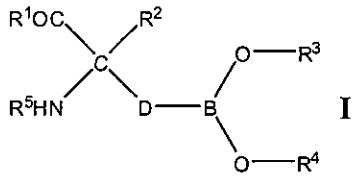
WE CLAIM:

1. A compound according to Formula I,



I

wherein

R^1 is selected from the group consisting of -OH, OR^a, and NR^bR^c;

R^a is selected from the group consisting of hydrogen, straight or branched chain (C_1-C_6)alkyl, (C_3-C_{14})aryl, (C_3-C_{14})heterocycloalkyl-(C_1-C_6)alkylene-, (C_3-C_{14})heteroaryl-(C_1-C_6)alkylene-, and (C_3-C_{14})aryl(C_1-C_6)alkylene-;

R^b and R^c are each independently selected from the group consisting of H, -OH, straight or branched (C_1-C_6)alkyl, $-S(O)_2-(C_1-C_6)$alkyl, (C_3-C_{14})aryl-$S(O)_2-$, (C_3-C_{14})heterocycloalkyl-(C_1-C_6)alkylene-, and (C_3-C_{14})heteroaryl-(C_1-C_6)alkylene-;

and wherein

(A) R^2 is selected from the group consisting of straight or branched (C_1-C_6)alkyl, straight or branched (C_2-C_6)alkenyl, straight or branched (C_2-C_6)alkynyl, (C_3-C_{14})aryl, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})aryl(C_1-C_6)alkylene-, (C_3-C_{14})heteroaryl-(C_1-C_6)alkylene-, (C_3-C_{14})heteroaryl, (C_3-C_{14})heterocycloalkyl, (C_3-C_{14})heterocycloalkyl-(C_1-C_6)alkylene-, (C_3-C_{14})heteroaryl-(C_3-C_6)heterocycloalkylene-, (C_3-C_{14})aryl-(C_3-C_{14})heterocycloalkylene-, (C_3-C_{14})-aryl-(C_1-C_6)alkyl-(C_3-C_{14})heterocycloalkylene-, (C_3-C_{14})heteroaryl-(C_1-C_6)alkyl-(C_3-C_{14})heterocycloalkylene-, (C_3-C_{14})heterocycloalkyl-(C_1-C_6)alkyl-(C_3-C_{14})heterocycloalkylene-, and $-(CH_2)_m-(X)_u-(CH_2)_n-(Y)_v-R^f$;

wherein

u and v are each independently 0 or 1, and $u + v \geq 1$;

m and n are each independently 0, 1, 2, 3, 4, 5, or 6, wherein m + n ≥1;

X and Y are independently selected from the group consisting of –NH, -O- and –S-;

R^f is selected from the group consisting of H, hydroxyl, straight or branched (C_1-C_6)alkyl and (C_3-C_{14})aryl; and

R^5 is selected from the group consisting of straight or branched (C_1-C_6) alkyl or (C_1-C_6)alkyl-C(O)-;

OR wherein

(B) R^2 is (C_3-C_{14})heterocycloalkyl-(C_1-C_2)alkylene- and
R^5 is selected from the group consisting of H, straight or branched (C_1-C_6) alkyl, and (C_1-C_6)alkyl-C(O)-;

and wherein

R^3 and R^4 are each independently selected from hydrogen, straight or branched (C_1-C_6)alkyl, and C(O)-R',

or R^3 and R^4 together with the boron atom to which they are bound form a 5- or 6-membered ring that is fully or partially saturated, and that optionally contains 1-3 additional heteroatom ring members selected from O, S, and N;

D is selected from the group consisting of straight or branched (C_1-C_6)alkylene, straight or branched (C_2-C_8)alkenylene, straight or branched (C_2-C_8)alkynylene, (C_3-C_{14})arylene, and (C_3-C_{14})cycloalkylene,

wherein one or more –CH_2- groups in D are optionally and independently replaced with a moiety selected from group the consisting of O, NR', S, SO, SO_2, and CR'R"; or

wherein any two adjacent –CH_2- groups optionally represent two members of a (C_3-C_{14})-cycloalkylenyl group;

and wherein any alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is optionally substituted with one or more members selected from the group consisting of halogen, oxo, -COOH, -CN, $-NO_2$, -OH, $-NR^dR^e$, $-NR^gS(O)_2R^h$, (C_1-C_6)alkoxy, and (C_3-C_{14})aryloxy;

wherein R^d, R^e, R^g, and R^h are each independently selected from the group consisting of H, straight or branched (C_1-C_6)alkyl, optionally substituted (C_3-C_{14})aryl(C_1-C_6)alkylene-, (C_1-C_6)alkoxy, optionally substituted (C_3-C_{14})aryl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)aminoalkyl, $H_2N(C_1-C_6)$alkylene-, optionally substituted (C_3-C_6)cycloalkyl, optionally substituted (C_3-C_{14})heterocycloalkyl, optionally substituted (C_3-C_{14})heteroaryl, optionally substituted (C_3-C_{14})aryl-(C_1-C_6)alkylene-, NR'R"C(O)-, and (C_3-C_6)aryl-(C_3-C_{14})-cycloalkylene-,

R' and R" are each independently selected from the group consisting of H, (C_1-C_8)alkyl, and (C_3-C_6)aryl; and

wherein any aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more members selected from the group consisting of halogen, -OH, oxo, -COOH, (C_3-C_{14})aryl(C_1-C_6)alkylene-, -CN, $-NO_2$, $-NH_2$, (C_1-C_6)alkyl-S-, (C_3-C_{14})cycloalkyl, (C_3-C_{14})heterocycloalkyl, (C_3-C_{14})aryl, (C_3-C_{14})heteroaryl, -C(O)NH-(C_1-C_6)alkyl, - NHC(O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, and (C_1-C_6)hydroxyalkyl;

or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof;

and wherein the compound is not 2-amino-4-borono-2-methylbutanoic acid.

2. The compound according to claim 1, wherein D is selected from the group consisting of:

$-L^1-L^2-CH_2-CH_2-$,

$-CH_2-L^1-L^2-CH_2-$,

$-CH_2-CH_2-L^1-L^2-$,

- L^1-CH_2-CH_2- L^2-,

-L^1-CH_2-L^2-CH_2-, and

-L^1-CH_2-CH_2-L^2-,

wherein L^1 and L^2 are independently selected from the group consisting of O, NR', S, SO, SO_2, and CR'R", wherein R' and R" are as defined in claim 1.

3. The compound according to claim 1, wherein D is straight or branched (C_1-C_6)alkylene.

4. The compound according to claim 3, wherein D is butylene.

5. The compound according to claim 3, wherein R^1 is –OH.

6. The compound according to claim 5, wherein

(A) R^2 is selected from the group consisting of straight or branched (C_1-C_6)alkyl, straight or branched (C_2-C_6)alkenyl, straight or branched (C_2-C_6)alkynyl, (C_3-C_{14})aryl, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})aryl(C_1-C_6)alkylene-, (C_3-C_{14})heteroaryl-(C_1-C_6)alkylene-, (C_3-C_{14})heteroaryl, (C_3-C_{14})heterocycloalkyl, (C_3-C_{14})heterocycloalkyl-(C_1-C_6)alkylene-,
(C_3-C_{14})heteroaryl-(C_3-C_6)heterocycloalkylene-, (C_3-C_{14})aryl-(C_3-C_{14})heterocycloalkylene-, (C_3-C_{14})-aryl-(C_1-C_6)alkyl-(C_3-C_{14})heterocycloalkylene-, (C_3-C_{14})heteroaryl-(C_1-C_6)alkyl-(C_3-C_{14})heterocycloalkylene-, (C_3-C_{14})heterocycloalkyl-(C_1-C_6)alkyl-(C_3-C_{14})heterocycloalkylene-, and -$(CH_2)_m$-$(X)_u$-$(CH_2)_n$-$(Y)_v$-R^f; and

each of $R^3$and R^4 is hydrogen

OR

(B) R^2 is (C_3-C_{14})heterocycloalkyl-(C_1-C_2)alkylene- and

each of R^3, and R^4 and R^5 is hydrogen.

7. The compound according to claim 6, wherein

R^2 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{14})$aryl, $(C_3\text{-}C_{14})$heteroaryl, $(C_3\text{-}C_{14})$heterocycloalkyl, $(C_3\text{-}C_{14})$heterocycloalkyl-$(C_1\text{-}C_6)$alkylene-, $(C_3\text{-}C_{14})$heteroaryl-$(C_1\text{-}C_6)$alkylene-, $(C_3\text{-}C_{14})$aryl-$(C_1\text{-}C_6)$alkylene- and $-(CH_2)_n\text{-}(X)_u\text{-}(CH_2)_m\text{-}(Y)_v\text{-}R^f$, and

R^5 is selected from the group consisting of straight or branched $(C_1\text{-}C_6)$ alkyl or $(C_1\text{-}C_6)$alkyl-C(O)-.

8. The compound according to claim 7, wherein any aryl, heterocycloalkyl, or heteroaryl is optionally substituted with members selected from the group consisting of -COOH, -OH, halogen, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$hydroxyalkyl, $(C_3\text{-}C_{14})$heterocycloalkyl and $(C_3\text{-}C_{14})$heteroaryl.

9. The compound according to claim 7, wherein R^2 is alkyl optionally substituted by hydroxyl or $-NR^dR^e$.

10. The compound according to claim 9, wherein each of R^d and R^e is independently selected from the group consisting of H, straight or branched $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$aminoalkyl, optionally substituted $(C_3\text{-}C_{14})$aryl$(C_1\text{-}C_6)$alkylene-, optionally substituted $(C_3\text{-}C_{14})$aryl, and optionally substituted $(C_3\text{-}C_6)$cycloalkyl.

11. The compound according to claim 10, wherein each of R^d and R^e is $(C_1\text{-}C_6)$aminoalkyl.

12. The compound according to claim 7, wherein R^2 is $-(CH_2)_n\text{-}(X)_u\text{-}(CH_2)_m\text{-}(Y)_v\text{-}R^f$.

13. The compound according to claim 12, wherein X and Y are each independently –NH-.

14. The compound according to claim 12, wherein m is 1 and n is 2.

15. The compound according to claim 12, wherein each of u and v is 1.

16. The compound according to claim 7, wherein R^2 is $(C_3\text{-}C_6)$heterocycloalkyl-$(C_1\text{-}C_2)$alkylene-.

17. The compound according to claim 16, wherein the $(C_3\text{-}C_6)$heterocycloalkyl is selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydro-2H-pyran, and thiomorpholinyl.

18. The compound according to claim 17, wherein the $(C_3\text{-}C_6)$heterocycloalkyl is piperidinyl or pyrrolidinyl.

19. The compound according to claim 18, wherein $(C_3\text{-}C_6)$heterocycloalkyl is optionally substituted with one or more members selected from the group consisting of -$(C_1\text{-}C_6)$alkoxy, -$(C_1\text{-}C_6)$alkyl, and -OH.

20. The compound according to claim 16, wherein the $(C_1\text{-}C_2)$alkylene is methylene.

21. The compound according to claim 16, wherein the $C_1\text{-}C_2)$alkylene is ethylene.

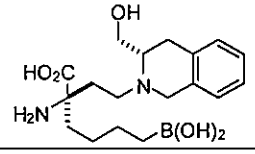
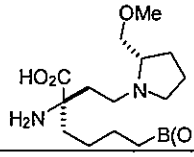
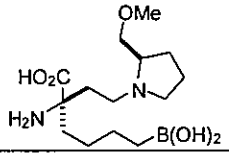
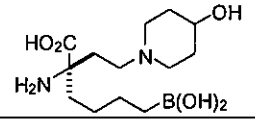
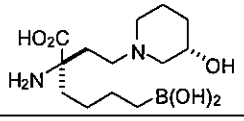
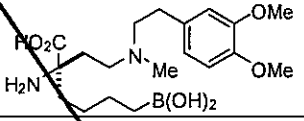
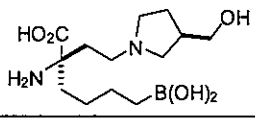
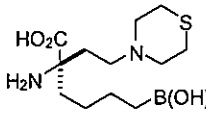
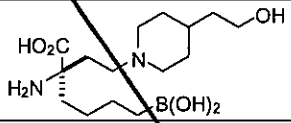
22. The compound according to claim 7, wherein R^2 is $(C_3\text{-}C_{14})$heteroaryl-$(C_1\text{-}C_6)$alkylene-.

