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(54) Title: ISOTHIAZOLE BASED PROTEIN KINASE INHIBITORS

(57) Abstract: Hydroxy containing isothiazole base derivatives have enhanced and unexpected drug properties as inhibitors of protein kinases and are useful in treating disorders related to abnormal protein kinase activities such as cancer.



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ISOTHIAZOLE BASED PROTEIN KINASE INHIBITORS

Description

Field of Invention:

The invention relates to protein kinase inhibitors and to their use in treating disorders related to abnormal protein kinase activities such as cancer and inflammation. More particularly, the invention relates to isothiazole based compounds and their pharmaceutically acceptable salts employable as protein kinase inhibitors.

Background:

Protein kinases are enzymes that catalyze the phosphorylation of hydroxyl groups of tyrosine, serine, and threonine residues of proteins. Many aspects of cell life (for example, cell growth, differentiation, proliferation, cell cycle and survival) depend on protein kinase activities. Furthermore, abnormal protein kinase activity has been related to a host of disorders such as cancer and inflammation. Therefore, considerable effort has been directed to identifying ways to modulate protein kinase activities. In particular, many attempts have been made to identify small molecules that act as protein kinase inhibitors.

Isothiazole based derivatives having activity as protein kinase inhibitors have been disclosed in International Patent Application WO 09962890 and in US Patent No. 6235764. What is needed is a class of modified isothiazole based derivatives having both activity as protein kinase inhibitors and enhanced drug properties.

Summary:

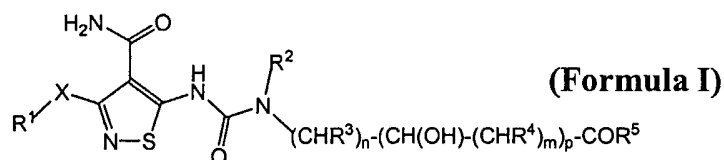
The invention is directed to hydroxy containing isothiazole derivatives and to their use as inhibitors of protein kinases. It is disclosed herein that hydroxy containing isothiazole derivatives have enhanced and unexpected drug properties that advantageously distinguish this class of compounds over known isothiazole derivatives having protein kinase inhibition activity. It is also disclosed herein that

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hydroxy containing isothiazole derivatives are useful in treating disorders related to abnormal protein kinase activities such as cancer.

This invention discloses that certain hydroxy compounds may have advantageous and unexpected properties that distinguish them from known compounds. They are therefore useful in treating disorders related to abnormal protein kinase activities such as cancer.

One aspect of the invention is directed to a compound represented by Formula (I):

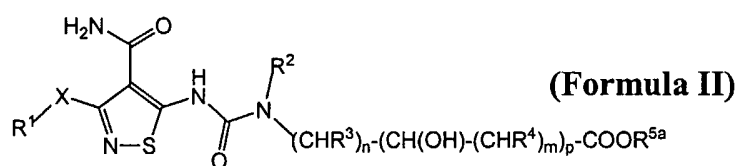


In Formula I, X is O or S; R¹ is selected from the group consisting of (C1-C6) alkyl, (C3-C8) cycloalkyl, (C6-C10) arylalkyl, (C5-C9) heteroarylalkyl, substituted (C6-C10) arylalkyl, and substituted (C5-C9) heteroarylalkyl; R² and R³ are independently hydrogen or (C1-C6) alkyl; R⁴ is selected from the group consisting of hydrogen, (C1-C6) alkyl, and hydroxyl; n and m are independently 0, 1, 2, or 3; p is independently 1, 2, or 3; R⁵ is selected from the group consisting of hydroxyl, (C1-C6) alkoxy, (C3-C8) cycloalkoxy, substituted or unsubstituted O-(C6-C10) aryl, and NR⁶R⁷; R⁶ and R⁷ are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy, (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C10) aryl, (C5-C9) heteroaryl, (C3-C8) cycloalkyl carboxylic acid; or R⁷ and R⁸ together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; or NR⁶R⁷ may form a cyclic ring containing 0-3 additional heteroatoms selected from N, O, or S; or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, prodrug thereof. It may also act as a prodrug.

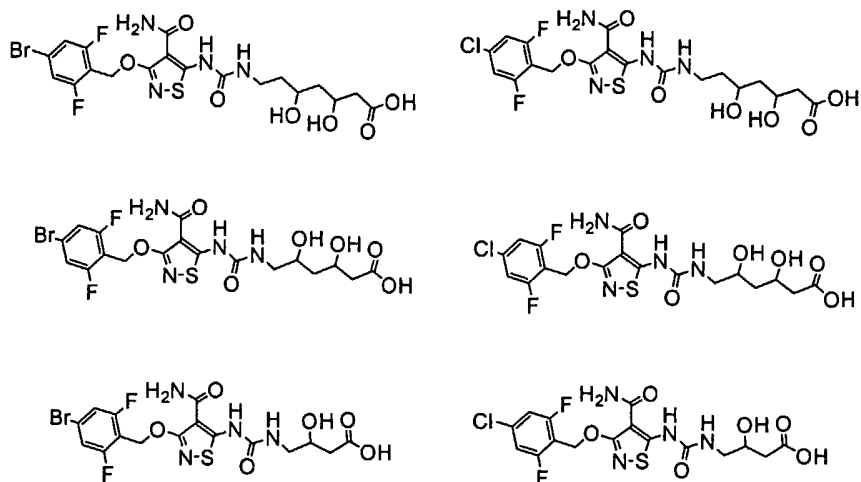
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It should be understood that a compound of Formula (I) where R^5 is OH may exist in its open-acid form or its cyclic-lactone form or the two forms may co-exist in solution or *in vivo* as illustrated in Figure 1. Furthermore, all compounds of Formula (I) have at least one asymmetric center and the stereochemistry at the asymmetric center(s) is(are) either *RS*, *R*, or *S*. Preferred acid species of this embodiment are represented in Figure 2. Preferred amide species of this embodiment are represented in Figure 3.

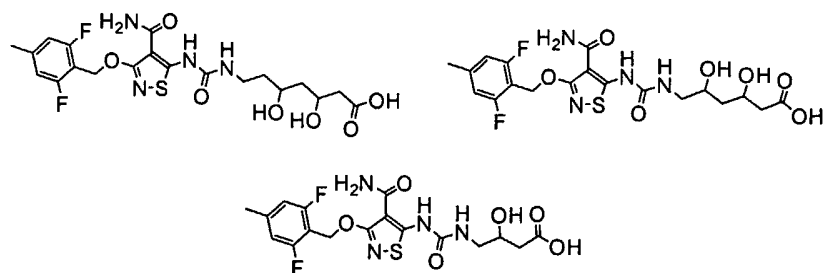
In a preferred embodiment of this first aspect of the invention, the compound, salt, tautomer, or prodrug is represented by Formula (II):



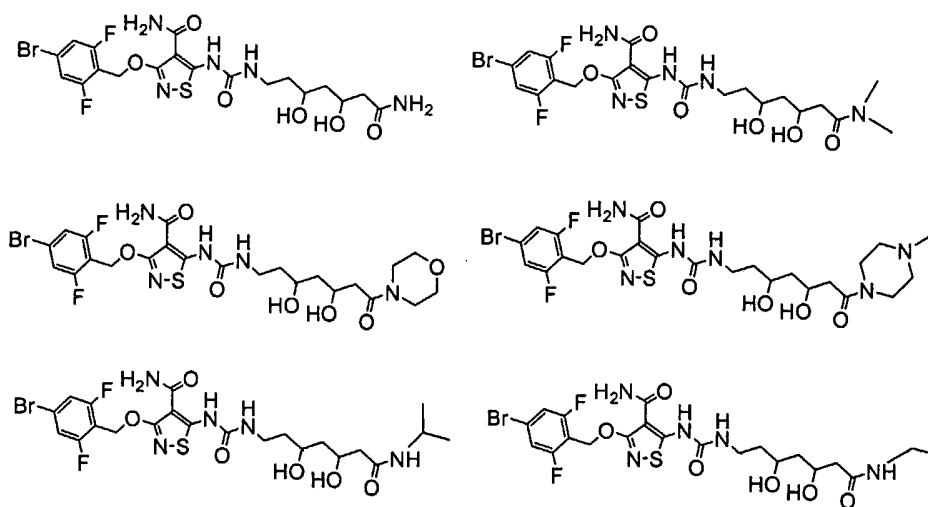
In Formula II, R^{5a} is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, and substituted or unsubstituted (C6-C10) aryl. In a subgroup of this first embodiment, X is O; R^1 is selected from the group consisting of optionally substituted (C6-C10) arylmethylene and (C5-C9) heteroaryl-methylene; R^2 and R^3 are hydrogen; and R^4 is selected from the group consisting of hydrogen and hydroxyl. Preferred species within this first embodiment are represented by the following structures:



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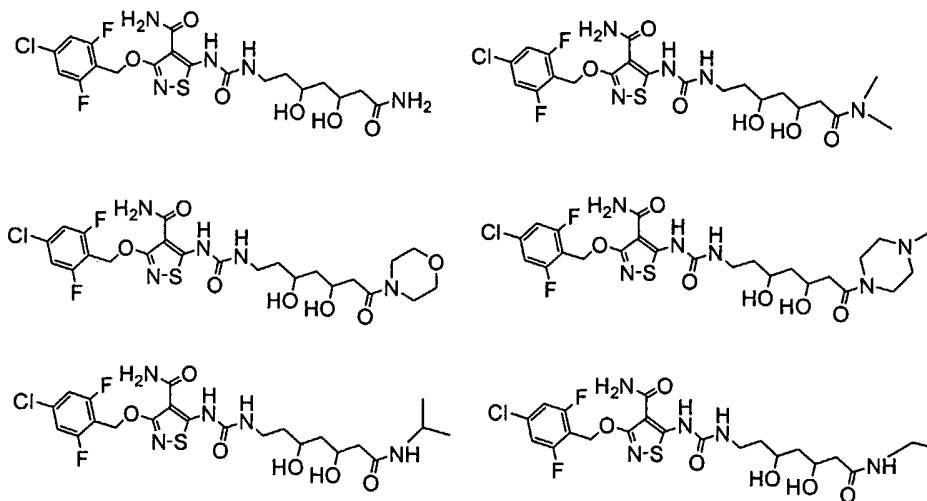


In the second embodiment of the first aspect of the invention, R^5 of Formula I is NR^6R^7 . In a subgroup of this second embodiment, X is O; R^1 is selected from the group consisting of optionally substituted (C6-C10) arylmethylene and (C5-C9) heteroaryl-methylene; R^2 and R^3 are hydrogen; and R^4 is selected from the group consisting of hydrogen and hydroxyl. A first group of preferred species is represented by the following structures:

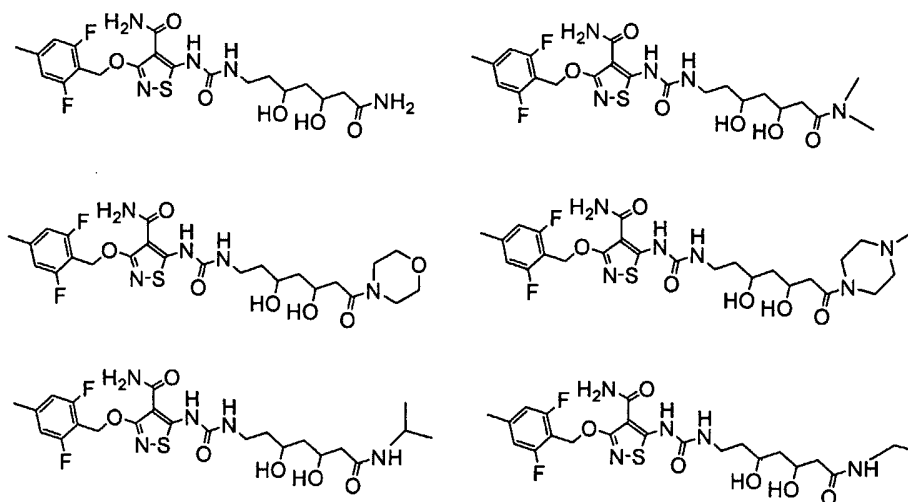


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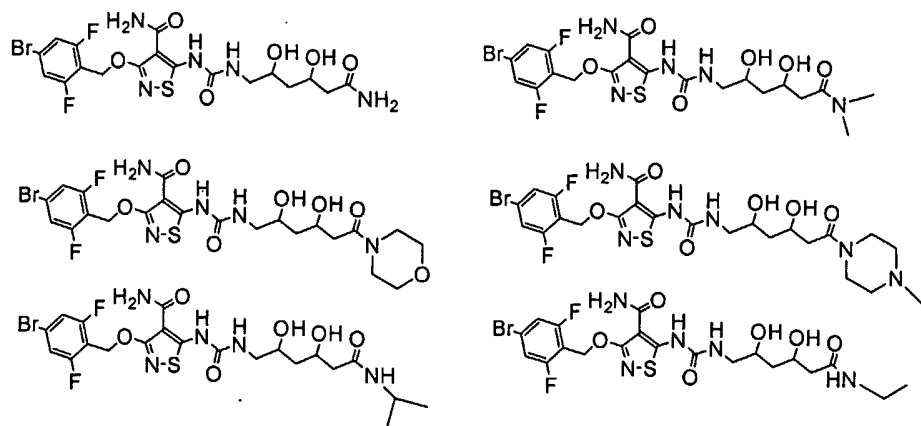
A second group of preferred species is represented by the following structures:



A third group of preferred species is represented by the following structures:

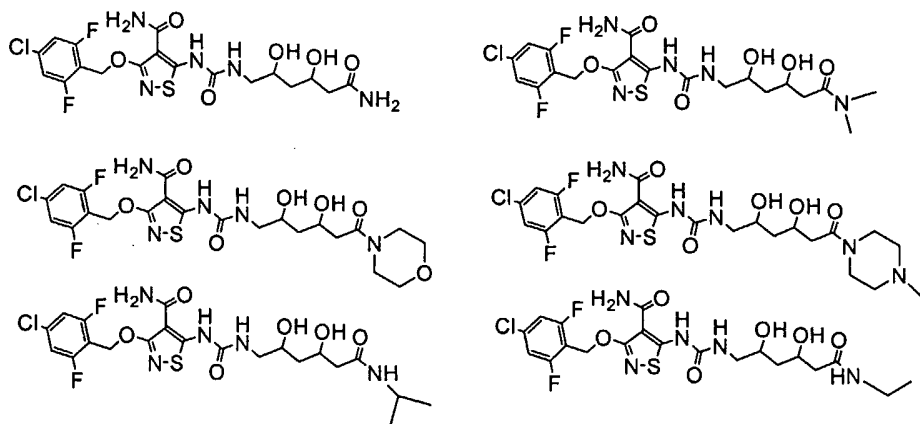


A fourth group of preferred species is represented by the following structures:

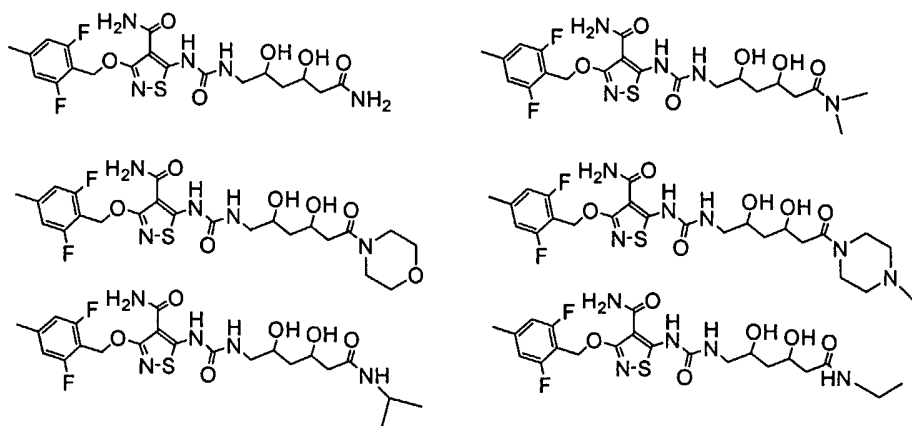


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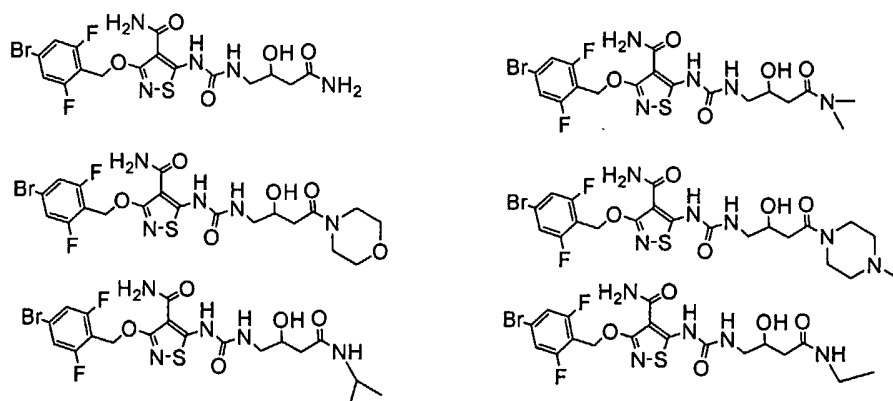
A fifth group of preferred species is represented by the following structures:



A sixth group of preferred species is represented by the following structures:

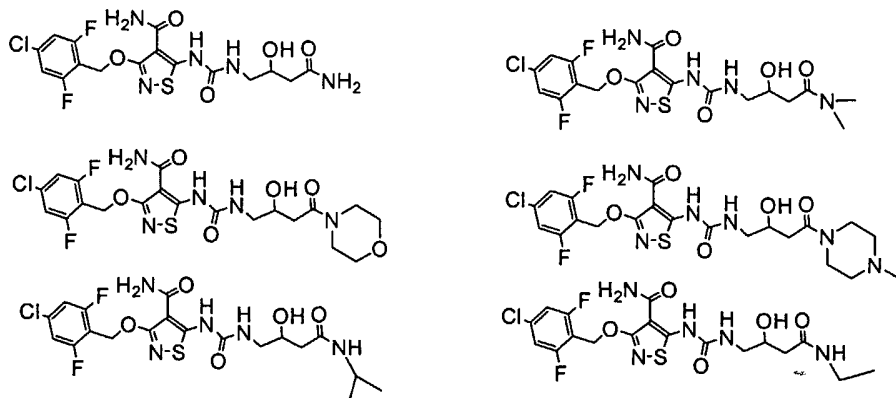


A seventh group of preferred species is represented by the following structures:

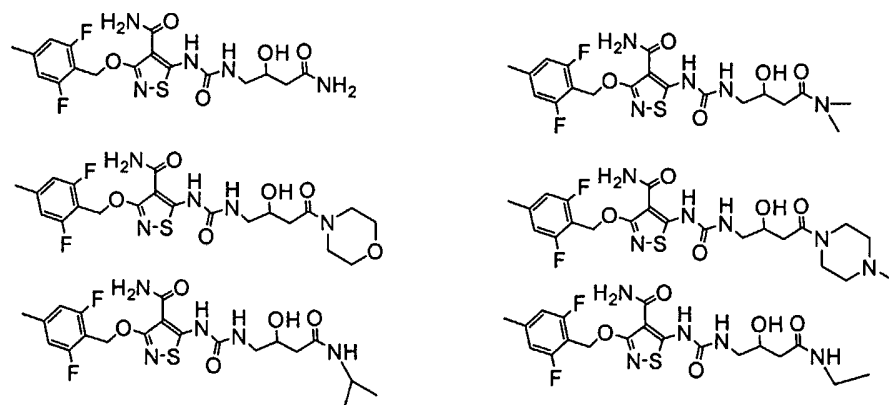


An eighth group of preferred species is represented by the following structures:

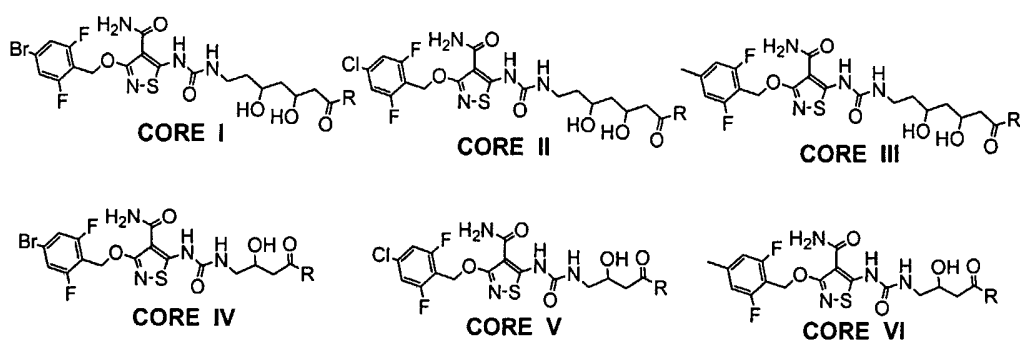
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A ninth group of preferred species is represented by the following structures:

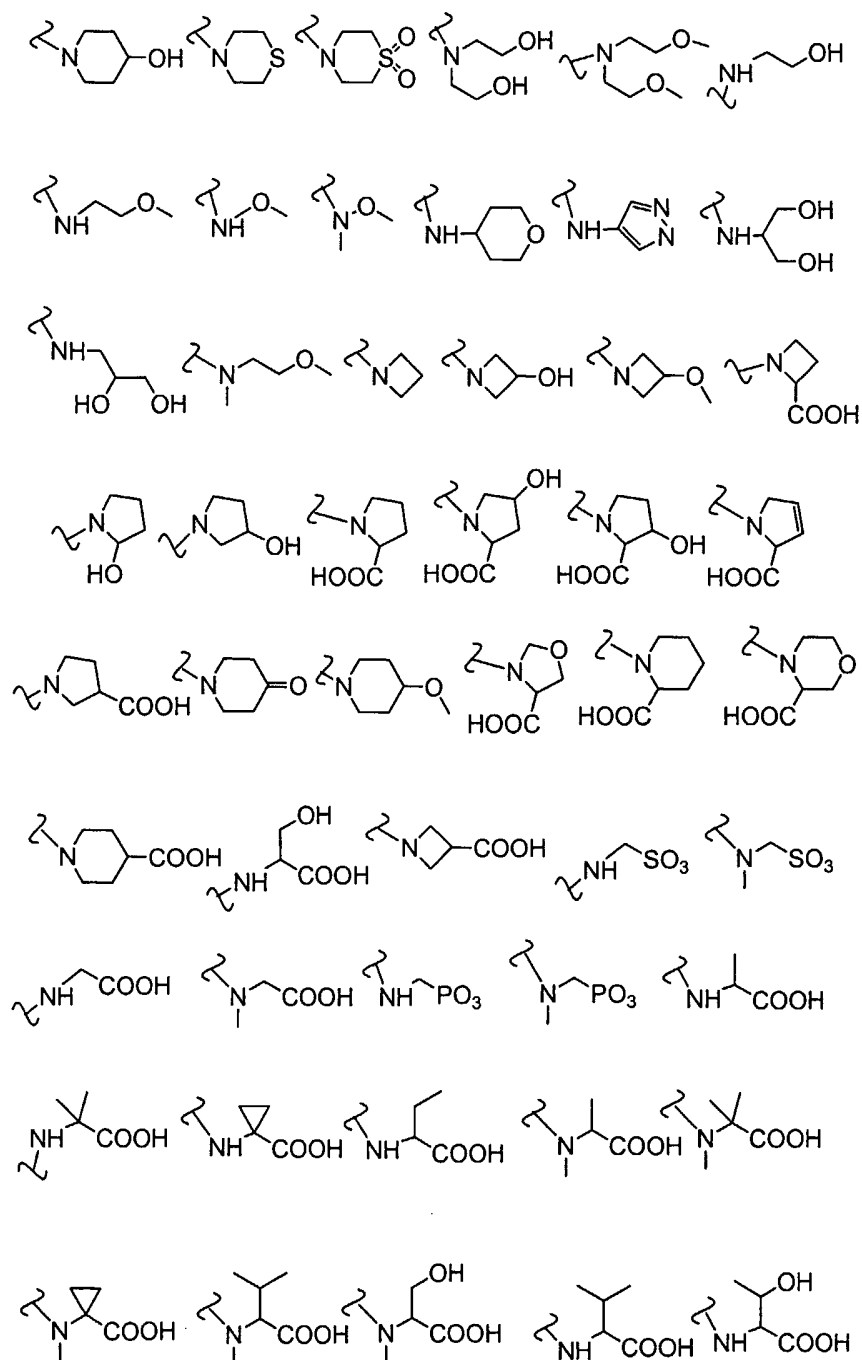


A tenth group of preferred species is represented by the following core structures:



In the above core structure, R is selected from the group consisting of radical represented by the following structures:

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Provisios may apply to any of the above subgroups or embodiments wherein any one or more of the other above described embodiments or species may be excluded from such subgroups or embodiments.

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Another aspect of the invention is directed to a method for the modulation of the catalytic activity of a protein kinase with a compound or salt of the first aspect of the invention. In a preferred mode, the protein kinase is selected from the group consisting of VEGF receptors and PDGF receptors.

Brief Description of the Drawings:

Figure 1 illustrates that the hydroxyl containing portion of the isothiazole based compound of the invention, and illustrates that this portion of the compound may exist in its open-acid form or its cyclic-lactone form or the two forms may co-exist in solution or *in vivo*.

Figure 2 illustrates preferred compounds of the invention in acid or open-chain form.

Figure 3 illustrates preferred compounds of the invention which are amides.

Figure 4 illustrates a scheme used to synthesize the acid compounds in Figure 2.

Figure 5 illustrates a method for completion of the synthesis of **1-10** which is representative of the acid compounds.

Figure 6 illustrates a scheme used for the synthesis of compounds like **2-3**.

Utility:

The present invention provides compounds capable of regulating and/or modulating protein kinase activities of, but not limited to, VEGFR (Vascular Endothelial Growth Factor Receptor) and/or FGFR (Fibroblast Growth Factor Receptor). Thus, the present invention provides a therapeutic approach to the treatment of disorders related to the abnormal functioning of these kinases. Such disorders include, but not limited to, solid tumors such as glioblastoma, melanoma, and Kaposi's sarcoma, and ovarian, lung, prostate, pancreatic, colon and epidermoid carcinoma. In addition, VEGFR/FGFR inhibitors may also be used in the treatment of restenosis and diabetic retinopathy.

Furthermore, this invention relates to the inhibition of vasculogenesis and angiogenesis by receptor-mediated pathways, including the pathways comprising VEGF receptors, and/or FGF receptors. Thus the present invention provides

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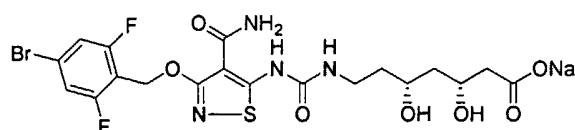
therapeutic approaches to the treatment of cancer and other diseases which involve the uncontrolled formation of blood vessels.

Synthesis of Acid and Ester Compounds

The compounds of this invention can be synthesized by following the published general procedures. But the following intermediates are specific to compounds of this invention and may be used in place of their respective counterparts in the published general procedures: (4*R*,6*R*)-*t*-butyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate; 4-amino-3-hydroxy-butanoic acid; 2-hydroxy-4-aminobutyric acid; and isoserine. These intermediates may be purchased from commercial sources (e.g. Fisher Scientific, Fairlawn, New Jersey and Sigma Aldrich, Milwaukee, Wisconsin). Another variation from the published general procedures is that in the synthesis of compounds using (4*R*,6*R*)-*t*-butyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate, the protecting groups need to be removed from the final product. These variations from the published general procedures can be understood and carried out by those skilled in the art. The amides of Figure 3 can be readily synthesized from the acids of Figure 2. Thus, the compounds of the present invention can be synthesized by those skilled in the art.

The compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

Example 1: (3*R*,5*R*)-7-{3-[3-(4-bromo-2,6-difluorobenzyloxy)-4-carbamoylisothiazol-5-yl]ureido}-3,5-dihydroxyheptanoic acid, sodium salt



The general synthetic sequence is depicted in Figure 4. The intermediates until isothiazole **1-6** were obtained according literature methods (Larson, E. R.; Noe, M. C.; Gant, T. G. Isothiazole Derivatives Useful As Anticancer Agents. International

publication number WO 99/62890; international publication date 12/09/1999. Larson, E. R.; Noe, M. C.; Gant, T. G. Isothiazole Derivatives Useful As Anticancer Agents. United States patent US 6,235,764. Date of patent 5/22/2001) and are not further described in this report. However, the purification method for **1-5** was changed significantly and this process is therefore detailed in the experimental section. Accordingly, crude **1-5** was purified by crystallization from hot DMF, which proved more convenient than the tedious, repeated centrifugation procedure given in the patents cited above.

Preparation of 1-5: (4-Carbamoyl-3-hydroxyisothiazol-5-yl)-carbamic acid phenyl ester

Solid (3-benzyloxy-4-cyanoisothiazol-5-yl)-carbamic acid phenyl ester (**1-4**, 38.7g, 0.11 mol) was added slowly to concentrated sulfuric acid (75 mL) over 1 h and the mixture was stirred for additional 3 h. The viscous solution was diluted by slow addition of ice (150 g) followed by vigorous stirring for an additional 1 h. The precipitate was filtered and pressed on the filter without washing with water. The wet solid was dissolved in DMF (250 mL) under heating to 120 °C. The mixture was then cooled to room temperature and kept at ca. 5 °C for 3 h. The crystals were filtered and washed with acetonitrile (3×50 mL). The formed solid was then washed with aqueous NaHCO₃ solution (80 mL) and acetone (50 mL) and dried in vacuum to give (4-carbamoyl-3-hydroxyisothiazol-5-yl)-carbamic acid phenyl ester (15.0 g, 50 %) as a solid, which was used in the next step without further purification. ¹H NMR (300 MHz, DMSO-d₆/TMS): δ 8.08 (s, 1H), 7.89 (s, 1H), 7.45-7.40 (m, 2H), 7.31-7.27 (m, 3H), 7.00 (br s, 1H). 4.00-3.70 (br, 1 H). ¹³C NMR (75 MHz, DMSO-d₆): δ 167.0, 164.8, 150.0, 130.0, 129.0, 126.0, 121.0, 117.4, 98.5. HMRS (LSIMS, nba): calcd for C₁₁H₁₀O₄N₃S (MH⁺): 280.0392; found: 280.0383.

Preparation of 1-Na: (3*R*,5*R*)-7-{3-[3-(4-bromo-2,6-difluorobenzyloxy)-4-carbamoylisothiazol-5-yl]ureido}-3,5-dihydroxyheptanoic acid, sodium salt

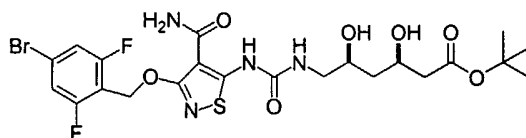
A solution of [3-(4-bromo-2,6-difluorobenzyloxy)-4-carbamoylisothiazol-5-yl]-carbamic acid phenyl ester (**1-6**, 2.55 g, 5.3 mmol) and (4*R*,6*R*)-[6-(2-aminoethyl)-

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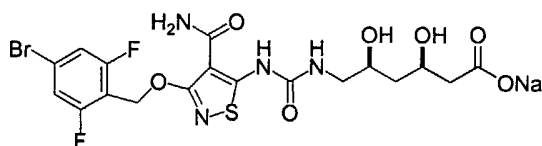
2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid *tert*-butyl ester (**1-7**, 1.43 g, 5.3 mmol) in THF (50 mL) was stirred at 45 °C overnight. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (silica gel, EtOAc:heptane = 1:1) to give crude (4*R*,6*R*)-[6-(2-{3-[3-(4-bromo-2,6-difluorobenzyloxy)-4-carbamoylisothiazol-5-yl]-ureido}-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid *tert*-butyl ester (**1-8**, 1.5 g, 43%) as an oil. ¹H NMR (300 MHz, DMSO-*d*₆/TMS): δ 7.25 (d, *J* = 7.2 Hz, 2H), 7.12 (br, 2 H), 6.75 (br, 1H), 6.05 (br, 1 H), 5.50 (s, 2H), 4.21-4.09 (m, 1H), 4.00-3.90 (m, 1H), 3.38-3.34 (m, 2H), 2.36-2.25 (m, 2H), 1.80-1.60 (m, 2H), 1.41 (s, 9H), 1.40-1.20 (m, 2 H), 1.39 (s, 3H), 1.29 (s, 3H). (4*R*,6*R*)-[6-(2-{3-[3-(4-Bromo-2,6-difluorobenzyloxy)-4-carbamoylisothiazol-5-yl]-ureido}-ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid *tert*-butyl ester (**1-8**, 0.5 g, 0.75 mmol) was added to MeOH (10 mL), concd aqueous HCl (0.5 mL) and THF (5 mL) and the mixture was stirred overnight at room temperature. The solvents were evaporated, the residue was extracted with EtOAc (50 mL), and the solution was dried over MgSO₄. After concentration, the solvent was evaporated and the residue was purified by column chromatography (CH₂Cl₂:MeOH = 10:1) to give a mixture of (3*R*,5*R*)-7-{3-[3-(4-bromo-2,6-difluorobenzyloxy)-4-carbamoylisothiazol-5-yl]ureido}-3,5-dihydroxyheptanoic acid (**1-9**) and its methyl ester (0.17 g). This residue was stirred in a solution of NaOH (11 mg, 0.028 mmol) in MeOH (10 mL) and water (0.5 mL) for 3 h. The solvent was evaporated, MeOH (10 mL) was added and the mixture was concentrated. The residue (light yellow solid) was washed with *i*-PrOH (5 mL), filtered, washed with Et₂O (20 mL) and dried in vacuum. The obtained solid (0.2 g) was dissolved in MeOH (20 mL) and filtered through Celite filter agent. The solvent was evaporated and the residual solid was stirred with Et₂O (10 mL) and MeOH (1 mL) at room temperature overnight. The precipitate was filtered and dried in vacuum to give (3*R*,5*R*)-7-{3-[3-(4-bromo-2,6-difluorobenzyloxy)-4-carbamoylisothiazol-5-yl]ureido}-3,5-dihydroxyheptanoic acid, sodium salt (**1-Na**, 0.17 g, 38 %) as a white solid. Mp 207-208 °C (decomposition). ¹H NMR (300 MHz, CD₃OD/TMS), δ 7.29 (d, *J* = 7.2 Hz, 2H), 5.50 (s, 2H), 4.10 (m, 1H), 3.86 (m, 1H), 3.37-3.30 (m, 2H), 2.36-2.30 (m, 2H), 1.80-1.50 (m, 4H). ¹³C NMR (75 MHz, CD₃OD): □ 180.3, 170.4, 167.0, 163.1 (dd, *J* = 254, 8 Hz), 162.6, 156.1, 124.4 (t, *J* = 13 Hz), 116.8 (d, *J* = 29 Hz), 113.0 (t, *J* = 19 Hz), 98.6, 69.1, 68.7, 58.9, 45.6, 45.2, 38.3, 38.2.

