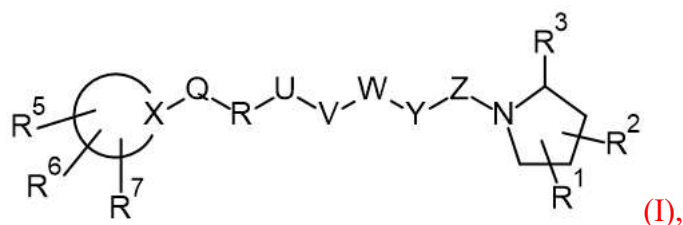


smaller primary tumors and, thus the possibility of earlier diagnosis, (ii) the detection of smaller metastasis and, thus a better assessment of tumor stage, (iii) precise intra-operative guidance facilitating complete surgical removal of tumor tissue, (iv) better differentiation between inflammation and tumor tissue, (v) more precise staging of patients with tumors, (vi) better follow up of tumor lesions after antitumor therapy, (vii) the opportunity to use the molecules as theranostic agents for diagnosis and therapy. Furthermore, the molecules can be used for the diagnosis and treatment of non-malignant diseases such as chronic inflammation, atherosclerosis, fibrosis, tissue remodeling and keloid disorders.

Summary

In a first aspect, the present disclosure provides a compound of Formula (I)



wherein

Q, R, and U are absent;

V, W, Y, and Z are individually present or absent under the proviso that at least three of V, W, Y, and Z are present;

V, W, Y, and Z are independently selected from the group consisting of O, CH₂, NR⁴, C=O, C=S, C=NR⁴, HCR⁴ and R⁴CR⁴, with the proviso that two Os are not directly adjacent to each other;

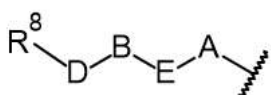
R¹ and R² are independently selected from the group consisting of -H, -OH, halo, C₁₋₆-alkyl, -O-C₁₋₆-alkyl, and S-C₁₋₆-alkyl;

R³ is selected from the group consisting of -H, -CN, -B(OH)₂, -C(O)-alkyl, -C(O)-aryl, -C=C-C(O)-aryl, -C=C-S(O)₂-aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R⁴ is selected from the group consisting of -H, -C₁₋₆-alkyl, -O-C₁₋₆-alkyl, -S-C₁₋₆-alkyl, alkenyl, heteroalkenyl, cycloalkenyl, cycloheteroalkenyl, alkynyl, aryl, and -C₁₋₆-aralkyl, each of said -C₁₋₆-alkyl being optionally substituted with from 1 to 3 substituents selected from -OH, oxo, and halo;

R⁵ is selected from the group consisting of -H, halo and C₁₋₆-alkyl;

R⁶, and R⁷ are independently selected from the group consisting of -H,



and , under the proviso that R^6 and R^7 are not at the same time H,

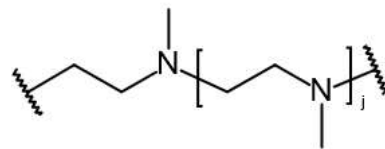
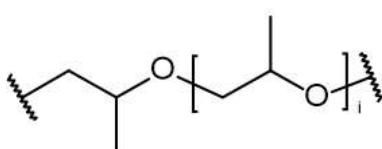
wherein D is present or absent,

wherein A, E, and B are present,

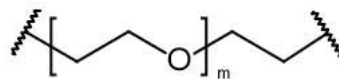
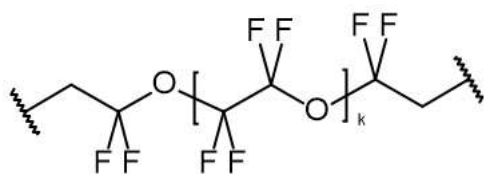
wherein when D is present: D is a linker;

A is selected from the group consisting of NR^4 , O, S, and CH_2 ;

E is selected from the group consisting of



C_{1-6} -alkyl,



and

;

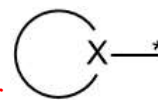
wherein i is 1, 2, or 3;

wherein j is 1, 2, or 3;

wherein k is 1, 2, or 3;

wherein m is 1, 2, or 3;

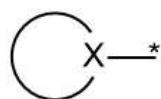
A and E together form a group selected from: a cycloalkyl, heterocycloalkyl, aryl and heteroaryl, preferably heterocycloalkyl, wherein A and E can be mono-, bi- and multicyclic, preferably monocyclic; each A and E being optionally substituted with 1 to 4 substituents selected from -H, $-C_{1-6}$ -alkyl, $-O-C_{1-6}$ -alkyl, $-S-C_{1-6}$ -alkyl, alkenyl, heteroalkenyl, cycloalkenyl, cycloheteroalkenyl, alkynyl, aryl, and $-C_{1-6}$ -aralkyl, each of said $-C_{1-6}$ -alkyl being optionally substituted with from 1 to 3 substituents selected



