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(71) Applicant(s)
Receptos LLC

(72) Inventor(s)
Tamiya, Junko;Turnbull, Philip;Enugurthi, Brahmachary;Huang, Liming;Yeager, Adam R.;Fowler, Thomas;Iacobini, Greg P.;Crittall, Matthew Richard

(74) Agent / Attorney
Davies Collison Cave Pty Ltd, Level 15 1 Nicholson Street, MELBOURNE, VIC, 3000, AU

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(71) Applicant: **CELGENE INTERNATIONAL II SARL**
[CH/CH]; Rue des Moulins, 2108 Couvet (CH).

(72) Inventors: **TAMIYA, Junko**; 934 Daisy Avenue, Carlsbad, California 92011 (US). **TURNBULL, Philip**; 3033 Science Park Road, Suite 300, San Diego, California 92121 (US). **ENUGURTHI, Brahmachary**; 6768 Elegante Way, San Diego, California 92130 (US). **HUANG, Liming**; 12788 Adolphia Court, San Diego, California 92129 (US). **YEAGER, Adam, R.**; 7958 Normal Avenue, La Mesa, California 91941 (US). **FOWLER, Thomas**; 15 Blacksmith End, Stathern, Melton Mowbray Leicestershire LE14 4EZ (GB). **IACOBINI, Greg, P.**; Pennyfoot Street, Bio City Nottinghamshire NG1 1GF (GB). **CRITTALL, Matthew, Richard**; Pennyfoot Street, BioCity Nottinghamshire NG1 1GF (GB).

(74) Agent: **HERMANN, Karl, R.** et al.; Seed Intellectual Property Law Group LLP, Suite 5400, 701 Fifth Avenue, Seattle, Washington 98104-7064 (US).

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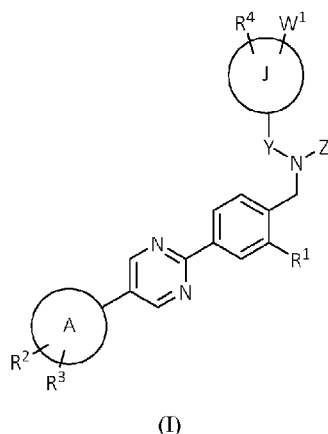
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(57) Abstract: Compounds are provided that modulate the glucagon-like peptide 1 (GLP-1) receptor, as well as products containing such compounds, and methods of their use and synthesis. Such compounds have the structure of Formula (I) below: (I) or pharmaceutically acceptable salts thereof, wherein A, J, W¹, Y, Z, R¹, R², R³ and R⁴ are as defined herein.



NOVEL GLP-1 RECEPTOR MODULATORS

TECHNICAL FIELD

The disclosure is directed to compounds that modulate the glucagon-like peptide 1 (GLP-1) receptor, as well as to related products and methods for their use and
5 synthesis.

BACKGROUND

Glucagon-like peptide 1 receptor (GLP-1R) belongs to Family B1 of the seven-transmembrane G protein-coupled receptors, and its natural agonist ligand is the peptide hormone glucagon-like peptide-1 (GLP-1). GLP-1 is a peptide hormone arising
10 by its alternative enzymatic cleavage from proglucagon, the prohormone precursor for GLP-1, which is highly expressed in enteroendocrine cells of the intestine, the alpha cells of the endocrine pancreas (islets of Langerhans), and the brain (Kieffer T. J. and Habener, J. F. *Endocrin. Rev.* 20:876-913 (1999); Drucker, D. J., *Endocrinology* 142:521-7 (2001); Holst, J. J., *Diabetes Metab. Res. Rev.* 18:430-41 (2002)). The initial
15 actions of GLP-1 observed were on the insulin-producing cells of the islets, where it stimulates glucose-dependent insulin secretion. Subsequently, multiple additional antidiabetogenic actions of GLP-1 were discovered including the stimulation of the growth and inhibition of the apoptosis of pancreatic beta cells (Drucker, D. J., *Endocrinology* 144:5145-8 (2003); Holz, G. G. and Chepurny O. G., *Curr. Med. Chem.*
20 10:2471-83 (2003); List, J. F. and Habener, J. F., *Am. J. Physiol. Endocrinol. Metab.* 286:E875-81 (2004)).

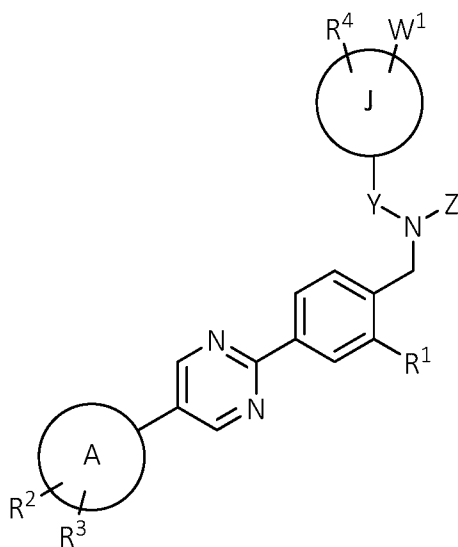
On activation, GLP-1 receptors couple to the α subunit of G protein, with subsequent activation of adenylate cyclase and increase of cAMP levels, thereby potentiating glucose-stimulated insulin secretion. Therefore, GLP-1 is an attractive
25 target to lower blood glucose levels and preserve the β -cells of the pancreas of diabetic patients. Glucagon has been used for decades in medical practice within diabetes and several glucagon-like peptides are being developed for various therapeutic indications. GLP-1 analogs and derivatives are being developed for the treatment for patients suffering from diabetes.

While advances have been made in this field, there remains a significant need for modulators of the GLP-1 receptor, particularly GLP-1 receptor agonists, as well as for products and methods related to the same. The present disclosure fulfills these and other needs, as described in more detail in the following detailed description.

5 SUMMARY OF INVENTION

The present invention is directed to compounds adapted to act as modulators of the GLP-1 receptor, particularly GLP-1 receptor agonists, as well as to related products and methods of their preparation and their use, such as in treatment of a malcondition mediated by GLP-1 receptor, or when modulation of GLP-1 receptor is medically indicated.

In one embodiment, compounds are provided having the structure of Formula (I):



(I)

15 or a pharmaceutically acceptable salts thereof, wherein A, J, W¹, Y, Z, R¹, R², R³ and R⁴ are as defined below.

In one embodiment, the compounds of Formula (I) include, but are not limited to, hydrates, hydrates and/or isotopes thereof, as well as stereoisomers to the extent such compounds contain one or more chiral centers.

In one embodiment, a pharmaceutical composition comprising a compound of Formula (I) together with at least one pharmaceutically acceptable carrier, diluent or excipient is provided.

In one embodiment, a method of modulation of a GLP-1 receptor is provided comprising contacting the receptor with a compound of Formula (I), or a pharmaceutical composition comprising a compound of Formula (I).

In one embodiment, a method is provided for treatment of a malcondition in a subject for which modulation of a GLP-1 receptor is medically indicate, comprising administering to the subject a compound of Formula (I), or a pharmaceutical composition comprising a compound of Formula (I).

In one embodiment, the malcondition is type I diabetes, type II diabetes, gestational diabetes, obesity, excessive appetite, insufficient satiety, or metabolic disorder.

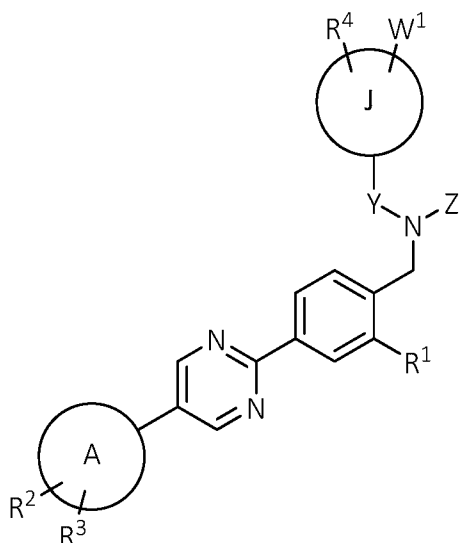
In one embodiment, the malcondition is non-alcoholic fatty liver disease (NAFLD) and/or non-alcoholic steatohepatitis (NASH).

In one embodiment, methods for synthesis of compounds of Formula (I) are provided, including preparation of intermediates associated with such methods.

DETAILED DESCRIPTION OF THE INVENTION

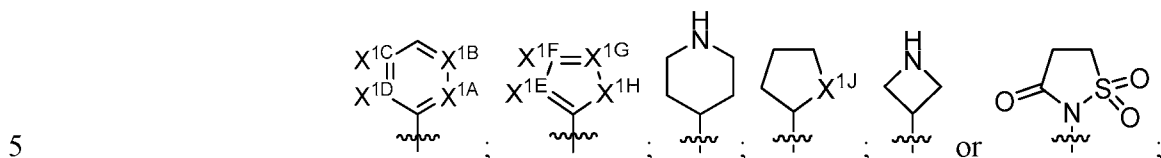
As mentioned above, the present invention provides compounds which modulate the GLP-1 receptor, particularly GLP-1 receptor agonists, as well as to methods of their preparation and use in the treatment of conditions mediated by the GLP-1 receptor, including (but not limited to) type I diabetes, type II diabetes, gestational diabetes, obesity, excessive appetite, insufficient satiety, metabolic disorder, non-alcoholic fatty liver disease (NAFLD) and/or non-alcoholic steatohepatitis (NASH).

In one embodiment, compounds are provided having the structure of Formula (I):



or a pharmaceutically acceptable salts thereof, wherein:

J is null or has the structure:



each of X^{1A}, X^{1B}, X^{1C}, X^{1D}, X^{1E}, X^{1F} and X^{1G} is C, CH or N;

X^{1H} is O or S;

X^{1J} is CH₂ or NH;

R¹ is H, alkyl or alkoxy;

10 Y is -C(O)-, -CH₂-, -C(O)-CH₂-, -CH₂-C(O)-,

-C(O)-(CR^aR^b)_n-N(R^c)-C(O)-(CR^aR^b)_n-, -C(O)-(CR^aR^b)_n-N(R^d)

where R^d may form a fused ring with J or with a fused J-R⁴-W¹ ring system,

-C(O)-(CR^aR^b)_n-N(R^c)-C(O)-(CR^aR^b)_n-N(R^c)-S(O)_k-(CR^aR^b)_n-,

15 -C(O)-(CR^aR^b)_n-N(R^c)-C(O)-(CR^aR^b)-N(R^d)- where R^d may form a fused ring with J or with a fused J-R⁴-W¹ ring system, or

-C(O)-(CR^aR^b)_n-N(R^c)-S(O)_k-(CR^aR^b)_n-;

Z is -(CR^aR^b)_n-C(O)-R⁷;

R⁷ is -OR³⁰, -NR³¹R³², -NH(CR^aR^b)_n-C(O)-R⁷, -NHSO₂R⁷ or

20 -(CO)-NH-SO₂-R⁷, or R³¹;

each R³⁰ is independently H or alkyl;

- each R³¹ and R³² is independently H or C₁-C₆ alkyl optionally substituted with one or more R³³, or taken together with the N atom to which they are attached can form a 3- to 7-membered heterocyclic ring;
- each R³³ is independently halo, hydroxyl, alkoxy, perhaloalkyl, perhaloalkoxy, carboxyl, -C(O)O-R³⁰, -OR³⁰, -N(R³⁰)₂ or heterocyclyl;
- each R⁴ is independently H, alkyl, alkoxy, or alkyl substituted with one or more R⁴³, halogen, perhaloalkyl, perhaloalkoxy, -CN, -OR⁴⁰ or -NR⁴¹R⁴²;
- each R⁴¹ and R⁴² is independently H, alkyl, -(CH₂)_n-C(O)O-R⁴⁰, -C(O)-R⁴⁰, aryl, heteroaryl; or R⁴¹ and R⁴², taken together with the N atom to which they are attached, can form a 3- to 7-membered heterocyclic ring;
- each R⁴³ is independently H, halo, hydroxyl, -NR⁴¹R⁴², or alkoxy;
- W¹ is -(CR^aR^b)_{i1}-L¹-(CR^aR^b)_{j1}-R⁶⁰ or R⁴; or W¹ and R⁴ taken together comprise a 5- or 6- membered carbocyclic or heterocyclic ring fused with the ring to which W¹ and R⁴ are attached and optionally having one, two or three heteroatoms where each such heteroatom is independently selected from O, N, and S, and where any ring atom of such heterocyclic ring may be optionally substituted with one or more -L¹-R¹³ or R¹³; or W¹ is a 5- or 6- membered heterocyclic ring fused with a phenyl ring and having one, two or three heteroatoms where each such heteroatom is independently selected from O, N, and S, and where any ring atom of such fused heterocyclic ring and phenyl ring moiety may be optionally substituted with one or more R¹⁴;
- L¹ is -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR¹⁰-, -C(O)NR¹⁰-, -N(R¹⁰)-(CH₂)_n-C(O)-, -N(R¹⁰)-C(O)-N(R¹⁰)-, -N(R¹⁰)-S(O)₂-, -S(O)₂-NR¹⁰-, or -N(S(O)₂-(CH₂)_n-R⁶⁰)₂;
- R⁶⁰ is R¹³, -O-(CH₂)_n-R¹³, or R¹⁰;
- each R¹⁰, R¹¹ and R¹² is independently H or alkyl;

5 R^{13} is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or a fused bicycle or tricycle of any two or three of such ring moieties, or R^{13} and R^{10} taken together with the N atom to which they are attached form a heterocyclic ring, where any ring atom of R_{13} may be optionally substituted with one or more R^{14} or R^{15} ;

each R^{14} is independently H, alkyl, halo, hydroxy, cyano, alkoxy, perhaloalkyl, and perhaloalkoxy, $-OR^{10}$, $-(CH_2)_n-C(O)OR^{10}$, $-SR^{10}$, $-SO-R^{10}$, $-S(O)_2-R^{10}$, $-(CH_2)_n-NR^{11}R^{12}$, $-NH-C(O)-(CH_2)_n-R^{12}$, $-N(R^{11})-C(O)-(CH_2)_n-R^{12}$, or $-NH(CH_2)_n-R^{12}$;

10 R^{15} is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or a fused bicycle of any two of such ring moieties, where any ring atom of R^{15} may be optionally substituted with one or more R^{14} ;

each R^5 is independently H, alkyl, alkoxy, alkyl substituted with one or more R_{53} , halogen, perhaloalkyl, perhaloalkoxy, $-CN$, $-OR^{50}$, or $-NR^{51}R^{52}$;

15

each R^{40} and R^{50} is independently H or alkyl;

each R^{51} and R^{52} is independently H or alkyl, $-(CH_2)_n-C(O)O-R^{50}$, $-C(O)-R^{50}$, aryl, heteroaryl, or two taken together with the N atom to which they are attached can form a 3- to 7-membered heterocyclic ring;

20

each R^a and R^b is independently H, hydroxy, alkyl, or aralkyl optionally substituted with hydroxyl; or both R^a and R^b attached to the same carbon are, taken together, oxo, or cycloalkyl;

each R^c and R^d is independently H, hydroxy, alkyl, $-S(O)_k-R^7$ or $-C(O)-R^7$;

25

A is cycloalkyl;

R^2 is alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or a fused bicycle of any two of such ring moieties, where any ring atom of R_2 may be optionally substituted with one or more R^3 ;

30

each R^3 is independently H, alkyl, or perhaloalkyl;

each n is independently 0, 1, 2, 3 or 4; and

each i_1 , i_2 , j_1 and j_2 is independently 0, 1, 2, 3 or 4.