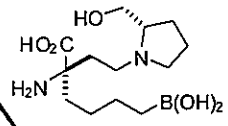
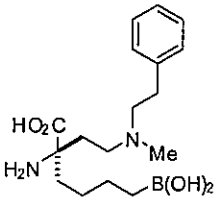
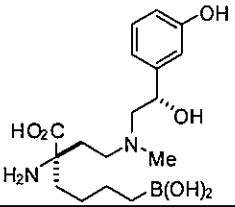
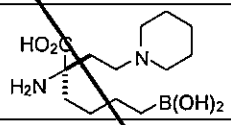
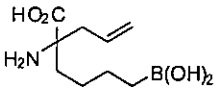
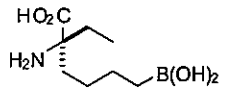
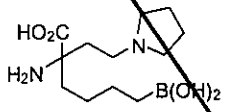
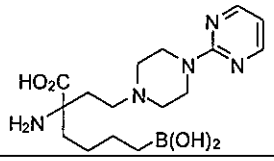
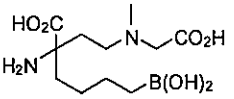
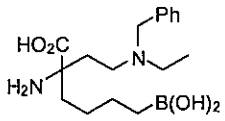
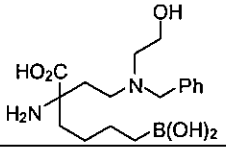
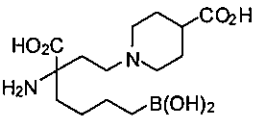
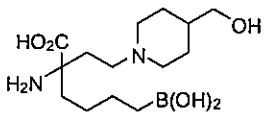
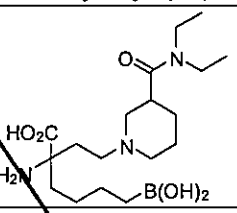
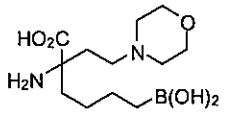
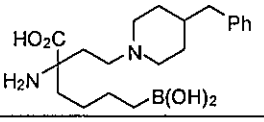
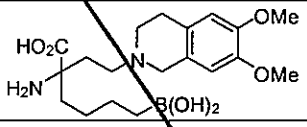
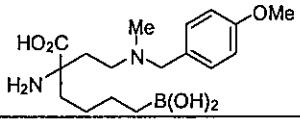
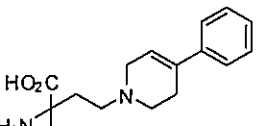
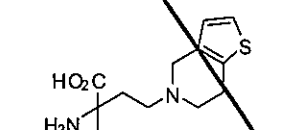
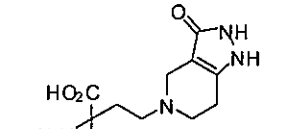
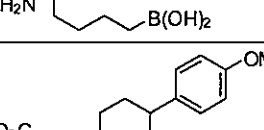
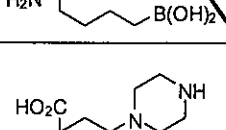
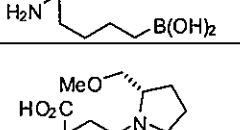
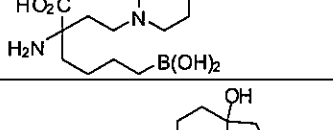
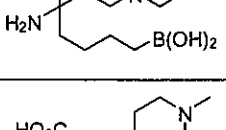
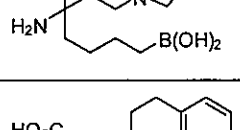
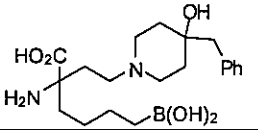
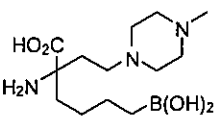
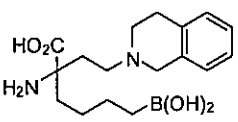
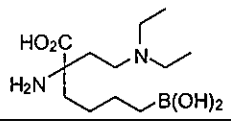
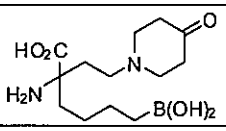
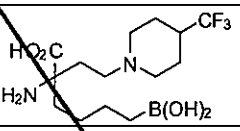
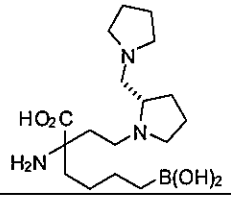
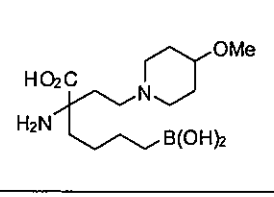
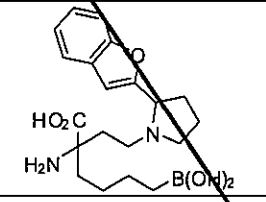
23. The compound of claim 22, wherein R^2 is $(C_3\text{-}C_6)$heteroaryl-$(C_1\text{-}C_6)$alkylene-.

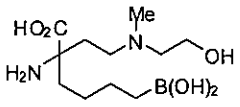
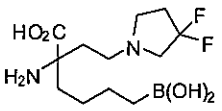
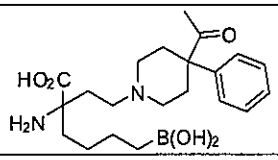
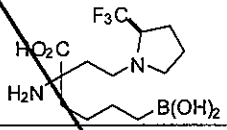
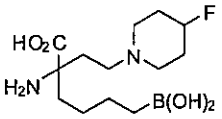
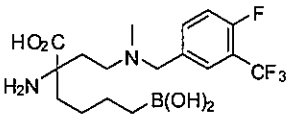
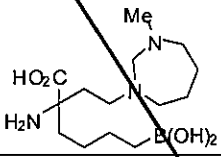
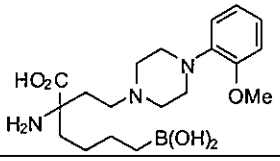
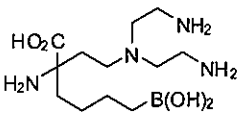
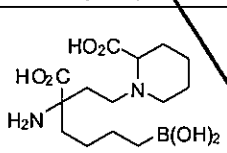
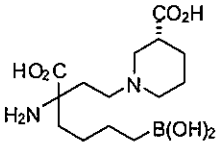
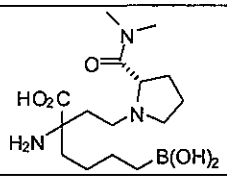
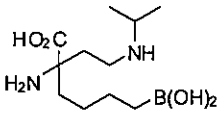
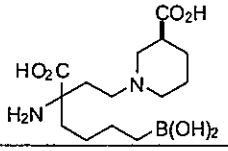
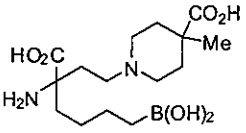
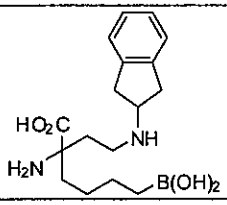
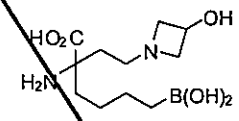
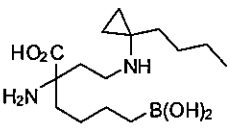
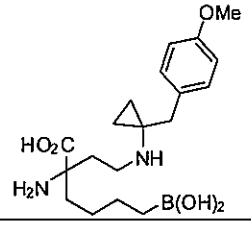
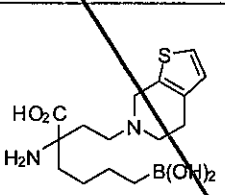
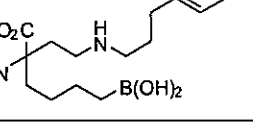
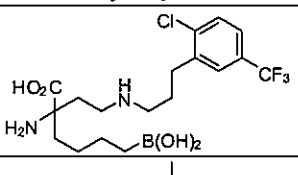
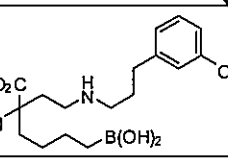
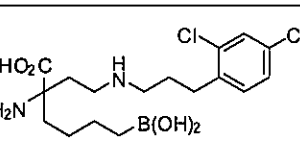
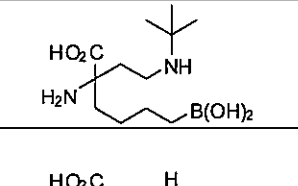
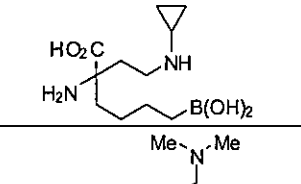
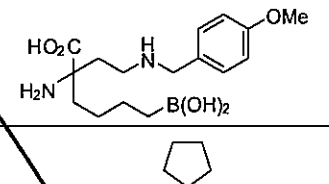
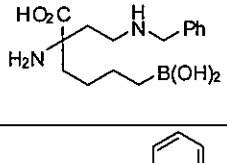
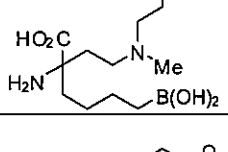
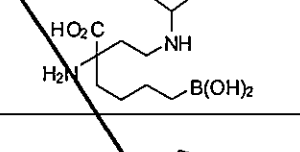
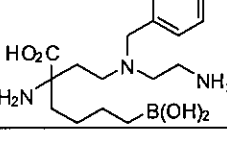
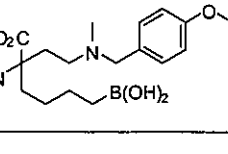
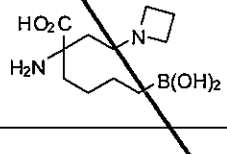
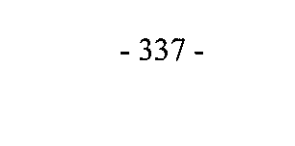
24. The compound according to claim 23, wherein the $(C_1\text{-}C_6)$alkylene is methylene.

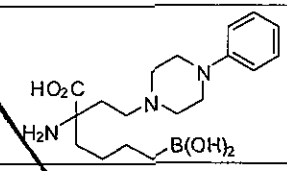
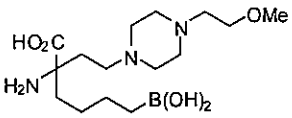
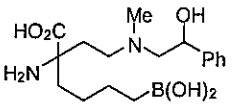
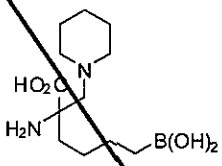
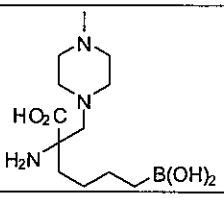
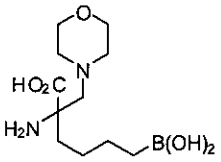
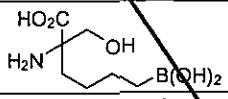
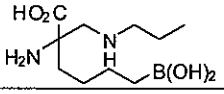
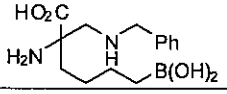
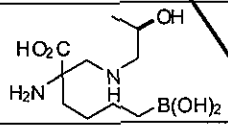
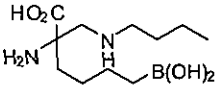
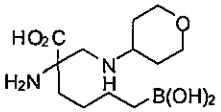
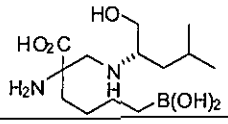
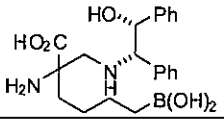
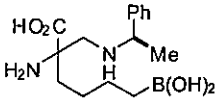
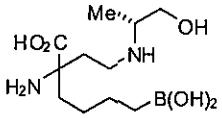
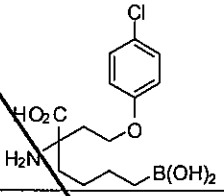
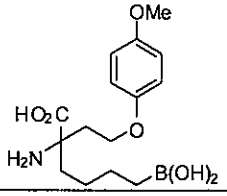
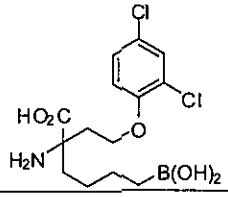
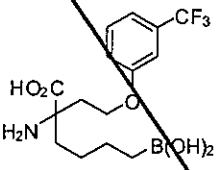
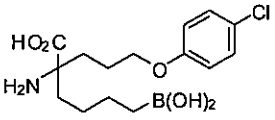
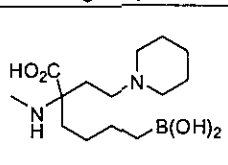
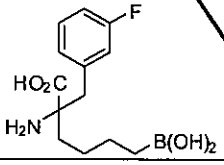
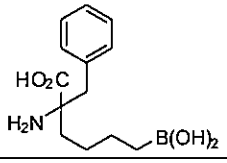
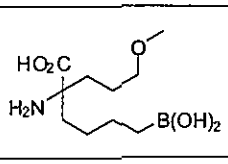
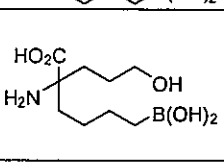
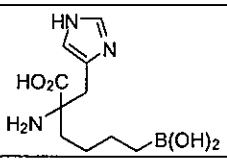
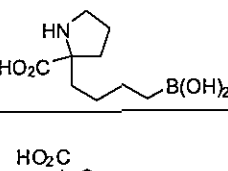
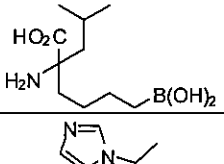
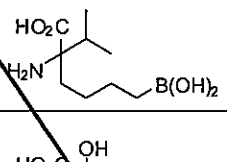
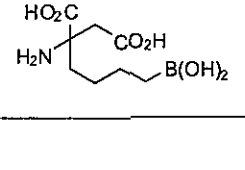
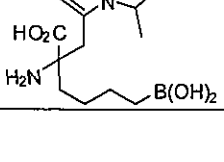
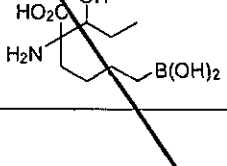
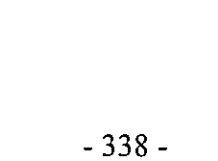
25. The compound according to claim 23, wherein the $(C_1\text{-}C_6)$alkylene is ethylene.