from -OH, oxo, halo; and optionally connected to A, B, D, E or

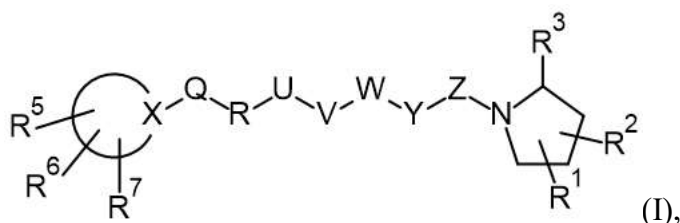
B is a 5- to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle optionally further comprising 1 or 2 heteroatoms selected from O, N, and S, wherein the N-containing heterocycle is substituted with 1 to 3 substituents selected the group consisting of C_{1-6} -alkyl, aryl, and C_{1-6} -aralkyl; and;

R^8 is selected from the group consisting of a radioactive moiety, a chelating agent, a fluorescent dye, a contrast agent and combinations thereof;



is a 1-naphthyl moiety or a 5 to 10- membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, wherein there are 2 ring atoms between the N atom and X; said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S; and X is a C atom; or a pharmaceutically acceptable tautomer, racemate, hydrate, solvate, or salt thereof.

In a ~~first aspect~~ one example, the present disclosure provides a compound of Formula (I)



wherein

Q, R, U, V, W, Y, Z are individually present or absent under the proviso that at least three of Q, R, U, V, W, Y, Z are present;

Q, R, U, V, W, Y, Z are independently selected from the group consisting of O, CH₂, NR⁴, C=O, C=S, C=NR⁴, HCR⁴ and R⁴CR⁴, with the proviso that two Os are not directly adjacent to each other;

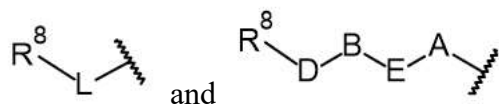
R¹ and R² are independently selected from the group consisting of -H, -OH, halo, C₁₋₆-alkyl, -O-C₁₋₆-alkyl, S-C₁₋₆-alkyl;

R³ is selected from the group consisting of -H, -CN, -B(OH)₂, -C(O)-alkyl, -C(O)-aryl, -C=C-C(O)-aryl, -C=C-S(O)₂-aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R⁴ is selected from the group consisting of -H, -C₁₋₆-alkyl, -O-C₁₋₆-alkyl, -S-C₁₋₆-alkyl, aryl, and -C₁₋₆-aryl, each of said -C₁₋₆-alkyl being optionally substituted with from 1 to 3 substituents selected from -OH, oxo, halo and optionally connected to Q, R, U, V, W, Y or Z;

R⁵ is selected from the group consisting of -H, halo and C₁₋₆-alkyl;

R⁶, and R⁷ are independently selected from the group consisting of -H,



, under the proviso that R⁶ and R⁷ are not at the same time H,

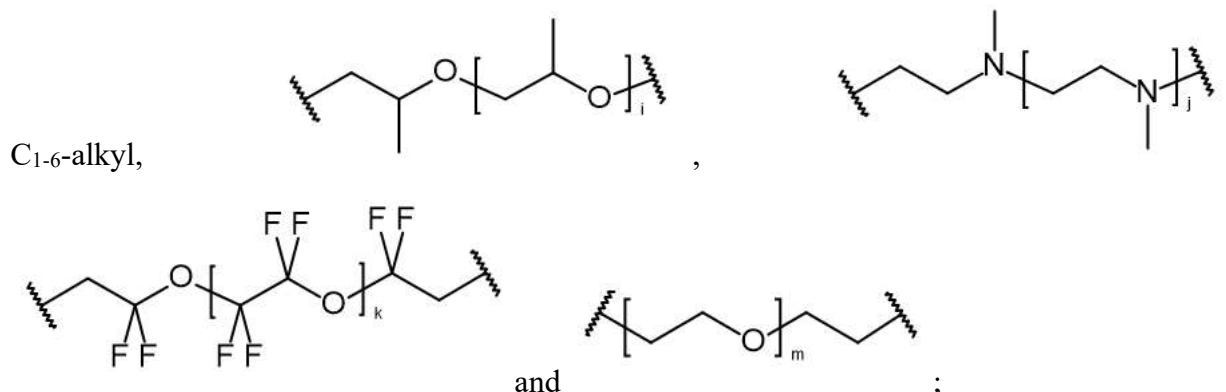
wherein L is a linker,

wherein D, A, E, and B are individually present or absent, preferably wherein at least A, E, and B are present, wherein when present:

D is a linker;

A is selected from the group consisting of NR^4 , O, S, and CH_2 ;

E is selected from the group consisting of



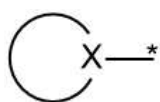
wherein i is 1, 2, or 3;

wherein j is 1, 2, or 3;

wherein k is 1, 2, or 3;