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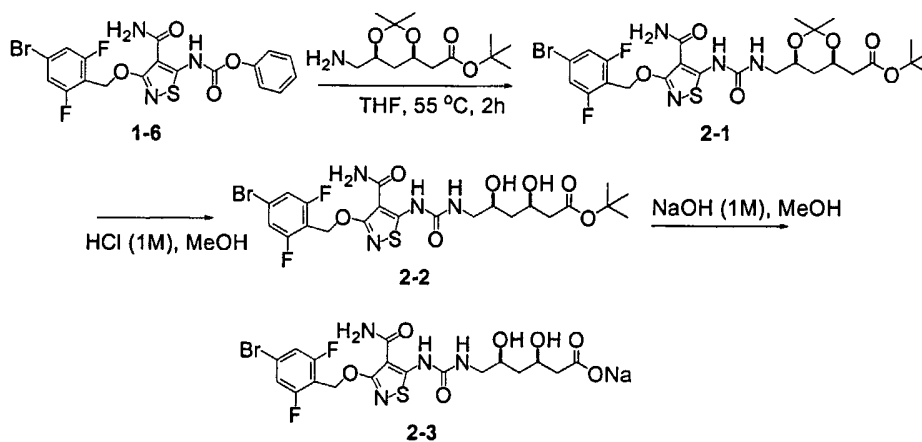
Example 2: (3R,5S)-6-{3-[3-(4-Bromo-2,6-difluoro-benzyloxy)-4-carbamoyl-isothiazol-5-yl]-ureido}-3,5-dihydroxy-hexanoic acid tert-butyl ester.



Example 3: (3R,5S)-6-{3-[3-(4-Bromo-2,6-difluoro-benzyloxy)-4-carbamoyl-isothiazol-5-yl]-ureido}-3,5-dihydroxy-hexanoic acid.



The preparation of Examples 2 and 3 are outlined in Scheme 1, below:



Scheme 1

Preparation of ((4R,6S)-6-Aminomethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester:



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Triflic anhydride 1.4mL (2.36g, 8.345mmol) was dropwise added at -78 °C to a solution of 2,6-lutidine 1.35mL (11.63mmol) and *t*-Butyl (3R,5S)-6-hydroxy-3,5-O-isopropylidene-3,5-dihydroxyhexanoate 1.981g (7.609 mmol, obtained from Kaneka Corp.) in dichloromethane (anh., 50mL) over 3 minutes. The mixture was stirred at -78 °C for 10 min, then placed on ice-slush bath and stirred at 0 °C for 45 min. The resulting pink mixture was transferred into ice-cooled solution of ammonia in methanol (7M solution, 200mL). The mixture was placed on ambient water bath and stirred at RT for 6 hours. The reaction mix was evaporated to dryness, the residue partitioned between ether (200mL) and aqueous potassium carbonate (6g in 200 mL of water), the aqueous phase re-extracted with ether (150mL). Combined organic extracts were dried (magnesium sulfate) and evaporated. The crude product was purified on a column of silica (125g) eluting with a mixture of chloroform-methanol-conc. aq. ammonia 100:10:1 (v/v) (1.5L) Y = 1.777g of a colorless liquid (90% th) ¹H (dDMSO, 400MHz): 4.167(m, 1H), 3.741 (m, 1H), 2.484 (m, 2H), 2.384 (ddAB, J=15.2Hz, 5.1Hz, 1H), 2.201(ddAB, J=15Hz, 7.8Hz, 1H), 1.533 (br d, J=12.5Hz, 1H), 1.373 (s, 9H), 1.363 (s, 3H), 1.250 (br s, 2H), 1.223 (s, 3H)

Preparation of compound 2-1. ((4R,6S)-6-Aminomethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester (0.39 mmol) was added to a solution of compound **1-6** (100 mg, 0.2 mmol), and DIEA (0.3 mmol) in THF (5 mL). After the solution was stirred at 55 °C overnight, the solvent was removed via evaporation under reduced pressure. The resulting residue was subjected to flash chromatography (ISCO system, 25% – 60% ethyl acetate in hexane, 22 min.) to get the final product **2-1** (93 mg, 72%). LC-MS: single peak at 254 nm, MH⁺ calcd. for C₂₅H₃₁BrF₂N₄O₇S: 650, obtained: 650. ¹H-NMR (DMSO-d₆, 400 MHz), δ 11.06 (s, 1H), 8.32 (t, J = 5.6 Hz, 1H), 7.57 (m, 3H), 6.82 (s, 1H), 5.42 (s, 2H), 4.20 (m, 1H), 3.95 (m, 1H), 3.12 (m, 2H), 2.38 (dd, J = 4.8 Hz, J = 14.0 Hz, 1H), 2.21 (dd, J = 4.8 Hz, J = 14.8 Hz, 1H), 1.53 (dd, J = 2.8 Hz, J = 8.0 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 9H), 1.27 (s, 3H), 1.15 (dd, J = 7.2 Hz, J = 14.4 Hz, 1H).

Synthesis of compound 2-2. Aqueous HCl (1.5 mL, 1.0M) was added to a solution of compound **2-1** (285 mg, 0.44 mmol) in MeOH (10 mL). A precipitation was observed immediately. After the suspension was stirred at 50 °C for 2.5h, the solution became clear, and LC-MS showed the reaction was complete. The MeOH

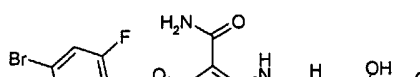
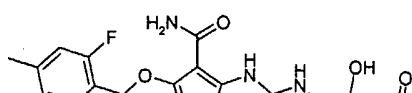
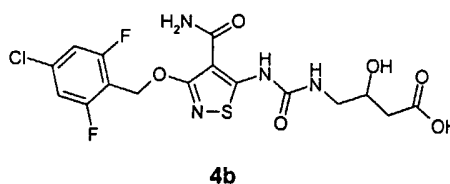
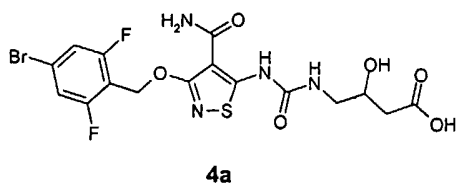
-15-

was removed via evaporation under reduced pressure. The resulting aqueous solution was extracted using ethyl acetate (3x 50 mL). The combined organic solution was dried over Na₂SO₄, and the ethyl acetate was evaporated under vacuum to obtain the crude product (261 mg). This crude material was used directly in the next step without further purification. A small portion of this crude product was subjected to preparative HPLC to obtain the pure product **2-2**. LC-MS: single peak at 254 nm, MH⁺ calcd. for C₂₂H₂₇BrF₂N₄O₇S: 610, obtained: 610. ¹H-NMR (DMSO-d₆, 400 MHz), δ 11.05 (s, 1H), 8.30 (t, *J* = 5.6 Hz, 1H), 7.57 (m, 3H), 6.81 (s, 1H), 5.42 (s, 2H), 4.82 (d, *J* = 4.8 Hz, 1H), 4.74 (d, *J* = 4.8 Hz, 1H), 3.94 (m, 1H), 3.65 (m, 1H), 3.19 (m, 1H), 3.04 (m, 1H), 2.30 (dd, *J* = 4.2 Hz, *J* = 14.8 Hz, 1H), 2.20 (dd, *J* = 8.0 Hz, *J* = 14.4 Hz, 1H), 1.47 (t, *J* = 6.0 Hz, 2H), 1.36 (s, 9H).

Synthesis of compound 2-3. Aqueous NaOH (2 mL, 1.0M) was added to a solution of compound **2-2** (93 mg, ~0.44 mmol. Crude from the previous step) in MeOH (2 mL). The solution was stirred at 25 °C for 1.5h, and LC-MS showed the reaction was complete. This solution was directly subjected to preparative HPLC to obtain the pure product **2-3** (62 mg, 71%). LC-MS: single peak at 254 nm, MH⁺ calcd. for C₁₈H₁₈BrF₂N₄O₇S: 554, obtained: 554. ¹H-NMR (DMSO-d₆, 400 MHz), δ 11.05 (s, 1H), 8.30 (t, *J* = 5.6 Hz, 1H), 7.57 (m, 3H), 6.81 (s, 1H), 5.40 (s, 2H), 5.05 (s, 1H), 4.15 (s, 1H), 3.76 (m, 1H), 3.64 (m, 1H), 3.13 (m, 1H), 2.99 (m, 1H), 2.02 (dd, *J* = 4.0 Hz, *J* = 14.8 Hz, 1H), 1.82 (dd, *J* = 8.4 Hz, *J* = 15.2 Hz, 1H), 1.42 (m, 1H), 1.34 (m, 1H).

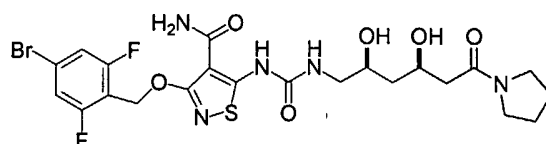
Example 4: 3-hydroxy-butyric acid derivatives.

Following the above procedures and procedures published in patents such as WO 09962890 and US 6235764, the following 3-hydroxy-butyric acid derivatives **4a-d** can be made using the commercially available 4-amino-3-hydroxy-butyric acid (e.g. Fisher Scientific, Fairlawn, New Jersey).

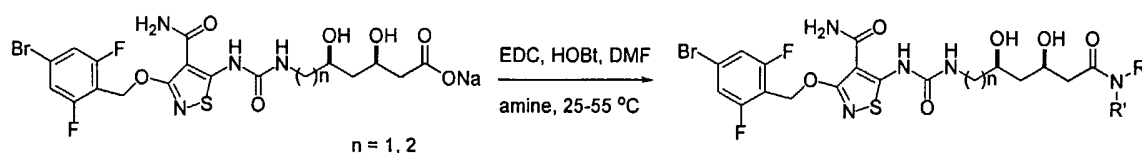


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Example 5: 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-((2S,4R)-2,4-dihydroxy-6-oxo-6-pyrrolidin-1-yl-hexyl)-ureido]-isothiazole-4-carboxylic acid amide



The general procedure for the synthesis of amides of Examples 1 and 3 is shown in **Scheme 3** below:



Scheme 3

An amine (3 equiv) was added to a solution of the sodium salt of a free acid (1 equiv), EDC (5 equiv), HOBT (5 equiv), and DIEA (5 equiv) in DMF. After the solution was stirred at 25 °C overnight (stirred at 55 °C for a couple of hours if necessary), DMF was removed via evaporation under reduced pressure. The resulting residue was suspended in ethyl acetate, washed by saturated NaHCO_3 (3x) and brine (3x), and dried over Na_2SO_4 . The ethyl acetate was removed under vacuum to give the crude product. This crude material was subjected to preparative HPLC to give the final product amide, which was subsequently characterized by LC-MS and NMR spectroscopy.

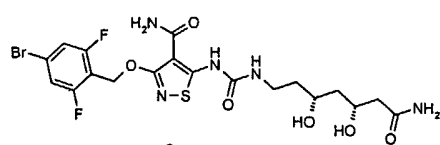
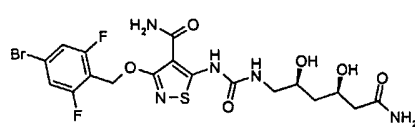
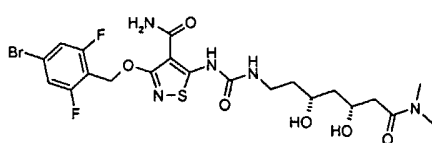
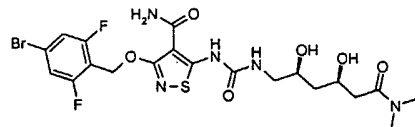
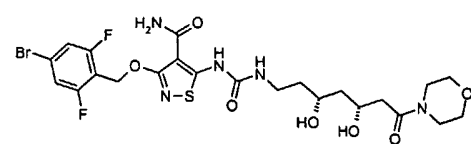
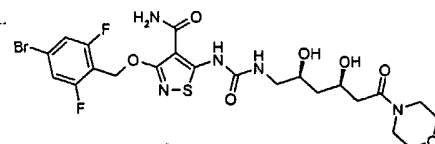
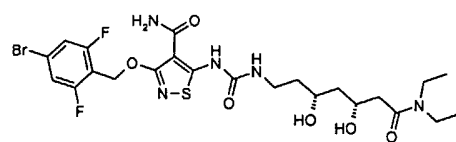
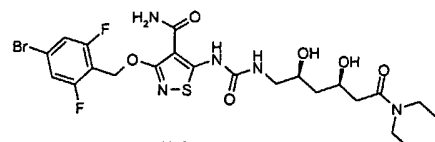
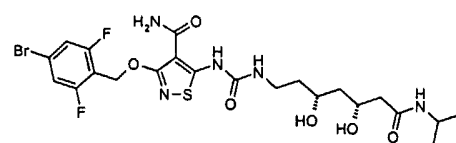
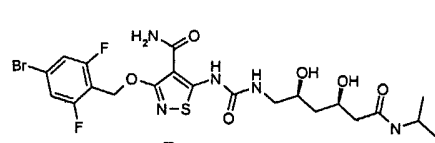
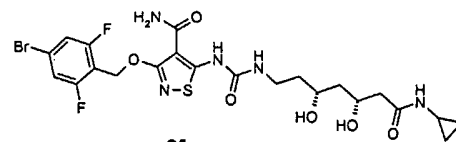
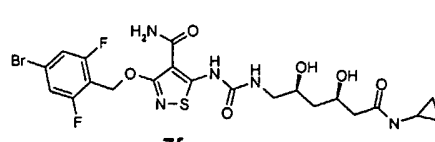
Synthesis of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-((2S,4R)-2,4-dihydroxy-6-oxo-6-pyrrolidin-1-yl-hexyl)-ureido]-isothiazole-4-carboxylic acid amide: An amount of 31 mg (92%) product was obtained after preparative HPLC from 32 mg (0.056 mmol) of the free acid sodium salt. LC-MS: single peak at 254 nm, MH^+ calcd. for $\text{C}_{22}\text{H}_{26}\text{BrF}_2\text{N}_5\text{O}_6\text{S}$: 607, obtained: 607. ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz), δ 11.05 (s, 1H), 8.31 (s, 1H), 7.57 (s, 2H), 7.55 (s, 1H), 6.81 (s, 1H), 5.42 (s, 2H), 4.82 (d, $J = 4.0$ Hz, 1H), 4.76 (d, $J = 4.0$ Hz, 1H), 4.02 (m, 1H), 3.68 (m, 1H), 3.42 (m, 2H),

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3.27 (m, 2H), 3.16 (m, 1H), 3.03 (m, 1H), 2.33 (m, 2H), 1.82 (m, 2H), 1.73 (m, 2H), 1.50 (m, 2H).

