and/or shortened biological inhibitory activity. To overcome such shortfalls, additional drug is typically administered to provide more drug and prolonged efficacy at the biological site of action. Hence, both the rapid clearance and the twice weekly frequency of dosing of carfilzomib leave room for possible improvements in efficacy, delivery and/or patient compliance.

Carfilzomib, as currently approved (Kyprolis®), is a sterile lyophilized formulation comprising sulfabutylether beta cyclodextrin (SBECD) and a sodium citrate buffer. The lyophilate is reconstituted with sterile water, and infused or injected into the patient. The SBECD excipient acts primarily as a solubilizing additive for carfilzomib, and forms a complex with carfilzomib thereby improving carfilzomib water solubility.

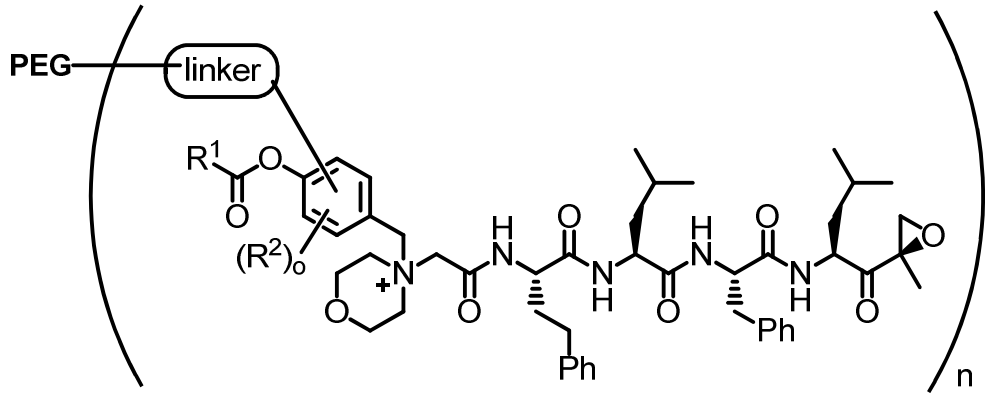
History has revealed that attempts to solve weaknesses of drug products have led to the preparation of alternative forms of these medicinal compounds, including production of pro-drug versions, in attempts to enhance their drug pK and/or PD properties. For instance, Greenwald et al disclose Prodrugs of Amine Containing Compounds (*J. Med. Chem.*, 1999, 42, 3657-3667). WO2005063777 discloses benzylphosphate and substituted benzylphosphate prodrugs for the treatment of pulmonary inflammation. WO20090152160 discloses inhaled carbaprotacyclin and prostacyclin prodrugs for the treatment of arterial hypertension. US patent publication no. 20040100225 discloses acyloxymethyl pro-drugs of imatinib (Gleevec®). Also, PCT publication WO2011084846 discloses acyloxymethyl pro-drugs of risperidone. These pro-drug disclosures teach alkyl-acyloxymethyl linked pro-drugs. Another example, US patent application publication no. US20140105921 describes carfilzomib and other epoxyketone proteasome inhibitor pro-drugs having an acyloxymethyl linker connecting the inhibitor to polyethylene glycol units (PEG). However, these carfilzomib pro-drug compounds have been found to release quinone methide byproducts during metabolism *in vivo*, which may be potentially toxic and may present a safety risk. To this end, it would be desirable to identify alternative forms of carfilzomib and/or alternative ways to deliver the active pharmaceutical ingredient carfilzomb to patients while maintaining or possibly improving the efficacy and/or safety of the currently approved carfilzomib treatments.

SUMMARY

The present disclosure provides novel polymeric carfilzomib compounds, i.e., modified structures of carfilomib, that deliver therapeutic anti-cancer benefits to the patient while maintaining comparable or longer carfilzomib plasma concentrations and

proteasome exposure. To this end, these polymeric carfilzomib compounds provide proteosomal inhibitory activity comparable to that of the currently approved carfilzomib cyclodextrin IV formulation.