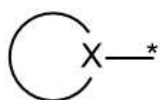
wherein m is 1, 2, or 3;

A and E together form a group selected from a cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein A and E can be mono-, bi- and multicyclic, preferably monocyclic. Each A and E being optionally substituted by 1 to 4 residues from the group consisting of -H, - C_{1-6} -alkyl, -O- C_{1-6} -alkyl, -S- C_{1-6} -alkyl, alkenyl, heteroalkenyl, cycloalkenyl, cycloheteroalkenyl, alkynyl, aryl, and - C_{1-6} -aralkyl, each of said - C_{1-6} -alkyl being optionally substituted with from 1 to 3 substituents selected from -OH, oxo, halo; and optionally connected to A, B, D, E or



B is selected from the group consisting of S, NR^4 , NR^4 -O, NR^4 - C_{1-6} -alkyl, NR^4 - C_{1-6} -alkyl- NR^4 , and a 5- to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, preferably further comprising 1 or 2 heteroatoms selected from O, N, and S, preferably further comprising 1 or 2 nitrogen atoms, preferably wherein NR^4 - C_{1-6} -alkyl- NR^4 and the N-containing heterocycle is substituted with 1 to 3 substituents selected from the group consisting of C_{1-6} -alkyl, aryl, C_{1-6} -aralkyl; and;

R^8 is selected from the group consisting of radioactive moiety, chelating agent, fluorescent dye, a contrast agent and combinations thereof;



is a 1-naphtyl moiety or a 5 to 10- membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, wherein there are 2 ring atoms between the N atom

and X; said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S; and X is a C atom;

or a pharmaceutically acceptable tautomer, racemate, hydrate, solvate, or salt thereof.

In another aspect, the present disclosure provides a pharmaceutical composition comprising at least one compound as described herein; and a pharmaceutically acceptable carrier.

In ~~a second aspect~~another example, the present disclosure relates to a pharmaceutical composition comprising or consisting of at least one compound of the first aspect, and, optionally, a pharmaceutically acceptable carrier and/or excipient.

In a third aspect, the present disclosure relates to use of the compound as described herein or the pharmaceutical composition of as described herein in the manufacture of a medicament for the diagnosis or treatment of a disease characterized by overexpression of fibroblast activation protein (FAP) in an animal or a human subject, preferably wherein the disease characterized by overexpression of fibroblast activation protein (FAP) is selected from the group consisting of cancer, chronic inflammation, atherosclerosis, fibrosis, tissue remodeling and keloid disorder, preferably wherein the cancer is selected from the group consisting of breast cancer, pancreatic cancer, small intestine cancer, colon cancer, rectal cancer, lung cancer, head and neck cancer, ovarian cancer, hepatocellular carcinoma, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus carcinoma, desmoid tumors, glioma, astrocytoma, cervix carcinoma and prostate cancer. Also disclosed herein is the compound of the first aspect or the pharmaceutical composition of the second aspect for use in the diagnosis or treatment of a disease characterized by overexpression of fibroblast activation protein (FAP) in an animal or a human subject.

In a fourth aspect, the present disclosure relates to a kit comprising or consisting of the compound of the first aspect or the pharmaceutical composition of the second aspect and instructions for the diagnosis or treatment of a disease.

List of Figures

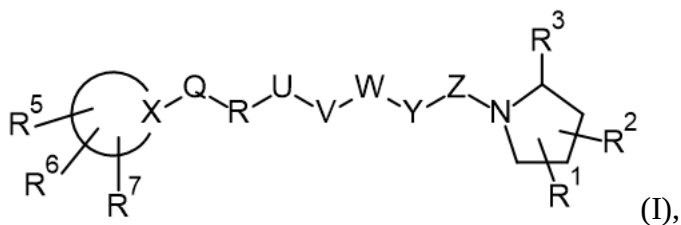
In the following, the content of the figures comprised in this specification is described. In this context please also refer to the detailed description of the invention above and/or below.

Figure 1: In vitro characterization of ^{125}I -FAP1-01 and ^{177}Lu -FAP1-02.

A. Binding of radiolabeled FAPI-01 and FAPI-02 to different human cancer cell lines as well as cell lines transfected with human FAP- α (HT-1080-FAP), murine FAP- α (HEK-muFAP) and human CD26 (HEK-CD26) after 60 min of incubation. **B.** Internalization of radiolabeled FAPI-01 and FAPI-02 into HT-1080-FAP cells after incubation for 10 min to 24 h. The internalized proportion is shown in grey and black, respectively; the extracellularly bound fraction is indicated by the white bars. **C.** Competitive binding of radiolabeled FAPI-01 and FAPI-02 to HT-1080-FAP cells after adding increasing concentrations of unlabeled FAPI-01 and Lu-FAPI-02. **D.** Internalization of FAPI-02 into FAP- α positive and negative cell lines. Blue: DAPI; green: FAPI-02-Atto488. **E+F.** Efflux kinetics of FAPI-01 and FAPI-02 after 1 h incubation of HT-1080-FAP cells with radiolabeled compounds followed by incubation with compound-free medium for 1 to 24 h. All values are given as percentage of total applied dose normalized to 1 million cells (%ID/1 mio cells).