Examples 6 and 7: Amide derivatives of Examples 1 and 3.

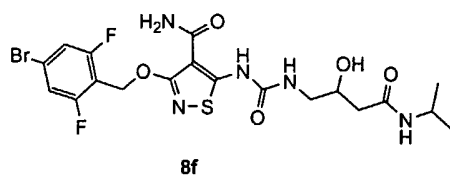
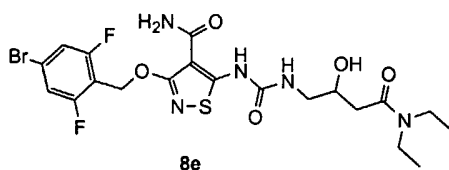
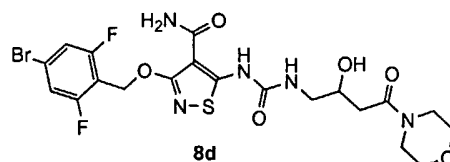
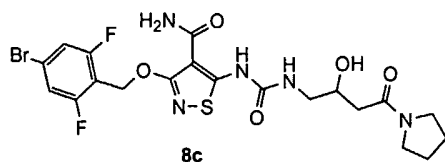
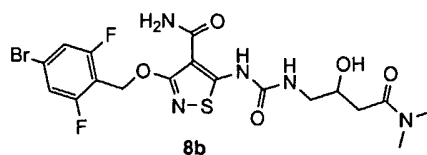
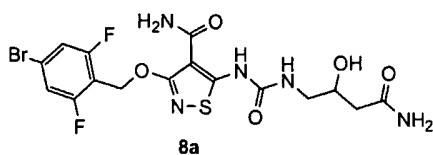
The following amide derivatives **6a-f**, **7a-f** of Examples 1 and 3 can be made by those skilled in the art following the above and/or known procedures.

**6a****7a****6b****7b****6c****7c****6d****7d****6e****7e****6f****7f**

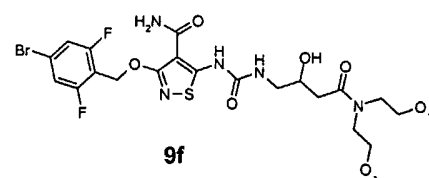
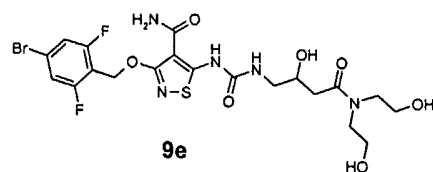
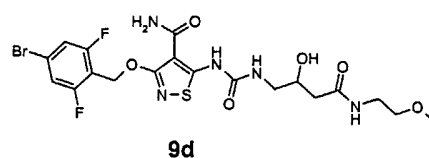
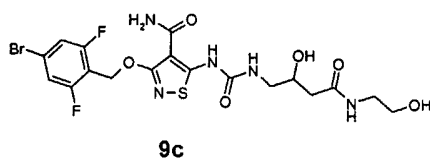
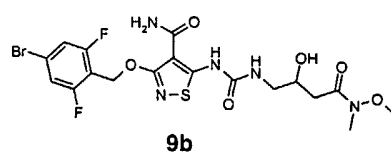
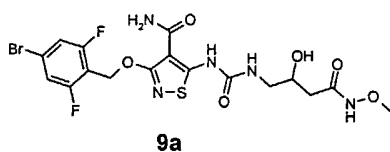
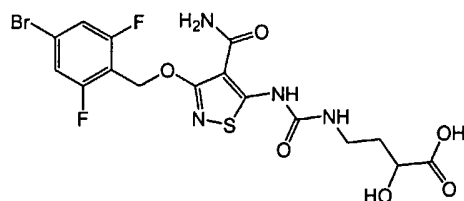
Example 8: Amide derivatives of Example 4.

The following amide derivatives **8a-f** of Example 4 can be made by those skilled in the art following known procedures.

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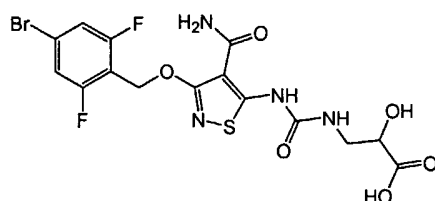
**Example 9: further amide derivatives of Example 4.**

The following amide derivatives **9a-f** of Example 4 can be made by those skilled in the art following known procedures.

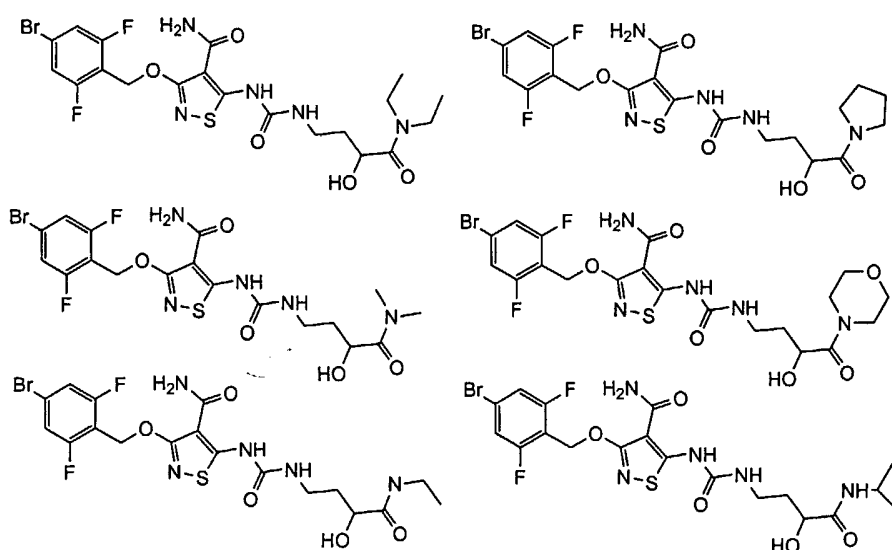
**Example A. 4-{3-[3-(4-Bromo-2,6-difluoro-benzyloxy)-4-carbamoyl-isothiazol-5-yl]-ureido}-2-hydroxy-butyrlic acid**

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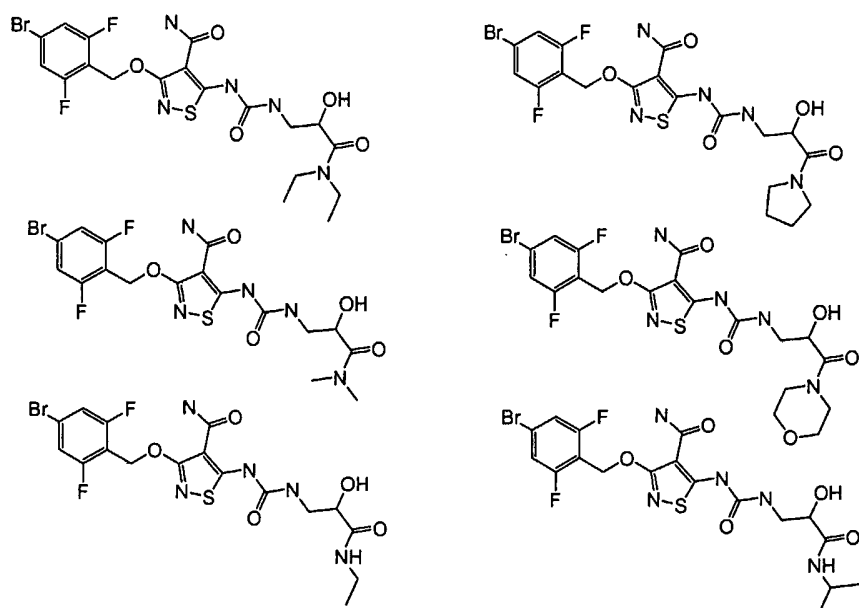
Example B. 3-{3-[3-(4-Bromo-2,6-difluoro-benzyloxy)-4-carbamoyl-isothiazol-5-yl]-ureido}-2-hydroxy-propionic acid

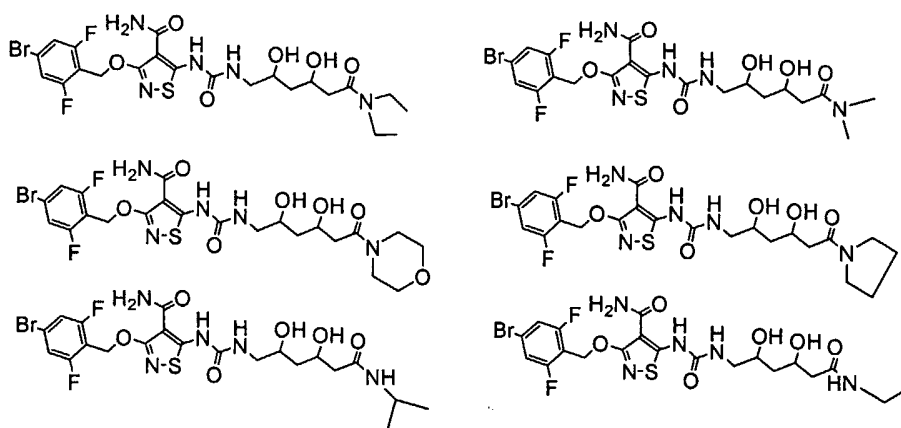


Example C. Amide examples of Example A.



Example D. Amide examples of Example B.

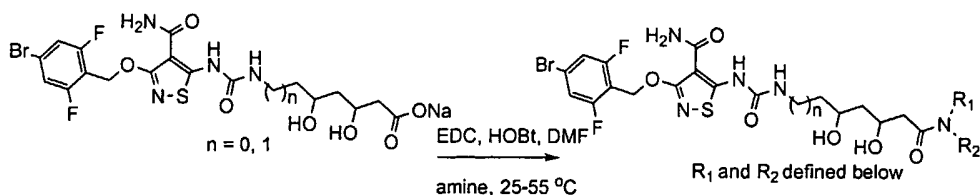


Example E: Amide examples of Example 3:**Synthesis of Amide Compounds**

The amide compounds of this invention can be readily synthesized by those skilled in the art starting from the acid compound disclosed herein.

The compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

Exemplary Synthesis. An exemplary synthesis of an amide compound is illustrated in Scheme 4 shown below:

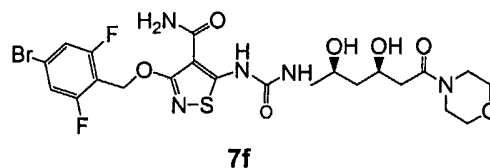
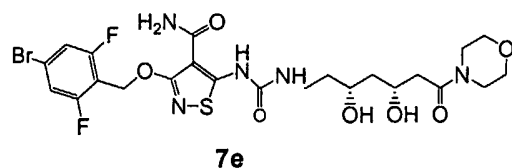
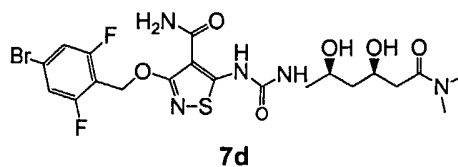
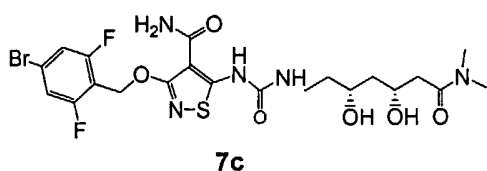
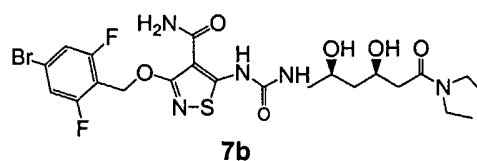
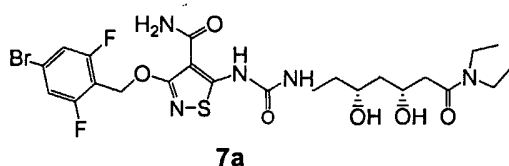
**Scheme 4**

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An amine (3 equiv) is added to a solution of the sodium salt of a free acid (1 equiv), EDC (5 equiv), HOBt (5 equiv), and DIEA (5 equiv) in DMF. After the solution is stirred at 25 °C overnight (stirred at 55 °C for a couple of hours if necessary), DMF is removed via evaporation under reduced pressure. The resulting residue is suspended in ethyl acetate, washed by saturated NaHCO₃ (3x) and brine (3x), and dried over Na₂SO₄. The ethyl acetate is removed under vacuum to give the crude product. This crude material is then subjected to preparative HPLC to give the final product amide, which may subsequently be characterized by LC-MS and NMR spectroscopy.

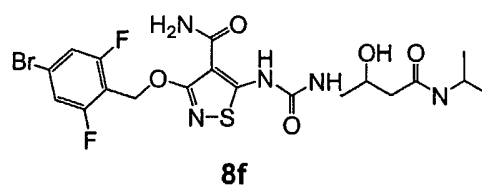
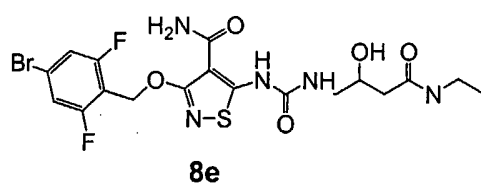
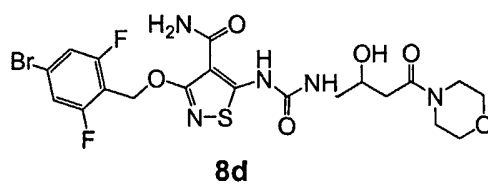
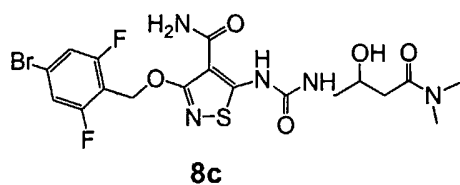
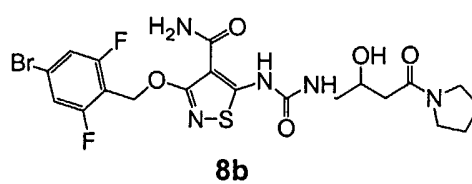
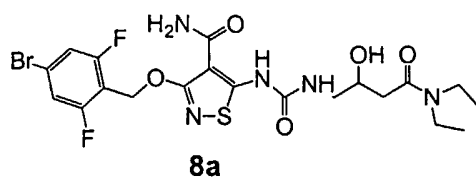
Example 7. Further amide derivatives of Scheme 4.

Following the above procedure described in Scheme 4 or other known procedures and employing the compounds of Examples 1-Na and 2-3 as starting materials, the following amides can be made.

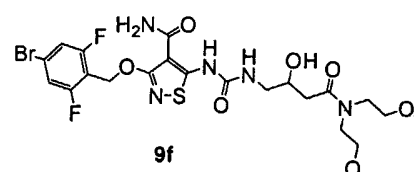
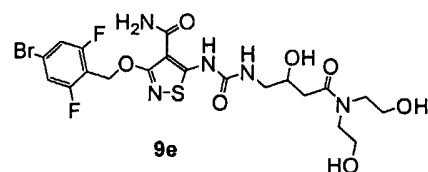
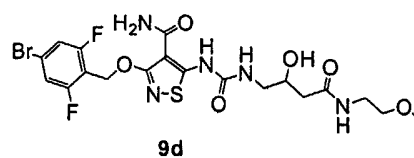
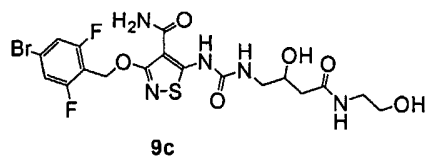
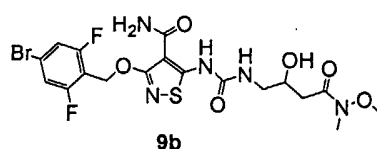
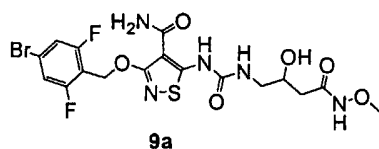
**Example 8. Amide derivatives of Example 4.**

Following the above procedure described in Scheme 4 or other known procedures and employing a monohydroxy compound corresponding to Example 2-3 as a starting material, the following compounds may be made:

-22-

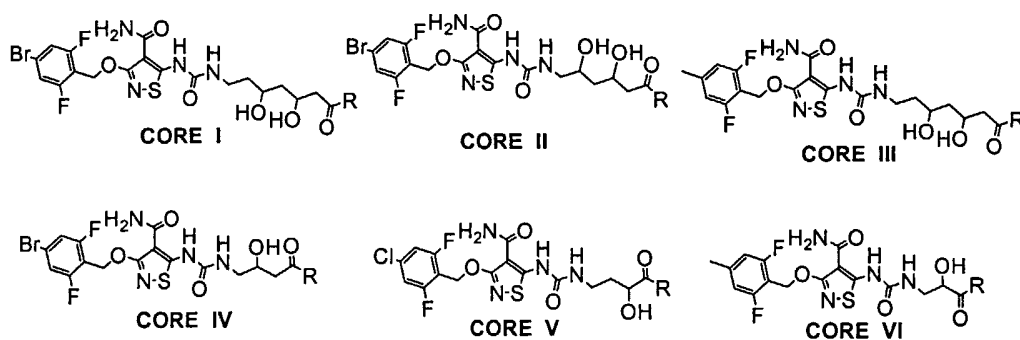
**Example 9: further amide derivatives of Example 4.**

The following amide derivatives **9a-f** of Example 4 can be made by those skilled in the art following known procedures.



