CLAIMS

What is claimed is:

1. A compound of formula (I), or a salt, geometric isomer, stereoisomer, or solvate thereof:

$$[TBM]_n—[Linker]_m—[LRP1BM]_o \text{ (I)},$$

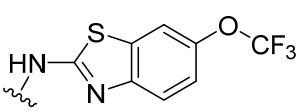
wherein

m is an integer from 0 to 15;

n and o are each independently an integer from 1 to 15;

[TBM] represents a target binding motif comprising or consisting of:

(a) a compound selected from: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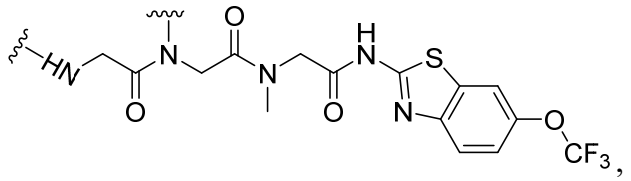
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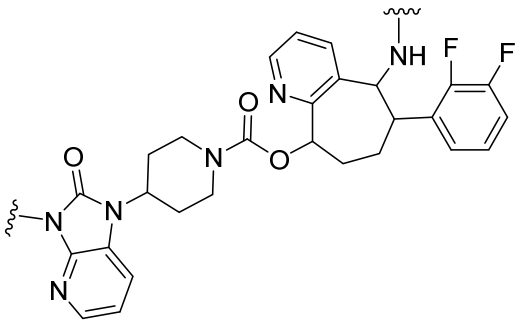
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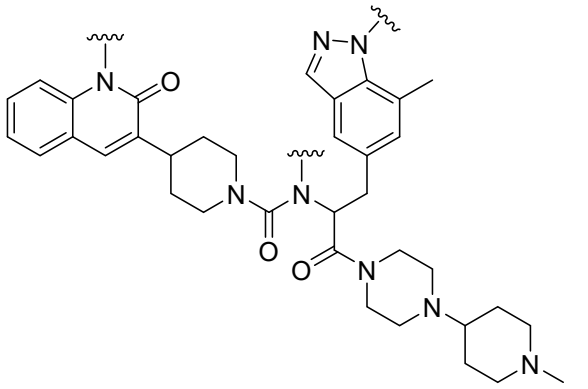
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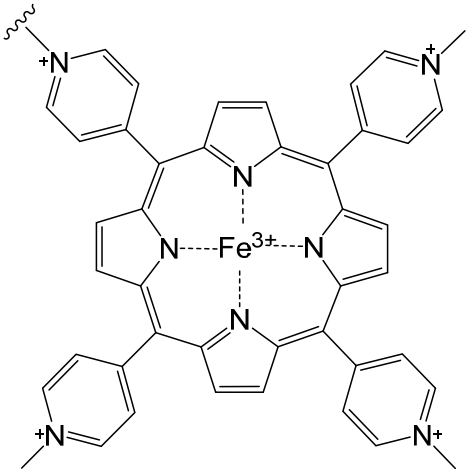
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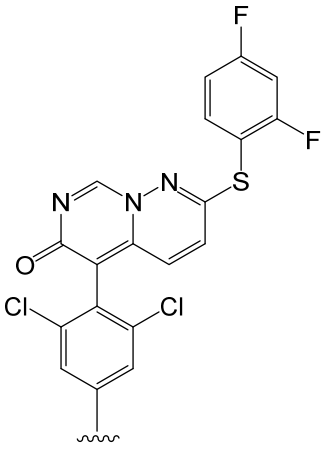
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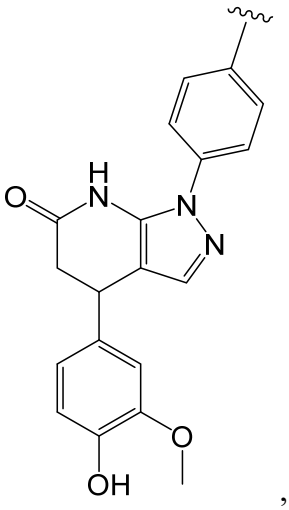
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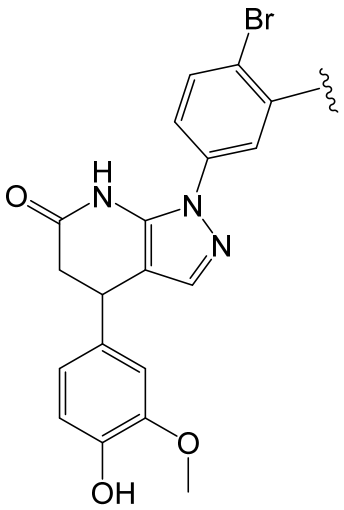
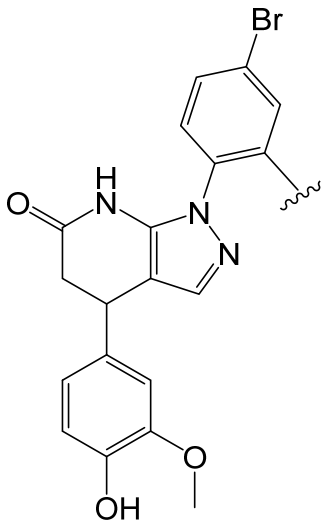
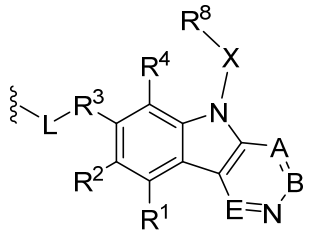