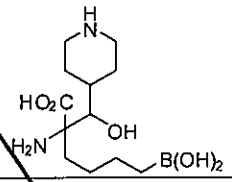
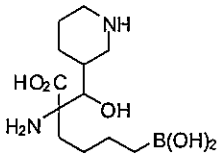
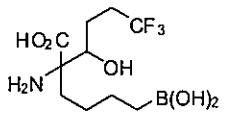
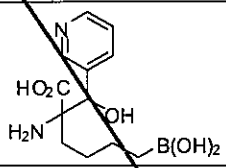
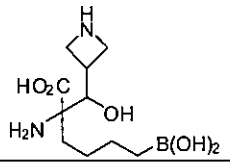
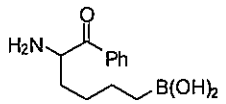
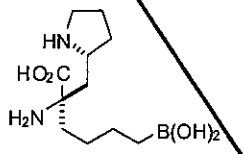
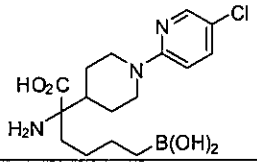
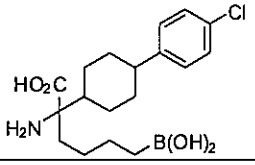
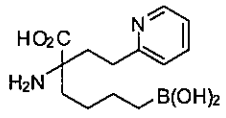
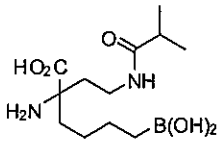
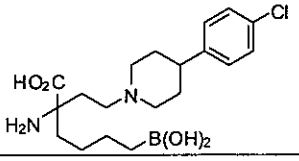
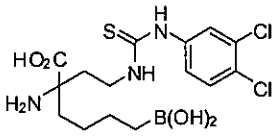
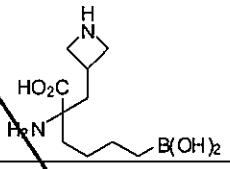
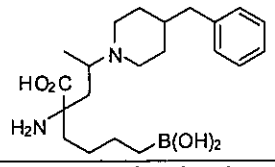
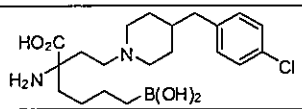
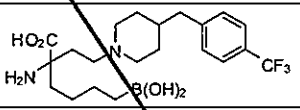
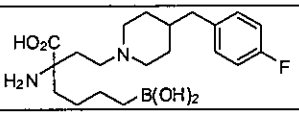
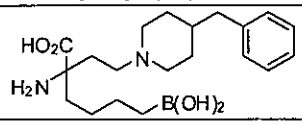
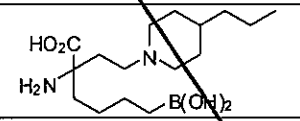
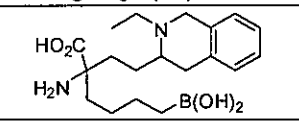
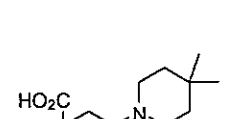
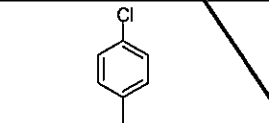
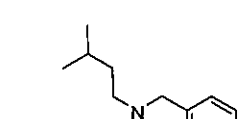
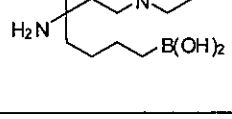
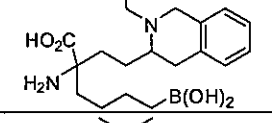
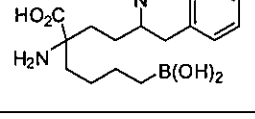
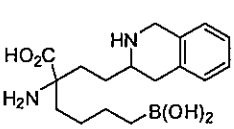
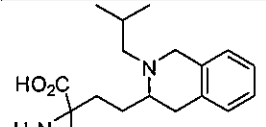
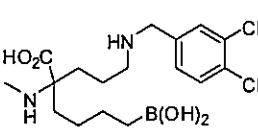
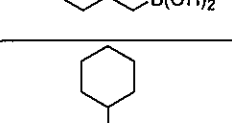
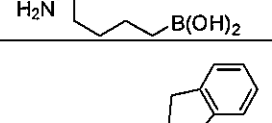
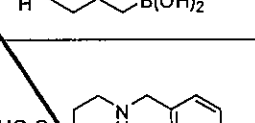
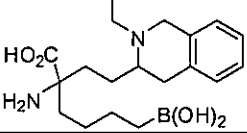
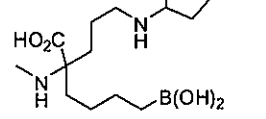
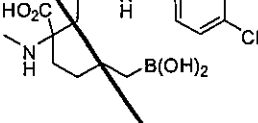
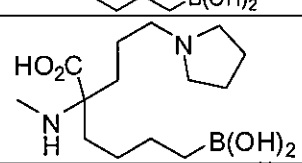
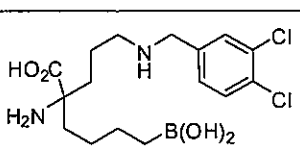
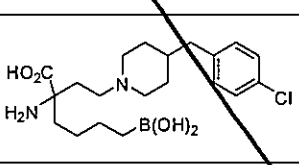
26. A compound that is selected from the following table:

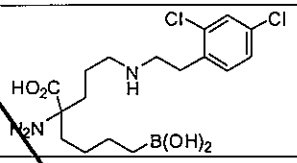
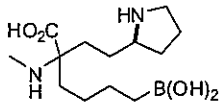
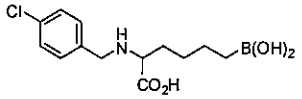
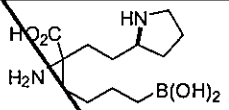
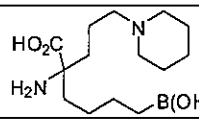
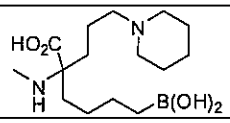
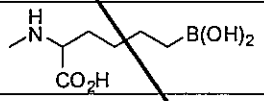
		
		
		

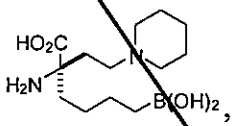
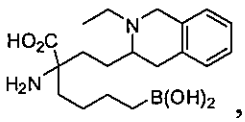
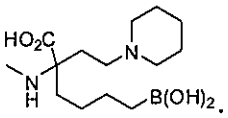
		
		
		
		
		
		
		
		
		
		
		
		

27. A compound according to claim 26 that is selected from the group consisting of:

,  , and .

28. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound according to claim 1, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof; and a pharmaceutically acceptable carrier.

29. A method for inhibiting arginase I, arginase II, or a combination thereof in a cell, comprising contacting the cell with at least one compound according to claim 1, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof.

30. A method for the treatment or prevention of a disease or condition associated with expression or activity of arginase I, arginase II, or a combination thereof in a subject, comprising administering to the subject therapeutically effective amount of at least one compound according to claim 1, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof.

31. The method according to claim 30, wherein the disease or condition is selected from the group consisting of cardiovascular disorders, gastrointestinal disorders, autoimmune disorders, immune disorders, infections, pulmonary disorders, and hemolytic disorders.

32. The method according to claim 31, wherein the disease or condition is a cardiovascular disorder selected from the group consisting of systemic hypertension, pulmonary arterial hypertension (PAH), pulmonary arterial hypertension in high altitude,

ischemia reperfusion (IR) injury, myocardial infarction, atherosclerosis, Peyronie's Disease, erectile dysfunction, reduced hepatic blood flow disorders, and cerebral vasospasm.

33. The method according to claim 31, wherein the disease or condition is a pulmonary disorder.

34. The method according to claim 33, wherein the disease or condition is selected from the group consisting of selected from the group consisting of chemically-induced lung fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma.

35. The method according to claim 31, wherein the disease or condition is an autoimmune disorder selected from the group consisting of selected from the group consisting of encephalomyelitis, multiple sclerosis, anti-phospholipid syndrome 1, autoimmune hemolytic anaemia, chronic inflammatory demyelinating polyradiculoneuropathy, dermatitis herpetiformis, dermatomyositis, myasthenia gravis, pemphigus, rheumatoid arthritis, stiff-person syndrome, type 1 diabetes, ankylosing spondylitis, paroxysmal nocturnal hemoglobinuria (PNH), paroxysmal cold hemoglobinuria, severe idiopathic autoimmune hemolytic anemia, and Goodpasture's syndrome.

36. The method according to claim 31, wherein the disease or condition is an immune disorder selected from the group consisting of myeloid-derived suppressor cell (MDSC) mediated T-cell dysfunction, human immunodeficiency virus (HIV), autoimmune encephalomyelitis, and ABO mismatch transfusion reaction.

37. The method according to claim 31, wherein the disease or condition is a hemolytic disorder selected from the group consisting of selected from the group consisting of sickle-cell disease, thalassemias, hereditary spherocytosis, stomatocytosis, microangiopathic hemolytic anemias, pyruvate kinase deficiency, infection-induced anemia, cardiopulmonary bypass and mechanical heart valve-induced anemia, and chemical induced anemia.

38. The method according to claim 31, wherein the disease or condition is a gastrointestinal disorder selected from the group consisting of gastrointestinal motility disorders, gastric cancers, inflammatory bowel disease, Crohn's disease, ulcerative colitis, and gastric ulcers.

39. The method according to claim 31, wherein the disease or condition is selected from the group consisting of renal disease, , inflammation, psoriasis, leishmaniasis, neurodegenerative diseases, wound healing, hepatitis B virus (HBV), *H. pylori* infections, fibrotic diseases, arthritis, candidiasis, periodontal disease, keloids, adenotonsilar disease, African sleeping sickness, and Chagas' disease.

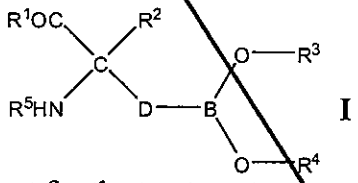
40. The method according to claim 39, wherein the disease or condition is selected from the group consisting of infected and uninfected wound healing,

41. The method according to claim 32, wherein the disease or condition is pulmonary arterial hypertension.

42. The method according to claim 32, wherein the disease or condition is erectile dysfunction.

43. The method according to claim 31, wherein the subject is a mammal selected from the group consisting of a human, dog, cat, horse, cow sheep, reptile and lamb.

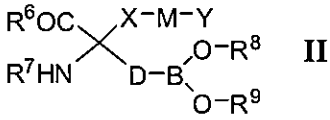
44. Use of a compound according to Formula I, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof:



I

in the manufacture of a medicament for the treatment or prevention of a disease or condition associated with expression or activity of arginase I, arginase II, or a combination thereof in a subject, wherein R^1, R^2, R^3, R^4, R^5, and D are as defined in claim 1.

45. A compound according to Formula II,



II

wherein

R^6 is selected from the group consisting of OR^a, and NR^bR^c;

R^a is selected from the group consisting of hydrogen, straight or branched chain (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_{14})aryl, (C_3-C_{14})heterocycloalkyl-(C_1-C_6)alkylene-, (C_3-C_{14})heteroaryl-(C_1-C_6)alkylene-, and (C_3-C_{14})aryl(C_1-C_6)alkylene-;

R^b and R^c are each independently selected from the group consisting of H, -OH, straight or branched (C_1-C_6)alkyl, -S(O)$_2$-(C_1-C_6)alkyl, (C_3-C_{14})aryl-S(O)$_2$-, (C_3-C_{14})heterocycloalkyl-(C_1-C_6)alkylene-, and (C_3-C_{14})heteroaryl-(C_1-C_6)alkylene-;

R^7 is selected from the group consisting of H, straight or branched (C_1-C_6) alkyl, (C_3-C_{14})aryl(C_1-C_6)alkylene-, (C_3-C_{14})heteroaryl-(C_1-C_6)alkylene-, (C_3-C_{14})heterocycloalkyl-(C_1-C_6)alkylene- and (C_1-C_6)alkyl-C(O)-;

X is selected from the group consisting of (C_3-C_{14})-cycloalkylene and (C_3-C_{14}) heterocycloalkylene,

Y is selected from the group consisting of H, (C_1-C_{14})alkyl, -NR'R", hydroxy(C_1-C_6)alkylene, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})-cycloalkyl-(C_1-C_6)alkylene, (C_3-C_{14})aryl, (C_3-C_{14})aryl-(C_1-C_6)alkylene, (C_3-C_{14})heterocycloalkyl, (C_3-C_{14})heterocycloalkyl-(C_1-C_6)alkylene, (C_3-C_{14})heteroaryl, (C_3-C_{14})heteroaryl-(C_1-C_6)alkylene, (C_3-C_{14})heteroaryl-(C_3-C_6)heterocycloalkylene-, (C_3-C_{14})aryl-(C_3-C_{14})heterocycloalkylene-, (C_3-C_{14})-aryl-(C_1-C_6)alkyl-(C_3-C_{14})heterocycloalkylene-, (C_3-C_{14})heteroaryl-(C_1-C_6)alkyl-(C_3-C_{14})heterocycloalkylene-, and (C_3-C_{14})heterocycloalkyl-(C_1-C_6)alkyl-(C_3-C_{14}) heterocycloalkylene-.;

M is selected from the group consisting of a bond, -(C_1-C_6)alkylene-, -O-, -C(O)-, -C(S)-, -C(O)NH-, -C(S)NH-, -S-, -S(O)-, -S(O)$_2$-, -NR'-, and –C=NR^{11}-;

R^8 and R^9 are independently selected from hydrogen, straight or branched (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_3-C_{14})aryl, and C(O)-R',

or R^8 and R^9 together with the boron atom to which they are bound form a 5- or 6-membered ring that is fully saturated, or partially saturated and that optionally contains 1-3 additional heteroatom ring members selected from O, S, and N,

wherein the ring is optionally fused with a cycloalkyl, heterocyclic or aromatic ring;

D is selected from the group consisting of straight or branched (C_3-C_5)alkylene, straight or branched (C_2-C_8)alkenylene, straight or branched (C_2-C_8)alkynylene, (C_3-C_{14})arylene, and (C_3-C_{14})cycloalkylene,

wherein one or more $-CH_2-$ groups in D are optionally and independently replaced with a moiety selected from group the consisting of O, NR', S, SO, SO_2, and CR'R"; or

wherein any two adjacent $-CH_2-$ groups optionally represent two members of a (C_3-C_{14})-cycloalkylenyl group; and

wherein no two adjacent $-CH_2-$ groups are O, NR', S, SO, or SO_2;

R' and R" are independently selected from the group consisting of H, (C_1-C_8)alkyl, -C(O)-(C_1-C_8)alkylene, optionally substituted (C_3-C_6)aryl, optionally substituted (C_3-C_{14})aryl(C_1-C_6)alkylene-, optionally substituted (C_1-C_6)aminoalkyl, optionally substituted (C_3-C_6)cycloalkyl, optionally substituted (C_3-C_{14})heterocycloalkyl, optionally substituted (C_3-C_{14})heteroaryl; and

wherein any alkyl, alkylene, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more members selected from the group consisting of halogen, oxo, -COOH, -CN, $-NO_2$, -OH, $-NR^dR^e$, $-NR^gS(O)_2R^h$, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, (C_1-C_6)alkoxy, (C_3-C_{14})aryl, (C_3-C_{14})heteroaryl, (C_3-C_{14})heterocycloalkyl, (C_3-C_{14})heteroaryl-(C_1-C_6)alkylene and (C_3-C_{14})aryloxy;

wherein R^d, R^e, R^g, and R^h are each independently selected from the group consisting of H, straight or branched (C_1-C_6)alkyl, optionally substituted (C_3-C_{14})aryl(C_1-C_6)alkylene-, optionally substituted (C_3-C_{14})aryl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)aminoalkyl, H_2N(C_1-C_6)alkylene-, optionally substituted (C_3-C_6)cycloalkyl, optionally substituted (C_3-C_{14})heterocycloalkyl, optionally substituted (C_3-C_{14})heteroaryl, optionally substituted (C_3-C_{14})aryl-(C_1-C_6)alkylene-, and NR'R"C(O)-,

or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof.

