REFERENCES

All publications, patent applications, patents, and other references mentioned in the specification are indicative of the level of those skilled in the art to which the presently disclosed subject matter pertains. All publications, patent applications, patents, and other references are herein incorporated by reference to the same extent as if each individual publication, patent application, patent, and other reference was specifically and individually indicated to be incorporated by reference. It will be understood that, although a number of patent applications, patents, and other references are referred to herein, such reference does not constitute an admission that

any of these documents forms part of the common general knowledge in the art. In case of a conflict between the specification and any of the incorporated references, the specification (including any amendments thereof, which may be based on an incorporated reference), shall control. Standard art-accepted meanings of terms are used herein unless indicated otherwise. Standard abbreviations for various terms are used herein.

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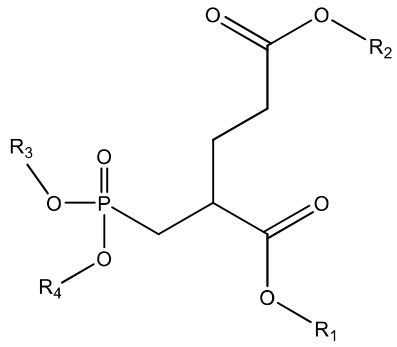
Although the foregoing subject matter has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be understood by those skilled in the art that certain changes and modifications can be practiced within the scope of the appended claims.

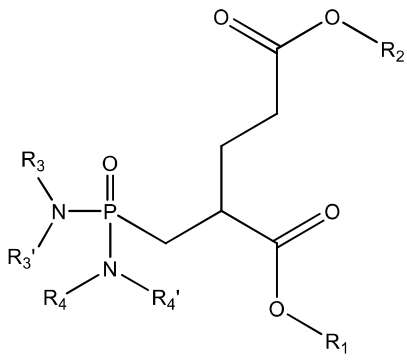
CLAIMS

1. Use of a prodrug of 2-(phosphonomethyl)pentanedioic acid (2-PMPA) in the manufacture of a medicament for preventing or reducing exposure of a prostate-specific membrane antigen (PSMA)-targeted imaging or therapeutic agent in off-target non-cancer tissues, wherein the prodrug of 2-PMPA is to be administered to a subject being treated with a PSMA-targeted agent in an amount effective to prevent or reduce binding of the PSMA-targeted agent to off-target non-cancer tissues,

wherein the prodrug of 2-PMPA comprises a compound of formula (I) or formula (II):



(I);



(II);

wherein:

each R_1, R_2, R_3, and R_4 is independently selected from the group consisting of H, C_1-C_{20} straight-chain or branched alkyl, Ar, -($CR_5R_6)_n$-Ar, -$(CR_5R_6)_n$-O-C(=O)-R_7, -$(CR_5R_6)_n$- C(=O)-O-R_7, -$(CR_5R_6)_n$-O-C(=O)-O-R_7,-$(CR_5R_6)_n$-O-R_7, -$(CR_5R_6)_n$-O-[$(CR_5R_6)_n$-O]$_m$-R_7, -$(CR_5R_6)_n$-Ar-O-C(=O)-R_7,-Ar-C(=O)-O-$(CR_5R_6)_n$-R_7, -$(CR_5R_6)_n$-NR_8R_9, and -$(CR_5R_6)_n$-C(=O)-NR_8R_9, wherein R_1, R_2, R_3, and R_4 cannot all be H at the same time;

wherein:

n is an integer from 1 to 20;

m is an integer from 1 to 20;

each R_3' and R_4' are independently H or C_1-C_4 straight-chain or branched alkyl;

each R_5 and R_6 is independently selected from the group consisting of H, C_1-C_4 straight-chain or branched alkyl, and alkylaryl;

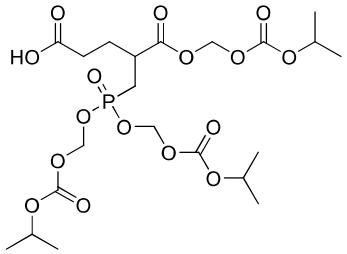
each R_7 is independently straightchain or branched C_1-C_{20} alkyl;

Ar is aryl, substituted aryl, heteroaryl or substituted heteroaryl; and

R_8 and R_9 are each independently H or C_1-C_4 straight-chain or branched alkyl; and

pharmaceutically acceptable salts thereof.