In one aspect, the present disclosure refers to a pegylated carfilzomib compound having a structure of formula I



Formula I

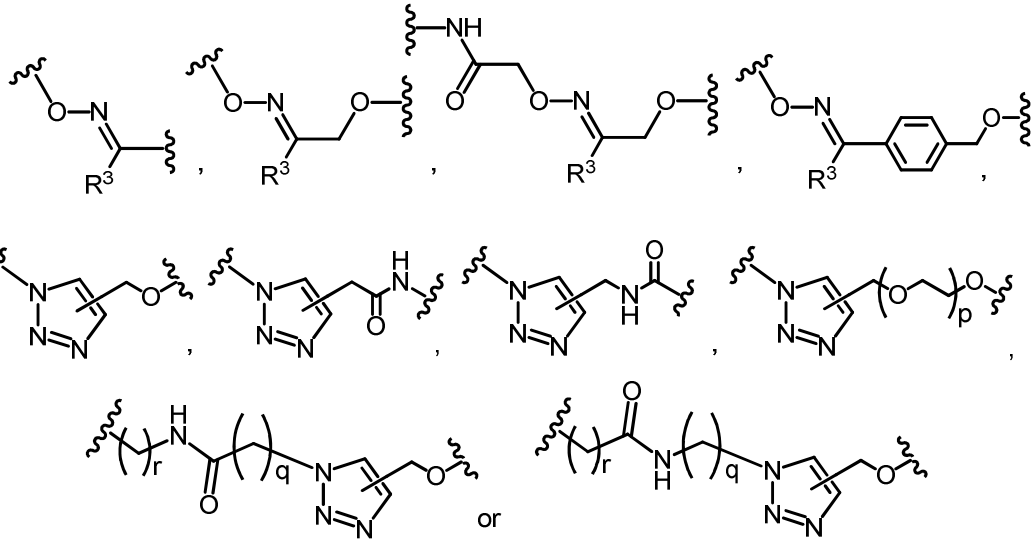
or a pharmaceutically acceptable salt thereof, wherein

R^1 is $C_{1\text{-}10}$alkyl or $C_{3\text{-}7}$cycloalkyl;

each R^2, independently, is $C_{1\text{-}6}$alkyl, $-OCH_3$ or halogen;

o is an integer selected from 0, 1, 2 or 3;

linker is a moiety having the structure of



wherein R^3 is H or CH_3;

n is an integer selected from 1, 2, 3 or 4;

p is an integer selected from 0, 1, 2, 3 or 4;

q is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8 or 9;

r is an integer selected from 0, 1, 2, 3, 4 or 5; and

PEG is a polyethylene glycol polymeric moiety having a molecular weight ranging from about 500 to about 20,000.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as disclosed herein and a pharmaceutically acceptable excipient, carrier or diluent.

In another aspect, the present disclosure refers to a use of the compound as disclosed herein or a composition as disclosed herein in the manufacture of a medicament for treating multiple myeloma.

Particularly, the present disclosure provides pegylated carfilzomib compounds, having improved water solubility, and which are useful to treat various types of cancer, including without limitation, multiple myeloma. More particularly, the pegylated compounds provided herewith maintain or exhibit suitable bioavailability and reduce or completely eliminate the need for solubilizing excipients or agents such as sulfobutylether-β-cyclodextrin. The present disclosure further provides a method of preparing the pegylated carfilzomib compounds, pharmaceutical compositions comprising the same, and methods of using the compounds and compositions for treating various forms of cancer such as multiple myeloma.