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Examples 16 – 315: Still further amide examples are shown in the following table:



Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
16	I	a	66	II	a	116	III	a
17	I	b	67	II	b	117	III	b
18	I	c	68	II	c	118	III	c
19	I	d	69	II	d	119	III	d
20	I	e	70	II	e	120	III	e
21	I	f	71	II	f	121	III	f
22	I	g	72	II	g	122	III	g
23	I	h	73	II	h	123	III	h
24	I	i	74	II	i	124	III	i
25	I	j	75	II	j	125	III	j
26	I	k	76	II	k	126	III	k
27	I	l	77	II	l	127	III	l
28	I	m	78	II	m	128	III	m
29	I	n	79	II	n	129	III	n
30	I	o	80	II	o	130	III	o

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Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
31	I	p	81	II	p	131	III	p
32	I	q	82	II	q	132	III	q
33	I	r	83	II	r	133	III	r
34	I	s	84	II	s	134	III	s
35	I	t	85	II	t	135	III	t
36	I	u	86	II	u	136	III	u
37	I	v	87	II	v	137	III	v
38	I	w	88	II	w	138	III	w
39	I	x	89	II	x	139	III	x
40	I	y	90	II	y	140	III	y
41	I	z	91	II	z	141	III	z
42	I	aa	92	II	aa	142	III	aa
43	I	ab	93	II	ab	143	III	ab
44	I	ac	94	II	ac	144	III	ac
45	I	ad	95	II	ad	145	III	ad
46	I	ae	96	II	ae	146	III	ae
47	I	af	97	II	af	147	III	af
48	I	ag	98	II	ag	148	III	ag
49	I	ah	99	II	ah	149	III	ah
50	I	ai	100	II	ai	150	III	ai
51	I	aj	101	II	aj	151	III	aj
52	I	ak	102	II	ak	152	III	ak
53	I	al	103	II	al	153	III	al
54	I	am	104	II	am	154	III	am
55	I	an	105	II	an	155	III	an
56	I	ao	106	II	ao	156	III	ao
57	I	ap	107	II	ap	157	III	ap
58	I	aq	108	II	aq	158	III	aq
59	I	ar	109	II	ar	159	III	ar
60	I	as	110	II	as	160	III	as
61	I	at	111	II	at	161	III	at
62	I	au	112	II	au	162	III	au
63	I	av	113	II	av	163	III	av
64	I	aw	114	II	aw	164	III	aw
65	I	ax	115	II	ax	165	III	ax

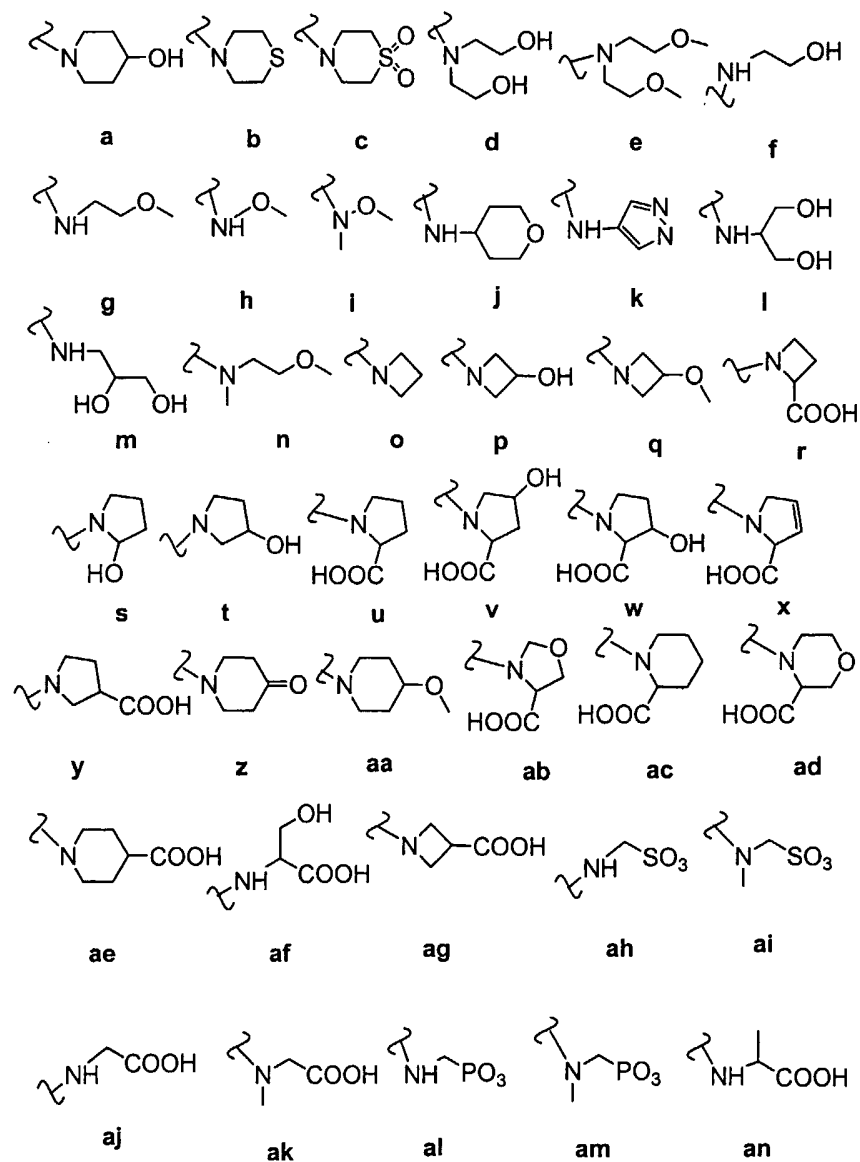
-25-

Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
166	IV	a	216	V	a	266	VI	a
167	IV	b	217	V	b	267	VI	b
168	IV	c	218	V	c	268	VI	c
169	IV	d	219	V	d	269	VI	d
170	IV	e	220	V	e	270	VI	e
171	IV	f	221	V	f	271	VI	f
172	IV	g	222	V	g	272	VI	g
173	IV	h	223	V	h	273	VI	h
174	IV	i	224	V	i	274	VI	i
175	IV	j	225	V	j	275	VI	j
176	IV	k	226	V	k	276	VI	k
177	IV	l	227	V	l	277	VI	l
178	IV	m	228	V	m	278	VI	m
179	IV	n	229	V	n	279	VI	n
180	IV	o	230	V	o	280	VI	o
181	IV	p	231	V	p	281	VI	p
182	IV	q	232	V	q	282	VI	q
183	IV	r	233	V	r	283	VI	r
184	IV	s	234	V	s	284	VI	s
185	IV	t	235	V	t	285	VI	t
186	IV	u	236	V	u	286	VI	u
187	IV	v	237	V	v	287	VI	v
188	IV	w	238	V	w	288	VI	w
189	IV	x	239	V	x	289	VI	x
190	IV	y	240	V	y	290	VI	y
191	IV	z	241	V	z	291	VI	z
192	IV	aa	242	V	aa	292	VI	aa
193	IV	ab	243	V	ab	293	VI	ab
194	IV	ac	244	V	ac	294	VI	ac
195	IV	ad	245	V	ad	295	VI	ad
196	IV	ae	246	V	ae	296	VI	ae
197	IV	af	247	V	af	297	VI	af
198	IV	ag	248	V	ag	298	VI	ag
199	IV	ah	249	V	ah	299	VI	ah
200	IV	ai	250	V	ai	300	VI	ai
201	IV	aj	251	V	aj	301	VI	aj
202	IV	ak	252	V	ak	302	VI	ak
203	IV	al	253	V	al	303	VI	al
204	IV	am	254	V	am	304	VI	am
205	IV	an	255	V	an	305	VI	an
206	IV	ao	256	V	ao	306	VI	ao
207	IV	ap	257	V	ap	307	VI	ap
208	IV	aq	258	V	aq	308	VI	aq
209	IV	ar	259	V	ar	309	VI	ar
210	IV	as	260	V	as	310	VI	as
211	IV	at	261	V	at	311	VI	at

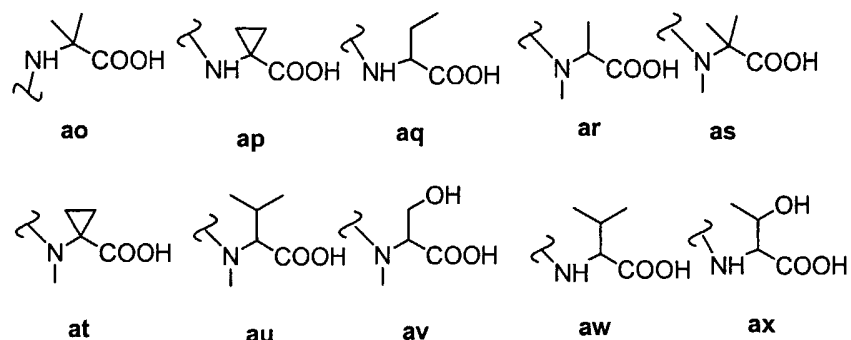
-26-

Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
212	IV	au	262	V	au	312	VI	au
213	IV	av	263	V	av	313	VI	av
214	IV	aw	264	V	aw	314	VI	aw
215	IV	ax	265	V	ax	315	VI	ax

In the above table, R is selected from the following radicals:



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These amide examples **16 - 315** can be made by those skilled in the art following the above procedure and/or known procedures.

VEGFR Biochemical Assay

The compounds were assayed for biochemical activity by Upstate Ltd at Dundee, United Kingdom, according to the following procedure. In a final reaction volume of 25 μ l, KDR (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.33 mg/ml myelin basic protein, 10 mM MgAcetate and [γ - ^{33} P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μ l of a 3% phosphoric acid solution. 10 μ l of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

Compounds of the present invention were tested in this assay and exhibited IC₅₀ between 1 – 5,000 nM.

Cellular Assay: HUVEC: VEGF induced proliferation

The compounds were assayed for cellular activity in the VEGF induced proliferation of HUVEC cells. HUVEC cells (Cambrex, CC-2517) were maintained in EGM (Cambrex, CC-3124) at 37°C and 5% CO₂. HUVEC cells were plated at a density 5000 cells/well (96 well plate) in EGM. Following cell attachment (1hour) the EGM-medium was replaced by EBM (Cambrex, CC-3129) + 0.1% FBS (ATTC , 30-2020) and the cells were incubated for 20 hours at 37°C. The medium was replaced by

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EBM +1% FBS, the compounds were serial diluted in DMSO and added to the cells to a final concentration of 0 – 5,000 nM and 1% DMSO. Following a 1 hour pre-incubation at 37°C cells were stimulated with 10ng/ml VEGF (Sigma, V7259) and incubated for 45 hours at 37°C. Cell proliferation was measured by BrdU DNA incorporation for 4 hours and BrdU label was quantitated by ELISA (Roche kit, 16472229) using 1M H₂SO₄ to stop the reaction. Absorbance was measured at 450nm using a reference wavelength at 690nm.

Detailed Description of Figures:

Figure 1 shows that a compound like the first structure may exist in its open-acid form or its cyclic- lactone form or the two forms may co-exist in solution or *in vivo*.

Figure 2 shows the preferred compounds of the invention in acid or open-chain form. There are two variable regions on these compounds. The first variable region is found on the “left end” of the molecule, as shown, which is the substitution on the phenyl ring of the 3-benzyl ether. The second variable region is the side chain on the 5-urea functionality.

Figure 3 shows the preferred compounds of the invention which are all amides. Both these structures and those from Figure 2 show the same core isothiazole ring with its 3-benzyl ether, 4- carboxamide and 5-urea functionality. The three variable regions on the amide compounds are found in the substitution of the phenyl ring of the benzyl ether, the length of the side chain on the 5- urea functionality and the type of substitution on the amide of the side chain.

Figure 4 shows the scheme used to synthesize the acid compounds in Figure 2. The intermediates until isothiazole **1-6** were obtained according literature methods (Larson, E. R.; Noe, M. C.; Gant, T. G. Isothiazole Derivatives Useful As Anticancer Agents. International publication number WO 99/62890; international publication date 12/09/1999. Larson, E. R.; Noe, M. C.; Gant, T. G. Isothiazole Derivatives Useful As Anticancer Agents. United States patent US 6,235,764. Date of patent 5/22/2001) and are not further described in this report. However, the purification method for **1-5** was changed significantly and this process is therefore

detailed in the experimental section. Accordingly, crude **1-5** was purified by crystallization from hot DMF, which proved more convenient than the tedious, repeated centrifugation procedure given in the patents cited above.

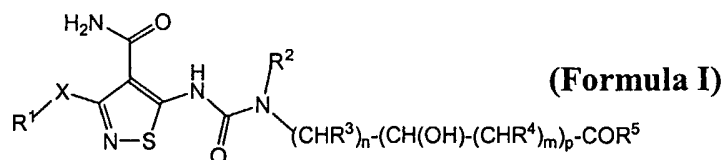
Figure 5 shows the completion of the synthesis of **1-10** which is representative of the acid compounds. Simple deprotection of the acetonide group is followed by neutralizing the carboxylic acid to give the desired sodium salt **1-10**.

Figure 6 shows the scheme used for the synthesis of compounds like **2-3**. This starts from compound **1-6** and substitutes a different primary amine for the urea formation than the earlier scheme in Figures 4 and 5.

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What is claimed is:

1. A compound of Formula (I):



wherein:

X is O or S;

R¹ is selected from the group consisting of (C1-C6) alkyl, (C3-C8) cycloalkyl, (C6-C10) arylalkyl, (C5-C9) heteroarylalkyl, substituted (C6-C10) arylalkyl, and substituted (C5-C9) heteroarylalkyl;

R² and R³ are independently hydrogen or (C1-C6) alkyl;

R⁴ is selected from the group consisting of hydrogen, (C1-C6) alkyl, and hydroxyl;

n and m are independently 0, 1, 2, or 3; p is independently 1, 2, or 3;

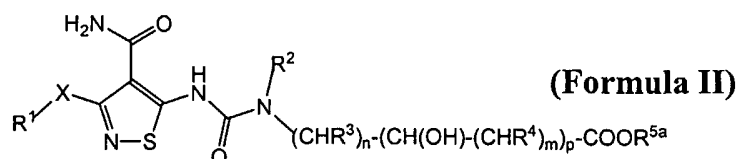
R⁵ is selected from the group consisting of hydroxyl, (C1-C6) alkoxy, (C3-C8) cycloalkoxy, substituted or unsubstituted O-(C6-C10) aryl, and NR⁶R⁷;

R⁶ and R⁷ are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy, (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C10) aryl, (C5-C9) heteroaryl, (C3-C8) cycloalkyl carboxylic acid; or R⁶ and R⁷ together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; or NR⁶R⁷ may form a cyclic ring containing 0-3 additional heteroatoms selected from N, O, or S;

or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or prodrug thereof.

2. The compound, salt, tautomer, or prodrug according to claim 1 represented by Formula (II):

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wherein:

R^{5a} is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, and substituted or unsubstituted (C6-C10) aryl.