Claims

1. A compound of Formula (I)



wherein

Q, R, ~~and U,~~ are absent;

V, W, Y, ~~and Z~~ are individually present or absent under the proviso that at least three of ~~Q,~~ ~~R,~~ ~~U,~~ V, W, Y, ~~and Z~~ are present;

~~Q, R, U,~~ V, W, Y, ~~and Z~~ are independently selected from the group consisting of O, CH₂, NR⁴, C=O, C=S, C=NR⁴, HCR⁴ and R⁴CR⁴, with the proviso that two Os are not directly adjacent to each other;

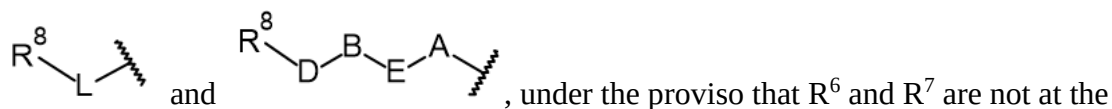
R¹ and R² are independently selected from the group consisting of -H, -OH, halo, C₁₋₆-alkyl, -O-C₁₋₆-alkyl, ~~and S-C₁₋₆-alkyl;~~

R³ is selected from the group consisting of -H, -CN, -B(OH)₂, -C(O)~~---~~alkyl, -C(O)~~---~~aryl, -C=C-C(O)~~---~~aryl, -C=C-S(O)₂-aryl, -CO₂H, -SO₃H, -SO₂NH₂, ~~-,~~ ~~---~~PO₃H₂, and 5-tetrazolyl;

R⁴ is selected from the group consisting of -H, -C₁₋₆-alkyl, -O-C₁₋₆-alkyl, -S-C₁₋₆-alkyl, alkenyl, heteroalkenyl, cycloalkenyl, cycloheteroalkenyl, alkynyl, aryl, and -C₁₋₆-aryl, each of said -C₁₋₆-alkyl being optionally substituted with from 1 to 3 substituents selected from -OH, oxo, ~~halo and optionally connected to Q, R, U, V, W, Y or Z and halo;~~

R⁵ is selected from the group consisting of -H, halo and C₁₋₆-alkyl;

R⁶, and R⁷ are independently selected from the group consisting of -H,



same time H,

~~wherein L is a linker,~~

wherein D, ~~A, E, and B~~ ~~are individually~~ is present or absent, ~~preferably~~

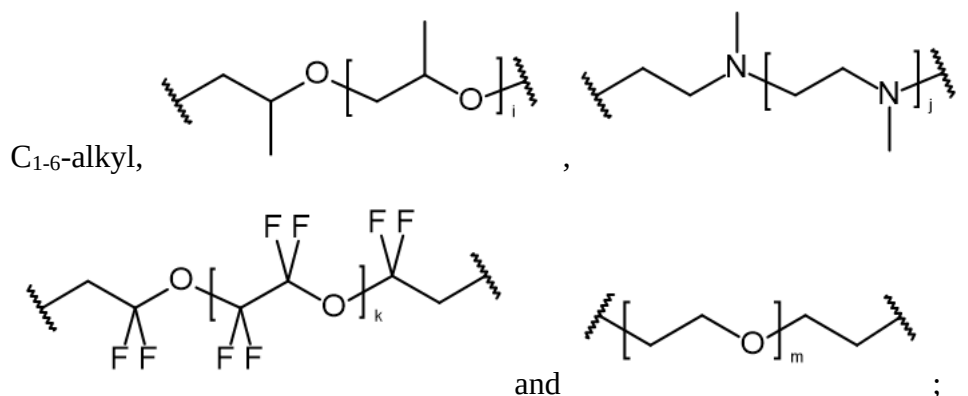
wherein ~~at least~~ A, E, and B are present,

wherein when D is present:

D is a linker;

A is selected from the group consisting of NR^4 , O, S, and CH_2 ;

E is selected from the group consisting of



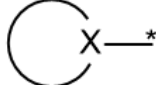
wherein i is 1, 2, or 3;

wherein j is 1, 2, or 3;

wherein k is 1, 2, or 3;

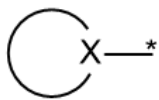
wherein m is 1, 2, or 3;

B is A and E together form a group selected from ~~the group consisting of S, NR^4 , NR^4 -O, NR^4 ; a cycloalkyl, heterocycloalkyl, aryl and heteroaryl, preferably heterocycloalkyl, wherein A and E can be mono-, bi- and multicyclic, preferably monocyclic; each A and E being optionally substituted with 1 to 4 substituents selected from -H, C_{1-6} -alkyl, NR^4 -O- C_{1-6} -alkyl- NR^4 , and, -S- C_{1-6} -alkyl, alkenyl, heteroalkenyl, cycloalkenyl, cycloheteroalkenyl, alkynyl, aryl, and - C_{1-6} -aralkyl, each of said - C_{1-6} -alkyl being optionally substituted with from 1 to 3 substituents selected from -OH, oxo, halo; and~~

optionally connected to A, B, D, E or  ;

