

# RADIOLABELLED FIBROBLAST ACTIVATION PROTEIN LIGANDS

## INTRODUCTION

### Field

The present invention relates to ligands of Fibroblast Activation Protein (FAP) for the active delivery of radioactive payloads at the site of disease. In particular, the present invention relates to the development of FAP ligands for the targeted delivery of radionuclides, such as <sup>18</sup>Fluorine, <sup>68</sup>Gallium, <sup>64</sup>Copper, <sup>111</sup>Indium, <sup>177</sup>Lutetium, and to diagnostic methods and/or methods for therapy or surgery in relation to a disease or disorder, such as cancer, inflammation or another disease characterized by overexpression of FAP.

### Background of the Invention

Fibroblast activation protein (FAP) is a membrane-bound gelatinase which promotes tumor growth and progression and is overexpressed in cancer-associated fibroblasts. FAP represents an ideal target for the development of targeted small molecule drug conjugates (SMDCs) and small molecule radio conjugates (SMRCs) due to its low expression in normal organs.

WO2019154886 and WO2019154859 describe heterocyclic compounds as fibroblast activation protein-alpha inhibitors used to treat different cancer types. WO2019118932 describes substituted N-containing cyclic compounds as fibroblast activation protein alpha inhibitors used to treat different pathological conditions. WO2019083990 describes imaging and radiotherapeutic targeting fibroblast-activation protein-alpha (FAP-alpha) compounds as FAP-alpha inhibitors used for imaging disease associated with FAP-alpha and to treat proliferative diseases. WO2013107820 describes substituted pyrrolidine derivatives used in the treatment of proliferative disorders such as cancers and diseases indicated by tissue remodeling or chronic inflammation such as osteoarthritis, and notes that the 4-isoquinolinoyl and 8-quinolinoyl derivatives described therein are characterized by very low FAP-affinity. WO2005087235 describes pyrrolidine derivatives as dipeptidyl peptidase IV inhibitors to treat Type II diabetes. WO2018111989 describes conjugates comprising fibroblast activation protein (FAP) inhibitor, bivalent linker and e.g. near infrared (NIR) dye, useful for removing cancer-associated fibroblasts, imaging population of cells in vitro, and treating cancer.

Tsutsumi et al. (J Med Chem 1994) describe the preparation and in vitro prolyl endopeptidase (PEP) inhibitory activity of a series of α-keto heterocyclic compounds. Hu et al. (Bioorg Med Chem Lett 2005) describe the structure-activity relationship of various N-alkyl Gly-boro-Pro derivatives against FAP and other two dipeptidyl peptidases. Edosada et al. (J Biol Chem 2006) describe the dipeptide substrate specificity of FAP and the development of a Ac-Gly-BoroPro FAP-selective inhibitor. Gilmore et al. (Biochem Biophys Res Commun 2006) describe the design, synthesis, and kinetic testing of a series of

dipeptide proline diphenyl phosphonates, against DPP-IV and FAP. Tran et al. (Bioorg Med Chem Lett 2007) describe the structure–activity relationship of various N-acyl-Gly-, N-acyl-Sar-, and N-blocked-boroPro derivatives against FAP. Tsai et al. (J Med Chem 2010) describe structure–activity relationship studies that resulted in a number of FAP inhibitors with excellent selectivity over DPP-IV, DPP-II, DPP8, and DPP9. Ryabtsova et al. (Bioorg Med Chem Lett 2012) describe the synthesis and the evaluation of FAP inhibition properties of a series of N-acylated glycyl-(2-cyano)pyrrolidines. Poplawski et al. (J Med Chem 2013) describe N-(pyridine-4-carbonyl)-D-Ala-boroPro as a potent and selective FAP inhibitor. Jansen et al. (ACS Med Chem Lett 2013) describe FAP inhibitors based on the N-(4-quinolinoyl)-Gly-(2-cyanopyrrolidine) scaffold. Jansen et al. (Med Chem Commun 2014) the structure–activity relationship of FAP inhibitors based on the linagliptin scaffold. Jansen et al. (Med Chem Commun 2014) describe xanthine-based FAP inhibitors with low micromolar potency. Jansen et al. (J Med Chem 2014) describe the structure–activity relationship of FAP inhibitors based on the N-4-quinolinoyl-Gly-(2S)-cyanoPro scaffold. Jackson et al. (Neoplasia 2015) describe the development of a pseudopeptide inhibitor of FAP. Meletta et al. (Molecules 2015) describe the use of a boronic-acid based FAP inhibitor as non-invasive imaging tracers of atherosclerotic plaques. Dvořáková et al. (J Med Chem 2017) describe the preparation of a polymer conjugate containing a FAP-specific inhibitor for targeting applications. Loktev et al. (J Nucl Med 2018) describe the development of an iodinated and a DOTA-coupled radiotracer based on a FAP-specific enzyme inhibitor. Lindner et al. (J Nucl Med 2018) describe the modification and optimization of FAP inhibitors for use as theranostic tracers. Giesel et al. (J Nucl Med 2019) describe the clinical imaging performance of quinoline-based PET tracers that act as FAP inhibitors.

Nevertheless, developing potent FAP binders with superior targeting properties, and SMDCs and SMRCs based thereon, remains a challenging task. Particularly desirable would be SMRCs exhibiting advantageous tumor-to-organ biodistribution, high activity labelling, and/or good compound stability, especially with respect to chemical and radiolytic stability and stability in in vitro and in vivo biological systems.

## PROBLEMS TO BE SOLVED BY THE INVENTION

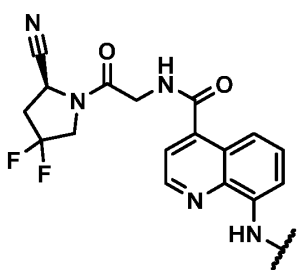
The present invention aims at the problem of providing improved compounds for targeted delivery, in particular SMRCs, which bind the fibroblast activation protein (FAP). The compounds (“binders”) should be suitable for therapeutic and/or diagnostic applications, and be capable of reaching a site afflicted by or at risk of disease or disorder characterized by overexpression of FAP. Preferably, the compound should form a stable complex with FAP, display a prolonged residence at the site of disease, and a lower accumulation in healthy organs.

## SUMMARY OF THE INVENTION

The present inventors have found novel compounds (in particular: SMRCs) binding fibroblast activation protein (FAP) which are particularly suitable for targeting applications, and are suitable for addressing the above-described problems.

- 5 The present invention provides a compound, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers, or a pharmaceutically acceptable salt thereof, wherein the compound structure comprises:

a moiety **A** represented by or comprising the following structure:



- 10 one or more diagnostic or therapeutic agent moieties **C**; and

a moiety **B** covalently connecting **A** to **C**, and comprising a carbocyclic or heterocyclic group.

The present invention further provides a pharmaceutical composition comprising said compound and a pharmaceutically acceptable excipient.

- 15 The present invention further provides said compound or pharmaceutical composition for use in a method for treatment of the human or animal body by surgery or therapy or a diagnostic method practiced on the human or animal body; as well as a method for treatment of the human or animal body by surgery or therapy or a diagnostic method practiced on the human or animal body comprising administering a therapeutically or diagnostically effective amount of said compound or pharmaceutical composition to a subject in need thereof.

- 20 The present invention further provides said compound or pharmaceutical composition for use in a method for therapy or prophylaxis of a subject suffering from or having risk for a disease or disorder; as well as a method for treatment therapy or prophylaxis of a disease or disorder comprising administering a therapeutically or diagnostically effective amount of said compound or pharmaceutical composition to a subject suffering from or having risk for said disease or disorder.

- 25 The present invention further provides said compound or pharmaceutical composition for use in a method for guided surgery practiced on a subject suffering from or having risk for a disease or disorder; as well as

a method for guided surgery comprising administering a therapeutically or diagnostically effective amount of said compound or pharmaceutical composition to a subject suffering from or having risk for a disease or disorder.

5 The present invention further provides said compound or pharmaceutical composition for use in a method for diagnosis of a disease or disorder, the method being practiced on the human or animal body and involving a nuclear medicine imaging technique, such as Positron Emission Tomography (PET); as well as a method for diagnosis of a disease or disorder, the method being practiced on the human or animal body and involving a nuclear medicine imaging technique, such as Positron Emission Tomography (PET), and comprising administering a therapeutically or diagnostically effective amount of said compound or  
10 pharmaceutical composition to a subject in need thereof.

The present invention further provides said compound or pharmaceutical composition for use in a method for targeted delivery of a therapeutic or diagnostic agent to a subject suffering from or having risk for a disease or disorder; as well as a method for targeted delivery of a therapeutically or diagnostically effective amount of said compound or pharmaceutical composition to a subject suffering from or having  
15 risk for a disease or disorder.

Preferably, the aforementioned disease or disorder is characterized by overexpression of FAP and is independently selected from cancer, 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, multi-drug resistant colon cancer, rectal cancer, colorectal  
20 cancer, metastatic colorectal cancer, lung cancer, non-small cell lung cancer, head and neck cancer, ovarian cancer, hepatocellular cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocarcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus cancer, desmoid tumors, glioma, astrocytoma, cervix cancer, skin cancer, kidney cancer, breast cancer, and prostate cancer. More preferably, the disease or disorder is selected from melanoma, breast cancer,  
25 and renal cell carcinoma.

## BRIEF DESCRIPTION OF THE DRAWINGS

**Figure 1.** ESV6-NODAGA-Al-F: Chromatographic purity of the labelling procedure measured by LC-UV-MS (Agilent 6100 Series Single Quadrupole MS System combined with Agilent 1200 Series LC  
30 System. Chromatographic method Water/ACN + 0.1% HCOOH 90:10 to 0:100 in 3 min) identified a single chemical species after labelling.

**Figure 2.** NanoHPLC chromatogram of ESV6-NODAGA-Al-F: By applying nanoHPLC, a chromatography with higher resolution, three different chemical species were identified: (i) ESV6-NODAGA-Al (at 15.34 min 883.31254 m/z) corresponding to the compound with a loss of the fluorine

anion (ii) ESV6-NODAGA-Al-OH (at 13.56 min 901.32311 m/z) corresponding to the compound with the fluorine anion substituted with a hydroxyl anion and (iii) ESV6-NODAGA-Al-F (at 16.42 min 903.31877 m/z). This figure indicates that ESV6-NODAGA labelling may results in a mixture of species.

**Figure 3.** ESV6-NOTA (Compound 1): Chromatographic purity of the labelling procedure measured by LC-UV-MS (Agilent 6100 Series Single Quadrupole MS System combined with Agilent 1200 Series LC System. Chromatographic method Water/ACN + 0.1% HCOOH 90:10 to 0:100 in 3 min) identified a single chemical species after labelling.

**Figure 4.** NanoHPLC chromatogram of ESV6-NOTA-Al-F (Compound AIF@1): By applying nanoHPLC, a chromatography with higher resolution, a single peak was identified (15.24 min and 857.31329 m/z) indicating a high degree of purity for the labelled version of ESV6-NOTA.

**Figure 5.** Schematic workflow of the *ex-vivo* biodistribution experiments: Mice were treated with either ESV6-NODAGA-Al-F (represented as a sum of the three species) or ESV6-NOTA-Al-F (Compound AIF@1) and euthanized after two hours. Tissues were harvested, deproteinized, cleaned up with two SPE in line, and analyzed with a nanoLC-HR-MS platform. As internal standard for the MS analysis, isotopically labelled derivative of the analytes at fixed concentrations were added to the samples prior to sample preparation.

**Figure 6.** *Ex vivo* biodistribution results: ESV6-NODAGA-Al-F (represented as a sum of the three species) and ESV6-NOTA-Al-F, are expressed as pmol/g in tumor and in selected organs 2 hours after injection. \*\*\* = p value < 0.001, Q = 0.003 with unpaired t test (95%). The preferential uptake of ESV6-NOTA-Al-F in the tumor is remarkable, and significantly superior compared to the tumor uptake presented by ESV6-NODAGA-Al-F.

**Figure 7.** Quantitative *in vivo* biodistribution results of ESV6-NOTA-[<sup>18</sup>F]Al-F in nude mice bearing subcutaneous HT-1080.hFAP tumors: results are expressed as the percentage of injected dose per gram of tissue (A) and as tumor to organs ratio (B). The preferential uptake of ESV6-NOTA-[<sup>18</sup>F]Al-F is remarkable while the uptake in normal organs is at negligible levels.

**Figure 8.** Coelution experiments with a) [<sup>68</sup>Ga]GaESV6-NOTA, b) [<sup>68</sup>Ga]GaESV6-NODAGA and c) ESV6-NOTA-[<sup>18</sup>F]Al-F and human FAP. In the presence of the human FAP the complexes are the only compounds present. Binding experiments demonstrate high affinity of all the radiolabelled ESV6 moieties towards human FAP.

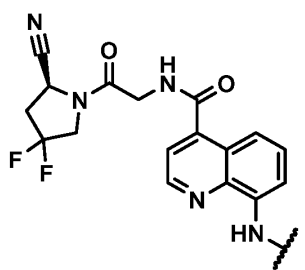
## DETAILED DESCRIPTION OF THE INVENTION

The present inventors have identified compounds, and in particular small molecule radio conjugates (SMRCs), which bind to the fibroblast activation protein (FAP), and are suitable for targeting applications. The SMRCs according to the invention provide good inhibition of FAP, good affinity for FAP and/or are suitable for targeted delivery of a payload, such as a therapeutic or diagnostic agent, to a site afflicted by or at risk of disease or disorder characterized by overexpression of FAP.

The compounds according to the present invention form a stable complex with FAP, display an increased affinity, increased inhibitory activity, a slower rate of dissociation from the complex, and/or prolonged residence at a disease site. The compounds according to the invention further can have an increased tumor-to-liver, tumor-to-kidney and/or tumor-to-intestine uptake ratio; a more potent anti-tumor effect (e.g., measured by mean tumor volume increase), and/or lower toxicity (e.g., as assessed by the evaluation of changes (%) in body weight). The compounds according to the invention preferably attain FAP-specific cellular binding; FAP-selective accumulation on the cell membrane; FAP-selective accumulation inside the cytosol. Further, the compounds according to the invention preferably can rapidly and homogeneously localize at the tumor site in vivo with a high tumor-to-organs selectivity, in particular for melanoma and/or renal cell carcinoma. Compounds according to the invention comprising a radioactive payload (e.g., <sup>18</sup>Fluorine) preferably attain dose-dependent response, e.g., with target saturation reached between 500 pmol/g and 1000 pmol/g reached and/or maintained at up to 12 h, more preferably 1 to 9 h, further more preferably 1 to 3 h after intravenous administration.

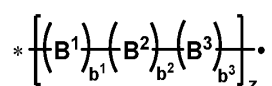
PET imaging is one of the preferred applications of the compounds described herein. Affinity for FAP, lipophilicity and stability of the compounds can be among the relevant factors determining the suitability of a SMRC for such applications. For instance, PET and gamma counting-based biodistribution can be used to assess tracer kinetics and uptake. Without wishing to be bound by theory, the compounds described herein, are believed to exhibit favourable biodistribution and kinetics with high and reliable uptake in cancer tissues, which is believed to result from the combination of the moiety A with a very high FAP binding affinity, the particular linking group B, and a radioactive therapeutic or diagnostic moiety C.

The present invention provides a compound, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers, or a pharmaceutically acceptable salt thereof, wherein the compound structure comprises a moiety A represented by or comprising the following structure:



**A** is a binding moiety (i.e., moiety binding to FAP), and is covalently connected to one or more one or more diagnostic or therapeutic agent moieties **C** (i.e., payload(s), such as a radioactive group comprising a radionuclide) through a moiety **B**.

- 5 **B** can be represented by the following structure:



wherein each  $b^1$  and  $b^3$  is independently an integer from 0 to 4, preferably 0 or 1;

each  $b^2$  is independently an integer from 1 to 4, preferably 1 or 2;

$z$  is an integer from 1 to 3, preferably 1 or 2;

- 10 each  $B^2$  is independently represented by  $*-Y \text{---} Z-\bullet$ , wherein:

$Y$  and  $Z$  are linking groups forming part of a carbocyclic or heterocyclic group, preferably a  $C_{3-13}$  carbocyclic or  $C_{2-12}$  heterocyclic group, wherein all valences are satisfied.

- 15  $*-Y$  preferably represents  $*-C$ ,  $*-CR$ ,  $*-N$ ,  $*-NR$ ,  $*-NRC(O)C$ ,  $*-NRC(O)CR$ ,  $*-NRC(O)CR_2C$ ,  $*-NRC(O)CR_2CR$ ,  $*-NRC(S)NRC$ ,  $*-NRC(S)NRCR$ ,  $*-NRC$ ,  $*-NRCR$ ,  $*-NRCR_2C$ , or  $*-NRCR_2CR$ ;

$Z-\bullet$  preferably represents  $C-\bullet$ ,  $CR-\bullet$ ,  $N-\bullet$ ,  $NR-\bullet$ ,  $CC(O)NRCRC(O)NR-\bullet$ ,  $CCR_2C(O)NR-\bullet$ ,  $CRCR_2C(O)NR-\bullet$ ,  $CNRC(S)NR-\bullet$ ,  $NRC(S)CRNR-\bullet$ ,  $CNR-\bullet$ ,  $CRNR-\bullet$ ,  $CCR_2NR-\bullet$ , or  $CRCR_2NR-\bullet$ ;

- 20 Each  $*$  represents a point of attachment closer to moiety **A** than to a moiety **C**; and each  $\bullet$  represents a point of attachment closer to a moiety **C** than to moiety **A**.

Each **B**<sup>3</sup> is independently a bond, alkylene, oxoalkylene, di(oxo)alkylene, C(O)alkylarylalkylene, C(S)N(R)arylalkylene, or heteroalkylene, said heteroalkylene comprising one or more heteroatoms selected from N and O; and is preferably a bond, alkylene, oxoalkylene, di(oxo)alkylene, C(O)alkylarylalkylene, or C(S)N(R)arylalkylene. The shortest path between **B**<sup>2</sup> and **C** preferably  
5 comprises 10 or less, more preferably 7 or less, most preferably 6 or less covalently connected atoms or is a bond.

Each of **B**<sup>1</sup>, **B**<sup>2</sup> and **B**<sup>3</sup> independently optionally substituted by one or more of R.

Each R is independently selected from H, OH, SH, NH<sub>2</sub>, halogen, cyano, oxo, carboxy, C(O)NH<sub>2</sub> C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C(O)C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylthio, C<sub>1-5</sub> heteroalkyl, C<sub>1-5</sub> heteroalkoxy, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkoxy, C<sub>6-10</sub> aryl, C<sub>6-10</sub> aryloxy, C<sub>5-10</sub> heteroaryl and C<sub>5-10</sub> heteroaryloxy, of which the SH, NH<sub>2</sub>, C(O)NH<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C(O)C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylthio, C<sub>1-5</sub> heteroalkyl, C<sub>1-5</sub> heteroalkoxy, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkoxy, C<sub>6-10</sub> aryl, C<sub>6-10</sub> aryloxy, C<sub>5-10</sub> heteroaryl and C<sub>5-10</sub> heteroaryloxy can be optionally substituted with one or more of OH, SH, NH<sub>2</sub>, halogen, cyano, oxo, carboxy, C<sub>1-6</sub> alkyl, C<sub>1-5</sub> heteroalkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>5-10</sub> heteroaryl, and two or more of R can be bound together  
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15 to form part of a carbocyclic or heterocyclic ring system.

A compound according to the present invention may be represented by Formula I:

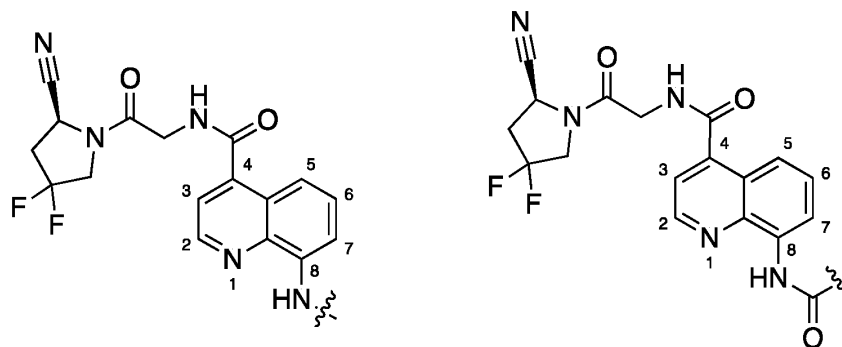


**I**

Therein, **B** is a covalent bond or a moiety comprising a chain of atoms covalently attaching **A** to **C**. **C** is a  
20 therapeutic or diagnostic agent, which may be, e.g., an atom, a molecule, a particle, or a radionuclide.

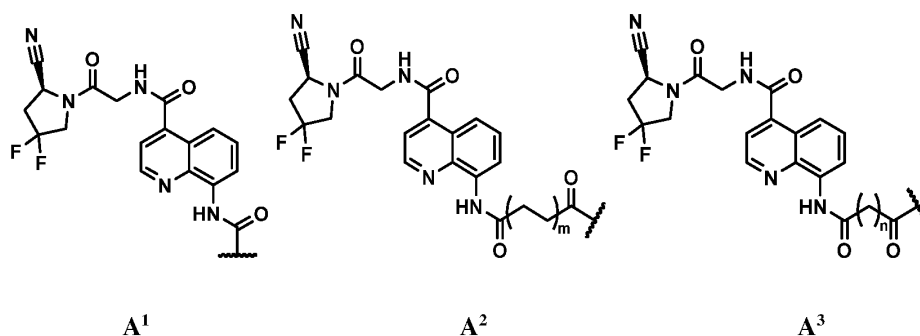
#### Moiety A

Without wishing to be bound by any theory, it is contemplated that some of the beneficial technical effects achieved by the compounds of the invention are associated with the particular structure of the binding moiety **A** wherein the quinoline ring is substituted at the 8-position by a nitrogen-containing group, such as an amino or amido group:  
25



It has been previously shown that the higher target protein affinity of a compound results in longer tumor residence *in vivo* (Wichert et al., *Nature Chemistry* 7, 241–249 (2015)). The compounds of the present invention have an increased affinity, slower dissociation rate with respect to FAP as compared to prior art compounds, and therefore are also considered to as having a prolonged residence at the disease site at a therapeutically or diagnostically relevant level, preferably beyond 1 h, more preferably beyond 6 h post injection. Preferably, the highest enrichment is achieved after 5 min, 10 min, 20 min, 30 min, 45 min, 1 h, 2 h, 3 h, 4 h, 5 h or 6 h; and/or enrichment in the disease site is maintained at a therapeutically or diagnostically relevant level, over a period of or at least for 5 min, 10 min, 20 min, 30 min, 45 min, 1 h, 2 h, 3 h, 4 h, 5 h or 6 h, more preferably beyond 6 h post injection. Compounds according to the invention comprising a radioactive payload (e.g., <sup>18</sup>Fluorine) may attain dose-dependent response, e.g., with target saturation reached between 500 pmol/g and 1000 pmol/g reached and/or maintained at up to 12 h, more preferably 1 to 9 h, further more preferably 1 to 3 h after intravenous administration.

Preferably, the binding moiety **A** has the following structure **A**<sup>1</sup>, **A**<sup>2</sup> or **A**<sup>3</sup>, wherein *m* is 0, 1, 2, 3, 4, or 5, preferably 1; and *n* is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, preferably 2:



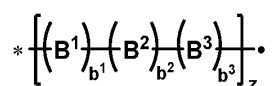
More preferably, moiety **A** has the structure **A**<sup>2</sup>, most preferably wherein *m* is 1.

#### Moiety B

Moiety **B** is a covalent bond or a moiety comprising a chain of atoms that covalently attaches **A** to the payload(s) **C**, i.e., through one or more covalent bond(s).

The moiety **B** links one or more payload and/or binder moieties to form the targeted conjugate of the invention. In some embodiments, the structure of the compound comprises one moiety **A** and more than one moieties **C** per molecule, e.g., 2, 3, 4, 5, 6, 7, 8, 9 or 10 moieties **C** per molecule. In such  
 5 embodiments, one moiety **C** can be attached to moiety **B** at the position indicated by • in any of the general formulae disclosed herein, and the remaining moieties **C** are attached as substituents at further positions on moiety **B**.

Moiety **B** can be represented by the following structure:



wherein each  $b^1$  and  $b^3$  is independently an integer from 0 to 4, preferably 0 or 1;

10 each  $b^2$  is independently an integer from 1 to 4, preferably 1 or 2;

$z$  is an integer from 1 to 3, preferably 1 or 2;

each **B**<sup>2</sup> is independently represented by , wherein **Y** and **Z** are linking groups forming part of a carbocyclic or heterocyclic group;

each \* represents a point of attachment closer to moiety **A** than to a moiety **C**;

15 each • represents a point of attachment closer to a moiety **C** than to moiety **A**;

each **B**<sup>1</sup> is independently a bond, alkylene, oxoalkylene, di(oxo)alkylene, C(O)alkylarylalkylene, C(S)N(R)arylalkylene, or heteroalkylene, said heteroalkylene comprising one or more heteroatoms selected from N and O;

20 each **B**<sup>3</sup> is independently a bond, alkylene, oxoalkylene, di(oxo)alkylene, C(O)alkylarylalkylene, C(S)N(R)arylalkylene, or heteroalkylene, said heteroalkylene comprising one or more heteroatoms selected from N and O;

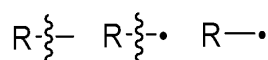
each of **B**<sup>1</sup>, **B**<sup>2</sup> and **B**<sup>3</sup> is independently optionally substituted by one or more of R;

each R is independently selected from H, OH, SH, NH<sub>2</sub>, halogen, cyano, oxo, carboxy, C(O)NH<sub>2</sub> C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C(O)C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylthio, C<sub>1-5</sub> heteroalkyl, C<sub>1-5</sub> heteroalkoxy, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkoxy, C<sub>6-10</sub> aryl, C<sub>6-10</sub> aryloxy, C<sub>5-10</sub> heteroaryl and C<sub>5-10</sub> heteroaryloxy, of which the SH, NH<sub>2</sub>, C(O)NH<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C(O)C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylthio, C<sub>1-5</sub> heteroalkyl, C<sub>1-5</sub> heteroalkoxy, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkoxy, C<sub>6-10</sub> aryl, C<sub>6-10</sub> aryloxy, C<sub>5-10</sub> heteroaryl and C<sub>5-10</sub> heteroaryloxy is  
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optionally substituted with one or more of OH, SH, NH<sub>2</sub>, halogen, cyano, oxo, carboxy, C<sub>1-6</sub> alkyl, C<sub>1-5</sub> heteroalkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>5-10</sub> heteroaryl, and two or more of R can be bound together to form part of a carbocyclic or heterocyclic ring system; and

all valences are satisfied.

- 5 In any of the embodiments described therein, \* represents a point of attachment to moiety **A** or a point of attachment for which the shortest path to moiety **A** comprises less atoms than that for •, as the case may be; and • represents a point of attachment a point of attachment to moiety **C** or a point of attachment to moiety **C** for which the shortest path to moiety **C** comprises less atoms than that for \*, as the case may be. The following notations and all have the meaning of a point of attachment of a certain group or atom (e.g.,  
10 R) to a further moiety:



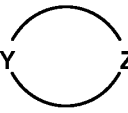
- Each **B**<sup>1</sup> is independently a bond, alkylene, oxoalkylene, di(oxo)alkylene, C(O)alkylarylalkylene, C(S)N(R)arylalkylene, or heteroalkylene, said heteroalkylene comprising one or more heteroatoms selected from N and O; and is preferably a bond, alkylene or heteroalkylene, said heteroalkylene  
15 comprising one or more heteroatoms selected from N and O. The shortest path between **A** and **B**<sup>2</sup> preferably comprises 6 or less, more preferably 3 or less, most preferably 2 or less covalently connected atoms or is a bond.

In a preferred embodiment, b<sup>1</sup> is 0 or 1; b<sup>2</sup> is 1; b<sup>3</sup> is 1; and z is 1.

- Preferably, **B**<sup>1</sup> is a bond, alkylene or heteroalkylene, said heteroalkylene comprising one or more  
20 heteroatoms selected from N and O.

Preferably, the shortest path between **A** and **B**<sup>2</sup> preferably comprises 6 or less, more preferably 3 or less, most preferably 2 or less covalently connected atoms or is a bond.

- Preferably, **B**<sup>3</sup> a bond, alkylene, oxoalkylene, di(oxo)alkylene, C(O)alkylarylalkylene, or C(S)N(R)arylalkylene; wherein the shortest path between **B**<sup>2</sup> and **C** preferably comprises 10 or less, more  
25 preferably 7 or less, most preferably 6 or less covalently connected atoms or is a bond.

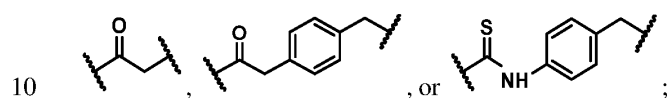
Preferably, \*—Y  Z—• is a C<sub>3-13</sub> carbocyclic or C<sub>2-12</sub> heterocyclic group.

Preferably, \*—Y represents \*—C, \*—CR, \*—N, \*—NR, \*—NRC(O)C, \*—NRC(O)CR, \*—NRC(O)CR<sub>2</sub>C, \*—NRC(O)CR<sub>2</sub>CR, \*—NRC(S)NRC, \*—NRC(S)NR<sub>2</sub>CR, \*—NRC, \*—NR<sub>2</sub>CR, \*—NR<sub>2</sub>CR<sub>2</sub>C, or \*—NR<sub>2</sub>CR<sub>2</sub>CR; and

$Z-$  represents  $C-$ ,  $CR-$ ,  $N-$ ,  $NR-$ ,  $CC(O)NRCRC(O)NR-$ ,  $CCR_2C(O)NR-$ ,  $CR_2C(O)NR-$ ,  $CNRC(S)NR-$ ,  $NRC(S)CRNR-$ ,  $CNR-$ ,  $CRNR-$ ,  $CCR_2NR-$ , or  $CR_2NR-$ .

In a preferred embodiment, each  $B^1$  is independently selected from bond;  $C_{1-10}$ , preferably  $C_{1-4}$ , more preferably  $C_{1-2}$  alkylene;  $C_{1-10}$ , preferably  $C_{1-4}$ , more preferably  $C_{1-2}$  heteroalkylene group comprising one or two N atoms;  $NR(C_{1-10}, C_{1-4}, \text{ or } C_{1-2} \text{ alkylene})NR$ ;  $(C_{1-10}, C_{1-4}, \text{ or } C_{1-2} \text{ alkylene})NR$ ;  $NR(C_{1-10}, C_{1-4}, \text{ or } C_{1-2} \text{ alkylene})$ ;  $C(O)$ ;  $C(O)CR_2$ ;  $C(O)(C_{6-10} \text{ aryl})CR_2$ ;  $C(O)(C_{1-10} \text{ alkylene})C(O)$ ;  $C(O)(C_{1-10} \text{ alkyl})C(O)NR$ ;  $C(O)(C_{5-10} \text{ heteroaryl})CR_2$ ;  $C(O)(C_{6-10} \text{ aryl})CR_2$ ;  $C(O)(C_{5-10} \text{ heteroaryl})CR_2$ ;  $C(S)NR$ ;  $C(S)NR(C_{6-10} \text{ aryl})CR_2$ ; and  $C(S)NR(C_{5-10} \text{ heteroaryl})CR_2$ .

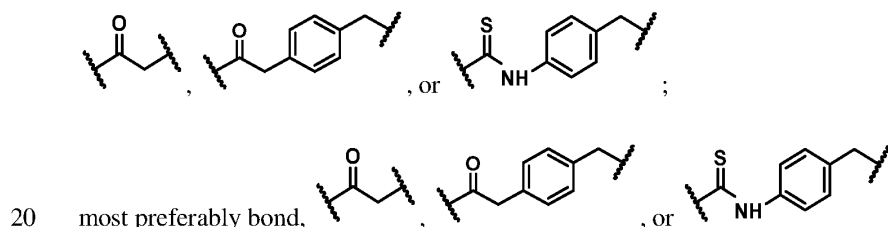
More preferably,  $B^1$  is bond,  $C(O)CH_2CH_2C(O)$ ,  $NHCH_2CH_2NH$ ,  $CH_2CH_2NH$ ,  $NHCH_2CH_2$ ,



most preferably bond or  $NHCH_2CH_2NH$ .

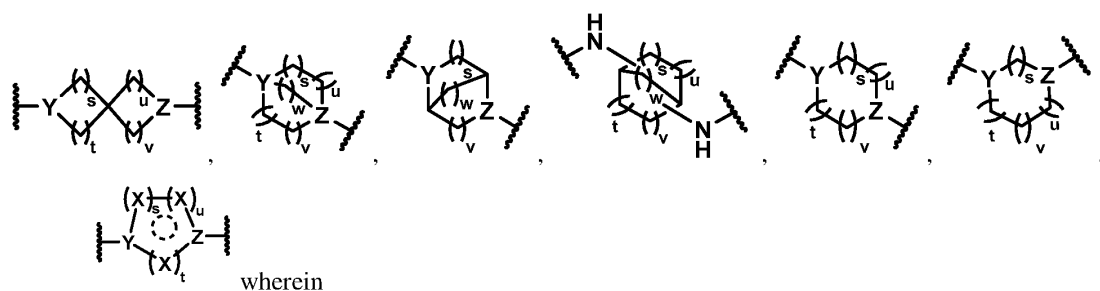
In a preferred embodiment, each  $B^3$  is independently selected from bond;  $C_{1-10}$ , preferably  $C_{1-4}$ , more preferably  $C_{1-2}$  alkylene;  $C_{1-10}$ , preferably  $C_{1-4}$ , more preferably  $C_{1-2}$  heteroalkylene group comprising one or two N atoms;  $NR(C_{1-10}, C_{1-4}, \text{ or } C_{1-2} \text{ alkylene})NR$ ;  $(C_{1-10}, C_{1-4}, \text{ or } C_{1-2} \text{ alkylene})NR$ ;  $NR(C_{1-10}, C_{1-4}, \text{ or } C_{1-2} \text{ alkylene})$ ;  $C(O)$ ;  $C(O)CR_2$ ;  $C(O)(C_{6-10} \text{ aryl})CR_2$ ;  $C(O)(C_{5-10} \text{ heteroaryl})CR_2$ ;  $C(O)(C_{6-10} \text{ aryl})CR_2$ ;  $C(O)(C_{5-10} \text{ heteroaryl})CR_2$ ;  $C(O)(C_{6-10} \text{ aryl})CR_2$ ;  $C(O)(C_{5-10} \text{ heteroaryl})CR_2$ ;  $C(S)NR$ ;  $C(S)NR(C_{6-10} \text{ aryl})CR_2$ ; and  $C(S)NR(C_{5-10} \text{ heteroaryl})CR_2$ .

More preferably,  $B^3$  is bond,  $C(O)CH_2CH_2C(O)$ ,  $NHCH_2CH_2NH$ ,  $CH_2CH_2NH$ ,  $NHCH_2CH_2$ ,



In a preferred embodiment, moiety  $A$  has the structure  $A^2$ ;  $m$  is 1;  $b^1$  is 0 or 1;  $b^2$  is 1;  $b^3$  is 1; and  $z$  is 1; and each of  $s$ ,  $u$ ,  $t$ , and  $v$ , if present, is 1, and  $w$  is 0 or 1.

In an embodiment,  $B^2$  is independently selected from:



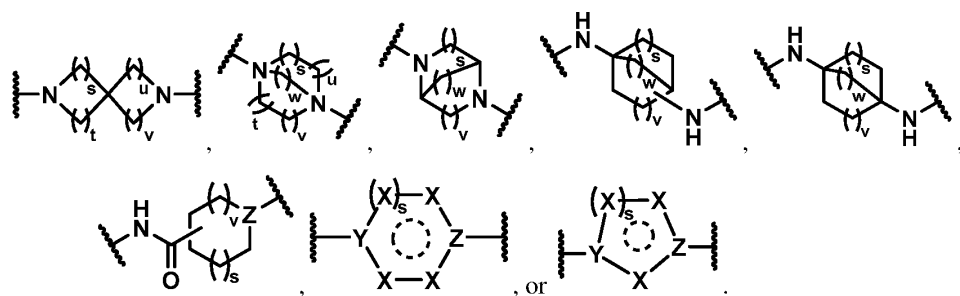
each s, u, t, and v is independently 0, 1, or 2;

each w is independently 0, 1, 2, or 3; and

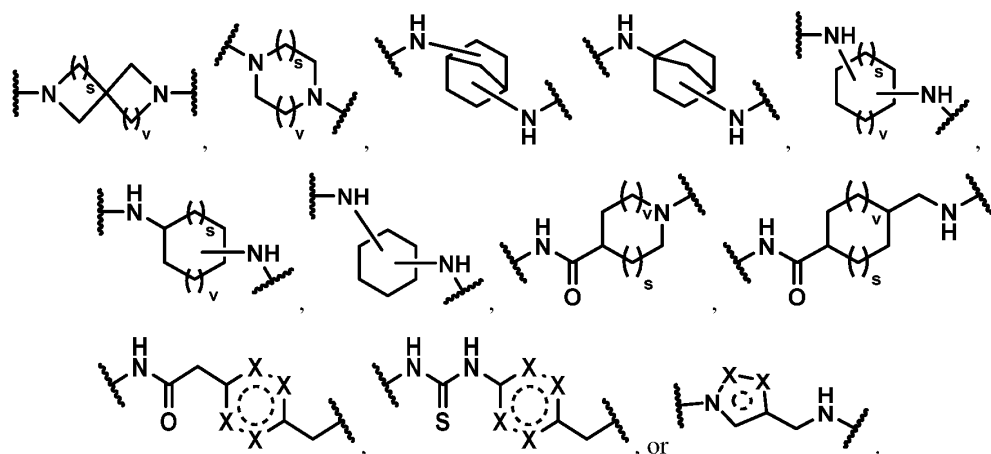
- 5 each X is independently N, NH, NR, S, S(O), SO<sub>2</sub>, O, C, CR, CH, CR<sub>2</sub> or CH<sub>2</sub>; preferably N.

