

IMIDAZOLINONE DERIVATIVE FOR USE IN THE TREATMENT OF TUMORS
IN COMBINATION WITH RDC

RELATED APPLICATIONS

5 This application claims priority to Chinese Application No. 202410273774.5 filed
March 11, 2024; Chinese Application No. 202410295753.3 filed March 15, 2024; Chinese
Application No. 202410376693.8 filed March 29, 2024; Chinese Application No.
202411058175.8 filed August 2, 2024; Chinese Application No. 202411332885.5 filed
September 24, 2024; and Chinese Application No. 202411379711.4 filed September 30,
10 2024, the contents of which are incorporated by reference in their entirety.

TECHNICAL FIELD

 The present invention relates to the use of an imidazolinone derivative for the
treatment of a tumor in combination with RDC.

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BACKGROUND

 Radiotherapy is one of the most important methods for the comprehensive treatment
of malignant tumors, and the neoadjuvant therapy based on conventional long-term
radiotherapy has become a standard regimen for treating various malignant tumors.

20 However, long-term clinical studies have found that the responses of patients with malignant
tumors to radiotherapy vary greatly. Although some patients can achieve complete
pathological remission at the end of a treatment cycle, there are still some patients who
cannot benefit from long-term treatment, and a few even develop worsening progress.
Studies have found that the enhanced DNA damage repair mechanism due to radiotherapy
25 is an important reason for the tolerance mechanism of tumors to radiotherapy.

 Radionuclide drug conjugates (RDC) are a new radiotherapy technology, which
consist mainly of four parts: targeted localization elements (antibodies or small molecules),
linking arms, chelators and radioactive isotopes.

30 DNA double-strand break (DSB) is a highly harmful form of DNA damage in cells,
and DNA double-strand breaks that are not repaired in time are closely associated with the
canceration of cells. Non-homologous end-joining (NHEJ) is one of the main pathways for
the repair of DNA double-strand breaks in cells. In NHEJ, the DSB end is first recognized
and bound by Ku70/80 and then binds to a DNA-dependent protein kinase catalytic subunit
(DNA-PKcs) to form a DNA-dependent protein kinase (DNAPK), i.e., an NHEJ initiation
35 complex (DNAPK). Subsequently, two DNAPKs bind to the ends of damaged DNA while
recruiting subsequent NHEJ repair factors (XRCC4 and XLF) and DNA ligase IV (LigIV) to
repair the damaged DNA. Studies have shown that DNA-PK activity is associated with drug

resistance due to radiotherapy, such that the killing effect of radiotherapy on tumor cells can be improved by inhibiting the DNA-PK activity in tumor cells. However, there are still no effective DNA-PK inhibitor drugs on the market. Therefore, developing a potent DNA-PK inhibitor as a radiosensitizing drug for tumor treatment has important clinical significance.

5 WO 2021209055 discloses the use of an imidazolinone derivative in the preparation of a drug for use in the treatment of a cancer, in which the compounds described in the specification have high selectivity and significant inhibitory activity against DNA-PK.

There remains a need to increase the sensitivity of tumors to radiotherapy.

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SUMMARY

An objective of the present invention is to provide the use of an imidazolinone derivative for the treatment of a tumor in combination with radionuclide drug conjugate (RDC), so as to overcome the deficiencies of the prior art. Thus, provided herein is a combination therapy comprising a compound of Formula I and a radionuclide drug conjugate. Also provided herein is a pharmaceutical combination comprising a compound of

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BRIEF DESCRIPTION OF THE DRAWINGS

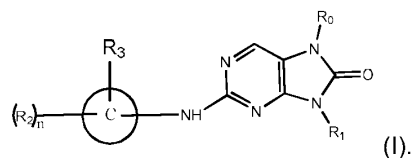
FIG. 1 shows the growth inhibitory effect of Compound A on LNCaP.

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FIG. 2 shows the growth inhibitory effect of ^{177}Lu -PSMA-617 used alone and in combination with Compound A on LNCaP.

DETAILED DESCRIPTION

25 Provided herein is combination therapy comprising a compound represented by formula (I), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt or co-crystal thereof as an active ingredient for the treatment of a tumor in combination with RDC:



30 When Compound A in the present application is used for treating tumors in combination with radiotherapy, radionuclide drug conjugates (RDC) may be preferred. The mechanism of action of a RDC is delivering cytotoxic molecules or imaging molecules, such as radionuclides, to the target site by using antibodies or small molecules to mediate specific targeting effects. This specific targeting allows the radiation generated by radioactive isotopes (radionuclides) to act locally on the tissue. Therefore, Compound A in the present

application can be used in combination with RDC for radiotherapy of tumors. When Compound A is used in combination with RDC for radiotherapy, it may be used preferably in combination with Pluvicto, Lutathera or a Radium[²²³Ra] dichloride injection solution. RDCs generally comprise radioligand therapies (RLTs): a radionuclide, and a targeting polypeptide.

- 5 The radionuclides may include, for example, ⁶⁸Ga, ¹⁷⁷Lu, ¹⁶¹Tb, ²²⁵Ac, and ²²⁶Ra, and the targeting polypeptides may include, for example, PSMA, SSTR and FAP.

As such, provided herein is a combination therapy comprising a compound of Formula I, e.g., Compound A, and a radionuclide drug conjugate for the treatment of cancers, such as prostate cancer. When combined with a RDC, Compound A exhibits
10 promising synergistic anti-tumor efficacy.

Definitions

Listed below are definitions of various terms used herein. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited
15 in specific instances, either individually or as part of a larger group.

Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and peptide chemistry are those well-known and
20 commonly employed in the art.

As used herein, the articles “a” and “an” refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

25 As used herein and throughout the disclosure, the term “about” can mean $\pm 10\%$.

The term “combination therapy” refers to the administration of two or more therapeutic compounds to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic compounds in a substantially simultaneous manner, such as in a single capsule having a
30 fixed ratio of active ingredients or in multiple, or in separate containers (e.g., capsules or IV administration) for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic compound in a sequential manner, either at approximately the same time or at different times. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described
35 herein.

As used herein, “pharmaceutical combination” or “combination” refers to formulations of the separate compounds with or without instructions for combined use. The combination

compounds may thus be entirely separate pharmaceutical dosage forms or in pharmaceutical compositions that are also sold independently of each other and where just instructions for their combined use are provided in the package equipment, e.g., leaflet or the like, or in other information, e.g., provided to physicians and medical staff (e.g. oral
5 communications, communications in writing or the like), for simultaneous or sequential use for being jointly active.

As used herein, the term “treating” or “treatment” refers to one or more of (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet
10 experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an
15 individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease. In some embodiments, the term “treating” or “treatment” refers to inhibiting or ameliorating the disease.

As used herein, the term “prevent” or “prevention” means no disorder or disease
20 development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

As used herein, the term “patient,” “individual,” or “subject” refers to a human or a non-human mammal. Non-human mammals include, for example, livestock and pets, such
25 as ovine, bovine, porcine, canine, feline and marine mammals. Preferably, the patient, subject, or individual is human.

As used herein, the terms “effective amount,” “pharmaceutically effective amount,” and “therapeutically effective amount” refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. That result may be reduction or alleviation of the signs,
30 symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate therapeutic amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

As used herein, the term “pharmaceutically acceptable” refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the
35 compound, and is relatively non-toxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term "pharmaceutically acceptable salt" refers to derivatives of the disclosed compounds wherein a parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali
5 or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts described herein include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts discussed herein can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods.
10 Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used. The phrase "pharmaceutically acceptable salt" is not limited to a mono, or 1:1, salt. For example, "pharmaceutically
15 acceptable salt" also includes bis-salts, such as a bis-hydrochloride salt. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Journal of Pharmaceutical Science, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

As used herein, the term "composition" or "pharmaceutical composition" refers to a
20 mixture of at least one compound with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the composition to a patient or subject. Multiple techniques of administering a compound exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

As used herein, the term "pharmaceutically acceptable carrier" means a
25 pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful to the patient such that it may perform its intended function. Typically, such constructs are carried or
30 transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation, including the compound disclosed herein, and not injurious to the patient. Some examples of materials that may serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn
35 starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed

oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; surface active agents; alginic acid; pyrogen-free water; isotonic saline; 5 Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

As used herein, "pharmaceutically acceptable carrier" also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of a compound disclosed herein, and are physiologically 10 acceptable to the patient. Supplementary active compounds may also be incorporated into the compositions. The "pharmaceutically acceptable carrier" may further include a pharmaceutically acceptable salt of the compound(s) disclosed herein. Other additional ingredients that may be included in the pharmaceutical compositions are known in the art and described, for example, in Remington's Pharmaceutical Sciences (Genaro, Ed., Mack 15 Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

The combination of agents described herein may display a synergistic effect. The term "synergistic effect" as used herein, refers to action of two agents such as, for example, a compound of Formula (I) and radionuclide drug conjugate (RDC), producing an effect, for example, slowing the symptomatic progression of cancer or symptoms thereof, which is 20 greater than the simple addition of the effects of each drug administered by themselves. A synergistic effect can be calculated, for example, using suitable methods such as the Sigmoid-Emax equation (Holford, N. H. G. and Scheiner, L. B., Clin. Pharmacokinet. 6: 429-453 (1981)), the equation of Loewe additivity (Loewe, S. and Muischnek, H., Arch. Exp. Pathol Pharmacol. 114: 313-326 (1926)) and the median-effect equation (Chou, T. C. and 25 Talalay, P., Adv. Enzyme Regul. 22: 27-55 (1984)). Each equation referred to above can be applied to experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, respectively.

30 As used herein, the term "synergy" refers to the effect achieved when the active ingredients, i.e., Compound A and ^{177}Lu -PSMA-617, used together is greater than the sum of the effects that results from using the compounds separately.

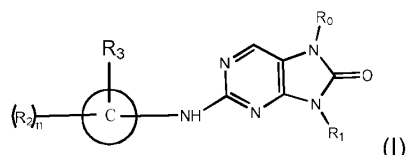
In an embodiment, provided herein is a combination therapy comprising an effective amount of a compound of Formula I and a radionuclide drug conjugate (RDC). An "effective 35 amount" of a combination of agents (i.e., a compound of Formula I (e.g., Compound A) and RDC (e.g., ^{177}Lu -PSMA-617)) is an amount sufficient to provide an observable improvement

over the baseline clinically observable signs and symptoms of the disorders treated with the combination.

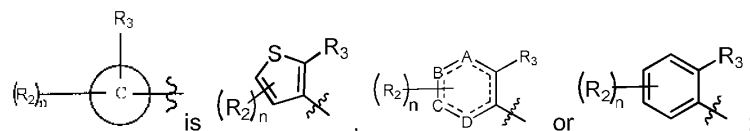
The term "unit dose" is used herein to mean simultaneous administration of both agents together, in one dosage form, to the patient being treated. In some embodiments, the unit dose is a single formulation. In certain embodiments, the unit dose includes one or more vehicles such that each vehicle includes an effective amount of at least one of the agents along with pharmaceutically acceptable carriers and excipients. In some embodiments, the unit dose is one or more tablets, capsules, pills, or patches administered to the patient at the same time. In some embodiments, the unit dose is an intravenous (IV) injection or infusion.

Methods and Uses

In one or more embodiments of the present application, there is provided the use of a compound of general formula (I), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt or co-crystal thereof as an active ingredient for the treatment of a tumor in combination with a radionuclide drug conjugate (RDC):



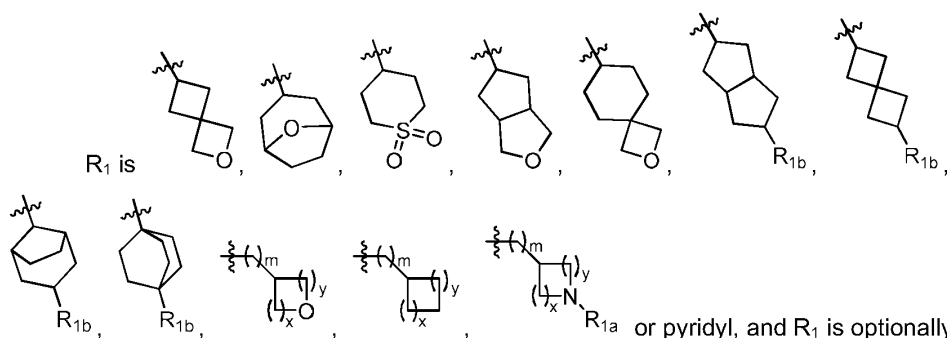
wherein



— is a single bond or double bond;

in , A, B, C, D are each independently C or N, and at least one of A, B, C and D is N;

R₀ is H, C₁₋₆ alkyl or cyclopropyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;



further substituted with 1 or 2 substituents selected from D, halogen, cyano, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy;

5 R_{1a} is H or C_{1-6} alkyl;

R_{1b} is H, OH, cyano, or hydroxyl substituted C_{1-6} alkyl;

R_2 is H, cyano, =O, carboxyl, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, C_{1-6} alkyl, halogen, $-S(=O)_2R_{2a}$ or $-C(=O)OC_{1-6}$ alkyl, wherein the C_{1-6} alkyl, $-C(=O)OC_{1-6}$ alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

10 R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D, halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1, 2 or 3 heteroatoms selected from N, O and S and is optionally further substituted with one or more substituents selected from C_{1-6} alkyl, OH and halogen;

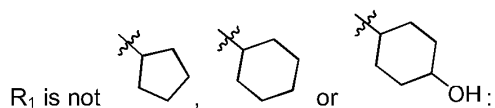
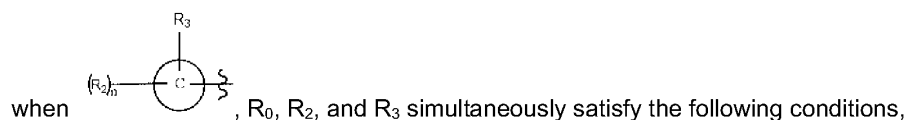
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

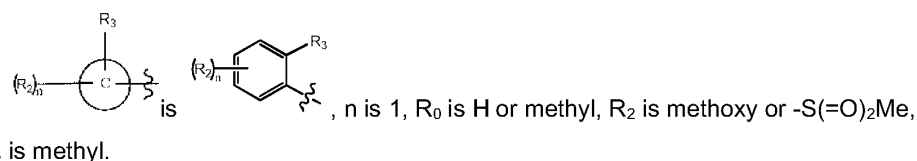
m is 0 or 1;

20 n is 0, 1 or 2; and

x and y are each independently 1, 2 or 3;

with the provisos that

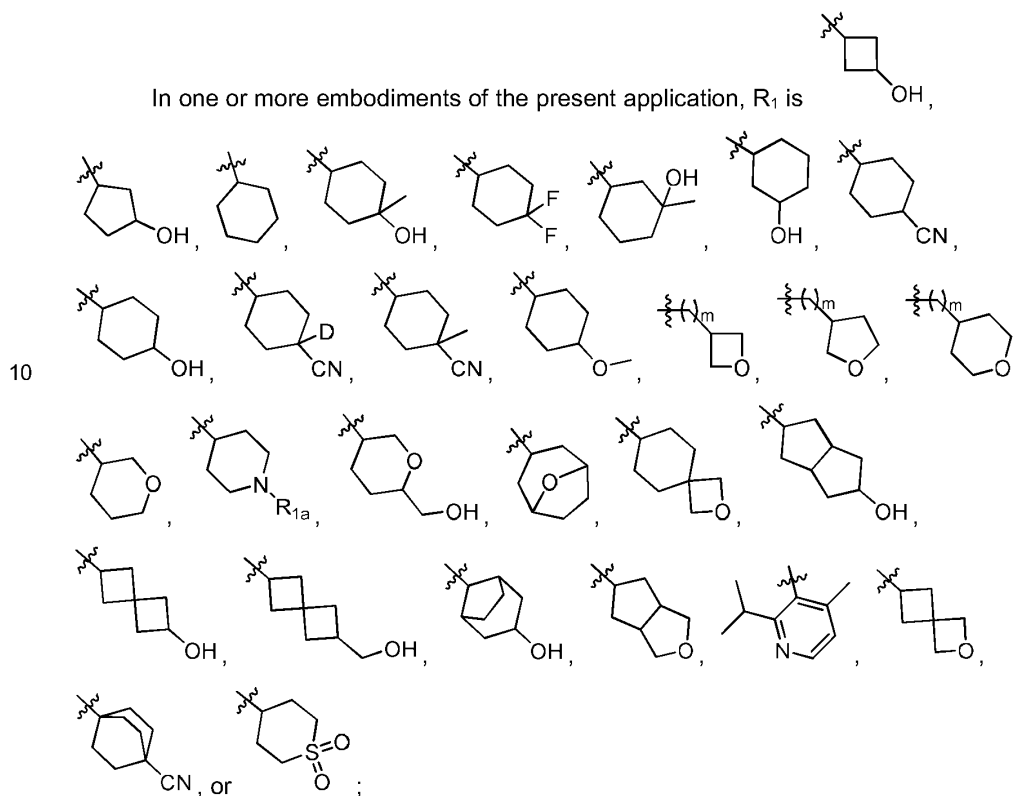




In an embodiment, R₁ is optionally further substituted with hydroxyl-substituted C₁₋₆ alkyl.