B is a 5- to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, ~~preferably optionally~~ further comprising 1 or 2 heteroatoms selected from O, N, and S, ~~preferably further comprising 1 or 2 nitrogen atoms, preferably wherein NR^4 - C_{1-6} -alkyl- NR^4 and~~ wherein the N-containing heterocycle is substituted with 1 to 3 substituents selected the group consisting of C_{1-6} -alkyl, aryl, and C_{1-6} -aralkyl; and;

R⁸ is selected from the group consisting of a radioactive moiety, a chelating agent, a fluorescent dye, a contrast agent and combinations thereof;



is a 1-~~naphthyl~~naphthyl moiety or a 5 to 10- membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, wherein there are 2 ring atoms between the N atom and X; said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S; and X is a C atom;
or a pharmaceutically acceptable tautomer, racemate, hydrate, solvate, or salt thereof.

2. The compound of claim 1, wherein

~~(i) Q, R, U are CH₂ and are individually present or absent;~~

~~(i)~~

V is CH₂, C=O, C=S or C=NR⁴;

W is NR⁴;

Y is HCR⁴; and

Z is C=O, C=S or C=NR⁴; and/or

(ii) ~~Q and R are absent;~~

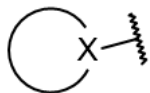
~~U is CH₂ and is present or absent;~~

R¹ and R² are independently selected from the group consisting of -H and halo;

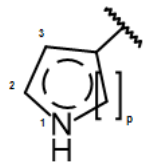
R³ is selected from the group consisting of -H, -CN, and -B(OH)₂;

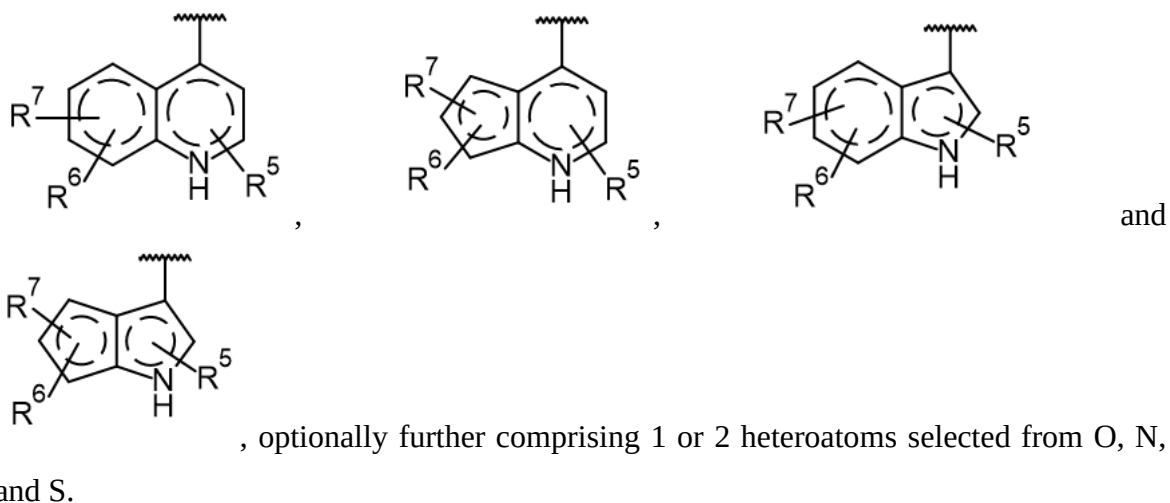
R⁴ is selected from the group consisting of -H and -C₁₋₆-alkyl, wherein the -C₁₋₆-alkyl is optionally substituted with from 1 to 3 substituents selected from -OH.