In a preferred embodiment, each of s, u, t, and v, if present, is 1, and w is 0 or 1.

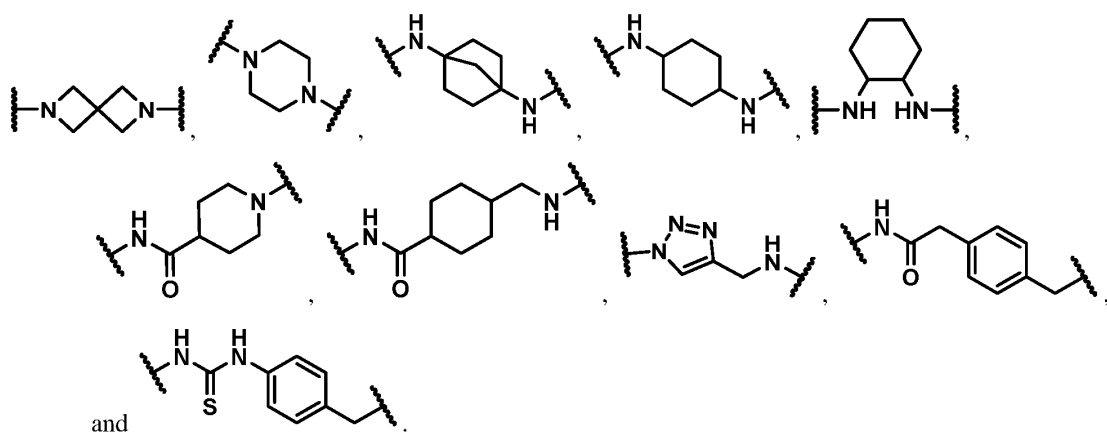
In a preferred embodiment, **B**<sup>2</sup> is selected from:



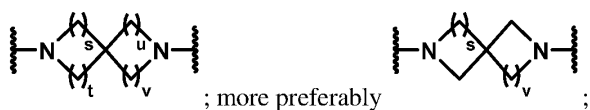
- 10 In a more preferred embodiment, **B**<sup>2</sup> is selected from:



In a most preferred embodiment, **B**<sup>2</sup> is selected from:

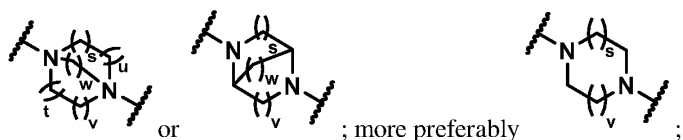


In one particular embodiment,  $B^2$  is

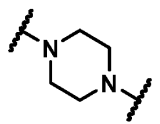


5 most preferably

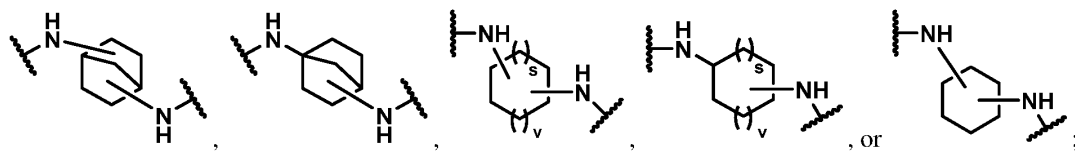
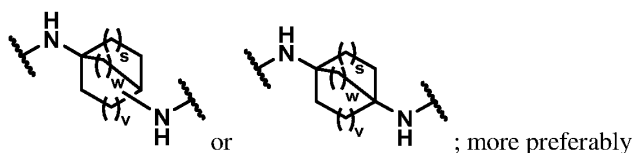
In another particular embodiment,  $B^2$  is



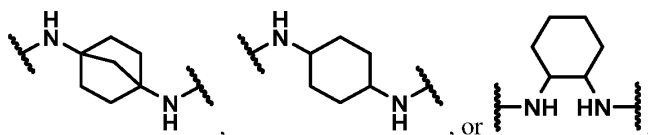
most preferably

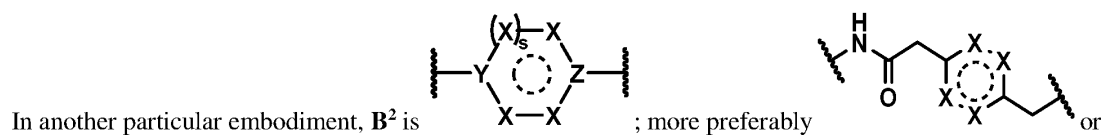
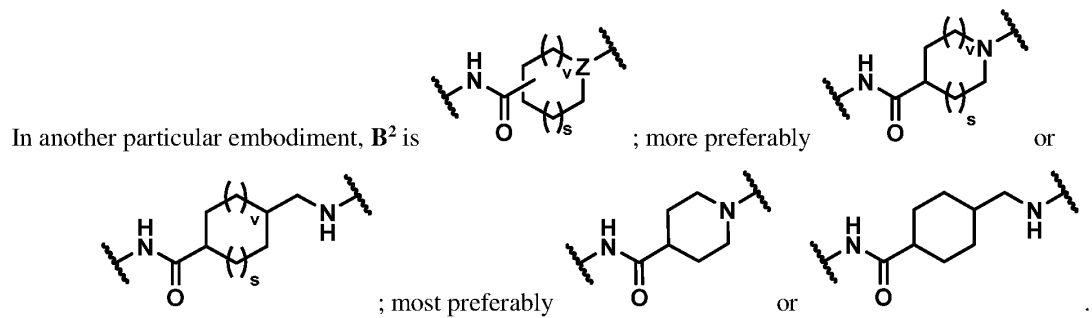


In another particular embodiment,  $B^2$  is

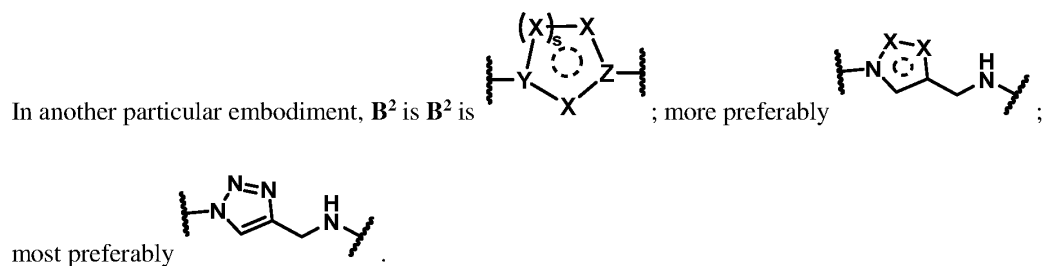


10 most preferably

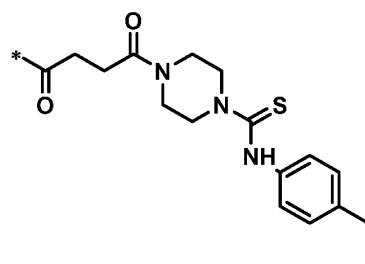
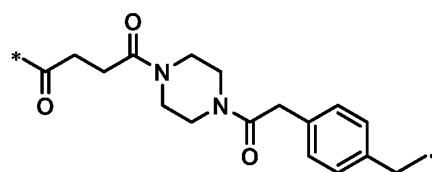
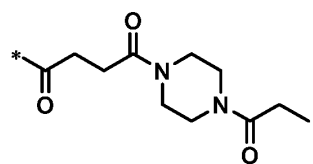
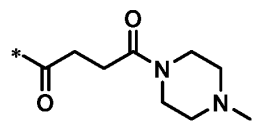
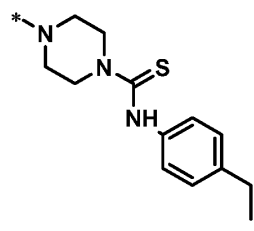
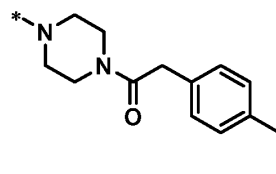
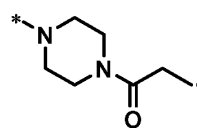
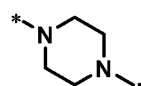
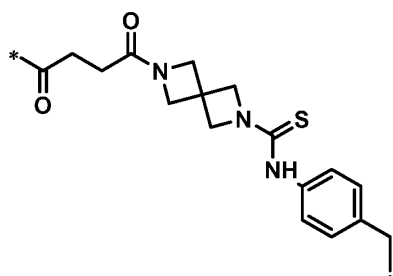
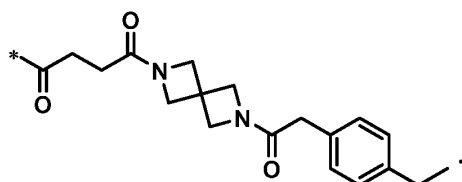
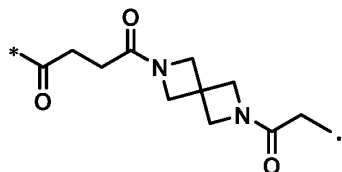
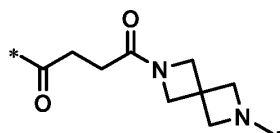
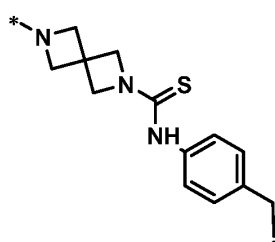
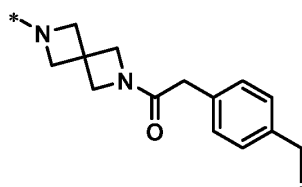
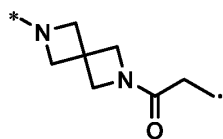
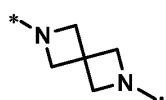


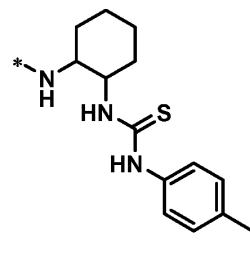
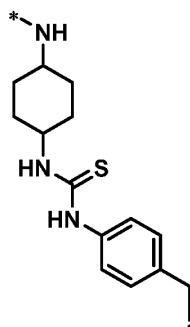
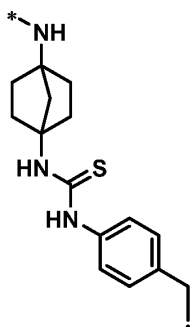
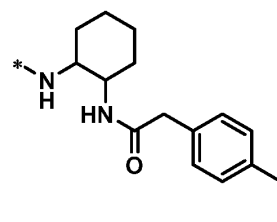
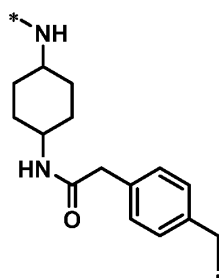
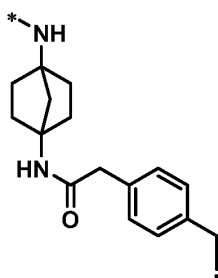
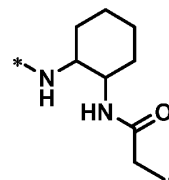
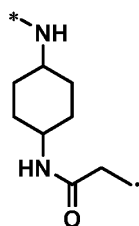
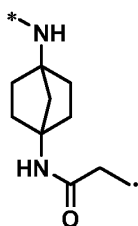
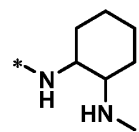
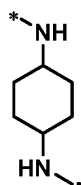
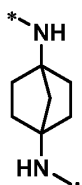


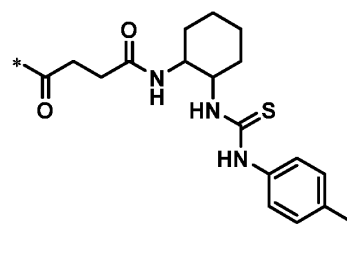
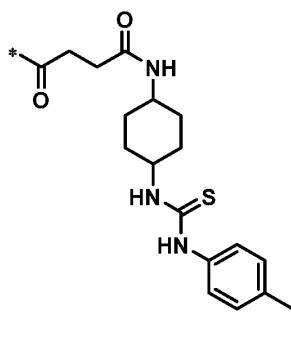
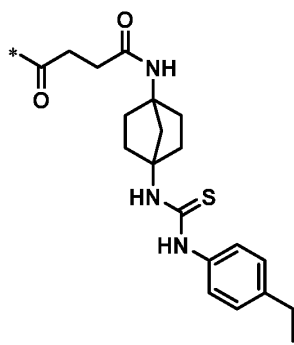
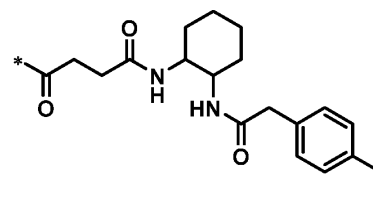
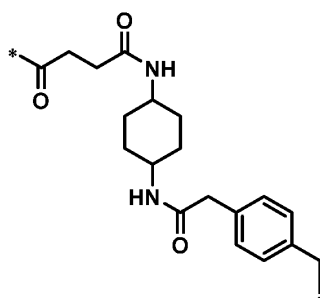
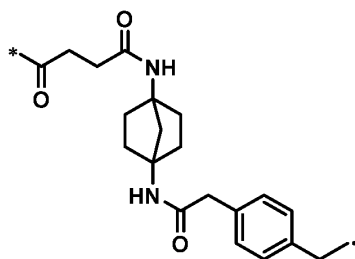
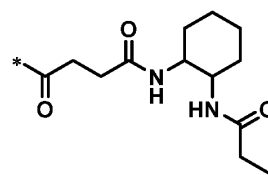
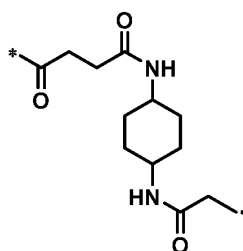
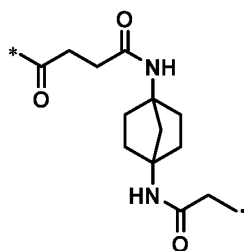
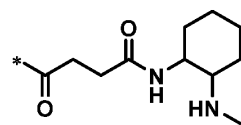
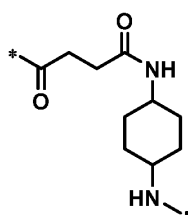
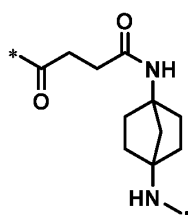
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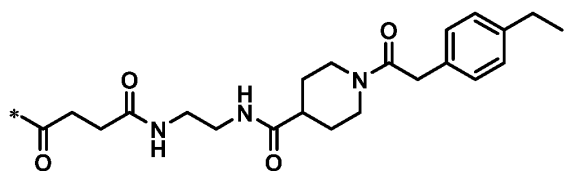
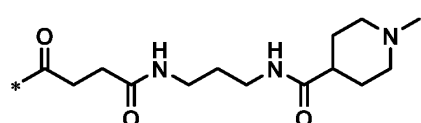
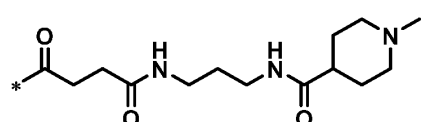
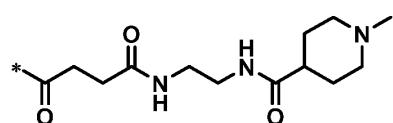
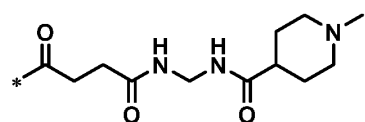
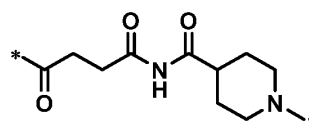
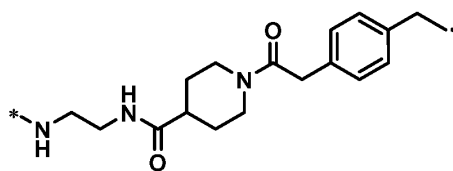
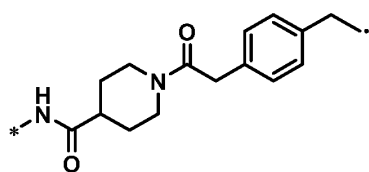
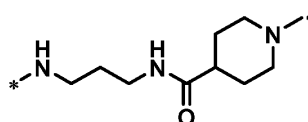
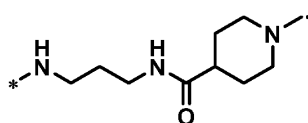
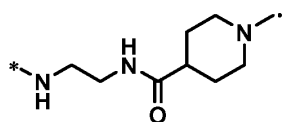
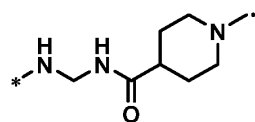
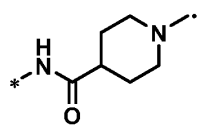


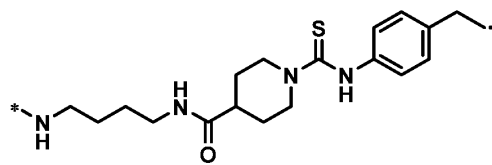
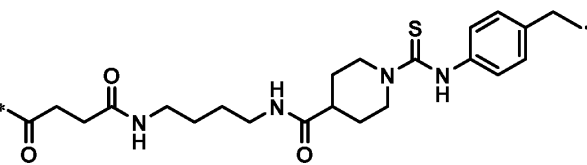
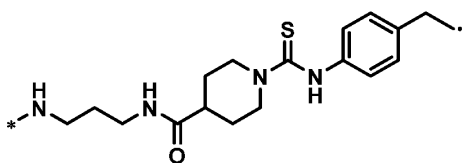
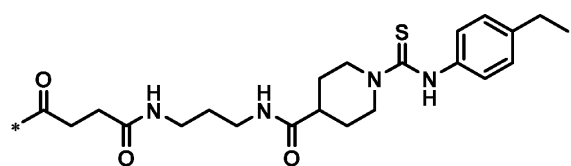
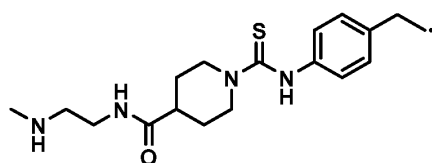
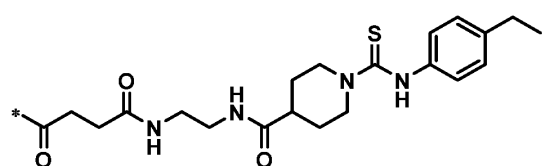
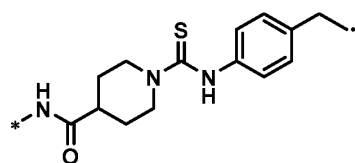
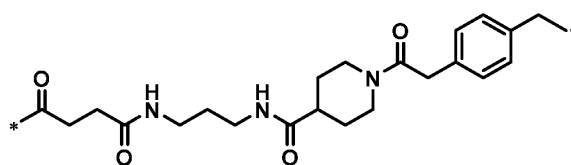
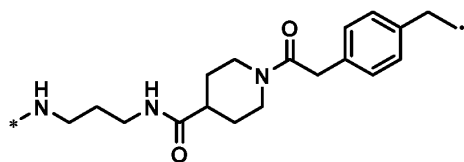
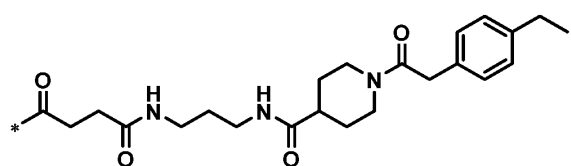
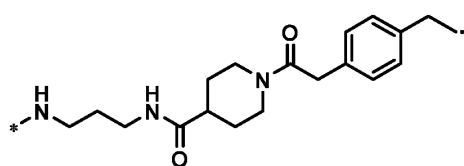
Moiety **B** preferably comprises, more preferably consists of a unit from the following list:

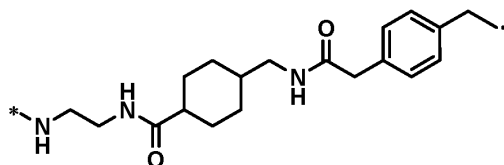
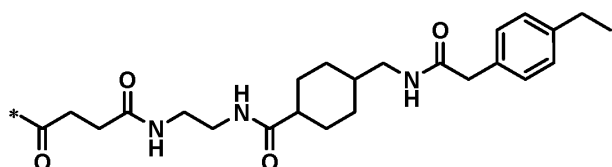
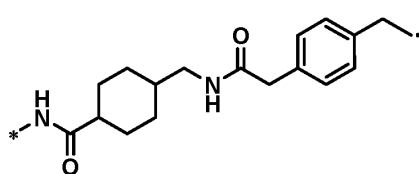
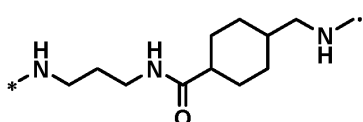
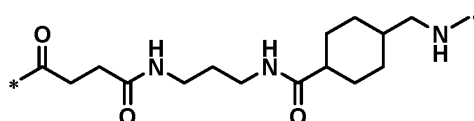
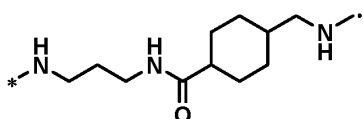
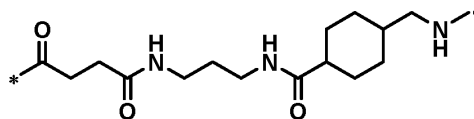
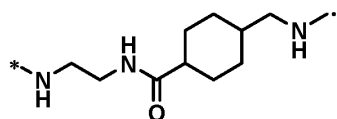
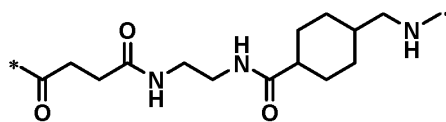
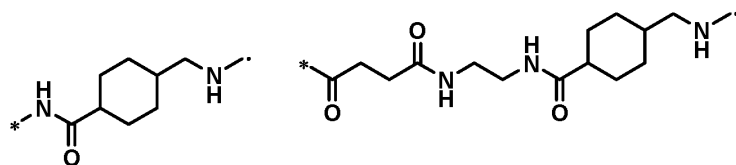


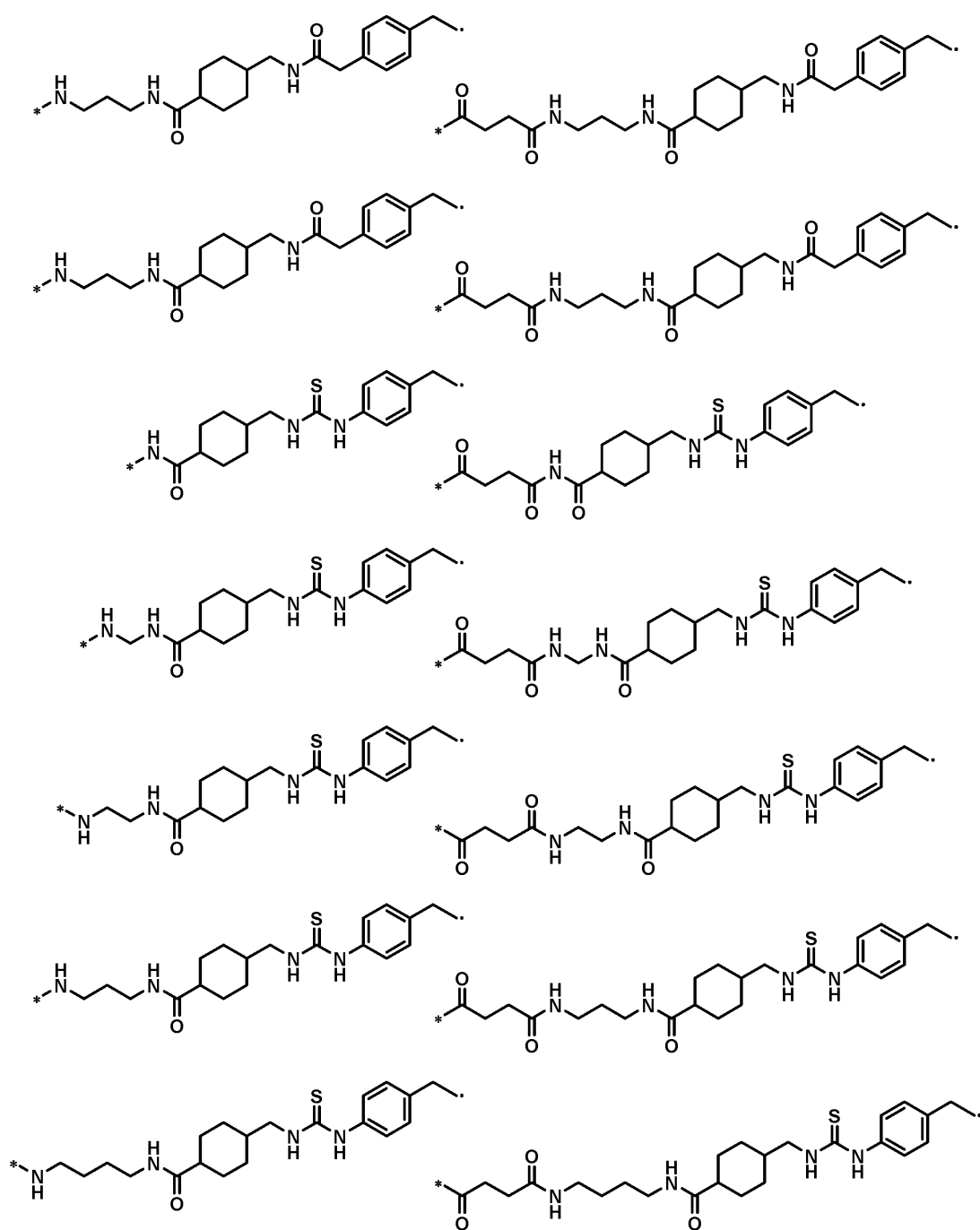


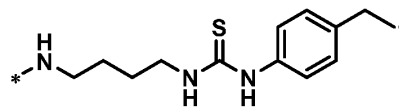
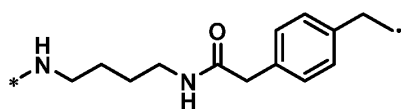
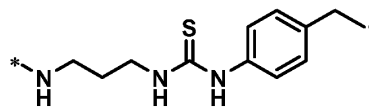
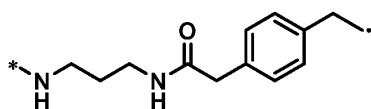
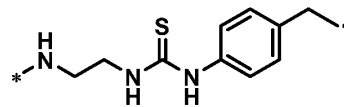
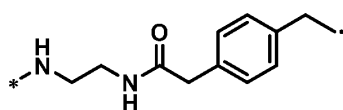
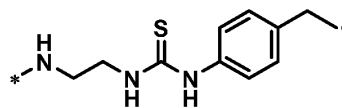
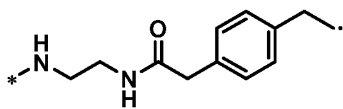
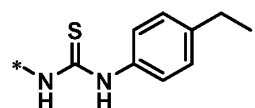
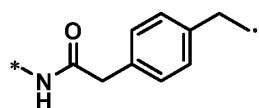


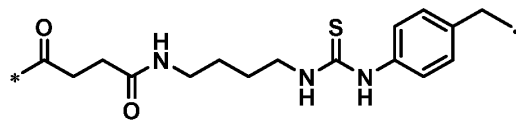
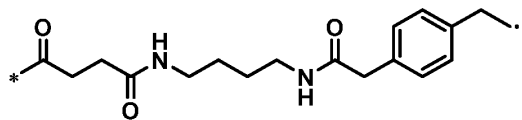
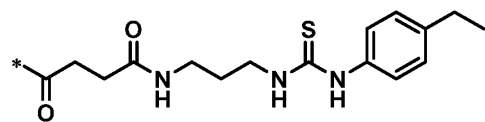
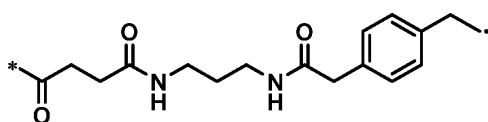
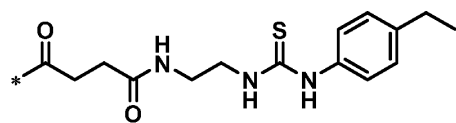
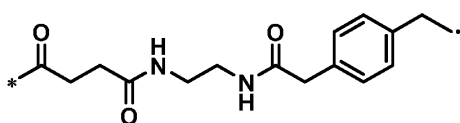
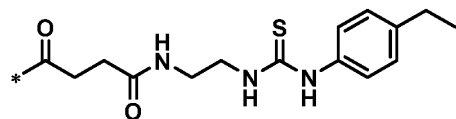
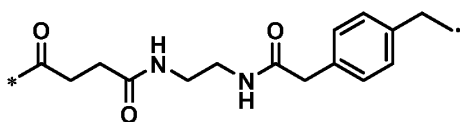
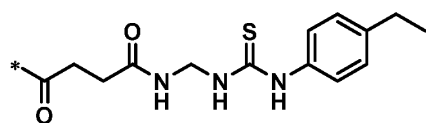
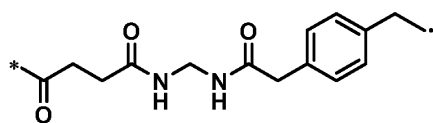
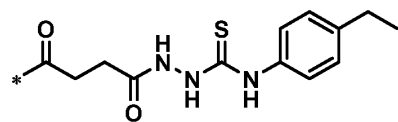
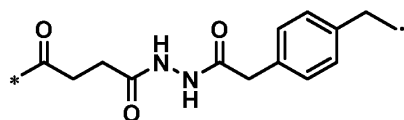
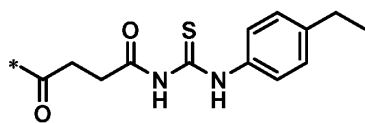
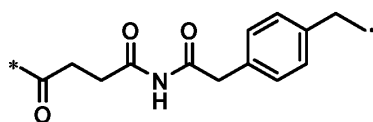


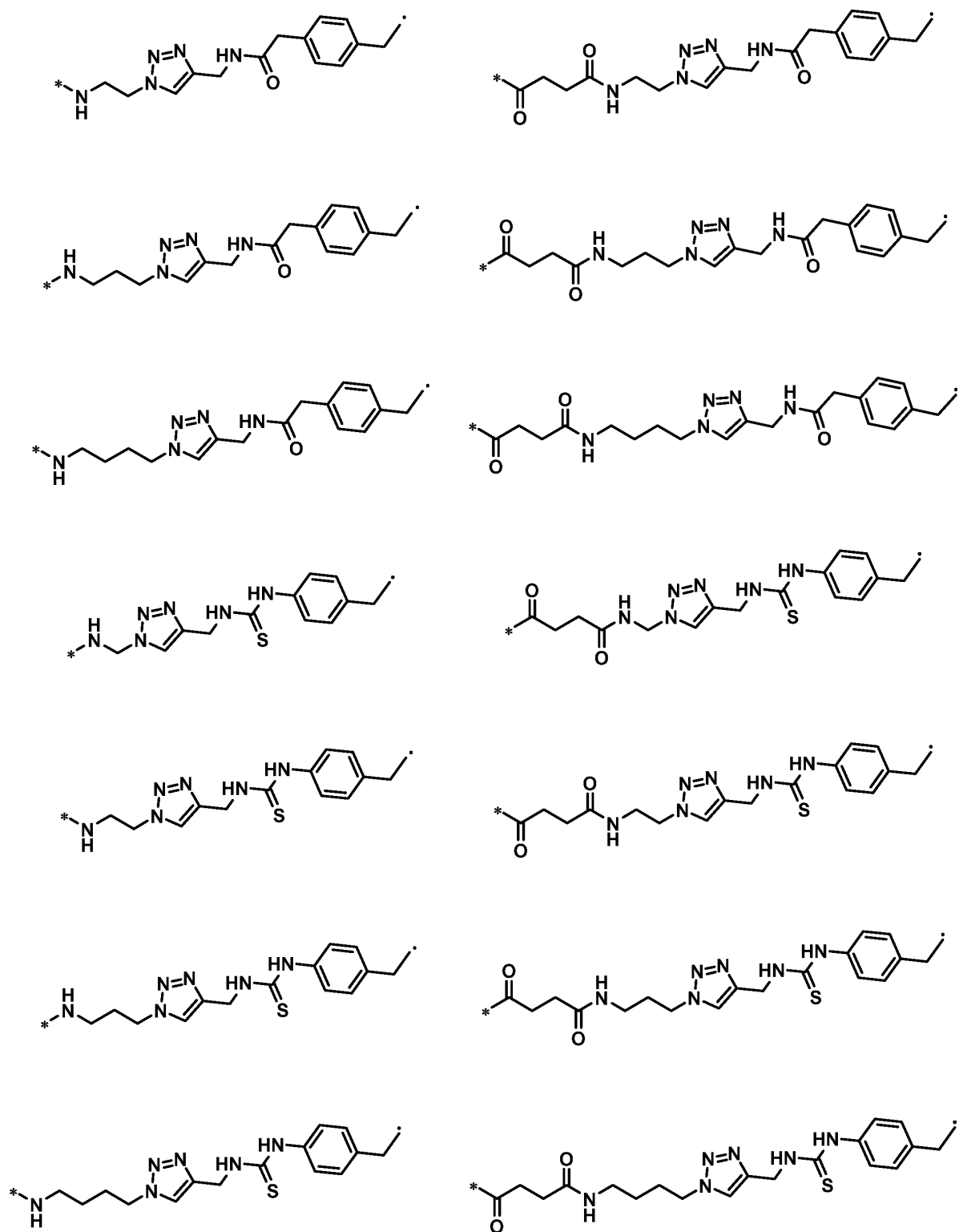












Moiety C

Moiety C in the present invention represents a payload, which can be generally any atom (including H), molecule or particle, and can function as a therapeutic or diagnostic agent. Preferably, moiety C is not a hydrogen atom, and may be selected from: a chelating agent group suitable for radiolabelling; a radioactive group comprising a radioisotope; a chelate of a radioactive isotope with a chelating agent; a fluorophore group; a cytotoxic and/or cytostatic agent; immunomodulator agent; or a protein

Payload moiety C may comprise or consist of a chelating agent (chelator) for radiolabeling.

Payload moiety C may be a radioactive group comprising or consisting of radioisotope including isotopes such as  $^{223}\text{Ra}$ ,  $^{89}\text{Sr}$ ,  $^{94\text{m}}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{203}\text{Pb}$ ,  $^{66}\text{Ga}$ ,  $^{67}\text{Ga}$ ,  $^{68}\text{Ga}$ ,  $^{43}\text{Sc}$ ,  $^{44}\text{Sc}$ ,  $^{47}\text{Sc}$ ,  $^{111}\text{In}$ ,  $^{97}\text{Ru}$ ,  $^{62}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{86}\text{Y}$ ,  $^{88}\text{Y}$ ,  $^{90}\text{Y}$ ,  $^{121}\text{Sn}$ ,  $^{161}\text{Tb}$ ,  $^{153}\text{Sm}$ ,  $^{166}\text{Ho}$ ,  $^{105}\text{Rh}$ ,  $^{177}\text{Lu}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{18}\text{F}$ ,  $^{211}\text{At}$ ,  $^{225}\text{Ac}$ ,  $^{89}\text{Sr}$ ,  $^{117\text{m}}\text{Sn}$  and  $^{169}\text{Er}$ . Preferably, In one preferred embodiment the radioisotopes are  $^{68}\text{Ga}$ ,  $^{62}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{111}\text{In}$ ,  $^{18}\text{F}$ .

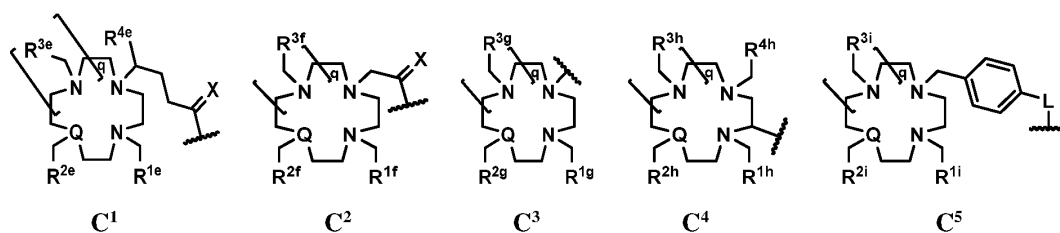
In a preferred embodiment,  $^{18}\text{F}$  is bound to a cation; more preferably, the cation is aluminium (Al) in any of its oxidation states.

The payload may be a chelate of an isotope, preferably of a radioactive isotope, listed under above.

Particularly preferred embodiments for the moiety C as well as the compound according to the present invention are shown in the appended claims.

The chelating agent group suitable for radiolabelling may be derived from 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA), 2,2',2''-(1,4,7-triazonane-1,4-diyl)diacetic acid (NODA), 2,2'-((2-((4-(2-amino-2-oxoethyl)benzyl)(carboxymethyl)amino)cyclohexyl)azanediyl)diacetic acid] (RESCA), sulfur colloid, diethylenetriaminepentaacetic acid (DTPA), ethylenediaminetetraacetic acid (EDTA), 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), [2,2',2''-(10-(4-((2-aminoethyl)amino)-1-carboxy-4-oxobutyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid DOTA-GA), [1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA), iminodiacetic acid, bis(carboxymethylimidazole)glycine, 6-Hydrazinopyridine-3-carboxylic acid (HYNIC).