46. The compound according to claim 45, wherein D is selected from the group consisting of:

$-L^1-L^2-CH_2-CH_2-$,

$-CH_2-L^1-L^2-CH_2-$,

$-CH_2-CH_2-L^1-L^2-$,

$-L^1-CH_2-CH_2-L^2-$,

$-L^1-CH_2-L^2-CH_2-$, and

$-L^1-CH_2-CH_2-L^2-$,

wherein

L^1 and L^2 are independently selected from the group consisting of O, NR', S, SO, SO_2, and CR'R", wherein R' and R" are as defined in claim 1 and

when L^1 and L^2 are adjacent to each other, then L^1 and L^2 are not simultaneously O, NR', S, SO, or SO_2.

47. The compound according to claim 46, wherein D is straight or branched (C_3-C_5)alkylene.

48. The compound according to claim 47, wherein D is butylene.

49. The compound according to claim 46, wherein R^6 is –OH.

50. The compound according to claim 49, wherein each of R^7, R^8 and R^9 is hydrogen.

51. The compound according to claim 46, wherein X is a (C_3-C_{14})cycloalkylene, M is selected from the group consisting of bond, -(C_1-C_6)alkylene-, -O-, -C(O)-, -C(S)-, -C(O)NH-, -C(S)NH-, -S-, -S(O)-, $-S(O)_2-$, -NR'-, and $-C=NR^{11}-$ and Y is –NR'R".

52. The compound according to claim 51, wherein M is a bond and Y is $-NH_2$.

53. The compound according to claim 45, wherein X is (C_3-C_{14})heterocycloalkylene.

54. The compound according to claim 53, wherein M is selected from the group consisting of bond, -(C_1-C_6)alkylene-, -O-, -C(O)-, -C(S)-, -C(O)NH-, -C(S)NH-, -S-, -S(O)-, -$S(O)_2$-, -NR'-, and –C=NR^{11}- and Y is selected from the group consisting of (C_3-C_{14})-cycloalkyl, (C_3-C_{14})aryl, (C_3-C_{14})aryl-(C_1-C_6)alkylene, (C_3-C_{14})heteroaryl and (C_3-C_{14})heteroaryl-(C_1-C_6)alkylene.

55. The compound according to claim 54, wherein Y is (C_3-C_{14})heteroaryl.

56. The compound according to claim 54, wherein Y is (C_3-C_{14})aryl-(C_1-C_6)alkylene.

57. The compound according to claim 54, wherein Y is (C_3-C_{14})aryl.

58. The compound according to claim 54, wherein Y is (C_3-C_{14})-cycloalkyl.

59. The compound according to claim 54, wherein M is selected from the group consisting of -C(O)NH-, -C(S)NH-, and -NR'-.

60. The compound according to claim 59, wherein R' is (C_1-C_4)alkylene.

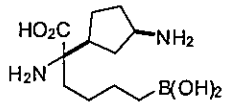
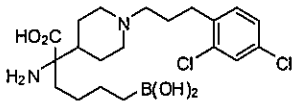
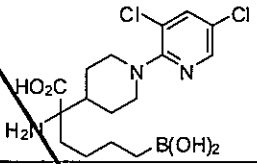
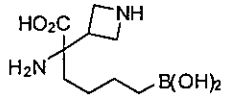
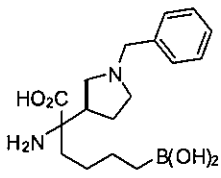
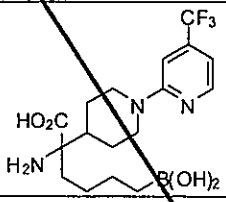
61. The compound according to claim 60, wherein R' is methylene or ethylene.

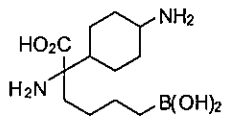
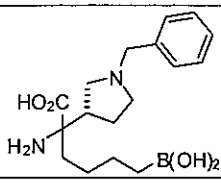
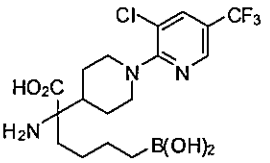
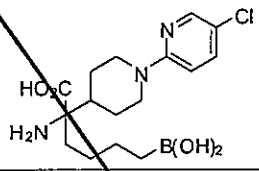
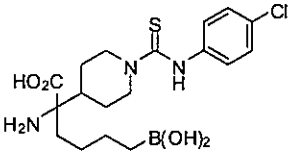
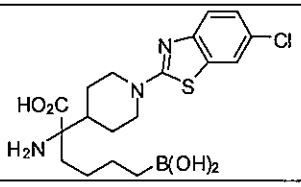
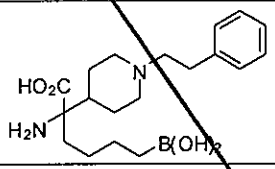
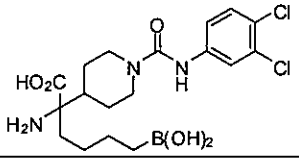
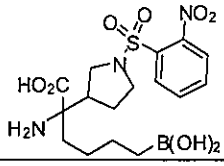
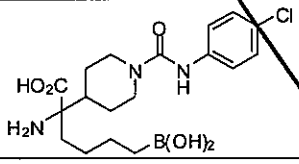
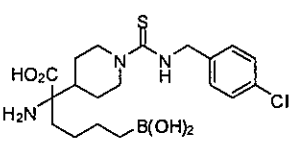
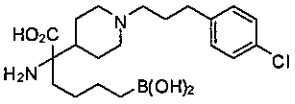
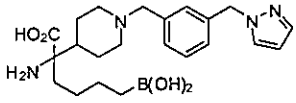
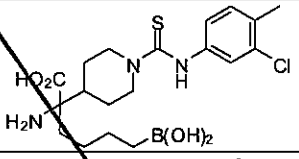
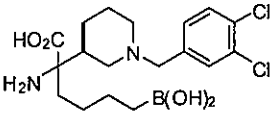
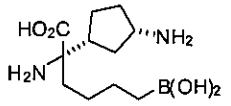
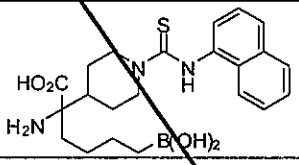
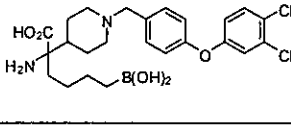
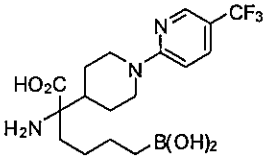
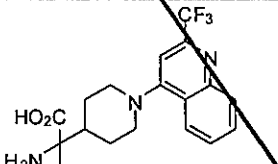
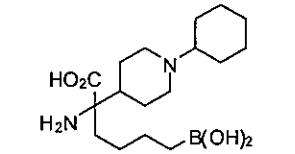
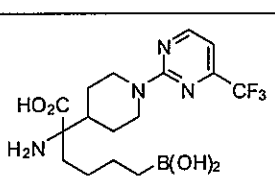
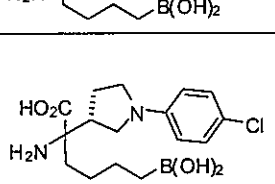
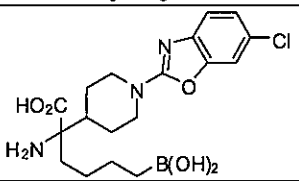
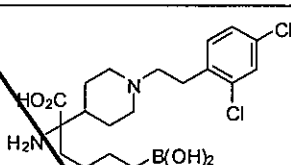
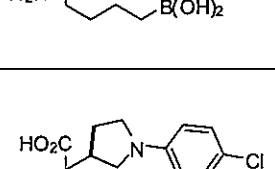
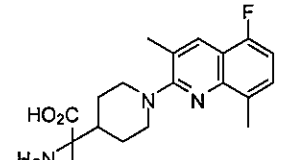
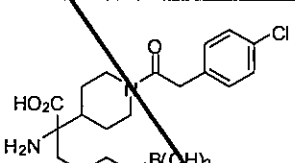
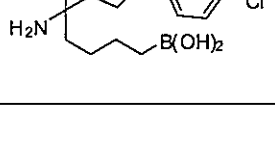
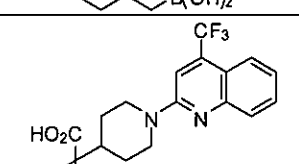
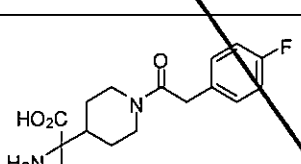
62. The compound according to claim 59, wherein R' is -C(O)-(C_1-C_8)alkylene.

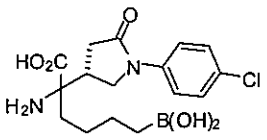
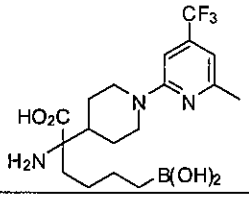
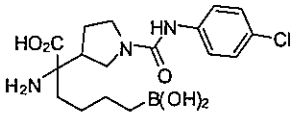
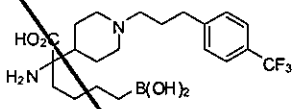
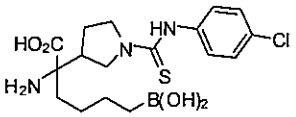
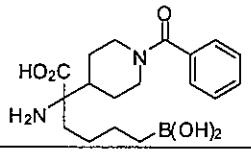
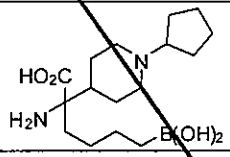
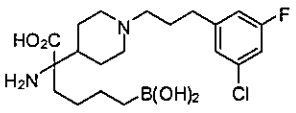
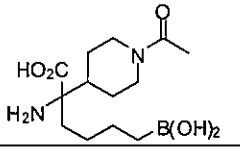
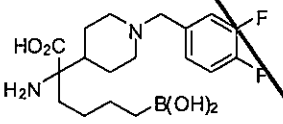
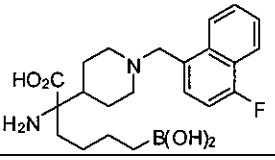
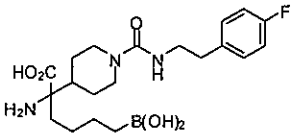
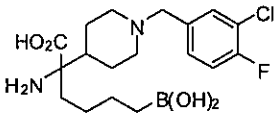
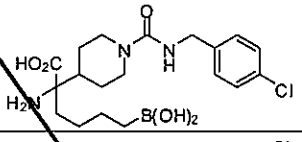
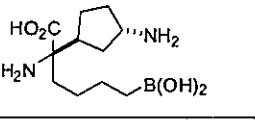
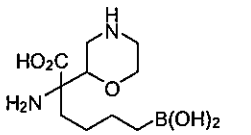
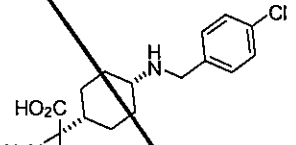
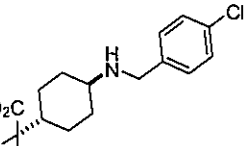
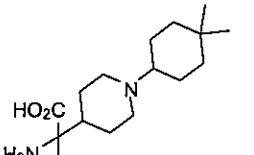
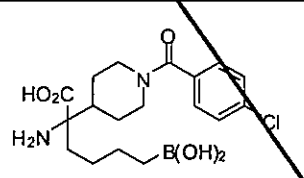
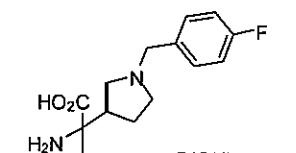
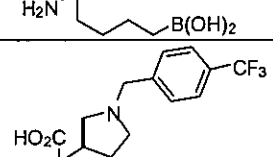
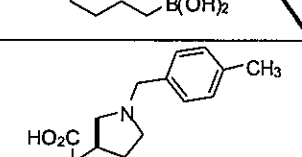
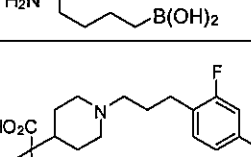
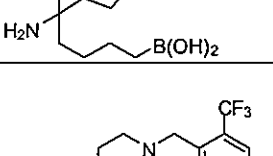
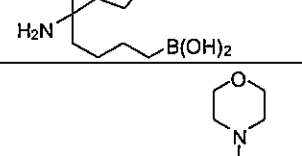
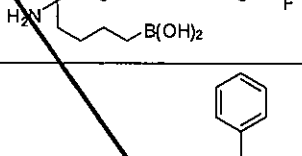
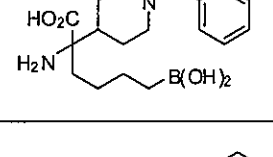
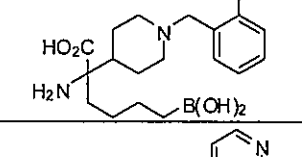
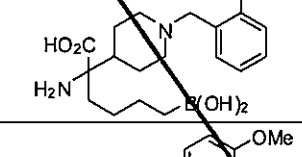
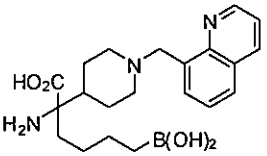
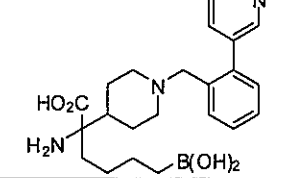
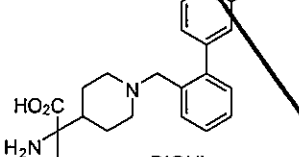
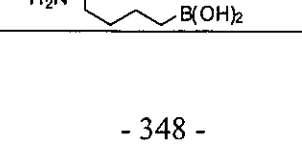
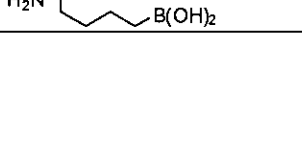
63. The compound according to claim 62, wherein R' is -C(O)-methylene.

