



Polymer-based drug delivery system

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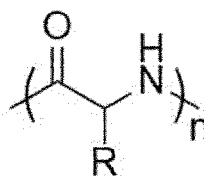
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A



(57) Abstract: The present invention relates to a polymer-based drug delivery system as such and its use in a method of treatment of a range of diseases and disorders, including cancer. The drug delivery system of the present invention is suitable for intracranial delivery and release of cytotoxic agents, in particular radioisotope-functionalized agents such as deoxyuridine.

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Polymer-based drug delivery system

Technical field

The present invention relates to polymer-based drug delivery system as such and its use in a method of treatment of a range of diseases and disorders, including cancer. The
5 drug delivery system of the present invention is suitable for intracranial delivery and release of cytotoxic agents, in particular radioisotope-functionalized agents such as deoxyuridine.

Background

10 Glioblastoma multiforme (GBM) is an aggressive and highly malignant primary brain tumour that originates in the glial cells of the central nervous system. Glioblastoma is the most common and deadliest type of primary brain tumour in adults, accounting for a significant portion of all brain malignancies. This complex and challenging tumour is characterized by its rapid growth, infiltrative nature, and resistance to traditional treatment approaches. Glioblastomas are known for their ability to invade nearby brain
15 tissue, making complete surgical removal often difficult or impossible. Despite advances in medicine, the prognosis for patients diagnosed with glioblastoma remains poor, with a median survival rate typically measured in months, even with rigorous treatment.

The treatment of glioblastoma typically involves a multidisciplinary approach, including surgery, radiation therapy, and chemotherapy. However, due to the tumour's infiltrative
20 nature, it is challenging to remove all cancerous cells, and recurrence is very common, leading to an average survival of only 5% after 18 months.

Alternative and improved treatments are therefore being sought where targeted drug delivery presents one possible alternative. However, drug delivery to the brain, particularly in the context of treating glioblastoma, presents a myriad of challenges that
25 stem from the intricate nature of the central nervous system and the unique characteristics of the tumour itself. One of the most common, but significant, challenges is the presence of the blood-brain barrier (BBB), a specialized barrier that tightly regulates the passage of substances between the bloodstream and the brain. Glioblastoma disrupts the BBB, causing increased permeability, but this phenomenon is
30 often heterogeneous and not uniform throughout the tumour. Even if drugs can breach the BBB, they often have limited penetration into the tumor tissue due to its complex microenvironment. The dense extracellular matrix and interstitial fluid pressure within the tumour can hinder uniform drug distribution.

The infiltrative nature of the GBM is imaginably the greatest challenge to effectively combat this cancer type, and demands a targeted and localized drug delivery approach to minimize collateral healthy cell damage.

5 Therapeutic agents such as the radionucleoside [¹²⁵I]UdR, inherently face challenges due to their instability or rapid metabolism, posing difficulties in achieving effective delivery to and within the brain over extended periods. Ensuring drug stability and therapeutic concentrations within the brain environment becomes imperative. This critical task can be achieved through the utilization of polymer-based nanocarriers where
10 enhanced bioavailability is often provided through means of a polyethylene glycol (PEG) surface modification to the polymer. While these advancements are noteworthy, there have emerged certain instances raising concerns in the realm of toxicology and immunology linked to PEG-modified drugs, encompassing phenomena like auto-immune response and accelerated blood clearance. Of particular note is the undesirable effect of
15 the latter, as it diminishes the therapeutic impact of nanocarriers, thereby necessitating more frequent administrations. This contradicts a primary advantage of nanocarriers – their capacity to prolonged sustainably deliver therapeutic agents.

20 Thus, there is a strong need for new therapeutic strategies that are able to effectively treat brain tumors that can overcome current limitations and improve therapeutic outcomes.

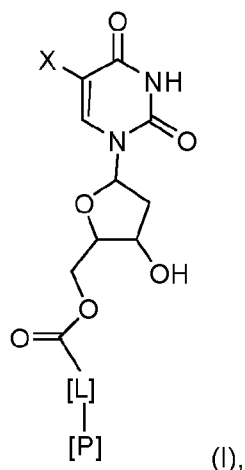
Summary

25 The present invention addresses the above-mentioned limitations in the treatment of brain cancer, and particularly brain tumors, by providing a composition which comprises a polymer, a cytotoxic agent comprising a radioisotope and a linker between the polymer and the cytotoxic agent.

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In one main aspect, the present disclosure provides a compound of formula (I)



wherein

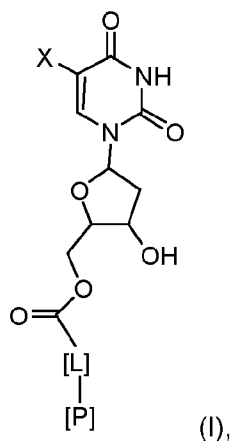
X is defined as $-R^1-R^A$, wherein R^1 is selected from the group consisting of $-C_{1-3}$ alkyl-, $-C_{1-3}$ haloalkyl-, $-C_{2-4}$ alkenyl-, $-C_{3-6}$ cycloalkyl-, $-C_{3-6}$ cycloaryl-, $-C_{3-6}$ cycloheteroaryl-, $-O-$, $-NH-$, $-C(O)-$, $-C(O)-O-(C_{1-6}$ alkyl)-, $-phenyl-$, $-O-phenyl-$, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope,

P is a polymer comprising at least one polypeptide and at least one polypeptoid,
and
L is a covalent linker.

In one aspect, the present disclosure provides the compound of formula (I) for use as a medicament.

In another main aspect, the present disclosure provides a pharmaceutical composition for use in a method of treatment of cancer, said composition comprising:

- a. a polymer [P];
- b. a cytotoxic agent; and
- c. a linker [L], which links the cytotoxic agent to the polymer, wherein the cytotoxic agent is of formula (I) or a derivative thereof, or a pharmaceutically acceptable salt thereof



wherein

X is defined as $-R^1-R^A$, wherein R^1 is selected from the group consisting of $-C_{1-3}$ alkyl-, $-C_{1-3}$ haloalkyl-, $-C_{2-4}$ alkenyl-, $-C_{3-6}$ cycloalkyl-, $-C_{3-6}$ cycloaryl-, $-C_{3-6}$ cycloheteroaryl-, $-O-$, $-NH-$, $-C(O)-$, $-C(O)-O-(C_{1-6}$ alkyl)-, $-phenyl-$, $-O-phenyl$, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope, P is a polymer comprising at least one polypeptide and at least one polypeptoid, and L is a covalent linker.

10 Preferably R^A comprises or consists of an Auger-emitting radioisotope and/or R^A comprises or consists of a radioisotope selected from the group consisting of ^{123}I , ^{124}I or ^{125}I , ^{77}Br , ^{76}Br , ^{80m}Br , ^{80}Br , ^{126}I , ^{131}I , ^{18}F , or ^{211}At .

15 In one aspect, the present invention provides for the use of the compound of formula (I) for the manufacture of a medicament for treatment of a disease, such as cancer.

20 The examples of the present disclosure demonstrate that the composition releases the active Auger-emitting nucleoside in the presence of linkage-breaking enzymes such as esterases and that the rate of release of active Auger-emitting nucleoside can be extended over long periods of time, thereby extending the window of time during which the Auger emitting nucleoside can be incorporated into the DNA of cancer cells. Preferably, the composition provided within the present disclosure is for use in a method of treatment of cancers and in particular brain cancer.

Thus, the present invention provides for a new modality of treatment of brain cancer wherein the efficiency of Auger emitting therapeutics is increased, thus allowing for better outcomes and quality of life for patients. Advantages of the invention are for example:

- 5 • Extended biological half-life and retention of Auger emitting nucleoside agents in the brain due to reduced wash-out from the intracerebral compartment.
- The release of active Auger-emitting nucleoside cytotoxic agents is controlled by by release from the polymer composition and conversion to the active Auger-emitting nucleoside in the presence of enzymes, like esterases.
- 10 • Tunable release via controlling the functionalization of sidechains and/or backbone of the polymer, also referred to herein as brushes of the peptobrush polymer, making the release rate adaptable to different Auger emitting isotopes or therapeutic modalities.
- Extended window of release of active Auger emitting radionucleosides provides an advantage in dealing with resistant cancer cells or slow-dividing cancer cells
- 15 with stem-cell like properties and extends the duration of a therapeutic concentration in the brain, making it more likely that dividing cancer cells are exposed to the Auger emitting nucleoside.
- Possibility to increase the distribution of the active Auger emitting nucleoside within the brain tissue.

20

Definitions

“Radioactive” refers to the property of a nuclide of undergoing spontaneous nuclear transformations with the emission of radiation. Radiation refers to electromagnetic waves and particles emitted during a nuclear process. Radioactive is used herein to describe

25 said property of compositions, compounds or agents comprising radioactive nuclei.

“Radioisotope” is a radioactive isotope of a specified element.

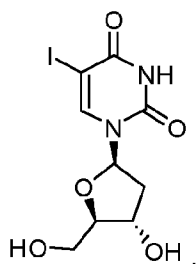
“Auger electron-emitting radioisotope” are radioisotopes that emit Auger electrons during their radioactive decay. Auger electrons differ from other forms of radiation therapy because the electrons emitted in the radioactive decay, the Auger electrons, are released

30 in large numbers with low kinetic energy, leading to high linear-energy-transfer (LET) effects. Because of their low energy these electrons exert their damaging effect on cellular structures over a very short nanometre scale range being less than the size of a single cell. This very short-range delivery of energy provides a highly targeted therapy because the radiation-emitting nuclide is located inside the cell to cause damage to the

genomic DNA. Non-limiting examples of Auger-emitting radioisotopes include ^{125}I , ^{123}I , ^{77}Br , and $^{99\text{m}}\text{Tc}$, ^{111}In , and ^{67}Ga , among others.

“Nucleoside” as use herein refers to nitrogen-containing biological compounds that contain a nucleobase (e.g., a purine or pyrimidine base, such as adenine, cytosine, 5 guanine, thymine or uracil) covalently bonded to a pentose sugar ribose or deoxyribose. Examples of nucleosides are thymidine, uridine, adenosine, cytidine, or guanosine, or any of their deoxy derivatives, such as 2'-deoxy derivative: deoxythymidine, deoxyuridine, deoxyadenosine, deoxycytidine or deoxyguanosine.

As used herein, the term nucleoside may refer to any nucleoside or an analogue or 10 derivative thereof formed by chemical modification of a nucleotide. For example, the nucleoside analogue or nucleoside derivative may be 5-iodo-2'-deoxyuridine, also referred to Idoxuridine, or IUdR, according to the formula below:



The term “hydrocarbon” as used herein refers to molecules or parts of molecules 15 consisting of carbon and hydrogen atoms only. A substituted hydrocarbon may however refer to molecules or parts of molecules wherein at least one hydrogen or carbon has been substituted with a different element or group. Substituted hydrocarbons may exemplary be those substituted with azide functionality and/or ester group functionality. A hydrocarbon group or chain may be specified by the number of carbon atoms. For 20 example, a C_6 hydrocarbon chain means a molecule or part of a molecule having 6 total carbon atoms. The hydrocarbon chain may comprise any number of branches unless otherwise specified. The term “alkyl” as used herein refers to a linear or branched hydrocarbon moiety.

The term “cycle” when referring to molecules, moieties or groups of atoms refers to cyclic 25 entities, also sometimes referred to as ring-systems. “Carbocycle” as also used herein refers to cyclic entities having an all-carbon backbone, and which may be either saturated or unsaturated, i.e. comprising at least one double bond in the cyclic structure, such as the non-limiting examples cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, phenyl, cyclooctene, cyclohexene and

derivatives of any of the foregoing. A "heterocycle" as used herein by extension refers to carbocycles having at least one carbon substituted for a heteroatom such as N, O, S, Se, As or P. Non-limiting examples may be piperidines, piperazines, pyridines, pyrimidines, triazines, tetrazines, pyrroles, imidazoles, pyrazoles, triazoles, and tetrazoles. Carbocycles and heterocycles as used herein may be polycyclic, i.e. having one or more closed rings of atoms wherein the rings share at least one atom, two or more rings of atoms sharing at least one atom, or two or more rings of atoms sharing two or three atoms.

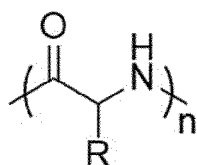
The term "treatment", as used anywhere herein comprises any type of therapy, which aims at terminating, preventing, ameliorating and/or reducing the susceptibility to a clinical condition as described herein. Thus, "treatment," "treating," and the like, as used herein, refer to obtaining a desired pharmacologic and/or physiologic effect, covering any treatment of a pathological and/or clinical condition or disorder in a mammal, including a human. The effect may be prophylactic in terms of completely or partially preventing a disorder or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disorder and/or adverse effect attributable to the disorder. That is, "treatment" includes (1) preventing the disorder or clinical condition from occurring or recurring in a subject, (2) inhibiting the disorder or clinical condition, such as arresting its development, (3) stopping or terminating the disorder or clinical condition or at least symptoms associated therewith, so that the host no longer suffers from the disorder or clinical condition or its symptoms, such as causing regression of the disorder or clinical condition or its symptoms, for example, by restoring or repairing a lost, missing or defective function, or stimulating an inefficient process, or (4) relieving, alleviating, or ameliorating the disorder or clinical condition, or symptoms associated therewith, where ameliorating is used in a broad sense to refer to at least a reduction in the magnitude of a parameter, such as inflammation, pain, and/or immune deficiency.

The terms "ameliorate", "ameliorating" and "amelioration", are also used separately herein to refer to a reduction of the severity of the occurrence of symptoms or characteristics of a disorder or clinical condition.

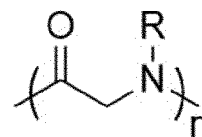
As used herein the term "peptobrush" refers to polypeptide-graft-polypeptoid polymers and has the same meaning as generally used and understood by skilled persons within the field. Polypeptoids differ from polypeptides in being a class of non-natural biomimetic oligomers having an N-substituted polyglycine backbone, as opposed to peptides which are normally alpha-carbon substituted leaving the amide unsubstituted (difference

illustrated below). Polymers defined herein may vary in size and shape, such as defined by the integers n, p, n1, n2, x1, x1, m1, m2 etc found within the present disclosure, in particular in formulas (II) and (III), including sub-formulas thereof (exemplary formula (III-a)). It is well understood by the skilled person that the listed values of these integers should be taken as an average of the polymer, and the polymer and/or peptobrush defined herein may comprise a multitude of different n, p, n1, n2, x1, x1, m1, and m2 with different values, which on average correspond to the listed integer value which may be between 10 and 1000 repeating units.

The difference between polypeptide and polypeptoid is shown below, wherein R represents an arbitrary non-hydrogen substitution and/or functionalization, and n indicates the polymeric nature of A and B by representing a generic repeating unit:



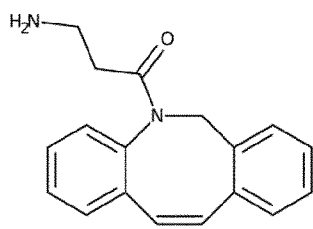
polypeptide

A

polypeptoid

B

As used herein, references to DBCO or dibenzocyclooctyne are to be understood as referring to azadibenzocyclooctyne-amine, DBCO-amine or ADIBO, and having CAS identifier 1255942-06-3. ADIBO has the following structure:



15

The term "natural abundance" as used herein refers to e.g. compounds or substances having their atoms in an isotopic abundance as naturally found in nature. Hence, compounds or substances that are not of natural abundance have an isotopic abundance of an isotope of an element different from the natural abundance and are usually not found in nature and are not naturally occurring substances. The "isotopic abundance" refers to the relative number of atoms of a particular isotope of an element relative to all isotopes of the element in a compound or substance.

20

Description of Drawings**Figure 1:**

Illustrative representation of differences between polypeptide (A) and polypeptoid (B) as used herein. R represents an arbitrary non-hydrogen substitution and/or functionalization, and n indicates the polymeric nature of A and B by representing a generic repeating unit.

Figure 2:

Illustrative representation of a peptobrush according to the present invention. The peptobrush comprises a backbone featuring pendent groups, wherein some pendent groups are synthetic modifications, such as polypeptides or polypeptoids, and wherein some pendent groups are specifically designed as a drug coupling site to receive a chemical payload.

Figure 3:

Release behaviours of [¹²⁵I]UdR from [¹²⁵I]UdR-PB in PBS buffer with or without esterase added. (a) Esterase mediated release of [¹²⁵I]UdR from [¹²⁵I]UdR-PB in PBS buffer at 37 °C, aliquots analyzed by radio-TLC. (b) Release of [¹²⁵I]UdR from [¹²⁵I]UdR-PB in the absence of esterase (control).

Figure 4:

In vitro DNA incorporation of [¹²⁵I]UdR-PB with or without esterase in LN229 cells after 4 and 24 hours of incubation. Data was represented in terms of the percentage of incorporation (IP%) based on the total added activity. Two-tail unpaired t-test P-values indicate statistical significance (*P < 0.05, **P < 0.01). Error bars shown are standard deviation.

Figure 5:

SPECT/CT scans of non-tumour bearing rat at 1 hour (A) and 24 hours (B) post intracranial injection with 25 μL [¹²⁵I]UdR-PB (approx. 256 kBq). A) SPECT/CT scan after 1 hour shows retention of [¹²⁵I]UdR-PB primarily in the brain with little uptake in the thyroid gland and stomach. B) SPECT/CT scan after 24 hours shows retention of [¹²⁵I]UdR-PB in the brain with an increased uptake in the thyroid gland and stomach.

The scale bar on the right reflects the intensity of the SPECT radioactivity signal of the areas marked with the lines (Brain, thyroid, stomach).

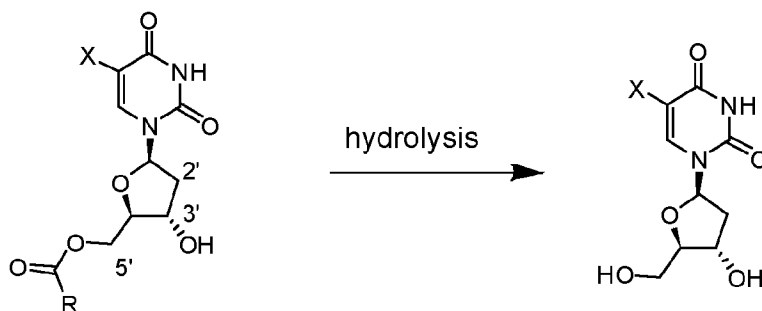
Detailed description

5 Alternative polymers with similar properties to PEG are hybrid materials consisting of polypeptides and polypeptoids, based on amino acids and N-methylated polysarcosine. Also known as PeptoBrush (PB), these have recently emerged as a substitute for PEG in various imaging or theranostic applications, since they are able to combine synthetic precision and high functionality of synthetic materials (e.g. unnatural amino acids). For
10 this purpose, the present inventors propose that PBs appear to be an ideal candidate for drug delivery in the brain. PBs can be used to build up core-shell structures that allow for high loading of lipophilic compounds, including chemical moieties that can connect the drug load onto the polymer, without the risk of aggregation and with the possibility to protect these moieties against degradation. They intrinsically combine a 3D structure
15 and the multi-functionality of polypeptides with the structural flexibility and "stealth-like" properties of polysarcosine. Moreover, these types of polymers are reported to be highly biocompatible, nontoxic and nonimmunogenic, and have been demonstrated to exhibit Enhanced Permeability and Retention (EPR)-mediated tumor accumulation due to their relatively small size. The latter is especially advantageous as smaller nanocarriers will
20 have a much better distribution when administered in the cerebral region, leading to increased therapeutic effectiveness, while covering a larger section of the cerebral tissue. From this, it is clear that PeptoBrush offers different and unique opportunities through its design as opposed to alternative nanocarriers, such as liposomes and polymeric micelles.

25 [125I]iododeoxyuridine, also referred to as [125I]IUdR, is a radiolabelled analogue of the nucleoside deoxyuridine that contains iodine-125. This compound serves as a valuable tool for labelling DNA or DNA precursors within cells, enabling the study of DNA synthesis and metabolism. This property also makes it effective in impairing the growth
30 of cancer cells, especially tracking down and compromising the effects of infiltrating glioblastoma stem-cells. When [125I]IUdR is incorporated into DNA, the radioactive decay of iodine-125 emits Auger electrons (half-life 59.8 days). These high-energy Auger electrons (ranging from 4 to 25 keV/ μm) cause disruption to the DNA's chemical bonds in the nearby vicinity, ultimately resulting in cellular death. Through this mechanism,

[¹²⁵I]UdR has demonstrated remarkable efficacy in eliminating glioblastoma cancer cells and retarding the metastatic processes.

