J* = 9.0 Hz, 1H), 3.91-4.02 (m, 2H), 2.95-3.18 (m, 4H), 1.41 (t, *J* = 7.5 Hz, 3H).

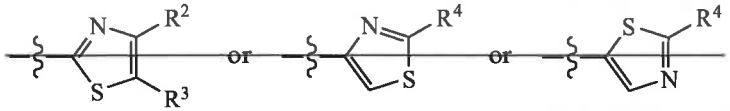


CLAIMS

1. The use of a compound for making a medicament for treating vascular leak syndrome, the compound having the formula:



~~wherein R is a substituted or unsubstituted thiazolyl unit having the formula:~~



R^2, ~~R^3~~, and R^4 are each independently:

~~i)~~ ~~hydrogen;~~

i) ~~ii)~~ substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

~~iii) substituted or unsubstituted C_2-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkenyl;~~

~~iv) substituted or unsubstituted C_2-C_6 linear or C_3-C_6 branched alkynyl;~~

ii) ~~v)~~ substituted or unsubstituted phenyl ~~C_6 or C_{10} aryl~~; or

iii) ~~vi)~~ substituted or unsubstituted ~~C_1-C_9~~ heteroaryl;

wherein the substitutions are chosen from C_1-C_4 linear or branched alkyl, C_1-C_4 linear or branched alkoxy and halogen;

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic; or~~

~~viii) R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms; wherein from 1 to 3 atoms can optionally be heteroatoms chosen from oxygen, nitrogen, and sulfur;~~

~~Z is a unit having the formula:~~

~~$-(L)_n-R^1$~~

R^1 is chosen from:

~~i)~~ ~~hydrogen;~~

~~ii) hydroxyl;~~

~~iii) amino;~~

i) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

ii) ~~v)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkoxy;

~~vi) substituted or unsubstituted C_6 or C_{10} aryl;~~

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic rings; or~~

~~viii) substituted or unsubstituted C_1-C_9 heteroaryl rings;~~

~~L is a linking unit having the formula:~~

~~$-[Q]_y[C(R^{5a}R^{5b})]_x[Q^1]_z[C(R^{6a}R^{6b})]_w-$~~

~~Q and Q^1 are each independently:~~

~~i) C(O) ;~~

~~ii) NH ;~~

~~iii) C(O)NH ;~~

~~iv) NHC(O) ;~~

~~v) NHC(O)NH ;~~

~~vi) NHC(O)O ;~~

~~vii) C(O)O ;~~

~~viii) C(O)NHC(O) ;~~

~~ix) O ;~~

~~x) S ;~~

~~xi) SO_2 ;~~

~~xii) C(=NH) ;~~

~~xiii) C(=NH)NH ;~~

~~xiv) NHC(=NH) ; or~~

~~xv) NHC(=NH)NH ;~~

R^{5a} is ~~and R^{5b} are each independently~~:

i) hydrogen;

~~ii) hydroxy;~~

~~iii) halogen;~~

ii) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear or C_3-C_6 branched alkyl; or

iii) ~~v)~~ a unit having the formula:

~~$-[C(R^{7a}R^{7b})]_tR^8$~~

$-[C(R^{7a}H)]_tR^8$

R^{7a} is ~~and R^{7b} are each independently:~~

i) hydrogen; or

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

R^8 is:

i) hydrogen;

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

iii) phenyl ~~substituted or unsubstituted C_6 or C_{10} aryl~~;

~~iv) substituted or unsubstituted C_1-C_9 heteroaryl; or~~

~~v) substituted or unsubstituted C_1-C_9 heterocyclic;~~

~~R^{6a} and R^{6b} are each independently:~~

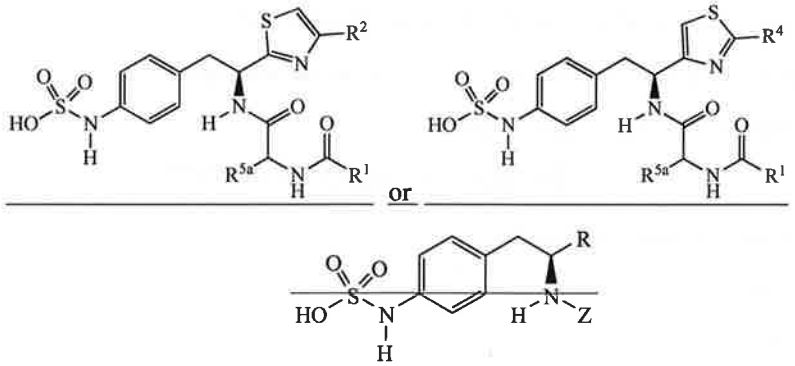
~~i) hydrogen; or~~

~~ii) C_1-C_4 linear or C_3-C_4 branched alkyl;~~

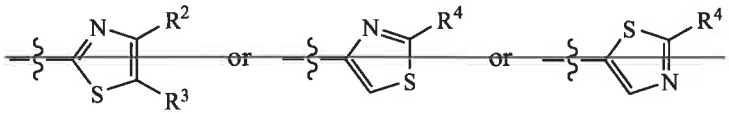
the index ~~n is 0 or 1; the indices~~ t is, ~~w and x are each independently from~~ 0 to 4~~; the indices y and z are each independently 0 or 1~~; or

a pharmaceutically acceptable salt thereof.

2. The use of a compound for making a medicament for treating vascular leakage in a subject having an inflammatory disease, the compound having the formula:



~~wherein R is a substituted or unsubstituted thiazolyl unit having the formula:~~



R^2, ~~R^3~~, and R^4 are each independently:

~~i) hydrogen;~~

i) ~~ii)~~ substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

~~iii) substituted or unsubstituted C_2-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkenyl;~~

~~iv) substituted or unsubstituted C_2-C_6 linear or C_3-C_6 branched alkynyl;~~

ii) ~~v)~~ substituted or unsubstituted phenyl ~~C_6 or C_{10} aryl~~; or

iii) ~~vi)~~ substituted or unsubstituted ~~C_1-C_9~~ heteroaryl;

wherein the substitutions are chosen from C_1-C_4 linear or branched alkyl, C_1-C_4 linear or branched alkoxy and halogen;

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic; or~~

viii) R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms; wherein from 1 to 3 atoms can optionally be heteroatoms chosen from oxygen, nitrogen, and sulfur;

Z is a unit having the formula:

$$-(L)_n-R^1$$

R^1 is chosen from:

i) hydrogen;

ii) hydroxyl;

iii) amino;

i) iv) substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

or

ii) v) substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkoxy;

vi) substituted or unsubstituted C_6 or C_{10} aryl;

vii) substituted or unsubstituted C_1-C_9 heterocyclic rings; or

viii) substituted or unsubstituted C_1-C_9 heteroaryl rings;

L is a linking unit having the formula:

$$-[Q]_y[C(R^{5a}R^{5b})]_x[Q^1]_z[C(R^{6a}R^{6b})]_w-$$

Q and Q^1 are each independently:

i) -C(O) ;

ii) -NH ;

iii) -C(O)NH ;

iv) -NHC(O) ;

v) -NHC(O)NH ;

vi) -NHC(O)O ;

vii) -C(O)O ;

viii) -C(O)NHC(O) ;

ix) -O ;

x) -S ;

xi) $-SO_2-$;

xii) -C(=NH) ;

xiii) -C(=NH)NH ;

xiv) -NHC(=NH) ; or

~~xv) —NHC(=NH)NH—;~~

R^{5a} is ~~and R^{5b} are each independently~~:

i) hydrogen;

~~ii) hydroxy;~~

~~iii) halogen;~~

ii) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear or C_3-C_6 branched alkyl; or

iii) ~~v)~~ a unit having the formula:

$$-[C(R^{7a}R^{7b})]_tR^8$$

$$-[C(R^{7a}H)]_tR^8$$

R^{7a} is ~~and R^{7b} are each independently:~~

i) hydrogen; or

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

R^8 is:

i) hydrogen;

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

iii) phenyl ~~substituted or unsubstituted C_6 or C_{10} aryl~~;

~~iv) substituted or unsubstituted C_1-C_9 heteroaryl; or~~

~~v) substituted or unsubstituted C_1-C_9 heterocyclic;~~

~~R^{6a} and R^{6b} are each independently:~~

~~i) hydrogen; or~~

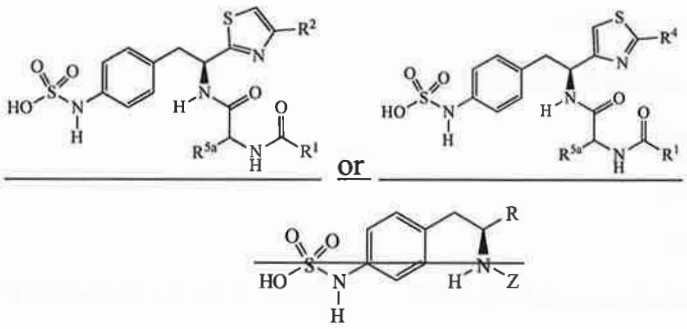
~~ii) C_1-C_4 linear or C_3-C_4 branched alkyl;~~

the index ~~n is 0 or 1; the indices~~ t is, ~~w and x are each independently from~~ 0 to 4~~; the indices y and z are each independently 0 or 1~~; or

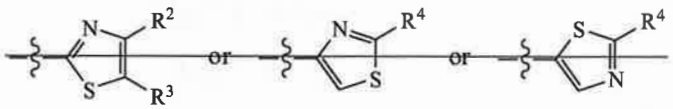
a pharmaceutically acceptable salt thereof.