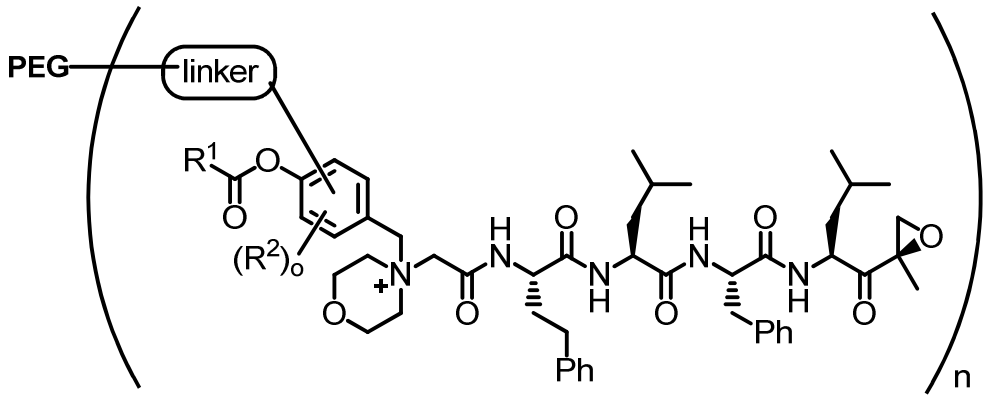
In one example of the disclosure, the pegylated carfilzomib compounds described herein include one or more covelantly linked PEG moieties that (i) can confer enhanced solubility, permeability, pharmacokinetics (pK) and/or pharmacodynamics (PD) properties to carfilzomib when compared with the corresponding approved carfilzomib product that does not contain such polymeric moieties; and (ii) can be cleaved or removed *in vivo* after administration to a subject thereby further providing free carfilzomib, that has proven safety and efficacy capabilities to treat various cancers, including without limitation, multiple myeloma.

The pegylated carfilzomib compounds provided by the present disclosure further provide potential benefits including, without limitation, extended release allowing for reduced dosing frequency, lower Cmax and, consequenetly, possibly reduced side effects when compared with the presently approved carfilzomib product. An improved safety profile of the compounds of the disclosure may also result from enhanced aqueous solubility which could facilitate alternative modes of administration, such as for example subcutaneous administration, from the presently

approved infusion mode of administration. A modified pK and/or biodistribution profile for the pegylated carfilzomib compounds of the disclosure may result in improved efficacy in treating cancers, including without limitation, multiple myeloma and solid tumors. Further, the pegylated carfilzomib compounds of the disclosure provide formulation options with potentially improved chemical and temperature stability, lower dosing volume and the potential to eliminate a lyophilization step, part of the manufacturing procedure for the currently approved carfilzomib drug product.

What is claimed is:

1. A pegylated carfilzomib compound having a structure of formula I



Formula I

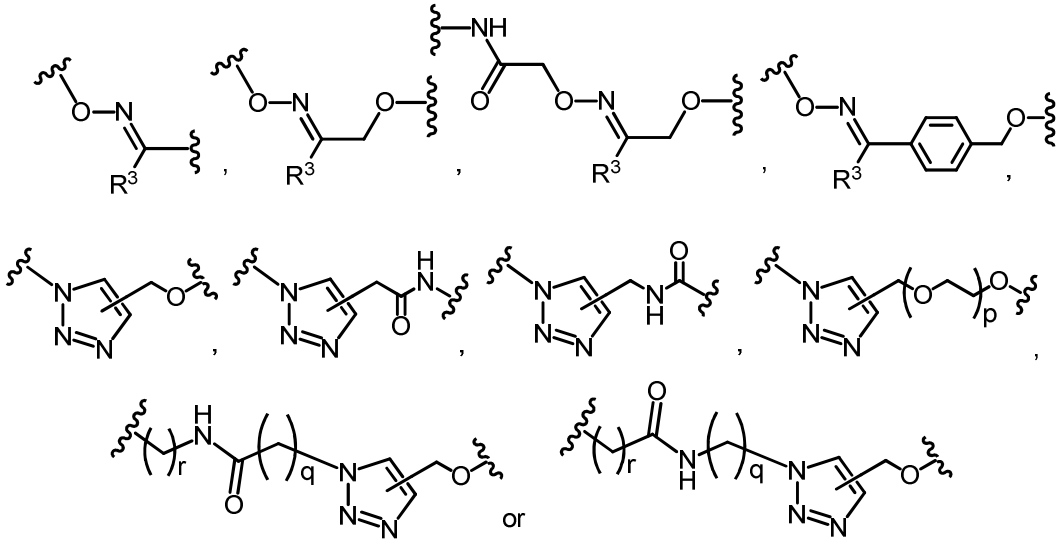
or a pharmaceutically acceptable salt thereof, wherein