In one embodiment, the compounds of Formula (I) include, but are not limited to, hydrates, hydrates and/or isotopes thereof. The compounds of Formula (I) also include stereoisomers to the extent that the compounds of Formula (I) contain one
5 or more chiral centers.

As used herein, the terms listed below have the following meaning.

“Alkyl” groups include straight chain and branched alkyl groups having from 1 to about 20 carbon atoms, and typically from 1 to 12 carbons (C_1 - C_{12} alkyl), or, in some embodiments, from 1 to 8 carbon atoms (C_1 - C_8 alkyl), or, in some
10 embodiments, from 1 to 4 carbon atoms (C_1 - C_4 alkyl). In the case of cycloalkyl groups, such groups have from 3-20 carbon atoms. Examples of straight chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-
15 dimethylpropyl groups.

“Alkenyl” groups include straight and branched chain alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Thus, alkenyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are
20 not limited to $-CH=CH_2$, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH_2$, $-C(CH_3)=CH(CH_3)$, $-C(CH_2CH_3)=CH_2$, $-CH=CHCH_2CH_3$, $-CH=CH(CH_2)_2CH_3$, $-CH=CH(CH_2)_3CH_3$, $-CH=CH(CH_2)_4CH_3$, vinyl, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others.

“Cycloalkyl” groups are alkyl groups forming a ring structure, which can
25 be substituted or unsubstituted, wherein the ring is either completely saturated, partially unsaturated, or fully unsaturated, wherein if there is unsaturation, the conjugation of the pi-electrons in the ring do not give rise to aromaticity. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group has 3 to 8 ring
30 members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 3 to 6, or 3 to 7. In some embodiments, cycloalkyl groups are partially unsaturated,

including, for example, but not limited to cyclohexenyl, cyclopentenyl, and cyclohexadienyl groups. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalanyl, and the like.

“Aryl” groups are cyclic aromatic hydrocarbons that do not contain heteroatoms. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain 6-14 carbons in the ring portions of the groups. The phrase “aryl groups” includes groups containing fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl, tetrahydronaphthyl, and the like).

“Aralkyl” groups are alkyl, alkenyl or alkynyl groups as defined above in which a hydrogen atom of an alkyl, alkenyl or alkynyl group is replaced with an aryl group as defined above. Representative aralkyl groups include benzyl (-CH₂phenyl), phenylethyl (-CH₂CH₂phenyl) and phenylethylene (-CH=CHphenyl) groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl.

“Heterocyclyl” or “heterocyclic” groups include aromatic and non-aromatic ring moieties containing 3 or more ring members, of which one or more is a heteroatom such as, but not limited to, N, O, S, or P. In some embodiments, heterocyclyl groups include 3 to 20 ring members, whereas other such groups have 3 to 15 ring members, including for example single ring systems containing 5, 6 or 7 ring members. At least one ring contains a heteroatom, but every ring in a polycyclic system need not contain a heteroatom. For example, a dioxolanyl ring and a benzodioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclyl groups within the meaning herein. A heterocyclyl group designated as a C₂-heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms, and so forth. Likewise a C₄-heterocyclyl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms.

The term “heterocyclyl” includes fused ring species including those having fused aromatic and non-aromatic groups. The phrase also includes polycyclic and/or bridging ring systems containing a heteroatom such as, but not limited to, quinuclidyl and 7-azabicyclo[2.2.1]heptane, and also includes heterocyclyl groups that have substituents, including but not limited to alkyl, halo, amino, hydroxy, cyano, carboxy, nitro, thio, or alkoxy groups, bonded to one of the ring members. A heterocyclyl group as defined herein can be a heteroaryl group or a partially or completely saturated cyclic group including at least one ring heteroatom. Heterocyclyl groups include, but are not limited to, pyrazinyl, pyrimidinyl, pyridazinyl, thiadiazolyl, oxadiazolyl, imidazolyl, hexahydropyrimidinyl, diazepanyl, triazinyl, imidazolyl, pyrrolidinyl, furanyl, tetrahydrofuranlyl, tetrahydro-2H-pyranlyl, dioxolanyl, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranlyl, dihydrobenzofuranlyl, indolyl, dihydroindolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups.

“Heteroaryl” groups are aromatic ring moieties containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. A heteroaryl group designated as a C₂-heteroaryl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C₄-heteroaryl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, pyrazinyl, pyrimidinyl, thiadiazolyl, imidazolyl, oxadiazolyl, thienyl, triazolyl, tetrazolyl, triazinyl, thiazolyl, thiophenyl, oxazolyl, isoxazolyl, benzothiophenyl, benzofuranlyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl,

quinoxaliny, and quinazoliny groups. The terms "heteroaryl" and "heteroaryl groups" include fused ring compounds such as wherein at least one ring, but not necessarily all rings, are aromatic, including tetrahydroquinoliny, tetrahydroisoquinoliny, indolyl and 2,3-dihydro indolyl.

5 Additional examples of aryl and heteroaryl groups include but are not limited to phenyl, biphenyl, indenyl, naphthyl (1-naphthyl, 2-naphthyl), N-hydroxytetrazolyl, N-hydroxytriazolyl, N-hydroxyimidazolyl, anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophenyl (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl), indolyl, oxadiazolyl (1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), thiadiazolyl
 10 (1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), isoxazolyl, quinazoliny, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridiny, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-
 15 thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), prazolo[1,5- α]pyridinyl, quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl),
 20 benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), isobenzofuranyl, 2,3-dihydrobenzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-
 25 benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydrobenzo[b]thiophenyl, (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-
 30 benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-

indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), benzo[d]isoxazolyl, carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), and the like.

By a "ring system" as the term is used herein is meant a moiety comprising one, two, three or more rings, which can be substituted with non-ring groups or with other ring systems, or both, which can be fully saturated, partially unsaturated, fully unsaturated, or aromatic, and when the ring system includes more than a single ring, the rings can be fused, bridging, or spirocyclic. By "spirocyclic" is meant the class of structures wherein two rings are fused at a single tetrahedral carbon atom, as is well known in the art.

When two "R" groups are said to be joined together or taken together to form a ring, it is meant that together with the carbon atom or a non-carbon atom (e.g., nitrogen atom), to which they are bonded, they may form a ring system. In general, they are bonded to one another to form a 3- to 7-membered ring, or a 5- to 7-membered ring. Non-limiting specific examples are the cyclopentyl, cyclohexyl, cycloheptyl, piperidinyl, piperazinyl, pyrrolidinyl, pyrrolyl, pyridinyl.

The term "alkoxy" refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined above. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, n-propoxy, n-butoxy, n-pentyloxy, n-hexyloxy, n-heptyloxy, n-octyloxy, n-nonyloxy, and the like. Examples of branched alkoxy include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy, and the like. Examples of cyclic alkoxy include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

An "acyl" group as the term is used herein refers to a group containing a carbonyl moiety wherein the group is bonded via the carbonyl carbon atom. The carbonyl carbon atom is also bonded to another carbon atom, which can be part of an alkyl, aryl, aralkyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl group or the like. In the special case wherein the carbonyl carbon atom is bonded to a hydrogen, the group is a "formyl" group, an acyl group as the term is defined herein. An acyl group can include 0 to about 12-20 additional carbon atoms bonded to the carbonyl group. An acyl group can include double or triple bonds within the meaning herein. An acryloyl group is an example of an acyl group. An acyl group can also include heteroatoms within the meaning here. A nicotinoyl group (pyridyl-3-carbonyl) group is an example of an acyl group within the meaning herein. Other examples include acetyl, benzoyl, phenylacetyl, pyridylacetyl, cinnamoyl, and acryloyl groups and the like. When the group containing the carbon atom that is bonded to the carbonyl carbon atom contains a halogen, the group is termed a "haloacyl" group. An example is a trifluoroacetyl group.

The term "amine" includes primary, secondary, and tertiary amines having, e.g., the formula $N(\text{group})_3$ wherein each group can independently be H or non-H, such as alkyl, aryl, and the like. Amines include but are not limited to $R-NH_2$, for example, alkylamines, arylamines, alkylarylamines; R_2NH wherein each R is independently selected, such as dialkylamines, diarylamines, aralkylamines, heterocyclylamines and the like; and R_3N wherein each R is independently selected, such as trialkylamines, dialkylarylamines, alkyldiarylamines, triarylamines, and the like. The term "amine" also includes ammonium ions as used herein.

An "amino" group is a substituent of the form $-NH_2$, $-NHR$, $-NR_2$, $-NR_3^+$, wherein each R is independently selected, and protonated forms of each. Accordingly, any compound substituted with an amino group can be viewed as an amine.

An "ammonium" ion includes the unsubstituted ammonium ion NH_4^+ , but unless otherwise specified, it also includes any protonated or quaternarized forms of amines. Thus, trimethylammonium hydrochloride and tetramethylammonium chloride are both ammonium ions, and amines, within the meaning herein.

The term "amide" or "amido" includes C- and N-amide groups, *i.e.*, -C(O)NR₂, and -NRC(O)R groups, respectively. Amide groups therefore include but are not limited to carbamoyl groups (-C(O)NH₂) and formamide groups (-NHC(O)H). A "carboxamido" group is a group of the formula C(O)NR₂, wherein R can
5 be H, alkyl, aryl, etc.

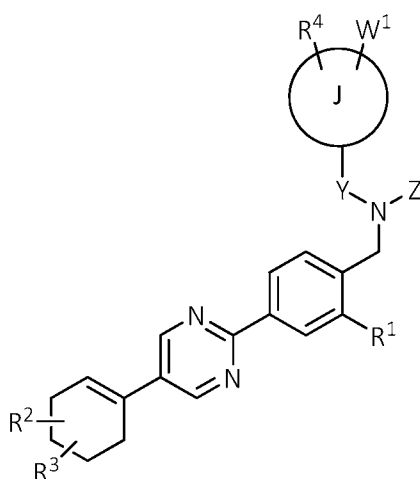
The term "carbonyl," refers to a -C(O)- group.

"Halo," "halogen," and "halide" include fluorine, chlorine, bromine and iodine.

The term "perhaloalkyl" refers to an alkyl group where all of the
10 hydrogen atoms are replaced by halogen atoms. Perhaloalkyl groups include, but are not limited to, -CF₃ and -C(CF₃)₃. The term "haloalkyl" refers to an alkyl group where some but not necessarily all of the hydrogen atoms are replaced by halogen atoms. Haloalkyl groups include but are not limited to -CHF₂ and -CH₂F.

The term "perhaloalkoxy" refers to an alkoxy group where all of the
15 hydrogen atoms are replaced by halogen atoms. Perhaloalkoxy groups include, but are not limited to, -OCF₃ and -OC(CF₃)₃. The term "haloalkoxy" refers to an alkoxy group where some but not necessarily all of the hydrogen atoms are replaced by halogen atoms. Haloalkoxy groups include but are not limited to -OCHF₂ and -OCH₂F.

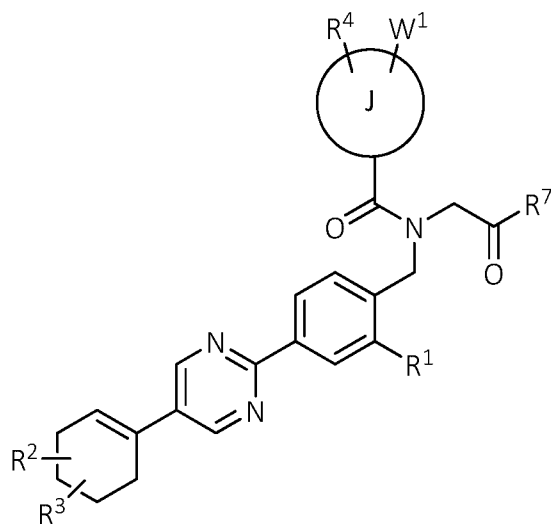
In one embodiment, compounds are provided having the structure of
20 Formula (II):



(II)

wherein J, W¹, Y, Z, R¹, R², R³ and R⁴ are as defined for Formula (I) above.