3. The use according to Claim 2, wherein the inflammatory disease is lupus, sepsis, or inflammatory bowel disease.

4. The use of a compound for making a medicament for controlling vascular leak syndrome in a subject undergoing a treatment for cancer, the compound having the formula:



wherein R is a substituted or unsubstituted thiazolyl unit having the formula:



R^2, R^3, and R^4 are each independently:

i) hydrogen;

i) ii) substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

iii) substituted or unsubstituted C_2-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkenyl;

iv) substituted or unsubstituted C_2-C_6 linear or C_3-C_6 branched alkynyl;

ii) v) substituted or unsubstituted phenyl C_6 or C_{10} aryl; or

iii) vi) substituted or unsubstituted C_4-C_9 heteroaryl;

wherein the substitutions are chosen from C_1-C_4 linear or branched alkyl, C_1-C_4 linear or branched alkoxy and halogen;

vii) substituted or unsubstituted C_4-C_9 heterocyclic; or

viii) R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms; wherein from 1 to 3 atoms can optionally be heteroatoms chosen from oxygen, nitrogen, and sulfur;

Z is a unit having the formula:

$$-(L)_n-R^1$$

R^1 is chosen from:

i) hydrogen;

ii) hydroxyl;

iii) amino;

i) iv) substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

ii) v) substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkoxy;

vi) substituted or unsubstituted C_6 or C_{10} aryl;

vii) substituted or unsubstituted C_1-C_9 heterocyclic rings; or

viii) substituted or unsubstituted C_1-C_9 heteroaryl rings;

L is a linking unit having the formula:

$$-[Q]_y[C(R^{5a}R^{5b})]_x[Q^1]_z[C(R^{6a}R^{6b})]_w-$$

~~Q and Q^1 are each independently:~~

~~i) -C(O) ;~~

~~ii) -NH ;~~

~~iii) -C(O)NH ;~~

~~iv) -NHC(O) ;~~

~~v) -NHC(O)NH ;~~

~~vi) -NHC(O)O ;~~

~~vii) -C(O)O ;~~

~~viii) -C(O)NHC(O) ;~~

~~ix) -O ;~~

~~x) -S ;~~

~~xi) -SO_2 ;~~

~~xii) -C(=NH) ;~~

~~xiii) -C(=NH)NH ;~~

~~xiv) -NHC(=NH) ; or~~

~~xv) -NHC(=NH)NH ;~~

R^{5a} is ~~and R^{5b} are each independently~~:

i) hydrogen;

~~ii) hydroxy;~~

~~iii) halogen;~~

ii) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear or C_3-C_6 branched alkyl; or

iii) ~~v)~~ a unit having the formula:

~~-[C($R^{7a}R^{7b}$)]$_t$$R^8$~~

-[C(R^{7a}H)]$_t$$R^8$

R^{7a} is ~~and R^{7b} are each independently:~~

i) hydrogen; or

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

R^8 is:

i) hydrogen;

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

iii) phenyl ~~substituted or unsubstituted C_6 or C_{10} aryl~~;

~~iv) substituted or unsubstituted C_1-C_9 heteroaryl; or~~

~~v)~~ ~~substituted or unsubstituted C_1-C_9 heterocyclic;~~

~~R^{6a} and R^{6b} are each independently:~~

~~i)~~ ~~hydrogen; or~~

~~ii)~~ ~~C_1-C_4 linear or C_3-C_4 branched alkyl;~~

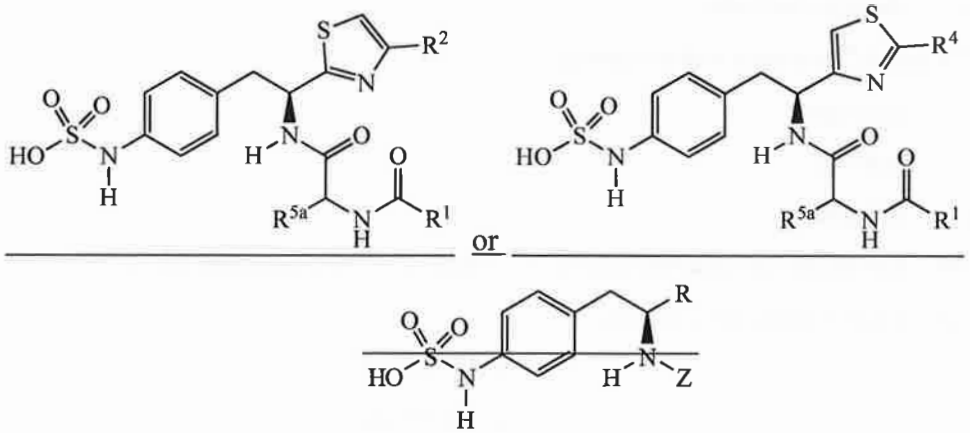
the index ~~n is 0 or 1; the indices~~ t is~~, w and x are each independently from~~ 0 to 4~~; the indices y and z are each independently 0 or 1~~; or

a pharmaceutically acceptable salt thereof.

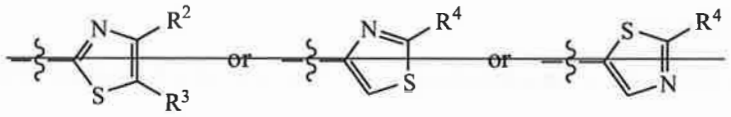
5. The use according to Claim 4, wherein the cancer is renal cell carcinoma or malignant melanoma.

6. The use according to Claim 4, wherein the cancer is medulloblastoma, ependymoma, ogliodendroglioma, pilocytic asrocytoma, diffuse astrocytoma, anaplasic astrocytoma, or glioblastoma.

7. The use of a compound for making a medicament for stabilizing the vasculature of a subject prior to the onset of or during the course of a cancer treatment, the compound having the formula:



~~wherein R is a substituted or unsubstituted thiazolyl unit having the formula:~~



R^2~~,~~ ~~R^3~~,~~ and R^4 are each independently:

~~i)~~ ~~hydrogen;~~

i) ~~ii)~~ substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

~~iii)~~ ~~substituted or unsubstituted C_2-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkenyl;~~

~~iv)~~ ~~substituted or unsubstituted C_2-C_6 linear or C_3-C_6 branched alkynyl;~~

ii) ~~v)~~ substituted or unsubstituted phenyl ~~C_6 or C_{10} aryl~~; or

iii) ~~vi)~~ substituted or unsubstituted ~~C_1-C_9~~ heteroaryl;

wherein the substitutions are chosen from C_1-C_4 linear or branched alkyl, C_1-C_4 linear or branched alkoxy and halogen;

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic; or~~

~~viii) R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms; wherein from 1 to 3 atoms can optionally be heteroatoms chosen from oxygen, nitrogen, and sulfur;~~

~~Z is a unit having the formula:~~

~~$-(L)_n-R^1$~~

R^1 is chosen from:

~~i) hydrogen;~~

~~ii) hydroxyl;~~

~~iii) amino;~~

i) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

ii) ~~v)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkoxy;

~~vi) substituted or unsubstituted C_6 or C_{10} aryl;~~

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic rings; or~~

~~viii) substituted or unsubstituted C_1-C_9 heteroaryl rings;~~

~~L is a linking unit having the formula:~~

~~$-[Q]_y[C(R^{5a}R^{5b})]_x[Q^1]_z[C(R^{6a}R^{6b})]_w-$~~

~~Q and Q^1 are each independently:~~

~~i) -C(O)-;~~

~~ii) -NH-;~~

~~iii) -C(O)NH-;~~

~~iv) -NHC(O)-;~~

~~v) -NHC(O)NH-;~~

~~vi) -NHC(O)O-;~~

~~vii) -C(O)O-;~~

~~viii) -C(O)NHC(O)-;~~

~~ix) -O-;~~

~~x) -S-;~~

~~xi) -SO_2-;~~

~~xii) -C(=NH)-;~~

~~xiii) —C(=NH)NH—;~~

~~xiv) —NHC(=NH)—; or~~

~~xv) —NHC(=NH)NH—;~~

R^{5a} is ~~and R^{5b} are each independently~~:

i) hydrogen;

~~ii) hydroxy;~~

~~iii) halogen;~~

ii) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear or C_3-C_6 branched alkyl; or

iii) ~~v)~~ a unit having the formula:

$$-[C(R^{7a}R^{7b})]_tR^8$$

$$-[C(R^{7a}H)]_tR^8$$

R^{7a} is ~~and R^{7b} are each independently:~~

i) hydrogen; or

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

R^8 is:

i) hydrogen;

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

iii) phenyl ~~substituted or unsubstituted C_6 or C_{10} aryl~~;

~~iv) substituted or unsubstituted C_1-C_9 heteroaryl; or~~

~~v) substituted or unsubstituted C_1-C_9 heterocyclic;~~

~~R^{6a} and R^{6b} are each independently:~~

~~i) hydrogen; or~~

~~ii) C_1-C_4 linear or C_3-C_4 branched alkyl;~~

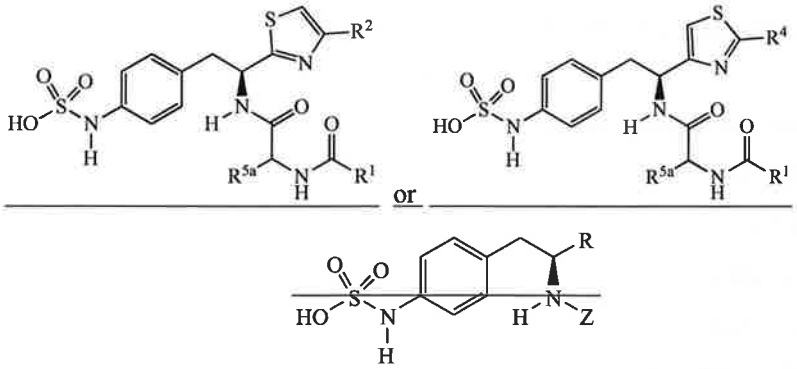
the index ~~n is 0 or 1; the indices~~ t is~~, w and x are each independently from~~ 0 to 4~~; the indices y and z are each independently 0 or 1~~; or

a pharmaceutically acceptable salt thereof.

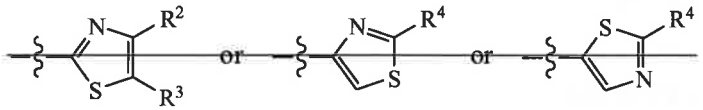
8. The use according to Claim 7, wherein the cancer is renal cell carcinoma or malignant melanoma.

9. The use according to Claim 7, wherein the cancer treatment comprises administering to the subject an effective amount of IL-2.

