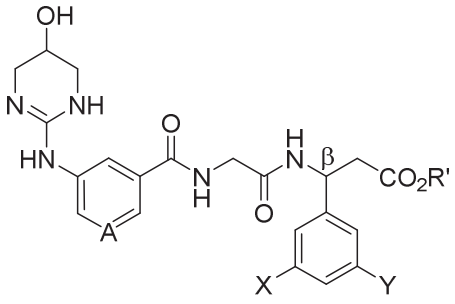
SUMMARY

The present disclosure provides novel integrin receptor antagonists, pharmaceutical compositions thereof, methods of manufacture thereof, and methods for their use.

In some aspects, the present disclosure provides compounds of the formula:



(I),

wherein:

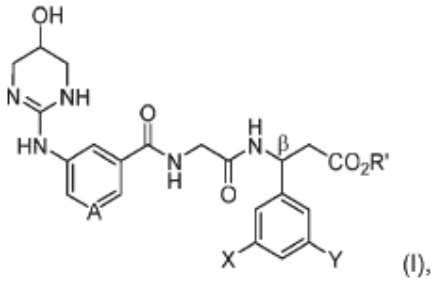
A is C–H, C–OH, or N;

R′ is hydrogen, $alkyl_{(C\leq 8)}$, substituted $alkyl_{(C\leq 8)}$, or a substituent convertible *in vivo* to hydrogen; and

X and Y are each independently cyano, halo, $fluoroalkoxy_{(C1-2)}$, $alkyl_{(C1-2)}$, or $fluoroalkyl_{(C1-2)}$, with the proviso that X and Y are not both cyano or $alkyl_{(C1-2)}$;

or a pharmaceutically acceptable salt or tautomer of the above formula.

In one aspect, the present disclosure provides compound of the formula:



(I),

wherein:

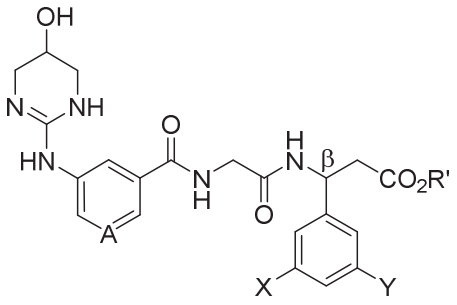
A is C-OH, or N;

R' is hydrogen; and

X and Y are each independently halo, $-OCF_3$, $-CH_3$, $-CF_3$ or $-CHF_2$, with the proviso that X and Y are not both $-CH_3$;

or a pharmaceutically acceptable salt or tautomer of the above formula.

In some embodiments, the compound is further defined as:



(I),

wherein:

A is C–OH or N;

R′ is hydrogen, alkyl$_{(C\leq 8)}$, substituted alkyl$_{(C\leq 8)}$, or a substituent convertible *in vivo* to hydrogen; and

b) an excipient.

In still yet another aspect, the present disclosure provides use of a compound described herein in the manufacture of a medicament for the treatment and/or prevention of a disease or a disorder in a patient in need thereof. In yet another aspect, the present disclosure provides a compound as disclosed herein for use in therapy. In some embodiments, the present disclosure provides methods of treating and/or preventing a disease or a disorder in a patient in need thereof, comprising administering to the patient a compound or composition described herein in an amount sufficient to treat and/or prevent the disease or disorder.

In some embodiments, the disease or disorder is associated with angiogenesis. In other embodiments, the disease or disorder is associated with fibrosis. In some embodiments, the disease or disorder is associated with fibrosis and/or angiogenesis.

In some embodiments, the disease or disorder is pulmonary, liver, renal, cardiac, and pancreatic fibrosis, scleroderma, scarring, retinopathy of prematurity, familial exudative vitreoretinopathy, proliferative vitreoretinopathies, macular degeneration, diabetic retinopathy, cancer, osteoporosis, autoimmune diseases, humoral hypercalcemia of malignancy, Paget's disease, periodontal disease, psoriasis, arthritis, restenosis, and infection. In some embodiments, the disease or disorder is pulmonary fibrosis. In other embodiments, the disease or disorder is liver fibrosis. In other embodiments, the disease or disorder is cardiac fibrosis. In other embodiments, the disease or disorder is renal fibrosis. In other embodiments, the disease or disorder is pancreatic fibrosis.

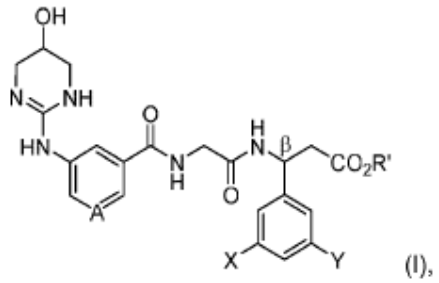
In other embodiments, the disease or disorder is scleroderma. In other embodiments, the disease or disorder is scarring. In some embodiments, the scarring is dermal scarring. In other embodiments, the scarring is retinal scarring. In other embodiments, the scarring is corneal scarring.