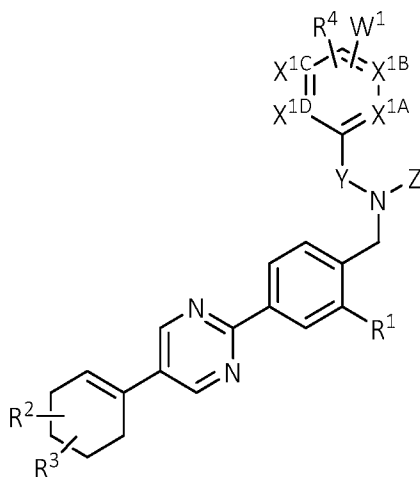
In one embodiment, compounds are provided having the structure of Formula (III):



(III)

5 wherein J, W¹, R¹, R², R³, R⁴, and R⁷ are as defined for Formula (I) above

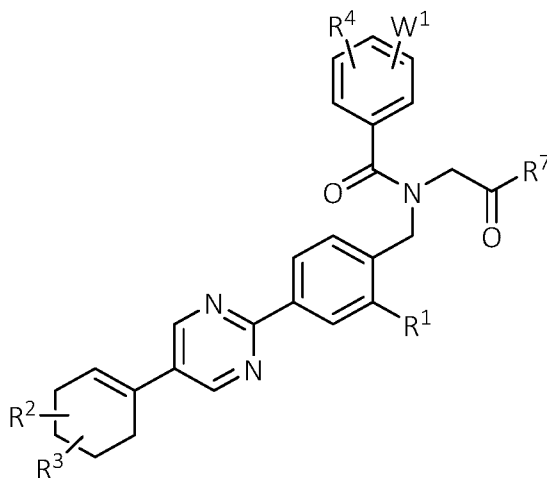
In one embodiment, compounds are provided having the structure of Formula (IV):



(IV)

10 wherein W¹, Y, Z, X^{1A}, X^{1B}, X^{1C}, X^{1D}, R¹, R², R³ and R⁴ are as defined for Formula (I) above.

In one embodiment, compounds are provided having the structure of Formula (V):

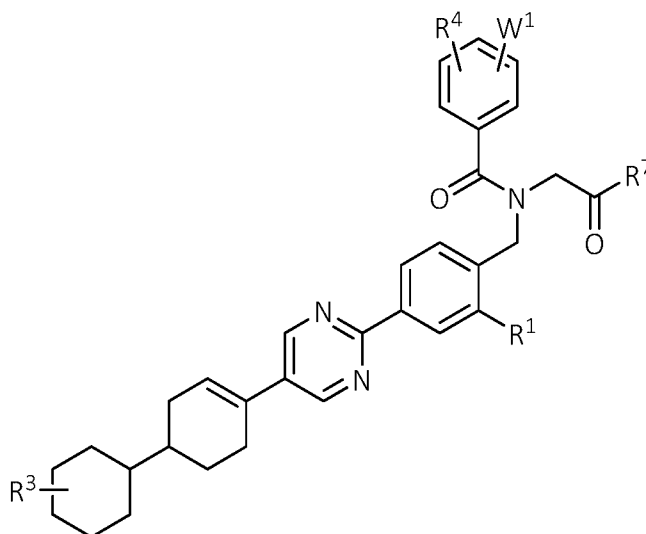


(V)

wherein W¹, R¹, R², R³, R⁴, and R⁷ are as defined for Formula (I) above.

In one embodiment, compounds are provided having the structure of

5 Formula (VI):

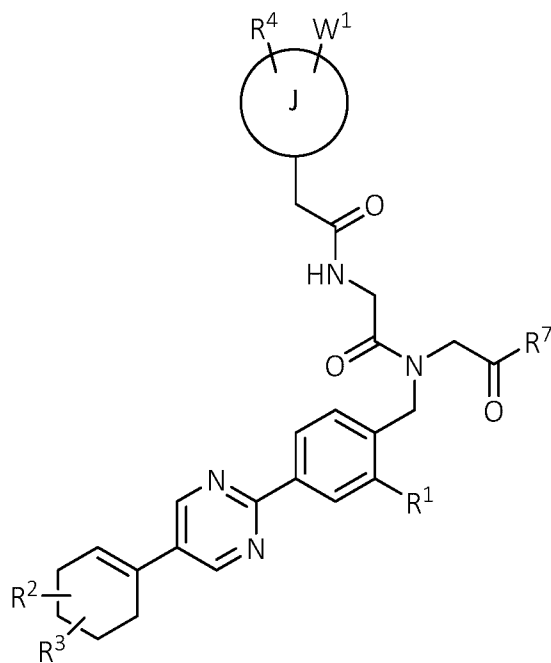


(VI)

wherein W¹, R³, R⁴, and R⁷ are as defined for Formula (I) above.

In one embodiment, compounds are provided having the structure of

10 Formula (VII):

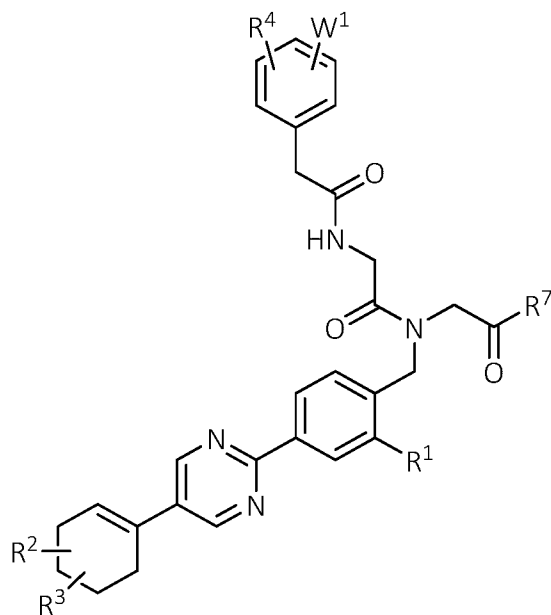


(VII)

wherein J, W¹, R¹, R², R³, R⁴, and R⁷ are as defined for Formula (I) above.

In one embodiment, compounds are provided having the structure of

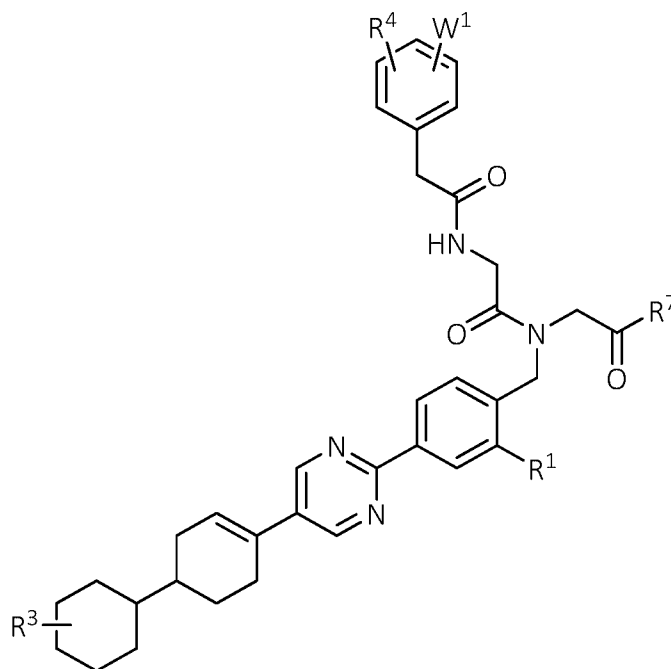
5 Formula (VIII):



(VIII)

wherein W¹, R¹, R², R³, R⁴, and R⁷ are as defined for Formula (I) above.

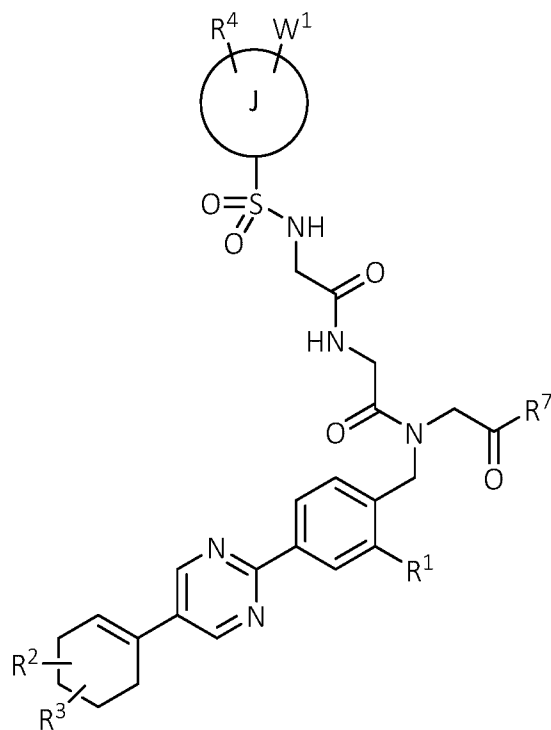
In one embodiment, compounds are provided having the structure of Formula (IX):



(IX)

5 wherein W¹, R¹, R³, R⁴, and R⁷ are as defined for Formula (I) above.

In one embodiment, compounds are provided having the structure of Formula (X):

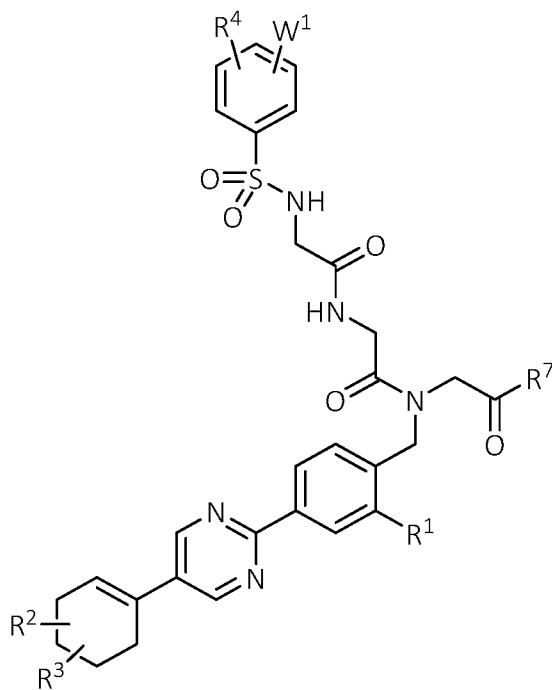


(X)

wherein J, W¹, R¹, R², R³, R⁴, and R⁷ are as defined for Formula (I) above.

In one embodiment, compounds are provided having the structure of

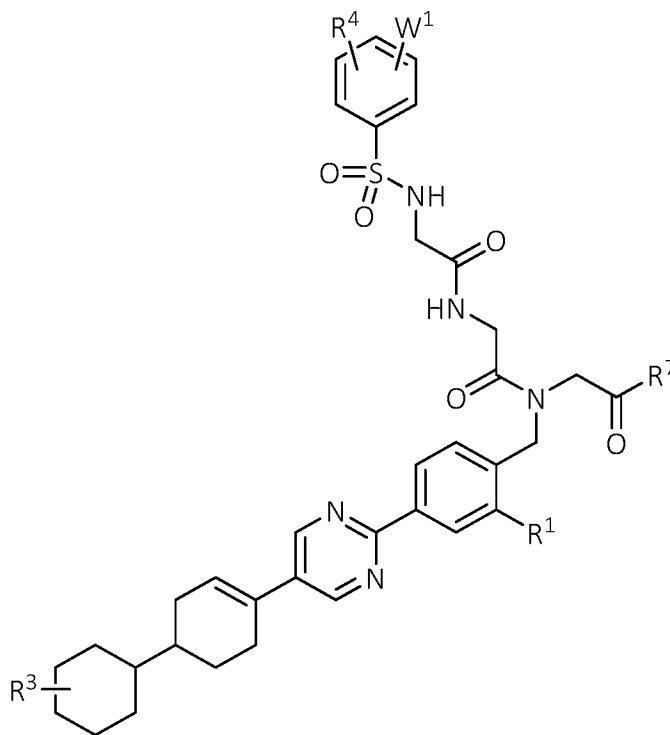
5 Formula (XI):



(XI)

wherein W^1 , R^1 , R^2 , R^3 , R^4 , and R^7 are as defined for Formula (I) above.

In one embodiment, compounds are provided having the structure of Formula (XII):



5

(XII)

wherein W^1 , R^1 , R^3 , R^4 , and R^7 are as defined for Formula (I) above.

The compounds of any one of Formulas (II) through (XII) above include, but are not limited to, hydrates, hydrates and/or isotopes thereof, as well as stereoisomers to the extent such compounds contain one or more chiral centers. The
 10 compounds of any one of Formulas (II) through (XII) above also include pharmaceutically acceptable salts.

In the following more specific embodiments, the various substituents (*e.g.*, A, J, W^1 , Y, Z, R^1 , R^2 , R^3 , R^4 , and R^7) are set forth in more detail with respect to the compounds of each of Formulas (I) through (XII) above, as applicable to the
 15 substituents being further defined. For example, reference to Y below is intended to further limit the compounds of Formulas (I), (II) and (IV) above, but not Formulas (III) or (V)-(XII) since the Y substituent has already been further defined in the same. Thus,

reference to the substituents below is intended to further modify Formulas (I)-(XII) to the extent such formulas recite that particular substituent as a variable.