10. The use of a compound for making a medicament for determining the course of treatment for a subject with an disease or illness wherein vascular leakage is present, the compound having the formula:



~~wherein R is a substituted or unsubstituted thiazolyl unit having the formula:~~



R^2, ~~R^3~~, and R^4 are each independently:

~~i)~~ ~~hydrogen;~~

i) ~~ii)~~ substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

~~iii) substituted or unsubstituted C_2-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkenyl;~~

~~iv) substituted or unsubstituted C_2-C_6 linear or C_3-C_6 branched alkynyl;~~

ii) ~~v)~~ substituted or unsubstituted phenyl ~~C_6 or C_{10} aryl~~; or

iii) ~~vi)~~ substituted or unsubstituted ~~C_1-C_9~~ heteroaryl;

wherein the substitutions are chosen from C_1-C_4 linear or branched alkyl, C_1-C_4 linear or branched alkoxy and halogen;

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic; or~~

~~viii) R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms; wherein from 1 to 3 atoms can optionally be heteroatoms chosen from oxygen, nitrogen, and sulfur;~~

~~Z is a unit having the formula:~~

~~$-(L)_n-R^1$~~

R^1 is chosen from:

~~i)~~ ~~hydrogen;~~

~~ii) hydroxyl;~~

~~iii) amino;~~

i) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

ii) ~~v)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkoxy;

~~vi) substituted or unsubstituted C_6 or C_{10} aryl;~~

~~vii) substituted or unsubstituted C_4-C_9 heterocyclic rings; or~~

~~viii) substituted or unsubstituted C_1-C_6 heteroaryl rings;~~

~~L is a linking unit having the formula:~~

~~$-[Q]_y[C(R^{5a}R^{5b})]_x[Q^1]_z[C(R^{6a}R^{6b})]_w-$~~

~~Q and Q^1 are each independently:~~

~~i) -C(O)-;~~

~~ii) -NH-;~~

~~iii) -C(O)NH-;~~

~~iv) -NHC(O)-;~~

~~v) -NHC(O)NH-;~~

~~vi) -NHC(O)O-;~~

~~vii) -C(O)O-;~~

~~viii) -C(O)NHC(O)-;~~

~~ix) -O-;~~

~~x) -S-;~~

~~xi) -SO_2-;~~

~~xii) -C(=NH)-;~~

~~xiii) -C(=NH)NH-;~~

~~xiv) -NHC(=NH)-; or~~

~~xv) -NHC(=NH)NH-;~~

R^{5a} is ~~and R^{5b} are each independently~~:

i) hydrogen;

~~ii) hydroxy;~~

~~iii) halogen;~~

ii) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear or C_3-C_6 branched alkyl; or

iii) ~~v)~~ a unit having the formula:

~~$-[C(R^{7a}R^{7b})]_tR^8$~~

$-[C(R^{7a}H)]_tR^8$

R^{7a} is ~~and R^{7b} are each independently:~~

i) hydrogen; or

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

R^8 is:

i) hydrogen;

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

iii) phenyl ~~substituted or unsubstituted C_6 or C_{10} aryl~~;

~~iv) substituted or unsubstituted C_1-C_9 heteroaryl; or~~

~~v) substituted or unsubstituted C_1-C_9 heterocyclic;~~

~~R^{6a} and R^{6b} are each independently:~~

~~i) hydrogen; or~~

~~ii) C_1-C_4 linear or C_3-C_4 branched alkyl;~~

the index ~~n is 0 or 1; the indices~~ t is~~, w and x are each independently from~~ 0 to 4~~; the indices y and z are each independently 0 or 1~~; or

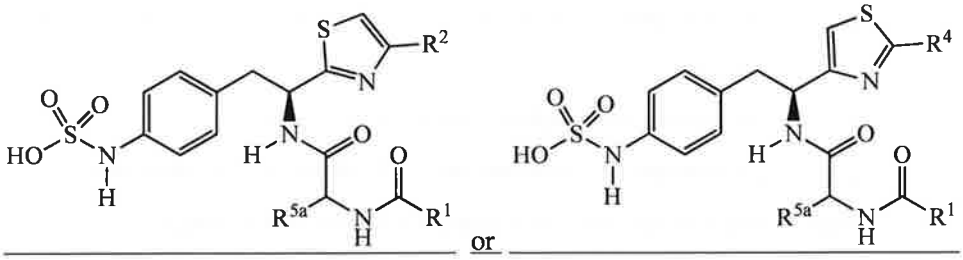
a pharmaceutically acceptable salt thereof,

wherein the subject being treated is monitored for the amount of angiopoietin-2 present during the course of treatment.

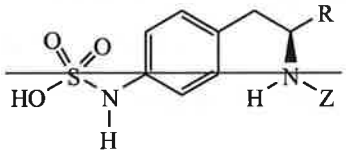
11. The use according to Claim 10, wherein the Angiopoietin-2 level is used to adjust the course of treatment or to establish a new course of treatment.

12. The use of a compound for making a medicament for determining the course of treatment for a subject suffering from vascular leak syndrome, the medicament comprising:

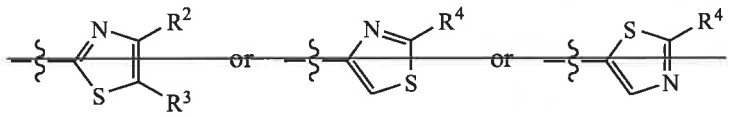
a) an effective amount of one or more compounds having the formula:



or



~~wherein R is a substituted or unsubstituted thiazolyl unit having the formula:~~



R^2, ~~R^3~~, and R^4 are each independently:

~~i) hydrogen;~~

i) ~~ii)~~ substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

~~iii) substituted or unsubstituted C_2-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkenyl;~~

~~iv) substituted or unsubstituted C_2-C_6 linear or C_3-C_6 branched alkynyl;~~

ii) ~~v)~~ substituted or unsubstituted phenyl ~~C_6 or C_{10} aryl~~; or

iii) ~~vi)~~ substituted or unsubstituted ~~C_1-C_9~~ heteroaryl;

wherein the substitutions are chosen from C_1-C_4 linear or branched alkyl, C_1-C_4 linear or branched alkoxy and halogen;

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic; or~~

~~viii) R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms; wherein from 1 to 3 atoms can optionally be heteroatoms chosen from oxygen, nitrogen, and sulfur;~~

~~Z is a unit having the formula:~~

~~$-(L)_n-R^1$~~

R^1 is chosen from:

~~i) hydrogen;~~

~~ii) hydroxyl;~~

~~iii) amino;~~

i) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

ii) ~~v)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkoxy;

~~vi) substituted or unsubstituted C_6 or C_{10} aryl;~~

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic rings; or~~

~~viii) substituted or unsubstituted C_1-C_9 heteroaryl rings;~~

~~L is a linking unit having the formula:~~

~~$-[Q]_y[C(R^{5a}R^{5b})]_x[Q^1]_z[C(R^{6a}R^{6b})]_w-$~~

~~Q and Q^1 are each independently:~~

~~i) -C(O)-;~~

~~ii) -NH-;~~

~~iii) -C(O)NH-;~~

~~iv) -NHC(O)-;~~

~~v) -NHC(O)NH-;~~

~~vi) -NHC(O)O-;~~

~~vii) —C(O)O—;~~

~~viii) —C(O)NHC(O)—;~~

~~ix) —O—;~~

~~x) —S—;~~

~~xi) —SO_2—;~~

~~xii) —C(=NH)—;~~

~~xiii) —C(=NH)NH—;~~

~~xiv) —NHC(=NH)—; or~~

~~xv) —NHC(=NH)NH—;~~

R^{5a} is ~~and R^{5b} are each independently~~:

i) hydrogen;

~~ii) hydroxy;~~

~~iii) halogen;~~

ii) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear or C_3-C_6 branched alkyl; or

iii) ~~v)~~ a unit having the formula:

~~—[C($R^{7a}R^{7b}$)]$_t$$R^8$~~

—[C(R^{7a}H)]$_t$$R^8$

R^{7a} is ~~and R^{7b} are each independently:~~

i) hydrogen; or

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

R^8 is:

i) hydrogen;

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

iii) phenyl ~~substituted or unsubstituted C_6 or C_{10} aryl~~;

~~iv) substituted or unsubstituted C_1-C_9 heteroaryl; or~~

~~v) substituted or unsubstituted C_1-C_9 heterocyclic;~~

~~R^{6a} and R^{6b} are each independently:~~

~~i) hydrogen; or~~

~~ii) C_1-C_4 linear or C_3-C_4 branched alkyl;~~

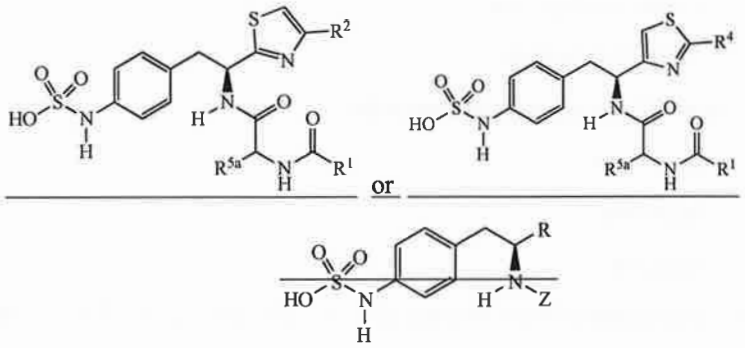
the index ~~n is 0 or 1; the indices~~ t is~~, w and x are each independently from~~ 0 to 4~~; the indices y and z are each independently 0 or 1~~; or

a pharmaceutically acceptable salt thereof; and

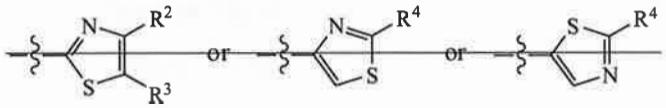
b) one or more adjunct ingredients;

wherein the medicament is adapted for use when the level of angiopoietin-2 in a subject is abnormal.