The chelating agent group may have a structure according to one of the following formulae C<sup>1</sup>, C<sup>2</sup>, C<sup>3</sup>, C<sup>4</sup>, and C<sup>5</sup>:



wherein:

each q is independently 0, 1, 2, 3, 4 or 5; preferably 0;

R<sup>1e</sup>, R<sup>1f</sup>, R<sup>1g</sup>, R<sup>1h</sup>, and R<sup>1i</sup> are each independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH;

- 5 R<sup>2e</sup>, R<sup>2f</sup>, R<sup>2g</sup>, R<sup>2h</sup>, and R<sup>2i</sup> are each independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH;

R<sup>3e</sup>, R<sup>3f</sup>, R<sup>3g</sup>, R<sup>3h</sup>, R<sup>4h</sup>, and R<sup>3i</sup> are each independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH; and

- and R<sup>4e</sup> is independently H, COOH, aryl-COOH or heteroaryl-COOH, with the proviso that when q is 0,  
10 R<sup>4e</sup> is H;

each X is independently NH, NR, S, O, CR<sub>2</sub>, or H,H; preferably O;

each Q is N or O, preferably N;

wherein when Q is O, CH<sub>2</sub>R<sup>2e</sup>, CH<sub>2</sub>R<sup>2f</sup>, CH<sub>2</sub>R<sup>2g</sup>, CH<sub>2</sub>R<sup>2h</sup>, and CH<sub>2</sub>R<sup>2i</sup> is absent; and

L is -CH<sub>2</sub>C(O)- or -NHC(S)-.

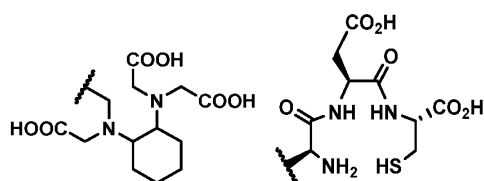
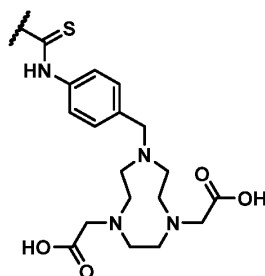
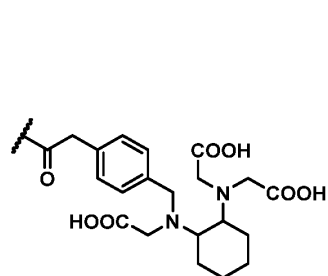
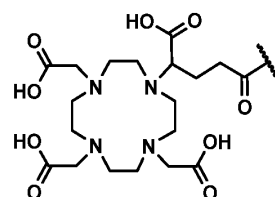
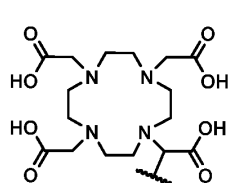
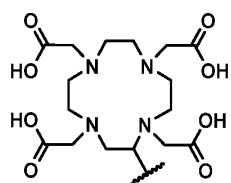
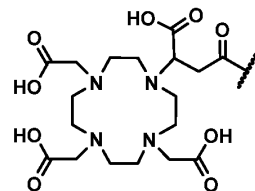
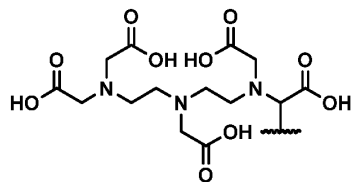
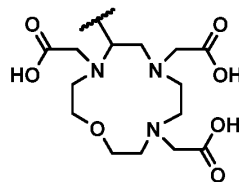
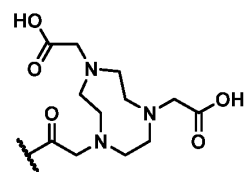
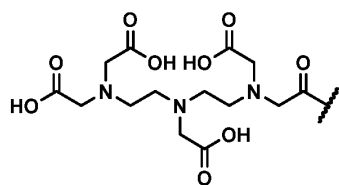
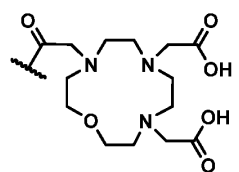
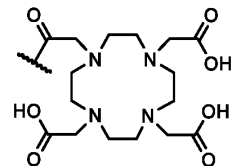
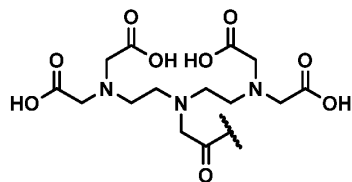
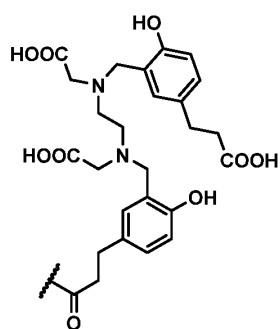
- 15 In a preferred embodiment, q is 0, R<sup>1e</sup>, R<sup>1f</sup>, R<sup>1g</sup>, R<sup>1h</sup>, R<sup>1i</sup>, R<sup>2e</sup>, R<sup>2f</sup>, R<sup>2g</sup>, R<sup>2h</sup>, and R<sup>2i</sup> are each independently COOH, aryl-COOH or heteroaryl-COOH; preferably COOH;

R<sup>3e</sup>, R<sup>3f</sup>, R<sup>3g</sup>, R<sup>3h</sup>, R<sup>4h</sup>, and R<sup>3i</sup> are each independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH; and

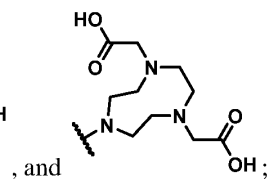
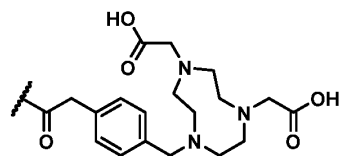
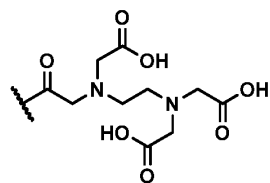
R<sup>4e</sup> is H; and

- 20 Q is N.

The chelating agent group may have a structure selected from the following:



5



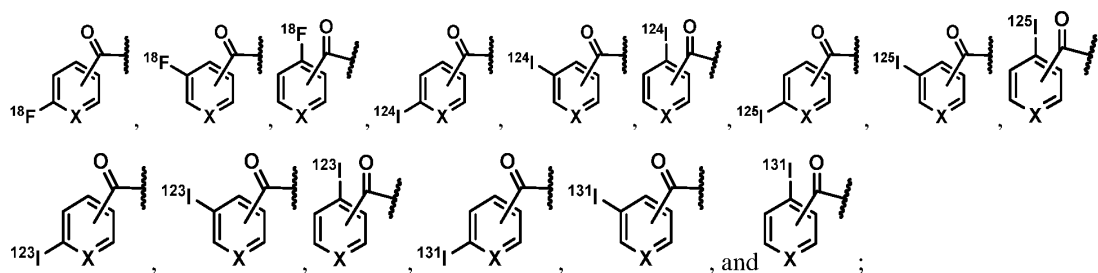
, and

The radioactive group, in general, may comprise a radioisotope is selected from  $^{223}\text{Ra}$ ,  $^{89}\text{Sr}$ ,  $^{94\text{m}}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{203}\text{Pb}$ ,  $^{67}\text{Ga}$ ,  $^{68}\text{Ga}$ ,  $^{47}\text{Sc}$ ,  $^{111}\text{In}$ ,  $^{97}\text{Ru}$ ,  $^{62}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{86}\text{Y}$ ,  $^{88}\text{Y}$ ,  $^{90}\text{Y}$ ,  $^{121}\text{Sn}$ ,  $^{161}\text{Tb}$ ,  $^{153}\text{Sm}$ ,  $^{166}\text{Ho}$ ,  $^{105}\text{Rh}$ ,  $^{177}\text{Lu}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{18}\text{F}$ ,  $^{211}\text{At}$ ,  $^{225}\text{Ac}$ ,  $^{89}\text{Sr}$ ,  $^{117\text{m}}\text{Sn}$  and  $^{169}\text{Er}$ .

In the radioactive groups useful in the present invention, e.g., chelate complexes with one or more of the chelators described herein,  $^{18}\text{F}$ , when present, is preferably bound to chelated Al, Zr, Si, Ga, or In, more preferably  $^{18}\text{F}$  is bound to Al chelated by the chelator. In the context of the present disclosure, also complexes of the chelators described herein are contemplated wherein F is present, which is preferably bound to chelated Al, Zr, Si, Ga, or In, wherein F can contain any isotope of fluorine, e.g.,  $^{18}\text{F}$  and/or  $^{19}\text{F}$ .

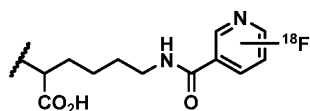
Particularly useful diagnostic or therapeutic agents **C** for use in the present invention are chelates of a radioactive isotope listed under above with any of the chelating agents listed under (a) above.

Alternatively, diagnostic or therapeutic agents **C** is a group selected from any of the following structures comprising covalently bound radioactive nuclides:



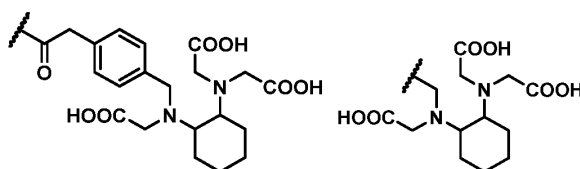
wherein X is as defined further above, and can be, e.g., N, S, S(O),  $\text{SO}_2$ , O, CR, CH; preferably CH or N.

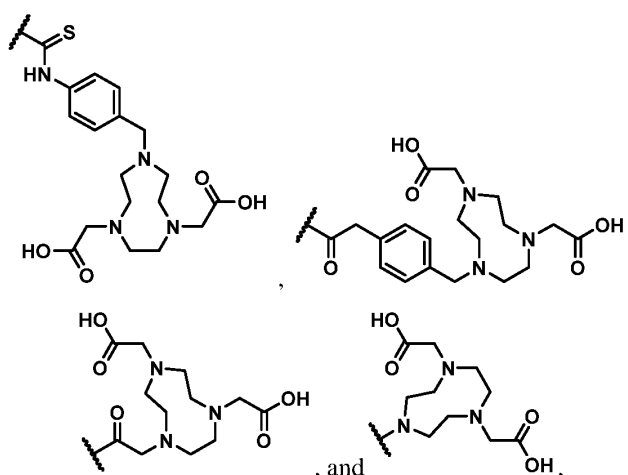
For instance, a preferred structure comprising covalently a bound radioactive nuclide is



In the context of the present disclosure, compounds are also contemplated wherein any isotope of F or I can be present instead of  $^{18}\text{F}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$  or  $^{131}\text{I}$ , as the case may be.

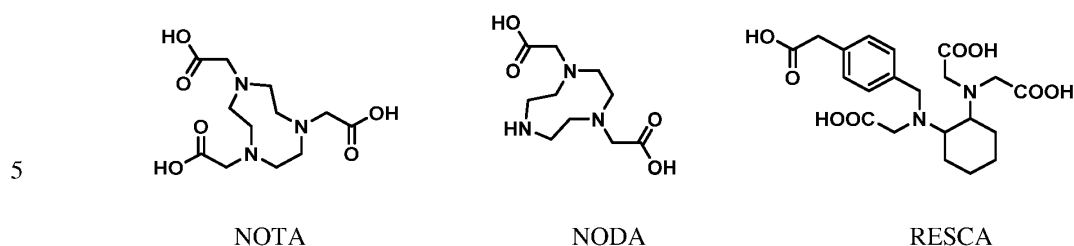
Most preferably, moiety **C** is a chelator selected from:





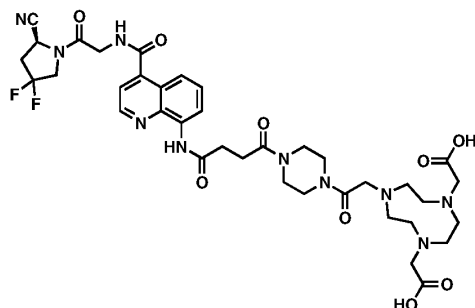
and even more preferably wherein  $^{18}\text{F}$  is bound to Al chelated by the chelator.

These chelators are derived from derived from:

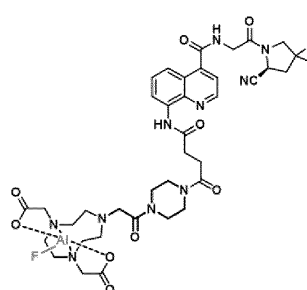


Without wishing to be bound by theory, it is believed that these chelators and their Al-F complexes are particularly advantageous from the viewpoint of activity labelling, stability, especially with respect to chemical and radiolytic stability and stability.

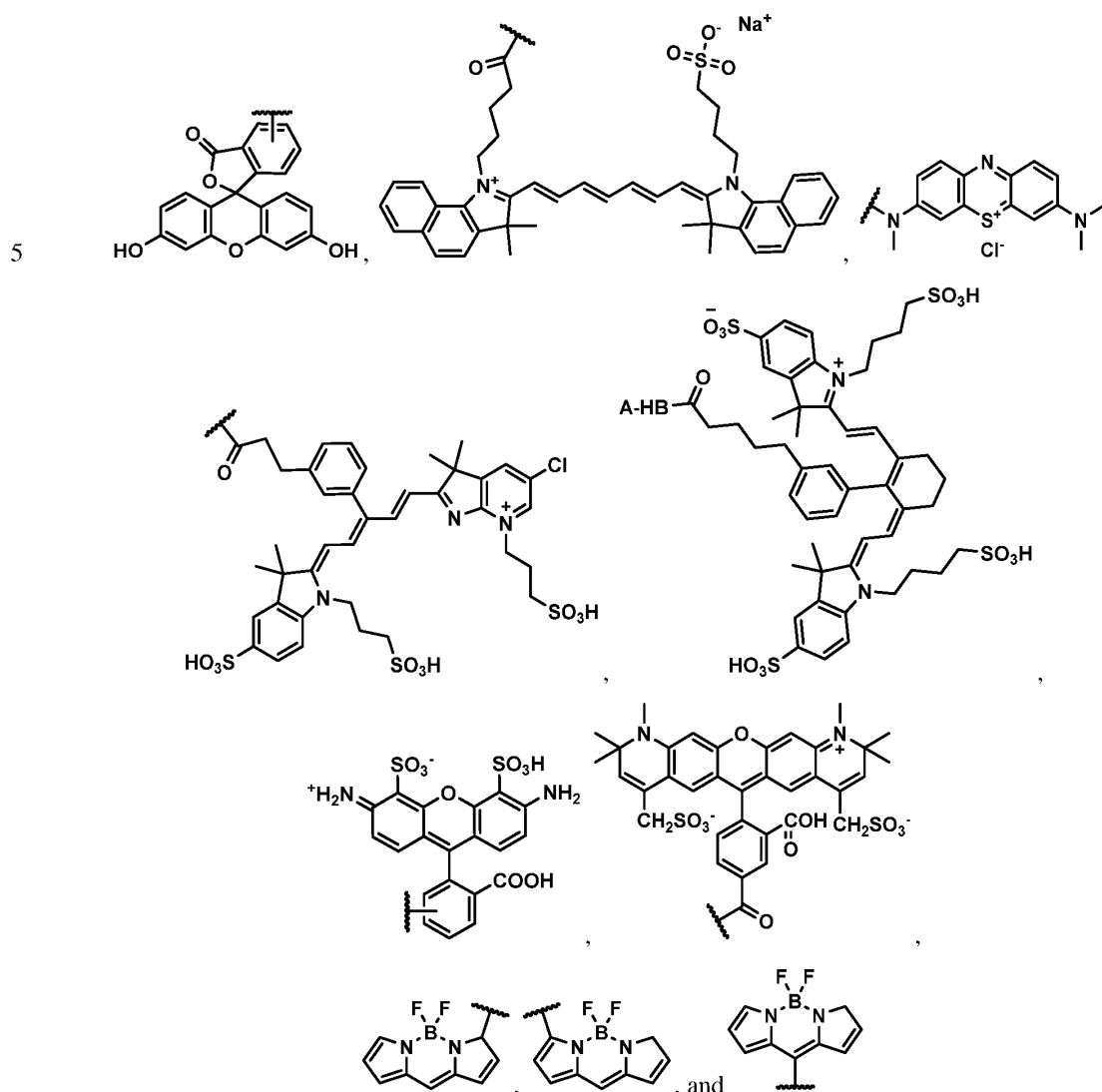
- 10 Preferred compounds are listed in the appended claims, especially claim 14, as well as chelate complexes of thereof with ions or radionuclides as listed above, such as AlF (containing, e.g.,  $^{18}\text{F}$  and/or  $^{19}\text{F}$  bound to Al), or Ga (e.g.,  $^{67}\text{Ga}$  and/or  $^{68}\text{Ga}$  in any oxidation state). Particularly preferred compounds are **1** and its AlF complex **AlF@1**, which can contain  $^{18}\text{F}$  and/or  $^{19}\text{F}$ , even more preferably  $^{18}\text{F}$ , bound to Al.



15

**1****AlF@1**

Alternatively, moiety **C** can be a fluorophore group. Preferably, the fluorophore group is selected from a xanthene dye, acridine dye, oxazine dye, cyanine dye, styryl dye, coumarine dye, porphine dye, fluorescent metal-ligand-complex, fluorescent protein, nanocrystals, perylene dye, boron-dipyrromethene dye and phthalocyanine dye. Preferred structures may be selected from the following:



Alternatively, moiety **C** can be a cytotoxic and/or cytostatic agent, e.g., a chemotherapeutic agent.

- 10 Preferably, such therapeutic agents are selected from the group consisting of topoisomerase inhibitors, alkylating agents, antimetabolites, antibiotics, mitotic disrupters, DNA intercalating agents, DNA synthesis inhibitors, DNA-RNA transcription regulator, enzyme inhibitors, gene regulators, hormone response modifiers, hypoxia-selective cytotoxins, epidermal growth factor inhibitors, anti-vascular agents and a combination of two or more thereof.

Such agents can inhibit or prevent the function of cells and/or cause destruction of cells. Examples of cytotoxic agents include radioactive isotopes, chemotherapeutic agents, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including synthetic analogues and derivatives thereof. The cytotoxic agent may be selected from the group consisting of an auristatin, a DNA minor groove binding agent, a DNA minor groove alkylating agent, an enediyne, a lexitropsin, a duocarmycin, a taxane, a puromycin, a dolastatin, a maytansinoid and a vinca alkaloid or a combination of two or more thereof. Preferred cytotoxic and/or cytostatic payload moieties are listed in claim 8 (c).

In one embodiment, the payload is a chemotherapeutic agent selected from the group consisting of a topoisomerase inhibitor, an alkylating agent (*e.g.*, nitrogen mustards; ethylenimines; alkylsulfonates; triazines; piperazines; and nitrosureas), an antimetabolite (*e.g.*, mercaptopurine, thioguanine, 5-fluorouracil), an antibiotics (*e.g.*, anthracyclines, dactinomycin, bleomycin, adriamycin, mithramycin, dactinomycin) a mitotic disrupter (*e.g.*, plant alkaloids – such as vincristine and/or microtubule antagonists – such as paclitaxel), a DNA methylating agent, a DNA intercalating agent (*e.g.*, carboplatin and/or cisplatin, daunomycin and/or doxorubicin and/or bleomycin and/or thalidomide), a DNA synthesis inhibitor, a DNA-RNA transcription regulator, an enzyme inhibitor, a gene regulator, a hormone response modifier, a hypoxia-selective cytotoxin (*e.g.*, tirapazamine), an epidermal growth factor inhibitor, an anti-vascular agent (*e.g.*, xanthenone 5,6-dimethylxanthenone-4-acetic acid), a radiation-activated prodrug (*e.g.*, nitroarylmethyl quaternary (NMQ) salts) or a bioreductive drug or a combination of two or more thereof. In some embodiments, the payload (*i.e.*, moiety **C**) is not derived from an anthracycline, preferably not derived from PNU 159682.

The chemotherapeutic agent may be selected from the group consisting of Erlotinib (TARCEVA®), Bortezomib (VELCADE®), Fulvestrant (FASLODEX®), Sutent (SU11248), Letrozole (FEMARA®), Imatinib mesylate (GLEEVEC®), PTK787/ZK 222584, Oxaliplatin (Eloxatin®), 5-FU (5-fluorouracil), Leucovorin, Rapamycin (Sirolimus, RAPAMUNE®), Lapatinib (GSK572016), Lonafermin (SCH 66336), Sorafenib (BAY43-9006), and Gefitinib (IRESSA®), AG1478, AG1571 (SU 5271; Sugen) or a combination of two or more thereof.

The chemotherapeutic agent may be an alkylating agent – such as thiotepa, CYTOXAN® and/or cyclophosphamide; an alkyl sulfonate – such as busulfan, improsulfan and/or piposulfan; an aziridine – such as benzodopa, carboquone, meturedopa and/or uredopa; ethylenimines and/or methylamelamines – such as altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and/or trimethylmelamine; acetogenin – such as bullatacin and/or bullatacinone; camptothecin; bryostatin; callystatin; cryptophycins; dolastatin; duocarmycin; eleutherobin; pancratistatin; sargactin; spongistatin; nitrogen mustards – such as chlorambucil, chlornaphazine, chlorthophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide and/or uracil mustard; nitrosureas – such as carmustine,

- chlorozotocin, fotemustine, lomustine, nimustine, and/or ranimustine; dynemicin; bisphosphonates - such as clodronate; an esperamicin; a neocarzinostatin chromophore; aclacinomysins, actinomycin, aithramycin, azaserine, bleomycins, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN®.
- 5 doxorubicin - such as morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and/or deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins - such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites - such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues - such as denopterin,
- 10 methotrexate, pteropterin, trimetrexate; purine analogues - such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogues - such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens - such as calusterone, dromostanolone propionate, epitio stanol, mepitio stanane, testolactone; anti-adrenals - such as aminogluthethimide, mitotane, trilostane; folic acid replenisher - such as frolinic acid; aceglatone;
- 15 aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; macrocyclic depsipeptides such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane;
- 20 rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes - such as verracurin A, roridin A and/or anguidine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside; cyclophosphamide; thiotepa; taxoids - such as TAXOL®, paclitaxel, abraxane, and/or TAXOTERE®, doxetaxel; chloranbucil; GEMZAR®, gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum
- 25 analogues - such as cisplatin and carboplatin; vinblastine; platinum; etoposide; ifosfamide; mitoxantrone; vincristine; NAVELBINE®, vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; topoisomerase inhibitor RFS 2000; difluoromethylomithine (DMFO); retinoids - such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids, derivatives or combinations of two or more of any of the above.
- 30 The payload may be a tubulin disruptor including but are not limited to: taxanes - such as paclitaxel and docetaxel, vinca alkaloids, discodermolide, epothilones A and B, desoxyepothilone, cryptophycins, curacin A, combretastatin A-4-phosphate, BMS 247550, BMS 184476, BMS 188791; LEP, RPR 109881A, EPO 906, TXD 258, ZD 6126, vinflunine, LU 103793, dolastatin 10, E7010, T138067 and T900607, colchicine, phenstatin, chalcones, indanocine, T138067, oncocidin, vincristine, vinblastine,
- 35 vinorelbine, vinflunine, halichondrin B, isohomohalichondrin B, ER-86526, pironetin, spongistatin 1, spiket P, cryptophycin 1, LU103793 (cematodin or cemadotin), rhizoxin, sarcodictyin, eleutherobin,

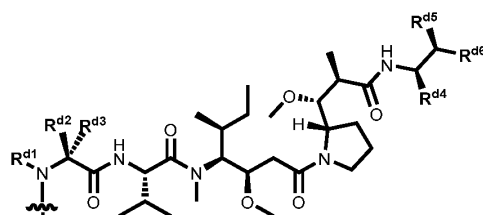
laulilamide, VP-16 and D-24851 and pharmaceutically acceptable salts, acids, derivatives or combinations of two or more of any of the above.

The payload may be a DNA intercalator including but are not limited to: acridines, actinomycins, anthracyclines, benzothiopyranoindazoles, pixantrone, crisnatol, brostallicin, CI-958, doxorubicin, (adriamycin), actinomycin D, daunorubicin (daunomycin), bleomycin, idarubicin, mitoxantrone, cyclophosphamide, melphalan, mitomycin C, bizelesin, etoposide, mitoxantrone, SN-38, carboplatin, cisplatin, actinomycin D, amsacrine, DACA, pyrazoloacridine, irinotecan and topotecan and pharmaceutically acceptable salts, acids, derivatives or combinations of two or more of any of the above.

The payload may be an anti-hormonal agent that acts to regulate or inhibit hormone action on tumours - such as anti-estrogens and selective estrogen receptor modulators, including, but not limited to, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and/or fareston toremifene and pharmaceutically acceptable salts, acids, derivatives or combinations of two or more of any of the above. The payload may be an aromatase inhibitor that inhibits the enzyme aromatase, which regulates estrogen production in the adrenal glands - such as, for example, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, AROMASIN®, exemestane, formestanie, fadrozole, RIVISOR®, vorozole, FEMARA®, letrozole, and ARIMIDEX® and/or anastrozole and pharmaceutically acceptable salts, acids, derivatives or combinations of two or more of any of the above.

The payload may be an anti-androgen such as flutamide, nilutamide, bicalutamide, leuprolide, goserelin and/or troxacitabine and pharmaceutically acceptable salts, acids, derivatives or combinations of two or more of any of the above.

In a preferred embodiment, moiety **C** is an auristatin (i.e., having a structure derived from an auristatin compound family member) or an auristatin derivative. More preferably, moiety **C** has a structure according to the following formula:



wherein:

$R^{1d}$  is independently H or C<sub>1</sub>-C<sub>6</sub> alkyl; preferably H or CH<sub>3</sub>;

$R^{2d}$  is independently C<sub>1</sub>-C<sub>6</sub> alkyl; preferably CH<sub>3</sub> or iPr;

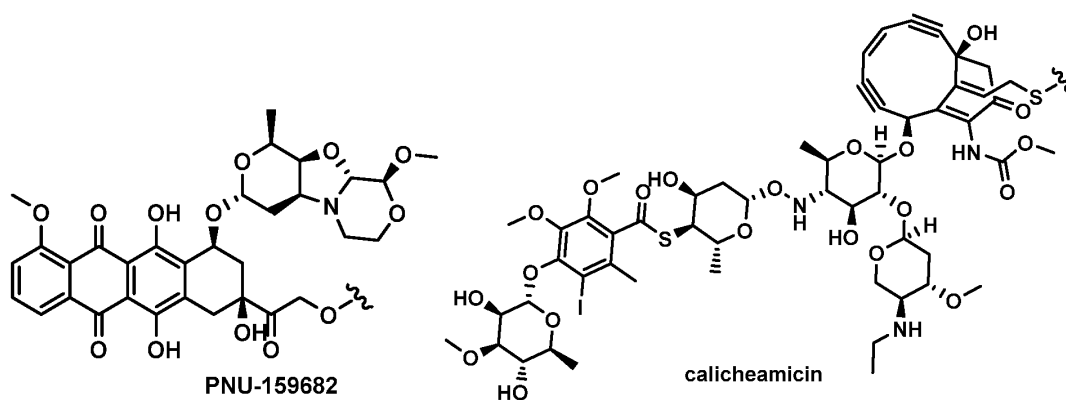
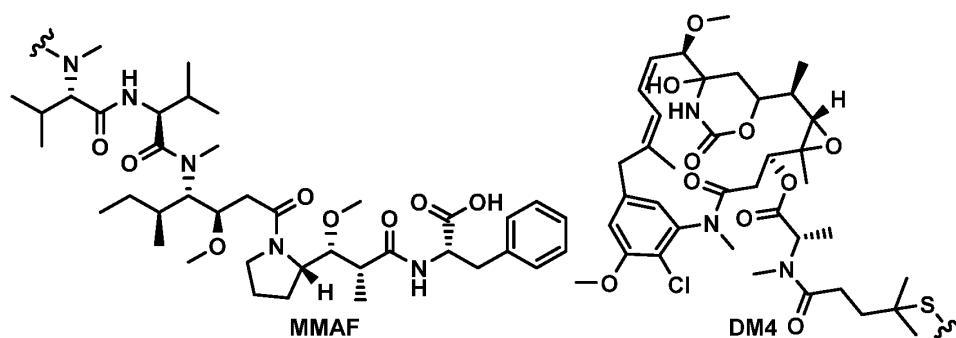
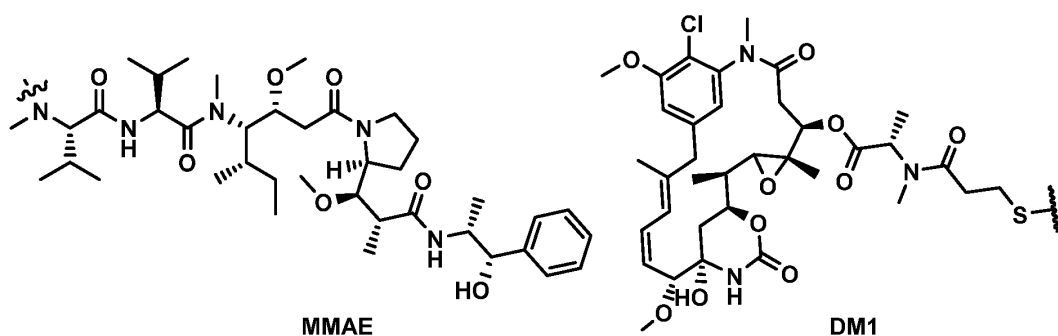
$R^{3d}$  is independently H or C<sub>1</sub>-C<sub>6</sub> alkyl; preferably H or CH<sub>3</sub>;

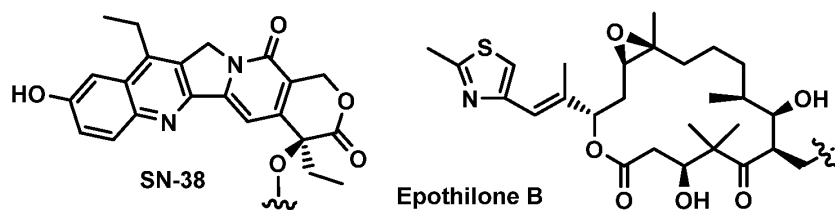
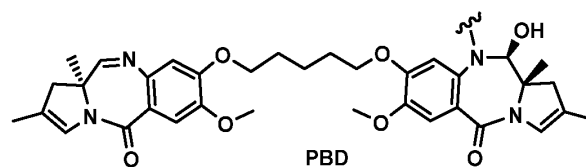
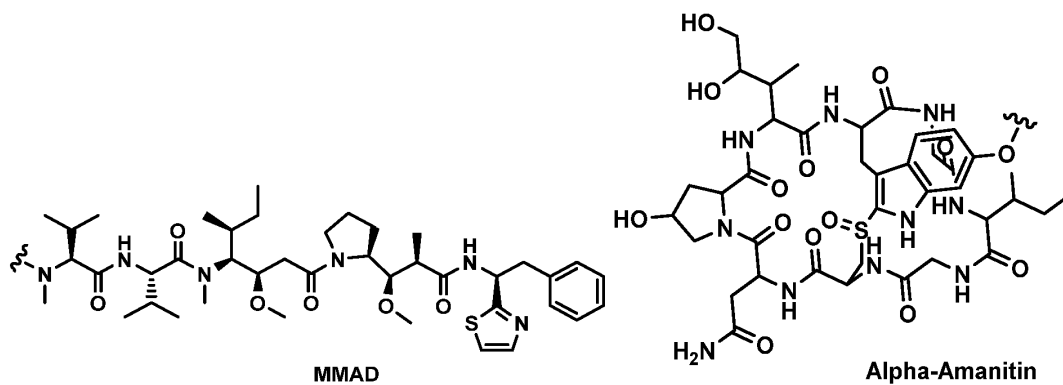
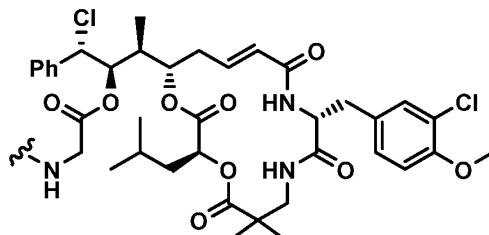
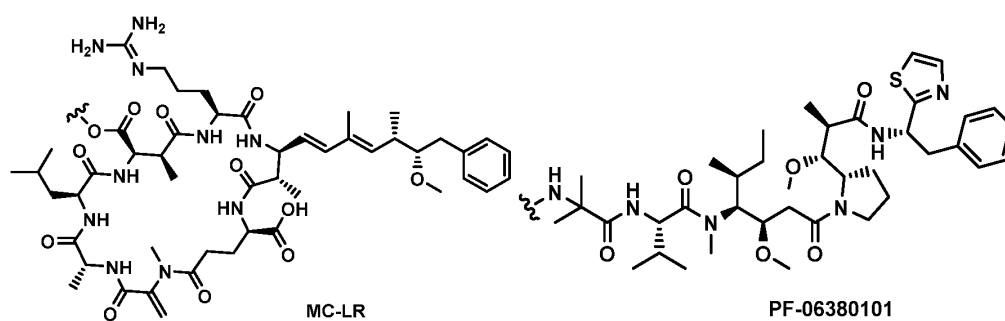
R<sup>4d</sup> is independently H, C<sub>1</sub>-C<sub>6</sub> alkyl, COO(C<sub>1</sub>-C<sub>6</sub> alkyl), CON(H or C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>3</sub>-C<sub>10</sub> aryl or C<sub>3</sub>-C<sub>10</sub> heteroaryl; preferably H, CH<sub>3</sub>, COOH, COOCH<sub>3</sub> or thiazolyl;

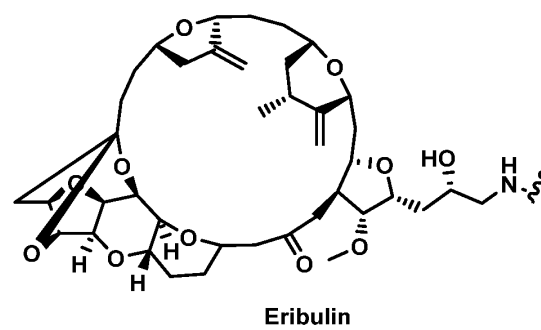
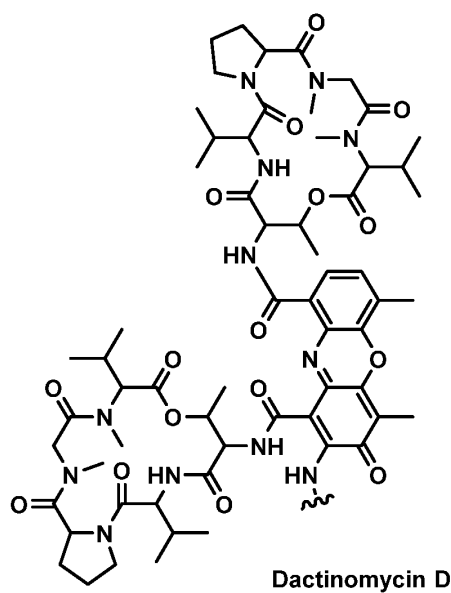
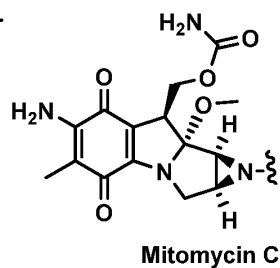
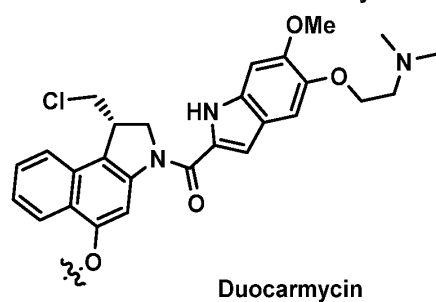
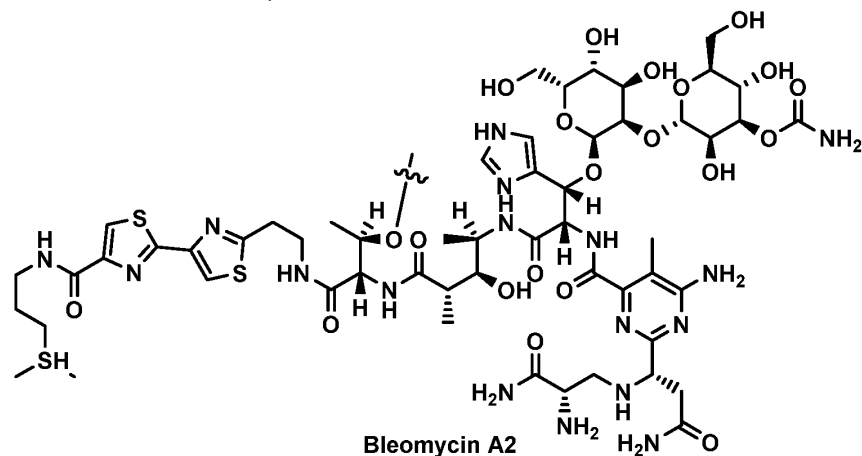
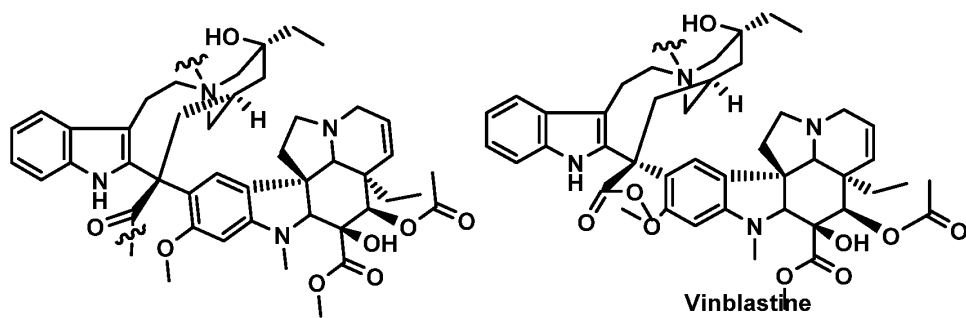
R<sup>5d</sup> is independently H, OH, C<sub>1</sub>-C<sub>6</sub> alkyl; preferably H or OH; and

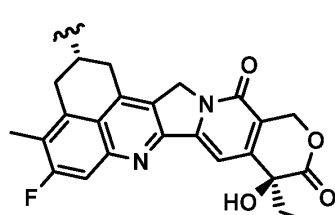
R<sup>6d</sup> is independently C<sub>3</sub>-C<sub>10</sub> aryl or C<sub>3</sub>-C<sub>10</sub> heteroaryl; preferably optionally substituted phenyl or pyridyl.

