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(54) **Title**: ORGANIC COMPOUNDS

(57) **Abstract**: The present invention relates to compounds and compositions useful for inhibiting and/or reducing platelet deposition, adhesion and/or aggregation. The present invention further relates to methods for the treatment or prophylaxis of thrombotic disorders, including stroke, myocardial infarction, unstable angina, peripheral vascular disease, abrupt closure following angioplasty or stent placement and thrombosis as a result of vascular surgery.

ORGANIC COMPOUNDS

The present invention was made with funding from National Institutes of Health Grant No. HL019278. The United States Government has certain rights in this invention.

Field of the Invention

[0001] The present invention relates to methods for screening compounds and compositions useful for inhibiting or reducing platelet deposition, adhesion and/or aggregation. The present invention further relates to methods of treatment or prophylaxis of thrombotic disorders, including stroke, myocardial infarction, unstable angina, abrupt closure following angioplasty or stent placement, thrombosis induced by peripheral vascular surgery, peripheral vascular disease or thrombotic disorders resulting from atrial fibrillation or inflammation.

Background

[0002] Platelet accumulation at sites of vascular injury is a dynamic process that mediates formation of both the primary hemostatic plug and pathologic thrombus formation. The mechanisms by which platelet surface proteins direct platelet recruitment to thrombi under flow conditions have been studied in detail. In addition to directing initial platelet adhesion, cell-surface receptor interactions activate intracellular signaling. Intracellular signaling stimulates the release of thrombogenic substances from platelet granules. Signaling also mediates activation of the platelet integrin αIIbβ3 that facilitates firm adhesion of the platelets at the sites of injury.

[0003] Arterial thrombosis mediates tissue infarction in coronary artery disease, cerebrovascular disease, and peripheral vascular disease, and, thus, is the single most common cause of morbidity and mortality in the United States. Platelets are key mediators of arterial thrombosis. Thus, the identification of compounds that inhibit platelet function is of great importance to medicine.

[0004] Platelets form the body's primary means of hemostasis and, as such, have developed an elaborate mechanism of surveying the vasculature for defects in endothelial integrity. This mechanism involves the ability to respond to subendothelial matrices, shear forces, neighboring platelets, the adrenal axis, as well

as soluble proteinacious, nucleotide, and lipid signals. Despite this plethora of physiologic activators, the platelet has only a small repertoire of major functional outputs. Upon activation, platelets change shape, aggregate, and secrete their granular contents. The process of platelet activation involves the expression of activities not shared by functionally intact resting platelets, including, for example, ATP release, serotonin release, lysosomal release, alpha granule release, dense granule release, and cell surface expression of markers of activated platelets [including, but not limited to P-selectin and activated αIIbβ3 (GPIIb/IIIa) receptor]. In addition, platelet activation results in the aggregation of platelets with each other and attachment to non-platelet surrounding cells. The granular contents of platelets supply additional adhesion molecules, growth factors, coagulation enzymes and other specialized molecules instrumental in the process of thrombus formation and the initiation of the healing process.

[0005] In addition to coronary artery disease/myocardial infarction, cerebrovascular disease and peripheral vascular disease, diseases and disorders associated with inappropriate platelet activity and arterial thrombosis also include, for example, stable and unstable angina, transient ischemic attacks, placental insufficiency, unwanted thromboses subsequent to surgical procedures (e.g., aortocoronary bypass surgery, angioplasty and stent placement, and heart valve replacement), or thromboses subsequent to atrial fibrillation. Inhibitors of platelet activity can provide therapeutic and preventive benefits for each of these diseases or disorders. It is also possible that inappropriate platelet activation plays a role in venous thrombosis, such that platelet inhibitors can be useful for the treatment or prophylaxis of disorders associated with such thromboses.

[0006] A connection is emerging between platelet activation and inflammation, particularly allergic inflammation (e.g., in asthma) and inflammation at the sites of atherosclerotic damage. Therefore, compounds that inhibit platelet activation can also be useful in the treatment or prophylaxis of disorders involving inflammation.

[0007] There are a number of agents presently available that target platelet function. For example, aspirin is a relatively weak platelet inhibitor. However, aspirin can cause life-threatening allergic reactions in sensitive individuals.

[0008] Another platelet inhibiting agent is ticlopidine (Ticlid.TM., Roche Pharmaceuticals). Because it requires the production of active metabolites to be effective, the effect of ticlopidine is delayed 24-48 hours. The drug can also cause thrombotic thrombocytopenic purpura as well as life threatening leukopenia, nausea, abdominal pain, dyspepsia, diarrhea and skin rash.

[0009] Clopidogrel (Plavix.TM., Bristol-Meyers Squibb/Sanofi Pharmaceuticals) is another platelet inhibitor that requires the generation of active metabolites for its therapeutic efficacy. Therefore, clopidogrel also has a delay of at least several hours for its effect. Clopidogrel can also cause thrombotic thrombocytopenia purpura. The drug has also been associated with a number of side effects, including rash, edema, hypertension, hypercholesterolemia, nausea, abdominal pain, dyspepsia, diarrhea, urinary tract infections, liver enzyme elevations and arthralgia.

[0010] Recently, prasugrel was approved as a $P2Y_{12}$ inhibitor for use as a platelet inhibitor, but similar to clopidogrel, major bleeding, including non-fatal as well as fatal bleeding was observed.

[0011] The platelet inhibitory agent abciximab (c7E3 Fab, Reopro®, manufacturer-Centocor B. V., distributor-Eli Lilly and Co.) is only available in a parenteral form. The drug can cause severe thrombocytopenia. Its antiplatelet effects last for several days unless platelet transfusions are given and, therefore, may complicate surgery that is sometimes required in the setting of life-threatening arterial occlusion (e.g., emergent cardiac surgery in the setting of a myocardial infarction).

[0012] There is only limited clinical experience with the oral anti-αIIbβ3 agents lamifiban, sibrafiban, orbofiban and xemilofiban, none of which are approved for human use. Similarly, clinical experience is limited with the phosphodiesterase inhibitors cilostazol, trapidil and trifusal. There is more clinical experience with the phosphodiesterase inhibitor dipyridamole, but its activity is relatively weak and so it is not frequently used unless combined with aspirin.

[0013] There is a need in the art for additional platelet adhesion and aggregation inhibitory agents for the treatment and prophylaxis of diseases or disorders associated with abnormalities in platelet adhesion and aggregation.

[0014] It is known that integrin αIIbβ3 is a receptor on the surface of human platelets. As a heterodimeric complex composed of both αIIb and β3 subunits, the

dimer is responsible for binding adhesive plasma proteins, most notably fibrinogen and von Willebrand factor (vWF). The binding of fibrinogen, vWF and other ligands by αIIbβ3 is mediated principally though the peptide recognition sequence Arg-Gly-Asp (RGD) or the fibrinogen γ chain dodecapeptide HHLGGAKQAGDV. Conformational changes in αIIbβ3 are thought to occur upon the binding of ligand to the receptor, leading to the exposure of ligand-induced binding sites (LIBS) as detected by LIBS-specific monoclonal antibodies (mAbs). Electron microscopy and crystal structures of the integrin in complex with various R(K)GD-like ligands support the theory that the integrin undergoes a major conformational change after or during ligand binding.

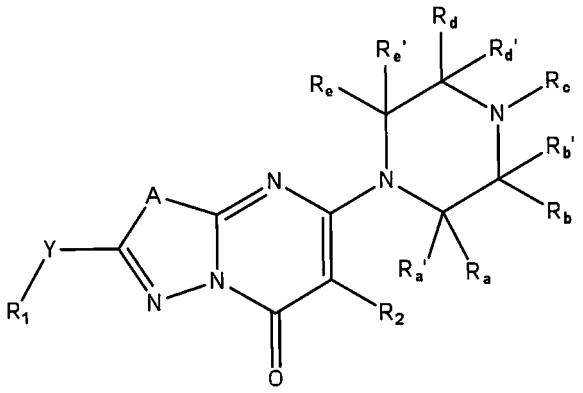
[0015] Currently two small molecule inhibitors of the αIIbβ3 exist: a cyclic homoarginine-glycine-aspartic acid peptide (eptifibatide) and an RGD peptidomimetic (tirofiban). Both inhibitors act by competitively blocking the binding site for fibrinogen. Although both compounds have demonstrated significant clinical benefit, tirofiban (Aggrastat.TM., Merck and Co., Inc.) is only available in a parenteral form and can cause thrombocytopenia, dizziness and vasovagal reactions. Eptifibatide (Integrilin.TM., COR Therapeutics, Inc., Key Pharmaceuticals Inc.) is also only available for parenteral administration and it too can cause thrombocytopenia and hypotension. Crystal structure studies of the αIIbβ3 headpiece demonstrates that these inhibitors bind to both αIIb and to the divalent cation in the β3 subunit's metal ion dependant adhesion site (MIDAS). It is believed that the interaction with the MIDAS metal ion induces conformational changes in the β3 which leads to the increased the risk for thrombotic complications following αIIbβ3 inhibitor therapy.

Summary of the Invention

[0016] Previously, our scientists have identified inhibitors of αIIbβ3, particularly 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one, that are capable of inhibiting fibrinogen binding and platelet aggregation without inducing the binding of one or more integrin β3 LIBS-specific monoclonal antibodies (mAbs). These inhibitors are disclosed in U.S. Patent Application No. 12/514,286 (equivalent to U.S. Pub. No. 2010/0150913), the contents of which are hereby incorporated by reference in their entirety. Our scientists have now identified further

inhibitors of αIIbβ3 that are capable of inhibiting fibrinogen binding and platelet aggregation without inducing the binding of integrin β3 LIBS. The present invention thus provides αIIbβ3 antagonists, pharmaceutical compositions comprising αIIbβ3 antagonists, new methods of treatment and prophylaxis using αIIbβ3 antagonists, and new methods to screen for αIIbβ3 antagonists that are capable of inhibiting fibrinogen binding without inducing β3 LIBS binding.

[0017] In the first aspect, the invention provides a compound of Formula P-I:



Formula P-I

wherein:

i) A is S, N(H), CH_2, or O;

ii) R_1 is

phenyl optionally substituted with one or more nitro, -C(O)N(R_5)(R_6)and/or -N(R_5)(R_6) and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

phenyl substituted with one or more nitro and/or -N(R_5)(R_6) and Y is a single bond;

phenyl substituted with -C(O)OR_3 and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

heteroaryl (e.g., pyridyl, pyrazolyl, isoxazolyl, furyl, thienyl) wherein said heteroaryl group is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene);

heteroaryl (e.g., pyridyl, pyrazolyl, thienyl or pyrimidyl) wherein said heteroaryl group is substituted with halo (e.g., fluoro), -C(O)OH, -CH_2C(O)OH, or –NH_2, and Y is arylene (e.g., phenylene), for example R_1 is (pyrazol-1-yl)-4-acetic acid (i.e., -(pyrazol-1-yl)-4-

$CH_2C(O)OH$), thiophen-4-yl-2-carboxylic acid (i.e., -(thiophen-4-yl)-2-C(O)OH), 2-fluoropyrid-4-yl or 2-amino-pyrimid-5-yl, and Y is phenylene;

pyrazolyl, isoxazolyl, furyl or thienyl and Y is arylene (e.g., phenylene) wherein said pyrazolyl, isoxazolyl, furyl or thienyl is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl), -C_{0-4}alkyl-C(O)OH, -$N(R_{13})(R_{14})$, or halo (e.g., fluoro); or

-$C(O)N(R_4)(CH_2)_{1-4}$-$C(O)OR_3$ (e.g., -$C(O)N(H)CH_2C(O)OH$) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$C(O)N(R_4)(CH_2)_{1-4}$-$N(R_{13})(R_{14})$ (e.g., -$C(O)N(H)CH_2$ CH_2NH_2) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$N(R_4)$-C(O)-heteroaryl (e.g., -$N(R_4)$-C(O)-pyridyl) wherein said heteroaryl is optionally substituted with halo (e.g., fluoro) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$N(R_4)$-C_{1-4}alkylene-heteroaryl (e.g., -$N(R_4)$-C_{1-4}alkylene-pyridyl) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$N(R_{10})$-C(O)-$[C(R_{11})(R_{12})]_{1-4}$-$N(R_{13})(R_{14})$, e.g., -$N(R_{10})$-C(O)-$[C(R_{11})(R_{12})]_2$-$N(R_{13})(R_{14})$ or -$N(R_{10})$-C(O)-$C(R_{11})(R_{12})$-$N(R_{13})(R_{14})$, and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene), for example, R_1 is –N(H)-C(O)-CH_2CH_2-NH_2 or –N(H)-C(O)-CH_2-NH_2 and Y is phenylene,

-$N(R_{10})$-C(O)-C_{3-10}heterocycloalkyl (e.g., -$N(R_{10})$-C(O)-piperidine) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

-$N(R_4)(CH_2)_{1-4}$-$C(O)OR_4$ (e.g., -$N(H)CH_2C(O)OH$) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

-$N(R_4)C(O)C(H)(NH_2)CH_2CH_2$-$C(O)OR_3$ and Y is arylene (e.g., phenylene);

-N(R_4)C(O)C(H)(NH_2)CH_2-heteroaryl (e.g., -N(R_4)C(O)C(H)(NH_2)CH_2-thiazol-4-yl and Y is arylene (e.g., phenylene);

-N(R_4)C(O)C(H)(CH_3)-NH_2 and Y is arylene (e.g., phenylene);

-N(R_4)C(O)CH_2CH_2C(H)(NH_2)-COOH and Y is arylene (e.g., phenylene);

-N(R_4)C(O)-C(H)(NH_2)CH_2CH_2-COOH and Y is arylene (e.g., phenylene); or

-N(R_4)C(O)-heteroaryl (-N(H)C(O)isoxazolyl) and Y is arylene (e.g., phenylene);

iii) R_2 is H, halo (e.g., fluoro) or -C_1-C_4alkyl (e.g., methyl);

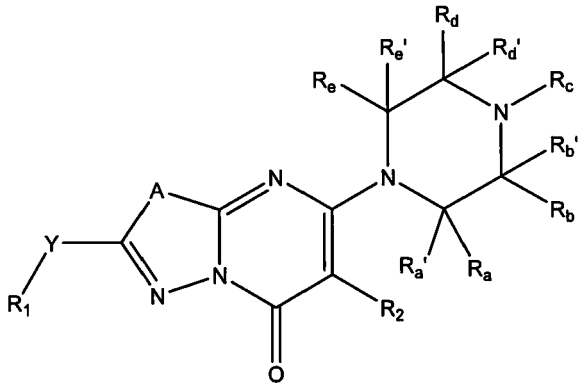
iv) R_a, R_a', R_b, R_b',R_c, R_d, R_d', R_e,and R_e' are independently H or C_1-C_4alkyl (e.g., methyl or ethyl);

v) R_3, R_4, R_5 and R_6 are independently H or C_1-C_4alkyl;

vi) R_{10}, R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl),

in free or salt form.

[0018] In a further embodiment of the first aspect, the invention provides a compound of Formula P-I, wherein said compound is a compound of Formula Q-I:



Formula Q-I

wherein:

i) A is S, N(H), CH_2, or O;

ii) R_1 is

phenyl optionally substituted with one or more nitro and/or -N(R_5)(R_6) and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

phenyl substituted with one or more nitro and/or -N(R_5)(R_6) and Y is a single bond;

phenyl substituted with -C(O)OR_3 and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

heteroaryl (e.g., pyridyl, pyrazolyl, isoxazolyl, furyl, thienyl) wherein said heteroaryl group is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene);

pyrazolyl, isoxazolyl, furyl or thienyl and Y is arylene (e.g., phenylene) wherein said pyrazolyl, isoxazolyl, furyl or thienyl is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl), -C_{0-4}alkyl-C(O)OH, -N(R_{13})(R_{14}), or halo (e.g., fluoro); or

-C(O)N(R_4)(CH_2)$_{1-4}$-C(O)OR_3 (e.g., -C(O)N(H)CH_2C(O)OH) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-C(O)N(R_4)(CH_2)$_{1-4}$-N(R_{13})(R_{14}) (e.g., -C(O)N(H)CH_2 CH_2NH_2) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-N(R_4)-C(O)-heteroaryl (e.g., -N(R_4)-C(O)-pyridyl) wherein said heteroaryl is optionally substituted with halo (e.g., fluoro) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-N(R_4)-C_{1-4}alkylene-heteroaryl (e.g., -N(R_4)-C_{1-4}alkylene-pyridyl) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-N(R_{10})-C(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14}) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-N(R_{10})-C(O)-C_{3-10}heterocycloalkyl (e.g., -N(R_{10})-C(O)-piperidine) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

-N(R_4)(CH_2)$_{1-4}$-C(O)OR_4 (e.g., -N(H)CH_2C(O)OH) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

-$N(R_4)C(O)C(H)(NH_2)CH_2CH_2$-$C(O)OR_3$ and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)C(H)(NH_2)CH_2$-heteroaryl (e.g., -$N(R_4)C(O)C(H)(NH_2)CH_2$-thiazol-4-yl and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)C(H)(CH_3)$-NH_2 and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)CH_2CH_2C(H)(NH_2)$-COOH and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)$-$C(H)(NH_2)CH_2CH_2$-COOH and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)$-heteroaryl (-N(H)C(O)isoxazolyl) and Y is arylene (e.g., phenylene);

iii) R_2 is H, halo (e.g., fluoro) or -C_1-C_4alkyl (e.g., methyl);

iv) R_a, R_a', R_b, R_b',R_c, R_d, R_d', R_e,and R_e' are independently H or C_1-C_4alkyl (e.g., methyl or ethyl);

v) R_3, R_4, R_5 and R_6 are independently H or C_1-C_4alkyl;

vi) R_{10}, R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl),

in free or salt form.

[0019] The invention further provides a compound of Formula P-I, as follows:

2.1. the compound of Formula P-I, wherein

R_1 is

phenyl optionally substituted with one or more nitro, -$C(O)N(R_5)(R_6)$ and/or -$N(R_5)(R_6)$ and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

phenyl substituted with one or more nitro and/or -$N(R_5)(R_6)$ and Y is a single bond;

phenyl substituted with -$C(O)OR_3$ and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

heteroaryl (e.g., pyridyl, pyrazolyl, isoxazolyl, furyl, thienyl) wherein said heteroaryl group is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene);

heteroaryl (e.g., pyridyl, pyrazolyl, thienyl or pyrimidyl) wherein said heteroaryl group is substituted with halo (e.g., fluoro), -C(O)OH, -$CH_2C(O)OH$, or $-NH_2$, and Y is arylene (e.g., phenylene), for example R_1 is (pyrazol-1-yl)-4-acetic acid (i.e., -(pyrazol-1-yl)-4-$CH_2C(O)OH$), thiophen-4-yl-2-carboxylic acid (i.e., -(thiophen-4-yl)-2-C(O)OH), 2-fluoropyrid-4-yl or 2-amino-pyrimid-5-yl, and Y is phenylene;

pyrazolyl, isoxazolyl, furyl or thienyl and Y is arylene (e.g., phenylene) wherein said pyrazolyl, isoxazolyl, furyl or thienyl is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl), -C_{0-4}alkyl-C(O)OH, -$N(R_{13})(R_{14})$, or halo (e.g., fluoro);

-$C(O)N(R_4)(CH_2)_{1-4}$-$C(O)OR_3$ (e.g., -$C(O)N(H)CH_2C(O)OH$) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$C(O)N(R_4)(CH_2)_{1-4}$-$N(R_{13})(R_{14})$ (e.g., -$C(O)N(H)CH_2$ CH_2NH_2) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$N(R_4)$-C(O)-heteroaryl (e.g., -$N(R_4)$-C(O)-pyridyl) wherein said heteroaryl is optionally substituted with halo (e.g., fluoro) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$N(R_4)$-C_{1-4}alkylene-heteroaryl (e.g., -$N(R_4)$-C_{1-4}alkylene-pyridyl) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$N(R_{10})$-C(O)-$[C(R_{11})(R_{12})]_{1-4}$-$N(R_{13})(R_{14})$, e.g., -$N(R_{10})$-C(O)-$C(R_{11})(R_{12})$-$N(R_{13})(R_{14})$, and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene), for example, R_1 is –N(H)-C(O)-CH_2CH_2-NH_2 and Y is phenylene,-$N(R_{10})$-C(O)-C_{3-10}heterocycloalkyl (e.g., -$N(R_{10})$-C(O)-piperidine) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

-$N(R_4)(CH_2)_{1-4}$-$C(O)OR_4$ (e.g., -$N(H)CH_2C(O)OH$) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

-$N(R_4)C(O)C(H)(NH_2)CH_2CH_2$-$C(O)OR_3$ and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)C(H)(NH_2)CH_2$-heteroaryl (e.g., -$N(R_4)C(O)C(H)(NH_2)CH_2$-thiazol-4-yl and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)C(H)(CH_3)$-NH_2 and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)CH_2CH_2C(H)(NH_2)$-COOH and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)$-$C(H)(NH_2)CH_2CH_2$-COOH and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)$-heteroaryl (-N(H)C(O)isoxazolyl) and Y is arylene (e.g., phenylene);

R_2 is H, halo (e.g., fluoro) or -C_1-C_4alkyl (e.g., methyl);

R_a, R_a', R_b, R_b',R_c, R_d, R_d', R_e,and R_e' are independently H or C_1-C_4alkyl (e.g., methyl or ethyl);

R_3, R_4, R_5 and R_6 are independently H or C_1-C_4alkyl;

R_{10}, R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl),

2.2. the compound of Formula P-I, or 2.1, wherein R_1 is phenyl optionally substituted with one or more nitro, -$C(O)N(R_5)(R_6)$ and/or -$N(R_5)(R_6)$ and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

2.3. the compound of Formula P-I, or 2.1 or 2.2, wherein R_1 is phenyl optionally substituted with one or more nitro and/or -$N(R_5)(R_6)$ and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

2.4. the compound of Formula P-I, or 2.1 or 2.2, wherein R_1 is phenyl optionally substituted with -$C(O)N(R_5)(R_6)$ and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

2.5. the compound of Formula P-I, or 2.1, wherein R_1 is heteroaryl (e.g., pyridyl, pyrazolyl, thienyl or pyrimidyl) wherein said heteroaryl group is substituted with halo (e.g., fluoro), -C(O)OH, -$CH_2C(O)OH$, or –NH_2, and Y is arylene (e.g., phenylene), for example R_1 is (pyrazol-1-yl)-4-acetic acid (i.e., -(pyrazol-1-yl)-4-$CH_2C(O)OH$), thiophen-4-yl-2-

carboxylic acid (i.e., -(thiophen-4-yl)-2-C(O)OH), 2-fluoropyrid-4-yl or 2-amino-pyrimid-5-yl, and Y is phenylene;

2.6. the compound of Formula P-I, 2.1 or 2.5, wherein R_1 is pyridyl substituted with halo (e.g., fluoro) and Y is arylene (e.g., phenylene), for example R_1 is 2-fluoropyrid-4-yl and Y is phenylene;

2.7. the compound of Formula P-I, 2.1 or 2.5, wherein R_1 is pyrimidyl substituted with $-NH_2$, and Y is arylene (e.g., phenylene), for example R_1 is 2-amino-pyrimid-5-yl, and Y is phenylene;

2.8. the compound of Formula P-I, or 2.1, wherein R_1 is $-N(R_{10})-C(O)-[C(R_{11})(R_{12})]_{1-4}-N(R_{13})(R_{14})$, e.g., $-N(R_{10})-C(O)-[C(R_{11})(R_{12})]_2-N(R_{13})(R_{14})$ or $-N(R_{10})-C(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14})$, and Y is a single bond, $-C_1-C_4$alkylene (e.g., methylene) or arylene (e.g., phenylene), for example, R_1 is $-N(H)-C(O)-CH_2CH_2-NH_2$ or $-N(H)-C(O)-CH_2-NH_2$ and Y is phenylene;

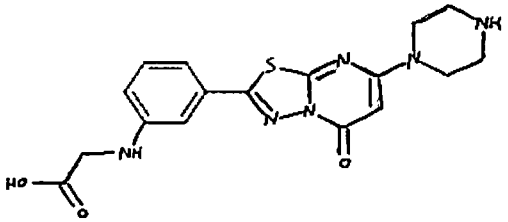
2.9. the compound of Formula P-I, or 2.8, wherein R_1 is $-N(R_{10})-C(O)-[C(R_{11})(R_{12})]_2-N(R_{13})(R_{14})$ or $-N(R_{10})-C(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14})$, and Y is arylene (e.g., phenylene);

2.10. the compound of Formula P-I, or 2.9, wherein R_1 is $-N(H)-C(O)-CH_2CH_2-NH_2$;

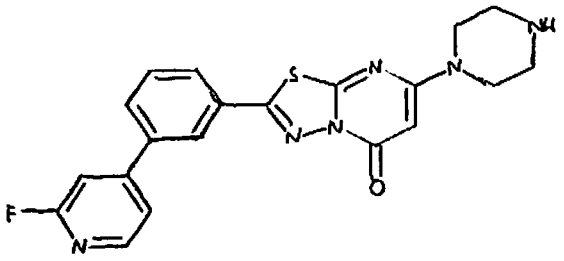
2.11. the compound of Formula P-I, or 2.9, wherein R_1 is $-N(H)-C(O)-CH_2-NH_2$;

2.12. the compound of Formula P-I, or any of formulae 2.1-2.11, wherein any of the substituents Y, R_1-R_{14}, R_a, R_a', R_b, R_b', R_c, R_d, R_d', R_e, and R_e', are independently defined in any of formulae 3.1-3.51, or the remaining substituents (i.e., substituents not yet defined in any of the above formulae) are as defined in any of formulae 3.1-3.51;

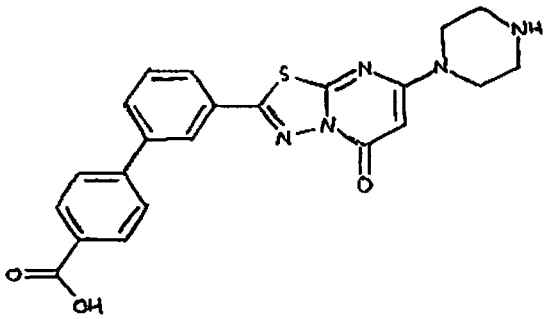
2.13. the compound of Formula P-I, or any of formulae 2.1-2.12, wherein said compound is selected from any of those disclosed in any of formulae 3.45-13.50, and the following:



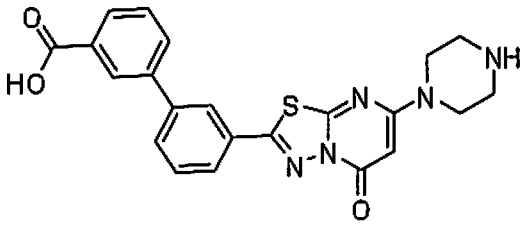
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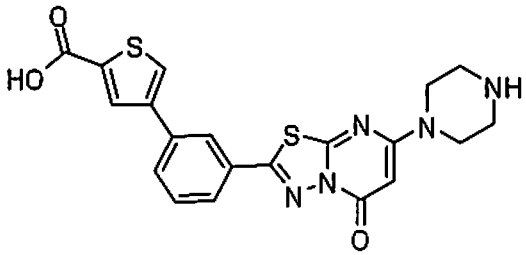
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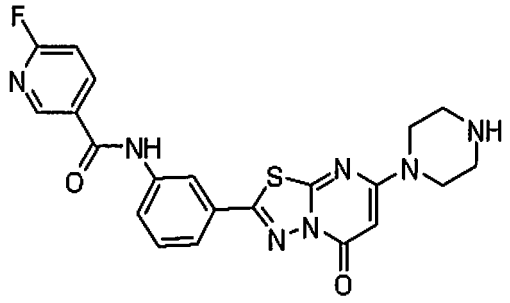
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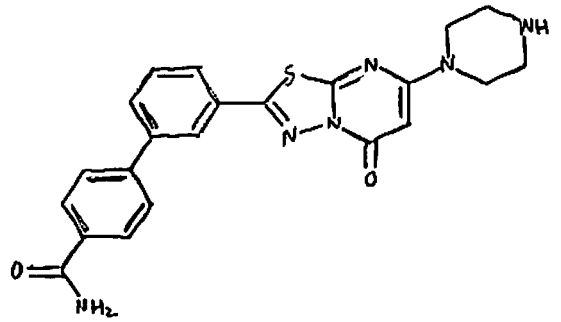
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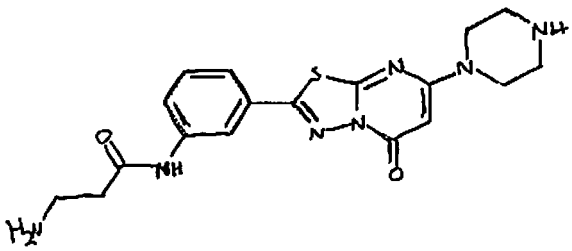
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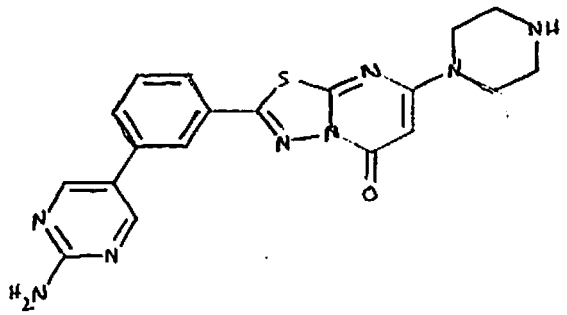
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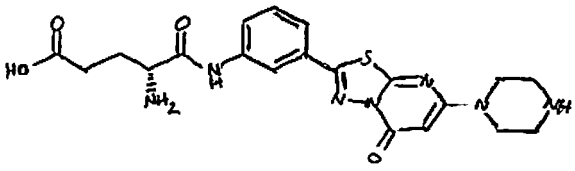
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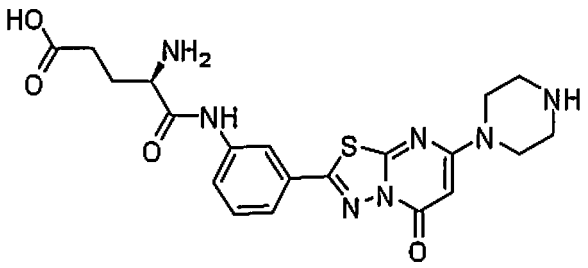
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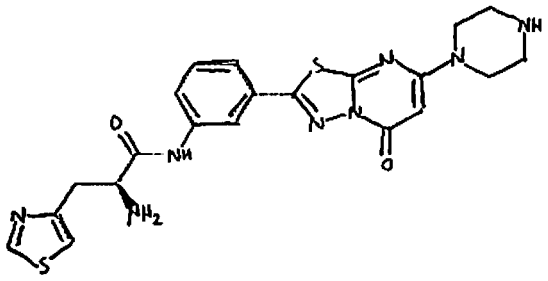
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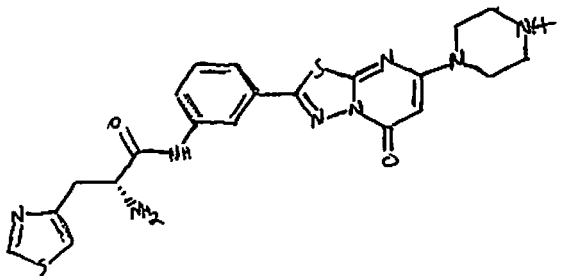
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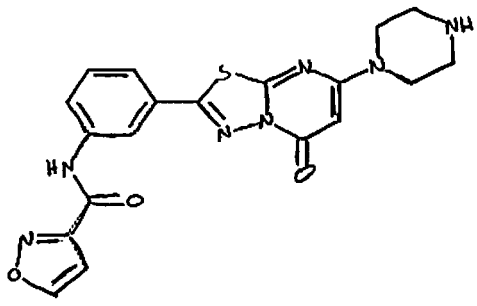
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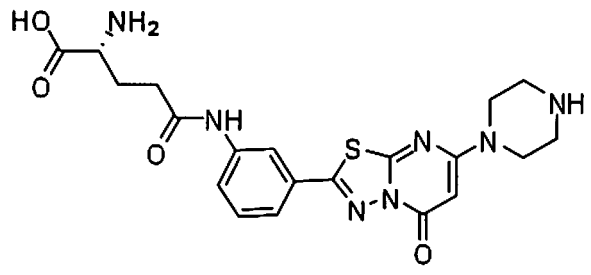
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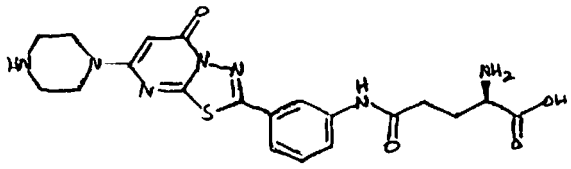
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in free or salt form.

