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(54) Title: CELL PERMEABLE CYCLIC PEPTIDE SCAFFOLDS

(57) Abstract: Aspects of the present disclosure include cell permeable cyclic peptide scaffolds that include a hexapeptide composed of naturally or non-naturally occurring amino acids. Pharmaceutical compositions having one or more of the cell permeable cyclic peptide scaffolds and pharmaceutically acceptable excipient are also provided. Methods for using the subject cell permeable cyclic peptide scaffolds are also described.



CELL PERMEABLE CYCLIC PEPTIDE SCAFFOLDS

CROSS-REFERENCE TO RELATED APPLICATION

Pursuant to 35 U.S.C. §119(e), this application claims priority to the filing date of United States Provisional Patent Application Serial No. 62/489,337 filed on April 24, 2017, the disclosure of which application is incorporated herein by reference.

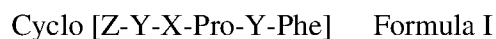
INTRODUCTION

Certain undruggable targets lack well defined binding pockets. Inhibitors of these undruggable targets may be larger and more complex than typical small molecule drugs. The targets of existing small molecule drugs make up only a small fraction of the protein encoding genome, and it is estimated that the total "druggable" genome (accessible to inhibition by classic small molecules) represents a small fraction of the total number of potential targets. The number of therapeutic targets that have been unexploited due to poor druggability, such as transcription factors and non-coding RNAs, therefore represent a vast opportunity to make therapeutic advances in virtually every disease category.

Macrocylic compounds, such as cyclic peptides exhibit therapeutic potential due to protein-protein interactions (PPIs). Cyclization can often improve potency in peptides as well as proteolytic stability. In addition, the synthesis of cyclic peptides is much more modular and straightforward than the synthesis of organic molecules of similar size and complexity. Large combinatorial libraries of cyclic peptides, derived from methods such as DNA-encoded synthesis, phage display and mRNA-display, have yielded potent inhibitors against a variety of undruggable or challenging targets, such as XIAP10 and E6AP11.

SUMMARY

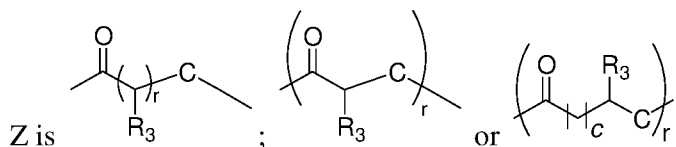
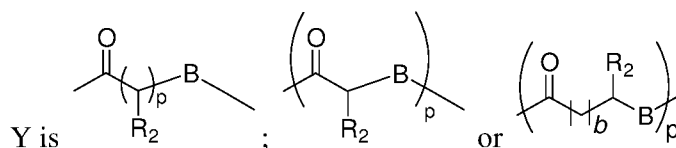
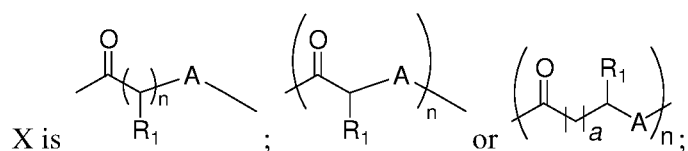
The present disclosure provides cell permeable cyclic peptide scaffolds, pharmaceutical compositions, and their methods of use, where the cell permeable cyclic peptide scaffolds include a hexapeptide composed of naturally or non-naturally occurring amino acids. In embodiments, the cyclic peptide scaffold is a compound of Formula I:



wherein:

Pro is L-proline or D-proline;

Phe is L-phenylalanine or D-phenylalanine;



- 5 each R_1 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;
- 10 each R_2 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;
- 15 each R_3 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;
- 20 A is selected from $-NR_a-$, $-O-$ or $-S-$;
 B is selected from $-NR_b-$, $-O-$ or $-S-$;
 C is selected from $-NR_c-$, $-O-$ or $-S-$;
 each R_a , R_b , R_c is independently selected from hydrogen, alkyl, substituted alkyl, aryl and substituted aryl, or
- 25 R_1 and R_a together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R_2 and R_b together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R_3 and R_c together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

- 5 n is an integer from one to 5 and a is an integer from one to 5;
 p is an integer from one to 5 and b is an integer from one to 5; and
 r is an integer from one to 5 and c is an integer from one to 5;
 or a pharmaceutical acceptable salt, solvate or hydrate thereof.

- Compositions containing one or more of the subject cell permeable cyclic peptide
10 scaffolds are also provided. In some embodiments, compositions include one or more of the cell
 permeable cyclic peptide scaffolds described herein, or pharmaceutically acceptable salt, solvate
 or hydrate thereof and a pharmaceutically acceptable vehicle. Dose units containing one or
 more of the subject compositions are also provided. A library having a plurality of the cell
 permeable cyclic peptide scaffolds are also described. For example, the library may include 50
15 or more of the subject cyclic peptides, each cyclic peptide independently being a compound of
 Formula I.

DEFINITION OF CERTAIN CHEMICAL TERMINOLOGY

- The following terms have the following meaning unless otherwise indicated. Any
20 undefined terms have their art recognized meanings.

- As used herein, the term "alkyl" by itself or as part of another substituent refers to a
 saturated branched or straight-chain monovalent hydrocarbon radical derived by the removal of
 one hydrogen atom from a single carbon atom of a parent alkane. Typical alkyl groups include,
 but are not limited to, methyl; ethyl, propyls such as propan-1-yl or propan-2-yl; and butyls such
25 as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl or 2-methyl-propan-2-yl. In some embodiments,
 an alkyl group comprises from 1 to 20 carbon atoms. In other embodiments, an alkyl group
 comprises from 1 to 10 carbon atoms. In still other embodiments, an alkyl group comprises
 from 1 to 6 carbon atoms, such as from 1 to 4 carbon atoms.

- "Alkanyl" by itself or as part of another substituent refers to a saturated branched,
30 straight-chain or cyclic alkyl radical derived by the removal of one hydrogen atom from a single
 carbon atom of an alkane. Typical alkanyl groups include, but are not limited to, methanyl;
 ethanyl; propyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, etc.; butanyls

such as butan-1-yl, butan-2-yl (sec-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (t-butyl), cyclobutan-1-yl, etc.; and the like.

"Alkylene" refers to a branched or unbranched saturated hydrocarbon chain, usually having from 1 to 40 carbon atoms, more usually 1 to 10 carbon atoms and even more usually 1 to 6 carbon atoms. This term is exemplified by groups such as methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{CH}_2-$), the propylene isomers (e.g., $-\text{CH}_2\text{CH}_2\text{CH}_2-$ and $-\text{CH}(\text{CH}_3)\text{CH}_2-$) and the like.

"Alkenyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of an alkene. The group may be in either the cis or trans conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, etc.; and the like.

"Alkynyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of an alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl, etc.; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, etc.; and the like.

"Acyl" by itself or as part of another substituent refers to a radical $-\text{C}(\text{O})\text{R}^{30}$, where R^{30} is hydrogen, alkyl, cycloalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl as defined herein and substituted versions thereof. Representative examples include, but are not limited to formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl, benzylcarbonyl, piperonyl, succinyl, and malonyl, and the like.

The term "aminoacyl" refers to the group $-\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, wherein R^{21} and R^{22} independently are selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{21} and R^{22} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl,

heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"Alkoxy" by itself or as part of another substituent refers to a radical $-OR^{31}$ where R^{31} represents an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, cyclohexyloxy and the like.

"Alkoxy carbonyl" by itself or as part of another substituent refers to a radical $-C(O)OR^{31}$ where R^{31} represents an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, cyclohexyloxycarbonyl and the like.

"Aryl" by itself or as part of another substituent refers to a monovalent aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of an aromatic ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like. In certain embodiments, an aryl group comprises from 6 to 20 carbon atoms. In certain embodiments, an aryl group comprises from 6 to 12 carbon atoms. Examples of an aryl group are phenyl and naphthyl.

"Arylalkyl" by itself or as part of another substituent refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl group. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. Where specific alkyl moieties are intended, the nomenclature arylalkanyl, arylalkenyl and/or arylalkynyl is used. In certain embodiments, an arylalkyl group is (C_7-C_{30}) arylalkyl, e.g., the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_1-C_{10}) and the aryl moiety is (C_6-C_{20}) . In certain embodiments, an arylalkyl group is (C_7-C_{20}) arylalkyl, e.g., the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_1-C_8) and the aryl moiety is (C_6-C_{12}) .

"Arylaryl" by itself or as part of another substituent, refers to a monovalent hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a ring system in which two or more identical or non-identical aromatic ring systems are joined directly together by a single bond, where the number of such direct ring junctions is one less than the

number of aromatic ring systems involved. Typical arylaryl groups include, but are not limited to, biphenyl, triphenyl, phenyl-naphthyl, binaphthyl, biphenyl-naphthyl, and the like. When the number of carbon atoms in an arylaryl group are specified, the numbers refer to the carbon atoms comprising each aromatic ring. For example, (C₅-C₁₄) arylaryl is an arylaryl group in which each aromatic ring comprises from 5 to 14 carbons, e.g., biphenyl, triphenyl, binaphthyl, phenyl-naphthyl, etc. In certain embodiments, each aromatic ring system of an arylaryl group is independently a (C₅-C₁₄) aromatic. In certain embodiments, each aromatic ring system of an arylaryl group is independently a (C₅-C₁₀) aromatic. In certain embodiments, each aromatic ring system is identical, e.g., biphenyl, triphenyl, binaphthyl, trinaphthyl, etc.

"Cycloalkyl" by itself or as part of another substituent refers to a saturated or unsaturated cyclic alkyl radical. Where a specific level of saturation is intended, the nomenclature "cycloalkanyl" or "cycloalkenyl" is used. Typical cycloalkyl groups include, but are not limited to, groups derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and the like. In certain embodiments, the cycloalkyl group is (C₃-C₁₀) cycloalkyl. In certain embodiments, the cycloalkyl group is (C₃-C₇) cycloalkyl.

"Cycloheteroalkyl" or "heterocyclyl" by itself or as part of another substituent, refers to a saturated or unsaturated cyclic alkyl radical in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atom(s) include, but are not limited to, N, P, O, S, Si, etc. Where a specific level of saturation is intended, the nomenclature "cycloheteroalkanyl" or "cycloheteroalkenyl" is used. Typical cycloheteroalkyl groups include, but are not limited to, groups derived from epoxides, azirines, thiiranes, imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine and the like.

"Heteroalkyl, Heteroalkanyl, Heteroalkenyl and Heteroalkynyl" by themselves or as part of another substituent refer to alkyl, alkanyl, alkenyl and alkynyl groups, respectively, in which one or more of the carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatomic groups. Typical heteroatomic groups which can be included in these groups include, but are not limited to, -O-, -S-, -S-S-, -O-S-, -NR³⁷R³⁸-, -N=N-, -N=N-, -N=N-NR³⁹R⁴⁰-, -PR⁴¹-, -P(O)₂-, -POR⁴²-, -O-P(O)₂-, -S-O-, -S-(O)-, -SO₂-, -SnR⁴³R⁴⁴- and the like, where R³⁷, R³⁸, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³ and R⁴⁴ are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl,

substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl.

"Heteroaryl" by itself or as part of another substituent, refers to a monovalent heteroaromatic radical derived by the removal of one hydrogen atom from a single atom of a heteroaromatic ring system. Typical heteroaryl groups include, but are not limited to, groups derived from acridine, arsindole, carbazole, β -carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, benzodioxole and the like. In certain embodiments, the heteroaryl group is from 5-20 membered heteroaryl. In certain embodiments, the heteroaryl group is from 5-10 membered heteroaryl. In certain embodiments, heteroaryl groups are those derived from thiophene, pyrrole, benzothiophene, benzofuran, indole, pyridine, quinoline, imidazole, oxazole and pyrazine.

"Heteroarylalkyl" by itself or as part of another substituent, refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkanyl, heteroarylalkenyl and/or heteroarylalkynyl is used. In certain embodiments, the heteroarylalkyl group is a 6-30 membered heteroarylalkyl, e.g., the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is 1-10 membered and the heteroaryl moiety is a 5-20-membered heteroaryl. In certain embodiments, the heteroarylalkyl group is 6-20 membered heteroarylalkyl, e.g., the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is 1-8 membered and the heteroaryl moiety is a 5-12-membered heteroaryl.

"Aromatic Ring System" by itself or as part of another substituent, refers to an unsaturated cyclic or polycyclic ring system having a conjugated π electron system. Specifically included within the definition of "aromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, fluorene, indane, indene, phenalene, etc. Typical aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene,

penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like.

"Heteroaromatic Ring System" by itself or as part of another substituent, refers to an aromatic ring system in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atoms include, but are not limited to, N, P, O, S, Si, etc. Specifically included within the definition of "heteroaromatic ring systems" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, arindole, benzodioxan, benzofuran, chromane, chromene, indole, indoline, xanthene, etc. Typical heteroaromatic ring systems include, but are not limited to, arindole, carbazole, β -carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene and the like.

"Substituted" refers to a group in which one or more hydrogen atoms are independently replaced with the same or different substituent(s). Typical substituents include, but are not limited to, alkylenedioxy (such as methylenedioxy), -M, -R⁶⁰, -O⁻, =O, -OR⁶⁰, -SR⁶⁰, -S⁻, =S, -NR⁶⁰R⁶¹, =NR⁶⁰, -CF₃, -CN, -OCN, -SCN, -NO, -NO₂, =N₂, -N₃, -S(O)₂O⁻, -S(O)₂OH, -S(O)₂R⁶⁰, -OS(O)₂O⁻, -OS(O)₂R⁶⁰, -P(O)(O⁻)₂, -P(O)(OR⁶⁰)(O⁻), -OP(O)(OR⁶⁰)(OR⁶¹), -C(O)R⁶⁰, -C(S)R⁶⁰, -C(O)OR⁶⁰, -C(O)NR⁶⁰R⁶¹, -C(O)O⁻, -C(S)OR⁶⁰, -NR⁶²C(O)NR⁶⁰R⁶¹, -NR⁶²C(S)NR⁶⁰R⁶¹, -NR⁶²C(NR⁶³)NR⁶⁰R⁶¹ and -C(NR⁶²)NR⁶⁰R⁶¹ where M is halogen; R⁶⁰, R⁶¹, R⁶² and R⁶³ are independently hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl, or optionally R⁶⁰ and R⁶¹ together with the nitrogen atom to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring; and R⁶⁴ and R⁶⁵ are independently hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl, or optionally R⁶⁴ and R⁶⁵ together with the nitrogen atom to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring. In certain embodiments, substituents include -M, -R⁶⁰, =O, -OR⁶⁰, -SR⁶⁰, -S⁻, =S, -NR⁶⁰R⁶¹, =NR⁶⁰, -CF₃, -CN, -OCN, -SCN, -NO, -NO₂,

$=N_2$, $-N_3$, $-S(O)_2R^{60}$, $-OS(O)_2O^-$, $-OS(O)_2R^{60}$, $-P(O)(O^-)_2$, $-P(O)(OR^{60})(O^-)$, $-OP(O)(OR^{60})(OR^{61})$, $-C(O)R^{60}$, $-C(S)R^{60}$, $-C(O)OR^{60}$, $-C(O)NR^{60}R^{61}$, $-C(O)O^-$, $-NR^{62}C(O)NR^{60}R^{61}$. In certain embodiments, substituents include $-M$, $-R^{60}$,

$=O$, $-OR^{60}$, $-SR^{60}$, $-NR^{60}R^{61}$, $-CF_3$, $-CN$, $-NO_2$, $-S(O)_2R^{60}$, $-P(O)(OR^{60})(O^-)$, $-OP(O)(OR^{60})(OR^{61})$, $-C(O)R^{60}$, $-C(O)OR^{60}$, $-C(O)NR^{60}R^{61}$, $-C(O)O^-$. In certain embodiments, substituents include $-M$, $-R^{60}$,

$=O$, $-OR^{60}$, $-SR^{60}$, $-NR^{60}R^{61}$, $-CF_3$, $-CN$, $-NO_2$, $-S(O)_2R^{60}$, $-OP(O)(OR^{60})(OR^{61})$, $-C(O)R^{60}$, $-C(O)OR^{60}$, $-C(O)O^-$, where R^{60} , R^{61} and R^{62} are as defined above. For example, a substituted group may bear a methylenedioxy substituent or one, two, or three substituents selected from a halogen atom, a (1-4C)alkyl group and a (1-4C)alkoxy group.

“PK profile” refers to a profile of drug concentration in blood or plasma. Such a profile can be a relationship of drug concentration over time (i.e., a “concentration-time PK profile”) or a relationship of drug concentration versus number of doses ingested (i.e., a “concentration-dose PK profile”). A PK profile is characterized by PK parameters.

“PK parameter” refers to a measure of drug concentration in blood or plasma, such as: 1) “drug Cmax”, the maximum concentration of drug achieved in blood or plasma; 2) “drug Tmax”, the time elapsed following ingestion to achieve Cmax; and 3) “drug exposure”, the total concentration of drug present in blood or plasma over a selected period of time, which can be measured using the area under the curve (AUC) of a time course of drug release over a selected period of time (t). Modification of one or more PK parameters provides for a modified PK profile.

“Pharmacodynamic (PD) profile” refers to a profile of the efficacy of a drug in a patient (or subject or user), which is characterized by PD parameters. “PD parameters” include “drug Emax” (the maximum drug efficacy), “drug EC50” (the concentration of drug at 50% of the Emax) and side effects.

“Pharmaceutical composition” refers to at least one compound and can further comprise a pharmaceutically acceptable carrier, with which the compound is administered to a patient.

“Pharmaceutically acceptable salt” refers to a salt of a compound, which possesses the desired pharmacological activity of the compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid,

3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the compound is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like.

The term "solvate" as used herein refers to a complex or aggregate formed by one or more molecules of a solute, *e.g.* a prodrug or a pharmaceutically-acceptable salt thereof, and one or more molecules of a solvent. Such solvates are typically crystalline solids having a substantially fixed molar ratio of solute and solvent. Representative solvents include by way of example, water, methanol, ethanol, isopropanol, acetic acid, and the like. When the solvent is water, the solvate formed is a hydrate.

"Pharmaceutically acceptable carrier" refers to a diluent, adjuvant, excipient or vehicle with, or in which a compound is administered.

"Preventing" or "prevention" or "prophylaxis" refers to a reduction in risk of occurrence of a condition, such as pain.

"Prodrug" refers to a derivative of an active agent that requires a transformation within the body to release the active agent. In certain embodiments, the transformation is an enzymatic transformation. Prodrugs are frequently, although not necessarily, pharmacologically inactive until converted to the active agent.

"Promoiety" refers to a form of protecting group that when used to mask a functional group within an active agent converts the active agent into a prodrug. Typically, the promoiety will be attached to the drug via bond(s) that are cleaved by enzymatic or non-enzymatic means *in vivo*.

"Treating" or "treatment" of any condition, such as pain, refers, in certain embodiments, to ameliorating the condition (*i.e.*, arresting or reducing the development of the condition). In certain embodiments "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the patient. In certain embodiments, "treating" or "treatment" refers to inhibiting the condition, either physically, (*e.g.*, stabilization of a

discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In certain embodiments, "treating" or "treatment" refers to delaying the onset of the condition.

"Therapeutically effective amount" means the amount of a compound that, when administered to a patient for preventing or treating a condition such as pain, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the condition and its severity and the age, weight, *etc.*, of the patient.

DETAILED DESCRIPTION

Before exemplary embodiments of the present invention are described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, some potential and exemplary methods and materials may now be described. Any and all publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. It is understood that the present disclosure supersedes any disclosure of an incorporated publication to the extent there is a contradiction.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for

example, reference to “a membrane anchored polynucleotide” includes a plurality of such membrane-anchored polynucleotides and reference to “the polynucleotide” includes reference to one or more polynucleotides, and so forth.

It is further noted that the claims may be drafted to exclude any element which may be optional. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely”, “only” and the like in connection with the recitation of claim elements, or the use of a “negative” limitation.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed. To the extent such publications may set out definitions of a term that conflicts with the explicit or implicit definition of the present disclosure, the definition of the present disclosure controls.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

CELL PERMEABLE CYCLIC PEPTIDE SCAFFOLDS

As summarized above, aspects of the present disclosure include cell permeable cyclic peptide scaffolds where the cell permeable cyclic peptide scaffolds include a hexapeptide composed of naturally or non-naturally occurring amino acids. Cell permeable cyclic peptide scaffolds according to some embodiments are permeable into cells. In certain embodiments, the cell permeable cyclic peptide scaffolds described herein are permeable into the nucleus of the cells. In embodiments of the present disclosure, cells permeable to the subject cyclic peptide scaffolds include eukaryotic cells (e.g., mammalian cells) and/or prokaryotic cells (e.g., bacterial cells or archaeal cells). Cells permeable to the subject cyclic peptide scaffolds may be obtained from an *in vitro* source (e.g., a suspension of cells from laboratory cells grown in culture) or from an *in vivo* source (e.g., a mammalian subject, a human subject, etc.). In some embodiments, the cells permeable to the subject cyclic peptide scaffolds are obtained from an *in vitro* source.

In vitro sources include, but are not limited to, prokaryotic (e.g., bacterial, archaeal) cell cultures, environmental samples that contain prokaryotic and/or eukaryotic (e.g., mammalian, protest, fungal, etc.) cells, eukaryotic cell cultures (e.g., cultures of established cell lines, cultures of known or purchased cell lines, cultures of immortalized cell lines, cultures of primary cells, cultures of laboratory yeast, etc.), tissue cultures, and the like.

In some embodiments, cells permeable to the subject cyclic peptide scaffolds are obtained from an *in vivo* source and can include samples obtained from tissues (e.g., cell suspension from a tissue biopsy, cell suspension from a tissue sample, etc.) and/or body fluids (e.g., whole blood, fractionated blood, plasma, serum, saliva, lymphatic fluid, interstitial fluid, etc.). In some cases, cells, fluids, or tissues derived from a subject are cultured, stored, or manipulated prior to evaluation. *In vivo* sources include living multi-cellular organisms and can yield non-diagnostic or diagnostic cellular samples.

In certain embodiments the source of the cells is a “mammal” or “mammalian”, where these terms are used broadly to describe organisms which are within the class mammalia, including the orders carnivore (e.g., dogs and cats), rodentia (e.g., mice, guinea pigs, and rats), and primates (e.g., humans, chimpanzees, and monkeys). In some instances, the subjects are humans. The methods may be applied to samples obtained from human subjects of both genders and at any stage of development (i.e., neonates, infant, juvenile, adolescent, adult), where in certain embodiments the human subject is a juvenile, adolescent or adult. While the present invention may be applied to samples from a human subject, it is to be understood that the methods may also be carried-out on samples from other animal subjects (that is, in “non-human subjects”) such as, but not limited to, birds, mice, rats, dogs, cats, livestock and horses.

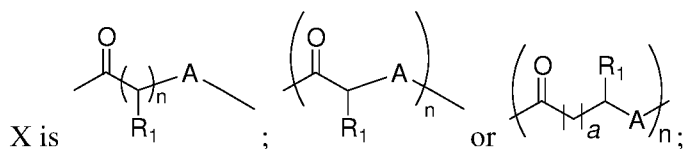
In embodiments, the cyclic peptide scaffold is a compound of Formula I:

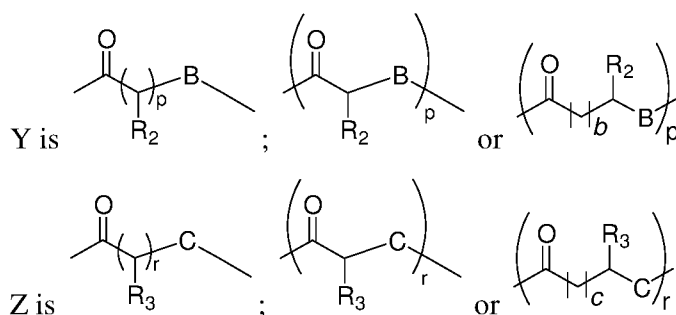
Cyclo [Z-Y-X-Pro-Y-Phe] Formula I

wherein:

Pro is L-proline or D-proline;

Phe is L-phenylalanine or D-phenylalanine;





each R_1 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

each R_2 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

each R_3 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

A is selected from $-NR_a-$, $-O-$ or $-S-$;

B is selected from $-NR_b-$, $-O-$ or $-S-$;

C is selected from $-NR_c-$, $-O-$ or $-S-$;

each R_a , R_b , R_c is independently selected from hydrogen, alkyl, substituted alkyl, aryl and substituted aryl, or

R_1 and R_a together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R_2 and R_b together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R_3 and R_c together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

n is an integer from one to 5 and a is an integer from one to 5;

p is an integer from one to 5 and b is an integer from one to 5; and
 r is an integer from one to 5 and c is an integer from one to 5;
or a pharmaceutical acceptable salt, solvate or hydrate thereof.

In some embodiments in the compounds of Formula I, each R_1 is independently selected
5 from a side chain of an amino acid selected from the group consisting of alanine, arginine,
asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine,
leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and
valine. In some instances, each R_1 is independently selected from a side chain of glycine,
leucine or phenylalanine. In one example, R_1 is a side chain of glycine. In another example, R_1
10 is a side chain of leucine. In yet another example, R_1 is a side chain of phenylalanine.

In some embodiments in the compounds of Formula I, each R_2 is independently selected
from a side chain of an amino acid selected from the group consisting of alanine, arginine,
asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine,
leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and
15 valine. In some instances, R_2 is selected from a side chain of leucine or glycine. In one
example, R_2 is a side chain of leucine. In another example, R_2 is a side chain of glycine.

In some embodiments in the compounds of Formula I, each R_3 is independently selected
from a side chain of an amino acid selected from the group consisting of alanine, arginine,
asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine,
20 leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and
valine. In some instances, R_3 is independently selected from a side chain of glycine, alanine or
phenylalanine. In one example, R_3 is a side chain of glycine. In another example, R_3 is a side
chain of alanine. In yet another example, R_3 is a side chain of phenylalanine.