In a further preferred embodiment, moiety C is selected from the following structures:

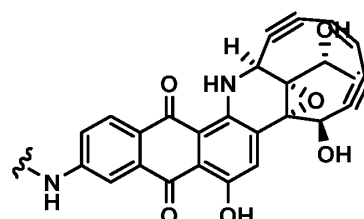




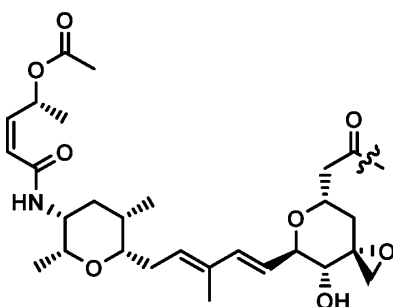




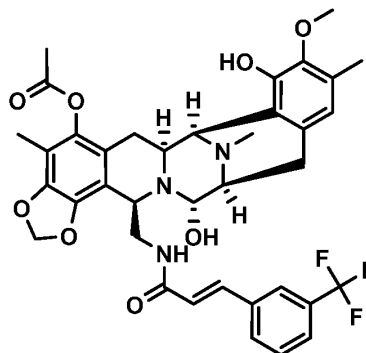
Camptothecin derivative



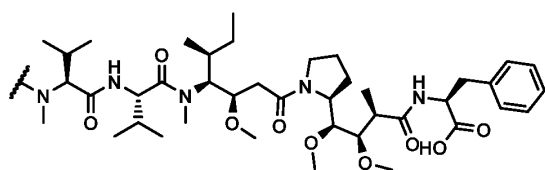
Uncialamycin



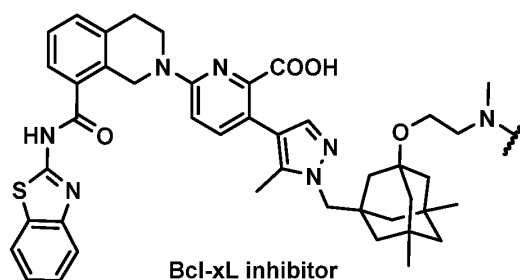
thailanstatin A



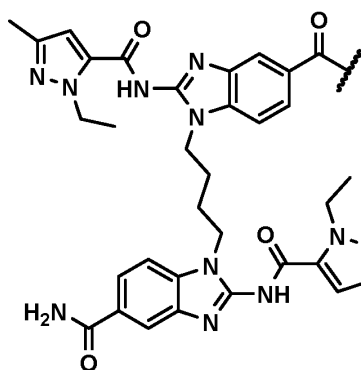
PM00104



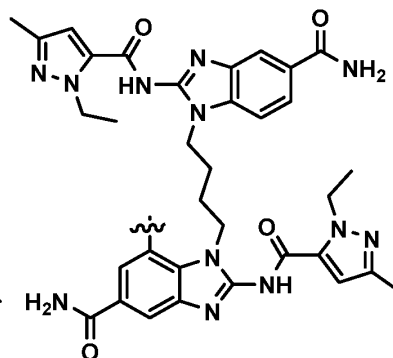
AS269



Bcl-xL inhibitor



STING agonist 1



STING agonist 2

5

Alternatively, moiety **C** can be a immunomodulator agent. The immunomodulator agent is preferably selected from molecules known to be able to modulate the immune system, such as ligands of CD3, CD25, TLRs, STING, 4-1BBL, 4-1BB, PD-1, mTor, PDL-1, NKG-2D IMiDs, wherein ligands can be agonists and/or antagonists.

Alternatively, moiety **C** can be a protein or an antibody. Preferably, the payload is a cytokine (e.g., an interleukin such as IL2, IL10, IL12, IL15; a member of the TNF superfamily; or an interferon such as interferon gamma.).

- Any payload may be used in unmodified or modified form. Combinations of payloads in which some are unmodified and some are modified may be used. For example, the payload may be chemically modified. One form of chemical modification is the derivatisation of a carbonyl group – such as an aldehyde.

#### Treatment

- The compounds described herein may be used to treat disease. The treatment may be therapeutic and/or prophylactic treatment, with the aim being to prevent, reduce or stop an undesired physiological change or disorder. The treatment may prolong survival as compared to expected survival if not receiving treatment.

The disease that is treated by the compound may be any disease that might benefit from treatment. This includes chronic and acute disorders or diseases including those pathological conditions which predispose to the disorder.

- The term "cancer" and "cancerous" is used in its broadest sense as meaning the physiological condition in mammals that is typically characterized by unregulated cell growth. A tumor comprises one or more cancerous cells.

- When treating cancer, the therapeutically effect that is observed may be a reduction in the number of cancer cells; a reduction in tumor size; inhibition or retardation of cancer cell infiltration into peripheral organs; inhibition of tumor growth; and/or relief of one or more of the symptoms associated with the cancer.

- In animal models, efficacy may be assessed by physical measurements of the tumor during the treatment, and/or by determining partial and complete remission of the cancer. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

Particularly preferred embodiments for the methods of treatment related to the present invention are shown in the appended claims.

- Herein disclosed are also methods for treatment of the human or animal body, e.g., by surgery or therapy, or diagnostic method practiced on the human or animal body, the methods involving a step of administering a therapeutically or diagnostically effective amount of a compound or a pharmaceutical composition as described herein to a subject in need thereof. More specifically, herein disclosed are methods for treatment, e.g., by therapy or prophylaxis, of a subject suffering from or having risk for a

disease or disorder; or by guided surgery practiced on a subject suffering from or having risk for a disease or disorder; method for diagnosis of a disease or disorder, e.g., diagnostic method practiced on the human or animal body and/or involving a nuclear medicine imaging technique, such as Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT); method for targeted  
5 delivery of a therapeutic or diagnostic agent to a subject suffering from or having risk for a disease or disorder. In the aforementioned methods, said disease or disorder may be independently selected from cancer, 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, multi-drug resistant colon cancer, rectal cancer, colorectal cancer, metastatic colorectal  
10 cancer, lung cancer, non-small cell lung cancer, head and neck cancer, ovarian cancer, hepatocellular cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocarcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus cancer, desmoid tumors, glioma, astrocytoma, cervix cancer, skin cancer, kidney cancer and prostate cancer. When used in the methods  
15 disclosed herein, the compound has a prolonged residence at the disease site at a therapeutically or diagnostically relevant level, preferably beyond 1 h, more preferably beyond 6 h post injection.

#### Pharmaceutical composition

Also disclosed is a pharmaceutical composition comprising the compound according to any of the preceding aspects, and a pharmaceutically acceptable excipient. Such pharmaceutical composition is also  
20 disclosed for use in: (a) a method for treatment of the human or animal body by surgery or therapy or a diagnostic method practiced on the human or animal body; or (b) a method for therapy or prophylaxis of a subject suffering from or having risk for a disease or disorder; or (c) a method for guided surgery practiced on a subject suffering from or having risk for a disease or disorder; or (d) a method for diagnosis of a disease or disorder, the method being practiced on the human or animal body and involving  
25 a nuclear medicine imaging technique, such as Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT); or (e) a method for targeted delivery of a therapeutic or diagnostic agent to a subject suffering from or having risk for a disease or disorder, wherein in each of the preceding (b)–(e), said disease or disorder is independently selected from cancer, inflammation, atherosclerosis, fibrosis, tissue remodeling and keloid disorder, preferably wherein the cancer is selected  
30 from the group consisting of breast cancer, pancreatic cancer, small intestine cancer, colon cancer, multi-drug resistant colon cancer, rectal cancer, colorectal cancer, metastatic colorectal cancer, lung cancer, non-small cell lung cancer, head and neck cancer, ovarian cancer, hepatocellular cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocarcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma,  
35 CUP (carcinoma of unknown primary), thymus cancer, desmoid tumors, glioma, astrocytoma, cervix cancer and prostate cancer; preferably wherein the compound has a prolonged residence at the disease site

at a therapeutically or diagnostically relevant level, preferably beyond 1 h, more preferably beyond 6 h post injection.

The compounds described herein may be in the form of pharmaceutical compositions which may be for human or animal usage in human and veterinary medicine and will typically comprise any one or more of a pharmaceutically acceptable diluent, carrier, or excipient. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as - or in addition to - the carrier, excipient or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilizing agent(s).

Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

There may be different composition/formulation requirements dependent on the different delivery systems. By way of example, the pharmaceutical composition may be formulated to be administered using a mini-pump or by a mucosal route, for example, as a nasal spray or aerosol for inhalation or ingestible solution, or parenterally in which the composition is formulated by an injectable form, for delivery, by, for example, an intravenous, intramuscular or subcutaneous route. Alternatively, the formulation may be designed to be administered by a number of routes.

If the agent is to be administered mucosally through the gastrointestinal mucosa, it should be able to remain stable during transit through the gastrointestinal tract; for example, it should be resistant to proteolytic degradation, stable at acid pH and resistant to the detergent effects of bile.

Where appropriate, the pharmaceutical compositions may be administered by inhalation, in the form of a suppository or pessary, topically in the form of a lotion, solution, cream, ointment or dusting powder, by use of a skin patch, orally in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavoring or coloring agents, or the pharmaceutical compositions can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, the compositions may be best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or monosaccharides to make the solution isotonic with blood. For buccal or sublingual administration, the compositions may be administered in the form of tablets or lozenges which can be formulated in a conventional manner.

The compound of the present invention may be administered in the form of a pharmaceutically acceptable or active salt. Pharmaceutically-acceptable salts are well known to those skilled in the art, and for example, include those mentioned by Berge et al, in J.Pharm.Sci., 66, 1-19 (1977). Salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

The routes for administration (delivery) may include, but are not limited to, one or more of oral (e.g. as a tablet, capsule, or as an ingestible solution), topical, mucosal (e.g. as a nasal spray or aerosol for inhalation), nasal, parenteral (e.g. by an injectable form), gastrointestinal, intraspinal, intraperitoneal, intramuscular, intravenous, intrauterine, intraocular, intradermal, intracranial, intratracheal, intravaginal, intracerebroventricular, intracerebral, subcutaneous, ophthalmic (including intravitreal or intracameral), transdermal, rectal, buccal, vaginal, epidural, sublingual.

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the individual undergoing therapy.

The formulations may be packaged in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for administration. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Exemplary unit dosage formulations contain a daily dose or unit daily sub-dose, or an appropriate fraction thereof, of the active ingredient.

#### Chemical synthesis

The compounds described herein may be prepared by chemical synthesis techniques.

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound. This may be achieved by conventional techniques, for example as described in "Protective Groups in Organic Synthesis" by T W Greene and P G M Wuts, John Wiley and Sons Inc. (1991), and by P.J.Kocienski, in "Protecting Groups", Georg Thieme Verlag (1994).

It is possible during some of the reactions that any stereocenters present could, under certain conditions, be epimerized, for example if a base is used in a reaction with a substrate having an optical center comprising a base-sensitive group. It should be possible to circumvent potential problems such as this by choice of reaction sequence, conditions, reagents, protection/deprotection regimes, etc. as is well-known  
5 in the art.

#### Definitions

**Derivative.** A derivative includes the chemical modification of a compound. Examples of such modifications include the replacement of a hydrogen by a halo group, an alkyl group, an acyl group or an amino group and the like. The modification may increase or decrease one or more hydrogen bonding  
10 interactions, charge interactions, hydrophobic interactions, van der Waals interactions and/or dipole interactions.

**Analog.** This term encompasses any enantiomers, racemates and stereoisomers, as well as all pharmaceutically acceptable salts and hydrates of such compounds.

Unless otherwise stated, the following definitions apply to chemical terms used in connection of  
15 compounds of the invention and compositions containing such compounds.

**Alkyl** refers to a branched or unbranched saturated hydrocarbyl radical. Suitably, the alkyl group comprises from 1 to 100, preferably 3 to 30, carbon atoms, more preferably from 5 to 25 carbon atoms. Preferably, alkyl refers to methyl, ethyl, propyl, butyl, pentyl, or hexyl.

**Alkenyl** refers to a branched or unbranched hydrocarbyl radical containing one or more carbon-carbon  
20 double bonds. Suitably, the alkenyl group comprises from 2 to 30 carbon atoms, preferably from 5 to about 25 carbon atoms.

**Alkynyl** refers to a branched or unbranched hydrocarbyl radical containing one or more carbon-carbon triple bonds. Suitably, the alkynyl group comprises from about 3 to about 30 carbon atoms, for example from about 5 to about 25 carbon atoms.

25 **Halogen** refers to fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

**Cycloalkyl** refers to an alicyclic moiety, suitably having 3, 4, 5, 6, 7 or 8 carbon atoms. The group may be a bridged or polycyclic ring system. More often cycloalkyl groups are monocyclic. This term includes reference to groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, bicyclo[2.2.2]octyl and the like.

30 **Aryl** refers to an aromatic carbocyclic ring system, suitably comprising 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring carbon atoms. Aryl may be a polycyclic ring system, having two or more rings, at least one of

which is aromatic. This term includes reference to groups such as phenyl, naphthyl fluorenyl, azulenyl, indenyl, anthryl and the like.

The prefix **“hetero”**, unless specified otherwise, signifies that one or more of the carbon atoms of the group may be substituted by nitrogen, oxygen, phosphorus, silicon or sulfur. Heteroalkyl groups include for example, alkyloxy groups and alkythio groups. Heterocycloalkyl or heteroaryl groups herein may have from 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, at least one of which is selected from nitrogen, oxygen, phosphorus, silicon and sulfur. In particular, a 3- to 10-membered ring or ring system and more particularly a 5- or 6-membered ring, which may be saturated or unsaturated. For example, selected from oxiranyl, aziranyl, 1,2-oxathiolanyl, imidazolyl, thienyl, furyl, tetrahydrofuryl, pyranal, thiopyranal, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2H-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, especially thiomorpholino, indoliziny, 1,3-Dioxo-1,3-dihydro-isoindolyl, 3H-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4H-quinoliziny, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnoliny, pteridinyl, carbazolyl, [beta]-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanal, chromanl, 3,4-dihydro-2H-isoquinolin-1-one, 3,4-dihydro-2H-isoquinoliny, and the like.

**“Substituted”**, unless specified otherwise, signifies that one or more, especially up to 5, more especially 1, 2 or 3, of the hydrogen atoms in said moiety are replaced independently of each other by the corresponding number of substituents. The term "optionally substituted" as used herein includes substituted or unsubstituted. It will, of course, be understood that substituents are only at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort whether a particular substitution is possible. For example, amino or hydroxy groups with free hydrogen may be unstable if bound to carbon atoms with unsaturated (e.g. olefinic) bonds. Preferably, the term “substituted” signifies one or more, especially up to 5, more especially 1, 2 or 3, of the hydrogen atoms in said moiety are replaced independently of each other by the corresponding number of substituents selected from OH, SH, NH<sub>2</sub>, halogen, cyano, carboxy, alkyl, cycloalkyl, aryl and heteroaryl. Additionally, the substituents described herein may themselves be substituted by any substituent, subject to the aforementioned restriction to appropriate substitutions as recognized by the skilled person. Preferably, any of the aforementioned substituents may be further substituted by any of the aforementioned substituents, each of which may be further substituted by any of the aforementioned substituents.

Substituents may suitably include halogen atoms and halomethyl groups such as CF<sub>3</sub> and CCl<sub>3</sub>; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, alkylamino, dialkylamino, cyano, azide and nitro; sulfur containing groups such as thiol, alkylthiol, sulfonyl and sulfoxide; heterocyclic groups which may themselves be substituted; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl. Alkyl includes substituted and unsubstituted benzyl.

More preferably, "substituted" signifies substitution by one or more groups selected from OH, SH, NH<sub>2</sub>, halogen, cyano, oxo, carboxy, C(O)NH<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C(O)C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylthio, C<sub>1-5</sub> heteroalkyl, C<sub>1-5</sub> heteroalkoxy, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkoxy, C<sub>6-10</sub> aryl, C<sub>6-10</sub> aryloxy, C<sub>5-10</sub> heteroaryl and C<sub>5-10</sub> heteroaryloxy, of which the SH, NH<sub>2</sub>, C(O)NH<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C(O)C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylthio, C<sub>1-5</sub> heteroalkyl, C<sub>1-5</sub> heteroalkoxy, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkoxy, C<sub>6-10</sub> aryl, C<sub>6-10</sub> aryloxy, C<sub>5-10</sub> heteroaryl and C<sub>5-10</sub> heteroaryloxy is optionally substituted with one or more of OH, SH, NH<sub>2</sub>, halogen, cyano, oxo, carboxy, C<sub>1-6</sub> alkyl, C<sub>1-5</sub> heteroalkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>5-10</sub> heteroaryl; two or more of the aforementioned groups can be bound together to form part of a carbocyclic or heterocyclic ring system.

Where two or more moieties are described as being "each independently" selected from a list of atoms or groups, this means that the moieties may be the same or different. The identity of each moiety is therefore independent of the identities of the one or more other moieties.

20

## MATERIAL & METHODS

General remarks and procedures

Yields refer to chromatographically purified compounds.

Mass Spectrometry (LC-MS-UV): spectra were recorded on an Agilent 6100 Series Single Quadrupole MS System combined with an Agilent 1200 Series LC System, using an InfinityLab Poroshell 120 EC-C18 column, 4.6 mm × 56 mm at a flow rate of 0.8 mL min<sup>-1</sup> with linear gradients of solvents A and B (A = Millipore water with 0.1% formic acid [FA], B = MeCN with 0.1% formic acid [FA]).

NanoHPLC-HR-MS: chromatographic separation was carried out on an Acclaim PepMap RSLC column (50 µm x 15 cm, particle size 2 µm, pore size, 100 Å, Thermo Scientific) with a gradient program from 95% A (0.1% FA), 5 % B (ACN 0.1 % FA) to 5 % A, 95 % B in 45 minutes on an Easy nanoLC 1000 (Thermo Scientific). Sample clean up and concentration was carried out with a pre column Acclaim PepMAP 100 (75 µm x 2 cm, particle size 3 µm, pore size 100 Å; Thermo Scientific) mounted on the system. The LC system was coupled to a Q-Exactive mass spectrometer (Thermo Fisher) via a Nano Flex

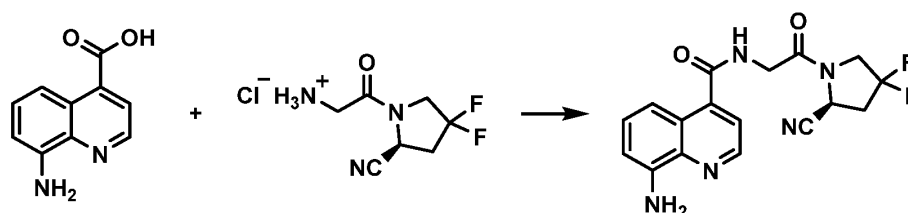
ion source (Thermo Scientific). Ionization was carried out with 2 kV of spray voltage, 250 °C of capillary temperature, 60 S-lens RF level. Mass spectrometry was working in Single ion Monitoring mode (SIM) following the mass range reported in Table 1. The detector was working in positive ion mode with the following parameters: resolution 70000 (FWHM at 400 m/z), AGC target  $5 \times 10^4$ , and maximum injection time 200 ms. Data analysis was carried out with Thermo Xcalibur Qual Browser v2.2 (Thermo Scientific) and Prism8 (GrapPhad).

Preparative reversed-phase high-pressure liquid chromatography (RP-HPLC) was performed on an Agilent 1200 Series System, using a Phenomenex Gemini® 5  $\mu\text{m}$  NX-C18 semipreparative column, 110 Å, 150 mm  $\times$  10 mm at a flow rate of 5 mL min<sup>-1</sup> with linear gradients of solvents A and B (A = Millipore water with 0.1% trifluoroacetic acid [TFA], B = MeCN with 0.1% trifluoroacetic acid [TFA]).

### Example 1: Preparation of “ESV6-NODAGA” and labelling

#### Synthesis

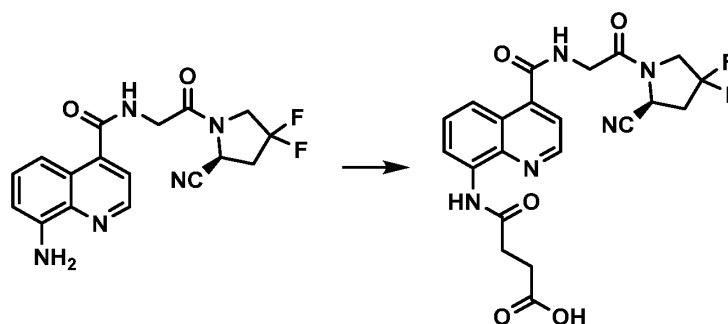
#### Synthesis of Intermediate I-1



In a 25 mL round bottom flask, 8-aminoquinoline-4-carboxylic acid (100 mg, 0.531 mmol, 1 eq), (S)-1-(2-aminoacetyl)-4,4-difluoropyrrolidine-2-carbonitrile hydrochloride (132 mg, 0.585 mmol, 1.1 eq) and HATU (202 mg, 0.531 mmol, 1 eq) were suspended in 900  $\mu\text{L}$  of DMF and 4 mL of DCM. DIPEA (371  $\mu\text{L}$ , 2.127 mmol, 4 eq) was added dropwise and the reaction was stirred until completion (checked via LC/MS with the method 90:10 Water/Acetonitrile 0.1% FA to 100% Acetonitrile 0.1% FA in 3min, Positive). The crude was diluted with DCM, washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent evaporated under vacuum. The dried crude was purified via CombiFlash Nextgen 300+ (parameters: flow 50 ml/min, 40 gr silica column, 100% DCM to 85:15 DCM/MeOH in 5 min) to obtain an amber oil (172 mg, 90% yield).

MS (ESI+) m/z 360.1 [M+H]<sup>+</sup>

#### Synthesis of Intermediate I-2

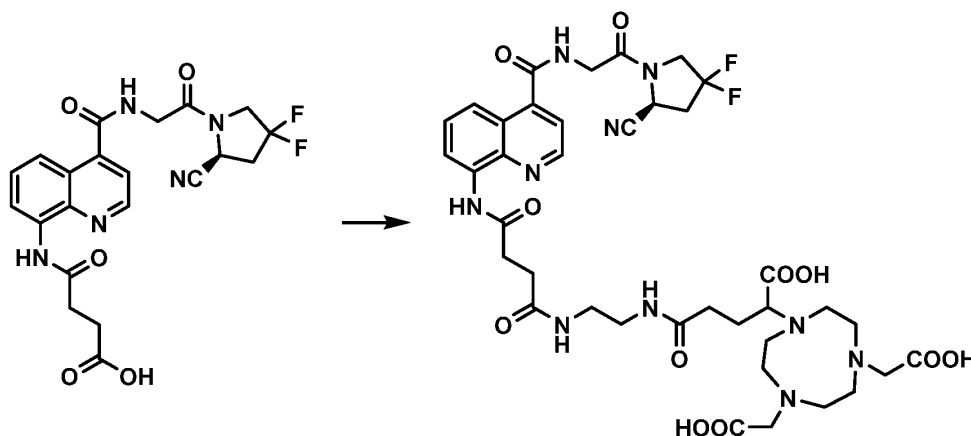


In a 25 mL round bottom flask, Intermediate A (48 mg, 0.134 mmol, 1 eq), succinic anhydride (669 mg, 6.683 mmol, 50 eq) and DMAP (8 mg, 0.067 mmol, 0.5 eq) were dissolved in 3 mL of THF. The reaction was heated at 60 °C for 6h and checked via LC/MS (method 90:10 Water/Acetonitrile 0.1% FA to 100% Acetonitrile 0.1% FA in 3min, Positive). The reaction was dried under vacuum, diluted with water, extracted with DCM, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under. The dried crude was purified via CombiFlash Nextgen 300+ (parameters: flow 30 ml/min, 24 gr silica column, DMC/MeOH 90:10 to 70:30 in 4 minutes) to obtain an amber oil (58 mg, 95% yield).

MS (ESI+) m/z 460.1 [M+H]<sup>+</sup>

10

From (S)-4-((4-((2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-8-yl)amino)-4-oxobutanoic acid (**I-2**) to **ESV6-NODAGA**

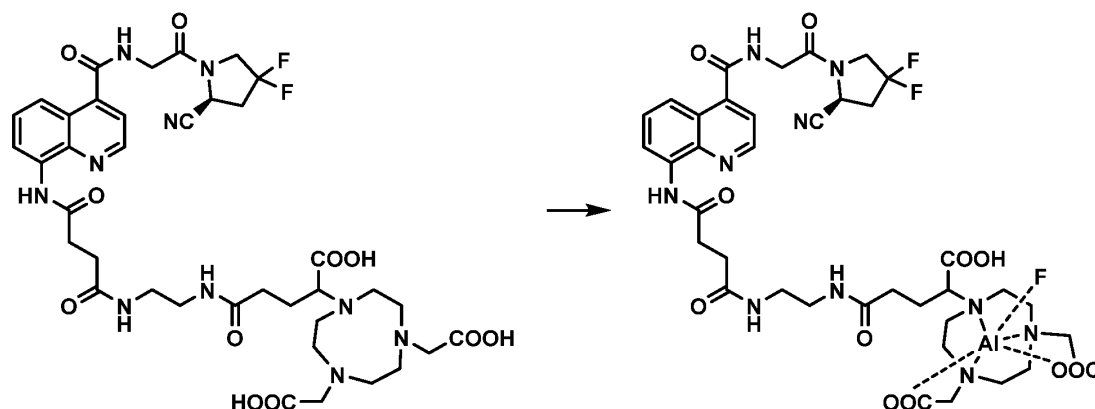


(S)-4-((4-((2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-8-yl)amino)-4-oxobutanoic acid (15 mg, 0.032 mmol, 1.0 eq) was dissolved in dry DMSO (400 μL). Dicyclohexylcarbodiimide (9 mg, 0.042 mmol, 1.3 eq) and N-hydroxysuccinimide (4.5 mg, 0.039 mmol, 1.3 eq) were added and the reaction was stirred overnight at room temperature, protected from light. 100 μL of PBS solution containing 2,2'-(7-(4-((2-aminoethyl)amino)-1-carboxy-4-oxobutyl)-1,4,7-triazonane-

1,4-diyl)diacetic acid (16.2 mg, 0.039 mmol, 1.2 eq) were added and the reaction was stirred for 2h. The crude product was purified by reversed phase HPLC (95:5 to 20:80 water/ACN + 0.1%TFA in 20 min) and lyophilized, to obtain a white solid. (21 mg, 75%).

MS (ESI+)  $m/z$  859.9  $[M+H]^+$

5 Labelling: from ESV6-NODAGA to ESV6-NODAGA-Al-F



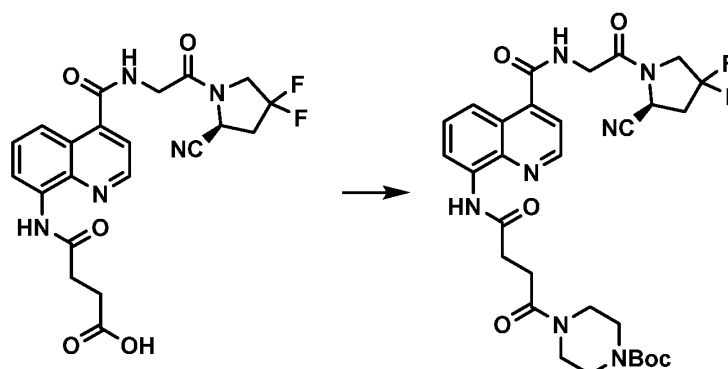
ESV6-NODAGA (1 mg, 1.16  $\mu\text{mol}$ , 1 eq) was dissolved in a mixture of DMSO (0.05 mL) and acetate buffer pH=4 (0.2 mL).  $\text{AlF}_3$  (1 mg, 11.6  $\mu\text{mol}$ , 10 eq.) was added and the mixture was heated at 95°C for 15 min. Then the mixture was purified via RP-HPLC (95:5 to 0:100 water/ACN + 0.1% TFA in 20 min) the desired fractions were collected and lyophilized to afford a white solid. (0.8 mg, 80%).

MS (ESI+)  $m/z$  903.4  $[M+H]^+$

## Example 2: Preparation of “ESV6-NOTA” and labelling

### Synthesis

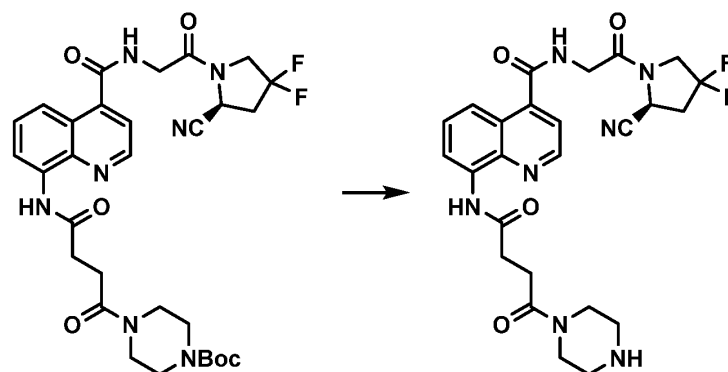
15 From (S)-4-((4-((2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-8-yl)amino)-4-oxobutanoic acid (**I-2**) to *tert*-butyl (S)-4-(4-((4-((2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-8-yl)amino)-4-oxobutanoyl)piperazine-1-carboxylate (**I-3**)



Intermediate **I-2** (50 mg, 0.11 mmol, 1 eq), *N*-Boc-piperazine (24 mg, 0.13 mmol, 1.2 eq) and HATU (49 mg, 0.13 mmol, 1.2 eq) was dissolved in DMF (1 mL). DIPEA (0.08 mL, 0.44 mmol, 4 eq) was added dropwise and the mixture was stirred for 30 min at room temperature. The mixture was purified via RP flash chromatography (2:98 to 100:0 ACN/water + 0.1% HCOOH in 40 min). The desired fractions were collected and lyophilized to afford a white solid. (40 mg, 58%).

MS (ESI+)  $m/z$  627.9 [M+H]<sup>+</sup>

From *tert*-butyl (*S*)-4-(4-((2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-8-yl)amino)-4-oxobutanoyl)piperazine-1-carboxylate (**I-3**) to (*S*)-*N*-(2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethyl)-8-(4-oxo-4-(piperazin-1-yl)butanamido)quinoline-4-carboxamide (**I-4**)

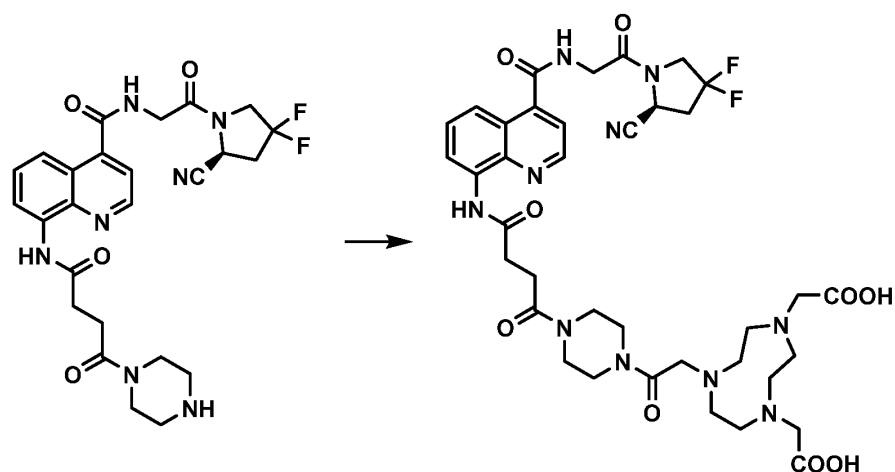


Intermediate **I-3** (40 mg, 0.06 mmol, 1 eq.) was dissolved in DCM (1 mL) and TFA (0.5 mL) was added dropwise. The mixture was stirred at room temperature for 3h then solvent was evaporated, and the crude was purified via RP flash chromatography (2:98 to 100:0 ACN/water + 0.1% HCOOH in 40 min). The desired fractions were collected and lyophilized to afford a colorless oil. (17 mg, 51%).

MS (ESI+)  $m/z$  527.9 [M+H]<sup>+</sup>

From (*S*)-*N*-(2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethyl)-8-(4-oxo-4-(piperazin-1-yl)butanamido)quinoline-4-carboxamide (**I-4**) to (*S*)-2,2'-(7-(2-(4-(4-((2-(2-cyano-4,4-

difluoropyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-8-yl)amino)-4-oxobutanoyl)piperazin-1-yl)-2-oxoethyl)-1,4,7-triazonane-1,4-diyl)diacetic acid (ESV6-NOTA; **1**).



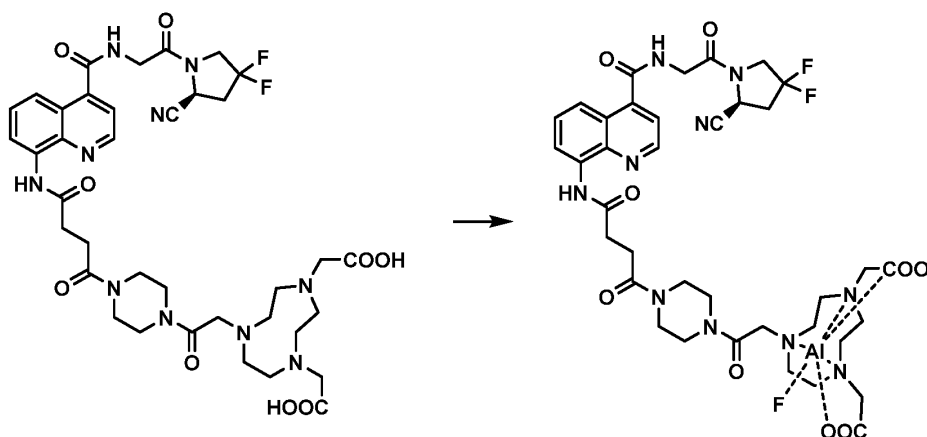
Intermediate **I-4** (8 mg, 0.02 mmol, 1 eq) and NOTA-NHS (19 mg, 0.04 mmol, 2 eq) was dissolved in  
 5 DMF (0.2 mL). DIPEA (0.01 mL, 0.08 mmol, 4 eq) was added to the mixture and stirred for 1h at room temperature. The mixture was purified via RP-HPLC (90:10 to 0:100 water/ACN + 0.1% TFA in 12 min). The desired fractions were collected and lyophilized to afford a white solid. (4 mg, 25%).

MS (ESI+)  $m/z$  812.7  $[M+H]^+$

Labelling: from ESV6-NOTA (**1**) to ESV6-NOTA-Al-F (**AlF@1**)

10

From (*S*)-2,2'-(7-(2-(4-(4-((4-((2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-8-yl)amino)-4-oxobutanoyl)piperazin-1-yl)-2-oxoethyl)-1,4,7-triazonane-1,4-diyl)diacetic acid (**1**) to ESV6-NOTA-Al-F (**AlF@1**)



Compound **1** (1 mg, 1.16  $\mu\text{mol}$ , 1 eq) was dissolved in a mixture of DMSO (0.05 mL) and acetate buffer pH=4 (0.2 mL).  $\text{AlF}_3$  (1 mg, 11.6  $\mu\text{mol}$ , 10 eq.) was added and the mixture was heated at 95°C for 15 min. Then the mixture was purified via RP-HPLC (95:5 to 0:100 water/ACN + 0.1% TFA in 20 min) the desired fractions were collected and lyophilized to afford a white solid. (0.8 mg, 80%).

- 5  $^{13}\text{C}_4$ -ESV6-NODAGA-Al-F was generated following the same procedure described for ESV6-NODAGA-Al-F, using  $^{13}\text{C}_4$  succinic anhydride as isotopically labelled building block for the synthesis of **1**.

$^{13}\text{C}_4$ -ESV6-NOTA-Al-F was generated following the same procedure described for ESV6-NOTA-Al-F, using  $^{13}\text{C}_4$  succinic anhydride as isotopically labelled building block for the synthesis of **1**.

10

### **Example 3: Ex vivo characterization of “ESV6-NODAGA-Al-F” and of “ESV6-NOTA-Al-F”**

All animal experiments were conducted in accordance with Swiss animal welfare laws and regulations under the license number ZH06 / 2021 granted by the Veterinäramt des Kantons Zürich.