[0020] The invention further provides a compound of Formula Q-I as follows:

3.1 a Compounds of Formula Q-I, wherein A is S, N(H), CH_2, or O;

3.2 a Compound of Formula Q-I or 3.1, wherein A is O;

3.3 a Compound of Formula Q-I or 3.1, wherein A is S;

3.4 a Compound of Formula Q-I, or any of 3.1-3.3, wherein R_1 is phenyl optionally substituted with one or more nitro and/or -$N(R_5)(R_6)$ and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

3.5 a Compound of Formula Q-I or any of 3.1-3.4, wherein R_1 is phenyl substituted with one or more nitro and/or -$N(R_5)(R_6)$ and Y is a single bond;

3.6 a Compound of Formula Q-I, or any of 3.1-3.4 wherein R_1 is phenyl substituted with -$C(O)OR_3$ and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

3.7 a Compound of Formula Q-I or any of 3.1-3.4, wherein R_1 is heteroaryl (e.g., pyridyl, pyrazolyl, isoxazolyl, furyl, thienyl) wherein said heteroaryl group is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl) and Y is a single bond or -C_1-C_4alkylene (e.g., methylene);

3.8 a Compound of Formula Q-I or any of 3.1-3.4, wherein R_1 is pyrazolyl, isoxazolyl, furyl or thienyl and Y is arylene (e.g., phenylene) wherein

pyrazolyl, isoxazolyl, furyl or thienyl is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl) or halo (e.g., fluoro);

3.9 a Compound of Formula Q-I or 3.8, wherein R_1 is pyrazolyl and Y is arylene (e.g., phenylene) wherein said pyrazolyl is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl) or halo (e.g., fluoro);

3.10 a Compound of Formula Q-I or or 3.8 or 3.9, wherein R_1 is pyrazolyl and Y is phenylene wherein said pyrazolyl is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl) or halo (e.g., fluoro);

3.11 formula 3.10, wherein said pyrazolyl is substituted on the meta-position of the phenylene (e.g., relative to the point of attachment);

3.12 a Compound of Formula Q-I or any of 3.1-3.4, wherein R_1 is -$C(O)N(R_4)(CH_2)_{1-4}$-$C(O)OR_3$ (e.g., -$C(O)N(H)CH_2C(O)OH$) , -$C(O)N(R_4)(CH_2)_{1-4}$-$N(R_{13})(R_{14})$ (e.g., -$C(O)N(H)CH_2$ CH_2NH_2), -$N(R_4)$-C(O)-heteroaryl (e.g., -$N(R_4)$-C(O)-pyridyl), -$N(R_4)$-C_{1-4}alkylene-heteroaryl (e.g., -$N(R_4)$-C_{1-4}alkylene-pyridyl), -$N(R_{10})$-C(O)-$C(R_{11})(R_{12})$-$N(R_{13})(R_{14})$, -$N(R_{10})$-C(O)-C_{3-10}heterocycloalkyl (e.g., -$N(R_{10})$-C(O)-piperidine) or -$N(R_4)(CH_2)_{1-4}$-$C(O)OR_4$ (e.g., -$N(H)CH_2C(O)OH$) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

3.13 a Compound of Formula Q-I or 3.12, wherein Y is an arylene (e.g., phenylene);

3.14 a Compound of Formula Q-I or any of 3.1-3.4, wherein:

R_1 is –

phenyl optionally substituted with one or more nitro and/or -$N(R_5)(R_6)$,

phenyl substituted with -$C(O)OR_3$,

pyrazolyl, isoxazolyl, furyl or thienyl wherein said pyrazolyl, isoxazolyl, furyl or thienyl is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl), -C_{0-4}alkyl-C(O)OH, -$N(R_{13})(R_{14})$, or halo (e.g., fluoro),

-$C(O)N(R_4)(CH_2)_{1-4}$-$C(O)OR_3$ (e.g., -$C(O)N(H)CH_2C(O)OH$),

-$C(O)N(R_4)(CH_2)_{1-4}$-$N(R_{13})(R_{14})$ (e.g., -$C(O)N(H)CH_2$ CH_2NH_2),

-N(R_4)-C(O)-heteroaryl (e.g., -N(R_4)-C(O)-pyridyl) wherein said heteroaryl is optionally substituted with halo (e.g., fluoro),
-N(R_4)-C_{1-4}alkylene-heteroaryl (e.g., -N(R_4)-C_{1-4}alkylene-pyridyl),
-N(R_{10})-C(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14}),
-N(R_{10})-C(O)-C_{3-10}heterocycloalkyl (e.g., -N(R_{10})-C(O)-piperidine),
-N(R_4)(CH_2)$_{1-4}$-C(O)OR_4 (e.g., -N(H)CH_2C(O)OH);
-N(R_4)C(O)C(H)(NH_2)CH_2CH_2-C(O)OR_3;
-N(R_4)C(O)C(H)(NH_2)CH_2-heteroaryl (e.g., -N(R_4)C(O)C(H)(NH_2)CH_2-thiazol-4-yl and Y is arylene (e.g., phenylene);
-N(R_4)C(O)C(H)(CH_3)-NH_2;
-N(R_4)C(O)CH_2CH_2C(H)(NH_2)-COOH,
-N(R_4)C(O)-C(H)(NH_2)CH_2CH_2-COOH or,
-N(R_4)C(O)-heteroaryl (-N(H)C(O)isoxazolyl),
and Y is arylene (e.g., phenylene);

3.15 a Compound of Formula Q-I or 3.12, 3.13 or 3.14, wherein Y is a phenylene;

3.16 formula 3.15, wherein R_1 is substituted on the meta-position of the phenylene (e.g., relative to the point of attachment);

3.17 a Compound of Formula Q-I or any of 3.12-3.16, wherein R_1 is -N(R_{10})-C(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14});

3.18 a Compound of Formula Q-I or any of 3.12-3.16, wherein R_1 is -N(R_{10})-C(O)-C_{3-10}heterocycloalkyl (e.g., -N(R_{10})-C(O)-piperidine);

3.19 a Compound of Formula Q-I or any of 3.12-3.18, wherein R_{10}, is H or C_{1-4}alkyl (e.g., methyl);

3.20 a Compound of Formula Q-I or any of 3.12-3.18, wherein R_{10} is H;

3.21 a Compound of Formula Q-I or any of 3.12-3.18, wherein R_{10} is C_{1-4}alkyl (e.g., methyl);

3.22 a Compound of Formula Q-I or any of 3.12-3.17 or 3.19-3.21, wherein R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl);

3.23 a Compound of Formula Q-I or any of 3.12-3.17 or 3.19-3.21, wherein R_{11} and R_{12} are both H;

3.24 a Compound of Formula Q-I or any of 3.12-3.17 or 3.19-3.21, wherein R_{11} is H and R_{12} is C_{1-4}alkyl (e.g., methyl);

3.25 a Compound of Formula Q-I or any of 3.12-3.17 or 3.19-3.21, wherein R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl);

3.26 a Compound of Formula Q-I or any of 3.12-3.17 or 3.19-3.21, wherein R_{13} and R_{14} are both H;

3.27 a Compound of Formula Q-I or any of 3.12-3.17 or 3.19-3.21, wherein R_{13} is H and R_{14} is C_{1-4}alkyl (e.g., methyl);

3.28 a Compound of Formula Q-I or any of 3.1-3.27, wherein R_2 is H, halo (e.g., fluoro) or C_1-C_4alkyl (e.g., methyl);

3.29 a Compound of Formula Q-I or any of 3.1-3.28, wherein R_2 is -C_1-C_4alkyl (e.g., methyl);

3.30 a Compound of Formula Q-I or any of 3.1-3.27, wherein R_2 is H or halo (e.g., fluoro);

3.31 a Compound of Formula Q-I or any of 3.1-3.27, wherein R_2 is H;

3.32 a Compound of Formula Q-I or any of 3.1-3.27, wherein R_2 is halo (e.g., fluoro);

3.33 a Compound of Formula Q-I or any of 3.1-3.32, wherein R_a, R_a', R_b, R_b',R_c, R_d, R_d', R_e,and R_e' are independently H or C_1-C_4alkyl (e.g., methyl or ethyl);

3.34 a Compound of Formula Q-I or any of 3.1-3.32, wherein R_a', R_b', R_d' and R_e' are H;

3.35 a Compound of Formula Q-I or any of 3.1-3.34, wherein R_a, R_b, R_c, R_d and R_e are independently H or C_1-C_4alkyl (e.g., methyl or ethyl);

3.36 a Compound of Formula Q-I or any of 3.1-3.34, wherein R_a, R_b, R_c, R_d and R_e are independently H;

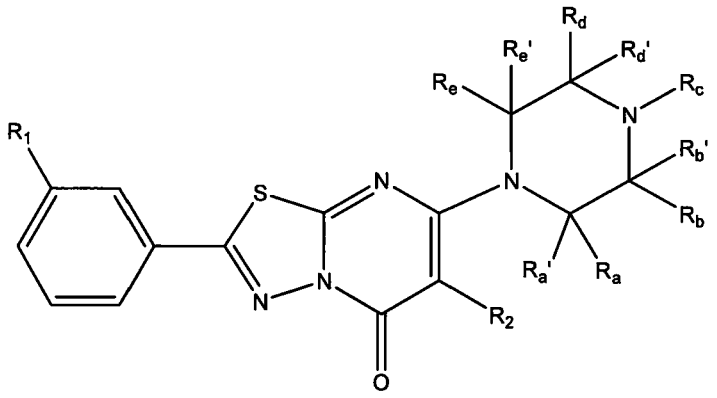
3.37 a Compound of Formula Q-I or any of 3.1-3.34, wherein R_a, R_b, R_c, R_d and R_e are independently C_1-C_4alkyl (e.g., methyl or ethyl);

3.38 a Compound of Formula Q-I or any of 3.1-3.37, wherein R_3, R_4, R_5 and R_6 are independently H or C_1-C_4alkyl;

3.39 a Compound of Formula Q-I or any of 3.1-3.37, wherein R_3, R_4, R_5 and R_6 are independently H;

3.40 a Compound of Formula Q-I or any of 3.1-3.37, wherein R_3, R_4, R_5 and R_6 are independently C_1-C_4alkyl;

3.41 a Compound of Formula Q-I or any of 3.1-3.40, wherein the compound is as shown below:



wherein

R_1 is:

phenyl optionally substituted with one or more nitro and/or -N(R_5)(R_6);

phenyl substituted with -C(O)OR_3;

pyrazolyl optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl) or halo (e.g., fluoro);

-C(O)N(R_4)(CH_2)$_{1-4}$-C(O)OR_3 (e.g., -C(O)N(H)CH_2C(O)OH);

-C(O)N(R_4)(CH_2)$_{1-4}$-N(R_{13})(R_{14}) (e.g., -C(O)N(H)CH_2 CH_2NH_2);

-N(R_4)-C(O)-heteroaryl (e.g., -N(R_4)-C(O)-pyridyl);

-N(R_4)-C_{1-4}alkylene-heteroaryl (e.g., -N(R_4)-C_{1-4}alkylene-pyridyl);

-N(R_{10})-C(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14});

-N(R_{10})-C(O)-C_{3-10}heterocycloalkyl (e.g., -N(R_{10})-C(O)-piperidine);

-N(R_4)(CH_2)$_{1-4}$-C(O)OR_4 (e.g., -N(H)CH_2C(O)OH);

-N(R_4)C(O)C(H)(NH_2)CH_2CH_2-C(O)OR_3;

-N(R_4)C(O)C(H)(NH_2)CH_2-heteroaryl (e.g., -N(R_4)C(O)C(H)(NH_2)CH_2-thiazol-4-yl;

-N(R_4)C(O)C(H)(CH_3)-NH_2;

-N(R_4)C(O)CH_2CH_2C(H)(NH_2)-COOH;

-N(R_4)C(O)-C(H)(NH_2)CH_2CH_2-COOH;

-N(R_4)C(O)-heteroaryl (-N(H)C(O)isoxazolyl);

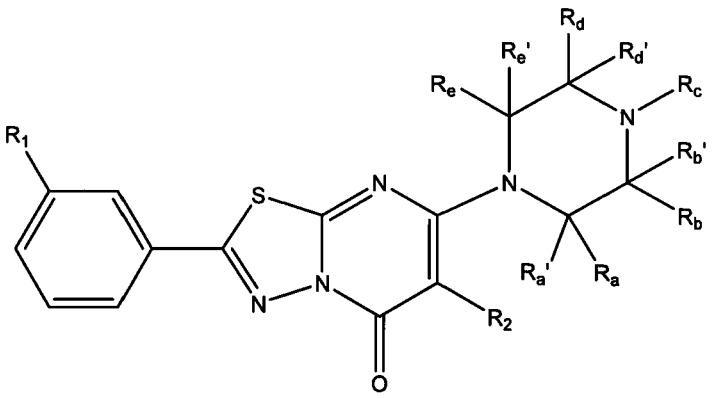
R_2 is H, halo (e.g., fluoro) or -C_1-C_4alkyl (e.g., methyl);

R_3, R_4, R_5 and R_6 are independently H or C_1-C_4alkyl;

R_{10}, R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl);

R_a, R_a', R_b, R_b', R_c, R_d, R_d', R_e,and R_e' are H;

3.42 a Compound of Formula Q-I or any of 3.1-3.40, wherein the compound is as shown below:



wherein

R_1 is:

phenyl optionally substituted with one or more nitro and/or -$N(R_5)(R_6)$;

phenyl substituted with -$C(O)OR_3$;

pyrazolyl optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl) or halo (e.g., fluoro);

$C(O)N(R_4)(CH_2)_{1-4}$-$C(O)OR_3$ (e.g., -$C(O)N(H)CH_2C(O)OH$);

-$N(R_4)$-C(O)-heteroaryl (e.g., -$N(R_4)$-C(O)-pyridyl); -$N(R_4)$-C_{1-4}alkylene-heteroaryl (e.g., -$N(R_4)$-C_{1-4}alkylene-pyridyl);

-$N(R_{10})$-C(O)-$C(R_{11})(R_{12})$-$N(R_{13})(R_{14})$;

-$N(R_{10})$-C(O)-C_{3-10}heterocycloalkyl (e.g., -$N(R_{10})$-C(O)-piperidine); or

-$N(R_4)(CH_2)_{1-4}$-$C(O)OR_4$ (e.g., -$N(H)CH_2C(O)OH$);

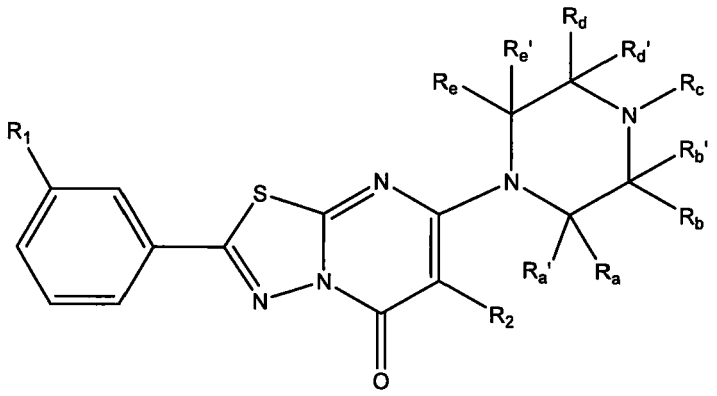
R_2 is H, halo (e.g., fluoro) or -C_1-C_4alkyl (e.g., methyl);

R_3, R_4, R_5 and R_6 are independently H or C_1-C_4alkyl;

R_{10}, R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl);

R_a, R_a', R_b, R_b', R_c, R_d, R_d', R_e,and R_e' are independently H or C_1-C_4alkyl (e.g., methyl or ethyl);

3.43 a Compound of Formula Q-I or any of 3.1-3.41, wherein the compound is as shown below:



wherein

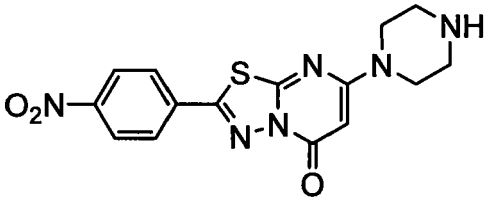
R_1 is $-N(R_{10})-C(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14})$, e.g., $-NHC(O)CH_2NH_2$;

R_2 is H or halo (e.g., fluoro);

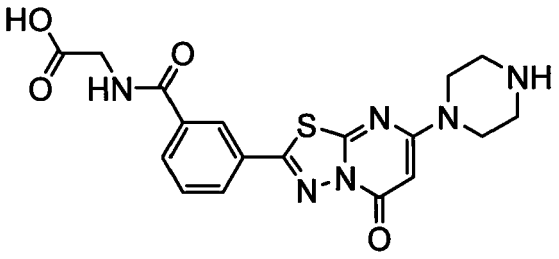
R_a, R_a', R_b, R_b', R_c, R_d, R_d', R_e,and R_e' are independently H or C_1-C_4alkyl (e.g., methyl or ethyl);

R_{10}, R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl);

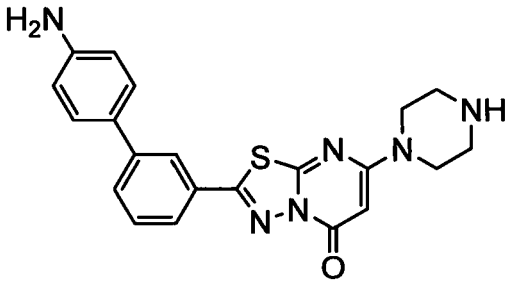
3.44 any of the preceding formulae 3.1-3.43, wherein the Compound of Formula Q-I is selected from any of the following:



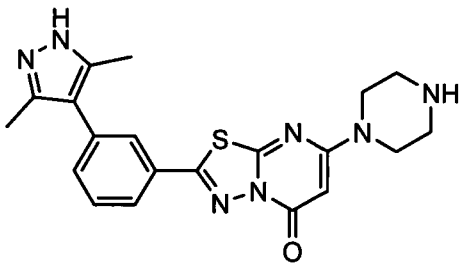
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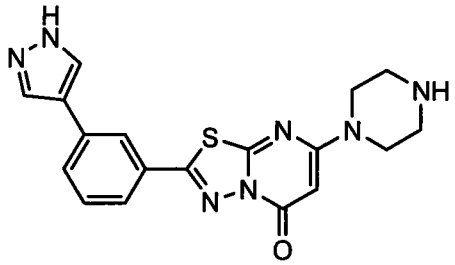
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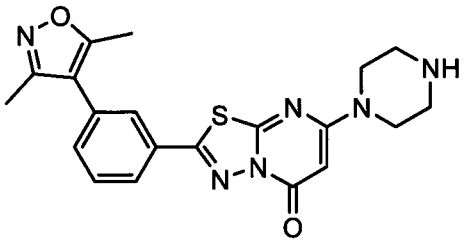
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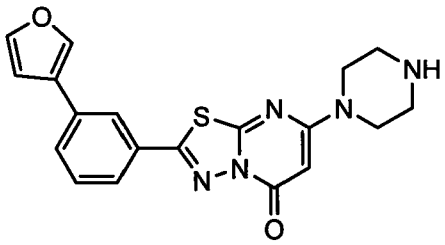
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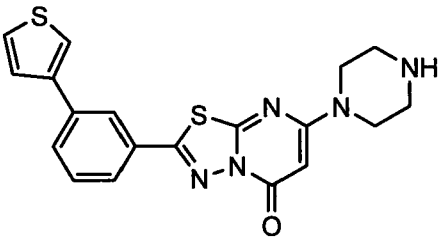
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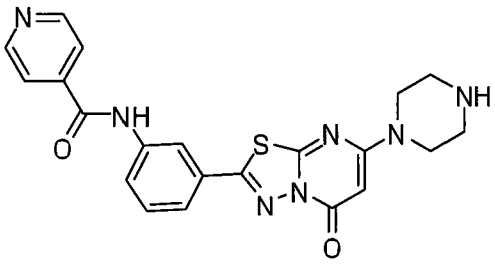
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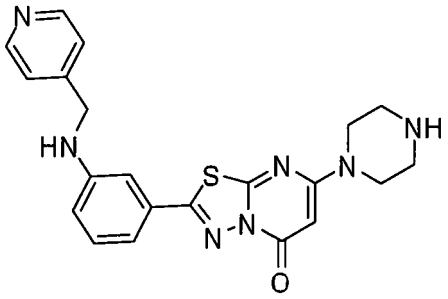
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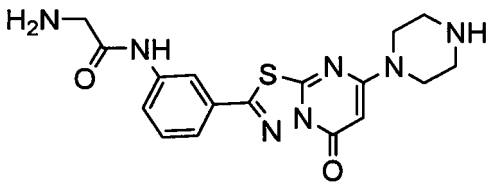


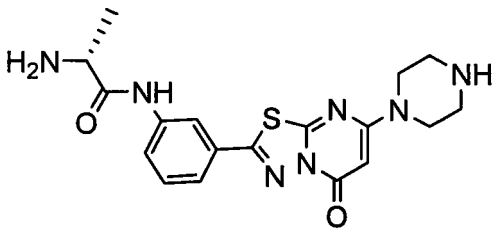
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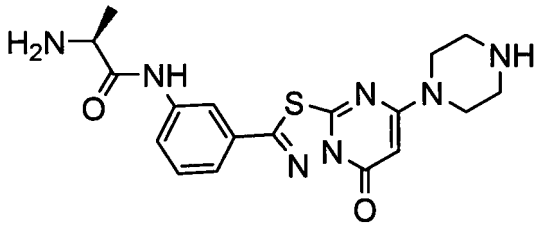


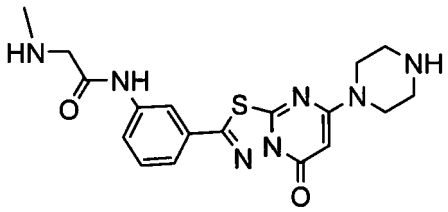
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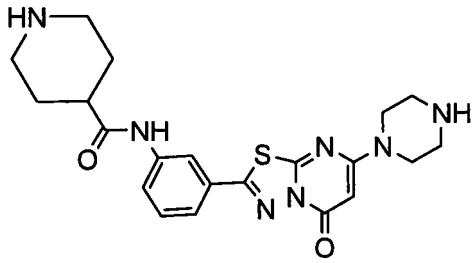

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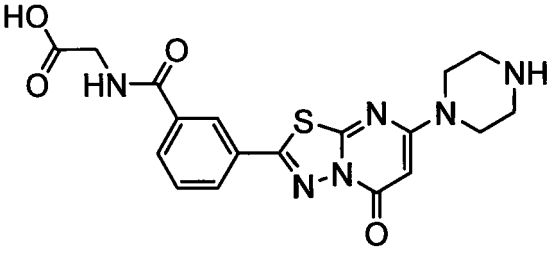

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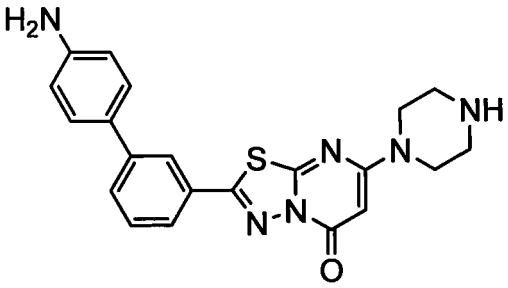
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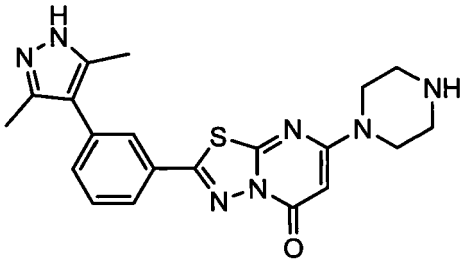
3.45 any of formulae 3.1-3.44, wherein the Compound of Formula Q-I is selected from any of the following:



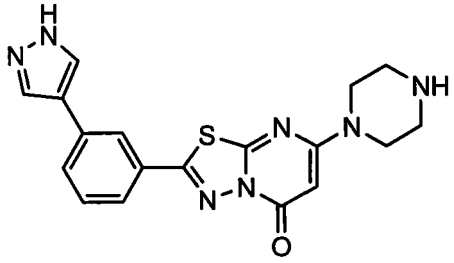
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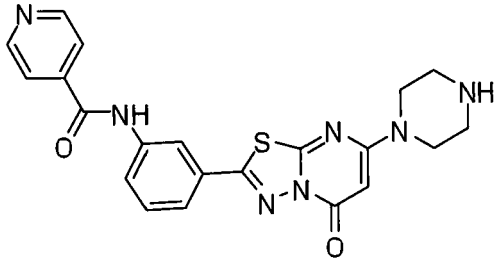
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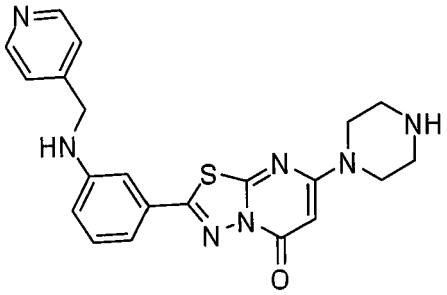
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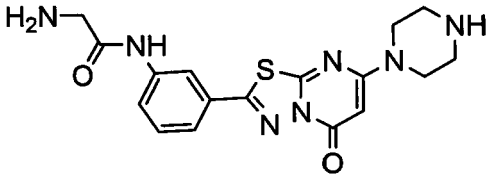
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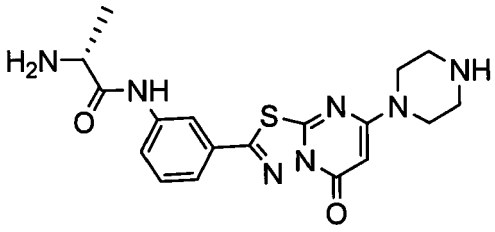
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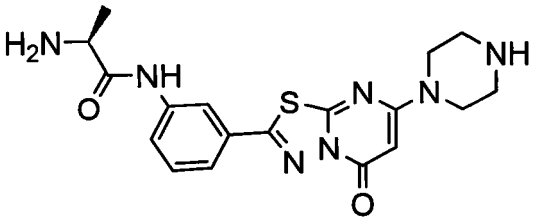
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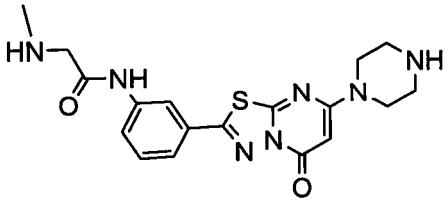


