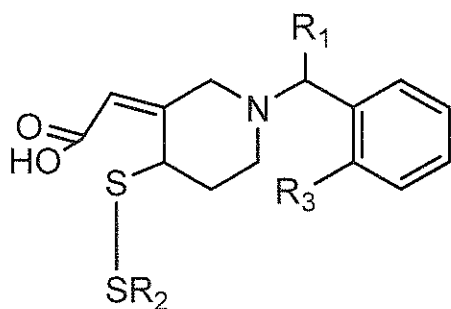
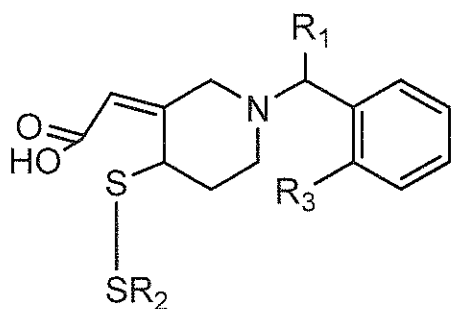


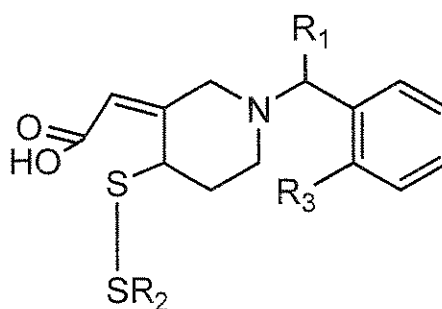
of developing embodiments for the present ~~disclosure~~ ~~invention~~ demonstrated that the mixed disulfide conjugates of thienopyridine compounds of the present ~~disclosure~~ ~~invention~~ are capable of producing active thienopyridine metabolites (e.g., active thienopyridine metabolites capable of antiplatelet activity) in the presence of endogenous glutathione (GSH) without the need for bioactivation by P450s. This approach not only bypasses the oxidative bioactivation process by P450s, but circumvents many of the drawbacks associated with thienopyridinyl drugs. For example, the mixed disulfide conjugates of thienopyridine compounds of the present ~~invention~~ ~~disclosure~~ improve dosing consistency because production of the active metabolite from the conjugates is predictable. In addition, use of the mixed disulfide conjugates of thienopyridine compounds of the present ~~invention~~ ~~disclosure~~ as antiplatelet agents reduce the toxicity as toxic reactive metabolites are not produced by the thiol-exchange reaction. In addition, the therapeutic onset time for the mixed disulfide conjugates of thienopyridine compounds of the present ~~invention~~ ~~disclosure~~ is shortened, which greatly benefits patients who experience acute cardiovascular events. For example, the standard regimen for thienopyridines requires continuously dosing patients for 3-5 days as only a small percentage of ingested thienopyridines are converted to the active metabolite. In contrast, the mixed disulfide conjugates of thienopyridine compounds of the present ~~invention~~ ~~disclosure~~ release the active metabolites with high yields in less than 30 min. In addition, the mixed disulfide conjugates of thienopyridine compounds of the present ~~invention~~ ~~disclosure~~ have superior stability over the active metabolites and therefore they can be used to quantitatively generate the active metabolites for basic and clinical research in vitro.

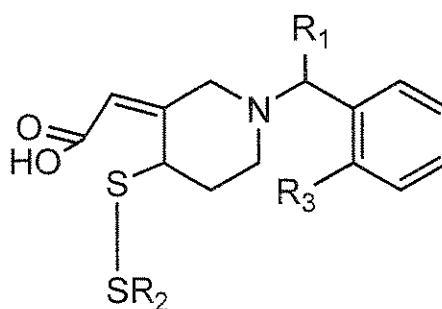
Accordingly, in certain embodiments, the present ~~invention~~ ~~disclosure~~ provides mixed disulfide conjugates of thienopyridine compounds capable of overcoming such drawbacks associated with thienopyridinyl compounds widely used as antiplatelet agents (e.g., Clopidogrel (Plavix), ticlopidine (Ticlid) and prasugrel (Effient)). The present ~~invention~~ ~~disclosure~~ is not limited to particular mixed disulfide conjugates of thienopyridine compounds. In a first aspect, there is provided a compound having Formula I:

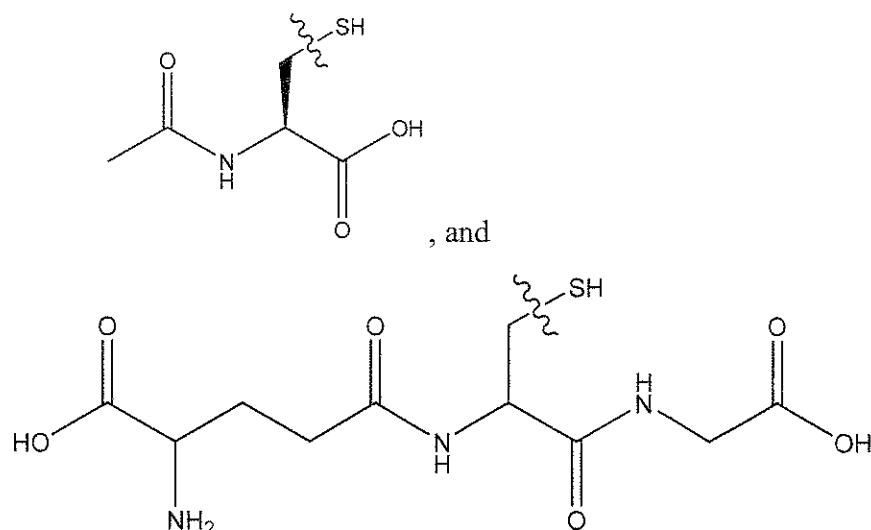


Formula I: . including pharmaceutically acceptable salts, solvates, and/or prodrugs thereof; wherein R1, R2, and R3 independently include any chemical moiety that renders the resulting compound capable of producing active thienopyridine metabolites upon interaction with endogenous glutathione (GSH).

5 In some ~~embodiments~~embodiments, the mixed disulfide conjugates of thienopyridine



compounds are described by Formula I: , including pharmaceutically acceptable salts, solvates, and/or prodrugs thereof; wherein R1, R2, and R3 independently include any chemical moiety



In a second aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a pharmaceutically acceptable carrier.

In certain embodiments, the present invention provides pharmaceutical compositions comprising a mixed disulfide conjugate of a thienopyridine compound and a pharmaceutically acceptable carrier.

In certain embodiments, the present invention provides pharmaceutical compositions comprising mixed disulfide conjugates of thienopyridine compounds configured for intravenous (IV) administration. In some embodiments, such pharmaceutical compositions comprising mixed disulfide conjugates of thienopyridine compounds configured for intravenous (IV) administration are used in the treatment, amelioration and prevention of atherothrombosis. In some embodiments, such pharmaceutical compositions comprising mixed disulfide conjugates of thienopyridine compounds configured for intravenous (IV) administration are used for rapid inhibition of platelet aggregation. In some embodiments, such pharmaceutical compositions comprising mixed disulfide conjugates of thienopyridine compounds configured for intravenous (IV) administration are used during percutaneous coronary intervention procedures (e.g., coronary angioplasty) for rapid inhibition of platelet aggregation.

In certain embodiments, the present invention provides methods of treating, ameliorating, or preventing a cardiovascular disease comprising administering to a patient a therapeutically effective amount of a mixed disulfide conjugate of a thienopyridine compound. In some embodiments, the administration is intravenous administration. In some embodiments, the cardiovascular disease is selected from the group consisting of coronary artery disease, peripheral vascular disease, and cerebrovascular disease. In some

embodiments, the compound reduces aggregation of platelets (e.g., through irreversible binding to P2Y₁₂ receptors) (e.g., through blocking ADP receptors). In some embodiments,

the compound is capable of producing active thienopyridine metabolites in the presence of endogenous glutathione without the need for bioactivation by P450s. In some embodiments, the methods further comprise co-administration of at least one agent selected from the group consisting of a HMG-CoA reductase inhibitor, an ACE Inhibitor, a Calcium Channel
5 Blocker, a Platelet Aggregation Inhibitor, a Polyunsaturated Fatty Acid, Fibrin Acid Derivative, a Bile Acid Sequestrant, an Antioxidant, and an Antianginal Agent.

In certain embodiments, the present ~~invention~~disclosure provides methods of treating, ameliorating, or preventing aggregation of platelets onto blood vessels in a patient, comprising administering to the patient a therapeutically effective amount of a mixed
10 disulfide conjugate of a thienopyridine compound. In some embodiments, the administration is intravenous administration. In some embodiments, the patient has or is at risk for developing cardiovascular disease (e.g., coronary artery disease, peripheral vascular disease, and cerebrovascular disease). In some embodiments, the treating, ameliorating, or preventing the aggregation of the platelets occurs through irreversible binding to P2Y₁₂ receptors. In
15 some embodiments, the treating, ameliorating, or preventing the aggregation of the platelets occurs through blocking ADP receptors. In some embodiments, the mixed disulfide conjugate of thienopyridine compound is capable of producing active thienopyridine metabolites in the presence of endogenous glutathione without the need for bioactivation by P450s.