2. The use of claim 1, wherein the compound of formula (I) is selected from the group consisting of: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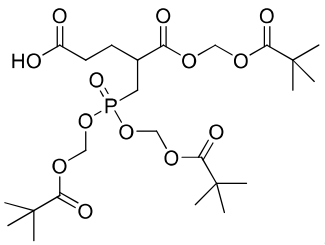
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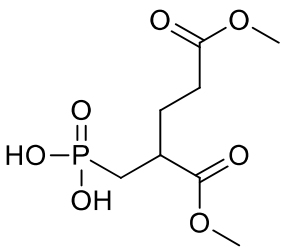
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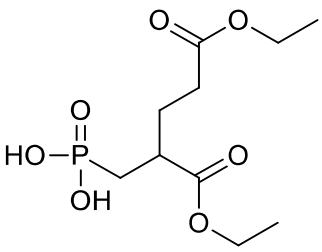
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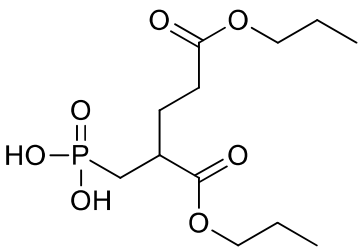
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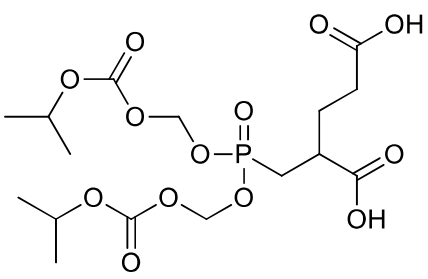
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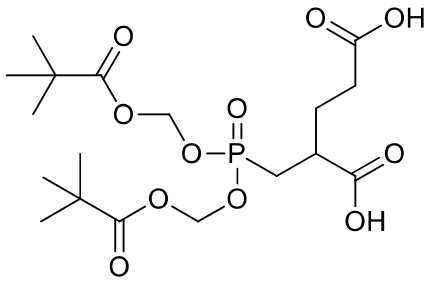
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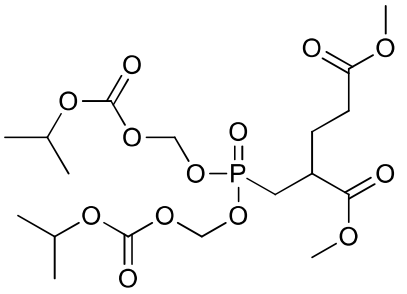
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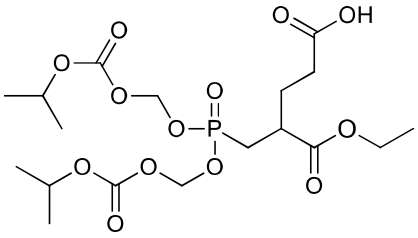
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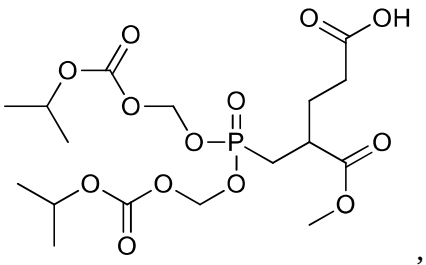
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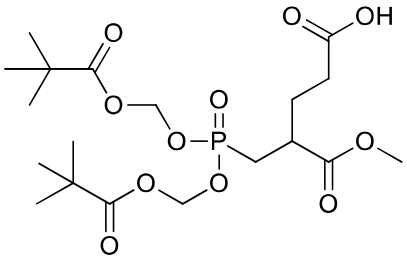
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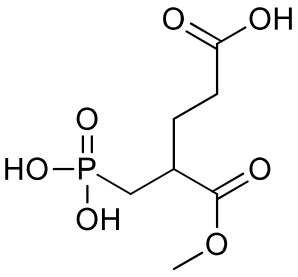
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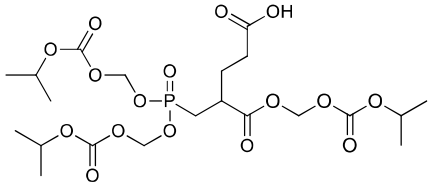
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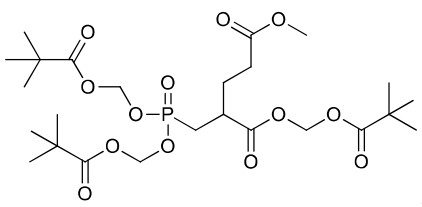
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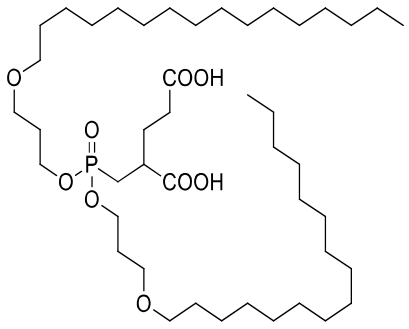