3. The compound of claim 1-~~or 2~~, wherein

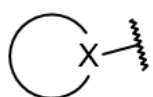


is selected from the group consisting of

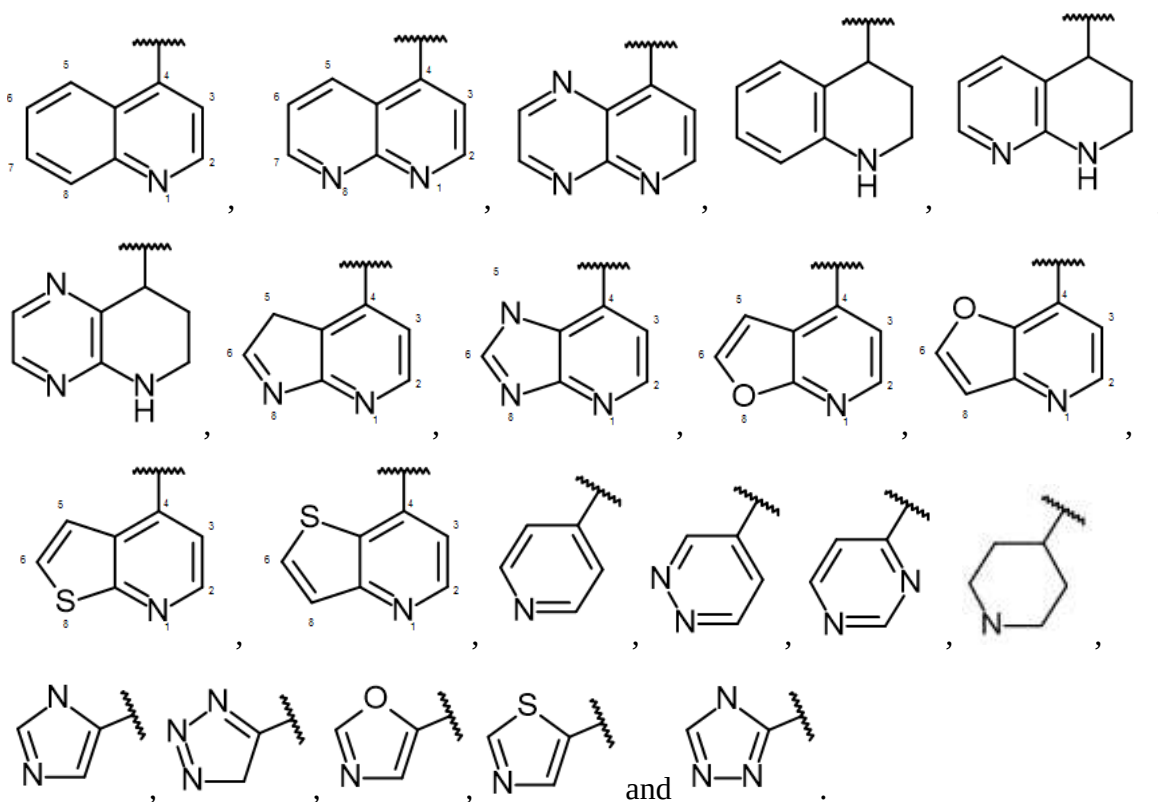




4. The compound of ~~any of the preceding claims~~claim 1, wherein



is selected from the group consisting of

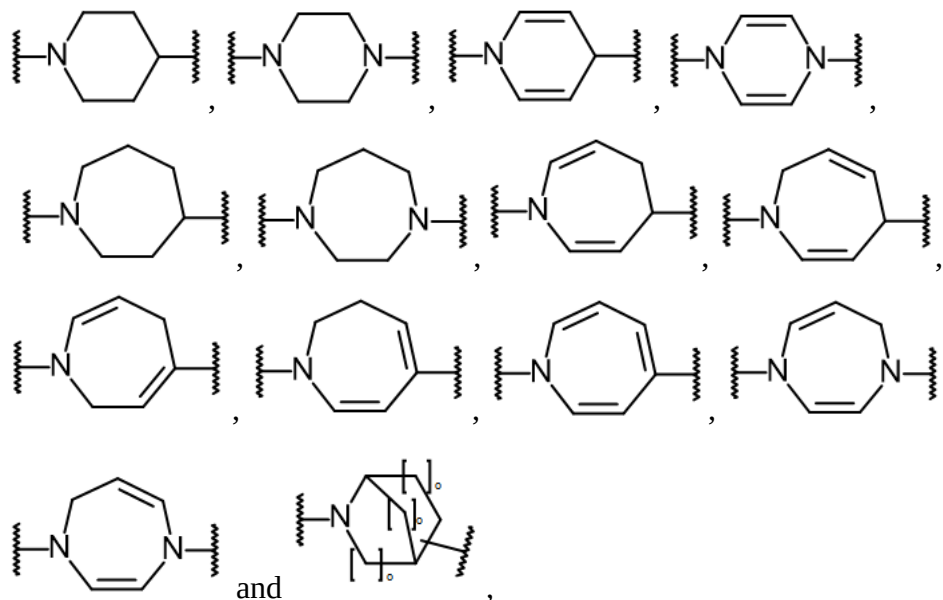


5. The compound of ~~any of the preceding claims~~claim 1, wherein

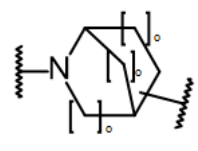
optionally wherein the N-containing heterocycle is substituted with a C₁₋₆-alkyl;

and/or

- (ii) the N-containing heterocycle comprised in B is selected from the group consisting of:



optionally wherein the N-containing heterocycle is substituted with a C₁₋₆-alkyl;