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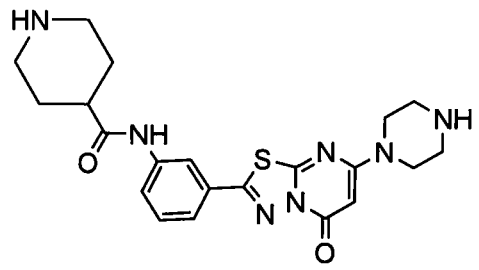
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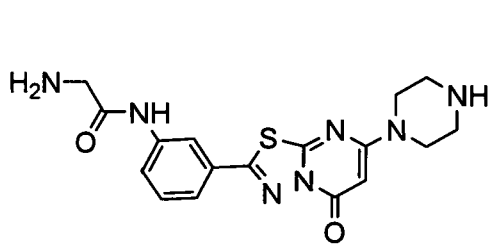
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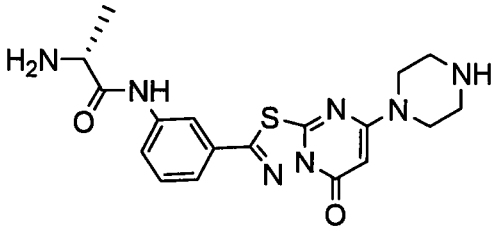


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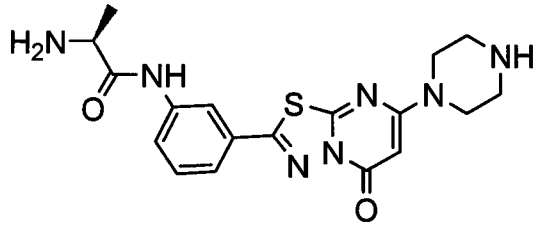
3.46 any of formulae 3.1-3.44 wherein the Compound of Formula Q-I is selected from any of the following:



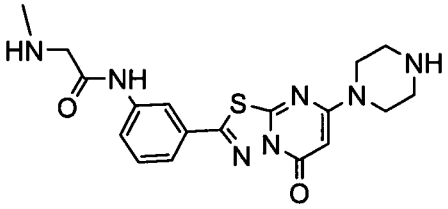
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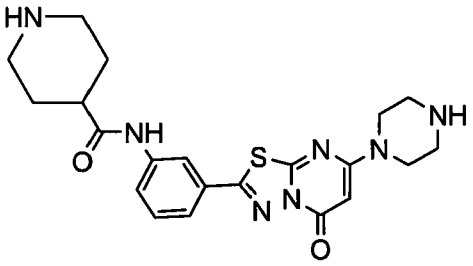
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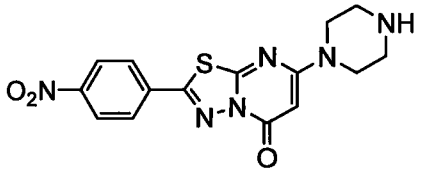


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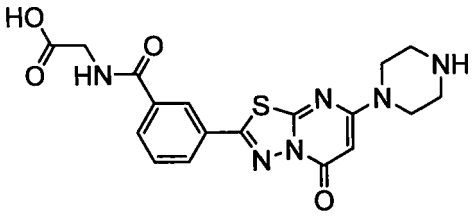
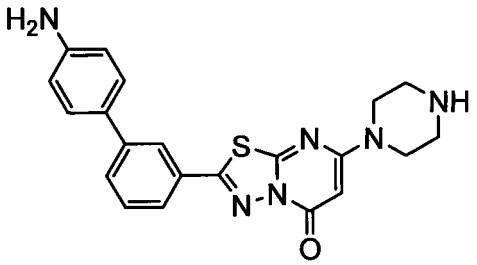
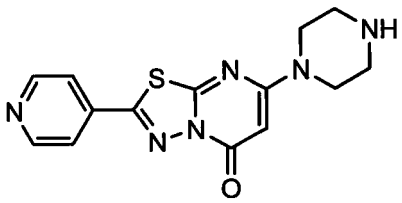
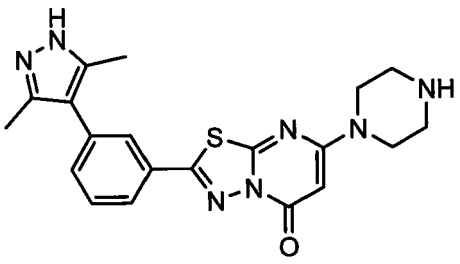
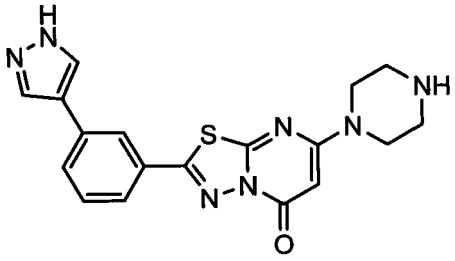


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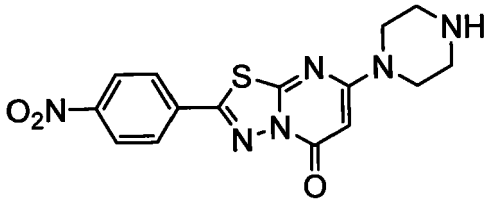
3.47 any of formulae 3.1-3.44 wherein the Compound of Formula Q-I is selected from any of the following:



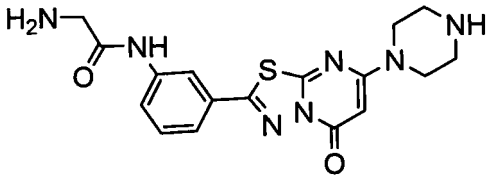
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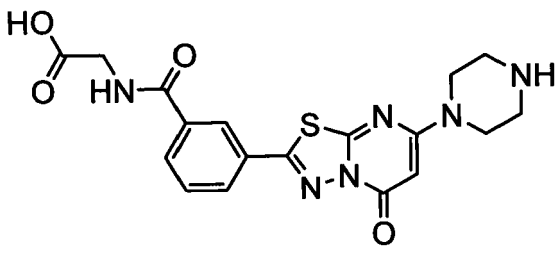
3.48 any of formulae 3.1-3.44 wherein the Compound of Formula Q-I is:


;

3.49 any of formulae 3.1-3.44 wherein the Compound of Formula Q-I is:


;

3.50 any of formulae 3.1-3.44 wherein the Compound of Formula Q-I is:


;

3.51 any of the preceding formulae wherein the compound of Formula Q-I has an IC_{50} value of less than 100 μM, preferably less than 75 μM, more

preferably less than 50 μM, most preferably, less than 25 μM in an aggregation assay as described in Example 44 and/or a percentage of inhibition of greater than 30%, preferably greater than 40%, more preferably, greater than 50%, more preferably, greater than 60%, most preferably greater than 70% at a concentration of 100μM or less in an adhesion assay as described in Example 44.

in free or salt form.

[0021] In a further embodiment of the first aspect, the invention provides a Compound of Formula P-I or Q-I, preferably formula 3.43, wherein:

R_1 is $-N(R_{10})-C(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14})$, e.g., $-NHC(O)CH_2NH_2$;

R_2 is H;

R_a, R_a', R_b, R_b', R_c, R_d, R_d', R_e and R_e' are independently H or C_1-C_4alkyl (e.g., methyl or ethyl);

R_{10}, R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl),

in free or salt form.

[0022] In a further embodiment of the first aspect, the invention provides a Compound of Formula P-I or Q-I, preferably formula 3.43, wherein:

R_1 is $-N(R_{10})-C(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14})$, e.g., $-NHC(O)CH_2NH_2$;

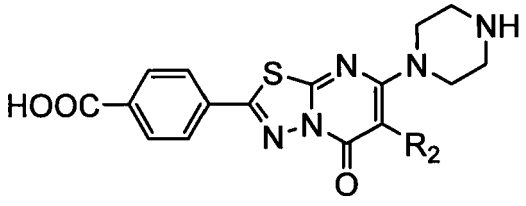
R_2 is H;

R_a, R_a', R_b, R_b', R_c, R_d, R_d', R_e and R_e' are H;

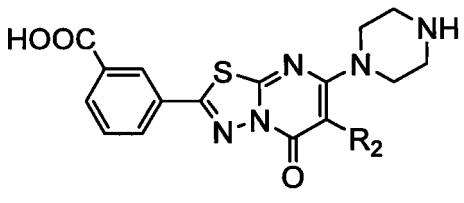
R_{10}, R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl),

in free or salt form.

[0023] In the second aspect, the Invention provides a Compound of Formula I-A selected from:

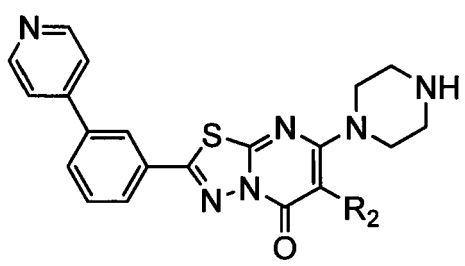


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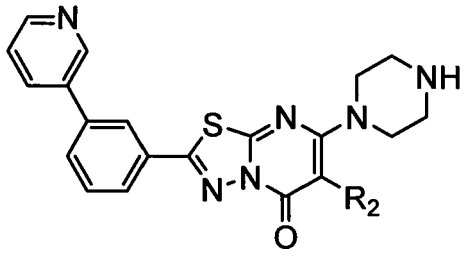


wherein R_2 is H, halo (e.g., fluoro) or C_1-C_4-alkyl (e.g., methyl), in free or salt form. In a particular embodiment, the Compound of Formula I-A is the compound having the para-substituted carboxylic acid and R_2 is H.

[0024] In the third aspect, the Invention provides a Compound of Formula I-B selected from:

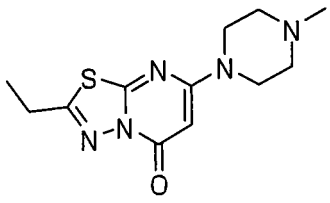
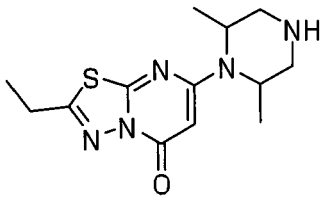
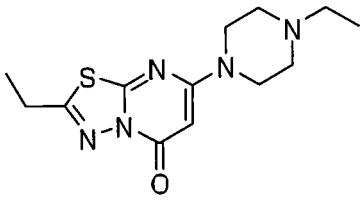
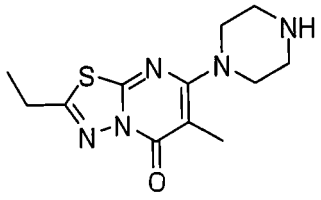
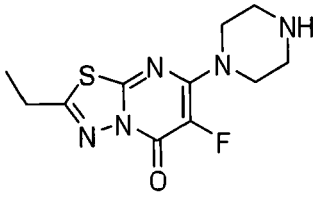
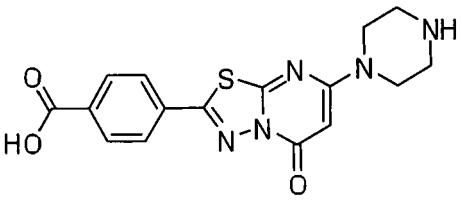
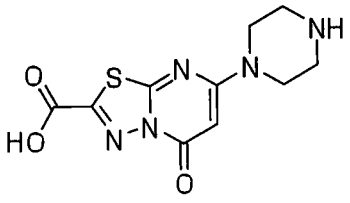
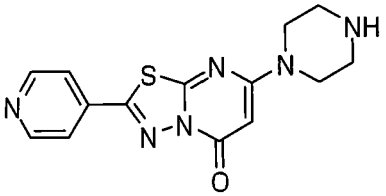
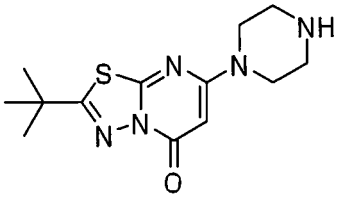
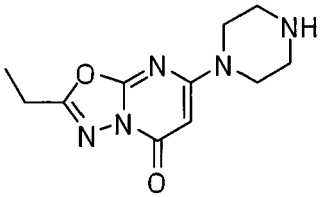


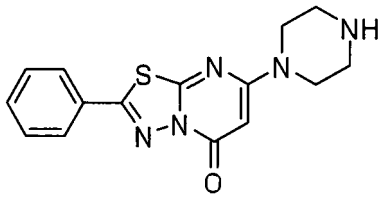
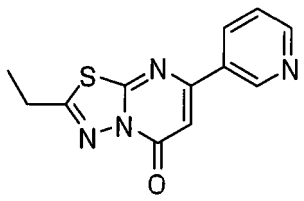
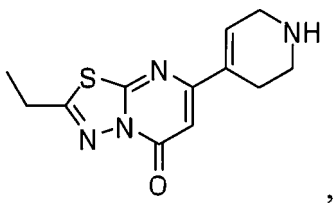
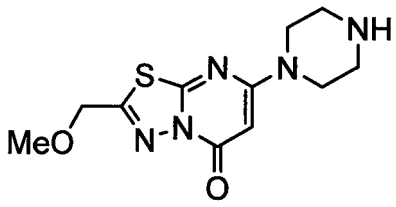
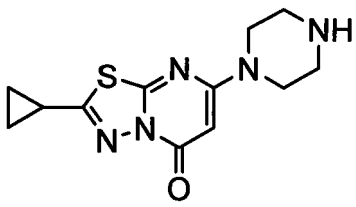
and



wherein R_2 is H, halo (e.g., fluoro) or C_1-C_4-alkyl (e.g., methyl), in free or salt form.

[0025] In the fourth aspect, the invention provides a Compound of Formula I-C selected from any one of the following:


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in free or salt form.

[0026] Preferably, the Compounds of the Present Invention (e.g., any of the compounds hereinbefore described, e.g. any of Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, as hereinbefore described, in free or salt form) are selected from the Compounds of Formula Q-I, e.g., any of 3.1-3.51, more preferably, the compounds of formula 3.45, most preferably formula 3.49, in free or salt form.

[0027] In the fifth aspect, the invention provides to a Pharmaceutical Composition (Composition Q-I) comprising a Compound of the Invention hereinbefore described, e.g., a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, preferably selected from the Compounds of Formula Q-I, e.g., any of 3.1-3.51, more preferably, the compounds of formula 3.45, most preferably 3.49, as hereinbefore described, in free or pharmaceutically acceptable salt form, in combination or association with a pharmaceutically acceptable diluent or carrier. Composition Q as hereinbefore described is useful, e.g., for preventing or inhibiting platelet adhesion and/or aggregation in treating thrombotic a disorder in a subject in need thereof. In a particular embodiment, the invention provides Composition Q-I as hereinbefore described, wherein the compound is a Compound of Formula Q-I, any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , more preferably, the compounds of formula 3.45, most preferably 3.49, in free or pharmaceutically acceptable salt form. In yet another embodiment, the invention provides a

Pharmaceutical Composition Q-I as hereinbefore described useful for inhibiting or reducing platelet aggregation and/or adhesion.

[0028] In the sixth aspect, the invention provides a method for inhibiting or reducing platelet aggregation and/or adhesion comprising administering to a subject in need thereof, an effective amount of a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] any of the Compound of Formula I-A, I-B or I-C, preferably a Compound of Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , more preferably, a compound of formula 3.45, most preferably 3.49, in free or pharmaceutically acceptable salt form, such that platelet aggregation and/or adhesion is reduced (Method Q-I).

[0029] The invention further provides for the following methods:

6.1 Method Q-I, wherein the compound is a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , more preferably, the compound of formula 3.45, most preferably 3.49, in free or pharmaceutically acceptable salt form;

6.2 Method Q-I or 6.1, wherein reduction of platelet aggregation and/or adhesion treats or inhibits a thrombotic disorder, e.g. selected from a group consisting of stroke, myocardial infarction, unstable angina, abrupt closure following angioplasty or stent placement, thrombosis induced by peripheral vascular surgery, peripheral vascular disease or thrombotic disorders resulting from atrial fibrillation or inflammation.

[0030] In a particular embodiment, the invention provides Method Q-I, e.g., formula 6.1 or 6.2, wherein both platelet aggregation and adhesion are reduced (Method Q-I').

[0031] In the seventh aspect, the invention provides a method for the treatment or prophylaxis of a thrombotic disorder comprising administering to a subject at risk of a thrombotic disorder, an effective amount of a compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, as hereinbefore described, in free or pharmaceutically acceptable salt form, such that platelet aggregation and/or adhesion is reduced (Method Q-II).

[0032] The invention further provides for the following methods:

7.1 Method Q-II, wherein said thrombotic disorder is selected from a group consisting of stroke, myocardial infarction, unstable angina, abrupt closure following angioplasty or stent placement, thrombosis induced by peripheral vascular surgery, peripheral vascular disease or thrombotic disorders resulting from atrial fibrillation or inflammation;

7.2 Method Q-II or 7.1, wherein said thrombotic disorder is thrombosis as a result of angioplasty or stent placement;

7.3 Method Q-II, 7.1 or 7.2, wherein subject at risk of thrombotic disorder is a subject who has a history of vascular surgery;

7.4 Method Q-II or any of Methods 7.1-7.3, further comprises administering to said subject an effective amount of at least one therapeutic agent selected from a group consisting of anti-coagulant, antiplatelet, and thrombolytic agents in conjunction with a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, as hereinbefore described, in free or pharmaceutically acceptable salt form;

7.5 Method Q-II, or any of Methods 7.1-7.4, further comprises administering to said subject an effective amount of at least one therapeutic agent selected from a group consisting of heparin, low molecular weight heparins, bivalirudin, Fondaparinux, warfarin, Acenocoumarol, Phenprocoumon, Phenindione, Abbokinase (urokinase), streptokinase, alteplase, retaplase, tenecteplase, prasugrel, aspirin, ticlopidine, clopidogrel, abciximab, eptifibatide and tirofiban in conjunction with a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, as hereinbefore described, in free or pharmaceutically acceptable salt form;

7.6 Method Q-II or any of Methods 7.1-7.4, further comprises administering to said subject an anticoagulant or thrombolytic agent in conjunction with a Compound of Formula P-I, any of 2.1-2.13,

Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, as hereinbefore described, in free or pharmaceutically acceptable salt form;

7.7 Method Q-II or any of Methods 7.1-7.4, further comprises administering to said subject an effective amount of heparin in conjunction with a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, as hereinbefore described, in free or pharmaceutically acceptable salt form.

7.8 Method Q-II or any of Methods 7.1-7.7, wherein the Compound of the Invention is a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , more preferably, the compounds of formula 3.45, most preferably formula 3.49, in free or pharmaceutically acceptable salt form.

[0033] The invention further provides any of the foregoing methods wherein the compounds of the present invention (a) reduce platelet inhibition with a percentage of inhibition of greater than 30%, preferably greater than 50% at a concentration of 100 μM or less; and/or (b) reduce platelet aggregation, e.g., with an IC_{50} of less than 100 μM, preferably less than 25 μM in an ADP or other agonist-induced platelet aggregation assay and/or in a fibrinogen binding assay as described in the examples below.

[0034] In a preferred embodiment, the invention is a method for the treatment or prophylaxis of a thrombotic disorder comprising administering an effective amount of a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , more preferably, the compounds of formula 3.44, most preferably 3.49 in free or pharmaceutically acceptable salt form.

[0035] In a particular embodiment, the invention is a method for the treatment or prophylaxis of a thrombotic disorder comprising administering heparin in conjunction with the Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g.,

any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, as hereinbefore described, in free or pharmaceutically acceptable salt form, preferably a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , more preferably, the compounds of formula 3.44, most preferably 3.49 in free or pharmaceutically acceptable salt form.

[0036] Without being bound to any theory, it is believed that binding of ligand by the receptor induces conformational changes in αIIbβ3, exposing the ligand-induced binding sites (LIBS). With traditional αIIbβ3-inhibitors such as tirofiban and eptifibatide, binding of these compounds to both the αIIb and to the divalent cation in the β3 subunit's metal ion dependant adhesion site (MIDAS) inhibits platelet adhesion. It is believed, however, that the interaction with the β3 subunit's metal ion dependant adhesion site (MIDAS) is likely to be responsible for initiating the conformational change which result in both the thrombocytopenia and the increased mortality rate of traditional αIIbβ3 antagonists. The present invention identifies αIIbβ3 inhibitors that are capable of inhibiting fibrinogen binding without inducing the binding of one more integrin β3 LIBS-specific mAbs. Therefore, in one embodiment, the Compounds of the Invention e.g., the Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, preferably, the compounds of formula 3.45, most preferably formula 3.49, in free or salt form may bind to αIIb, and in some cases induce αIIb LIBS exposure, without inducing β3 LIBS exposure. Such compounds thus demonstrate specific binding to αIIbβ3 integrin and inhibition of platelet adhesion without the disadvantage of inducing the change in conformation of the β3 and consequent risk of complications following dissociation of the compounds from the αIIbβ3.

[0037] In the eighth aspect, the invention provides a drug-eluting stent wherein the drug or drugs eluted comprise a Platelet Inhibitor of the Invention, or a Compound of P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, preferably, the Compound of Formula Q-I, more preferably, the compounds of formula 3.45, most preferably formula 3.49, in free or pharmaceutically acceptable salt form as hereinbefore described. For example, the

invention provides a stent, e.g., an arterial stent, for example a coronary artery or carotid artery stent, which comprises a biocompatible polymer matrix which comprises or is associated with a Compound of P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, in free or pharmaceutically acceptable salt form as hereinbefore described. The stent may be made of metal, plastic, biodegradable or bioabsorbable material or combination thereof, e.g., stainless steel, nickel-titanium alloy, colbalt-alloy, tantalum, silicone, polytetrafluoroethylene, magnesium alloy or poly-L-lactide. For example, a stent may be a metallic stent (e.g., stainless steel, nickel-titanium alloy, colbalt alloy, or tantalum) partially or wholly coated with a biocompatible polymer, e.g., a plastic (e.g., polytetrafluoroethylene) or a polymeric carrier (e.g., phosphorylcholine or polylactic acid) which polymer comprises or is associated with a Compound of P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, preferably, the compounds of formula Q-I, more preferably, formula 3.45, most preferably formula 3.49, in free or pharmaceutically acceptable salt form as hereinbefore described, e.g., such that said Compound is presented or released in a manner and amount effective to inhibit platelet adhesion and/or aggregation in the vicinity of the stent. The stent may further comprise or be associated with an additional drug or drugs, e.g., an antiproliferative agent, e.g., sirolimus, everolimus, zotarolimus, tacrolimus, or paclitaxel, and/or an anticoagulant, e.g., heparin.

[0038] In the nineth aspect, the invention provides a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, preferably, Compounds of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , more preferably, the compounds of formula 3.45, most preferably formula 3.49, in free or pharmaceutically acceptable salt form as hereinbefore described, for use as a pharmaceutical, e.g. use of a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, preferably Compounds of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in

paragraph [0021] or [0022] , more preferably, the compounds of formula 3.45, most preferably formula 3.49, in free or pharmaceutically acceptable salt form as hereinbefore described, e.g., (in the manufacture of a medicament) for the treatment or prophylaxis of a thrombotic disorder, e.g., according to any of Method Q-I, e.g., formula 6.1 or 6.2, or Method Q-II or any of methods 7.1-7.8.

[0039] In the tenth aspect, the invention provides a Pharmaceutical Composition comprising a Compound of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , any of the Compound of Formula I-A, I-B or I-C, preferably, Compounds of Formula P-I, any of 2.1-2.13, Formula Q-I, e.g., any of 3.1-3.51, or the compound described in paragraph [0021] or [0022] , more preferably, the compounds of formula 3.45, most preferably formula 3.49, in free or pharmaceutically acceptable salt form as hereinbefore described, for use as a pharmaceutical e.g., (in the manufacture of a medicament) for the treatment or prophylaxis of a thrombotic disorder, e.g., according to any of Method Q-I, e.g., formula 6.1 or 6.2, or Method Q-II or any of methods 7.1-7.8.

Detailed Description of the Invention

[0040] As used herein, the term "αIIbβ3" or "integrin αIIbβ3" refers to the receptor on the surface of human platelets. It is a heterodimeric complex composed of both αIIb and β3 subunits responsible for binding adhesive plasma proteins, most notably fibrinogen and von Willebrand factor.

[0041] The term "antagonist" refers to any ligand or molecule that binds to receptors and competitively or noncompetitively blocks the binding of ligand to that receptor. Therefore, "αIIbβ3 antagonist" refers to any ligand or molecule that competitively or noncompetitively blocks αIIbβ3.

[0042] "LIBS" refers to ligand-induced binding sites on αIIbβ3 that are presented or exposed upon the binding of a ligand or antagonist by the receptor.

[0043] "LIBS-specific mAbs" refers to monoclonal antibodies that bind to the exposed ligand-induced binding sites of αIIbβ3. Examples of LIBS-specific mAbs include AP5, PMI-1 and LIBS1.

[0044] The term "thrombotic disorders" refers to disorders characterized by formation of a thrombus that obstructs vascular blood flow. Examples of thrombotic

disorders include stroke, myocardial infarction, stable or unstable angina, peripheral vascular disease, abrupt closure following angioplasty or stent placement and thrombosis induced by vascular surgery. Thrombotic disorders also include disorders characterized by formation of a thrombus caused by atrial fibrillation or inflammation.

[0045] The phrase "subject at risk of thrombotic disorders" or "subject in need thereof" includes subjects who have a history of vascular intervention (e.g. angioplasty, stent placement, aortocoronary bypass or insertion of prosthetic heart valves), cardiovascular abnormality (e.g. atrial fibrillation) or a family history of vascular diseases (e.g., coronary artery disease (CAD), systemic hypertension, diabetes mellitus, hyperlipidemia, bicuspid aortic valve, hypertrophic cardiomyopathy or mitral valve prolapse). The term "subject" may include human or non-human (e.g., an animal).

[0046] The term "platelet adhesion" refers to the binding of platelet membrane proteins to fibrinogen, collagen, von Willebrand factor (vWF) or other adhesive glycoproteins (e.g., fibronectin, laminin).

[0047] The term "platelet aggregation" refers to the attachment of activated platelets one to another, which results in the formation of aggregates or clumps of activated platelets.

[0048] The phrase "inhibit or reduce platelet adhesion and/or aggregation" is intended to mean at least a 30% inhibition of platelet activity at a concentration of 100 μM or lower in a given assay, relative to platelet activity in the absence of the compound.

[0049] The phrase "antagonist known to expose β3 LIBS" herein refers to agents that induce conformational in β3, for example tirofiban.

[0050] The term "anticoagulants" herein refers to any compound or substance that either stimulates natural inhibitor of coagulant proteases or blocks the coagulation cascade. Examples of anticoagulants include, but are not limited to heparin, warfarin, phenprocoumon, fondaparinux, lepirudin, bivalirudin, argatroban, danaparoid and drotrecogin alfa.

[0051] The term "anti-platelet agents" herein refers to compound or substance that prevents platelet adhesion and/or aggregation. Examples of anti-platelet agents include, but are not limited to prasugrel, aspirin, ticlopidine, clopidogrel, abciximab, eptifibatide and tirofiban.

[0052] The term "fibrinolytic agents" therefore refers to any compound or substance that lyses pathological thrombi. "Thrombolytic agents" are agents that are fibrinolytic, i.e., agents that convert plasminogen to plasmin, which lyses fibrin. Examples of fibrinolytic agents include but are not limited to streptokinase and tissue plasminogen activator (t-PA).

[0053] The term "stent" herein refers to expandable wire form or perforated tube that is inserted into a natural conduit of the body, such as an artery, usually a coronary artery, to prevent or counteract a disease-induced localized flow constriction.

[0054] The term "optionally substituted" is intended to mean substituted with the substituents defined or unsubstituted. For example, phenyl optionally substituted with one or more nitro means in some instances, the phenyl is substituted with one or more nitro groups and in other instances, the phenyl is unsubstituted.

[0055] The binding of LIBS-specific mAbs to αIIbβ3 may be measured by comparing the binding of LIBS-specific mAbs to αIIbβ3 in the presence of testing compound with the binding of LIBS-specific mAbs to αIIbβ3 in the absence or presence of a control such as untreated platelets and/or other known αIIbβ3 inhibitors that are known to cause β3 LIBS exposure, e.g., tirofiban. For example, the test compound may bind to αIIb and optionally increases binding of at least one αIIb LIBS-specific mAb relative to binding to unactivated platelets without increasing the binding of one or more β3 LIBS-specific mAbs relative to binding to unactivated platelets and/or produces less binding relative to binding in the presence of an agent known to bind to and directly activate αIIbβ3 so as to expose β3 LIBS.

[0056] As used herein, the term "alkyl" or "alkyl chain" or "alkylene" refers to a linear or branched, saturated or unsaturated, aliphatic hydrocarbon. Unless otherwise specified, alkyl refers to a hydrocarbon chain containing one to four carbon atoms. Examples of alkyl may include, but are not limited to methyl, ethyl, tert-butyl and the like as well as alkenyl or alkynyl substituents.