, or 

, or a derivative or prodrug thereof, wherein

≋ indicates possible points of covalent attachment to a [Linker] or a [LRP1BM];

(b) a compound of formula (I):



, or a derivative or prodrug thereof,

wherein:

A is N or CR^5;

B is N or CR^6;

E is N or CR^7;

L is a substituted or unsubstituted alkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted carbocyclylene, substituted or unsubstituted heterocyclylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene, substituted or unsubstituted heteroalkylene, a bond, -O-, -NR^A-, -S-, -C(=O)-, -C(=O)O-, -C(=O)NR^A-, -NR^AC(=O)-, -NR^AC(=O)R^A-, -C(=O)R^A-, -NR^AC(=O)O-, -NR^AC(=O)N(R^A)-, -OC(=O)-, -OC(=O)O-, -OC(=O)N(R^A)-, -$S(O)_2NR^A$-, -$NR^AS(O)_2$-, or a combination thereof;

X is a bond or substituted or unsubstituted C_{1-12} alkylene, wherein one or more carbon is optionally replaced with C(=O), O, S, SO_2, NH, or NC_{1-6} alkyl optionally substituted with halogen, OH, or C_{1-6} alkyl;

R^8 is hydrogen, -N_3, alkynyl, OH, halogen, NH_2, N(C_{1-6} alkyl)$_2$, aryl, heteroaryl, or a

protecting group, wherein the aryl and heteroaryl are optionally substituted with halogen, SO_2, NH_2, or C_{1-6} alkyl optionally substituted with halogen or C_{3-8} cycloalkyl;

R^3 is $-(CH_2)_n-$, $-(CH_2)_n-C(=O)$, $-(CH_2)_n-C(=O)-O-$, $-(CH_2)_n-O-$, $-A-(CH_2)_n-O-$, $-(CH_2)_n-A-O-$, $-A-O-(CH_2)_n-(C=O)NR^A-$, $-(CH_2)_n-S-$, $-A-(CH_2)_n-S-$, $-(CH_2)_n-A-S-$, $-A-S-(CH_2)_n-(C=O)NR^A-$, $-(CH_2)_n-NR^A-$, $-A-(CH_2)_n-NR^A-$, $-(CH_2)_n-A-NR^A-$, $-(CH_2)_n-(C=O)NR^A-$, $-A-(CH_2)_n-(C=O)NR^A-$, $-(CH_2)_n-A-(C=O)NR^A-$, $-A-NR^A-(CH_2)_n-(C=O)NR^A-$, $-(CH_2)_n-S(O)_2NR^A-$, $-A-(CH_2)_n-S(O)_2NR^A-$, or $-(CH_2)_n-A-S(O)_2NR^A-$;

each occurrence of R^A is independently selected from hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group when attached to a nitrogen atom, or two R^A groups are joined to form a substituted or unsubstituted heterocyclic ring;

each occurrence of A is independently selected from substituted or unsubstituted heterocyclylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^1, R^2, and R^4-R^8 are each independently hydrogen, OH, halogen, NH_2, CH_3, SO_2, NO_2, a leaving group, a protecting group, aryl, heteroaryl, NHR^{12} , $N(R^{12})_2$ C_{3-8} cycloalkyl, $N(R^{12})_2$ heterocyclyl, or $-(CH_2)_n-R^{12}$;