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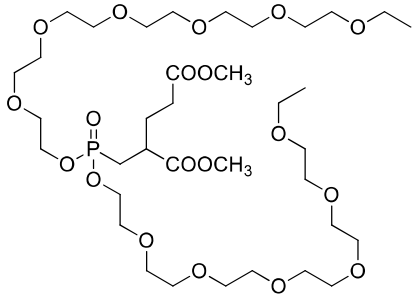
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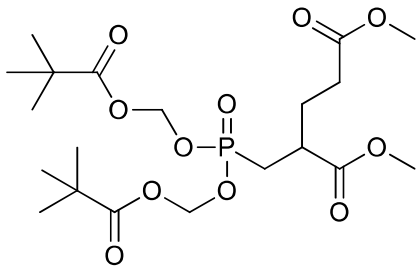
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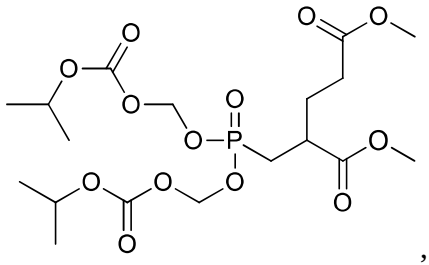
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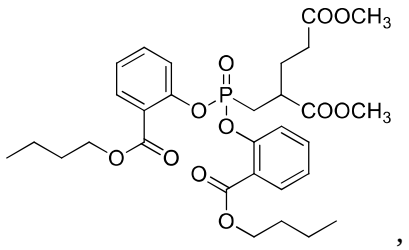
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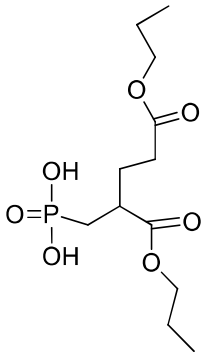
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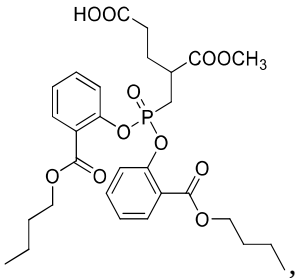
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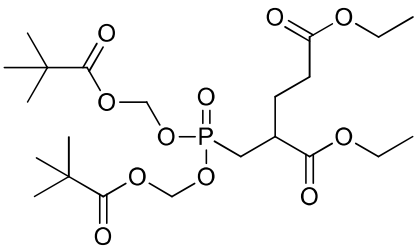
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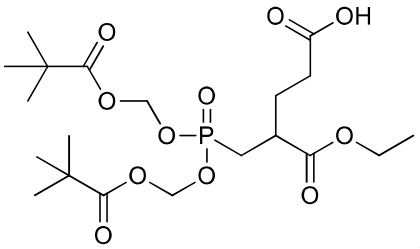
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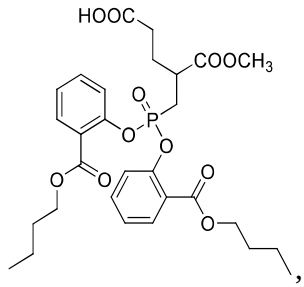
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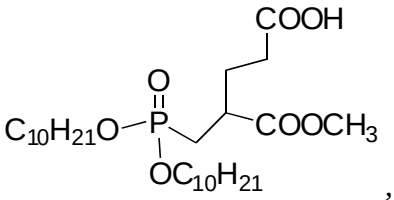
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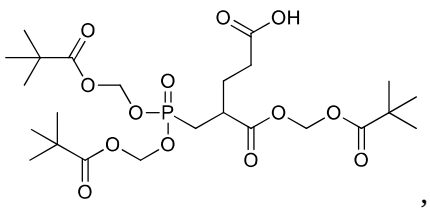
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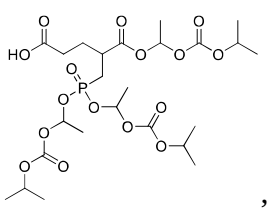
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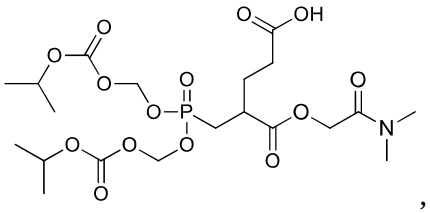
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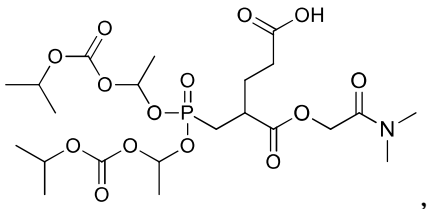
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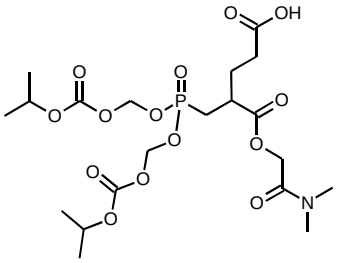