- 5 In an aspect, provided herein is a method of treating a tumor in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a RDC.

In one or more embodiments of the present application, R₁ is



R_{1a} is H or C₁₋₆ alkyl;

- 15 R₂ is H, cyano, -C(=O)NR_{2a}R_{2b}, C₁₋₆ alkoxy, halogen, -S(=O)₂R_{2a} or -C(=O)OC₁₋₆ alkyl, wherein the -C(=O)OC₁₋₆ alkyl or C₁₋₆ alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

- R_{2a} and R_{2b} are each independently H, C₁₋₆ alkyl, or 3- to 5-membered cycloalkyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from OH, D or halogen;
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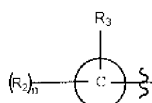
alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S and is optionally further substituted with one or more substituents selected from OH and halogen;

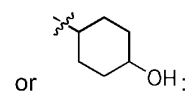
- 5 R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

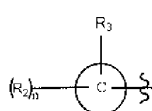
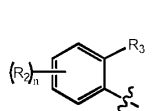
m is 0 or 1; and

n is 0, 1 or 2;

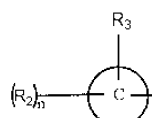
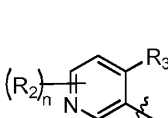
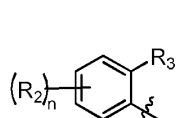
with the provisos that

- 10 when , R_0 , R_2 , and R_3 simultaneously satisfy the following conditions,

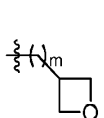
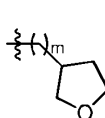
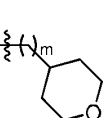
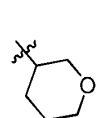
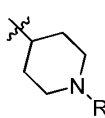
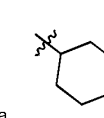
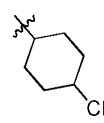
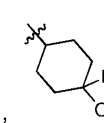
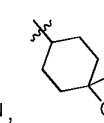
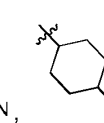
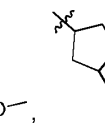
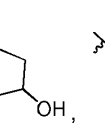
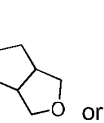
R_1 is not ,  or ;

 is , n is 1, R_0 is H or methyl, R_2 is methoxy or - $S(=O)_2Me$, and R_3 is methyl.

In one or more embodiments of the present application,

- 15  is  or ;

R_0 is H, C_{1-4} alkyl or cyclopropyl, wherein the C_{1-4} alkyl is optionally further substituted with one or more substituents selected from halogen and D;

R_1 is , , , , , , , , , , ,  or ;

- 20 R_{1a} is H, C_{1-6} alkyl or $-C(=O)C_{1-6}$ alkyl;

R_2 is H, cyano, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, $-S(=O)_2R_{2a}$ or $-C(=O)OC_{1-6}$ alkyl, wherein the $-C(=O)OC_{1-6}$ alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D and halogen;

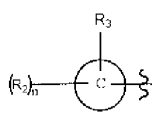
alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S and is also optionally further substituted with one or more substituents selected from OH and halogen;

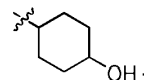
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

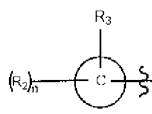
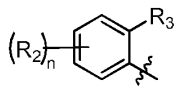
m is 0 or 1; and

n is 0, 1 or 2;

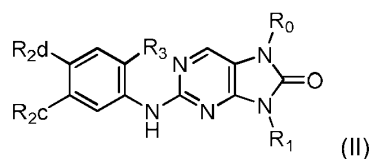
with the provisos that

when , R_0 , R_2 , and R_3 simultaneously satisfy the following conditions,

R_1 is not ,  or :

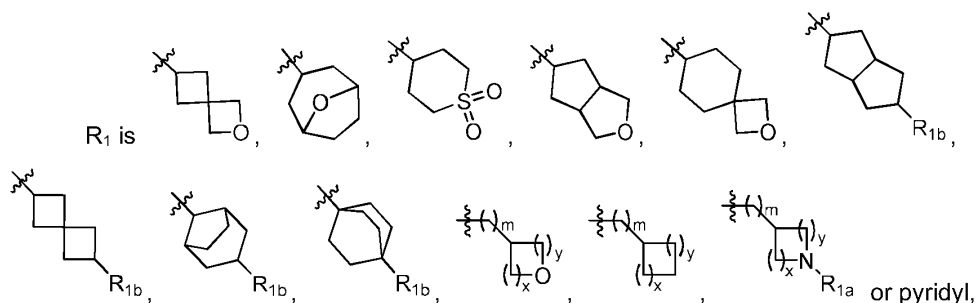
when  is , n is 1, R_0 is H or methyl, R_2 is methoxy or -S(=O)₂Me, and R_3 is methyl.

In one or more embodiments of the present application, there is provided the use of a compound of general formula (II), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt or co-crystal thereof as an active ingredient for the treatment of a tumor in combination with RDC:



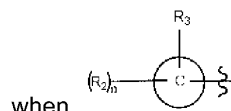
wherein

R_0 is H, C_{1-6} alkyl or cyclopropyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

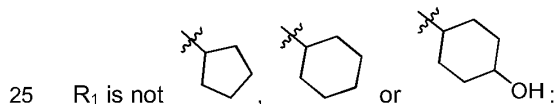


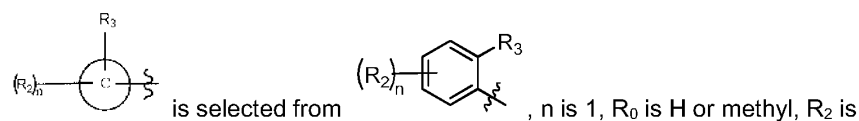
and R₁ is optionally further substituted with 1 to 2 substituents selected from D, halogen, cyano, hydroxyl, C₁₋₆ alkyl and C₁₋₆ alkoxy;

- 5 R_{1a} is H or C₁₋₆ alkyl;
R_{1b} is H, OH, cyano, or hydroxyl substituted C₁₋₆ alkyl;
R_{2c} is H, cyano, halogen or C₁₋₆ alkoxy;
R_{2d} is H, cyano, carboxyl, -C(=O)NR_{2a}R_{2b}, C₁₋₆ alkyl, halogen, -S(=O)₂R_{2a} or -
C(=O)OC₁₋₆ alkyl, wherein the C₁₋₆ alkyl and -C(=O)OC₁₋₆ alkyl is optionally substituted with
10 one or more substituents selected from halogen and deuterium;
R_{2a} and R_{2b} are H, C₁₋₆ alkyl, or 3- to 5-membered cycloalkyl, wherein the C₁₋₆ alkyl is
optionally further substituted with one or more substituents selected from OH, D, halogen,
C₁₋₆ alkyl and C₁₋₆ alkoxy;
alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a
15 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S
and is optionally further substituted with one or more substituents selected from C₁₋₆ alkyl,
OH and halogen;
R₃ is halogen or C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally further substituted with
1 to 3 substituents selected from D and halogen;
20 m is 0 or 1;
n is 0, 1 or 2; and
x and y are each independently 1, 2 or 3;
with the provisos that



when $\bigcirc_{\frac{1}{2}h}$, R_0 , R_2 , and R_3 simultaneously satisfy the following conditions,

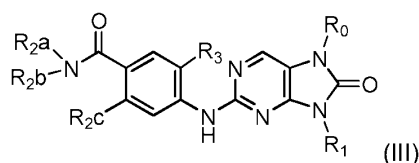




methoxy or -S(=O)₂Me, and R₃ is methyl.

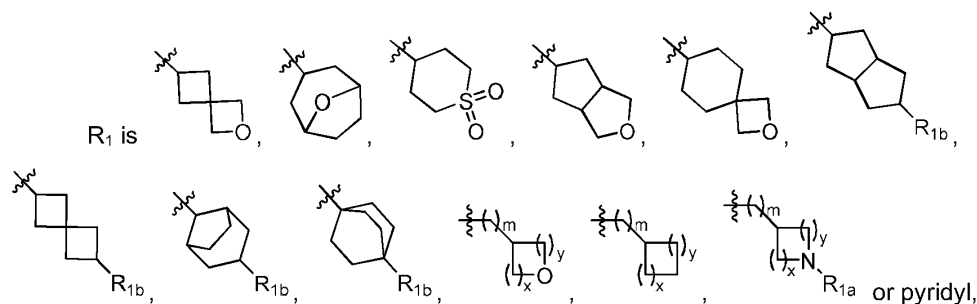
In one or more embodiments of the present application, there is provided the use of a compound of general formula (III), or a stereoisomer, solvate, prodrug, metabolite,

- 5 pharmaceutically acceptable salt or co-crystal thereof as an active ingredient for the treatment of a tumor in combination with RDC:



wherein

- 10 R₀ is H, C₁₋₆ alkyl or cyclopropyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;



and R₁ is optionally further substituted with 1 to 2 substituents selected from D, halogen, cyano, hydroxyl, C₁₋₆ alkyl and C₁₋₆ alkoxy;

- 15 R_{1b} is H, OH, cyano, or hydroxyl substituted C₁₋₆ alkyl;

R_{2a} and R_{2b} are each independently H, C₁₋₆ alkyl, or 3- to 5-membered cycloalkyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from D or halogen;

- 20 alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S and is optionally further substituted with one or more substituents selected from C₁₋₆ alkyl, OH and halogen;

R_{2c} is H, cyano, halogen or C₁₋₆ alkoxy, wherein the C₁₋₆ alkoxy is optionally substituted with one or more deuterium;

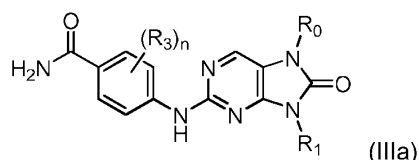
- 25 R₃ is halogen or C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally further substituted with 1 to 3 substituents selected from D or halogen;

m is 0 or 1;

n is 0, 1 or 2; and

x and y are each independently 1, 2 or 3.

In an embodiment, the compound of Formula I is a compound of Formula IIIa:



or a pharmaceutically acceptable salt thereof;

wherein

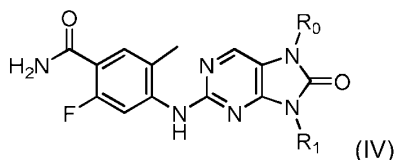
R₀ is H, C₁₋₆ alkyl or cyclopropyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium; and

R₁ is -(CH)_m-4- to 7-membered carbocyclyl, -(CH)_m-4- to 7-membered heterocyclyl, -(CH)_m-8- to 12-membered bridged ring, -(CH)_m-7- to 12-membered spiro ring, wherein the -(CH)_m-4- to 7-membered carbocyclyl, -(CH)_m-4- to 7-membered heterocyclyl, -(CH)_m-8- to 12-membered bridged ring, or -(CH)_m-7- to 12-membered spiro ring is optionally further substituted with one or more substituents selected from hydroxy, cyano, halogen, =O, C₁₋₆ alkyl, C₁₋₆ alkoxy, and hydroxy substituted C₁₋₆ alkyl;

each R₃ is independently halogen or C₁₋₆ alkyl; and

n is 2.

In one or more embodiments of the present application, there is provided the use of a compound of general formula (IV), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt or co-crystal thereof as an active ingredient for the treatment of a tumor in combination with RDC:



wherein

R₀ is H, C₁₋₆ alkyl or cyclopropyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium; and

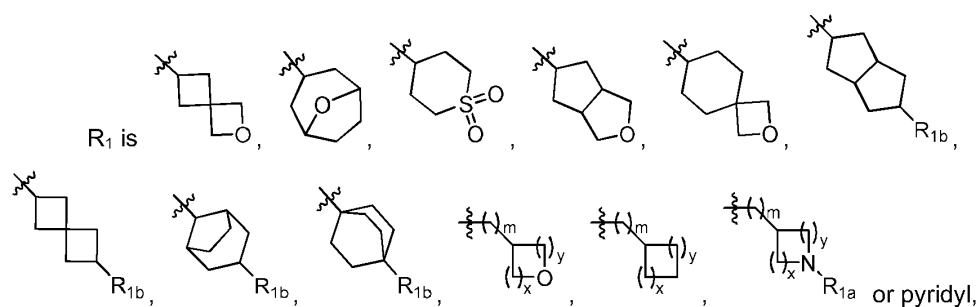
R₁ is -(CH)_m-4- to 7-membered carbocyclyl, -(CH)_m-4- to 7-membered heterocyclyl, -(CH)_m-8- to 12-membered bridged ring, -(CH)_m-7- to 12-membered spiro ring, wherein the -(CH)_m-4- to 7-membered carbocyclyl, -(CH)_m-4- to 7-membered heterocyclyl, -(CH)_m-8- to 12-membered bridged ring, or -(CH)_m-7- to 12-membered spiro ring is optionally further

substituted with one or more substituents selected from hydroxy, cyano, halogen, =O, C₁₋₆ alkyl, C₁₋₆ alkoxy, and hydroxy substituted C₁₋₆ alkyl.