[0057] The term "C_3-C_{10}cycloalky" or "C_{3-10}cycloalky" refers to fully or partially saturated, carbocyclic, non-aromatic hydrocarbon radicals having three to eight carbon atoms. Examples of C_3-C_{10}cycloalkyl optionally containing one or more heteroatoms selected from a group consisting of O or N include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl or cyclohexenyl,

piperidinyl, piperazinyl, morpholinyl, imidazolinyl, pyrrolidinyl. These cycloalkyl systems may be attached via the heteroatom or any other carbon on the system. C_3-C_{10}cycloalky may also refer to non-aromatic cyclic system fused to an aromatic cyclic system. An example of this includes tetrahydroquinolinyl.

[0058] The term "aryl" refers to any aromatic ring system. Aromatic compounds include phenyl, naphthyl and their derivatives.

[0059] The term "heteroaryl" is intended to mean a stable 5- to 6-membered monocyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to another ring.

[0060] The term "acyl" is intended to encompass R-C(O)- wherein R is C_{1-4}alkyl wherein said alkyl is optionally substituted with one or more halo, hydroxy, or C_{1-4}alkoxy.

[0061] The Compounds of the Invention may comprise one or more chiral carbon atoms. The compounds thus exist in individual isomeric, e.g., enantiomeric or diasteriomeric form or as mixtures of individual forms, e.g., racemic/diastereomeric mixtures. Any isomer may be present in which the asymmetric center is in the (*R*)-, (*S*)-, or (*R,S*)- configuration. The invention is to be understood as embracing both individual optically active isomers as well as mixtures (e.g., racemic/diasteromeric mixtures) thereof. Accordingly, the Compound of the Invention may be a racemic mixture or it may be predominantly, e.g., in pure, or substantially pure, isomeric form, e.g., greater than 70% enantiomeric excess ("ee"), preferably greater than 80% ee, more preferably greater than 90% ee, most preferably greater than 95% ee. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art (e.g., column chromatography, preparative TLC, preparative HPLC, simulated moving bed and the like)

[0062] Compounds of the Invention may exist in free or salt form, e.g., as acid addition salts (e.g., hydrochloric acid, toluene sulfonic acid, methane sulfonic acid, benzene sulfonic acid, trifluoroacetic acid, and the like). In this specification unless otherwise indicated language such as Compounds of the Invention is to be understood as embracing the compounds in any form, for example free or acid addition salt form,

or where the compounds contain acidic substituents, in base addition salt form. The Compounds of the Invention are intended for use as pharmaceuticals, therefore pharmaceutically acceptable salts are preferred. Salts which are unsuitable for pharmaceutical uses may be useful, for example, for the isolation or purification of free Compounds of the Invention or their pharmaceutically acceptable salts, are therefore also included. In particular embodiment, the salt of the compound of the invention is a trifluoroacetic acid addition salt.

[0063] Compounds of the Invention may in some cases also exist in prodrug form. A prodrug form is compound which converts in the body to a Compound of the Invention. For example, when the Compounds of the Invention contain hydroxy or carboxy substituents, these substituents may form physiologically hydrolysable and acceptable esters. As used herein, "physiologically hydrolysable and acceptable ester" means esters of Compounds of the Invention which are hydrolysable under physiological conditions to yield acids (in the case of Compounds of the Invention which have hydroxy substituents) or alcohols (in the case of Compounds of the Invention which have carboxy substituents) which are themselves physiologically tolerable at doses to be administered. For example, wherein the compounds of the invention contains a hydroxy group (e.g., Drug-OH), the prodrug (e.g., Drug-O-C(O)-CH_3) may hydrolyze under physiological conditions to yield hydroxy (Drug-OH) on the one hand and acid, e.g., carboxylic acid on the other (e.g., CH_3COOH), which are themselves physiologically tolerable at doses to be administered. Similarly, wherein the compounds of the invention contains a carboxylic acid group (e.g., Drug-C(O)OH), its prodrug (e.g., Drug-C(O)-O-CH_2CH_3) may hydrolyze under physiological conditions to yield the carboxylic acid (Drug-C(O)OH) on the one hand and alcohol, e.g., ethanol on the other (e.g., CH_3CH_2OH), which are themselves physiologically tolerable at doses to be administered. As will be appreciated the term thus embraces conventional pharmaceutical prodrug forms.

[0064] Compounds of the present invention may be administered orally or parenterally, including intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration. The compounds useful in the invention may generally be provided in the form of tablets or capsules, as a powder or granules, or as an aqueous solution or suspension. Tablets for oral use may include the active ingredients mixed

with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

[0065] Dosages of the compounds of the invention will vary depending upon the condition to be treated or prevented and on the identity of the inhibitor being used. Estimates of effective dosages and in vivo half-lives for the individual compounds encompassed by the invention can be made on the basis of in vivo testing using an animal model, such as the mouse model described herein or an adaptation of such method to larger mammals. Appropriate dosage may range from 0.01mg to 5000 mg. For example, one appropriate dosage may be 0.01-30mg/Kg, e.g., 26.5mg/Kg, e.g., 12mg/Kg.

[0066] In addition to their administration singly, the compounds useful according to the invention can be administered in combination or in conjunction with other known therapeutic agents useful for thrombotic disorders such as anticoagulants (e.g., heparin, warfarin, phenprocoumon, fondaparinux, lepirudin, bivalirudin, argatroban, danaparoid, drotrecogin alfa), fibrinolytic agents (e.g., streptokinase or tissue plasminogen activator (t-PA) or other anti-platelet agents (e.g., prasugrel, aspirin, ticlopidine, clopidogrel, abciximab, eptifibatide and tirofiban). In any event, the administering physician can adjust the amount and timing of drug administration on the basis of results observed using standard measures of platelet activity known in the art or described herein.

EXAMPLES

Example 1

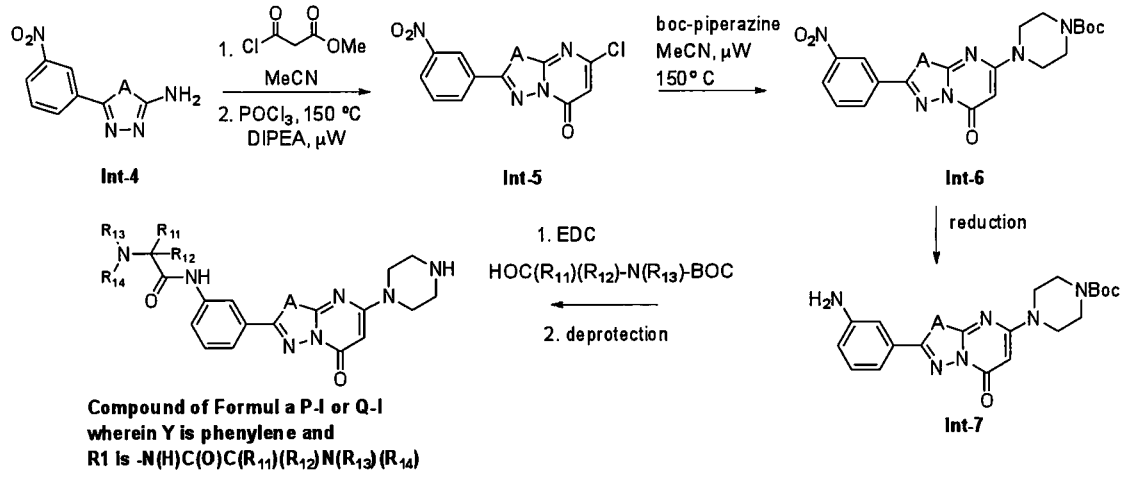
[0067] ***Synthesis of Compounds of the present invention.*** The compounds described herein and their pharmaceutically acceptable salts may be made using the methods as described and exemplified herein and by methods similar thereto and by

methods known in the chemical art. In the description of the synthetic methods described herein, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. Therefore, at times, reaction may require to be run at elevated temperature, for a longer or shorter period of time or in the presence of an acid or base. It is understood by one skilled in the art of organic synthesis that functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. If not commercially available, starting materials for these processes may be made by procedures, which are selected from the chemical art using techniques similar or analogous to the synthesis of known compounds. Significances of the substituents are as set forth in the formulae hereinbefore defined unless otherwise specified. All references cited herein are hereby incorporated in their entirety by reference.

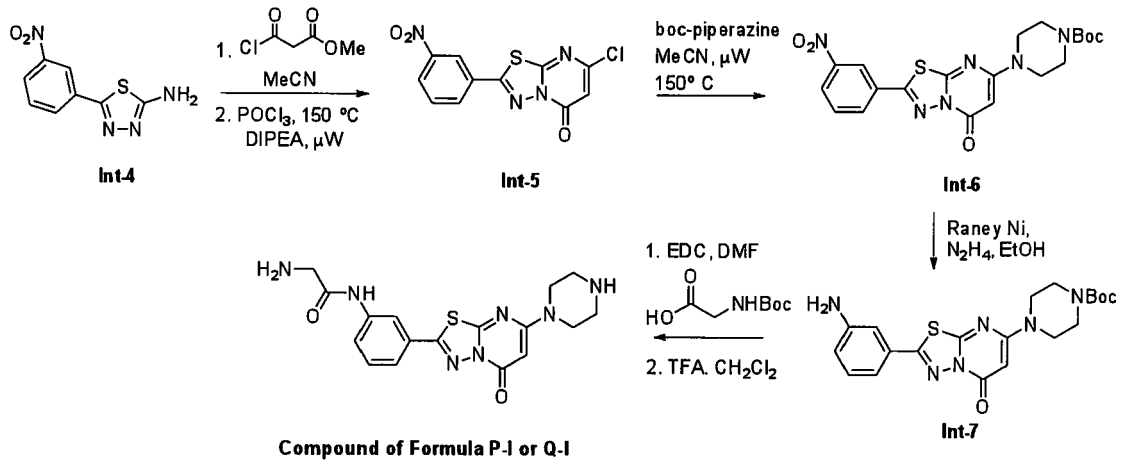
[0068] All commercially available reagents and solvents are purchased and used without further purification. All microwave reactions are carried out in a sealed microwave vial equipped with a magnetic stir bar and heated in a Biotage Initiator Microwave Synthesizer. All compounds for biological testing are purified using a Waters semi-preparative HPLC equipped with a Phenomenex Luna® C18 reverse phase (5 micron, 30 x 75 mm) column having a flow rate of 45 mL/min. The mobile phase is a mixture of acetonitrile and H_2O each containing 0.1% trifluoroacetic acid. During purification, a gradient of 30% to 80% acetonitrile over 8 minutes is used with fraction collection triggered by UV detection (220 nM). Pure fractions passed through PL-HCO_3 MP SPE (Varian) to remove trifluoroacetic acid and concentrated under vacuum on a lyophilizer. ^1H spectra are recorded using an Inova 400 (100) MHz spectrometer (Varian).

[0069] The Compounds of Formula P-I, any of 2.1-2.13, Formula Q-I, wherein R_2 is H, Y is phenylene and R_1 is as defined in Formula P-I, any of 2.1-2.13, or Formula Q-I, for example R_1 is –N(H)-C(O)-C(R_{11})(R_{12})-N(R_{14})(R_{15}), or –N(H)-C(O)-heterocycloalkyl, preferably –N(H)-C(O)-CH_2NH_2 or –N(H)-C(O)-CH_2-piperidine, may be prepared by first reacting 5-(3-nitrophenyl)-1,3,4-thiadiazol-2-amine (Int-4) with methyl 3-chloro-3-oxopropanoate, which product is then halogenated, e.g., reacting with phosphorous oxychloride in the presence of a base,

e.g., diisopropyl ethyl amine or the like, optionally with heat, e.g., up to about 150°C, e.g., using microwave to produce 7-chloro-2-(3-nitrophenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one, (Int-5). Boc-protected piperazine is then reacted with Int-5 optionally in the presence of heat, e.g., up to about 150°C, e.g., using a microwave, to produce tert-butyl 4-(2-(3-nitrophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate, Int-6. The nitro group on Int-6 is then reduced to an amine, e.g., by catalytic hydrogenation, e.g., using Raney Nickel and hydrazine to produce tert-butyl 4-(2-(3-aminophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate, Int-7. Int-7 is then reacted with $HOC(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14})$ in the presence of a activating agent, e.g., 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC). Wherein R_{13} and/or R_{14} are H, $HOC(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14})$ is preferably protected with a protecting group, e.g., a BOC protecting group, e.g. $HOC(O)-C(R_{11})(R_{12})-N(R_{13})$-BOC or $HOC(O)-C(R_{11})(R_{12})-N(R_{14})$-BOC. The resulting compound of Formula P-I, any of 2.1-2.13, or Formula Q-I is then deprotected, e.g., using acid, e.g., trifluoroacetic acid to provide the Compound of Formula P-I, any of 2.1-2.13, or Formula Q-I wherein R_1 is $-N(H)-C(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14})$, e.g., $-N(H)-C(O)-CH_2NH_2$. The synthesis may be summarized in the reaction scheme below:



Specifically, the synthesis for the Compound of Formula P-I, any of 2.1-2.13, or Formula Q-I, wherein A is S, R_2 is H and R_1 is $-N(H)-C(O)-CH_2NH_2$ may be summarized in the reaction scheme below:



[0070] ***General Synthetic Procedures.*** The synthesis methods described above and/or the following general procedures are used to synthesize compounds having different but analogous structures. All final compounds differed only in the substitution off of the commercially available starting material.

Terms and abbreviations:

ACN = acetonitrile,

DCM = dichloromethane,

DMF = *N,N*-dimethylforamide,

DCM = dichloromethane

DIPEA = diisopropylethylamine

DMSO = dimethyl sulfoxide,

EDC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide

EtOAc = ethyl acetate,

h = hour(s),

HCl = hydrochloric acid

HPLC = high performance liquid chromatography,

K_2CO_3 = potassium carbonate,

m = multiplet,

min. = minute(s)

MeOH = methanol,

MeCN = acetonitrile

$MgSO_4$ = magnesium sulfate

$NaHCO_3$ = sodium bicarbonate,

NMR = nuclear magnetic resonance,

p = pentet,

$POCl_3$ = phosphorous oxychloride

rt = room temperature,

s = singlet,

t = triplet,

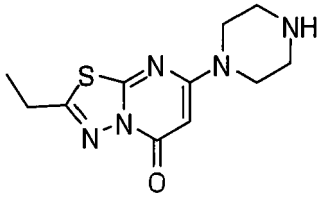
TFA = trifluoroacetic acid,

THF = tetrahydrofuran,

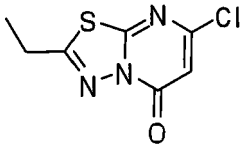
TLC = thin layer chromatography.

Example 1

2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one

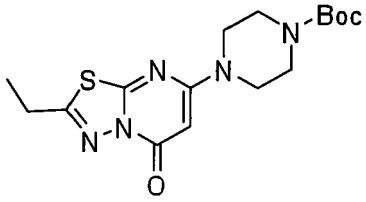


Step 1: 7-chloro-2-ethyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



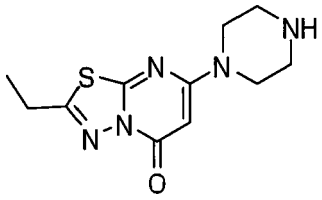
[0071] To a solution of 5-ethyl-1,3,4-thiadiazol-2-amines (5 g, 38.7 mmol, 1.0 equiv) in 200 mL anhydrous acetonitrile is added to methyl 3-chloro-3-oxopropionate (4.97 mL, 46.4 mmol, 1.2 equiv) and the mixture is stirred for 2 h at room temperature. After consumption of the starting material, phosphorous (V) oxychloride (40 mL, 429 mmol, 27 equiv) is added along with *N,N*-diisopropylethylamine (6.76 mL, 38.7 mmol, 1.0 equiv). The mixture is stirred at 150 °C for 25 min after which it is concentrated *in vacuo* and taken up in chloroform, poured over ice and washed with saturated $NaHCO_3$, water and brine. The organic layer is dried ($MgSO_4$) and concentrated *in vacuo* to give a dark, red oil. The residue is purified by column chromatography (silica gel, 0-10% EtOAc/Dichloromethane) to give 7-chloro-2-ethyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one (2.35 g, 28.2 % yield) as a tan solid.

Step 2: *tert*-butyl 4-(2-ethyl-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate



[0072] To a solution of 7-chloro-2-ethyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one (2.0 g, 9.27 mmol, 1.0 equiv) in 50 mL of anhydrous acetonitrile in a microwave vial is added *tert*-butyl 1-piperazinecarboxylate (2.073 g, 11.13 mmol, 1.2 equiv) followed by *N,N*-diisopropylethylamine (4.86 mL, 27.8 mmol, 3.0 equiv). The mixture is heated in a microwave reactor for 25 min at 150 °C. Upon completion, the mixture is concentrated *in vacuo* to give crude *tert*-butyl 4-(2-ethyl-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate as a yellow oil. This material is advanced directly to the next step.

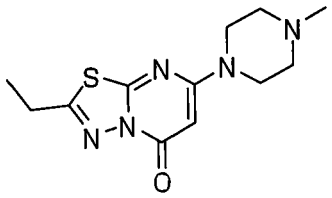
Step 3: 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0073] To a solution of *tert*-butyl 4-(2-ethyl-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (3.39 g, 9.28 mmol, 1.0 equiv) in 40 mL of dichloromethane is added trifluoroacetic acid (10 ml, 130 mmol, 14 equiv). The mixture stirred for 18 h, after which it is concentrated *in vacuo* and azeotroped with dichloroethane to give a yellow solid. The crude residue is dissolved in MeOH and purified by HPLC to give 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one (2.053 g, 83 % yield) as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 5.30 (s, 1 H), 3.37 - 3.44 (m, 4 H), 2.94 (q, *J*=7.56 Hz, 2 H), 2.64 - 2.73 (m, 4 H), 1.25 (t, 3 H); LCMS: (electrospray +ve), *m/z* 266.0 $(MH)^+$; HPLC: t_R = 2.71 min,UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{11}H_{16}N_5OS$ $[M+H]^+$ 266.1069, found 266.1073.

Example 2

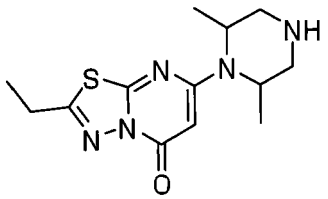
2-ethyl-7-(4-methylpiperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0074] This example is prepared by following the same procedures as described in Example 1 above except substituting 1-methylpiperazine for Boc-piperazine. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 5.51 (s, 1 H), 4.32 (br. s., 2 H), 3.39 - 3.75 (m, 4 H), 3.01 (q, *J*=7.50 Hz, 2 H), 2.83 (s, 3 H), 1.96 - 2.55 (m, 2 H), 1.41 (t, 3 H); LCMS: (electrospray +ve), *m/z* 280.1 $(MH)^+$; HPLC: t_R = 2.69 min,UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{12}H_{18}N_5OS$ $[M+H]^+$ 280.1226, found 280.1224.

Example 3

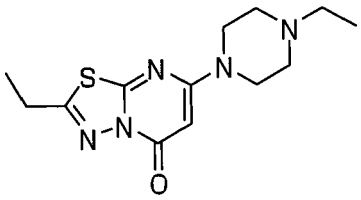
7-(2,6-dimethylpiperazin-1-yl)-2-ethyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0075] This example is prepared by following the same procedures as described in Example 1 above except substituting tert-butyl 3,5-dimethylpiperazine-1-carboxylate for Boc-piperazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.32 (s, 1 H), 4.03 (d, *J*=9.78 Hz, 2 H), 2.92 (q, *J*=7.43 Hz, 2 H), 2.53 - 2.66 (m, 2 H), 2.18 - 2.30 (m, 2 H), 1.23 (t, *J*=7.43 Hz, 3 H), 0.94 (d, 6 H); LCMS: (electrospray +ve), *m/z* 294.2 $(MH)^+$; HPLC: t_R = 2.86 min,UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{13}H_{20}N_5OS$ $[M+H]^+$ 294.1383, found 294.1382.

Example 4

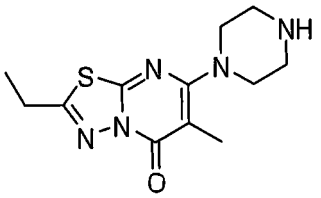
2-ethyl-7-(4-ethylpiperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0076] This example is prepared by following the same procedures as described in Example 1 above except substituting N-ethylpiperazine for Boc-piperazine. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 5.49 (s, 1 H), 4.33 (br. s., 2 H), 3.42 - 3.75 (m, 4 H), 3.12 (q, *J*=7.37 Hz, 2 H), 3.01 (q, *J*=7.50 Hz, 2 H), 2.76 (br. s., 2 H), 1.32 - 1.45 (m, 6 H); LCMS: (electrospray +ve), *m/z* 294.1 $(MH)^+$; HPLC: t_R = 2.76 min,UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{13}H_{20}N_5OS$ $[M+H]^+$ 294.1383, found 294.1381.

Example 5

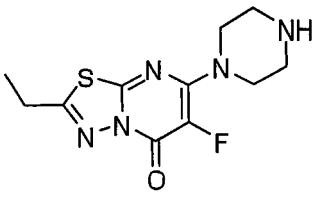
2-ethyl-6-methyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0077] This example is prepared by following the same procedures as described in Example 1 above except substituting 3-ethoxy-2-methyl-3-oxopropanoic acid for 3-ethoxy-3-oxopropanoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.09 - 3.16 (m, 4 H), 2.94 (q, *J*=7.43 Hz, 2 H), 2.66 - 2.75 (m, 4 H), 1.88 (s, 3 H), 1.24 (t, *J*=7.63 Hz, 3 H); LCMS: (electrospray +ve), *m/z* 280.1 $(MH)^+$; HPLC: t_R = 2.82 min,UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{12}H_{18}N_5OS$ $[M+H]^+$ 280.1227, found 280.1230.

Example 6

2-ethyl-6-fluoro-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one

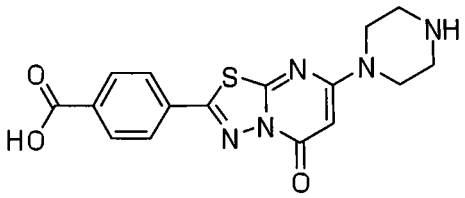


[0078] This example is prepared by following the same procedures as described in Example 1 above except substituting 3-ethoxy-2-fluoro-3-oxopropanoic

acid for 3-ethoxy-3-oxopropanoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.46 - 3.55 (m, 4 H), 2.96 (q, *J*=7.43 Hz, 2 H), 2.68 - 2.76 (m, 4 H), 1.26 (t, 3 H); LCMS: (electrospray +ve), *m/z* 284.1 $(MH)^+$; HPLC: t_R = 2.59 min,UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{11}H_{15}N_5OS$ $[M+H]^+$ 284.0975, found 284.0974.

Example 7

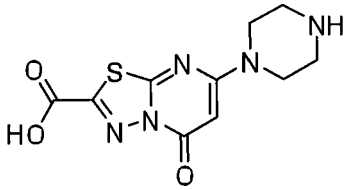
4-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)benzoic acid



[0079] This example is prepared by following the same procedures as described in Example 1 above except substituting methyl 4-(5-amino-1,3,4-thiadiazol-2-yl)benzoate for 5-ethyl-1,3,4-thiadiazol-2-amine to obtain tert-butyl 4-(2-(4-(methoxycarbonyl)phenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate as a yellow oil. This oil (99 mg, 0.21 mmol, 1.0 equiv) is taken up in a 1:1 THF/water mixture (3.0 mL), and to it is added lithium hydroxide (10 mg, 0.420 mmol, 2.0 equiv). After stirring for 2 h, the mixture is filtered and concentrated to give a yellow oil which is taken on crude to the same deprotection step mentioned above to give 4-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)benzoic acid as a tan solid (33 mg, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.86 (br. s., 1 H), 8.07 - 8.14 (m, 2 H), 7.99 - 8.06 (m, 2 H), 5.59 (s, 1 H), 4.06 (br. s., 1 H), 3.69 - 3.81 (m, 4 H), 3.08 - 3.21 (m, 4 H); LCMS: (electrospray +ve), *m/z* 358.1 $(MH)^+$; HPLC: t_R = 3.03 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{16}H_{16}N_5O_3S$ $[M+H]^+$ 358.0969, found 358.0969.

Example 8

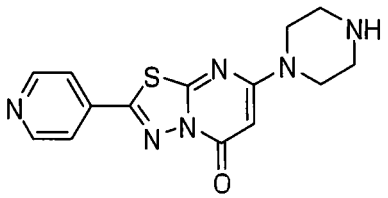
5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-carboxylic acid



[0080] This example is prepared by following the same procedures as described in Example 1 above except substituting methyl 5-amino-1,3,4-thiadiazole-2-carboxylate for methyl 4-(5-amino-1,3,4-thiadiazol-2-yl)benzoate. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.58 (br. s., 1 H), 5.90 (s, 1 H), 3.68 - 3.78 (m, 4 H), 3.10 - 3.19 (m, 4 H); LCMS: (electrospray +ve), *m/z* 282.0 $(MH)^+$; HPLC: t_R = 0.55 min, UV_{254} = 95%. HRMS (ESI): *m/z* calcd for $C_{10}H_{12}N_5O_3S$ $[M+H]^+$ 282.0655, found 282.0658.

Example 9

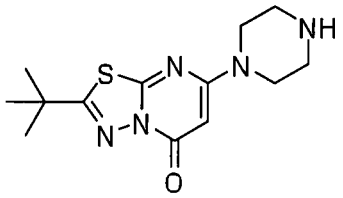
7-(piperazin-1-yl)-2-(pyridin-4-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0081] This example is prepared by following the same procedures as described in Example 1 above except substituting 5-(pyridin-4-yl)-1,3,4-thiadiazol-2-amine for 5-ethyl-1,3,4-thiadiazol-2-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (dd, *J*=4.30, 1.57 Hz, 2 H), 7.85 (dd, *J*=4.30, 1.57 Hz, 2 H), 5.40 (s, 1 H), 3.42 - 3.51 (m, 4 H), 2.66 - 2.75 (m, 4 H); LCMS: (electrospray +ve), *m/z* 315.0 $(MH)^+$; HPLC: t_R = 2.55 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{14}H_{15}N_6OS$ $[M+H]^+$ 315.1023, found 315.1024.

Example 10

2-tert-butyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one

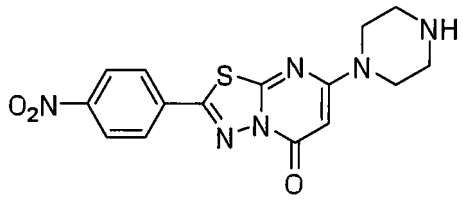


[0082] This example is prepared by following the same procedures as described in Example 1 above except substituting 5-tert-butyl-1,3,4-thiadiazol-2-amine for 5-ethyl-1,3,4-thiadiazol-2-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.32 (s, 1 H), 3.40 (m, 4 H), 2.67 (m, 4 H), 1.35 (s, 9 H); LCMS: (electrospray +ve),

m/z 294.1 $(MH)^+$; HPLC: t_R = 2.52 min (4 min method), UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{13}H_{20}N_5OS$ $[M+H]^+$ 294.1383, found 294.1382.

Example 11

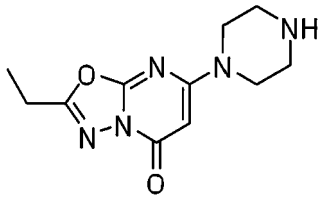
2-(4-nitrophenyl)-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0083] This example is prepared by following the same procedures as described in Example 1 above except substituting 5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine for 5-ethyl-1,3,4-thiadiazol-2-amine. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.39 (d, *J*=9.00 Hz, 2 H), 8.12 - 8.20 (m, 2 H), 5.40 (s, 1 H), 3.43 - 3.51 (m, 4 H), 2.64 - 2.75 (m, 4 H); LCMS: (electrospray +ve), *m/z* 359.1 $(MH)^+$; HPLC: t_R = 2.60 min (4 min method), UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{15}H_{15}N_6O_3S$ $[M+H]^+$ 359.0921, found 359.0919.

Example 12

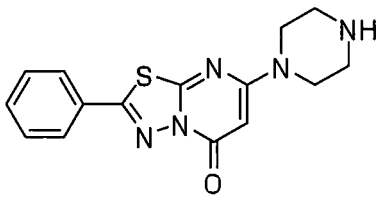
2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]oxadiazolo[3,2-a]pyrimidin-5-one



[0084] This example is prepared by following the same procedures as described in Example 1 above except substituting 5-ethyl-1,3,4-oxadiazol-2-amine for 5-ethyl-1,3,4-thiadiazol-2-amine. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 5.23 (s, 1 H), 3.35 - 3.43 (m, 4 H), 2.80 (q, *J*=7.56 Hz, 2 H), 2.64 - 2.73 (m, 4 H), 1.23 (t, 3 H); LCMS: (electrospray +ve), *m/z* 250.1 $(MH)^+$; HPLC: t_R = 2.41 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{11}H_{16}N_5O_2$ $[M+H]^+$ 250.1299, found 250.1302.