13. The use of a compound for making a medicament for providing vascular stabilization in a subject infected with a pathogen, a compound having the formula



~~wherein R is a substituted or unsubstituted thiazolyl unit having the formula:~~



R^2~~,~~ ~~R^3~~,~~ and R^4 are each independently:

~~i)~~ ~~hydrogen;~~

i) ~~ii)~~ substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

~~iii) substituted or unsubstituted C_2-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkenyl;~~

~~iv) substituted or unsubstituted C_2-C_6 linear or C_3-C_6 branched alkynyl;~~

ii) ~~v)~~ substituted or unsubstituted phenyl ~~C_6 or C_{10} aryl~~; or

iii) ~~vi)~~ substituted or unsubstituted ~~C_1-C_9~~ heteroaryl;

wherein the substitutions are chosen from C_1-C_4 linear or branched alkyl, C_1-C_4 linear or branched alkoxy and halogen;

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic; or~~

~~viii) R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms; wherein from 1 to 3 atoms can optionally be heteroatoms chosen from oxygen, nitrogen, and sulfur;~~

~~Z is a unit having the formula:~~

~~$-(L)_n-R^1$~~

R^1 is chosen from:

~~i)~~ ~~hydrogen;~~

~~ii)~~ ~~hydroxyl;~~

~~iii) amino;~~

i) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

ii) ~~v)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkoxy;

~~vi) substituted or unsubstituted C_6 or C_{10} aryl;~~

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic rings; or~~

~~viii) substituted or unsubstituted C_1-C_9 heteroaryl rings;~~

~~L is a linking unit having the formula:~~

~~$-[Q]_y[C(R^{5a}R^{5b})]_x[Q^1]_z[C(R^{6a}R^{6b})]_w-$~~

~~Q and Q^1 are each independently:~~

~~i) -C(O)-;~~

~~ii) -NH-;~~

~~iii) -C(O)NH-;~~

~~iv) -NHC(O)-;~~

~~v) -NHC(O)NH-;~~

~~vi) -NHC(O)O-;~~

~~vii) -C(O)O-;~~

~~viii) -C(O)NHC(O)-;~~

~~ix) -O-;~~

~~x) -S-;~~

~~xi) -SO_2-;~~

~~xii) -C(=NH)-;~~

~~xiii) -C(=NH)NH-;~~

~~xiv) -NHC(=NH)-; or~~

~~xv) -NHC(=NH)NH-;~~

R^{5a} is ~~and R^{5b} are each independently~~:

i) hydrogen;

~~ii) hydroxy;~~

~~iii) halogen;~~

ii) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear or C_3-C_6 branched alkyl; or

iii) ~~v)~~ a unit having the formula:

~~$-[C(R^{7a}R^{7b})]_tR^8$~~

$-[C(R^{7a}H)]_tR^8$

R^{7a} is ~~and R^{7b} are each independently:~~

i) hydrogen; or

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

R^8 is:

i) hydrogen;

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

iii) phenyl ~~substituted or unsubstituted C_6 or C_{10} aryl~~;

~~iv) substituted or unsubstituted C_1-C_9 heteroaryl; or~~

~~v) substituted or unsubstituted C_1-C_9 heterocyclic;~~

~~R^{6a} and R^{6b} are each independently:~~

~~i) hydrogen; or~~

~~ii) C_1-C_4 linear or C_3-C_4 branched alkyl;~~

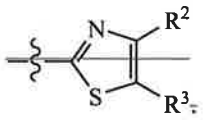
the index ~~n is 0 or 1; the indices~~ t is~~, w and x are each independently from~~ 0 to 4~~; the indices y and z are each independently 0 or 1~~; or

a pharmaceutically acceptable salt thereof.

14. The use according to Claim 13, wherein the pathogen is chosen from bacteria, viruses, yeasts, fungi, or protozoa.

15. The use as defined in Claim 13, further comprising administering to the subject an effective amount of an antibacterial agent, an antiviral agent, a fungicide, or combination thereof.

~~16. The use according to any one of Claim 1 to 15, wherein R has the formula:~~



~~17. The use according to any one of Claim 1 to 15, wherein R^2 and R^3 are each independently hydrogen or substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl.~~

~~18~~16. The use according to any of Claim 1 to 15, wherein R^2 is chosen from methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *iso*-butyl, *sec*-butyl, and *tert*-butyl; and R^3 is hydrogen.

~~19~~17. The use according to any of Claim 1 to 15, wherein R^2 is methyl or ethyl.

~~20. The use according to any one of Claim 1 to 15, wherein R^2 is an alkyl unit wherein one or more hydrogen atoms are substituted with one or more substitutions chosen from:~~

~~i) halogen;~~

~~ii) $N(R^{11})_2$; and~~

~~iii) OR^{11};~~

~~wherein each R^{11} is independently hydrogen or C_1-C_4 linear or C_3-C_4 branched alkyl.~~

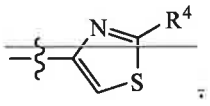
~~21~~18. The use according to any of Claim 1 to 15, wherein R^2 is ~~substituted or unsubstituted~~ phenyl ~~and R^3 is hydrogen~~.

~~22~~19. The use according to any of Claim 1 to 15, wherein R^2 is ~~substituted or unsubstituted~~ heteroaryl ~~and R^3 is hydrogen~~.

~~23. The use according to any one of Claim 1 to 15, wherein R^2 is a heteroaryl unit chosen from 1,2,3,4-tetrazol-1-yl ,1,2,3,4-tetrazol-5-yl, [1,2,3]triazol-4-yl, [1,2,3]triazol-5-yl, [1,2,4]triazol-4-yl, [1,2,4]triazol-5-yl, imidazol-2-yl, imidazol-4-yl, pyrrol-2-yl, pyrrol-3-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]oxadiazol-5-yl, [1,3,4]oxadiazol-2-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,2,4]thiadiazol-3-yl, [1,2,4]thiadiazol-5-yl, or [1,3,4]thiadiazol-2-yl.~~

~~24~~20. The use according to any of Claim 1 to 15, wherein R^2 is thiophen-2-yl or thiophen-3-yl.

~~25. The use according to any one of Claim 1 to 15, wherein R has the formula:~~



~~26. The use according to any one of Claim 1 to 15, wherein R^4 is hydrogen or substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl.~~

~~27~~21. The use according to any of Claim 1 to 15, wherein R^4 is chosen from methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *iso*-butyl, *sec*-butyl, and *tert*-butyl; and R^3 is hydrogen.

~~28~~22. The use according to any of Claim 1 to 15, wherein R^4 is methyl or ethyl.

~~29~~23. The use according to any of Claim 1 to 15, wherein R^4 is ~~substituted or unsubstituted~~ phenyl ~~and R^3 is hydrogen~~.

~~30. The use according to any one of Claim 1 to 15, wherein R^4 is an alkyl unit wherein one or more hydrogen atoms are substituted with one or more substitutions chosen from:~~

~~i) halogen;~~

~~ii) $N(R^{11})_2$; and~~

~~iii) OR^{11};~~

~~wherein each R^{11} is independently hydrogen or C_1-C_4 linear or C_3-C_4 branched alkyl.~~

~~31. The use according to any one of Claim 1 to 15, wherein R^4 is substituted or unsubstituted heteroaryl.~~

~~32. The use according to any one of Claim 1 to 15, wherein R^4 is a heteroaryl unit chosen from 1,2,3,4-tetrazol-1-yl ,1,2,3,4-tetrazol-5-yl, [1,2,3]triazol-4-yl, [1,2,3]triazol-5-yl, [1,2,4]triazol-4-yl, [1,2,4]triazol-5-yl, imidazol-2-yl, imidazol-4-yl, pyrrol-2-yl, pyrrol-3-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-~~

~~yl, isoxazol-5-yl, [1,2,4]oxadiazol-3-yl, [1,2,4]oxadiazol-5-yl, [1,3,4]oxadiazol-2-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, [1,2,4]thiadiazol-3-yl, [1,2,4]thiadiazol-5-yl, and [1,3,4]thiadiazol-2-yl.~~

~~33~~24. The use according to any of Claim 1 to 15, wherein R^4 is thiophen-2-yl or thiophen-3-yl.

~~34~~25. The use according to any of Claim 1 to 15, wherein R^1 is ~~hydrogen~~, methyl, methoxy, ~~ethyl,~~ *tert*-butyl, or *tert*-butoxy ~~methyl substituted with phenyl~~.

~~35. The use according to any one of Claim 1 to 15, wherein L has the formula:~~

~~$C(O)[C(R^{5a}R^{5b})]_xNHC(O)$~~

~~R^{5a} is hydrogen, substituted or unsubstituted phenyl, and substituted or unsubstituted heteroaryl; the index x is 1 or 2.~~

~~36. The use according to any one of Claim 1 to 15, wherein R^{5a} has the formula:~~

~~$[C(R^{7a}R^{7b})]_wR^8$~~

~~each R^{7a} is independently hydrogen, methyl, or ethyl; each R^{7b} is hydrogen; R^8 is hydrogen, substituted or unsubstituted C_1-C_4 linear, C_3-C_4 branched, or C_3-C_4 cyclic alkyl, or substituted or unsubstituted phenyl, wherein the substitutions are chosen from one or more hydroxy, halogen, or C_1-C_4 alkyl; R^{5b} is hydrogen; the index w is 1 or 2.~~

~~37. The use according to any one of Claim 1 to 15, wherein L has the formula chosen from:~~

~~i) $C(O)[C(R^{5a}H)]NHC(O)O$;~~

~~ii) $C(O)[C(R^{5a}H)][CH_2]NHC(O)O$;~~

~~ii) $C(O)[CH_2][C(R^{5a}H)]NHC(O)O$;~~

~~iv) $C(O)[C(R^{5a}H)]NHC(O)$;~~

~~v) $C(O)[C(R^{5a}H)][CH_2]NHC(O)$; or~~

vi) —C(O)[CH_2][C(R^{5a}H)]NHC(O)—;

wherein R^{5a} is:

i) hydrogen;

ii) methyl;

iii) ethyl;

iv) isopropyl;

v) phenyl;

vi) benzyl;

vii) 4-hydroxybenzyl;

viii) hydroxymethyl; or

ix) 1-hydroxyethyl.

38. The use according to any one of Claim 1 to 15, wherein R^1 is chosen from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, and 3,5-dimethoxyphenyl.