In other embodiments, the disease or disorder is retinopathy of prematurity. In other embodiments, the disease or disorder is familial exudative vitreoretinopathy. In other embodiments, the disease or disorder is proliferative vitreoretinopathies. In other embodiments, the disease or disorder is macular degeneration. In other embodiments, the disease or disorder is diabetic retinopathy.

In other embodiments, the disease or disorder is cancer. In some embodiments, the cancer includes solid tumor growth or neoplasia. In some embodiments, the cancer includes tumor metathesis. In some embodiments, the cancer is of the bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder, genitalia, genitourinary tract, head, kidney, larynx, liver, lung, muscle tissue, neck, oral or nasal mucosa, ovary, pancreas, prostate, skin, spleen, small intestine, large intestine, stomach,

Clams

1. A compound of the formula:



(I),

wherein:

A is C-OH, or N;

R' is hydrogen; and

X and Y are each independently halo, $-OCF_3$, $-CH_3$, $-CF_3$ or $-CHF_2$, with the proviso that X and Y are not both $-CH_3$;

or a pharmaceutically acceptable salt or tautomer of the above formula.

2. The compound of claim 1, wherein A is N.

3. The compound of claim 1, wherein A is C-OH.

4. The compound according to any one of claims 1-3, wherein X is –Cl or –Br.

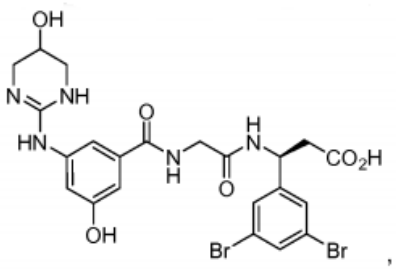
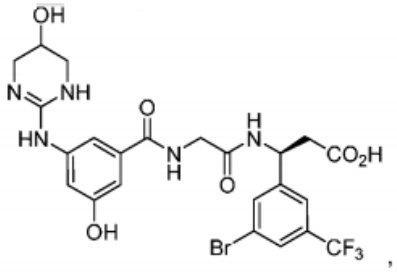
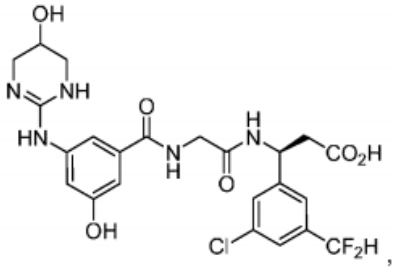
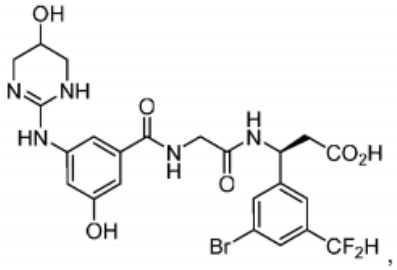
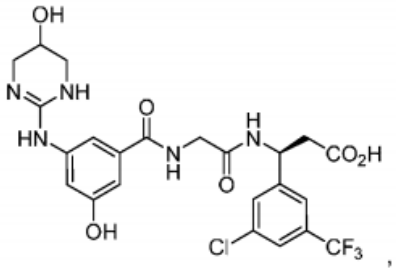
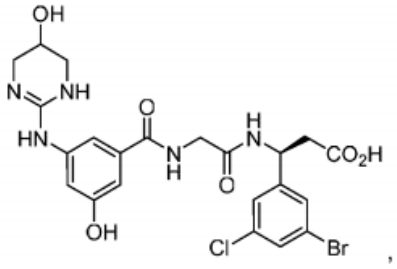
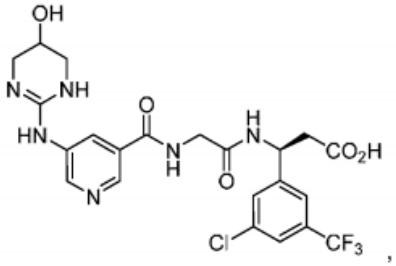
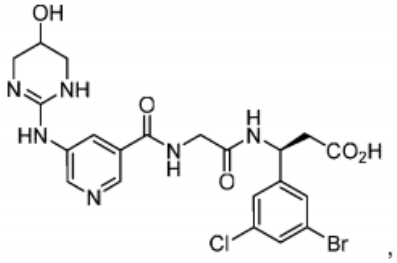
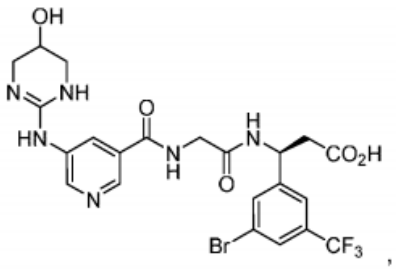
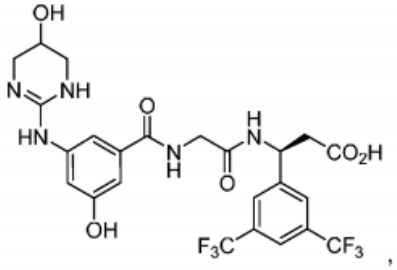
5. The compound according to any one of claims 1-4, wherein Y is $–OCF_3$.