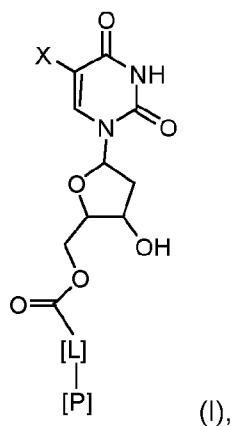
5 It is within the scope of the present disclosure to demonstrate and provide the potential synergistic effects of combining radioisotope labelled nucleosides such as deoxyuridine (UdR), and in particular such as iododeoxyuridine (IUdR) and PeptoBrushes (PB) as a novel therapeutic approach for use in a method of treatment of cancers, and more preferably brain cancers such as glioblastoma such as glioblastoma multiforme, by leveraging the distinct attributes of both exemplary [¹²⁵I]UdR, or other UdR-modified
10 Auger-emitting cytotoxic agents capable of high DNA damage to glioblastoma cells, and the PeptoBrush, a polypeptoid nanocarrier which allows precise synthetic pre-functionalization. Within the scope of the present disclosure, a cytotoxic agent modified with a radioisotope such as an Auger-emitting cytotoxic agent may also be referred to as radioactive agents. To combine these entities according to the teachings of the present
15 disclosure, the PeptoBrush of the present disclosure was functionalized with a bio-conjugative coupling handle, while the Auger-emitting nucleoside was functionalized with a concomitant and/or matching coupling partner. In one embodiment this strategic approach enables the direct covalent binding of deoxyuridines onto the PB polymer. Notably, the linker that connects the deoxyuridines to its coupling partner comprise in
20 one embodiment an ester linkage, but may in other embodiments comprise an amide linkage. As an exemplary embodiment, ester linkages possess the capability to undergo *in vivo* hydrolysis through various mechanisms of action, including esterases, enzymes that break down ester moieties. Esterase-mediated hydrolysis may in one embodiment of the present disclosure serve as a means for drug activation and controlled release.
25 The prodrugs or drug carriers of the present disclosure therefore may remain inert until encountering esterases *in vivo*, triggering hydrolysis of the ester bond, leading to the release of nucleosides such as [¹²⁵I]UdR or other radiolabeled UdRs in its active form, as shown below.



This approach allows for the precise modulation of drug activity and localized therapeutic effects. Other enzymes, such as amidases and lipases, can also contribute to the breakdown of specific chemical bonds, thereby providing a diverse array of enzymes facilitating the targeted release and activation of e.g., [¹²⁵I]UdR *in vivo* from the PB in a facile manner.

One embodiment of the present disclosure is a pharmaceutical composition for use in a method of treatment of cancer, said composition comprising:

- a. a polymer [P];
- b. a cytotoxic agent; and
- c. a linker [L], which links the cytotoxic agent to the polymer, wherein the cytotoxic agent is of formula (I) or a derivative thereof, or a pharmaceutically acceptable salt thereof



wherein

X is defined as -R¹-R^A, wherein R¹ is selected from the group consisting of -C₁₋₃ alkyl-, -C₁₋₃ haloalkyl-, -C₂₋₄ alkenyl-, -C₃₋₆ cycloalkyl-, -C₃₋₆ cycloaryl-, -C₃₋₆ cycloheteroaryl-, -O-, -NH-, -C(O)-, -C(O)-O-(C₁₋₆ alkyl)-, -phenyl-, -O-phenyl, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope.

20

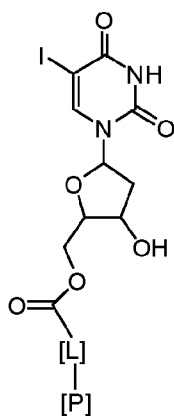
In one embodiment of the present disclosure, R^A comprises an Auger electron-emitting radioisotope and/or R^A comprises a radioisotope selected from the group consisting of ¹²³I, ¹²⁴I or ¹²⁵I, ⁷⁷Br, ⁷⁶Br, ^{80m}Br, ⁸⁰Br, ¹²⁶I, ¹³¹I, ¹⁸F, or ²¹¹At. In one embodiment of the present disclosure, R¹ is absent and R^A comprises an Auger electron-emitting radioisotope and/or R^A comprises a radioisotope selected from the group consisting of ¹²³I, ¹²⁴I or ¹²⁵I, ⁷⁷Br, ⁷⁶Br, ^{80m}Br, ⁸⁰Br, ¹²⁶I, ¹³¹I, ¹⁸F, or ²¹¹At.

25

In one embodiment of the present disclosure, R^1 is absent and R^A consists of a radioisotope of a halogen, such as ^{123}I , ^{124}I or ^{125}I , ^{77}Br , ^{76}Br , $^{80\text{m}}\text{Br}$, ^{80}Br , ^{126}I , ^{131}I , ^{18}F , or ^{211}At , preferably a radioisotope of iodine or bromine, such as ^{123}I or ^{125}I or ^{77}Br .

In one embodiment of the present disclosure, R^1 is absent and R^A comprises a radioisotope of a iodine, such as consists essentially of a radioisotope of iodine. In one embodiment, R^1 is absent and R^A comprises or consists of ^{125}I . In another embodiment, R^1 is absent and R^A comprises or consists of ^{123}I . In another embodiment, R^1 is absent and R^A comprise or consist of ^{77}Br .

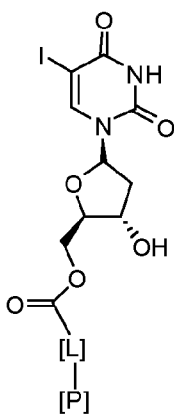
In one embodiment of the present disclosure, the compound of formula (I) is



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wherein [L] and [P] are as defined herein.

In one embodiment of the present disclosure, the compound of formula (I) is



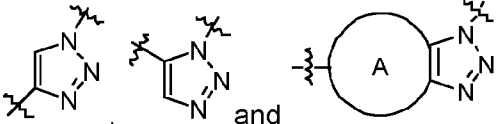
wherein [L] and [P] are as defined herein.

15 One embodiment of the present disclosure is the compound of formula (I), wherein R^A is not of natural abundance, such as wherein all elements of formula (I) are of natural abundance except for R^A which is not of natural abundance.

In one embodiment, the level of isotope enrichment in the compound of formula (I) with isotopes that are not of natural abundance is 2% or more, 5% or more, 10% or more, 20% or more, 50% or more, 75% or more, 90% or more, or 95% or more, such as is 95%, 96%, 97%, 98%, 99% or 100%.

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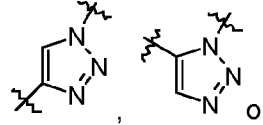
Within the present disclosure, the linker [L] is defined as comprising or consisting of a bivalent, saturated or unsaturated, straight or branched, C₂-C₁₂ hydrocarbon chain wherein one or more methylene groups are individually and optionally replaced by one or more of the groups selected from -O-, -NH-, -N(R^{L1})-, OC(=O)-, -C(=O)O-, C(=O)-, -N(H)C(=O), -N(R^{L1})C(=O)-, -C(=O)N(H)-, -NHC(O)NH-, -NHC(O)O-, -C(=O)N(R^{L1})-, -S-, -S(=O)-, -S(=O)₂-, -N(R^{L1})S(=O)₂-, -S(=O)₂N(R^{L1})-; an optionally substituted aromatic group; an optionally substituted carbocycle; an optionally substituted heterocycle; an optionally substituted aromatic heterocycle,


 ; wherein R^{L1} is selected from the group consisting of C₁₋₅ alkyl and the moiety 'A' comprises or consists of any monocyclic or polycyclic carbocycle or heterocycle.

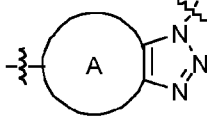
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In one embodiment of the present disclosure, [L] comprises or consists of a bivalent, saturated or unsaturated, straight or branched, C₂-C₁₂ hydrocarbon chain, such as a C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ or C₁₂ hydrocarbon chain, wherein one or more methylene groups such as 1, 2, 3, 4, or 5 methylene groups are each individually and optionally replaced by one or more of the groups selected from -O-, -N(H)-, -N(R^{L1})-, -OC(=O)-, -C(=O)O-, -C(=O)-, -N(H)C(=O)-, -N(R^{L1})C(=O)-, -C(=O)N(H)-, -C(=O)N(R^{L1})-, -S-, -S(=O)-, -S(=O)₂-, -N(R^{L1})S(=O)₂-, -S(=O)₂N(R^{L1})-, -CH₂-CH₂-O-, an optionally

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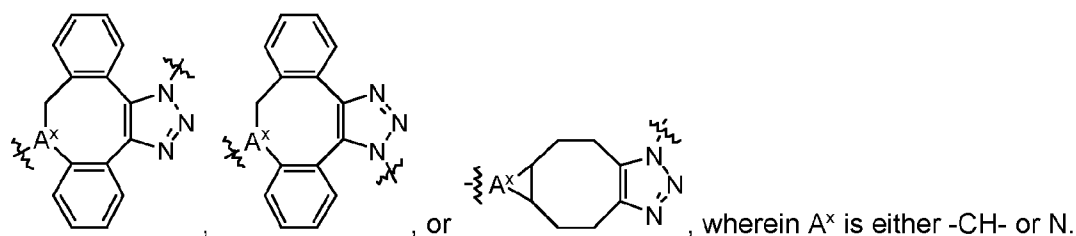
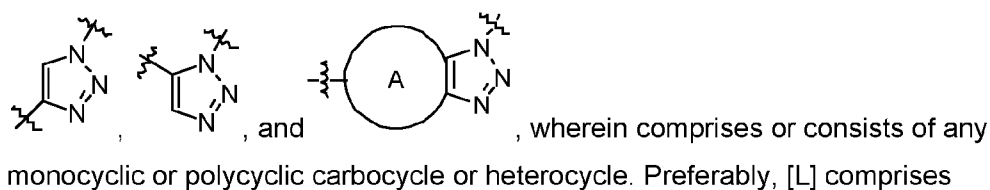
substituted carbocycle; an optionally substituted heterocycle,
 
 or

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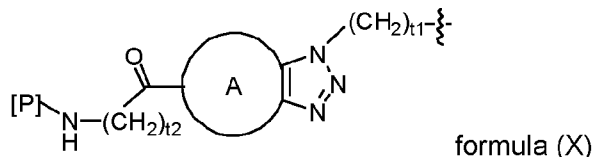

 ; wherein R^{L1} is C₁₋₅ alkyl and A comprises or consists of any monocyclic or polycyclic carbocycle or heterocycle.

The linker moiety [L] of formula (I) may within the present disclosure be formed by a click-reaction between an alkyne group and an azide, such as in a copper-assisted click reaction (CuAAC) or copper-free click reaction (SPAAC).

- 5 In one embodiment, [L] comprises one selected from the group consisting of:



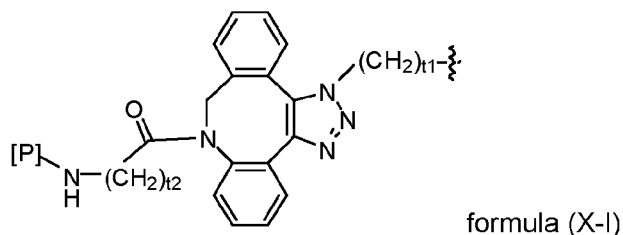
- 10 In a further embodiment of the present disclosure, [L] is according to formula (X):



wherein A comprises or consists of any monocyclic or polycyclic carbocycle or heterocycle; and

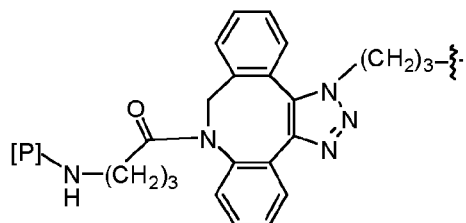
- 15 t_1 and t_2 are each integers individually selected from 1, 2, 3, 4, or 5, and wherein the polymer [P] is as defined herein.

In one embodiment, A comprises an 8-membered carbocycle or heterocycle. Thus, in a more preferred embodiment, [L] is according to formula (X-I):



wherein each of t1 and t2 are each integers individually selected from 1, 2, 3, 4, or 5, and wherein the polymer [P] is as defined herein.

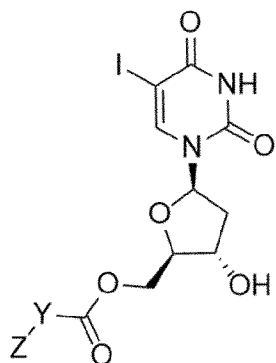
In a further embodiment of the present disclosure, [L] is defined as



, wherein the polymer [P] is as defined herein.

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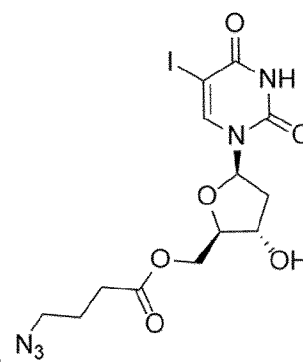
Provided herein are also compounds of formula (V)



formula (V),

wherein Z is alkyne or azide, and wherein Y is C₁₋₆ alkyl, preferably propyl or ethyl or butyl or pentyl.

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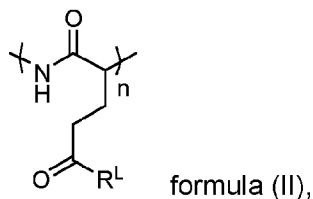


In one embodiment, the compound of formula (V) is

Such compounds may find use as prodrugs of IUdR, and thereby also for use in treatment of cancers, in particular brain cancers. When contemplated for use in such methods of treatment, the iodine is preferably a radioemitting isotope such as an Auger-emitting isotope of iodine, preferable ¹²³I or ¹²⁵I.

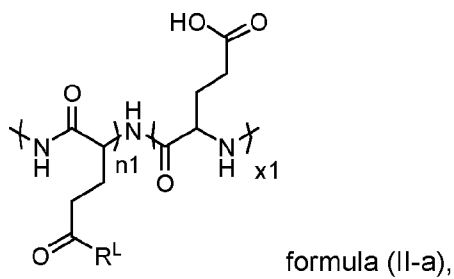
15

In one embodiment of the present disclosure, [P] comprises formula (II)



5 or a diastereomer, enantiomer, regioisomer or stereoisomer thereof, wherein n is an integer from 10 to 1000; and R^L denotes the attachment to [L] of formula (I) and formula (I) is as described herein.

In one embodiment, [P] comprises formula (II-a)

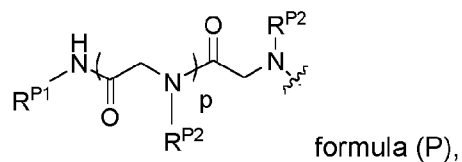


10 or a diastereomer, enantiomer, regioisomer or stereoisomer thereof, wherein n_1 is an integer from 10 to 500, x_1 is an integer from 10 to 500, and R^L denotes attachment to [L] of formula (I) and formula (I) is as described herein.

In one embodiment, [P] comprises formula (II-b)

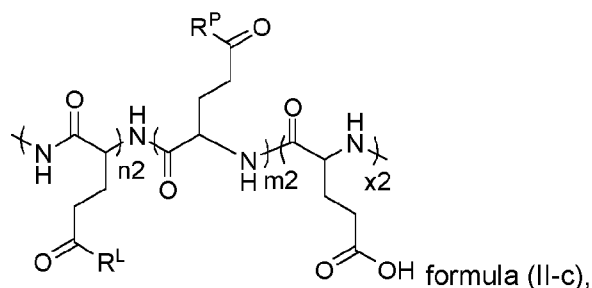


15 or a diastereomer, enantiomer, regioisomer or stereoisomer thereof, wherein R^L denotes attachment to [L] of formula (I) and formula (I) is as described herein, n_1 is an integer from 10 to 500, m_1 is an integer from 10 to 500, R^P is according to formula (P)



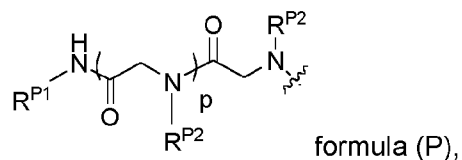
wherein R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl and p is an integer from 10 to 500.

5 In one embodiment, [P] comprises formula (II-c)



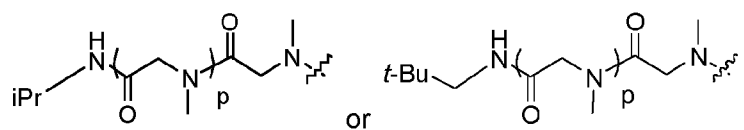
or a diastereomer, enantiomer, regioisomer or stereoisomer thereof, wherein n_2 is an integer from 10 to 500, m_2 is an integer from 10 to 500, x_2 is an integer from 0 to 500, R^L denotes attachment to [L] of formula (I) and formula (I) is as described herein, R^P is according to formula (P):

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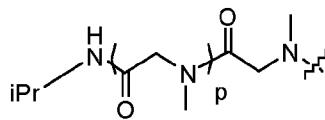
wherein R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl and p is an integer from 10 to 500.

15 In one embodiment, R^P as defined herein is



wherein p is an integer from 10 to 500.

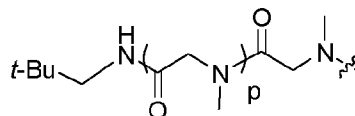
In one embodiment, R^P as defined herein is



, wherein p is an

integer from 10 to 500.

In one embodiment, R^P as defined herein is

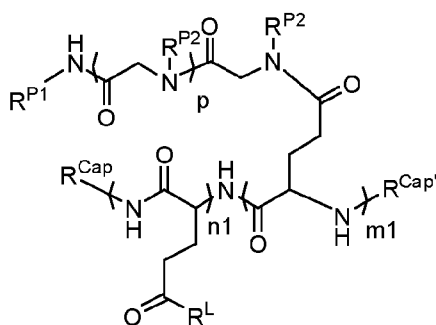


wherein p is

an integer from 10 to 500.

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In one embodiment, [P] comprises formula (III)



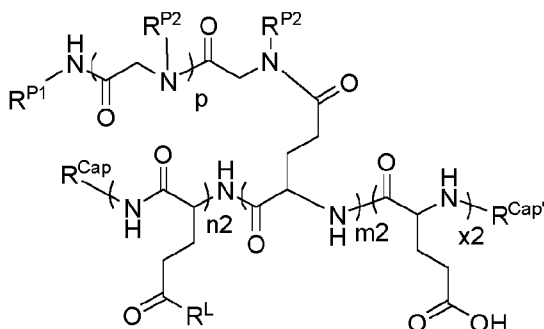
formula (III),

or a diastereomer, enantiomer, regioisomer or stereoisomer thereof, wherein n_1 is an integer from 10 to 500, m_1 is an integer from 10 to 500, p is an integer from 10 to 500,

10 R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl, R^{Cap} is a C_1 - C_6 alkyl, $R^{Cap'}$ is $-C(O)-C_{1-6}$ -alkyl or $-C(O)$ -aryl; and

R^L denotes attachment to [L] of formula (I) and formula (I) is as described herein.

In one embodiment, [P] comprises formula (III-a)



formula (III-a),

15 or a diastereomer, enantiomer, regioisomer or stereoisomer thereof, wherein n_2 is an integer from 10 to 500, m_2 is an integer from 10 to 500, x_2 is an integer from 0 to 500,

p is an integer from 10 to 500, R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl, R^{Cap} is a C_1 - C_6 alkyl, $R^{Cap'}$ is $-C(=O)-C_{1-6}$ alkyl or $-C(=O)$ -aryl; and R^L denotes attachment to [L] of formula (I) and formula (I) is as described herein.

In one embodiment of the present disclosure, R^{P2} is C_1 alkyl, C_2 alkyl, C_3 alkyl or C_4 alkyl, preferably R^{P2} is methyl.

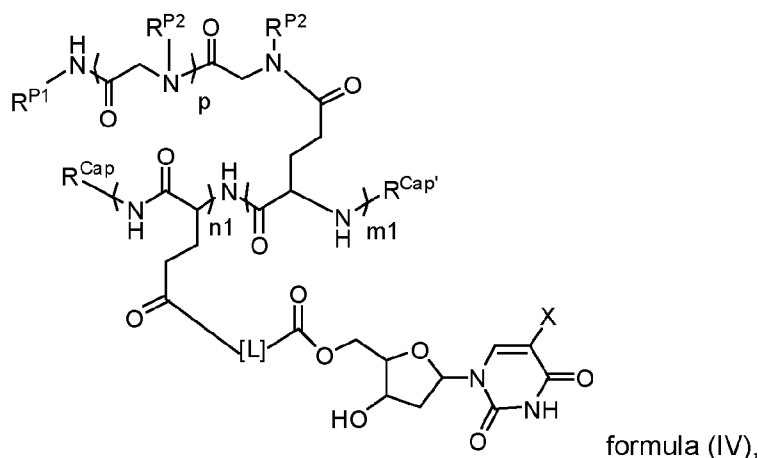
In one embodiment of the present disclosure, R^{P1} is C_1 alkyl, C_2 alkyl, C_3 alkyl or C_4 alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or sec-butyl. In one embodiment, R^{P1} is isopropyl.