In embodiments, n ranges from 1 to 10, such as where n is 1, such as where n is 2, such
25 as where n is 3, such as where n is 4, such as where n is 5, such as where n is 6, such as where n
is 7, such as where n is 8, such as where n is 9 and including where n is 10. In certain
embodiments, n ranges from 1 to 5. In one example, n is 1. In this example where n is 1, X
may be a naturally occurring amino acid, as described below. In another example, n is 2. In this
example where n is 2, X may be a non-naturally occurring amino acid, such as a non-naturally
30 occurring glycine or phenylalanine residue.

In embodiments, p ranges from 1 to 10, such as where p is 1, such as where p is 2, such
as where p is 3, such as where p is 4, such as where p is 5, such as where p is 6, such as where p
is 7, such as where p is 8, such as where p is 9 and including where p is 10. In certain

embodiments, p ranges from 1 to 5. In one example, p is 1. In this example where p is 1, Y may be a naturally occurring amino acid, such as a glycine or leucine residue. In another example, p is 2. In this example where p is 2, Y may be a non-naturally occurring amino acid.

In embodiments, r ranges from 1 to 10, such as where r is 1, such as where r is 2, such as where r is 3, such as where r is 4, such as where r is 5, such as where r is 6, such as where r is 7, such as where r is 8, such as where r is 9 and including where r is 10. In certain embodiments, r ranges from 1 to 5. In one example, r is 1. In this example where r is 1, Z may be a naturally occurring amino acid, as described below. In another example, r is 2. In this example where r is 2, Z may be a non-naturally occurring amino acid, such as a non-naturally occurring glycine or phenylalanine residue.

In certain embodiments, n is 2 and each R_1 is selected from a side chain of glycine or phenylalanine. In other embodiments, r is 2 and each R_3 is selected from a side chain of glycine or phenylalanine. In still other embodiments, p is 1 and R_2 is glycine or leucine.

A may be $-NR_a-$, $-O-$ or $-S-$. In some instances, A is O . In other instances, A is S . In certain instances, A is NR_a where R_a is hydrogen, alkyl or aryl. In certain embodiments, R_a is hydrogen. In other embodiments, R_a is aryl, such as benzyl. In yet other instances, R_a is alkyl, such as methyl or propyl.

B may be $-NR_b-$, $-O-$ or $-S-$. In some instances, B is O . In other instances, B is S . In certain instances, B is NR_b where R_b is hydrogen, alkyl or aryl. In certain embodiments, R_b is hydrogen. In other embodiments, R_b is aryl, such as benzyl. In yet other instances, R_b is alkyl, such as methyl or propyl.

C may be $-NR_b-$, $-O-$ or $-S-$. In some instances, C is O . In other instances, C is S . In certain instances, C is NR_c where R_c is hydrogen, alkyl or aryl. In certain embodiments, R_c is hydrogen. In other embodiments, R_c is aryl, such as benzyl. In yet other instances, R_c is alkyl, such as methyl or propyl.

In some embodiments, X is a residue of a D-amino acid or L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof. In some instances, X is a D-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof. For example, X may be D-leucine or an N-alkyl derivative thereof, such as

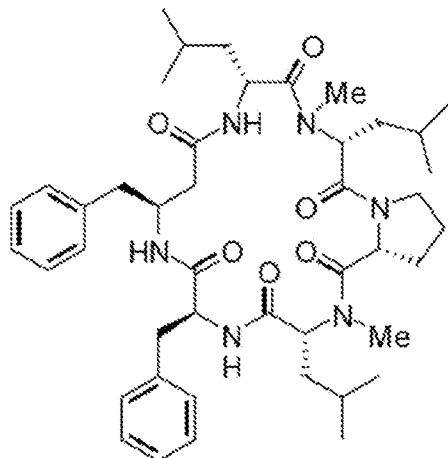
N-methyl D-leucine. In other instances, X is an L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof. For example, X may be L-leucine or an N-alkyl derivative thereof, such as N-methyl L-leucine. In other instances, X is L- β -homophenylalanine or an alkyl derivative thereof. In yet other instances, X is glycine or an N-alkyl derivative thereof, such as N-benzyl glycine.

In some embodiments, Y is a residue of a D-amino acid or L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof. In some instances, Y is a D-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof. For example, Y may be D-leucine or an N-alkyl derivative thereof, such as N-methyl D-leucine. In other instances, Y is an L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof. For example, Y may be L-leucine or an N-alkyl derivative thereof, such as N-methyl L-leucine. In yet other instances, Y is glycine or an N-alkyl derivative thereof, such as N-benzyl glycine.

In some embodiments, Z is a residue of a D-amino acid or L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof. In some instances, Z is a D-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof. For example, Z may be D-alanine or an N-alkyl derivative thereof, such as N-methyl D-leucine. In other instances, Z is an L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine,

tryptophan, tyrosine and valine or an N-alkyl derivative thereof. For Example, Z may be L-alanine or an N-alkyl derivative thereof, such as N-methyl L-alanine. In yet other instances, Z is L- β -homophenylalanine or an alkyl derivative thereof. In still other instances, Z is glycine or an N-alkyl derivative thereof, such as N-propyl glycine.

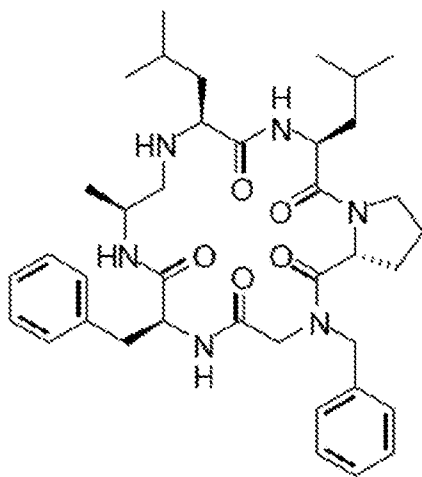
- 5 In certain embodiments, a cell permeable cyclic peptide scaffold of interest includes a compound of Formula 1:



Formula 1.

or a pharmaceutical acceptable salt, solvate or hydrate thereof.

- 10 In other embodiments, a cell permeable cyclic peptide scaffold of interest includes a compound of Formula 2:

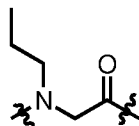


Formula 2

or a pharmaceutical acceptable salt, solvate or hydrate thereof.

- 15 In certain embodiments, cell permeable cyclic peptide scaffolds of interest include the compounds as set forth in Table 1, wherein each compound has a cyclic hexapeptide structure, (i.e., cyclo[A-B-C-X-Y-Z]) having a sequence of amino acids as set forth in Table 1, wherein:

LA02 = Pro-peptoid



= Pr-Peptoid (propyl-peptoid)

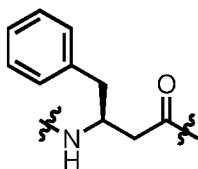
5 MA = N-methyl L-alanine

Ma = N-methyl D-alanine

A = L-alanine

a = D-alanine

BHF = L-β-Homophenylalanine



10

ML*** = N-methyl L-leucine

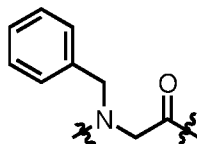
MI = N-methyl D-leucine

L*** = L-leucine

l = D-leucine

15

LA08 = Benzylpeptoid



P = L-proline

p = D-proline

20

F = L-Phenylalanine.

Table 1

<u>Compound No.</u>	<u>Cyclic Peptide Sequence</u>	<u>Compound No.</u>	<u>Cyclic Peptide Sequence</u>
1	BHF,L***,BHF,p,L***,F	621	MA,LA08,L***,p,l,F
2	BHF,l,MI,p,MI,F	622	Ma,LA08,L***,P,l,F
3	A,L***,L***,p,LA08,F	623	a,LA08,L***,P,LA08,F
4	BHF,l,MI,p,l,F	624	A,L***,MI,p,MI,F
5	BHF,L***,l,P,L***,F	625	LA02,ML***,LA08,p,LA08,F
6	Ma,MI,L***,P,l,F	626	A,l,LA08,P,LA08,F
7	A,L***,l,p,l,F	627	LA02,LA08,ML***,P,l,F
8	A,MI,BHF,P,l,F	628	BHF,MI,BHF,p,MI,F
9	A,MI,l,p,ML***,F	629	LA02,ML***,L***,p,l,F
10	a,MI,l,P,MI,F	630	Ma,L***,MI,p,l,F
11	MA,MI,MI,P,MI,F	631	LA02,MI,LA08,p,ML***,F
12	A,l,BHF,p,l,F	632	MA,MI,MI,p,MI,F

13	BHF,I,MI,P,MI,F	633	a,ML***,I,p,MI,F
14	MA,MI,MI,P,ML***,F	634	A,ML***,L***,P,I,F
15	MA,LA08,MI,P,I,F	635	Ma,I,I,p,I,F
16	MA,MI,L***,P,MI,F	636	BHF,MI,MI,P,MI,F
17	BHF,I,ML***,P,ML***,F	637	LA02,LA08,LA08,p,I,F
18	BHF,L***,BHF,p,I,F	638	a,ML***,I,P,MI,F
19	MA,LA08,L***,P,MI,F	639	a,MI,BHF,P,I,F
20	BHF,MI,MI,P,MI,F	640	a,LA08,LA08,P,LA08,F
21	LA02,I,MI,P,MI,F	641	LA02,I,LA08,P,LA08,F
22	a,MI,ML***,p,I,F	642	LA02,I,I,P,LA08,F
23	a,L***,L***,p,MI,F	643	LA02,MI,MI,p,LA08,F
24	BHF,MI,MI,p,MI,F	644	LA02,MI,LA08,p,LA08,F
25	BHF,MI,MI,P,MI,F	645	MA,I,LA08,P,LA08,F
26	Ma,L***,ML***,P,MI,F	646	A,I,LA08,p,MI,F
27	MA,ML***,LA08,P,LA08,F	647	A,L***,MI,P,MI,F
28	MA,MI,MI,P,MI,F	648	Ma,ML***,BHF,p,LA08,F
29	BHF,MI,MI,p,I,F	649	MA,ML***,BHF,p,LA08,F
30	a,ML***,L***,p,I,F	650	MA,L***,ML***,p,LA08,F
31	Ma,MI,L***,P,ML***,F	651	a,MI,MI,P,MI,F
32	A,MI,MI,p,I,F	652	Ma,MI,MI,p,MI,F
33	A,MI,L***,p,MI,F	653	a,L***,MI,P,I,F
34	A,LA08,MI,p,L***,F	654	A,MI,LA08,p,MI,F
35	A,MI,L***,P,MI,F	655	Ma,L***,I,P,LA08,F
36	a,MI,BHF,p,MI,F	656	Ma,I,I,P,L***,F
37	Ma,ML***,I,P,ML***,F	657	Ma,I,I,p,LA08,F
38	A,MI,MI,P,ML***,F	658	MA,MI,LA08,p,LA08,F
39	MA,I,MI,P,ML***,F	659	BHF,MI,I,p,MI,F
40	A,MI,MI,p,LA08,F	660	LA02,LA08,I,P,LA08,F
41	MA,MI,ML***,P,MI,F	661	LA02,I,BHF,p,L***,F
42	BHF,MI,MI,P,MI,F	662	LA02,LA08,LA08,p,I,F
43	Ma,MI,I,P,MI,F	663	LA02,I,MI,p,MI,F
44	Ma,MI,I,P,MI,F	664	LA02,MI,ML***,p,ML***,F
45	LA02,MI,LA08,P,MI,F	665	A,LA08,ML***,P,MI,F
46	LA02,MI,LA08,P,MI,F	666	a,MI,ML***,p,L***,F
47	A,L***,BHF,p,I,F	667	a,LA08,LA08,p,I,F
48	MA,MI,MI,P,L***,F	668	BHF,ML***,LA08,P,I,F
49	Ma,MI,MI,P,MI,F	669	BHF,L***,ML***,p,LA08,F
50	Ma,ML***,MI,P,MI,F	670	BHF,I,BHF,P,I,F
51	MA,I,MI,P,I,F	671	MA,L***,LA08,p,LA08,F
52	A,MI,ML***,P,MI,F	672	A,I,LA08,p,L***,F
53	A,L***,MI,p,ML***,F	673	BHF,I,I,P,LA08,F
54	MA,L***,MI,P,MI,F	674	a,L***,LA08,P,LA08,F
55	A,I,LA08,p,I,F	675	LA02,LA08,LA08,P,LA08,F

56	Ma,Ml,ML***,P,Ml,F	676	LA02,LA08,LA08,P,L***,F
57	MA,Ml,LA08,P,ML***,F	677	LA02,L***,L***,p,LA08,F
58	A,Ml,BHF,P,Ml,F	678	a,L***,l,P,Ml,F
59	BHF,l,l,p,Ml,F	679	BHF,LA08,l,P,l,F
60	a,L***,BHF,p,l,F	680	A,L***,l,P,Ml,F
61	a,L***,LA08,P,L***,F	681	a,Ml,l,P,l,F
62	BHF,L***,l,p,Ml,F	682	LA02,ML***,LA08,P,LA08,F
63	a,Ml,L***,p,Ml,F	683	Ma,ML***,l,P,l,F
64	MA,ML***,Ml,P,Ml,F	684	a,Ml,LA08,p,LA08,F
65	Ma,l,ML***,P,ML***,F	685	A,L***,l,p,Ml,F
66	BHF,Ml,Ml,p,Ml,F	686	Ma,LA08,L***,P,l,F
67	MA,ML***,L***,p,Ml,F	687	LA02,ML***,LA08,P,LA08,F
68	a,ML***,Ml,P,l,F	688	BHF,L***,BHF,p,Ml,F
69	A,Ml,Ml,p,Ml,F	689	a,ML***,l,P,L***,F
70	A,ML***,BHF,P,L***,F	690	Ma,L***,Ml,p,L***,F
71	A,L***,L***,p,l,F	691	LA02,l,BHF,p,Ml,F
72	Ma,ML***,Ml,P,L***,F	692	Ma,l,BHF,p,LA08,F
73	A,l,ML***,p,l,F	693	A,L***,LA08,P,l,F
74	A,Ml,BHF,p,Ml,F	694	Ma,L***,LA08,P,LA08,F
75	MA,l,Ml,P,LA08,F	695	a,L***,l,P,ML***,F
76	A,Ml,BHF,p,Ml,F	696	A,LA08,l,P,LA08,F
77	LA02,Ml,BHF,P,L***,F	697	BHF,L***,Ml,P,ML***,F
78	A,Ml,l,p,LA08,F	698	LA02,ML***,BHF,P,L***,F
79	A,Ml,l,p,Ml,F	699	BHF,L***,ML***,p,l,F
80	A,Ml,L***,p,ML***,F	700	LA02,Ml,L***,p,ML***,F
81	Ma,Ml,L***,P,LA08,F	701	LA02,Ml,ML***,p,Ml,F
82	A,l,Ml,p,Ml,F	702	BHF,L***,LA08,P,l,F
83	a,Ml,L***,P,Ml,F	703	MA,l,BHF,p,LA08,F
84	MA,Ml,Ml,p,Ml,F	704	A,L***,LA08,p,l,F
85	A,L***,LA08,p,Ml,F	705	LA02,L***,BHF,P,L***,F
86	MA,L***,Ml,P,Ml,F	706	MA,Ml,l,P,LA08,F
87	MA,Ml,Ml,P,LA08,F	707	LA02,l,Ml,p,Ml,F
88	LA02,Ml,L***,P,l,F	708	a,l,BHF,p,l,F
89	Ma,L***,Ml,P,ML***,F	709	BHF,L***,L***,P,LA08,F
90	Ma,ML***,L***,P,Ml,F	710	LA02,LA08,BHF,P,L***,F
91	A,Ml,BHF,P,Ml,F	711	a,LA08,l,P,LA08,F
92	Ma,Ml,Ml,P,Ml,F	712	a,Ml,l,P,L***,F
93	a,Ml,BHF,p,Ml,F	713	BHF,l,BHF,p,LA08,F
94	BHF,Ml,Ml,P,Ml,F	714	LA02,L***,l,P,l,F
95	a,Ml,L***,P,ML***,F	715	BHF,LA08,BHF,P,L***,F
96	BHF,L***,LA08,P,L***,F	716	A,LA08,ML***,P,ML***,F
97	A,Ml,L***,p,l,F	717	a,l,LA08,P,LA08,F
98	LA02,Ml,BHF,P,Ml,F	718	LA02,l,L***,p,L***,F
99	A,Ml,L***,P,ML***,F	719	BHF,Ml,BHF,P,l,F

100	MA,ML***,I,P,MI,F	720	a,I,BHF,p,MI,F
101	Ma,MI,MI,P,MI,F	721	BHF,LA08,I,P,MI,F
102	a,MI,BHF,p,MI,F	722	A,ML***,LA08,p,MI,F
103	LA02,MI,MI,P,MI,F	723	MA,L***,L***,p,MI,F
104	MA,MI,ML***,P,LA08,F	724	A,MI,BHF,P,L***,F
105	LA02,L***,I,P,L***,F	725	BHF,L***,ML***,P,LA08,F
106	MA,I,L***,p,ML***,F	726	BHF,LA08,MI,p,MI,F
107	Ma,L***,MI,p,ML***,F	727	LA02,L***,BHF,p,I,F
108	MA,MI,I,P,ML***,F	728	a,LA08,ML***,p,ML***,F
109	MA,L***,MI,P,ML***,F	729	A,LA08,ML***,P,I,F
110	BHF,L***,MI,P,L***,F	730	A,MI,MI,p,MI,F
111	Ma,ML***,MI,P,LA08,F	731	LA02,LA08,L***,p,LA08,F
112	a,LA08,MI,p,L***,F	732	BHF,I,ML***,p,LA08,F
113	LA02,I,MI,P,MI,F	733	Ma,L***,L***,p,MI,F
114	A,L***,LA08,p,I,F	734	LA02,MI,MI,P,MI,F
115	a,ML***,MI,P,LA08,F	735	BHF,MI,I,P,ML***,F
116	a,I,LA08,p,I,F	736	Ma,MI,L***,p,I,F
117	a,MI,LA08,p,I,F	737	BHF,LA08,ML***,P,L***,F
118	A,I,L***,P,L***,F	738	BHF,ML***,MI,p,MI,F
119	LA02,MI,MI,p,MI,F	739	a,I,LA08,p,ML***,F
120	A,I,L***,p,L***,F	740	a,MI,LA08,P,L***,F
121	LA02,MI,I,P,I,F	741	LA02,LA08,I,p,L***,F
122	a,MI,BHF,P,MI,F	742	BHF,I,L***,p,ML***,F
123	A,L***,LA08,p,LA08,F	743	LA02,I,L***,p,L***,F
124	A,I,L***,p,MI,F	744	A,I,I,p,LA08,F
125	a,MI,L***,p,I,F	745	LA02,L***,MI,p,LA08,F
126	Ma,MI,BHF,P,MI,F	746	MA,ML***,BHF,p,LA08,F
127	Ma,MI,I,P,LA08,F	747	a,L***,L***,P,LA08,F
128	MA,I,ML***,P,ML***,F	748	BHF,L***,I,P,LA08,F
129	BHF,MI,MI,p,MI,F	749	LA02,MI,I,P,LA08,F
130	Ma,MI,I,P,I,F	750	MA,MI,L***,p,I,F
131	Ma,LA08,MI,P,L***,F	751	a,LA08,I,p,MI,F
132	Ma,L***,MI,P,L***,F	752	LA02,L***,I,p,I,F
133	a,MI,I,P,ML***,F	753	Ma,MI,BHF,P,I,F
134	BHF,I,MI,P,I,F	754	MA,LA08,ML***,P,MI,F
135	BHF,I,L***,p,ML***,F	755	MA,LA08,I,p,LA08,F
136	a,MI,LA08,p,ML***,F	756	Ma,MI,BHF,p,I,F
137	MA,I,MI,P,MI,F	757	BHF,MI,L***,P,LA08,F
138	MA,MI,I,P,MI,F	758	LA02,MI,BHF,p,MI,F
139	BHF,MI,MI,P,MI,F	759	BHF,I,I,p,L***,F
140	A,L***,MI,P,L***,F	760	a,LA08,BHF,p,ML***,F
141	a,MI,L***,p,ML***,F	761	a,MI,MI,P,MI,F
142	MA,L***,MI,P,I,F	762	BHF,MI,L***,p,I,F
143	LA02,MI,I,P,MI,F	763	a,LA08,I,P,LA08,F

144	Ma,LA08,I,P,MI,F	764	Ma,L***,I,p,LA08,F
145	MA,MI,BHF,P,MI,F	765	LA02,ML***,MI,P,LA08,F
146	BHF,I,I,P,ML***,F	766	BHF,LA08,BHF,p,I,F
147	Ma,L***,I,P,ML***,F	767	A,L***,MI,P,I,F
148	Ma,L***,I,P,L***,F	768	A,MI,I,P,I,F
149	MA,I,LA08,P,ML***,F	769	Ma,ML***,LA08,p,MI,F
150	BHF,MI,MI,p,MI,F	770	A,ML***,LA08,P,I,F
151	MA,MI,I,P,MI,F	771	a,LA08,LA08,p,I,F
152	MA,MI,I,P,MI,F	772	BHF,L***,LA08,p,MI,F
153	LA02,L***,L***,P,MI,F	773	Ma,I,BHF,P,MI,F
154	a,LA08,MI,P,MI,F	774	A,I,BHF,P,I,F
155	MA,MI,MI,P,I,F	775	a,ML***,BHF,P,LA08,F
156	MA,MI,MI,P,I,F	776	A,MI,LA08,p,MI,F
157	Ma,I,MI,P,MI,F	777	BHF,MI,LA08,P,MI,F
158	LA02,I,L***,p,MI,F	778	LA02,I,MI,P,MI,F
159	Ma,LA08,MI,P,MI,F	779	Ma,LA08,ML***,P,I,F
160	LA02,I,L***,P,ML***,F	780	LA02,MI,I,p,I,F
161	A,I,ML***,p,MI,F	781	BHF,ML***,LA08,p,LA08,F
162	Ma,MI,BHF,P,MI,F	782	MA,I,LA08,p,LA08,F
163	a,LA08,ML***,P,MI,F	783	Ma,ML***,BHF,p,I,F
164	LA02,L***,I,P,MI,F	784	Ma,LA08,BHF,P,L***,F
165	Ma,MI,BHF,P,MI,F	785	LA02,I,I,p,LA08,F
166	A,MI,MI,p,MI,F	786	a,L***,I,p,MI,F
167	a,ML***,L***,p,ML***,F	787	Ma,I,L***,P,LA08,F
168	LA02,MI,MI,P,MI,F	788	LA02,ML***,I,P,L***,F
169	A,MI,ML***,p,L***,F	789	LA02,I,BHF,p,L***,F
170	MA,I,I,P,LA08,F	790	BHF,LA08,L***,p,MI,F
171	a,MI,L***,P,LA08,F	791	LA02,MI,LA08,p,ML***,F
172	A,L***,ML***,p,MI,F	792	MA,MI,MI,P,MI,F
173	BHF,I,MI,p,L***,F	793	BHF,LA08,LA08,p,I,F
174	a,LA08,MI,p,ML***,F	794	A,I,I,P,MI,F
175	MA,ML***,LA08,P,LA08,F	795	a,L***,I,p,LA08,F
176	BHF,ML***,LA08,p,ML***,F	796	a,MI,BHF,P,LA08,F
177	BHF,L***,MI,p,I,F	797	MA,L***,I,P,L***,F
178	LA02,I,ML***,P,MI,F	798	BHF,MI,I,P,MI,F
179	Ma,ML***,L***,p,MI,F	799	a,LA08,MI,p,I,F
180	MA,I,ML***,P,LA08,F	800	A,I,BHF,P,ML***,F
181	A,ML***,MI,P,MI,F	801	A,LA08,MI,p,L***,F
182	Ma,I,ML***,P,I,F	802	MA,MI,LA08,p,L***,F
183	BHF,L***,I,p,LA08,F	803	MA,MI,BHF,P,MI,F
184	LA02,L***,I,p,ML***,F	804	A,LA08,I,P,I,F
185	LA02,ML***,I,p,ML***,F	805	A,I,L***,P,L***,F
186	Ma,I,ML***,p,ML***,F	806	BHF,MI,ML***,P,ML***,F
187	MA,MI,L***,p,ML***,F	807	MA,MI,MI,P,MI,F

188	LA02,MI,BHF,P,MI,F	808	MA,ML***,BHF,p,l,F
189	LA02,ML***,l,p,LA08,F	809	A,l,BHF,P,LA08,F
190	MA,l,LA08,p,ML***,F	810	a,l,BHF,P,ML***,F
191	Ma,L***,MI,P,LA08,F	811	a,LA08,MI,P,LA08,F
192	Ma,MI,MI,P,l,F	812	BHF,MI,l,p,ML***,F
193	A,L***,BHF,P,ML***,F	813	a,L***,MI,p,l,F
194	a,MI,l,p,ML***,F	814	a,l,BHF,P,LA08,F
195	A,MI,MI,P,L***,F	815	a,LA08,L***,p,L***,F
196	a,MI,MI,P,l,F	816	LA02,l,l,P,MI,F
197	A,MI,ML***,p,l,F	817	A,l,BHF,p,MI,F
198	Ma,L***,MI,P,l,F	818	BHF,L***,LA08,p,LA08,F
199	A,L***,L***,p,MI,F	819	LA02,l,LA08,p,LA08,F
200	A,l,L***,P,LA08,F	820	MA,L***,L***,p,LA08,F
201	A,ML***,MI,P,ML***,F	821	BHF,L***,MI,p,ML***,F
202	LA02,MI,MI,P,l,F	822	A,l,l,P,L***,F
203	BHF,MI,MI,p,MI,F	823	MA,L***,BHF,p,LA08,F
204	LA02,MI,MI,p,MI,F	824	BHF,MI,L***,p,ML***,F
205	LA02,MI,MI,P,MI,F	825	BHF,L***,L***,P,l,F
206	LA02,l,L***,P,l,F	826	a,MI,MI,P,MI,F
207	a,MI,MI,p,MI,F	827	MA,l,MI,P,l,F
208	a,LA08,ML***,P,ML***,F	828	Ma,L***,l,p,MI,F
209	MA,l,ML***,p,l,F	829	LA02,LA08,LA08,p,LA08,F
210	a,L***,LA08,p,l,F	830	LA02,L***,L***,P,l,F
211	Ma,ML***,MI,p,MI,F	831	LA02,l,l,p,L***,F
212	A,MI,MI,p,MI,F	832	A,L***,l,P,l,F
213	A,LA08,L***,P,MI,F	833	MA,l,LA08,P,L***,F
214	LA02,l,L***,p,ML***,F	834	a,l,L***,P,LA08,F
215	Ma,ML***,L***,P,l,F	835	Ma,l,LA08,P,LA08,F
216	BHF,L***,MI,p,L***,F	836	LA02,L***,LA08,p,L***,F
217	LA02,L***,MI,P,MI,F	837	a,LA08,l,P,l,F
218	LA02,l,l,P,L***,F	838	Ma,l,ML***,p,L***,F
219	a,MI,BHF,P,MI,F	839	BHF,MI,MI,P,l,F
220	BHF,l,ML***,P,l,F	840	a,ML***,BHF,P,l,F
221	BHF,L***,l,p,l,F	841	BHF,MI,l,p,ML***,F
222	A,l,MI,P,LA08,F	842	LA02,LA08,LA08,P,L***,F
223	A,MI,l,P,LA08,F	843	Ma,l,LA08,p,LA08,F
224	BHF,l,MI,P,MI,F	844	MA,LA08,LA08,P,LA08,F
225	MA,L***,MI,P,LA08,F	845	a,l,LA08,P,MI,F
226	LA02,MI,l,p,ML***,F	846	BHF,L***,MI,P,LA08,F
227	a,ML***,L***,P,MI,F	847	A,l,l,p,ML***,F
228	A,MI,BHF,P,MI,F	848	MA,L***,L***,P,MI,F
229	Ma,LA08,l,P,l,F	849	Ma,LA08,BHF,p,ML***,F
230	LA02,ML***,ML***,p,MI,F	850	LA02,MI,BHF,p,MI,F
231	a,l,l,P,L***,F	851	A,MI,BHF,P,l,F