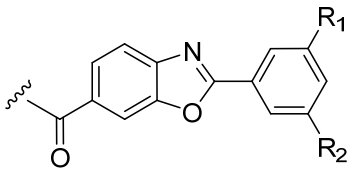
R^{12} is hydrogen, $-CH_3$, aryl, or heteroaryl; and

n is 0-12;

wherein one or more carbon of R^1-R^7 is optionally replaced with C(=O), O, S, SO_2, NH, NH-C_{1-6} alkyl, NC_{1-6} alkyl, NH_2, or N(C_{1-6} alkyl)$_2$; and

$\lesssim$ indicates the point of covalent attachment to a [Linker] or a [LRP1BM];

(c) a compound of formula (II):



, or a derivative or prodrug thereof,

wherein

R_1 and R_2 are each independently selected from hydrogen, N_3, alkynyl, OH, halogen, NH_2, N(C_{1-6} alkyl)$_2$, C_{1-6} alkyl, aryl, heteroaryl, NHR^{12}, $N(R^{12})_2$ C_{3-8} cycloalkyl, $N(R^{12})_2$ heterocyclyl, or $-(CH_2)_n-R^{12}$;

wherein the aryl and heteroaryl are optionally substituted with halogen, -SO_2, NO_2, -NH_2, or C_{1-6} alkyl optionally substituted with halogen or C_{3-8} cycloalkyl;

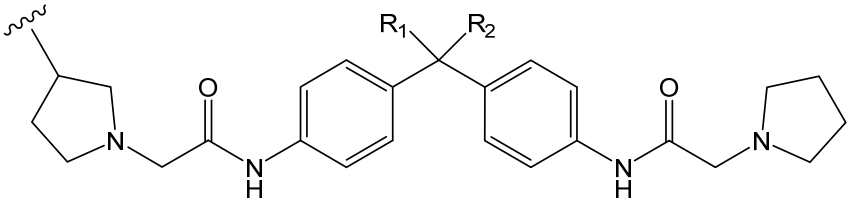
R^{12} is hydrogen, -CH_3, aryl, or heteroaryl; and

n is 0-12;

wherein one or more carbon of R^1 or R^2 is optionally replaced with C(=O), O, S, SO_2, NH, NH-C_{1-6} alkyl, NC_{1-6} alkyl, NH_2, or N(C_{1-6} alkyl)$_2$; and

≋ indicates the point of covalent attachment to a [Linker] or a [LRP1BM];

(d) a compound of formula (III):



, or a derivative or prodrug thereof,

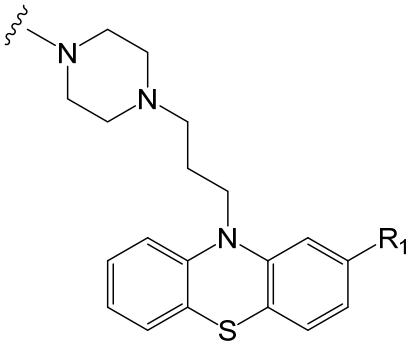
wherein

R_1 is selected from benzene, phenyl, cyclohexyl, hydrogen, and CF_3;

R_2 is selected from hydrogen and CF_3; and

≋ indicates the point of covalent attachment to a [Linker] or a [LRP1BM];

(e) a compound of formula (IV):



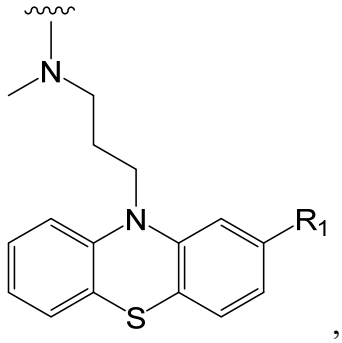
, or a derivative or prodrug thereof,

wherein

R_1 is selected from hydrogen, Cl, OMe, SMe, and CF_3, and

≋ indicates the point of covalent attachment to a [Linker] or a [LRP1BM];

(f) a compound of formula (V):



, or a derivative or prodrug thereof,

wherein

R_1 is selected from hydrogen, Cl, OMe, SMe, and CF_3, and

§ indicates the point of covalent attachment to a [Linker] or a [LRP1BM]; or

(g) an amino acid sequence selected from:

SVWIWYE,

DVWIINKKLK,

MLRTKDLIWTLFFLGTAVS-NH_2,

MLRTKDLIWTLFFLGTAVS-KKRPKP-NH_2, and

MLRTKDLIWTLFFLGTAVS-KKLVFF-NH_2;

[LRP1BM] represents a low density lipoprotein receptor-related protein 1 (LRP1) receptor binding motif comprising one of the following amino acid sequences:

TFFYGGSRGKRNNFKTEEYC-OH (or -NH_2),

TWPKHFDKHTFYSILKLGKH-OH,

EAKIEKHNHYQKK/C-NH_2,

EAKIEKHNHYQKQLEIAHEKLRK/C-NH_2,

R_8AKIEKHS_5HYQKK/C-NH_2, wherein R_8 represents (R)-2-(7-octenyl)Ala-OH, S_5 represents (S)-2-(4-pentenyl)Ala-OH, and there is a hydrocarbon bridge between position 1 and 8,

LRKLRKRLLRDADDLLRKLRKRLLRDADDL-NH_2,

TEELRVRLASHLRKLRKRLL-NH_2,

Ac-VKFNKPFVFLNleIEQNTK-NH_2, wherein Nle represents norleucine,

VKFNKPFVFLMIEQNTK,

TFFYGGCRGKRNNFKTEEYC-OH (or -NH_2),

TFFYGGSRGKRNNFRTEEYC-OH (or -NH_2),

TFFYGGSRGRRNNFRTEEYC-OH (or -NH_2),

cyeetkfnnrkGrsGGyfft-OH (or-NH_2),

TFFYGGCRAKRNNFKRAKY,

TFFYGGCRGKKNNFKRAKY,

PFFYGGCRGKRNNFKTEEY,

TFFYGGKRGKRNNFKTKEY,

TFFYGGCRGKRNNFKTKRY,

TFFYGGKRGKRNNFKTAEY,

TFFYGGKRGKRNNFKREKY,

RFKYGGCLGNKNNFLRLKY, and

RFKYGGCLGNKNNYLRLKY,

wherein the underlined amino acids in the above sequences indicate that the amino acids may be present or absent and underlined K/C indicates that either K or C may be present; and

[Linker] represents a polyethylene glycol containing linker having 1-12 ethylene glycol residues, or [Linker] represents a Linking group comprising:

(a) $-CH_2CH_2(OCH_2CH_2)_mOCH_2-$, $-(CH_2)_mCH_2-$, or $-[N(R^a)-CH(R^b)(C=O)]_m-$,

or a polypropylene glycol or polypropylene-co-polyethylene glycol group containing 1-100 alkylene glycol units;

wherein each R^a is independently H, C_1-C_3 alkyl, or C_1-C_6 alkanol, or combines with R^b to form a pyrrolidine or hydroxypyrroline group;

wherein each R^b is independently selected from the group consisting of hydrogen, methyl, isopropyl, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-(CH_2)_3$-guanidine, $-CH_2C(=O)NH_2$, $-CH_2C(=O)OH$, $-CH_2SH$, $-(CH_2)_2C(=O)NH_2$, $-(CH_2)_2C(=O)OH$, $-(CH_2)$imidazole, $-(CH_2)_4NH_2$, $-CH_2CH_2SCH_3$, benzyl, $-CH_2OH$, $-CH(OH)CH_3$, $-(CH_2)$imidazole, or $-(CH_2)$phenol; and

wherein m is an integer ranging from 1 to 15;

(b) $-[N(R'-(CH_2)_{1\text{-}15}-C(=O)]_m-$, wherein R' is H or a C_1-C_3 alkyl optionally substituted with 1-2 hydroxyl groups, and m is an integer ranging from 1 to 100;

(c) -Z-D-Z'-, wherein:

Z and Z' are each independently a bond, $-(CH_2)_i-O-$, $-(CH_2)_i-S-$, $-(CH_2)_i-N(R)-$, , $-(CH_2)_i-C(R^2)=C(R^2)-$ (cis or trans), -

$(CH_2)_i$-≡-, or -Y-C(=O)-Y-,

each R is independently H, C_1-C_3 alkyl, or C_1-C_6 alkanol,

each R^2 is independently H or C_1-C_3 alkyl,

each Y is independently a bond, O, S, or N(R),

each i is independently 0 to 100,

D is a bond, -$(CH_2)_i$-Y-C(=O)-Y-$(CH_2)_i$-, -$(CH_2)_{m'}$-, or -[$(CH_2)_n$-X_1)]$_j$-, with the proviso that Z, Z', and D are not each simultaneously bonds;