In one embodiment of the present disclosure, R^{Cap} is C_1 - C_5 alkyl, such as methyl, ethyl, propyl, butyl, isopropyl, sec-butyl, tert-butyl or neopentyl.

In one embodiment of the present disclosure, $R^{Cap'}$ is $-C(=O)-C_{1-6}$ alkyl or $-C(=O)$ -aryl, such as $-C(=O)-CH_3$.

Provided herein are also compounds of formula (IV) and/or compositions comprising a compound of formula (IV) or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound according to formula (IV) or a pharmaceutically acceptable salt thereof is

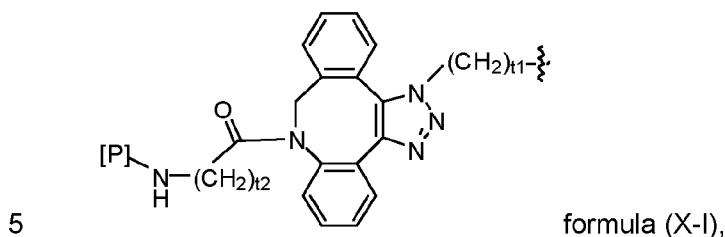


or a diastereomer, enantiomer, regioisomer or stereoisomer thereof, wherein

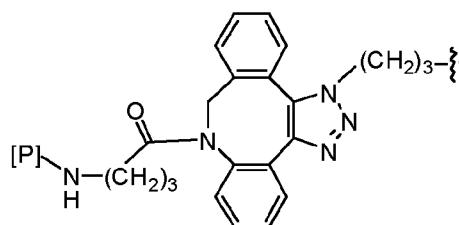
n_1 is an integer from 10 to 500, m_1 is an integer from 10 to 500, p is an integer from 10 to 500, R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl, R^{Cap} is a C_1 - C_6 alkyl, $R^{Cap'}$ is $-C(O)-C_{1-6}$ alkyl or $-C(O)$ -aryl; and

X is defined as $-R^1-R^A$, wherein R^1 is selected from the group consisting of $-C_{1-3}$ alkyl-, $-C_{1-3}$ haloalkyl-, $-C_{2-4}$ alkenyl-, $-C_{3-6}$ cycloalkyl-, $-C_{3-6}$ cycloaryl-, $-C_{3-6}$ cycloheteroaryl-

, -O-, -NH-, -C(O)-, -C(O)-O-(C₁₋₆ alkyl)-, -phenyl-, -O-phenyl, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope; and [L] is a covalent linker as defined herein, but preferably, [L] may in one embodiment be according to formula (X-I)



wherein each of t1 and t2 are each integers individually selected from 1, 2, 3, 4, or 5.



In more preferred embodiments, [L] is

10 In one embodiment of the present disclosure, X of formula (IV) is selected from ¹²³I, ¹²⁴I, ¹²⁵I, ⁷⁷Br, ⁷⁶Br, ^{80m}Br, ⁸⁰Br, ¹²⁶I, ¹³¹I, ¹⁸F and ²¹¹At; more preferably selected from ¹²³I, ¹²⁴I, ¹²⁵I, ¹³¹I, and ⁷⁷Br, more preferably selected from ¹²³I and ¹²⁵I.

In one embodiment of the present disclosure, n is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200, such as from 10 to 100, such as from 500 to 1000, such as from 200 to 500.

15 In one embodiment of the present disclosure, (n1 + x1) is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200, such as from 10 to 100, such as from 500 to 1000, such as from 200 to 500.

In one embodiment of the present disclosure, the ratio of n1:x1 is approximately 0.1-3.0:7.0-9.9, such as approximately 0.5-1.5:8.5-9.5, such as about 1:9 as determined by ¹H-NMR by relation of signal of known protons, such as change in signal ratios.

20 In one embodiment of the present disclosure, (n1 + m1) is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200, such as from 10 to 100, such as from 500 to 1000, such as from 200 to 500.

In one embodiment of the present disclosure, the ratio of $n_1:m_1$ is approximately 0.1-3.0:7.0-9.9, such as approximately 0.5-1.5:8.5-9.5, such as about 1:9, e.g. as determined by $^1\text{H-NMR}$ by relation of signal of known protons, such as change in signal ratios.

- 5 In one embodiment of the present disclosure, $(n_2+m_2+x_2)$ is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200, such as from 10 to 100, such as from 500 to 1000, such as from 200 to 500.

- 10 In one embodiment of the present disclosure, the ratio of $n_2:(m_2+x_2)$ is approximately 0.1-3.0:7.0-9.9, such as approximately 0.5-1.5:8.5-9.5, such as about 1:9, e.g. as determined by $^1\text{H-NMR}$ by relation of signal of known protons, such as change in signal ratios.

In one embodiment of the present disclosure, p is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200, such as from 10 to 100, such as from 500 to 1000, such as from 200 to 500.

- 15 As used herein, when integers are used to refer to the number of repeating units of a polymer formula, it is understood that they refer to an average number across chains. As used herein, when different repeating units are depicted in a polymer formula, it is referred to as these units being randomly distributed through the polymer backbone.

- 20 For polypeptoids defined by repeating units of glutamic acid, or a derivative thereof, in the backbone, in one preferred embodiment each of the units corresponding to glutamic acid, or a derivative thereof, corresponds to the L-isomer of glutamic acid or derivative thereof.

- 25 In one embodiment of the present disclosure, the average molecular weight number (M_n) of the polymer is from 250 kg/mol to 500 kg/mol, such as from 250 kg/mol to 300 kg/mol, from 300 kg/mol to 350 kg/mol, from 350 kg/mol to 400 kg/mol, from 400 kg/mol to 450 kg/mol such as from 450 kg/mol to 500 kg/mol, such as determined by size exclusion chromatography (SEC) using a known standard as reference.

Treatment of brain cancer

- 30 The methods, uses, compounds, and compositions provided herein are generally intended for, or for use in, treating and/or ameliorating any type of cancer, and in particular any type of brain cancer and/or brain tumor, or intracerebral neoplasm. In one

embodiment, this includes all tumors inside the human skull (cranium) or in the central spinal canal.

The tumor may originate from the brain itself, but also from lymphatic tissue, blood vessels, the cranial nerves, the brain envelopes (meninges), skull, pituitary gland, or pineal gland. Within the brain itself, the involved cells may be neurons or glial cells (which include astrocytes, oligodendrocytes, and ependymal cells). Brain tumors may also spread from cancers primarily located in other organs (metastatic tumors).

Numerous systems exist for grading tumors of the central nervous system (CNS), such as the “2021 World Health Organization (WHO) Classification of Tumor of the Central Nervous System” (WHO CN5). Thus, in one embodiment, the brain cancer is any type of glioma, glioneuronal tumor or neuronal tumor according to the WHO CN5 classification. In one embodiment, the brain tumor is astrocytoma, glioblastoma, diffuse midline glioma, diffuse hemispheric glioma or diffuse paediatric-type high-grade glioma according to the WHO CN5 classification.

In one preferred embodiment, the brain cancer is a brain tumor involving glial cells, and in a preferred embodiment, the methods, uses, agents, compositions and kits-of-parts provided herein are intended for treating and/or ameliorating a high-grade glioma. In one preferred embodiment, the high-grade glioma is glioblastoma.

Another grading systems in use, is the previous World Health Organization (WHO) grading system for astrocytoma, under which tumors are graded with roman numerals from I (least advanced disease - best prognosis) to IV (most advanced disease - worst prognosis). In this grading system, high-grade gliomas are categorized by the World Health Organization (WHO) as grade III and IV gliomas. These tumors are malignant and carry a worse prognosis. Thus, in one embodiment, the brain cancer is a WHO grade III or WHO grade IV according to the classification prior to 2021.

Thus, in one embodiment, the methods, uses, agents, and compositions provided herein are intended for use in a method of treating and/or ameliorating a high-grade glioma or glioblastoma.

Cancer cells with stem cell-like properties have been found in glioblastomas. The presence of cancer stem cells is a likely cause of the resistance of glioblastomas to conventional treatments, and their high recurrence rate. These cells are harder to treat with chemotherapeutic agent as they divide more slowly.

The composition according to the present disclosure provides: a) a longer residence time of the composition in the intra-cerebral compartment (i.e. increased biological half-life ($t_{1/2}$) of the composition and/or drug); and b) release of Auger-emitting nucleosides for

extended periods of time. This gives the opportunity to extend the window of time it can be incorporated into the DNA of cancer cells, and treat cancer more efficiently. Therefore, the compositions of the present disclosure may be able to deal more effectively with resistant cancer cells or slowly dividing cancer cells, such as cancer cells with stem-cell like properties.

In one embodiment of the present disclosure, the cytotoxic agent comprised in formula (I) is released from the polymer [P] in aqueous solutions in the presence of a degrading enzyme over the course of 1 to 6 days.

Preferred degrading enzymes within the scope of the present disclosure are proteases, esterases, and amidases.

In one embodiment of the present disclosure, the cytotoxic agent comprised in formula (I) is released from the polymer [P] in aqueous solutions in the presence of an esterase over the course of 1 to 6 days.

In one embodiment of the present disclosure, the cytotoxic agent comprised in formula (I) is released from the polymer [P] in aqueous solutions in the presence of an esterase (0.1 U/mL) over the course of 1 to 6 days.

In one embodiment of the present disclosure, at least 50% of the cytotoxic is present in and/or associated with the polymer 24 hours after administration, such as in one embodiment, at least 50% of the radioactive agent is not released from the polymer 24 hours after administration.

In one embodiment of the present disclosure, at least 20% or at least 10% of the cytotoxic agent is present in the polymer 96 hours after administration, such as in one embodiment, at least 20% or at least 10% of the radioactive agent is not released from the polymer 96 hours after administration.

In one embodiment of the present disclosure, the activity of radiation from the radioisotope is maintained in the intracerebral compartment for at least 6h, such as at least 24h, such as at least 48h, such as at least 72h, such as at least 96h, such as at least 120h.

In one embodiment, the retention of activity of the radioisotope in the intracranial compartment upon intracerebral administration of the composition for use as described herein is increased compared to the retention of an equivalent amount of activity of the a free Auger electron-emitting nucleoside analog, particularly an equivalent amount of activity of the free Auger electron-emitting 2'-deoxyuridine analog, such as free [¹²⁵I]UdR or free [¹²³I]UdR.

Route of administration

The composition for use as described herein may be administered locally to the brain by direct intracerebral administration or to the spinal cord by intrathecal injection. In one embodiment, the composition for use as described herein, may be formulated in any physiologically acceptable liquid suitable for intracerebral administration. In one embodiment, the composition for use as described herein is formulated or provided in an isotonic saline buffer or PBS buffer.

Convection enhanced delivery (CED) is a local delivery approach that delivers therapeutics to the tumor site under positive pressure via an implanted catheter, thereby circumventing brain-blood-barrier (BBB) constraints. Convection-enhanced delivery involves the continuous infusion of a therapeutic compound under positive pressure. One or more catheters can be placed using intraoperative neuronavigation into areas of residual tumor, preferably after surgical resection of the tumor. The one or more catheters are then connected to a pump, either an internal or external pump depending on the duration of the infusion. This convection-enhanced delivery bypasses the blood-brain barrier and allows the creation of higher concentrations of the radioactive agent in the brain with no or very little systemic toxicity.

Thus, in one embodiment, the composition for use as described herein is administered by CED. In one embodiment, the composition for use as described herein is provided or prepared in a buffer suitable for convection-enhanced delivery.

In one embodiment, the infusion rate is adjusted to a level that ensures sufficient delivery of the composition, while avoiding adverse effects resulting from increased intracranial pressure, for example, the infusion rate is from 0.1 to 5.0 mL/hour. The infusion rate should generally be about 0.1-5 ml/hour, and preferably between 0.1-4 ml/hour, such as 0.1-3 ml/hour, such as 0.1-2 ml/hour, such as preferably 0.1-1 ml/hour. Alternatively, the infusion rate is between 0.2-4 ml/hour, such as 0.2-3 ml/hour, such as 0.2-2 ml/hour, such as 0.3-2 ml/hour, such as 0.3-1.5 ml/hour, such as preferably 0.3-1.0 ml/hour, such as 0.3-0.9 ml/hour, such as 0.3-0.7 ml/hour, such as about 0.5 ml/hour.

In one embodiment, the infusion rate is from 0.1 $\mu\text{L}/\text{min}$ per catheter to 1000 $\mu\text{L}/\text{min}$ per catheter. In one embodiment, the infusion rate is from 1.0 $\mu\text{L}/\text{min}$ per catheter to 10 $\mu\text{L}/\text{min}$ per catheter, such as from 1.0 to 2.0, from 2.0 to 3.0, from 3.0 to 4.0, such as from 4.0 to 5.0, such as from 5.0 to 6.0, such as from 6.0 to 7.0, such as from 7.0 to 8.0, such as from 8.0 to 9.0, such as from 9.0 to 10.0 $\mu\text{L}/\text{min}$ per catheter.

In one embodiment, the composition is administered in one or more fractions, such as in 1 to 20 fractions, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 fractions.

The time between each fraction may vary depending on the patient response and practical considerations. The time between each fraction will usually vary between a few hours and several days. In a preferred embodiment, one fraction per day is provided, but the fractions may also be provided once a week.

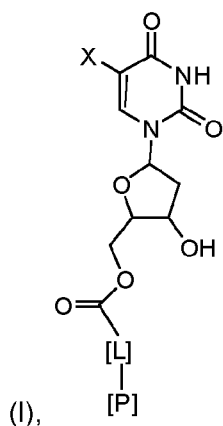
Each provided fraction may comprise between 1 kBq to 50 GBq activity of radioactive composition and/or compound. "Bq" refers to the SI unit of measure of radioactivity the Becquerel. The radioactive composition content and/or compound of each fraction can be between 1 kBq to 50 GBq, such as 100 kBq to 40 GBq, such as 1 MBq to 40 GBq, such as 500 MBq to 30 GBq, such as 0.1 GBq to 20 GBq, such as 0.1-10 GBq, such as 0.1-9 GBq, such as 0.1-8 GBq, such as 0.1-7 GBq, such as 0.1-6 GBq, such as 0.1-5 GBq, such as 0.1-4 GBq, such as 0.1-3.7 GBq, such as 0.1-3 GBq, such as 0.1-2 GBq.

In a preferred embodiment, the radioactive composition content of each fraction is 0.1-3.7 GBq, more specifically 0.1-3.0, such as 0.1-2.0 GBq, such as 0.2-2.0 GBq, such as 0.3-2.0 GBq, such as 0.4-2.0 GBq, such as 0.5-2.0 GBq, such as 0.6-2.0 GBq, such as 0.7-2.0 GBq, such as 0.8-2.0 GBq, such as 0.9-2 GBq, such as 1-2 GBq. In one embodiment, each fraction comprise 0.1-3.7 GBq, such as 0.2-3.7 GBq, such as 0.3-3.7 GBq, such as 0.4-3.7 GBq, such as 0.5-3.7 GBq, such as 0.6-3.7 GBq, such as 0.7-3.7 GBq, such as 0.8-3.7 GBq, such as 0.9-3.7 GBq, such as 1.0-3.7 GBq, such as 1.1-3.7 GBq, such as 1.2-3.7 GBq, such as 1.3-3.7 GBq, such as 1.4-3.7 GBq, such as 1.5-3.7 GBq, such as 1.6-3.7 GBq, such as 1.7-3.7 GBq, such as 1.8-3.7 GBq, such as 1.9-3.7 GBq, such as 2.0-3.7 GBq, such as 2.1-3.7 GBq, such as 2.2-3.7 GBq, such as 2.3-3.7 GBq, such as 2.4-3.7 GBq, such as 2.5-3.7 GBq, such as 2.6-3.7 GBq, such as 2.7-3.7 GBq, such as 2.8-3.7 GBq, such as 2.9-3.7 GBq, such as 3.0-3.7 GBq, 3.1-3.7 GBq, such as 3.2-3.7 GBq, such as 3.3-3.7 GBq, such as 3.4-3.7 GBq, such as 3.5-3.7 GBq, such as 3.6-3.7 GBq.

In one embodiment, a further therapeutic agent is administered. In one embodiment, the further therapeutic agent is a chemotherapeutic agent. In one embodiment, the further chemotherapeutic agent is administered enterally or parenterally.

5 Items

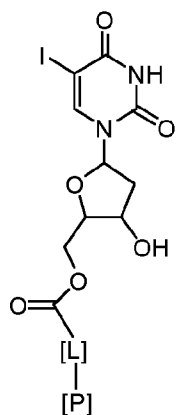
1. A pharmaceutical composition for use in a method of treatment of cancer, said composition comprising:
 - a. a polymer [P];
 - b. a cytotoxic agent; and
 - 10 c. a linker [L], which links the cytotoxic agent to the polymer, wherein the cytotoxic agent is of formula (I) or a derivative thereof, or a pharmaceutically acceptable salt thereof



wherein

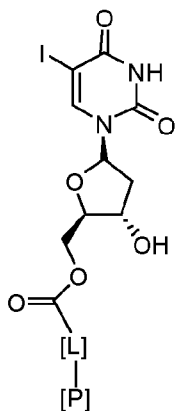
- 15 X is defined as $-R^1-R^A$, wherein R^1 is selected from the group consisting of $-C_{1-3}$ alkyl-, $-C_{1-3}$ haloalkyl-, $-C_{2-4}$ alkenyl-, $-C_{3-6}$ cycloalkyl-, $-C_{3-6}$ cycloaryl-, $-C_{3-6}$ cycloheteroaryl-, $-O-$, $-NH-$, $-C(O)-$, $-C(O)-O-(C_{1-6}$ alkyl)-, $-phenyl-$, $-O-phenyl$, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope.
- 20 2. The pharmaceutical composition for use according to any one of the preceding items, wherein R^1 is absent and R^A comprises a radioisotope of a halogen, such as ^{123}I , ^{124}I or ^{125}I , ^{77}Br , ^{76}Br , ^{80m}Br , ^{80}Br , ^{126}I , ^{131}I , ^{18}F , or ^{211}At .
- 25 3. The pharmaceutical composition for use according to any one of the preceding items, wherein R^1 is absent and R^A comprises an Auger electron-emitting radioisotope.

4. The pharmaceutical composition for use according to any one of the preceding items, wherein R^1 is absent and R^A comprises or consists of a radioisotope, which is ^{123}I , ^{125}I or ^{77}Br .
5. The pharmaceutical composition for use according to any one of the preceding items, wherein R^1 is absent and R^A consists essentially of a radioisotope of iodine.
6. The pharmaceutical composition for use according to any one of the preceding items, wherein the compound of formula (I) is



wherein [L] and [P] are as defined in any one of the preceding items.

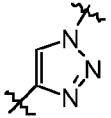
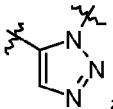
7. The pharmaceutical composition for use according to any one of the preceding items, wherein the compound of formula (I) is

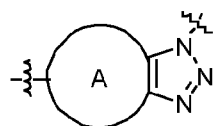


wherein [L] and [P] are as defined in any one of the preceding items.

8. The pharmaceutical composition for use according to any one of the preceding items, wherein R^A is ^{123}I or ^{125}I .
9. The pharmaceutical composition for use according to any one of the preceding items, wherein R^A is ^{125}I .

10. The pharmaceutical composition for use according to any one of the preceding items, wherein R^A is ¹²³I.
11. The pharmaceutical composition for use according to any one of the preceding items, wherein R^A is not of natural abundance.
- 5 12. The pharmaceutical composition for use according to any one of the preceding items, wherein all elements of formula (I) are of natural abundance except for R^A which is not of natural abundance.
13. The pharmaceutical composition for use according to any one of the preceding items, wherein the level of isotope enrichment in the compound of formula (I) with
10 isotopes that are not of natural abundance is 2% or more, 5% or more, 10% or more, 20% or more, 50% or more, 75% or more, 90% or more, or 95% or more.
14. The pharmaceutical composition for use according to any one of the preceding items, wherein the level of isotope enrichment in the compound of formula (I) with isotopes that are not of natural abundance is 95% or more.
- 15 15. The pharmaceutical composition for use according to any one of the preceding items, wherein the level of isotope enrichment in the compound of formula (I) with isotopes that are not of natural abundance is 95%, 96%, 97%, 98%, 99% or 100%.
16. The pharmaceutical composition for use according to any one of the preceding items, wherein [L] comprises a triazole moiety formed by the click-reaction
20 between an alkyne group and an azide.
17. The pharmaceutical composition for use according to any one of the preceding items, wherein [L] comprises a triazole moiety formed by the copper-free click-reaction between an alkyne group and an azide.
18. The pharmaceutical composition for use according to any one of the preceding items, wherein [L] comprises or consists of a bivalent, saturated or unsaturated,
25 straight or branched, C₂-C₁₂ hydrocarbon chain wherein one or more methylene groups are individually and optionally replaced by one or more of the groups selected
from: -O-, -N(H)-, -N(R^{L1})-, -OC(=O)-, -C(=O)O-, -C(=O)-, -N(H)C(=O)-,
30 -N(R^{L1})C(=O)-, -C(=O)N(H)-, -NHC(O)NH-, -NHC(O)O- -C(=O)N(R^{L1})-, -S-,
-S(=O)-, -S(=O)₂-, -N(R^{L1})S(=O)₂-, -S(=O)₂N(R^{L1})-; an optionally substituted aromatic group; an optionally substituted carbocycle; an optionally substituted

heterocycle; an optionally substituted aromatic heterocycle, ,  and

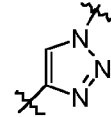
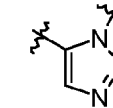


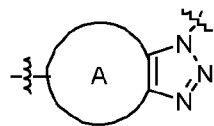
; wherein R^{L1} is selected from the group consisting of C_{1-5} alkyl

and

A comprises or consists of any monocyclic or polycyclic carbocycle or heterocycle.