R^1 is $C_{1\text{-}10}$alkyl or $C_{3\text{-}7}$cycloalkyl;

each R^2, independently, is $C_{1\text{-}6}$alkyl, $-OCH_3$ or halogen;

o is an integer selected from 0, 1, 2 or 3;

linker is a moiety having the structure of



wherein R^3 is H or CH_3;

n is an integer selected from 1, 2, 3 or 4;

p is an integer selected from 0, 1, 2, 3 or 4;

q is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8 or 9;

r is an integer selected from 0, 1, 2, 3, 4 or 5; and

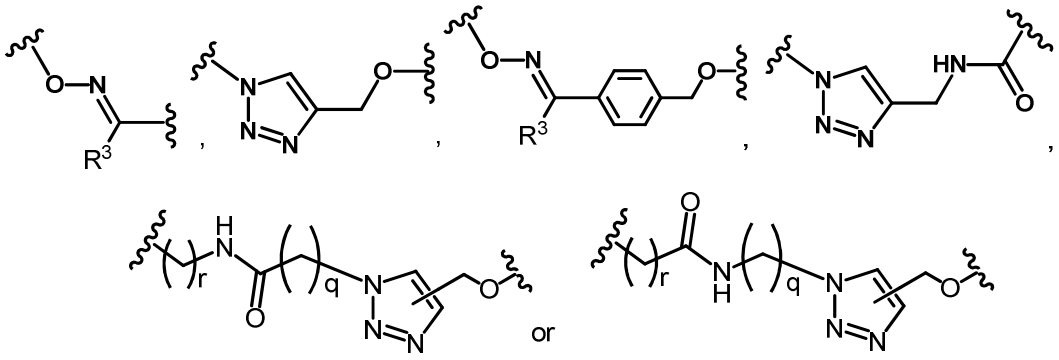
PEG is a polyethylene glycol polymeric moiety having a molecular weight ranging from about 500 to about 20,000.

2. The compound of claim 1 wherein R^1 is C_{1-10}alkyl.

3. The compound of any one of claims 1 and 2 wherein each o is 0 or 1 and R^2 is CH_3 or halogen.

4. The compound of any one of claims 1, 2 and 3 wherein each o is 0 or 1 and R^2 is CH_3 or F.

5. The compound of any one of claims 1, 2, 3 and 4 wherein the linker is a moiety having the structure of

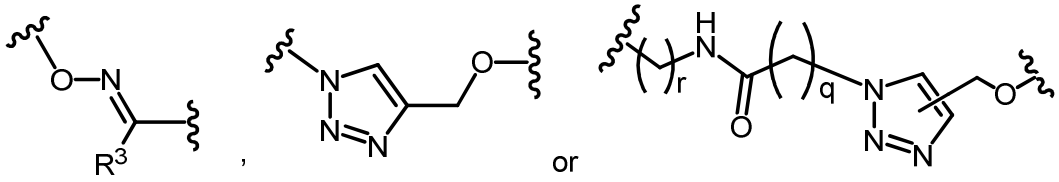


wherein R^3 is H or CH_3;

q is an integer selected from 1, 2, 3, 4 or 5; and

r is an integer selected from 0, 1, 2, 3 or 4.

6. The compound of any one of claims 1, 2, 3, 4 and 5 wherein the linker is



wherein R^3 is H or CH_3;

q is 4 ; and

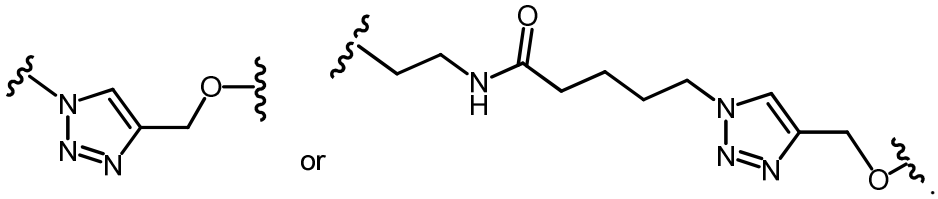
r is 2.