- In one embodiment, Y is $-\text{C}(\text{O})-$.
- In one embodiment, Y is $-\text{C}(\text{O})-\text{CH}_2-$.
- 5 In one embodiment, Y is $-\text{C}(\text{O})-\text{CH}_2-\text{NH}-\text{C}(\text{O})-\text{CH}_2-$.
- In one embodiment, Y is $-\text{C}(\text{O})-\text{CH}_2-\text{NH}-\text{C}(\text{O})-\text{CH}_2-\text{NH}-\text{S}(\text{O})_2-\text{CH}_2-$.
- In one embodiment, Y is $-\text{C}(\text{O})-\text{CH}_2-\text{NH}-\text{C}(\text{O})-\text{CH}_2-\text{NH}-$.
- In one embodiment, Y is $-\text{C}(\text{O})-\text{CH}_2-\text{NH}-\text{C}(\text{O})-\text{CH}_2-\text{NH}-\text{S}(\text{O})_2-\text{CH}_2-$.
- In one embodiment, Z is $-\text{CH}_2\text{C}(\text{O})\text{OH}$.
- 10 In one embodiment, W^1 is attached to one of $\text{X}^{1\text{A}}$, $\text{X}^{1\text{B}}$, $\text{X}^{1\text{C}}$, $\text{X}^{1\text{D}}$, $\text{X}^{1\text{E}}$, $\text{X}^{1\text{F}}$ or $\text{X}^{1\text{G}}$.
- In one embodiment, the ring atom of $\text{X}^{1\text{A}}$, $\text{X}^{1\text{B}}$, $\text{X}^{1\text{C}}$, $\text{X}^{1\text{D}}$, $\text{X}^{1\text{E}}$, $\text{X}^{1\text{F}}$ and $\text{X}^{1\text{G}}$ to which W^1 is attached is C.
- In one embodiment, W^1 is attached to $\text{X}^{1\text{G}}$ and $\text{X}^{1\text{G}}$ is C.
- 15 In one embodiment, each of $\text{X}^{1\text{A}}$, $\text{X}^{1\text{B}}$, $\text{X}^{1\text{C}}$ and $\text{X}^{1\text{D}}$ is C or CH.
- In one embodiment, one of $\text{X}^{1\text{A}}$, $\text{X}^{1\text{B}}$, $\text{X}^{1\text{C}}$ and $\text{X}^{1\text{D}}$ is N.
- In one embodiment, two of $\text{X}^{1\text{A}}$, $\text{X}^{1\text{B}}$, $\text{X}^{1\text{C}}$, and $\text{X}^{1\text{D}}$ is N.
- In one embodiment, one of $\text{X}^{1\text{E}}$, $\text{X}^{1\text{F}}$ and $\text{X}^{1\text{G}}$ is N.
- In one embodiment, $\text{X}^{1\text{F}}$ is N.
- 20 In one embodiment, $\text{X}^{1\text{H}}$ is O.
- In one embodiment, $\text{X}^{1\text{H}}$ is S.
- In one embodiment, W^1 is attached in the para position.
- In one embodiment, W^1 is $-(\text{CR}^{\text{a}}\text{R}^{\text{b}})_{\text{i}1}-\text{L}^1-(\text{CR}^{\text{a}}\text{R}^{\text{b}})_{\text{j}1}-\text{R}^{60}$.
- In one embodiment, W^1 is $-\text{NH}-\text{C}(\text{O})-(\text{CH}_2)_n-\text{R}^{60}$.
- 25 In one embodiment, W^1 is $-\text{NH}-\text{C}(\text{O})-\text{CH}_2-\text{R}^{60}$.
- In one embodiment, W^1 is $-\text{OR}^{10}$, $-\text{NHCO}(\text{CH}_2)_n-\text{R}^{60}$, $-\text{N}(\text{CH}_3)\text{CO}(\text{CH}_2)_n-\text{R}^{60}$ or $-\text{NH}(\text{CH}_2)_n-\text{R}^{60}$.
- In one embodiment, $i1$ is 0, in another embodiment $i1$ is 1, and in a further embodiment $i1$ is 2.
- 30 In one embodiment, $j1$ is 0, in another embodiment $j1$ is 1, and in a further embodiment $j1$ is 2.

In one embodiment, L^1 is $-NR^{10}C(O)-$.

In one embodiment, L^1 is $-NR^{10}-$.

In one embodiment, L^1 is $-N(R^{10})SO_2-$.

In one embodiment, R^{10} is $-H$.

5 In one embodiment, R^{60} is R^{13} .

In one embodiment, R^{60} is $-O-(CH_2)_n-R^{13}$, in another embodiment R^{60} is $-O-R^{13}$, and in a further embodiment R^{60} is $-O-CH_2-R^{13}$.

In one embodiment, R^{13} is aryl optionally substituted with one or more R^{14} , and in another embodiment R^{13} is phenyl.

10 In one embodiment, R^{13} is cycloalkyl or heterocycloalkyl, and in another embodiment, R^{13} is cyclopentyl, cyclohexyl, thiazolyl, tetrahydrofuranyl, oxazolyl, thiophenyl, 1,2,4-oxadiazolyl, furanyl, tetrahydro-2H-pyranyl, or piperidinyl.

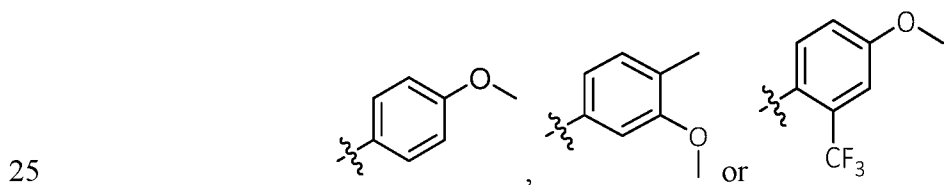
In one embodiment, R^{13} is unsubstituted or substituted at one or more ring position with methyl, ethyl, isopropyl, t-butyl, $-CF_3$, methoxy, ethoxy, hydroxyl, $-OCF_3$, halogen (F, Cl, Br or I), methylthio or $-SO_2CH_3$. In another embodiment, R^{13} is substituted with one or more of methyl, methoxy, F or $-CF_3$.

In one embodiment, R^{13} is cycloalkyl, aryl or heteroaryl, where any ring atom of R^{13} may be optionally substituted with R^{14} .

20 In one embodiment, each R^{14} is independently H, alkyl, halo, alkoxy, perhaloalkyl or perhaloalkoxy. In another embodiment, R^{14} is halo, alkoxy, perhaloalkyl or perhaloalkoxy. In a further embodiment, R^{14} is alkoxy or perhaloalkyl.

In one embodiment, each R^{31} and R^{32} is independently H, alkyl or alkyl substituted with carboxyl. In another embodiment, at least one of R^{31} and R^{32} is H.

In one embodiment, R^{60} is:



In one embodiment, each of R^a and R^b is H. In another embodiment, at least one of R^a and R^b is methyl.

In one embodiment, at least one of R^a and R^b is isopropyl.

In one embodiment, at least one of R^a and R^b is benzyl or hydroxybenzyl.

In one embodiment, at least one pair of R^a and R^b is, taken together, oxo or cycloalkyl.

5 In one embodiment, A is a fully saturated cycloalkyl. In another embodiment, A is a partially saturated cycloalkyl. In a further embodiment, A is a fully unsaturated cycloalkyl. In such embodiment, if there is unsaturation, the conjugation of the pi-electrons in the ring do not give rise to aromaticity. In another embodiment, A is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropenyl,
10 cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

In one embodiment, R^2 is alkyl. In another embodiment, R^2 is methyl, ethyl, isopropyl or t-butyl.

In one embodiment, R^2 is cycloalkyl. In another embodiment, R^2 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropenyl,
15 cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

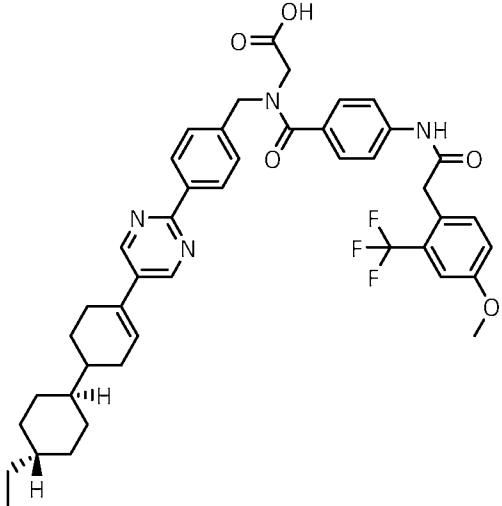
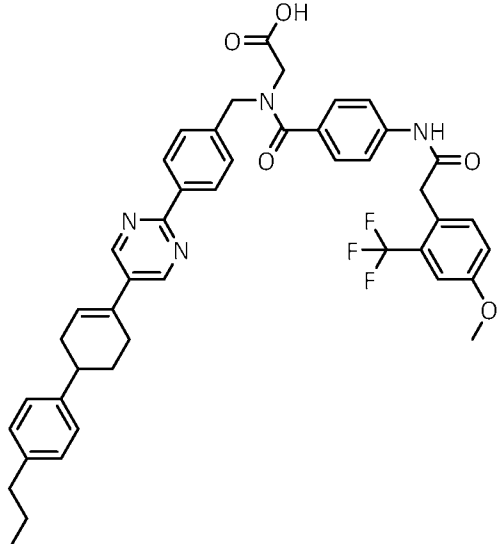
In one embodiment, R^2 is aryl. In another embodiment, R^2 is phenyl.

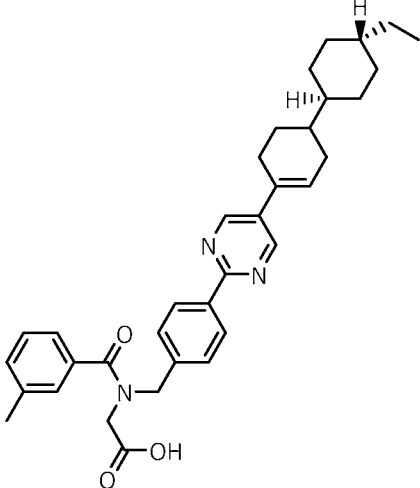
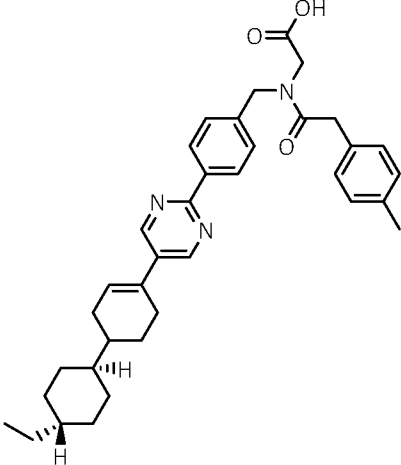
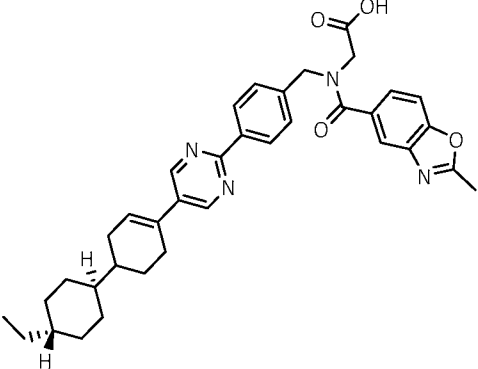
In one embodiment, R^2 is substituted with at least one R^3 .

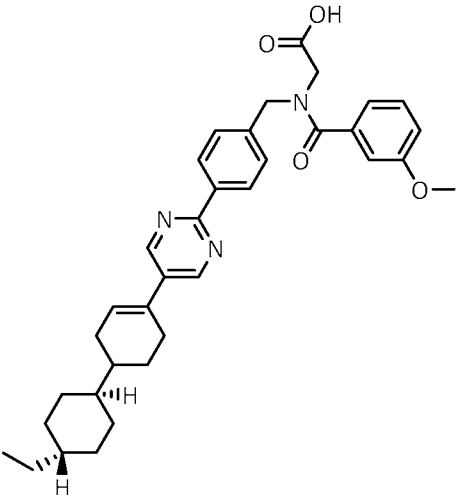
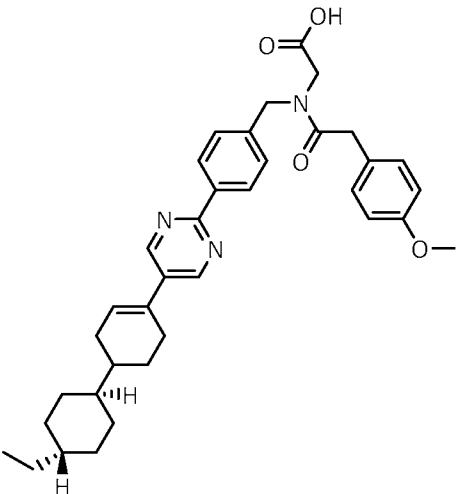
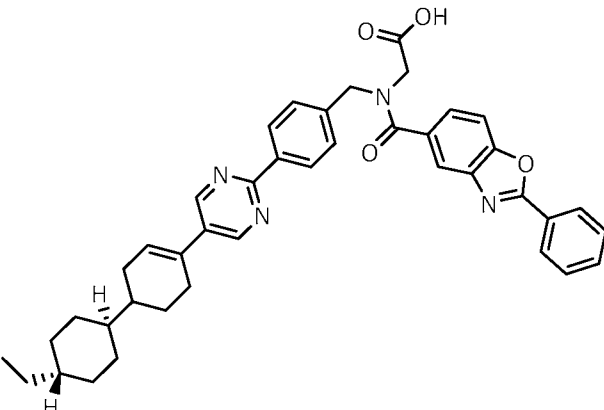
In one embodiment, R^3 is halo, alkyl, alkoxy, perhaloalkyl or perhaloalkoxy. In another embodiment, R^3 is methyl, ethyl, n-propyl, iso-propyl, n-
20 butyl, iso-butyl, tert-butyl, n-pentyl or $-CF_3$.