In a third aspect, there is provided the use of a compound as defined above for the
20 manufacture of a medicament for the treatment, amelioration, or prevention of a cardiovascular disease in a patient.

In a fourth aspect, there is provided the use of a compound as defined above for the
manufacture of a medicament for the treatment, amelioration, or prevention of aggregation of
platelets onto blood vessels in a patient.

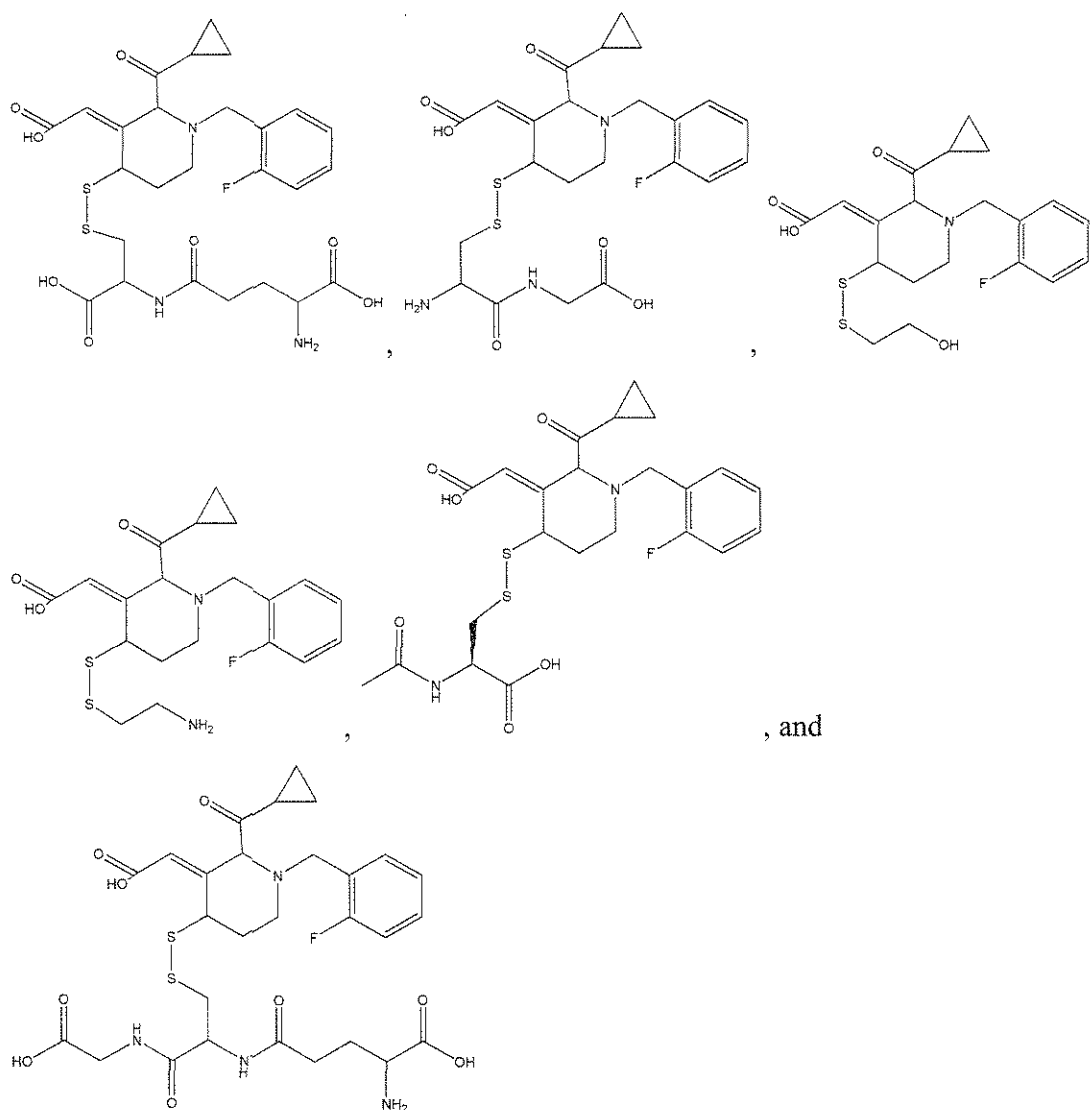
BRIEF DESCRIPTION OF DRAWINGS

Figure 1 shows effects of thiol reductants on the formation of the active metabolite (AM) of clopidogrel. The AM was produced in 0.1 ml of 50 mM KP buffer (pH 7.4) containing 0.2 mg/ml HLM, 0.1 mM 2-oxoclopidogrel, the NADPH-regenerating system, and
30 the thiol reductants. The concentrations of the thiol reductants were 1 mM except for CPT, DFT and NPT which were 0.3 mM each. The reaction was initiated by the addition of 5 units of G6PD and incubated at 37 °C for 20 min. The active metabolite was then quantitated as the

MP derivative as described in Materials and Methods. The reported rates were averaged over three separate measurements. Abbreviations for the thiol compounds are provided in Table 1.