7. The compound of any one of claims 2- 6 wherein R^1 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl or heptyl.

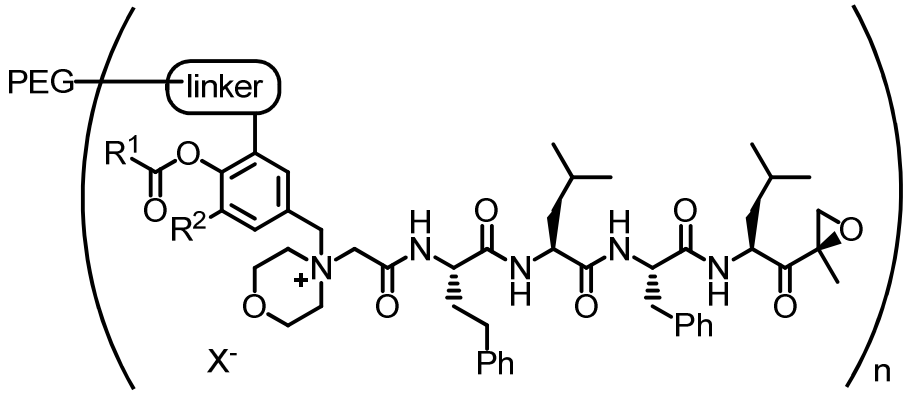
8. The compound of any one of claims 1, 2, 3, 4, 5, 6 and 7 wherein

R^1 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl or heptyl; and

the linker is



9. The pegylated carfilzomib compound of claim 1 having a structure of Formula II



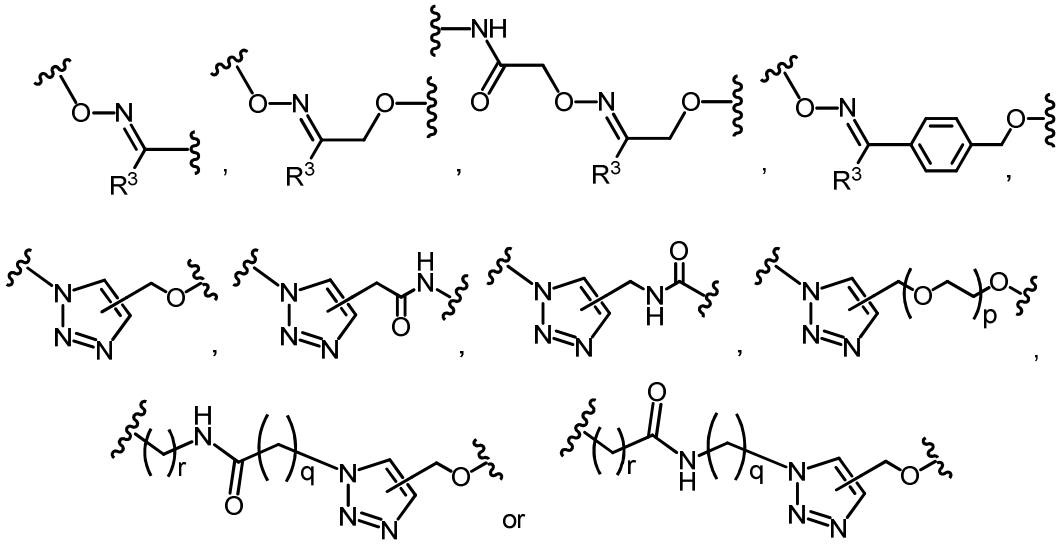
Formula II

wherein

R^1 is $C_{1\text{-}10}$alkyl or $C_{3\text{-}7}$cycloalkyl;

R^2 is $C_{1\text{-}6}$alkyl, -OCH_3 or halogen;

linker is a moiety having the structure of



wherein R^3 is H or CH_3;

n is an integer selected from 1, 2, 3 or 4;

p is an integer selected from 0, 1, 2, 3 or 4;

q is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8 or 9;

r is an integer selected from 0, 1, 2, 3, 4 or 5;