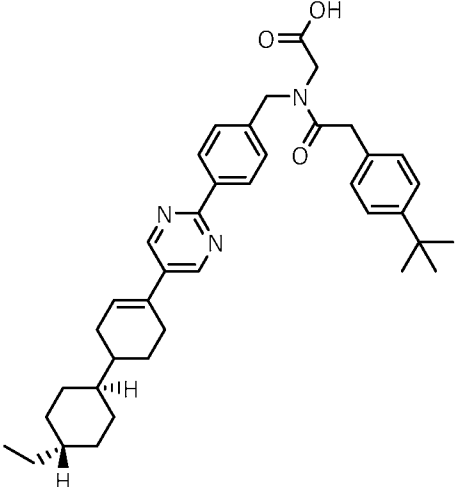
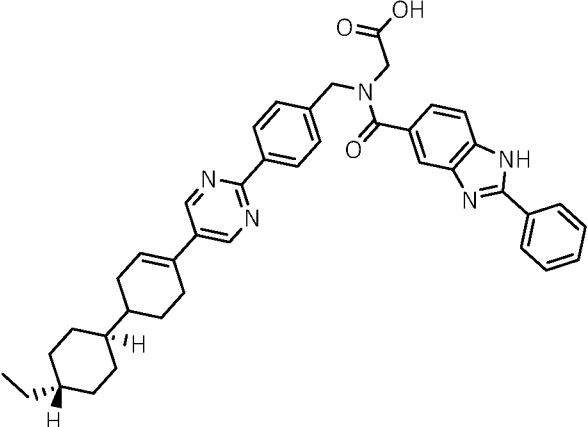
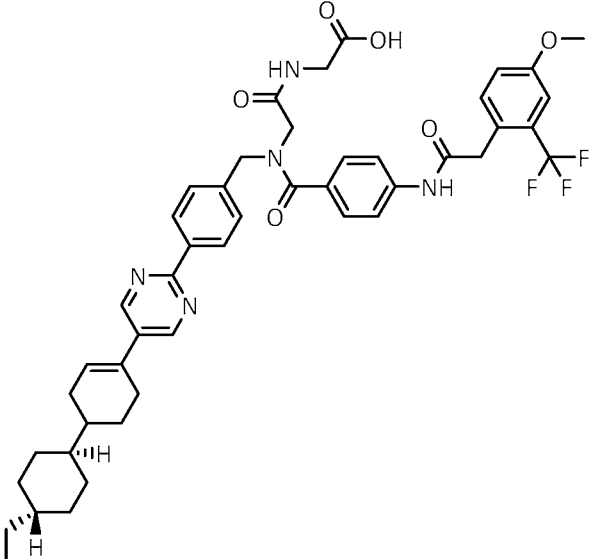
In one embodiment, a compound is provided having the structure any one of compound numbers 1-153 as shown in the following Table 1, or a stereoisomer, hydrate, solvate, isotope or pharmaceutically acceptable salts thereof.

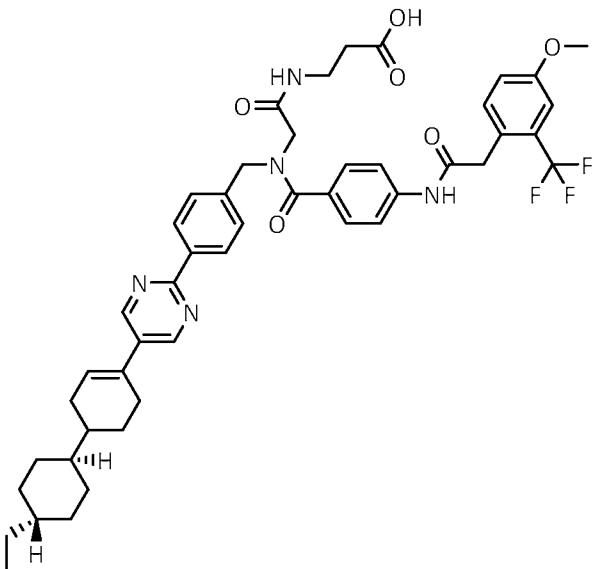
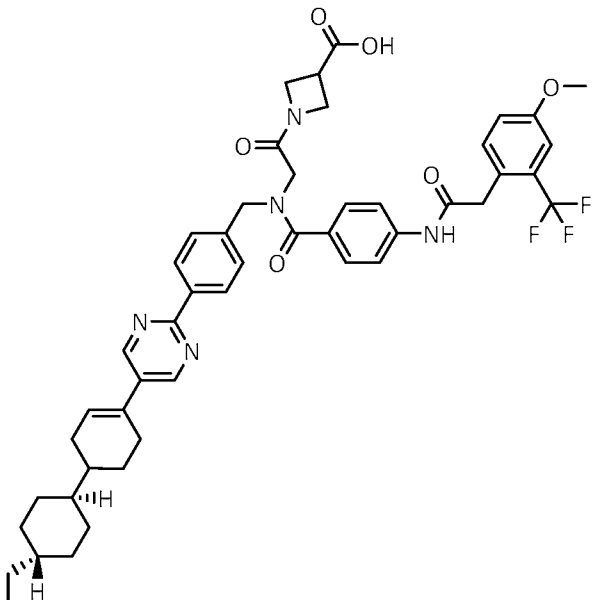
Table 1
Representative Compounds

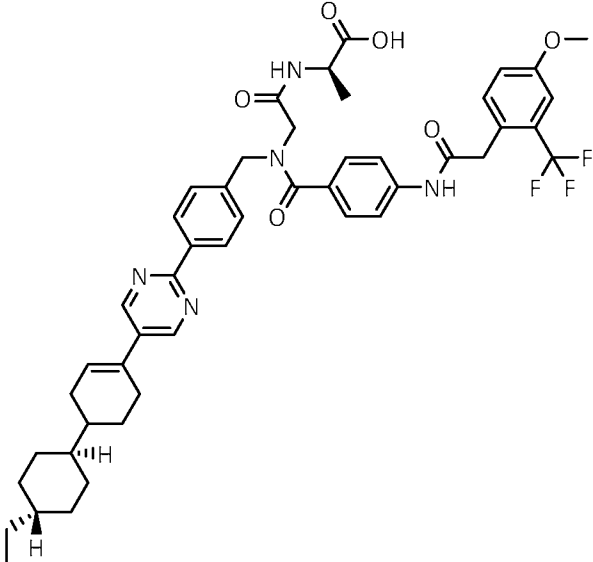
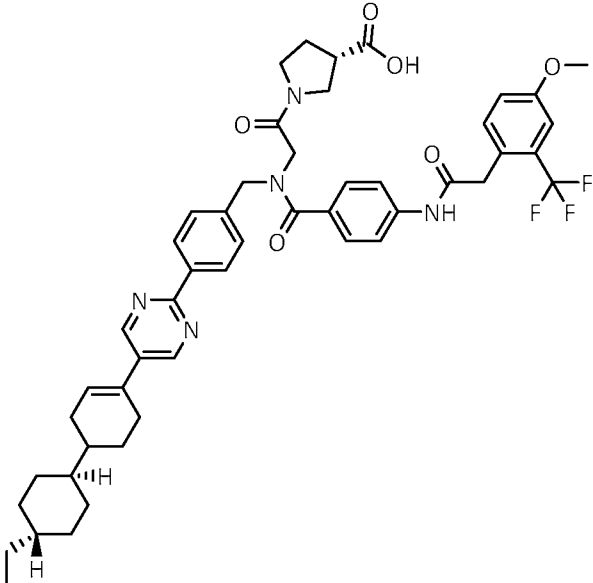
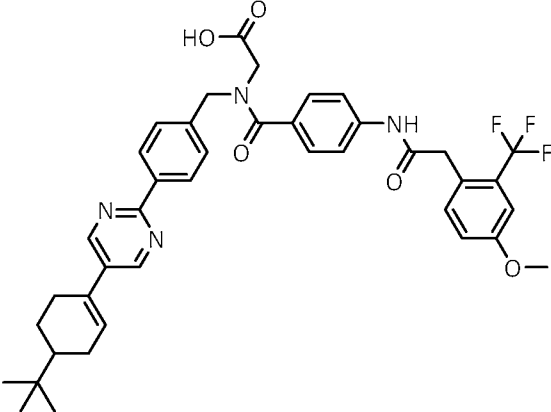
Structure	Cpd. No.
 <p>Chemical structure of Compound 1: A complex molecule featuring a central benzimidazole ring system. One benzimidazole nitrogen is substituted with a 4-(2-iodoethyl)cyclohexyl group. The other benzimidazole nitrogen is substituted with a 4-(2-(2-(2,2,2-trifluoroethyl)acetyl)aminoethyl)phenyl group. The 2-(2-(2,2,2-trifluoroethyl)acetyl)aminoethyl group is further substituted with a 4-methoxyphenyl ring.</p>	1
 <p>Chemical structure of Compound 2: A complex molecule featuring a central benzimidazole ring system. One benzimidazole nitrogen is substituted with a 4-(2-propylphenyl)cyclohexyl group. The other benzimidazole nitrogen is substituted with a 4-(2-(2-(2,2,2-trifluoroethyl)acetyl)aminoethyl)phenyl group. The 2-(2-(2,2,2-trifluoroethyl)acetyl)aminoethyl group is further substituted with a 4-methoxyphenyl ring.</p>	2

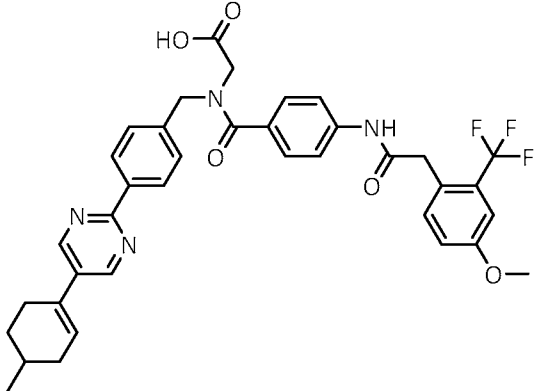
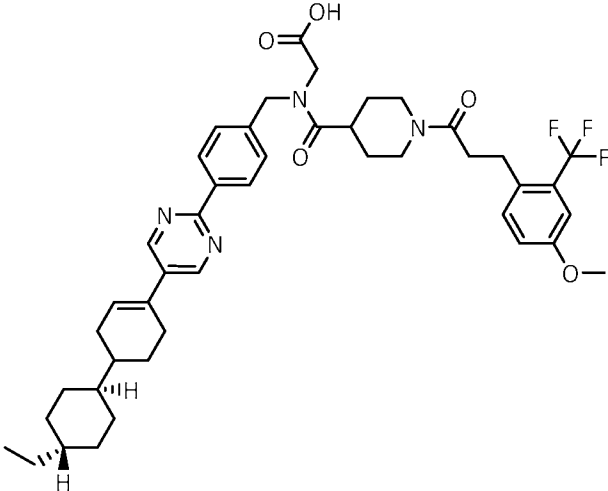
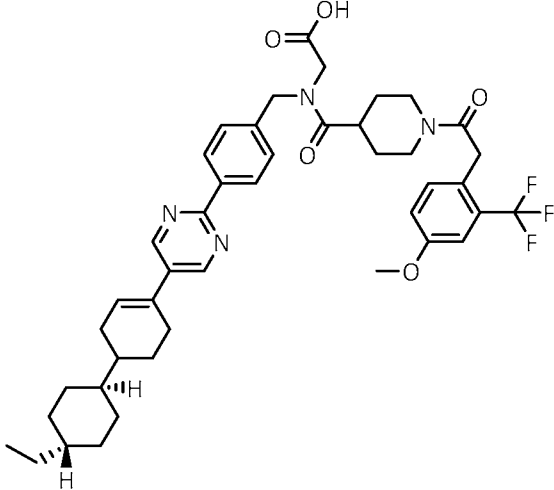
Structure	Cpd. No.
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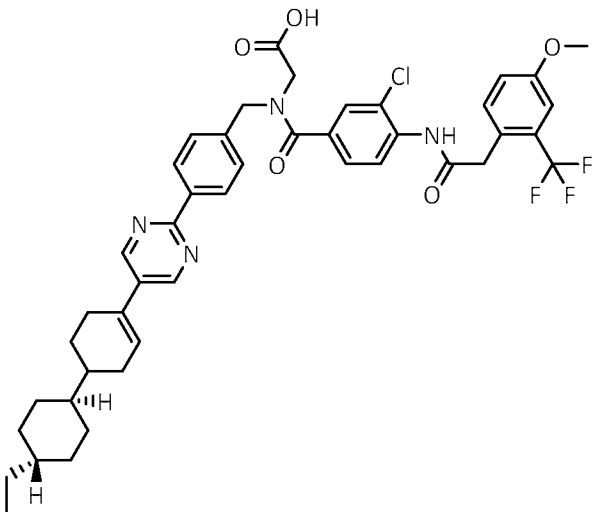
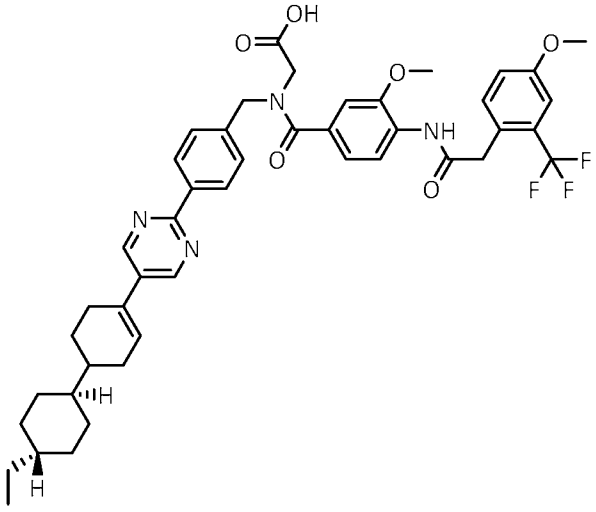
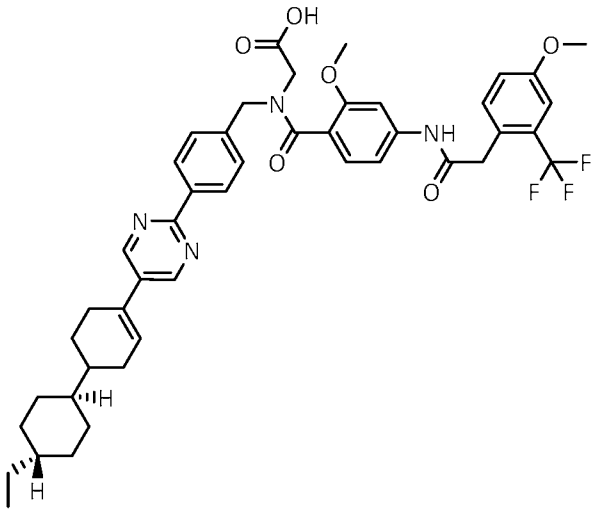
Structure	Cpd. No.
 <p>Chemical structure of compound 6: A bicyclic system consisting of two fused six-membered rings. The left ring is a cyclohexane with a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring is a cyclohexane with a hydrogen atom on a wedged bond. This bicyclic system is connected to a pyrimidine ring, which is further connected to a benzene ring. This benzene ring is linked via a methylene group to a nitrogen atom. The nitrogen atom is part of a carbamate group, with a hydroxyl group attached to the carbonyl carbon and a methylene group attached to the nitrogen. This methylene group is connected to another benzene ring, which has a methoxy group at the para position.</p>	6
 <p>Chemical structure of compound 7: Similar to compound 6, but the carbamate group is attached to a benzene ring with a methoxy group at the para position, and the nitrogen atom is also attached to a methylene group which is connected to another benzene ring with a methoxy group at the para position.</p>	7
 <p>Chemical structure of compound 8: Similar to compound 6, but the carbamate group is attached to a benzene ring with a methoxy group at the para position, and the nitrogen atom is also attached to a methylene group which is connected to another benzene ring with a methoxy group at the para position. The nitrogen atom is also attached to a methylene group which is connected to another benzene ring with a methoxy group at the para position.</p>	8