In one or more embodiments of the present application,

R₀ is H, C₁₋₆ alkyl or cyclopropyl, wherein the C₁₋₆ alkyl is optionally further substituted

5 with one or more substituents selected from halogen and deuterium;



and R₁ is optionally further substituted with 1 to 2 substituents selected from D, halogen, cyano, hydroxyl, C₁₋₆ alkyl and C₁₋₆ alkoxy;

10 R_{1a} is H or C₁₋₆ alkyl;

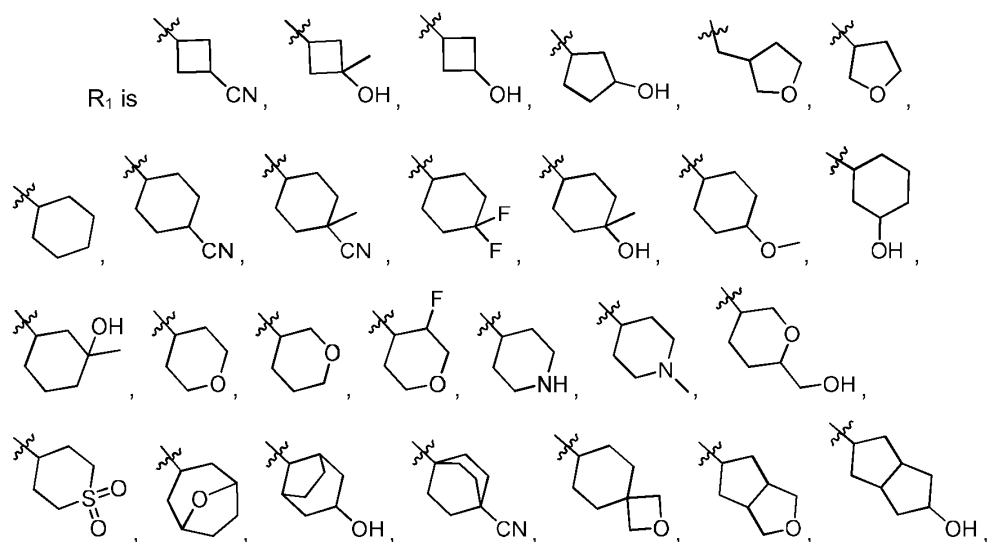
R_{1b} is H, OH, cyano, or hydroxyl substituted C₁₋₆ alkyl;

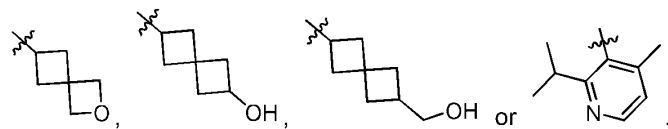
m is 0 or 1; and

x and y are each independently 1, 2 or 3.

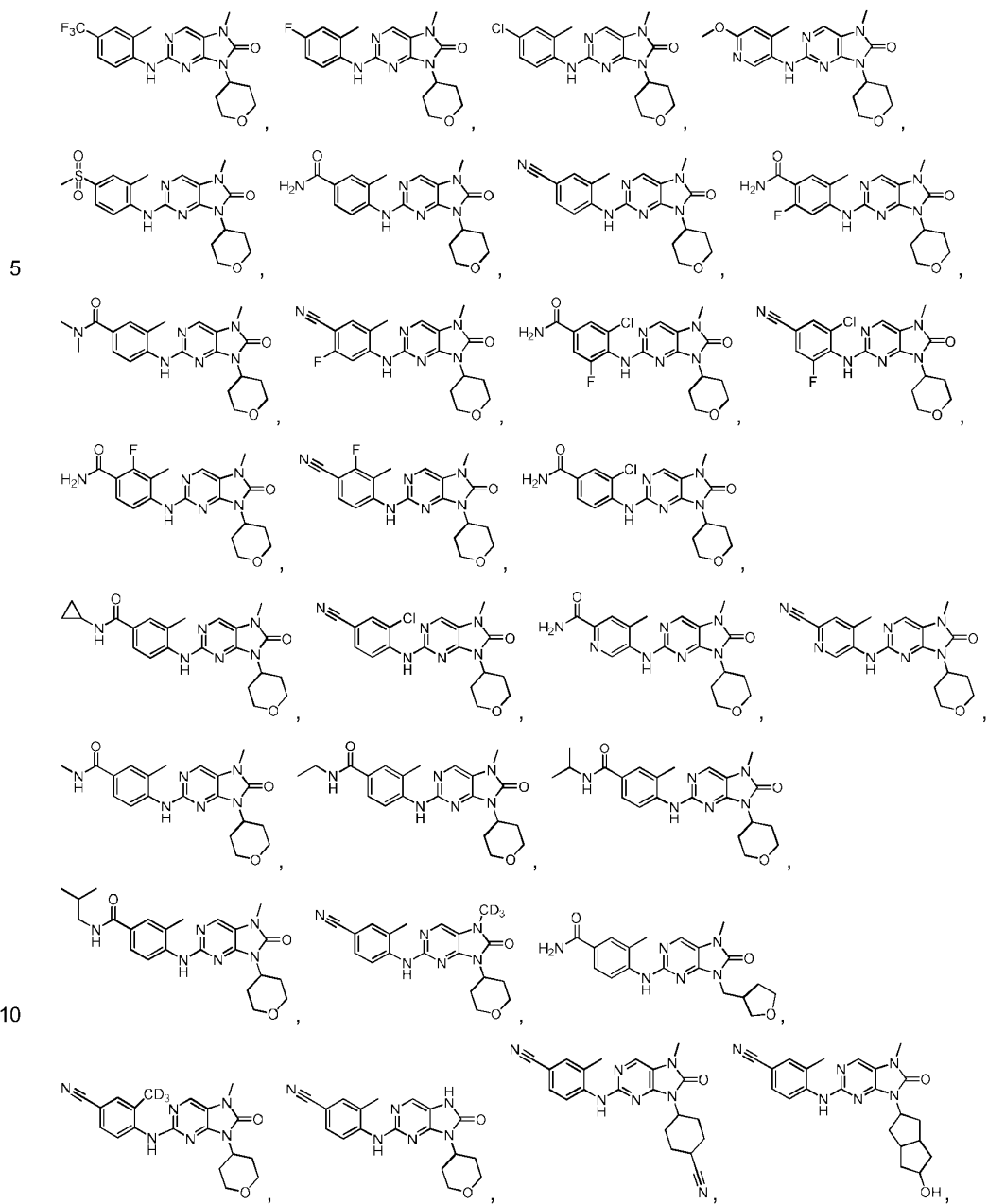
In one or more embodiments of the present application,

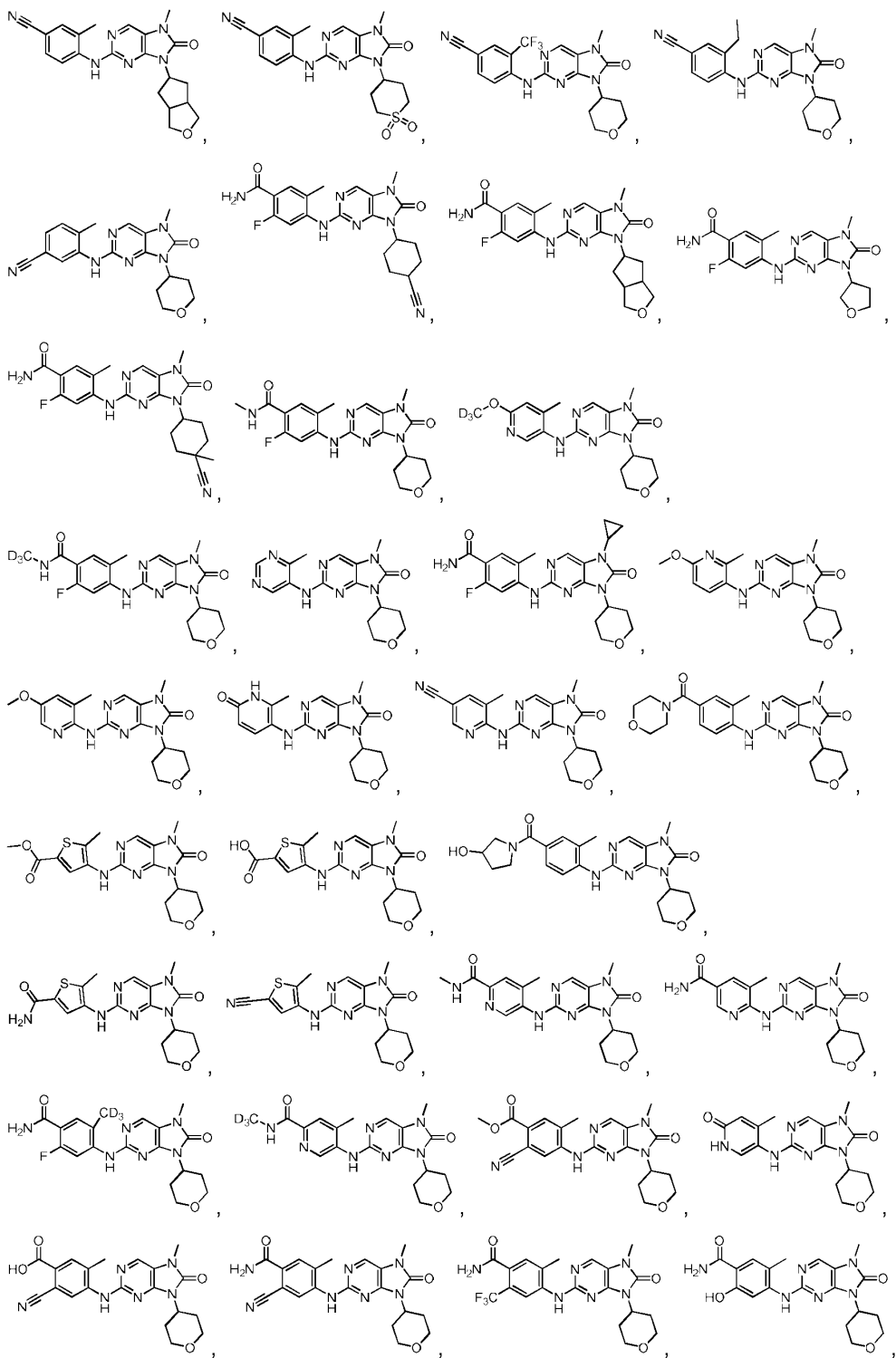
15 R₀ is C₁₋₄ alkyl, wherein the C₁₋₄ alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium; and

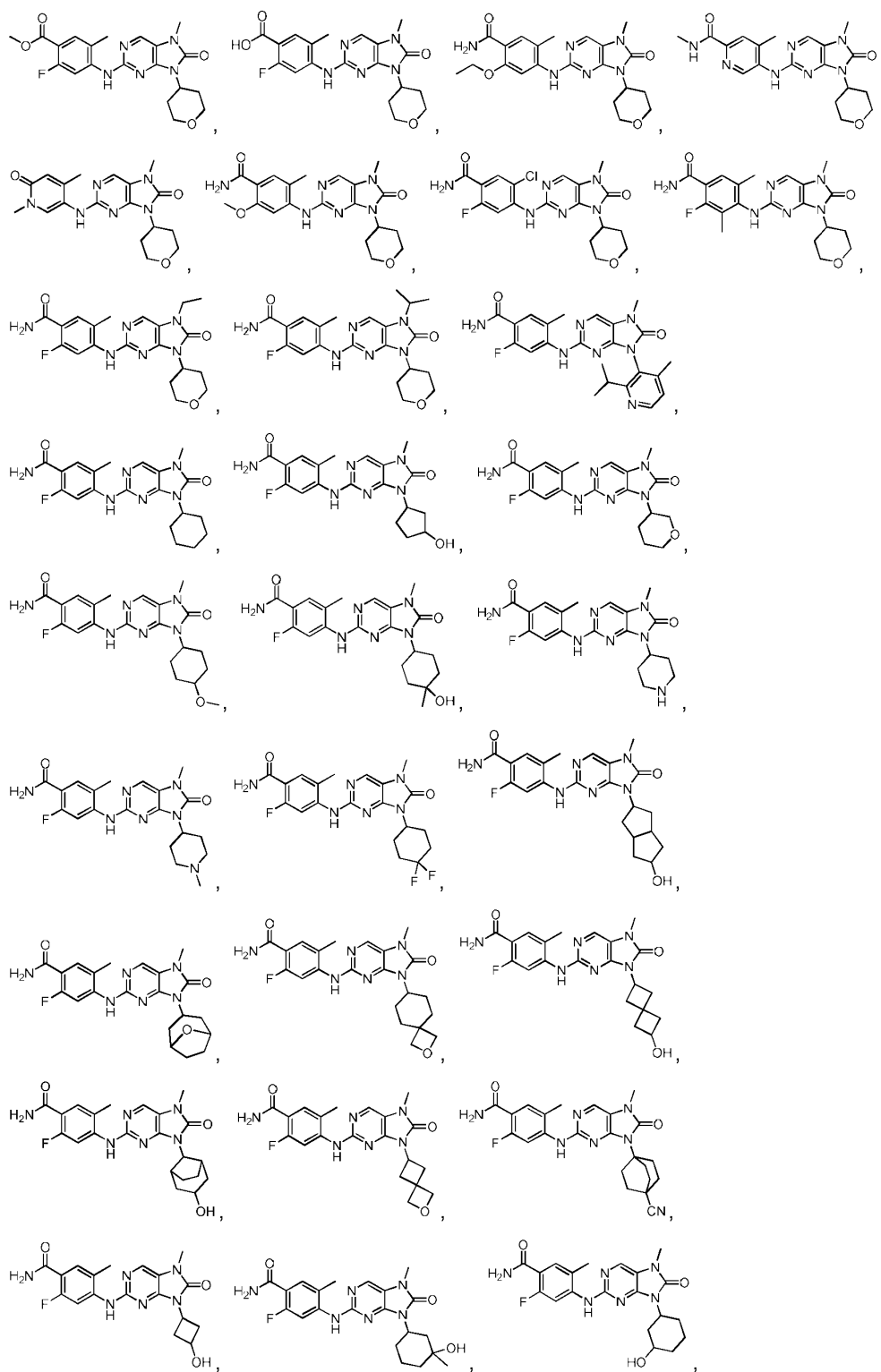


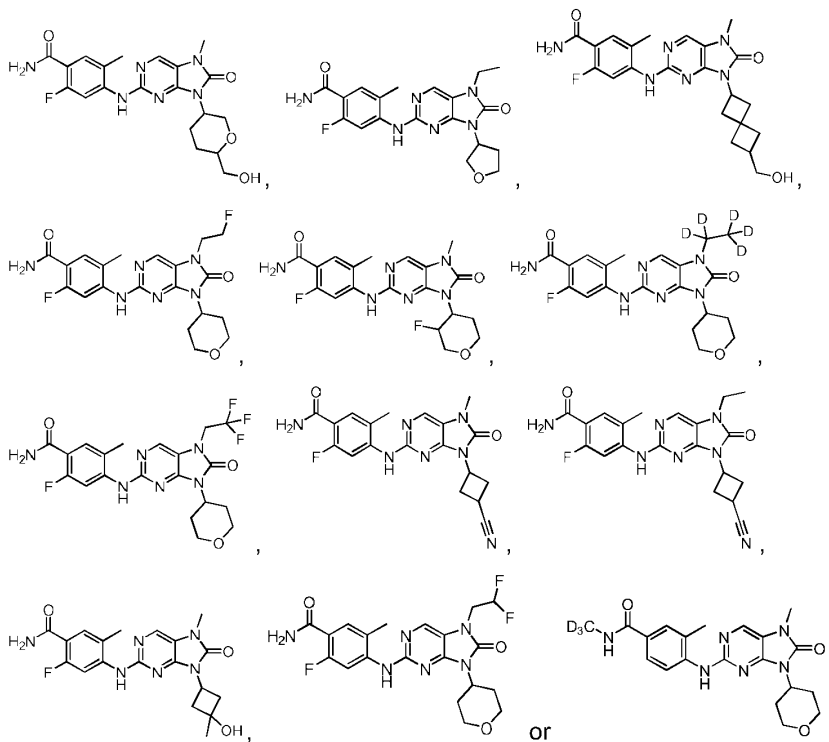


In one or more embodiments of the present application, the active ingredient is selected from:

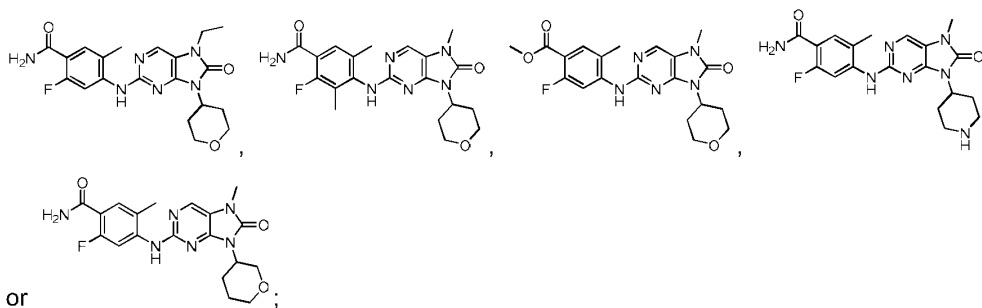






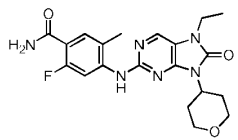


In an embodiment, the compound of Formula I is



or a stereoisomer, solvate, or pharmaceutically acceptable salt.