6. The compound according to any one of claims 1-4, wherein Y is $-CHF_2$ or $-CF_3$.

7. The compound according to any one of claims 1-4, wherein Y is $-CH_3$.

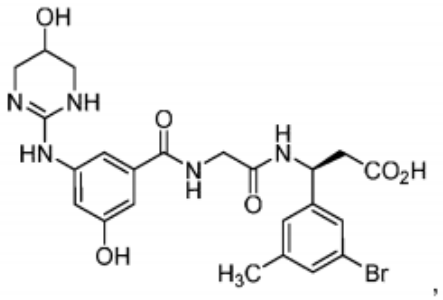
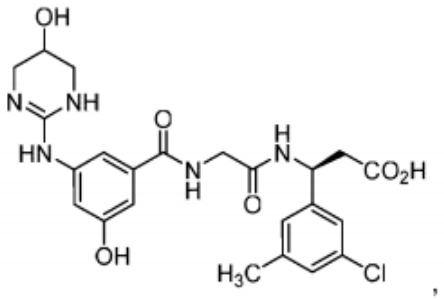
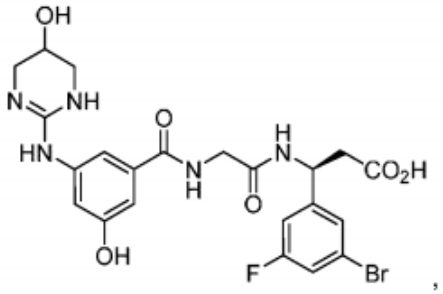
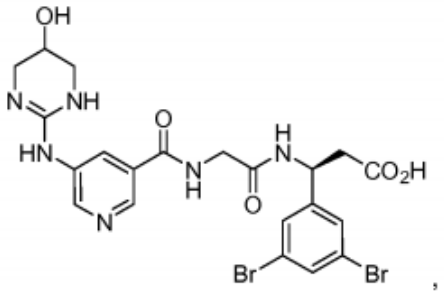
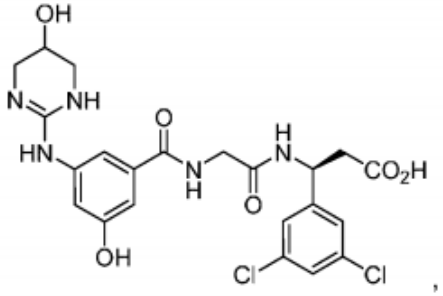
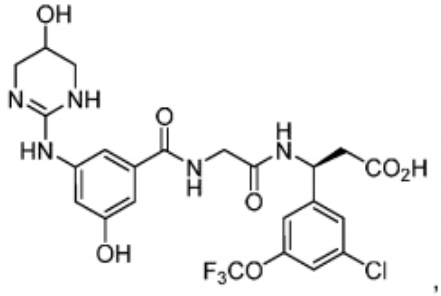
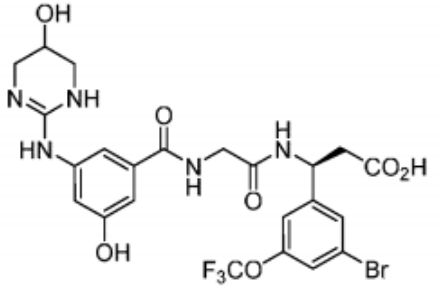
8. The compound according to any one of claims 1-7, wherein the carbon atom labeled β is in the *S* configuration.

9. The compound of claim 1, further defined as:


,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

, or


or a pharmaceutically acceptable salt or tautomer of any of the above formulas.

10. A pharmaceutical composition comprising:

a) the compound according to any one of claims 1-9; and

b) an excipient.

11. Use of a compound according to any one of claims 1-9 in the manufacture of a medicament for the treatment and/or prevention of a disease or a disorder in a patient in need thereof.

12. The use according to claim 11, wherein the disease or disorder is associated with fibrosis.

13. The use according to claim 11, wherein the disease or disorder is selected from the group consisting of pulmonary, liver, renal, cardiac, and pancreatic fibrosis, scleroderma, scarring, retinopathy of prematurity, familial exudative vitreoretinopathy, proliferative vitreoretinopathies, macular degeneration, diabetic retinopathy, cancer, osteoporosis, autoimmune diseases, humoral hypercalcemia of malignancy, Paget's disease, periodontal disease, psoriasis, arthritis, restenosis, and infection.

14. The use according to claim 11, wherein the disease or disorder is pulmonary fibrosis.

15. The use according to claim 11, wherein the disease or disorder is liver fibrosis.

16. A compound according to any one of claims 1-9 for use in therapy.