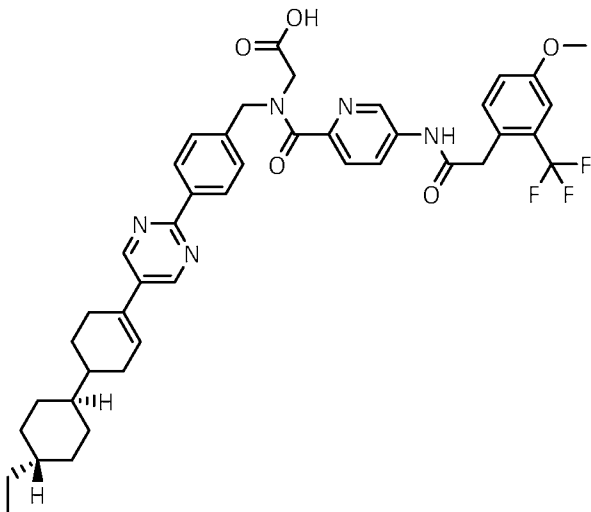
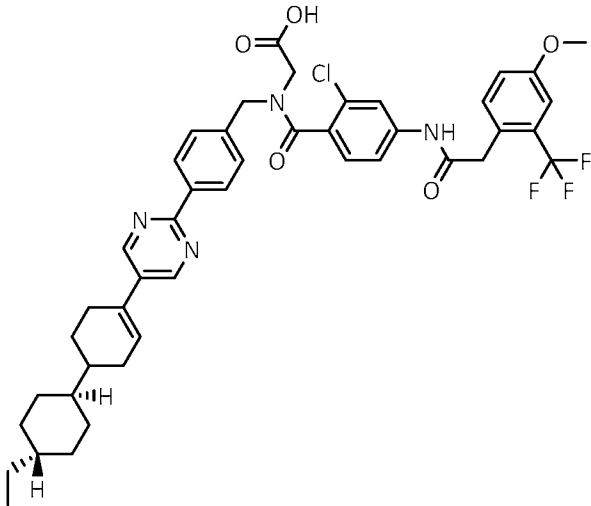
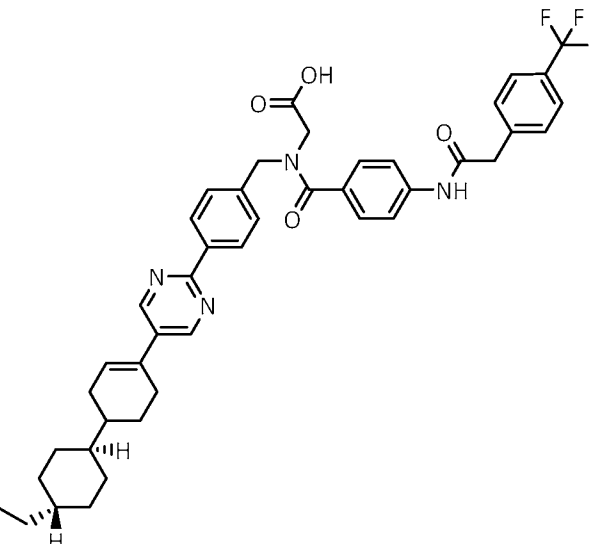
Structure	Cpd. No.
 <p>Chemical structure of compound 9: A bicyclic core consisting of two fused cyclohexane rings. The left ring has a methyl group on a wedge and a hydrogen on a dash. The right ring has a hydrogen on a dash. A phenyl ring is attached to the right ring, which is further connected to a pyrimidine ring. The pyrimidine ring is linked to a benzene ring, which is connected to a nitrogen atom. This nitrogen atom is part of a chain: -N(CH2)2-C(=O)-CH2-C(=O)-O-CH2-COOH. The nitrogen atom is also bonded to a benzene ring with a tert-butyl group at the para position.</p>	9
 <p>Chemical structure of compound 10: A bicyclic core consisting of two fused cyclohexane rings. The left ring has a methyl group on a wedge and a hydrogen on a dash. The right ring has a hydrogen on a dash. A phenyl ring is attached to the right ring, which is further connected to a pyrimidine ring. The pyrimidine ring is linked to a benzene ring, which is connected to a nitrogen atom. This nitrogen atom is part of a chain: -N(CH2)2-C(=O)-CH2-C(=O)-O-CH2-COOH. The nitrogen atom is also bonded to a benzene ring with an indazole ring at the para position.</p>	10
 <p>Chemical structure of compound 11: A bicyclic core consisting of two fused cyclohexane rings. The left ring has a methyl group on a wedge and a hydrogen on a dash. The right ring has a hydrogen on a dash. A phenyl ring is attached to the right ring, which is further connected to a pyrimidine ring. The pyrimidine ring is linked to a benzene ring, which is connected to a nitrogen atom. This nitrogen atom is part of a chain: -N(CH2)2-C(=O)-NH-CH2-COOH. The nitrogen atom is also bonded to a benzene ring with a trifluoromethyl group and a methoxy group at the para position.</p>	11

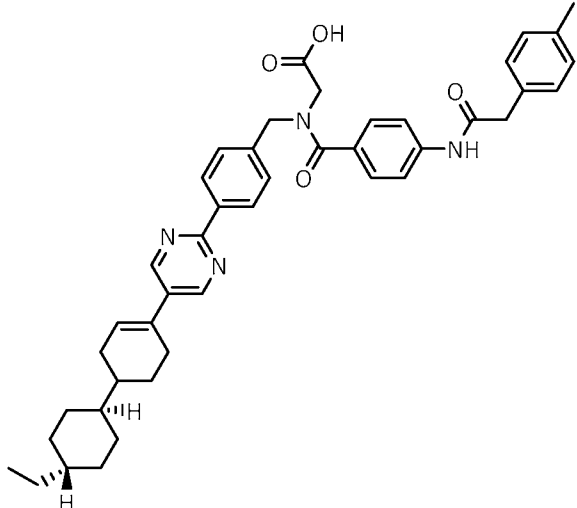
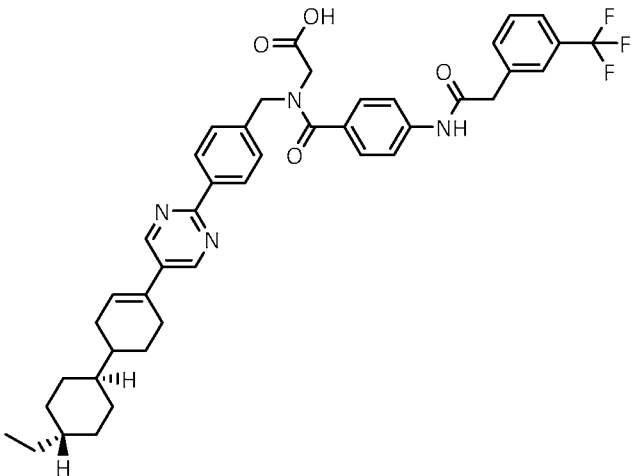
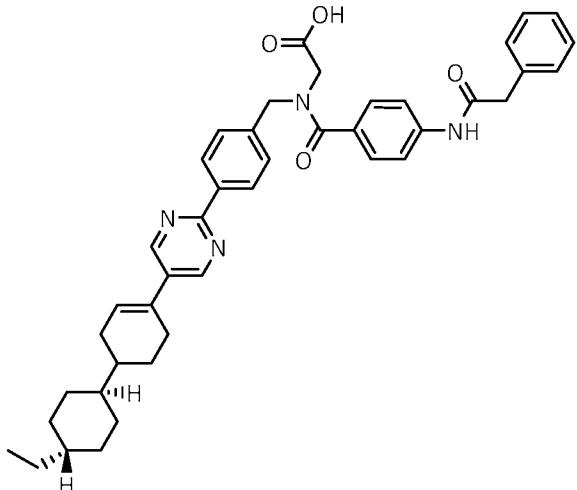
Structure	Cpd. No.
 <p>Chemical structure of compound 12. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. One of the cyclohexane rings is substituted with a pyrimidine ring. The pyrimidine ring is further substituted with a benzene ring. This benzene ring is connected via a methylene group to a nitrogen atom, which is part of a chain containing a carbonyl group and a secondary amide group. The secondary amide group is further substituted with a propionic acid chain. Another branch from the nitrogen atom is a benzamide group, which is substituted with a 4-methoxy-2,2,2-trifluoroethyl group.</p>	12
 <p>Chemical structure of compound 13. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. One of the cyclohexane rings is substituted with a pyrimidine ring. The pyrimidine ring is further substituted with a benzene ring. This benzene ring is connected via a methylene group to a nitrogen atom, which is part of a chain containing a carbonyl group and a secondary amide group. The secondary amide group is further substituted with a propionic acid chain. Another branch from the nitrogen atom is a benzamide group, which is substituted with a 4-methoxy-2,2,2-trifluoroethyl group.</p>	13

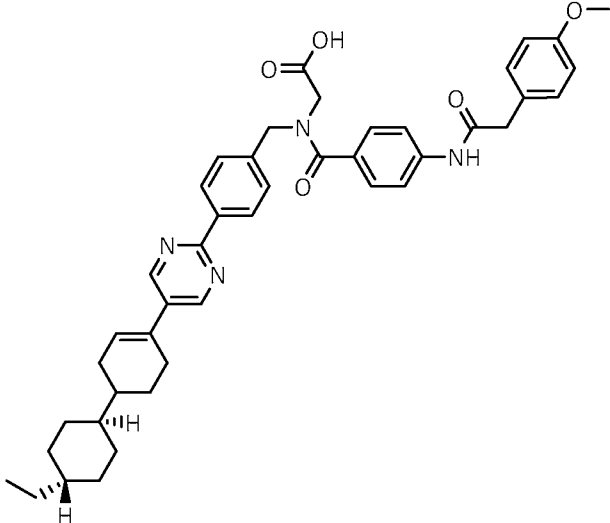
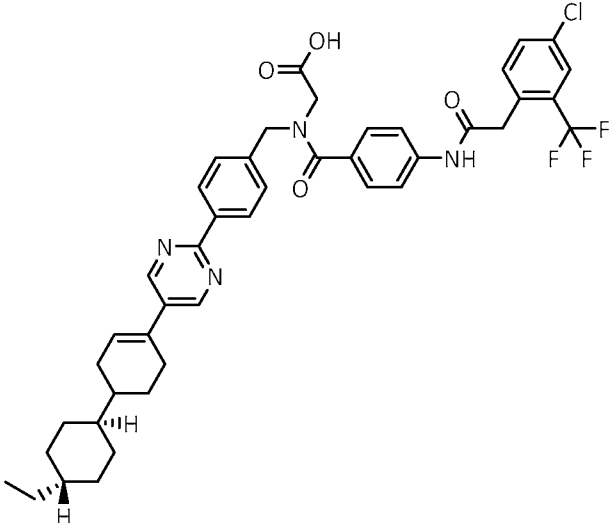
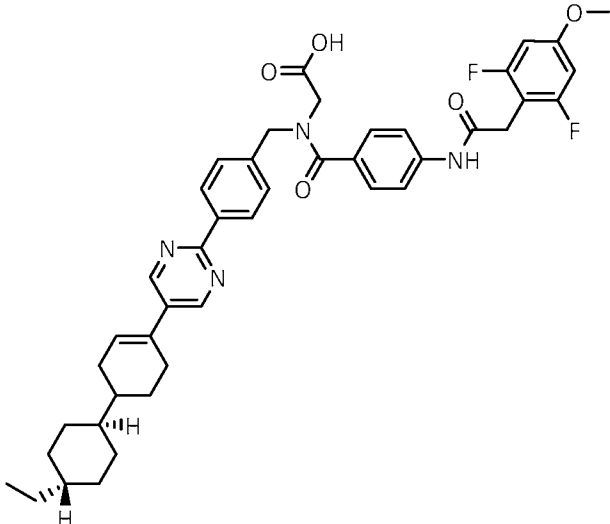
Structure	Cpd. No.
 <p>Chemical structure of compound 14: A complex molecule featuring a bicyclic core consisting of two cyclohexane rings connected at the 1 and 4 positions. The core is substituted with a pyrimidine ring at the 2-position. This pyrimidine ring is further substituted with a benzene ring at the 5-position. The benzene ring is connected via a methylene group to a nitrogen atom, which is part of a secondary amide linkage. This nitrogen is also bonded to a propionic acid chain (CH2-CH2-COOH) and a para-substituted benzene ring. The para-substituted benzene ring is connected via an amide linkage to another benzene ring, which is substituted with a methoxy group and a trifluoromethyl group.</p>	14
 <p>Chemical structure of compound 15: Similar to compound 14, but the propionic acid chain is replaced by a pyrrolidine ring substituted with a carboxylic acid group.</p>	15
 <p>Chemical structure of compound 16: Similar to compound 14, but the bicyclic core is substituted with a tert-butyl group instead of a hydrogen atom at the 1-position of the cyclohexane ring.</p>	16