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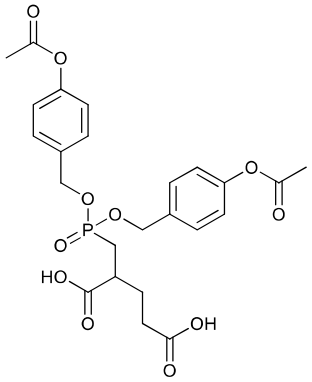
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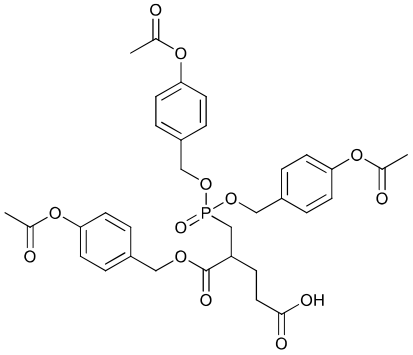
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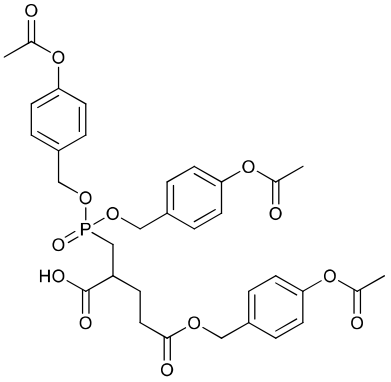
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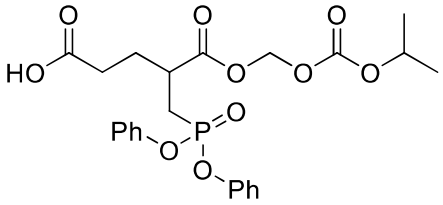
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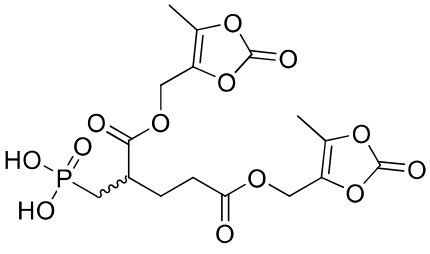
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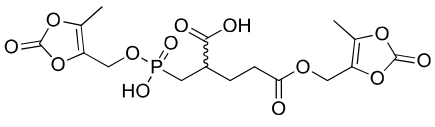
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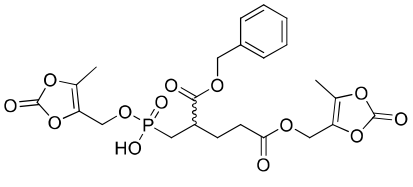
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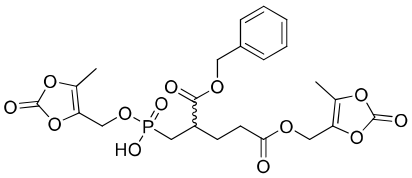
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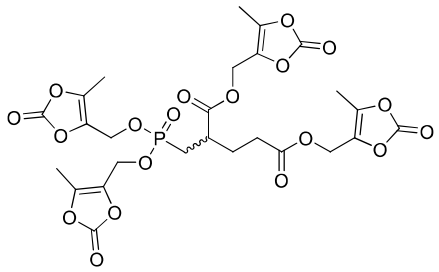
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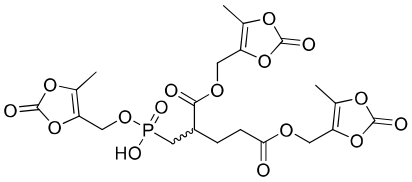
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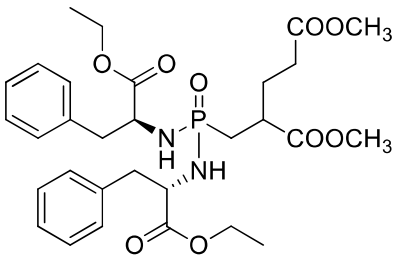
3. The use of claim 1, wherein the compound of formula (II) is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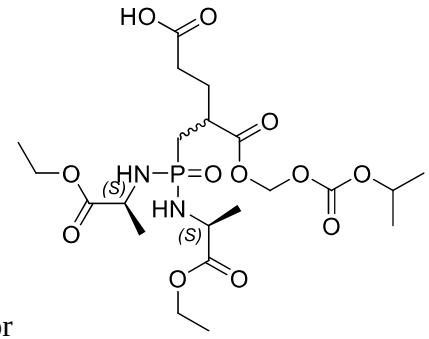
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4. The use of claim 1, wherein the prodrug of 2-PMPA is to be administered in combination with a PSMA-targeted imaging or therapeutic agent.