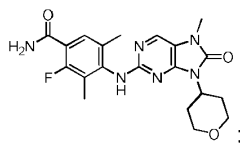
In an embodiment, the compound of Formula I is Compound A:



10

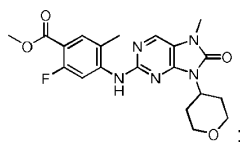
or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

In an embodiment, the compound of Formula I is:



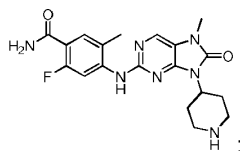
or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

In an embodiment, the compound of Formula I is:



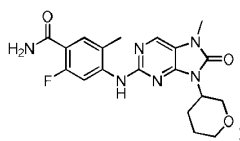
5 or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

In an embodiment, the compound of Formula I is:



or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

In an embodiment, the compound of Formula I is:



10

or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

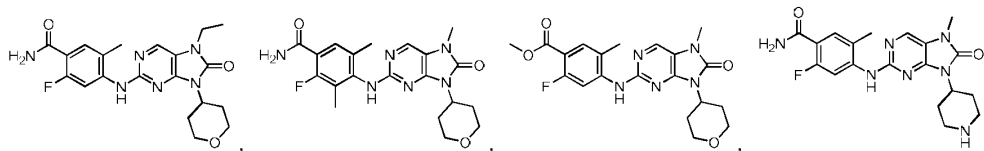
In an embodiment, the compound of formula (I) is a compound of formula (I), or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

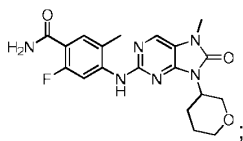
In an embodiment, the RDC is ^{177}Lu -PSMA-617.

15 In an embodiment, the compound of formula (I) is Compound A, or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof, and the RDC is ^{177}Lu -PSMA-617.

In an aspect, provided herein is a method of treating a tumor in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a RDC. In an

20 embodiment of this method, the compound of Formula I is

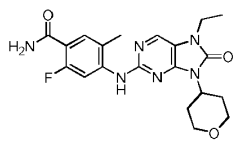




or

or a stereoisomer, solvate, or pharmaceutically acceptable salt.

In another embodiment of the method, the compound of Formula I is Compound A:



5 or a stereoisomer, solvate, or pharmaceutically acceptable salt.

In still another embodiment of the method, the RDC is 177Lu-PSMA-617.

The tumor can be a solid tumor, e.g., prostate cancer.

In one or more embodiments of the present application, the active ingredient, when used in combination with RDC, has the effect of increasing the sensitivity of tumors to radiotherapy.

In one or more embodiments of the present application, the tumor is selected from a solid tumor.

In one or more embodiments of the present application, the tumor is selected from neuroendocrine tumors, esophageal cancer, lung cancer, head and neck cancer, gastric cancer, pleural mesothelioma, thymic carcinoma, kidney cancer, bladder cancer, hepatocellular carcinoma, colorectal cancer, lymphoma, nasopharyngeal cancer, ovarian cancer, breast cancer, fibrosarcoma, myosarcoma, liposarcoma, chondrosarcoma, osteoblastic sarcoma, malignant tumors of urethra, thyroid cancer, malignant tumors of anal canal, malignant tumors of bone and soft tissue, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, pancreatic cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, hepatocellular carcinoma, cholangiocarcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, small cell lung cancer, epithelial cancer, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, chronic leukemia, polycythemia vera, multiple myeloma, Waldenstrom's macroglobulinemia or heavy chain disease, or any combination thereof.

In an embodiment, the tumor is prostate cancer. In an embodiment, the tumor is an adenocarcinoma. In an embodiment, the tumor is androgen-sensitive prostate adenocarcinoma or hormone-sensitive prostate cancer (HSPC).

In one or more embodiments of the present application, the neuroendocrine tumor
5 comprises SSTR-positive neuroendocrine tumors of the gastrointestinal tract and pancreas, an SSTR-positive bronchial neuroendocrine tumors, unresectable or metastatic SSTR-positive neuroendocrine tumors, aggressive neuroendocrine tumors of the gastrointestinal tract and pancreas, neuroendocrine tumors of the gastrointestinal tract with liver metastases, bronchial neuroendocrine tumors with liver metastases, neuroendocrine tumors of unknown
10 primary site with liver metastases, and other SSTR-positive neuroendocrine tumors; the prostate cancer comprises PSMA-positive metastatic castration-resistant prostate cancer, metastatic neuroendocrine prostate cancer, metastatic castration-resistant prostate cancer without chemotherapy, and progressive metastatic castration-resistant prostate cancer; the neuroblastoma comprises SSTR-positive refractory or relapsed neuroblastoma; the
15 glioblastoma comprises newly diagnosed glioblastoma, progressive glioblastoma, and relapsed glioblastoma; the leukemia is selected from acute lymphocytic leukemia or acute myeloblastic leukemia, and the acute myeloblastic leukemia comprises myeloblastic leukemia, promyelocytic leukemia, myelomonocytic leukemia, monocytic leukemia and/or erythroleukemia; the chronic leukemia comprises chronic myelogenous/granulocytic
20 leukemia and/or chronic lymphocytic leukemia; the lymphoma comprises Hodgkin lymphoma and/or non-Hodgkin lymphoma; the gastric cancer comprises gastric adenocarcinoma; the head and neck cancer comprises tongue adenoid cystic carcinoma and/or adenoid cystic carcinoma; the lung cancer comprises limited-stage small cell lung cancer, extensive-stage small-cell lung cancer, non-small cell lung cancer, pulmonary large-cell neuroendocrine
25 carcinoma, lung adenocarcinoma, pulmonary sarcomatoid carcinoma, and/or lung squamous cell carcinoma and CNS metastatic lung cancer; the cervical cancer comprises cervical squamous cell carcinoma; the breast cancer comprises invasive ductal carcinoma, ductal carcinoma, relapsed breast cancer, and CNS metastatic breast cancer; and the ovarian cancer comprises ovarian clear cell carcinoma or ovarian serous carcinoma.

30 In an embodiment of the methods and uses, the method or use involves the administration of a therapeutically effective amount of a combination or composition comprising compounds provided herein, or pharmaceutically acceptable salts thereof, to a subject (including, but not limited to a human or animal) in need of treatment (including a subject identified as in need).

35 In another embodiment of the methods and uses, the treatment includes co-administering the compound of Formula I and the RDC. In an embodiment, the compound of Formula I and the RDC are in a single formulation or unit dosage form. In still other

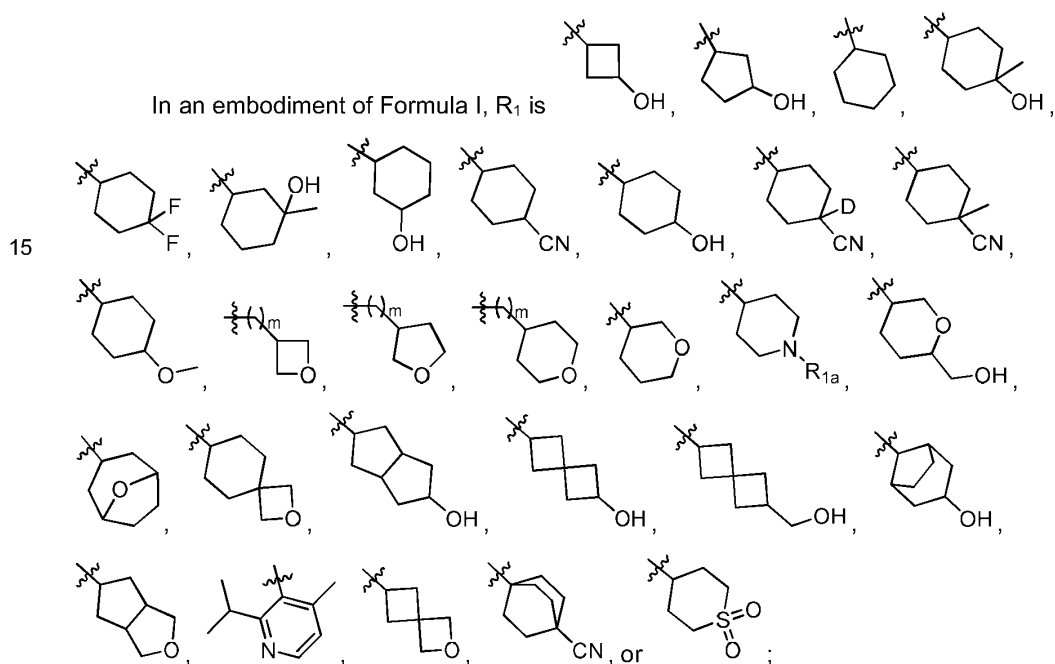
embodiments, the compound of Formula I and the RDC are in a separate formulations or unit dosage forms.

- In the foregoing methods, the treatment can include administering the compound of Formula I and the RDC at substantially the same time or administering the compound of Formula I and the RDC at different times. In some embodiments of the foregoing methods, the compound of Formula I and/or the RDC is administered at dosages that would not be effective when one or both of the compound of Formula I and the RDC is administered alone, but which amounts are effective in combination.

10 *Pharmaceutical Combinations*

In an aspect, provided herein is a pharmaceutical combination comprising a compound of Formula I, or pharmaceutically acceptable salt thereof, and a radionuclide drug conjugate (RDC).

In an embodiment of Formula I, R_1 is



R_{1a} is H or C_{1-6} alkyl;

- 20 R_2 is H, cyano, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, $-S(=O)_2R_{2a}$ or $-C(=O)OC_{1-6}$ alkyl, wherein the $-C(=O)OC_{1-6}$ alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

- R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D or halogen;
- 25

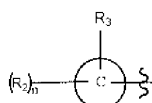
alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S and is optionally further substituted with one or more substituents selected from OH and halogen;

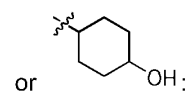
- 5 R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

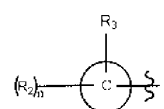
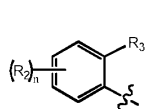
m is 0 or 1; and

n is 0, 1 or 2;

with the provisos that

- 10 when , R_0 , R_2 , and R_3 simultaneously satisfy the following conditions,

R_1 is not , , or ;

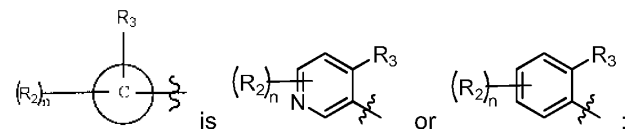
 is , n is 1, R_0 is H or methyl, R_2 is methoxy or -

$S(=O)_2Me$, and R_3 is methyl.

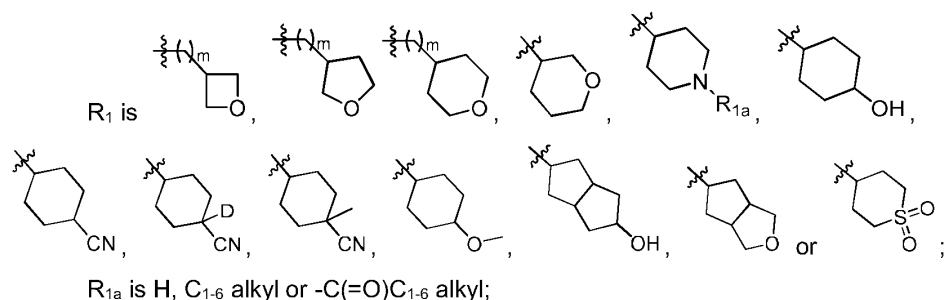
In an embodiment, R_1 is optionally further substituted with hydroxyl substituted C_{1-6} alkyl.

- 15 alkyl.

In another embodiment of Formula I,



- 20 R_0 is H, C_{1-4} alkyl or cyclopropyl, wherein the C_{1-4} alkyl is optionally further substituted with one or more substituents selected from halogen and D;



R_2 is H, cyano, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, $-S(=O)_2R_{2a}$ or $-C(=O)OC_{1-6}$ alkyl, wherein the $-C(=O)OC_{1-6}$ alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl,
 5 wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D and halogen;

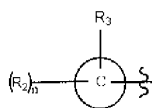
alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S and is also optionally further substituted with one or more substituents selected from OH and
 10 halogen;

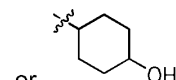
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

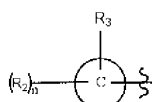
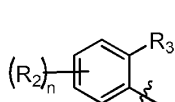
m is 0 or 1; and

n is 0, 1 or 2;

15 with the provisos that

when , R_0 , R_2 , and R_3 simultaneously satisfy the following conditions,

R_1 is not ,  or ;

when  is , n is 1, R_0 is H or methyl, R_2 is methoxy or $-S(=O)_2Me$, and R_3 is methyl.

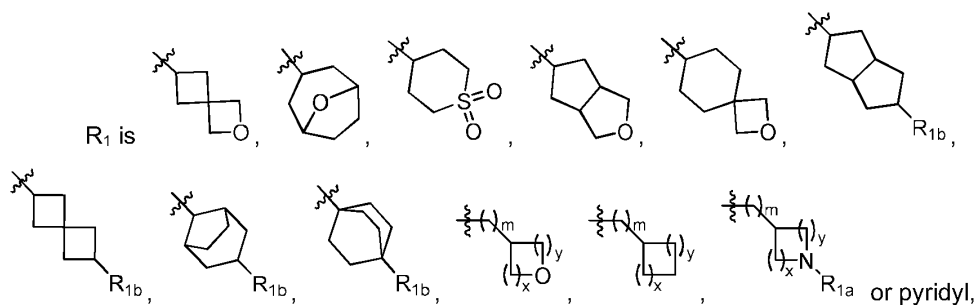
20 In another aspect, provided herein is a pharmaceutical combination comprising a compound of Formula II, or pharmaceutically acceptable salt thereof, and a radionuclide drug conjugate (RDC).