3. The compound, salt, tautomer, or prodrug according to claim 2 represented by Formula (II): wherein:

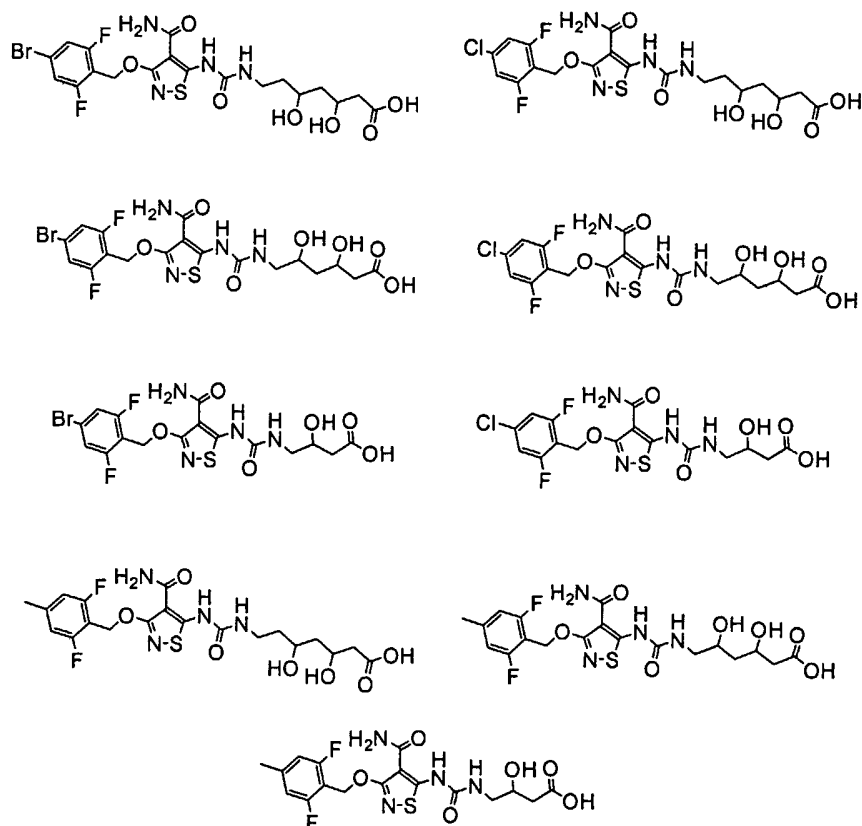
X is O;

R^1 is selected from the group consisting of optionally substituted (C6-C10) arylmethylene and (C5-C9) heteroarylmethylene;

R^2 and R^3 are hydrogen; and

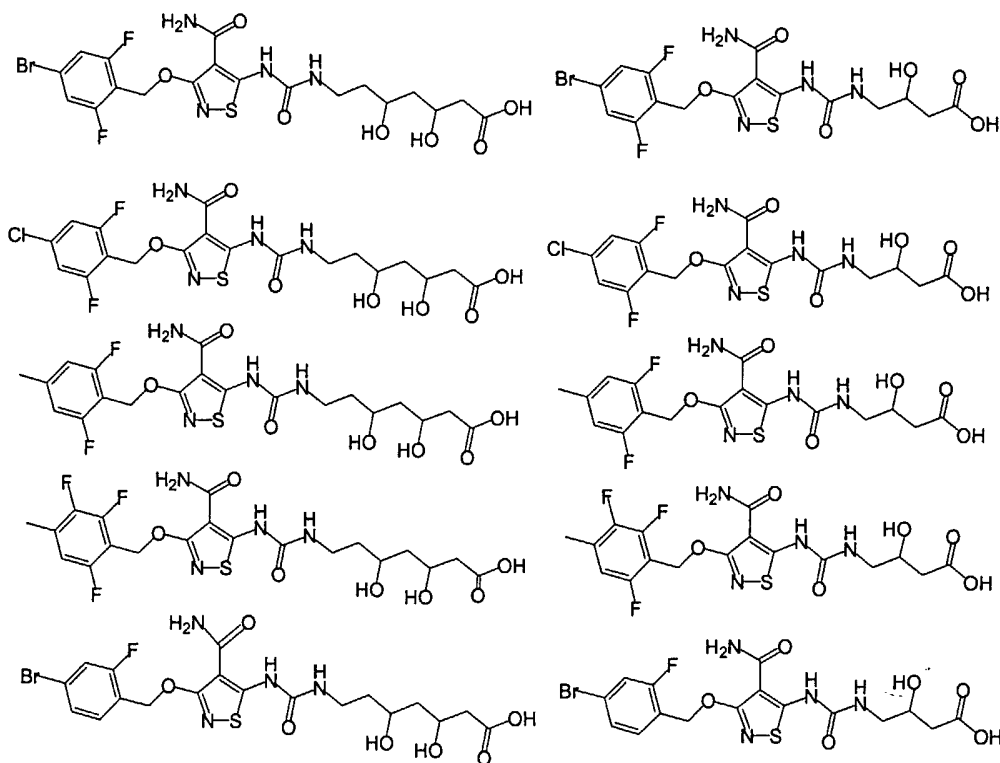
R^4 is selected from the group consisting of hydrogen and hydroxyl.

4. The compound, salt, tautomer, or prodrug according to claim 2 selected from the group represented by the following structures:

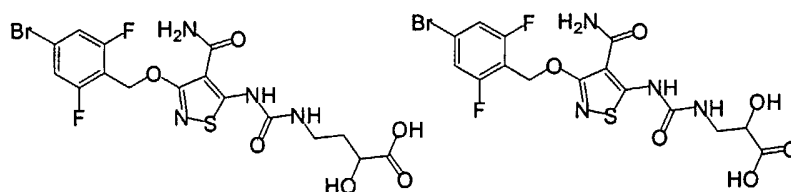


-32-

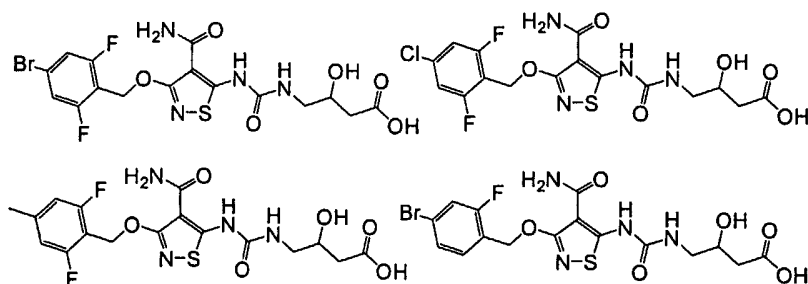
5. The compound, salt, tautomer, or prodrug according to claim 2 selected from the group represented by the following structures:



6. The compound, salt, tautomer, or prodrug according to claim 2 selected from the group represented by the following structures:



7. The compound, salt, tautomer, or prodrug according to claim 2 selected from the group represented by the following structures:



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8. The compound, salt, tautomer, or prodrug according to claim 1 wherein R^5 is NR^6R^7 .

9. The compound, salt, tautomer, or prodrug according to claim 8 wherein:

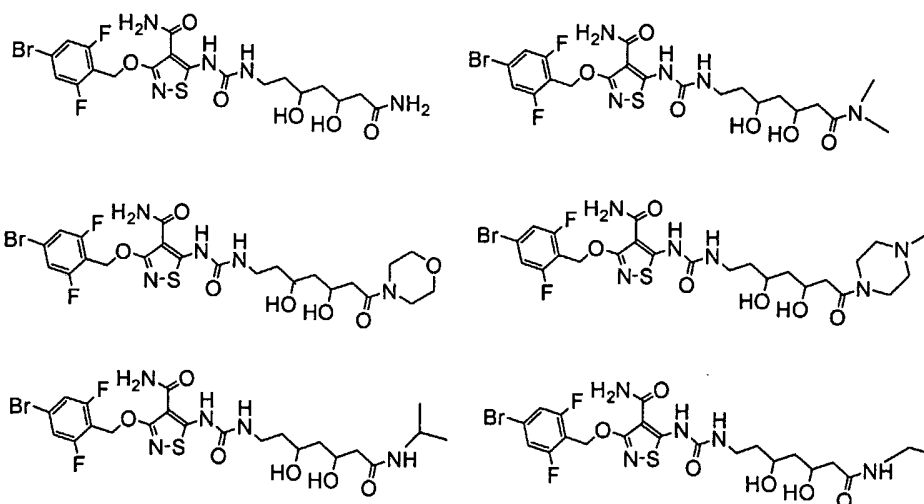
X is O;

R^1 is selected from the group consisting of optionally substituted (C6-C10) arylmethylene and (C5-C9) heteroarylmethylene;

R^2 and R^3 are hydrogen; and

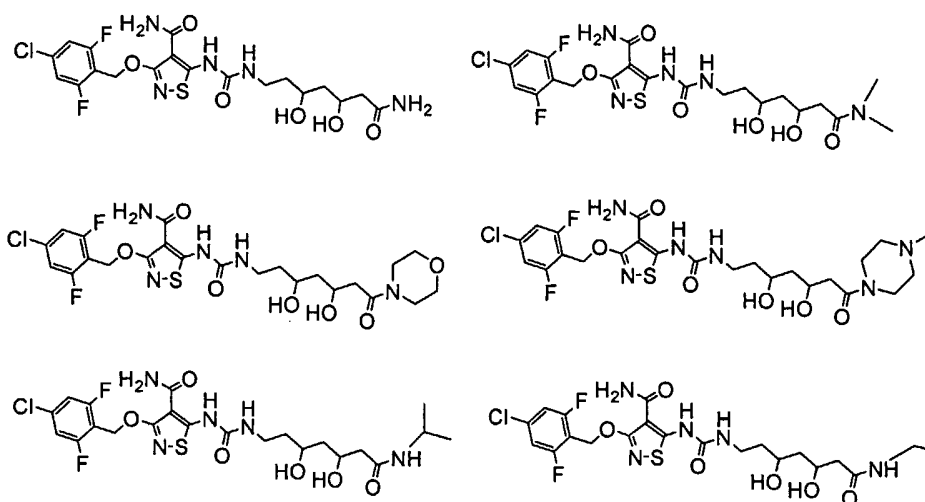
R^4 is selected from the group consisting of hydrogen and hydroxyl.

10. The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:

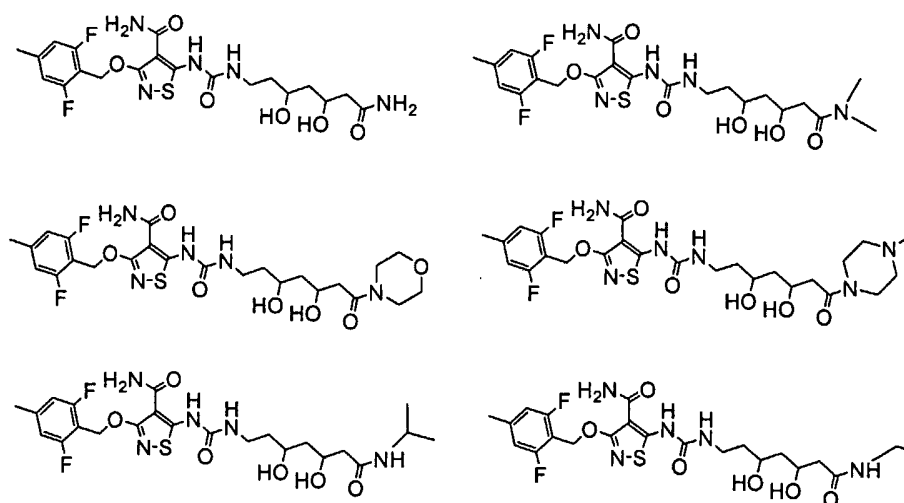


-34-

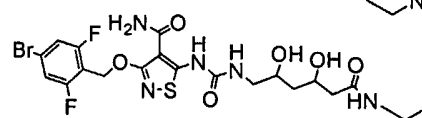
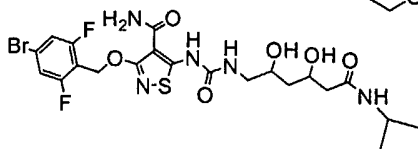
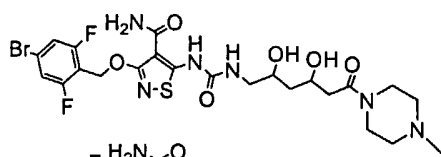
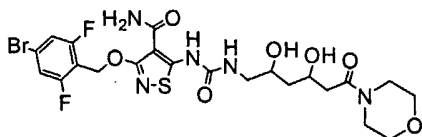
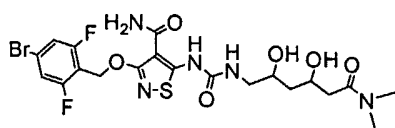
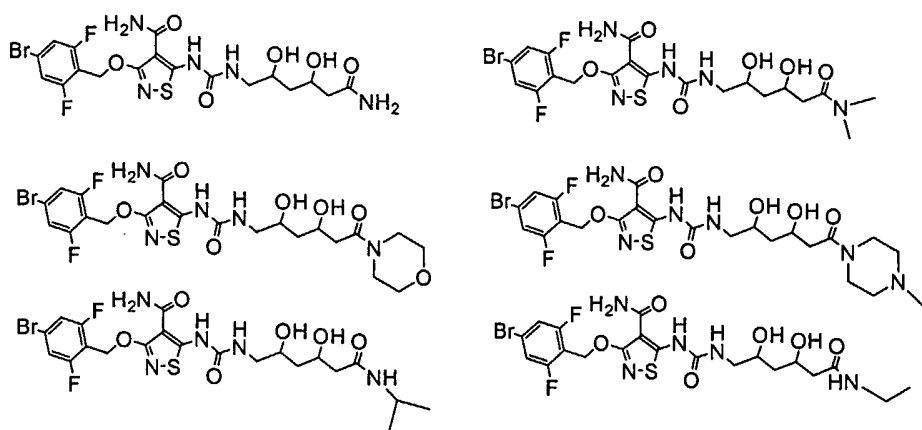
11 . The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:



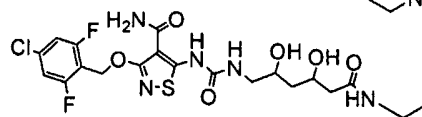
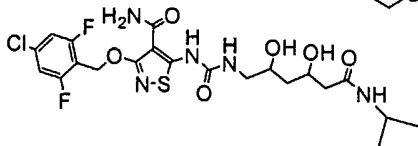
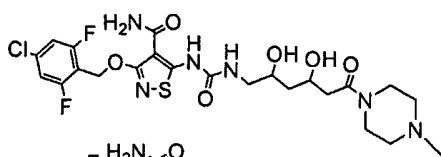
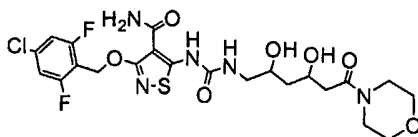
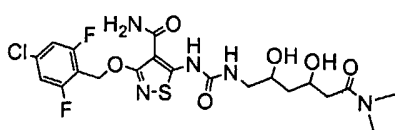
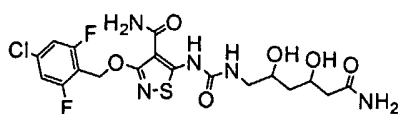
12 . The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:



13 . The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:

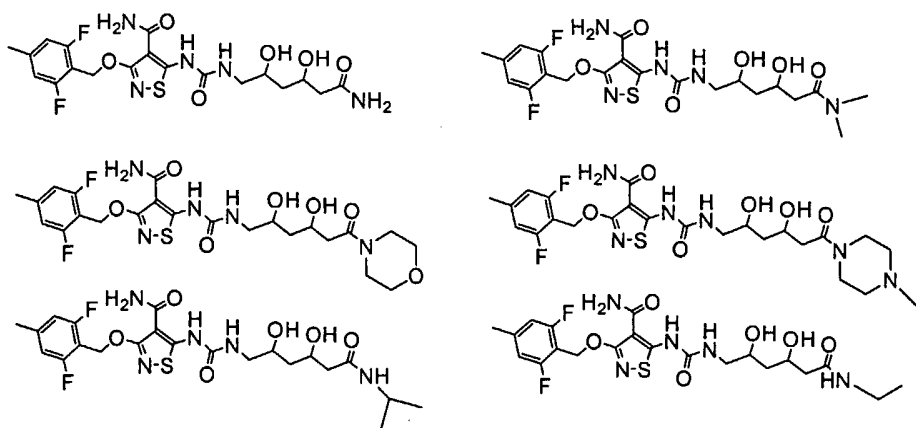


14 . The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:

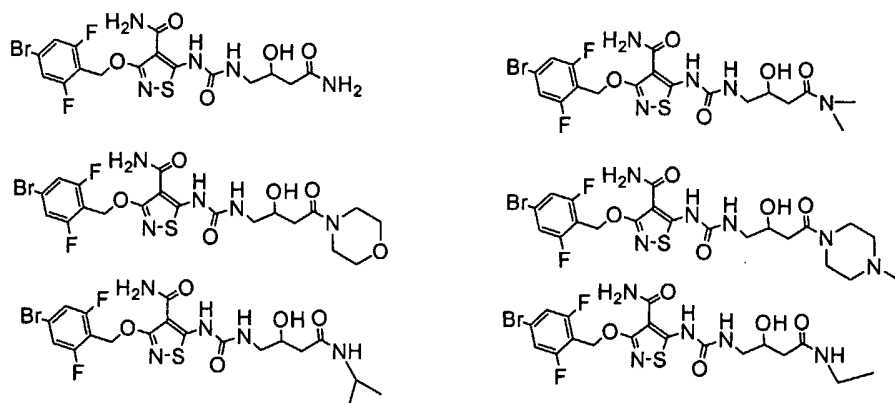


-36-

15 . The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:

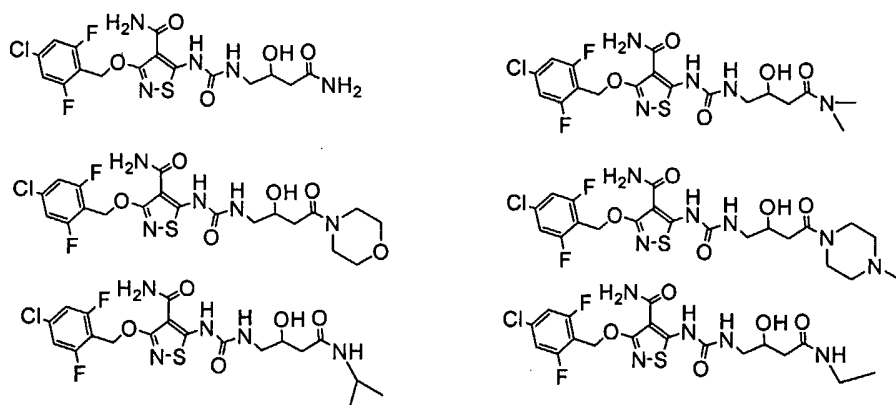


16 . The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:

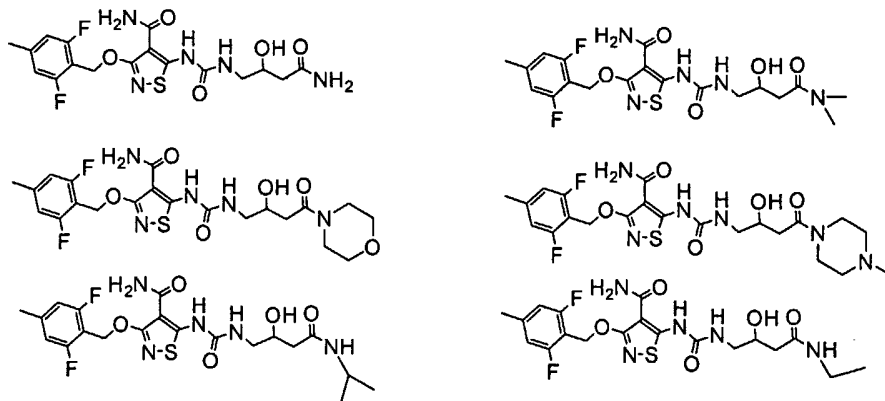


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17 . The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:

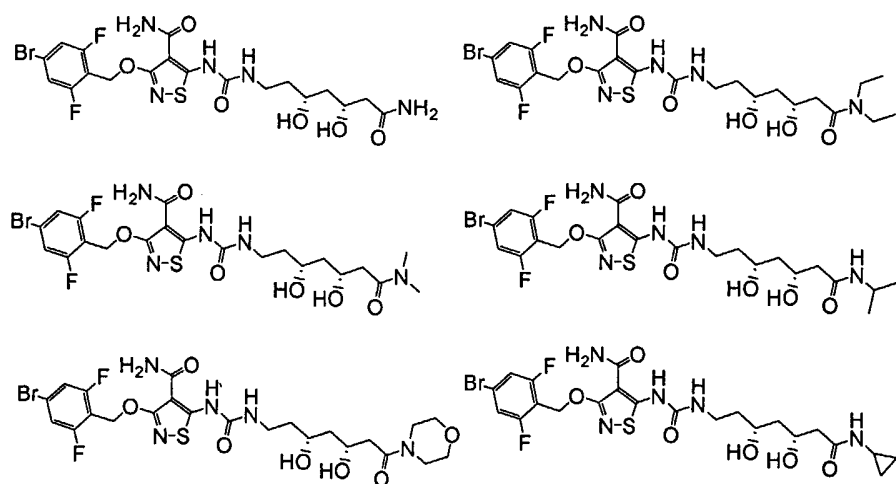


18 . The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:

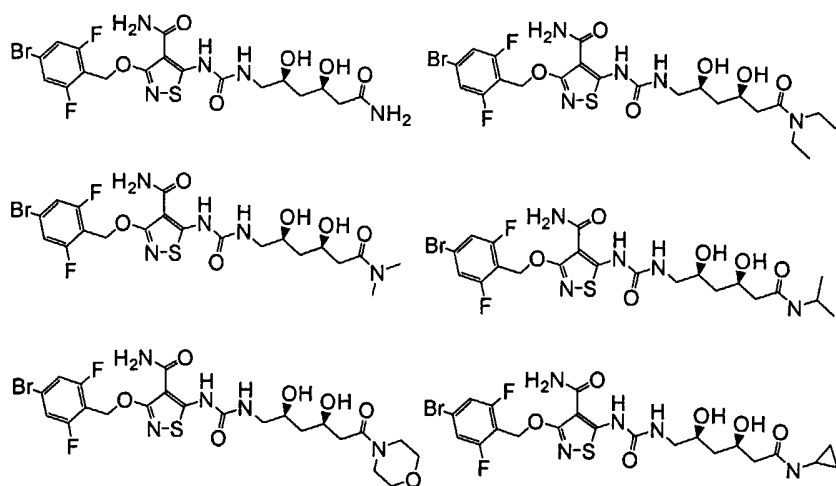


-38-

19. The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:

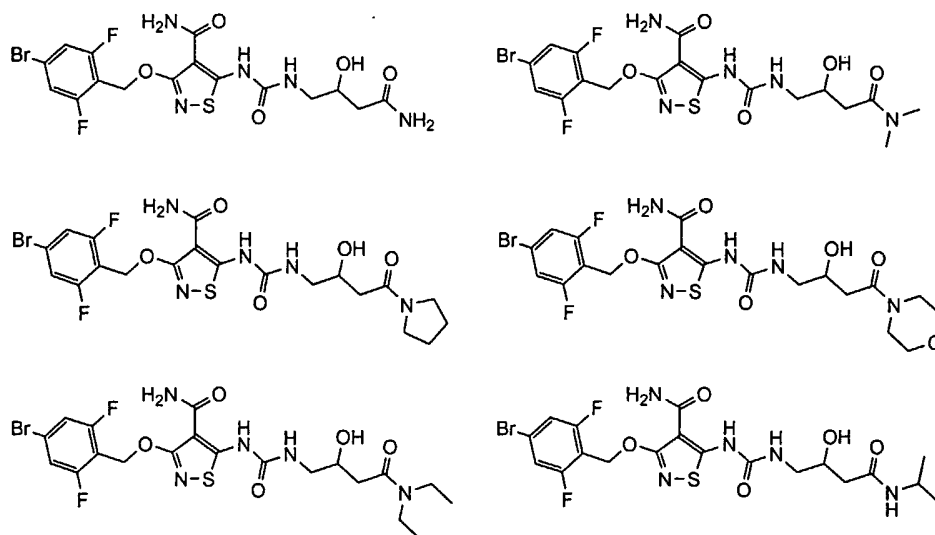


20. The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:

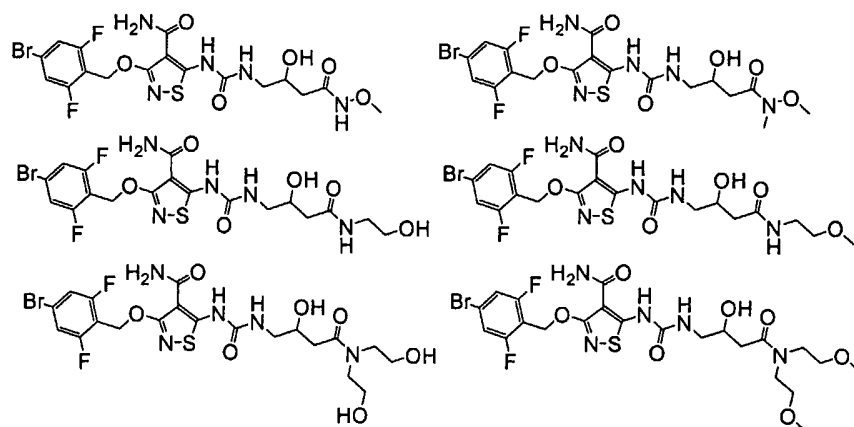


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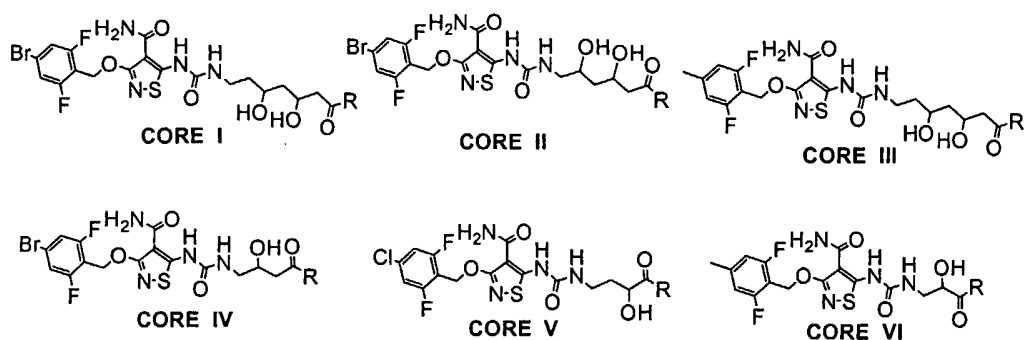
21. The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:



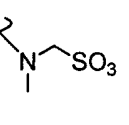
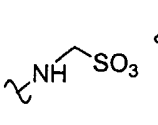
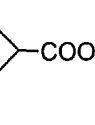
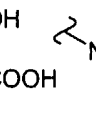
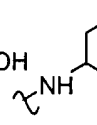
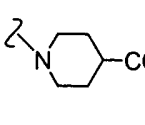
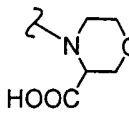
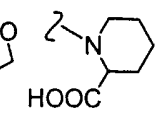
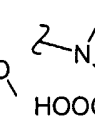
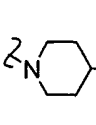
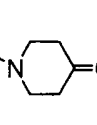
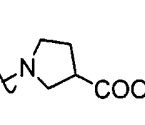
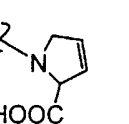
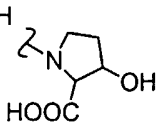
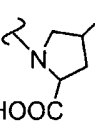
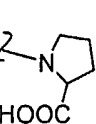
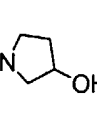
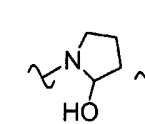
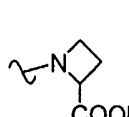
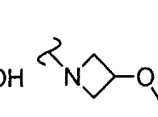
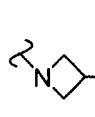
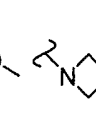
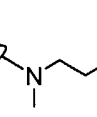
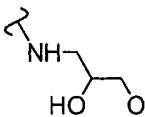
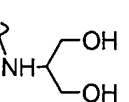
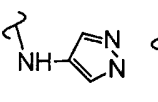
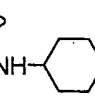
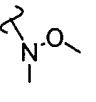
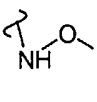
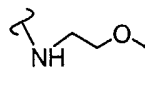
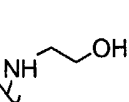
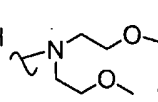
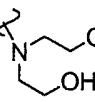
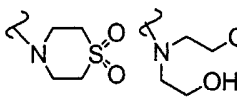
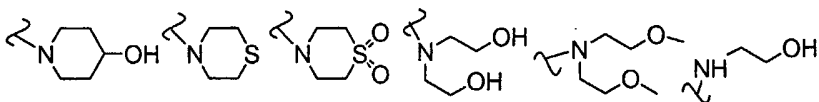
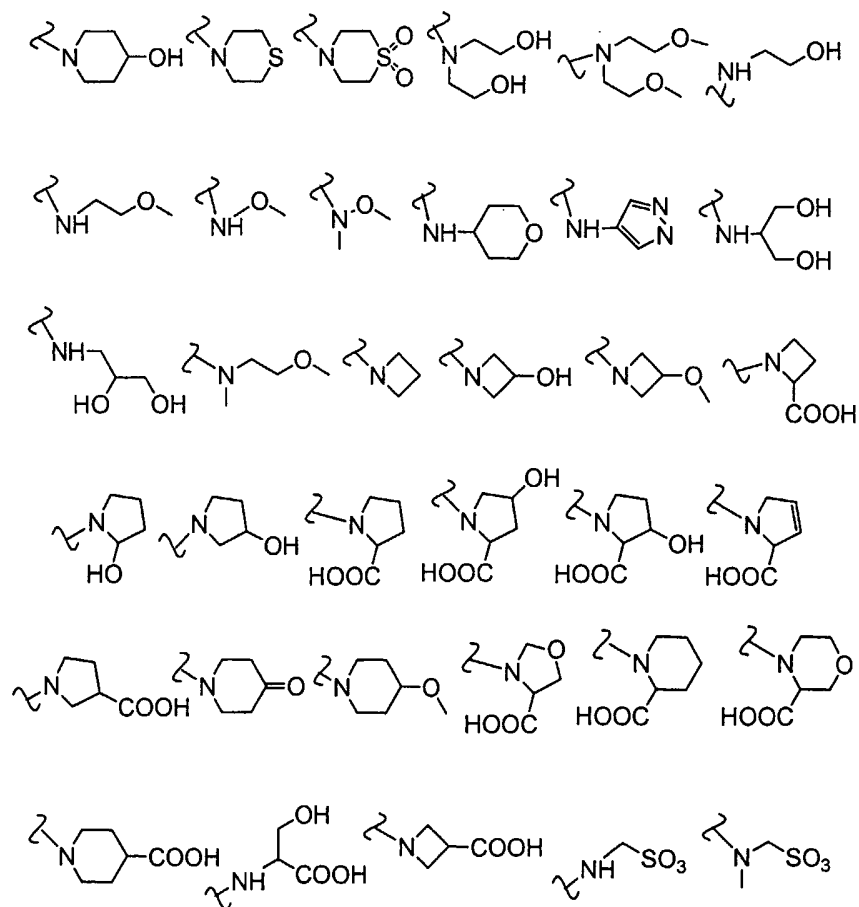
22. The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:



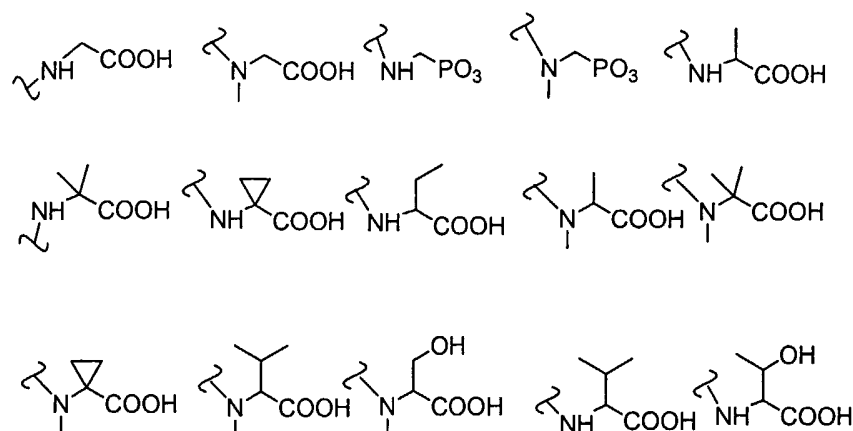
23 . The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:



wherein: R is selected from the group consisting of radical represented by the following structures:



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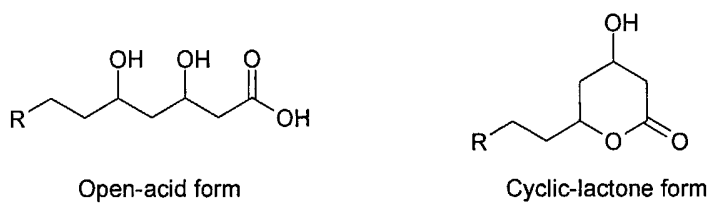
24. The compound, salt, tautomer, or prodrug according to any of claims 1-23 with the following provisos:

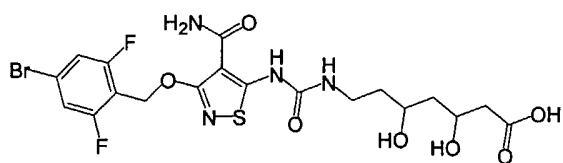
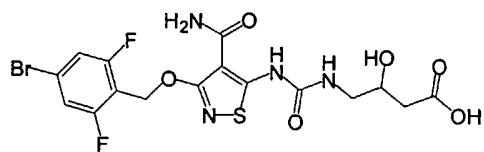
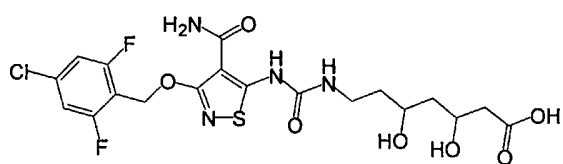
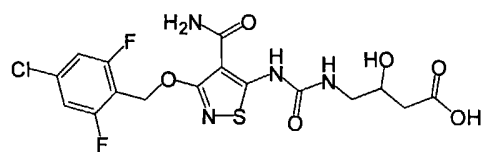
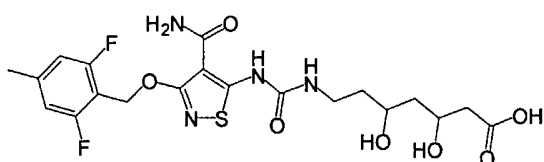
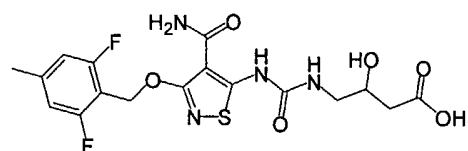
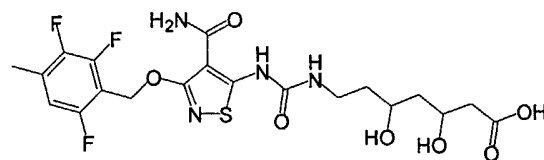
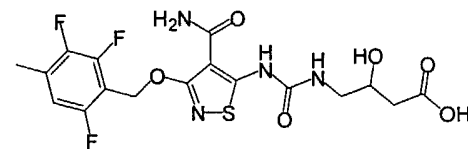
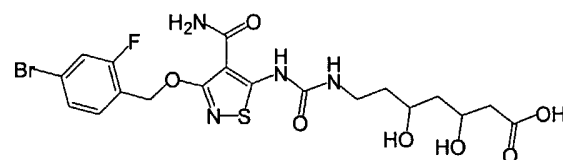
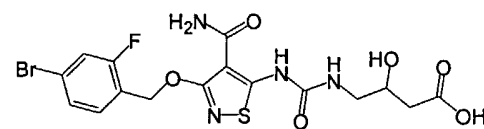
the compound, salt, tautomer, or prodrug of claim 2 is excluded or
the compound, salt, tautomer, or prodrug of claim 3 is excluded or
the compound, salt, tautomer, or prodrug of claim 4 is excluded or
the compound, salt, tautomer, or prodrug of claim 5 is excluded or
the compound, salt, tautomer, or prodrug of claim 6 is excluded or
the compound, salt, tautomer, or prodrug of claim 7 is excluded or
the compound, salt, tautomer, or prodrug of claim 8 is excluded or
the compound, salt, tautomer, or prodrug of claim 9 is excluded or
the compound, salt, tautomer, or prodrug of claim 10 is excluded or
the compound, salt, tautomer, or prodrug of claim 11 is excluded or
the compound, salt, tautomer, or prodrug of claim 12 is excluded or
the compound, salt, tautomer, or prodrug of claim 13 is excluded or
the compound, salt, tautomer, or prodrug of claim 14 is excluded or
the compound, salt, tautomer, or prodrug of claim 15 is excluded or
the compound, salt, tautomer, or prodrug of claim 16 is excluded or
the compound, salt, tautomer, or prodrug of claim 17 is excluded or
the compound, salt, tautomer, or prodrug of claim 18 is excluded or
the compound, salt, tautomer, or prodrug of claim 19 is excluded or
the compound, salt, tautomer, or prodrug of claim 20 is excluded or
the compound, salt, tautomer, or prodrug of claim 21 is excluded or
the compound, salt, tautomer, or prodrug of claim 22 is excluded or
the compound, salt, tautomer, or prodrug of claim 23 is excluded.

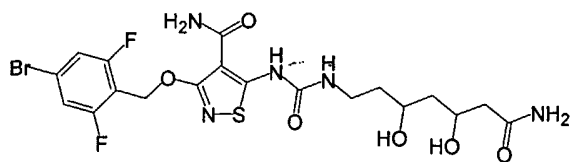
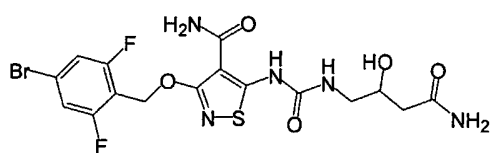
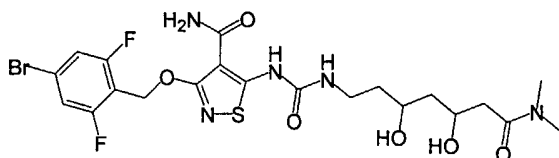
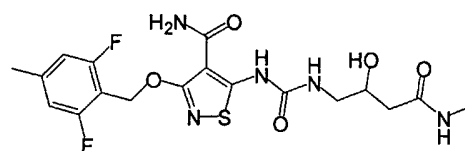
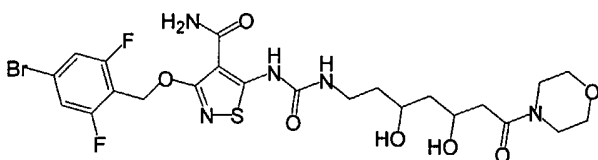
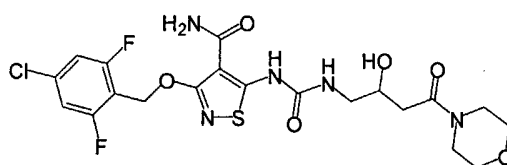
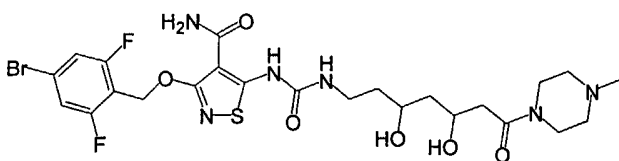
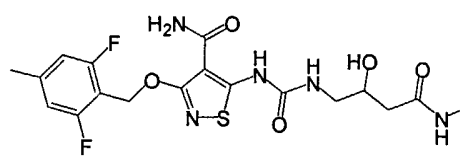
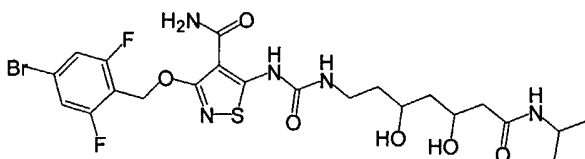
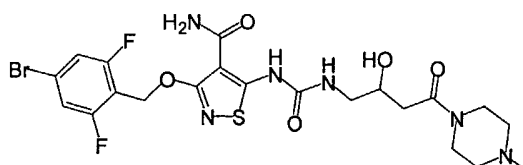
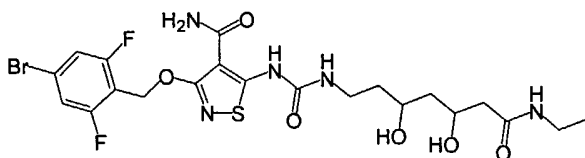
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25. A method for the modulation of the catalytic activity of a protein kinase with a compound or salt of any one of claims 1-24.

26 . The method of claim 25, wherein said protein kinase is selected from the group consisting of VEGF receptors, PDGF receptors.

**Figure 1**

**1****2****3****4****5****6****7****8****9****10****Figure 2**

**11****12****13****14****15****16****17****18****19****20****21****Figure 3**

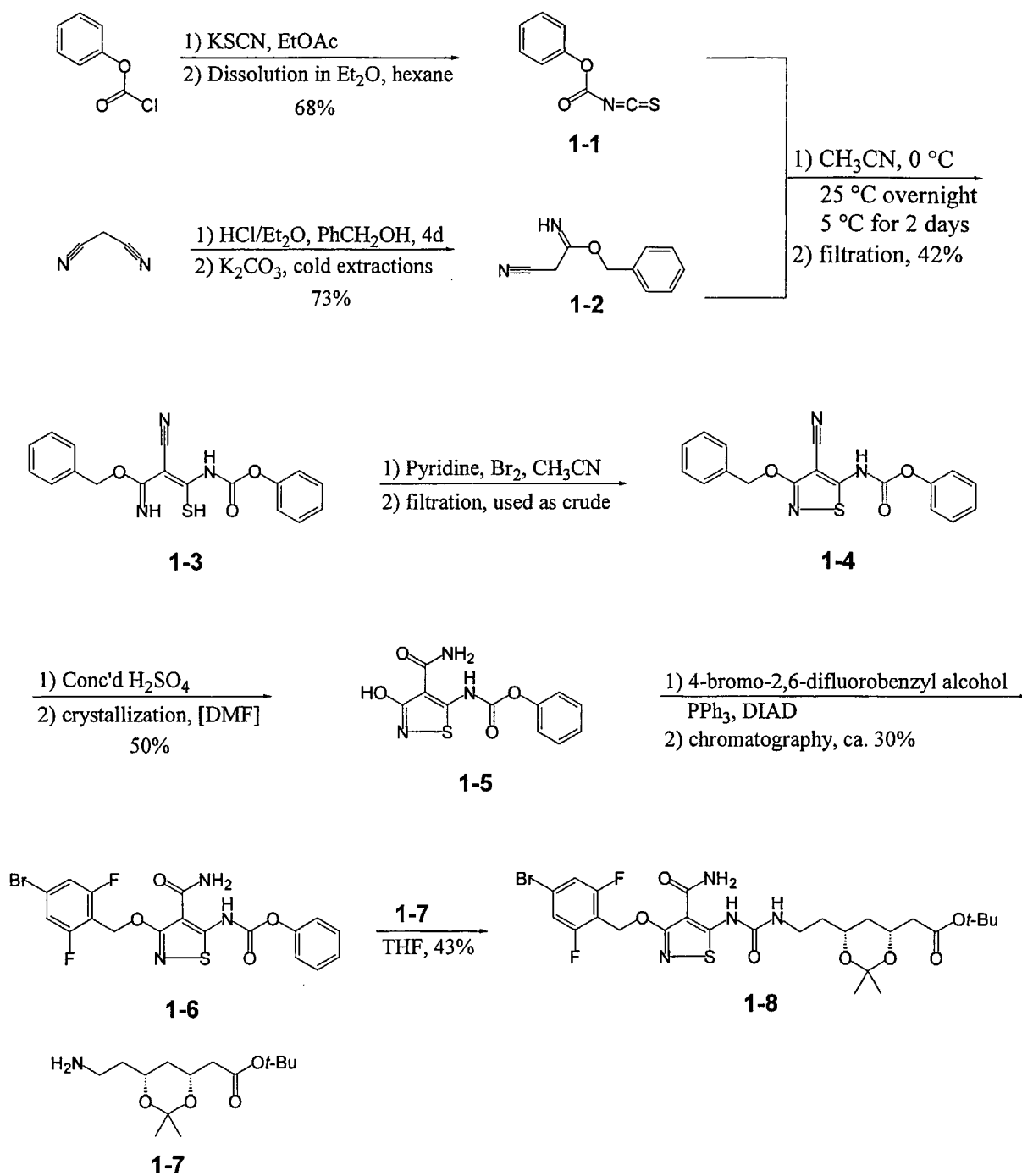


Figure 4

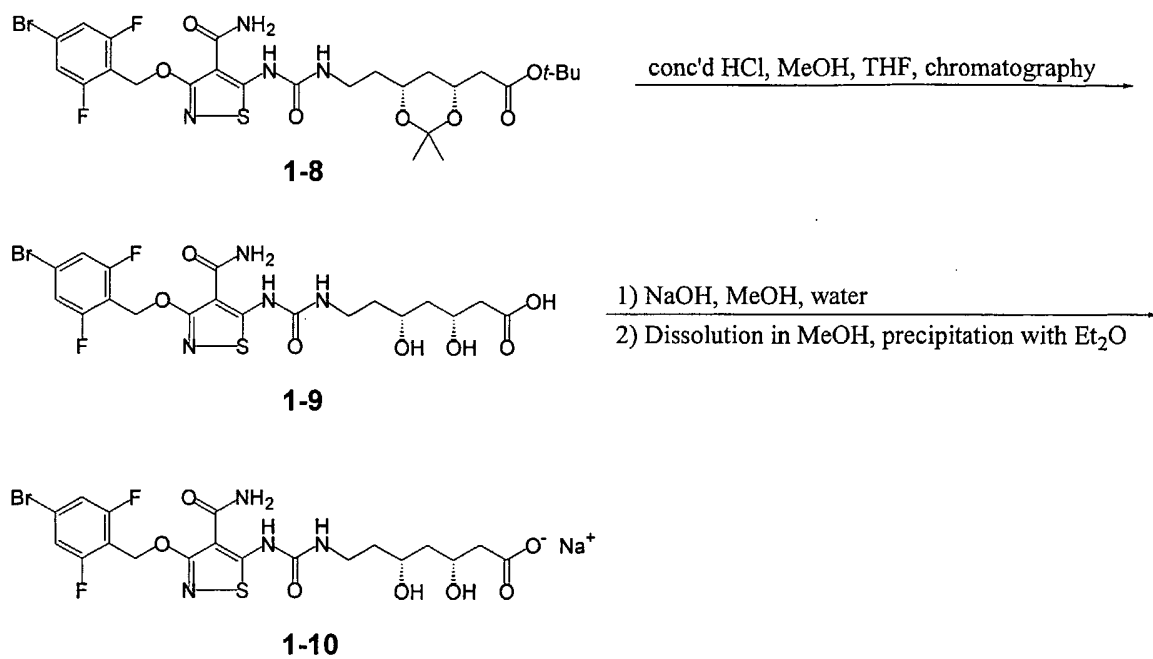


Figure 5

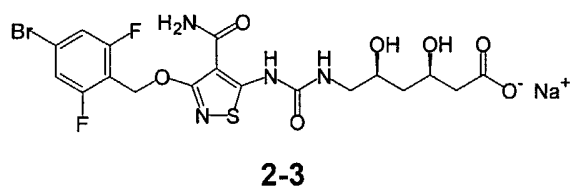
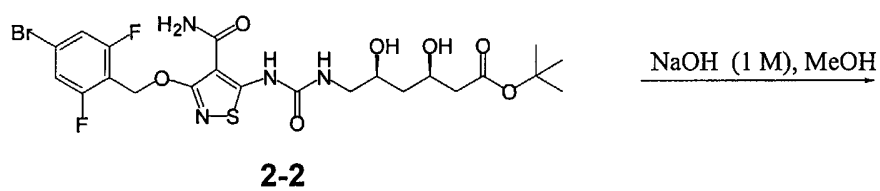
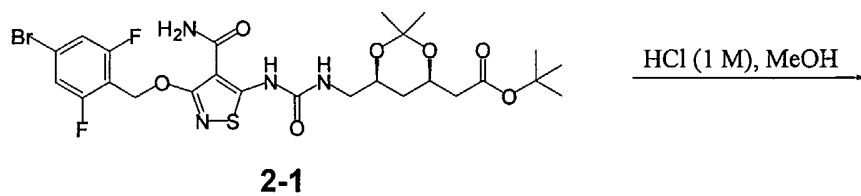
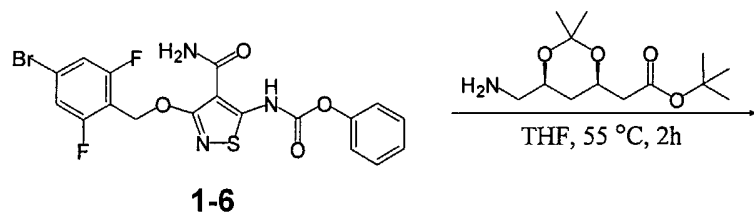


Figure 6