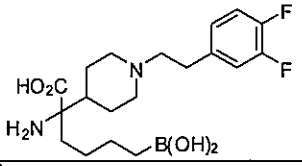
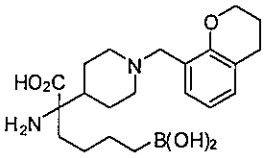
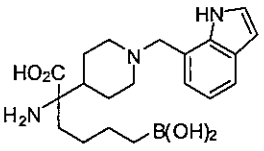
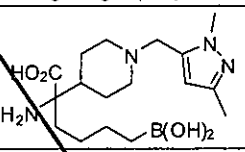
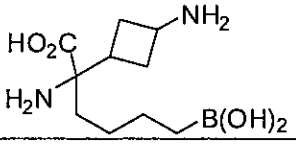
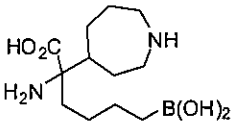
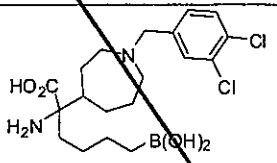
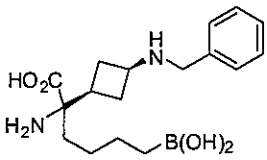
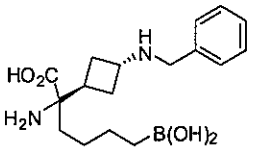
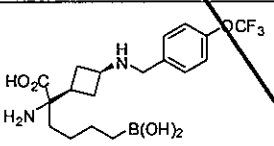
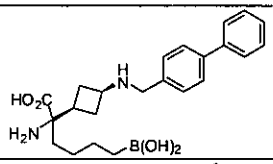
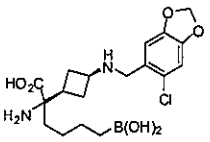
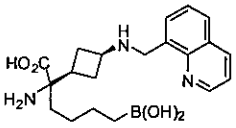
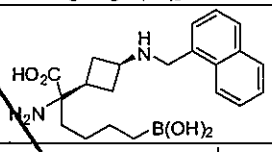
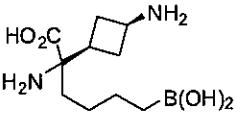
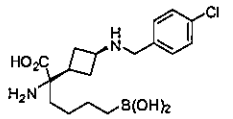
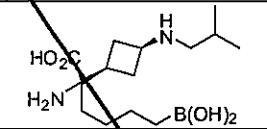
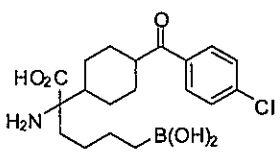
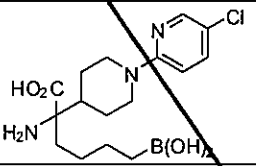
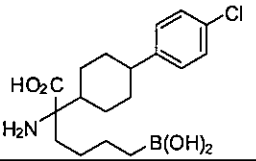
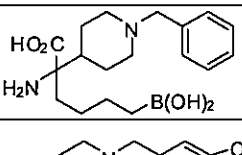
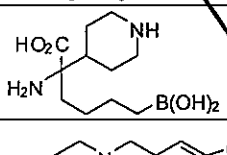
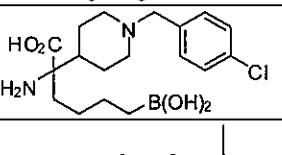
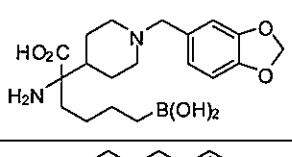
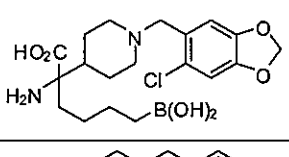
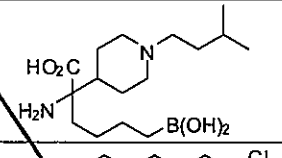
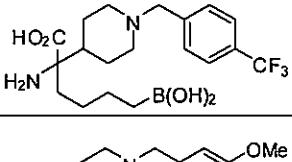
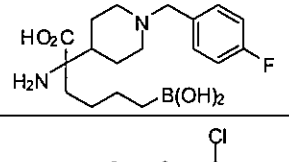
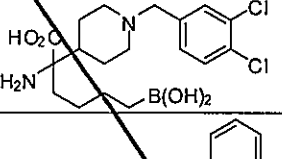
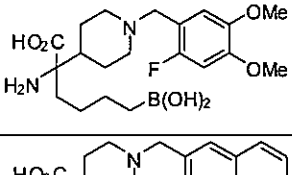
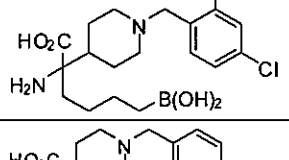
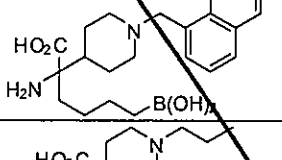
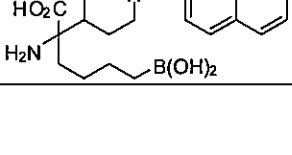
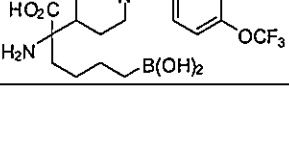
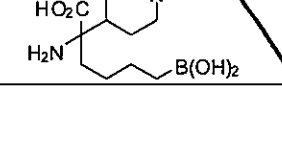
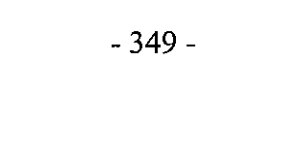
64. The compound according to claim 54, wherein M is a bond.

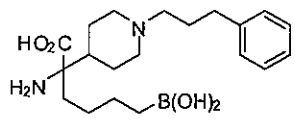
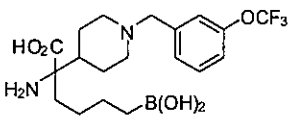
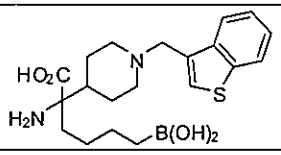
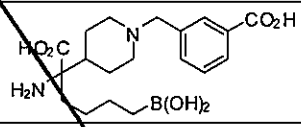
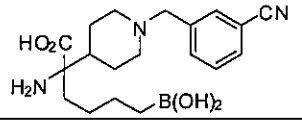
65. The compound according to claim 45 that is selected from the following table:

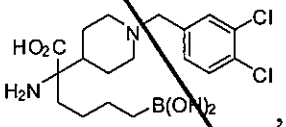
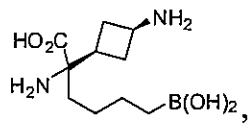
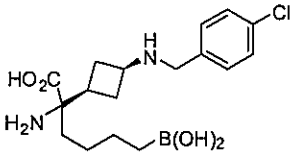
		
		
		
		
		
		
		
		
		
		
		

66. A compound according to claim 65 that is selected from the group consisting of:

, , and 

67. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound according to claim 45, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof; and a pharmaceutically acceptable carrier.

68. A method for inhibiting arginase I, arginase II, or a combination thereof in a cell, comprising contacting the cell with at least one compound according to claim 45, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof.

69. A method for the treatment or prevention of a disease or condition associated with expression or activity of arginase I, arginase II, or a combination thereof in a subject, comprising administering to the subject therapeutically effective amount of at least one compound according to claim 45, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof.

70. The method according to claim 69, wherein the disease or condition is selected from the group consisting of cardiovascular disorders, gastrointestinal disorders, autoimmune disorders, immune disorders, infections, pulmonary disorders, and hemolytic disorders.

71. The method according to claim 70, wherein the disease or condition is a cardiovascular disorder selected from the group consisting of systemic hypertension, pulmonary arterial hypertension (PAH), pulmonary arterial hypertension in high altitude,

ischemia reperfusion (IR) injury, myocardial infarction, atherosclerosis, Peyronie's Disease, erectile dysfunction, reduced hepatic blood flow disorders, and cerebral vasospasm.

72. The method according to claim 70, wherein the disease or condition is a pulmonary disorder.

73. The method according to claim 72, wherein the disease or condition is selected from the group consisting of selected from the group consisting of chemically-induced lung fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma.

74. The method according to claim 70, wherein the disease or condition is an autoimmune disorder selected from the group consisting of selected from the group consisting of encephalomyelitis, multiple sclerosis, anti-phospholipid syndrome 1, autoimmune hemolytic anaemia, chronic inflammatory demyelinating polyradiculoneuropathy, dermatitis herpetiformis, dermatomyositis, myasthenia gravis, pemphigus, rheumatoid arthritis, stiff-person syndrome, type 1 diabetes, ankylosing spondylitis, paroxysmal nocturnal hemoglobinuria (PNH), paroxysmal cold hemoglobinuria, severe idiopathic autoimmune hemolytic anemia, and Goodpasture's syndrome.

75. The method according to claim 70, wherein the disease or condition is an immune disorder selected from the group consisting of myeloid-derived suppressor cell (MDSC) mediated T-cell dysfunction, human immunodeficiency virus (HIV), autoimmune encephalomyelitis, and ABO mismatch transfusion reaction.

76. The method according to claim 70, wherein the disease or condition is a hemolytic disorder selected from the group consisting of selected from the group consisting of sickle-cell disease, thalassemias, hereditary spherocytosis, stomatocytosis, microangiopathic hemolytic anemias, pyruvate kinase deficiency, infection-induced anemia, cardiopulmonary bypass and mechanical heart valve-induced anemia, and chemical induced anemia.

77. The method according to claim 70, wherein the disease or condition is a gastrointestinal disorder selected from the group consisting of gastrointestinal motility disorders, gastric cancers, inflammatory bowel disease, Crohn's disease, ulcerative colitis, and gastric ulcers.

78. The method according to claim 69, wherein the disease or condition is selected from the group consisting of renal disease, inflammation, psoriasis, leishmaniasis, neurodegenerative diseases, wound healing, hepatitis B virus (HBV), *H. pylori* infections, fibrotic diseases, arthritis, candidiasis, periodontal disease, keloids, adenotonsilar disease, African sleeping sickness, and Chagas' disease.

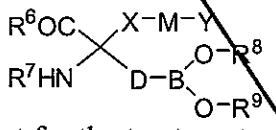
79. The method according to claim 78, wherein the disease or condition is selected from the group consisting of infected and uninfected wound healing,

80. The method according to claim 71, wherein the disease or condition is pulmonary arterial hypertension.

81. The method according to claim 71, wherein the disease or condition is erectile dysfunction.

82 The method according to claim 69, wherein the subject is a mammal selected from the group consisting of a human, dog, cat, horse, cow sheep, reptile and lamb.

83. Use of a compound according to Formula II or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof:



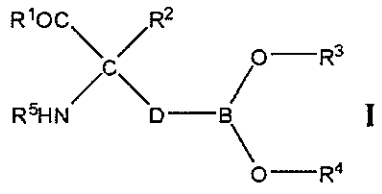
II

in the manufacture of a medicament for the treatment or prevention of a disease or condition associated with expression or activity of arginase I, arginase II, or a combination thereof in a subject, wherein R^6, R^7, R^8, R^9, X, M, Y and D are as defined in claim 45.

CLAIMS

[Claim 1]

A compound according to Formula I:



I

wherein

R1 is selected from the group consisting of-OH, ORa, and NRbRc;

Ra is selected from the group consisting of hydrogen, straight or branched chain (C1-C6)alkyl, (C3-C14)aryl, (C3-C14)heterocycloalkyl-(C1-C6)alkylene-, (C3-C14)heteroaryl-(C1-C6)alkylene-, and (C3-C14)aryl(C1-C6)alkylene-;

Rb and Rc are each independently selected from the group consisting of H,-OH, straight or branched (C1-C6)alkyl,-S(O)2-(C1-C6)alkyl, (C3-C14)aryl-S(O)2-, (C3-C14)heterocycloalkyl-(C1-C6)alkylene-, and (C3-C14)heteroaryl-(C1-C6)alkylene-;

and wherein

(A) R2 is selected from the group consisting of straight or branched (C1-C6)alkyl, straight or branched (C2-C6)alkenyl, straight or branched (C2-C6)alkynyl, (C3-C14)aryl, (C3-C14)-cycloalkyl, (C3-C14)aryl(C1-C6)alkylene-, (C3-C14)heteroaryl-(C1-C6)alkylene-, (C3-C14)heteroaryl, (C3-C14)heterocycloalkyl, (C3-C14)heterocycloalkyl-(C1-C6)alkylene-, (C3-C14)heteroaryl-(C3-C6)heterocycloalkylene-, (C3-C14)aryl-(C3-C14)heterocycloalkylene-, (C3-C14)-aryl-(C1-C6)alkylene-(C3-C14)heterocycloalkylene-, (C3-C14)heteroaryl-(C1-C6)alkylene-(C3-C14)heterocycloalkylene-, (C3-C14)heterocycloalkyl-(C1-C6)alkylene-(C3-C14)heterocycloalkylene-, and-(CH2)m-(X)u-(CH2)n-(Y)v-Rf;

wherein

u and v are each independently 0 or 1, and u+v ≥1;

m and n are each independently 0, 1, 2, 3, 4, 5, or 6, wherein m+n ≥ 1;

X and Y are independently selected from the group consisting of-NH,-O-and –S-;

Rf is selected from the group consisting of H, hydroxyl, straight or branched (C1-C6)alkyl and (C3-C14)aryl; and