39. The use according to any one of Claim 1 to 15, wherein R^2 is methyl or ethyl, R^3 is hydrogen, and L has the formula —C(O)CH_2—.

40. The use according to any one of Claim 1 to 15, wherein R^2 is methyl or ethyl, R^3 is hydrogen, and L has the formula —C(O)CH_2CH_2—.

41. The use according to any one of Claim 1 to 15, wherein R^4 is methyl, ethyl, phenyl, thiophen-2-yl, thiazol-2-yl, oxazol-2-yl, and isoxazol-3-yl; and L has the formula —C(O)CH_2—.

42. The use according to any one of Claim 1 to 15, wherein R^4 is methyl, ethyl, phenyl, thiophen-2-yl, thiazol-2-yl, oxazol-2-yl, and isoxazol-3-yl; and L has the formula $-C(O)CH_2CH_2-$.

43. The use according to any one of Claim 1 to 15, wherein R^1 is a substituted or unsubstituted heteroaryl unit, said substitutions chosen from:

i) C_1-C_6 linear, branched, and cyclic alkyl;

ii) substituted or unsubstituted phenyl and benzyl;

iii) substituted of unsubstituted heteroaryl;

iv) $C(O)R^9$; or

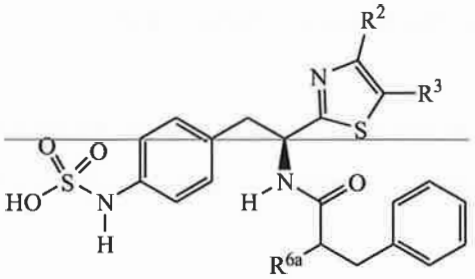
v) $NHC(O)R^9$;

R^9 is C_1-C_6 linear or C_3-C_6 branched alkyl; C_1-C_6 linear or C_3-C_6 branched alkoxy; or $NHCH_2C(O)R^{10}$; R^{10} is chosen from hydrogen, methyl, ethyl, or *tert*-butyl.

44. The use according to any one of Claim 1 to 15, wherein R^1 is a heteroaryl unit substituted by an alkyl unit chosen from methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *iso*-butyl, *sec*-butyl, or *tert*-butyl.

45. The use according to any one of Claim 1 to 15, wherein R^1 is a heteroaryl unit substituted by a carboxy unit having the formula $NHC(O)R^9$; R^9 is chosen from methyl, methoxy, ethyl, ethoxy, *tert*-butyl, and *tert*-butoxy.

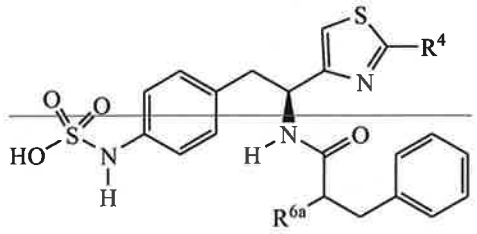
46. The use according to any one of Claim 1 to 15, wherein the compound has the formula:



wherein R^2 is methyl or ethyl, R^3 is hydrogen, R^{6a} is chosen from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-

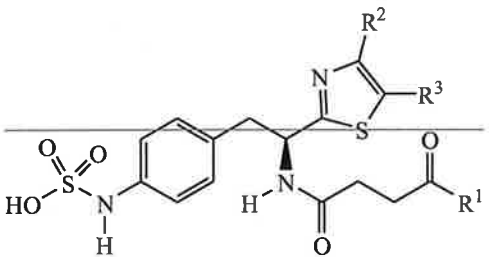
~~difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3-methyl-1,2,4-oxadiazol-5-yl, thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, or isoxazol-3-yl.~~

~~47. The use according to any one of Claim 1 to 15, wherein the compound has the formula:~~



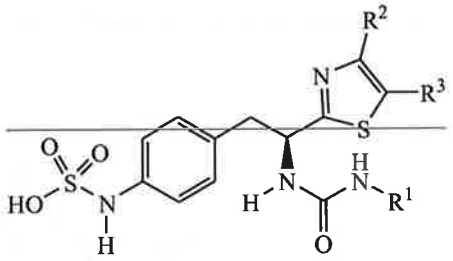
~~wherein R^4 is methyl, ethyl, phenyl, or thiophen-2-yl, R^{6a} is chosen from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3-methyl-1,2,4-oxadiazol-5-yl, thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, or isoxazol-3-yl.~~

~~48. The use according to any one of Claim 1 to 15, wherein the compound has the formula:~~



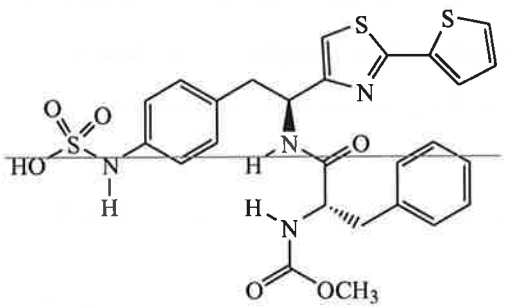
wherein R^2 is chosen from methyl, ethyl, phenyl, and thiophen-2-yl, R^3 is hydrogen or methyl; R^1 is chosen from phenyl, thiophen-2-yl, thiophen-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, and isoxazol-3-yl.

49. The use according to any one of Claim 1 to 15, wherein the compound has the formula:



wherein R^2 and R^3 are each independently hydrogen, methyl or ethyl; R^1 is chosen from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, and 3,5-dimethoxyphenyl.

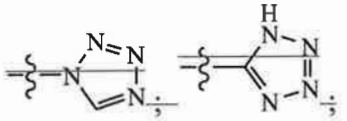
50. The use according to any one of Claim 1 to 15, wherein the compound has the formula:



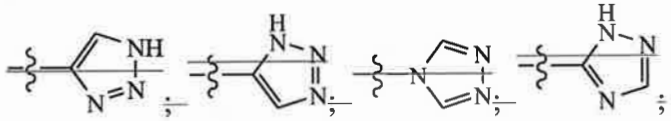
or the ammonium salt thereof.

51. The use according to any one of Claim 1 to 15, wherein R^1 is a substituted or unsubstituted heteroaryl unit chosen from:

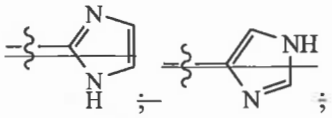
i) 1,2,3,4-tetrazol-1-yl and 1,2,3,4-tetrazol-5-yl having the respective formulae:



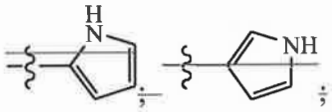
ii) [1,2,3]triazol-4-yl, [1,2,3]triazol-5-yl, [1,2,4]triazol-4-yl, and [1,2,4]triazol-5-yl having the respective formulae:



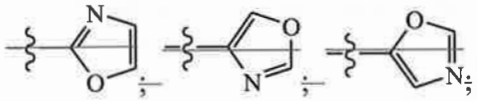
iii) imidazol-2-yl and imidazol-4-yl having the respective formulae:



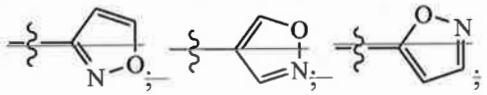
iv) pyrrol-2-yl and pyrrol-3-yl having the respective formulae:



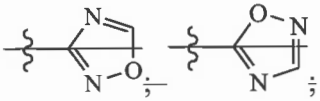
v) oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl having the respective formulae:



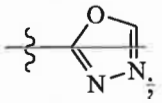
vi) isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl having the respective formulae:



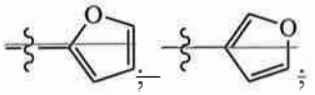
vii) [1,2,4]oxadiazol-3-yl and [1,2,4]oxadiazol-5-yl having the respective formulae:



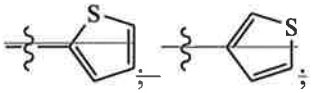
viii) [1,3,4]oxadiazol-2-yl having the formula:



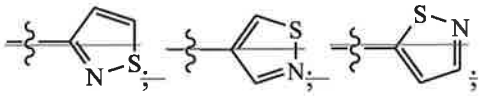
ix) furan-2-yl and furan-3-yl having the respective formulae:



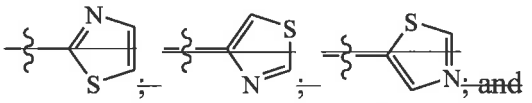
x) thiophen-2-yl and thiophen-3-yl having the respective formulae:



xi) isothiazol-3-yl, isothiazol-4-yl and isothiazol-5-yl having the respective formulae:

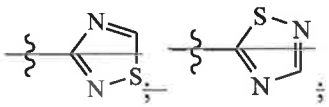


xii) thiazol-2-yl, thiazol-4-yl and thiazol-5-yl having the respective formulae:



; and

xiii) [1,2,4]thiadiazol-3-yl and [1,2,4]thiadiazol-5-yl having the respective formulae:



said heteroaryl unit substitutions chosen from:

i) C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 alkyl;

ii) substituted or unsubstituted phenyl and benzyl;

iii) substituted of unsubstituted heteroaryl;

iv) $C(O)R^9$; and

v) $NHC(O)R^9$;

R^9 is C_1-C_6 linear and C_3-C_6 branched alkyl; C_1-C_6 linear and C_3-C_4 branched alkoxy; or $NHCH_2C(O)R^{10}$; R^{10} is chosen from hydrogen, methyl, ethyl, and *tert*-butyl;

R^4 is a unit chosen from:

i) hydrogen;

ii) substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

iii) substituted or unsubstituted C_2-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkenyl;

iv) substituted or unsubstituted C_2-C_6 linear or C_3-C_6 branched alkynyl;

v) substituted or unsubstituted C_6 or C_{10} aryl;

vi) substituted or unsubstituted C_1-C_9 heteroaryl;

vii) substituted or unsubstituted C_1-C_9 heterocyclic.

