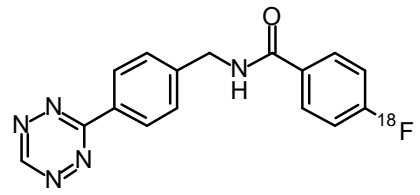
Beyond brain penetrant large molecules, the other requisite for any successful CNS pretargeted imaging studies is the availability of brain-penetrant, fast-clearing, reactive yet stable, small molecule chasers containing tetrazine reactive groups. Several ^{11}C- and ^{18}F-labeled small molecule tetrazine chasers have been reported to have appreciable brain uptake (see, Hannes Mikula et al. *Bioconjugate Chem.* 2016, 27, 7, 1707-1712; Hannes Mikula et al. *Angew. Chem. Int. Ed.* 2014, 53, 9655 –9659). However, their application in CNS pretargeted imaging studies have not been reported.

In 2019, Brendon Cook and collaborators reported the first case of CNS pretargeted imaging to study the distribution of an antisense oligonucleotide (ASO) in rat brain (World Molecular Imaging Congress Conference Poster 139). Rats were intrathecally administered 2.5 mM ASO-TCO conjugate in 30 μL saline solution and followed with an intravenous injection of a CNS-penetrant tetrazine, [^{18}F]-537-Tz, 24 and 168 hours post ASO-TCO. Static PET-CT scans were performed 75-90 minutes after administration of [^{18}F]-537-Tz. Higher radiotracer uptake was observed in the brain and spine of the animals that received ASO-TCO relative to the control group. It was also reported that [^{18}F]-537-Tz showed brain uptake (1.7 ± 0.9 %ID by 10 min P.I.) in wild type mice by dynamic PET imaging.

By comparison, dynamic PET imaging of [^{18}F]-N-(4-(1,2,4,5-tetrazin-3-yl)benzyl)-4-fluorobenzamide in WT mice showed that this compound readily crosses the blood-brain-barrier and reaches a peak brain uptake of 4.1 ± 0.3 %ID/g approximately 2.5 min post injection, followed by a steady clearance of tracer to 0.8 ± 0.1 %ID/g by 60 minutes. An agent that possesses robust brain penetration and rapid and complete washout from the brain provides a larger window to achieve higher signal to background ratios resulting in better image quality. Thus, we expect [^{18}F]-N-(4-(1,2,4,5-tetrazin-3-yl)benzyl)-4-fluorobenzamide to provide an advantage for pretargeted CNS imaging.

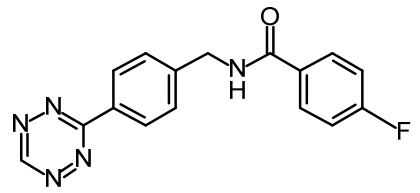
Summary

In one aspect of the present disclosure, there is provided a compound of the formula:



or pharmaceutically acceptable salt thereof.

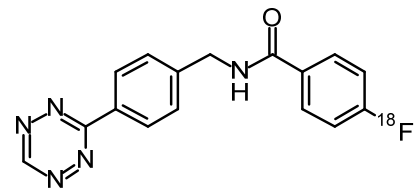
In another aspect of the present disclosure, there is provided a compound of the formula:



or pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof disclosed herein, with one or more pharmaceutically acceptable carriers, diluents or excipients.

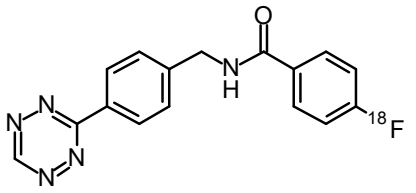
In another aspect of the present disclosure, there is provided a composition comprising:



;

or a pharmaceutically acceptable salt thereof, and ethanol and PBS buffer.

In a further aspect of the present disclosure, there is provided a compound of the formula:



or a pharmaceutically acceptable salt thereof,

for use in a method of pretargeted imaging comprising:

a. introducing into a mammal a detectable quantity of the compound or a pharmaceutically acceptable salt thereof, and

b. detecting said compound in PET imaging, wherein the compound is introduced after a biologics-TCO conjugate was introduced into the mammal.

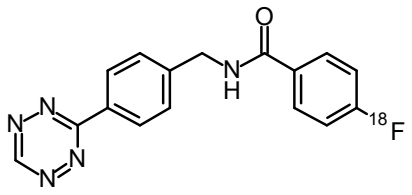
In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof disclosed herein, with one or more pharmaceutically acceptable carriers, diluents or excipients,

for use in a method of pretargeted imaging comprising:

a. introducing into a mammal a detectable quantity of the composition;

b. detecting the composition.