- 15 Implantation of subcutaneous tumors

Tumor cells were grown to 80% confluence and detached with Trypsin-EDTA 0.05%. SK-RC-52.hFAP, cells (FAP positive cells) were resuspended in Hanks' Balanced Salt Solution medium. Aliquots of 5 to  $10 \times 10^6$  cells (100 to 150  $\mu\text{L}$  of suspension) were injected subcutaneously in the right or left flanks of female athymic Balb/c AnNRj-Foxn1 mice (6 to 8 wk of age, Janvier).

- 20 *Ex Vivo* biodistribution experiments.

Mice bearing subcutaneous SK-RC-52.hFAP tumors were injected intravenously with ESV6-NODAGA-Al-F and ESV6-NOTA-Al-F (10 nmol dissolved in sterile PBS, pH 7.4). Animals were sacrificed 2 h after intravenous injection, organs and tumor were subsequently excised, snap frozen at such, and stored at  $-80^\circ\text{C}$ .

- 25 Sample Preparation

50 mg of mice tissues were resuspended in 600  $\mu\text{L}$  of a solution containing 95 % ACN and 0.1 % FA to induce protein precipitation. In parallel 50  $\mu\text{L}$  of a solution 600 nM of internal standard ( $^{13}\text{C}_4$ -ESV6-NODAGA-Al-F or  $^{13}\text{C}_4$ -ESV6-NOTA-Al-F) were also added to the solution. Samples were then homogenized with a tissue lyser (TissueLyser II, QIAGEN) for 15 minutes at 30 Hz. After

homogenization, samples were centrifugated at 14000 g for 10 minutes and supernatants were dried at room temperature with a vacuum centrifuge.

Samples were then resuspended in 1 mL solution containing 3% ACN and 0.1 % of TFA and subsequently cleaned up using Oasis HLB SPE columns (Waters). Eluted samples were again dried under vacuum at room temperature, resuspended in 1 mL 3% ACN and 0.1 % of TFA and cleaned up using Sep-Pak SPE columns (Waters). Eluted samples were then dried under vacuum at room temperature.

Dry samples were finally resuspended in 30 µL of a solution containing 3 % of ACN and 0.1 % of FA. 3 µL of each sample (10% of the total) were then injected in the nanoLC-HR-MS system (as depicted in Figure 5).

#### 10 nanoLC-HR-MS analysis

Chromatographic separation was carried out on an Acclaim PepMap RSLC column (50 µm x 15 cm, particle size 2 µm, pore size, 100 Å) with a gradient program from 95% A (0.1% FA), 5 % B (ACN 0.1 % FA) to 5 % A, 95 % B in 45 minutes on an Easy nanoLC 1000. Sample clean up and concentration was carried out with a pre column Acclaim PepMAP 100 (75 µm x 2 cm, particle size 3 µm, pore size 100 Å) mounted on the system. The LC system was coupled to a Q-Exactive mass spectrometer via a Nano Flex ion source. Ionization was carried out with 2 kV of spray voltage, 250 °C of capillary temperature, 60 S-lens RF level. Mass spectrometry was working in Single ion Monitoring mode (SIM) following the mass range reported in Table 1. The detector was working in positive ion mode with the following parameters: resolution 70000 (FWHM at 400 m/z), AGC target  $5 \times 10^4$ , and maximum injection time 200 ms. Data analysis was carried out with Thermo Xcalibur Qual Browser v2.2 and Prism8.

**Table 1:** Mass range windows for the SIM mode of the mass spectrometer.

| Compound                                               | Mass Range (m/z)  |
|--------------------------------------------------------|-------------------|
| ESV6-NODAGA-Al-F, $^{13}\text{C}_4$ ESV6-NODAGA-Al-F   | 901.8188–910.8188 |
| ESV6-NODAGA-Al, $^{13}\text{C}_4$ ESV6-NODAGA-Al       | 881.8106–890.8106 |
| ESV6-NODAGA-Al-OH, $^{13}\text{C}_4$ ESV6-NODAGA-Al-OH | 889.8208–908.8208 |
| ESV6-NOTA-Al-F, $^{13}\text{C}_4$ - ESV6-NOTA-Al-F     | 855.8133–864.8133 |

The results shown in Figure 6 indicate a remarkable tumor-to-organ ratio for ESV6-NOTA-Al-F.

#### **Example 4: Quantitative *in vivo* biodistribution of “ESV6-NOTA-[ $^{18}\text{F}$ ]Al-F”**

#### 25 Animal studies

All animal experiments were conducted in accordance with Swiss animal welfare laws and regulations under the license number ZH06/2021 granted by the Veterinäramt des Kantons Zürich.

### Implantation of subcutaneous tumors

HT-1080.hFAP cells (FAP positive tumor cells) were grown to 80% confluence in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% Fetal Bovine Serum and 1% antibiotic-antimycotic and detached with Trypsin-EDTA 0.05%. Cells were resuspended in Hanks' Balanced Salt Solution medium.

- 5 Aliquots of  $5 \times 10^6$  cells (100  $\mu$ L of suspension) were injected subcutaneously in the right flanks of female athymic Balb/c AnNRj-Foxn1 mice (6 to 8 wk of age).

### Biodistribution studies in tumour bearing mice

Female athymic Balb/c AnNRj-Foxn1 mice (6 to 8 wk of age) implanted in the right flank with HT-1080.hFAP tumors as described above were allowed to grow to an average tumor volume of 250 mm<sup>3</sup>.

- 10 Mice were randomized (n = 5 per group) and injected intravenously with radiolabeled preparations of ESV6-NOTA-[<sup>18</sup>F]Al-F (10 nmol/mice; 77 KBq). Mice were euthanized 1h after the injection by CO<sub>2</sub> asphyxiation. Organs were extracted, weighted, and radioactivity was measured with a Gamma Counter. Values are expressed as percent ID/g  $\pm$  SD. Results are reported in Figure 7.

### 15 Radiolabelling of ESV6-NOTA

Radiolabelling of ESV6-NOTA (200-300  $\mu$ g) with <sup>18</sup>F was performed via aluminium (Al<sup>3+</sup>) fluoride complex using FASTlab 2 synthesis module and the cassette. During the placement of vials and reagents on the cassette, the 5 mL reactor vessel was prefilled with 25  $\mu$ L of 2mM aluminium chloride (AlCl<sub>3</sub>, anhydrous, powder, 99.999% trace metals basis) in sodium acetate buffer (0.1 M, pH=4.1). [<sup>18</sup>F]-fluoride was transferred to the module and trapped on a Sep-Pak light Accel plus QMA cartridge (Cl<sup>-</sup> form:). The cartridge was washed with 6 mL of water (HPCE grade). [<sup>18</sup>F]-fluoride was eluted from the QMA cartridge into reactor vessel with 500  $\mu$ L of the eluent solution (250  $\mu$ L NaCl 0.9%; 99.999% trace metals basis NaCl;) in water for injection and 250  $\mu$ L absolute ethanol). The solution was stirred for 5 min at room temperature under gentle nitrogen flow to form [<sup>18</sup>F]AlF. The precursor solution (600  $\mu$ L of 350  $\mu$ g/mL ESV6-NOTA in sodium acetate 0.1M pH 4.5) was added to the reactor which was sealed and heated for 10 min at 95°C. Next, the reactor was cooled to 40°C and the reaction mixture was diluted with 3.5 mL of NaCl 0.9% and sent through the preactivated C18 cartridge, C18 was washed with 5 mL of NaCl 0.9% and eluted with 1.5 mL of absolute EtOH. The product was diluted with NaCl 0.9% to obtain the final formulation. The radiochemical purity for each batch of ESV6-NOTA-[<sup>18</sup>F]Al-F was determined by radio-HPLC and reported in Table 2.

| Radiosynthesis of ESV6-NOTA-[ <sup>18</sup> F]Al-F |         |         |         |
|----------------------------------------------------|---------|---------|---------|
|                                                    | Batch 1 | Batch 2 | Batch 3 |
| Precursor ( $\mu$ g)                               | 200     | 250     | 300     |
| Reaction time (min)                                | 25      | 25      | 25      |
| Reaction temperature (°C)                          | 95      | 95      | 95      |

|                               |       |       |       |
|-------------------------------|-------|-------|-------|
| <b>Reaction pH</b>            | 4.5   | 4.5   | 4.5   |
| <b>Initial activity (MBq)</b> | 3811  | 9250  | 16280 |
| <b>Product activity (MBq)</b> | 644   | 1750  | 2967  |
| <b>RCY %</b>                  | 16.9  | 18.9  | 18.2  |
| <b>RCY decav corrected %</b>  | 18.7  | 20.9  | 20.2  |
| <b>Final pH</b>               | 5.5   | 5.5   | 5.5   |
| <b>Final Volume (mL)</b>      | 24    | 24    | 24    |
| <b>Purity %</b>               | 91.97 | 89.64 | 90.52 |

TABLE 2

### Example 5: Radiosynthesis of [<sup>68</sup>Ga]GaESV6-NODAGA and of [<sup>68</sup>Ga]GaESV6-NOTA

[<sup>68</sup>Ga]GaESV6-NODAGA/NOTA (15-25 µg) were synthesized in an FASTlab 2 synthesis module using the cassette. The synthesis is carried out using <sup>68</sup>Ga (t<sub>1/2</sub> = 68 min, β<sup>+</sup> = 89%, and EC = 11%) obtained by a Eckert & Ziegler generator (1850 MBq, GalliaPharm), eluted with HCl (4.5ml, 0.1M TRASIS ALLinONE reagent kit). 4 ml of [<sup>68</sup>Ga]GaCl<sub>3</sub> was transferred to the reactor vessel, the precursor dissolved in sodium acetate (750 µL, 0.7M TRASIS ALLinONE reagent kit) is aspirated into the reactor, the solution was stirred for 5 min at room temperature under gentle nitrogen flow. Next, the reaction mixture is sent through the preactivated C18 cartridge, washed with NaCl 0.9% (5ml, TRASIS ALLinONE reagent kit) and eluted with eluent solution (700 µL of absolute ethanol and 800 µL of water for injection). The product is diluted with NaCl 0.9% to obtain the final formulation. The radiochemical purity for each batch of [<sup>68</sup>Ga]GaESV6-NODAGA/NOTA is determined by radio-HPLC and reported in Table 3 and 4 respectively.

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| <b>Radiosynthesis [<sup>68</sup>Ga]GaESV6-NODAGA</b> |         |         |         |
|------------------------------------------------------|---------|---------|---------|
|                                                      | Batch 1 | Batch 2 | Batch 3 |
| <b>µg DOTAGA-OncoFAP</b>                             | 15.00   | 20      | 25.00   |
| <b>Reaction Time min</b>                             | 10      | 5       | 5       |
| <b>Reaction</b>                                      | 90.00   | 90.00   | 90.00   |
| <b>Reaction pH</b>                                   | 4.2     | 4.2     | 4.2     |
| <b>Starting Activity MBq</b>                         | 750     | 875     | 950     |
| <b>Final Activity MBq</b>                            | 615     | 735     | 808     |
| <b>RCY %</b>                                         | 82      | 84      | 85      |
| <b>RCY decav</b>                                     | 94      | 90      | 91      |
| <b>Final pH</b>                                      | 5.0     | 5.0     | 5.0     |
| <b>Final Volume ml</b>                               | 12.00   | 12.00   | 12.00   |
| <b>Purity %</b>                                      | 99.65   | 99.68   | 99.70   |

TABLE 3

| <b>Radiosynthesis [<sup>68</sup>Ga]GaESV6-NOTA</b> |         |         |         |
|----------------------------------------------------|---------|---------|---------|
|                                                    | Batch 1 | Batch 2 | Batch 3 |
| <b>µg DOTAGA-OncoFAP</b>                           | 15.00   | 20      | 25.00   |
| <b>Reaction Time min</b>                           | 10      | 5       | 5       |
| <b>Reaction</b>                                    | 90.00   | 90.00   | 90.00   |
| <b>Reaction pH</b>                                 | 4.2     | 4.2     | 4.2     |
| <b>Starting Activity MBq</b>                       | 590     | 635     | 675     |
| <b>Final Activity MBq</b>                          | 460     | 515     | 560     |
| <b>RCY %</b>                                       | 78      | 81      | 83      |

|                        |              |       |       |       |
|------------------------|--------------|-------|-------|-------|
| <b>RCY</b>             | <b>decav</b> | 89.6  | 87    | 89.2  |
| <b>Final pH</b>        |              | 5.0   | 5.0   | 5.0   |
| <b>Final Volume ml</b> |              | 12.00 | 12.00 | 12.00 |
| <b>Purity %</b>        |              | 99.67 | 99.75 | 99.77 |

TABLE 4

The acceptance criteria and the average results of synthesis are reported in Table 5

| Parameters                                | Acceptance criteria       | Average<br>NOTA-ESV6         | Average<br>NODAGA-ESV6       |
|-------------------------------------------|---------------------------|------------------------------|------------------------------|
| <b>[<sup>68</sup>Ga]-labeled activity</b> | 200 a 1300 MBq            | 460-560                      | 750 - 950 MBq                |
| <b>Radiopharmaceutical volume</b>         | 12 ml                     | 12 ml                        | 12 ml                        |
| <b>Aspect</b>                             | Clear colourless solution | Clear colourless<br>solution | Clear colourless<br>solution |
| <b>Half-life</b>                          | 62-74 min                 | 66.8                         | 66.9                         |
| - <sup>68</sup> Ga <sup>3+</sup>          | ≤ 2%                      | <0.20%                       | < 0.10%                      |
| - <sup>68</sup> Ga colloidal              | ≤ 3%                      | <0.30%                       | < 0.25%                      |
| - Radiochemical purity                    | ≥ 95%                     | > 99.52%                     | > 99.65%                     |
| <b>Ethanol v/v</b>                        | < 10%                     | 4.9% ±0.5%                   | 4.8% ±0.5%                   |
| <b><sup>68</sup>Ga breakthrough</b>       | < 10 <sup>-3</sup> %      | < 10 <sup>-4</sup> %         | < 10 <sup>-4</sup> %         |
| <b>pH</b>                                 | 4.0-8.0                   | 5.0 ± 0.3                    | 5.0 ± 0.3                    |
| <b>Bacterial endotoxins</b>               | < 175 EU/V                | < 0.5EU/ml                   | < 0.5EU/ml                   |
| <b>Filter integrity</b>                   | ≥ 50 psi                  | > 50 psi                     | > 50 psi                     |
| <b>Sterility</b>                          | Sterile                   | Sterile                      | Sterile                      |

#### 5 Example 6: Characterization of [<sup>68</sup>Ga]GaESV6-NODAGA, [<sup>68</sup>Ga]GaESV6-NOTA and of ESV6-NOTA-[<sup>18</sup>F]Al-F binding to human FAP

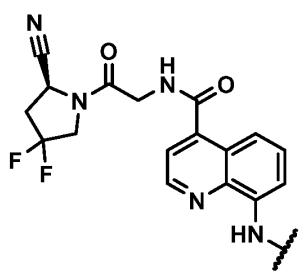
Radiolabelled ESV6-derivatives binding to hFAP were tested by loading a solution of preincubated of either <sup>68</sup>Ga/[<sup>18</sup>F]AlF-ESV6 derivatives (500KBq) and human FAP (2 μM, 100μl) on PD-10 columns preequilibrated with running buffer (50 mM Tris, 100 mM NaCl, and 1 mM ethylenediaminetetraacetic acid [EDTA], pH = 7.4), and flushed with running buffer. Fractions of the flow through (500 μL) were collected in 3ml test tube, and the radioactivity intensity associated with the concentration of radiocompounds was measured immediately on a gamma counter (λ=511KeV for <sup>68</sup>Ga and <sup>18</sup>F).

For all the radiolabelled compounds the coelution experiments of the radiopharmaceutical in the absence and in the presence of the human FAP protein show an excellent affinity towards their biological target as can be seen from Figure 8.

## CLAIMS

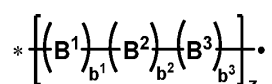
1. A compound, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers, or a pharmaceutically acceptable salt thereof, wherein the compound structure comprises:

a moiety **A** represented by or comprising the following structure:



one or more diagnostic or therapeutic agent moieties **C**; and

a moiety **B** covalently connecting **A** to **C**, which is represented by the following structure:



wherein each  $b^1$  and  $b^3$  is independently an integer from 0 to 4, preferably 0 or 1;

each  $b^2$  is independently an integer from 1 to 4, preferably 1 or 2;

$z$  is an integer from 1 to 3, preferably 1 or 2;

each  $B^2$  is independently represented by  $*-Y \text{---} Z-\bullet$ , wherein:

**Y** and **Z** are linking groups forming part of a carbocyclic or heterocyclic group, preferably a  $C_{3-13}$  carbocyclic or  $C_{2-12}$  heterocyclic group;

$*-Y$  represents  $*-C$ ,  $*-CR$ ,  $*-N$ ,  $*-NR$ ,  $*-NRC(O)C$ ,  $*-NRC(O)CR$ ,  $*-NRC(O)CR_2C$ ,  $*-NRC(O)CR_2CR$ ,  $*-NRC(S)NRC$ ,  $*-NRC(S)NRCR$ ,  $*-NRC$ ,  $*-NRCR$ ,  $*-NRCR_2C$ , or  $*-NRCR_2CR$ ;

$Z-\bullet$  represents  $C-\bullet$ ,  $CR-\bullet$ ,  $N-\bullet$ ,  $NR-\bullet$ ,  $CC(O)NRCRC(O)NR-\bullet$ ,  $CCR_2C(O)NR-\bullet$ ,  $CR_2C(O)NR-\bullet$ ,  $CNRC(S)NR-\bullet$ ,  $NRC(S)CRNR-\bullet$ ,  $CNR-\bullet$ ,  $CRNR-\bullet$ ,  $CCR_2NR-\bullet$ , or  $CR_2NR-\bullet$ ;

each \* represents a point of attachment closer to moiety **A** than to a moiety **C**;

each • represents a point of attachment closer to a moiety **C** than to moiety **A**;

each **B<sup>1</sup>** is independently a bond, alkylene, oxoalkylene, di(oxo)alkylene, C(O)alkylarylalkylene, C(S)N(R)arylalkylene, or heteroalkylene, said heteroalkylene comprising one or more heteroatoms selected from N and O; and is preferably a bond, alkylene or heteroalkylene, said heteroalkylene comprising one or more heteroatoms selected from N and O; wherein the shortest path between **A** and **B<sup>2</sup>** preferably comprises 6 or less, more preferably 3 or less, most preferably 2 or less covalently connected atoms or is a bond;

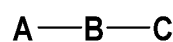
each **B<sup>3</sup>** is independently a bond, alkylene, oxoalkylene, di(oxo)alkylene, C(O)alkylarylalkylene, C(S)N(R)arylalkylene, or heteroalkylene, said heteroalkylene comprising one or more heteroatoms selected from N and O; and is preferably a bond, alkylene, oxoalkylene, di(oxo)alkylene, C(O)alkylarylalkylene, or C(S)N(R)arylalkylene; wherein the shortest path between **B<sup>2</sup>** and **C** preferably comprises 10 or less, more preferably 7 or less, most preferably 6 or less covalently connected atoms or is a bond;

each of **B<sup>1</sup>**, **B<sup>2</sup>** and **B<sup>3</sup>** can be independently substituted by one or more of R;

each R is independently selected from H, OH, SH, NH<sub>2</sub>, halogen, cyano, oxo, carboxy, C(O)NH<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C(O)C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylthio, C<sub>1-5</sub> heteroalkyl, C<sub>1-5</sub> heteroalkoxy, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkoxy, C<sub>6-10</sub> aryl, C<sub>6-10</sub> aryloxy, C<sub>5-10</sub> heteroaryl and C<sub>5-10</sub> heteroaryloxy, of which the SH, NH<sub>2</sub>, C(O)NH<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C(O)C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylthio, C<sub>1-5</sub> heteroalkyl, C<sub>1-5</sub> heteroalkoxy, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkoxy, C<sub>6-10</sub> aryl, C<sub>6-10</sub> aryloxy, C<sub>5-10</sub> heteroaryl and C<sub>5-10</sub> heteroaryloxy can be optionally substituted with one or more of OH, SH, NH<sub>2</sub>, halogen, cyano, oxo, carboxy, C<sub>1-6</sub> alkyl, C<sub>1-5</sub> heteroalkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>5-10</sub> heteroaryl, and two or more of R can be bound together to form part of a carbocyclic or heterocyclic ring system; and

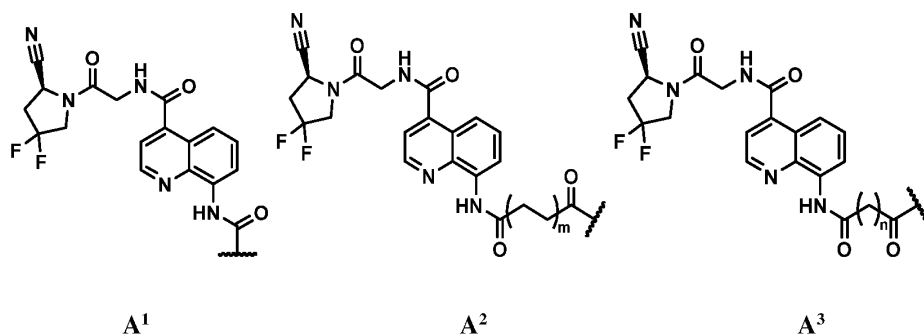
all valences are satisfied.

2. The compound of claim 1, which is represented by the following Formula I:

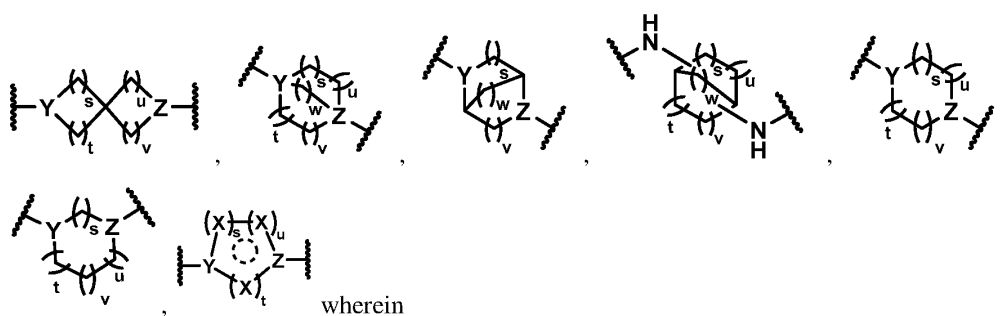


**I**

3. The compound according to any one of the preceding claims, wherein moiety **A** has the following structure **A<sup>1</sup>**, **A<sup>2</sup>** or **A<sup>3</sup>**, preferably **A<sup>2</sup>**, wherein *m* is 0, 1, 2, 3, 4, or 5, preferably 1; and *n* is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, preferably 2:



4. The compound of any one of the preceding claims, wherein each **B**<sup>2</sup> is independently selected from:

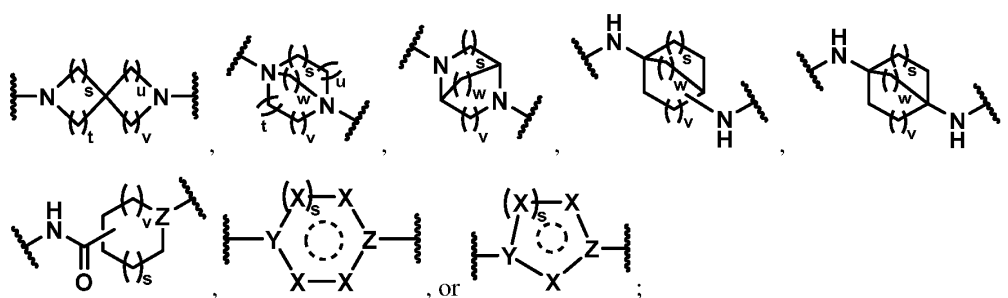


each s, u, t, and v is independently 0, 1, or 2;

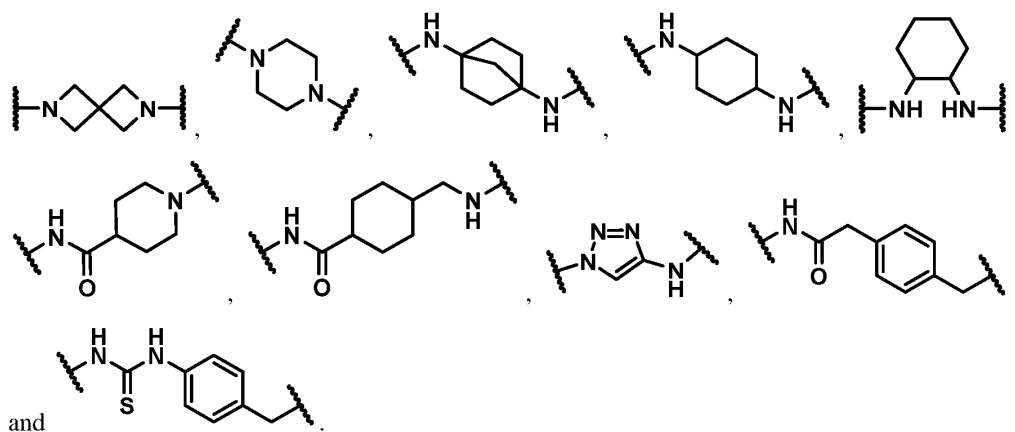
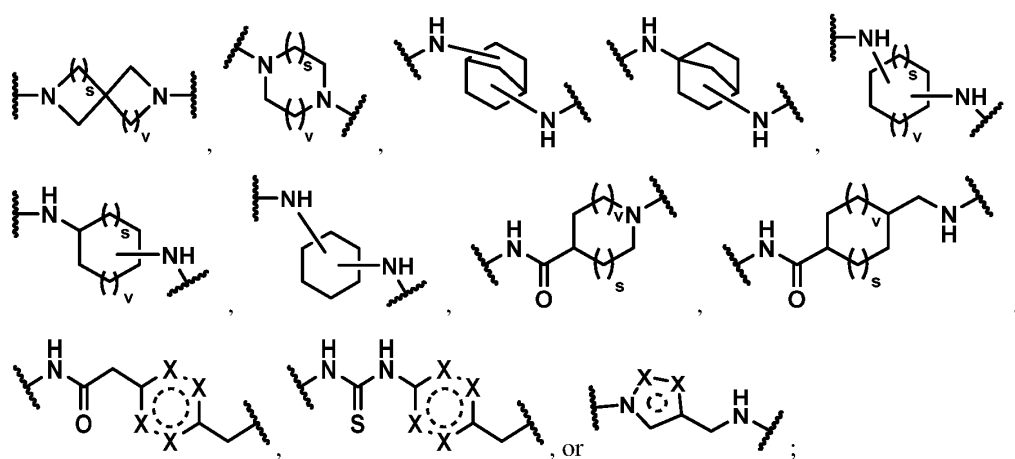
each w is independently 0, 1, 2, or 3; and

each X is independently N, NH, NR, S, S(O), SO<sub>2</sub>, O, C, CR, CH, CR<sub>2</sub> or CH<sub>2</sub>; and

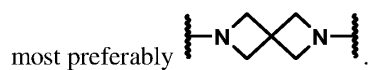
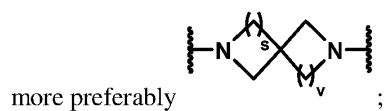
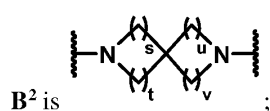
preferably, **B**<sup>2</sup> is selected from:



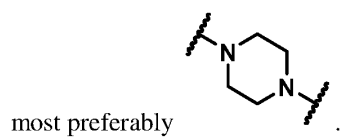
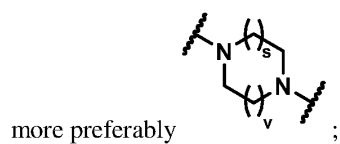
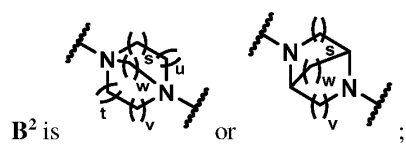
more preferably, **B**<sup>2</sup> is selected from:



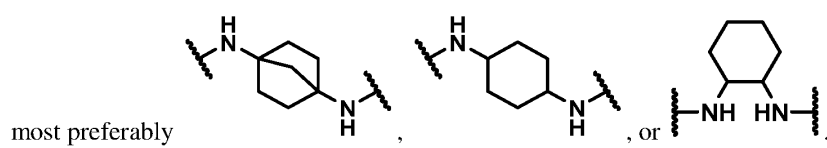
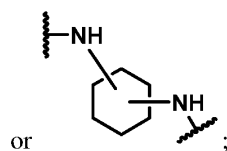
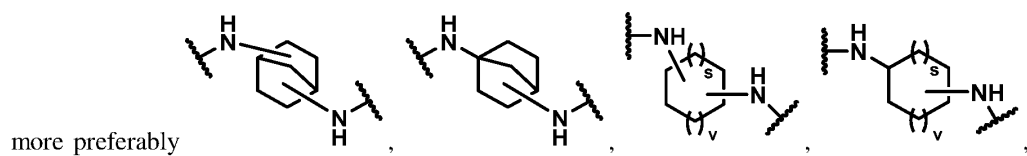
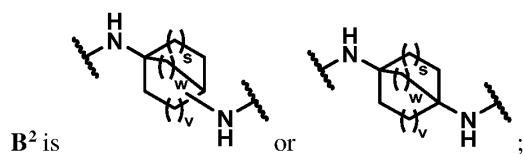
5. The compound of any one of claims 1 to 4, wherein



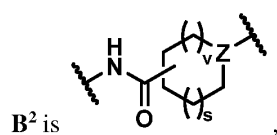
6. The compound of any one of claims 1 to 4, wherein

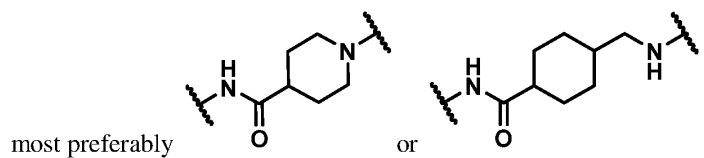
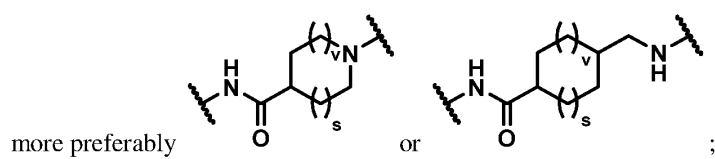


7. The compound of any one of claims 1 to 4, wherein

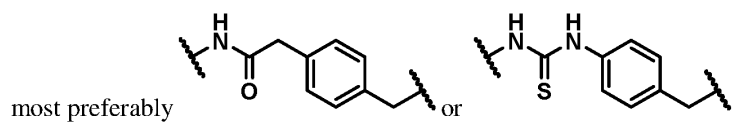
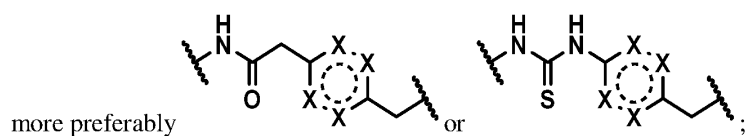
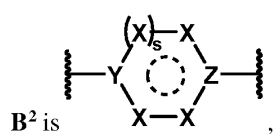


8. The compound of any one of claims 1 to 4, wherein:

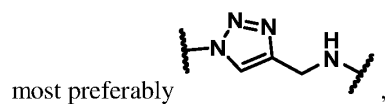
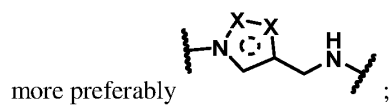
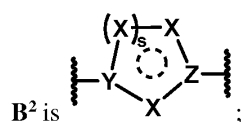




9. The compound of any one of claims 1 to 4, wherein

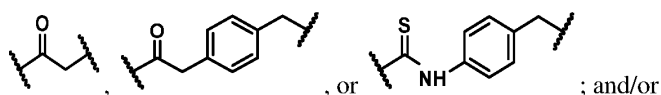


10. The compound of any one of claims 1 to 4, wherein

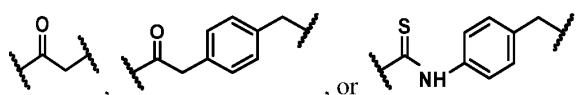


11. The compound of any one of the preceding claims, wherein:

each **B**<sup>1</sup> is independently selected from bond; C<sub>1-10</sub>, preferably C<sub>1-4</sub>, more preferably C<sub>1-2</sub> alkylene; C<sub>1-10</sub>, preferably C<sub>1-4</sub>, more preferably C<sub>1-2</sub> heteroalkylene group comprising one or two N atoms; NR(C<sub>1-10</sub>, C<sub>1-4</sub>, or C<sub>1-2</sub> alkylene)NR; (C<sub>1-10</sub>, C<sub>1-4</sub>, or C<sub>1-2</sub> alkylene)NR; NR(C<sub>1-10</sub>, C<sub>1-4</sub>, or C<sub>1-2</sub> alkylene); C(O); C(O)CR<sub>2</sub>; C(O)(C<sub>6-10</sub> aryl)CR<sub>2</sub>; C(O)(C<sub>1-10</sub> alkylene)C(O); C(O)(C<sub>1-10</sub> alkyl)C(O)NR; C(O)(C<sub>5-10</sub> heteroaryl)CR<sub>2</sub>; C(O)(C<sub>6-10</sub> aryl)CR<sub>2</sub>; C(O)(C<sub>5-10</sub> heteroaryl)CR<sub>2</sub>; C(S)NR; C(S)NR(C<sub>6-10</sub> aryl)CR<sub>2</sub>; and C(S)NR(C<sub>5-10</sub> heteroaryl)CR<sub>2</sub>; and is preferably bond, C(O)CH<sub>2</sub>CH<sub>2</sub>C(O), NHCH<sub>2</sub>CH<sub>2</sub>NH, CH<sub>2</sub>CH<sub>2</sub>NH, NHCH<sub>2</sub>CH<sub>2</sub>,



each **B**<sup>3</sup> is independently selected from bond; C<sub>1-10</sub>, preferably C<sub>1-4</sub>, more preferably C<sub>1-2</sub> alkylene; C<sub>1-10</sub>, preferably C<sub>1-4</sub>, more preferably C<sub>1-2</sub> heteroalkylene group comprising one or two N atoms; NR(C<sub>1-10</sub>, C<sub>1-4</sub>, or C<sub>1-2</sub> alkylene)NR; (C<sub>1-10</sub>, C<sub>1-4</sub>, or C<sub>1-2</sub> alkylene)NR; NR(C<sub>1-10</sub>, C<sub>1-4</sub>, or C<sub>1-2</sub> alkylene); C(O); C(O)CR<sub>2</sub>; C(O)(C<sub>6-10</sub> aryl)CR<sub>2</sub>; C(O)(C<sub>5-10</sub> heteroaryl)CR<sub>2</sub>; C(O)(C<sub>6-10</sub> aryl)CR<sub>2</sub>; C(O)(C<sub>5-10</sub> heteroaryl)CR<sub>2</sub>; C(O)(C<sub>6-10</sub> aryl)CR<sub>2</sub>; C(O)(C<sub>5-10</sub> heteroaryl)CR<sub>2</sub>; C(S)NR; C(S)NR(C<sub>6-10</sub> aryl)CR<sub>2</sub>; and C(S)NR(C<sub>5-10</sub> heteroaryl)CR<sub>2</sub>; and is preferably bond, C(O)CH<sub>2</sub>CH<sub>2</sub>C(O), NHCH<sub>2</sub>CH<sub>2</sub>NH, CH<sub>2</sub>CH<sub>2</sub>NH, NHCH<sub>2</sub>CH<sub>2</sub>,

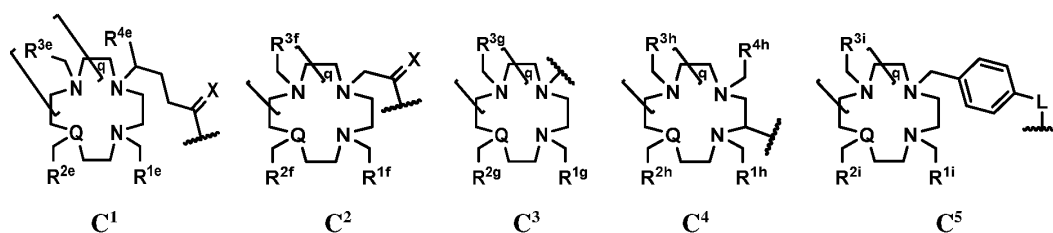


12. The compound according to any one of the preceding claims, wherein the moiety **C** is selected from: a chelating agent group suitable for radiolabelling; a radioactive group comprising a radioisotope; a chelate of a radioactive isotope with a chelating agent; a fluorophore group; a cytotoxic and/or cytostatic agent; immunomodulator agent; or a protein,

wherein preferably, **C**:

- (a) is chelating agent group suitable for radiolabelling:
- (i) derived from 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA), 2,2',2''-(1,4,7-triazonane-1,4-diyl)diacetic acid (NODA), 2,2'-((2-((4-(2-amino-2-oxoethyl)benzyl)(carboxymethyl)amino)cyclohexyl)azanediy)diacetic acid] (RESCA), sulfur colloid, diethylenetriaminepentaacetic acid (DTPA), ethylenediaminetetraacetic acid (EDTA), 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), [2,2',2''-(10-(4-((2-aminoethyl)amino)-1-carboxy-4-oxobutyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (DOTA-GA), [1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA), iminodiacetic acid, bis(carboxymethylimidazole)glycine, 6-Hydrazinopyridine-3-carboxylic acid (HYNIC); or