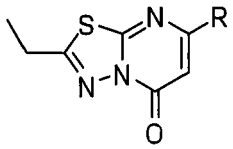
Example 13

2-phenyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0085] This example is prepared by following the same procedures as described in Example 1 above except substituting 5-phenyl-1,3,4-thiadiazol-2-amine for 5-ethyl-1,3,4-thiadiazol-2-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.84 - 7.93 (m, 2 H), 7.53 - 7.66 (m, 3 H), 5.38 (s, 1 H), 3.40 - 3.51 (m, 4 H), 2.65 - 2.77 (m, 4 H); LCMS: (electrospray +ve), *m/z* 314.1 $(MH)^+$; HPLC: t_R = 3.37 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{15}H_{16}N_5OS$ $[M+H]^+$ 314.1070, found 314.1073.

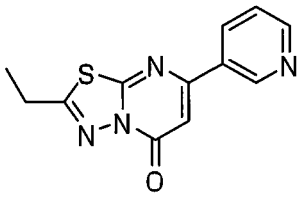
Examples 14-15 are prepared by using General procedure described below:



[0086] In a microwave vial is added 7-chloro-2-ethyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one (50 mg, 0.232 mmol, 1.0 equiv) followed by the R-boronic acid (0.464 mmol, 2.0 equiv), sodium carbonate (73.7 mg, 0.696 mmol, 3.0 equiv), and tetrakis(triphenylphosphine)palladium(0) (13.40 mg, 0.012 mmol, 0.05 equiv). The solids are taken up in DMF (1.4 mL), Ethanol (0.700 mL), and Water (0.350 mL). The mixture is then heated in the microwave at 120 °C for 25 min. Upon completion, the mixture is taken up in ethyl acetate and saturated potassium hydrogen sulfate. The layers are separated and the aqueous layer is extracted with ethyl acetate. The combined organic extracts are then washed with saturated sodium bicarbonate, water, and brine. They are dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil which is purified by HPLC to give 2-ethyl-7-aryl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-ones (20-40%) as tan solids.

Example 14

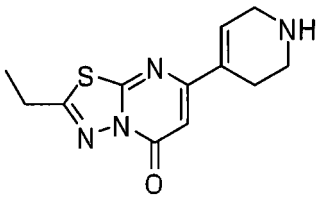
2-ethyl-7-(pyridin-3-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0087] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (d, J=2.35 Hz, 1 H), 8.61 - 8.68 (m, 1 H), 8.40 (ddd, J=8.02, 2.15, 1.96 Hz, 1 H), 7.49 (dd, J=8.02, 4.89 Hz, 1 H), 7.07 (s, 1 H), 3.04 (q, J=7.43 Hz, 2 H), 1.30 (t, 3 H); LCMS: (electrospray +ve), *m/z* 259.1 $(MH)^+$; HPLC: t_R = 2.98 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{12}H_{11}N_4OS$ $[M+H]^+$ 259.0648, found 259.0639.

Example 15

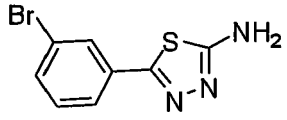
2-ethyl-7-(1,2,3,6-tetrahydropyridin-4-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0088] This example are prepared by following the same general procedure above for examples 14-15 to obtain tert-butyl 4-(2-ethyl-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)-5,6-dihydropyridine-1(2H)-carboxylate, which is taken on to the same deprotection procedure as with 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one described in step 3 of Example 1. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.94 - 7.00 (m, 1 H), 6.21 (s, 1 H), 3.36 (d, J=3.13 Hz, 2 H), 2.99 (q, J=7.43 Hz, 2 H), 2.81 (t, J=5.48 Hz, 2 H), 2.21 (d, 2 H), 1.26 (t, J=7.43 Hz, 3 H); LCMS: (electrospray +ve), *m/z* 263.0 $(MH)^+$; HPLC: t_R = 2.32 min (4 min method), UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{12}H_{15}N_4OS$ $[M+H]^+$ 263.0960, found 263.0958.

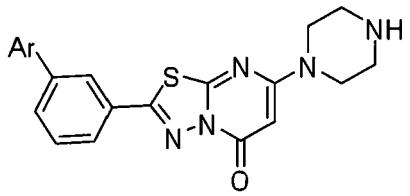
Examples 16-26 are prepared using the general procedures below:

Step 1: 5-(3-bromophenyl)-1,3,4-thiadiazol-2-amine



[0089] To a solution of thiosemicarbazide (0.493 g, 5.40 mmol, 1.0 equiv) in 6 mL of water at 70 °C is added a solution of 3-bromobenzaldehyde (0.633 ml, 5.40 mmol, 1.0 equiv) in 4.5 mL ethanol. After the precipitate formed, iron(III) chloride hexahydrate (2.92 g, 10.81 mmol, 2.0 equiv) in 6 mL water is added and the mixture is stirred for 2.5 h at 85 °C. Upon completion, the mixture is allowed to cool to room temperature and the resulting precipitate is collected by filtration and taken up in 12 mL pyridine. Ice water is then added to the pyridine slurry. The mixture is cooled then filtered to give 5-(3-bromophenyl)-1,3,4-thiadiazol-2-amine (553 mg, 39.9 % yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.85 - 7.88 (m, 1 H), 7.67 (d, J=8.22 Hz, 1 H), 7.53 - 7.59 (m, 1 H), 7.45 (s, 2 H), 7.36 (t, J=8.02 Hz, 1 H);

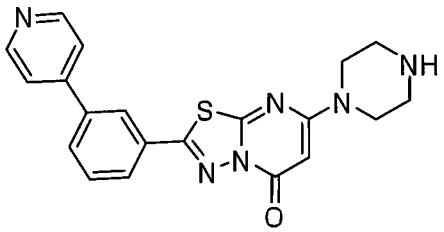
Step 2:



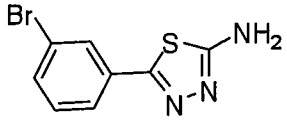
[0090] Boc-protected 2-(3-bromophenyl)-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one may be prepared as similarly described in step 2 of Example 1. To a solution of *tert*-butyl 4-(2-(3-bromophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (40 mg, 0.081 mmol, 1.0 equiv) in 1 mL DMF, 0.5 mL ethanol and 0.25 mL water in a microwave vial is added the boronic acid (0.162 mmol, 2.0 equiv), sodium carbonate (25.8 mg, 0.244 mmol, 3.0 equiv), and tetrakis(triphenylphosphine)palladium(0) (4.69 mg, 4.06 μmol, 0.05 equiv). The mixture is heated in a microwave reactor for 30 min at 120 °C. Upon completion the mixture is filtered through a thiol-SPE column (Stratospheres) and the resulting solution is concentrated *in vacuo* to give crude *tert*-butyl 4-(5-oxo-2-(3-(aryl-4-yl)phenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate as a yellow oil. The residue is then taken on crude to the next reaction, which followed the same deprotection procedure as described in step 3 of Example 1 to give 7-(piperazin-1-yl)-2-(3-(aryl-4-yl)phenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-ones (30-50%) as tan solids.

Example 16

7-(piperazin-1-yl)-2-(3-(pyridin-4-yl)phenyl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one

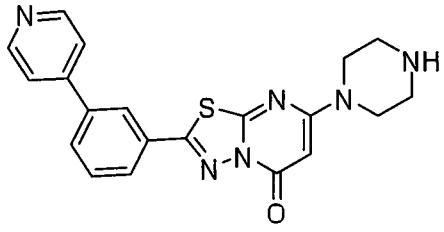


Step 1: 5-(3-bromophenyl)-1,3,4-thiadiazol-2-amine



[0091] To a solution of thiosemicarbazide (0.493 g, 5.40 mmol, 1.0 equiv) in 6 mL of water at 70 °C is added a solution of 3-bromobenzaldehyde (0.633 ml, 5.40 mmol, 1.0 equiv) in 4.5 mL ethanol. After the precipitate is formed, iron(III) chloride hexahydrate (2.92 g, 10.81 mmol, 2.0 equiv) in 6 mL water is added and the mixture is stirred for 2.5 h at 85 °C. Upon completion, the mixture is allowed to cool to room temperature and the resulting precipitate is collected by filtration and taken up in 12 mL pyridine. Ice water is then added to the pyridine slurry. The mixture is cooled then filtered to give 5-(3-bromophenyl)-1,3,4-thiadiazol-2-amine (553 mg, 39.9 % yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.85 - 7.88 (m, 1 H), 7.67 (d, J=8.22 Hz, 1 H), 7.53 - 7.59 (m, 1 H), 7.45 (s, 2 H), 7.36 (t, J=8.02 Hz, 1 H);

Step 2: 7-(piperazin-1-yl)-2-(3-(pyridin-4-yl)phenyl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one

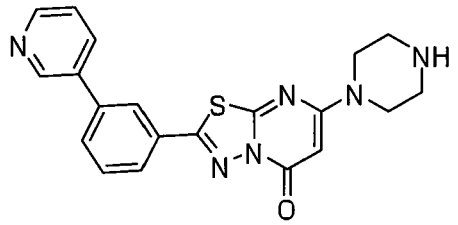


[0092] Boc-protected 2-(3-bromophenyl)-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one may be prepared as similarly described above (or in Steps 1 and 2 of Example 1), except 5-(3-bromophenyl)-1,3,4-thiadiazol-2-amine is used as the starting material in step 1.

[0093] To a solution of *tert*-butyl 4-(2-(3-bromophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (40 mg, 0.081 mmol, 1.0 equiv) in 1 mL DMF, 0.5 mL ethanol and 0.25 mL water in a microwave vial is added 4-pyridineboronic acid (19.97 mg, 0.162 mmol, 2.0 equiv), sodium carbonate (25.8 mg, 0.244 mmol, 3.0 equiv), and tetrakis(triphenylphosphine)palladium(0) (4.69 mg, 4.06 μmol, 0.05 equiv). The mixture is heated in a microwave reactor for 30 min at 120 °C. Upon completion the mixture is filtered through a thiol-SPE column (Stratospheres) and the resulting solution is concentrated *in vacuo* to give crude *tert*-butyl 4-(5-oxo-2-(3-(pyridin-4-yl)phenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate as a yellow oil. The residue is then taken on crude to the next reaction, which follows the same deprotection procedure as described in Step 3 of Example 1 to give 7-(piperazin-1-yl)-2-(3-(pyridin-4-yl)phenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one (12 mg, 38%) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.67 (dd, *J*=4.30, 1.57 Hz, 2 H), 8.18 (s, 1 H), 8.02 (dd, *J*=16.43, 8.22 Hz, 2 H), 7.70 - 7.82 (m, 3 H), 5.40 (s, 1 H), 3.42 - 3.51 (m, 4 H), 2.68 - 2.75 (m, 4 H); LCMS: (electrospray +ve), *m/z* 391.1 $(MH)^+$; HPLC: t_R = 2.82 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{20}H_{19}N_6OS$ $[M+H]^+$ 391.1321, found 391.1322.

Example 17

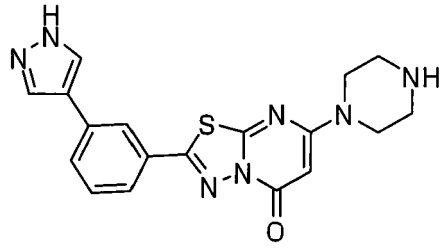
7-(piperazin-1-yl)-2-(3-(pyridin-3-yl)phenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0094] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.96 (d, *J*=1.57 Hz, 1 H), 8.61 (dd, *J*=4.70, 1.57 Hz, 1 H), 8.14 - 8.20 (m, 1 H), 8.12 (s, 1 H), 7.93 - 8.01 (m, 2 H), 7.72 (t, *J*=7.83 Hz, 1 H), 7.52 (dd, *J*=8.41, 5.28 Hz, 1 H), 5.39 (s, 1 H), 3.41 - 3.50 (m, 4 H), 2.66 - 2.75 (m, 4 H); LCMS: (electrospray +ve), *m/z* 391.1 $(MH)^+$; HPLC: t_R = 2.87 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{20}H_{19}N_6OS$ $[M+H]^+$ 391.1334, found 391.1337.

Example 18

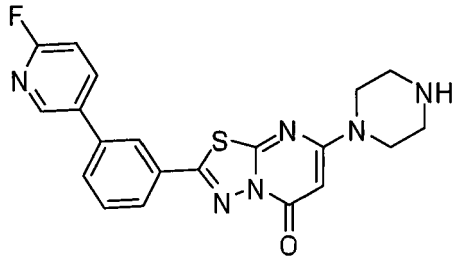
2-(3-(1H-pyrazol-4-yl)phenyl)-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0100] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.06 (br. s., 1 H), 8.16 (s, 2 H), 8.00 (s, 1 H), 7.85 (d, *J*=7.83 Hz, 1 H), 7.70 (d, *J*=8.61 Hz, 1 H), 7.55 (t, *J*=7.83 Hz, 1 H), 5.39 (s, 1 H), 3.44 (d, *J*=5.09 Hz, 4 H), 2.65 - 2.74 (m, 4 H); LCMS: (electrospray +ve), *m/z* 380.1 $(MH)^+$; HPLC: t_R = 3.53 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{18}H_{18}N_7OS$ $[M+H]^+$ 380.1288, found 380.1290.

Example 19

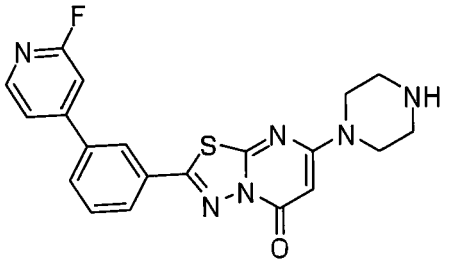
2-(3-(6-fluoropyridin-3-yl)phenyl)-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0101] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.64 (d, *J*=2.74 Hz, 1 H), 8.39 (td, *J*=8.22, 2.74 Hz, 1 H), 8.11 (s, 1 H), 7.97 (dd, *J*=8.22, 1.56 Hz, 2 H), 7.72 (t, *J*=8.02 Hz, 1 H), 7.32 (dd, *J*=8.61, 2.35 Hz, 1 H), 5.40 (s, 1 H), 3.42 - 3.50 (m, 4 H), 2.67 - 2.75 (m, 4 H); LCMS: (electrospray +ve), *m/z* 409.0 $(MH)^+$; HPLC: t_R = 3.81 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{20}H_{18}FN_6OS$ $[M+H]^+$ 409.1242, found 409.1233.

Example 20

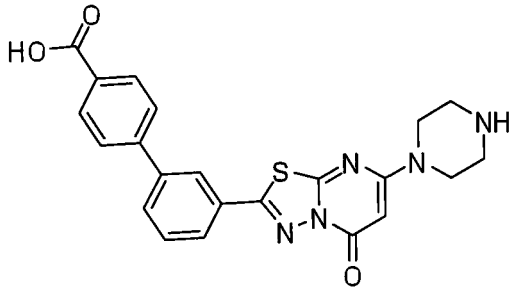
2-(3-(2-fluoropyridin-4-yl)phenyl)-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0102] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.34 (d, J=5.28 Hz, 1 H), 8.21 (t, J=1.66 Hz, 1 H), 8.00 - 8.12 (m, 2 H), 7.71 - 7.81 (m, 2 H), 7.65 (s, 1 H), 5.39 (s, 1 H), 3.41 - 3.48 (m, 4 H), 2.66 - 2.75 (m, 4 H); LCMS: (electrospray +ve), *m/z* 409.1 $(MH)^+$; HPLC: t_R = 3.82 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{20}H_{18}FN_6OS$ $[M+H]^+$ 409.1244, found 409.1246.

Example 21

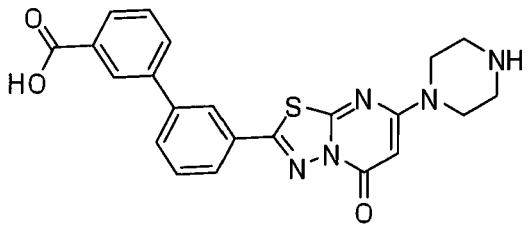
3'-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)biphenyl-4-carboxylic acid



[0103] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.04 (br. s., 1 H), 8.76 (br. s., 1 H), 8.14 - 8.18 (m, 1 H), 8.05 (d, J=8.61 Hz, 2 H), 7.94 - 8.03 (m, 2 H), 7.88 (d, J=8.61 Hz, 2 H), 7.73 (t, J=8.02 Hz, 1 H), 5.61 (s, 1 H), 3.71 - 3.82 (m, 4 H), 3.16 (br. s., 4 H); LCMS: (electrospray +ve), *m/z* 434.1 $(MH)^+$; HPLC: t_R = 3.79 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{22}H_{20}N_5O_3S$ $[M+H]^+$ 434.1281, found 434.1270.

Example 22

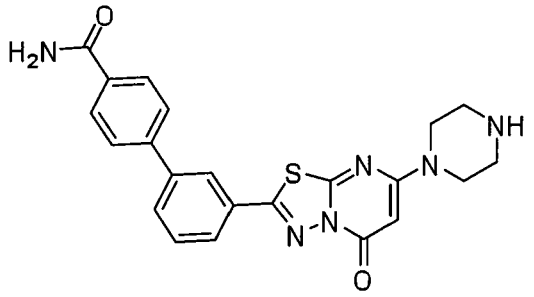
3'-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)biphenyl-3-carboxylic acid



[0104] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.15 (br. s., 1 H), 8.76 (br. s., 1 H), 8.23 (t, J=1.57 Hz, 1 H), 8.14 (t, J=1.66 Hz, 1 H), 7.90 - 8.05 (m, 4 H), 7.72 (t, J=7.92 Hz, 1 H), 7.64 (t, J=7.83 Hz, 1 H), 5.61 (s, 1 H), 3.69 - 3.83 (m, 4 H), 3.16 (br. s., 4 H); LCMS: (electrospray +ve), m/z 434.1 $(MH)^+$; HPLC: t_R = 3.94 min, UV_{254} = 100%. HRMS (ESI): m/z calcd for $C_{22}H_{20}N_5O_3S$ $[M+H]^+$ 434.1282, found 434.1281.

Example 23

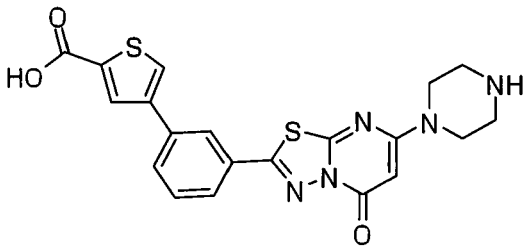
3'-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)biphenyl-4-carboxamide



[0105] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.12 (t, J=1.66 Hz, 1 H), 8.02 - 8.06 (m, 1 H), 7.89 - 8.01 (m, 3 H), 7.79 - 7.86 (m, 2 H), 7.70 (t, J=7.83 Hz, 1 H), 7.39 (br. s., 1 H), 5.40 (s, 1 H), 3.41 - 3.50 (m, 4 H), 2.66 - 2.76 (m, 4 H); LCMS: (electrospray +ve), m/z 433.1 $(MH)^+$; HPLC: t_R = 3.56 min, UV_{254} = 100%. HRMS (ESI): m/z calcd for $C_{22}H_{20}N_6O_2S$ $[M+H]^+$ 433.1441, found 433.1447.

Example 24

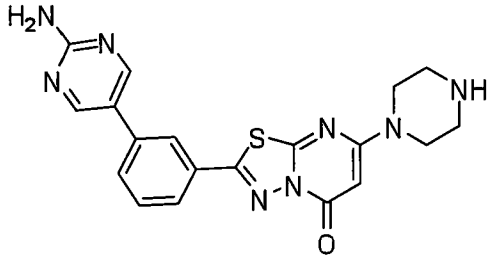
4-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)thiophene-2-carboxylic acid



[0106] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.27 (br. s., 1 H), 8.77 (br. s., 1 H), 8.37 (d, *J*=1.56 Hz, 1 H), 8.24 (d, *J*=1.56 Hz, 1 H), 8.15 (t, *J*=1.66 Hz, 1 H), 8.03 (ddd, *J*=8.12, 1.47, 1.17 Hz, 1 H), 7.89 (ddd, *J*=8.22, 1.37, 0.98 Hz, 1 H), 7.65 (t, *J*=7.92 Hz, 1 H), 5.60 (s, 1 H), 3.70 - 3.83 (m, 4 H), 3.08 - 3.22 (m, 4 H); LCMS: (electrospray +ve), *m/z* 440.1 $(MH)^+$; HPLC: t_R = 3.70 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{20}H_{18}N_5O_3S_2$ $[M+H]^+$ 440.0845, found 440.0852.

Example 25

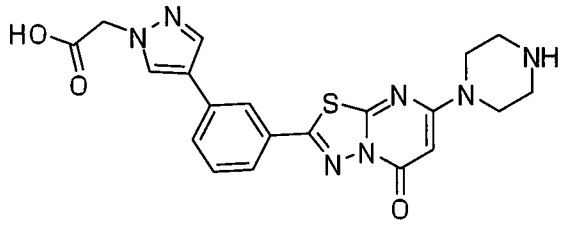
2-(3-(2-aminopyrimidin-5-yl)phenyl)-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one



[0107] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.64 (d, *J*=2.93 Hz, 2 H), 8.00 (d, *J*=1.17 Hz, 1 H), 7.85 (dd, *J*=9.10, 8.12 Hz, 2 H), 7.58 - 7.68 (m, 1 H), 6.87 (s, 2 H), 5.39 (d, *J*=2.54 Hz, 1 H), 3.45 (br. s., 4 H), 2.71 (d, 4 H); LCMS: (electrospray +ve), *m/z* 407.1 $(MH)^+$; HPLC: t_R = 3.10 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{19}H_{19}N_8OS$ $[M+H]^+$ 407.1389, found 407.1385.

Example 26

2-(4-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)-1H-pyrazol-1-yl)acetic acid

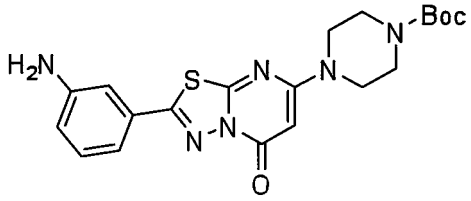


[0108] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.14 (br. s., 1 H), 8.79 (br. s., 1 H), 8.33 (d, *J*=0.78 Hz, 1 H), 7.96 - 8.05 (m, 2 H), 7.81 - 7.89 (m, 1 H), 7.70 - 7.77 (m, 1 H), 7.58 (t, *J*=8.02 Hz, 1 H), 5.60 (s, 1 H), 4.97 (s, 2 H), 3.70 - 3.82 (m, 4 H), 3.16 (br. s., 4 H); LCMS: (electrospray +ve), *m/z* 438.1 $(MH)^+$; HPLC: t_R = 3.34 min,

UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{20}H_{20}N_7O_3S$ $[M+H]^+$ 438.1343, found 438.1338.

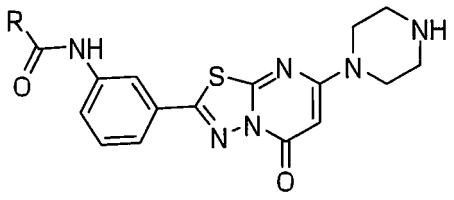
Examples 27-40 are prepared using general procedures below:

Step 1: *tert*-butyl 4-(2-(3-aminophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate



[0109] *tert*-butyl 4-(2-(3-nitrophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (220, 0.480 mmol, 1.0 equiv) is dissolved in 5 mL methanol. To the solution is added palladium on carbon (51.1 mg). The reaction is stirred under an atmosphere of hydrogen for 3 h. Upon completion, the mixture is filtered through celite and concentrated *in vacuo* to give crude *tert*-butyl 4-(2-(3-aminophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.37 (s, 1 H), 7.20 - 7.29 (m, 1 H), 7.13 (d, *J*=7.83 Hz, 1 H), 6.83 (dd, *J*=7.63, 1.76 Hz, 1 H), 5.46 (s, 1 H), 3.87 (s, 2 H), 3.45 - 3.65 (m, 8 H), 1.48 (m, 9 H);

step 2:

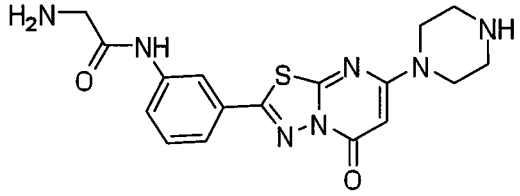


[0110] Crude tert-butyl 4-(2-(3-aminophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (60 mg, 0.140 mmol, 1.0 equiv) prepared as described in step 1 above, is taken up in DMF (1.5 mL) and to it is added the carboxylic acid (0.210 mmol, 1.5 equiv) then EDC (40.3 mg, 0.210 mmol, 1.5 equiv). The mixture is stirred at r.t. for 24 h. Upon completion, the reaction is then taken up in water and ethyl acetate. The layers are separated and the aqueous layer is extracted with ethyl acetate. The combined organic extracts are then

washed with water twice, then brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow solid which is chromatographed with 2-7% MeOH/DCM gradient to give N-acylated tert-butyl 4-(2-(3-aminophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylates. The residue is then taken on to the next reaction, which follows the same deprotection procedure to give N-acylated 2-(3-aminophenyl)-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-ones (40-60%) as tan solids after HPLC purification.

Example 27

2-amino-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)acetamide



[0111] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.31 (s, 1 H), 7.86 (d, J=7.43 Hz, 1 H), 7.48 - 7.58 (m, 2 H), 5.38 (s, 1 H), 3.46 (br. s., 4 H), 3.29 (s, 2 H), 2.67 - 2.76 (m, 4 H); LCMS: (electrospray +ve), *m/z* 386.1 $(MH)^+$; HPLC: t_R = 2.70 min,UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{17}H_{20}N_7O_2S$ $[M+H]^+$ 386.1394, found 386.1393.

[0112] In a particular instance, the compound of this example is prepared as described or similarly described as follows: To 5-(3-nitrophenyl)-1,3,4-thiadiazol-2-amine (**2**) (3.0 g, 13.50 mmol) in MeCN (120 ml) is added methyl 3-chloro-3-oxopropanoate (1.735 mL, 16.20 mmol). The mixture is stirred at room temperature for 2 hours. After consumption of the starting material, $POCl_3$ (60 mL, 644 mmol) is added along with DIPEA (2.358 mL, 13.50 mmol) in MeCN (10 mL). The mixture is heated in the microwave at 150 °C for 25 min, cooled, and concentrated *in vacuo*. The resulting slurry is taken up in chloroform, poured over ice and washed with saturated $NaHCO_3$, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a dark red oil which is purified via column chromatography on a 100 g snap column with 0-10% EtOAc/DCM gradient elution to give 7-chloro-2-(3-nitrophenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one (1.36 g, 4.41 mmol, 32.6 % yield) as an orange solid.

[0113] To 7-chloro-2-(3-nitrophenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one (1.0 g, 3.24 mmol) in MeCN (30 ml) in a microwave vial is added *tert*-butyl 1-piperazinecarboxylate (0.724 g, 3.89 mmol) followed by DIPEA (1.697 ml, 9.72 mmol). The mixture is heated in the microwave to 150 °C for 25 min., cooled and concentrated *in vacuo* and purified via column chromatography on a 50 g snap column with 0-10% MeOH/DCM gradient elution to give tert-butyl 4-(2-(3-nitrophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (1.44 g, 3.14 mmol, 97 % yield) as a tan solid.

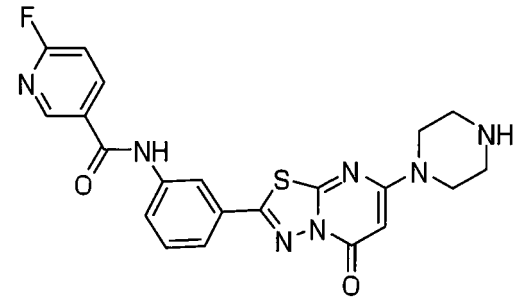
[0114] To a solution of tert-butyl 4-(2-(3-nitrophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (769 mg, 1.677 mmol) in EtOH (12 ml) at room temperature is added Raney® 2400 nickel (98 mg, 1.677 mmol) followed by hydrazine (0.526 ml, 16.77 mmol) dropwise and the mixture is stirred at room temperature for 4 hours. The reaction is monitored by TLC and LMCMS and additional nickel and hydrazine is added until completion. The mixture is filtered over celite and concentrated *in vacuo* to give crude tert-butyl 4-(2-(3-aminophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (443 mg, 1.034 mmol, 61.6 % yield) as a tan solid.

[0115] Crude tert-butyl 4-(2-(3-aminophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (60 mg, 0.140 mmol) is taken up in DMF (1.5 mL) and to it is added the Boc-glycine (37 mg, 0.210 mmol) then EDC (40.3 mg, 0.210 mmol). The mixture is stirred at room temperature for 24 hours and the reaction mixture is then taken up in water and ethyl acetate. The layers are separated and the aqueous layer is extracted with ethyl acetate. The combined organic extracts are then washed with water twice, then brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow solid which is purified via column chromatography with 2-7% MeOH/DCM gradient to give tert-butyl 4-(2-(3-(2-(tert-butoxycarbonylamino)acetamido)phenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (crude material confirmed by LCMS analysis). The residue is then taken up in 2 mL of dichloromethane and trifluoroacetic acid (1 ml, 13.0 mmol) is added and the mixture is stirred for 18 hours. The solution is then concentrated *in vacuo* and washed with dichloroethane to give a crude yellow solid that is dissolved in methanol and purified by preparative HPLC to

give 2-amino-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)acetamide (40 mg, 49%) as a tan solid after HPLC purification.