232	A,ML***,I,P,LA08,F	852	A,ML***,I,p,L***,F
233	LA02,Ml,ML***,P,Ml,F	853	A,ML***,I,p,Ml,F
234	Ma,Ml,BHF,P,Ml,F	854	A,I,ML***,P,I,F
235	BHF,I,L***,P,ML***,F	855	a,Ml,BHF,p,Ml,F
236	A,I,ML***,P,ML***,F	856	MA,I,BHF,P,ML***,F
237	LA02,Ml,Ml,p,Ml,F	857	MA,Ml,Ml,P,Ml,F
238	Ma,Ml,Ml,p,Ml,F	858	BHF,Ml,Ml,P,Ml,F
239	BHF,L***,I,P,I,F	859	MA,Ml,I,p,L***,F
240	a,Ml,Ml,P,Ml,F	860	a,LA08,LA08,p,LA08,F
241	A,I,LA08,p,LA08,F	861	BHF,L***,BHF,P,ML***,F
242	A,L***,I,p,LA08,F	862	Ma,I,I,P,Ml,F
243	A,I,ML***,P,Ml,F	863	BHF,ML***,LA08,p,Ml,F
244	A,ML***,LA08,P,Ml,F	864	a,L***,L***,P,Ml,F
245	BHF,Ml,I,p,I,F	865	a,I,LA08,p,Ml,F
246	BHF,I,L***,P,L***,F	866	a,L***,I,p,I,F
247	LA02,Ml,L***,P,Ml,F	867	Ma,L***,LA08,p,LA08,F
248	BHF,L***,I,P,ML***,F	868	LA02,I,BHF,P,LA08,F
249	LA02,ML***,L***,P,I,F	869	LA02,I,I,p,Ml,F
250	A,I,ML***,P,LA08,F	870	A,L***,L***,P,I,F
251	A,Ml,ML***,P,LA08,F	871	MA,L***,I,P,I,F
252	Ma,LA08,I,P,Ml,F	872	BHF,ML***,LA08,p,I,F
253	Ma,L***,LA08,P,ML***,F	873	A,ML***,I,P,I,F
254	LA02,Ml,ML***,P,ML***,F	874	BHF,Ml,Ml,P,I,F
255	MA,I,L***,p,Ml,F	875	MA,ML***,L***,P,I,F
256	a,L***,Ml,p,ML***,F	876	a,LA08,ML***,p,LA08,F
257	A,Ml,LA08,p,ML***,F	877	LA02,ML***,L***,p,LA08,F
258	MA,I,Ml,p,I,F	878	a,Ml,LA08,P,I,F
259	LA02,L***,I,p,Ml,F	879	MA,Ml,BHF,p,I,F
260	Ma,I,L***,P,Ml,F	880	LA02,LA08,L***,p,ML***,F
261	BHF,I,ML***,p,I,F	881	A,Ml,I,p,L***,F
262	MA,L***,I,P,ML***,F	882	Ma,Ml,LA08,p,LA08,F
263	A,Ml,I,P,Ml,F	883	LA02,ML***,LA08,p,L***,F
264	A,L***,Ml,P,LA08,F	884	a,Ml,I,p,I,F
265	a,Ml,I,P,LA08,F	885	MA,Ml,L***,P,I,F
266	LA02,Ml,Ml,P,Ml,F	886	LA02,Ml,I,P,LA08,F
267	Ma,L***,LA08,P,Ml,F	887	Ma,I,BHF,P,L***,F
268	LA02,Ml,LA08,P,LA08,F	888	A,L***,I,P,I,F
269	A,I,ML***,p,ML***,F	889	BHF,I,LA08,P,LA08,F
270	a,I,L***,p,Ml,F	890	Ma,I,BHF,p,Ml,F
271	LA02,Ml,BHF,p,Ml,F	891	Ma,I,BHF,P,LA08,F
272	BHF,Ml,Ml,P,Ml,F	892	A,I,BHF,P,L***,F
273	MA,Ml,Ml,P,Ml,F	893	BHF,Ml,I,P,LA08,F
274	A,ML***,LA08,p,LA08,F	894	a,L***,Ml,p,L***,F
275	MA,I,Ml,P,L***,F	895	MA,Ml,I,p,I,F

276	LA02,I,BHF,P,L***,F	896	BHF,MI,LA08,P,ML***,F
277	MA,MI,MI,P,MI,F	897	a,MI,BHF,P,MI,F
278	BHF,I,I,p,I,F	898	a,MI,BHF,p,LA08,F
279	BHF,I,I,p,I,F	899	BHF,ML***,LA08,p,MI,F
280	Ma,I,BHF,P,I,F	900	a,L***,I,P,LA08,F
281	A,ML***,I,p,LA08,F	901	a,MI,LA08,p,L***,F
282	MA,I,ML***,p,ML***,F	902	LA02,L***,ML***,p,LA08,F
283	a,ML***,LA08,P,ML***,F	903	MA,LA08,BHF,p,I,F
284	BHF,L***,L***,p,MI,F	904	BHF,LA08,LA08,P,I,F
285	A,MI,MI,P,MI,F	905	BHF,MI,L***,P,MI,F
286	A,MI,MI,P,MI,F	906	Ma,LA08,BHF,p,I,F
287	A,LA08,BHF,p,I,F	907	Ma,MI,MI,p,MI,F
288	a,LA08,MI,P,L***,F	908	BHF,LA08,MI,P,LA08,F
289	a,I,ML***,p,MI,F	909	LA02,MI,MI,p,I,F
290	BHF,I,I,p,LA08,F	910	MA,ML***,I,p,LA08,F
291	LA02,I,LA08,P,MI,F	911	A,LA08,LA08,p,L***,F
292	a,LA08,MI,P,L***,F	912	a,L***,I,P,I,F
293	LA02,MI,ML***,p,I,F	913	BHF,LA08,BHF,P,I,F
294	MA,MI,ML***,p,MI,F	914	a,MI,MI,p,MI,F
295	BHF,MI,L***,P,I,F	915	Ma,LA08,I,p,L***,F
296	BHF,MI,I,P,I,F	916	BHF,MI,ML***,P,MI,F
297	MA,LA08,ML***,p,I,F	917	A,I,I,P,I,F
298	a,MI,L***,p,L***,F	918	a,ML***,I,P,I,F
299	A,MI,LA08,P,L***,F	919	MA,I,MI,p,L***,F
300	A,I,LA08,P,L***,F	920	Ma,LA08,LA08,P,LA08,F
301	BHF,LA08,I,P,MI,F	921	a,I,MI,p,I,F
302	Ma,ML***,MI,P,LA08,F	922	Ma,I,I,P,LA08,F
303	BHF,LA08,L***,P,L***,F	923	LA02,MI,BHF,p,MI,F
304	LA02,MI,BHF,p,MI,F	924	Ma,L***,ML***,p,I,F
305	A,MI,MI,P,MI,F	925	MA,MI,MI,P,MI,F
306	BHF,I,LA08,p,I,F	926	A,MI,I,p,I,F
307	A,MI,ML***,P,ML***,F	927	Ma,LA08,I,p,L***,F
308	MA,ML***,LA08,p,MI,F	928	Ma,MI,MI,p,MI,F
309	A,MI,MI,p,MI,F	929	a,I,LA08,P,I,F
310	BHF,I,I,P,MI,F	930	LA02,ML***,BHF,p,MI,F
311	MA,MI,BHF,p,MI,F	931	a,L***,LA08,P,I,F
312	BHF,I,L***,P,I,F	932	MA,ML***,BHF,P,I,F
313	MA,I,L***,p,I,F	933	MA,L***,I,P,LA08,F
314	BHF,I,BHF,p,MI,F	934	a,MI,MI,p,I,F
315	a,MI,I,P,MI,F	935	LA02,ML***,BHF,p,LA08,F
316	BHF,I,BHF,p,I,F	936	LA02,L***,L***,p,I,F
317	A,MI,LA08,P,ML***,F	937	BHF,MI,LA08,P,ML***,F
318	a,I,L***,p,LA08,F	938	Ma,MI,BHF,P,MI,F
319	LA02,ML***,MI,P,I,F	939	a,I,L***,P,ML***,F

320	BHF,I,LA08,P,I,F	940	BHF,ML***,LA08,P,LA08,F
321	A,ML***,L***,p,I,F	941	A,I,I,p,I,F
322	MA,I,L***,p,LA08,F	942	MA,I,LA08,p,L***,F
323	BHF,MI,L***,p,L***,F	943	a,I,MI,P,MI,F
324	A,LA08,L***,P,MI,F	944	MA,MI,L***,P,L***,F
325	A,MI,LA08,p,MI,F	945	Ma,I,I,p,ML***,F
326	LA02,MI,MI,p,MI,F	946	Ma,I,BHF,p,MI,F
327	A,MI,L***,p,LA08,F	947	Ma,LA08,BHF,p,MI,F
328	LA02,MI,L***,p,I,F	948	MA,MI,MI,p,I,F
329	Ma,L***,I,P,MI,F	949	A,I,I,p,MI,F
330	A,LA08,I,P,LA08,F	950	a,MI,LA08,p,MI,F
331	LA02,MI,I,p,MI,F	951	MA,I,ML***,P,L***,F
332	A,MI,BHF,p,MI,F	952	a,L***,BHF,p,I,F
333	A,I,BHF,p,ML***,F	953	BHF,ML***,MI,P,LA08,F
334	LA02,ML***,MI,p,MI,F	954	a,I,I,P,LA08,F
335	LA02,I,L***,p,I,F	955	MA,I,I,P,MI,F
336	MA,MI,LA08,p,ML***,F	956	BHF,ML***,LA08,P,LA08,F
337	LA02,ML***,MI,P,MI,F	957	MA,LA08,BHF,P,I,F
338	LA02,MI,BHF,P,MI,F	958	BHF,LA08,LA08,p,MI,F
339	LA02,LA08,MI,P,I,F	959	A,I,BHF,P,MI,F
340	LA02,MI,MI,P,LA08,F	960	a,L***,MI,p,MI,F
341	LA02,ML***,LA08,p,MI,F	961	MA,I,BHF,P,I,L***,F
342	Ma,LA08,MI,p,I,F	962	BHF,L***,LA08,P,LA08,F
343	Ma,ML***,LA08,P,LA08,F	963	MA,L***,LA08,P,I,F
344	A,I,LA08,P,MI,F	964	BHF,MI,LA08,p,I,F
345	a,ML***,MI,P,LA08,F	965	a,I,MI,p,ML***,F
346	LA02,ML***,I,P,I,F	966	Ma,MI,BHF,p,LA08,F
347	MA,MI,LA08,P,LA08,F	967	BHF,ML***,LA08,p,ML***,F
348	BHF,I,L***,P,ML***,F	968	BHF,I,LA08,p,LA08,F
349	A,L***,MI,P,ML***,F	969	MA,I,I,P,L***,F
350	Ma,MI,MI,p,MI,F	970	MA,MI,BHF,P,MI,F
351	Ma,MI,L***,p,L***,F	971	MA,MI,LA08,P,I,F
352	a,LA08,MI,p,MI,F	972	a,LA08,I,p,I,F
353	a,ML***,LA08,p,MI,F	973	MA,I,BHF,P,MI,F
354	A,MI,MI,P,LA08,F	974	MA,I,BHF,P,MI,F
355	Ma,LA08,I,p,ML***,F	975	a,ML***,I,p,ML***,F
356	BHF,I,L***,p,MI,F	976	Ma,LA08,LA08,p,LA08,F
357	a,LA08,ML***,p,ML***,F	977	a,I,LA08,P,L***,F
358	A,MI,ML***,p,LA08,F	978	a,L***,L***,p,I,F
359	BHF,I,L***,P,LA08,F	979	MA,LA08,LA08,p,LA08,F
360	BHF,MI,BHF,P,I,L***,F	980	BHF,ML***,LA08,P,MI,F
361	MA,MI,MI,P,MI,F	981	BHF,ML***,MI,P,MI,F
362	A,MI,I,P,L***,F	982	MA,I,BHF,p,L***,F
363	BHF,I,ML***,P,I,F	983	MA,I,L***,p,L***,F

364	Ma,Ml,ML***,p,Ml,F	984	BHF,LA08,L***,P,LA08,F
365	MA,l,ML***,P,l,F	985	BHF,l,LA08,P,LA08,F
366	LA02,L***,Ml,p,l,F	986	BHF,ML***,ML***,P,LA08,F
367	LA02,ML***,l,p,LA08,F	987	Ma,L***,BHF,P,L***,F
368	A,LA08,L***,P,LA08,F	988	BHF,LA08,BHF,P,Ml,F
369	a,ML***,l,p,l,F	989	MA,Ml,BHF,P,l,F
370	LA02,ML***,l,p,Ml,F	990	Ma,l,l,p,Ml,F
371	BHF,Ml,BHF,P,l,F	991	a,L***,l,p,l,F
372	a,LA08,LA08,P,ML***,F	992	BHF,Ml,BHF,p,Ml,F
373	MA,Ml,Ml,P,Ml,F	993	BHF,ML***,LA08,p,LA08,F
374	A,LA08,l,p,l,F	994	MA,l,l,p,LA08,F
375	MA,l,BHF,p,Ml,F	995	MA,LA08,L***,P,l,F
376	MA,Ml,l,P,l,F	996	Ma,LA08,l,p,l,F
377	Ma,Ml,BHF,P,L***,F	997	BHF,LA08,LA08,p,L***,F
378	A,Ml,Ml,P,Ml,F	998	Ma,L***,l,P,l,F
379	A,Ml,BHF,p,l,F	999	MA,Ml,Ml,p,l,F
380	LA02,l,LA08,p,Ml,F	1000	BHF,Ml,l,p,LA08,F
381	MA,l,ML***,P,Ml,F	1001	Ma,Ml,Ml,P,l,F
382	BHF,L***,l,P,Ml,F	1002	a,l,BHF,P,Ml,F
383	LA02,L***,LA08,P,Ml,F	1003	Ma,L***,l,P,LA08,F
384	a,Ml,l,p,Ml,F	1004	MA,L***,l,p,LA08,F
385	Ma,l,LA08,p,Ml,F	1005	BHF,ML***,ML***,P,Ml,F
386	MA,l,L***,P,ML***,F	1006	MA,LA08,L***,p,LA08,F
387	a,ML***,LA08,p,ML***,F	1007	BHF,ML***,LA08,p,Ml,F
388	BHF,ML***,LA08,P,Ml,F	1008	MA,L***,BHF,p,l,F
389	A,ML***,l,P,Ml,F	1009	a,l,l,p,l,F
390	Ma,ML***,l,P,LA08,F	1010	MA,L***,L***,p,l,F
391	a,l,BHF,p,ML***,F	1011	Ma,Ml,Ml,p,l,F
392	A,LA08,ML***,P,LA08,F	1012	MA,l,l,p,L***,F
393	a,l,ML***,p,LA08,F	1013	LA02,Ml,ML***,p,L***,F
394	Ma,l,LA08,P,LA08,F	1014	BHF,Ml,L***,p,Ml,F
395	Ma,Ml,L***,p,ML***,F	1015	Ma,L***,l,p,l,F
396	Ma,Ml,Ml,P,Ml,F	1016	a,l,l,P,Ml,F
397	A,LA08,Ml,P,LA08,F	1017	BHF,LA08,LA08,p,Ml,F
398	BHF,l,l,P,l,F	1018	Ma,Ml,Ml,p,l,F
399	MA,l,LA08,p,ML***,F	1019	MA,l,L***,P,L***,F
400	Ma,L***,LA08,P,LA08,F	1020	Ma,L***,L***,P,l,F
401	LA02,L***,L***,p,Ml,F	1021	a,l,l,p,LA08,F
402	A,LA08,LA08,p,L***,F	1022	Ma,l,l,p,LA08,F
403	LA02,l,l,P,Ml,F	1023	a,l,LA08,p,L***,F
404	Ma,Ml,LA08,p,ML***,F	1024	a,l,Ml,p,Ml,F
405	Ma,ML***,L***,p,LA08,F	1025	a,l,l,P,l,F
406	BHF,LA08,Ml,p,Ml,F	1026	LA02,LA08,BHF,p,Ml,F
407	BHF,l,L***,p,ML***,F	1027	BHF,LA08,BHF,P,LA08,F

408	MA,L***,BHF,p,L***,F	1028	BHF,ML***,BHF,P,LA08,F
409	LA02,Ml,Ml,p,Ml,F	1029	Ma,l,L***,p,L***,F
410	A,L***,l,P,LA08,F	1030	BHF,Ml,ML***,p,Ml,F
411	LA02,l,BHF,P,Ml,F	1031	MA,Ml,BHF,P,L***,F
412	a,ML***,ML***,P,LA08,F	1032	a,LA08,LA08,p,L***,F
413	A,l,L***,P,Ml,F	1033	BHF,Ml,BHF,P,LA08,F
414	MA,ML***,LA08,p,LA08,F	1034	a,L***,l,P,l,F
415	MA,l,Ml,p,LA08,F	1035	MA,l,l,P,LA08,F
416	A,l,LA08,p,ML***,F	1036	BHF,Ml,LA08,P,LA08,F
417	Ma,l,ML***,p,l,F	1037	BHF,ML***,LA08,p,ML***,F
418	Ma,LA08,L***,p,Ml,F	1038	BHF,LA08,LA08,P,LA08,F
419	A,l,Ml,P,Ml,F	1039	BHF,LA08,L***,p,ML***,F
420	A,Ml,Ml,p,Ml,F	1040	a,l,l,P,l,F
421	a,ML***,l,P,ML***,F	1041	a,l,l,p,Ml,F
422	LA02,L***,L***,P,LA08,F	1042	BHF,Ml,BHF,P,ML***,F
423	MA,L***,L***,P,Ml,F	1043	Ma,Ml,Ml,p,l,F
424	LA02,l,ML***,p,L***,F	1044	Ma,L***,l,p,L***,F
425	a,Ml,BHF,P,L***,F	1045	a,l,L***,p,L***,F
426	LA02,Ml,LA08,p,Ml,F	1046	BHF,LA08,BHF,p,Ml,F
427	BHF,LA08,l,P,L***,F	1047	Ma,L***,L***,p,l,F
428	A,L***,LA08,P,LA08,F	1048	a,L***,l,p,L***,F
429	A,Ml,LA08,p,Ml,F	1049	MA,L***,L***,P,l,F
430	BHF,Ml,Ml,p,Ml,F	1050	BHF,LA08,LA08,p,LA08,F
431	MA,l,LA08,P,Ml,F	1051	MA,LA08,Ml,p,LA08,F
432	MA,LA08,L***,p,ML***,F	1052	Ma,Ml,BHF,p,Ml,F
433	a,L***,Ml,P,L***,F	1053	Ma,l,l,P,l,F
434	Ma,Ml,Ml,P,Ml,F	1054	MA,l,l,P,l,F
435	a,LA08,L***,P,L***,F	1055	MA,l,l,p,l,F
436	A,ML***,l,P,L***,F	1056	LA02,L***,L***,p,L***,F
437	MA,L***,l,P,Ml,F	1057	BHF,LA08,BHF,p,LA08,F
438	LA02,l,ML***,P,LA08,F	1058	a,Ml,BHF,p,Ml,F
439	A,Ml,Ml,P,l,F	1059	LA02,Ml,BHF,P,Ml,F
440	MA,Ml,ML***,p,LA08,F	1060	BHF,ML***,BHF,p,ML***,F
441	MA,Ml,L***,p,LA08,F	1061	BHF,Ml,BHF,P,Ml,F
442	A,l,LA08,P,ML***,F	1062	a,Ml,BHF,p,Ml,F
443	a,LA08,l,P,L***,F	1063	BHF,Ml,BHF,p,Ml,F
444	LA02,LA08,ML***,P,Ml,F	1064	BHF,Ml,BHF,p,Ml,F
445	MA,ML***,L***,p,LA08,F	1065	A,Ml,Ml,p,Ml,F
446	LA02,Ml,ML***,P,l,F	1066	a,Ml,Ml,p,Ml,F
447	LA02,l,ML***,p,l,F	1067	A,Ml,Ml,P,Ml,F
448	A,Ml,LA08,p,L***,F	1068	a,Ml,Ml,P,Ml,F
449	Ma,l,ML***,p,LA08,F	1069	MA,Ml,Ml,P,Ml,F
450	MA,l,l,p,l,F	1070	Ma,Ml,Ml,P,Ml,F
451	A,Ml,L***,p,L***,F	1071	Ma,l,l,p,l,F

452	Ma,l,L***,P,ML***,F	1072	MA,l,l,p,l,F
453	a,LA08,L***,P,LA08,F	1073	MA,l,l,p,l,F
454	BHF,ML***,ML***,P,LA08,F	1074	Ma,MI,BHF,P,MI,F
455	LA02,LA08,l,p,L***,F	1075	a,l,l,p,l,F
456	LA02,LA08,MI,P,LA08,F	1076	MA,LA08,LA08,P,LA08,F
457	A,MI,MI,P,MI,F	1077	A,MI,BHF,p,MI,F
458	a,MI,LA08,P,MI,F	1078	MA,MI,BHF,P,MI,F
459	Ma,L***,LA08,p,MI,F	1079	a,MI,MI,p,MI,F
460	a,l,ML***,p,ML***,F	1080	BHF,l,l,P,MI,F
461	A,L***,LA08,p,L***,F	1081	LA02,MI,BHF,P,ML***,F
462	LA02,MI,LA08,p,MI,F	1082	Ma,MI,MI,P,ML***,F
463	Ma,LA08,l,p,ML***,F	1083	LA02,ML***,BHF,p,MI,F
464	a,MI,MI,P,MI,F	1084	Ma,ML***,ML***,P,l,F
465	A,ML***,l,P,ML***,F	1085	MA,L***,LA08,P,LA08,F
466	MA,MI,l,p,MI,F	1086	Ma,L***,L***,p,ML***,F
467	Ma,l,L***,p,MI,F	1087	MA,MI,MI,P,ML***,F
468	MA,LA08,ML***,p,ML***,F	1088	MA,MI,MI,P,ML***,F
469	LA02,l,BHF,P,L***,F	1089	Ma,L***,ML***,p,MI,F
470	BHF,MI,BHF,p,l,F	1090	MA,l,l,p,MI,F
471	MA,l,L***,P,MI,F	1091	Ma,L***,L***,P,ML***,F
472	LA02,L***,ML***,p,MI,F	1092	a,l,ML***,P,MI,F
473	LA02,MI,L***,p,MI,F	1093	MA,l,l,P,ML***,F
474	LA02,l,L***,p,LA08,F	1094	A,LA08,BHF,p,L***,F
475	Ma,LA08,L***,p,ML***,F	1095	MA,MI,ML***,P,l,F
476	Ma,MI,LA08,p,l,F	1096	LA02,ML***,ML***,P,LA08,F
477	LA02,MI,LA08,p,LA08,F	1097	MA,l,l,p,ML***,F
478	MA,LA08,L***,p,L***,F	1098	BHF,l,ML***,p,ML***,F
479	LA02,LA08,L***,p,L***,F	1099	A,MI,BHF,p,L***,F
480	BHF,l,ML***,P,ML***,F	1100	a,ML***,ML***,p,l,F
481	Ma,l,LA08,P,MI,F	1101	Ma,MI,ML***,p,L***,F
482	a,MI,LA08,P,ML***,F	1102	MA,MI,LA08,P,MI,F
483	BHF,LA08,l,p,l,F	1103	Ma,L***,MI,p,l,F
484	A,LA08,l,P,L***,F	1104	A,l,MI,p,MI,F
485	LA02,MI,L***,P,LA08,F	1105	Ma,ML***,LA08,p,l,F
486	A,L***,LA08,P,MI,F	1106	BHF,ML***,L***,p,MI,F
487	A,l,l,p,l,F	1107	BHF,ML***,L***,p,MI,F
488	LA02,MI,LA08,p,MI,F	1108	A,l,BHF,p,L***,F
489	LA02,MI,BHF,p,l,F	1109	a,ML***,LA08,P,ML***,F
490	BHF,l,ML***,P,L***,F	1110	MA,L***,LA08,p,LA08,F
491	BHF,MI,BHF,P,MI,F	1111	a,ML***,ML***,p,l,F
492	BHF,ML***,LA08,P,l,F	1112	A,ML***,BHF,P,l,F
493	BHF,L***,BHF,P,L***,F	1113	MA,L***,l,p,l,F
494	a,LA08,BHF,P,l,F	1114	Ma,l,L***,p,ML***,F
495	MA,MI,LA08,p,MI,F	1115	BHF,ML***,L***,P,MI,F