- 5 19. The pharmaceutical composition for use according to any one of the preceding items, wherein [L] comprises or consists of a bivalent, saturated or unsaturated, straight or branched, C_2 - C_{12} hydrocarbon chain, such as a C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} or C_{12} hydrocarbon chain, wherein one or more methylene groups such as 1, 2, 3, 4, or 5 methylene groups are each individually and optionally replaced by
- 10 one or more of the groups selected from -O-, -N(H)-, -N(R^{L1})-, -OC(=O)-, -C(=O)O-, -C(=O)-, -N(H)C(=O)-, -N(R^{L1})C(=O)-, -C(=O)N(H)-, -C(=O)N(R^{L1})-, -S-, -S(=O)-, -S(=O)₂-, -N(R^{L1})S(=O)₂-, -S(=O)₂N(R^{L1})-, -CH₂-CH₂-O-, an optionally substituted

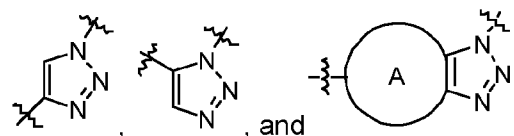
carbocycle; an optionally substituted heterocycle, ,  or

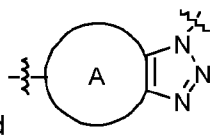


; wherein R^{L1} is C_{1-5} alkyl and A comprises or consists of any

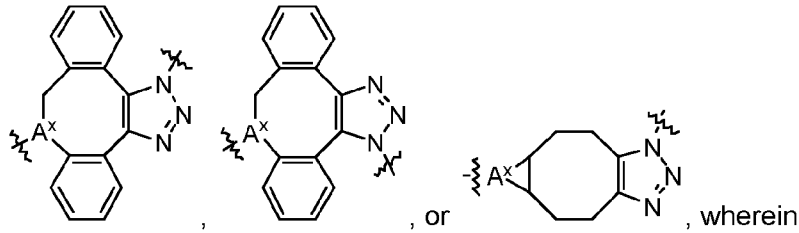
- 15 monocyclic or polycyclic carbocycle or heterocycle.

20. The pharmaceutical composition for use according to any one of the preceding items, wherein [L] comprises one selected from the group consisting of:



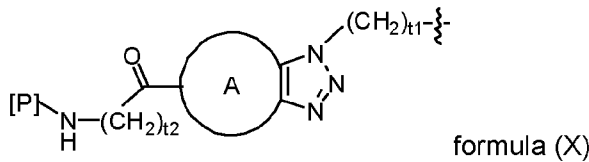
, and , wherein A comprises or consists of any monocyclic or polycyclic carbocycle or heterocycle.

21. The pharmaceutical composition for use according to any one of the preceding items, wherein [L] comprises:



A^x is either -CH- or N.

5 22. The pharmaceutical composition for use according to any one of the preceding items, wherein [L] is according to formula (X):

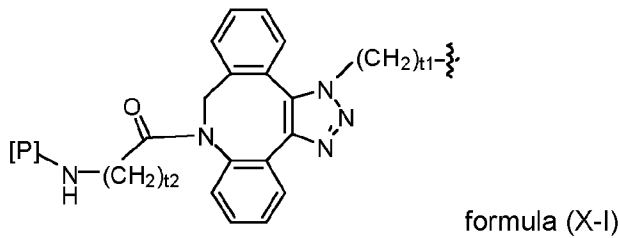


wherein A comprises or consists of any monocyclic or polycyclic carbocycle or heterocycle; and

10 t₁ and t₂ are each integers individually selected from 1, 2, 3, 4, or 5.

23. The pharmaceutical composition for use according to any one of the preceding items, wherein A comprises an 8-membered carbocycle or heterocycle.

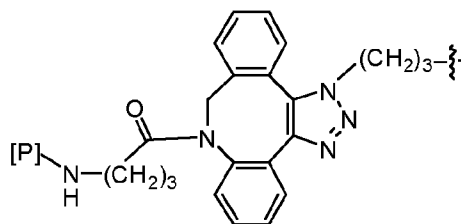
24. The pharmaceutical composition for use according to any one of the preceding items, wherein [L] is according to formula (X-I):



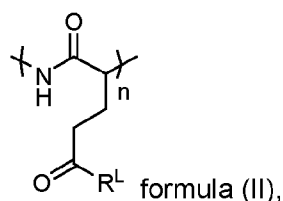
15

wherein each of t₁ and t₂ are each integers individually selected from 1, 2, 3, 4, or 5.

25. The pharmaceutical composition for use according to any one of the preceding items, wherein [L] is



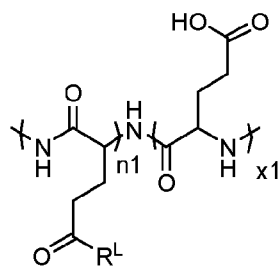
26. The pharmaceutical composition for use according to any one of the preceding items, wherein [P] comprises formula (II):



wherein n is an integer from 10 to 1000; and

R^L denotes the attachment to formula (I) and formula (I) is as defined in any one of the preceding items.

27. The pharmaceutical composition for use according to any one of the preceding items, wherein [P] comprises formula (II-a):



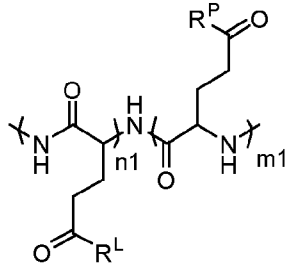
formula (II-a), wherein

n_1 is an integer from 10 to 500,

x_1 is an integer from 10 to 500, and

- R^L denotes attachment to formula (I) and formula (I) is as defined in any one of the preceding items.

28. The pharmaceutical composition for use according to any one of the preceding items, wherein [P] comprises formula (II-b):



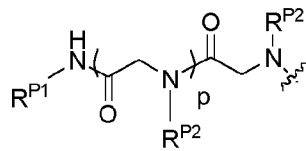
, formula (II-b); wherein,

R^L denotes attachment to formula (I) and formula (I) is as defined in any one of the preceding items;

n_1 is an integer from 10 to 500,

m_1 is an integer from 10 to 500,

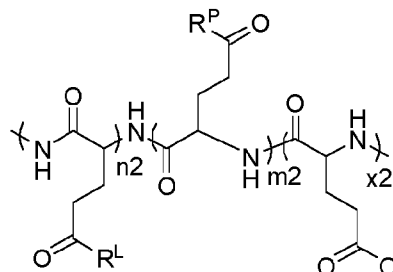
R^P is according to formula (P):



formula (P), wherein R^{P1} and R^{P2} are each independently

selected from C_1 - C_4 alkyl and p is an integer from 10 to 500.

29. The pharmaceutical composition for use according to any one of the preceding items, wherein [P] comprises formula (II-c):



formula (II-c), wherein

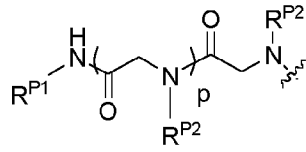
n_2 is an integer from 10 to 500,

m_2 is an integer from 10 to 500,

x_2 is an integer from 0 to 500,

R^L denotes attachment to formula (I) and formula (I) is as defined in any one of the preceding items,

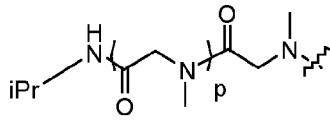
R^P is according to formula (P):



formula (P), wherein R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl and p is an integer from 10 to 500.

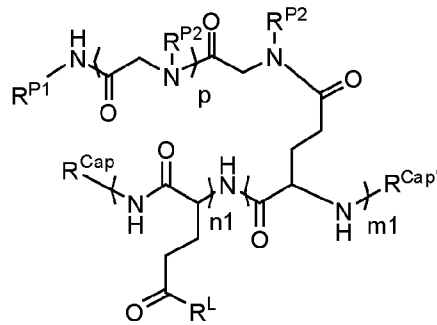
30. The pharmaceutical composition for use according to any one of the preceding items, wherein R^P is

5



wherein p is an integer from 10 to 500.

31. The pharmaceutical composition for use according to any one of the preceding items, wherein [P] is according to formula (III),



10

formula (III), wherein

$n1$ is an integer from 10 to 500

$m1$ is an integer from 10 to 500

p is an integer from 10 to 500

R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl

15

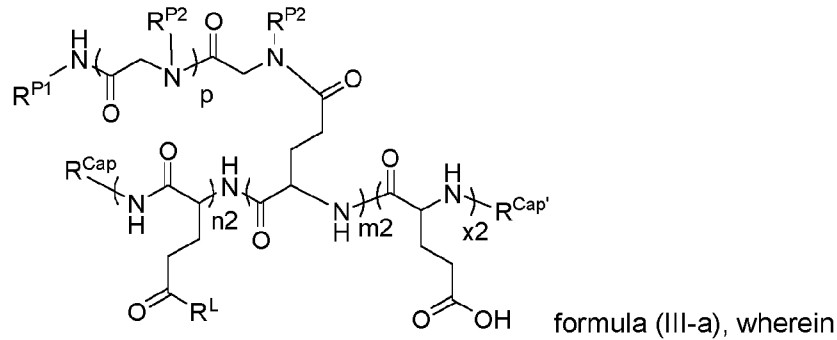
R^{Cap} is a C_1 - C_6 alkyl,

$R^{Cap'}$ is $-C(O)-C_1-6$ alkyl or $-C(O)-aryl$; and

R^L denotes attachment of formula (I) and formula (I) is as defined in any one of the preceding items.

20

32. The pharmaceutical composition for use according to any one of the preceding items, wherein [P] is according to formula (III-a),

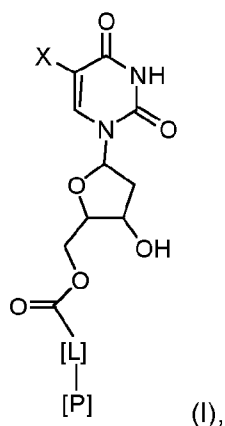


- 5 n_2 is an integer from 10 to 500
 m_2 is an integer from 10 to 500
 x_2 is an integer from 0 to 500
 p is an integer from 10 to 500
 R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl,
 10 R^{Cap} is a C_1 - C_6 alkyl,
 $R^{Cap'}$ is $-C(=O)-C_{1-6}$ alkyl or $-C(=O)$ -aryl; and
 R^L denotes attachment of formula (I) and formula (I) is as defined in any one of the preceding items.
- 15 33. The pharmaceutical composition for use according to any one of the preceding items, wherein ;
 n is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200; or
 $(n + x_1)$ is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200; or
 20 $(n + m_1)$ is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200; or
 $(n_2+m_2+x_2)$ is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200.
- 25 34. The pharmaceutical composition for use according to any one of the preceding items, wherein p is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200.
35. The pharmaceutical composition for use according to any one of the preceding items, wherein
 the ratio of $n_1:m_1$ is approximately 0.1-3.0:7.0-9.9, such as approximately 0.5-

- 1.5:8.5-9.5, such as about 1:9; or
the ratio of $n_1:x_1$ is approximately 0.1-3.0:7.0-9.9, such as approximately 0.5-1.5:8.5-9.5, such as about 1:9; or
the ratio of $n_2:(m_2+x_2)$ is approximately 0.1-3.0:7.0-9.9, such as approximately
5 0.5-1.5:8.5-9.5, such as about 1:9;
e.g. as determined by $^1\text{H-NMR}$ by relation of signal of known protons.
36. The pharmaceutical composition for use according to any one of the preceding items, wherein R^{P2} is C_1 alkyl, C_2 alkyl, C_3 alkyl or C_4 alkyl.
37. The pharmaceutical composition for use according to any one of the preceding
10 items, wherein R^{P2} is methyl.
38. The pharmaceutical composition for use according to any one of the preceding items, wherein R^{P1} is C_1 alkyl, C_2 alkyl, C_3 alkyl or C_4 alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or sec-butyl.
39. The pharmaceutical composition for use according to any one of the preceding
15 items, wherein R^{Cap} is C_1 - C_5 alkyl, such as methyl, ethyl, propyl, butyl, isopropyl, sec-butyl, tert-butyl or neopentyl.
40. The pharmaceutical composition for use according to any one of the preceding items, wherein R^{Cap} is $-C(=O)-C_{1-6}$ alkyl or $-C(=O)-$ aryl, such as $-C(=O)-CH_3$.
41. The pharmaceutical composition for use according to any one of the preceding
20 items, wherein the average molecular weight number (M_n) of the polymer is higher from 250 kg/mol to 500 kg/mol, such as from 250 kg/mol to 300 kg/mol, from 300 kg/mol to 350 kg/mol, from 350 kg/mol to 400 kg/mol, from 400 kg/mol to 450 kg/mol such as from 450 kg/mol to 500 kg/mol, e.g. as determined by size exclusion chromatography (SEC) relative to known standards.
- 25 42. The pharmaceutical composition for use according to any one of the preceding items, wherein the cancer is brain cancer.
43. The pharmaceutical composition for use according to any one of the preceding items, wherein the brain cancer is a brain tumor or an intracerebral neoplasm.
44. The pharmaceutical composition for use according to any one of the preceding
30 items, wherein the brain tumor or intracerebral neoplasm involves glial cells.
45. The pharmaceutical composition for use according to any one of the preceding items, wherein the brain tumor or intracerebral neoplasm is a glioma.

46. The pharmaceutical composition for use according to any one of the preceding items, wherein the intracerebral neoplasm is a high grade glioma, i.e. grade III or grade IV glioma.
- 5 47. The pharmaceutical composition for use according to any one of the preceding items, wherein the glioma is astrocytoma, glioblastoma, diffuse midline glioma, diffuse hemispheric glioma or diffuse paediatric-type high-grade glioma.
48. The pharmaceutical composition for use according to any one of the preceding items, wherein the composition is administered by direct intracerebral administration or by intrathecal administration.
- 10 49. The pharmaceutical composition for use according to any one of the preceding items, wherein the composition is formulated or provided in a isotonic saline buffer or PBS buffer.
50. The pharmaceutical composition for use according to any one of the preceding items, wherein the composition is administered by convection-enhanced delivery (CED).
- 15 51. The pharmaceutical composition for use according to any one of the preceding items, wherein the infusion rate is adjusted to a level that ensures sufficient delivery of the composition, while avoiding adverse effects resulting from increased intracranial pressure, for example, the infusion rate is from 0.1 to 5.0 mL/hour.
- 20 52. The pharmaceutical composition for use according to any one of the preceding items, wherein the composition is administered in one or more fractions, such as in 1 to 20 fractions, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 fractions.
53. The pharmaceutical for use according to any one of the preceding items, wherein the composition comprises 1kBq to 50 GBq of activity.
- 25 54. The pharmaceutical for use according to any one of the preceding items, wherein a further chemotherapeutic agent is administered.
55. The pharmaceutical for use according to any one of the preceding items, wherein the further chemotherapeutic agent is administered enterally or parenterally.
- 30 56. The pharmaceutical for use according to any one of the preceding items, wherein the radioactive agent is released from the polymer in aqueous solutions in the presence of esterase over the course of 1 to 6 days.

57. The pharmaceutical for use according to any one of the preceding items, wherein the radioactive agent is released from the polymer in aqueous solutions in the presence of esterase (0.1 U/mL) over the course of 1 to 6 days.
58. The pharmaceutical composition for use according to any one of the preceding items, wherein at least 50% of the radioactive agent is present in the polymer 24 hours after administration.
59. The pharmaceutical composition for use according to any one of the preceding items, wherein at least 20% or at least 10% of the radioactive agent is present in the polymer 96 hours after administration.
60. The pharmaceutical composition for use according to any one of the preceding items, wherein the activity of radiation from the radioisotope is maintained in the intracerebral compartment for at least 6h, such as at least 24h, such as at least 48h, such as at least 72h, such as at least 96h, such as at least 120h.
61. A compound according to formula (I):



wherein

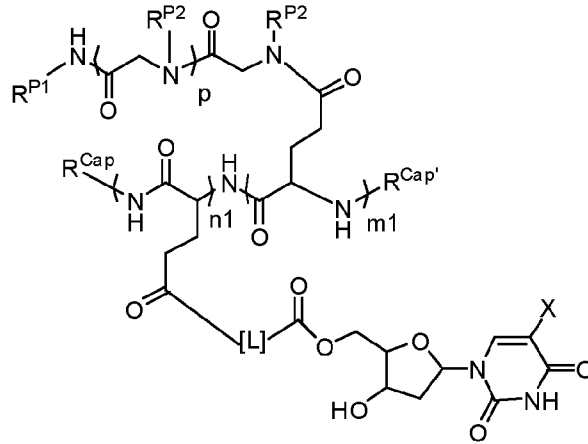
X is defined as $-R^1-R^A$, wherein R^1 is selected from the group consisting of $-C_{1-3}$ alkyl-, $-C_{1-3}$ haloalkyl-, $-C_{2-4}$ alkenyl-, $-C_{3-6}$ cycloalkyl-, $-C_{3-6}$ cycloaryl-, $-C_{3-6}$ cycloheteroaryl-, $-O-$, $-NH-$, $-C(O)-$, $-C(O)-O-(C_{1-6}$ alkyl)-, $-phenyl-$, $-O-phenyl-$, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope,

P is a polymer comprising at least one polypeptide and at least one polypeptoid, and

L is a covalent linker.

62. The compound according to item 61, wherein [P] is as defined in any one of items 26 to 41.

63. The compound according to any one of items 61 to 62, wherein the compound comprises or consists of formula (IV):



5

formula (IV), or a pharmaceutically

acceptable salt thereof, wherein

n1 is an integer from 10 to 500

m1 is an integer from 10 to 500

p is an integer from 10 to 500

10 R^{P1} and R^{P2} are each independently selected from C₁-C₄ alkyl

R^{Cap} is a C₁-C₆ alkyl,

R^{Cap'} is -C(O)-C₁₋₆alkyl or -C(O)-aryl; and

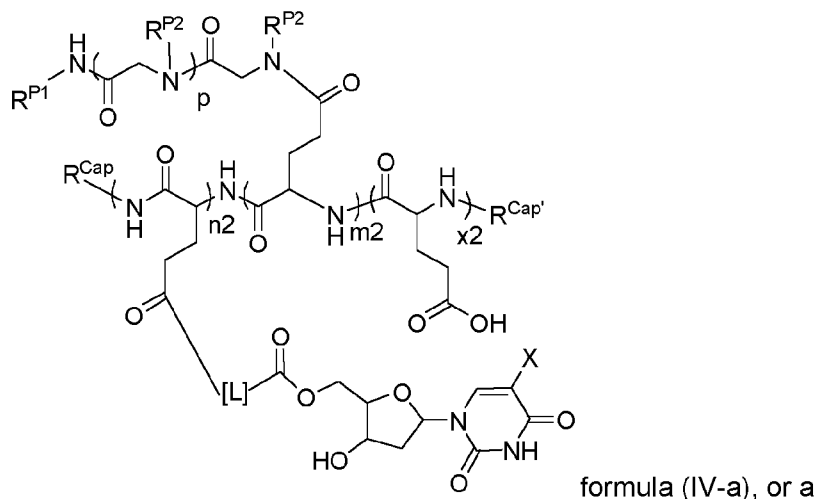
15 X is defined as -R¹-R^A, wherein R¹ is selected from the group consisting of -C₁₋₃ alkyl-, -C₁₋₃ haloalkyl-, -C₂₋₄ alkenyl-, -C₃₋₆ cycloalkyl-, -C₃₋₆ cycloaryl-, -C₃₋₆ cycloheteroaryl-, -O-, -NH-, -C(O)-, -C(O)-O-(C₁₋₆ alkyl)-, -phenyl-, -O-phenyl, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope; and

L is a covalent linker.