In another aspect, provided herein is a pharmaceutical combination comprising a compound of Formula III, or pharmaceutically acceptable salt thereof, and a radionuclide
 25 drug conjugate (RDC).

In another aspect, provided herein is a pharmaceutical combination comprising a compound of Formula IV, or pharmaceutically acceptable salt thereof, and a radionuclide drug conjugate (RDC).

In an embodiment of the formulae,

30 R_0 is H, C_{1-6} alkyl or cyclopropyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

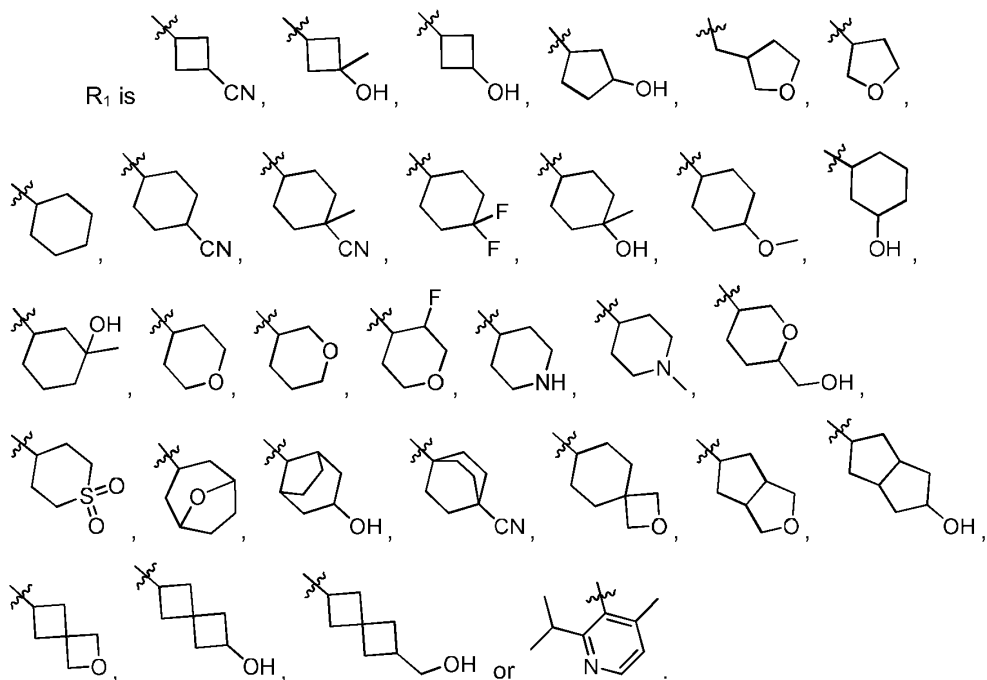


and R₁ is optionally further substituted with 1 to 2 substituents selected from D, halogen, cyano, hydroxyl, C₁₋₆ alkyl and C₁₋₆ alkoxy;

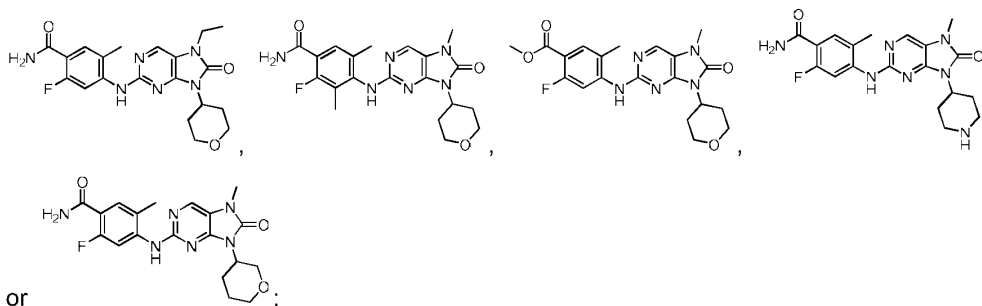
- 5 R_{1a} is H or C₁₋₆ alkyl;
 R_{1b} is H, OH, cyano, or hydroxyl substituted C₁₋₆ alkyl;
 m is 0 or 1; and
 x and y are each independently 1, 2 or 3.

In another embodiment of the formulae,

- 10 R₀ is C₁₋₄ alkyl, wherein the C₁₋₄ alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium; and



In another embodiment, the compound of Formulae I, II, III, and IV is selected from the compounds disclosed *supra*. In another embodiment, the compound of Formulae I, II, III, and IV is



or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound of Formulae I, II, III, and IV is Compound A. In

5 another embodiment, the RDC is ^{177}Lu -PSMA-617.

In an embodiment, the pharmaceutical combination comprises Compound A, or a pharmaceutically acceptable salt thereof, and ^{177}Lu -PSMA-617.

In an embodiment, the pharmaceutical combination is for use in the treatment of a tumor. In an embodiment, the tumor is a solid tumor. In an embodiment, the tumor is

10 prostate cancer. In an embodiment, the tumor is an adenocarcinoma. In an embodiment, the tumor is androgen-sensitive prostate adenocarcinoma or hormone-sensitive prostate cancer (HSPC).

In an embodiment, the pharmaceutical combination comprises:

a compound of Formula I, II, III, or IV, or pharmaceutically acceptable salt thereof,

15 and a pharmaceutically acceptable carrier; and

a radionuclide drug conjugate (RDC) and a pharmaceutically acceptable carrier.

The administration of a pharmaceutical combination provided herein may result in a beneficial effect, e.g. a synergistic therapeutic effect, e.g., with regard to alleviating, delaying progression of or inhibiting the symptoms, and may also result in further surprising beneficial

20 effects, e.g., fewer side-effects, an improved quality of life or a decreased morbidity, compared with a monotherapy applying only one of the pharmaceutically active ingredients used in the combination of the invention.

The syntheses and activity of the compounds of Formula I disclosed herein, including Compound A, are described in WO 2021/209055, which is incorporated by

25 reference in its entirety.

Pharmaceutical Compositions

In an aspect, provided herein is a pharmaceutical composition comprising a compound of Formula I, or pharmaceutically acceptable salt thereof, a radionuclide drug

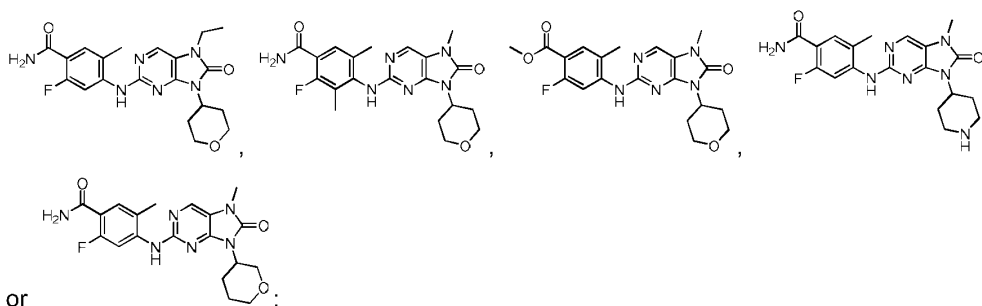
30 conjugate (RDC), and a pharmaceutically acceptable carrier.

In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula II, or pharmaceutically acceptable salt thereof, a radionuclide drug conjugate (RDC), and a pharmaceutically acceptable carrier.

In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula III, or pharmaceutically acceptable salt thereof, a radionuclide drug conjugate (RDC), and a pharmaceutically acceptable carrier.

In an aspect, provided herein is a pharmaceutical composition comprising a compound of Formula IV, or pharmaceutically acceptable salt thereof, a radionuclide drug conjugate (RDC), and a pharmaceutically acceptable carrier.

In another embodiment, the compound of Formulae I, II, III, and IV is selected from the compounds disclosed *supra*. In another embodiment, the compound of Formulae I, II, III, and IV is



or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound of Formulae I, II, III, and IV is Compound A. In another embodiment, the RDC is ^{177}Lu -PSMA-617. In an embodiment, the pharmaceutical composition comprises Compound A, or a pharmaceutically acceptable salt thereof, ^{177}Lu -PSMA-617, and a pharmaceutically acceptable carrier.

In an embodiment, the pharmaceutical composition is for use in the treatment of a tumor. In an embodiment, the tumor is a solid tumor. In an embodiment, the tumor is prostate cancer. In an embodiment, the tumor is an adenocarcinoma. In an embodiment, the tumor is androgen-sensitive prostate adenocarcinoma or hormone-sensitive prostate cancer (HSPC).

Pharmaceutical Formulations

Pharmaceutical formulations or pharmaceutical products are included herein. Such pharmaceutical formulations (e.g., packaged pharmaceutical formulation) include, for example, one or more pharmaceutical formulations comprising a combination of a compound of Formula I and a RDC. The combination in formulated form is contained in a container. The

package typically contains instructions for using the formulation to treat an animal (typically a human patient) suffering from cancer.

In certain embodiments the pharmaceutical formulation (e.g., packaged pharmaceutical formulation) or pharmaceutical product contains the combination described herein in a container with instructions for administering the dosage forms on a fixed schedule. In some of these embodiments, the combination is provided in separate unit dosage forms. In an embodiment, the compound of Formula I and RDC are in a unit dose form. In an embodiment, the compound of Formula I and RDC are in separate unit dose forms.

In a particular embodiment, the combination components can be dosed on the same schedule, whether by administering a single formulation or unit dosage form containing all of the components of the combination, or by administering separate formulations or unit dosage forms of the components of the combination. However, some of the components used in the combination may be administered more frequently than once per day, or with different frequencies than other components in the combination. Therefore, in one embodiment the pharmaceutical formation (e.g., packaged pharmaceutical formulation) contains a formulation or unit dosage form containing all of the components in the combination, and an additional formulation or unit dosage form that includes one of the components in the combination, with no additional active compound, in a container, with instructions for administering the dosage forms on a fixed schedule.

The packaged pharmaceutical formulations provided herein include comprise prescribing information, for example, to a patient or health care provider, or as a label in a packaged pharmaceutical formulation. Prescribing information may include for example efficacy, dosage and administration, contraindication and adverse reaction information pertaining to the pharmaceutical formulation.

In all of the foregoing the combination of components of the present disclosure can be administered alone, as mixtures, or with additional active agents.

Administration / Dosage / Formulations

In another aspect, provided herein is a pharmaceutical composition or pharmaceutical combination comprising the components disclosed herein, together with a pharmaceutically acceptable carrier.

Administration of the combination includes administration of the combination in a single formulation or unit dosage form, administration of the individual agents of the combination concurrently but separately, or administration of the individual agents of the combination sequentially by any suitable route. The dosage of the individual agents of the combination may require more frequent administration of one of the agent(s) as compared to

the other agent(s) in the combination. Therefore, to permit appropriate dosing, packaged pharmaceutical products may contain one or more dosage forms that contain the combination of agents, and one or more dosage forms that contain one of the combination of agents, but not the other agent(s) of the combination.

5 Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

10 In particular, the selected dosage level will depend upon a variety of factors including the activity of the particular agent employed, the time of administration, the rate of excretion of the agent, the duration of the treatment, other drugs, compounds or materials used in combination with the agent, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

15 A medical doctor, e.g., physician or veterinarian, having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could begin administration of the pharmaceutical composition to dose the disclosed agent at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

20 In certain embodiments, a compound of Formula I (e.g., a compound of Formula A) is administered at a dose per day of about 1-3000 mg, for example, about 1-2000 mg (e.g., about 1-1000 mg, or about 1-500 mg). The total daily dose of the compound of Formula I may be administered according to, but not limited to, the following regimen of once a day, twice a day, three times a day, four times a day, five times a day, once a week, twice a
25 week, three times per week, four times per week, five times per week, six times per week, once a month, twice per month, three times per month, four times per month, five times per month, six times per month, seven times per month, eight times per month, nine times per month, or ten or more times per month.

30 Provided herein are methods of administering a therapeutically effective amount of a radionuclide drug conjugate (RDC) in combination with a therapeutically effective amount of the compound of Formula I. In particular embodiments, the dosing of a radionuclide drug conjugate to be administered to a human or other mammal host in single or divided doses may be referred to as administered activity to be delivered to the subject (e.g., human or other mammal host). Administered activity of radionuclide drug conjugates (RDC) is given in
35 units of radioactive disintegrations per unit time (SI units Becquerels (BQ), imperial units Curies (Ci)). The total dose will vary depending on a variety of factors, such as the purpose, i.e., for imaging and/or therapy, and the number of cycles of administration. Dosing may also

be based on energy deposited per unit of mass, i.e., the absorbed dose, usually given in J/kg or Gy).

In some embodiments, the total dose (over the course of a treatment regimen, also referred to herein as a “cumulative dose”) of the radionuclide drug conjugate (RDC), is from about 1 GBq to about 200 GBq. In some embodiments, the radionuclide drug conjugate (RDC) is administered in a total dose to deliver from 40 to 100 GBq of radiation. In some embodiments, the radionuclide drug conjugate (RDC) is administered in a single dose (once within a 24-hour period) to deliver from about 1 to about 20 GBq of radiation. In some embodiments, the radionuclide drug conjugate (RDC) is administered in a single dose (once within a 24-hour period) to deliver from about 3 to about 15 GBq of radiation. In some embodiments, the radionuclide drug conjugate (RDC) is administered in a single dose (once within a 24-hour period) to deliver from about 5 to about 10 GBq of radiation. In some embodiments, the radionuclide drug conjugate (RDC) is administered in a single dose (once within a 24-hour period) to deliver about 7.4 GBq (e.g., 7.4 GBq) of radiation.

In some embodiments, the total dose (over the course of a treatment regimen) of the radionuclide drug conjugate (RDC), is from about 1 MBq to about 100 MBq. In some embodiments, the radionuclide drug conjugate (RDC) is administered in a total dose of from about 20 to about 80 MBq of radiation. In some embodiments, the radionuclide drug conjugate (RDC) is administered in a single dose (once within a 24-hour period) to deliver from about 1 to about 40 MBq of radiation. In some embodiments, the radionuclide drug conjugate (RDC) is administered in a single dose (once within a 24-hour period) to deliver from about 5 to about 40 MBq of radiation. In some embodiments, the radionuclide drug conjugate (RDC) is administered in a single dose (once within a 24-hour period) to deliver from about 5 to about 25 MBq of radiation.

In some embodiments, the radionuclide drug conjugate (RDC) is administered on alternate days, weeks, or months. For example, the radionuclide drug conjugate (RDC) described herein may be administered every two days, or every three days, or every four days, or every five days, or every six days, or every week, or every month. The radionuclide drug conjugate (RDC) described herein may be administered every two weeks, or every three weeks, or every four weeks, or every five weeks, or every six weeks, or every seven weeks, or every eight weeks, or every nine weeks, or every ten weeks. In some embodiments, the radionuclide drug conjugate (RDC) is administered once about every 2 weeks to 10 weeks. In some embodiments, the radionuclide drug conjugate (RDC) is administered once about every 3 weeks to 4 weeks. In some embodiments, the radionuclide drug conjugate (RDC) is administered once about every 4 weeks to 6 weeks (e.g., once about every four weeks, once about every 5 weeks, or once about every 6 weeks).