496	BHF,I,LA08,P,L***,F	1116	Ma,l,l,p,L***,F
497	A,Ml,BHF,p,Ml,F	1117	BHF,ML***,L***,p,LA08,F
498	BHF,I,ML***,p,l,F	1118	Ma,L***,ML***,p,LA08,F
499	MA,LA08,l,P,l,F	1119	MA,Ml,Ml,P,l,F
500	LA02,ML***,l,p,l,F	1120	Ma,Ml,LA08,p,L***,F
501	A,l,L***,P,ML***,F	1121	A,ML***,BHF,P,LA08,F
502	Ma,Ml,Ml,P,Ml,F	1122	BHF,ML***,L***,P,LA08,F
503	MA,Ml,LA08,p,ML***,F	1123	BHF,Ml,L***,p,LA08,F
504	BHF,Ml,BHF,p,Ml,F	1124	LA02,ML***,L***,P,LA08,F
505	LA02,LA08,L***,P,ML***,F	1125	a,l,l,p,ML***,F
506	a,ML***,LA08,P,l,F	1126	MA,l,BHF,P,LA08,F
507	LA02,Ml,LA08,p,l,F	1127	BHF,ML***,LA08,p,LA08,F
508	A,ML***,BHF,p,l,F	1128	Ma,Ml,Ml,P,ML***,F
509	LA02,ML***,ML***,p,l,F	1129	LA02,L***,L***,p,LA08,F
510	A,l,ML***,p,L***,F	1130	Ma,Ml,l,p,Ml,F
511	A,l,L***,p,ML***,F	1131	MA,Ml,ML***,p,Ml,F
512	a,ML***,L***,p,Ml,F	1132	MA,ML***,ML***,P,l,F
513	Ma,ML***,LA08,p,LA08,F	1133	a,l,l,p,L***,F
514	A,ML***,Ml,P,l,F	1134	a,ML***,BHF,p,LA08,F
515	LA02,Ml,ML***,P,LA08,F	1135	Ma,ML***,LA08,p,Ml,F
516	LA02,LA08,l,P,l,F	1136	LA02,Ml,l,P,Ml,F
517	LA02,l,Ml,P,l,F	1137	a,Ml,l,p,L***,F
518	LA02,l,Ml,P,l,F	1138	a,ML***,l,p,L***,F
519	BHF,Ml,BHF,P,l,F	1139	a,l,l,P,ML***,F
520	LA02,Ml,LA08,p,LA08,F	1140	Ma,l,L***,P,L***,F
521	LA02,ML***,Ml,p,l,F	1141	a,L***,ML***,P,Ml,F
522	LA02,l,LA08,p,ML***,F	1142	a,Ml,Ml,P,l,F
523	MA,Ml,L***,P,ML***,F	1143	BHF,ML***,L***,p,L***,F
524	A,l,LA08,P,l,F	1144	BHF,ML***,LA08,p,ML***,F
525	A,LA08,Ml,P,Ml,F	1145	A,ML***,BHF,p,LA08,F
526	a,Ml,L***,P,l,F	1146	MA,L***,l,p,LA08,F
527	a,Ml,ML***,p,LA08,F	1147	BHF,LA08,BHF,p,L***,F
528	LA02,l,l,p,ML***,F	1148	a,l,Ml,P,Ml,F
529	A,l,l,P,LA08,F	1149	A,l,l,p,L***,F
530	Ma,l,L***,p,LA08,F	1150	BHF,Ml,LA08,p,Ml,F
531	LA02,LA08,Ml,P,l,F	1151	a,ML***,BHF,P,L***,F
532	A,Ml,ML***,p,L***,F	1152	Ma,L***,BHF,p,l,F
533	Ma,l,L***,p,l,F	1153	Ma,Ml,l,p,Ml,F
534	MA,Ml,ML***,p,L***,F	1154	BHF,ML***,L***,p,LA08,F
535	LA02,l,ML***,p,ML***,F	1155	a,l,BHF,P,L***,F
536	LA02,Ml,Ml,p,Ml,F	1156	BHF,Ml,Ml,P,LA08,F
537	LA02,L***,LA08,P,LA08,F	1157	Ma,ML***,L***,P,L***,F
538	MA,Ml,Ml,p,Ml,F	1158	LA02,LA08,BHF,P,ML***,F
539	LA02,Ml,LA08,P,ML***,F	1159	MA,ML***,L***,p,L***,F

540	LA02,LA08,l,p,l,F	1160	BHF,L***,BHF,p,L***,F
541	LA02,LA08,l,p,Ml,F	1161	Ma,L***,BHF,p,L***,F
542	a,ML***,L***,P,l,F	1162	A,Ml,LA08,P,l,F
543	Ma,L***,Ml,p,LA08,F	1163	Ma,ML***,BHF,P,LA08,F
544	Ma,L***,L***,P,Ml,F	1164	a,l,Ml,p,LA08,F
545	MA,l,LA08,P,Ml,F	1165	A,L***,L***,P,LA08,F
546	BHF,LA08,Ml,p,l,F	1166	Ma,ML***,L***,p,L***,F
547	A,LA08,LA08,P,LA08,F	1167	BHF,l,ML***,p,LA08,F
548	a,LA08,BHF,P,L***,F	1168	MA,L***,BHF,p,L***,F
549	LA02,Ml,L***,p,LA08,F	1169	A,ML***,L***,p,ML***,F
550	A,LA08,ML***,P,LA08,F	1170	A,L***,Ml,p,l,F
551	Ma,Ml,LA08,P,LA08,F	1171	MA,ML***,l,p,L***,F
552	a,LA08,Ml,P,LA08,F	1172	a,l,Ml,p,Ml,F
553	BHF,LA08,Ml,P,L***,F	1173	BHF,Ml,BHF,p,l,F
554	a,Ml,l,p,LA08,F	1174	LA02,L***,BHF,p,L***,F
555	Ma,Ml,ML***,p,LA08,F	1175	a,l,Ml,P,ML***,F
556	A,LA08,Ml,P,l,F	1176	MA,Ml,Ml,P,l,F
557	A,L***,L***,P,LA08,F	1177	BHF,Ml,ML***,p,LA08,F
558	LA02,ML***,BHF,p,l,F	1178	BHF,ML***,LA08,p,L***,F
559	a,Ml,BHF,P,ML***,F	1179	BHF,ML***,LA08,p,L***,F
560	BHF,l,BHF,p,LA08,F	1180	A,l,Ml,p,L***,F
561	MA,l,l,P,l,F	1181	A,l,ML***,P,L***,F
562	BHF,Ml,L***,P,ML***,F	1182	A,Ml,Ml,P,l,F
563	BHF,l,BHF,p,ML***,F	1183	LA02,l,LA08,p,l,F
564	A,LA08,BHF,P,L***,F	1184	Ma,ML***,l,p,ML***,F
565	a,ML***,Ml,p,LA08,F	1185	a,l,Ml,p,L***,F
566	LA02,ML***,L***,p,Ml,F	1186	LA02,Ml,LA08,P,LA08,F
567	Ma,L***,ML***,P,l,F	1187	A,LA08,L***,p,L***,F
568	LA02,ML***,l,p,L***,F	1188	Ma,L***,LA08,p,ML***,F
569	A,LA08,LA08,p,LA08,F	1189	Ma,L***,BHF,p,LA08,F
570	BHF,L***,Ml,P,l,F	1190	MA,Ml,l,P,L***,F
571	MA,Ml,Ml,p,Ml,F	1191	A,L***,l,p,l,F
572	BHF,ML***,l,p,Ml,F	1192	a,L***,ML***,P,l,F
573	MA,l,ML***,p,L***,F	1193	BHF,ML***,BHF,p,LA08,F
574	A,ML***,LA08,p,LA08,F	1194	BHF,L***,LA08,p,l,F
575	A,L***,L***,P,Ml,F	1195	Ma,l,LA08,P,L***,F
576	MA,l,l,P,Ml,F	1196	A,L***,ML***,p,l,F
577	MA,l,BHF,p,l,F	1197	MA,L***,LA08,p,L***,F
578	a,LA08,Ml,P,l,F	1198	a,ML***,BHF,p,Ml,F
579	MA,l,L***,P,LA08,F	1199	a,Ml,LA08,P,Ml,F
580	a,Ml,L***,p,LA08,F	1200	BHF,L***,Ml,P,LA08,F
581	BHF,Ml,L***,P,L***,F	1201	MA,l,LA08,p,l,F
582	LA02,Ml,BHF,P,Ml,F	1202	LA02,ML***,BHF,P,L***,F
583	LA02,l,LA08,p,L***,F	1203	BHF,Ml,LA08,P,l,F

584	a,L***,MI,P,ML***,F	1204	A,MI,LA08,p,LA08,F
585	BHF,LA08,L***,p,l,F	1205	BHF,MI,L***,p,ML***,F
586	Ma,MI,LA08,P,LA08,F	1206	Ma,l,LA08,p,L***,F
587	BHF,L***,L***,P,MI,F	1207	BHF,MI,LA08,p,ML***,F
588	BHF,l,LA08,p,MI,F	1208	MA,L***,LA08,P,LA08,F
589	BHF,l,L***,p,LA08,F	1209	a,MI,BHF,p,LA08,F
590	A,l,ML***,P,l,F	1210	MA,L***,BHF,P,l,F
591	BHF,l,L***,p,LA08,F	1211	MA,LA08,BHF,P,L***,F
592	A,LA08,L***,P,LA08,F	1212	a,ML***,LA08,p,LA08,F
593	LA02,LA08,MI,p,LA08,F	1213	MA,LA08,BHF,p,L***,F
594	a,MI,BHF,p,ML***,F	1214	A,l,L***,p,L***,F
595	LA02,L***,L***,p,LA08,F	1215	a,LA08,ML***,p,ML***,F
596	Ma,MI,L***,p,LA08,F	1216	Ma,MI,LA08,P,l,F
597	BHF,l,L***,p,l,F	1217	a,l,ML***,p,L***,F
598	MA,LA08,MI,p,l,F	1218	BHF,MI,MI,P,ML***,F
599	LA02,MI,LA08,p,ML***,F	1219	Ma,ML***,LA08,P,l,F
600	A,l,MI,p,ML***,F	1220	Ma,l,BHF,p,ML***,F
601	BHF,MI,L***,P,MI,F	1221	BHF,MI,MI,p,LA08,F
602	A,LA08,MI,P,LA08,F	1222	Ma,MI,BHF,p,l,F
603	a,LA08,l,p,ML***,F	1223	MA,MI,BHF,p,l,F
604	Ma,l,l,P,l,F	1224	LA02,LA08,MI,P,MI,F
605	Ma,MI,MI,p,MI,F	1225	MA,ML***,LA08,P,l,F
606	Ma,l,BHF,P,ML***,F	1226	MA,LA08,ML***,P,l,F
607	Ma,l,L***,P,l,F	1227	Ma,LA08,L***,p,MI,F
608	MA,ML***,L***,p,l,F	1228	a,LA08,MI,p,L***,F
609	A,LA08,l,p,L***,F	1229	a,LA08,l,P,ML***,F
610	a,L***,MI,P,LA08,F	1230	A,LA08,MI,p,ML***,F
611	LA02,LA08,BHF,P,MI,F	1231	a,LA08,L***,p,l,F
612	a,ML***,l,p,LA08,F	1232	MA,LA08,L***,p,l,F
613	LA02,LA08,MI,p,MI,F	1233	a,LA08,LA08,p,L***,F
614	MA,l,LA08,p,MI,F	1234	LA02,LA08,L***,p,LA08,F
615	LA02,MI,BHF,P,MI,F	1235	MA,LA08,LA08,P,L***,F
616	LA02,MI,L***,P,LA08,F	1236	a,LA08,LA08,p,L***,F
617	a,MI,BHF,p,l,F	1237	a,LA08,LA08,p,L***,F
618	LA02,LA08,BHF,P,l,F	1238	A,l,MI,p,MI,F
619	LA02,MI,MI,p,MI,F	1239	BHF,l,MI,p,l,F
620	BHF,l,BHF,P,ML***,F	1240	Ma,MI,MI,P,ML***,F

PHARMACEUTICAL COMPOSITIONS AND METHODS OF USE

The pharmaceutical composition according to the embodiments can further comprise a pharmaceutically acceptable carrier. The composition is conveniently formulated in a form suitable for oral (including buccal and sublingual) administration, for example as a tablet,

capsule, thin film, powder, suspension, solution, syrup, dispersion or emulsion. The composition can contain components conventional in pharmaceutical preparations, e.g. one or more carriers, binders, lubricants, excipients, pH modifiers, sweeteners, bulking agents, coloring agents or further active agents.

5 As described above, patients can be humans, and also other mammals, such as livestock, zoo animals and companion animals, such as a cat, dog or horse.

In some embodiments, the present disclosure provides cyclic peptide scaffolds for use in the treatment of a patient.

10 In another aspect, the embodiments provide a method of treating a patient requiring treatment, which comprises administering an effective amount of one or more of the cyclic peptide scaffolds or pharmaceutical composition as described hereinabove. The amount of the one or more of the cyclic peptide scaffolds or pharmaceutical composition disclosed herein to be administered to a patient to be effective will depend upon the bioavailability of the particular composition, as well as other factors, such as the species, age, weight, sex, and condition of the patient, manner of administration and judgment of the prescribing physician. In general, the composition dose can be such that the cyclic peptide is in the range of from 0.01 milligrams per kilogram to 20 milligrams per kilogram (mg/kg) body weight. For example, a composition comprising a cyclic peptide scaffold compound can be administered at a dose equivalent to administration in the range of from 0.02 to 0.5 mg/kg body weight or 0.01 mg/kg to 10 mg/kg body weight or 0.01 to 2 mg/kg body weight.

The present disclosure also provides dose units of the subject cyclic peptide scaffold compounds that can provide for a desired pharmacokinetic (PK) profile. Dose units can provide a modified PK profile compared to a reference PK profile as disclosed herein. It will be appreciated that a modified PK profile can provide for a modified pharmacodynamic (PD) profile. Ingestion of multiples of such a dose unit can also provide a desired PK profile. The term dose unit is used herein to refer to a composition that provides a therapeutically effective amount of drug (i.e., a sufficient amount of drug to effect a therapeutic effect, e.g., a dose within the respective drug's therapeutic window, or therapeutic range). "Multiple dose units" or "multiples of a dose unit" or a "multiple of a dose unit" refers to at least two single dose units.

30 As used herein, a "PK profile" refers to a profile of drug concentration in blood or plasma. Such a profile can be a relationship of drug concentration over time (i.e., a "concentration-time PK profile") or a relationship of drug concentration versus number of doses

ingested (i.e., a “concentration-dose PK profile”.) A PK profile is characterized by PK parameters.

As used herein, a “PK parameter” refers to a measure of drug concentration in blood or plasma, such as: 1) “drug C_{max}”, the maximum concentration of drug achieved in blood or plasma; 2) “drug T_{max}”, the time elapsed following ingestion to achieve C_{max}; and 3) “drug exposure”, the total concentration of drug present in blood or plasma over a selected period of time, which can be measured using the area under the curve (AUC) of a time course of drug release over a selected period of time (t). Modification of one or more PK parameters provides for a modified PK profile.

For purposes of describing the features of dose units of the present disclosure, “PK parameter values” that define a PK profile include drug C_{max} (e.g., phenolic opioid C_{max}), total drug exposure (e.g., area under the curve) and 1/(drug T_{max}) (such that a decreased 1/T_{max} is indicative of a delay in T_{max} relative to a reference T_{max}). Thus a decrease in a PK parameter value relative to a reference PK parameter value can indicate, for example, a decrease in drug C_{max}, a decrease in drug exposure, and/or a delayed T_{max}.

Dose units of the present disclosure can be adapted to provide for a modified PK profile, e.g., a PK profile that is different from that achieved from dosing a given dose of the cyclic peptide scaffold compound. For example, dose units can provide for at least one of decreased drug C_{max}, delayed drug T_{max} and/or decreased drug exposure.

As used herein, “a pharmacodynamic (PD) profile” refers to a profile of the efficacy of a drug in a patient (or subject or user), which is characterized by PD parameters. “PD parameters” include “drug E_{max}” (the maximum drug efficacy), “drug EC₅₀” (the concentration of drug at 50% of the E_{max}), and side effects.

A dose unit can be adapted to provide for a desired PK profile (e.g., a concentration-time PK profile) following ingestion of a single dose. A dose unit can be adapted to provide for a desired PK profile (e.g., a concentration-dose PK profile) following ingestion of multiple dose units (e.g., at least 2, at least 3, at least 4 or more dose units).

In compositions of the present disclosure, the compounds disclosed herein may be administered in the form of their pharmaceutically acceptable salts, or they may also be used alone or in appropriate association, as well as in combination, with other pharmaceutically active compounds. The following methods and excipients are merely exemplary and are in no way limiting.

The cyclic peptide scaffold compounds can be administered to a host using any available conventional methods and routes suitable for delivery of conventional drugs, including systemic or localized routes. In general, routes of administration contemplated include but are not necessarily limited to, enteral, parenteral, or inhalational routes, such as intrapulmonary or intranasal delivery.

Conventional and pharmaceutically acceptable routes of administration include intranasal, intrapulmonary, intramuscular, intratracheal, subcutaneous, intradermal, topical application, intravenous, rectal, nasal, oral and other parenteral routes of administration. Routes of administration may be combined, if desired, or adjusted depending upon the agent and/or the desired effect. The composition can be administered in a single dose or in multiple doses.

For oral preparations, the subject compounds can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, for example, with conventional additives, such as lactose, mannitol, corn starch or potato starch; with binders, such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators, such as corn starch, potato starch or sodium carboxymethylcellulose; with lubricants, such as talc or magnesium stearate; and if desired, with diluents, buffering agents, moistening agents, preservatives and flavoring agents. If oral administration is desired, the subject compounds may optionally be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

Parenteral routes of administration other than inhalation administration include, but are not necessarily limited to, topical, transdermal, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, and intravenous routes. Parenteral administration can be carried to effect systemic or local delivery of the agent. Where systemic delivery is desired, administration typically involves invasive or systemically absorbed topical or mucosal administration of pharmaceutical preparations. Where local delivery is desired, administration typically involves administering the composition to a desired target tissue, such as a liver, heart, spine, etc. For local delivery, the administration may be by injection or by placement of the composition in the desired tissue or organ by surgery, for example.

Methods of administration of the agent through the skin or mucosa include, but are not necessarily limited to, topical application of a suitable pharmaceutical preparation, transdermal transmission, injection and epidermal administration. For transdermal transmission, absorption

promoters or iontophoresis are suitable methods. Iontophoretic transmission may be accomplished using commercially available "patches" which deliver their product continuously via electric pulses through unbroken skin for periods of several days or more.

The subject compounds of the invention can be formulated into preparations for injection by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

The subject compounds can also be delivered to the subject by enteral administration. Enteral routes of administration include, but are not necessarily limited to, oral and rectal (e.g., using a suppository) delivery.

Furthermore, the subject compounds can be made into suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. The compounds of the present invention can be administered rectally via a suppository. The suppository can include vehicles such as cocoa butter, carbowaxes and polyethylene glycols, which melt at body temperature, yet are solidified at room temperature.

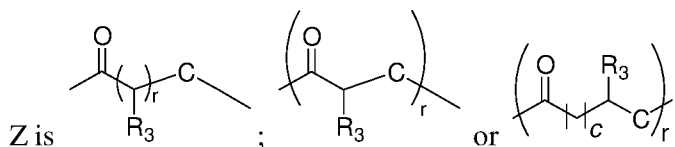
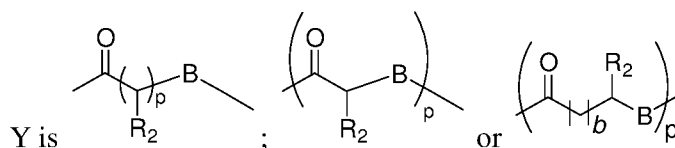
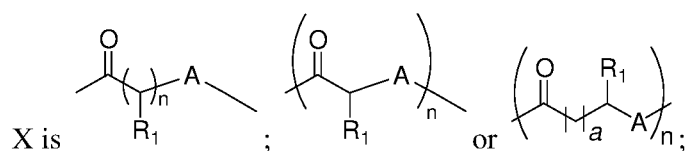
Aspects of the present disclosure also include a library having 5 or more of the cell permeable cyclic peptide scaffolds described hereinabove, such as 10 or more, such as 15 or more, such as 20 or more, such as 25 or more, such as 30 or more, such as 35 or more, such as 40 or more, such as 45 or more, such as 50 or more, such as 75 or more and including a library having 100 or more of the subject cell permeable cyclic peptide scaffolds. The library of compounds may include cyclic peptide scaffolds having similar amino acid sequences, conformation structures, or cell permeability values as desired. In embodiments, libraries of interest include 5 or more cell permeable cyclic peptide scaffolds, each having a structure according to Formula I:

Cyclo [Z-Y-X-Pro-Y-Phe] Formula I

wherein:

Pro is L-proline or D-proline;

Phe is L-phenylalanine or D-phenylalanine;



- 5 each R_1 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;
- 10 each R_2 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;
- 15 each R_3 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;
- 20 A is selected from $-NR_a-$, $-O-$ or $-S-$;
 B is selected from $-NR_b-$, $-O-$ or $-S-$;
 C is selected from $-NR_c-$, $-O-$ or $-S-$;
 each R_a , R_b , R_c is independently selected from hydrogen, alkyl, substituted alkyl, aryl and substituted aryl, or
- 25 R_1 and R_a together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R_2 and R_b together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R_3 and R_c together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

- 5 n is an integer from one to 5 and a is an integer from one to 5;
 p is an integer from one to 5 and b is an integer from one to 5; and
 r is an integer from one to 5 and c is an integer from one to 5;
 or a pharmaceutical acceptable salt, solvate or hydrate thereof.

EXAMPLES

- 10 As can be appreciated from the disclosure provided above, the present disclosure has a wide variety of applications. Accordingly, the following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only
- 15 experiments performed. Those of skill in the art will readily recognize a variety of noncritical parameters that could be changed or modified to yield essentially similar results. Thus, the following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended
- 20 to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, dimensions, etc.) but some experimental errors and deviations should be accounted for.

General

- 25 All starting reagents were commercially available and used without further purification except where mentioned. Purification was performed on a Biotage Isolera Prime HPLC using various solvent systems and columns (listed individually). Composition and purity were tested by HPLC (Waters 1525) with an attached mass spectrometer (Micromass ZQ, waters) and PDA detector (Waters 2998) through a 3.5 μ m C18 column (XBridge BEH C18 4.6 $\times$ 50 mm). A
- 30 mixture of water (0.1% formic acid) and ACN (0.1% formic acid) was used as an eluent, with results being analyzed by MassLynx4.1. Runs were 12 minutes long with 1.2 ml/min flow rate; ACN concentration was increased stepwise from its starting concentration (30% 0-2 min, linear

increase to 100% 2-10 min, 100% 10-12 min). Tandem MS runs and LC-MS analyses for PAMPA were performed on an UHPLC (UltiMate 3000, Dionex) with attached mass spectrometer (Orbitrap Velos Pro, Thermo Scientific) through a 2.2 μ m C18 column (Acclaim 120 2.1 $\times$ 250 mm, Thermo Scientific). A mixture of water (0.1% formic acid) and ACN (0.1% formic acid) was used as an eluent, with results being analyzed by XCALIBUR version 2.2 SP1.48. Runs were 32.7 minutes long with 0.5 ml/min flow rate; ACN concentration was increased stepwise from its starting concentration (40% 0-2 min, linear increase to 85% 2-22 min, 100% 22-27 min, 40% 27-32.7 min).

Fmoc addition to isotopically labeled leucine

Fmoc was added to unprotected isotopically labeled leucine. The procedure used herein was adapted from Malkov A et al, Journal of Organic Chemistry 74, 5839-5849, 2009 (including supporting information) which incorporated by reference herein. One gram of isotopically labeled leucine was added to a separate flask containing 30ml of distilled water 80% saturated with sodium bicarbonate, then agitated by sonication until dissolved. 2.82g (1 molar equivalent) of Fmoc succinimide was added to a separate round-bottom flask in an ice bath containing 30ml dioxane. The dissolved leucine was added dropwise to the Fmoc solution over 10 minutes with rapid stirring. The mixture was stirred 2 hours on ice, then allowed to come to room temperature overnight with continued stirring. The mixture was then evaporated at 25 degrees Celsius and brought up in a minimal volume of DMF before reverse-phase purification over a SNAP Ultra C18 30g cartridge (Biotage), eluting with water (0.1% TFA)/ACN (0.1% TFA). The resulting fractions were analyzed on the Waters LC-MS system, pooled, and evaporated to a white solid.

N-methylation of Fmoc amino acids

All N-methylated amino acids used in the library synthesis were synthesized via the following procedure: Fmoc amino acid and paraformaldehyde (1:1 by mass) were added to a round-bottom flask containing 75ml toluene per 5g of amino acid. The flask was heated to 90 degrees Celsius before 0.2 molar equivalents of camphorsulfonic acid was added. The flask was stirred for at least 2 hours, then the solution was evaporated to 3ml volume per gram of amino acid. 5ml of ethyl acetate per gram of amino acid was added. The solution was then transferred to a separatory funnel and washed twice with an equal volume of water saturated with sodium bicarbonate and once with an equal volume of brine. The organic layer was dried with magnesium sulfate, filtered into a round-bottom flask, then evaporated to a minimal volume.

2ml of DCM per gram of amino acid was added to the flask and the oil or solid thoroughly dissolved. Once dissolved, an equal volume of trifluoroacetic acid was added, then stirred for 5 minutes. Finally, 3 molar equivalents of triethylsilane was added and let stir overnight. The solution was then evaporated to minimal volume before addition of 5ml ethyl acetate per gram of amino acid, transferred to a separatory funnel and washed twice with an equal volume of distilled water and once with an equal volume of brine. The organic layer was dried, filtered into a round-bottom flask, and evaporated to a white solid, then analyzed for purity.