X is a counter ion salt selected from a chloride, a bisulfate, a sulfate, a nitrate, a phosphate, an alky-sulfonate or an aryl-sulfonate; and

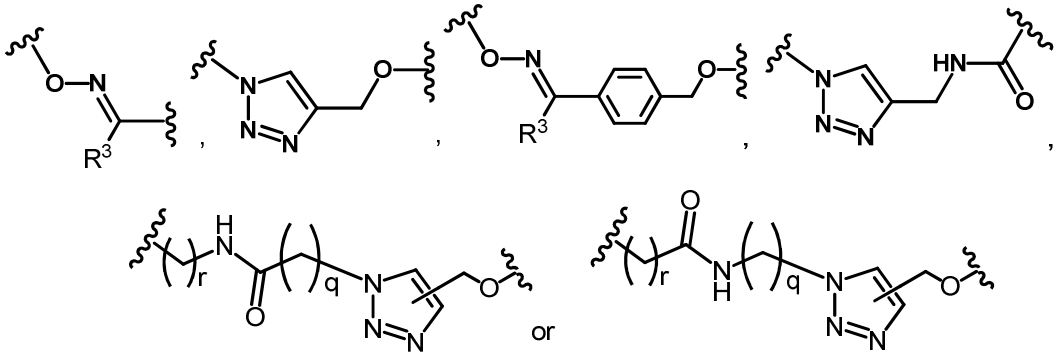
PEG is a polyethylene glycol polymeric moiety having a molecular weight ranging from about 2000 to about 20,000.

10. The compound of claim 9 wherein R^1 is $C_{1\text{-}10}$alkyl.

11. The compound of any one of claims 9 and 10 wherein R^2 is H, CH_3 or halogen.

12. The compound of any one of claims 9, 10 and 11 wherein R^2 is H, CH_3 or F.

13. The compound of any one of claims 9, 10, 11 and 12 wherein the linker is a moiety having the structure of

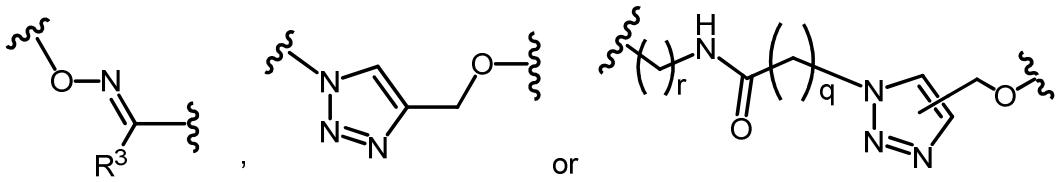


wherein R^3 is H or CH_3;

q is an integer selected from 1, 2, 3, 4 or 5; and

r is an integer selected from 0, 1, 2, 3 or 4.

14. The compound of any one of claims 9-13 wherein the linker is



wherein R^3 is H or CH_3;

q is 4 ; and

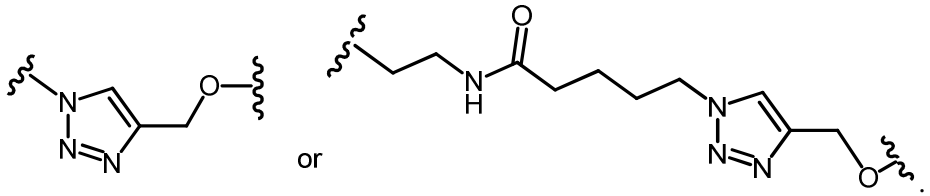
r is 2.

15. The compound of any one of claims 9- 14 wherein R^1 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl or heptyl.