5226. The use according to any of Claim 1 to 15, wherein the compound is chosen from:

(*S*)-4-[2-Benzamido-2-(4-ethylthiazol-2-yl)ethyl]phenylsulfamic acid;

(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(2-fluorophenyl)acetamido]ethyl}phenyl-sulfamic acid;

(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-fluorophenyl)acetamido)ethyl)phenylsulfamic acid;

(*S*)-4-(2-(2-(2,3-Difluorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid;

(*S*)-4-(2-(2-(3,4-Difluorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid;

(*S*)-4-(2-(2-(2-Chlorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenylsulfamic acid;

(*S*)-4-(2-(2-(3-Chlorophenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid;

(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-hydroxyphenyl)acetamido)ethyl)phenyl-sulfamic acid;

(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(2-methoxyphenyl)acetamido)ethyl)phenyl-sulfamic acid;

(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(2-(3-methoxyphenyl)acetamido)ethyl)phenyl-sulfamic acid;

(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-phenylpropanamido)ethyl)phenylsulfamic acid;

(*S*)-4-(2-(2-(3,4-Dimethoxyphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)-phenylsulfamic acid;

(*S*)-4-(2-(2-(2,3-Dimethoxyphenyl)acetamido)-2-(4-ethylthiazol-2-yl)ethyl)-phenylsulfamic acid;

(*S*)-4-(2-(3-(3-Chlorophenyl)propanamido)-2-(4-ethylthiazol-2-yl)ethyl)phenyl-sulfamic acid;

(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(2-methoxyphenyl)propanamido)ethyl)phenyl-sulfamic acid;

(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(3-methoxyphenyl)propanamido)ethyl)phenylsulfamic acid;

(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(3-(4-methoxyphenyl)propanamido)ethyl)phenyl-sulfamic acid;

(*S*)-4-{2-[2-(4-Ethyl-2,3-dioxopiperazin-1-yl)acetamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;

(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetamide]ethyl}phenylsulfamic acid;

(*S*)-4-[2-(Benzo[*d*][1,3]dioxole-5-carboxamido)-2-(4-ethylthiazol-2-yl)ethyl]-phenylsulfamic acid;

4-((*S*)-2-(2-(2-Chlorophenyl)acetamido)-2-(2-(thiophene2-yl)thiazol-4-yl)ethyl)-phenylsulfamic acid;

4-((*S*)-2-(2-(3-Methoxyphenyl)acetamido)-2-(2-(thiophene2-yl)thiazol-4-yl)ethyl)-phenylsulfamic acid;

4-{(*S*)-2-(3-Phenylpropanamido)-2-[2-(thiophene2-yl)thiazol-4-yl]ethyl}phenyl-sulfamic acid;

4-{(*S*)-2-(3-(3-Chlorophenyl)propanamido)-2-[2-(thiophene2-yl)thiazol-4-yl]ethyl}-phenylsulfamic acid;

4-{(*S*)-2-[2-(3-Fluorophenyl)acetamide]-2-[2-(thiophene2-yl)thiazol-4-yl]ethyl}-phenylsulfamic acid;

(*S*)-4-{2-[2-(2,5-Dimethylthiazol-4-yl)acetamide]-2-(4-ethylthiazol-2-yl]ethyl}-phenylsulfamic acid;

(*S*)-4-{2-[2-(2,4-Dimethylthiazol-5-yl)acetamide]-2-(4-methylthiazol-2-ylethyl}-phenylsulfamic acid;

(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[3-(thiazol-2-yl)propanamido]ethyl}phenylsulfamic acid;

(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(4-ethylthiazol-2-yl)acetamide]ethyl}phenyl-sulfamic acid;

(*S*)-4-{2-[2-(3-Methyl-1,2,4-oxadiazol-5-yl)acetamide]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid;

4-{(*S*)-2-[2-(4-Ethyl-2,3-dioxopiperazin-1-yl)acetamide]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;

(*S*)-4-(2-(2,3-Diphenylpropanamido)-2-(4-ethylthiazol-2-yl)ethyl)phenylsulfamic acid;

(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(2-methoxyphenyl)-3-phenylpropanamido]-ethyl)phenylsulfamic acid;

(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(3-fluorophenyl)-3-phenylpropanamido]-ethyl}phenylsulfamic acid;

(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(3-methoxyphenyl)-3-phenylpropanamido]-ethyl}phenylsulfamic acid;

4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[2-(3-methyl-1,2,4-oxadiazol-5-yl)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

(*S*)-4-[2-(4-Ethylthiazol-2-yl)-2-(4-oxo-4-phenylbutanamido)-ethyl]phenylsulfamic acid;

(*S*)-4-(2-(4-Ethylthiazol-2-yl)-2-(5-methyl-4-oxohexanamido)ethyl)phenylsulfamic acid;

(*S*)-4-{2-[4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;

(*S*)-4-{2-[4-(2,3-Dimethoxyphenyl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;

(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[4-oxo-4-(pyridin-2-yl)butanamido]ethyl}phenyl-sulfamic acid;

(S)-4-{2-[4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-4-oxobutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;

(*S*)-4-[2-(4-*tert*-Butoxy-4-oxobutanamido)-2-(4-ethylthiazol-2-yl)ethyl]phenyl-sulfamic acid;

(*S*)-4-[2-(4-Ethoxy-4-oxobutanamido)-2-(4-ethylthiazol-2-yl)ethyl]phenylsulfamic acid;

(S)-4-(2-(3-Benzylureido)-2-(4-ethylthiazol-2-yl)ethyl)phenylsulfamic acid;

4-{[(*S*)-2-(2-Ethylthiazol-4-yl)-2-(3-(*R*)-1methoxy-1-oxo-3-phenylpropan-2-yl)ureido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-(3-Benzylureido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;

4-(*S*)-[2-Phenylmethanesulfonylamino-2-(2-(thiophen-2-yl)thiazol-4-yl)ethyl]-phenylsulfamic acid;

4-{(S)-2-[(2-Methylthiazol-4-yl)methylsulfonamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;

{4-(*S*)-[2-Phenylmethanesulfonylamino-2-(2-ethylthiazol-4-yl)ethyl]phenyl}-sulfamic acid;

{4-(*S*)-[2-(3-Methoxyphenyl)methanesulfonylamino-2-(2-ethylthiazol-4-yl)ethyl]phenyl}sulfamic acid;

(*S*)-4-{[1-(2-Ethylthiazol-4-yl)-2-(4-sulfoaminophenyl)ethylsulfamoyl]methyl}-benzoic acid methyl ester;

(*S*)-4-[2-(2-Ethylthiazol-4-yl)-2-(1-methyl-1*H*-imidazol-4-sulfonamido)ethyl]-phenylsulfamic acid;

4-{(*S*)-2-[2-(Thiophen-2-yl)thiazol-4-yl]-2-(2,2,2-trifluoroethylsulfonamido)-ethyl}phenylsulfamic acid;

{4-(*S*)-[2-(Phenylethanesulfonylamino)-2-(2thiophen-2-ylthiazol-4-yl)ethyl]-phenyl}sulfamic acid;

{4-(*S*)-[3-(Phenylpropanesulfonylamino)-2-(2thiophen-2-ylthiazol-4-yl)ethyl]-phenyl}sulfamic acid;

(*S*)-{4-[2-(4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonylamino)-2-(2-thiophen-2-ylthiazol-4-yl)ethyl]phenyl}sulfamic acid;

4-{(*S*)-2-(4-Acetamidophenylsulfonamido)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;

4-{(S)-2-(2-cyclopropylthiazol-4-yl)-2-[4-(3-methoxyphenyl)-thiazol-2-ylamino]ethyl}phenylsulfamic acid;

(*S*)-4-(2-(4-((2-Methoxy-2-oxoethyl)carbamoyl)thiazole-5-ylamino)2-(2-ethylthiazole-4-yl)ethyl)phenylsulfamic acid;

4-((*S*)-2-(5-(1-*N*-(2-Methoxy-2-oxoethyl)-1-*H*-indol-3-yl)oxazole-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl))phenylsulfamic acid;

4-((S)-2-(5-(2-Methoxyphenyl)oxazol-2-ylamino)-2-(2-methylthiazol-4-yl)ethyl)-phenylsulfamic acid;

4-((*S*)-2-(5-((*S*)-1-(*tert*-Butoxycarbonyl)-2-phenylethyl)oxazole-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl)phenylsulfamic acid;

(*S*)-4-(2-(5-(4-Methoxycarbonyl)phenyl)oxazole-2-ylamino)2-(2-methylthiazole-4-yl)ethyl)phenylsulfamic acid;

(*S*)-4-(2-(5-(3-Methoxybenzyl)oxazole-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl)-phenylsulfamic acid;

(*S*)-4-(2-(2-Methylthiazole-4-yl)2-(5-phenyloxazole-2-ylamino)ethyl)phenyl-sulfamic acid;

4-((S)-2-(2-Cyclopropylthiazol-4-yl)-2-(4-(3-methoxyphenyl)thiazol-2-ylamino)-ethyl)phenylsulfamic acid;

(*S*)-4-(2-(2-cyclopropylthiazol-4-yl)-2-(4-(4-fluorophenyl)thiazol-2-ylamino)ethyl)-phenylsulfamic acid;

4-((*S*)-2-(2-cyclopropylthiazol-4-yl)-2-(4-(2-methoxyphenyl)thiazol-2-ylamino)-ethyl)phenylsulfamic acid;

4-((*S*)-2-(2-cyclopropylthiazol-4-yl)-2-(4-(2,4-difluorophenyl)thiazol-2-ylamino)-ethyl)phenylsulfamic acid;

(*S*)-4-(2-(4-(3-methoxybenzyl)thiazol-2-ylamino)-2-(2-cyclopropylthiazol-4-yl)ethyl)phenylsulfamic acid;

(*S*)-{5-[1-(2-Ethylthiazol-4-yl)-2-(4-sulfoaminophenyl)ethylamino]-2-methyl-2H-[1,2,4]triazole-3-yl}carbamic acid methyl ester;

4-{(S)-2-[4-(2-Methoxyphenyl)thiazol-2-ylamino)-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[5-(3-Methoxyphenyl)oxazole-2-ylamino]-2-(2-phenylthiazole-4-yl)ethyl}phenylsulfamic acid;

4-{(*S*)-2-[4-(2,4-Difluorophenyl)thiazol-2-ylamino]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;