Example 28

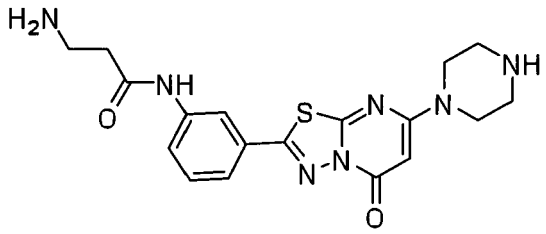
6-fluoro-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)nicotinamide



[0116] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.72 (s, 1 H), 8.84 (d, *J*=2.74 Hz, 1 H), 8.52 (td, *J*=8.12, 2.54 Hz, 1 H), 8.40 (s, 1 H), 8.04 (dt, *J*=7.43, 1.96 Hz, 1 H), 7.52 - 7.65 (m, 2 H), 7.37 (dd, *J*=8.61, 2.35 Hz, 1 H), 5.38 (s, 1 H), 3.40 - 3.49 (m, 4 H), 2.65 - 2.76 (m, 4 H); LCMS: (electrospray +ve), *m/z* 452.1 $(MH)^+$; HPLC: t_R = 3.65 min,UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{18}H_{28}FN_7O_2S$ $[M+H]^+$ 452.1300, found 452.1305.

Example 29

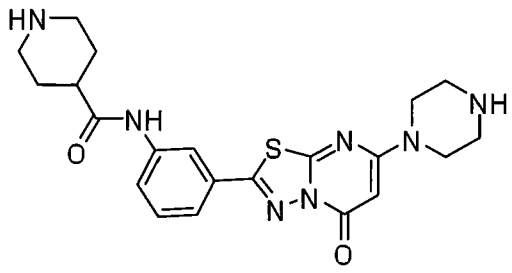
3-amino-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)propanamide



[0117] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.26 (d, *J*=1.57 Hz, 1 H), 7.77 (dt, *J*=6.41, 2.47 Hz, 1 H), 7.46 - 7.54 (m, 2 H), 5.37 (s, 1 H), 3.40 - 3.49 (m, 4 H), 2.82 (t, *J*=6.46 Hz, 2 H), 2.65 - 2.74 (m, 4 H), 2.39 (t, 2 H); LCMS: (electrospray +ve), *m/z* 400.1 $(MH)^+$; HPLC: t_R = 3.27 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{18}H_{22}N_7O_2S$ $[M+H]^+$ 400.1549, found 400.1546.

Example 30

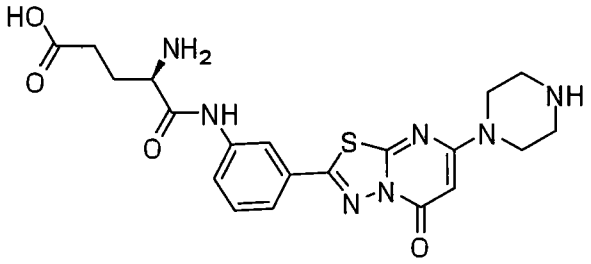
N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)piperidine-4-carboxamide



[0118] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.12 (s, 1 H), 8.27 (s, 1 H), 7.79 (d, *J*=7.04 Hz, 1 H), 7.49 (s, 2 H), 5.37 (s, 1 H), 3.44 (br. s., 4 H), 2.93 (br. s., 2 H), 2.70 (br. s., 4 H), 2.40 (m, 2 H), 1.65 (br. s., 2 H), 1.50 (br. s., 2 H); LCMS: (electrospray +ve), *m/z* 440.2 $(MH)^+$; HPLC: t_R = 2.90 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{21}H_{26}N_7O_2S$ $[M+H]^+$ 440.1862, found 440.1860.

Example 31

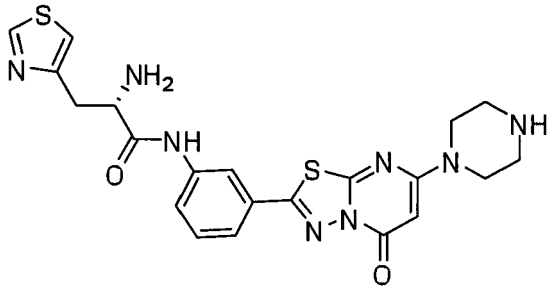
(R)-4-amino-5-oxo-5-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenylamino)pentanoic acid



[0119] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.26 (t, *J*=1.76 Hz, 1 H), 7.83 (ddd, *J*=7.97, 1.81, 1.57 Hz, 1 H), 7.52 - 7.67 (m, 2 H), 5.57 (s, 1 H), 3.95 (t, *J*=6.46 Hz, 1 H), 3.70 - 3.81 (m, 4 H), 3.09 - 3.18 (m, 4 H), 2.32 - 2.42 (m, 2 H), 2.01 - 2.11 (m, 2 H); LCMS: (electrospray +ve), *m/z* 458.2 $(MH)^+$; HPLC: t_R = 2.66 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{20}H_{24}N_7O_4S$ $[M+H]^+$ 458.1605, found 458.1602.

Example 32

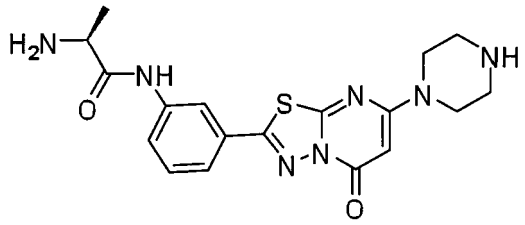
(S)-2-amino-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)-3-(thiazol-4-yl)propanamide



[0120] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.79 (s, 1 H), 9.10 (d, J=1.96 Hz, 1 H), 8.86 (br. s., 1 H), 8.33 (br. s., 2 H), 8.22 (t, J=1.76 Hz, 1 H), 7.76 (ddd, J=8.07, 1.71, 1.37 Hz, 1 H), 7.53 - 7.63 (m, 1 H), 7.51 (d, J=1.96 Hz, 1 H), 5.57 (s, 1 H), 4.29 (br. s., 1 H), 3.70 - 3.81 (m, 4 H), 3.34 - 3.45 (m, 2 H), 3.10 - 3.20 (m, 4 H); LCMS: (electrospray +ve), *m/z* 483.0 $(MH)^+$; HPLC: t_R = 3.00 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{21}H_{23}N_8O_2S_2$ $[M+H]^+$ 483.1379, found 483.1376.

Example 33

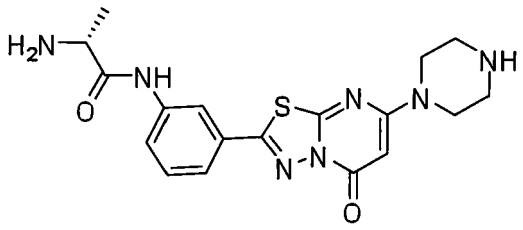
(S)-2-amino-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)propanamide



[0121] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.71 (s, 1 H), 8.83 (br. s., 1 H), 8.26 (t, J=1.66 Hz, 1 H), 8.14 - 8.23 (m, 2 H), 7.82 (ddd, J=7.87, 1.81, 1.66 Hz, 1 H), 7.53 - 7.66 (m, 2 H), 5.57 (s, 1 H), 4.01 (br. s., 1 H), 3.71 - 3.80 (m, 4 H), 3.16 (br. s., 4 H), 1.46 (d, 3 H); LCMS: (electrospray +ve), *m/z* 400.2 $(MH)^+$; HPLC: t_R = 2.79 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{18}H_{22}N_7O_2S$ $[M+H]^+$ 400.1550, found 400.1545.

Example 34

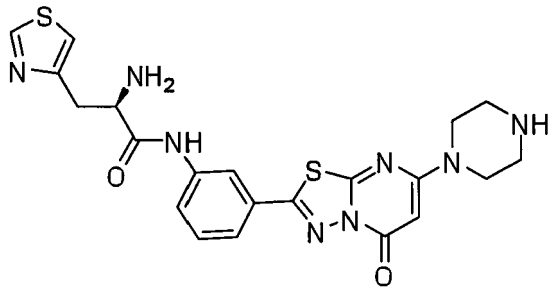
(R)-2-amino-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)propanamide



[0122] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.71 (s, 1 H), 8.83 (br. s., 1 H), 8.26 (t, *J*=1.66 Hz, 1 H), 8.13 - 8.23 (m, 2 H), 7.82 (ddd, *J*=7.87, 1.81, 1.66 Hz, 1 H), 7.52 - 7.67 (m, 2 H), 5.57 (s, 1 H), 4.01 (br. s., 1 H), 3.70 - 3.81 (m, 4 H), 3.16 (br. s., 4 H), 1.46 (d, 3 H); LCMS: (electrospray +ve), *m/z* 400.2 $(MH)^+$; HPLC: t_R = 2.82 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{18}H_{22}N_7O_2S$ $[M+H]^+$ 400.1550, found 400.1547.

Example 35

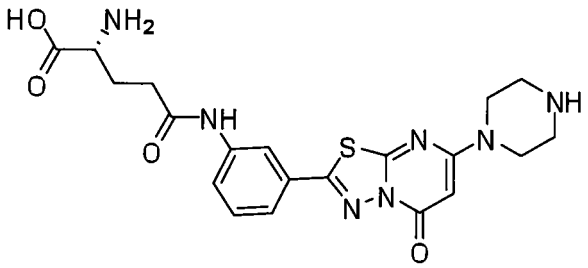
(R)-2-amino-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)-3-(thiazol-4-yl)propanamide



[0123] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.79 (s, 1 H), 9.10 (d, *J*=1.96 Hz, 1 H), 8.86 (br. s., 1 H), 8.33 (br. s., 2 H), 8.22 (t, *J*=1.76 Hz, 1 H), 7.76 (ddd, *J*=8.07, 1.71, 1.37 Hz, 1 H), 7.53 - 7.63 (m, 1 H), 7.51 (d, *J*=1.96 Hz, 1 H), 5.57 (s, 1 H), 4.29 (br. s., 1 H), 3.70 - 3.81 (m, 4 H), 3.34 - 3.45 (m, 2 H), 3.10 - 3.20 (m, 4 H); LCMS: (electrospray +ve), *m/z* 483.2 $(MH)^+$; HPLC: t_R = 3.02 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{21}H_{23}N_8O_2S_2$ $[M+H]^+$ 483.1380, found 483.1381.

Example 36

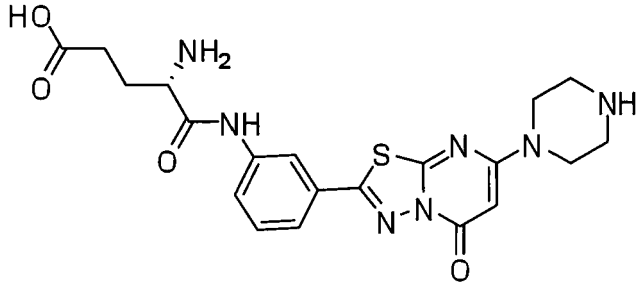
(R)-2-amino-5-oxo-5-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenylamino)pentanoic acid



[0124] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.44 (s, 1 H), 8.33 (s, 1 H), 7.71 - 7.80 (m, 1 H), 7.45 - 7.56 (m, 2 H), 5.57 (s, 1 H), 3.74 (br. s., 4 H), 3.14 (d, *J*=4.70 Hz, 4 H), 2.55 (m, 1 H), 2.50 (s, 2 H), 2.03 (br. s., 2 H); LCMS: (electrospray +ve), *m/z* 458.2 $(MH)^+$; HPLC: t_R = 2.82 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{20}H_{24}N_7O_4S$ $[M+H]^+$ 458.1603, found 458.1598.

Example 37

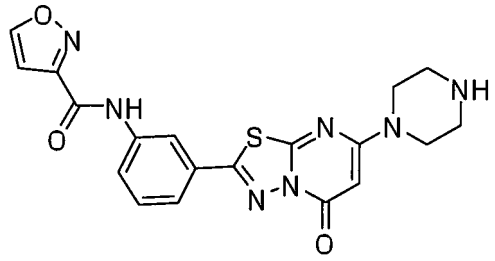
(S)-4-amino-5-oxo-5-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenylamino)pentanoic acid



[0125] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.26 (t, *J*=1.76 Hz, 1 H), 7.83 (ddd, *J*=7.97, 1.81, 1.57 Hz, 1 H), 7.51 - 7.67 (m, 2 H), 5.57 (s, 1 H), 3.96 (t, *J*=6.46 Hz, 1 H), 3.70 - 3.81 (m, 4 H), 3.09 - 3.18 (m, 4 H), 2.33 - 2.42 (m, 2 H), 2.01 - 2.11 (m, 2 H); LCMS: (electrospray +ve), *m/z* 458.2 $(MH)^+$; HPLC: t_R = 2.78 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{20}H_{24}N_7O_4S$ $[M+H]^+$ 458.1604, found 458.1620.

Example 38

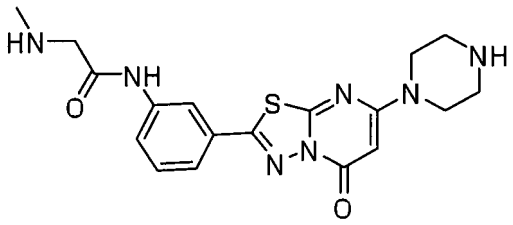
N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)isoxazole-3-carboxamide



[0126] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.03 (s, 1 H), 9.16 (d, *J*=1.76 Hz, 1 H), 8.72 (br. s., 1 H), 8.48 (t, *J*=1.86 Hz, 1 H), 8.02 (ddd, *J*=8.07, 2.10, 1.17 Hz, 1 H), 7.63 - 7.70 (m, 1 H), 7.59 (t, *J*=8.02 Hz, 1 H), 7.02 (d, *J*=1.76 Hz, 1 H), 5.58 (s, 1 H), 3.70 - 3.79 (m, 4 H), 3.10 - 3.19 (m, 4 H); LCMS: (electrospray +ve), *m/z* 424.1 $(MH)^+$; HPLC: t_R = 3.54 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{19}H_{18}N_7O_3S$ $[M+H]^+$ 424.1186, found 424.1181.

Example 39

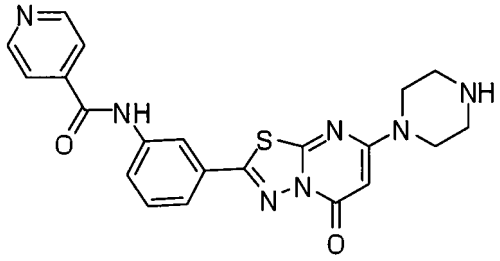
2-(methylamino)-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)acetamide



[0127] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.27 (t, *J*=1.66 Hz, 1 H), 7.78 (ddd, *J*=7.68, 1.91, 1.76 Hz, 1 H), 7.53 - 7.64 (m, 2 H), 5.57 (s, 1 H), 3.94 (s, 2 H), 3.70 - 3.79 (m, 4 H), 3.10 - 3.20 (m, 4 H), 2.63 (s, 3 H); LCMS: (electrospray +ve), *m/z* 400.2 $(MH)^+$; HPLC: t_R = 2.74 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{18}H_{22}N_7O_2S$ $[M+H]^+$ 400.1557, found 400.1547.

Example 40:

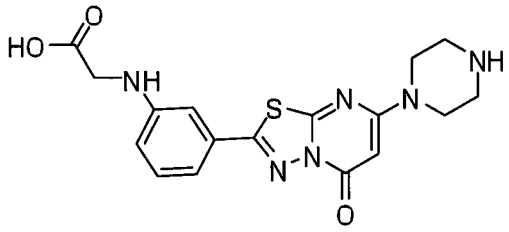
***N*-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)isonicotinamide**



[0128] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.77 (s, 1 H), 8.75 - 8.82 (m, 2 H), 8.42 (s, 1 H), 8.02 - 8.10 (m, 1 H), 7.86 - 7.91 (m, 2 H), 7.54 - 7.67 (m, 2 H), 5.38 (s, 1 H), 3.40 - 3.50 (m, 4 H), 2.67 - 2.75 (m, 4 H); LCMS: (electrospray +ve), *m/z* 434.1 $(MH)^+$; HPLC: t_R = 3.08 min, UV_{254} = 100%. HRMS (ESI): *m/z* calcd for $C_{21}H_{20}N_7O_2S$ $[M+H]^+$ 434.1399, found 434.1393.

Example 41

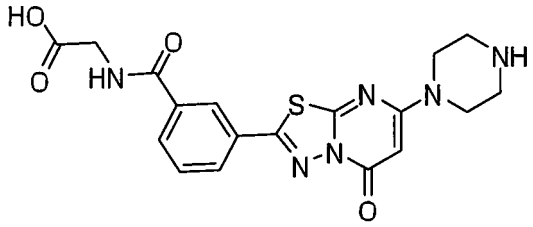
2-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenylamino)acetic acid



[0129] To a solution of *tert*-butyl 4-(2-(3-aminophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (50 mg, 0.117 mmol, 1.0 equiv) in 1.0 mL tetrahydrofuran is added dropwise a solution of *tert*-butyl bromoacetate (0.069 mL, 0.467 mmol, 4.0 equiv) in 0.5 mL tetrahydrofuran and a solution of *N,N*-diisopropylethylamine (0.082 mL, 0.467 mmol, 4.0 equiv) in 0.5 mL tetrahydrofuran. The mixture is heated in a microwave reactor for 30 min at 120 °C. Upon completion, the mixture is taken up in water and EtOAc. The layers are separated and the aqueous layer is back-extracted with EtOAc. The combined organic extracts are washed with water and brine, and concentrated *in vacuo* to give crude *tert*-butyl 4-(2-(3-(2-*tert*-butoxy-2-oxoethylamino)phenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate as a yellow solid. The residue is then taken on crude to the next reaction, which followed the same deprotection procedure as above to give 2-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenylamino)acetic acid (18 mg, 40%) as a tan solid.

Example 42:

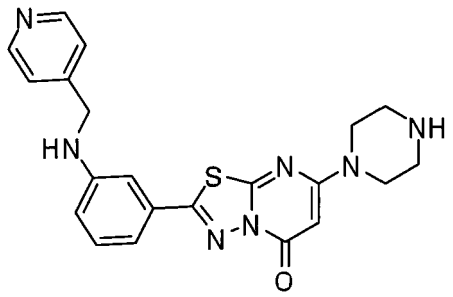
2-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)benzamido)acetic acid



[0130] 3-(7-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)benzoic acid (45 mg, 0.098 mmol, 1.0 equiv), is prepared using the procedure similarly described in Example 7, is dissolved in 1 mL in dimethylformamide. To the solution is added glycine *tert*-butyl ester (0.016 ml, 0.118 mmol, 1.2 equiv), PyBOP (77 mg, 0.148 mmol, 1.5 equiv), then *N,N*-diisopropylamine (0.052 ml, 0.295 mmol, 3.0 equiv). The mixture stirred at room temperature for 18 h. Upon completion, the mixture is taken up in water and EtOAc. The layers are separated and the aqueous layer is back-extracted with EtOAc. The combined organic extracts are then washed with water twice, then brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil which is purified by chromatography (silica gel, 2-5% MeOH/dichloromethane) to give *tert*-butyl 4-(2-(3-(2-*tert*-butoxy-2-oxoethylcarbamoyl)phenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (41 mg, 73.0 % yield) as a yellow oil. The residue is then taken on to the next reaction, which follows the same deprotection procedure as above to give 2-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)benzamido)acetic acid (16 mg, 53.7 % yield) as a white solid.

Example 43:

[0131] **7-(piperazin-1-yl)-2-(3-(pyridin-4-ylmethylamino)phenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one**



[0132] To a solution of *tert*-butyl 4-(2-(3-aminophenyl)-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate (60 mg, 0.140 mmol, 1.0 equiv) and 4-pyridinecarboxaldehyde (0.013 mL, 0.140 mmol, 1.0 equiv)

in 1 mL tetrahydrofuran in a microwave vial is added dibutyltin dichloride (4.25 mg, 0.014 mmol, 0.1 equiv) and Phenylsilane (0.035 mL, 0.280 mmol, 2.0 equiv). The mixture is heated in a microwave reactor for 10 min at 100 °C. Upon completion, the reaction mixture is filtered through a thiol-SPE collumn (Stratospheres) and concentrated *in vacuo* to give crude *tert*-butyl 4-(5-oxo-2-(3-(pyridin-4-ylmethylamino)phenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-yl)piperazine-1-carboxylate as a yellow oil. The residue is then taken on crude to the next reaction, which followed the same procedure as above to give 7-(piperazin-1-yl)-2-(3-(pyridin-4-ylmethylamino)phenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one (10 mg, 18%) as a white solid.

Example 44 - Platelet adhesion and/or aggregation

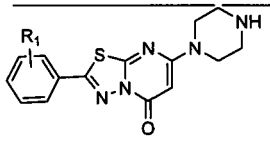
[0133] The platelet adhesion assay is conducted by a modification of the assay as described in Blue et al., *Blood* **2008**, *111*, 1248, the contents of which are incorporated by reference in their entirety. Thirty microliters of human fibrinogen (50 μg/mL) in Tris/saline (100 mM NaCl, 50 mM Tris/HCl, pH 7.4; American Diagnostica, Stamford, CT) are added to black, clear-bottom, untreated polystyrene, nonsterile 384-well microtiter plate wells (Corning no. 3711; Acton, MA). After incubating at 22°C for 1 hour, plates are washed 3 times with Tris/saline, and wells are then blocked with HBMT (138 mM NaCl, 12 mM $NaHCO_3$, 10 mM HEPES, 2.7 mM KCl, 0.4 mM NaH_2PO_4, 0.1% glucose, 0.35% BSA, pH 7.4) for at least 1 hour. An additional wash is performed using HBMT with 1 mM $MgCl_2$ and 2 mM $CaCl_2$. Calcein-labeled platelets (final concentration 1 x 10^{11}/L) are treated with selected Compounds of the Invention (final concentration of 100 μM, 30 μM, 10 μM or 1 μM) at 22°C for 20 minutes. Thirty microliters of platelets are then added to the wells. After 1 hour of adhesion, wells are washed 3 times with HBMT-1 mM $MgCl_2$/2 mM $CaCl_2$ and the plates are read by a fluorescent microtiter plate reader (Envision;Perkin Elmer) to detect calcein fluorescence (490 nm excitation and 515 nm emission). Negative controls consist of wells containing platelets without compounds of the invention. Positive controls are wells containing platelets and known inhibitors of αIIbβ3, including mAbs 7E3 and 10E5, and EDTA.

[0134] The platelet aggregation assay is conducted by modification of the assay as disclosed in Blue et al., *Blood* **2008**, *111*, 1248, the contents of which are

incorporated by reference in their entirety. Citrated platelet-rich plasma (PRP), generated by the centrifugation of whole blood at 650 g for 4 minutes at 22°C, is incubated in aggregometer cuvettes with selected Compounds of the Invention (final concentration of 100 μM, 30 μM, 10 μM or 1 μM) or controls for 15 minutes at 37°C. After 30 seconds in the aggregometer (Kowa AF-10E; Tokyo, Japan) at 37°C with stirring, ADP (5 – 20 μM) is added to induce aggregation and the light transmittance is measured for 8 minutes. The initial slopes of aggregation in the presence of different concentrations of the Compound being tested are used to generate an IC_{50}.

[0135] Platelet adhesion and/or aggregation studies of various Compounds of the Invention show that various exemplified compounds of the invention exhibit an IC_{50} value of less than 100 μM in a platelet aggregation study and/or inhibition of greater than 20% , in some instances, greater than 30% at a concentration of 100 μM in a platelet adhesion study. Selected results are shown in Table 1 below:

Table 1



18-22

#	R_1	*P.Ad.A.*[a] *% inhibition*[d]	*P.Ad.A.*[a] IC_{50}[d]	*P.Ag.A.*[a] IC_{50}[d]
18	3-(2-aminoacetamide)	92%[b]	1.1 μM	0.163 μM
19	3-((S)-2-aminopropanamide)	35%[c]	8.2 μM	0.916 μM
20	3-((R)-2-aminopropanamide)	69%[c]	> 20 μM	5.9 μM
21	3-(2-(methylamino)acetamide)	24%[c]	ND	ND
22	3-(piperidine-4-carboxamide)	64%[c]	> 20 μM	8.6 μM

[a] P.Ad.A. = platelet adhesion assay. P.Ag.A. = platelet aggregation assay;[b] % inhibition at 30 μM; [c] % inhibition at 100 μM [d] % inhibition and IC_{50} values were determined utilizing the platelet adhesion assay and platelet aggregation assay as described in Blue et al, Blood 2008, 111, 1248. ND = not determined.

[0136] In 5 separate experiments, Compound #18 described in Table 1 above (or 2-amino-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)acetamide of Example 27 of the current invention) produces 83±7% (mean ± SD) inhibition of platelet adhesion to fibrinogen at a concentration of 100 μM, 80±13% inhibition at 30 μM, and 66±10% inhibition at 10 μM; the comparable values for 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one (a compound disclosed and claimed in U.S. Serial No. 12/514,286) at the same concentrations are 70±15%, 38±10%, and 22±8%. For further comparison, tirofiban produces 87± 9% inhibition at 10 μM.

[0137] Compound #18 described in Table 1 above (or the compound of Example 27 of the current invention) also inhibits ADP-induced platelet aggregation

of citrated PRP with an IC_{50} of 90 ± 20 nM (n=4). By comparison, 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286 has an IC_{50} of 12 and 18 μM when tested twice under the same conditions. When PPACK is used as the anticoagulant instead of citrate, the IC_{50} for Compound #18 (or Example 27 of the current invention) is nearly 3-fold higher (220 nM; n=4). Therefore, the compound of Example 27 of the current invention is more than one hundred-fold more potent in inhibiting platelet aggregation than 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286.

Example 45:

[0138] The effects of the Compounds of the Invention on platelet adhesion and/or aggregation may be studied as described in the examples below.

[0139] ***Human αIIb and murine β3 (hαIIb/mβ3) platelets.*** The production of mice transgenic for the hαIIb gene locus may be produced as described in Thorton et al., *Blood* (2005) 112:1180-1188, the contents of which are incorporated by reference in their entirety. These mice may be crossed with mice homozygous for targeted disruption of the mαIIb gene (*Itga2b*). The resulting mice are a mixture of C57Bl/6 and SV129 backgrounds. The genotypes of mice containing the hαIIb transgene and homozygous for the targeted disruption of mαIIb may be confirmed by PCR and direct assessment of surface expression of the receptors may be performed on washed platelets prepared from platelet-rich plasma (PRP) as previously in Eslin et al., *Blood* (2004) 104:3173-3180; Basani et al., *Blood* (2009) 113:902-910. FITC-conjugated anti-human CD41 (HIP8; eBioscience, San Diego, CA) antibody is used to detect hαIIb and phycoerythrin-conjugated anti-mouse CD41 (MWReg30; BD Biosciences, San Jose, CA) antibody is used to detect mαIIb.

[0140] ***Murine αIIb and human β3 (mαIIb/hβ) platelets.*** Human normal β3 cDNA may be excised from the pcDNA3 mammalian expression vector (a kind gift of Dr. Peter Newman) and ligated into the mouse stem cell virus MigR1 vector containing an internal ribosome entry site (IRES)-green fluorescent protein (GFP) insertion prior to the polyadenylation signal. Virus containing hβ3 cDNA is then generated using Ecopack 2-293 cells (ATCC, Manassas, VA). Supernatant containing the virus may be collected 72 h after transfection, passed through a 0.45 μm filter, and stored at -70°C until further use.

[0141] Fetal liver cell transplantation may be performed as per Zou et al., *Blood* (2007) 109:3284-3290, with minor modifications. Fetal liver cells are harvested from *Itgb3*-/- embryos on a mixed C57Bl/6 and 129S6/SVEV background at E14.5-E16.5 and the cell suspension is enriched for CD34+ hematopoietic progenitors using negative selection (EasySep, StemCell Technologies, Vancouver, BC, Canada). Enriched cells may be then cultured overnight in media containing murine stem cell factor (100 ng/ml), murine interleukin 6 (10 ng/ml) and murine interleukin 3 (20 ng/ml; all from PeproTech, Rocky Hill, NJ). Fetal cell cultures may be infected at 0.5 transducing units (TDU) per cell on two consecutive days with MigR1-β3 viral supernatant in the presence of stem cell factor, interleukins 3 and 6 (concentrations as above), and hexadimethrine bromide (8 μg/ml; polybrene, Sigma). Infected cells (approximately 1.5 - 2 x 10^6/mouse; approximately 60% expressing GFP and hβ3) may then be injected i.v. into a lethally irradiated WT (i.e., *Itgβ3*+/+) mouse (900 rads of X-rays in two divided doses, three hours apart). Platelet studies may be performed with blood obtained 5 weeks or more after transplantation.

[0142] ***Platelet aggregation:*** Blood may be drawn via cardiac puncture from anesthetized Sprague Dawley rats (Taconic, Hudson, NY), WT C57Bl/6 mice (Jackson Laboratories, Bar Harbor, ME), and mice expressing hαIIb/mβ3 and diluted 1:1 with a mixture of 4 parts 0.165 mM NaCl, 0.01 mM HEPES, pH 7.4 containing 2 mM $CaCl_2$ and 1 mM $MgCl_2$. Blood from consenting human volunteers is obtained from a peripheral vein using a 19 gauge needle and anticoagulated with 1:10 vol 3.8% sodium citrate. Platelet-rich plasma (PRP) may be isolated by centrifugation at 22°C at 350 *g* for 10 minutes (rats); 250 *g* for 2.5 minutes (mice); or 650 *g* for 4 minutes (human). Mouse PRP samples may be adjusted to 400,000 platelets/μl with the buffer used for dilution and human PRP may be adjusted to 300,000 platelets/μl with platelet-poor plasma. Samples of PRP may be either untreated or incubated for 5 minutes at 37°C with the Compounds of the Invention (100 μM). Platelet aggregation may be induced by adding to PRP adenosine diphosphate (ADP) at 30 μM (rats and WT mice), 20 or 30 μM (hαIIb/mβ3 mice), or 5 μM (humans), and light transmission may be measured over time in an aggregometer (Kowa AG-10E, Tokyo, Japan) with stirring. Percent inhibition may be calculated by comparing the initial slope of untreated samples to the samples treated with the Compounds of the Invention.