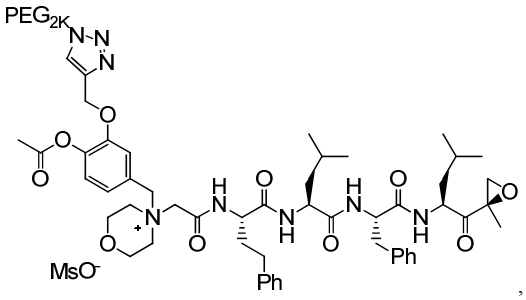
16. The compound of any one of claims 9-15 wherein

R^1 is methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl or heptyl; and

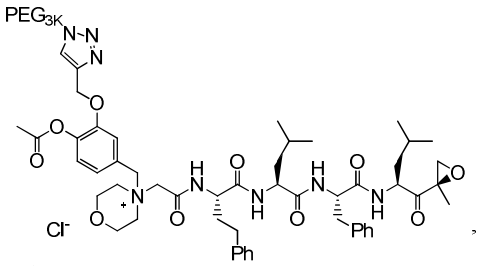
the linker is



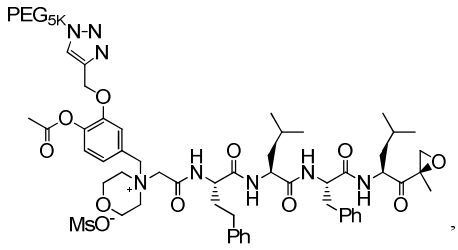
17. The compound of any one of claims 1-16, having the structure of