(*S*)-4-{2-[4-(Ethoxycarbonyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}-phenylsulfamic acid;

(*S*)-4-{2-[4-(2-Ethoxy-2-oxoethyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid;

(*S*)-4-{2-[4-(4-Acetamidophenyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid;

(S)-4-[2-(4-Phenylthiazol-2-ylamino)-2-(2-phenylthiazol-4-yl)ethyl]phenylsulfamic acid;

(*S*)-4-{2-[4-(4-(Methoxycarbonyl)phenyl)thiazol-2-ylamino]-2-(2-phenylthiazol-4-yl)ethyl}phenylsulfamic acid;

4-{(S)-2-[4-(Ethoxycarbonyl)thiazol-2-ylamino]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;

(*S*)-4-[2-(4-(Methoxycarbonyl)thiazol-5-ylamino)-2-(2-phenylthiazole-4-yl)ethyl]-phenylsulfamic acid;

~~(*S*)-4-[2-(5-Phenyloxazole-2-ylamino)]-2-(2-phenylthiazole-4-yl)phenylsulfamic acid;~~

~~(*S*)-4-{2-[5-(4-Acetamidophenyl)oxazole-2-ylamino]-2-(2-phenylthiazole-4-yl)ethyl}phenylsufamic acid;~~

~~4-((*S*)-2-(5-(2,4-Difluorophenyl)oxazole-2-ylamino)-2-(2-phenylthiazole-4-yl)ethyl)phenylsulfamic acid;~~

~~4-{(*S*)-2-[5-(3-Methoxyphenyl)oxazol-2-ylamino]-2-[(2-thiophen-2-yl)thiazole-4-yl]ethyl}phenylsulfamic acid;~~

~~(*S*)-4-[2-(4,6-Dimethylpyrimidene-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl]-phenylsulfamic acid;~~

~~(*S*)-4-[2-(4-Hydroxy-6-methylpyrimidine-2-ylamino)-2-(2-methylthiazole-4-yl)ethyl]phenylsulfamic acid;~~

4-{(S)-2-[(S)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*R*)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;

{1-[1-(5-Ethylthiazol-2-yl)-(*S*)-2-(4-sulfoaminophenyl)ethylcarbamoyl]-(*S*)-2-phenylethyl}methyl carbamic acid *tert*-butyl ester;

{(*S*)-2-Phenyl-1-[1-(4-phenylthiazol-2-yl)-(*S*)-2-(4-sulfoaminophenyl)ethyl-carbamoyl]ethyl}carbamic acid *tert*-butyl ester;

4-{(*S*)-2-(*S*)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropaneamido-2-(2-phenylthiazole-4-yl)}phenylsulfamic acid;

4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenyl-propanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-(thiazol-2-yl)ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-(4-methylthiazol-2-yl)ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-(4-propylthiazol-2-yl)ethyl}phenylsulfamic acid;

4-{(*S*)-2-(4-*tert*-Butylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-(4-Cyclopropylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-(4-Cyclohexylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-(4,5-Dimethylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

~~4-{(*S*)-2-Phenyl-1-[1-(2-phenylthiazol-4-yl)-(*S*)-2-(4-sulfoaminophenyl)ethylcarbamoyl]ethyl}carbamic acid *tert*-butyl ester;~~

4-{(*S*)-2-(4-Ethyl-5-methylthiazol-2-yl)-2-[(S)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(S)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-[4-(2,2,2-trifluoroethyl)thiazol-2-yl]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-[4-(3,3,3-trifluoropropyl)thiazol-2-yl]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[4-(2,2-Difluorocyclopropyl)thiazol-2-yl]-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-[4-(methoxymethyl)thiazol-2-yl]ethyl}phenylsulfamic acid;

4-{(*S*)-2-(4-(Ethoxycarbonylamino)thiazol-2-yl)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-(5-phenylthiazol-2-yl))ethyl}phenylsulfamic acid;

4-{(*S*)-2-(4-*tert*-Butylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-(4-Ethyl-5-phenylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[4-(3,4-Dimethylphenyl)thiazol-2-yl]-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(S)-2-[4-(4-Chlorophenyl)thiazol-2-yl]-2-[(S)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-(4-phenylthiazol-2-yl)ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-[4-(thiophen-2-yl)thiazol-2-yl]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-[4-(thiophen-3-yl)thiazol-2-yl]ethyl}phenylsulfamic acid;

4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbinyl)-3-phenylpropion-amido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-(5,6-Dihydro-4*H*-cyclopenta[*d*]thiazol-2-yl)-2-[(*S*)-2-(methoxy-carbonyl)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-(4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-yl)ethyl}phenylsulfamic acid;

4-{(*S*)-2-[4-(5-Chlorothiophen-2-yl)thiazol-2-yl]-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Ethoxycarbonylamino)-3-phenylpropanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-(2-ethylthiazol-4-yl) ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-(2-methyl-thiazol-4-yl)ethyl}phenylsulfamic acid;

4-{(S)-2-(2-Ethylthiazole-4-yl)-2-[(S)-2-(methoxycarbonylamino)-3-phenylpropan-amido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-(2-Isopropylthiazol-4-yl)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenyl-propan-amido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-(2-Cyclopropylthiazol-4-yl)-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(S)-2-{2-[(4-Chlorophenylsulfonyl)methyl]thiazol-4-yl}-2-[(S)-2-(methoxy-carbonyl)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(S)-2-[2-(*tert*-Butylsulfonylmethyl)thiazol-4-yl]-2-[(S)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropionamido]-2-(2-phenyl-thiazole-4-yl)ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[2-(3-Chlorothiophen-2-yl)thiazol-4-yl]-2-[(*S*)-2-(methoxycarbonylamino)-3-phenylpropanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-[2-(3-methylthiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;

4-{[(*S*)-2-(2-(Furan-2-yl)thiazol-4-yl]-2-[(*S*)-2-(methoxycarbonylamino)-3-phenyl-propanamido]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-[2-(2-methyl-thiazole-4-yl)thiazol-4yl]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-(2-pyrazine-2-yl)thiazole-4-yl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonylamino)-3-phenylpropanamido]-2-[2-(6-methyl-pyridin-3-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;

4-[(*S*)-2-((*S*)-2-Acetamido-3-phenylpropanamido)-2-(4-ethylthiazol-2-yl)ethyl]-phenylsulfamic acid ;

4-[(*S*)-2-((*S*)-2-Acetamido-3-phenylpropanamido)-2-(4-*tert*-butylthiazol-2-yl)ethyl]-phenylsulfamic acid;

4-{(*S*)-2-((*S*)-2-Acetamido-3-phenylpropanamido)-2-[4-(thiophen-3-yl)thiazol-2-yl]ethyl)phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(*tert*-Butoxycarbonyl)-3-methylbutanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;

(*S*)-4-{2-[2-(*tert*-Butoxycarbonyl)acetamide]-2-(4-ethylthiazol-2-yl)ethyl}phenyl-sulfamic acid;

(*S*)-4-{2-(4-Ethylthiazol-2-yl)-2-[2-(methoxycarbonyl)acetamido]ethyl}phenyl-sulfamic acid;

4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonyl)-3-methylbutanamido]-ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(*tert*-Butoxycarbonyl)-4-methylpentanamido]-2-(4-ethylthiazol-2-yl)ethyl}phenylsulfamic acid;

4-{(*S*)-2-(4-Ethylthiazol-2-yl)-2-[(*S*)-2-(methoxycarbonyl)-4-methylpentanamido]ethyl}phenylsulfamic acid;

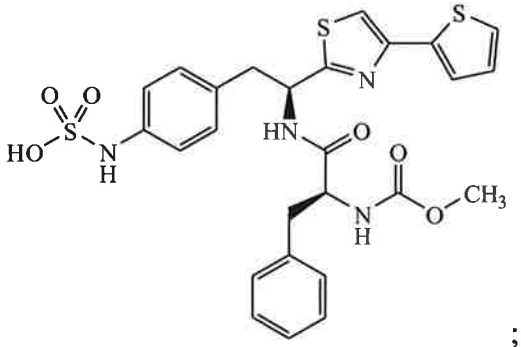
~~4-((*S*)-2-(4-Ethylthiazol-2-yl)-2-{(*S*)-2-[2-(methoxycarbonyl)acetamido]-3-phenylpropanamido}ethyl)phenylsulfamic acid;~~

4-{(*S*)-2-[(*S*)-2-(*tert*-Butoxycarbonyl)-4-methylpentanamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid;

4-{(*S*)-2-[(*S*)-2-(Methoxycarbonyl)-4-methylpentanamido]-2-[2-(thiophen-2-yl)thiazol-4-yl]ethyl}phenylsulfamic acid; and

(*S*)-4-{2-[2-(*tert*-Butoxycarbonyl)acetamide]-2-(4-ethylthiazol-2-yl)ethyl}-phenylsulfamic acid.

~~53~~27. The use according to any of Claim 1 to 15, wherein the compound has the formula:



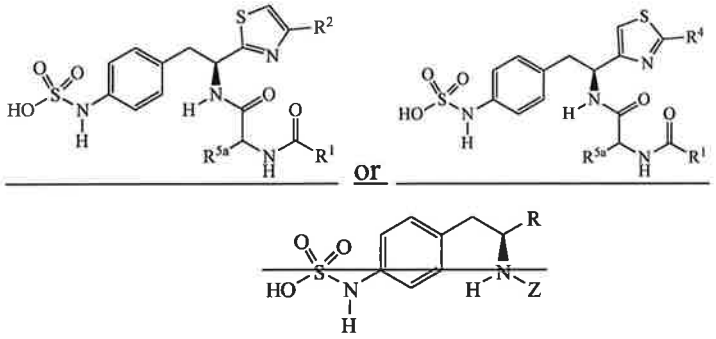
; and

pharmaceutically acceptable salts thereof.

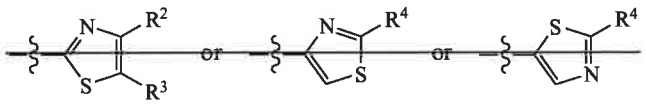
~~54~~28. The use according to any of Claim 1 to 15 and 16 to 53, wherein the compound is in the form of a salt of a cation chosen from ammonium, sodium, lithium, potassium, calcium, magnesium, bismuth, and lysine.