20

25

64. The compound according to item 63, wherein the compound comprises or consists of formula (IV-a):



pharmaceutically acceptable salt thereof, or a diastereomer, enantiomer, regioisomer or stereoisomer thereof, wherein

5

n_2 is an integer from 10 to 500

m_2 is an integer from 10 to 500

x_2 is an integer from 0 to 500

p is an integer from 10 to 500

10

R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl,

R^{Cap} is a C_1 - C_6 alkyl,

$R^{Cap'}$ is $-C(=O)-C_{1-6}$ alkyl or $-C(=O)$ -aryl; and

15

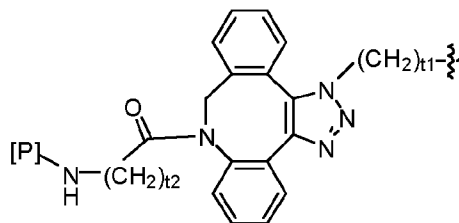
X is defined as $-R^1-R^A$, wherein R^1 is selected from the group consisting of $-C_{1-3}$ alkyl-, $-C_{1-3}$ haloalkyl-, $-C_{2-4}$ alkenyl-, $-C_{3-6}$ cycloalkyl-, $-C_{3-6}$ cycloaryl-, $-C_{3-6}$ cycloheteroaryl-, $-O$ -, $-NH$ -, $-C(O)$ -, $-C(O)-O-(C_{1-6}$ alkyl)-, $-phenyl$ -, $-O-phenyl$, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope; and

L is a covalent linker.

20

65. The compound according to any one of items 61 to 64, wherein $[L]$ is as defined in any one of items 16 to 25.

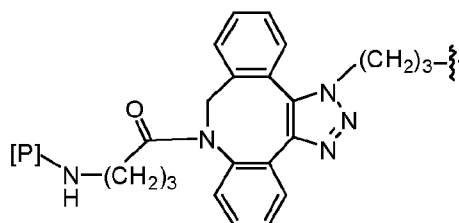
66. The compound according to item 65, wherein [L] is according to formula (X-I):



formula (X-I)

wherein each of t1 and t2 are each integers individually selected from 1, 2, 3, 4, or 5.

5 67. The compound according to item 66, wherein [L] is



68. The compound according to any one of items 61 to 67, wherein X is ^{123}I , ^{124}I , ^{125}I , ^{77}Br , ^{76}Br , $^{80\text{m}}\text{Br}$, ^{80}Br , ^{126}I , ^{131}I , ^{18}F or ^{211}At .

10 69. The compound according to any one of items 61 to 68, wherein X is ^{123}I , ^{124}I , ^{125}I , or ^{131}I .

70. The compound according to any one of items 61 to 69, wherein X is ^{123}I , ^{125}I or ^{77}Br .

Examples

Materials

All reagents and solvents were bought from commercial suppliers; VWR International, Sigma-Aldrich, ABCR Chemicals, FluoroChem or TCI Chemicals, and were used as received. Dry dimethylformamide (DMF) was degassed by three freeze-pump thaw cycles to remove residual dimethylamine before using. Tetrahydrofuran (THF) and *n*-hexane were dried over sodium and THF was freshly distilled before use. Milli-Q water was prepared by using a Milli-Q Reference A+ System and used at a resistivity of 18.2 M Ω and TOC < 3 ppm. *N,N*-triethylamine (TEA) and neopentylamine were dried over sodium hydroxide and distilled on molecular sieves. Iodine-125 (¹²⁵I) was bought from PerkinElmer (NEZ0330##MC, where ## is the amount of mCi, e.g. 10 mCi = 10, NEZ033010MC) as a [¹²⁵I]NaI/NaOH in H₂O solution (Specific Activity: 1 Ci/mg, 0.1M NaOH, pH = 12–14). Deuterated solvents were obtained from Deutero GmbH. Dialysis was carried out using Spectra/Por membranes (Roth) with 6-8 kDa molecular weight cut-off.

Methods

¹H NMR and diffusion-ordered spectra were recorded at room temperature on Bruker Avance III 400 and Avance I 500 spectrometers. Spectra were calibrated using the solvent signals and analysis of the spectra were performed using MestReNova 12.0.4 (Mestrelab Research S.L.).

The hydrodynamic diameter (\varnothing_{hyd}) and zeta potential were measured by dynamic light scattering (DLS) on a ZetaPALS (Brookhaven Instruments Limited, USA). Unless stated otherwise, \varnothing_{hyd} and analysis were performed in isotonic HEPES buffer (150 mM NaCl, 10 mM HEPES, pH 7.4) at 25°C, and were done in quintuplets. Osmolarity was measured on a Gonotec Osmomat 010/030-D (Gonotec GmbH, Germany).

Radio-HPLC was performed on a Hitachi Chromaster equipped with a Hitachi 5160 manual purge quaternary gradient pump, coupled to a Hitachi 5260 thermostat loop autosampler, a Hitachi 5310 column oven, a Hitachi 5430 UV-Vis multi-channel detector and a radio-detector (gamma) with analogue output and ca. 0.2 min signal delay.

Unless stated otherwise, routine HPLC analysis was performed using a Luna C18(2) ($\varnothing = 2.5 \mu\text{m}$, 100 \AA) column using a 20 min program, with a 0-100 $\text{H}_2\text{O}/\text{MeCN} + 0.1\%$ TFA gradient. Routine quantification of radioactivity was performed on a Capintec CRC-55tR dose calibrator (DoseCall) and reported in Becquerel (Bq).

5

If applicable, liquid scintillation counting (LSC) measurements were performed on a HIDEX 425-034 LSC for routine analysis, or on a HIDEX 300-SL LSC for large batch analysis, and reported in Becquerel (Bq), or counts per minute (cpm).

10 Radio-TLC analysis was performed with a PerkinElmer Cyclone Plus phosphor imager on commercially TLC pre-coated aluminium sheets ($4 \times 10 \text{ cm}$, Merck Silica gel 60), and unless stated otherwise run in 10% MeOH in DCM. Radio chemical conversion (RCC) is always based on the relative converted substance, judged by radio-TLC. Radio chemical yield (RCY) is based on the collected activity of the radiolabeled product, judged by
15 DoseCall or LSC, and (if stated) decay corrected.

Metal content (ICP, Inductively Coupled Plasma) was performed on an ICP-OES iCAP 7000 Plus Series (Thermo Fisher Scientific), using the relevant reference metal standard curve, prepared with metal-free 1% HCl in H_2O .

20

Size exclusion purification was performed on DP-10 (PD MidiTrap G-25 columns contain Sephadex G-25 resin) bought from Cytiva Sweden, using the relevant buffer (e.g., PBS ($\text{pH} = 7.4$), or HEPES ($\text{pH} = 7.3$) at $25 \text{ }^\circ\text{C}$ in MiliQ- H_2O ($18.2 \text{ M}\Omega \cdot \text{cm}$).

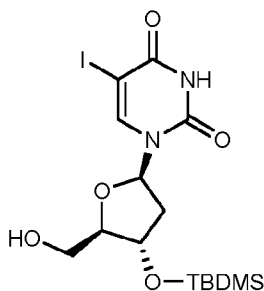
25 Analytical gel permeation chromatography (GPC) was carried out at $40 \text{ }^\circ\text{C}$ with a flow rate of 1.0 mL/min using hexafluoroisopropanol (HFIP) as eluent, equipped with 3 g/L potassium trifluoroacetate. Column material was modified silica gel (PFG columns, particle size: $7 \mu\text{m}$, porosity: $100 \text{ } 100 \text{ \AA}$ and 4000 \AA). The system was equipped with a UV detector (Jasco UV-2075 plus) set at a wavelength of 230 nm (unless otherwise
30 mentioned) and an RI detector (Jasco RI-2031). Molecular weights were determined by using a calibration with poly(methyl methacrylate) (PMMA) standards (Polymer Standards Services GmbH, Germany) and toluene as an internal standard. The elution diagram was evaluated with PSS WinGPC (Polymer Standard Service GmbH, Germany). Degree of polymerization (DP) of polysarcosine (pSar) was determined by
35 calibration of apparent M_n against a series of pSar standards characterized by static light

scattering to obtain absolute molecular weights. The samples were filtered through polytetrafluoroethylene (PTFE) syringe filters with a pore size of 0.2 μm .

5 Single-angle dynamic light scattering (DLS) and zeta potential measurements were performed on a Zetasizer Ultra (Malvern Panalytical Ltd.) at an angle of 173° and a wavelength of 633 nm at 25 °C. The measurements were done using disposable micro polystyrene cuvettes (Carl Roth GmbH & Co. KG, Germany). Size distribution (intensity weighted) histograms were calculated based on the autocorrelation function of samples using automated position seeking and attenuator selection at multiple scans, with
10 fluorescence filter. The samples were filtered through 0.2 μm GHP membrane filters (Pall Corporation, Port Washington, USA).

Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy was performed on a FT/IR-4600 spectrometer (Jasco Corporation) equipped with a Jasco
15 ATR Pro ONE unit using Jasco spectra manager 2.15.18 for data analysis.

Synthesis of 3'-TBDMS-IUdR



20 *1-((2R,4S,5R)-4-((tert-butyl dimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-iodopyrimidine-2,4(1H,3H)-dione*

In a flask equipped with a stirring bar, unprotected IUdR (354 mg) was added and dissolved in anhydrous DMF (10 mL) and cooled down to 0 °C. After this, TBDMS-Cl (302 mg, 2.0 mmol, 2.0 equiv.) and imidazole (136 mg, 2.0 mmol, 2.0 equiv.) was added to the stirring reaction mixture. The reaction was then allowed to warm up to
25 room temperature for 2 hours, and monitored by TLC. After complete consumption of the starting material, the crude was diluted with EtOAc (20 mL) and extracted with LiCl in H₂O (20 mL, 1M) three times to remove excess DMF. The organic layers were collected, dried with MgSO₄, filtered and concentrated *in vacuo* to give intermediate *bis*-3',5'-TBDMS-IUdR () as crude product. This crude can be optionally run over a

short plug of silica (2% MeOH in DCM) to remove some of the impurities. The collected intermediate product was then concentrated and used directly. Hereafter the intermediate crude was placed inside a round bottom flask, equipped with a stirring bar and dissolved into anhydrous MeOH (10 mL). The solution was cooled down to -10 °C (with a NaCl ice bath), and stirred for 10 minutes. Hereafter, acetyl chloride (15 μL, 0.2 mmol, 0.1 equiv.) was added dropwise and the mixture was stirred, sealed and allowed to warm up to 0 °C and stirred for 3 hours. The reaction was quenched with sat. NaHCO₃ in H₂O and diluted with EtOAc, extracted with 1 M HCl, NaHCO₃ in H₂O and brine. The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was further purified by column chromatography (2% MeOH in DCM), which afforded the title compound as an off-white solid (40-65% yield).

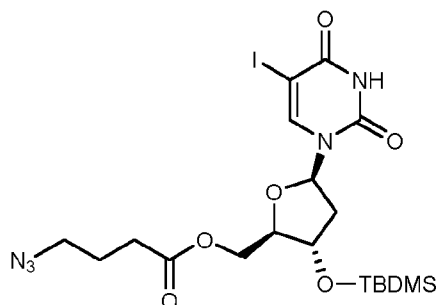
TLC (5% MeOH in DCM) R_f = 0.22, (25% EtOAc in Hexane) R_f = 0.12.

¹H-NMR (400 MHz, CDCl₃) δ 9.17 (s, 1H), 8.22 (s, 1H), 6.16 (t, J = 6.4 Hz, 1H), 4.48 (td, J = 5.1, 3.5 Hz, 1H), 3.96 (dt, J = 6.0, 2.9 Hz, 2H), 3.79 (d, J = 11.6 Hz, 1H), 2.55 (s, 1H), 2.32 – 2.22 (m, 2H), 0.88 (s, 9H), 0.08 (s, 6H).

¹³C-NMR (101 MHz, CDCl₃) δ 160.28, 150.07, 146.00, 87.95, 86.99, 71.47, 68.19, 61.84, 41.44, 25.83, 18.07, -4.56, -4.73.

MS (LC-ESI) calculated for C₁₅H₂₆I N₂O₅Si [M+H] 469.06, found 469.45 [M+H], 491.45 [M+Na], 937.30 [2M+H].

Synthesis of 3'-TBDMS-IUdR-N₃.



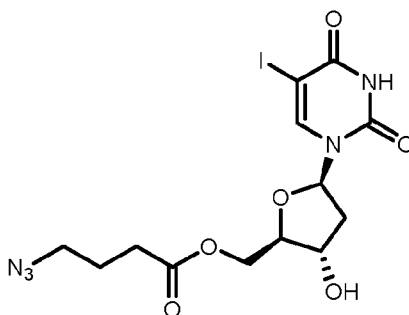
((2R,3S,5R)-3-((tert-butyl dimethylsilyl)oxy)-5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl 4-azidobutanoate

In a flask equipped with a stirring bar, 1-((2R,4S,5R)-4-((tert-butyl dimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-iodopyrimidine-2,4(1H,3H)-dione (3'-OTBDMS-IUdR) (468 mg, 1 mmol), 4-azidobutanoic acid (260 mg, 2 mmol, 2 equiv.) was added and dissolved in DMF (15 mL). After this, the mixture was cooled down to 0 °C and

DCC (216 mg, 1.05 mmol, 1.05 equiv.) was added in a single portion, and a single grain of DMAP (10 mg, 0.01 mmol) was added. This mixture was sealed with a rubber septum, the atmosphere was replaced with argon, and the mixture was stirred at 0 °C for 3 hours. After 3 hours, the reaction mixture was allowed to warm up to room temperature and stirred for another 18 hours. After complete consumption of the starting material, the reaction was diluted with 1M LiCl in H₂O, transferred to an extraction funnel, and then extracted with EtOAc, three times. The combined organic layers were collected and dried over MgSO₄ and then concentrated under reduced pressure and used directly without any further purification.

10

Synthesis of IUdR-N₃



((2R,3S,5R)-3-hydroxy-5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl 4-azidobutanoate.

15 A round-bottom flask was equipped with a stirring bar and charged with 3'-TBDMS-IUdR-N₃ (250 mg, 0.44 mmol), prepared according to the above procedure, and dissolved into dry THF (10 mL). The mixture was cooled down to 0 °C, using an ice-bath. To this mixture was added dropwise a solution of TBAF in THF (1M, 1 mL, 1 mmol) while stirring at 0 °C. After 10 minutes, the ice-bath was removed, and the mixture was allowed to warm up to room temperature. The reaction was monitored by TLC (10% MeOH in DCM), until all starting material was consumed. If full consumption was not reached after 2 hours stirring at room temperature, an extra portion of TBAF in THF (1 M, 0.25 mL, 0.25 mmol) was added dropwise. After complete consumption of the starting material, the reaction mixture was diluted with EtOAc (25 mL) and transferred into an extraction funnel. The organic mixture was washed consecutively with 1 M HCl, sat. NaHCO₃ in H₂O and brine. The combined organic layers were collected and dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was then further purified by SiO₂ column chromatography (5% MeOH in DCM) to give the title product as a glassy substance (200

mg, 95% yield). The compound can be crystallized using CHCl_3 , to give a clear white solid powder.

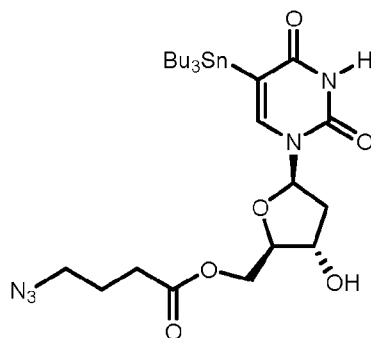
TLC (5% MeOH in DCM) $R_f = 0.15$.

5 $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.89 (s, 1H), 6.12 (t, $J = 6.4$ Hz, 1H), 4.32 (dd, $J = 12.3, 4.1$ Hz, 1H), 4.28 – 4.19 (m, 3H), 4.07 (q, $J = 3.8$ Hz, 1H), 3.36 – 3.28 (m, 6H), 2.50 (q, $J = 7.1$ Hz, 3H), 2.36 (ddd, $J = 13.8, 6.4, 4.3$ Hz, 1H), 2.05 (dt, $J = 13.5, 6.5$ Hz, 1H), 1.88 (p, $J = 7.0$ Hz, 2H).

10 $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ 172.68, 160.73, 150.19, 144.37, 85.80, 84.45, 70.53, 70.20, 68.65, 63.76, 50.47, 41.37, 31.18, 24.10.

MS (LC-ESI) Calculated for $\text{C}_{13}\text{H}_{16}\text{N}_5\text{O}_6$ $[\text{M}+\text{H}]$ 465.01, found 465.45 $[\text{M}+\text{H}]$, 487.45 $[\text{M}+\text{Na}]$.

Synthesis of $\text{Bu}_3\text{Sn-IUdR-N}_3$



((2R,3S,5R)-5-(2,4-dioxo-5-(tributylstannyl)-3,4-dihydropyrimidin-1(2H)-yl)-3-hydroxytetrahydrofuran-2-yl)methyl 4-azidobutanoate.

20 A flask with IUdR- N_3 (93.5 mg, 0.2 mmol, 1 equiv.) in 1,4-dioxane (2 mL) and bis(triphenylphosphine) palladium dichloride (6 mg, 2.5 mol%) was prepared. The vial was sealed with a rubber septum, and argon bubbled through the solvent for 10 minutes. To this solution was added, 1,1,1,2,2,2-hexabutyldistannane (256 mg, 0.44 mmol, 2.2 equiv.). The reaction mixture was heated to 120 °C and stirred for 12 hours. After this, the reaction mixture was cooled down to room temperature, diluted with EtOAc and filtered over a pad of Celite (0.5 cm). The combined organic layers were concentrated *in vacuo*, and further purified by silica column chromatography (0% - 5% MeOH in DCM) to obtain the title compound 3 as an off-white solid (75% yield).

25

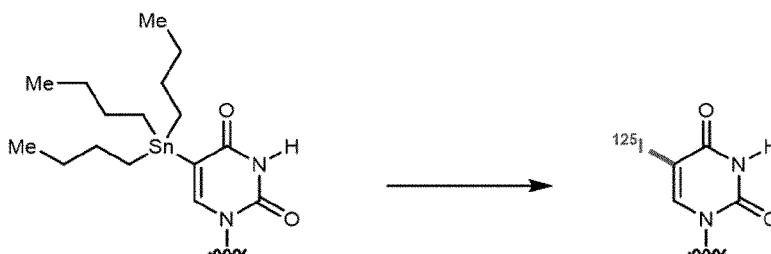
TLC (5% MeOH in DCM) $R_f = 0.25$.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.89 (s, 1H), 6.12 (t, $J = 6.4$ Hz, 1H), 4.32 (dd, $J = 12.3, 4.1$ Hz, 1H), 4.28 – 4.19 (m, 3H), 4.07 (q, $J = 3.8$ Hz, 1H), 3.36 – 3.28 (m, 6H), 2.50 (q, $J = 7.1$ Hz, 3H), 2.36 (ddd, $J = 13.8, 6.4, 4.3$ Hz, 1H), 2.05 (dt, $J = 13.5, 6.5$ Hz, 1H), 1.88 (p, $J = 7.0$ Hz, 2H).

5 $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ 172.67, 160.77, 150.17, 144.35, 85.85, 84.43, 70.52, 70.22, 68.65, 63.76, 50.47, 41.37, 40.25, 39, 11, 31.18, 24.10, 22.09.

MS (LC-ESI) Calculated for $\text{C}_{13}\text{H}_{16}\text{N}_5\text{O}_6$ $[\text{M}+\text{H}]$ 629.37, found 630.05 $[\text{M}+\text{H}]$, 651.35 $[\text{M}+\text{Na}]$.

10 **Synthesis of $[\text{}^{125}\text{I}]\text{IUdR-N}_3$**



((2R,3S,5R)-3-hydroxy-5-(5-(iodo- ^{125}I)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl 4-azidobutanoate.