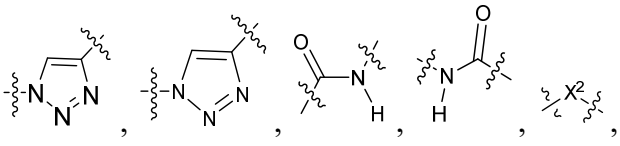
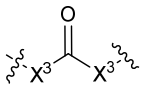
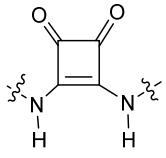
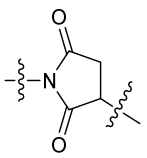
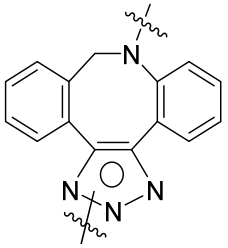
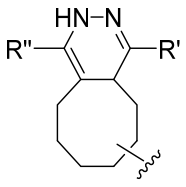
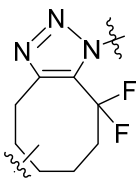
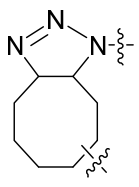
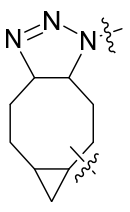
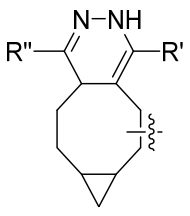
X_1 is O, S, or N(R),

j is an integer ranging from 1 to 100,

m' is an integer ranging from 1 to 100,

n is an integer ranging from 1 to 100;

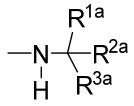
(d) -CH_2-$(OCH_2CH_2)_n$-CH_2-, -$(CH_2CH_2O)_{n'}CH_2CH_2$-, or -$(CH_2CH_2CH_2O)_n$-, wherein each n and n' is independently an integer ranging from 1 to 25;

(e) -PEG-CON-PEG-, wherein each PEG is independently a polyethylene glycol group containing from 1-12 ethylene glycol residues and CON is selected from  , , , , ,  ,  ,  ,  ,  ,  ,  ,  , or  , wherein R' and R" are each independently H, methyl, or a bond;

(f) -PEG-CON-PEG-, wherein each PEG is independently a polyethylene glycol group containing from 1-12 ethylene glycol residues and CON comprises a diamide structure selected from -C(=O)-N(R^1)-$(CH_2)_{n''}$-

$N(R^1)C(=O)$-, -$N(R^1)$-$C(=O)(CH_2)_{n''}$-$C(=O)N(R^1)$-, or -$N(R^1)$-$C(=O)(CH_2)_{n''}$-$N(R^1)C(=O)$ -, wherein each R^1 is independently H or C_1-C_3 alkyl, and n'' is independently an integer from 0 to 8;

(g) -PEG-CON-PEG-, wherein each PEG is independently a polyethylene glycol group containing from 1-12 ethylene glycol residues and CON comprises a structure



wherein:

R^{1a}, R^{2a} and R^{3a} are each independently H, -$(CH_2)_{M1}$-, -$(CH_2)_{M2}C(=O)_{M3}(NR^4)_{M3}$-$(CH_2)_{M2}$-, -$(CH_2)_{M2}(NR^4)_{M3}C(O)_{M3}$-$(CH_2)_{M2}$-, or -$(CH_2)_{M2}O$-$(CH_2)_{M1}$-$C(O)NR^4$-, with the proviso that R^{1a}, R^{2a} and R^{3a} are not simultaneously H;

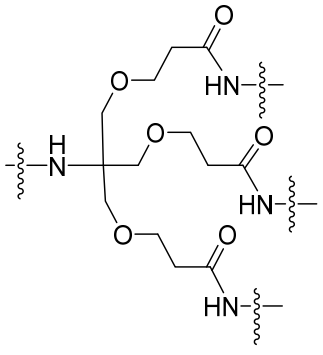
each M1 is independently 1, 2, 3, or 4; in certain embodiments, 1 or 2;

each M2 is independently 0, 1, 2, 3, or 4; in certain embodiments, 0, 1 or 2;

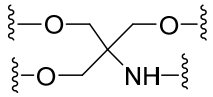
each M3 is independently 0 or 1; and

each R^4 is independently H, C_1-C_3 alkyl, C_1-C_6 alkanol, or -$C(=O)(C_1$-C_3 alkyl), with the proviso that M2, and M3 within the same R^{1a}, R^{2a} and R^{3a} cannot all be simultaneously 0;