- (ii) having a structure according to one of the following formulae **C<sup>1</sup>**, **C<sup>2</sup>**, **C<sup>3</sup>**, **C<sup>4</sup>**, and **C<sup>5</sup>**:



wherein:

each q is independently 0, 1, 2, 3, 4 or 5; preferably 0;

R<sup>1e</sup>, R<sup>1f</sup>, R<sup>1g</sup>, R<sup>1h</sup>, and R<sup>1i</sup> are each independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH;

R<sup>2e</sup>, R<sup>2f</sup>, R<sup>2g</sup>, R<sup>2h</sup>, and R<sup>2i</sup> are each independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH;

R<sup>3e</sup>, R<sup>3f</sup>, R<sup>3g</sup>, R<sup>3h</sup>, R<sup>4h</sup>, and R<sup>3i</sup> are each independently H, COOH, aryl-COOH or heteroaryl-COOH; preferably COOH; and

and R<sup>4e</sup> is independently H, COOH, aryl-COOH or heteroaryl-COOH, with the proviso that when q is 0, R<sup>4e</sup> is H;

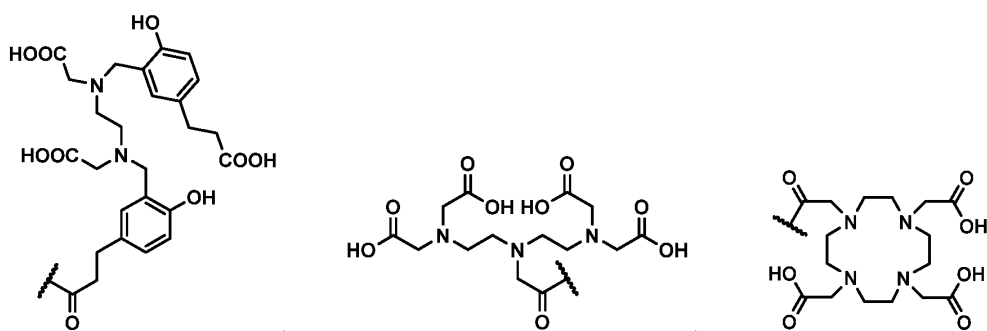
each X is independently NH, NR, S, O, CR<sub>2</sub>, or H,H; preferably O;

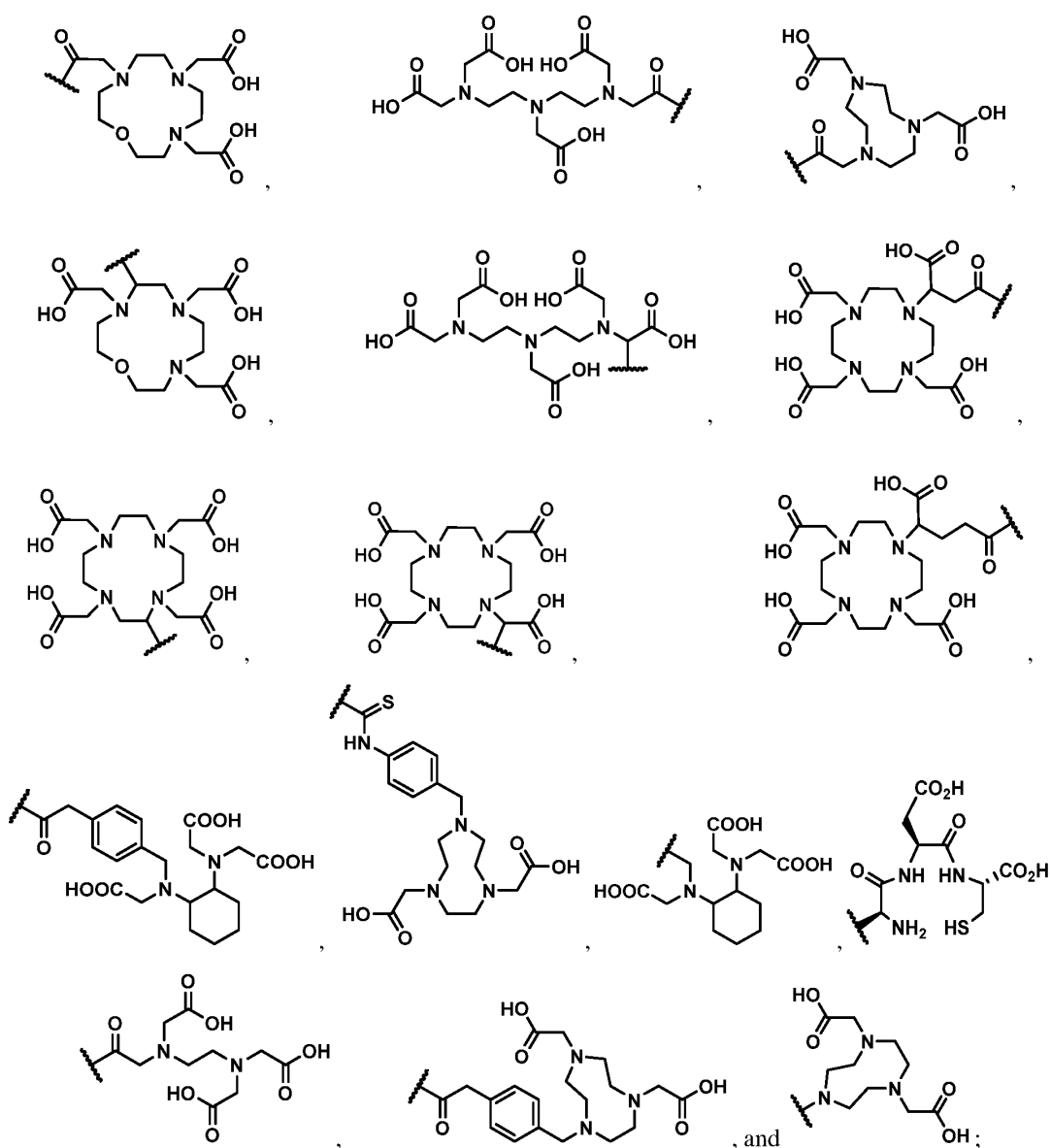
each Q is N or O, preferably N;

wherein when Q is O, CH<sub>2</sub>R<sup>2e</sup>, CH<sub>2</sub>R<sup>2f</sup>, CH<sub>2</sub>R<sup>2g</sup>, CH<sub>2</sub>R<sup>2h</sup>, and CH<sub>2</sub>R<sup>2i</sup> is absent; and

L is -CH<sub>2</sub>C(O)- or -NHC(S)-; or

- (iii) having a structure selected from the following:

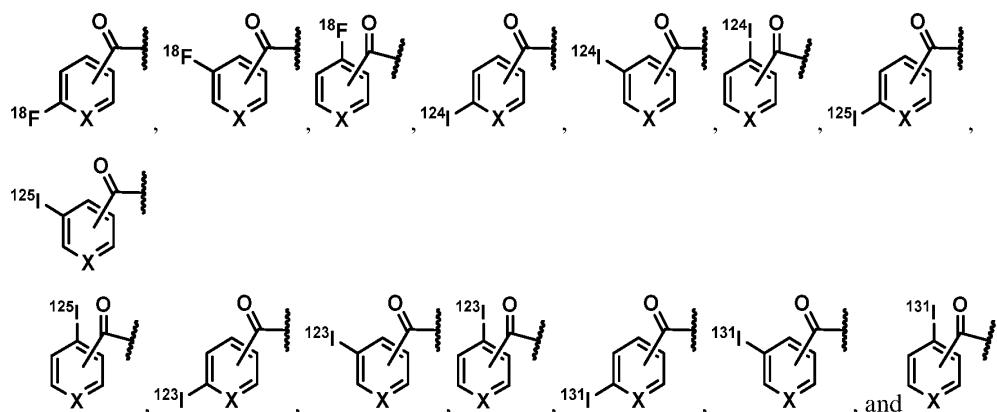




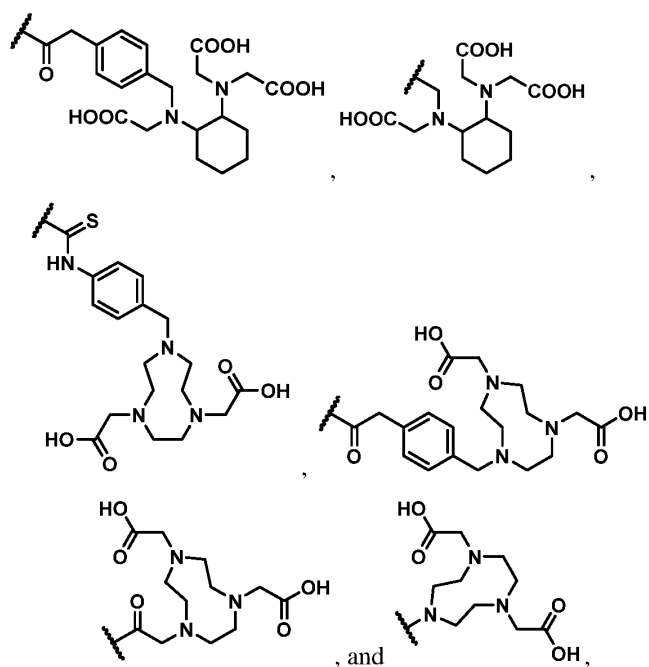
- (b) radioactive group comprising a radioisotope is selected from  $^{223}\text{Ra}$ ,  $^{89}\text{Sr}$ ,  $^{94\text{m}}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{203}\text{Pb}$ ,  $^{67}\text{Ga}$ ,  $^{68}\text{Ga}$ ,  $^{47}\text{Sc}$ ,  $^{111}\text{In}$ ,  $^{97}\text{Ru}$ ,  $^{62}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{86}\text{Y}$ ,  $^{88}\text{Y}$ ,  $^{90}\text{Y}$ ,  $^{121}\text{Sn}$ ,  $^{161}\text{Tb}$ ,  $^{153}\text{Sm}$ ,  $^{166}\text{Ho}$ ,  $^{105}\text{Rh}$ ,  $^{177}\text{Lu}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{18}\text{F}$ ,  $^{211}\text{At}$ ,  $^{225}\text{Ac}$ ,  $^{89}\text{Sr}$ ,  $^{117\text{m}}\text{Sn}$  and  $^{169}\text{Er}$ ,

wherein  $^{18}\text{F}$  is preferably bound to chelated Al, Zr, Si, Ga, or In, more preferably  $^{18}\text{F}$  is bound to Al chelated by the chelator;

- (c) chelate of a radioactive isotope is a chelate of an isotope listed under (b) above and/or with a chelating agent listed under (a) above; or moiety C is a group selected from any of the following structures:



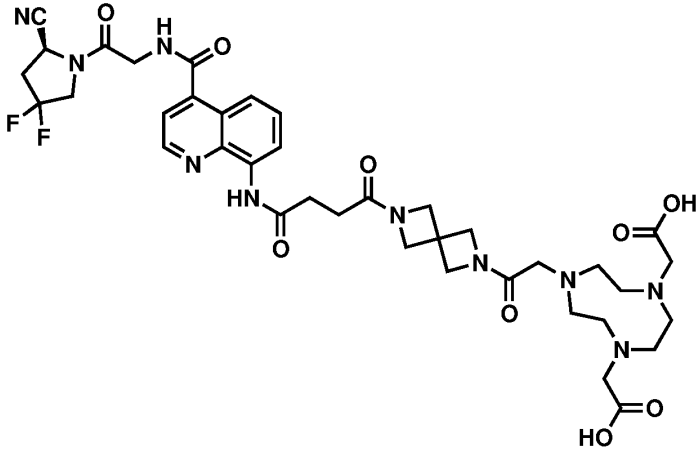
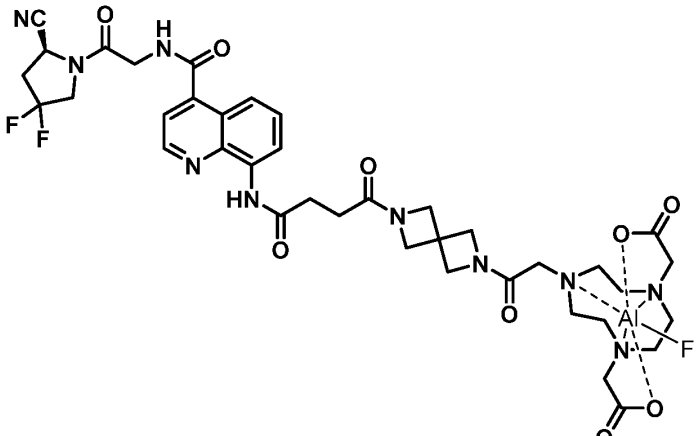
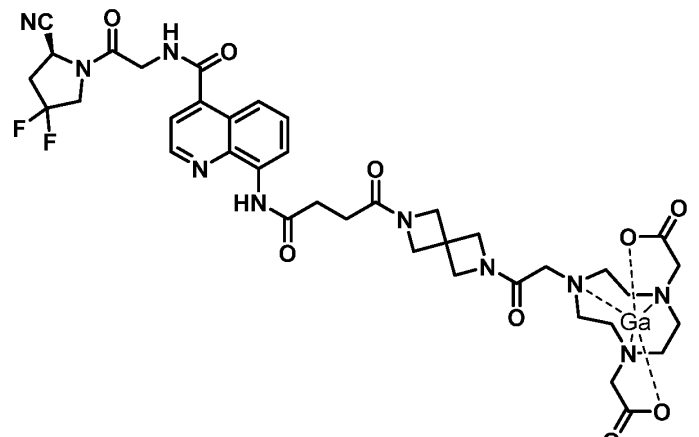
13. The compound of any one of claims 4 to 10, wherein C is a chelator selected from

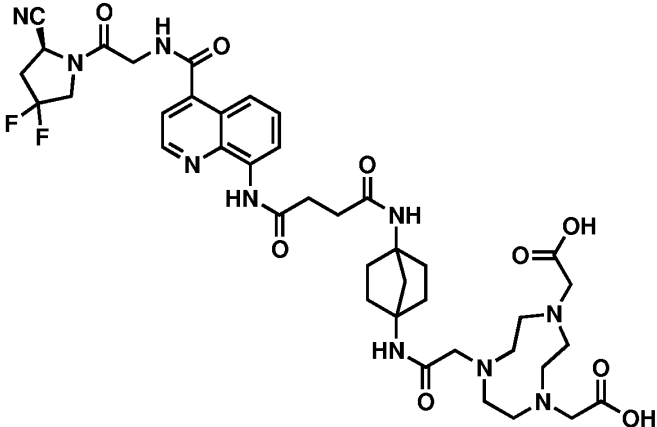
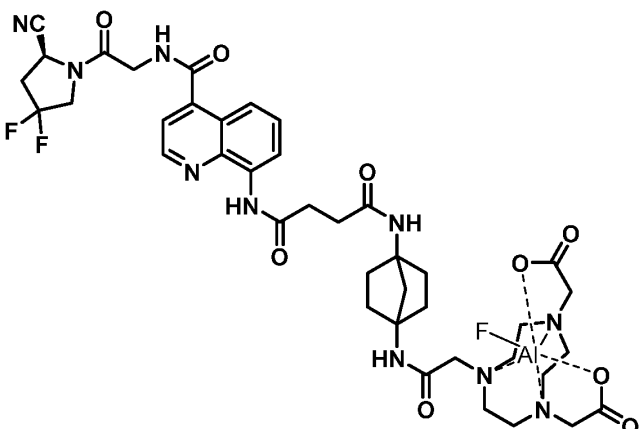
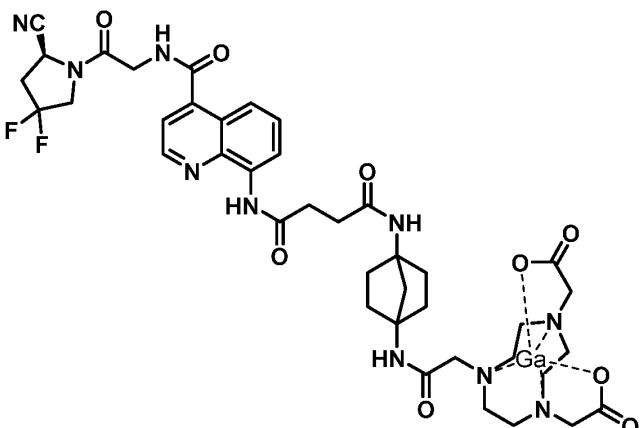


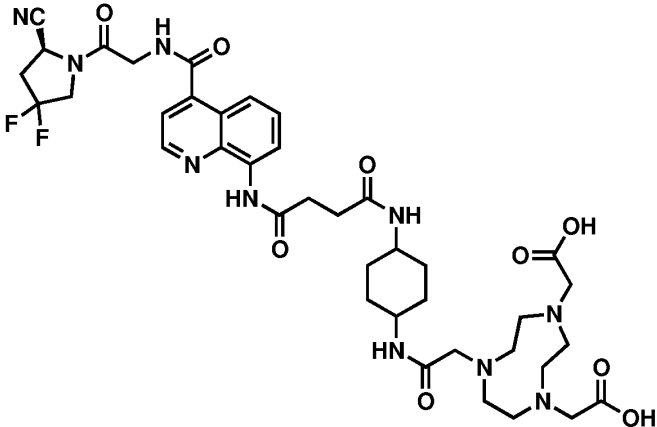
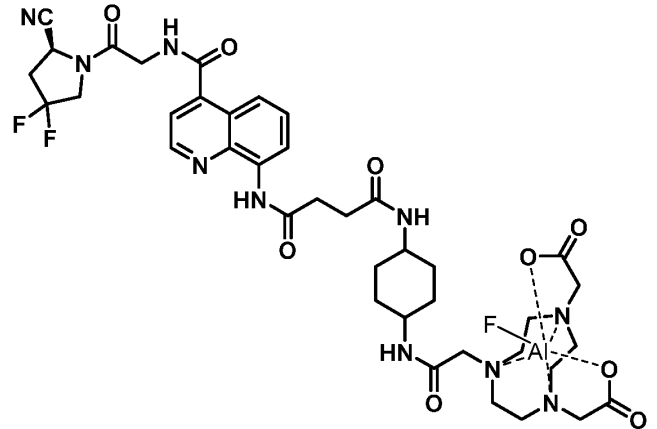
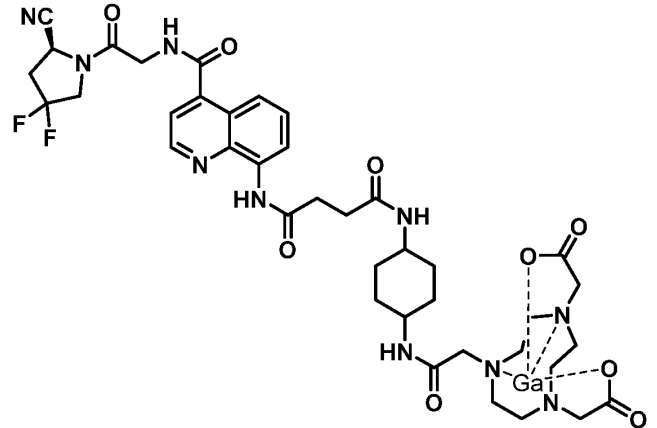
preferably wherein  $^{18}\text{F}$  is bound to Al chelated by the chelator.

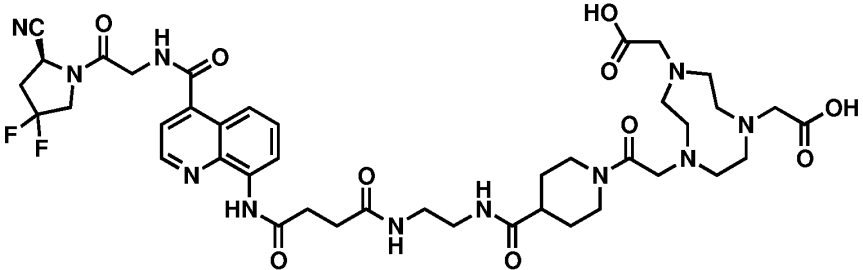
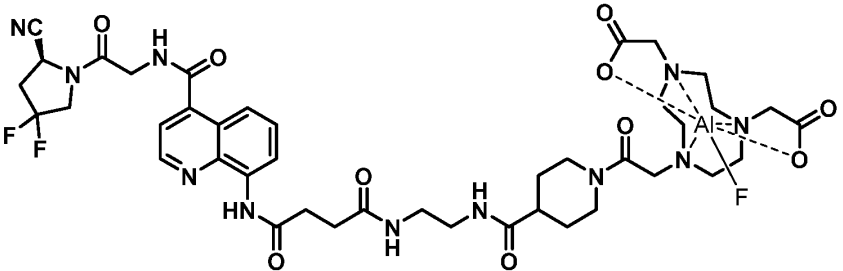
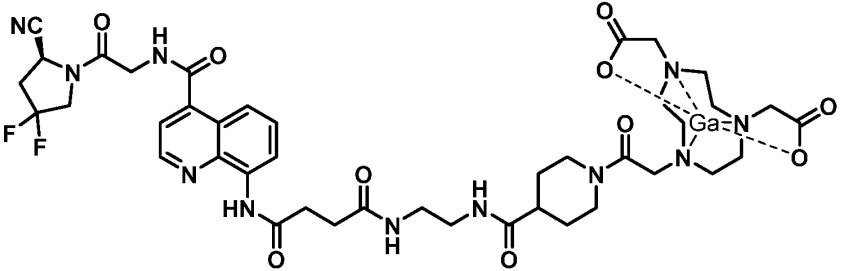
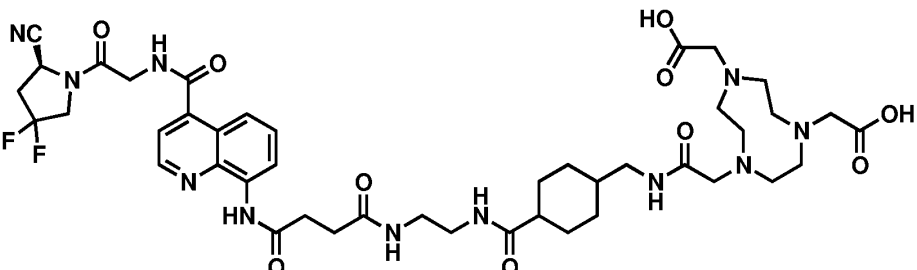
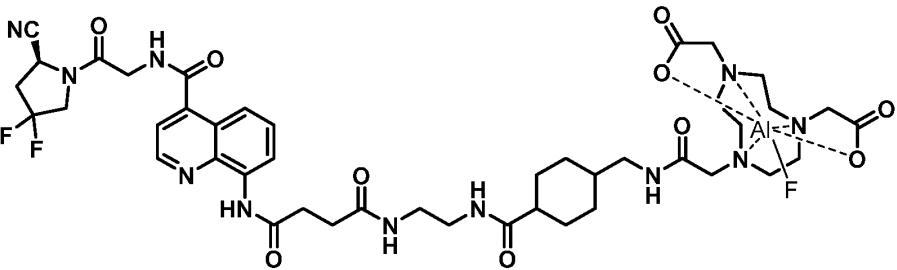
14. A compound, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers, or a pharmaceutically acceptable salt thereof, having a structure selected from the following:

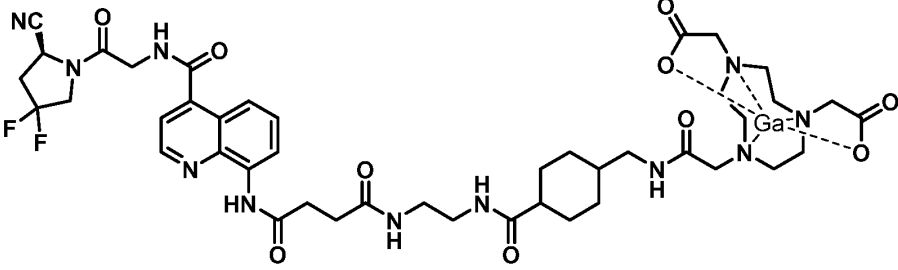
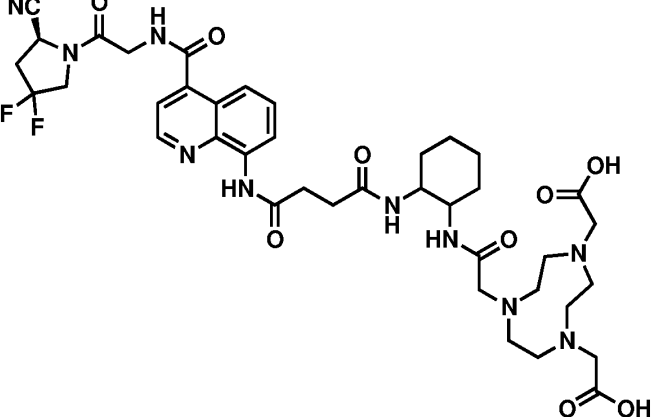
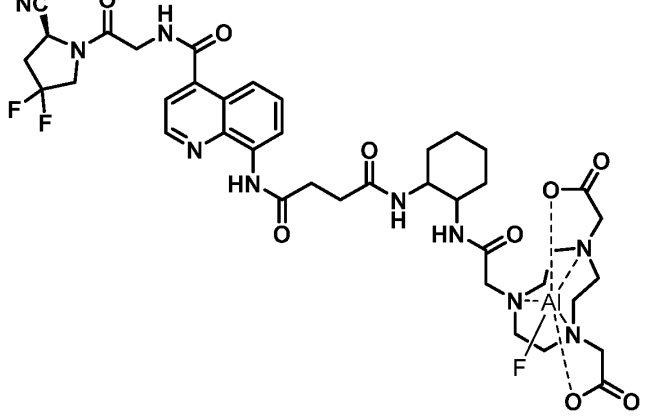
|       |  |
|-------|--|
| 1     |  |
| AlF@1 |  |
| Ga@1  |  |

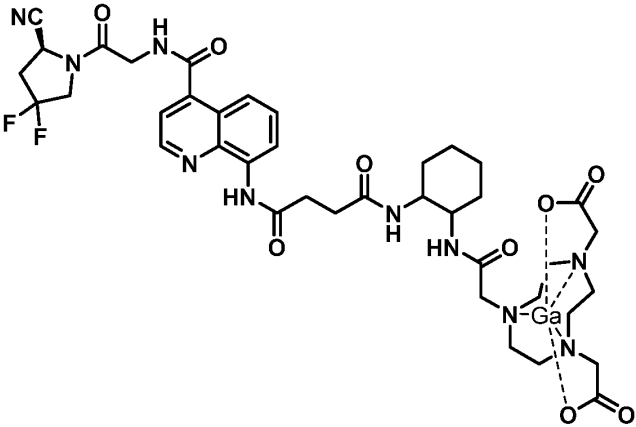
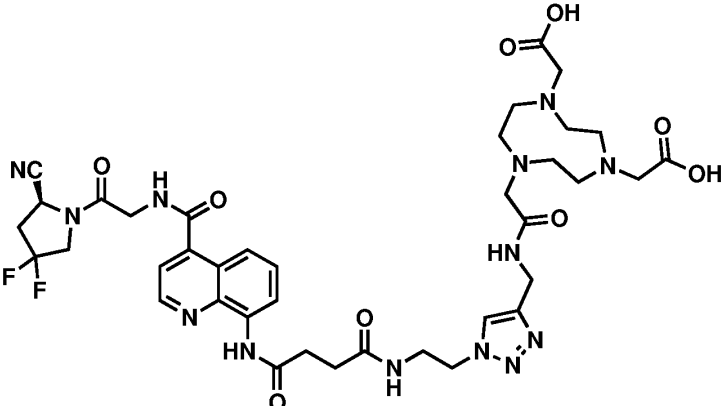
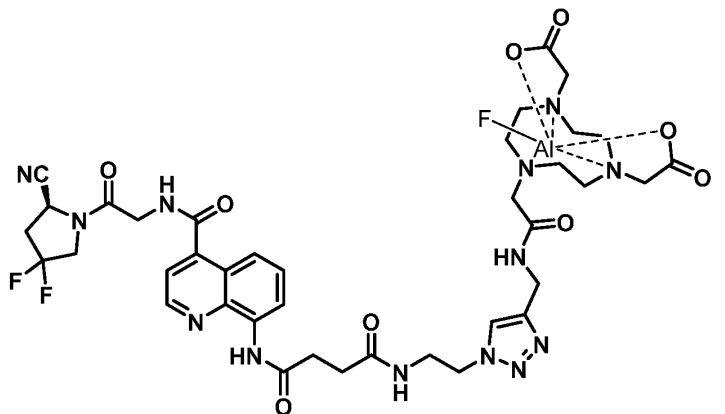
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|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3     |  <p>Chemical structure of compound 3: A complex molecule featuring a 2,2,2-trifluoroethyl group attached to a carbonyl, which is linked to a quinoline ring. The quinoline ring is further connected to a carboxylic acid group, which is linked to a cyclobutane ring. The cyclobutane ring is connected to a carboxylic acid group, which is linked to a 2,2,2-trifluoroethyl group.</p>                                                                                                                         |
| AlF@3 |  <p>Chemical structure of compound AlF@3: A complex molecule featuring a 2,2,2-trifluoroethyl group attached to a carbonyl, which is linked to a quinoline ring. The quinoline ring is further connected to a carboxylic acid group, which is linked to a cyclobutane ring. The cyclobutane ring is connected to a carboxylic acid group, which is linked to a 2,2,2-trifluoroethyl group. The molecule is shown with a fluorine atom (F) and an aluminum atom (Al) coordinated to the carboxylic acid group.</p> |
| Ga@3  |  <p>Chemical structure of compound Ga@3: A complex molecule featuring a 2,2,2-trifluoroethyl group attached to a carbonyl, which is linked to a quinoline ring. The quinoline ring is further connected to a carboxylic acid group, which is linked to a cyclobutane ring. The cyclobutane ring is connected to a carboxylic acid group, which is linked to a 2,2,2-trifluoroethyl group. The molecule is shown with a fluorine atom (F) and a gallium atom (Ga) coordinated to the carboxylic acid group.</p>   |

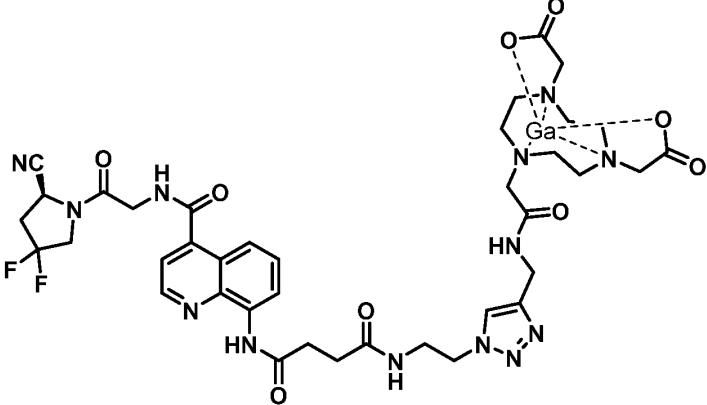
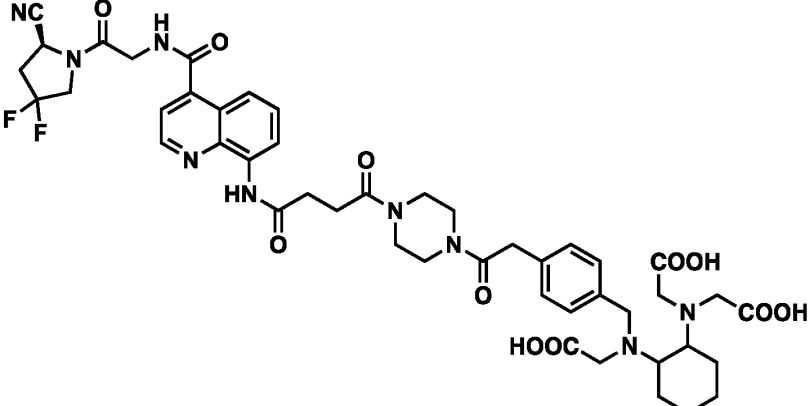
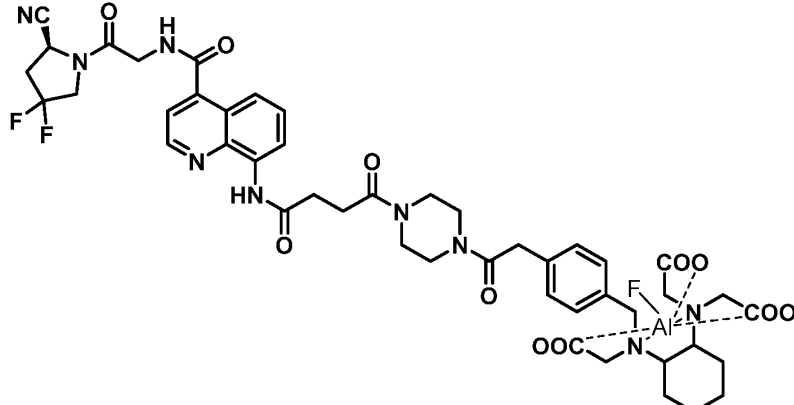
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|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4     |  <p>Chemical structure of compound 4, a complex molecule featuring a 2,2,2-trifluoroethyl group, a nitrile group, a quinoline ring system, a carboxylic acid group, and a bicyclic amine moiety.</p> |
| AlF@4 |  <p>Chemical structure of compound AlF@4, which is a complex molecule similar to compound 4, but with a fluorine atom coordinated to the aluminum atom (Al) in the bicyclic amine moiety.</p>       |
| Ga@4  |  <p>Chemical structure of compound Ga@4, which is a complex molecule similar to compound 4, but with a fluorine atom coordinated to the gallium atom (Ga) in the bicyclic amine moiety.</p>        |

|       |                                                                                                                                                                                                                                                                                                                |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5     |  <p>Chemical structure of compound 5, a complex molecule featuring a 2,2,2-trifluoroethyl group, a nitrile group, a quinoline ring system, a cyclohexane ring, and a macrocyclic structure with a carboxylic acid group.</p> |
| AlF@5 |  <p>Chemical structure of compound AlF@5, showing the same core structure as compound 5, but with an aluminum atom (Al) coordinated to the macrocyclic structure, indicated by dashed lines.</p>                            |
| Ga@5  |  <p>Chemical structure of compound Ga@5, showing the same core structure as compound 5, but with a gallium atom (Ga) coordinated to the macrocyclic structure, indicated by dashed lines.</p>                              |

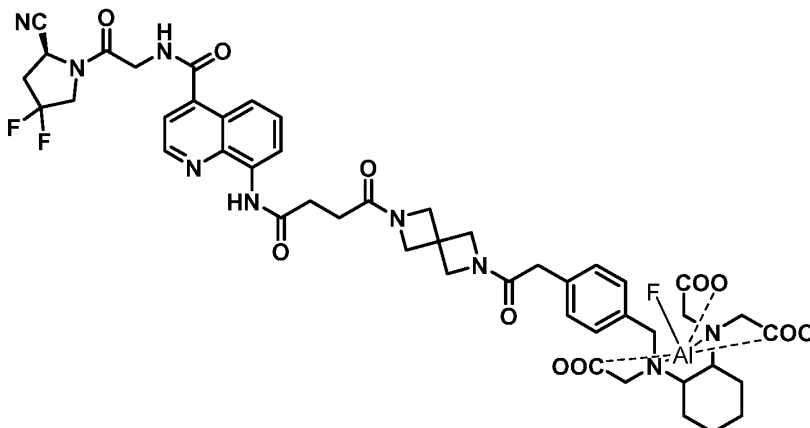
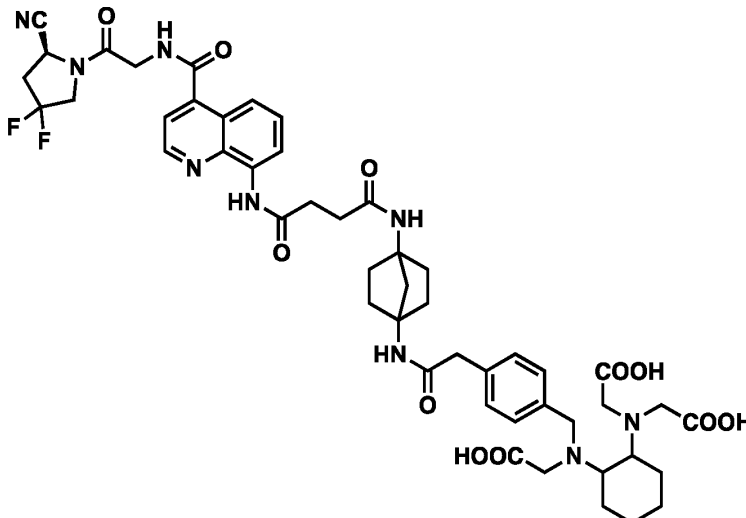
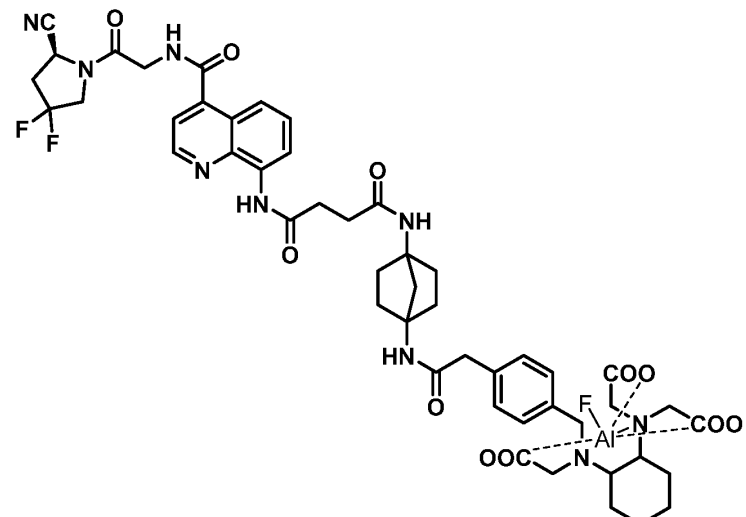
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|-------|--------------------------------------------------------------------------------------|
| 6     |    |
| AlF@6 |    |
| Ga@6  |   |
| 7     |  |
| AlF@7 |  |