[0143] ***Soluble fibrinogen binding***: Whole blood from WT mice, mice expressing hαIIb/mβ3, or mice expressing mαIIb/hβ3 on their platelets may be drawn from the retro-bulbar venous plexus into an equal volume of 200 μM PPACK (Calbiochem, Gibbstown, NJ) in 165 mM NaCl. Samples may be diluted in HEPES-modified Tyrode buffer [HBMT; 138 mM NaCl, 12 mM $NaHCO_3$, 10 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid), 2.7 mM KCl, 0.4 mM NaH_2PO_4, 0.1 % glucose, 0.35% BSA, pH 7.4] containing 50 μM PPACK, 2 mM $CaCl_2$, 1 mM $MgCl_2$, and may be left untreated or incubated with the Compounds of the Invention (20 or 100 μM), RGDS (1 mM) or EDTA (10 mM). Alexa488-fibrinogen (WT and hαIIb/mβ3 mice; 200 μg/ml; Invitrogen, Carlsbad, CA) or Alexa647-fibrinogen (mαIIb/hβ3 mice) may be added, and samples may be activated with a PAR-4-activating peptide (AYPGKF, 200 μM) and incubated at 37°C for 30 minutes. Samples may then be diluted 1:10 in HBMT containing $CaCl_2$ and $MgCl_2$ as above and analyzed by flow cytometry. Fibrinogen binding may be calculated from the geometric mean fluorescence intensity of platelets (gated by forward and side scatter for WT and hαIIb/mβ3 mice, and GFP intensity for mαIIb/hβ3 mice). Fibrinogen binding to unactivated samples may be defined as background binding and PAR-4 peptide-induced fibrinogen binding to untreated samples may be used to establish maximal (100%) binding. Studies performed on WT platelets to assess whether the dilution step performed prior to analysis resulted in fibrinogen dissociation demonstrated that samples analyzed immediately after dilution in buffer without or with Alexa488-fibrinogen (to maintain the same fibrinogen concentration) may have similar net geometric mean fluorescent intensities (133 and 124 units, respectively). When analyzed 15 min after dilution, the values may be identical (115 units), representing 86 and 93% of the immediate values.

[0144] ***Ferric chloride ($FeCl_3$) carotid artery injury model***: The protocol for $FeCl_3$-induced injury to the carotid artery may be adapted from Yorovoi et al., *Blood* (2003) 102-4006-4013 with minor changes. Four C57BL/6 WT mice, 6 WT mice on a mixed C57BL/6 and SV129 background, and 16 hαIIb/mβ3 mice may be anesthetized by intraperitoneal (i.p.) injection of pentobarbital (80 mg/kg Nembutol; Ovation Pharmaceuticals, Deerfield, IL). After 10 min, mice may be injected i.p. with 10 mM one of the Compounds of the Invention (26.5 mg/kg) (n=8) or the vehicle [1% (n=2) or 10% (n=6) dimethyl sulfoxide (DMSO) in 0.165 M NaCl]. The carotid artery may

then be isolated by blunt dissection and a Doppler flow probe (Model 0.5VB; Transonic Systems, Ithaca, NY) may be positioned around the vessel. Approximately 25 min after the compound or vehicle control is administered, a 1 x 2 mm^2 piece of filter paper (#1; Whatman International, Maidstone, Kent, UK) soaked in 20% $FeCl_3$ may be placed on the artery for 3 min and then removed. The area may then be flushed with distilled water and blood flow through the artery is monitored for 30 minutes. Arterial flow rate data may be analyzed as both "percent reduction in flow" (calculated as the area above the line of the plot of observed flow rate versus observation time, divided by the product of the initial flow rate and the total observation time) and "time to occlusion" (defined as the time from the application of the $FeCl_3$-soaked filter paper until arterial blood flow became undetectable for at least 10 min).

[0145] Carotid arteries from one hαIIb/mβ3 mouse treated with 10% DMSO and one treated with the Compounds of the Invention may be fixed in formaldehyde, cross-sectioned, and stained with hematoxylin and eosin. The sections may be visualized with a 20X objective using an Olympus BX60 microscope (Melville, NY), photographed with a Nikon D5-5M camera, and captured in Adobe Photoshop 6.0.

[0146] ***Laser microvascular injury and intravital microscopy:*** The protocols for laser microvascular injury in blood vessels in the cremaster muscle and intravital microscopic evaluation of subsequent thrombus formation are described in Neyman et al., *Blood* (2008) 112-1104-1108. Briefly, male mice expressing hαIIb/β3 (three in each group) that are anesthetized with pentobarbitol (11 mg/kg; Abbott Laboratories, North Chicago, IL) may have their cremaster arterioles (20 to 40 μm) studied using an Olympus BX61WI microscope (Olympus, Tokyo, Japan or Center Valley, PA) with a 40x/0.8 numeric aperture (NA) water-immersion objective lens. Arteriole laser injuries may be done using an SRS NL100 Nitrogen Laser system (Photonic Instruments, St Charles, IL) at 65% energy level. Visual confirmation of the extravasation of small amounts of blood cells may be made for each studied blood vessel as an assurance that a consistent injury had been produced. After the surgery to expose the blood vessels is performed, animals may be injected i.p. with 10 mM the Compounds of the Invention or 10% DMSO. Three arterioles may be injured in each mouse. Injuries may be initiated 25-35 min after injection of the Compounds of the Invention or DMSO, and 5 min after the i.v. injection of labeled antibodies that react

with murine platelet GPIbβ (DyLight^{488}; Emfret Analytics, Eibelstadt, Germany) and fibrin (Alexa^{647}) into the cannulated jugular vein. Data may be collected over 2.5 min at 5 frames per second (750 frames per study) and then averaged at each time point.

RESULTS

[0147] ***Platelet aggregation*:** It will be observed that the Compounds of the Invention at 100 μM will dramatically inhibits aggregation of platelets from humans, and mice expressing the hybrid hαIIb/mβ3 receptors, but not WT mice or rats. In a particular experiment, it is actually observed that at doses that nearly completely inhibited platelet aggregation, the compound of Example 27 of the current invention at 1 μM does not inhibit either mouse or rat platelet aggregation induced by ADP. In sharp contrast, this compound essentially completely inhibits the aggregation of platelets from a mouse expressing human αIIb and β3 (hαIIb/mβ3). Therefore, it is shown that the compound of Example 27 of the current invention is selective for αIIbβ3 compared to αVβ3 and is further selective for human αIIbβ3 compared to mouse or rat αIIbβ3.

[0148] ***Soluble fibrinogen binding.*** Activated platelets from WT mice will bind fibrinogen, and this binding is expected to only minimally be inhibited by various Compounds of the Invention at 20 or 100 μM. Fibrinogen may also bind to activated platelets from mice expressing mαIIb/hβ3 and these receptors are also not expected to be inhibited by various Compounds of the Invention. In sharp contrast, binding of fibrinogen to activated platelets from hαIIb/mβ3 mice is expected to be inhibited at a concentration of 20 μM and at 100 μM by one of the Compounds of the Invention. For comparison EDTA will inhibit the binding of fibrinogen to WT mouse platelets and hαIIb/mβ3 mouse platelets. Thus, the effects of the Compounds of the Invention on fibrinogen binding to WT and hαIIb/mβ3 platelets will parallel its effects on platelet aggregation.

[0149] ***The Compounds of the Invention will protect hαIIb/mβ3 mice, but not WT mice, against occlusive carotid artery thrombi.*** The platelet counts and αIIbβ3 expression levels of mice receiving the DMSO vehicle control solutions or the Compounds of the Invention will not differ significantly. All 8 hαIIb/mβ3 mice treated with DMSO (1 or 10%) will have reductions in carotid artery blood flow after $FeCl_3$ injury. The hαIIb/mβ3 mice may be treated with the Compounds of the

Invention. These mice will exhibit much less reduction in blood flow and will not develop an occlusive thrombus.

[0150] Cross sections of the hαIIb/mβ3 mouse carotid artery after $FeCl_3$ treatment will reveal nearly complete packing of the lumen with platelet-rich thrombus. The deposits of $FeCl_3$ will be visible as golden granules on the luminal side of the blood vessel. The lumen of the mouse carotid artery treated with the Compounds of the Invention will contain regions of loosely packed erythrocytes, which will demonstrate the patency of the artery. Golden $FeCl_3$ granules will also be visible on the luminal side of the blood vessel.

[0151] ***The Compounds of the Invention will decrease thrombus formation in response to microvascular laser injury.*** Cremaster arteriole injury studies will permit in situ visualization of thrombus development in real time. There will be no difference in thrombus formation in mice that are either untreated or pre-injected with the carrier, 10% DMSO, prior to injury (comparison not shown). Both groups will demonstrate rapid platelet adhesion followed by progressive incorporation of platelets into the thrombi over the first ~20 sec. In addition, after a delay of ~35 sec, both groups will demonstrate progressive incorporation of fibrin into the thrombi. The animals pre-injected with the Compounds of the Invention prior to injury will not develop platelet accumulation or fibrin deposition over a comparable time period.

Example 46 – Platelet Adhesion/Aggregation to Collagen; αVβ3-Mediated Cell Adhesion to Vitronectin; and αIIbβ3-Mediated Cell Adhesion to Fibrinogen

[0152] Washed platelets are prepared as per the primary screening assay, suspended in HBMT containing 1 mM $MgCl_2$ (platelet adhesion to collagen) or 2 mM $CaCl_2$/1 mM $MgCl_2$ (platelet adhesion to fibrinogen) and adjusted to a count of 250 x 10^9/L. HEK293 cells stably expressing normal human αVβ3 or normal human αIIbβ3 are suspended in HBMT containing either 1 mM $MgCl_2$ (HEK293 cells expressing αVβ3 for adhesion to vitronectin) or 2 mM $CaCl_2$/1 mM $MgCl_2$ (HEK293 cells expressing αIIbβ3 for adhesion to fibrinogen); the cell counts are adjusted to 10^6/mL. Polystyrene 96-well microtiter plates (Nunc) are coated with either fibrinogen (50 μg/mL), vitronectin (5 μg/mL), or collagen (33 μg/mL, rat tail type 1; Becton Dickinson) for 1 hour, and blocked with HBMT for at least 1 hour. Platelets and cells are treated with the compound of Example 27 of the current invention or 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No.

12/514,286 in the presence or absence of anti-α2β1 mAb 6F1, anti-αIIbβ3 mAb 10E5, anti-αIIbβ3 mAb 10E5 + αVβ3 mAb 7E3, αVβ3-specific mAb LM609, or anti-αVβ3 + αIIbβ3 mAb 7E3, for 15 minutes at 37°C before being added to the microtiter wells. After adhering for 1 hour at either 22°C (platelets) or 37°C (cells), nonadherent platelets or cells are removed by washing 3 times with HBMT containing the same ion composition as the buffer used for adhesion. Adherent platelets or cells are quantified by their endogenous acid phosphatase activity on p-nitrophenyl phosphate (pNPP) as previously described in Law DA, Nannizzi-Alaimo L, Ministri K, et al., *Blood* (1999) 93:2645-2652, the contents of which are incorporated by reference in their entirety (1 mg/mL in 0.1 M sodium citrate, 0.1% Triton X-100, pH 5.4). In other experiments, 8-chambered glass coverslips (Nunc) are coated with collagen (33 μg/mL) for 1 hour at 22°C. Washed platelets are allowed to adhere for 1 hour at 22°C and the coverslips are stained with the Alexa-488–conjugated β3-specific mAb 7H2. Adherent platelets are imaged using a Zeiss LSM-510 confocal system with Axiovert 200 microscope (Carl Zeiss, Heidelberg, Germany) using a Plan-Apochromat 100/1.4 NA oil DIC objective.

[0153] This experiment shows that anti-α2β1 mAb 6F1 produced 95 % inhibition of platelet adhesion/aggregation to collagen, whereas the anti-αIIbβ3 mAb 10E5 and the anti-αIIbβ3 + αVβ3 mAb 7E3 produce ~30% inhibition. The compound of Example 27 of the current invention at 1-100 μM also inhibits adhesion/aggregation by about ~30%, and combining the compound of Example 27 of the current invention with the anti- αIIbβ3 antibody 10E5 does not further inhibit adhesion /aggregation. Microscopic analysis indicates that the compound of Example 27 of the current invention does not decrease platelet adhesion to collagen, but rather decreases the recruitment of additional platelets to the adherent platelets.

[0154] Further, the αVβ3-specific mAb LM609 inhibits adhesion of HEK293 cells expressing αVβ3 to vitronectin by 74±27% (n=4) at 20 μg/ml and the anti-αVβ3 + αIIbβ3 mAb 7E3 inhibits adhesion by 80±12% (n=4) at 40 μg/ml. In sharp contrast, 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286 at 100 μM produced only 5±7% (n=4) inhibition and 2-amino-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)acetamide at 10 μM produced only 6±15% (n=4). These data are both similar to the 2±9 % (n=3) inhibition produced by the αIIbβ3-specific mAb 10E5.

[0155] αVβ3-specific mAb LM609 does not inhibit the adhesion of HEK293 cells expressing αIIbβ3 to fibrinogen, whereas 10E5 produces 79±10% inhibition, 7E3 produces 87±9% inhibition, 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286 produced 55±5% inhibition, and the compound of Example 27 of the current invention of the current invention produces 65±5% inhibition (all n=4) at the same concentrations indicated for the αVβ3 experiments.

Example 47 – Induction of Ligand-Induced Binding Site (LIBS) Epitopes

[0156] Washed platelets are prepared in HBMT containing 2 mM $CaCl_2$/1 mM $MgCl_2$. Platelet count is adjusted to 250 X 10^9/L and the compound of Example 27 of the current invention (100 μM), 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one (a compound disclosed and claimed in U.S. Serial No. 12/514,286), eptifibatide (10μM), EDTA (10mM), or mAb 10E5 (20μg/mL) is added to samples (30 μL) and incubated for 15 minutes at 37°C. Fluorescently labeled monoclonal antibodies (PMI-1, LIBS-1, AP5, or 10E5; Alexa-488 conjugated; Invitrogen) are then added (20 μL, final concentration: 5 μg/mL) and incubated for 30 minutes at 22°C in the dark, after which samples are diluted 1:10 in HBMT with $CaCl_2$/$MgCl_2$ for analysis by flow cytometry (FACSCalibur; Becton Dickinson, Franklin Lakes, NJ). Antibody binding is reported as the geometric mean fluorescence intensity; nonspecific binding is determined by adding a 50-fold excess of unlabeled antibody before adding the labeled antibody. The net normalized fluorescence intensity in the presence of eptifibatide (10 μM, 30 min incubation at 22°C) is assigned the value of 100%

[0157] This experiment shows that untreated platelets bind 7±3% (n=5) of the amount of AP5 in the presence of eptifibatide. In the presence of 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286, platelets bind 10±4% of the amount in the presence of eptifibatide. In the presence of the compound of Example 27 of the current invention, platelets bind 18±5% of the amount in the presence of eptifibatide. The comparable data for LIBS1 binding after 30 min are 22±3% (n=5) for untreated platelets, 18±2% for platelets in the presence of 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one (a compound disclosed and claimed in U.S. Serial No. 12/514,286), and 21±3%

for platelets in the presence of the compound of Example 27 of the current invention . Untreated platelets bind 46±5% (n=4) of the amount of PMI-1 that platelets treated with eptifibatide bound; both 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286 and the compound of Example 27 of the current invention increase PMI-1 binding to similar extents (73± 9% and 82±13, respectively).

[0158] In summary, Examples 46-47 show that the compound of Example 27 of the current invention as well as 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286 produce much less exposure than does eptifibatide of the β3 PSI epitope recognized by mAb AP5. The compound of Example 27 of the current invention does, however, produce significantly more exposure than does 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286 (18 and 10% of the eptifibatide value, respectively), with untreated platelets binding ~7% of the eptifibatide value. Both 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286 and the compound of Example 27 of the current invention induce exposure of the αIIb leg region epitope recognized by PMI-1, although they are less effective than eptifibatide. Thus, both compounds clearly affect the conformation of the αIIb subunit, but have much less effect than eptifibatide, a prototypic RGD-mimetic antagonist, in inducing a conformational change in the β3 subunit.

Example 48 – the Effect of the Compound of the Invention on Induction of Extension of Purified αIIbβ3 as Judged by Electron Microscopy

[0159] ***Purification of integrin αIIβ3***: αIIbβ3 is purified from outdated single donor platelet concentrates obtained from the New York Blood Center by washing platelets in the presence of PGE_1; removing contaminating blood cells by centrifugation; lysing the resuspended platelets at 4°C in 5% (w/v) n-octyl-β-D-glucoside (OG) in 150 mM NaCl, 20 mM HEPES, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 μM leupeptin, pH 7.4; performing Con A affinity chromatography [binding buffer: 150 mM NaCl, 1% (w/v) OG, 20 mM HEPES, 1 mM $CaCl_2$, 1 mM $MgCl_2$, pH 7.4; washing buffer: binding buffer + 20 mM α-methyl glucoside; elution buffer: binding buffer + 1M α-methyl glucoside]; performing heparin affinity chromatography;

applying the flow through fraction to Q-Sepharose [binding buffer: 75 mM NaCl, 1% (w/v) OG, 10 mM HEPES, 1 mM $CaCl_2$, 1 mM $MgCl_2$, pH 7.4; washing buffer: binding buffer + 200 mM NaCl; elution buffer: binding buffer + 400 mM NaCl]; and performing gel size exclusion chromatography on Sephacryl S300 HR [running buffer: 150 mM NaCl, 1% (w/v) OG, 10 mM HEPES, 1 mM $CaCl_2$, 1 mM $MgCl_2$, pH 7.4].

[0160] ***Preparation of αIIbβ3-containing nanodiscs***: αIIbβ3-containing nanodiscs are prepared by a modification of the techniques described by Ritchie et al., Babyurt and Sligar, and Ye et al[2-4], the contents of which are incorporated by reference in their entirety. In brief, the His-tagged membrane scaffold protein is prepared as a recombinant protein in E. coli and purified by Nickel affinity chromatography and anion exchange chromatography. Final assembly consists of solubilizing an equimolar mixture of 1,2-dimyristoyl-sn-glycero-3-phosphocholine and 1,2-dimyristoyl-sn-glycero-3-phospho-(1'-rac-glycerol) in octylglucoside and cholate and then adding the purified αIIbβ3. The detergents are removed with macroporous polymeric beads (Bio-Bead SM-2) and then the αIIbβ3 nanodiscs are separated from the empty nanodiscs by gel filtration.

[0161] ***Negative staining electron microscopy and evaluation of αIIbβ3 nanodisc particle size***: αIIbβ3 nanodiscs are treated with eptifibatide, tirofiban, 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286, or the compound of Example 27 of the current invention for 1 hour at room temperature at concentrations up to 100 μM for 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one (a compound claimed in U.S. Serial No. 12/514,286) and at concentrations up to 10 μM for 2-amino-N-(3-(5-oxo-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-2-yl)phenyl)acetamide of Example 27. Samples are loaded onto carbon-coated copper grids that are glow-discharged by a carbon coating unit (Edwards; Crowley, UK), and then stained with 2% uranyl acetate, followed by drying. Imaging of αIIbβ3 nanodiscs is performed using a JOEL JEM 100CX transmission electron microscope (Jeol Ltd; Tokyo, Japan) at 80 kV and magnifications of 33,000X and 50,000X. Individual nanodiscs containing αIIbβ3 are manually selected for analysis using Image J (NIH, Bethesda, MD). The distance from the bottom of the nanodisc to the height of the αIIbβ3 complex (nanodisc-integrin length; NIL) is measured as an indicator of integrin extension. The frequency

distribution of NIL values is then analyzed for untreated αIIbβ3 nanodiscs and αIIbβ3 nanodiscs in the presence of different compounds.

[0162] This experiment shows that in the absence of compound, αIIbβ3 primarily adopts a compact conformation adjacent to the nanodisc, giving nanodisc-integrin length (NIL) values primarily between 11 and 17 nm. Occasional nanodiscs, however, contain αIIbβ3 molecules that are extended, giving NIL values between 18 and 23. As a result, the NIL frequency distribution shows a bimodal pattern, with a marked predominance of αIIbβ3 nanodiscs in the range of 11 to 17 nm, and a small subpopulation in the range 18 to 23 nm. Both eptifibatide and tirofiban shift the distribution in a dose-dependent manner such that at the highest doses the majority of αIIbβ3 nanodiscs has NIL values in the 18 to 23 nm range ($p<0.001$ and $p<0.001$, respectively). In sharp contrast, neither 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286 at concentrations up to 100 μM nor the compound of Example 27 of the current invention at concentrations up to 10 μM produce a significant shift in NIL values ($p=0.23$ and $p=0.37$, respectively). In other words, the compound of Example 27 of the current invention and 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286 at these concentrations do not induce receptor extension as judged by electron microscopy.

Example 49 - The Effect of Mg^{2+} Concentration on Platelet Adhesion to Fibrinogen in the Presence of the Compound of the Invention:

[0163] Washed platelets in buffers containing 1 mM Ca^{2+} plus 1 mM, 20 mM, or 50 mM Mg^{2+} are added to wells pre-coated with fibrinogen (50 μg/ml) for 60 min at 22°C. After washing, adherent platelets are detected by acid phosphatase activity. Results are expressed as mean ± SD (n=3 for the compound of Example 27 of the current invention and 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one (a compound disclosed and claimed in U.S. Serial No. 12/514,286); n=2 for tirofiban).

[0164] In three separate experiments, the IC_{50} for the compound of Example 27 of the current invention increases from 0.29 ± 0.1 μM (mean ± SD) at 1 mM Mg^{2+} to 0.91 ± 0.21 μM at 20 mM Mg^{2+} ($p<0.01$), and to 1.3 ± 0.35 μM at 50 mM Mg^{2+} ($p<0.01$). Thus, in going from 1 to 50 mM Mg^{2+}, there is an ~4.5-fold increase in

IC_{50}, corresponding to nearly an ~80% decrease in affinity. Neither 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286 nor tirofiban shows a comparable increase in IC_{50} at higher Mg^{2+} concentrations.

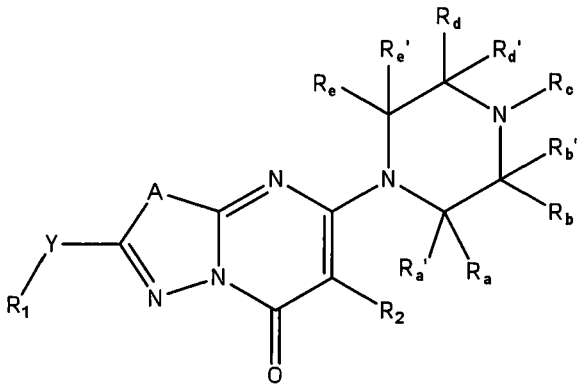
Example 50 - Effect of Mg^{2+} on Platelet Aggregation Induced by ADP in the Presence of Test Compound:

[0165] Washed platelets are resuspended in buffer containing fibrinogen (200 μg/ml) and 1 mM Mg^{2+} in combination with either 1 mM or 20 mM Mg^{2+}. Aggregation is induced by adding a thrombin receptor activating peptide (SFLLRN) at 10 μM.

[0166] The inhibitory effect of the compound of Example 27 of the current invention (1 μM) on platelet aggregation induced by a thrombin receptor activating peptide (SFLLRN) at different Mg^{2+} concentrations is clearly attenuated at 20 mM Mg^{2+}, whereas the effect on 2-ethyl-7-(piperazin-1-yl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidin-5-one of U.S. Serial No. 12/514,286 (100 μM) is much less evident. This experiment shows that the compound of Example 27 binds by a novel mechanism leading to loss of the MIDAS metal ion while producing only minor changes in the conformation of αIIbβ3.

What is claimed is:

1. A compound of Formula P-I:



Formula P-I

wherein:

i) A is S, N(H), CH_2, or O;

ii) R_1 is:

phenyl optionally substituted with one or more nitro, -C(O)N(R_5)(R_6)and/or -N(R_5)(R_6) and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

phenyl substituted with one or more nitro and/or -N(R_5)(R_6) and Y is a single bond;

phenyl substituted with -C(O)OR_3 and Y is a -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

heteroaryl (e.g., pyridyl, pyrazolyl, isoxazolyl, furyl, thienyl) wherein said heteroaryl group is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene);

heteroaryl (e.g., pyridyl, pyrazolyl, thienyl or pyrimidyl) wherein said heteroaryl group is substituted with halo (e.g., fluoro), -C(O)OH, -CH_2C(O)OH, or –NH_2, and Y is arylene (e.g., phenylene), for example R_1 is (pyrazol-1-yl)-4-acetic acid (i.e., -(pyrazol-1-yl)-4-CH_2C(O)OH), thiophen-4-yl-2-carboxylic acid (i.e., -(thiophen-4-yl)-2-C(O)OH), 2-fluoropyrid-4-yl or 2-amino-pyrimid-5-yl, and Y is phenylene;

pyrazolyl, isoxazolyl, furyl or thienyl and Y is arylene (e.g., phenylene) wherein said pyrazolyl, isoxazolyl, furyl or thienyl is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl), -C_{0-4}alkyl-C(O)OH, -$N(R_{13})(R_{14})$, or halo (e.g., fluoro); or

-$C(O)N(R_4)(CH_2)_{1-4}$-$C(O)OR_3$ (e.g., -$C(O)N(H)CH_2C(O)OH$) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$C(O)N(R_4)(CH_2)_{1-4}$-$N(R_{13})(R_{14})$ (e.g., -$C(O)N(H)CH_2$ CH_2NH_2) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$N(R_4)$-C(O)-heteroaryl (e.g., -$N(R_4)$-C(O)-pyridyl) wherein said heteroaryl is optionally substituted with halo (e.g., fluoro) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$N(R_4)$-C_{1-4}alkylene-heteroaryl (e.g., -$N(R_4)$-C_{1-4}alkylene-pyridyl) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-$N(R_{10})$-C(O)-$[C(R_{11})(R_{12})]_{1-4}$-$N(R_{13})(R_{14})$, e.g., e.g., -$N(R_{10})$-C(O)-$[C(R_{11})(R_{12})]_2$-$N(R_{13})(R_{14})$ or -$N(R_{10})$-C(O)-$C(R_{11})(R_{12})$-$N(R_{13})(R_{14})$, and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene), for example, R_1 is –N(H)-C(O)-CH_2CH_2-NH_2 or –N(H)-C(O)-CH_2-NH_2 and Y is phenylene,-$N(R_{10})$-C(O)-C_{3-10}heterocycloalkyl (e.g., -$N(R_{10})$-C(O)-piperidine) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

-$N(R_4)(CH_2)_{1-4}$-$C(O)OR_4$ (e.g., -$N(H)CH_2C(O)OH$) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

-$N(R_4)C(O)C(H)(NH_2)CH_2CH_2$-$C(O)OR_3$ and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)C(H)(NH_2)CH_2$-heteroaryl (e.g., -$N(R_4)C(O)C(H)(NH_2)CH_2$-thiazol-4-yl and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)C(H)(CH_3)$-NH_2 and Y is arylene (e.g., phenylene);

$-N(R_4)C(O)CH_2CH_2C(H)(NH_2)$-COOH and Y is arylene (e.g., phenylene);

$-N(R_4)C(O)-C(H)(NH_2)CH_2CH_2$-COOH and Y is arylene (e.g., phenylene); or

$-N(R_4)C(O)$-heteroaryl (-N(H)C(O)isoxazolyl) and Y is arylene (e.g., phenylene);

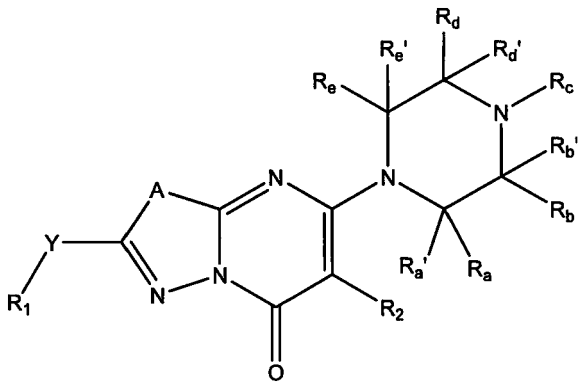
iii) R_2 is H, halo (e.g., fluoro) or $-C_1$-C_4alkyl (e.g., methyl);

iv) R_a, R_a', R_b, R_b',R_c, R_d, R_d', R_e,and R_e' are independently H or C_1-C_4alkyl (e.g., methyl or ethyl);

v) R_3, R_4, R_5 and R_6 are independently H or C_1-C_4alkyl;

vi) R_{10}, R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl), in free or salt form.