Cyclic peptomer synthesis

Linear peptomers were synthesized on 2-chlorotrityl resin (0.14 mmol/g) using extended Fmoc coupling (Fmoc amino acid/HATU/DIPEA in DMF, overnight) and peptoid synthesis conditions (bromoacetic acid/DIC in DMF, 1hr, then amine in DMF, overnight). The linear peptomers were cleaved from resin with 30% HFIP in DCM. Cyclization was performed in dilute conditions (<3 mM peptomer in a solution of 1:1 ACN:THF) with COMU (2 equiv) and DIPEA (10 equiv) and stirred overnight at room temperature. Each sublibrary was briefly purified using Isolute 103 SPE cartridge (200 mg/6 mL, Biotage).

Resin loading procedure

Phenylalanine and 2-Chlorotrityl resin were placed in a vacuum desiccator with phosphorous pentoxide overnight. The phenylalanine was added to a flame-dried round-bottom flask. Dry DCM of sufficient volume for the resin to float freely and 4 molar equivalents of dry DIPEA was added to the flask, which was then sonicated until the phenylalanine dissolved completely. The resin was added to the flask and the flask purged of air with a flow of argon, after which the flask was agitated for 4hrs. The resin was transferred to a solid-phase synthesis tube/manifold and washed with 2 resin-volumes of DMF (3x), then 2 resin-volumes DCM (3x), always keeping the solvent level above the resin. Finally, the resin was capped with a solution of 17:2:1 DCM:MeOH:DIPEA (2 resin-volumes, 3x, 15min incubation each). Loading value was calculated via resin cleavage (1% TFA) followed by quantification by UV absorbance at 280nm.

Fmoc deprotection

Two resin-volumes of 2% DBU 2% piperidine in DMF was added to the resin and the tube was capped and agitated for 20 minutes. The resin was then drained and washed with 2 resin-volumes of DMF (x3) and 2 resin-volumes of DCM (x3).

Amino Acid Couplings

Due to low resin loading value, 12 molar equivalents of Fmoc amino acid, 11.4 molar equivalents of HATU, and 15 molar equivalents of DIPEA were used to maintain high concentration in a DMF volume large enough to cover the resin. Fmoc amino acid, HATU, and dipea were added to a vial, then solubilized in the minimal amount of DMF which covers the resin-volume. The vial was set aside to react for 15 minutes before its contents were added to the resin. The SPPS tube was then capped and agitated overnight. The resin was then drained and washed with 2 resin-volumes of DMF (x3) and 2 resin-volumes of DCM (x3).

Peptoid Synthesis

For the same reasons as above, the 30 molar equivalents of bromoacetic acid was added to a vial and solubilized in a minimal volume of DMF which still covers the resin volume. 18 molar equivalents of DIC was then added, and the vial capped, mixed, and reacted for 15 minutes. The vial's contents were then added to the resin. The SPPS tube was then capped and agitated for 1 hour, after which the resin was drained and washed as above. 30 molar equivalents of the amine of choice was then added directly to the resin and the volume was increased with a minimal amount of DMF before capping the tube and agitating overnight (although the extended reaction time likely had little bearing on the results!). Finally, the resin was drained and washed as above.

Peptide cleavage

Two resin-volumes of 30% HFIP in DCM was added to the resin, the tube capped, then agitated for 30 minutes. The tube was then drained into a vial, and was further washed with an equal volume of DCM three times. This above was then repeated with the addition of a further wash step of an equal volume of acetone. The contents of the vial were then evaporated.

Peptide cyclization

5ml ACN and 10 molar equivalents of DIPEA were added to each vial containing a cleaved sublibrary. The vials were then sonicated until all peptides were totally dissolved before addition of 5ml THF, diluting the peptides to <3mM. 2 molar equivalents of COMU were added to each vial, all of which were stirred overnight. Finally, each vial was evaporated to a solid or oil.

Purification of sublibraries

Purification of each sublibrary was performed on individual Isolute 103 ENV+ flash chromatography columns (200mg/6ml). Each sublibrary was dissolved in a minimal volume of DMF (75ul or less) and loaded onto the dry column. The column was washed with 10ml of water, followed by elution with 10ml of methanol into tared vials. The methanol was then evaporated and the vials weighed for final yield.

Verification of Synthesis

The composition and purity of each sublibrary were tested by LC-MS (Waters system). Expected UV absorbance and masses for the library and possible truncations were observed to verify synthesis and purity.

MSMS and PAMPA LC-MS data acquisition

PAMPA LC-MS data was acquired as above with no modifications. Tandem MS data was acquired by taking the 5 most intense non-isotopic peaks (Xcalibur setting) for MS2 acquisition at every MS1 acquisition.

Parallel Artificial Membrane Permeability Assay procedure

Parallel Artificial Membrane Permeability Assay (PAMPA) was performed with a 96-well filter donor plate with 0.45 μ m hydrophobic Immobilon-P membrane supports (Millipore) and a 96-well teflon acceptor plate. The donor plate filter was loaded with 5 μ L of 1% lecithin in n-dodecane. 1NMe3, a well-characterized cyclic peptide, was added as a standard in each well at a concentration of 10uM. 150ul of each sublibrary (including standard) in PBS (containing 5% DMSO) was loaded into the donor plate (300uM theoretical concentration, or ~2uM per compound). The acceptor plate was loaded with 300ul of PBS with 5% DMSO. The donor filter plate was then loaded into the acceptor plate and was left in a damp chamber at 25 °C for 18 hours. The concentration of each compound in the donor and acceptor wells was quantified by LC-MS to calculate Pe.

PAMPA Data Analysis

For each well, single ion chromatograms for each library mass were extracted, followed by peak-finding by first differential. The peak boundaries were found by following outward

from peaks until the second differential met a detection threshold at a point sufficiently below the intensity of the peak center-point. Peaks and peak boundaries which were incorrectly detected were manually corrected. Integration was performed by fitting a Gaussian distribution to each peak and calculating its area.

- 5 Peaks were matched by retention time and peak number across wells to get acceptor and donor well intensities for each peak. A time independent permeability value was then calculated via the following equations:

$$C_{eq} = \frac{C_D \times V_D + C_A \times V_A}{V_D + V_A}$$

$$\%T = \frac{C_A}{C_{eq}} \times 100$$

$$P_e = \frac{-\ln(1 - \frac{C_A}{C_{eq}})}{(\frac{1}{V_D} + \frac{1}{V_A}) \times Area \times Time}$$

- 10 Wherein C is concentration, V is well volume, $\%T$ is percent transmittance to the acceptor well, and P_e is the desired time-independent permeability value. The subscript eq stands for equilibrium, A for acceptor and D for donor. For these calculations, concentration has been substituted for intensity under the peak since the ionization intensity of a compound should not vary overly much between two wells. Finally, the P_e values were corrected based on the known P_e of the 1NMe3 standard.

- 15 Permeability values for the compounds of Table 1 were determined as described above and are summarized in Table 2.

<u>Compound No.</u>	<u>Peptomer Sequence</u>	<u>Permeability Value</u> (x 10 ⁻⁶ cm/s)
1	BHF,L***,BHF,p,L***,F	56.19061214
2	BHF,l,Ml,p,Ml,F	50.8282355
3	A,L***,L***,p,LA08,F	48.71672758
4	BHF,l,Ml,p,l,F	46.22198458
5	BHF,L***,l,P,L***,F	42.78148279
6	Ma,Ml,L***,P,l,F	41.14185131
7	A,L***,l,p,l,F	36.44199332
8	A,Ml,BHF,P,l,F	34.07095274
9	A,Ml,l,p,Ml***,F	33.27688014
10	a,Ml,l,P,Ml,F	32.88796918
11	MA,Ml,Ml,P,Ml,F	32.57897584
12	A,l,BHF,p,l,F	30.68291478

13	BHF,l,Ml,P,Ml,F	29.1942956
14	MA,Ml,Ml,P,ML***,F	28.52497238
15	MA,LA08,Ml,P,l,F	28.50650176
16	MA,Ml,L***,P,Ml,F	28.33829512
17	BHF,l,ML***,P,ML***,F	27.98815431
18	BHF,L***,BHF,p,l,F	27.68606544
19	MA,LA08,L***,P,Ml,F	27.41715714
20	BHF,Ml,Ml,P,Ml,F	27.07177771
21	LA02,l,Ml,P,Ml,F	26.82931976
22	a,Ml,ML***,p,l,F	26.82301824
23	a,L***,L***,p,Ml,F	26.76564435
24	BHF,Ml,Ml,p,Ml,F	26.70634473
25	BHF,Ml,Ml,P,Ml,F	26.55043548
26	Ma,L***,ML***,P,Ml,F	26.50654657
27	MA,ML***,LA08,P,LA08,F	26.32870586
28	MA,Ml,Ml,P,Ml,F	26.22773297
29	BHF,Ml,Ml,p,l,F	26.17265039
30	a,ML***,L***,p,l,F	26.1105021
31	Ma,Ml,L***,P,ML***,F	25.94258816
32	A,Ml,Ml,p,l,F	25.80002884
33	A,Ml,L***,p,Ml,F	25.78220373
34	A,LA08,Ml,p,L***,F	25.55775971
35	A,Ml,L***,P,Ml,F	25.36713829
36	a,Ml,BHF,p,Ml,F	25.35607442
37	Ma,ML***,l,P,ML***,F	25.10086123
38	A,Ml,Ml,P,ML***,F	25.09089699
39	MA,l,Ml,P,ML***,F	25.0861927
40	A,Ml,Ml,p,LA08,F	25.03162272
41	MA,Ml,ML***,P,Ml,F	25.01886329
42	BHF,Ml,Ml,P,Ml,F	24.87040135
43	Ma,Ml,l,P,Ml,F	24.82810692
44	Ma,Ml,l,P,Ml,F	24.82810692
45	LA02,Ml,LA08,P,Ml,F	24.5926188
46	LA02,Ml,LA08,P,Ml,F	24.5926188
47	A,L***,BHF,p,l,F	24.57015331
48	MA,Ml,Ml,P,L***,F	24.38438951
49	Ma,Ml,Ml,P,Ml,F	24.38348673
50	Ma,ML***,Ml,P,Ml,F	24.31080278
51	MA,l,Ml,P,l,F	24.17124034
52	A,Ml,ML***,P,Ml,F	24.16377896
53	A,L***,Ml,p,ML***,F	24.16030909
54	MA,L***,Ml,P,Ml,F	23.92605054
55	A,l,LA08,p,l,F	23.91283292

56	Ma,Ml,ML***,P,Ml,F	23.73833678
57	MA,Ml,LA08,P,ML***,F	23.72007441
58	A,Ml,BHF,P,Ml,F	23.59143159
59	BHF,l,l,p,Ml,F	23.53463022
60	a,L***,BHF,p,l,F	23.26495371
61	a,L***,LA08,P,L***,F	23.22930206
62	BHF,L***,l,p,Ml,F	23.10492023
63	a,Ml,L***,p,Ml,F	23.0837236
64	MA,ML***,Ml,P,Ml,F	22.86097011
65	Ma,l,ML***,P,ML***,F	22.72909836
66	BHF,Ml,Ml,p,Ml,F	22.65698306
67	MA,ML***,L***,p,Ml,F	22.65481294
68	a,ML***,Ml,P,l,F	22.58524245
69	A,Ml,Ml,p,Ml,F	22.48095643
70	A,ML***,BHF,P,L***,F	22.47943243
71	A,L***,L***,p,l,F	22.35705255
72	Ma,ML***,Ml,P,L***,F	22.21408662
73	A,l,ML***,p,l,F	22.16308149
74	A,Ml,BHF,p,Ml,F	22.04952601
75	MA,l,Ml,P,LA08,F	21.9422274
76	A,Ml,BHF,p,Ml,F	21.89615654
77	LA02,Ml,BHF,P,L***,F	21.85502465
78	A,Ml,l,p,LA08,F	21.78328972
79	A,Ml,l,p,Ml,F	21.65504441
80	A,Ml,L***,p,ML***,F	21.64904102
81	Ma,Ml,L***,P,LA08,F	21.58462332
82	A,l,Ml,p,Ml,F	21.47967737
83	a,Ml,L***,P,Ml,F	21.43740026
84	MA,Ml,Ml,p,Ml,F	21.43183575
85	A,L***,LA08,p,Ml,F	21.40673824
86	MA,L***,Ml,P,Ml,F	21.2633048
87	MA,Ml,Ml,P,LA08,F	21.25660811
88	LA02,Ml,L***,P,l,F	21.21198624
89	Ma,L***,Ml,P,ML***,F	21.1569649
90	Ma,ML***,L***,P,Ml,F	20.98978613
91	A,Ml,BHF,P,Ml,F	20.9628871
92	Ma,Ml,Ml,P,Ml,F	20.76313119
93	a,Ml,BHF,p,Ml,F	20.74335994
94	BHF,Ml,Ml,P,Ml,F	20.73949965
95	a,Ml,L***,P,ML***,F	20.73281225
96	BHF,L***,LA08,P,L***,F	20.72754175
97	A,Ml,L***,p,l,F	20.51626729
98	LA02,Ml,BHF,P,Ml,F	20.41552774
99	A,Ml,L***,P,ML***,F	20.2928769

100	MA,ML***,l,P,Ml,F	20.24070307
101	Ma,Ml,Ml,P,Ml,F	20.2032426
102	a,Ml,BHF,p,Ml,F	20.10606447
103	LA02,Ml,Ml,P,Ml,F	20.05269969
104	MA,Ml,ML***,P,LA08,F	19.92606853
105	LA02,L***,l,P,L***,F	19.78870101
106	MA,l,L***,p,ML***,F	19.73554909
107	Ma,L***,Ml,p,ML***,F	19.73186827
108	MA,Ml,l,P,ML***,F	19.69291384
109	MA,L***,Ml,P,ML***,F	19.6567569
110	BHF,L***,Ml,P,L***,F	19.61804884
111	Ma,ML***,Ml,P,LA08,F	19.53234979
112	a,LA08,Ml,p,L***,F	19.52903752
113	LA02,l,Ml,P,Ml,F	19.51724784
114	A,L***,LA08,p,l,F	19.5156128
115	a,ML***,Ml,P,LA08,F	19.49874601
116	a,l,LA08,p,l,F	19.49562529
117	a,Ml,LA08,p,l,F	19.47372828
118	A,l,L***,P,L***,F	19.46627882
119	LA02,Ml,Ml,p,Ml,F	19.45529183
120	A,l,L***,p,L***,F	19.36475021
121	LA02,Ml,l,P,l,F	19.28813728
122	a,Ml,BHF,P,Ml,F	19.25184441
123	A,L***,LA08,p,LA08,F	19.22735011
124	A,l,L***,p,Ml,F	19.15078912
125	a,Ml,L***,p,l,F	19.11174655
126	Ma,Ml,BHF,P,Ml,F	19.08802734
127	Ma,Ml,l,P,LA08,F	19.04687727
128	MA,l,ML***,P,ML***,F	18.99987845
129	BHF,Ml,Ml,p,Ml,F	18.94392122
130	Ma,Ml,l,P,l,F	18.93627832
131	Ma,LA08,Ml,P,L***,F	18.91178744
132	Ma,L***,Ml,P,L***,F	18.89699421
133	a,Ml,l,P,ML***,F	18.86867707
134	BHF,l,Ml,P,l,F	18.8550913
135	BHF,l,L***,p,ML***,F	18.84710992
136	a,Ml,LA08,p,ML***,F	18.80246438
137	MA,l,Ml,P,Ml,F	18.79110041
138	MA,Ml,l,P,Ml,F	18.79110041
139	BHF,Ml,Ml,P,Ml,F	18.77564569
140	A,L***,Ml,P,L***,F	18.76412648
141	a,Ml,L***,p,ML***,F	18.75454855
142	MA,L***,Ml,P,l,F	18.72629726
143	LA02,Ml,l,P,Ml,F	18.57443693

144	Ma,LA08,l,P,Ml,F	18.56149677
145	MA,Ml,BHF,P,Ml,F	18.49316068
146	BHF,l,l,P,ML***,F	18.45259647
147	Ma,L***,l,P,ML***,F	18.32419316
148	Ma,L***,l,P,L***,F	18.30172016
149	MA,l,LA08,P,ML***,F	18.26363562
150	BHF,Ml,Ml,p,Ml,F	18.22781209
151	MA,Ml,l,P,Ml,F	18.20517238
152	MA,Ml,l,P,Ml,F	18.20517238
153	LA02,L***,L***,P,Ml,F	18.18720053
154	a,LA08,Ml,P,Ml,F	18.15357743
155	MA,Ml,Ml,P,l,F	17.98832753
156	MA,Ml,Ml,P,l,F	17.98832753
157	Ma,l,Ml,P,Ml,F	17.98816681
158	LA02,l,L***,p,Ml,F	17.98540374
159	Ma,LA08,Ml,P,Ml,F	17.9484773
160	LA02,l,L***,P,ML***,F	17.8677765
161	A,l,ML***,p,Ml,F	17.83963166
162	Ma,Ml,BHF,P,Ml,F	17.82220647
163	a,LA08,ML***,P,Ml,F	17.80862671
164	LA02,L***,l,P,Ml,F	17.79963046
165	Ma,Ml,BHF,P,Ml,F	17.7337768
166	A,Ml,Ml,p,Ml,F	17.72766039
167	a,ML***,L***,p,ML***,F	17.70135387
168	LA02,Ml,Ml,P,Ml,F	17.67238466
169	A,Ml,ML***,p,L***,F	17.66551964
170	MA,l,l,P,LA08,F	17.65724109
171	a,Ml,L***,P,LA08,F	17.62447466
172	A,L***,ML***,p,Ml,F	17.6142183
173	BHF,l,Ml,p,L***,F	17.57956415
174	a,LA08,Ml,p,ML***,F	17.5486073
175	MA,ML***,LA08,P,LA08,F	17.54234433
176	BHF,ML***,LA08,p,ML***,F	17.51418039
177	BHF,L***,Ml,p,l,F	17.49544027
178	LA02,l,ML***,P,Ml,F	17.46829141
179	Ma,ML***,L***,p,Ml,F	17.40797742
180	MA,l,ML***,P,LA08,F	17.3559126
181	A,ML***,Ml,P,Ml,F	17.31337854
182	Ma,l,ML***,P,l,F	17.30863947
183	BHF,L***,l,p,LA08,F	17.30227074
184	LA02,L***,l,p,ML***,F	17.28279029
185	LA02,ML***,l,p,ML***,F	17.10834035
186	Ma,l,ML***,p,ML***,F	17.09109135
187	MA,Ml,L***,p,ML***,F	17.04239744

188	LA02,Ml,BHF,P,Ml,F	17.00852323
189	LA02,ML***,l,p,LA08,F	16.98977471
190	MA,l,LA08,p,ML***,F	16.93095047
191	Ma,L***,Ml,P,LA08,F	16.9245817
192	Ma,Ml,Ml,P,l,F	16.8735617
193	A,L***,BHF,P,ML***,F	16.86530105
194	a,Ml,l,p,ML***,F	16.85433362
195	A,Ml,Ml,P,L***,F	16.84945047
196	a,Ml,Ml,P,l,F	16.83154675
197	A,Ml,ML***,p,l,F	16.79150455
198	Ma,L***,Ml,P,l,F	16.7716384
199	A,L***,L***,p,Ml,F	16.7279933
200	A,l,L***,P,LA08,F	16.71717023
201	A,ML***,Ml,P,ML***,F	16.71659758
202	LA02,Ml,Ml,P,l,F	16.71497558
203	BHF,Ml,Ml,p,Ml,F	16.61938228
204	LA02,Ml,Ml,p,Ml,F	16.61477747
205	LA02,Ml,Ml,P,Ml,F	16.53444871
206	LA02,l,L***,P,l,F	16.51415444
207	a,Ml,Ml,p,Ml,F	16.50115041
208	a,LA08,ML***,P,ML***,F	16.47863675
209	MA,l,ML***,p,l,F	16.47315765
210	a,L***,LA08,p,l,F	16.47314921
211	Ma,ML***,Ml,p,Ml,F	16.41152869
212	A,Ml,Ml,p,Ml,F	16.40602598
213	A,LA08,L***,P,Ml,F	16.38356976
214	LA02,l,L***,p,ML***,F	16.37435754
215	Ma,ML***,L***,P,l,F	16.35782285
216	BHF,L***,Ml,p,L***,F	16.30049653
217	LA02,L***,Ml,P,Ml,F	16.25446901
218	LA02,l,l,P,L***,F	16.24185622
219	a,Ml,BHF,P,Ml,F	16.22333019
220	BHF,l,ML***,P,l,F	16.2199749
221	BHF,L***,l,p,l,F	16.21290967
222	A,l,Ml,P,LA08,F	16.13438796
223	A,Ml,l,P,LA08,F	16.13150772
224	BHF,l,Ml,P,Ml,F	16.11552468
225	MA,L***,Ml,P,LA08,F	16.11353439
226	LA02,Ml,l,p,ML***,F	16.06160444
227	a,ML***,L***,P,Ml,F	16.03460499
228	A,Ml,BHF,P,Ml,F	15.99903862
229	Ma,LA08,l,P,l,F	15.97290745
230	LA02,ML***,ML***,p,Ml,F	15.96856352
231	a,l,l,P,L***,F	15.95794462

232	A,ML***,l,P,LA08,F	15.93909991
233	LA02,Ml,ML***,P,Ml,F	15.9017328
234	Ma,Ml,BHF,P,Ml,F	15.86578743
235	BHF,l,L***,P,ML***,F	15.79262297
236	A,l,ML***,P,ML***,F	15.71564676
237	LA02,Ml,Ml,p,Ml,F	15.70403365
238	Ma,Ml,Ml,p,Ml,F	15.69511476
239	BHF,L***,l,P,l,F	15.69315428
240	a,Ml,Ml,P,Ml,F	15.63313769
241	A,l,LA08,p,LA08,F	15.58997604
242	A,L***,l,p,LA08,F	15.56273971
243	A,l,ML***,P,Ml,F	15.54088864
244	A,ML***,LA08,P,Ml,F	15.53169555
245	BHF,Ml,l,p,l,F	15.5025513
246	BHF,l,L***,P,L***,F	15.5017172
247	LA02,Ml,L***,P,Ml,F	15.49541105
248	BHF,L***,l,P,ML***,F	15.4724259
249	LA02,ML***,L***,P,l,F	15.43740559
250	A,l,ML***,P,LA08,F	15.41168385
251	A,Ml,ML***,P,LA08,F	15.38459523
252	Ma,LA08,l,P,Ml,F	15.38085543
253	Ma,L***,LA08,P,ML***,F	15.37105241
254	LA02,Ml,ML***,P,ML***,F	15.21410223
255	MA,l,L***,p,Ml,F	15.19253259
256	a,L***,Ml,p,ML***,F	15.15432076
257	A,Ml,LA08,p,ML***,F	15.06505249
258	MA,l,Ml,p,l,F	15.04796558
259	LA02,L***,l,p,Ml,F	15.03779291
260	Ma,l,L***,P,Ml,F	15.03506168
261	BHF,l,ML***,p,l,F	15.02224354
262	MA,L***,l,P,ML***,F	15.00436914
263	A,Ml,l,P,Ml,F	14.98102179
264	A,L***,Ml,P,LA08,F	14.89646656
265	a,Ml,l,P,LA08,F	14.89615672
266	LA02,Ml,Ml,P,Ml,F	14.88908064
267	Ma,L***,LA08,P,Ml,F	14.78884386
268	LA02,Ml,LA08,P,LA08,F	14.71448863
269	A,l,ML***,p,ML***,F	14.68900781
270	a,l,L***,p,Ml,F	14.61652756
271	LA02,Ml,BHF,p,Ml,F	14.60273571
272	BHF,Ml,Ml,P,Ml,F	14.59898542
273	MA,Ml,Ml,P,Ml,F	14.59463904
274	A,ML***,LA08,p,LA08,F	14.58763062
275	MA,l,Ml,P,L***,F	14.57290574

276	LA02,l,BHF,P,L***,F	14.54063724
277	MA,Ml,Ml,P,Ml,F	14.53241073
278	BHF,l,l,p,l,F	14.53035014
279	BHF,l,l,p,l,F	14.53035014
280	Ma,l,BHF,P,l,F	14.51066215
281	A,ML***,l,p,LA08,F	14.49020071
282	MA,l,ML***,p,ML***,F	14.47722646
283	a,ML***,LA08,P,ML***,F	14.47295475
284	BHF,L***,L***,p,Ml,F	14.46686498
285	A,Ml,Ml,P,Ml,F	14.41367424
286	A,Ml,Ml,P,Ml,F	14.41367424
287	A,LA08,BHF,p,l,F	14.37489535
288	a,LA08,Ml,P,L***,F	14.3588776
289	a,l,ML***,p,Ml,F	14.34321989
290	BHF,l,l,p,LA08,F	14.32015491
291	LA02,l,LA08,P,Ml,F	14.31637679
292	a,LA08,Ml,P,L***,F	14.28954986
293	LA02,Ml,ML***,p,l,F	14.25635378
294	MA,Ml,ML***,p,Ml,F	14.25599002
295	BHF,Ml,L***,P,l,F	14.25275906
296	BHF,Ml,l,P,l,F	14.23889246
297	MA,LA08,ML***,p,l,F	14.23396924
298	a,Ml,L***,p,L***,F	14.16251831
299	A,Ml,LA08,P,L***,F	14.15268194
300	A,l,LA08,P,L***,F	14.07794459
301	BHF,LA08,l,P,Ml,F	14.00927789
302	Ma,ML***,Ml,P,LA08,F	13.98383886
303	BHF,LA08,L***,P,L***,F	13.96167677
304	LA02,Ml,BHF,p,Ml,F	13.94351241
305	A,Ml,Ml,P,Ml,F	13.93909716
306	BHF,l,LA08,p,l,F	13.92082944
307	A,Ml,ML***,P,ML***,F	13.85607019
308	MA,ML***,LA08,p,Ml,F	13.8343356
309	A,Ml,Ml,p,Ml,F	13.81799304
310	BHF,l,l,P,Ml,F	13.80170138
311	MA,Ml,BHF,p,Ml,F	13.78906142
312	BHF,l,L***,P,l,F	13.77226775
313	MA,l,L***,p,l,F	13.74395145
314	BHF,l,BHF,p,Ml,F	13.73456859
315	a,Ml,l,P,Ml,F	13.71285744
316	BHF,l,BHF,p,l,F	13.69640691
317	A,Ml,LA08,P,ML***,F	13.68166075
318	a,l,L***,p,LA08,F	13.64865683
319	LA02,ML***,Ml,P,l,F	13.62670989