(h) -PEG-CON-PEG-, wherein each PEG is independently a polyethylene glycol group containing from 1-12 ethylene glycol residues and CON comprises a structure:



or



;

(i) a natural or an unnatural amino acid;

(j) $[Gly\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Ser]_n$, where n is 1, 2, 3, 4, 5 or 6;

(k) $[Ser\text{-}Ser\text{-}Ser\text{-}Ser\text{-}Gly]_y$, where y is ≧1; or

(l) Ser-Gly-Ser-Ser-Ser-Ser-Gly-Ser-Ser-Ser-Ser-Gly-Ser.

2. The compound of claim 1, wherein the valence of the Linker is 1, 2, or 3.

3. The compound of claim 1, wherein m is 1, 2, or 3.

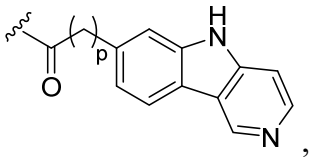
4. The compound of claim 1, wherein n and o are each independently 1, 2, or 3.

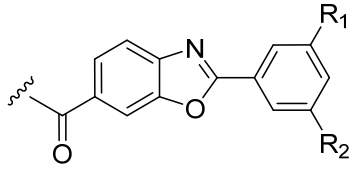
5. The compound of claim 1, wherein the target binding motif binds noncovalently to an extracellular protein or a cell surface protein.

6. The compound of claim 5, wherein the extracellular or cell surface protein comprises a calcitonin gene-related peptide (CGRP), a CGRP receptor, an N-methyl-D-aspartate (NMDA) receptor, myeloperoxidase (MPO), α-synuclein, IAPP, transthyretin, extracellular tau, amyloid precursor protein, a prion protein, or amyloid beta.

7. The compound of claim 5 or 6, wherein the extracellular or cell surface protein comprises extracellular tau or amyloid beta.

8. The compound of any one of claims 5-7, wherein the extracellular or cell surface protein is found in the brain or the central nervous system.

9. The compound of claim 1, wherein [TBM] is selected from 

, wherein p is an integer from 1-6; and 

, wherein R_1 and R_2 are each independently selected from F, Cl, Br, and I.

10. The compound of claim 1, wherein the LRP1BM comprises the peptide of SEQ ID NO: 1.

11. The compound of claim 10, wherein the C-terminal cysteine residue is absent from the peptide of SEQ ID NO: 1.

12. The compound of claim 11, wherein the peptide of SEQ ID NO: 1 is attached to the Linker through its N-terminal tyrosine (Tyr1), Lys10, or Lys15.

13. A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and at least one compound of claim 1.

14. The pharmaceutical composition of claim 13, further comprising another therapeutically active compound.

15. A composition comprising at least one compound of claim 1, or a salt, geometric isomer, stereoisomer, or solvate thereof for use as a medicament.

16. Use of a therapeutically effective amount of a composition comprising at least one compound of claim 1, or a salt, geometric isomer, stereoisomer, or solvate thereof in the manufacture of a medicament for treating, ameliorating, or preventing a neurological disease or disorder in a subject.

17. The use of claim 16, wherein the neurological disease or disorder is at least one of Huntington's Disease (HD), Parkinson's Disease (PD), Amyotropic Lateral Sclerosis (ALS), multiple system atrophy (MSA), Alzheimer's Disease, Lewy body dementia, Multiple System Atrophy, spinal and bulbar muscular atrophy (Kennedy's disease), Tourette Syndrome, spinocerebellar ataxia (SCA), schizophrenia, age associated memory impairment, autism, migraines, Rett syndrome, complex regional pain syndrome (CRPS), obsessive-compulsive disorder (OCD), attention-deficit disorder, bipolar disorder, hereditary cerebral angiopathy, ATTR amyloidosis, or depression.

18. The use of claim 16, wherein the neurological disease or disorder is Alzheimer’s Disease.

19. The use of claim 16, wherein the subject is to be further administered at least one additional therapeutic agent that treats, ameliorates, or prevents the disease or disorder.

20. The use of claim 16, wherein the subject is a mammal.

21. The use of claim 16, wherein the subject is a human.

22. The use of claim 16, wherein the composition comprises at least one pharmaceutically acceptable carrier or excipient.