In a 2 mL HPLC-vial equipped with a small stirring bar was added a mixture of Bu_3Sn -IUdR derivative (0.5 mg, 0.97 – 0.60 μmol) in DMF (100 μL). To this was added in a sequential manner, acetic acid (5 μL), chloramine-T solution (1 mg, 10 μL of H_2O), and then $[\text{}^{125}\text{I}]\text{NaI}$ in 0.1 M NaOH (2 - 10 MBq for method optimization, 20 - 50 MBq for primary use, anything above 50 MBq follows a slightly adapted procedure). If the reaction mixture was non-homogeneous, an extra amount of DMF solvent was added (50 μL). The vial was sealed with a screw cap and stirred for 30 min at 25 $^\circ\text{C}$. After this, radio-TLC analysis was done to check consumption of the $[\text{}^{125}\text{I}]\text{NaI}$ (RCC_1). Upon completion, KI in H_2O (10 μL , 0.1 M) was added, and the reaction was stirred for another 10 min at 25 $^\circ\text{C}$. Hereafter the reaction was terminated using a sodium meta-bisulfite solution (2 mg in 20 μL of H_2O). After this, an aliquot was taken for radio-HPLC or radio-TLC analysis to give the radio chemical conversion of the reaction (RCC_2). Hereafter the reaction mixture was diluted with MeCN (2 mL), taken up and filtered through a pre-activated SiO_2 cartridge (Sep-Pak Silica Plus Light Cartridge, 129 mg Sorbent) to remove residual salts (RCC_3). After this the product can be further purified by removing most of the MeCN under a flow of nitrogen at 65 $^\circ\text{C}$, followed by redissolving the material in H_2O (2-50 mL, see specific compound data for details) followed by trapping on a pre-activated C18 cartridge (Sep-

Pak C18 Plus Short Cartridge, 360 mg Sorbent). The C18 cartridge was then eluted with a series of solutions to release the radio-iodinated compound; in consecutive order H₂O (2 mL), 20% MeCN in H₂O (2 mL), 70% MeCN in H₂O (2 mL), 100% MeCN (2 mL) or 100% EtOH (2 mL) were slowly eluted over the C18 cartridge (depending on the specific
5 compound, see details below). All solutions were collected individually and analysed by radio-TLC. The desired fractions were collected and concentrated using a steady flow of N₂ (1 L min⁻¹) at 65 °C, with several ventilation needles onto the vial. The obtained dried compound was further analysed and used directly (see specific compound data below for details).

10

In cases where RCC₁ was less than 75%, as judged by radio-TLC analysis; additional DMF, AcOH, and chloramine-T solution can be added to further the reaction.

Synthesis of Homopolymers

15

Poly(5-benzyl-L-glutamic acid) (pGlu(OBn)). The synthesis was adapted from literature (Steen, et al., 2020). Prior to solvation in dry dimethylformamide (DMF, 5 mL) 5-benzyl-L-glutamate N-Carboxyanhydride (Glu(OBn)NCA) (CAS: 3190-71-4) (480 mg, 1.82 mmol) was transferred into a pre-dried Schlenk flask equipped with a stir bar under nitrogen counter flow. The Glu(OBn)NCA was dried under high vacuum, dissolved and
20 a stock solution of neopentylamine (1.59 mg, 0.02 mmol, 1 eq) in absolute DMF (500 µL) was added to the solution to initiate the polymerization. The mixture was allowed to stir at 0 °C under nitrogen atmosphere for 72 h. Progress of the reaction was monitored by FTIR Spectroscopy and showed disappearance of the NCA peaks (1855 and 1788 cm⁻¹). After completion of the polymerization the amine end group was capped by adding
25 acetic anhydride (26.9 mg, 0.09 mmol, 5 eq) and triethylamine (18.5 mg, 0.18 mmol, 10 eq) to the solution and allowed to stir overnight at room temperature. The polymer was precipitated into diethyl ether and centrifuged (5000 rpm at 4 °C for 10 min). After the liquid fraction was discarded the polymer was resuspended in diethyl ether and centrifuged again. This step was repeated one more time and the polymer was dried
30 under high vacuum to afford a colorless solid (362 mg, 90% yield).

¹H NMR (400 MHz, CD₂Cl₂) δ 8.42 (s, 60H), 7.58 – 7.04 (m, 435H), 5.08 (s, 170H), 4.01 (s, 82H), 2.50 (d, J = 136.3 Hz, 327H), 0.94 (d, J = 11.0 Hz, 9H).

Polyglutamic Acid, pGlu(COOH). Deprotection was adapted from literature (Steen, et al., 2020). pGlu(OBn)₁₀₀ (263 mg) was transferred in a Schlenk flask equipped with a stir bar and dissolved in trifluoroacetic acid (TFA) (2.5 mL). Hydrobromic acid (HBr, 48% v/v) (240 μ L, 2 eq) was added to the mixture dropwise and the solution was allowed to stir
5 overnight at room temperature. The polymer was precipitated into cold diethyl ether and centrifuged (5000 rpm at 4 °C for 10 min). After the liquid fraction was discarded the polymer was resuspended in diethyl ether and again centrifuged. This step was repeated one more time. The crude product was dissolved in water and lyophilized to obtain a colorless solid of polyglutamic acid (pGlu(COOH)) (105 mg, 92% yield).

10 ¹H NMR (400 MHz, D₂O) δ 4.18 (dd, J = 9.0, 5.5 Hz, 112H), 2.13 (tdd, J = 15.3, 12.2, 7.9 Hz, 232H), 1.97 – 1.72 (m, 233H), 0.75 (s, 9H).

Polysarcosine, pSar. Synthesis was carried out according to literature in a similar way as previously described (Steen, et al., 2020). N-Methylglycine (Sarcosine, sar) N-carboxyanhydride (NCA) (1077.3 mg, 9.36 mmol) was transferred into a pre-dried Schlenk
15 flask equipped with a stir bar under nitrogen counter flow. The Sar-NCA was dried under high vacuum and dissolved in dry DMF (10 mL). A stock solution of neopentylamine (8.2 mg, 0.09 mmol, 1 eq) in DMF (0.5 mL) was added to the Sar-NCA to initiate the polymerization. Progress of the reaction was detected by FTIR Spectroscopy and showed disappearance of the NCA peaks (1855 and 1788 cm^{-1}). After completion of the
20 polymerization the mixture was precipitated into diethyl ether and centrifuged (5000 rpm at 4 °C for 10 min). The crude product was resuspended in diethyl ether and again centrifuged. This procedure was repeated for one more time. The polymer was dried, dissolved in water and lyophilized to obtain a colorless fluffy polymer (662.5 mg, 98 % yield).

25 ¹H NMR (400 MHz, DMSO) δ 4.51 – 3.81 (m, 215H), 3.17 – 2.56 (m, 331H), 0.85 (d, J = 9.6 Hz, 9H).

DBCO Functionalization

DBCO-pGlu(COOH). In a Schlenk flask equipped with a stir bar, was added pGlu(COOH) (88.3 mg, 0.01 mmol) dissolved in MQ water (8 mL) and NaHCO₃ (339.9 mg, 3.39 mmol,
30 5 eq) as well as 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl morpholinium chloride (DMTMMCl) (187.9 mg, 0.67 mmol, 1 eq) were added to the solution. Hereafter, azadibenzocyclooctyne-amine (DBCO-NH₂) (56.28 mg, 0.20 mmol, 0.3 eq) was

dissolved in DMSO (1.6 mL) and added to the reaction mixture while stirring. The solution was allowed to stir at room temperature for 24 h before adding additional DMTMMCl (187.9 mg, 0.67 mmol, 1 eq). The crude product was purified using dialysis against a 6 – 8 kDa molecular weight cut-off (MWCO) for 3 days against DMSO with daily change of the solvent. After 3 days the product was dialysed against MQ water for one day and lyophilized under obtaining a colorless solid (180.6 mg, 83 % yield).

¹H NMR (600 MHz, DMSO) δ 7.77 – 6.90 (m, 134H), 5.33 (s, 2H), 5.02 (d, J = 15.4 Hz, 8H), 4.01 (d, J = 95.3 Hz, 20H), 2.28 – 1.62 (m, 68H), 0.93 – 0.72 (m, 9H).

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Polysarcosinylation

DBCO-PeptoBrush(PB). DBCO-pGlu(COOH) functionalized backbone (22.7 mg, 0.001 mmol, 1 eq), polysarcosine (357.9 mg, 0.04 mmol, 0.4 eq) and NaHCO₃ (85.8 mg, 1.02 mmol, 10 eq) were transferred into a Schlenk flask equipped with a stir bar and dissolved in a mixture of MQ water (7 mL) and DMSO (1.4 mL). To the solution DMTMMCl (28.3 mg, 0.12 mmol, 1 eq) was added and the mixture was allowed to stir at room temperature for 24 h. After 24 h, additional DMTMMCl (28.3 mg, 0.12 mmol, 1 eq) was added and stirred overnight. Progress of the reaction was monitored by size exclusion chromatography (SEC) analysis. The solution was purified using spinfiltration (MWCO of 20 kDa, volume of 2 mL, 2 x 30 min, 5000 rpm). After centrifugation steps the filtrates were removed and the crude concentrated product was redissolved in MQ water until the volume of 2 mL and centrifuged again. The procedure was repeated for 10 times. The product was lyophilized under obtaining the purified final PeptoBrush product (120 mg, 60 % yield) designated PB-DBCO.

25

[¹²⁵I]IUdR radiolabelling of peptobrush dibenzoazacyclooctyne (PB-DBCO) via Copper-free click reaction (synthesis of [¹²⁵I]IUdR-PB).

3 MBq of [¹²⁵I]IUdR-N₃ in 200 μL MeCN was transferred to a HPLC vial and dried down under argon flow, then 50 μL of DMSO was added to the HPLC vial and vomit gently. 2 mg of PB-DBCO in 200 μL PBS was added to the reaction vial. The vial was then incubated at 40 °C degrees for 60 min. Withdraw an aliquot (1 μL) from the crude product and apply it onto a TLC plate that using 10% MeOH in DCM as mobile phase. The TLC plate was then analysed using the Cyclone. After 1h, 300 μL of PBS was added to the crude reaction before applied to a size exclusion Minitrap column. Fractions were collected every 0.5 mL, for a total of 5 mL. Fractions 2 and 3 were pulled together as the

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Esterase mediated release of [¹²⁵I]UdR from [¹²⁵I]UdR-PB

To characterize [¹²⁵I]UdR release from [¹²⁵I]UdR-PB, a series of experiments were carried out in PBS buffer (pH = 7.4) at 37 °C, with and without the presence of esterase. The release profile of [¹²⁵I]UdR from [¹²⁵I]UdR-PB in the presence of added esterase was monitored by radio-TLC (**Figure 3a**). In the first 24 hours, 4.4 % of [¹²⁵I]UdR was released from the polymer. This release of [¹²⁵I]UdR continued, culminating in a 53% release after 480 hours. On the other hand, the release of [¹²⁵I]UdR from [¹²⁵I]UdR-PB without esterase, was also investigated (**Figure 3b**). The first 24 hours showed a much lower 1.9% release of [¹²⁵I]UdR from [¹²⁵I]UdR-PB. By the 480-hour mark, the release of [¹²⁵I]UdR had reached 22.8%, again indicating slower release. Over the 480-hour period, the amount of released [¹²⁵I]UdR in esterase-rich environment was roughly 2 times that of the non-esterase control group, with an increase in the release of [¹²⁵I]UdR from [¹²⁵I]UdR-PB by 1.6-fold. This relatively moderate difference in release rate was attributed to the brush-like topology of the [¹²⁵I]UdR-PB polymer, rendering a dynamic but sterically hindered environment. The densely packed brush structure was thought to act as a physical barrier slowing down and limiting the access of esterases to the ester linkers of [¹²⁵I]UdR.

Release of [¹²⁵I]UdR from [¹²⁵I]UdR-PB in brain homogenate

To obtain brain homogenate (BH), rats were administered subcutaneous ketamine (100 mg/kg) and dexmedetomidine (0.5 mg/kg) for anesthesia. When the loss of response to painful stimuli was confirmed, the rats were then euthanized and their brains were promptly extracted and divided into four sections. Each section was then homogenized in 5 mL of PBS using a homogenizer. The resulting BH samples were stored at a temperature of -80 °C until further utilization.

Then BH (200 µL) was diluted 1:1 (v/v) with PBS buffer (200 µL) in a HPLC vial. Penicillin-streptomycin solution (6 µL, 10,000 U/mL) was added, followed by [¹²⁵I]UdR-PB dispersion in PBS buffer (200 µL, 50 kBq). The vial was continuously stirred at 37 °C. At various time intervals, 0, 0.5, 1, 3, 6, 24, 48, 120, and 480 hours, aliquots of 5 µL were extracted from the vials. These aliquots were immediately mixed with 15 µL of tetrahydrofuran (THF) to quench the enzymatic hydrolysis and disrupt the brush structure. The resulting mixture was then subjected to analysis using radio-TLC to quantify the ratios of [¹²⁵I]UdR, [¹²⁵I]UdR-PB as well as any unidentified spots ('others').

DNA incorporation of [¹²⁵I]UdR from [¹²⁵I]UdR-PB

The integration of [¹²⁵I]UdR as released from [¹²⁵I]UdR-PB with (+) and without (-) esterase (E), into the DNA of dividing LN229 cells was explored. (Figure 4). LN229 is a human brain glioblastoma cell line.

5 Briefly, LN-229 cells were grown in Dulbecco's modified Eagle's medium (DMEM) growth medium with a pH = 7.4, supplemented with 5% fetal bovine serum (FBS), 100 U/mL of penicillin, 2 mM glutamine, and 100 µg/mL of streptomycin according to supplier instructions. Cell cultures were maintained in flasks and grown at 37 °C in a humidified atmosphere of 5% CO₂ in air. LN229 cells were seeded on 6-well plates at a density of
10 0.5×10⁶ cells per well before placed in an incubator for 24 hours incubation. Following this, 3 mL of PB-[¹²⁵I]UdR (5 kBq/mL) and esterase-containing PB-[¹²⁵I]UdR (5 kBq/mL, 0.1 U/mL of esterase) were added to each plate in triplicate. The plates were subsequently incubated for either 4 or 24 hours. At the end of the incubation period, the cellular DNA was collected using the DNA isolation protocol provided by the E.Z.N.A.®
15 Tissue DNA Kit. A 20 µL aliquot of each DNA solution was then utilized for liquid scintillation counting (LSC) measurements. The degree of DNA integration was quantified based on radioactivity measured by liquid scintillation counting (LSC), referred to the percent incorporated from the theoretical maximum as IP% (Figure 4).

20 The IP% of [¹²⁵I]UdR-PB+E after 4 hours incubation was 0.48% and increased to 1.0% after 24 hours incubation. This also revealed the accelerated rate of release of [¹²⁵I]UdR from [¹²⁵I]UdR-PB with the addition of esterase. The results also indicated that even in the absence of esterase, [¹²⁵I]UdR-PB can release a small amount of active [¹²⁵I]UdR which then undergoes incorporation into DNA, from 0.22% to 0.53% at 4 and 24 h.

25 A comparison between the groups with and without esterase shows a clear difference in IP% after 24 hours. In general, these results show that the incorporation of [¹²⁵I]UdR into DNA is possible and increases over time in both test groups. At the 24 hours time point, the incorporation of [¹²⁵I]UdR into DNA with added esterase approximately
30 doubles that of the non-esterase group which is in good agreement with the *in vitro* release data (Figure 3). Moreover, it is expected and made plausible that the IP% difference between groups with and without esterase would become increasingly distinct as time progressed (Figure 4).

35 **Cell viability study**

To assess the cytotoxicity of PB- ^{125}I IUdR against LN-229 cells, an in vitro cell viability assay is performed using CellTiter-Blue from Promega. LN-229 cells are seeded in 96-well plates at a density of 300 cells per well and incubated for 24 hours at 37 °C. The samples are divided into five groups for cytotoxicity evaluation: (1) PB- ^{125}I IUdR, (2) PB- ^{125}I IUdR+esterase, (3) ^{125}I IUdR- N_3 , (4) ^{125}I IUdR, and (5) PB. Appropriate amounts of PB- ^{125}I IUdR, ^{125}I IUdR- N_3 (dissolved in DMSO), and ^{125}I IUdR are diluted with complete DMEM culture medium to achieve the desired final radioactivity levels of 0.23, 0.49, 0.98, 1.97, 3.75, 7.5, 15, and 30 kBq/mL. The esterase concentration in group (2) will be 0.1 U/mL. The PB group has concentrations of 0.0156, 0.0312, 0.0625, 0.125, 0.25, 0.5, 1, and 2 mg/mL. The plates are incubated for 7 days before being mixed with CellTiter-Blue solution (20 μL per well). Following a 4-hour incubation, the absorbance measured using a microplate reader at 570 and 600 nm. The results are expressed as the percentage of cell viability, calculated as (mean optical density (OD) of treated cells/mean OD of untreated cells) \times 100%.

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In vivo biodistribution (SPECT/CT imaging)

Material and Methods

One female Sprague-Dawley (250 g, breed in-house at the Biomedical Laboratory, University of Southern Denmark) was anesthetized with a mixture of hypnorm/midazolam subcutaneously. The rat was placed in a stereotactic frame (Model 900, David Kopf Instruments, Tujunga, USA). Following this, a midline scalp incision was made and a burr hole was made one mm anteriorly and two mm laterally to bregma and 25 μL ^{125}I IUdR-PB (approx. 256 kBq) was injected slowly. SPECT/CT scans were performed with a Siemens Inveon small-animal scanner. For imaging, the rat was anesthetized with 1.5-2% isoflurane in 100% oxygen. The rat was scanned 1 hour and 24 hours post injection.

20
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Results

The 1 hour scan of ^{125}I IUdR-PB demonstrate a high retention in the brain and little uptake in thyroid gland and stomach (**Figure 5A**). The 24 hour scan, likewise, demonstrates retention in the brain, and a higher uptake in thyroid and stomach compared to the early scan (**Figure 5B**). Uptake in thyroid gland and stomach are expected within the normal biodistribution of iodine in rodents/humans due to the expression of the sodium-iodide symporter in the thyroid gland and stomach lining.

30
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Conclusion

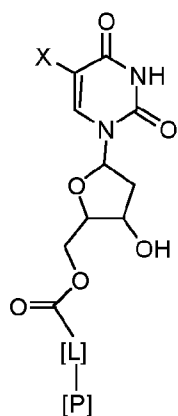
The results demonstrate high retention of [¹²⁵I]UdR-PB in the brain of a non-tumour bearing rat at 1 hour and moderate retention at 24 hours post intracranial injection.

5 References

E. J. L. Steen et al., ACS Nano, 2020, 14, 1, 568–584,
<https://doi.org/10.1021/acsnano.9b06905>

Claims

1. A pharmaceutical composition for use in a method of treatment of cancer, said composition comprising:
- 5 a. a polymer [P];
- b. a cytotoxic agent; and
- c. a linker [L], which links the cytotoxic agent to the polymer, wherein the cytotoxic agent is of formula (I) or a derivative thereof, or a pharmaceutically acceptable salt thereof



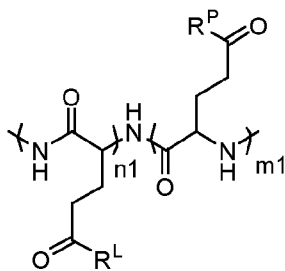
10 formula (I),

wherein

X is defined as $-R^1-R^A$, wherein R^1 is selected from the group consisting of $-C_{1-3}$ alkyl-, $-C_{1-3}$ haloalkyl-, $-C_{2-4}$ alkenyl-, $-C_{3-6}$ cycloalkyl-, $-C_{3-6}$ cycloaryl-, $-C_{3-6}$ cycloheteroaryl-, $-O-$, $-NH-$, $-C(O)-$, $-C(O)-O-(C_{1-6}$ alkyl)-, $-phenyl-$, $-O-phenyl$, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope;

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[P] comprises formula (II-b):

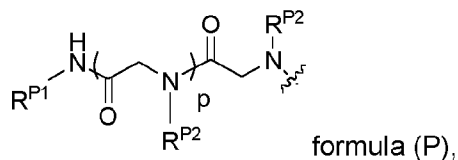


formula (II-b),

wherein

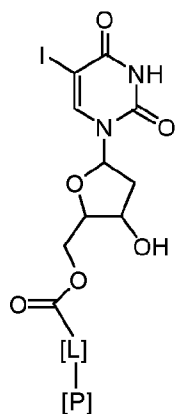
- 20 R^L denotes attachment to formula (I),
- n_1 is an integer from 10 to 500,
- m_1 is an integer from 10 to 500,

R^P is according to formula (P):

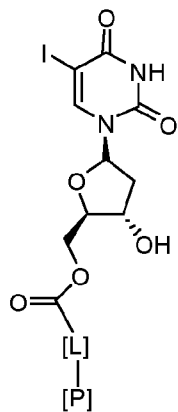


wherein R^{P1} and R^{P2} are each independently selected from C₁-C₄ alkyl and p is an integer from 10 to 500.