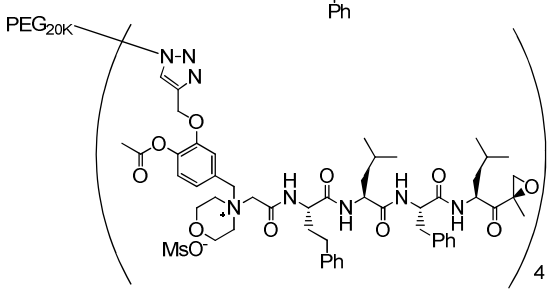
,



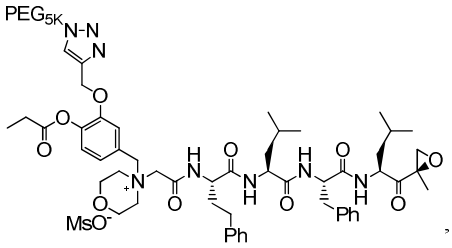
,



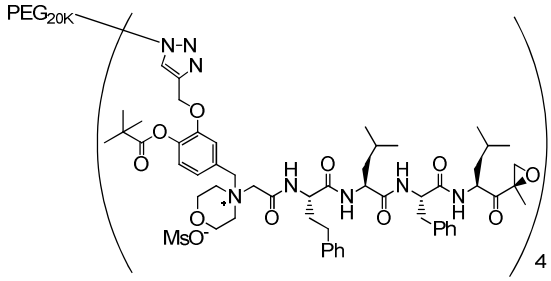
,



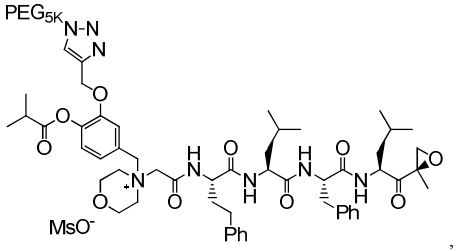
,



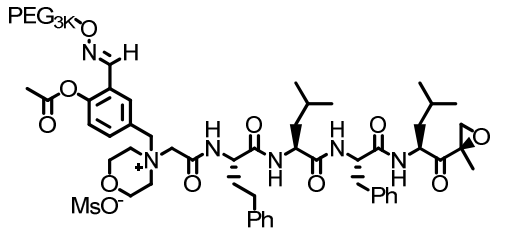
,



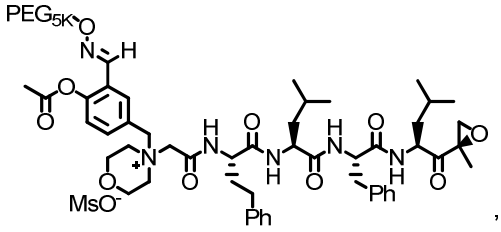
,



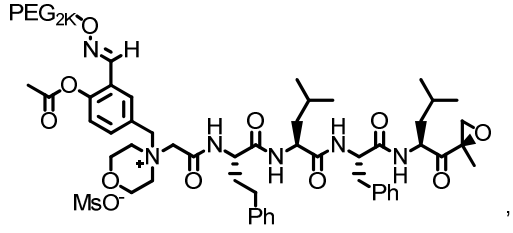
,



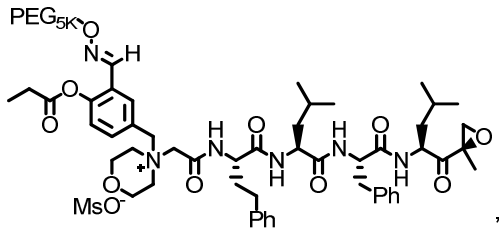
,



,

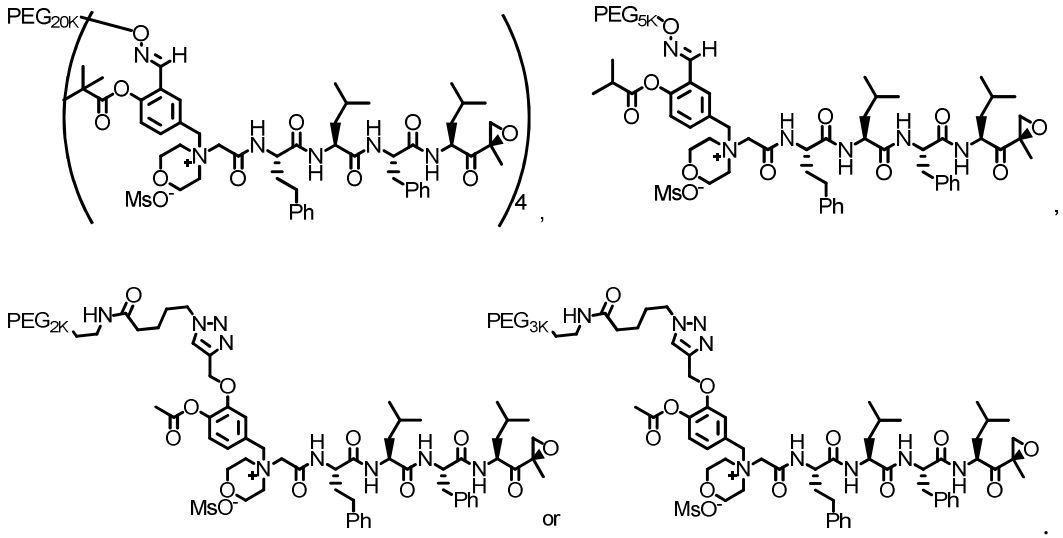


,



,

5



18. The compound of any one of claims 1- 16 wherein the PEG has a weight ranging from about 2K to about 20K.

19. The compound of any one of claims 1- 16 wherein the PEG has a weight of 2K, 3K, 5K or 20K.

20. The compound of any one of claims 1- 16 that is a pharmaceutically acceptable salt comprising a counter anion selected from a chloride anion, a bisulfate anion, a sulfate anion, a nitrate anion, a phosphate anion, an alky-sulfonate anion or an aryl-sulfonate anion.

21. The compound of claim 20 wherein the counter anion is a chloride anion or an alky-sulfonate anion.

22. A pharmaceutical composition comprising the compound according to any one of claims 1-21 and a pharmaceutically acceptable excipient, carrier or diluent.

23. The pharmaceutical composition of claim 22 that is to be administered orally or by infusion or injection.

24. Use of the compound of any one of claims 1-20 or a composition of any one of claims 22-23 in the manufacture of a medicament for treating multiple myeloma.

25. The use of claim 24 wherein the multiple myeloma is relapsed, refractory or relapsed and refractory multiple myeloma.

26. The use of claim 24 wherein the multiple myeloma is newly diagnosed multiple myeloma.