320	BHF,I,LA08,P,I,F	13.60501049
321	A,ML***,L***,p,I,F	13.59271209
322	MA,I,L***,p,LA08,F	13.57036188
323	BHF,M,I,L***,p,L***,F	13.56602015
324	A,LA08,L***,P,M,I,F	13.54743987
325	A,M,I,LA08,p,M,I,F	13.53244538
326	LA02,M,I,M,I,p,M,I,F	13.51585557
327	A,M,I,L***,p,LA08,F	13.51368794
328	LA02,M,I,L***,p,I,F	13.51085873
329	Ma,L***,I,P,M,I,F	13.47557403
330	A,LA08,I,P,LA08,F	13.46652765
331	LA02,M,I,I,p,M,I,F	13.46651411
332	A,M,I,BHF,p,M,I,F	13.46034782
333	A,I,BHF,p,ML***,F	13.42999756
334	LA02,ML***,M,I,p,M,I,F	13.41658601
335	LA02,I,L***,p,I,F	13.38203284
336	MA,M,I,LA08,p,ML***,F	13.37827685
337	LA02,ML***,M,I,P,M,I,F	13.35044535
338	LA02,M,I,BHF,P,M,I,F	13.32074194
339	LA02,LA08,M,I,P,I,F	13.27845085
340	LA02,M,I,M,I,P,LA08,F	13.27788945
341	LA02,ML***,LA08,p,M,I,F	13.26225567
342	Ma,LA08,M,I,p,I,F	13.24549565
343	Ma,ML***,LA08,P,LA08,F	13.23173168
344	A,I,LA08,P,M,I,F	13.22457132
345	a,ML***,M,I,P,LA08,F	13.21467684
346	LA02,ML***,I,P,I,F	13.17537765
347	MA,M,I,LA08,P,LA08,F	13.16825196
348	BHF,I,L***,P,ML***,F	13.1671722
349	A,L***,M,I,P,ML***,F	13.16677535
350	Ma,M,I,M,I,p,M,I,F	13.15497613
351	Ma,M,I,L***,p,L***,F	13.15137152
352	a,LA08,M,I,p,M,I,F	13.13765997
353	a,ML***,LA08,p,M,I,F	13.11783791
354	A,M,I,M,I,P,LA08,F	13.0552946
355	Ma,LA08,I,p,ML***,F	13.05294248
356	BHF,I,L***,p,M,I,F	13.02817814
357	a,LA08,ML***,p,ML***,F	12.99665604
358	A,M,I,ML***,p,LA08,F	12.98699884
359	BHF,I,L***,P,LA08,F	12.97614593
360	BHF,M,I,BHF,P,L***,F	12.96211767
361	MA,M,I,M,I,P,M,I,F	12.86418892
362	A,M,I,I,P,L***,F	12.83953132
363	BHF,I,ML***,P,I,F	12.83540366

364	Ma,Ml,ML***,p,Ml,F	12.82155693
365	MA,l,ML***,P,l,F	12.78167723
366	LA02,L***,Ml,p,l,F	12.77806535
367	LA02,ML***,l,p,LA08,F	12.76568836
368	A,LA08,L***,P,LA08,F	12.75886886
369	a,ML***,l,p,l,F	12.74944654
370	LA02,ML***,l,p,Ml,F	12.72752444
371	BHF,Ml,BHF,P,l,F	12.60378433
372	a,LA08,LA08,P,ML***,F	12.59939348
373	MA,Ml,Ml,P,Ml,F	12.54321102
374	A,LA08,l,p,l,F	12.48129444
375	MA,l,BHF,p,Ml,F	12.47101605
376	MA,Ml,l,P,l,F	12.40018963
377	Ma,Ml,BHF,P,L***,F	12.36119896
378	A,Ml,Ml,P,Ml,F	12.35053235
379	A,Ml,BHF,p,l,F	12.34098032
380	LA02,l,LA08,p,Ml,F	12.33153725
381	MA,l,ML***,P,Ml,F	12.32844411
382	BHF,L***,l,P,Ml,F	12.29193608
383	LA02,L***,LA08,P,Ml,F	12.29073611
384	a,Ml,l,p,Ml,F	12.25785791
385	Ma,l,LA08,p,Ml,F	12.22560074
386	MA,l,L***,P,ML***,F	12.21173435
387	a,ML***,LA08,p,ML***,F	12.20097919
388	BHF,ML***,LA08,P,Ml,F	12.16312141
389	A,ML***,l,P,Ml,F	12.13945126
390	Ma,ML***,l,P,LA08,F	12.05950752
391	a,l,BHF,p,ML***,F	12.02350374
392	A,LA08,ML***,P,LA08,F	12.02339437
393	a,l,ML***,p,LA08,F	11.98988226
394	Ma,l,LA08,P,LA08,F	11.97735999
395	Ma,Ml,L***,p,ML***,F	11.97433204
396	Ma,Ml,Ml,P,Ml,F	11.95760508
397	A,LA08,Ml,P,LA08,F	11.94247557
398	BHF,l,l,P,l,F	11.93620769
399	MA,l,LA08,p,ML***,F	11.91440886
400	Ma,L***,LA08,P,LA08,F	11.90580391
401	LA02,L***,L***,p,Ml,F	11.89457829
402	A,LA08,LA08,p,L***,F	11.8916768
403	LA02,l,l,P,Ml,F	11.89148268
404	Ma,Ml,LA08,p,ML***,F	11.87951487
405	Ma,ML***,L***,p,LA08,F	11.8657429
406	BHF,LA08,Ml,p,Ml,F	11.86354209
407	BHF,l,L***,p,ML***,F	11.8465143

408	MA,L***,BHF,p,L***,F	11.81568914
409	LA02,Ml,Ml,p,Ml,F	11.81300096
410	A,L***,l,P,LA08,F	11.80634988
411	LA02,l,BHF,P,Ml,F	11.78306695
412	a,ML***,ML***,P,LA08,F	11.76930838
413	A,l,L***,P,Ml,F	11.75739516
414	MA,ML***,LA08,p,LA08,F	11.75012842
415	MA,l,Ml,p,LA08,F	11.7066321
416	A,l,LA08,p,ML***,F	11.69139032
417	Ma,l,ML***,p,l,F	11.69018972
418	Ma,LA08,L***,p,Ml,F	11.68097375
419	A,l,Ml,P,Ml,F	11.67215488
420	A,Ml,Ml,p,Ml,F	11.6708824
421	a,ML***,l,P,ML***,F	11.62755806
422	LA02,L***,L***,P,LA08,F	11.60051198
423	MA,L***,L***,P,Ml,F	11.58242904
424	LA02,l,ML***,p,L***,F	11.53970127
425	a,Ml,BHF,P,L***,F	11.53741255
426	LA02,Ml,LA08,p,Ml,F	11.50816966
427	BHF,LA08,l,P,L***,F	11.49086837
428	A,L***,LA08,P,LA08,F	11.46140752
429	A,Ml,LA08,p,Ml,F	11.45827993
430	BHF,Ml,Ml,p,Ml,F	11.43468181
431	MA,l,LA08,P,Ml,F	11.41533436
432	MA,LA08,L***,p,ML***,F	11.39463489
433	a,L***,Ml,P,L***,F	11.38840445
434	Ma,Ml,Ml,P,Ml,F	11.38484272
435	a,LA08,L***,P,L***,F	11.37202846
436	A,ML***,l,P,L***,F	11.34763032
437	MA,L***,l,P,Ml,F	11.3403253
438	LA02,l,ML***,P,LA08,F	11.31935215
439	A,Ml,Ml,P,l,F	11.31550664
440	MA,Ml,ML***,p,LA08,F	11.31270331
441	MA,Ml,L***,p,LA08,F	11.26658443
442	A,l,LA08,P,ML***,F	11.25340711
443	a,LA08,l,P,L***,F	11.24073126
444	LA02,LA08,ML***,P,Ml,F	11.2240681
445	MA,ML***,L***,p,LA08,F	11.21773269
446	LA02,Ml,ML***,P,l,F	11.2038765
447	LA02,l,ML***,p,l,F	11.19139945
448	A,Ml,LA08,p,L***,F	11.17294641
449	Ma,l,ML***,p,LA08,F	11.17154455
450	MA,l,l,p,l,F	11.15483763
451	A,Ml,L***,p,L***,F	11.15384133

452	Ma,l,L***,P,ML***,F	11.14084235
453	a,LA08,L***,P,LA08,F	11.13170381
454	BHF,ML***,ML***,P,LA08,F	11.1300007
455	LA02,LA08,l,p,L***,F	11.12077509
456	LA02,LA08,Ml,P,LA08,F	11.11239467
457	A,Ml,Ml,P,Ml,F	11.10605987
458	a,Ml,LA08,P,Ml,F	11.08040848
459	Ma,L***,LA08,p,Ml,F	11.06700862
460	a,l,ML***,p,ML***,F	11.05716762
461	A,L***,LA08,p,L***,F	11.04762588
462	LA02,Ml,LA08,p,Ml,F	11.01911964
463	Ma,LA08,l,p,ML***,F	11.00753821
464	a,Ml,Ml,P,Ml,F	10.99483912
465	A,ML***,l,P,ML***,F	10.99059111
466	MA,Ml,l,p,Ml,F	10.98389537
467	Ma,l,L***,p,Ml,F	10.96931203
468	MA,LA08,ML***,p,ML***,F	10.95272724
469	LA02,l,BHF,P,L***,F	10.94048337
470	BHF,Ml,BHF,p,l,F	10.90683173
471	MA,l,L***,P,Ml,F	10.89476174
472	LA02,L***,ML***,p,Ml,F	10.85672407
473	LA02,Ml,L***,p,Ml,F	10.81739315
474	LA02,l,L***,p,LA08,F	10.81720781
475	Ma,LA08,L***,p,ML***,F	10.81173878
476	Ma,Ml,LA08,p,l,F	10.80968441
477	LA02,Ml,LA08,p,LA08,F	10.8082134
478	MA,LA08,L***,p,L***,F	10.80759226
479	LA02,LA08,L***,p,L***,F	10.76342435
480	BHF,l,ML***,P,ML***,F	10.74069253
481	Ma,l,LA08,P,Ml,F	10.67978794
482	a,Ml,LA08,P,ML***,F	10.66489775
483	BHF,LA08,l,p,l,F	10.65589664
484	A,LA08,l,P,L***,F	10.64954297
485	LA02,Ml,L***,P,LA08,F	10.64731224
486	A,L***,LA08,P,Ml,F	10.61764419
487	A,l,l,p,l,F	10.616968
488	LA02,Ml,LA08,p,Ml,F	10.61411526
489	LA02,Ml,BHF,p,l,F	10.61411526
490	BHF,l,ML***,P,L***,F	10.61055238
491	BHF,Ml,BHF,P,Ml,F	10.60337842
492	BHF,ML***,LA08,P,l,F	10.59249394
493	BHF,L***,BHF,P,L***,F	10.58270593
494	a,LA08,BHF,P,l,F	10.56527141
495	MA,Ml,LA08,p,Ml,F	10.54209193

496	BHF,I,LA08,P,L***,F	10.52391316
497	A,Ml,BHF,p,Ml,F	10.49832262
498	BHF,I,ML***,p,l,F	10.48610492
499	MA,LA08,I,P,l,F	10.47587086
500	LA02,ML***,l,p,l,F	10.47248244
501	A,l,L***,P,ML***,F	10.4452417
502	Ma,Ml,Ml,P,Ml,F	10.44310076
503	MA,Ml,LA08,p,ML***,F	10.38960721
504	BHF,Ml,BHF,p,Ml,F	10.38811427
505	LA02,LA08,L***,P,ML***,F	10.38303635
506	a,ML***,LA08,P,l,F	10.38125717
507	LA02,Ml,LA08,p,l,F	10.35501938
508	A,ML***,BHF,p,l,F	10.34392486
509	LA02,ML***,ML***,p,l,F	10.33568023
510	A,l,ML***,p,L***,F	10.31645393
511	A,l,L***,p,ML***,F	10.30829187
512	a,ML***,L***,p,Ml,F	10.30294089
513	Ma,ML***,LA08,p,LA08,F	10.30260088
514	A,ML***,Ml,P,l,F	10.29020859
515	LA02,Ml,ML***,P,LA08,F	10.23700271
516	LA02,LA08,l,P,l,F	10.22478091
517	LA02,l,Ml,P,l,F	10.19247245
518	LA02,l,Ml,P,l,F	10.19247245
519	BHF,Ml,BHF,P,l,F	10.0880796
520	LA02,Ml,LA08,p,LA08,F	9.987721562
521	LA02,ML***,Ml,p,l,F	9.985820738
522	LA02,l,LA08,p,ML***,F	9.975015248
523	MA,Ml,L***,P,ML***,F	9.964912872
524	A,l,LA08,P,l,F	9.962388042
525	A,LA08,Ml,P,Ml,F	9.952205367
526	a,Ml,L***,P,l,F	9.855274575
527	a,Ml,ML***,p,LA08,F	9.839043457
528	LA02,l,l,p,ML***,F	9.825155355
529	A,l,l,P,LA08,F	9.812290975
530	Ma,l,L***,p,LA08,F	9.778237191
531	LA02,LA08,Ml,P,l,F	9.77761088
532	A,Ml,ML***,p,L***,F	9.770813193
533	Ma,l,L***,p,l,F	9.764531664
534	MA,Ml,ML***,p,L***,F	9.750745143
535	LA02,l,ML***,p,ML***,F	9.739676705
536	LA02,Ml,Ml,p,Ml,F	9.72873097
537	LA02,L***,LA08,P,LA08,F	9.720623957
538	MA,Ml,Ml,p,Ml,F	9.688707921
539	LA02,Ml,LA08,P,ML***,F	9.672273612

540	LA02,LA08,l,p,l,F	9.632201764
541	LA02,LA08,l,p,Ml,F	9.631578926
542	a,ML***,L***,P,l,F	9.610381805
543	Ma,L***,Ml,p,LA08,F	9.598223554
544	Ma,L***,L***,P,Ml,F	9.576568139
545	MA,l,LA08,P,Ml,F	9.569340747
546	BHF,LA08,Ml,p,l,F	9.565372495
547	A,LA08,LA08,P,LA08,F	9.558499572
548	a,LA08,BHF,P,L***,F	9.513743034
549	LA02,Ml,L***,p,LA08,F	9.454798609
550	A,LA08,ML***,P,LA08,F	9.450444361
551	Ma,Ml,LA08,P,LA08,F	9.447880793
552	a,LA08,Ml,P,LA08,F	9.432127808
553	BHF,LA08,Ml,P,L***,F	9.358572929
554	a,Ml,l,p,LA08,F	9.312301232
555	Ma,Ml,ML***,p,LA08,F	9.305536018
556	A,LA08,Ml,P,l,F	9.275517312
557	A,L***,L***,P,LA08,F	9.266477273
558	LA02,ML***,BHF,p,l,F	9.240056979
559	a,Ml,BHF,P,ML***,F	9.195542246
560	BHF,l,BHF,p,LA08,F	9.169735085
561	MA,l,l,P,l,F	9.156141386
562	BHF,Ml,L***,P,ML***,F	9.128480075
563	BHF,l,BHF,p,ML***,F	9.06582977
564	A,LA08,BHF,P,L***,F	9.060761253
565	a,ML***,Ml,p,LA08,F	9.048478377
566	LA02,ML***,L***,p,Ml,F	9.047716444
567	Ma,L***,ML***,P,l,F	9.021357089
568	LA02,ML***,l,p,L***,F	8.993329364
569	A,LA08,LA08,p,LA08,F	8.989392592
570	BHF,L***,Ml,P,l,F	8.988047245
571	MA,Ml,Ml,p,Ml,F	8.974656881
572	BHF,ML***,l,p,Ml,F	8.957058001
573	MA,l,ML***,p,L***,F	8.949936716
574	A,ML***,LA08,p,LA08,F	8.949298386
575	A,L***,L***,P,Ml,F	8.924944906
576	MA,l,l,P,Ml,F	8.923494816
577	MA,l,BHF,p,l,F	8.850533896
578	a,LA08,Ml,P,l,F	8.84662479
579	MA,l,L***,P,LA08,F	8.843453166
580	a,Ml,L***,p,LA08,F	8.843156174
581	BHF,Ml,L***,P,L***,F	8.837774041
582	LA02,Ml,BHF,P,Ml,F	8.801957256
583	LA02,l,LA08,p,L***,F	8.799123611

584	a,L***,Ml,P,ML***,F	8.783351487
585	BHF,LA08,L***,p,l,F	8.764049129
586	Ma,Ml,LA08,P,LA08,F	8.757968504
587	BHF,L***,L***,P,Ml,F	8.708349082
588	BHF,l,LA08,p,Ml,F	8.698036413
589	BHF,l,L***,p,LA08,F	8.666959869
590	A,l,ML***,P,l,F	8.649168455
591	BHF,l,L***,p,LA08,F	8.624324092
592	A,LA08,L***,P,LA08,F	8.615162882
593	LA02,LA08,Ml,p,LA08,F	8.589641782
594	a,Ml,BHF,p,ML***,F	8.573690092
595	LA02,L***,L***,p,LA08,F	8.567734244
596	Ma,Ml,L***,p,LA08,F	8.510300222
597	BHF,l,L***,p,l,F	8.478559661
598	MA,LA08,Ml,p,l,F	8.476980949
599	LA02,Ml,LA08,p,ML***,F	8.453291457
600	A,l,Ml,p,ML***,F	8.423428825
601	BHF,Ml,L***,P,Ml,F	8.416794288
602	A,LA08,Ml,P,LA08,F	8.379323649
603	a,LA08,l,p,ML***,F	8.37012376
604	Ma,l,l,P,l,F	8.346444716
605	Ma,Ml,Ml,p,Ml,F	8.332435709
606	Ma,l,BHF,P,ML***,F	8.30570999
607	Ma,l,L***,P,l,F	8.269826169
608	MA,ML***,L***,p,l,F	8.261007071
609	A,LA08,l,p,L***,F	8.2447995
610	a,L***,Ml,P,LA08,F	8.228769492
611	LA02,LA08,BHF,P,Ml,F	8.216852927
612	a,ML***,l,p,LA08,F	8.203081879
613	LA02,LA08,Ml,p,Ml,F	8.191493245
614	MA,l,LA08,p,Ml,F	8.145248107
615	LA02,Ml,BHF,P,Ml,F	8.127230269
616	LA02,Ml,L***,P,LA08,F	8.118609252
617	a,Ml,BHF,p,l,F	8.102601635
618	LA02,LA08,BHF,P,l,F	8.091902464
619	LA02,Ml,Ml,p,Ml,F	8.087341698
620	BHF,l,BHF,P,ML***,F	8.087125042
621	MA,LA08,L***,p,l,F	8.085861541
622	Ma,LA08,L***,P,l,F	8.054472566
623	a,LA08,L***,P,LA08,F	8.048127709
624	A,L***,Ml,p,Ml,F	8.046713312
625	LA02,ML***,LA08,p,LA08,F	8.046674225
626	A,l,LA08,P,LA08,F	8.044443501
627	LA02,LA08,ML***,P,l,F	8.019399396

628	BHF,Ml,BHF,p,Ml,F	8.010904406
629	LA02,ML***,L***,p,l,F	8.004570537
630	Ma,L***,Ml,p,l,F	7.993062212
631	LA02,Ml,LA08,p,ML***,F	7.97665354
632	MA,Ml,Ml,p,Ml,F	7.937880559
633	a,ML***,l,p,Ml,F	7.893355922
634	A,ML***,L***,P,l,F	7.867367418
635	Ma,l,l,p,l,F	7.864537078
636	BHF,Ml,Ml,P,Ml,F	7.851231014
637	LA02,LA08,LA08,p,l,F	7.837222558
638	a,ML***,l,P,Ml,F	7.813251831
639	a,Ml,BHF,P,l,F	7.793065895
640	a,LA08,LA08,P,LA08,F	7.758108471
641	LA02,l,LA08,P,LA08,F	7.748292417
642	LA02,l,l,P,LA08,F	7.731597276
643	LA02,Ml,Ml,p,LA08,F	7.730253597
644	LA02,Ml,LA08,p,LA08,F	7.688530783
645	MA,l,LA08,P,LA08,F	7.674105266
646	A,l,LA08,p,Ml,F	7.628702763
647	A,L***,Ml,P,Ml,F	7.623092282
648	Ma,ML***,BHF,p,LA08,F	7.615059868
649	MA,ML***,BHF,p,LA08,F	7.607566237
650	MA,L***,ML***,p,LA08,F	7.599284711
651	a,Ml,Ml,P,Ml,F	7.59776048
652	Ma,Ml,Ml,p,Ml,F	7.594492079
653	a,L***,Ml,P,l,F	7.575968604
654	A,Ml,LA08,p,Ml,F	7.56853665
655	Ma,L***,l,P,LA08,F	7.553279146
656	Ma,l,l,P,L***,F	7.54894806
657	Ma,l,l,p,LA08,F	7.465613977
658	MA,Ml,LA08,p,LA08,F	7.464612233
659	BHF,Ml,l,p,Ml,F	7.453519149
660	LA02,LA08,l,P,LA08,F	7.43726545
661	LA02,l,BHF,p,L***,F	7.429402282
662	LA02,LA08,LA08,p,l,F	7.419630776
663	LA02,l,Ml,p,Ml,F	7.402734165
664	LA02,Ml,ML***,p,ML***,F	7.391575169
665	A,LA08,ML***,P,Ml,F	7.34042489
666	a,Ml,ML***,p,L***,F	7.323662362
667	a,LA08,LA08,p,l,F	7.302210643
668	BHF,ML***,LA08,P,l,F	7.293312811
669	BHF,L***,ML***,p,LA08,F	7.267970912
670	BHF,l,BHF,P,l,F	7.266800993
671	MA,L***,LA08,p,LA08,F	7.258863301

672	A,l,LA08,p,L***,F	7.225489084
673	BHF,l,l,P,LA08,F	7.212470041
674	a,L***,LA08,P,LA08,F	7.188958972
675	LA02,LA08,LA08,P,LA08,F	7.175169234
676	LA02,LA08,LA08,P,L***,F	7.160087694
677	LA02,L***,L***,p,LA08,F	7.115171485
678	a,L***,l,P,Ml,F	7.113170196
679	BHF,LA08,l,P,l,F	7.041035412
680	A,L***,l,P,Ml,F	7.040603365
681	a,Ml,l,P,l,F	7.03870328
682	LA02,ML***,LA08,P,LA08,F	7.035647254
683	Ma,ML***,l,P,l,F	7.017011869
684	a,Ml,LA08,p,LA08,F	7.011283929
685	A,L***,l,p,Ml,F	6.975808294
686	Ma,LA08,L***,P,l,F	6.959702972
687	LA02,ML***,LA08,P,LA08,F	6.943695894
688	BHF,L***,BHF,p,Ml,F	6.935705496
689	a,ML***,l,P,L***,F	6.917928868
690	Ma,L***,Ml,p,L***,F	6.916143735
691	LA02,l,BHF,p,Ml,F	6.903212049
692	Ma,l,BHF,p,LA08,F	6.882744451
693	A,L***,LA08,P,l,F	6.875531808
694	Ma,L***,LA08,P,LA08,F	6.824900307
695	a,L***,l,P,ML***,F	6.822741577
696	A,LA08,l,P,LA08,F	6.81157788
697	BHF,L***,Ml,P,ML***,F	6.809746689
698	LA02,ML***,BHF,P,L***,F	6.791270429
699	BHF,L***,ML***,P,l,F	6.755272298
700	LA02,Ml,L***,p,ML***,F	6.749230183
701	LA02,Ml,ML***,p,Ml,F	6.747900026
702	BHF,L***,LA08,P,l,F	6.720235555
703	MA,l,BHF,p,LA08,F	6.685521839
704	A,L***,LA08,p,l,F	6.682576235
705	LA02,L***,BHF,P,L***,F	6.681723993
706	MA,Ml,l,P,LA08,F	6.654625468
707	LA02,l,Ml,p,Ml,F	6.603141301
708	a,l,BHF,p,l,F	6.601010658
709	BHF,L***,L***,P,LA08,F	6.596594725
710	LA02,LA08,BHF,P,L***,F	6.590767157
711	a,LA08,l,P,LA08,F	6.542426979
712	a,Ml,l,P,L***,F	6.532408763
713	BHF,l,BHF,P,LA08,F	6.499409236
714	LA02,L***,l,P,l,F	6.436337086
715	BHF,LA08,BHF,P,L***,F	6.320166945

716	A,LA08,ML***,P,ML***,F	6.291937124
717	a,l,LA08,P,LA08,F	6.253940796
718	LA02,l,L***,p,L***,F	6.250077616
719	BHF,Ml,BHF,P,l,F	6.245065973
720	a,l,BHF,p,Ml,F	6.230284798
721	BHF,LA08,l,P,Ml,F	6.204256998
722	A,ML***,LA08,p,Ml,F	6.186737279
723	MA,L***,L***,p,Ml,F	6.180292332
724	A,Ml,BHF,P,L***,F	6.173418821
725	BHF,L***,ML***,P,LA08,F	6.166490266
726	BHF,LA08,Ml,p,Ml,F	6.152430163
727	LA02,L***,BHF,p,l,F	6.127555176
728	a,LA08,ML***,p,ML***,F	6.114988928
729	A,LA08,ML***,P,l,F	6.102511913
730	A,Ml,Ml,p,Ml,F	6.094306779
731	LA02,LA08,L***,p,LA08,F	6.080538292
732	BHF,l,ML***,p,LA08,F	6.073384376
733	Ma,L***,L***,p,Ml,F	6.062607317
734	LA02,Ml,Ml,P,Ml,F	6.043175019
735	BHF,Ml,l,P,ML***,F	6.039999151
736	Ma,Ml,L***,p,l,F	6.038344336
737	BHF,LA08,ML***,P,L***,F	6.029179956
738	BHF,ML***,Ml,p,Ml,F	5.962395369
739	a,l,LA08,p,ML***,F	5.952173707
740	a,Ml,LA08,P,L***,F	5.952015047
741	LA02,LA08,l,p,L***,F	5.849625283
742	BHF,l,L***,p,ML***,F	5.8405699
743	LA02,l,L***,p,L***,F	5.834238188
744	A,l,l,p,LA08,F	5.801327507
745	LA02,L***,Ml,p,LA08,F	5.796177059
746	MA,ML***,BHF,p,LA08,F	5.796105762
747	a,L***,L***,P,LA08,F	5.774621052
748	BHF,L***,l,P,LA08,F	5.762289714
749	LA02,Ml,l,P,LA08,F	5.732089574
750	MA,Ml,L***,p,l,F	5.729766862
751	a,LA08,l,p,Ml,F	5.722356207
752	LA02,L***,l,p,l,F	5.681169623
753	Ma,Ml,BHF,P,l,F	5.679997044
754	MA,LA08,ML***,P,Ml,F	5.642892187
755	MA,LA08,l,p,LA08,F	5.628456201
756	Ma,Ml,BHF,p,l,F	5.6180916
757	BHF,Ml,L***,P,LA08,F	5.614251779
758	LA02,Ml,BHF,p,Ml,F	5.604317419
759	BHF,l,l,p,L***,F	5.598423026