- 5 2. The pharmaceutical composition for use according to claim 1, wherein R¹ is absent and R^A comprises a radioisotope of a halogen, such as ¹²³I, ¹²⁴I, ¹²⁵I, ⁷⁷Br, ⁷⁶Br, ^{80m}Br, ⁸⁰Br, ¹²⁶I, ¹³¹I, ¹⁸F, or ²¹¹At.
- 10 3. The pharmaceutical composition for use according to any one of the preceding claims, wherein R¹ is absent and R^A comprises an Auger electron-emitting radioisotope.
- 15 4. The pharmaceutical composition for use according to any one of the preceding claims, wherein R¹ is absent and R^A comprises or consists of a radioisotope, which is ¹²³I, ¹²⁵I, or ⁷⁷Br.
- 15 5. The pharmaceutical composition for use according to any one of the preceding claims, wherein R¹ is absent and R^A consists essentially of a radioisotope of iodine.
- 20 6. The pharmaceutical composition for use according to any one of the preceding claims, wherein the compound of formula (I) is



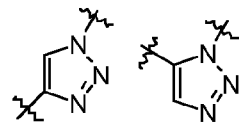
- 20 7. The pharmaceutical composition for use according to any one of the preceding items, wherein the compound of formula (I) is

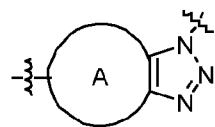


wherein [L] and [P] are as defined in claim 1.

8. The pharmaceutical composition for use according to any one of the preceding claims, wherein R^A is ^{123}I or ^{125}I .
9. The pharmaceutical composition for use according to any one of the preceding claims, wherein R^A is ^{125}I .
10. The pharmaceutical composition for use according to any one of the preceding claims, wherein R^A is ^{123}I .
11. The pharmaceutical composition for use according to any one of the preceding claims, wherein R^A is not of natural abundance.
- 10 12. The pharmaceutical composition for use according to any one of the preceding claims, wherein all elements of formula (I) are of natural abundance except for R^A which is not of natural abundance.
13. The pharmaceutical composition for use according to any one of the preceding claims, wherein the level of isotope enrichment in formula (I) with isotopes that are not of natural abundance is 2% or more, 5% or more, 10% or more, 20% or more, 50% or more, 75% or more, 90% or more, or 95% or more.
- 15 14. The pharmaceutical composition for use according to any one of the preceding claims, wherein the level of isotope enrichment in formula (I) with isotopes that are not of natural abundance is 95% or more.
- 20 15. The pharmaceutical composition for use according to any one of the preceding claims, wherein the level of isotope enrichment in formula (I) with isotopes that are not of natural abundance is 95%, 96%, 97%, 98%, 99% or 100%.

16. The pharmaceutical composition for use according to any one of the preceding claims, wherein [L] comprises a triazole moiety formed by the click-reaction between an alkyne group and an azide.
17. The pharmaceutical composition for use according to any one of the preceding claims, wherein [L] comprises a triazole moiety formed by the copper-free click-reaction between an alkyne group and an azide.
18. The pharmaceutical composition for use according to any one of the preceding claims, wherein [L] comprises or consists of a bivalent, saturated or unsaturated, straight or branched, C₂-C₁₂ hydrocarbon chain wherein one or more methylene groups are individually and optionally replaced by one or more of the groups selected
- from: -O-, -N(H)-, -N(R^{L1})-, -OC(=O)-, -C(=O)O-, -C(=O)-, -N(H)C(=O)-, -N(R^{L1})C(=O)-, -C(=O)N(H)-, -NHC(O)NH-, -NHC(O)O-, -C(=O)N(R^{L1})-, -S-, -S(=O)-, -S(=O)₂-, -N(R^{L1})S(=O)₂-, -S(=O)₂N(R^{L1})-; an optionally substituted aromatic group; an optionally substituted carbocycle; an optionally substituted

heterocycle; an optionally substituted aromatic heterocycle,  and

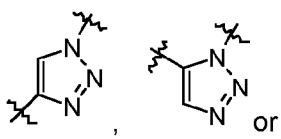
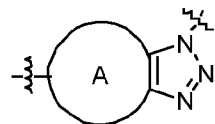


; wherein R^{L1} is selected from the group consisting of C₁₋₅ alkyl;

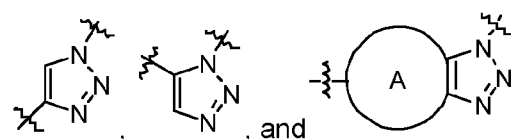
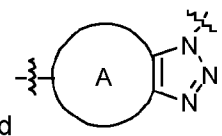
and

A comprises or consists of any monocyclic or polycyclic carbocycle or heterocycle.

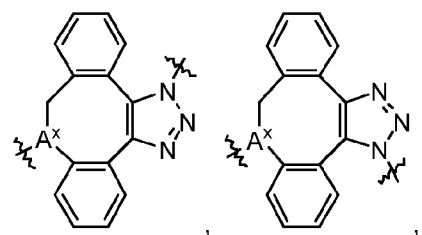
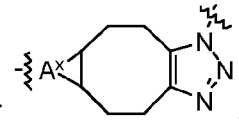
19. The pharmaceutical composition for use according to any one of the preceding claims, wherein [L] comprises or consists of a bivalent, saturated or unsaturated, straight or branched, C₂-C₁₂ hydrocarbon chain, such as a C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ or C₁₂ hydrocarbon chain, wherein one or more methylene groups such as 1, 2, 3, 4, or 5 methylene groups are each individually and optionally replaced by one or more of the groups selected from -O-, -N(H)-, -N(R^{L1})-, -OC(=O)-, -C(=O)O-, -C(=O)-, -N(H)C(=O)-, -N(R^{L1})C(=O)-, -C(=O)N(H)-, -C(=O)N(R^{L1})-, -S-, -S(=O)-, -S(=O)₂-, -N(R^{L1})S(=O)₂-, -S(=O)₂N(R^{L1})-, -CH₂-CH₂-O-, an optionally substituted

carbocycle; an optionally substituted heterocycle,  or ; wherein R^{L1} is C₁₋₅ alkyl and A comprises or consists of any monocyclic or polycyclic carbocycle or heterocycle.

20. The pharmaceutical composition for use according to any one of the preceding claims, wherein [L] comprises one selected from the group consisting of:

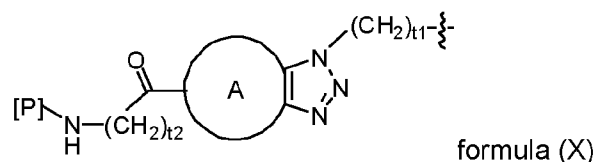
, and , wherein A comprises or consists of any monocyclic or polycyclic carbocycle or heterocycle.

21. The pharmaceutical composition for use according to any one of the preceding claims, wherein [L] comprises:

, or , wherein

A^x is either -CH- or N.

22. The pharmaceutical composition for use according to any one of the preceding claims, wherein [L] is according to formula (X):

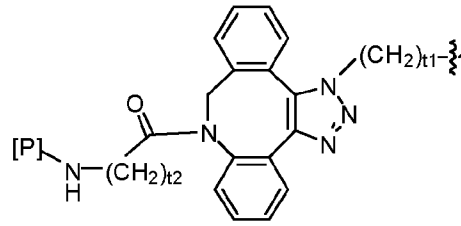


15 wherein A comprises or consists of any monocyclic or polycyclic carbocycle or heterocycle; and

t₁ and t₂ are each integers individually selected from 1, 2, 3, 4, or 5.

23. The pharmaceutical composition for use according to any one of the preceding claims, wherein A comprises an 8-membered carbocycle or heterocycle.

24. The pharmaceutical composition for use according to any one of the preceding claims, wherein [L] is according to formula (X-I):

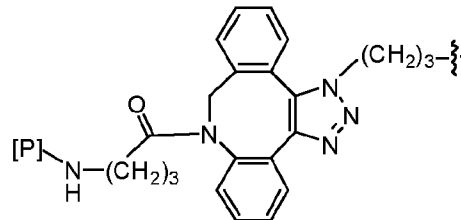


formula (X-I)

wherein each of t1 and t2 are each integers individually selected from 1, 2, 3, 4, or 5.

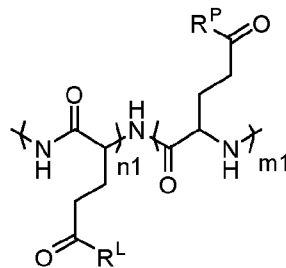
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25. The pharmaceutical composition for use according to any one of the preceding claims, wherein [L] is



26. The pharmaceutical composition for use according to any one of the preceding claims, wherein [P] comprises formula (II-b):

10



formula (II-b),

wherein

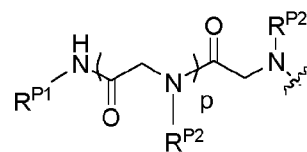
R^L denotes attachment to formula (I) and formula (I) is as defined in any one of the preceding claims;

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n1 is an integer from 10 to 500,

m1 is an integer from 10 to 500,

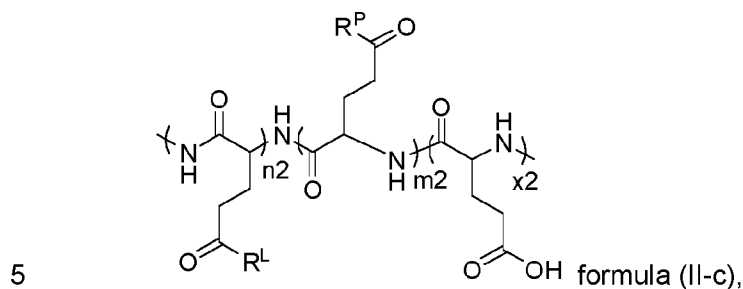
R^P is according to formula (P):



formula (P), wherein R^{P1} and R^{P2} are each independently

selected from C₁-C₄ alkyl and p is an integer from 10 to 500.

27. The pharmaceutical composition for use according to any one of the preceding claims, wherein [P] comprises formula (II-c):



wherein

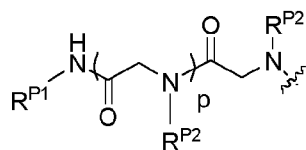
n₂ is an integer from 10 to 500,

m₂ is an integer from 10 to 500,

x₂ is an integer from 0 to 500,

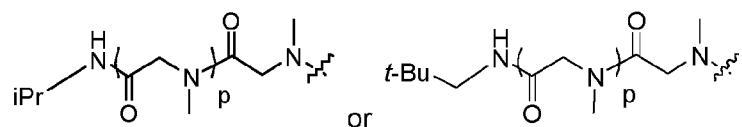
10 R^L denotes attachment to formula (I) and formula (I) is as defined in any one of the preceding claims,

R^P is according to formula (P):



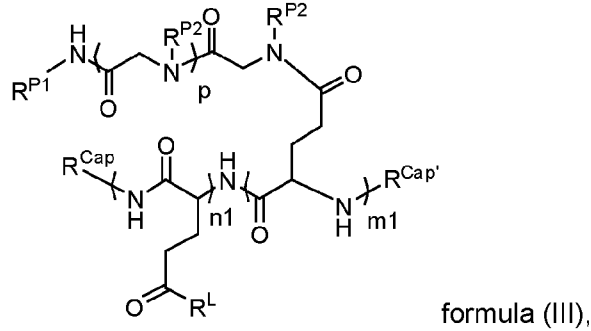
15 formula (P), wherein R^{P1} and R^{P2} are each independently selected from C₁-C₄ alkyl and p is an integer from 10 to 500.

28. The pharmaceutical composition for use according to any one of the preceding claims, wherein R^P is



20 wherein p is an integer from 10 to 500.

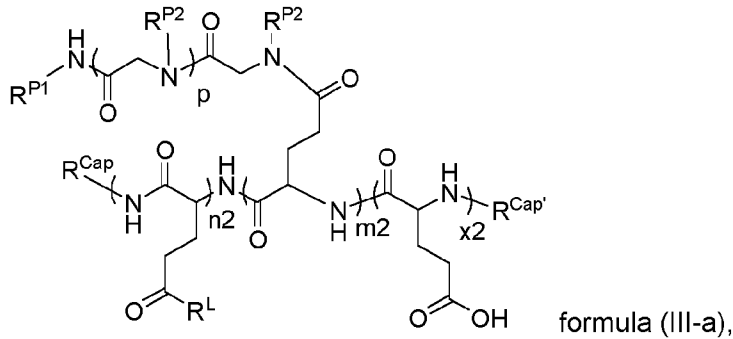
29. The pharmaceutical composition for use according to any one of the preceding claims, wherein [P] is according to formula (III),



wherein

- 5 n1 is an integer from 10 to 500,
 m1 is an integer from 10 to 500,
 p is an integer from 10 to 500,
 R^{P1} and R^{P2} are each independently selected from C₁-C₄ alkyl,
 R^{Cap} is a C₁-C₆ alkyl,
 10 R^{Cap'} is -C(O)-C₁₋₆alkyl or -C(O)-aryl; and
 R^L denotes attachment of formula (I) and formula (I) is as defined in any one of the preceding claims.

30. The pharmaceutical composition for use according to any one of the preceding claims, wherein [P] is according to formula (III-a),



wherein

- 20 n2 is an integer from 10 to 500,
 m2 is an integer from 10 to 500,
 x2 is an integer from 0 to 500,
 p is an integer from 10 to 500,

R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl,

R^{Cap} is a C_1 - C_6 alkyl,

$R^{Cap'}$ is $-C(=O)-C_{1-6}$ alkyl or $-C(=O)$ -aryl; and

R^L denotes attachment of formula (I) and formula (I) is as defined in any one of the preceding claims.

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31. The pharmaceutical composition for use according to any one of the preceding claims, wherein

($n_1 + m_1$) is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200; or

10

($n_2+m_2+x_2$) is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200.

32. The pharmaceutical composition for use according to any one of the preceding claims, wherein p is an integer from 10 to 1000, such as from 10 to 500, such as from 10 to 200.

15

33. The pharmaceutical composition for use according to any one of the preceding claims, wherein

the ratio of $n_1:m_1$ is approximately 0.1-3.0:7.0-9.9, such as approximately 0.5-1.5:8.5-9.5, such as about 1:9; or

20

the ratio of $n_2:(m_2+x_2)$ is approximately 0.1-3.0:7.0-9.9, such as approximately 0.5-1.5:8.5-9.5, such as about 1:9;

e.g. as determined by 1H -NMR by relation of signal of known protons.

34. The pharmaceutical composition for use according to any one of the preceding claims, wherein R^{P2} is C_1 alkyl, C_2 alkyl, C_3 alkyl or C_4 alkyl.

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35. The pharmaceutical composition for use according to any one of the preceding claims, wherein R^{P2} is methyl.

36. The pharmaceutical composition for use according to any one of the preceding claims, wherein R^{P1} is C_1 alkyl, C_2 alkyl, C_3 alkyl or C_4 alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or sec-butyl.

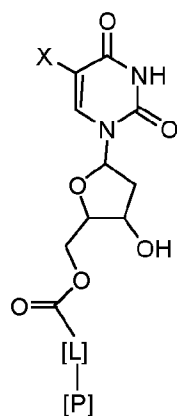
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37. The pharmaceutical composition for use according to any one of the preceding claims, wherein R^{Cap} is C_1 - C_5 alkyl, such as methyl, ethyl, propyl, butyl, isopropyl, sec-butyl, tert-butyl or neopentyl.

38. The pharmaceutical composition for use according to any one of the preceding claims, wherein R^{Cap'} is -C(=O)-C₁₋₆-alkyl or -C(=O)-aryl, such as -C(=O)-CH₃.
39. The pharmaceutical composition for use according to any one of the preceding claims, wherein the average molecular weight number (Mn) of the polymer is from 250 kg/mol to 500 kg/mol, such as from 250 kg/mol to 300 kg/mol, from 300 kg/mol to 350 kg/mol, from 350 kg/mol to 400 kg/mol, from 400 kg/mol to 450 kg/mol such as from 450 kg/mol to 500 kg/mol, e.g. as determined by size exclusion chromatography (SEC) .
40. The pharmaceutical composition for use according to any one of the preceding claims, wherein the cancer is brain cancer.
41. The pharmaceutical composition for use according to any one of the preceding claims, wherein the brain cancer is a brain tumor or an intracerebral neoplasm.
42. The pharmaceutical composition for use according to any one of the preceding claims, wherein the brain tumor or intracerebral neoplasm involves glial cells.
43. The pharmaceutical composition for use according to any one of the preceding claims, wherein the brain tumor or intracerebral neoplasm is a glioma.
44. The pharmaceutical composition for use according to any one of the preceding claims, wherein the intracerebral neoplasm is a high grade glioma, i.e. grade III or grade IV glioma.
45. The pharmaceutical composition for use according to any one of the preceding claims, wherein the glioma is astrocytoma, glioblastoma, diffuse midline glioma, diffuse hemispheric glioma or diffuse paediatric-type high-grade glioma.
46. The pharmaceutical composition for use according to any one of the preceding claims, wherein the composition is administered by direct intracerebral administration or by intrathecal administration.
47. The pharmaceutical composition for use according to any one of the preceding claims, wherein the composition is formulated or provided in an isotonic saline buffer or PBS buffer.
48. The pharmaceutical composition for use according to any one of the preceding claims, wherein the composition is administered by convection-enhanced delivery (CED).

49. The pharmaceutical composition for use according to any one of the preceding claims, wherein the infusion rate is adjusted to a level that ensures sufficient delivery of the composition, while avoiding adverse effects resulting from increased intracranial pressure, for example, the infusion rate is from 0.1 to 5.0 mL/hour.
- 5 50. The pharmaceutical composition for use according to any one of the preceding claims, wherein the composition is administered in one or more fractions, such as in 1 to 20 fractions, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 fractions.
- 10 51. The pharmaceutical for use according to any one of the preceding claims, wherein the composition comprises 1 kBq to 50 GBq of activity.
52. The pharmaceutical for use according to any one of the preceding claims, wherein a further chemotherapeutic agent is administered.
53. The pharmaceutical for use according to any one of the preceding claims, wherein the further chemotherapeutic agent is administered enterally or parenterally.
- 15 54. The pharmaceutical for use according to any one of the preceding claims, wherein the cytotoxic agent is released from the polymer in aqueous solutions in the presence of esterase over the course of 1 to 6 days.
- 20 55. The pharmaceutical for use according to any one of the preceding claims, wherein the cytotoxic agent is released from the polymer in aqueous solutions in the presence of esterase (0.1 U/mL) over the course of 1 to 6 days.
56. The pharmaceutical composition for use according to any one of the preceding claims, wherein at least 50% of the cytotoxic agent is present in the polymer 24 hours after administration.
- 25 57. The pharmaceutical composition for use according to any one of the preceding claims, wherein at least 20% or at least 10% of the cytotoxic agent is present in the polymer 96 hours after administration.
- 30 58. The pharmaceutical composition for use according to any one of the preceding claims, wherein the activity of radiation from the radioisotope is maintained in the intracerebral compartment for at least 6h, such as at least 24h, such as at least 48h, such as at least 72h, such as at least 96h, such as at least 120h.

59. A compound according to formula (I):

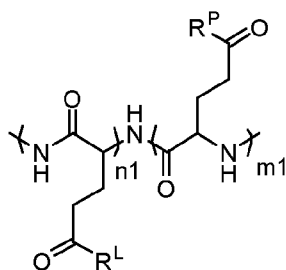


formula (I),

wherein

X is defined as $-R^1-R^A$, wherein R^1 is selected from the group consisting of $-C_{1-3}$ alkyl-, $-C_{1-3}$ haloalkyl-, $-C_{2-4}$ alkenyl-, $-C_{3-6}$ cycloalkyl-, $-C_{3-6}$ cycloaryl-, $-C_{3-6}$ cycloheteroaryl-, $-O-$, $-NH-$, $-C(O)-$, $-C(O)-O-(C_{1-6}$ alkyl)-, $-phenyl-$, $-O-phenyl-$, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope;

[L] is a covalent linker, and
[P] comprises formula (II-b):



formula (II-b),

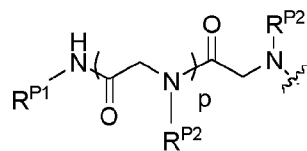
wherein

R^L denotes attachment to formula (I),

n_1 is an integer from 10 to 500,

m_1 is an integer from 10 to 500,

R^P is according to formula (P):

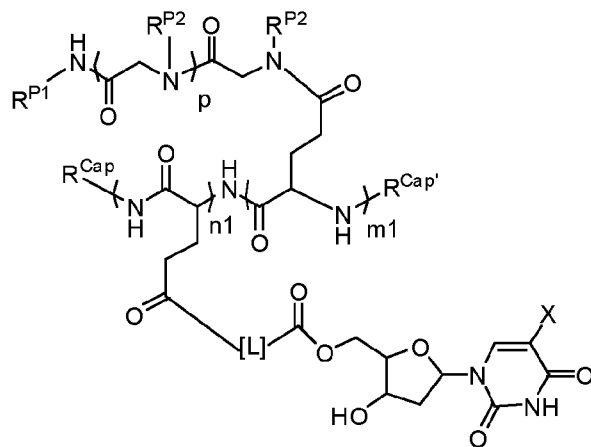


formula (P),

wherein R^{P1} and R^{P2} are each independently selected from C_1-C_4 alkyl and p is an integer from 10 to 500.