In some embodiments, provided are methods of treating a tumor in a subject in need thereof, wherein the method comprises administering to the subject: (1) a therapeutically effective amount of a compound of Formula I (e.g., a compound of Formula A), for example, wherein the therapeutically effective amount of a compound of Formula I is a dose per day of about 1-2000 mg (e.g., about 1-1000 mg), and (2) a therapeutically effective amount of a radionuclide drug conjugate (RDC) (e.g., ^{177}Lu -PSMA-617). In some embodiments, provided are methods of treating a tumor in a subject in need thereof, wherein the method comprises administering to the subject: (1) a therapeutically effective amount of a compound of Formula I (e.g., a compound of Formula A), for example, wherein the therapeutically effective amount of a compound of Formula I is a dose of about 1-2000 mg (e.g., about 1-1000 mg), and (2) a single dose (once within a 24-hour period) to deliver about 7.4 GBq of radiation of the radionuclide drug conjugate (RDC) (e.g., ^{177}Lu -PSMA-617) intravenously once about every 4 weeks to 6 weeks (e.g., once about every four weeks, once about every 5 weeks, or once about every 6 weeks, for example, once about every 6 weeks), for up to 6 doses. In some embodiments, the method comprises administering a single dose (once within a 24-hour period) to deliver about 7.4 GBq of radiation of the radionuclide drug conjugate (RDC) (e.g., ^{177}Lu -PSMA-617) intravenously once about every 4 weeks to 6 weeks (e.g., once about every four weeks, once about every 5 weeks, or once about every 6 weeks), for up to 6 doses. In some embodiments, the method comprises administering a single dose (once within a 24-hour period) to deliver about 7.4 GBq of radiation of the radionuclide drug conjugate (RDC) (e.g., ^{177}Lu -PSMA-617) intravenously once about every 6 weeks for up to 6 doses.

Routes of administration of any of the compositions discussed herein include oral, nasal, rectal, intravaginal, parenteral, buccal, sublingual or topical. The compounds may be formulated for administration by any suitable route, such as for oral or parenteral, for example, transdermal, transmucosal (e.g., sublingual, lingual, (trans)buccal, (trans)urethral, vaginal (e.g., trans- and perivaginally), (intra)nasal and (trans)rectal), intravesical, intrapulmonary, intraduodenal, intragastric, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical administration.

Suitable compositions and dosage forms include, for example, tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. It should be understood that the formulations and compositions are not limited to the particular formulations and compositions that are described herein.

For oral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gel caps. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic

5 pharmaceutically excipients that are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay the release of the active ingredients. Formulations for

10 oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

For parenteral administration, the disclosed compounds may be formulated for injection or infusion, for example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose or continuous infusion. Suspensions, solutions

15 or emulsions in an oily or aqueous vehicle, optionally containing other formulatory agents such as suspending, stabilizing or dispersing agents may be used.

The implementation process and beneficial effects of the present invention are described in detail below through specific examples, which are intended to help readers better understand the essence and characteristics of the present invention, and are not

20 intended to limit the scope of implementation of the present invention.

EXAMPLES

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments,

25 claims, and examples described herein. Such equivalents were considered to be within the scope of this disclosure and covered by the claims appended hereto. For example, it should be understood, that modifications in experimental conditions with art-recognized alternatives and using no more than routine experimentation, are within the scope of the present application.

30 It is to be understood that wherever values and ranges are provided herein, all values and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present disclosure. Moreover, all values that fall within these ranges, as well as the upper or lower limits of a range of values, are also contemplated by the present application.

35 The following examples further illustrate aspects of the present disclosure. However, they are in no way a limitation of the teachings of the present disclosure as set forth.

Experimental Example**I. Studies of in vitro cell viability of compound A in combination with various doses of ¹⁷⁷Lu-PSMA-617**

1) LNCaP cells in the logarithmic growth phase were adjusted to a density of 6×10^4 cells/mL, and seeded in a 96-well flat-bottom plate at 50 μ L/well for adherent culturing overnight in a 5% CO₂ cell incubator at 37°C.

2) Compound A was formulated into a 3 μ M working solution for later use. ¹⁷⁷Lu-PSMA-617 was formulated into a 60 MBq/mL working solution, which was then subjected to 2-fold dilution to obtain 30, 15, 7.5, 3.75, 1.875, 0.9375, 0.4688, and 0.2344 MBq/mL working solutions for later use. ¹⁷⁷Lu-PSMA-617 was purchased from Eczacıbaşı-Monrol Nuclear Products Co. (Monrol).

3) The compound A working solution was added at 50 μ L/well in the combined treatment group, and an equal volume of a cell culture medium was added in the normal control group, blank control group, nuclide-based drug group and solvent control group, followed by incubation for 1 h under conditions of 37°C and 5% CO₂.

4) The ¹⁷⁷Lu-PSMA-617 working solution was added at 50 μ L/well in the nuclide-based drug group and combined treatment group, an equal volume of a cell culture medium was added in the normal control group and blank control group, and a solvent-diluted solution of ¹⁷⁷Lu-PSMA-617 was added at 50 μ L/well to the solvent control group.

5) The cells and drug were incubated in a 5% CO₂ cell incubator at 37°C for 4 days and observed under the microscope every 24 h during incubation.

6) The cell culture medium was discarded, and the cells were washed 2-3 times with PBS then supplemented again with a cell culture medium at 100 μ L/well for CCK-8 cell viability detection.

Blank control group: 150 μ L cell culture medium.

Normal control group: 50 μ L cell suspension and 100 μ L cell culture medium.

Nuclide-based drug group: 50 μ L cell suspension, 50 μ L ¹⁷⁷Lu-PSMA-617, and 50 μ L cell culture medium, with the dose of ¹⁷⁷Lu-PSMA-617 decreased gradually (10, 5, 2.5, 1.25, 0.625, 0.3125, 0.1563, 0.0781, and 0 MBq/mL) from left to right.

Combined treatment group: 50 μ L cell suspension, 50 μ L ¹⁷⁷Lu-PSMA-617, and 50 μ L compound A, with the dose of ¹⁷⁷Lu-PSMA-617 decreased gradually (10, 5, 2.5, 1.25, 0.625, 0.3125, 0.1563, 0.0781, and 0 MBq/mL) from left to right.

Solvent control: 50 μ L cell suspension, 50 μ L solvent-diluted solution of ¹⁷⁷Lu-PSMA-617, and 50 μ L cell culture medium.

CCK8 cell viability detection

1) A CCK-8 solution was added at an amount of 10% by volume of the cell culture medium per well to avoid the generation of bubbles.

2) Incubation was carried out in a CO₂ cell incubator for 1-4 h.

5 3) The absorbance at 450 nm was measured with a microplate reader.

Data analysis

Calculation formula of cell viability:

$$\text{Cell viability}\% = \left| \frac{A - C}{B - C} \right| \times 100\%$$

10 Notes: A: Optical density (OD) value of the experimental group (containing a culture medium, cells, a drug, and a CCK-8 solution);

B: OD value of the experimental control group (containing a culture medium, cells, and a CCK-8 solution); and

15 C: OD value of the blank control group (containing a culture medium, and a CCK-8 solution).

The statistical analysis of the detection results was conducted using Excel and Graphpad prism, followed by plotting. The results are shown in Table 1, Table 2, FIG. 1 and FIG. 2.

Table 1 Inhibitory effect of Compound A

LNCaP	4 days
Group	IC₅₀ (μM)
Compound A	5.903

20

Table 2 Combined inhibitory effect

LNCaP	4 days
Group	IC₅₀ (MBq/mL)
¹⁷⁷ Lu-PSMA-617	0.6572
¹⁷⁷ Lu-PSMA-617 + 1 μM compound A	0.06276

Conclusion: the compound A in the present application can significantly enhance the growth inhibitory effect of ¹⁷⁷Lu-PSMA-617 on LNCaP.

25

II. Clinical evaluation

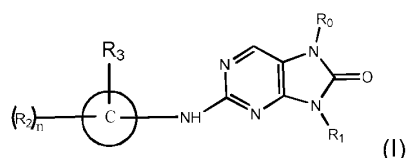
The results of the clinical studies show that the combined treatment regimens of the present application when applied to patients with tumors such as prostate cancer and

neuroendocrine tumor, result in a strong synergistic therapeutic effect, and throughout the treatment, the patients are safe, have a good tolerance, and are significantly benefited.

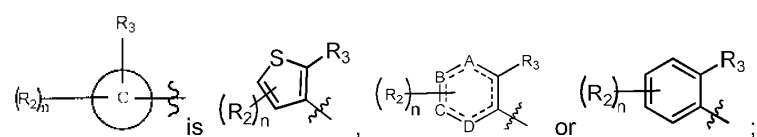
Specific embodiments are described in detail in the description of the present invention. A person skilled in the art should recognize that the embodiments described above are exemplary and cannot be construed as limiting the present invention. Additionally, a person skilled in the art can make several improvements and modifications to the present invention without departing from the principle of the present invention, and the technical solutions obtained based on these improvements and modifications also fall within the scope of protection of the claims of the present invention.

CLAIMS

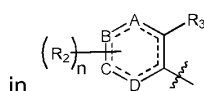
1. Use of a compound represented by formula (I), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt or co-crystal thereof as an active ingredient for the treatment of a tumor in combination with RDC;



wherein

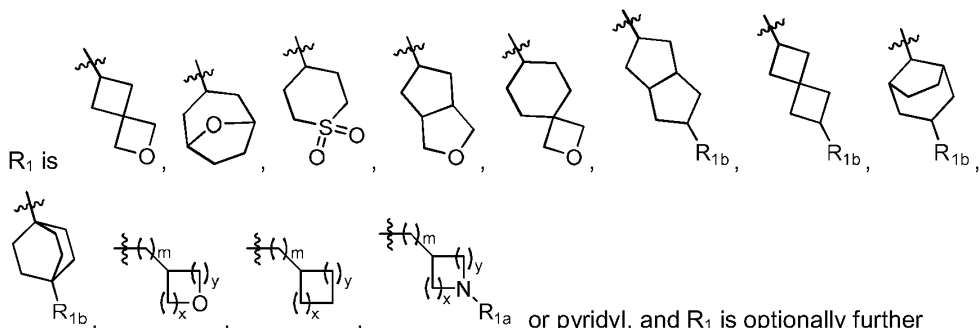


== is a single bond or double bond:



in , A, B, C, D are each independently C or N, and at least one of A, B, C and D is N;

R₀ is H, C₁₋₆ alkyl or cyclopropyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;



substituted with 1 or 2 substituents selected from D, halogen, cyano, hydroxyl, C₁₋₆ alkyl and C₁₋₆ alkoxy;

R_{1a} is H or C₁₋₆ alkyl;

R_{1b} is H, OH, cyano, or hydroxyl substituted C₁₋₆ alkyl;

R₂ is H, cyano, =O, carboxyl, -C(=O)NR_{2a}R_{2b}, C₁₋₆ alkoxy, C₁₋₆ alkyl, halogen, -S(=O)₂R_{2a} or -C(=O)OC₁₋₆ alkyl, wherein the C₁₋₆ alkyl, -C(=O)OC₁₋₆ alkyl or C₁₋₆ alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D, halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1, 2 or 3 heteroatoms selected from N, O and S and is optionally further substituted with one or more substituents selected from C_{1-6} alkyl, OH and halogen;

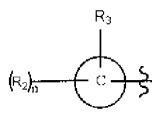
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

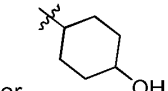
m is 0 or 1;

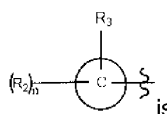
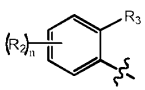
n is 0, 1 or 2; and

x and y are each independently 1, 2 or 3;

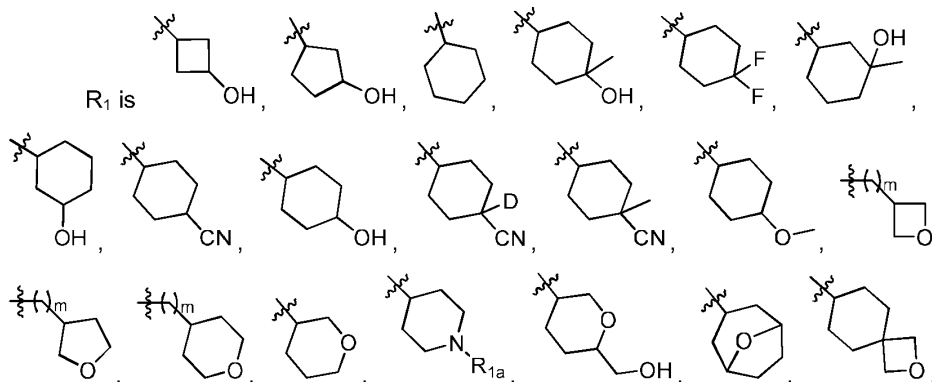
with the provisos that

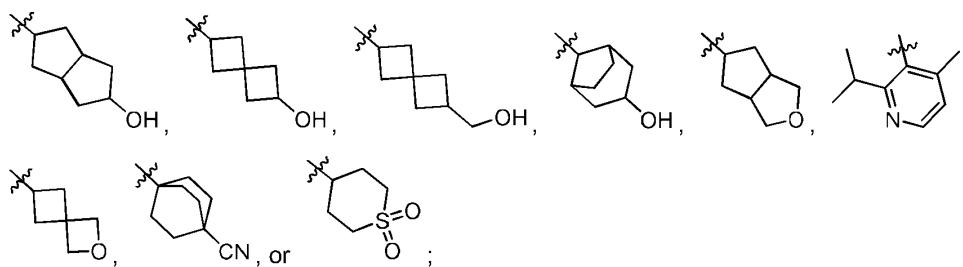
when , R_0 , R_2 , and R_3 simultaneously satisfy the following conditions,

R_1 is not ,  or :

 is , n is 1, R_0 is H or methyl, R_2 is methoxy or $-S(=O)_2Me$, and R_3 is methyl.

2. The use according to claim 1, wherein the active ingredient is a compound of formula (I), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt or co-crystal thereof, wherein





R_{1a} is H or C_{1-6} alkyl;

R_2 is H, cyano, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, $-S(=O)_2R_{2a}$ or $-C(=O)OC_{1-6}$ alkyl, wherein the $-C(=O)OC_{1-6}$ alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D or halogen;

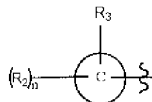
alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S and is optionally further substituted with one or more substituents selected from OH and halogen;

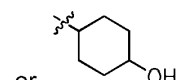
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

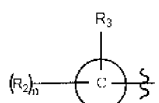
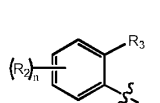
m is 0 or 1; and

n is 0, 1 or 2;

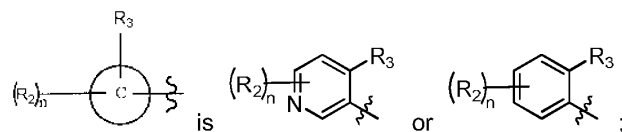
with the provisos that

when , R_0 , R_2 , and R_3 simultaneously satisfy the following conditions,

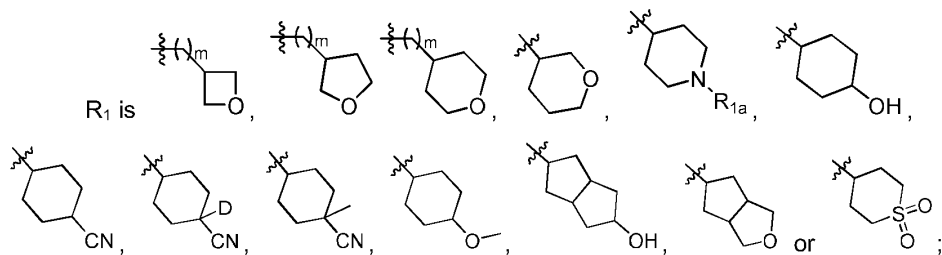
R_1 is not ,  or .

 is , n is 1, R_0 is H or methyl, R_2 is methoxy or $-S(=O)_2Me$, and R_3 is methyl.