~~55~~29. A composition for providing vascular stabilization in a subject, comprising:

A) an effective amount of one or more compounds having the formula



~~wherein R is a substituted or unsubstituted thiazolyl unit having the formula:~~



R^2, ~~R^3~~, and R^4 are each independently:

~~i)~~ ~~hydrogen;~~

i) ~~ii)~~ substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

~~iii) substituted or unsubstituted C_2-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkenyl;~~

~~iv) substituted or unsubstituted C_2-C_6 linear or C_3-C_6 branched alkynyl;~~

ii) ~~v)~~ substituted or unsubstituted phenyl ~~C_6 or C_{10} aryl~~; or

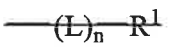
iii) ~~vi)~~ substituted or unsubstituted ~~C_1-C_9~~ heteroaryl;

wherein the substitutions are chosen from C_1-C_4 linear or branched alkyl, C_1-C_4 linear or branched alkoxy and halogen;

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic; or~~

~~viii) R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms; wherein from 1 to 3 atoms can optionally be heteroatoms chosen from oxygen, nitrogen, and sulfur;~~

~~Z is a unit having the formula:~~



R^1 is chosen from:

~~i)~~ ~~hydrogen;~~

~~ii) hydroxyl;~~

~~iii) amino;~~

i) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

ii) ~~v)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkoxy;

~~vi) substituted or unsubstituted C_6 or C_{10} aryl;~~

~~vii) substituted or unsubstituted C_4-C_9 heterocyclic rings; or~~

~~viii) substituted or unsubstituted C_1-C_9 heteroaryl rings;~~

~~L is a linking unit having the formula:~~

~~$-[Q]_y[C(R^{5a}R^{5b})]_x[Q^1]_z[C(R^{6a}R^{6b})]_w-$~~

~~Q and Q^1 are each independently:~~

~~i) -C(O)-;~~

~~ii) -NH-;~~

~~iii) -C(O)NH-;~~

~~iv) -NHC(O)-;~~

~~v) -NHC(O)NH-;~~

~~vi) -NHC(O)O-;~~

~~vii) -C(O)O-;~~

~~viii) -C(O)NHC(O)-;~~

~~ix) -O-;~~

~~x) -S-;~~

~~xi) -SO_2-;~~

~~xii) -C(=NH)-;~~

~~xiii) -C(=NH)NH-;~~

~~xiv) -NHC(=NH)-; or~~

~~xv) -NHC(=NH)NH-;~~

R^{5a} is ~~and R^{5b} are each independently~~:

i) hydrogen;

~~ii) hydroxy;~~

~~iii) halogen;~~

ii) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear or C_3-C_6 branched alkyl; or

iii) ~~v)~~ a unit having the formula:

~~$-[C(R^{7a}R^{7b})]_tR^8$~~

$-[C(R^{7a}H)]_tR^8$

R^{7a} is ~~and R^{7b} are each independently:~~

i) hydrogen; or

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

R^8 is:

i) hydrogen;

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

iii) phenyl ~~substituted or unsubstituted C_6 or C_{10} aryl~~;

~~iv) substituted or unsubstituted C_1-C_9 heteroaryl; or~~

~~v) substituted or unsubstituted C_1-C_9 heterocyclic;~~

~~R^{6a} and R^{6b} are each independently:~~

~~i) hydrogen; or~~

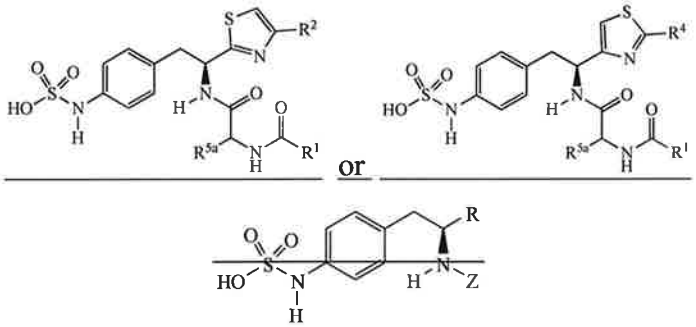
~~ii) C_1-C_4 linear or C_3-C_4 branched alkyl;~~

the index ~~n is 0 or 1; the indices~~ t is~~, w and x are each independently from~~ 0 to 4~~; the indices y and z are each independently 0 or 1~~; or

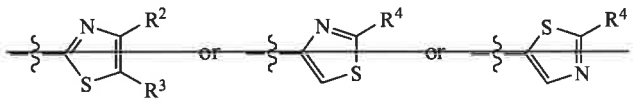
a pharmaceutically acceptable salt thereof; and

B) one or more pharmaceutically acceptable ingredients.

~~56~~30. A use of a compound for making a medicament for treating vascular leak syndrome, the compound having the formula:



~~wherein R is a substituted or unsubstituted thiazolyl unit having the formula:~~



R^2, ~~R^3~~, and R^4 are each independently:

~~i) hydrogen;~~

i) ~~ii)~~ substituted or unsubstituted C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

~~iii) substituted or unsubstituted C_2-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkenyl;~~

~~iv) substituted or unsubstituted C_2-C_6 linear or C_3-C_6 branched alkynyl;~~

ii) ~~v)~~ substituted or unsubstituted phenyl ~~C_6 or C_{10} aryl~~; or

iii) ~~vi)~~ substituted or unsubstituted ~~C_1-C_9~~ heteroaryl;

wherein the substitutions are chosen from C_1-C_4 linear or branched alkyl, C_1-C_4 linear or branched alkoxy and halogen;

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic; or~~

~~viii) R^2 and R^3 can be taken together to form a saturated or unsaturated ring having from 5 to 7 atoms; wherein from 1 to 3 atoms can optionally be heteroatoms chosen from oxygen, nitrogen, and sulfur;~~

~~Z is a unit having the formula:~~

~~$-(L)_n-R^1$~~

R^1 is chosen from:

~~i) hydrogen;~~

~~ii) hydroxyl;~~

~~iii) amino;~~

i) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl; or

ii) ~~v)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkoxy;

~~vi) substituted or unsubstituted C_6 or C_{10} aryl;~~

~~vii) substituted or unsubstituted C_1-C_9 heterocyclic rings; or~~

~~viii) substituted or unsubstituted C_1-C_9 heteroaryl rings;~~

~~L is a linking unit having the formula:~~

~~$-[Q]_y[C(R^{5a}R^{5b})]_x[Q^1]_z[C(R^{6a}R^{6b})]_w-$~~

~~Q and Q^1 are each independently:~~

~~i) -C(O)-;~~

~~ii) -NH-;~~

~~iii) -C(O)NH-;~~

~~iv) -NHC(O)-;~~

~~v) -NHC(O)NH-;~~

~~vi) -NHC(O)O-;~~

~~vii) -C(O)O-;~~

~~viii) -C(O)NHC(O)-;~~

~~ix) -O-;~~

~~x) -S-;~~

~~xi) $-SO_2-$;~~

~~xii) -C(=NH)-;~~

~~xiii) —C(=NH)NH—;~~

~~xiv) —NHC(=NH)—; or~~

~~xv) —NHC(=NH)NH—;~~

R^{5a} is ~~and R^{5b} are each independently~~:

i) hydrogen;

~~ii) hydroxy;~~

~~iii) halogen;~~

ii) ~~iv)~~ ~~substituted or unsubstituted~~ C_1-C_6 linear or C_3-C_6 branched alkyl; or

iii) ~~v)~~ a unit having the formula:

$$-[C(R^{7a}R^{7b})]_tR^8$$

$$-[C(R^{7a}H)]_tR^8$$

R^{7a} is ~~and R^{7b} are each independently:~~

i) hydrogen; or

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

R^8 is:

i) hydrogen;

ii) ~~substituted or unsubstituted~~ C_1-C_6 linear, C_3-C_6 branched, or C_3-C_6 cyclic alkyl;

or

iii) phenyl ~~substituted or unsubstituted C_6 or C_{10} aryl~~;

~~iv) substituted or unsubstituted C_1-C_9 heteroaryl; or~~

~~v) substituted or unsubstituted C_1-C_9 heterocyclic;~~

~~R^{6a} and R^{6b} are each independently:~~

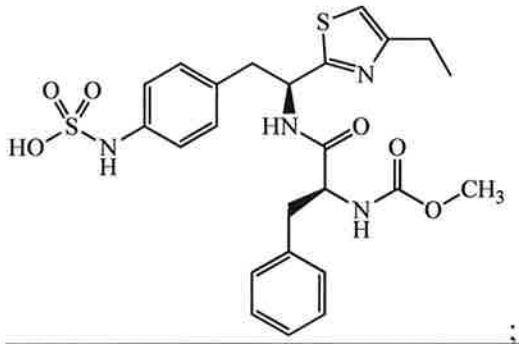
~~i) hydrogen; or~~

~~ii) C_1-C_4 linear or C_3-C_4 branched alkyl;~~

the index ~~n is 0 or 1; the indices~~ t is~~, w and x are each independently from~~ 0 to 4~~; the indices y and z are each independently 0 or 1~~; or

a pharmaceutically acceptable salt thereof.

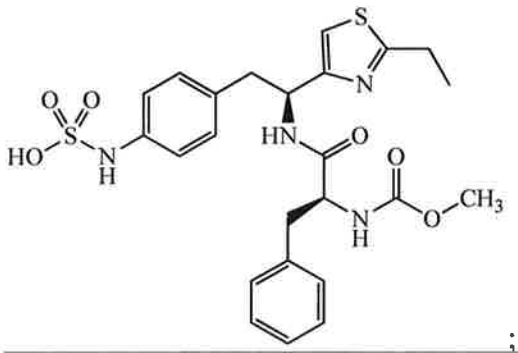
31. The medicament according to any of Claims 1-15, wherein the compound has the formula:



; and

pharmaceutically acceptable salts thereof.

32. The medicament according to any of Claims 1-15, wherein the compound has the formula:



; and

pharmaceutically acceptable salts thereof.