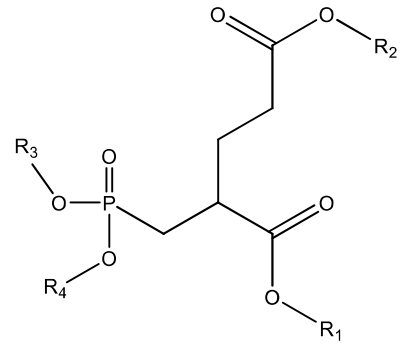
5. The use of claim 4, wherein the prodrug of 2-PMPA is to be administered to the subject before the PSMA-targeted imaging or therapeutic agent is administered.

6. The use of claim 4, wherein the prodrug of 2-PMPA is to be administered to the subject simultaneously with the PSMA-targeted imaging or therapeutic agent.

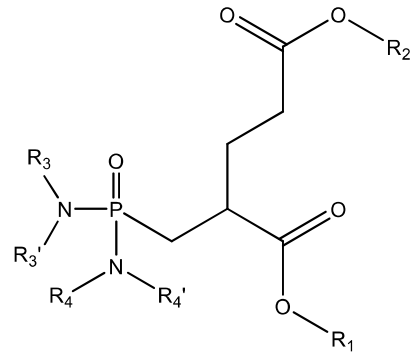
7. The use of claim 1, wherein the off-target tissue is in an organ selected from the group consisting of kidney, lacrimal glands, and salivary glands.

8. The use of claim 1, wherein the PSMA-targeted imaging or therapeutic agent is a small molecule inhibitor of glutamate carboxypeptidase bearing a glutamate moiety, including but not limited to PSMA-11, PSMA-617, or PSMA I&T.