760	a,LA08,BHF,p,ML***,F	5.595643211
761	a,Ml,Ml,P,Ml,F	5.58553753
762	BHF,Ml,L***,p,l,F	5.582865938
763	a,LA08,l,P,LA08,F	5.564052656
764	Ma,L***,l,p,LA08,F	5.54833614
765	LA02,ML***,Ml,P,LA08,F	5.539608771
766	BHF,LA08,BHF,p,l,F	5.523929465
767	A,L***,Ml,P,l,F	5.498324786
768	A,Ml,l,P,l,F	5.467952168
769	Ma,ML***,LA08,p,Ml,F	5.462668405
770	A,ML***,LA08,P,l,F	5.450254902
771	a,LA08,LA08,p,l,F	5.3981743
772	BHF,L***,LA08,p,Ml,F	5.384658442
773	Ma,l,BHF,P,Ml,F	5.37358175
774	A,l,BHF,P,l,F	5.333276911
775	a,ML***,BHF,P,LA08,F	5.322246179
776	A,Ml,LA08,p,Ml,F	5.303308773
777	BHF,Ml,LA08,P,Ml,F	5.299551298
778	LA02,l,Ml,P,Ml,F	5.291625049
779	Ma,LA08,ML***,P,l,F	5.279177817
780	LA02,Ml,l,p,l,F	5.276656133
781	BHF,ML***,LA08,p,LA08,F	5.268923867
782	MA,l,LA08,p,LA08,F	5.259222912
783	Ma,ML***,BHF,p,l,F	5.255010107
784	Ma,LA08,BHF,P,L***,F	5.251781145
785	LA02,l,l,p,LA08,F	5.237026512
786	a,L***,l,p,Ml,F	5.197078286
787	Ma,l,L***,P,LA08,F	5.18849604
788	LA02,ML***,l,P,L***,F	5.170969683
789	LA02,l,BHF,p,L***,F	5.163029145
790	BHF,LA08,L***,p,Ml,F	5.157084708
791	LA02,Ml,LA08,p,ML***,F	5.140152542
792	MA,Ml,Ml,P,Ml,F	5.125129024
793	BHF,LA08,LA08,p,l,F	5.110278738
794	A,l,l,P,Ml,F	5.110183983
795	a,L***,l,p,LA08,F	5.05005887
796	a,Ml,BHF,P,LA08,F	5.026004109
797	MA,L***,l,P,L***,F	5.022181461
798	BHF,Ml,l,P,Ml,F	5.014468783
799	a,LA08,Ml,p,l,F	5.01218403
800	A,l,BHF,P,ML***,F	5.008957941
801	A,LA08,Ml,p,L***,F	4.999599179
802	MA,Ml,LA08,p,L***,F	4.987967246
803	MA,Ml,BHF,P,Ml,F	4.98242252

804	A,LA08,l,P,l,F	4.971700529
805	A,l,L***,P,L***,F	4.955513875
806	BHF,Ml,ML***,P,ML***,F	4.949040241
807	MA,Ml,Ml,P,Ml,F	4.925309949
808	MA,ML***,BHF,p,l,F	4.92064853
809	A,l,BHF,P,LA08,F	4.920431357
810	a,l,BHF,P,ML***,F	4.918630557
811	a,LA08,Ml,P,LA08,F	4.887620717
812	BHF,Ml,l,p,ML***,F	4.853776703
813	a,L***,Ml,p,l,F	4.818220363
814	a,l,BHF,P,LA08,F	4.798780921
815	a,LA08,L***,p,L***,F	4.730771203
816	LA02,l,l,P,Ml,F	4.679523254
817	A,l,BHF,p,Ml,F	4.661421409
818	BHF,L***,LA08,p,LA08,F	4.650276938
819	LA02,l,LA08,p,LA08,F	4.645548262
820	MA,L***,L***,p,LA08,F	4.645204105
821	BHF,L***,Ml,p,ML***,F	4.560491954
822	A,l,l,P,L***,F	4.558809103
823	MA,L***,BHF,p,LA08,F	4.558093826
824	BHF,Ml,L***,p,ML***,F	4.540809527
825	BHF,L***,L***,P,l,F	4.496476521
826	a,Ml,Ml,P,Ml,F	4.489806331
827	MA,l,Ml,P,l,F	4.481489595
828	Ma,L***,l,p,Ml,F	4.439123536
829	LA02,LA08,LA08,p,LA08,F	4.413765128
830	LA02,L***,L***,P,l,F	4.397697324
831	LA02,l,l,p,L***,F	4.379675726
832	A,L***,l,P,l,F	4.343619858
833	MA,l,LA08,P,L***,F	4.292368636
834	a,l,L***,P,LA08,F	4.292139985
835	Ma,l,LA08,P,LA08,F	4.285097752
836	LA02,L***,LA08,p,L***,F	4.230986934
837	a,LA08,l,P,l,F	4.207597614
838	Ma,l,ML***,p,L***,F	4.20015786
839	BHF,Ml,Ml,P,l,F	4.186196982
840	a,ML***,BHF,P,l,F	4.18179341
841	BHF,Ml,l,p,ML***,F	4.157185489
842	LA02,LA08,LA08,P,L***,F	4.140926176
843	Ma,l,LA08,p,LA08,F	4.138746826
844	MA,LA08,LA08,P,LA08,F	4.06024523
845	a,l,LA08,P,Ml,F	4.047409136
846	BHF,L***,Ml,P,LA08,F	4.027404683
847	A,l,l,p,ML***,F	3.998229076

848	MA,L***,L***,P,MI,F	3.99591015
849	Ma,LA08,BHF,p,ML***,F	3.986868127
850	LA02,MI,BHF,p,MI,F	3.943742224
851	A,MI,BHF,P,l,F	3.940021
852	A,ML***,l,p,L***,F	3.9357447
853	A,ML***,l,p,MI,F	3.933263636
854	A,l,ML***,P,l,F	3.912148737
855	a,MI,BHF,p,MI,F	3.822583984
856	MA,l,BHF,P,ML***,F	3.816794499
857	MA,MI,MI,P,MI,F	3.799446452
858	BHF,MI,MI,P,MI,F	3.792816741
859	MA,MI,l,p,L***,F	3.78573774
860	a,LA08,LA08,p,LA08,F	3.779480912
861	BHF,L***,BHF,P,ML***,F	3.77844294
862	Ma,l,l,P,MI,F	3.75684075
863	BHF,ML***,LA08,p,MI,F	3.702677784
864	a,L***,L***,P,MI,F	3.701467648
865	a,l,LA08,p,MI,F	3.68847873
866	a,L***,l,p,l,F	3.680001237
867	Ma,L***,LA08,p,LA08,F	3.674158941
868	LA02,l,BHF,P,LA08,F	3.672058035
869	LA02,l,l,p,MI,F	3.670730924
870	A,L***,L***,P,l,F	3.661227149
871	MA,L***,l,P,l,F	3.648335683
872	BHF,ML***,LA08,p,l,F	3.646265202
873	A,ML***,l,P,l,F	3.639896025
874	BHF,MI,MI,P,l,F	3.614011685
875	MA,ML***,L***,P,l,F	3.613970739
876	a,LA08,ML***,p,LA08,F	3.565440407
877	LA02,ML***,L***,p,LA08,F	3.513531711
878	a,MI,LA08,P,l,F	3.509375384
879	MA,MI,BHF,p,l,F	3.47207946
880	LA02,LA08,L***,p,ML***,F	3.468532214
881	A,MI,l,p,L***,F	3.467292771
882	Ma,MI,LA08,p,LA08,F	3.449889179
883	LA02,ML***,LA08,p,L***,F	3.422626161
884	a,MI,l,p,l,F	3.413045384
885	MA,MI,L***,P,l,F	3.411058229
886	LA02,MI,l,P,LA08,F	3.398787948
887	Ma,l,BHF,P,L***,F	3.363638424
888	A,L***,l,P,l,F	3.342324735
889	BHF,l,LA08,P,LA08,F	3.336977214
890	Ma,l,BHF,p,MI,F	3.328291543
891	Ma,l,BHF,P,LA08,F	3.29864556

892	A,l,BHF,P,L***,F	3.283361952
893	BHF,Ml,l,P,LA08,F	3.282990164
894	a,L***,Ml,p,L***,F	3.265382315
895	MA,Ml,l,p,l,F	3.24089528
896	BHF,Ml,LA08,P,ML***,F	3.233604517
897	a,Ml,BHF,P,Ml,F	3.219899095
898	a,Ml,BHF,p,LA08,F	3.209271364
899	BHF,ML***,LA08,p,Ml,F	3.203077023
900	a,L***,l,P,LA08,F	3.192997038
901	a,Ml,LA08,p,L***,F	3.188836831
902	LA02,L***,ML***,p,LA08,F	3.186920091
903	MA,LA08,BHF,p,l,F	3.170561209
904	BHF,LA08,LA08,P,l,F	3.16955984
905	BHF,Ml,L***,P,Ml,F	3.163553756
906	Ma,LA08,BHF,p,l,F	3.158294592
907	Ma,Ml,Ml,p,Ml,F	3.150790127
908	BHF,LA08,Ml,P,LA08,F	3.096760797
909	LA02,Ml,Ml,p,l,F	3.09466279
910	MA,ML***,l,p,LA08,F	3.090144419
911	A,LA08,LA08,p,L***,F	3.064018713
912	a,L***,l,P,l,F	3.054271484
913	BHF,LA08,BHF,P,l,F	3.051380451
914	a,Ml,Ml,p,Ml,F	3.049366565
915	Ma,LA08,l,p,L***,F	3.010185207
916	BHF,Ml,ML***,P,Ml,F	2.995666887
917	A,l,l,P,l,F	2.99007427
918	a,ML***,l,P,l,F	2.946257625
919	MA,l,Ml,p,L***,F	2.944306232
920	Ma,LA08,LA08,P,LA08,F	2.918329696
921	a,l,Ml,p,l,F	2.887948226
922	Ma,l,l,P,LA08,F	2.86571319
923	LA02,Ml,BHF,p,Ml,F	2.864702906
924	Ma,L***,ML***,p,l,F	2.86160219
925	MA,Ml,Ml,P,Ml,F	2.831646367
926	A,Ml,l,p,l,F	2.827508693
927	Ma,LA08,l,p,L***,F	2.817673975
928	Ma,Ml,Ml,p,Ml,F	2.779684151
929	a,l,LA08,P,l,F	2.750737412
930	LA02,ML***,BHF,p,Ml,F	2.743938266
931	a,L***,LA08,P,l,F	2.722944496
932	MA,ML***,BHF,P,l,F	2.710500596
933	MA,L***,l,P,LA08,F	2.709421124
934	a,Ml,Ml,p,l,F	2.704207233
935	LA02,ML***,BHF,p,LA08,F	2.631383083

936	LA02,L***,L***,p,l,F	2.616954756
937	BHF,Ml,LA08,P,ML***,F	2.609283785
938	Ma,Ml,BHF,P,Ml,F	2.5838208
939	a,l,L***,P,ML***,F	2.573450027
940	BHF,ML***,LA08,P,LA08,F	2.558926316
941	A,l,l,p,l,F	2.552894905
942	MA,l,LA08,p,L***,F	2.546867999
943	a,l,Ml,P,Ml,F	2.53015786
944	MA,Ml,L***,P,L***,F	2.507583547
945	Ma,l,l,p,ML***,F	2.483452527
946	Ma,l,BHF,p,Ml,F	2.482115084
947	Ma,LA08,BHF,p,Ml,F	2.45866909
948	MA,Ml,Ml,p,l,F	2.430356628
949	A,l,l,p,Ml,F	2.392962435
950	a,Ml,LA08,p,Ml,F	2.366270393
951	MA,l,ML***,P,L***,F	2.343324006
952	a,L***,BHF,p,l,F	2.340204055
953	BHF,ML***,Ml,P,LA08,F	2.334566318
954	a,l,l,P,LA08,F	2.322052743
955	MA,l,l,P,Ml,F	2.321953035
956	BHF,ML***,LA08,P,LA08,F	2.317827141
957	MA,LA08,BHF,P,l,F	2.315571818
958	BHF,LA08,LA08,p,Ml,F	2.28082983
959	A,l,BHF,P,Ml,F	2.267306184
960	a,L***,Ml,p,Ml,F	2.262653009
961	MA,l,BHF,P,L***,F	2.236342237
962	BHF,L***,LA08,P,LA08,F	2.224107332
963	MA,L***,LA08,P,l,F	2.220888577
964	BHF,Ml,LA08,p,l,F	2.200773477
965	a,l,Ml,p,ML***,F	2.150885314
966	Ma,Ml,BHF,p,LA08,F	2.130913971
967	BHF,ML***,LA08,p,ML***,F	2.113078776
968	BHF,l,LA08,p,LA08,F	2.097299106
969	MA,l,l,P,L***,F	2.097240979
970	MA,Ml,BHF,P,Ml,F	2.084457722
971	MA,Ml,LA08,P,l,F	2.019124535
972	a,LA08,l,p,l,F	1.986395902
973	MA,l,BHF,P,Ml,F	1.976703241
974	MA,l,BHF,P,Ml,F	1.976703241
975	a,ML***,l,p,ML***,F	1.949056916
976	Ma,LA08,LA08,p,LA08,F	1.931680012
977	a,l,LA08,P,L***,F	1.917554286
978	a,L***,L***,p,l,F	1.896665982
979	MA,LA08,LA08,p,LA08,F	1.891875636

980	BHF,ML***,LA08,P,Ml,F	1.889646603
981	BHF,ML***,Ml,P,Ml,F	1.884015652
982	MA,l,BHF,p,L***,F	1.878245365
983	MA,l,L***,p,L***,F	1.808753284
984	BHF,LA08,L***,P,LA08,F	1.800796374
985	BHF,l,LA08,P,LA08,F	1.800065615
986	BHF,ML***,ML***,P,LA08,F	1.771227842
987	Ma,L***,BHF,P,L***,F	1.764502925
988	BHF,LA08,BHF,P,Ml,F	1.749745372
989	MA,Ml,BHF,P,l,F	1.702128466
990	Ma,l,l,p,Ml,F	1.644239055
991	a,L***,l,p,l,F	1.607246122
992	BHF,Ml,BHF,p,Ml,F	1.571943589
993	BHF,ML***,LA08,p,LA08,F	1.569937417
994	MA,l,l,p,LA08,F	1.505486657
995	MA,LA08,L***,P,l,F	1.505202515
996	Ma,LA08,l,p,l,F	1.497100343
997	BHF,LA08,LA08,p,L***,F	1.489150081
998	Ma,L***,l,P,l,F	1.480181817
999	MA,Ml,Ml,p,l,F	1.462990076
1000	BHF,Ml,l,p,LA08,F	1.447153033
1001	Ma,Ml,Ml,P,l,F	1.390305635
1002	a,l,BHF,P,Ml,F	1.33946399
1003	Ma,L***,l,P,LA08,F	1.326574827
1004	MA,L***,l,p,LA08,F	1.324580747
1005	BHF,ML***,ML***,P,Ml,F	1.324471746
1006	MA,LA08,L***,p,LA08,F	1.314797814
1007	BHF,ML***,LA08,p,Ml,F	1.210283521
1008	MA,L***,BHF,p,l,F	1.198411999
1009	a,l,l,p,l,F	1.167434745
1010	MA,L***,L***,p,l,F	1.159476244
1011	Ma,Ml,Ml,p,l,F	1.15303301
1012	MA,l,l,p,L***,F	1.140630815
1013	LA02,Ml,ML***,p,L***,F	1.136297368
1014	BHF,Ml,L***,p,Ml,F	1.127409942
1015	Ma,L***,l,p,l,F	1.116819581
1016	a,l,l,P,Ml,F	1.110903769
1017	BHF,LA08,LA08,p,Ml,F	1.103406979
1018	Ma,Ml,Ml,p,l,F	1.040434901
1019	MA,l,L***,P,L***,F	1.029054628
1020	Ma,L***,L***,P,l,F	1.025434776
1021	a,l,l,p,LA08,F	1.018947064
1022	Ma,l,l,p,LA08,F	0.970181534
1023	a,l,LA08,p,L***,F	0.963388403

1024	a,l,Ml,p,Ml,F	0.937026383
1025	a,l,l,P,l,F	0.932844583
1026	LA02,LA08,BHF,p,Ml,F	0.916820282
1027	BHF,LA08,BHF,P,LA08,F	0.901184923
1028	BHF,ML***,BHF,P,LA08,F	0.881944575
1029	Ma,l,L***,p,L***,F	0.876722677
1030	BHF,Ml,ML***,p,Ml,F	0.867335833
1031	MA,Ml,BHF,P,L***,F	0.860854334
1032	a,LA08,LA08,p,L***,F	0.860791996
1033	BHF,Ml,BHF,P,LA08,F	0.860571037
1034	a,L***,l,P,l,F	0.837694591
1035	MA,l,l,P,LA08,F	0.806641355
1036	BHF,Ml,LA08,P,LA08,F	0.763202189
1037	BHF,ML***,LA08,p,ML***,F	0.747831927
1038	BHF,LA08,LA08,P,LA08,F	0.743104171
1039	BHF,LA08,L***,p,ML***,F	0.737624873
1040	a,l,l,P,l,F	0.736545175
1041	a,l,l,p,Ml,F	0.713310536
1042	BHF,Ml,BHF,P,ML***,F	0.670525435
1043	Ma,Ml,Ml,p,l,F	0.644183993
1044	Ma,L***,l,p,L***,F	0.602912753
1045	a,l,L***,p,L***,F	0.592490913
1046	BHF,LA08,BHF,p,Ml,F	0.523175137
1047	Ma,L***,L***,p,l,F	0.478053842
1048	a,L***,l,p,L***,F	0.424511465
1049	MA,L***,L***,P,l,F	0.41125112
1050	BHF,LA08,LA08,p,LA08,F	0.361255187
1051	MA,LA08,Ml,p,LA08,F	0.342058957
1052	Ma,Ml,BHF,p,Ml,F	
1053	Ma,l,l,P,l,F	
1054	MA,l,l,P,l,F	
1055	MA,l,l,p,l,F	
1056	LA02,L***,L***,p,L***,F	
1057	BHF,LA08,BHF,p,LA08,F	
1058	a,Ml,BHF,p,Ml,F	
1059	LA02,Ml,BHF,P,Ml,F	
1060	BHF,ML***,BHF,p,ML***,F	
1061	BHF,Ml,BHF,P,Ml,F	
1062	a,Ml,BHF,p,Ml,F	
1063	BHF,Ml,BHF,p,Ml,F	
1064	BHF,Ml,BHF,p,Ml,F	
1065	A,Ml,Ml,p,Ml,F	
1066	a,Ml,Ml,p,Ml,F	
1067	A,Ml,Ml,P,Ml,F	

1068	a,Ml,Ml,P,Ml,F	
1069	MA,Ml,Ml,P,Ml,F	
1070	Ma,Ml,Ml,P,Ml,F	
1071	Ma,l,l,p,l,F	
1072	MA,l,l,p,l,F	
1073	MA,l,l,p,l,F	
1074	Ma,Ml,BHF,P,Ml,F	
1075	a,l,l,p,l,F	
1076	MA,LA08,LA08,P,LA08,F	
1077	A,Ml,BHF,p,Ml,F	
1078	MA,Ml,BHF,P,Ml,F	
1079	a,Ml,Ml,p,Ml,F	
1080	BHF,l,l,P,Ml,F	
1081	LA02,Ml,BHF,P,ML***,F	
1082	Ma,Ml,Ml,P,ML***,F	
1083	LA02,ML***,BHF,p,Ml,F	
1084	Ma,ML***,ML***,P,l,F	
1085	MA,L***,LA08,P,LA08,F	
1086	Ma,L***,L***,p,ML***,F	
1087	MA,Ml,Ml,P,ML***,F	
1088	MA,Ml,Ml,P,ML***,F	
1089	Ma,L***,ML***,p,Ml,F	
1090	MA,l,l,p,Ml,F	
1091	Ma,L***,L***,P,ML***,F	
1092	a,l,ML***,P,Ml,F	
1093	MA,l,l,P,ML***,F	
1094	A,LA08,BHF,p,L***,F	
1095	MA,Ml,ML***,P,l,F	
1096	LA02,ML***,ML***,P,LA08,F	
1097	MA,l,l,p,ML***,F	
1098	BHF,l,ML***,p,ML***,F	
1099	A,Ml,BHF,p,L***,F	
1100	a,ML***,ML***,p,l,F	
1101	Ma,Ml,ML***,p,L***,F	
1102	MA,Ml,LA08,P,Ml,F	
1103	Ma,L***,Ml,p,l,F	
1104	A,l,Ml,p,Ml,F	
1105	Ma,ML***,LA08,p,l,F	
1106	BHF,ML***,L***,p,Ml,F	
1107	BHF,ML***,L***,p,Ml,F	
1108	A,l,BHF,p,L***,F	
1109	a,ML***,LA08,P,ML***,F	
1110	MA,L***,LA08,p,LA08,F	
1111	a,ML***,ML***,p,l,F	

1112	A,ML***,BHF,P,l,F	
1113	MA,L***,l,p,l,F	
1114	Ma,l,L***,p,ML***,F	
1115	BHF,ML***,L***,P,Ml,F	
1116	Ma,l,l,p,L***,F	
1117	BHF,ML***,L***,p,LA08,F	
1118	Ma,L***,ML***,p,LA08,F	
1119	MA,Ml,Ml,P,l,F	
1120	Ma,Ml,LA08,p,L***,F	
1121	A,ML***,BHF,P,LA08,F	
1122	BHF,ML***,L***,P,LA08,F	
1123	BHF,Ml,L***,p,LA08,F	
1124	LA02,ML***,L***,P,LA08,F	
1125	a,l,l,p,ML***,F	
1126	MA,l,BHF,P,LA08,F	
1127	BHF,ML***,LA08,p,LA08,F	
1128	Ma,Ml,Ml,P,ML***,F	
1129	LA02,L***,L***,p,LA08,F	
1130	Ma,Ml,l,p,Ml,F	
1131	MA,Ml,ML***,p,Ml,F	
1132	MA,ML***,ML***,P,l,F	
1133	a,l,l,p,L***,F	
1134	a,ML***,BHF,p,LA08,F	
1135	Ma,ML***,LA08,p,Ml,F	
1136	LA02,Ml,l,P,Ml,F	
1137	a,Ml,l,p,L***,F	
1138	a,ML***,l,p,L***,F	
1139	a,l,l,P,ML***,F	
1140	Ma,l,L***,P,L***,F	
1141	a,L***,ML***,P,Ml,F	
1142	a,Ml,Ml,P,l,F	
1143	BHF,ML***,L***,p,L***,F	
1144	BHF,ML***,LA08,p,ML***,F	
1145	A,ML***,BHF,p,LA08,F	
1146	MA,L***,l,p,LA08,F	
1147	BHF,LA08,BHF,p,L***,F	
1148	a,l,Ml,P,Ml,F	
1149	A,l,l,p,L***,F	
1150	BHF,Ml,LA08,p,Ml,F	
1151	a,ML***,BHF,P,L***,F	
1152	Ma,L***,BHF,p,l,F	
1153	Ma,Ml,l,p,Ml,F	
1154	BHF,ML***,L***,p,LA08,F	
1155	a,l,BHF,P,L***,F	

1156	BHF,Ml,Ml,P,LA08,F	
1157	Ma,ML***,L***,P,L***,F	
1158	LA02,LA08,BHF,P,ML***,F	
1159	MA,ML***,L***,p,L***,F	
1160	BHF,L***,BHF,p,L***,F	
1161	Ma,L***,BHF,p,L***,F	
1162	A,Ml,LA08,P,l,F	
1163	Ma,ML***,BHF,P,LA08,F	
1164	a,l,Ml,p,LA08,F	
1165	A,L***,L***,P,LA08,F	
1166	Ma,ML***,L***,p,L***,F	
1167	BHF,l,ML***,p,LA08,F	
1168	MA,L***,BHF,p,L***,F	
1169	A,ML***,L***,p,ML***,F	
1170	A,L***,Ml,p,l,F	
1171	MA,ML***,l,p,L***,F	
1172	a,l,Ml,p,Ml,F	
1173	BHF,Ml,BHF,p,l,F	
1174	LA02,L***,BHF,p,L***,F	
1175	a,l,Ml,P,ML***,F	
1176	MA,Ml,Ml,P,l,F	
1177	BHF,Ml,ML***,p,LA08,F	
1178	BHF,ML***,LA08,p,L***,F	
1179	BHF,ML***,LA08,p,L***,F	
1180	A,l,Ml,p,L***,F	
1181	A,l,ML***,P,L***,F	
1182	A,Ml,Ml,P,l,F	
1183	LA02,l,LA08,p,l,F	
1184	Ma,ML***,l,p,ML***,F	
1185	a,l,Ml,p,L***,F	
1186	LA02,Ml,LA08,P,LA08,F	
1187	A,LA08,L***,p,L***,F	
1188	Ma,L***,LA08,p,ML***,F	
1189	Ma,L***,BHF,p,LA08,F	
1190	MA,Ml,l,P,L***,F	
1191	A,L***,l,p,l,F	
1192	a,L***,ML***,P,l,F	
1193	BHF,ML***,BHF,p,LA08,F	
1194	BHF,L***,LA08,p,l,F	
1195	Ma,l,LA08,P,L***,F	
1196	A,L***,ML***,p,l,F	
1197	MA,L***,LA08,p,L***,F	
1198	a,ML***,BHF,p,Ml,F	
1199	a,Ml,LA08,P,Ml,F	

1200	BHF,L***,MI,P,LA08,F	
1201	MA,l,LA08,p,l,F	
1202	LA02,ML***,BHF,P,L***,F	
1203	BHF,MI,LA08,P,l,F	
1204	A,MI,LA08,p,LA08,F	
1205	BHF,MI,L***,p,ML***,F	
1206	Ma,l,LA08,p,L***,F	
1207	BHF,MI,LA08,p,ML***,F	
1208	MA,L***,LA08,P,LA08,F	
1209	a,MI,BHF,p,LA08,F	
1210	MA,L***,BHF,P,l,F	
1211	MA,LA08,BHF,P,L***,F	
1212	a,ML***,LA08,p,LA08,F	
1213	MA,LA08,BHF,p,L***,F	
1214	A,l,L***,p,L***,F	
1215	a,LA08,ML***,p,ML***,F	
1216	Ma,MI,LA08,P,l,F	
1217	a,l,ML***,p,L***,F	
1218	BHF,MI,MI,P,ML***,F	
1219	Ma,ML***,LA08,P,l,F	
1220	Ma,l,BHF,p,ML***,F	
1221	BHF,MI,MI,p,LA08,F	
1222	Ma,MI,BHF,p,l,F	
1223	MA,MI,BHF,p,l,F	
1224	LA02,LA08,MI,P,MI,F	
1225	MA,ML***,LA08,P,l,F	
1226	MA,LA08,ML***,P,l,F	
1227	Ma,LA08,L***,p,MI,F	
1228	a,LA08,MI,p,L***,F	
1229	a,LA08,l,P,ML***,F	
1230	A,LA08,MI,p,ML***,F	
1231	a,LA08,L***,p,l,F	
1232	MA,LA08,L***,p,l,F	
1233	a,LA08,LA08,p,L***,F	
1234	LA02,LA08,L***,p,LA08,F	
1235	MA,LA08,LA08,P,L***,F	
1236	a,LA08,LA08,p,L***,F	
1237	a,LA08,LA08,p,L***,F	
1238	A,l,MI,p,MI,F	
1239	BHF,l,MI,p,l,F	
1240	Ma,MI,MI,P,ML***,F	

MSMS Processing

Centroided MS2 spectra first had their parent ion mass corrected to high resolution by locating the closest high resolution mass in the MS1 spectrum, then filtered down to those spectra matching masses of the sublibrary of interest. MS2 spectra were then grouped per their source-peak, before using the most intense as a base spectrum for intensity combination.