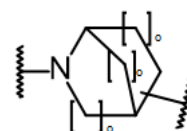


wherein if the N-containing heterocycle comprised in B is

the heterocycle optionally further comprises 1 or 2 heteroatoms selected from O, N and S, optionally further comprises 1 nitrogen, optionally comprises one or more (e.g. amino acid-derived) side chains;

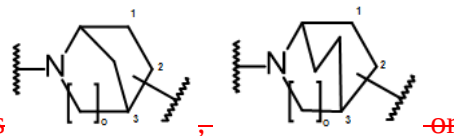
 is attached to position 1, 2, or 3, ~~preferably to position 2;~~ and

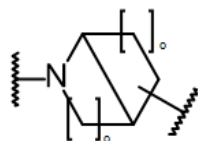
O is 1 or 2, ~~and~~



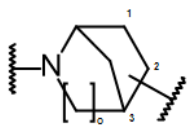
~~preferably, if the N-containing heterocycle comprised in B is~~ preferably, if the N-containing heterocycle comprised in B is ~~, the N-~~

containing heterocycle comprised in B is

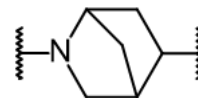




; more preferably, if the N-containing heterocycle comprised in B is



, the N-containing heterocycle comprised in B is



or



;

7. The compound of ~~any of the preceding claims~~ claim 1, wherein

~~Q, R, U are absent;~~

V is C=O;

W is NH;

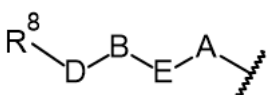
Y is CH₂;

Z is C=O;

R¹ and R² are independently selected from the group consisting of -H and halo;

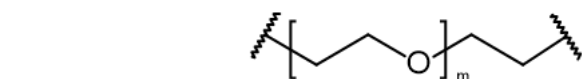
R³ is -CN;

R⁵ and R⁶ are H;

R⁷ is , wherein

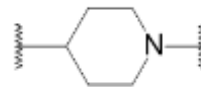
D is absent;

A is O, S, CH₂, NH, NCH₃;

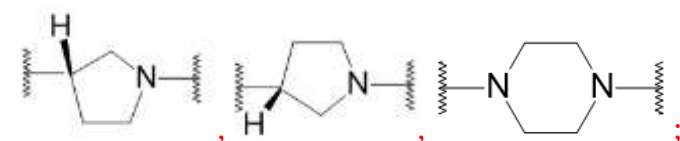


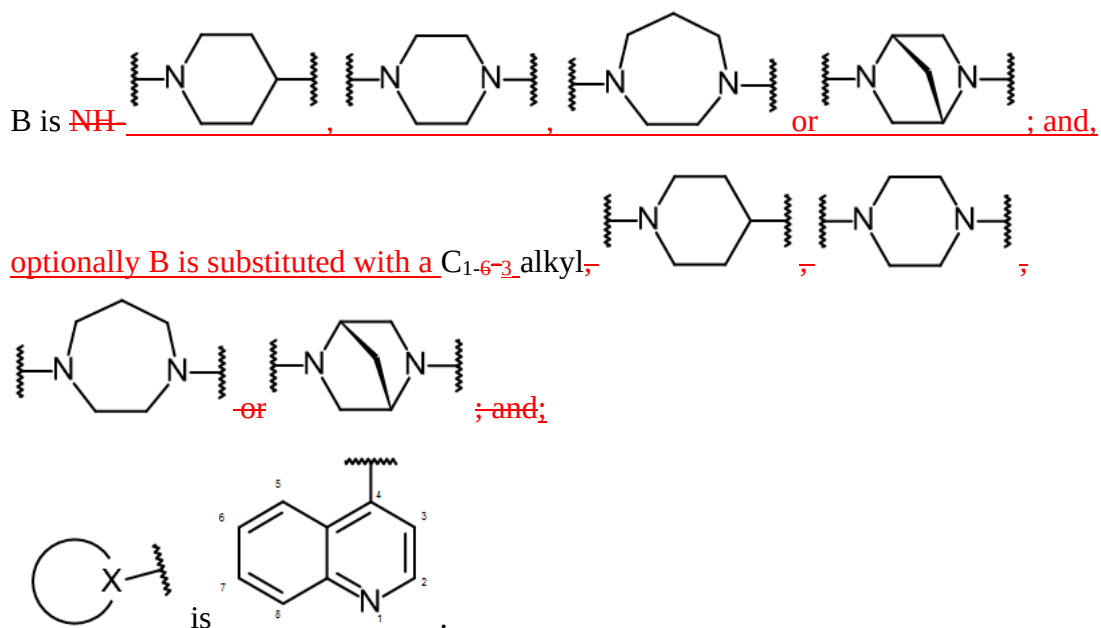
E is C₁₋₆-alkyl or

, wherein m is 1, 2, or 3; or



A and E together form a group selected from:





8. The compound of ~~any of the preceding claims~~ claim 1, wherein C₁₋₆-alkyl is selected from the group consisting of methyl, ethyl, propyl, i-propyl, butyl, sec-butyl, tert-butyl, pentyl and hexyl, and/or wherein C₁₋₆-aralkyl is selected from the group consisting of benzyl, phenyl-ethyl, phenyl-propyl, and phenyl-butyl.
9. The compound of any of the preceding claims, wherein R⁸ is a radioactive moiety, ~~wherein the radioactive moiety is a fluorescent isotope, a radioisotope, a radioactive drug or combinations thereof,~~
10. The compound according to claim 9, preferably wherein the radioactive moiety is selected from the group consisting of alpha radiation emitting isotopes, beta radiation emitting isotopes, gamma radiation emitting isotopes, Auger electron emitting isotopes, X-ray emitting isotopes, fluorescence emitting isotopes, such as ¹⁸F, ⁵¹Cr, ⁶⁷Ga, ⁶⁸Ga, ¹¹¹In, ^{99m}Tc, ¹⁸⁶Re, ¹⁸⁸Re, ¹³⁹La, ¹⁴⁰La, ¹⁷⁵Yb, ¹⁵³Sm, ¹⁶⁶Ho, ⁸⁸Y, ⁹⁰Y, ¹⁴⁹Pm, ¹⁶⁵Dy, ¹⁶⁹Er, ¹⁷⁷Lu, ⁴⁷Sc, ¹⁴²Pr, ¹⁵⁹Gd, ²¹²Bi, ²¹³Bi, ⁷²As, ⁷²Se, ⁹⁷Ru, ¹⁰⁹Pd, ¹⁰⁵Rh, ^{101m}Rh, ¹¹⁹Sb, ¹²⁸Ba, ¹²³I, ¹²⁴I, ¹³¹I, ¹⁹⁷Hg, ²¹¹At, ¹⁵¹Eu, ¹⁵³Eu, ¹⁶⁹Eu, ²⁰¹Tl, ²⁰³Pb, ²¹²Pb, ⁶⁴Cu, ⁶⁷Cu, ¹⁸⁸Re, ¹⁸⁶Re, ¹⁹⁸Au, ²²⁵Ac, ²²⁷Th and ¹⁹⁹Ag.

- ~~1011.~~ The compound of ~~any of claims 1 to 8~~claim 1, wherein R⁸ is a fluorescent dye ~~select~~selected from the group consisting of the following classes of fluorescent dyes: ~~Xanthenes~~Xanthenes, Acridines, Oxazines, Cynines, Styryl dyes, Coumarines, Porphines, Metal-Ligand-Complexes, Fluorescent proteins, Nanocrystals, Perylenes, Boron-dipyrromethenes and Phthalocyanines~~Phthalocyanines~~ as well as conjugates and combinations of these classes of dyes.
- ~~1112.~~ The compound of ~~any of claims~~claim 1 to 8, wherein R⁸ is a chelating agent ~~which forms a complex with divalent or trivalent metal cations, preferably wherein the chelating agent is~~ selected from the group consisting of 1,4,7,10-tetraazacyclododecane-N,N',N,N'-tetraacetic acid (DOTA), ethylenediaminetetraacetic acid (EDTA), 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), triethylenetetramine (TETA), iminodiacetic acid, diethylenetriamine-N,N,N',N',N''-pentaacetic acid (DTPA), bis-(carboxymethylimidazole)glycine and 6-Hydrazinopyridine-3-carboxylic acid (HYNIC).
- ~~1213.~~ The compound of ~~any of claims~~claim 1 to 8, wherein R⁸ is a contrast agent which comprises ~~or consists of~~ a paramagnetic agent, ~~preferably, wherein the paramagnetic agent comprises or consists of paramagnetic nanoparticles.~~
- ~~1314.~~ ~~A Pharmaceutical~~pharmaceutical composition comprising ~~or consisting of~~ at least one compound according to ~~any of claims~~claim 1 to 12; and, ~~optionally~~, a pharmaceutically acceptable carrier ~~and/or excipient~~.
- ~~1415.~~ Use of the compound of any of claims 1 to ~~12-13~~13-14 or the pharmaceutical composition of claim ~~13-14~~13-14 in the manufacture of a medicament for the diagnosis or treatment of a disease characterized by overexpression of fibroblast activation protein (FAP) in an animal or a human subject, preferably wherein the disease characterized by overexpression of fibroblast activation protein (FAP) is selected from the group consisting of cancer, chronic inflammation, atherosclerosis, fibrosis, tissue remodeling and keloid disorder, preferably wherein the cancer is selected from the group consisting of breast cancer, pancreatic cancer, small intestine cancer, colon cancer, rectal cancer, lung cancer, head and neck cancer,

ovarian cancer, hepatocellular carcinoma, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus carcinoma, desmoid tumors, glioma, astrocytoma, cervix carcinoma and prostate cancer.

1516. A kit comprising or consisting of the compound of any of claims 1 to ~~12-13~~ or the pharmaceutical composition of claim ~~13-14~~ and instructions for the diagnosis or treatment of a disease.