R5 is selected from the group consisting of straight or branched (C1-C6) alkyl or (C1-C6)alkyl-C(O)-;

OR wherein

(B) R2 is (C3-C14)heterocycloalkyl-(C1-C2)alkylene-and

R5 is selected from the group consisting of H, straight or branched (C1-C6) alkyl, and (C1-C6)alkyl-C(O)-;

and wherein

R3 and R4 are each independently selected from hydrogen, straight or branched (C1-C6)alkyl, and C(O)-R',
or R3 and R4 together with the boron atom to which they are bound form a 5-or 6-membered ring that is fully or partially saturated, and that optionally contains 1-3 additional heteroatom ring members selected from O, S, and N;
D is-CH2CH2CH2CH2-,
wherein one or more-CH2-groups in D are optionally and independently replaced with a moiety Q that is selected from O, NR', S, SO, SO2, and CR'R"; or
wherein any two adjacent-CH2-groups optionally are replaced by two members of a (C3-C14)-cycloalkylenyl group;
provided that D does not contain two adjacent Q moieties selected from O, NR', S, SO, and SO2;
and wherein any alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is optionally substituted with one or more members selected from the group consisting of halogen, oxo,-COOH,-CN,-NO2,-OH,-NRdRe,-NRgS(O)2Rh, (C1-C6)alkoxy, and (C3-C14)aryloxy;
wherein Rd, Re, Rg, and Rh are each independently selected from the group consisting of H, straight or branched (C1-C6)alkyl, optionally substituted (C3-C14)aryl(C1-C6)alkylene-, (C1-C6)alkoxy, optionally substituted (C3-C14)aryl, (C1-C6)hydroxyalkyl, (C1-C6)aminoalkyl, H2N(C1-C6)alkylene-, optionally substituted (C3-C6)cycloalkyl, optionally substituted (C3-C14)heterocycloalkyl, optionally substituted (C3-C14)heteroaryl, optionally substituted (C3-C14)aryl-(C1-C6)alkylene-, NR'R"C(O)-, and (C3-C6)aryl-(C3-C14)-cycloalkylene-,
R' and R" are each independently selected from the group consisting of H, (C1-C8)alkyl, and (C3-C6)aryl; and
wherein any aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more members selected from the group consisting of halogen,-OH, oxo,-COOH, (C3-C14)aryl(C1-C6)alkylene-,-CN,-NO2,-NH2, (C1-C6)alkyl-S-, (C3-C14)cycloalkyl, (C3-C14)heterocycloalkyl, (C3-C14)aryl,
(C3-C14)heteroaryl,-C(O)NH-(C1-C6)alkyl,-NHC(O)-(C1-C6)alkyl, (C1-C6)alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, (C1-C6)alkoxy, (C1-C6)haloalkyl, and (C1-C6)hydroxyalkyl;
or a pharmaceutically acceptable salt, stereoisomer, or tautomer.

[Claim 2]

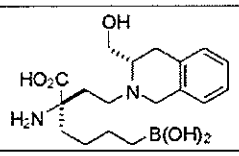
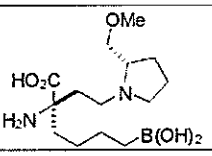
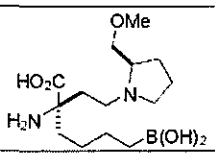
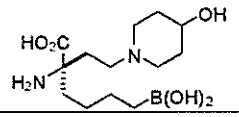
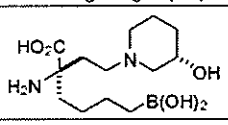
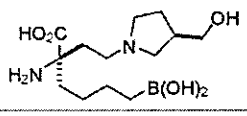
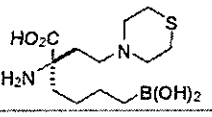
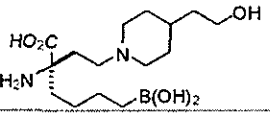
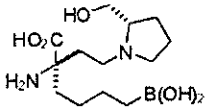
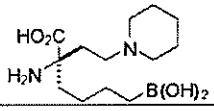
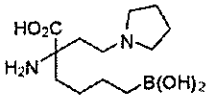
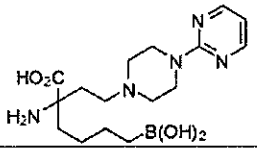
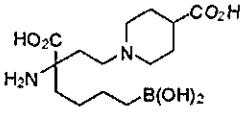
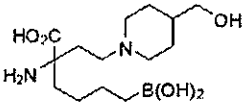
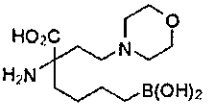
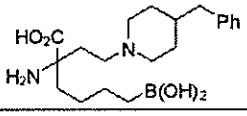
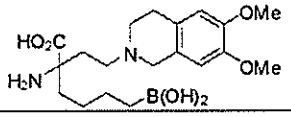
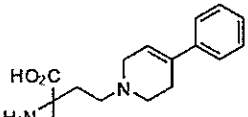
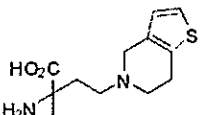
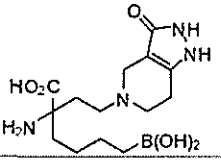
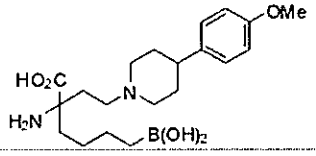
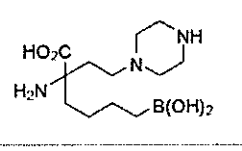
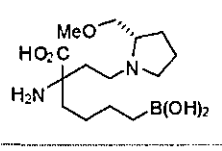
The compound according to claim 1, wherein D is butylene and R1 is-OH.

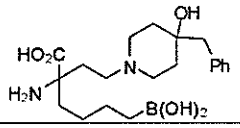
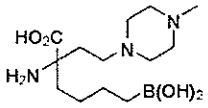
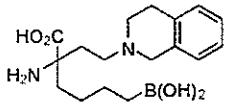
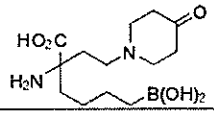
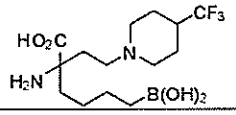
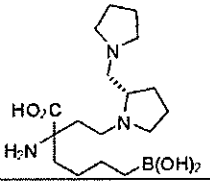
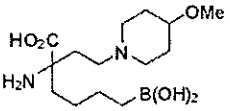
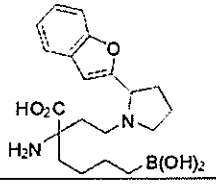
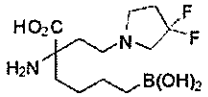
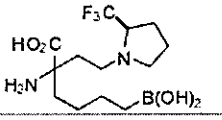
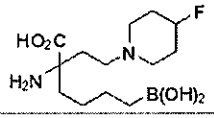
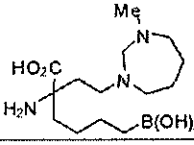
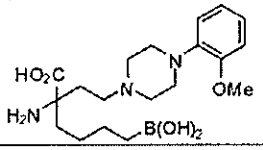
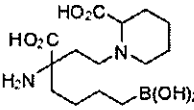
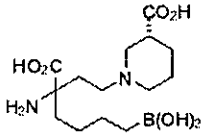
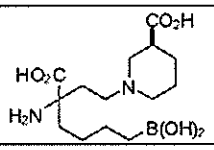
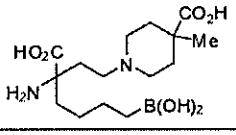
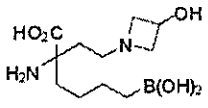
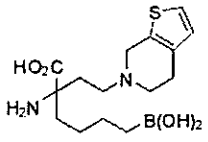
[Claim 3]

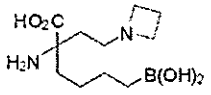
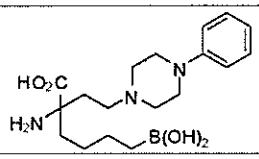
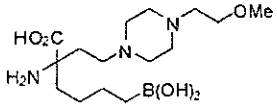
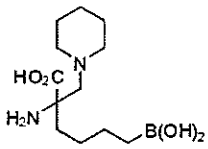
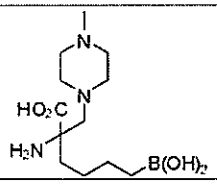
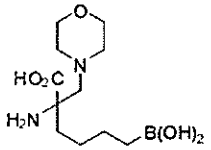
The compound according to claim 2, wherein

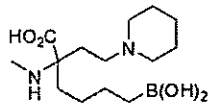
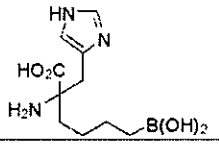
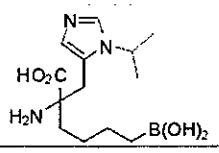
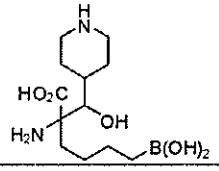
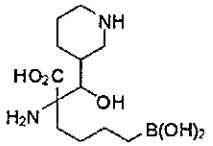
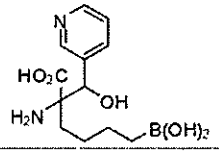
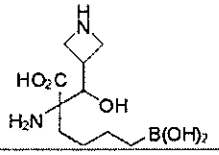
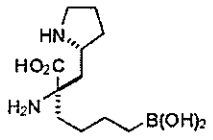
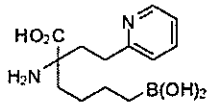
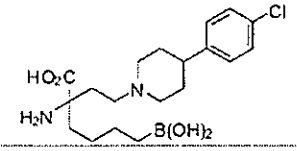
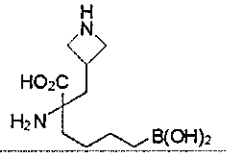
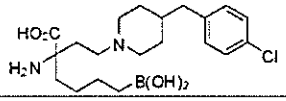
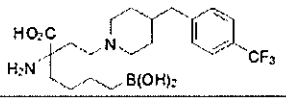
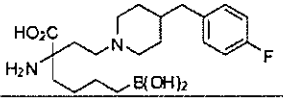
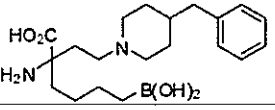
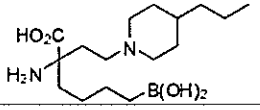
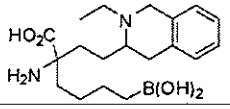
(A) R2 is selected from the group consisting of straight or branched (C1-C6)alkyl, straight or branched (C2-C6)alkenyl, straight or branched (C2-C6)alkynyl, (C3-C14)aryl, (C3-C14)-cycloalkyl, (C3-C14)aryl(C1-C6)alkylene-, (C3-C14)heteroaryl-(C1-C6)alkylene-, (C3-C14)heteroaryl, (C3-C14)heterocycloalkyl, (C3-C14)heterocycloalkyl-(C1-C6)alkylene-, (C3-C14)heteroaryl-(C3-C6)heterocycloalkylene-, (C3-C14)aryl-(C3-C14)heterocycloalkylene-, (C3-C14)-aryl-(C1-C6)alkylene-(C3-C14)heterocycloalkylene-, (C3-C14)heteroaryl-(C1-C6)alkylene-(C3-C14)heterocycloalkylene-, (C3-C14)heterocycloalkyl-(C1-C6)alkylene-(C3-C14)heterocycloalkylene-, and-(CH2)m-(X)u-(CH2)n-(Y)v-Rf; and

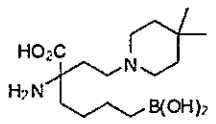
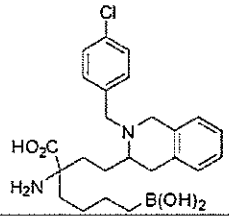
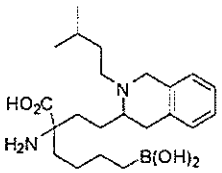
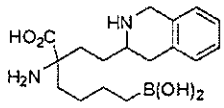
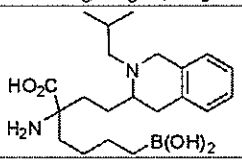
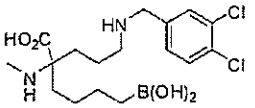
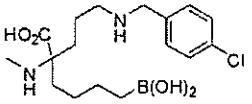
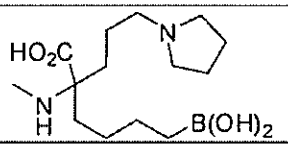
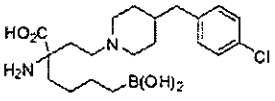
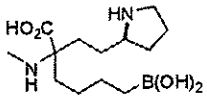
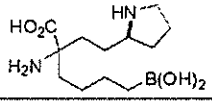
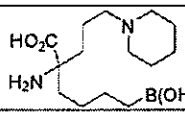
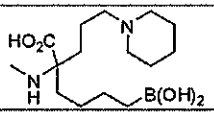
each of R3and R4 is hydrogen
OR
(B) R2 is (C3-C14)heterocycloalkyl-(C1-C2)alkylene-and
each of R3, and R4 and R5 is hydrogen.
[Claim 4]
The compound according to claim 3, wherein
R2 is selected from the group consisting of (C1-C6)alkyl, (C3-C14)aryl, (C3-C14)heteroaryl, (C3-C14)heterocycloalkyl, (C3-C14)heterocycloalkyl-(C1-C6)alkylene-, (C3-C14)heteroaryl-(C1-C6)alkylene-, (C3-C14)aryl-(C1-C6)alkylene-and-(CH2)n-(X)u-(CH2)m-(Y)v-Rf, and
R5 is selected from the group consisting of straight or branched (C1-C6) alkyl or (C1-C6)alkyl-C(O)-.
[Claim 5]
The compound according to claim 4, wherein R2 is (C3-C6)heterocycloalkyl-(C1-C2)alkylene optionally substituted with one or more members selected from the group consisting of-(C1-C6)alkoxy,-(C1-C6)alkyl, and-OH.
[Claim 6]
The compound according to claim 4 wherein R2 is (C3-C14)heteroaryl-(C1-C6)alkylene-.
[Claim 7]
The compound according to claim 1 that is selected from compounds of the following table:

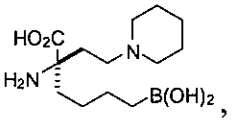
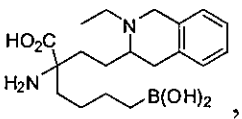
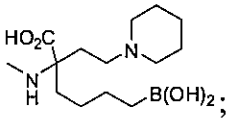
		
		
		
		
		
		
		
		
		
		

or a pharmaceutically acceptable salt or stereoisomer thereof.