Figure 2 shows extracted ion chromatograms (EIC) of representative mixed disulfide conjugates of clopidogrel. The mixed disulfide conjugates were produced in 0.2 ml of 50 mM KPi buffer (pH 7.4) containing 1 mg/ml HLMS, 0.1 mM 2-oxoclopidogrel, various thiol reductants and the NADPH-regenerating system at 37 °C for 30 min. MS analyses were performed as described in Materials and Methods. (A), EIC for the BME conjugate at m/z

5



7. A pharmaceutical composition comprising a compound of any one of claims 1-6 and a pharmaceutically acceptable carrier.

8. The pharmaceutical composition of claim 7, wherein said pharmaceutical composition is configured for intravenous administration.

9. Use of a compound of claim 1 for the manufacture of a medicament for the ~~A method of~~ treatment, amelioration, or prevention of a cardiovascular disease in a patient comprising ~~administering to said patient a therapeutically effective amount of the compound of any one of~~ claims 1-7.

10. The ~~method-use~~ of claim 9, wherein said ~~administration is selected from the group consisting of~~ medicament is formulated for oral administration and intravenous administration.
11. The ~~method-use~~ of claim 9, wherein said cardiovascular disease is selected from the group consisting of coronary artery disease, peripheral vascular disease, atherothrombosis, and cerebrovascular disease.
12. The ~~method-use~~ of claim 9, wherein said compound reduces aggregation of platelets.
13. The ~~method-use~~ of claim 12, wherein said reduces aggregation of said platelets occurs through irreversible binding to P2Y₁₂ receptors.
14. The ~~method-use~~ of claim 12, wherein said reduces aggregation of said platelets occurs through blocking ADP receptors.
15. The ~~method-use~~ of claim ~~9~~12, wherein said compound is capable of producing active thienopyridine metabolites in the presence of endogenous glutathione without the need for bioactivation by P450s.
16. The ~~method-use~~ of claim ~~9~~12, further comprising ~~co-administration of~~ at least one agent selected from the group consisting of a HMG-CoA reductase inhibitor, an ACE Inhibitor, a Calcium Channel Blocker, a Platelet Aggregation Inhibitor, a Polyunsaturated Fatty Acid, Fibrin Acid Derivative, a Bile Acid Sequestrant, an Antioxidant, a Thrombolytic Agent, and an Antianginal Agent.
17. Use of a compound of claim 1 for the manufacture of a medicament for the~~A method of treating, amelioration~~g, or prevention~~g of aggregation of platelets onto blood vessels in a patient, comprising administering to said patient a therapeutically effective amount of the compound of any one of claims 1-7.~~
18. The ~~method-use~~ of claim 17, wherein said ~~administration is selected from the group consisting of~~ medicament is formulated for oral administration and intravenous administration.

19. The ~~method~~use of claim 18, wherein said treating, ameliorating, or preventing said aggregation of said platelets occurs through irreversible binding to P2Y₁₂ receptors.

20. The ~~method~~use of claim 18, wherein said treating, ameliorating, or preventing said aggregation of said platelets occurs through blocking ADP receptors.

21. ~~The method of claim 18, wherein said compound is capable of producing active thienopyridine metabolites in the presence of endogenous glutathione without the need for bioactivation by P450s.~~

22. ~~The method of claim 18, further comprising co-administration of at least one agent selected from the group consisting of a HMG-CoA reductase inhibitor, an ACE Inhibitor, a Calcium Channel Blocker, a Platelet Aggregation Inhibitor, a Polyunsaturated Fatty Acid, Fibrin Acid Derivative, a Bile Acid Sequestrant, an Antioxidant, a Thrombolytic Agent, and an Antianginal Agent.~~

23. ~~A pharmaceutical composition comprising mixed disulfide conjugates of thienopyridine compounds a therapeutically effective amount of the compound of any one of claims 1-7, wherein said pharmaceutical composition is configured for intravenous administration.~~

24. ~~The pharmaceutical composition of claim 23, wherein said pharmaceutical composition is intravenously administered to a patient in the treatment, amelioration and prevention of atherothrombosis.~~

25. ~~The pharmaceutical composition of claim 23, wherein said pharmaceutical composition is intravenously administered to a patient during a percutaneous coronary intervention procedure.~~

26. ~~The pharmaceutical composition of claim 25, wherein said percutaneous coronary intervention procedure is coronary angioplasty.~~