In a further aspect of the present disclosure, there is provided a composition comprising:



;

or a pharmaceutically acceptable salt thereof, and ethanol and PBS buffer,

for use in a method of pretargeted imaging comprising:

a. introducing into a mammal a detectable quantity of the composition;

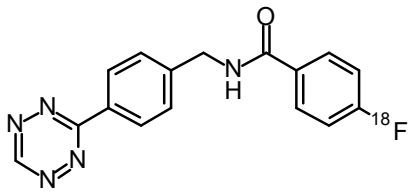
b. detecting the composition.

Description

The present embodiments provide novel compounds, compositions, formulations and methods for pretargeted imaging. This type of improved technology advancing the capacity to image patients is thus also needed to expand the clinical benefits and impact of diagnostic imaging. An improved imaging agent will provide enhanced pretargeted images, as compared with currently known agents.

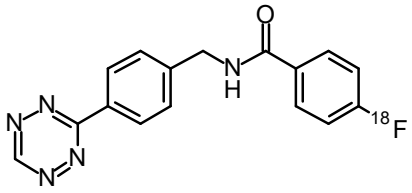
We Claim:

1. A compound of the formula:



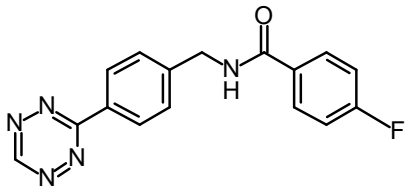
or pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, which is



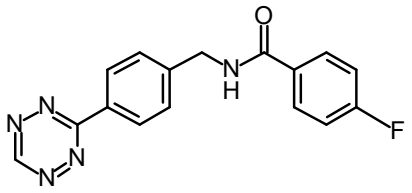
.

3. A compound of the formula:



or pharmaceutically acceptable salt thereof.

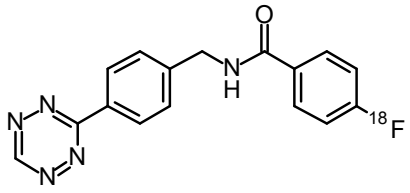
4. The compound according to claim 3, which is



.

5. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to claim 1 or claim 3, with one or more pharmaceutically acceptable carriers, diluents or excipients.

6. A composition comprising:

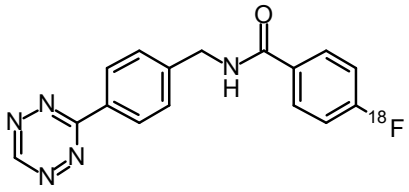


;

or a pharmaceutically acceptable salt thereof, and ethanol and PBS buffer.

7. A composition of claim 6, wherein the composition does not include ascorbate or ascorbic acid.

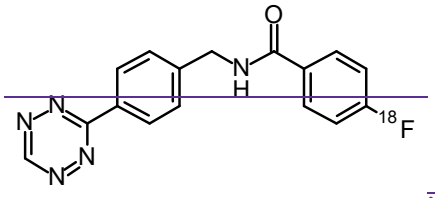
8. A compound of the formula:



or a pharmaceutically acceptable salt thereof,

for use in a method of pretargeted imaging comprising:

a. introducing into a mammal a detectable quantity of the compound:



or a pharmaceutically acceptable salt thereof, and

b. detecting said compound in PET imaging, wherein the compound is introduced after a biologics-TCO conjugate was introduced into the mammal.

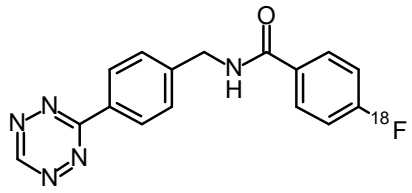
9. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to claim 1 or claim 3, with one or more pharmaceutically acceptable carriers, diluents or excipients,

for use in a method of pretargeted imaging comprising:

a. introducing into a mammal a detectable quantity of the~~a~~ composition ~~of any of claims 5 or 6~~;

b. detecting the composition.

10. A composition comprising:



;

or a pharmaceutically acceptable salt thereof, and ethanol and PBS buffer,

for use in a method of pretargeted imaging comprising:

a. introducing into a mammal a detectable quantity of the composition;

b. detecting the composition.