- 5 Combination occurred by a one-to-one m/z correspondence rule with the closest m/z being matched between spectra. In a separate process, all MS2 spectra (pre-filtration) had their peak intensities collected into a single dataset, which was filtered to the lowest 90% and used to generate a kernel density estimate of the noise distribution. From that noise distribution, a noise threshold was decided by setting it to the p-value of 0.05 of a noise peak having intensity equal
10 to or greater than the threshold. Finally, intensity-combined MS2 spectra were filtered by peak intensity at that threshold.

Sequencing

- Each MS2 spectrum was first matched at high resolution (0.015 m/z) to all possible parent compounds from the library design. All possible fragment masses were belonging to
15 those possible parent compounds were generated, then matched against the MS2 spectrum peaks. Based on those matches, a best candidate was identified. Number of matches, identity of matches, and peak intensity were all included in the scoring of each candidate molecule.

Data Correlation

- 20 Permeability data and sequencing data were correlated by mass and retention time matches within large precision gaps to account for inter-run variability (time precision = 3 seconds, mass precision = 0.03). The data were then pruned of those peaks for which no Pe value could be calculated and with unacceptably low sequencing quality (generally due to poor MS2 data quality).

25

Abbreviations

- ACN, acetonitrile; COMU, (1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate; DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene; DCM, dichloromethane; DMF, N,N-dimethylformamide;
30 DIPEA, diisopropylethylamine, DMSO, dimethylsulfoxide; Fmoc, 9-fluorenylmethoxycarbonyl; HATU, 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate; LCMS, liquid chromatography mass spectrometry; MeOH, methanol; N2,

nitrogen; PTFE, Polytetrafluoroethylene; RP, reverse phase; SPPS, solid phase peptide synthesis; TFA, trifluoroacetic acid.

PAMPA Permeability of Resynthesized Compounds

- 5 A set of hexapeptomers were resynthesized and the parallel artificial membrane permeability assay was performed to determine the permeability values. Each peptomer sequence with determined permeability (Pe) value is shown in Table 3.

Table 3

<u>Compound No.</u>	<u>Peptomer Sequence</u>	<u>Bulk Permeability Value</u> (x 10⁻⁶ cm/s)	<u>Pure Permeability Value</u> (x 10⁻⁶ cm/s)
1	a,L,L,p,l,F	0.58	2.51
2	BHF,ML,L,p,ML,F	0.74	3.27
3	BHF,l,BHF,p,l,F	4.08	7.43
4	Ma,l,L,p,l,F	2.94	11.34
5	A,L,L,P,ML,F	2.65	5.1
6	a,l,l,p,ML,F	0.17	1.91
7	Ma,L,BHF,p,l,F	0.16	6.65
8	A,L,BHF,P,ML,F	4.53	> 22
9	BHF,L,l,P,L,F	12.76	> 22
10	BHF,l,L,p,l,F	2.52	8.02
11	BHF,L,l,p,l,F	4.94	7.48
12	BHF,L,L,P,l,F	1.43	6.92

10

Aspects, including embodiments, of the subject matter described herein may be beneficial alone or in combination, with one or more other aspects or embodiments. Without limiting the description, certain non-limiting aspects of the disclosure numbered 1-68 are provided below. As will be apparent to those of skill in the art upon reading this disclosure, each of the individually numbered aspects may be used or combined with any of the preceding of following individually numbered aspects. This is intended to provide support for all such combinations of aspects and is not limited to combinations of aspects explicitly provided below:

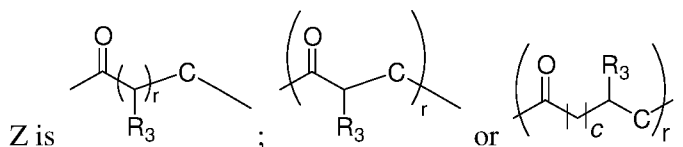
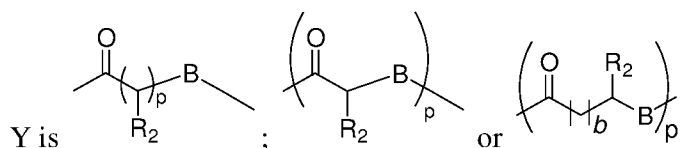
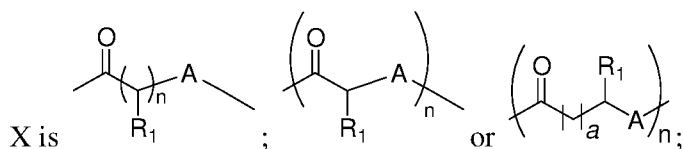
15

1. A compound of Formula I:

20

Cyclo [Z-Y-X-Pro-Y-Phe] Formula I

wherein:



5

each R_1 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R_1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl

10 ring;

each R_2 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R_2 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl

15 ring;

each R_3 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R_3 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl

20 ring;

A is selected from $-NR_a-$, $-O-$ or $-S-$;

B is selected from $-NR_b-$, $-O-$ or $-S-$;

C is selected from $-NR_c-$, $-O-$ or $-S-$;

each R_a , R_b , R_c is independently selected from hydrogen, alkyl, substituted alkyl, aryl

25 and substituted aryl, or

R_1 and R_a together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R_2 and R_b together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

5 R_3 and R_c together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

n is an integer from one to 5 and a is an integer from one to 5;

p is an integer from one to 5 and b is an integer from one to 5; and

r is an integer from one to 5 and c is an integer from one to 5;

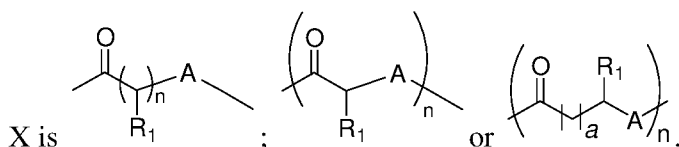
10 or a pharmaceutical acceptable salt, solvate or hydrate thereof.

2. The compound according to 1, wherein each R_1 is independently selected from a side chain of an amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

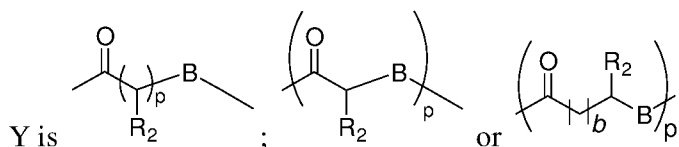
15 3. The compound according to 2, wherein each R_1 is independently selected from a side chain of glycine, leucine or phenylalanine.

4. The compound according to any one of 1-3, wherein each R_2 is independently selected from a side chain of an amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

5. The compound according to any one of 1-3, wherein:



6. The compound according to any one of 1-3, wherein:



7. The compound according to 6, wherein each R_2 is independently selected from a side chain of leucine or glycine.

8. The compound according to any one of 1-7, wherein each R_3 is independently selected from a side chain of an amino acid selected from the group consisting of alanine,

arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

9. The compound according to 8, wherein each R_3 is independently selected from a side chain of glycine, alanine or phenylalanine.

10. The compound according to any one of 1-9, wherein n is 2 and each R_1 is selected from a side chain of glycine or phenylalanine.

11. The compound according to any one of 1-10, wherein r is 2 and each R_3 is selected from a side chain of glycine or phenylalanine.

12. The compound according to any one of 1-11, wherein p is 1 and R_2 is glycine or leucine.

13. The compound according to any one of 1-12, wherein A is NR_a .

14. The compound according to 13, wherein R_a is selected from hydrogen, alkyl or aryl.

15. The compound according to 14, wherein the alkyl is methyl or propyl.

16. The compound according to 14, wherein the aryl is benzyl.

17. The compound according to any one of 1-16, wherein B is NR_b .

18. The compound according to 17, wherein R_b is selected from hydrogen, alkyl or aryl.

19. The compound according to 18, wherein the alkyl is methyl.

20. The compound according to 18, wherein the aryl is benzyl.

21. The compound according to any one of 1-20, wherein C is NR_c .

22. The compound according to 21, wherein R_c is selected from hydrogen, alkyl or aryl.

23. The compound according to 22, wherein the alkyl is methyl.

24. The compound according to 22, wherein the aryl is benzyl.

25. The compound according to any one of 1-24, wherein X is a residue of a D-amino acid or L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof.

26. The compound according to 25, wherein X is a D-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine,

isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof.

27. The compound according to 26, wherein X is D-leucine or an N-alkyl derivative thereof.

5 28. The compound according to 27, wherein X is D-leucine.

29. The compound according to 27, wherein X is N-methyl D-leucine.

30. The compound according to 25, wherein X is an L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof.

10 31. The compound according to 30, wherein X is L-leucine or an N-alkyl derivative thereof.

32. The compound according to 27, wherein X is L-leucine.

33. The compound according to 27, wherein X is N-methyl L-leucine.

15 34. The compound according to 30, wherein X is L- β -homophenylalanine or an alkyl derivative thereof.

35. The compound according to 30, wherein X is L- β -homophenylalanine.

36. The compound according to 25, wherein X is glycine or an N-alkyl derivative thereof.

20 37. The compound according to 36, wherein X is N-benzyl glycine.

38. The compound according to any one of 1-37, wherein Y is a residue of a D-amino acid or L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof.

25 39. The compound according to 38, wherein Y is a D-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof.

30 40. The compound according to 39, wherein Y is D-leucine or an N-alkyl derivative thereof.

41. The compound according to 40, wherein Y is D-leucine.

42. The compound according to 40, wherein Y is N-methyl D-leucine.

43. The compound according to 38, wherein Y is an L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof.

5 44. The compound according to 43, wherein Y is L-leucine or an N-alkyl derivative thereof.

45. The compound according to 44, wherein Y is L-leucine.

46. The compound according to 44, wherein Y is N-methyl L-leucine.

47. The compound according to 38, wherein Y is glycine or an N-alkyl derivative
10 thereof.

48. The compound according to 47, wherein Y is N-benzyl glycine.

49. The compound according to any one of 1-48, wherein Z is a residue of a D-amino acid or L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine,
15 phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof.

50. The compound according to 49, wherein Z is a D-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine,
20 threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof.

51. The compound according to 50, wherein Z is D-alanine or an N-alkyl derivative thereof.

52. The compound according to 51, wherein Z is D-alanine.

53. The compound according to 51, wherein Z is N-methyl D-leucine.

25 54. The compound according to 49, wherein Z is an L-amino acid selected from alanine, arginine, asparagine, aspartic acid, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, β -homophenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine or an N-alkyl derivative thereof.

55. The compound according to 54, wherein Z is L-alanine or an N-alkyl derivative
30 thereof.

56. The compound according to 55, wherein Z is L-alanine.

57. The compound according to 55, wherein Z is N-methyl L-alanine.

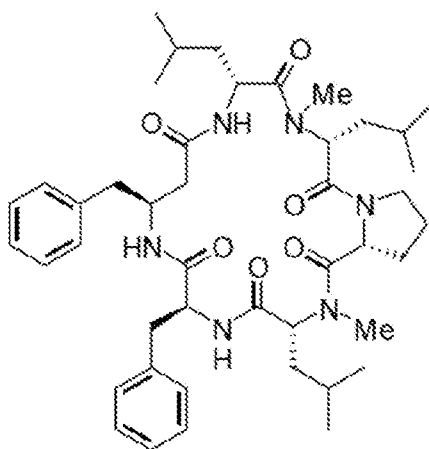
58. The compound according to 49, wherein Z is L- β -homophenylalanine or an alkyl derivative thereof.

59. The compound according to 30, wherein Z is L- β -homophenylalanine.

60. The compound according to 49, wherein Z is glycine or an N-alkyl derivative thereof.

61. The compound according to 36, wherein Z is N-propyl glycine.

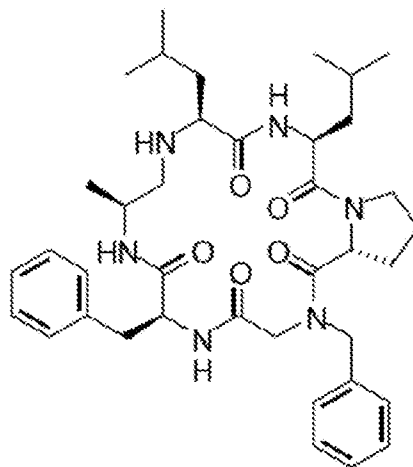
62. A compound of Formula 1:



Formula 1

or a pharmaceutical acceptable salt, solvate or hydrate thereof.

63. A compound of Formula 2:



Formula 2

or a pharmaceutical acceptable salt, solvate or hydrate thereof.

64. A composition comprising:

a compound or pharmaceutically acceptable salt, solvate or hydrate thereof

according to any one of 1-63; and

a pharmaceutically acceptable vehicle.

65. The composition according to 64, wherein the composition comprises:
a compound according to any one of 1-63; and
a pharmaceutically acceptable vehicle.

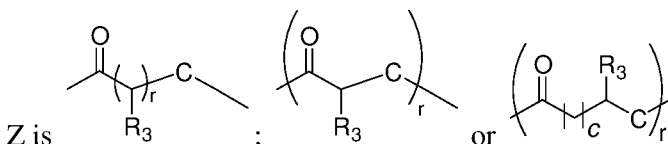
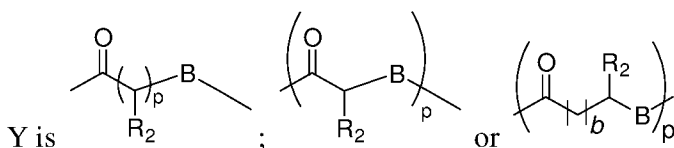
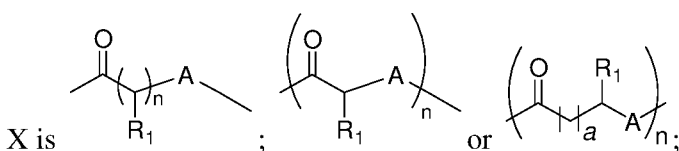
66. A method comprising administering a compound or pharmaceutically acceptable
5 salt, solvate or hydrate thereof according to any one of 1-63 to a subject.

67. A method comprising administering a composition according to any one of 64-65
to a subject.

68. A library comprising 50 or more cyclic peptides, each cyclic peptide
independently having a Formula I:

10 Cyclo [Z-Y-X-Pro-Y-Phe] Formula I

wherein:



each R₁ is independently selected from hydrogen, alkyl, substituted alkyl, aryl,
substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl,
substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R₁ together
with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl
20 ring;

each R₂ is independently selected from hydrogen, alkyl, substituted alkyl, aryl,
substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl,
substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R₂ together
with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl
25 ring;

each R_3 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R_1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

A is selected from $-NR_a-$, $-O-$ or $-S-$;

B is selected from $-NR_b-$, $-O-$ or $-S-$;

C is selected from $-NR_c-$, $-O-$ or $-S-$;

each R_a , R_b , R_c is independently selected from hydrogen, alkyl, substituted alkyl, aryl and substituted aryl, or

R_1 and R_a together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R_2 and R_b together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R_3 and R_c together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

n is an integer from one to 5 and a is an integer from one to 5;

p is an integer from one to 5 and b is an integer from one to 5; and

r is an integer from one to 5 and c is an integer from one to 5;

or a pharmaceutical acceptable salt, solvate or hydrate thereof.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Accordingly, the preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the

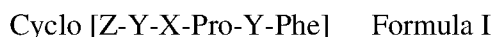
invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional
5 equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims.

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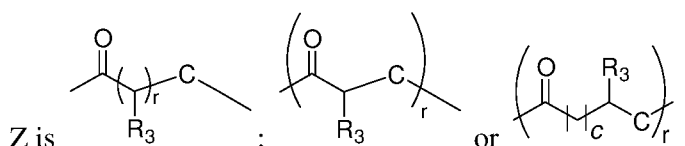
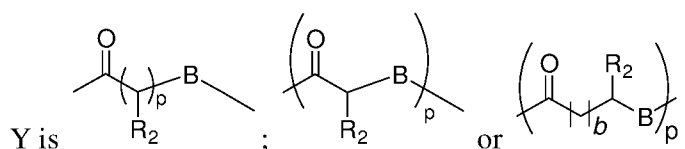
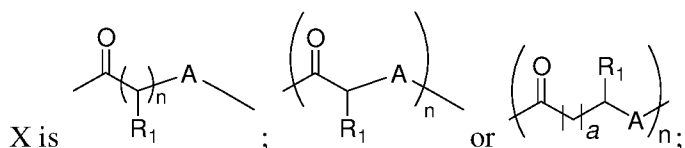
CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula I:



wherein:



each R_1 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R_1 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl

ring;

each R_2 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R_2 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl

ring;

each R_3 is independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R_3 together with the atoms to which it is bonded form a cycloheteroalkyl or substituted cycloheteroalkyl

ring;

A is selected from $-NR_a-$, $-O-$ or $-S-$;

B is selected from $\text{-NR}_b\text{-}$, -O- or -S- ;

C is selected from $\text{-NR}_c\text{-}$, -O- or -S- ;

each R_a , R_b , R_c is independently selected from hydrogen, alkyl, substituted alkyl, aryl and substituted aryl, or

5 R_1 and R_a together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R_2 and R_b together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

10 R_3 and R_c together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

n is an integer from one to 5 and a is an integer from one to 5;

p is an integer from one to 5 and b is an integer from one to 5; and

r is an integer from one to 5 and c is an integer from one to 5;

or a pharmaceutical acceptable salt, solvate or hydrate thereof.

15

2. The compound according to claim 1, wherein:

A is $\text{-NR}_a\text{-}$;

R_a is selected from hydrogen, alkyl or aryl;

a is an integer from 1 to 5;

20

n is an integer from 1 to 5;

R_1 is independently selected from a side chain of glycine, leucine or phenylalanine or N-alkyl derivative thereof.

3. The compound according to claim 2, wherein R_a is methyl or propyl.

25

4. The compound according to claim 2, wherein R_a is benzyl.

5. The compound according to claim 2, wherein n is 1.

30

6. The compound according to claim 1, wherein:

B is $\text{-NR}_b\text{-}$;

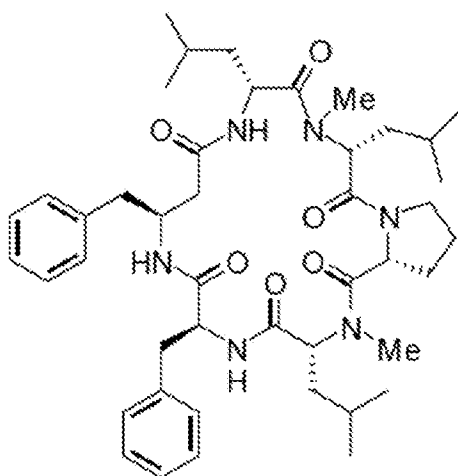
R_b is selected from hydrogen, alkyl or aryl;

b is an integer from 1 to 5;

p is an integer from 1 to 5;

R₂ is independently selected from a side chain of glycine or leucine or an N-alkyl derivative thereof.

- 5 7. The compound according to claim 6, wherein R_b is methyl or benzyl.
8. The compound according to claim 6, wherein p is 1.
9. The compound according to claim 1, wherein:
- 10 C is -NR_c-;
- R_c is selected from hydrogen, alkyl or aryl;
- c is an integer from one to 5;
- r is an integer from one to 5;
- R₃ is independently selected from a side chain of alanine or leucine or an N-alkyl
- 15 derivative thereof.
10. The compound according to R_c is methyl or benzyl.
11. The compound according to claim 1, wherein X is selected from L-leucine, N-
- 20 methyl L-leucine, D-leucine, N-methyl D-leucine, L-β-homophenylalanine and benzylpeptoid.
12. The compound according to claim 1, wherein Y is selected from L-leucine, N-
- methyl L-leucine, D-leucine, N-methyl D-leucine and benzylpeptoid.
- 25 13. The compound according to claim 1, wherein Z is selected from L-alanine, N-
- methyl L-alanine, N-methyl D-alanine, propyl peptoid and L-β-homophenylalanine.
14. The compound according to claim 1, wherein the compound is a compound of
- Formula 1:

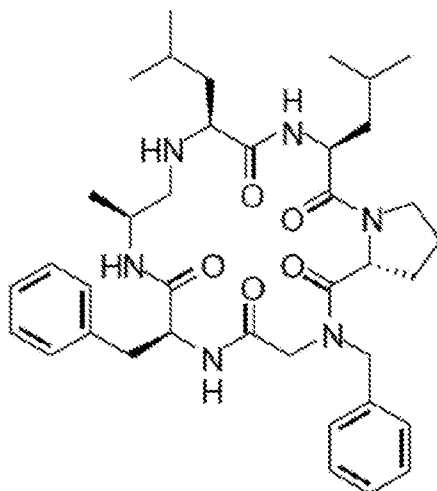


Formula 1

or a pharmaceutical acceptable salt, solvate or hydrate thereof.

15. The compound according to claim 1, wherein the compound is a compound of

5 Formula 2:



Formula 2

or a pharmaceutical acceptable salt, solvate or hydrate thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/028832

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/00; A61K 38/04; A61K 38/08; C07K 7/00; C07K 7/06; C07K 7/64 (2018.01)

CPC - A61K 38/00; A61K 38/04; A61K 38/08; C07K 7/00; C07K 7/06; C07K 7/64 (2018.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 514/9; 514/21.1; 530/317 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011/0256567 A1 (BERTHELOT et al) 20 October 2011 (20.10.2011) entire document	1
A	US 5,866,540 A (JONCZYK et al) 02 February 1999 (02.02.1999) entire document	1
A	PUBCHEM, Substance Record for SID 85759687, Available Date: 15 December 2009 [retrieved on 22 June 2018]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/85759687 >. entire document	1

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

11 September 2018

Date of mailing of the international search report

25 SEP 2018

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/028832

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/028832

Continued from Box No. III Observations where unity of invention is lacking

Claim 1 has been analyzed subject to the restriction that the claim reads on a compound of Formula I wherein X is the first shown structure; Y is the first shown structure; Z is the first shown structure; each R1 is independently hydrogen; each R2 is independently hydrogen; each R3 is independently hydrogen; A is -NRa-; B is -NRb-; C is -NRC-; each Ra, Rb, Rc is independently hydrogen; n is 1; p is 1; and r is 1; or a pharmaceutical acceptable salt, solvate or hydrate thereof.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-15 are drawn to compounds of Formula I or a pharmaceutical acceptable salt, solvate or hydrate thereof.

The first invention of Group I+ is restricted to a compound of Formula I wherein X is the first shown structure; Y is the first shown structure; Z is the first shown structure; each R1 is independently hydrogen; each R2 is independently hydrogen; each R3 is independently hydrogen; A is -NRa-; B is -NRb-; C is -NRC-; each Ra, Rb, Rc is independently hydrogen; n is 1; p is 1; and r is 1; or a pharmaceutical acceptable salt, solvate or hydrate thereof. It is believed that claim 1 reads on this first named invention and thus this claim will be searched without fee to the extent that it reads on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of Formula I wherein X is the second shown structure; Y is the first shown structure; Z is the first shown structure; each R1 is independently hydrogen; each R2 is independently hydrogen; each R3 is independently hydrogen; A is -NRa-; B is -NRb-; C is -NRC-; each Ra, Rb, Rc is independently hydrogen; n is 1; p is 1; and r is 1; or a pharmaceutical acceptable salt, solvate or hydrate thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables Z, Y, X, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structure of Formula I or a pharmaceutical acceptable salt, solvate or hydrate thereof, these shared technical features do not represent a contribution over the prior art as disclosed by Substance Record for SID 85759687 to PubChem.

Substance Record for SID 85759687 to PubChem teaches a compound having the core structure of Formula I (Pg. 3;...see shown structure...).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.