3. The use according to claim 1, wherein the active ingredient is the compound of formula (I), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt or co-crystal thereof, wherein



R_0 is H, C_{1-4} alkyl or cyclopropyl, wherein the C_{1-4} alkyl is optionally further substituted with one or more substituents selected from halogen and D;



R_{1a} is H, C_{1-6} alkyl or $-C(=O)C_{1-6}$ alkyl;

R_2 is H, cyano, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, $-S(=O)_2R_{2a}$ or $-C(=O)OC_{1-6}$ alkyl, wherein the $-C(=O)OC_{1-6}$ alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D and halogen;

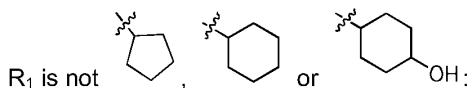
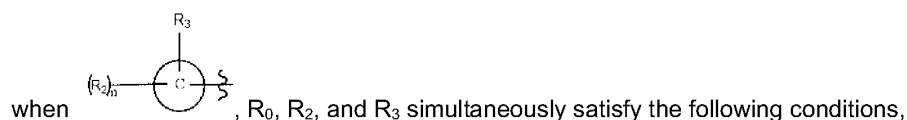
alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocycl, which contains 1 to 3 heteroatoms selected from N, O and S and is also optionally further substituted with one or more substituents selected from OH and halogen;

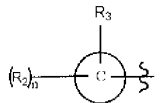
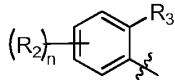
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

m is 0 or 1; and

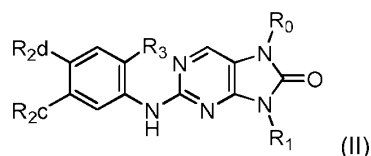
n is 0, 1 or 2;

with the provisos that



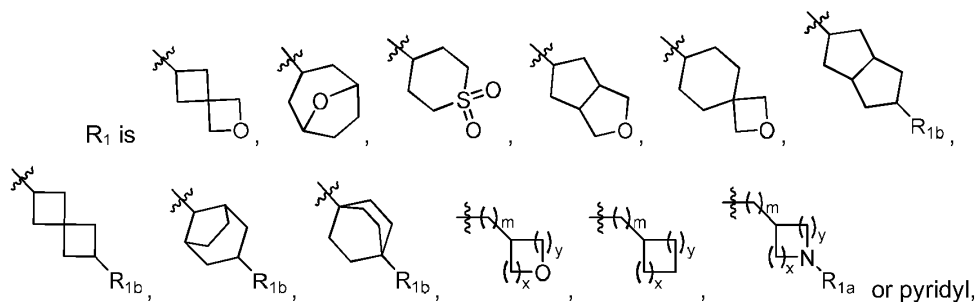
when  is , n is 1, R₀ is H or methyl, R₂ is methoxy or -S(=O)₂Me, and R₃ is methyl.

4. The use according to claim 1, wherein the active ingredient is selected from a compound of formula (II), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt or co-crystal thereof:



wherein

R₀ is H, C₁₋₆ alkyl or cyclopropyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;



and R₁ is optionally further substituted with 1 to 2 substituents selected from D, halogen, cyano, hydroxyl, C₁₋₆ alkyl and C₁₋₆ alkoxy;

R_{1a} is H or C₁₋₆ alkyl;

R_{1b} is H, OH, cyano, or hydroxyl substituted C₁₋₆ alkyl;

R_{2c} is H, cyano, halogen or C₁₋₆ alkoxy;

R_{2d} is H, cyano, carboxyl, -C(=O)NR_{2a}R_{2b}, C₁₋₆ alkyl, halogen, -S(=O)₂R_{2a} or -C(=O)OC₁₋₆ alkyl, wherein the C₁₋₆ alkyl and -C(=O)OC₁₋₆ alkyl is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are H, C₁₋₆ alkyl, or 3- to 5-membered cycloalkyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from OH, D, halogen, C₁₋₆ alkyl and C₁₋₆ alkoxy;

alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S

and is optionally further substituted with one or more substituents selected from C₁₋₆ alkyl, OH and halogen;

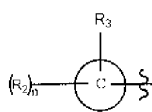
R₃ is halogen or C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

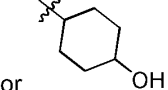
m is 0 or 1;

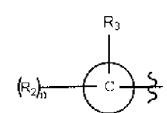
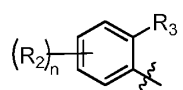
n is 0, 1 or 2; and

x and y are each independently 1, 2 or 3;

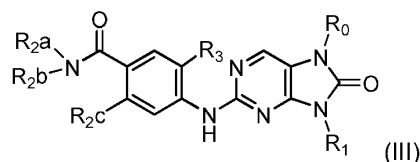
with the provisos that

when , R₀, R₂, and R₃ simultaneously satisfy the following conditions,

R₁ is not , , or :

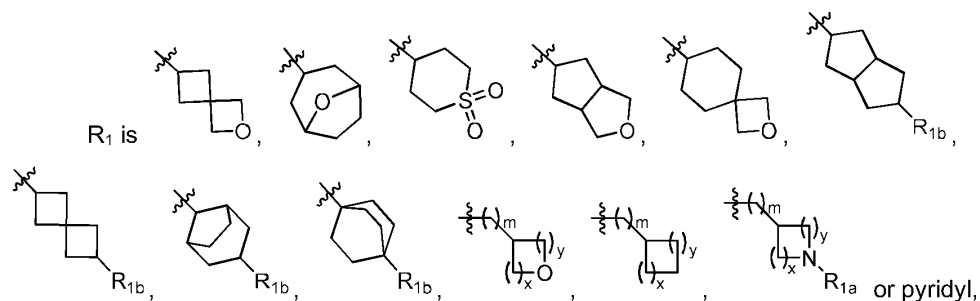
 is selected from , n is 1, R₀ is H or methyl, R₂ is methoxy or -S(=O)₂Me, and R₃ is methyl.

5. The use according to claim 4, wherein the active ingredient is selected from a compound of formula (III), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt or co-crystal thereof:



wherein

R₀ is H, C₁₋₆ alkyl or cyclopropyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;



and R₁ is optionally further substituted with 1 to 2 substituents selected from D, halogen, cyano, hydroxyl, C₁₋₆ alkyl and C₁₋₆ alkoxy;

R_{1b} is H, OH, cyano, or hydroxyl substituted C₁₋₆ alkyl;

R_{2a} and R_{2b} are each independently H, C₁₋₆ alkyl, or 3- to 5-membered cycloalkyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from D or halogen;

alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S and is optionally further substituted with one or more substituents selected from C₁₋₆ alkyl, OH and halogen;

R_{2c} is H, cyano, halogen or C₁₋₆ alkoxy, wherein the C₁₋₆ alkoxy is optionally substituted with one or more deuterium;

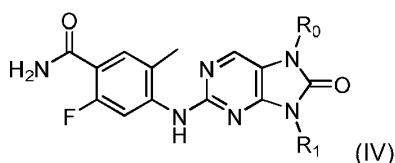
R₃ is halogen or C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally further substituted with 1 to 3 substituents selected from D or halogen;

m is 0 or 1;

n is 0, 1 or 2; and

x and y are each independently 1, 2 or 3.

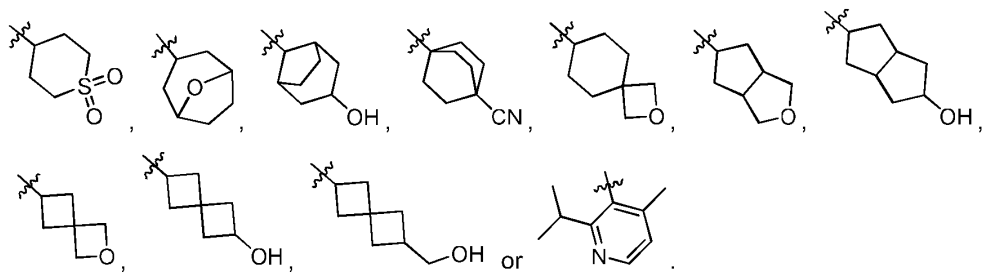
6. The use according to claim 1, wherein the active ingredient is selected from a compound of formula (IV), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt or co-crystal thereof:



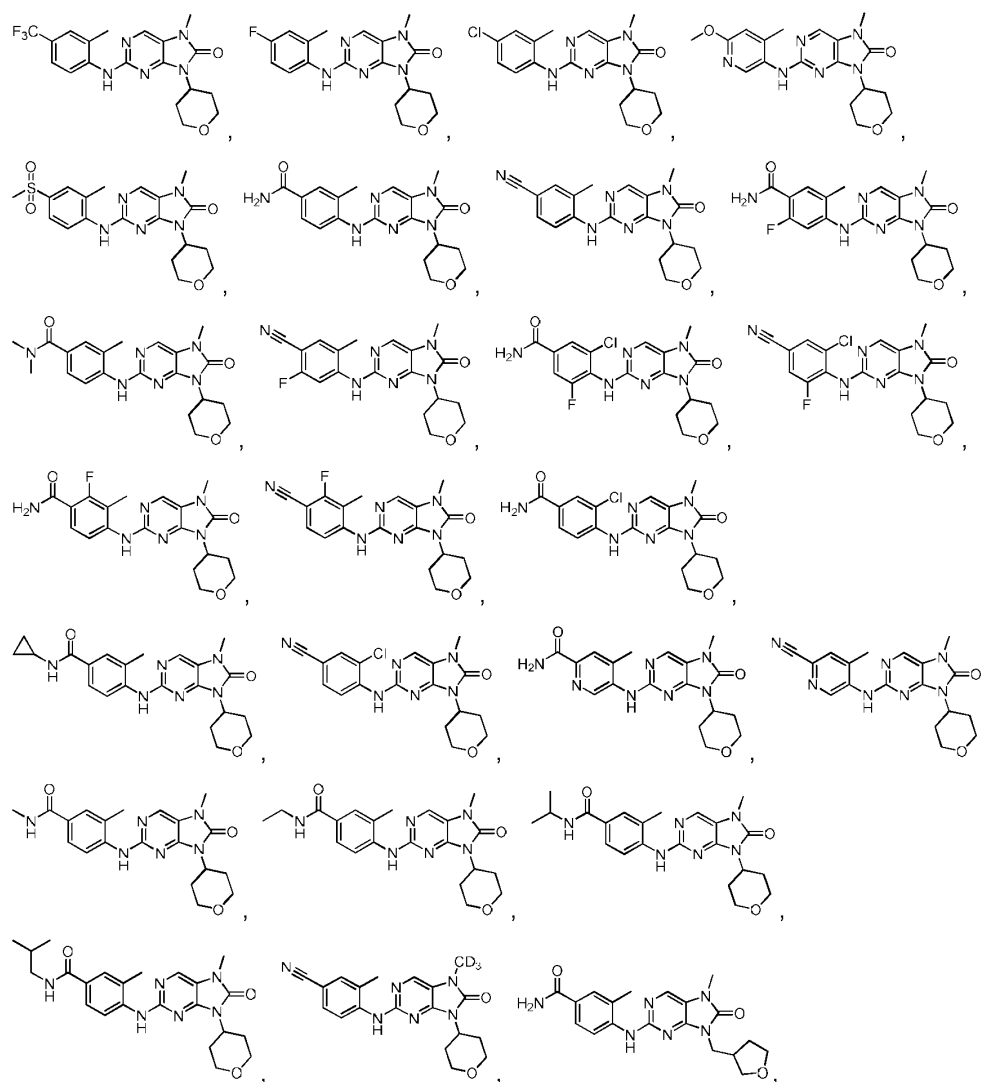
wherein

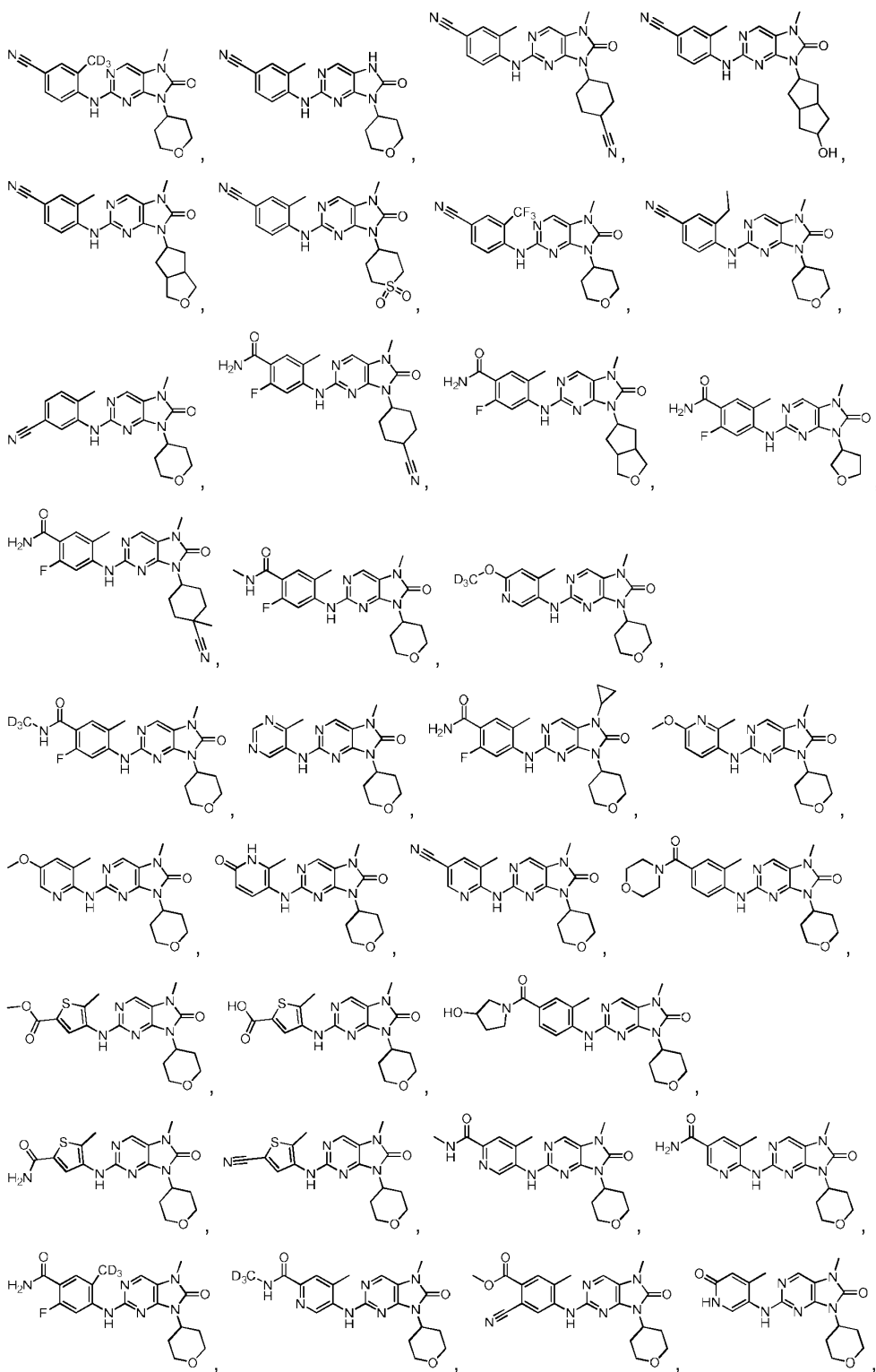
R₀ is H, C₁₋₆ alkyl or cyclopropyl, wherein the C₁₋₆ alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium; and