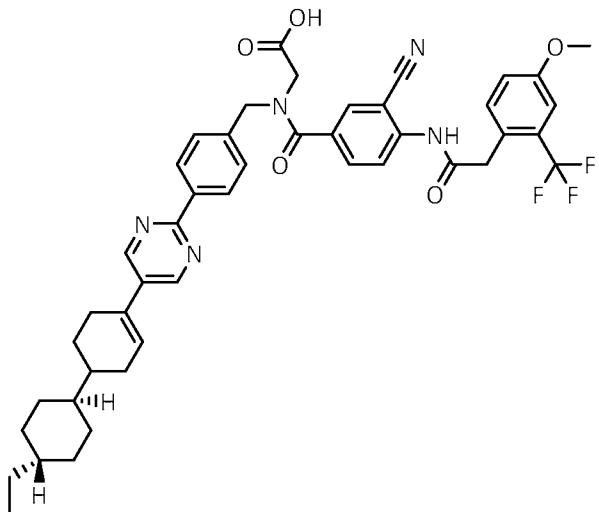
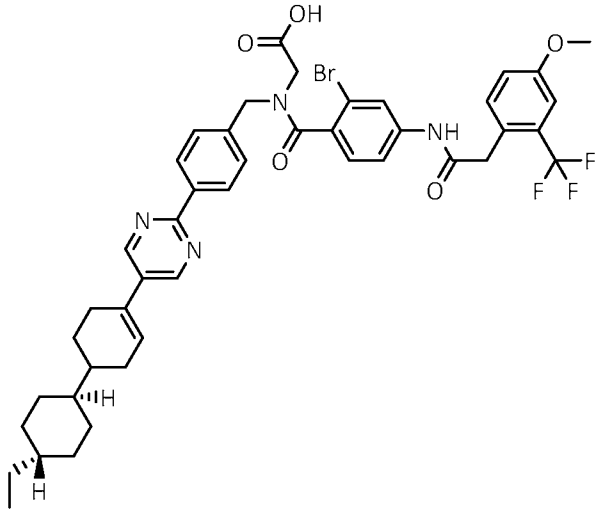
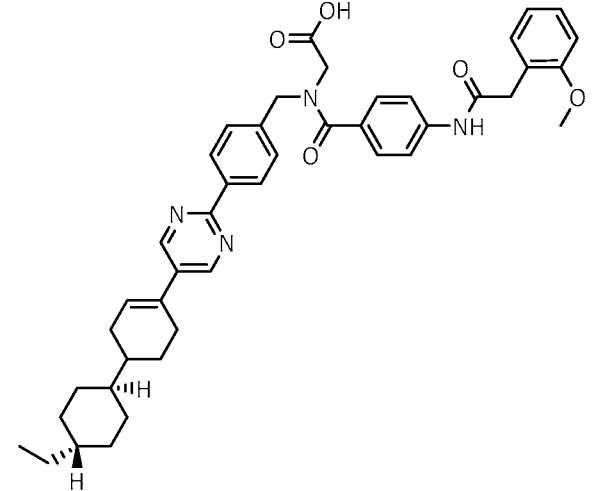
Structure	Cpd. No.
 <p>Chemical structure of compound 17: A central benzamide core is substituted with a 2-(4-methylphenyl)imidazo[1,2-a]pyridin-5-ylmethyl group at the 2-position, a propionic acid group at the 1-position, and a 2-(4-methoxyphenyl)propanoate group at the 4-position.</p>	17
 <p>Chemical structure of compound 18: A central piperazine core is substituted with a propionic acid group at the 2-position, a 2-(4-methoxyphenyl)propanoate group at the 4-position, and a 2-(4-methylphenyl)imidazo[1,2-a]pyridin-5-ylmethyl group at the 1-position. The piperazine ring is also substituted with a 4-methylpiperidin-2-yl group at the 3-position.</p>	18
 <p>Chemical structure of compound 19: A central piperazine core is substituted with a propionic acid group at the 2-position, a 2-(4-methoxyphenyl)propanoate group at the 4-position, and a 2-(4-methylphenyl)imidazo[1,2-a]pyridin-5-ylmethyl group at the 1-position. The piperazine ring is also substituted with a 4-methylpiperidin-2-yl group at the 3-position.</p>	19

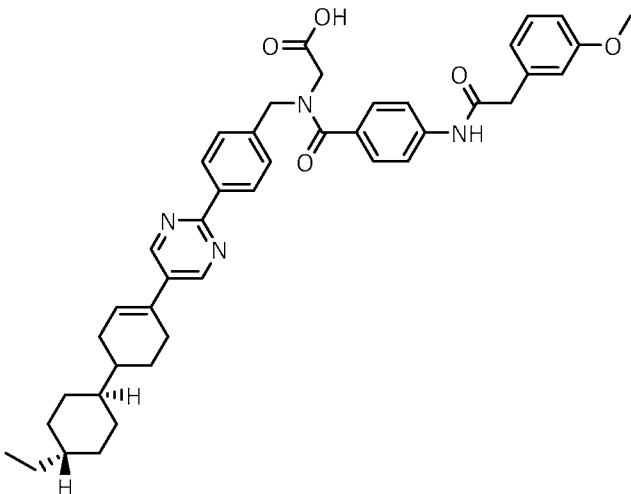
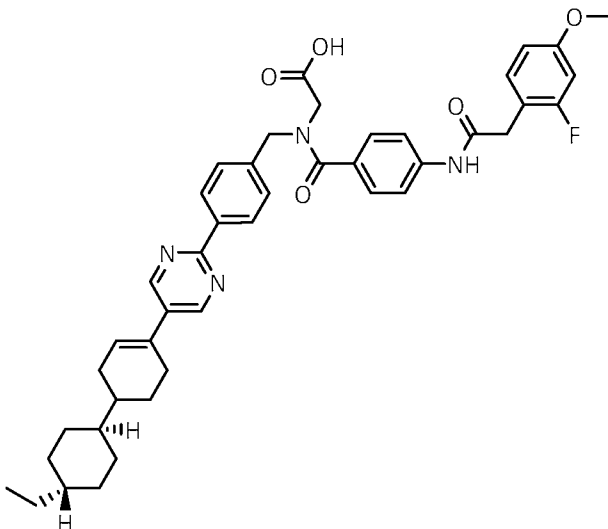
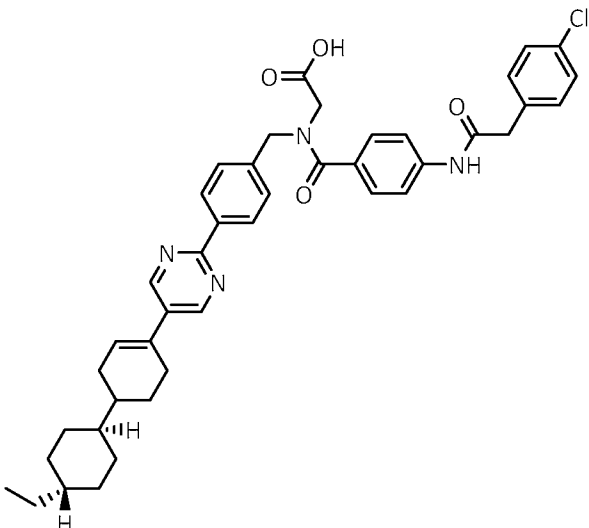
Structure	Cpd. No.
 <p>Chemical structure of compound 20: A bicyclic system consisting of two fused cyclohexane rings. The front ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The back ring is substituted with a pyrimidine ring at the para position. The pyrimidine ring is further substituted with a benzene ring at the 2-position. This benzene ring is substituted with a methylene group at the para position, which is connected to a nitrogen atom. The nitrogen atom is part of a chain: -N(CH₂)-C(=O)-O-CH₂-COOH. The nitrogen atom is also bonded to a benzene ring substituted with a chlorine atom at the meta position and an amide group (-NH-) at the para position. The amide group is connected to a methylene group, which is further connected to a benzene ring substituted with a methoxy group (-OCH₃) at the para position and a trifluoromethyl group (-CF₃) at the meta position.</p>	20
 <p>Chemical structure of compound 21: A bicyclic system consisting of two fused cyclohexane rings. The front ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The back ring is substituted with a pyrimidine ring at the para position. The pyrimidine ring is further substituted with a benzene ring at the 2-position. This benzene ring is substituted with a methylene group at the para position, which is connected to a nitrogen atom. The nitrogen atom is part of a chain: -N(CH₂)-C(=O)-O-CH₂-COOH. The nitrogen atom is also bonded to a benzene ring substituted with a methoxy group (-OCH₃) at the meta position and an amide group (-NH-) at the para position. The amide group is connected to a methylene group, which is further connected to a benzene ring substituted with a methoxy group (-OCH₃) at the para position and a trifluoromethyl group (-CF₃) at the meta position.</p>	21
 <p>Chemical structure of compound 22: A bicyclic system consisting of two fused cyclohexane rings. The front ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The back ring is substituted with a pyrimidine ring at the para position. The pyrimidine ring is further substituted with a benzene ring at the 2-position. This benzene ring is substituted with a methylene group at the para position, which is connected to a nitrogen atom. The nitrogen atom is part of a chain: -N(CH₂)-C(=O)-O-CH₂-COOH. The nitrogen atom is also bonded to a benzene ring substituted with a methoxy group (-OCH₃) at the meta position and an amide group (-NH-) at the para position. The amide group is connected to a methylene group, which is further connected to a benzene ring substituted with a methoxy group (-OCH₃) at the para position and a trifluoromethyl group (-CF₃) at the meta position.</p>	22

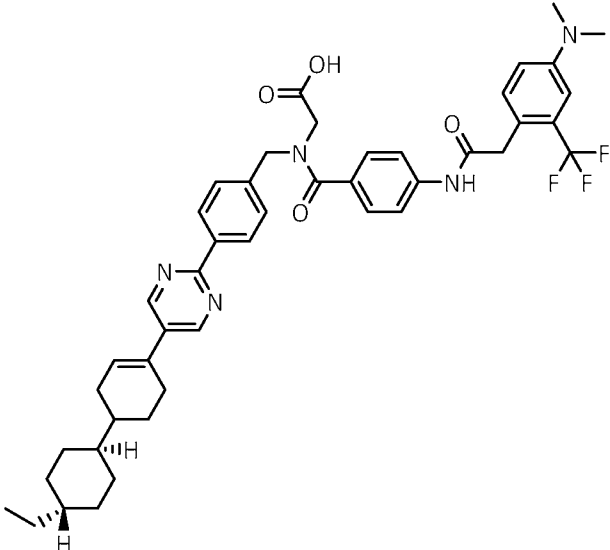
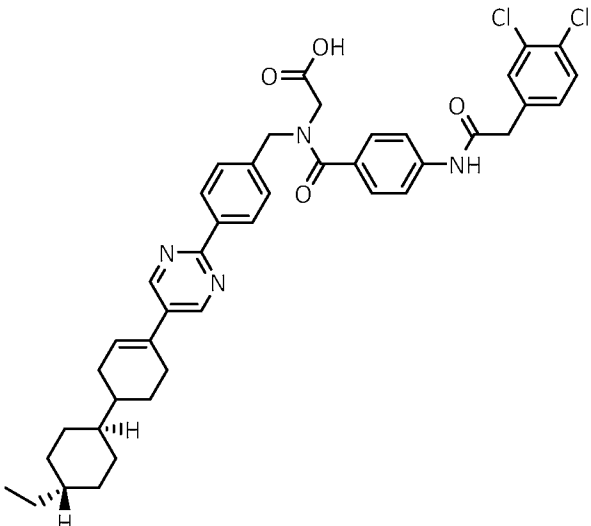
Structure	Cpd. No.
 <p>Chemical structure of compound 23: A bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring has a hydrogen atom on a dashed bond. A pyrimidine ring is attached to the right ring. This pyrimidine ring is further substituted with a benzene ring, which is connected via a methylene group to a nitrogen atom. This nitrogen atom is part of a chain: -N(CH2)-C(=O)-CH2-COOH. The nitrogen atom is also bonded to a pyridine ring, which is connected via an amide group (-NH-) to a benzene ring. This benzene ring has a methoxy group (-OCH3) at the para position and a trifluoromethyl group (-CF3) at the ortho position.</p>	23
 <p>Chemical structure of compound 24: Similar to compound 23, but the pyridine ring is substituted with a chlorine atom at the 3-position.</p>	24
 <p>Chemical structure of compound 25: Similar to compound 23, but the pyridine ring is substituted with a trifluoromethyl group (-CF3) at the 3-position.</p>	25