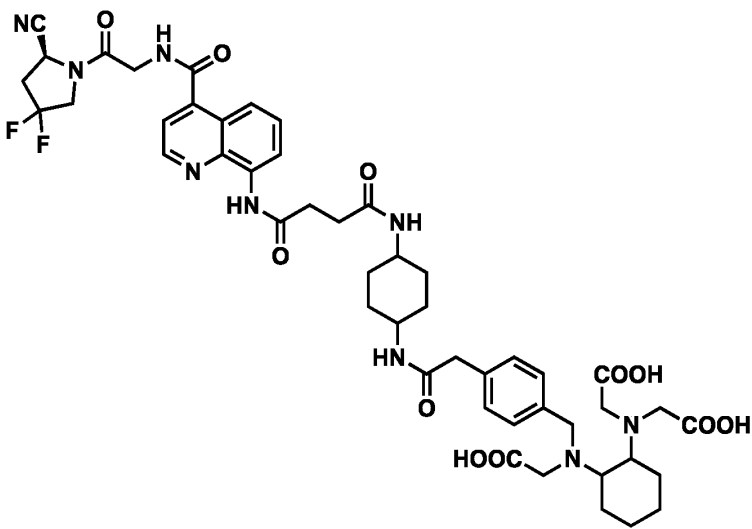
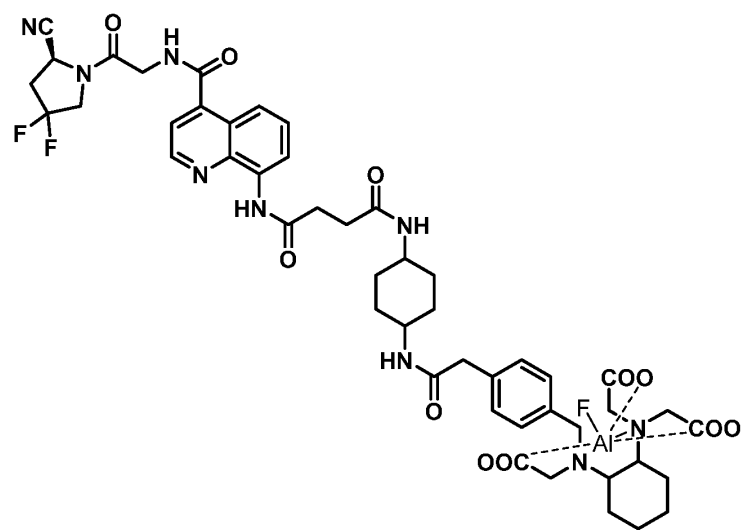
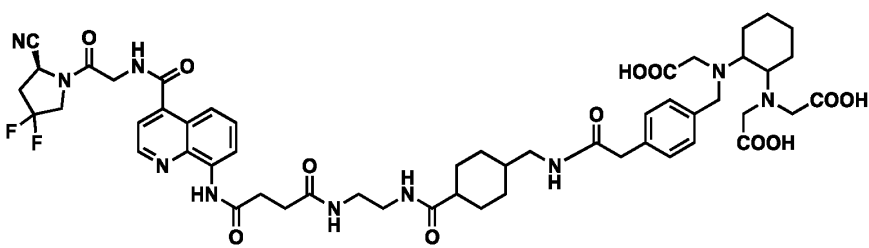
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|-------|--------------------------------------------------------------------------------------|
| Ga@7  |    |
| 8     |   |
| AlF@8 |  |

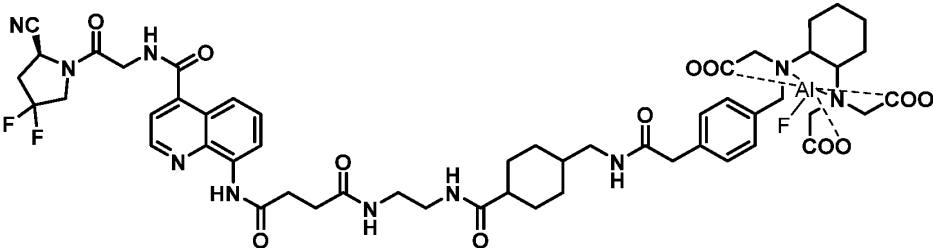
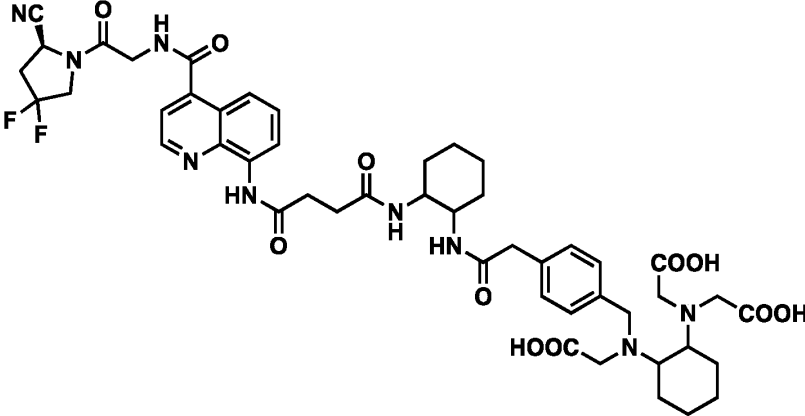
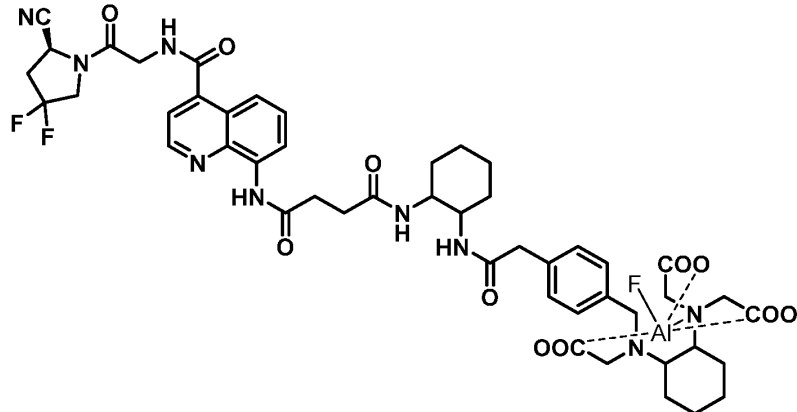
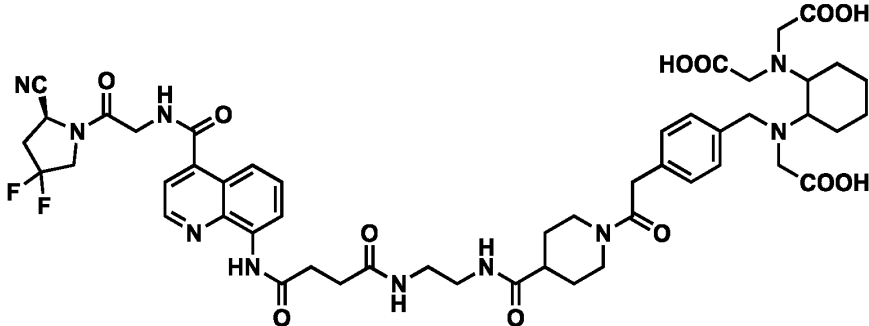
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|-------|--------------------------------------------------------------------------------------|
| Ga@8  |    |
| 9     |   |
| AlF@9 |  |

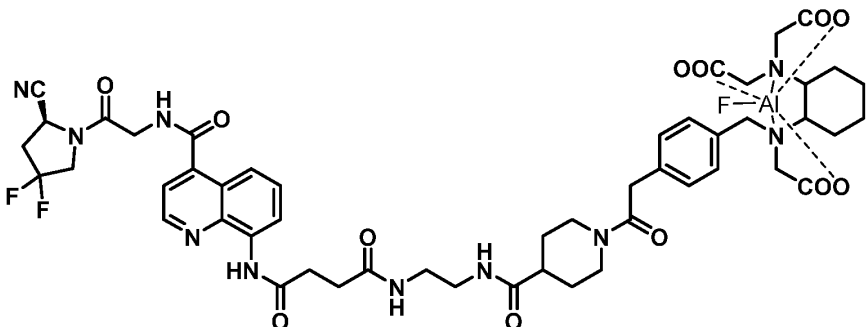
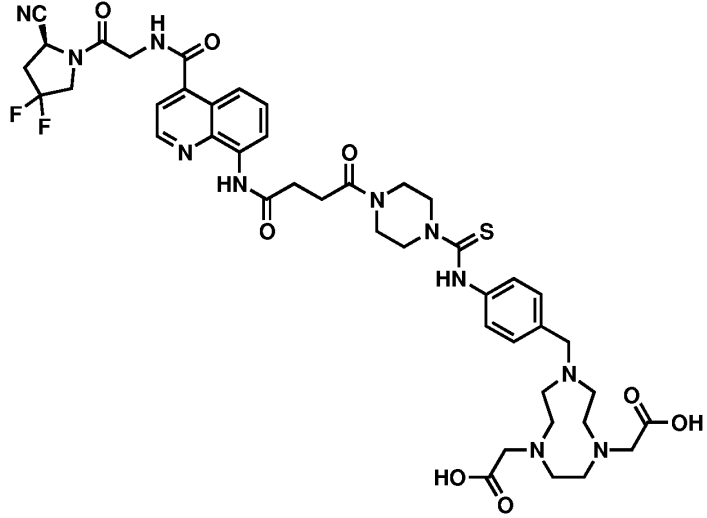
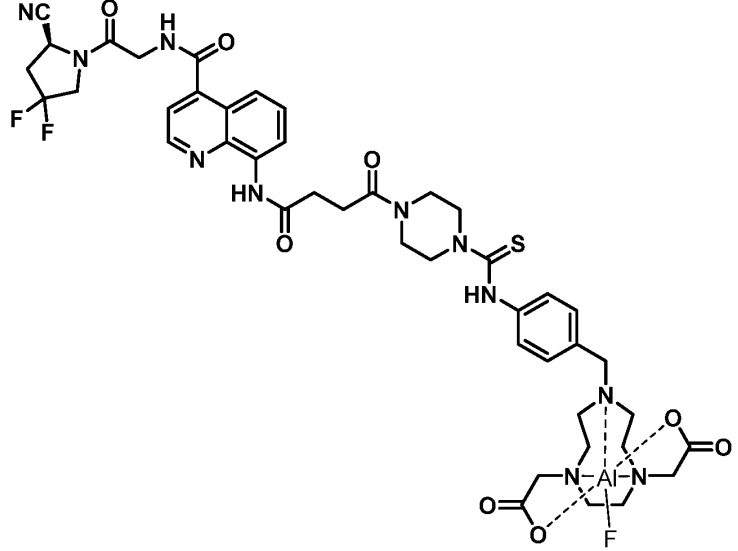
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| Ga@9   |    |
| 12     |   |
| AlF@12 |  |

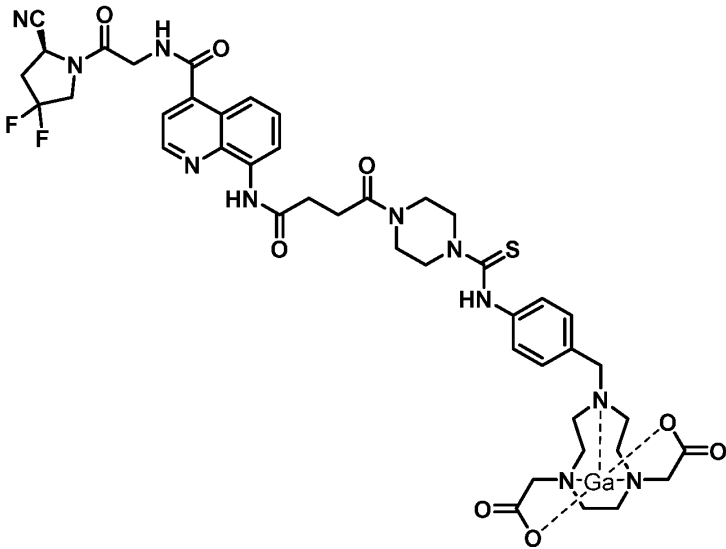
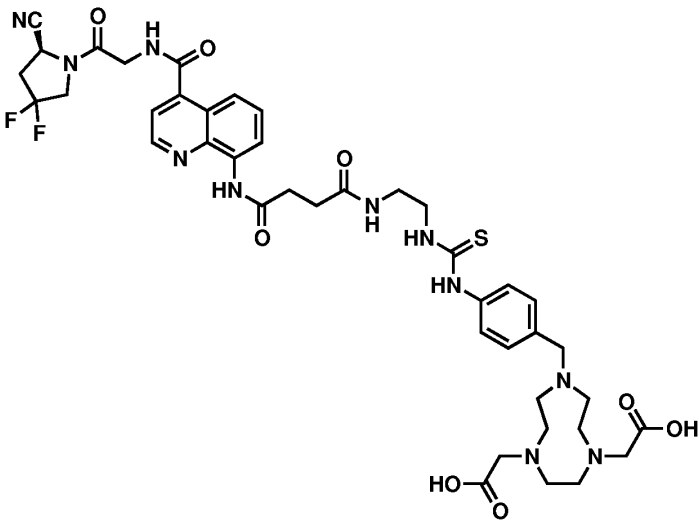
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|--------|--|
| 13     |  |
| AlF@13 |  |
| 14     |  |

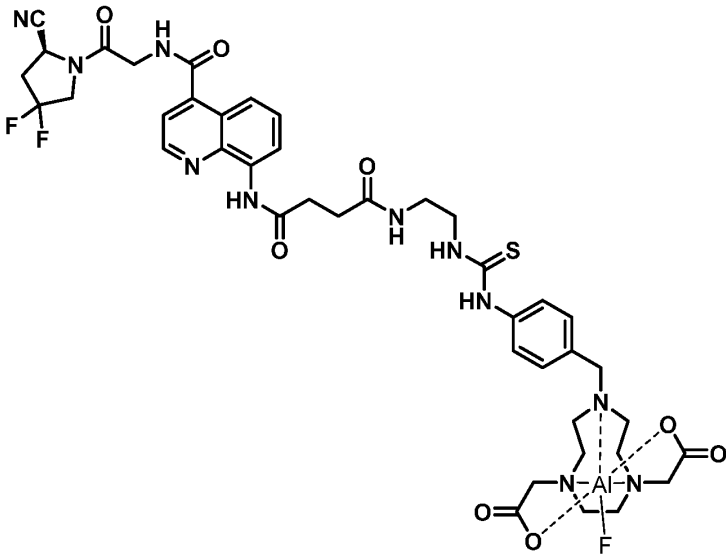
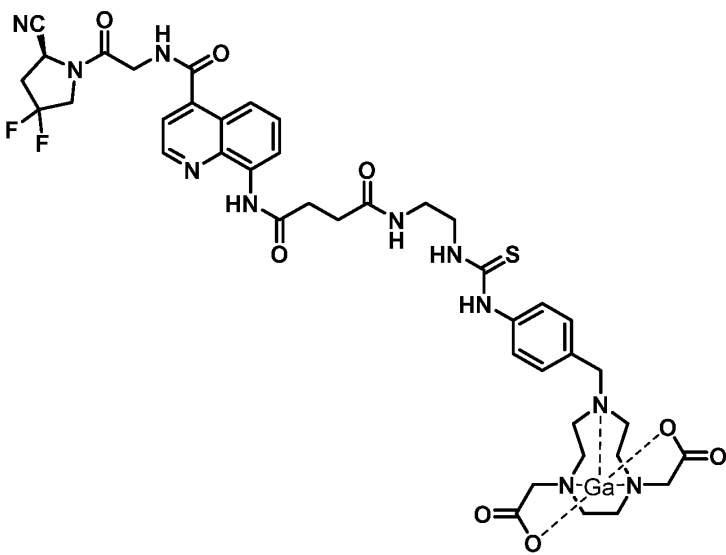
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|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AlF@14 |  <p>Chemical structure of AlF@14, a macrocyclic molecule. It features a central aluminum atom (Al) coordinated by a fluorine atom (F) and three nitrogen atoms (N) of a macrocyclic ligand. The macrocycle is composed of a 1,3-difluoro-4-cyano-5-oxo-5,5-dihydro-1H-imidazolidine-2-ylidene group, a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group, a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group, and a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group. The macrocycle is further substituted with a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group and a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group. The macrocycle is further substituted with a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group and a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group.</p>   |
| 15     |  <p>Chemical structure of 15, a macrocyclic molecule. It features a central aluminum atom (Al) coordinated by a fluorine atom (F) and three nitrogen atoms (N) of a macrocyclic ligand. The macrocycle is composed of a 1,3-difluoro-4-cyano-5-oxo-5,5-dihydro-1H-imidazolidine-2-ylidene group, a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group, a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group, and a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group. The macrocycle is further substituted with a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group and a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group. The macrocycle is further substituted with a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group and a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group.</p>      |
| AlF@15 |  <p>Chemical structure of AlF@15, a macrocyclic molecule. It features a central aluminum atom (Al) coordinated by a fluorine atom (F) and three nitrogen atoms (N) of a macrocyclic ligand. The macrocycle is composed of a 1,3-difluoro-4-cyano-5-oxo-5,5-dihydro-1H-imidazolidine-2-ylidene group, a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group, a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group, and a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group. The macrocycle is further substituted with a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group and a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group. The macrocycle is further substituted with a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group and a 4-oxo-4,5-dihydro-1H-imidazolidine-2-ylidene group.</p> |

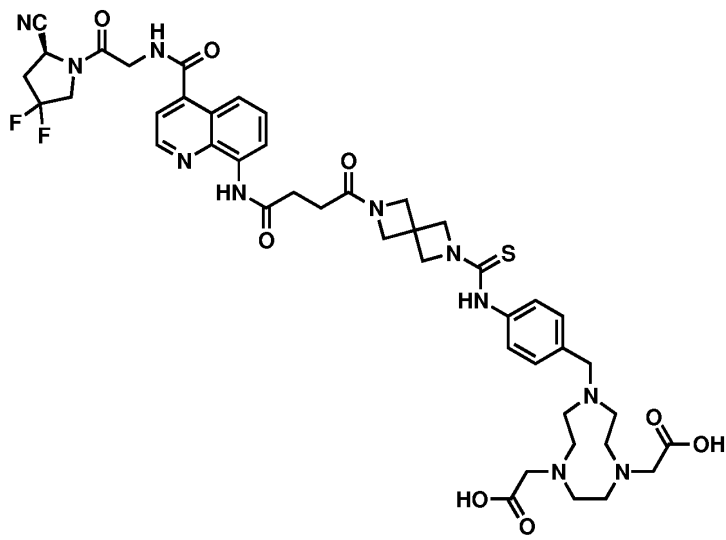
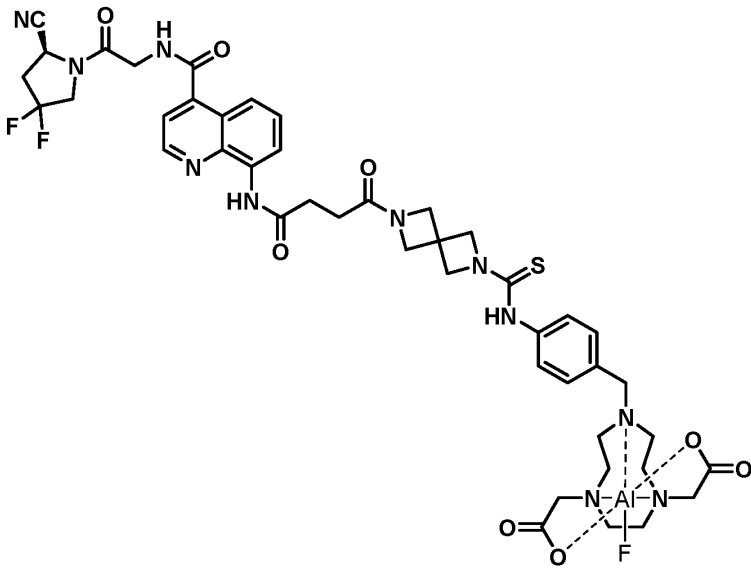
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| 16     |    |
| AlF@16 |   |
| 17     |  |

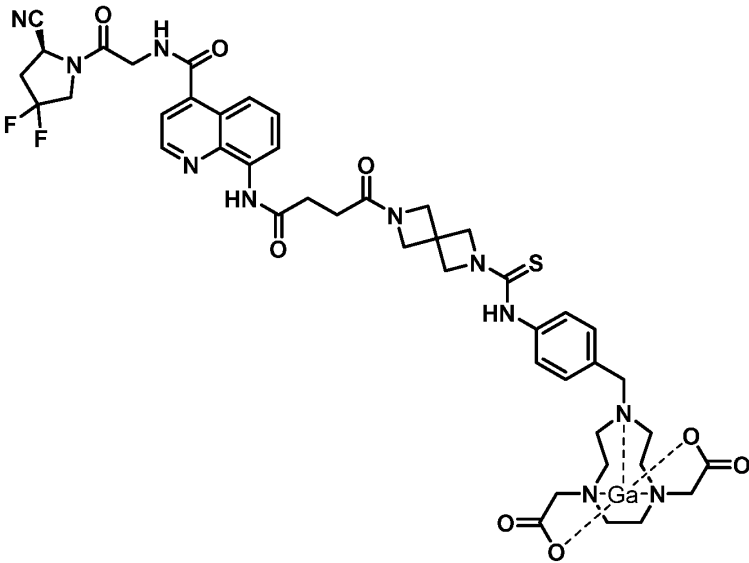
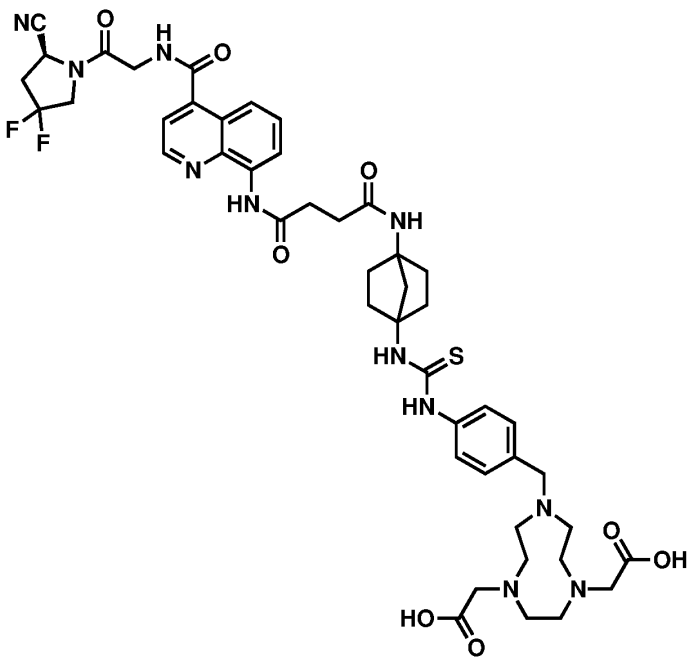
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| AlF@17 |    |
| 18     |    |
| AlF@18 |  |
| 19     |  |

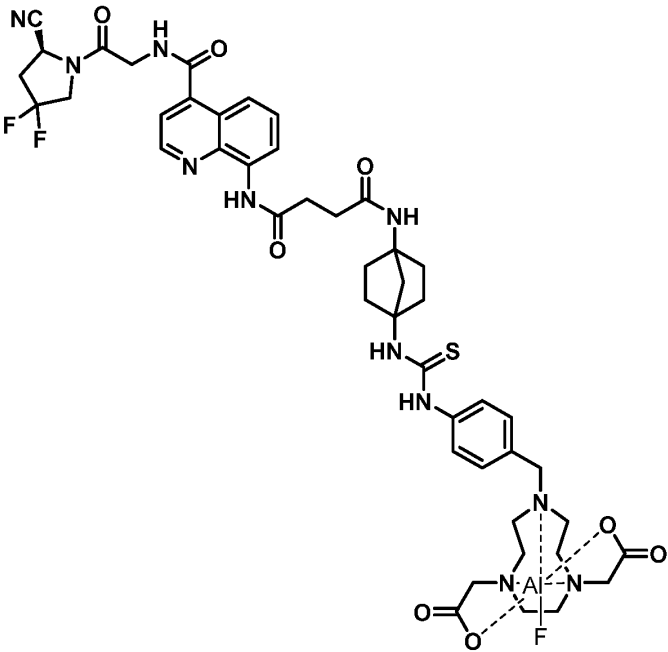
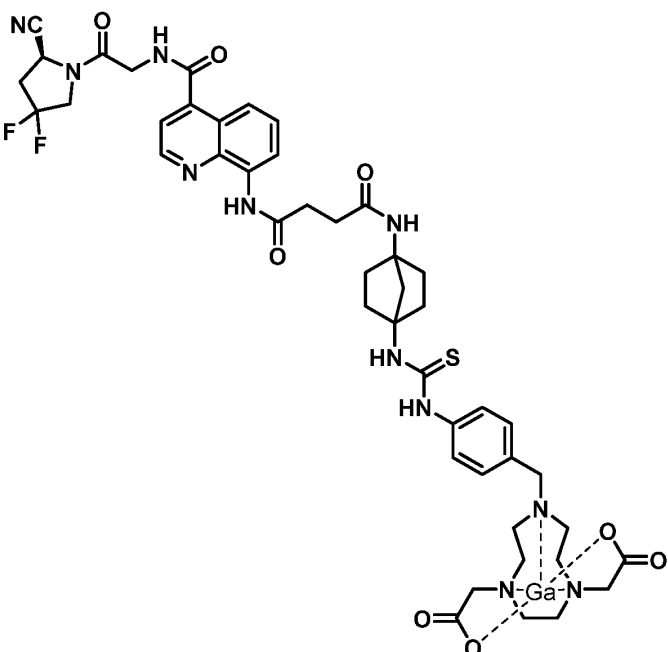
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| AlF@19 |  <p>Chemical structure of AlF@19, a macrocyclic cage with an aluminum atom coordinated by a fluorine atom and two carboxylate groups. The cage is substituted with a long chain containing a quinoxaline core, a nitrile group, and a piperidine ring.</p>   |
| 20     |  <p>Chemical structure of 20, a macrocyclic cage with a long chain containing a quinoxaline core, a nitrile group, and a piperidine ring, ending in a carboxylic acid group.</p>                                                                            |
| AlF@20 |  <p>Chemical structure of AlF@20, a macrocyclic cage with an aluminum atom coordinated by a fluorine atom and two carboxylate groups. The cage is substituted with a long chain containing a quinoxaline core, a nitrile group, and a piperidine ring.</p> |

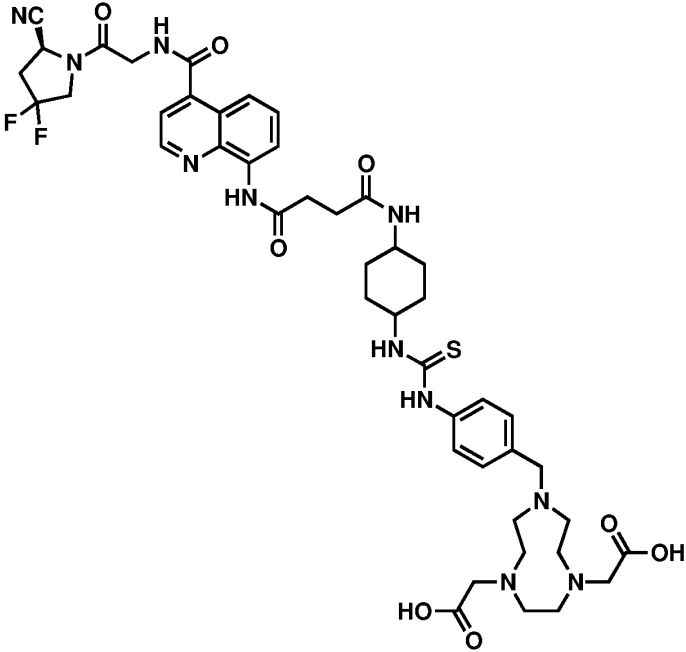
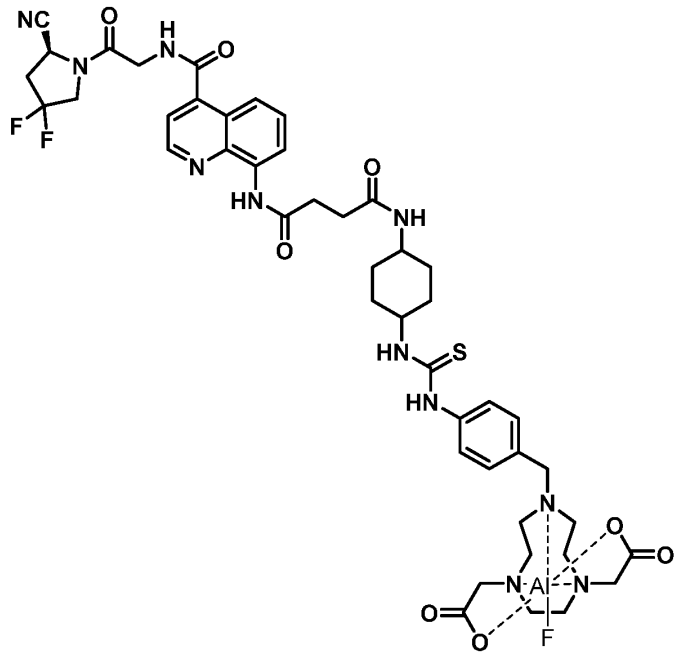
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| Ga@20 |  <p>Chemical structure of compound Ga@20. It features a 2,2,2-trifluoroethyl group attached to a carbonyl, which is linked to a quinoline ring. The quinoline ring is further connected to a chain containing a carbonyl, a piperazine ring, and a thiourea group. The thiourea group is attached to a phenyl ring, which is connected to a bicyclic cage structure. The cage structure contains a gallium atom (Ga) coordinated by two nitrogen atoms and two oxygen atoms, forming a complex cage-like structure.</p> |
| 21    |  <p>Chemical structure of compound 21. It features a 2,2,2-trifluoroethyl group attached to a carbonyl, which is linked to a quinoline ring. The quinoline ring is further connected to a chain containing a carbonyl, a piperazine ring, and a thiourea group. The thiourea group is attached to a phenyl ring, which is connected to a bicyclic cage structure. The cage structure contains two nitrogen atoms and two carboxylic acid groups, forming a complex cage-like structure.</p>                            |

|               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>AlF@21</b> |  <p>The chemical structure of AlF@21 shows a central aluminum atom (Al) coordinated by three nitrogen atoms of a macrocyclic ligand and one fluorine atom (F). The macrocycle is substituted with two carboxylate groups. A long, complex organic chain is attached to one of the nitrogens of the macrocycle. This chain includes a 4-mercaptophenyl group, a 1,3-bis(amide)propane linker, a 5-aminoquinoline-2-carboxamide moiety, and a 2,2,2-trifluoroethyl carbamate group.</p> |
| <b>Ga@21</b>  |  <p>The chemical structure of Ga@21 is identical to that of AlF@21, except that the central metal atom is gallium (Ga) instead of aluminum (Al).</p>                                                                                                                                                                                                                                                                                                                                 |

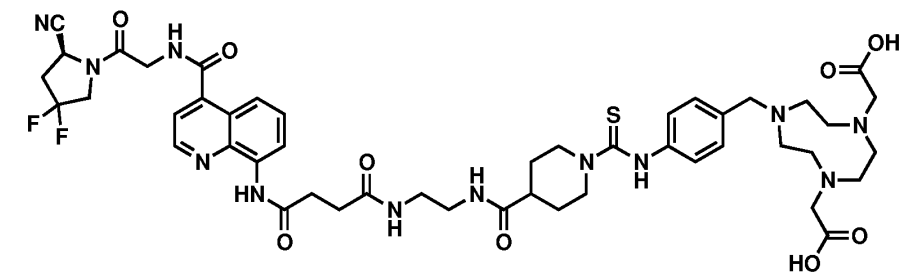
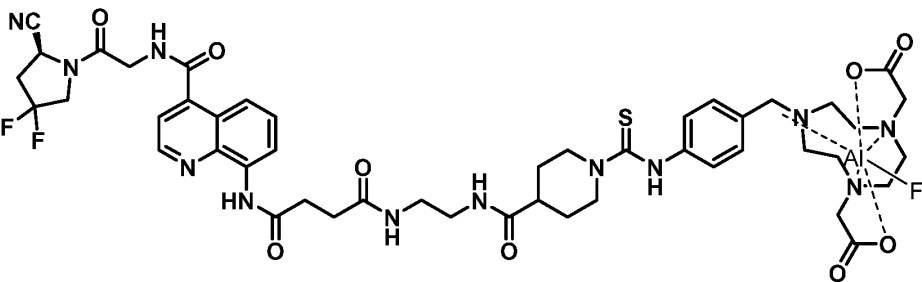
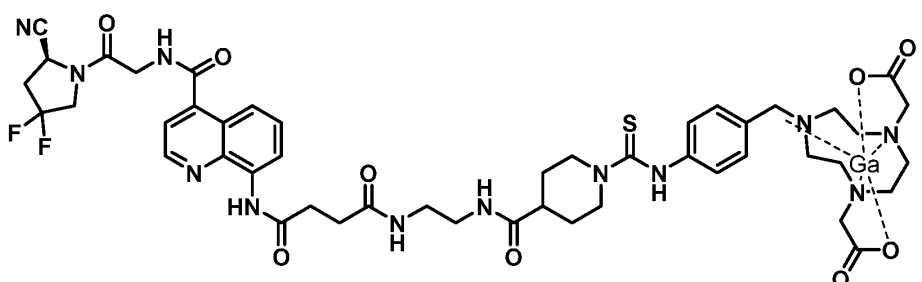
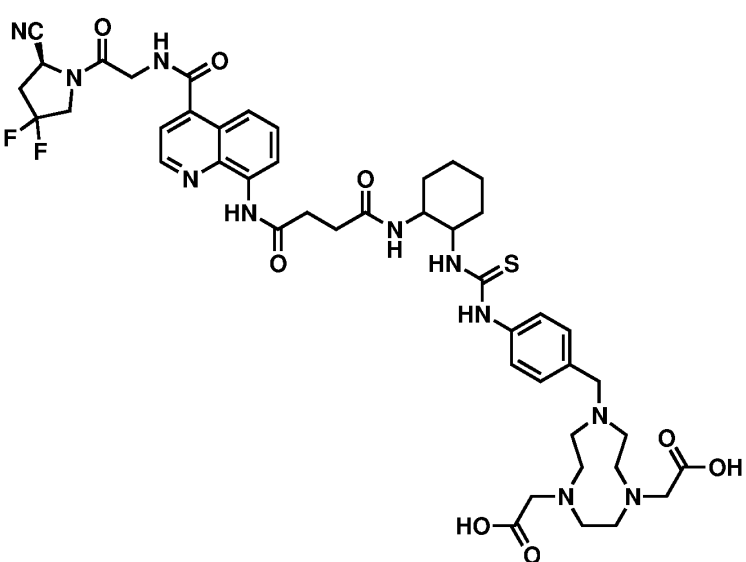
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| 22     |  <p>Chemical structure of compound 22: A complex molecule featuring a 2,2-difluoro-1-(cyano)ethyl group connected via an amide bond to a quinoline ring. The quinoline ring is further substituted with an amide group, which is linked to a 1,3-dioxane ring. This ring is connected to a 1,3-dioxane ring, which is further linked to a 1,3-dioxane ring. The molecule terminates in a carboxylic acid group.</p>                                                                                                                                                                       |
| AlF@22 |  <p>Chemical structure of compound AlF@22: A complex molecule featuring a 2,2-difluoro-1-(cyano)ethyl group connected via an amide bond to a quinoline ring. The quinoline ring is further substituted with an amide group, which is linked to a 1,3-dioxane ring. This ring is connected to a 1,3-dioxane ring, which is further linked to a 1,3-dioxane ring. The molecule terminates in a carboxylic acid group. The structure is shown with a fluorine atom (F) and an aluminum atom (Al) coordinated to the nitrogen atoms of the 1,3-dioxane rings, indicated by dashed lines.</p> |