60. The compound according to claim 59, wherein [P] is as defined in any one of claims 26 to 39.

61. The compound according to any one of claims 59 to 60, wherein the compound comprises or consists of formula (IV):



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formula (IV), or a pharmaceutically

acceptable salt thereof, wherein

$n1$ is an integer from 10 to 500,

$m1$ is an integer from 10 to 500,

p is an integer from 10 to 500,

10 R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl,

R^{Cap} is a C_1 - C_6 alkyl,

$R^{Cap'}$ is $-C(O)-C_{1-6}$ -alkyl or $-C(O)$ -aryl; and

X is defined as $-R^1-R^A$, wherein R^1 is selected from the group consisting of $-C_{1-3}$

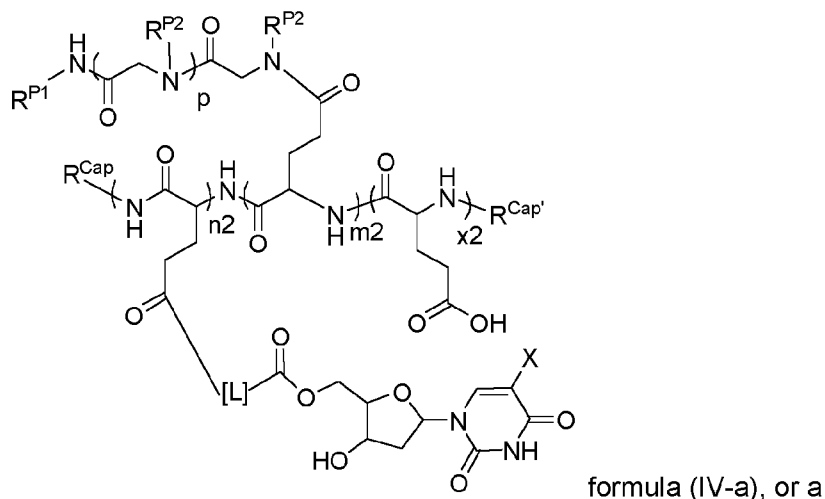
15 cycloheteroaryl-, $-O$ -, $-NH$ -, $-C(O)$ -, $-C(O)-O-(C_{1-6}$ alkyl)-, $-phenyl$ -, $-O-phenyl$ -, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope; and

$[L]$ is a covalent linker.

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62. The compound according to claim 61, wherein the compound comprises or consists of formula (IV-a):



pharmaceutically acceptable salt thereof, or a diastereomer, enantiomer, regioisomer or stereoisomer thereof, wherein

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n_2 is an integer from 10 to 500,

m_2 is an integer from 10 to 500,

x_2 is an integer from 0 to 500,

p is an integer from 10 to 500,

10

R^{P1} and R^{P2} are each independently selected from C_1 - C_4 alkyl,

R^{Cap} is a C_1 - C_6 alkyl,

$R^{Cap'}$ is $-C(=O)-C_{1-6}$ -alkyl or $-C(=O)$ -aryl; and

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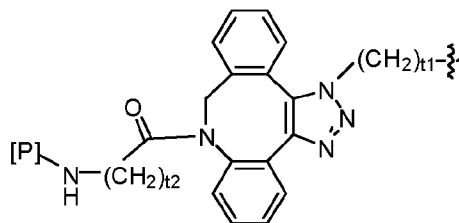
X is defined as $-R^1-R^A$, wherein R^1 is selected from the group consisting of $-C_{1-3}$ alkyl-, $-C_{1-3}$ haloalkyl-, $-C_{2-4}$ alkenyl-, $-C_{3-6}$ cycloalkyl-, $-C_{3-6}$ cycloaryl-, $-C_{3-6}$ cycloheteroaryl-, $-O$ -, $-NH$ -, $-C(O)$ -, $-C(O)-O-(C_{1-6}$ alkyl)-, $-phenyl$ -, $-O-phenyl$ -, 5-membered heteroaryl, a bond, or absent, and wherein R^A comprises a radioisotope; and

$[L]$ is a covalent linker.

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63. The compound according to any one of claims 59 to 62, wherein $[L]$ is as defined in any one of claims 16 to 25.

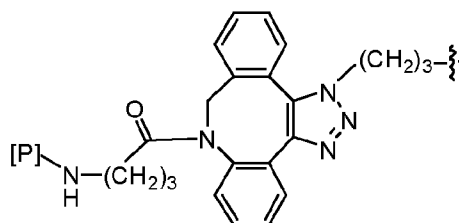
64. The compound according to claim 63, wherein [L] is according to formula (X-I):



formula (X-I)

wherein each of t1 and t2 are each integers individually selected from 1, 2, 3, 4, or 5.

5 65. The compound according to claim 64, wherein [L] is



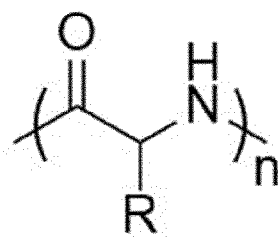
66. The compound according to any one of claims 59 to 65, wherein X is ^{123}I , ^{124}I , ^{125}I , ^{77}Br , ^{76}Br , $^{80\text{m}}\text{Br}$, ^{80}Br , ^{126}I , ^{131}I , ^{18}F , or ^{211}At .

10 67. The compound according to any one of claims 59 to 66, wherein X is ^{123}I , ^{124}I , ^{125}I , or ^{131}I .

68. The compound according to any one of claims 59 to 67, wherein X is ^{123}I , ^{125}I , or ^{77}Br .

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A



B

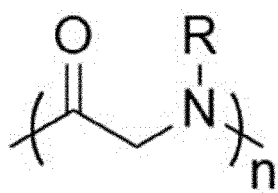


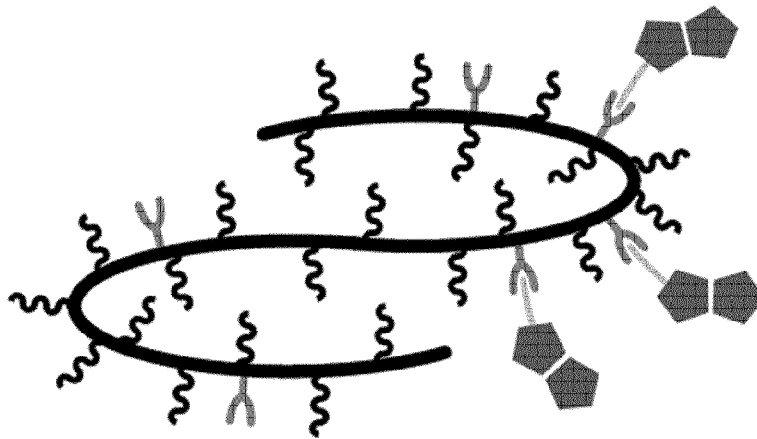
Fig. 1

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 = Synthetic modifications

 = Drug coupling sites

 = Chemical payload



Pepto-Brush Polyoids

Fig. 2

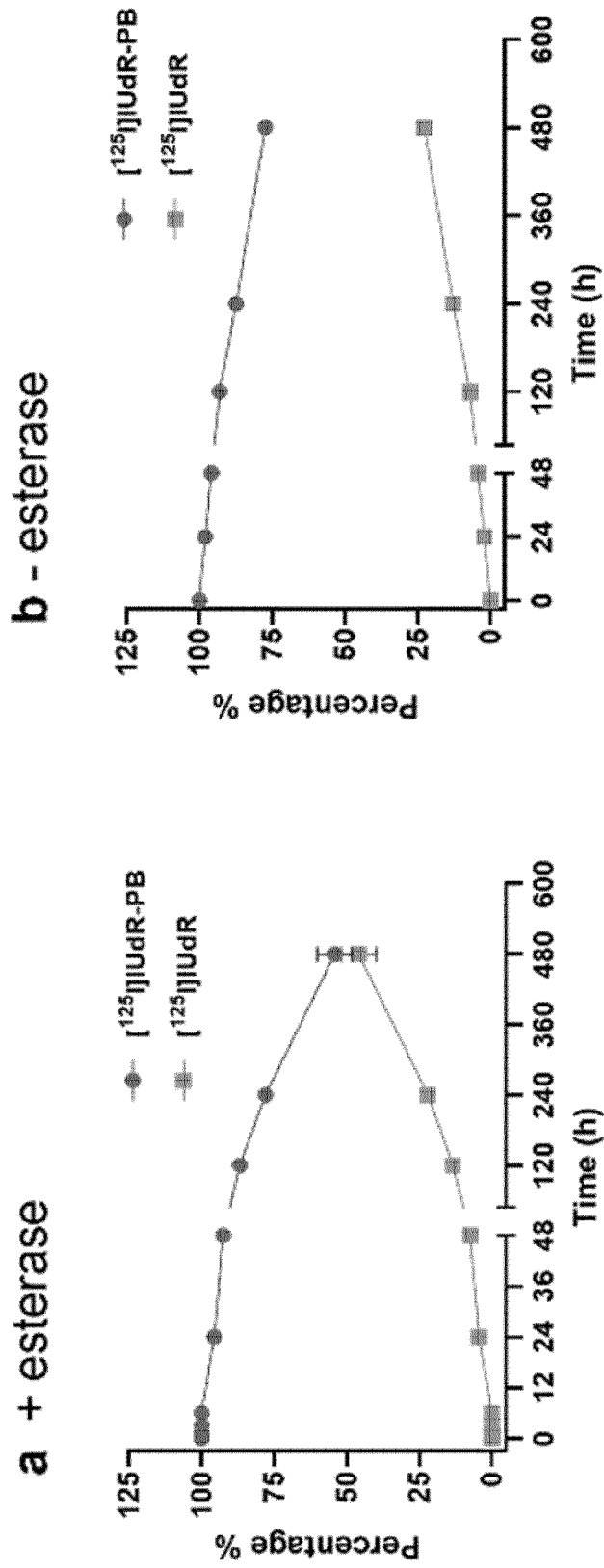


Fig. 3

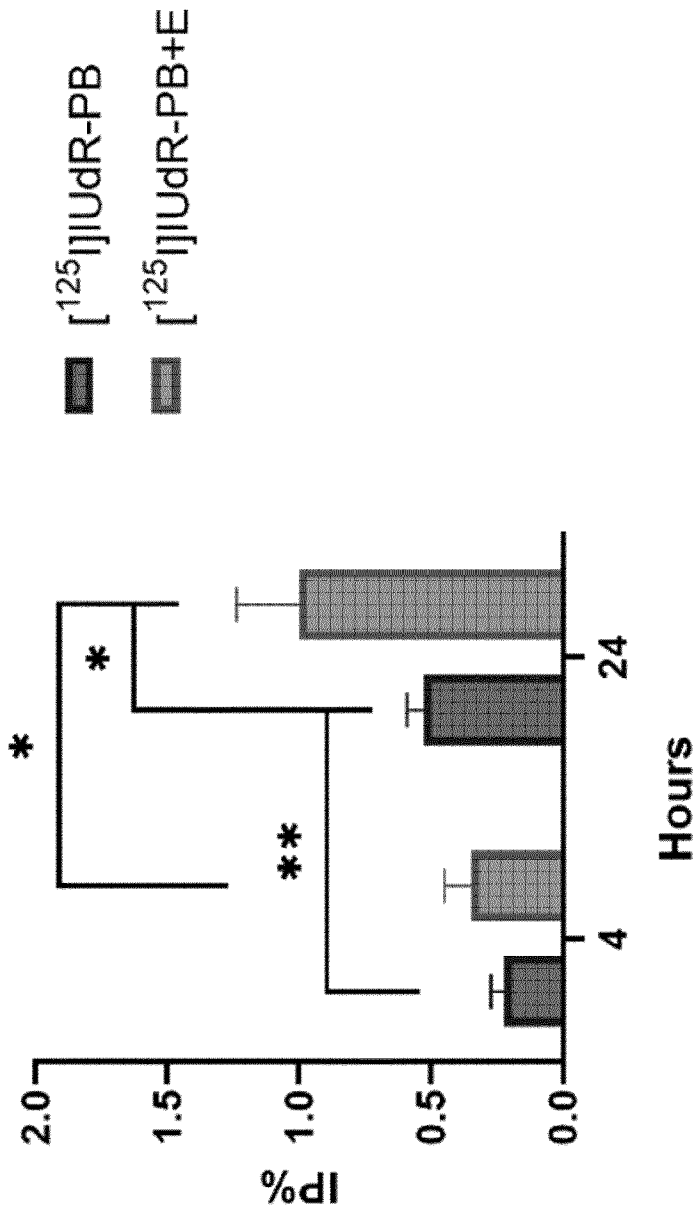


Fig. 4

A

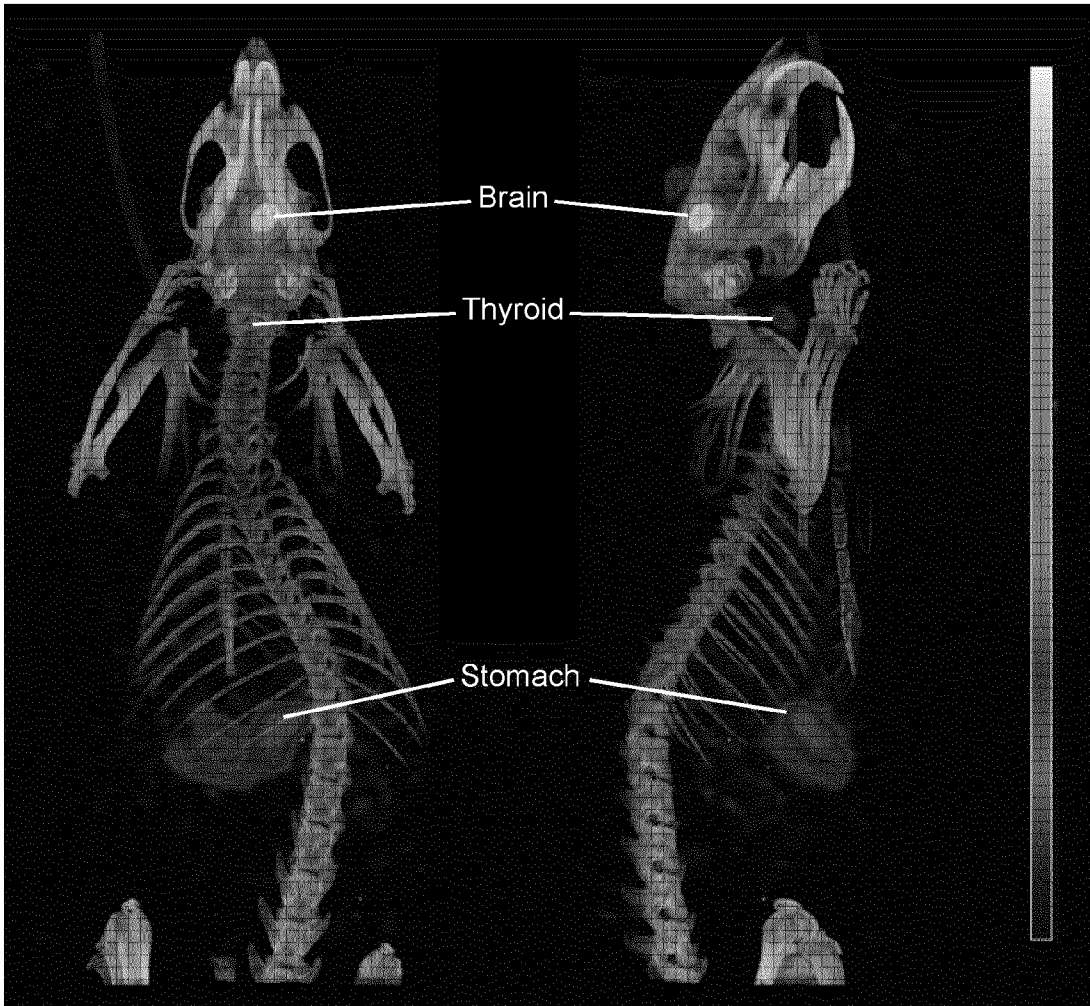


Fig. 5

B

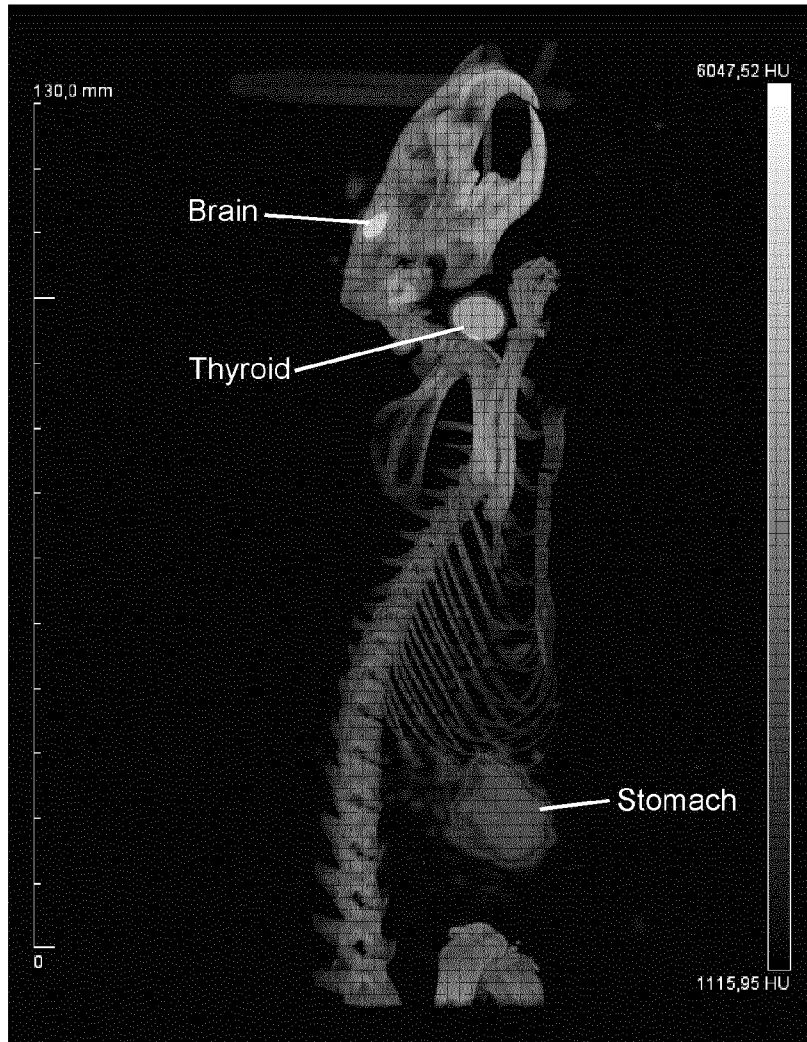


Fig. 5 cont.

INTERNATIONAL SEARCH REPORT

| |
|---|
| International application No PCT/EP2024/084070 |
|---|

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K51/06 A61K101/02 A61P35/00 A61K47/59
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | <p>WO 2017/053834 A1 (UNIV NEBRASKA [US]) 30 March 2017 (2017-03-30) page 8, line 9 - line 26 claims; examples</p> <p style="text-align: center;">----- -/--</p> | 1 - 68 |

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

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| Date of the actual completion of the international search 13 February 2025 | Date of mailing of the international search report 12/03/2025 |
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| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016 | Authorized officer <p style="text-align: center;">Ceyte, Mathilde</p> |
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2024/084070

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|-----------------------|
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | <p>KORTYLEWICZ ZBIGNIEW P. ET AL: "Norepinephrine-Transporter-Targeted and DNA-Co-Targeted Theranostic Guanidines", JOURNAL OF MEDICINAL CHEMISTRY , vol. 63, no. 5 24 June 2019 (2019-06-24), pages 2051-2073, XP055774850, US ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.9b00437 Retrieved from the Internet: URL:https://pubs.acs.org/doi/pdf/10.1021/a cs.jmedchem.9b00437 page 2052; figure 1 abstract</p> <p style="text-align: center;">-----</p> | 1 - 68 |
| A | <p>XIAO-HONG YANG: "[beta]-Cyclodextrin Complexes of Hydrolyzable Adamantanoyl-IUdR Prodrugs - Radioiodination and Biodistribution in Mice Bearing Implanted KBALB Tumours", CURRENT RADIOPHARMACEUTICALS, vol. 2, no. 2, 1 April 2009 (2009-04-01), pages 137-142, XP093163177, NL ISSN: 1874-4710, DOI: 10.2174/1874471010902020137 the whole document</p> <p style="text-align: center;">-----</p> | 1 - 68 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2024/084070

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | CA 3037835 A1 | 30-03-2017 |
| | | EP 3352746 A1 | 01-08-2018 |
| | | US 2018256761 A1 | 13-09-2018 |
| | | WO 2017053834 A1 | 30-03-2017 |
| ----- | | | |