2. The compound according to claim 1, wherein said compound is a compound of Formula Q-I:



Formula Q-I

wherein:

i) A is S, N(H), CH_2, or O;

ii) R_1 is

phenyl optionally substituted with one or more nitro and/or $-N(R_5)(R_6)$ and Y is a $-C_1$-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

phenyl substituted with one or more nitro and/or $-N(R_5)(R_6)$ and Y is a single bond;

phenyl substituted with $-C(O)OR_3$ and Y is a $-C_1$-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

heteroaryl (e.g., pyridyl, pyrazolyl, isoxazolyl, furyl, thienyl) wherein said heteroaryl group is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene);

pyrazolyl, isoxazolyl, furyl or thienyl and Y is arylene (e.g., phenylene) wherein said pyrazolyl, isoxazolyl, furyl or thienyl is optionally substituted with one or more -C_1-C_4alkyl (e.g., methyl), -C_{0-4}alkyl-C(O)OH, -N(R_{13})(R_{14}), or halo (e.g., fluoro); or -C(O)N(R_4)(CH_2)$_{1-4}$-C(O)OR_3 (e.g., -C(O)N(H)CH_2C(O)OH) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-C(O)N(R_4)(CH_2)$_{1-4}$-N(R_{13})(R_{14}) (e.g., -C(O)N(H)CH_2 CH_2NH_2) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-N(R_4)-C(O)-heteroaryl (e.g., -N(R_4)-C(O)-pyridyl) wherein said heteroaryl is optionally substituted with halo (e.g., fluoro) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-N(R_4)-C_{1-4}alkylene-heteroaryl (e.g., -N(R_4)-C_{1-4}alkylene-pyridyl) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-N(R_{10})-C(O)-C(R_{11})(R_{12})-N(R_{13})(R_{14}) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene),

-N(R_{10})-C(O)-C_{3-10}heterocycloalkyl (e.g., -N(R_{10})-C(O)-piperidine) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

-N(R_4)(CH_2)$_{1-4}$-C(O)OR_4 (e.g., -N(H)CH_2C(O)OH) and Y is a single bond, -C_1-C_4alkylene (e.g., methylene) or arylene (e.g., phenylene);

-N(R_4)C(O)C(H)(NH_2)CH_2CH_2-C(O)OR_3 and Y is arylene (e.g., phenylene);

-N(R_4)C(O)C(H)(NH_2)CH_2-heteroaryl (e.g., -N(R_4)C(O)C(H)(NH_2)CH_2-thiazol-4-yl and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)C(H)(CH_3)$-NH_2 and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)CH_2CH_2C(H)(NH_2)$-COOH and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)$-$C(H)(NH_2)CH_2CH_2$-COOH and Y is arylene (e.g., phenylene);

-$N(R_4)C(O)$-heteroaryl (-N(H)C(O)isoxazolyl) and Y is arylene (e.g., phenylene);

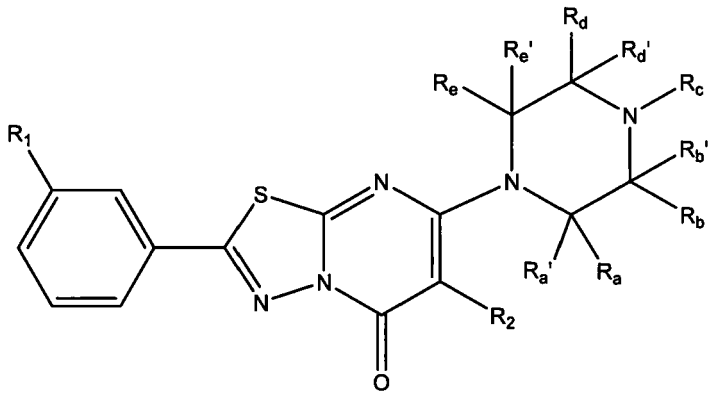
iii) R_2 is H, halo (e.g., fluoro) or -C_1-C_4alkyl (e.g., methyl);

iv) R_a, R_a', R_b, R_b', R_c, R_d, R_d', R_e,and R_e' are independently H or C_1-C_4alkyl (e.g., methyl or ethyl);

v) R_3, R_4, R_5 and R_6 are independently H or C_1-C_4alkyl;

vi) R_{10}, R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl), in free or salt form.

3. The compound according to claim 1 or 2 wherein said compound is:



wherein

R_1 is -$N(R_{10})$-$C(O)$-$C(R_{11})(R_{12})$-$N(R_{13})(R_{14})$, e.g., -$NHC(O)CH_2NH_2$;

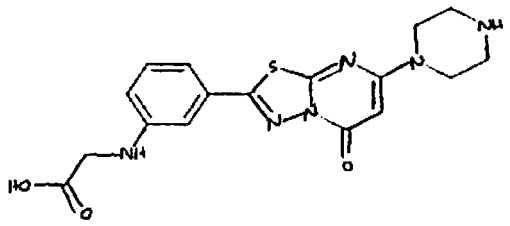
R_2 is H or halo (e.g., fluoro);

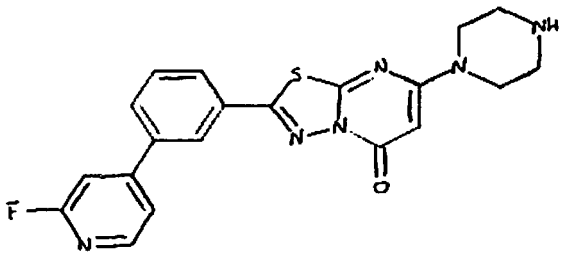
R_a, R_a', R_b, R_b', R_c, R_d, R_d', R_e,and R_e' are independently H or C_1-C_4alkyl (e.g., methyl or ethyl);

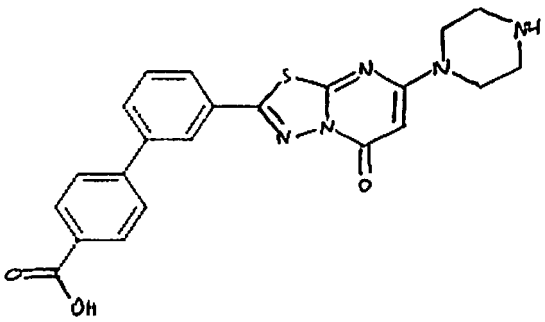
R_{10}, R_{11}, R_{12} R_{13} and R_{14} are independently H or C_{1-4}alkyl (e.g., methyl); in free or salt form.

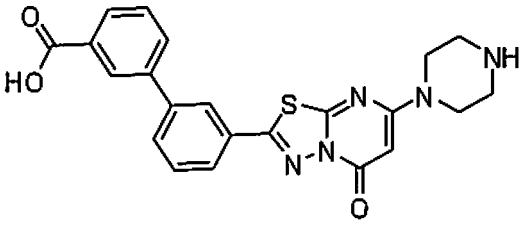
4. The Compound according any of claims 1-4, wherein the compound is a compound selected from any of formulae 3.44-3.49 and 2.13, in free or salt form.

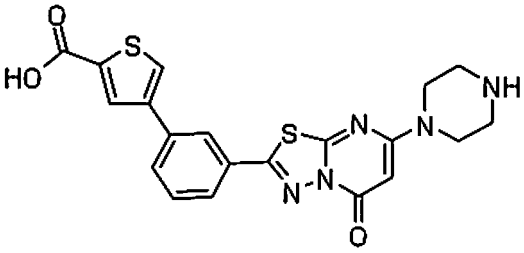
5. The Compound according any of claims 1-4, wherein the compound is a compound selected from any of the following:

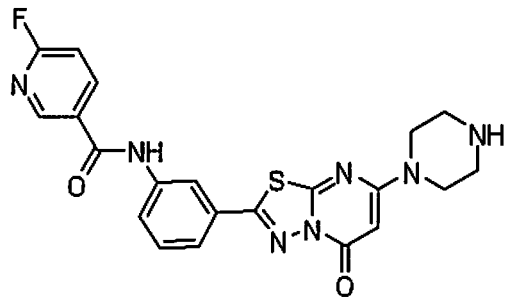

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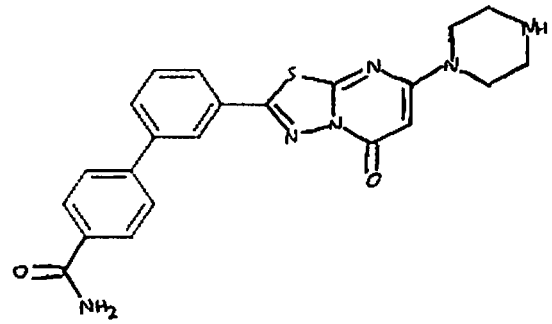

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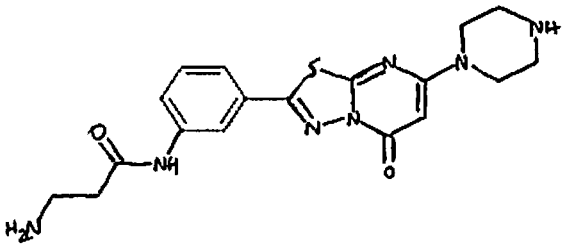

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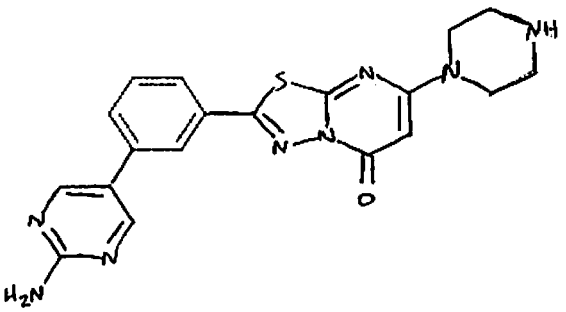
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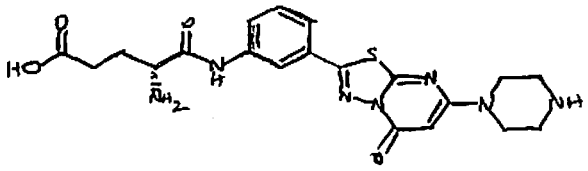
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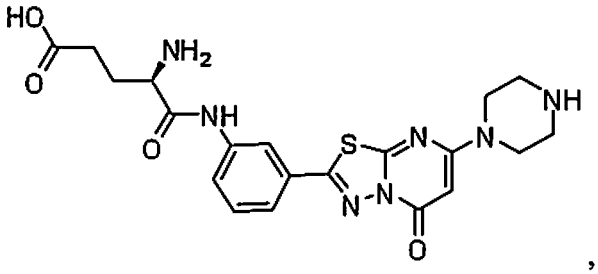
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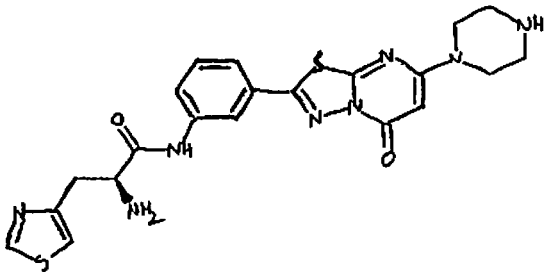
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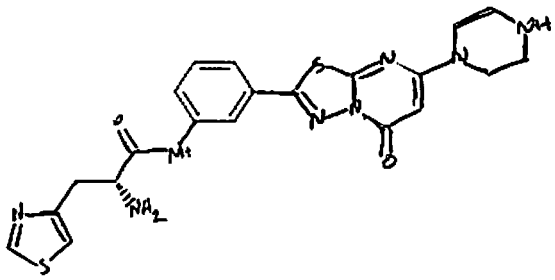
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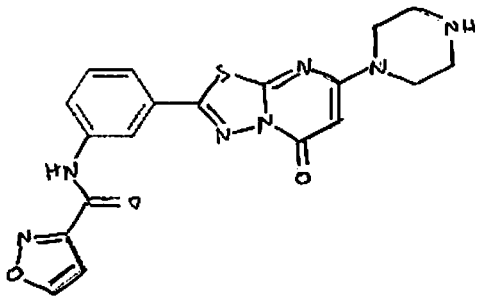
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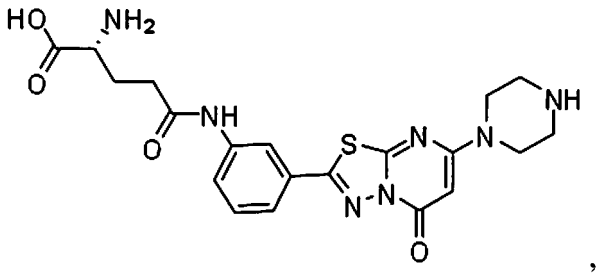
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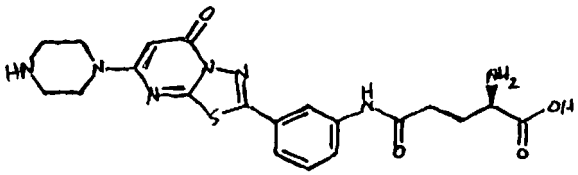
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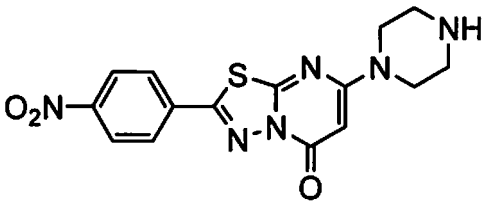
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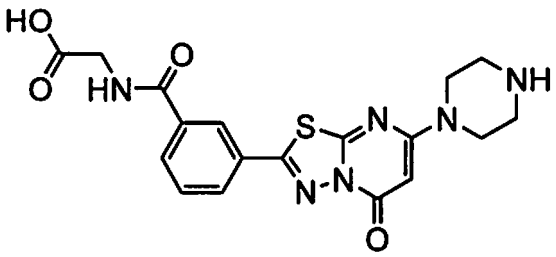
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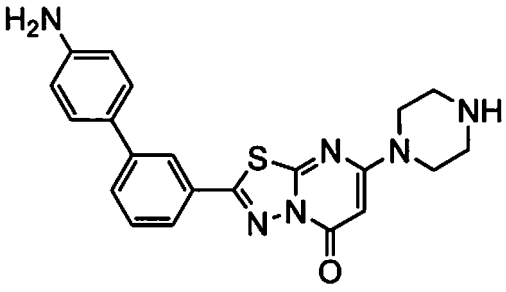
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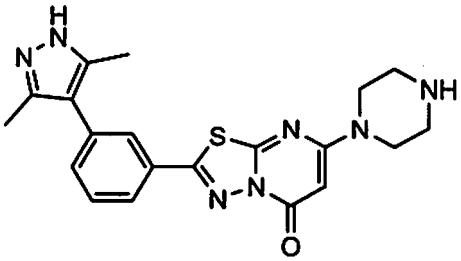
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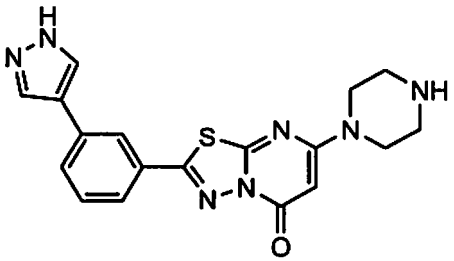
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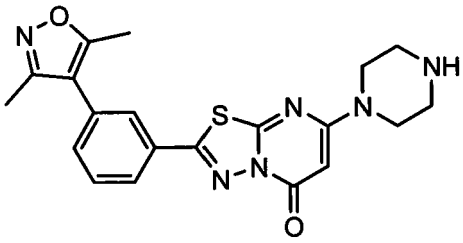
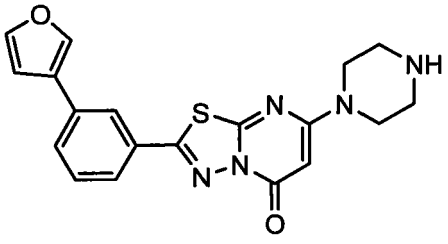
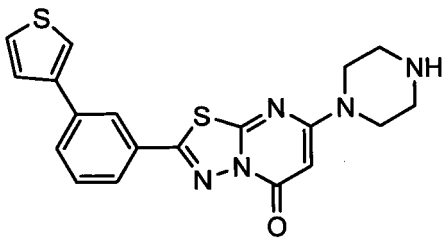
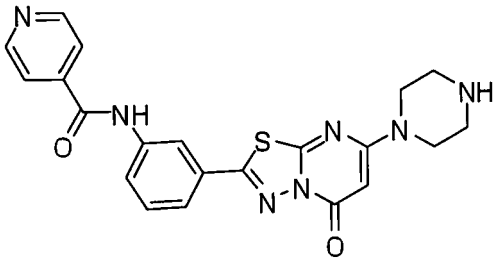
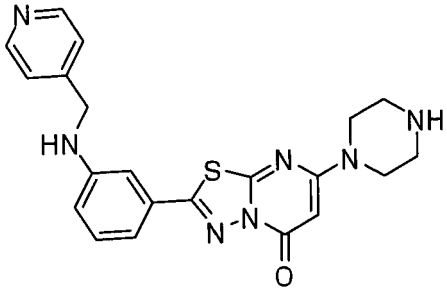
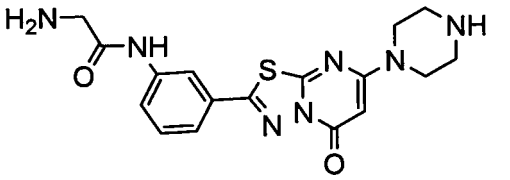
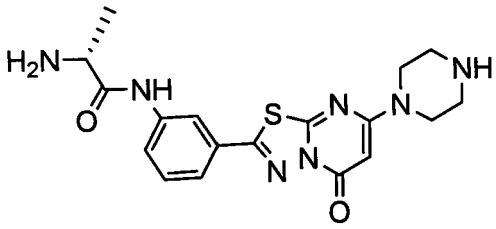
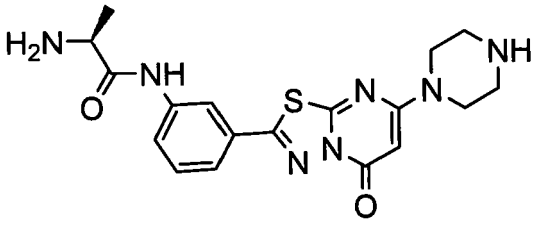
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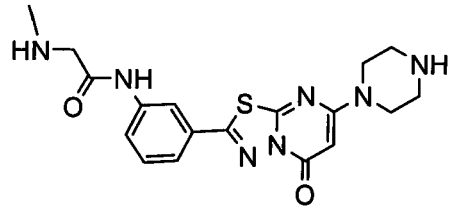


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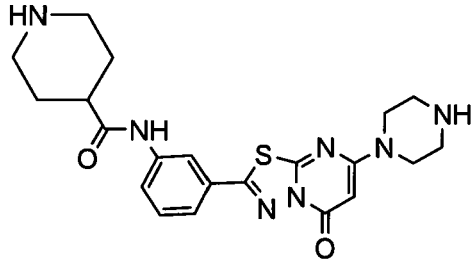


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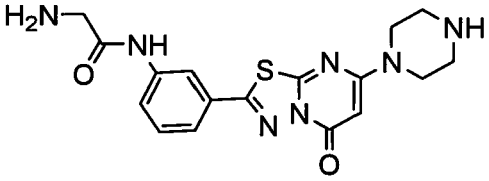
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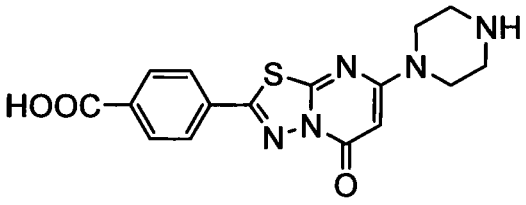
in free or salt form.

6. The compound according to any of claims 1-5, wherein said compound is:



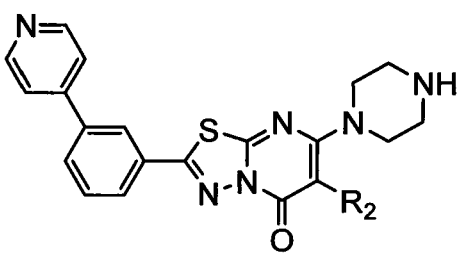
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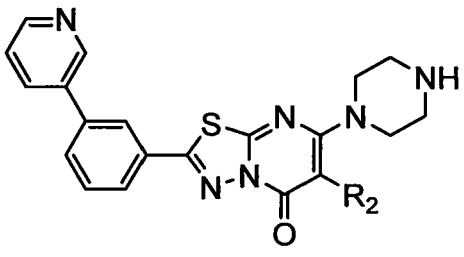
7. A compound of Formula I-A:



in free or salt form.

8. A compound of Formula I-B:

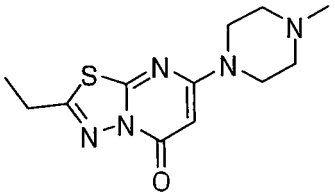
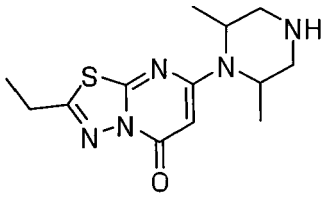
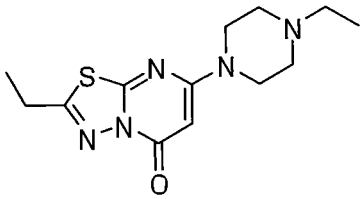
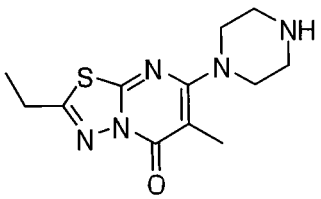
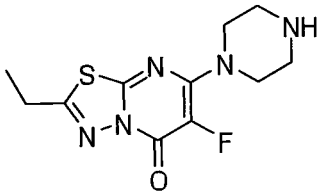
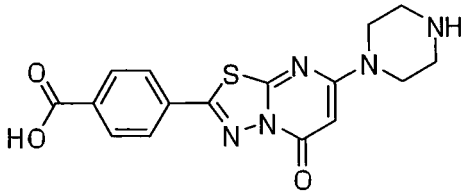
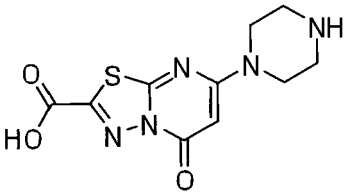
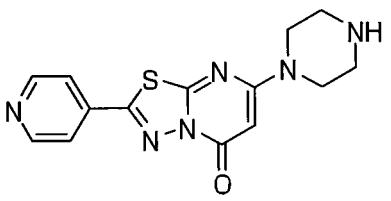
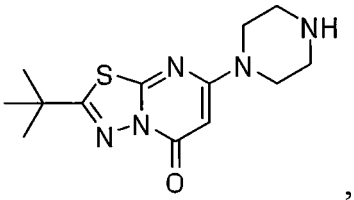
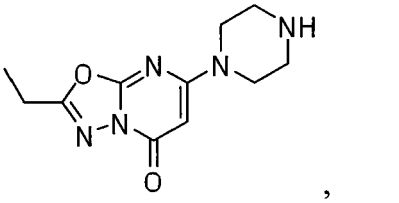




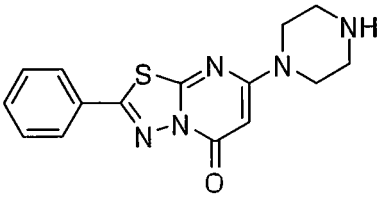
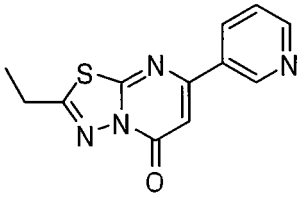
and

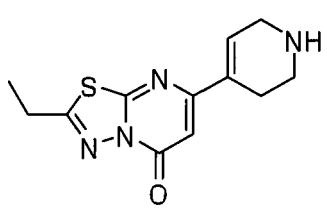
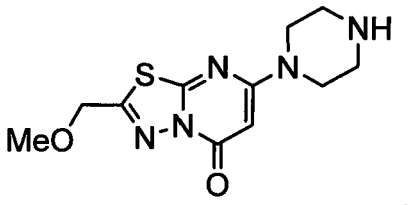
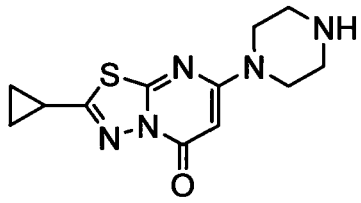
wherein R_2 is H, halo (e.g., fluoro) or C_1-C_4-alkyl (e.g., methyl), in free or salt form.

9. A compound of Formula I-C selected from any of the following:


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in free or salt form.

10. A pharmaceutical composition comprising a compound according to any of claims 1-9, in combination or association with a pharmaceutically acceptable diluent or carrier.

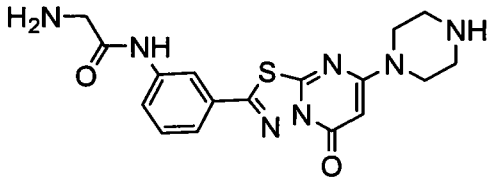
11. A method for the treatment or prophylaxis of a thrombotic disorder comprising administering to a subject at risk of thrombotic disorder an effective amount of a compound according to any of claims 1-9, in free or pharmaceutically acceptable salt form, or a pharmaceutical composition according to claim 10, such that platelet aggregation and/or adhesion is reduced.

12. The method according to claim 11, wherein both platelet aggregation and adhesion are reduced.

13. The method according to claim 11 or 12, wherein said thrombotic disorders is selected from a group consisting of stroke, myocardial infarction, unstable angina, abrupt closure following angioplasty or stent placement, thrombosis induced by peripheral vascular surgery, peripheral vascular disease or thrombotic disorders resulting from atrial fibrillation or inflammation.

14. The method according to any of claims 11-13, wherein said thrombotic disorder is thrombosis induced by peripheral vascular surgery.

15. The method according to any of claims 11-14, wherein said Compound is:



in free or pharmaceutically acceptable salt form.

16. The method according to any of claims 11-15, further comprises administering to said subject an effective amount of at least one therapeutic agent selected from a group consisting of anti-coagulant, antiplatelet, and fibrinolytic agents in conjunction with a compound according to any of claims 1-9, in free or pharmaceutically acceptable salt form.

17. The method according to claim 16, wherein said therapeutic agent is selected from a group consisting of heparin, low molecular weight heparins, bivalirudin, Fondaparinux, warfarin, Acenocoumarol, Phenprocoumon, Phenindione, Abbokinase (urokinase), streptokinase, alteplase, retaplase, tenecteplase, prasugrel, aspirin, ticlopidine, clopidogrel, abciximab, eptifibatide and tirofiban.

18. The method according to any of claims 11-17, further comprises administering heparin.

19. A method for inhibiting or reducing platelet aggregation and adhesion comprising administering an effective amount of a compound according to any of claims 1-9, in free or pharmaceutically acceptable salt form, such that platelet aggregation and adhesion is reduced.

20. Use of a Compound according to any of claims 1-9, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for the treatment or prophylaxis of a thrombotic disorder.

21. The Pharmaceutical composition according to claim 10 for use in the manufacture of a medicament for the prophylaxis or treatment of a thrombotic disorder.

22. A drug-eluting stent wherein the drug eluted comprises a compound described in any of claims 1-9, in free or pharmaceutically acceptable salt form.

23. The stent according to claim 22, wherein said stent is a metal stent coated with a biocompatible polymer comprising or associated with a compound as described in any of claims 1-9, in free or pharmaceutically acceptable salt form.

24. The stent according to claim 22 or 23, wherein said apparatus further comprises at least one agent selected from a group consisting of an antiproliferative agent or an anticoagulant.

25. The stent according to claim 24, wherein said antiproliferative agent is selected from a group consisting of sirolimus, everolimus, zotarolimus, tacrolimus and paclitaxel.

26. The stent according to claim 25, wherein said anticoagulant is heparin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/44267

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/497 (2011.01)
USPC - 514/252.16
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/252.16

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/133.1; 514/252.12, 514/252.13, 514/253.11, 514/254.07, 514/256, 514/257, 514/430, 514/433, 514/434, 514/438, 514/439; 544/255 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
*** Databases: WEST (PGPB, USPT, USOC, EPAB, JPAB); Google, Google Scholar *** Search Terms Used: Rockefeller, Coller, Thomas, Filizola, reduces, reducing, inhibits, inhibiting, platelet, deposits, depositing, adheres, adhering, aggregates, aggregating, pyrimidone, piperazine, piperazinyl, thiadiazolo, oxadiazolo, triazolo, amino, compound, formu

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2010/0150913 A1 (Blue et al.) 17 June 2010 (17.06.2010) para [0022]-[0024], [0075]	1-2, 7-9 --------- 3
Y	Blue et al. Structural and therapeutic insights from the species specificity and in vivo antithrombotic activity of a novel .alpha.IIb-specific .alpha.IIb.beta.3 antagonist. Blood, 2009, Vol 114, Iss 1, pp 195-201; especially abstract; pg 195, col 1, para 1; pg 196, Fig 1; pg 199, col 2, para 2-3	3
Y	Blue et al. Application of high throughput screening to identify a novel .alpha.IIb-specificsmall molecule inhibitor of .alpha.IIb.beta.3-mediated platelet interaction with fibrinogen. Blood, 2007, Vol 111, No 3, pp1248-1256; especially abstract; pg 1253, col 1, para 1; pg 1254, Fig 7; pg 1255, col 1, para 1	3

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2011 (22.11.2011)	06 DEC 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/44267

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-6 and 10-26
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.