[Claim 8]

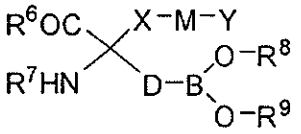
A compound according to claim 7 that is selected from the group consisting of:

 ,  , and  ;

or a pharmaceutically acceptable salt or stereoisomer thereof.

[Claim 9]

A compound according to Formula II,

 **II**

wherein

R6 is selected from the group consisting of ORa, and NRbRc;

Ra is selected from the group consisting of hydrogen, straight or branched chain (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C14)aryl, (C3-C14)heterocycloalkyl-(C1-C6)alkylene-, (C3-C14)heteroaryl-(C1-C6)alkylene-, and (C3-C14)aryl(C1-C6)alkylene-;

Rb and Rc are each independently selected from the group consisting of H,-OH, straight or branched (C1-C6)alkyl,-S(O)2-(C1-C6)alkyl, (C3-C14)aryl-S(O)2-, (C3-C14)heterocycloalkyl-(C1-C6)alkylene-, and (C3-C14)heteroaryl-(C1-C6)alkylene-;

R7 is selected from the group consisting of H, straight or branched (C1-C6) alkyl, (C3-C14)aryl(C1-C6)alkylene-, (C3-C14)heteroaryl-(C1-C6)alkylene-, (C3-C14)heterocycloalkyl-(C1-C6)alkylene-and (C1-C6)alkyl-C(O)-;
X is selected from the group consisting of (C3-C14)-cycloalkylene and (C3-C14) heterocycloalkylene,
Y is selected from the group consisting of H, (C1-C14)alkyl,-NR'R", hydroxy(C1-C6)alkylene, (C3-C14)-cycloalkyl, (C3-C14)-cycloalkyl-(C1-C6)alkylene, (C3-C14)aryl, (C3-C14)aryl-(C1-C6)alkylene, (C3-C14)heterocycloalkyl, (C3-C14)heterocycloalkyl-(C1-C6)alkylene, (C3-C14)heteroaryl, (C3-C14)heteroaryl-(C1-C6)alkylene, (C3-C14)heteroaryl-(C3-C6)heterocycloalkylene-, (C3-C14)aryl-(C3-C14)heterocycloalkylene-, (C3-C14)-aryl-(C1-C6)alkylene-(C3-C14)heterocycloalkylene-, (C3-C14)heteroaryl-(C1-C6)alkylene-(C3-C14)heterocycloalkylene-, and (C3-C14)heterocycloalkyl-(C1-C6)alkylene-(C3-C14) heterocycloalkylene-;
M is selected from the group consisting of a bond,-(C1-C6)alkylene-,-O-,-C(O)-,-C(S)-,-C(O)NH-,-C(S)NH-,-S-,-S(O)-,-S(O)2-,-NR'-, and-C=NR11-;
R8 and R9 are independently selected from hydrogen, straight or branched (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C14)aryl, and C(O)-R',
or R8 and R9 together with the boron atom to which they are bound form a 5-or 6-membered ring that is fully saturated, or partially saturated and that optionally contains 1-3 additional heteroatom ring members selected from O, S, and N,
wherein the ring is optionally fused with a cycloalkyl, heterocyclic or aromatic ring;
D is CH2CH2CH2CH2,
wherein one or more-CH2-groups in D are optionally and independently replaced with a moiety Q that is selected from O, NR', S, SO, SO2, and CR'R"; or
wherein any two adjacent –CH2-groups optionally are replaced by two members of a (C3-C14)-cycloalkylenyl group; and
provided that D does not contain two adjacent Q moieties selected from O, NR', S, SO, and SO2;
R' and R" are independently selected from the group consisting of H, (C1-C8)alkyl,-C(O)-(C1-C8)alkylene, optionally substituted (C3-C6)aryl, optionally substituted (C3-C14)aryl(C1-C6)alkylene-, optionally substituted (C1-C6)aminoalkyl, optionally substituted (C3-C6)cycloalkyl, optionally substituted (C3-C14)heterocycloalkyl, optionally substituted (C3-C14)heteroaryl; and
wherein any alkyl, alkylene, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more members selected from the group consisting of halogen, oxo,-COOH,-CN,-NO2,-OH,-NRdRe,-NRgS(O)2Rh, (C1-C6)alkyl, (C1-C6)haloalkyl, (C1-C6)haloalkoxy, (C1-C6)alkoxy, (C3-C14)aryl, (C3-C14)heteroaryl, (C3-C14)heterocycloalkyl, (C3-C14)heteroaryl-(C1-C6)alkylene and (C3-C14)aryloxy;
wherein Rd, Re, Rg, and Rh are each independently selected from the group consisting of H, straight or branched (C1-C6)alkyl, optionally substituted (C3-C14)aryl(C1-C6)alkylene-, optionally substituted (C3-C14)aryl, (C1-C6)hydroxyalkyl, (C1-C6)aminoalkyl,

H2N(C1-C6)alkylene-, optionally substituted (C3-C6)cycloalkyl, optionally substituted (C3-C14)heterocycloalkyl, optionally substituted (C3-C14)heteroaryl, optionally substituted (C3-C14)aryl-(C1-C6)alkylene-, and NR'R"C(O)-,
or a pharmaceutically acceptable salt, stereoisomer, or tautomer.

[Claim 10]

The compound according to claim 9, wherein D is butylene; R6 is-OH; and each of R7, R8 and R9 is hydrogen.

[Claim 11]

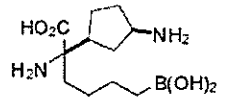
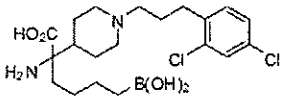
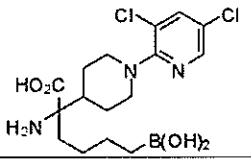
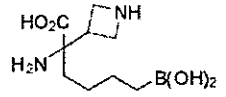
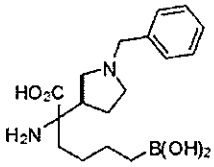
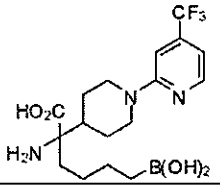
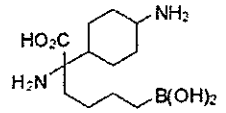
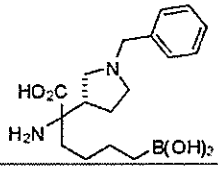
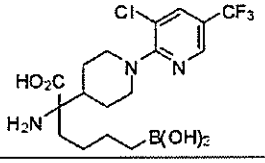
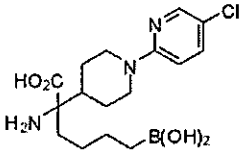
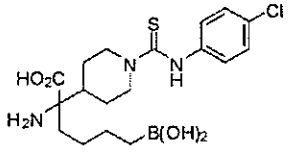
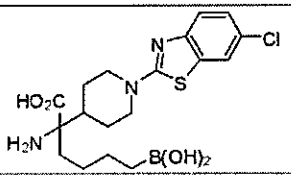
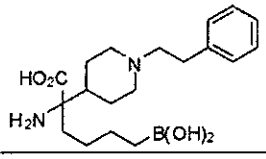
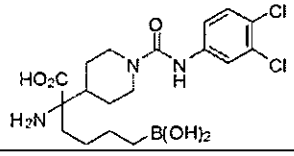
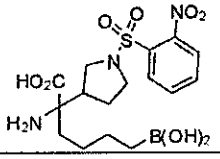
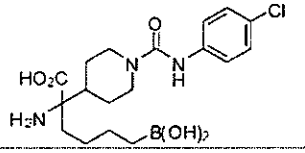
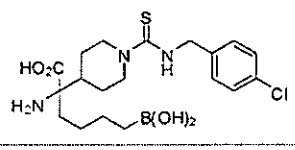
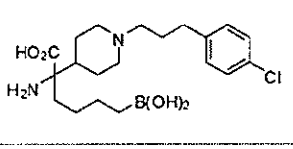
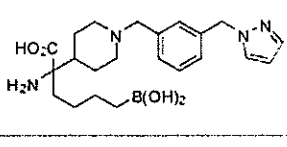
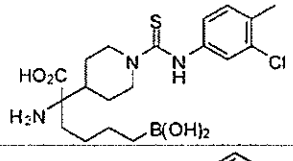
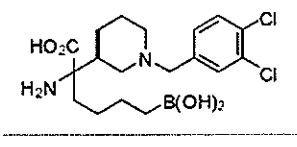
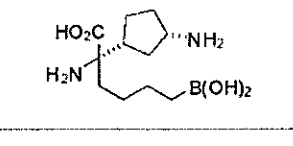
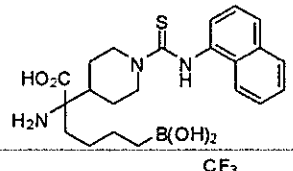
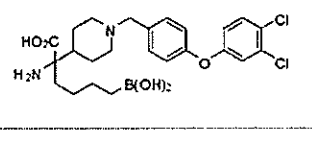
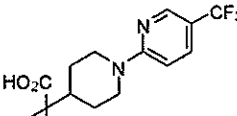
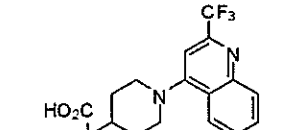
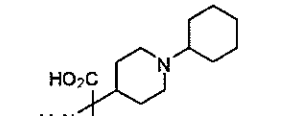
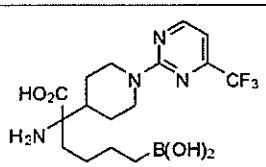
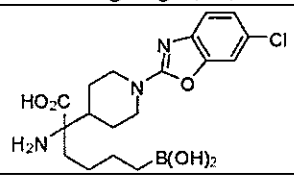
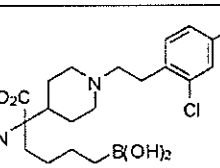
The compound according to claim 9, wherein X is a (C3-C14)-cycloalkylene, and M is selected from the group consisting of
bond,-(C1-C6)alkylene-,-O-,-C(O)-,-C(S)-,-C(O)NH-,-C(S)NH-,-S-,-S(O)-,-S(O)2-,-NR'-, and-C=NR11-and Y is-NR'R".

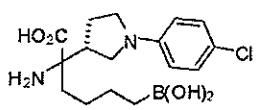
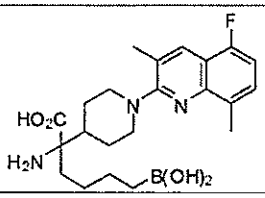
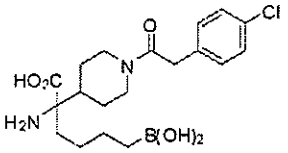
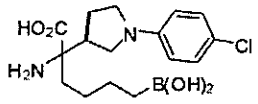
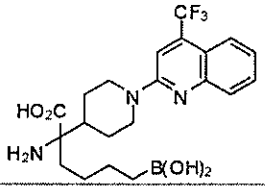
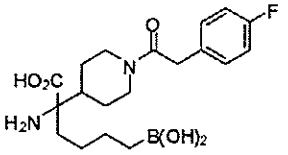
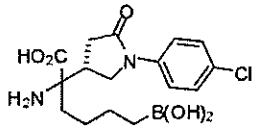
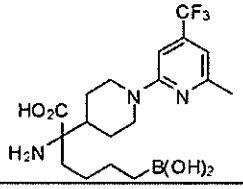
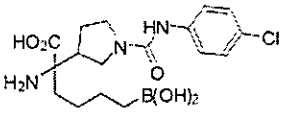
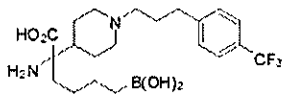
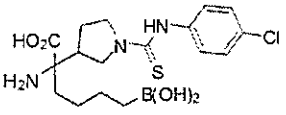
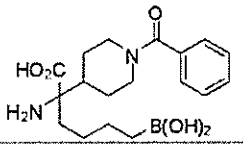
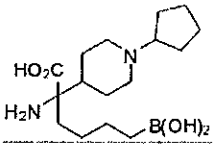
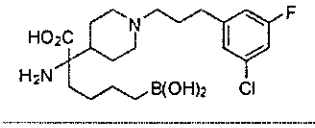
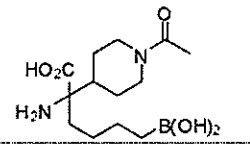
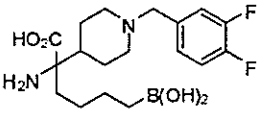
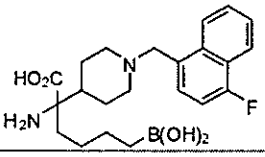
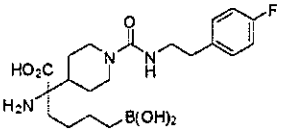
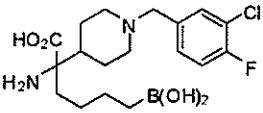
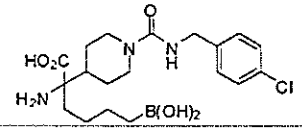
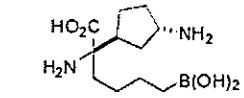
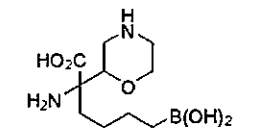
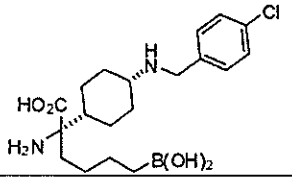
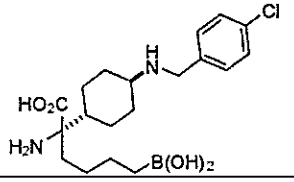
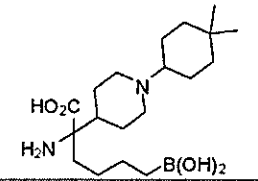
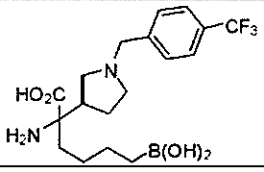
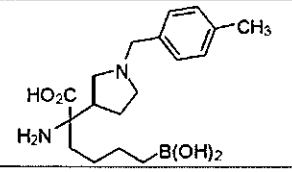
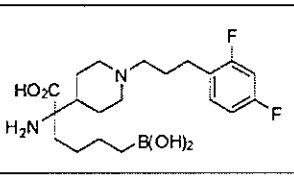
[Claim 12]