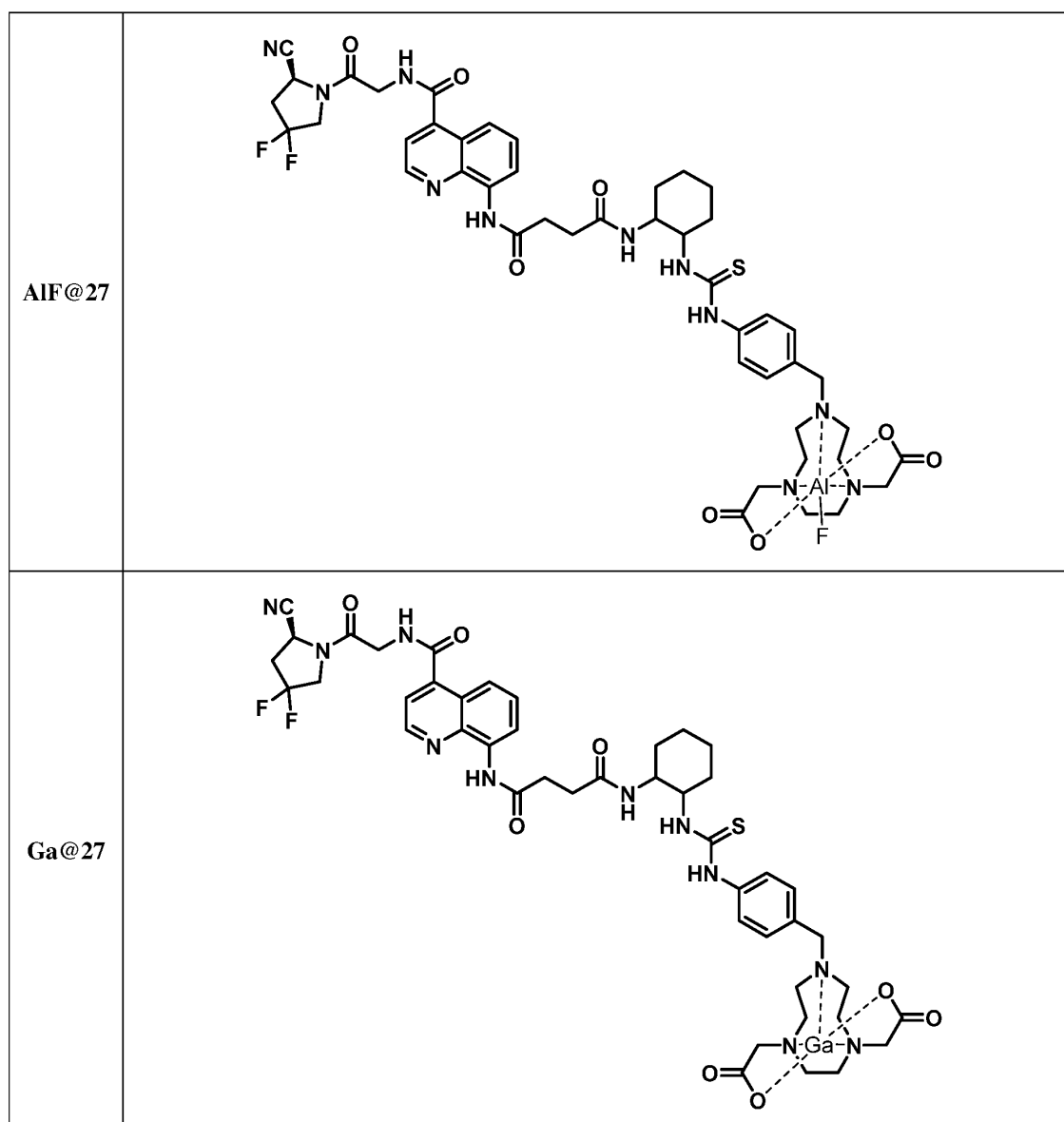
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| Ga@22 |  <p>Chemical structure of compound Ga@22. The molecule features a 2,2-difluoro-1-(cyano)ethyl group connected via an amide bond to a quinoline ring. The quinoline ring is further substituted with an amide group, which is linked to a 1,3-dioxane ring. This dioxane ring is connected to a 1,3-dioxane ring, which is in turn linked to a 1,3-dioxane ring. The final dioxane ring is connected to a 1,3-dioxane ring, which is linked to a 1,3-dioxane ring. The molecule is shown as a gallium complex, with the gallium atom coordinated to the nitrogen atoms of the dioxane rings and the oxygen atoms of the amide groups.</p> |
| 23    |  <p>Chemical structure of compound 23. The molecule features a 2,2-difluoro-1-(cyano)ethyl group connected via an amide bond to a quinoline ring. The quinoline ring is further substituted with an amide group, which is linked to a 1,3-dioxane ring. This dioxane ring is connected to a 1,3-dioxane ring, which is in turn linked to a 1,3-dioxane ring. The final dioxane ring is connected to a 1,3-dioxane ring, which is linked to a 1,3-dioxane ring. The molecule is shown as a gallium complex, with the gallium atom coordinated to the nitrogen atoms of the dioxane rings and the oxygen atoms of the amide groups.</p>   |

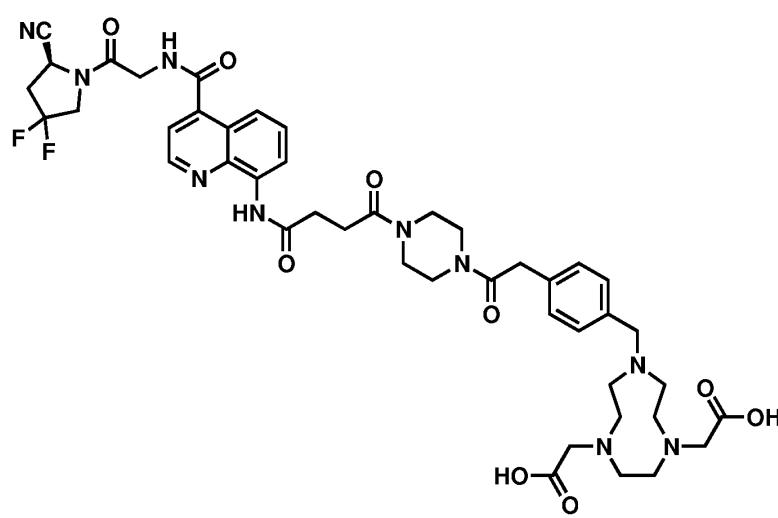
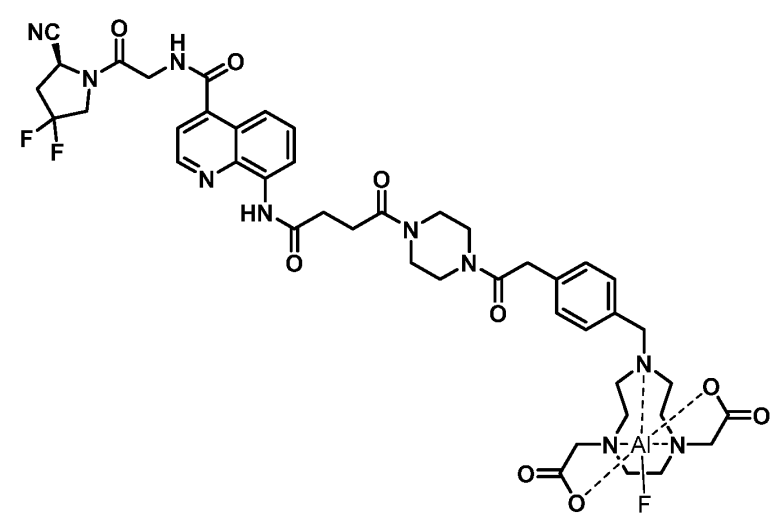
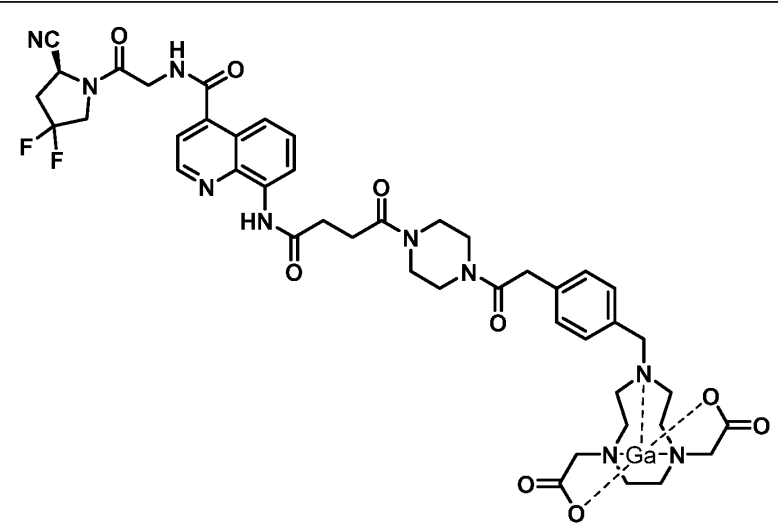
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|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>AlF@23</b> |  <p>The chemical structure of AlF@23 is a complex molecule. It features a central aluminum atom (Al) coordinated by a fluorine atom (F) and three nitrogen atoms (N) of a cage-like structure. The cage is composed of two cyclohexane rings and two nitrogen atoms, with a fluorine atom bridging the two nitrogens. The cage is further substituted with a carboxylate group (COO-) and a sulfonamide group (SO<sub>2</sub>NH-). The sulfonamide group is connected to a phenyl ring, which is in turn connected to a biphenyl system. The biphenyl system is further substituted with a carboxylate group (COO-) and a sulfonamide group (SO<sub>2</sub>NH-). The sulfonamide group is connected to a phenyl ring, which is in turn connected to a biphenyl system. The biphenyl system is further substituted with a carboxylate group (COO-) and a sulfonamide group (SO<sub>2</sub>NH-).</p> |
| <b>Ga@23</b>  |  <p>The chemical structure of Ga@23 is a complex molecule. It features a central gallium atom (Ga) coordinated by a fluorine atom (F) and three nitrogen atoms (N) of a cage-like structure. The cage is composed of two cyclohexane rings and two nitrogen atoms, with a fluorine atom bridging the two nitrogens. The cage is further substituted with a carboxylate group (COO-) and a sulfonamide group (SO<sub>2</sub>NH-). The sulfonamide group is connected to a phenyl ring, which is in turn connected to a biphenyl system. The biphenyl system is further substituted with a carboxylate group (COO-) and a sulfonamide group (SO<sub>2</sub>NH-). The sulfonamide group is connected to a phenyl ring, which is in turn connected to a biphenyl system. The biphenyl system is further substituted with a carboxylate group (COO-) and a sulfonamide group (SO<sub>2</sub>NH-).</p>  |

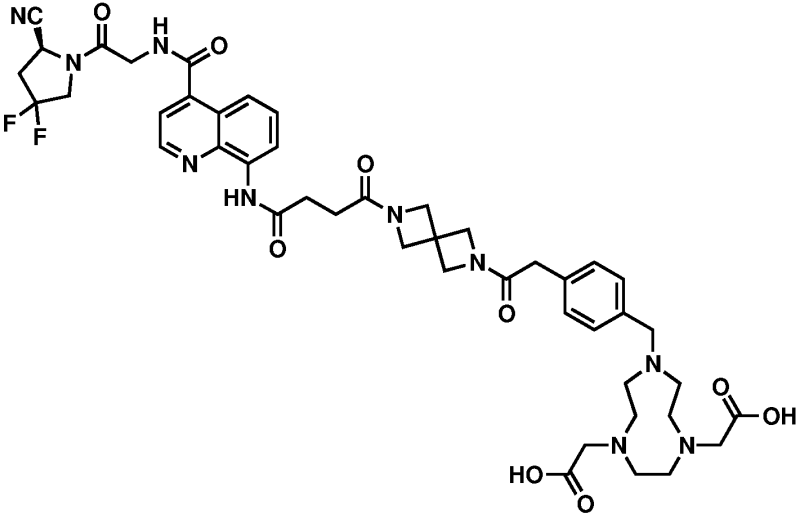
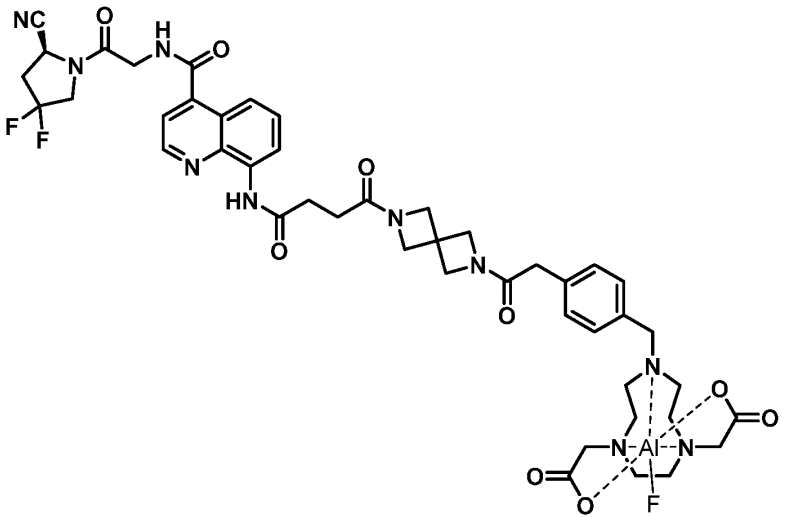
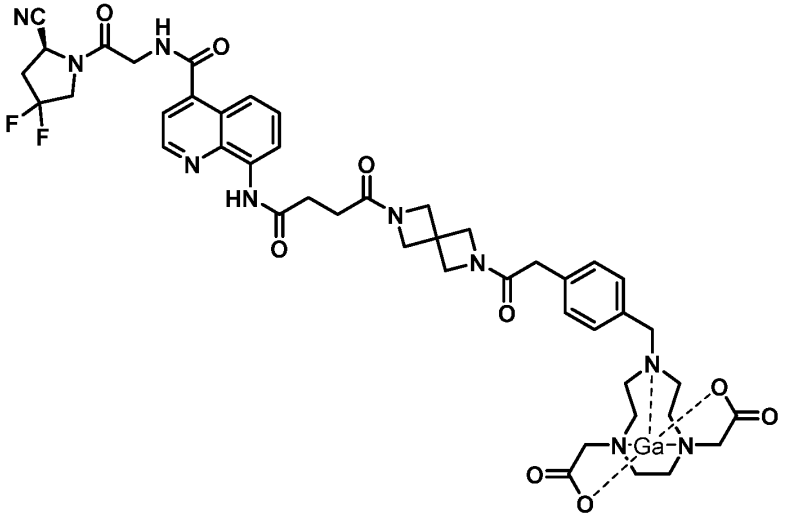
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| 24     |   |
| AIF@24 |  |

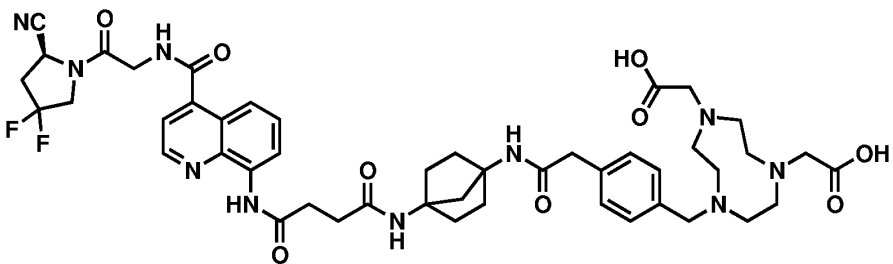
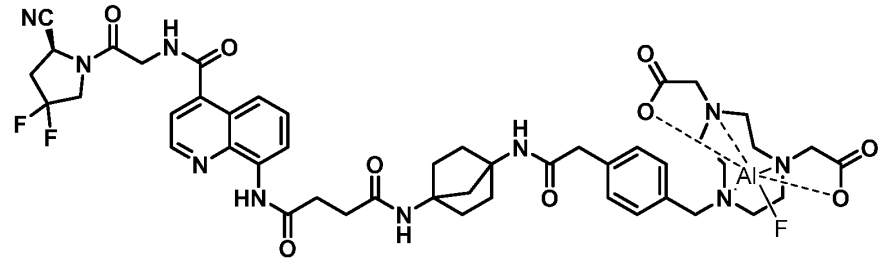
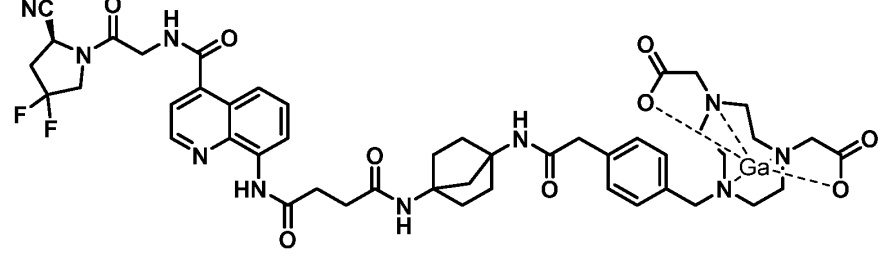
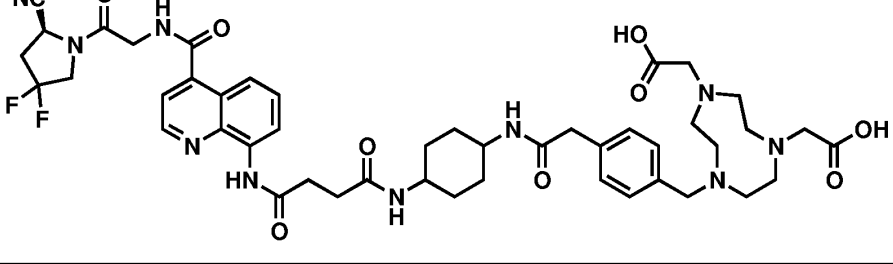
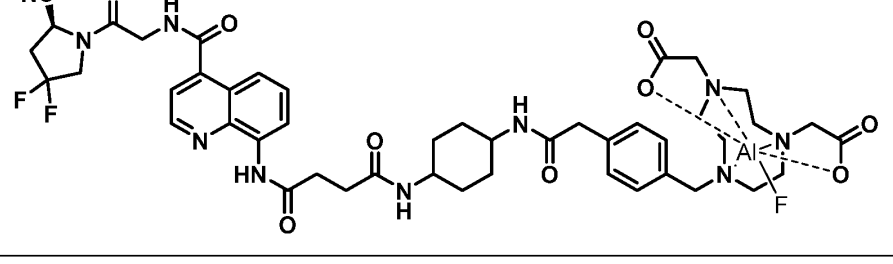
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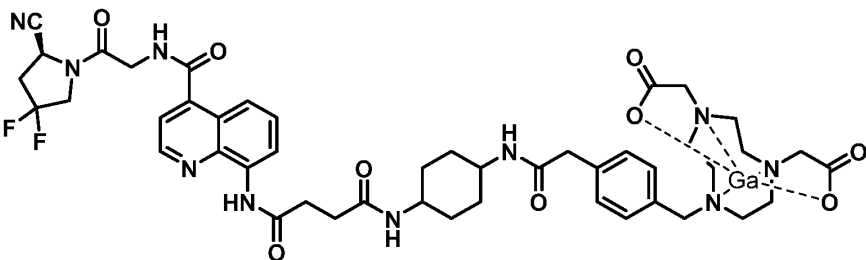
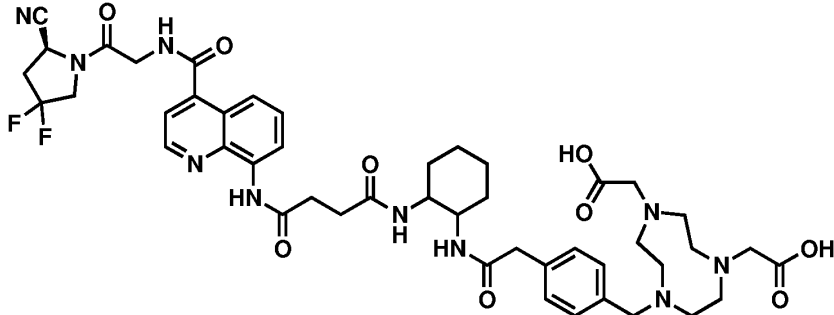
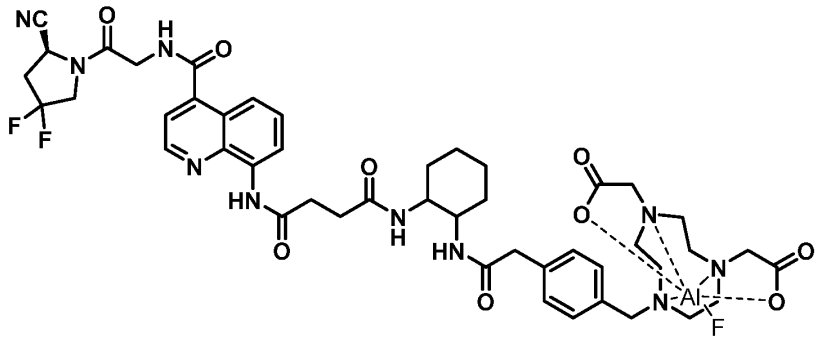
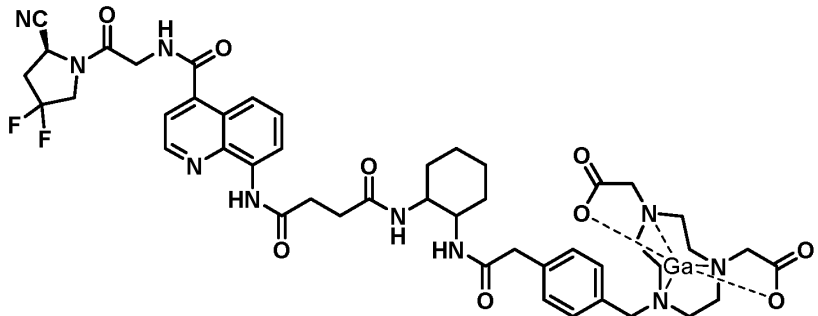
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|--------|--------------------------------------------------------------------------------------|
| 26     |    |
| AlF@26 |    |
| Ga@26  |   |
| 27     |  |

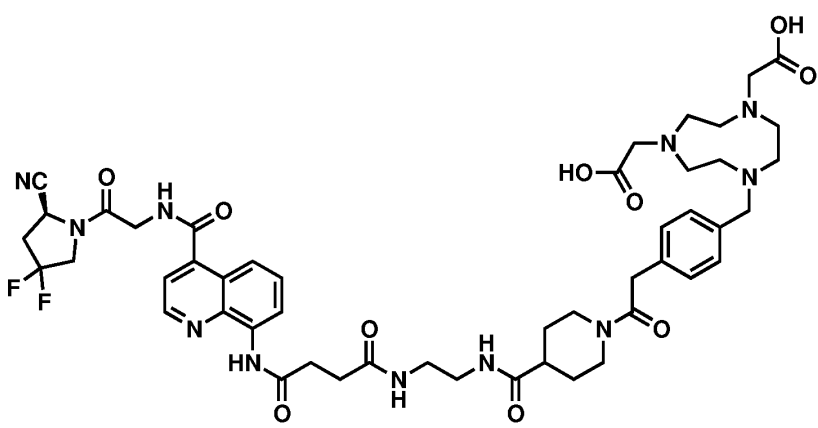
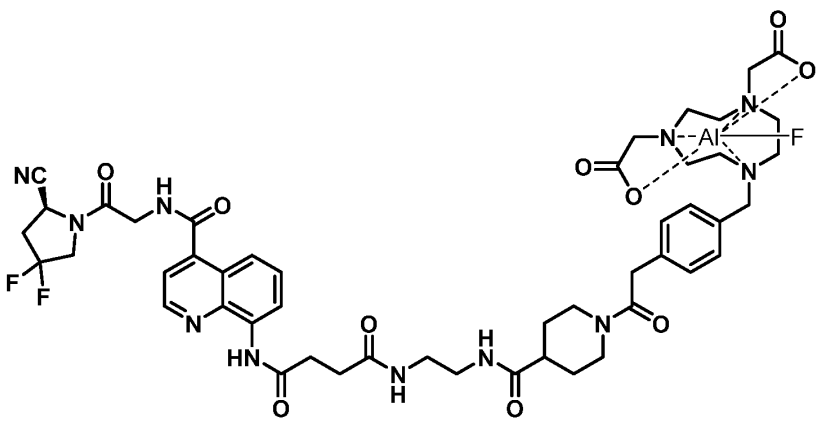
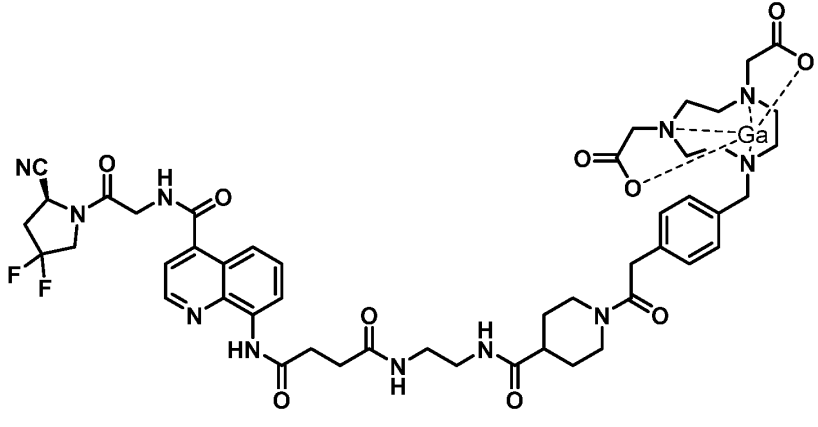
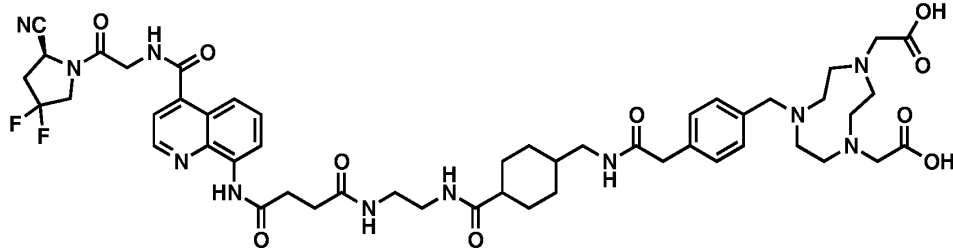


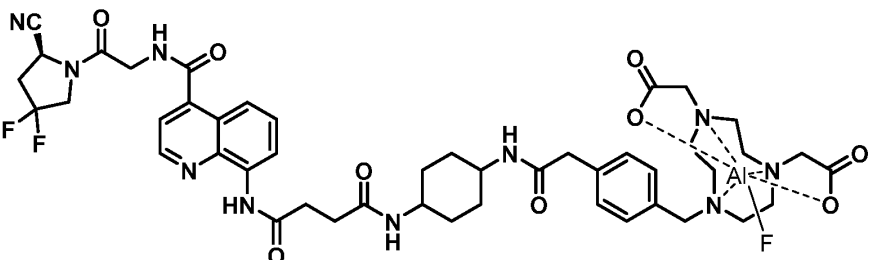
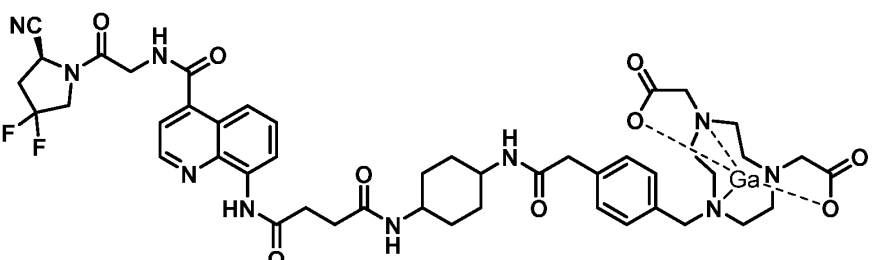
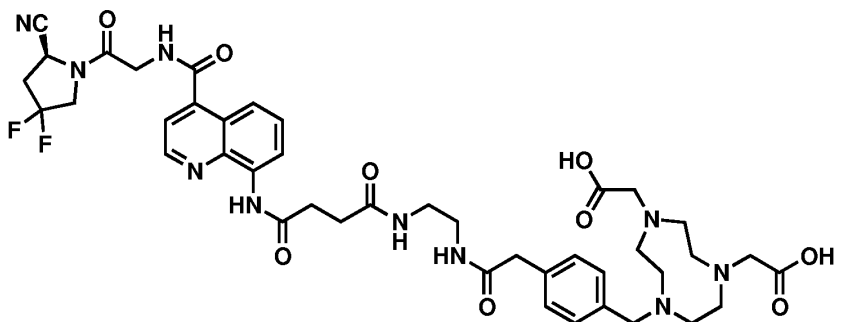
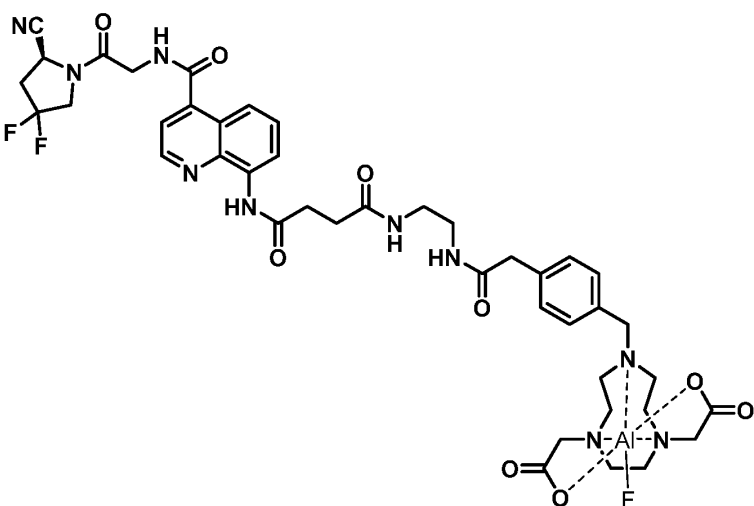
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| 28     |  <p>Chemical structure of compound 28, a complex molecule featuring a 2,2,2-trifluoroethyl group, a nitrile group, a quinoline ring system, a piperazine ring, and a carboxylic acid group.</p>                                                                |
| AlF@28 |  <p>Chemical structure of AlF@28, showing the molecule 28 encapsulated within a cage-like structure, likely a metal-organic framework (MOF) or a similar porous material, with a fluorine atom (F) and an aluminum atom (Al) coordinated within the cage.</p> |
| Ga@28  |  <p>Chemical structure of Ga@28, showing the molecule 28 encapsulated within a cage-like structure, likely a metal-organic framework (MOF) or a similar porous material, with a fluorine atom (F) and a gallium atom (Ga) coordinated within the cage.</p>   |

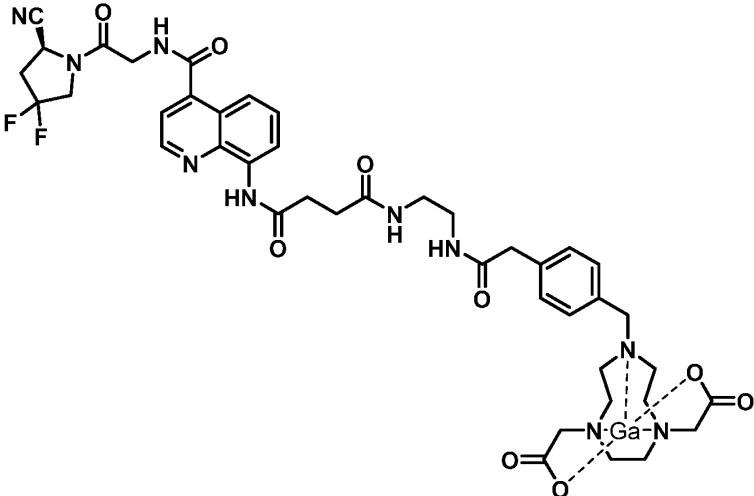
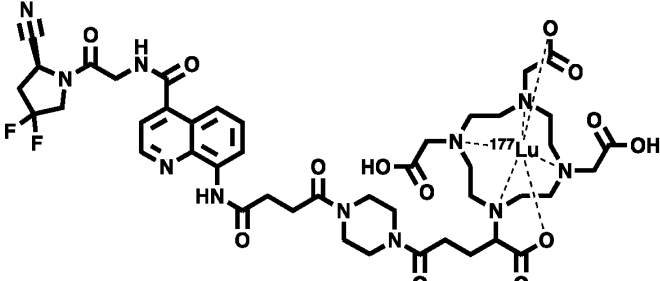
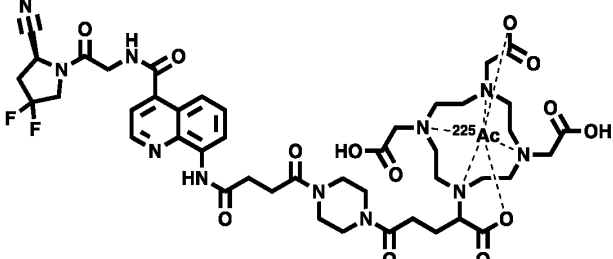
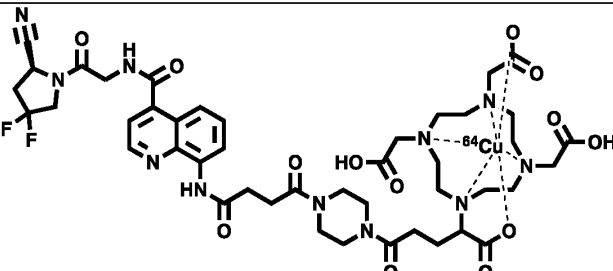
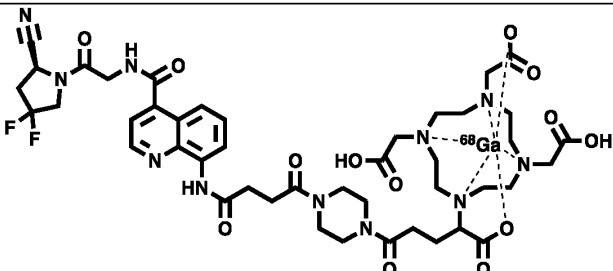
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|--------|--------------------------------------------------------------------------------------|
| 29     |    |
| AlF@29 |   |
| Ga@29  |  |

|        |                                                                                      |
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| 30     |    |
| AlF@30 |    |
| Ga@30  |   |
| 31     |  |
| AlF@31 |  |

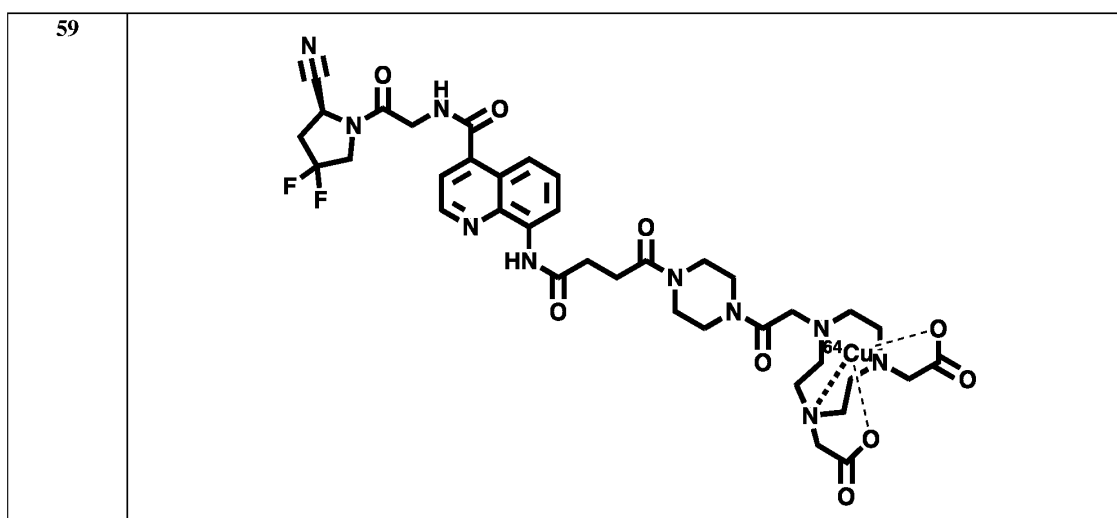
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| Ga@31  |    |
| 32     |    |
| AlF@32 |   |
| Ga@32  |  |

|        |                                                                                      |
|--------|--------------------------------------------------------------------------------------|
| 33     |    |
| AlF@33 |   |
| Ga@33  |  |
| 34     |  |

|        |                                                                                      |
|--------|--------------------------------------------------------------------------------------|
| AlF@34 |    |
| Ga@34  |    |
| 35     |   |
| AlF@35 |  |

|       |                                                                                      |
|-------|--------------------------------------------------------------------------------------|
| Ga@35 |    |
| 51    |   |
| 52    |  |
| 53    |  |
| 54    |  |

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| 56 |  |
| 57 |  |
| 58 |  |



15. The compound according to any one of the preceding claims for use in:
- (a) a method for treatment of the human or animal body by surgery or therapy or a diagnostic method practised on the human or animal body; or
  - (b) a method for therapy or prophylaxis of a subject suffering from or having risk for a disease or disorder; or
  - (c) a method for guided surgery practised on a subject suffering from or having risk for a disease or disorder; or
  - (d) a method for diagnosis of a disease or disorder, the method being practised on the human or animal body and involving a nuclear medicine imaging technique, such as Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT); or
  - (e) a method for targeted delivery of a therapeutic or diagnostic agent to a subject suffering from or having risk for a disease or disorder,

wherein in each of the preceding (b)–(e), said disease or disorder is independently selected from cancer, inflammation, atherosclerosis, fibrosis, tissue remodelling and keloid disorder, preferably wherein the cancer is selected from the group consisting of breast cancer, pancreatic cancer, small intestine cancer, colon cancer, multi-drug resistant colon cancer, rectal cancer, colorectal cancer, metastatic colorectal cancer, lung cancer, non-small cell lung cancer, head and neck cancer, ovarian cancer, hepatocellular cancer, oesophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocarcinoma, clear cell renal carcinoma, neuroendocrine tumour, oncogenic osteomalacia, sarcoma, CUP (carcinoma of

unknown primary), thymus cancer, desmoid tumours, glioma, astrocytoma, cervix cancer, skin cancer, kidney cancer, breast cancer, and prostate cancer;

and wherein in each of the preceding uses or methods, the compound preferably has a prolonged residence at the disease site at a therapeutically or diagnostically relevant level, preferably beyond 1 h, more preferably beyond 6 h post injection.