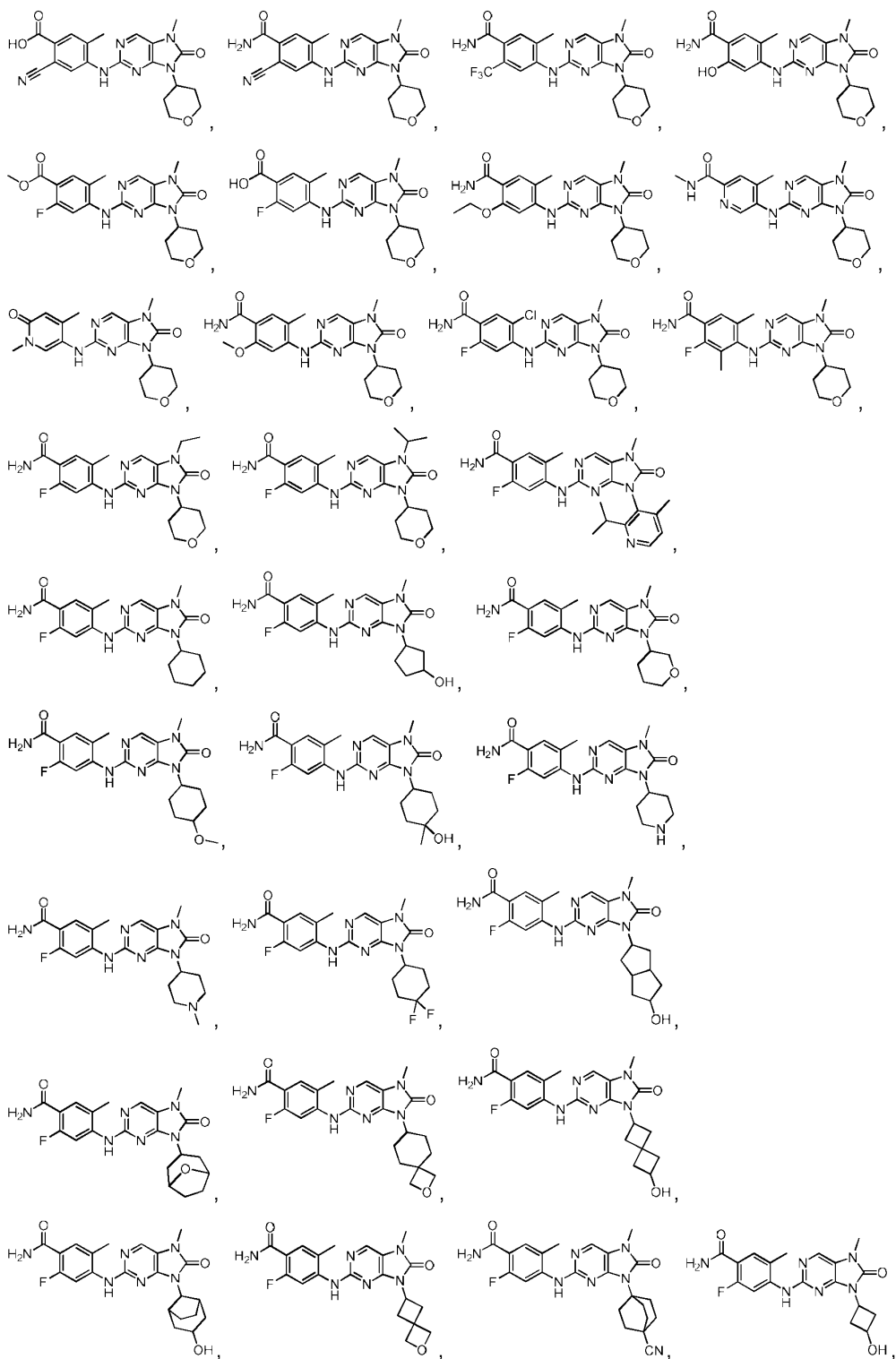
R₁ is -(CH)_m-4- to 7-membered carbocyclyl, -(CH)_m-4- to 7-membered heterocyclyl, -(CH)_m-8- to 12-membered bridged ring, -(CH)_m-7- to 12-membered spiro ring, wherein the -(CH)_m-4- to 7-membered carbocyclyl, -(CH)_m-4- to 7-membered heterocyclyl, -(CH)_m-8- to 12-membered bridged ring, or -(CH)_m-7- to 12-membered spiro ring is optionally further substituted with one or more substituents selected from hydroxy, cyano, halogen, =O, C₁₋₆ alkyl, C₁₋₆ alkoxy, and hydroxy substituted C₁₋₆ alkyl.

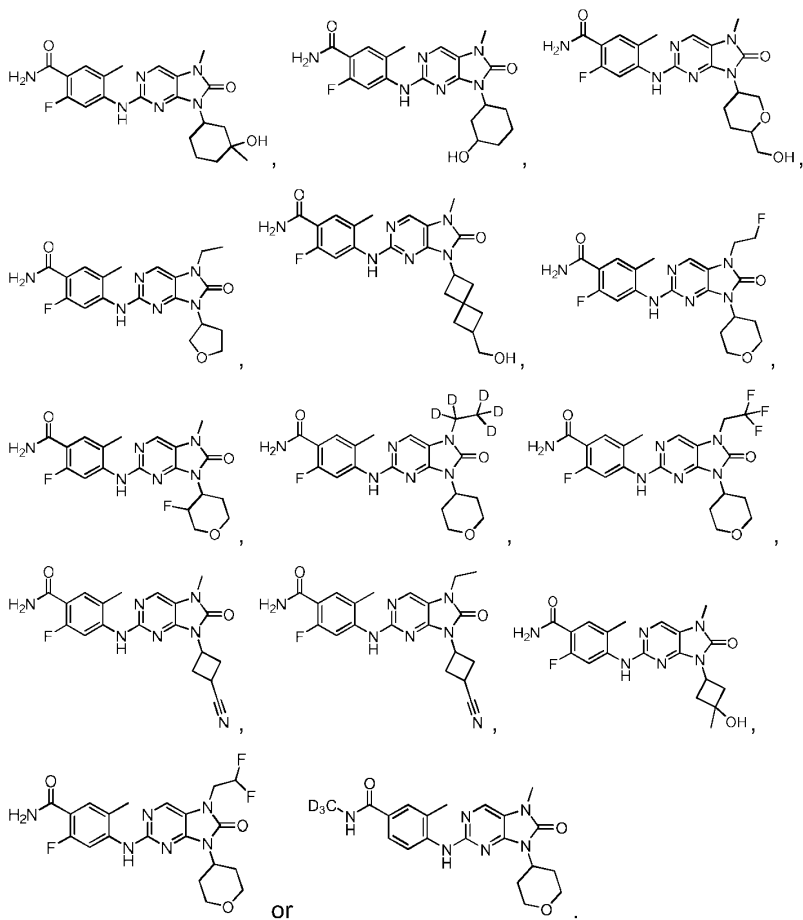


9. The use according to claims 1-8, wherein the active ingredient is selected from:

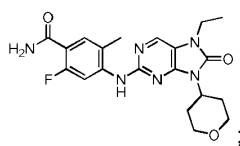






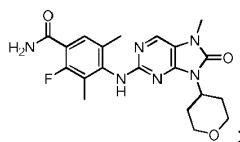


10. The use according to any one of claims 1 to 9, wherein the compound of Formula I is Compound A:



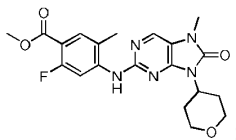
or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

11. The use according to any one of claims 1 to 9, wherein the compound of Formula I is:



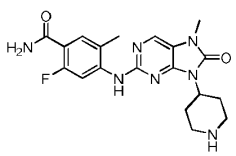
or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

12. The use according to any one of claims 1 to 9, wherein the compound of Formula I is:



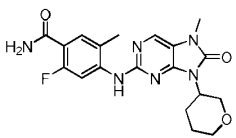
or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

13. The use according to any one of claims 1 to 9, wherein the compound of Formula I is:



or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

14. The use according to any one of claims 1 to 9, wherein the compound of Formula I is:



or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

15. The use according to any one of claims 1 to 14, wherein the RDC is ^{177}Lu -PSMA-617.

16. The use according to any one of claims 1 to 15, wherein the tumor is selected from a solid tumor.

17. The use according to any one of claims 1 to 16, wherein the tumor is selected from neuroendocrine tumors, esophageal cancer, lung cancer, head and neck cancer, gastric cancer, pleural mesothelioma, thymic carcinoma, kidney cancer, bladder cancer, hepatocellular carcinoma, colorectal cancer, lymphoma, nasopharyngeal cancer, ovarian cancer, breast cancer, fibrosarcoma, myosarcoma, liposarcoma, chondrosarcoma,

osteoblastic sarcoma, malignant tumors of urethra, thyroid cancer, malignant tumors of anal canal, malignant tumors of bone and soft tissue, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, pancreatic cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, hepatocellular carcinoma, cholangiocarcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, small cell lung cancer, epithelial cancer, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, chronic leukemia, polycythemia vera, multiple myeloma, Waldenstrom's macroglobulinemia or heavy chain disease, or any combination thereof.

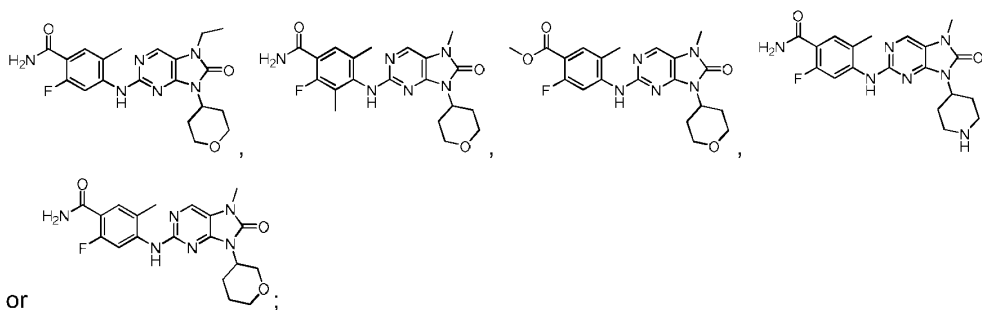
18. The use according to any one of claims 1 to 16, wherein the tumor is prostate cancer.

19. The use according to claim 17, wherein the neuroendocrine tumor comprises SSTR-positive neuroendocrine tumors of the gastrointestinal tract and pancreas, an SSTR-positive bronchial neuroendocrine tumors, unresectable or metastatic SSTR-positive neuroendocrine tumors, aggressive neuroendocrine tumors of the gastrointestinal tract and pancreas, neuroendocrine tumors of the gastrointestinal tract with liver metastases, bronchial neuroendocrine tumors with liver metastases, neuroendocrine tumors of unknown primary site with liver metastases, and other SSTR-positive neuroendocrine tumors; the prostate cancer comprises PSMA-positive metastatic castration-resistant prostate cancer, metastatic neuroendocrine prostate cancer, metastatic castration-resistant prostate cancer without chemotherapy, and progressive metastatic castration-resistant prostate cancer; the neuroblastoma comprises SSTR-positive refractory or relapsed neuroblastoma; the glioblastoma comprises newly diagnosed glioblastoma, progressive glioblastoma, and relapsed glioblastoma; the leukemia is selected from acute lymphocytic leukemia or acute myeloblastic leukemia, and the acute myeloblastic leukemia comprises myeloblastic leukemia, promyelocytic leukemia, myelomonocytic leukemia, monocytic leukemia and/or erythroleukemia; the chronic leukemia comprises chronic myelogenous/granulocytic leukemia and/or chronic lymphocytic leukemia; the lymphoma comprises Hodgkin lymphoma and/or non-Hodgkin lymphoma; the gastric cancer comprises gastric adenocarcinoma; the head and neck cancer comprises tongue adenoid cystic carcinoma and/or adenoid cystic

carcinoma; the lung cancer comprises limited-stage small cell lung cancer, extensive-stage small-cell lung cancer, non-small cell lung cancer, pulmonary large-cell neuroendocrine carcinoma, lung adenocarcinoma, CNS metastatic lung cancer, pulmonary sarcomatoid carcinoma, and/or lung squamous cell carcinoma; the cervical cancer comprises cervical squamous cell carcinoma; the breast cancer comprises invasive ductal carcinoma, ductal carcinoma, relapsed breast cancer, and CNS metastatic breast cancer; and the ovarian cancer comprises ovarian clear cell carcinoma or ovarian serous carcinoma.

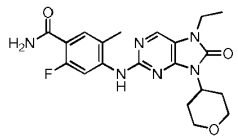
20. A pharmaceutical combination comprising a compound of Formula I, or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof, and a RDC.

21. The pharmaceutical combination of claim 20, wherein the compound of Formula I is



or a stereoisomer, solvate, or pharmaceutically acceptable salt.

22. The pharmaceutical combination according to claim 20 or 21, wherein the compound of Formula I is Compound A:

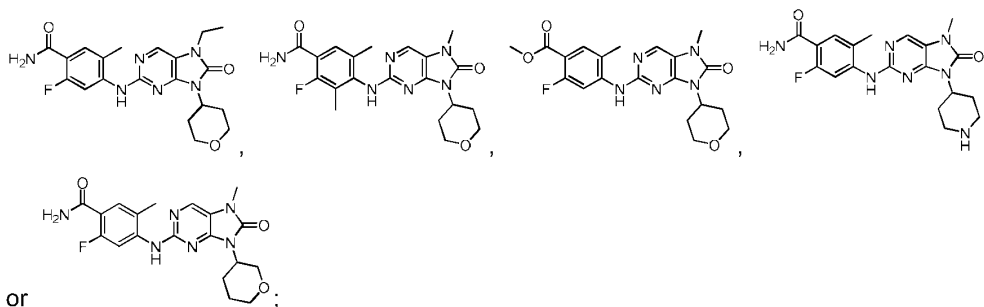


or a stereoisomer, solvate, or pharmaceutically acceptable salt.

23. The pharmaceutical combination according to any one of claims 20 to 22, wherein the RDC is ^{177}Lu -PSMA-617.

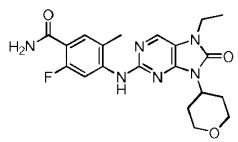
24. A method of treating a tumor in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a RDC.

25. The method according to claim 24, wherein the compound of Formula I is



or a stereoisomer, solvate, or pharmaceutically acceptable salt.

26. The method according to claim 24 or 25, wherein the compound of Formula I is Compound A:



or a stereoisomer, solvate, or pharmaceutically acceptable salt.

27. The method according to any one of claims 24 to 26, wherein the RDC is ^{177}Lu -PSMA-617.

28. The method according to any one of claims 24 to 27, wherein the tumor is a solid tumor.

29. The method according to any one of claims 24 to 28, wherein the tumor is prostate cancer.