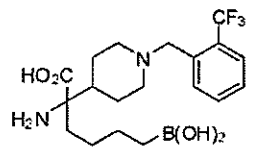
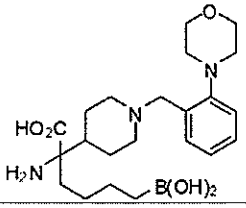
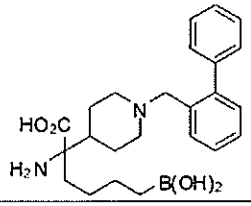
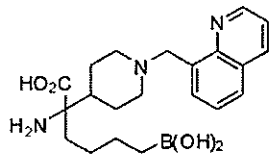
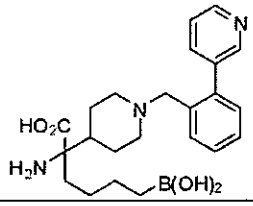
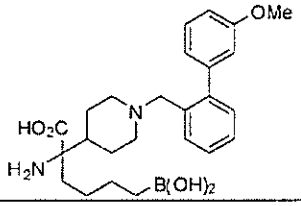
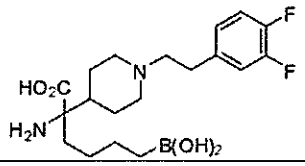
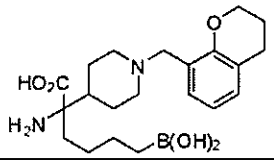
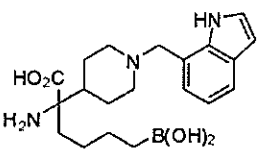
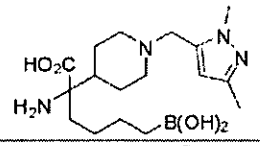
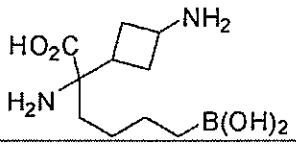
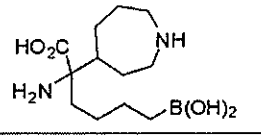
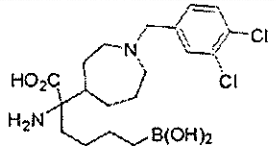
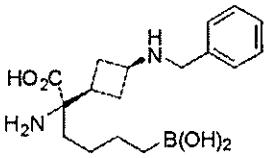
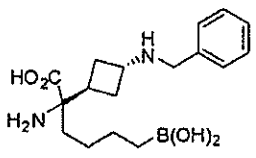
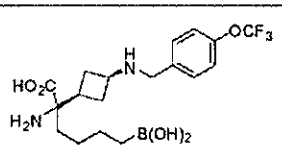
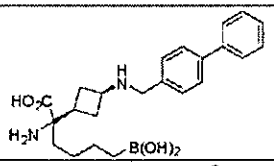
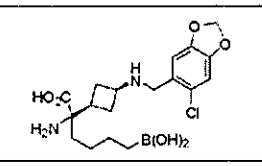
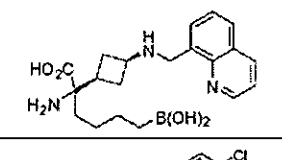
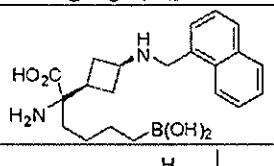
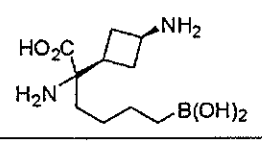
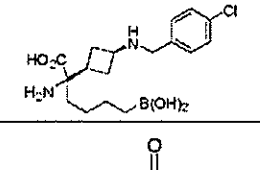
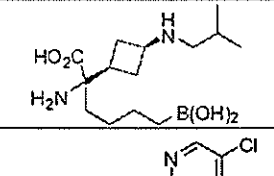
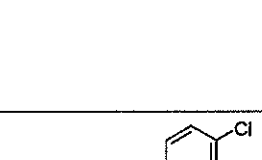
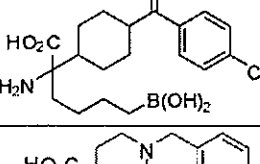
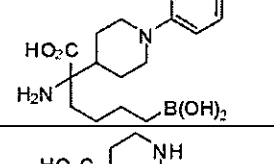
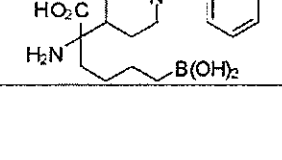
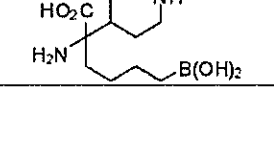
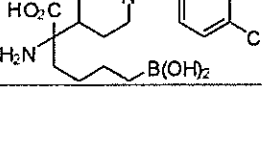
The compound according to claim 9, wherein
X is (C3-C14)heterocycloalkylene;
M is selected from the group consisting of
bond,-(C1-C6)alkylene-,-O-,-C(O)-,-C(S)-,-C(O)NH-,-C(S)NH-,-S-,-S(O)-,-S(O)2-,-NR'-, and-C=NR11-; and
Y is selected from the group consisting of (C3-C14)-cycloalkyl, (C3-C14)aryl, (C3-C14)aryl-(C1-C6)alkylene, (C3-C14)heteroaryl and (C3-C14)heteroaryl-(C1-C6)alkylene.

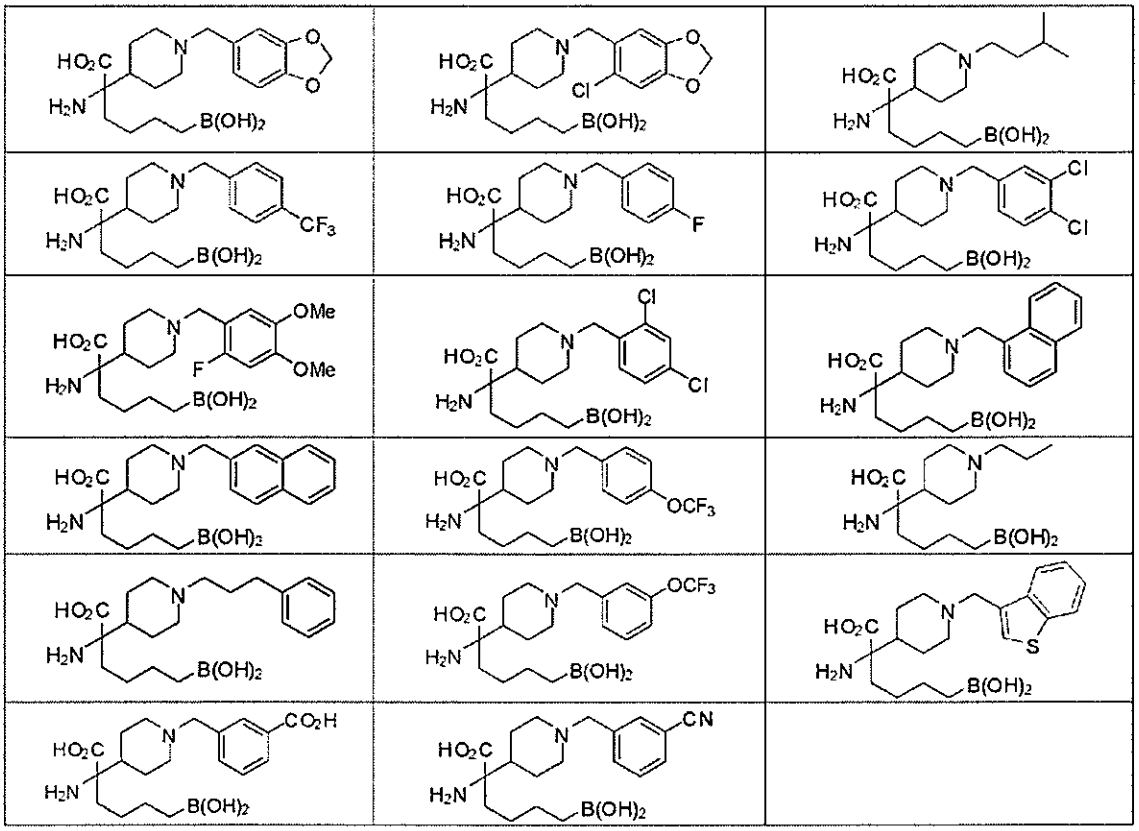
[Claim 13]

The compound according to claim 9 that is selected from compounds of the following table:

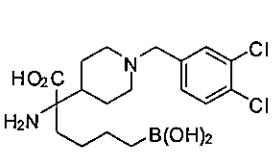
		
		
		
		
		
		
		
		
		
		
		



or a pharmaceutically acceptable salt or stereoisomer thereof.

[Claim 14]

A compound according to claim 13 that is selected from the group consisting of: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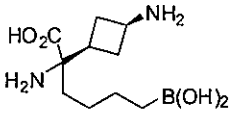
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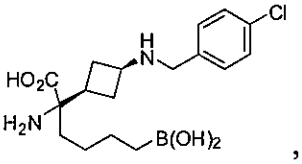
,

or a pharmaceutically acceptable salt or stereoisomer thereof.

[Claim 15]

A pharmaceutical composition comprising at least one compound according to any one of claims 1-14, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof; and a pharmaceutically acceptable carrier.

[Claim 16]

Use of a compound according to any one of claims 1-14, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof in the manufacture of a medicament for inhibiting arginase I, arginase II, or a combination thereof in a cell.

[Claim 17]

Use of a compound according to any one of claims 1-14, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof in the manufacture of a medicament for the treatment or prevention of a disease or condition associated with expression or activity of arginase I, arginase II, or a combination thereof in a subject.

[Claim 18]

The use according to claim 17, wherein the disease or condition is selected from the

group consisting of cardiovascular disorders, gastrointestinal disorders, autoimmune disorders, immune disorders, infections, pulmonary disorders, and hemolytic disorders.

[Claim 19]

The use according to claim 18, wherein the disease or condition is a cardiovascular disorder selected from the group consisting of systemic hypertension, pulmonary arterial hypertension (PAH), pulmonary arterial hypertension in high altitude, ischemia reperfusion (IR) injury, myocardial infarction, atherosclerosis, Peyronie's Disease, erectile dysfunction, reduced hepatic blood flow disorders, and cerebral vasospasm.

[Claim 20]

The use according to claim 18, wherein the disease or condition is a pulmonary disorder.

[Claim 21]

The use according to claim 19, wherein the disease or condition is pulmonary arterial hypertension.

[Claim 22]

The use according to claim 19, wherein the disease or condition is erectile dysfunction.

[Claim 23]

The use according to claim 20, wherein the disease or condition is selected from the group consisting of chemically-induced lung fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma.

[Claim 24]

The use according to claim 18, wherein the disease or condition is an autoimmune disorder selected from the group consisting of encephalomyelitis, multiple sclerosis, anti-phospholipid syndrome 1, autoimmune hemolytic anaemia, chronic inflammatory demyelinating polyradiculoneuropathy, dermatitis herpetiformis, dermatomyositis, myasthenia gravis, pemphigus, rheumatoid arthritis, stiff-person syndrome, type 1 diabetes, ankylosing spondylitis, paroxysmal nocturnal hemoglobinuria (PNH), paroxysmal cold hemoglobinuria, severe idiopathic autoimmune hemolytic anemia, and Goodpasture's syndrome.

[Claim 25]

The use according to claim 18, wherein the disease or condition is an immune disorder selected from the group consisting of myeloid-derived suppressor cell (MDSC) mediated T-cell dysfunction, human immunodeficiency virus (HIV), autoimmune encephalomyelitis, and ABO mismatch transfusion reaction.

[Claim 26]

The use according to claim 18, wherein the disease or condition is a hemolytic disorder selected from the group consisting of sickle-cell disease, thalassemias, hereditary spherocytosis, stomatocytosis, microangiopathic hemolytic anemias, pyruvate kinase deficiency, infection-induced anemia, cardiopulmonary bypass and mechanical heart valve-induced anemia, and chemical induced anemia.

[Claim 27]

The use according to claim 18, wherein the disease or condition is a gastrointestinal disorder selected from the group consisting of gastrointestinal motility disorders, gastric cancers, inflammatory bowel disease, Crohn's disease, ulcerative colitis, and gastric ulcers.

[Claim 28]

The use according to claim 18, wherein the disease or condition is selected from the group consisting of renal disease, inflammation, psoriasis, leishmaniasis, neurodegenerative diseases, wound healing, hepatitis B virus (HBV), H. pylori infections, fibrotic diseases, arthritis, candidiasis, periodontal disease, keloids, adenotonsilar disease, African sleeping sickness, and Chagas' disease.

[Claim 29]

The use according to claim 28, wherein the disease or condition is selected from the group consisting of infected and uninfected wound healing.

[Claim 30]

The use according to claim 17, wherein the disease or condition is cancer.

[Claim 31]

The use according to claim 30, wherein the cancer is renal cell carcinoma, prostate cancer, colorectal cancer, breast cancer, skin cancer, lung cancer, ovarian cancer, or gastric cancer.