9. Use of a prodrug of 2-PMPA in the manufacture of a medicament for reducing tissue damage to salivary glands, kidneys, or lacrimal glands in a patient receiving PSMA-targeted radiotherapy for cancer, wherein the prodrug of 2-PMPA comprises a compound of formula (I) or formula (II):



(I);



(II);

wherein:

each R_1, R_2, R_3, and R_4 is independently selected from the group consisting of H, C_1-C_{20} straight-chain or branched alkyl, Ar, -($CR_5R_6)_n$-Ar, -$(CR_5R_6)_n$-O-C(=O)-R_7, -$(CR_5R_6)_n$- C(=O)-O-R_7, -$(CR_5R_6)_n$-O-C(=O)-O-R_7,-$(CR_5R_6)_n$-O-R_7, -$(CR_5R_6)_n$-O-[$(CR_5R_6)_n$-O]$_m$-R_7, -$(CR_5R_6)_n$-Ar-

O-C(=O)-R_7,-Ar-C(=O)-O-$(CR_5R_6)_n$-R_7, -$(CR_5R_6)_n$-NR_8R_9, and -$(CR_5R_6)_n$-C(=O)-NR_8R_9, wherein R_1, R_2, R_3, and R_4 cannot all be H at the same time;

wherein:

n is an integer from 1 to 20;

m is an integer from 1 to 20;

each R_3' and R_4' are independently H or C_1-C_4 straight-chain or branched alkyl;

each R_5 and R_6 is independently selected from the group consisting of H, C_1-C_4 straight-chain or branched alkyl, and alkylaryl;

each R_7 is independently straightchain or branched C_1-C_{20} alkyl;

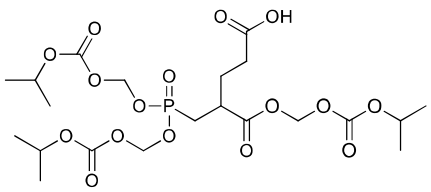
Ar is aryl, substituted aryl, heteroaryl or substituted heteroaryl; and

R_8 and R_9 are each independently H or C_1-C_4 straight-chain or branched alkyl; and

pharmaceutically acceptable salts thereof.

10. The use of claim 9, wherein the salivary gland damage gives rise to a side effect selected from the group consisting of xerostomia, thickened saliva, reduced saliva, mouth sores, hoarseness, trouble swallowing, loss of taste, and combinations thereof.

11. The use of claim 9 or claim 10, wherein the prodrug of 2-PMPA is selected from the group consisting of:



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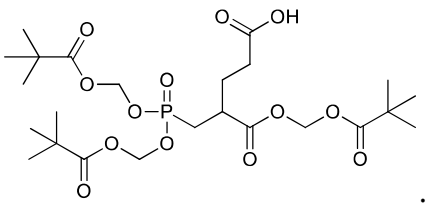

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12. The use of claim 9, wherein the PSMA-targeted imaging or therapeutic agent is selected from the group consisting of 117Lu-PSMA-617, 131I-MIP-1095, 177Lu-PSMA-I&T, 177Lu-PSMA-R2, 225Ac-PSMA-617, 227Th-PSMA-ADC, CTT1403, CTT1700, 68Ga-PSMA-11, 18F-DCFPyL, CTT1057, 68Ga-PSMA-R2, and 68Ga-PSMA-617.

13. The use of claim 9, wherein the PSMA-targeted therapeutic is a radiotherapeutic to be administered in a cumulative amount from about 3 GBq to about 100 GBq.

14. The use of claim 13, wherein the PSMA-targeted radiotherapeutic is to be administered in a cumulative amount from about 52 GBq to about 100 GBq.

15. The use of claim 9, wherein the PSMA-targeted therapeutic and 2-PMPA prodrug are to be administered for about 1 to about 15 treatment cycles.

16. The use of claim 15, wherein the PSMA-targeted therapeutic and 2-PMPA prodrug are to be administered for about 6 to about 15 treatment cycles.

17. The use of claim 9, wherein the patient has not received previous treatment for cancer.

18. The use of claim 9, wherein the cancer is prostate cancer.