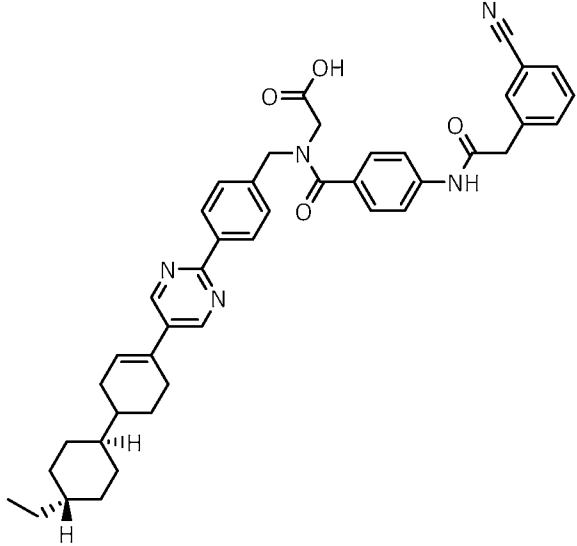
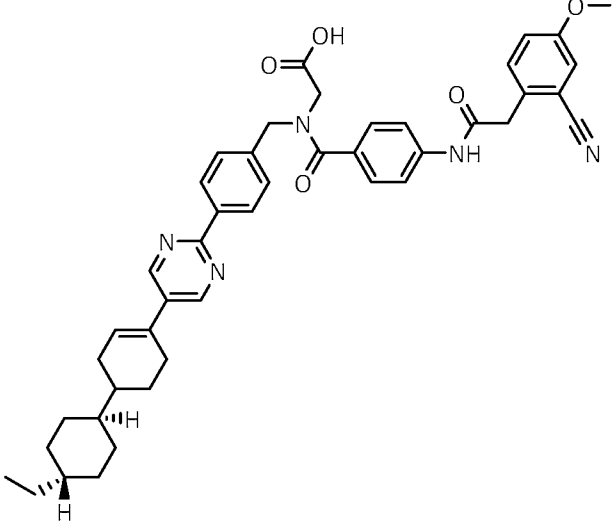
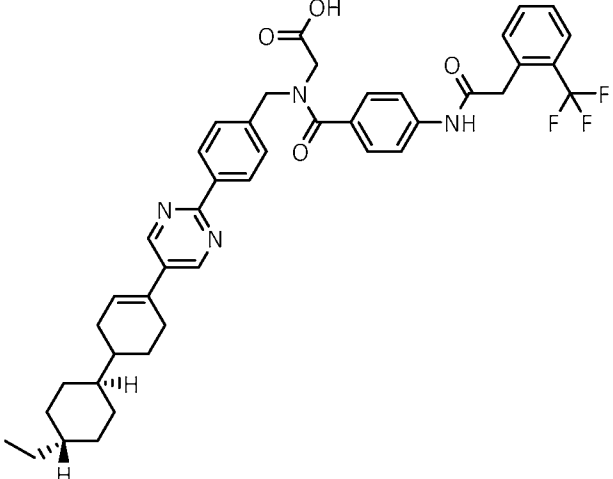
Structure	Cpd. No.
 <p>Chemical structure of compound 26: A bicyclic core consisting of two fused cyclohexane rings. The left ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring has a hydrogen atom on a dashed bond. This core is connected via a cyclohexane ring to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is linked to a methylene group. This methylene group is attached to a nitrogen atom that is also bonded to a hydroxymethyl group (-CH₂OH) and a carbonyl group (-C(=O)-). The carbonyl group is connected to another benzene ring, which is further connected to an amide group (-NH-). The amide group is attached to a methylene group, which is finally connected to a benzene ring with a methyl group at the para position.</p>	26
 <p>Chemical structure of compound 27: Similar to compound 26, but the terminal benzene ring is substituted with a trifluoromethyl group (-CF₃) at the para position.</p>	27
 <p>Chemical structure of compound 28: Similar to compound 26, but the terminal benzene ring is unsubstituted (phenyl group).</p>	28

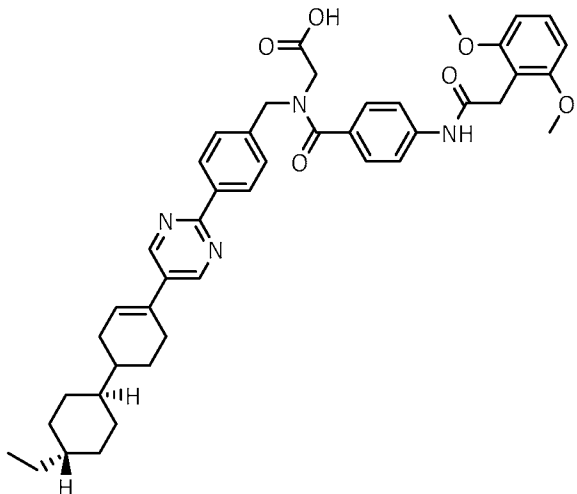
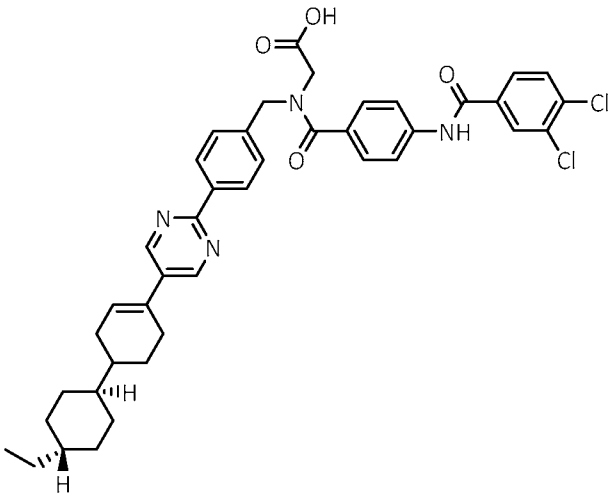
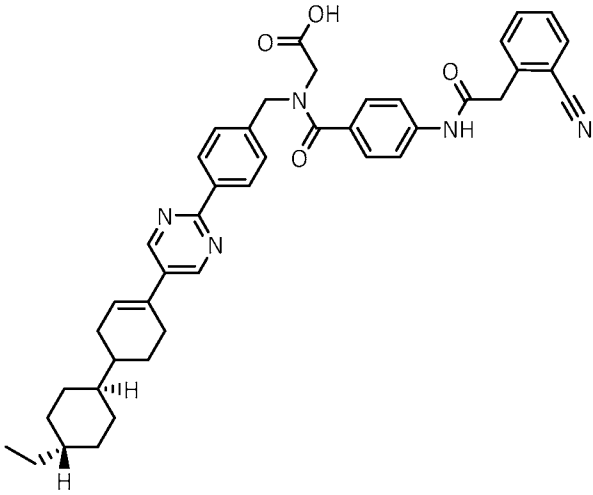
Structure	Cpd. No.
 <p>Chemical structure of compound 29: A bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group at the bottom-left position and a hydrogen atom at the bottom-right position, both shown with wedged bonds. The right ring has a hydrogen atom at the top-right position, also shown with a wedged bond. This bicyclic core is connected via a methylene group to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring. This benzene ring is linked to a nitrogen atom, which is part of a chain containing a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). The carbonyl group is connected to another benzene ring, which is in turn connected to an amide group (-NH-). This amide group is linked to a methylene group, which is connected to a benzene ring with a methoxy group (-OCH₃) at the para position.</p>	29
 <p>Chemical structure of compound 30: Similar to compound 29, but the terminal benzene ring has a chlorine atom (-Cl) at the para position and a trifluoromethyl group (-CF₃) at the meta position relative to the amide linkage.</p>	30
 <p>Chemical structure of compound 31: Similar to compound 29, but the terminal benzene ring has a methoxy group (-OCH₃) at the para position and two fluorine atoms (-F) at the meta positions relative to the amide linkage.</p>	31

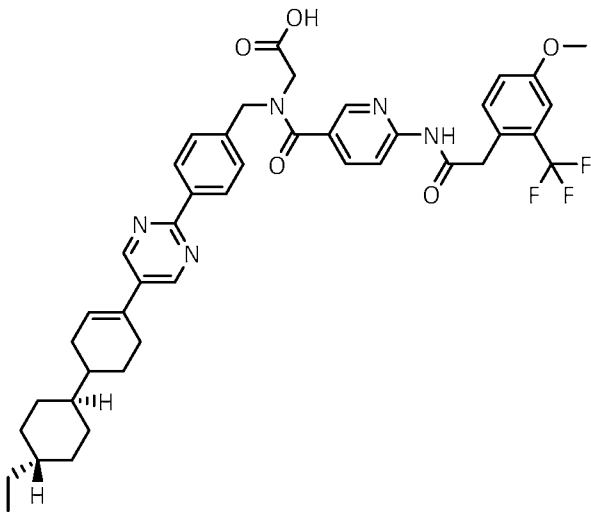
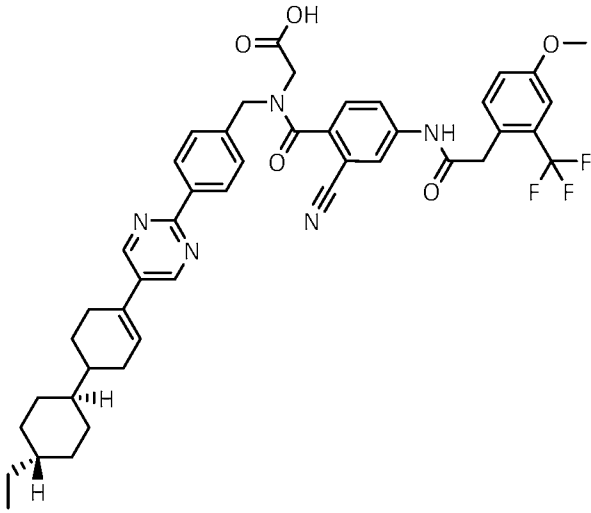
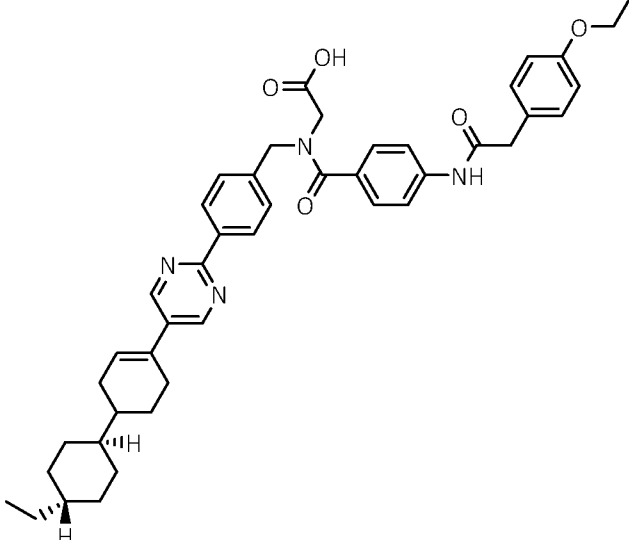
Structure	Cpd. No.
 <p>Chemical structure of compound 32: A bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring has a hydrogen atom on a dashed bond. A piperazine ring is attached to the right ring. The piperazine ring is further substituted with a benzimidazole ring, which is connected to a benzene ring. This benzene ring is part of a chain that includes a carbonyl group, a nitrogen atom, and a carboxylic acid group. The chain continues to another benzene ring with a cyano group and an amide group. The amide group is connected to a benzene ring with a methoxy group and a trifluoromethyl group.</p>	32
 <p>Chemical structure of compound 33: Similar to compound 32, but the benzene ring in the chain has a bromine atom instead of a cyano group.</p>	33
 <p>Chemical structure of compound 34: Similar to compound 32, but the bicyclic core has a methyl group on a wedged bond and a hydrogen atom on a dashed bond. The chain is shorter, ending in a benzimidazole ring connected to a benzene ring with a methoxy group.</p>	34

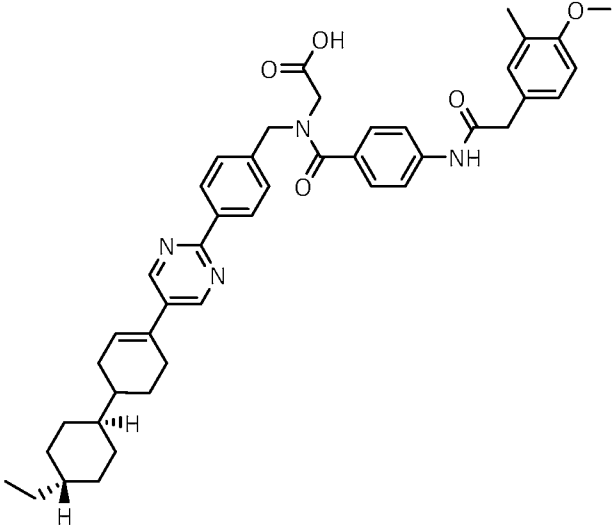
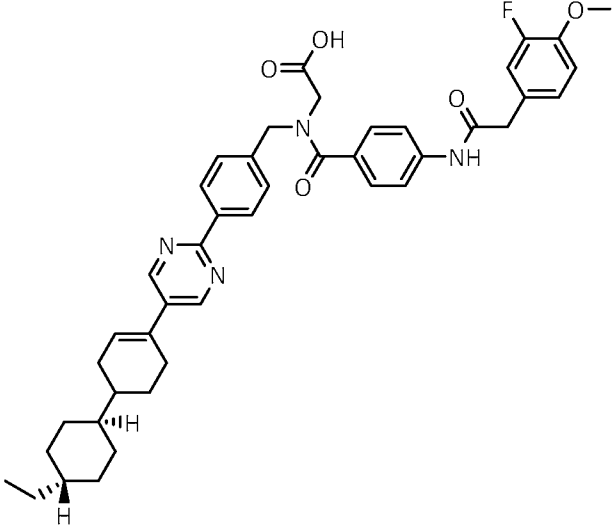
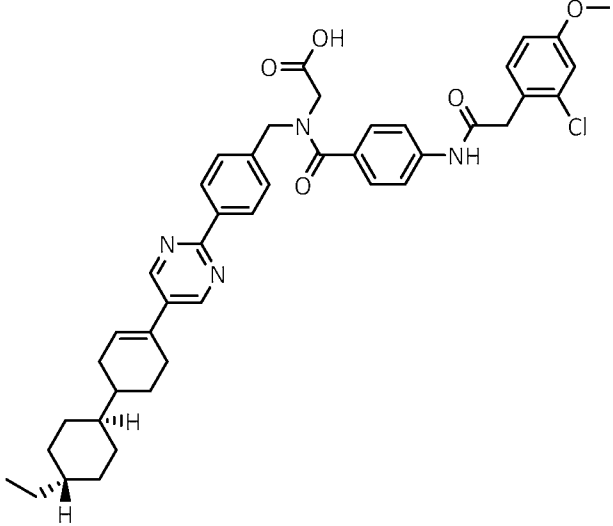
Structure	Cpd. No.
 <p>Chemical structure of compound 35: A bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring has a hydrogen atom on a dashed bond. This core is connected via a cyclohexane ring to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is linked to a nitrogen atom. This nitrogen atom is part of a chain containing a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). The carbonyl group is connected to another benzene ring, which is linked to an amide group (-NH-). The amide group is connected to a methylene group, which is further connected to a benzene ring with a methoxy group (-OCH₃) at the para position.</p>	35
 <p>Chemical structure of compound 36: Similar to compound 35, but the benzene ring at the end of the chain has a fluorine atom (-F) at the meta position and a methoxy group (-OCH₃) at the para position.</p>	36
 <p>Chemical structure of compound 37: Similar to compound 35, but the benzene ring at the end of the chain has a chlorine atom (-Cl) at the para position.</p>	37

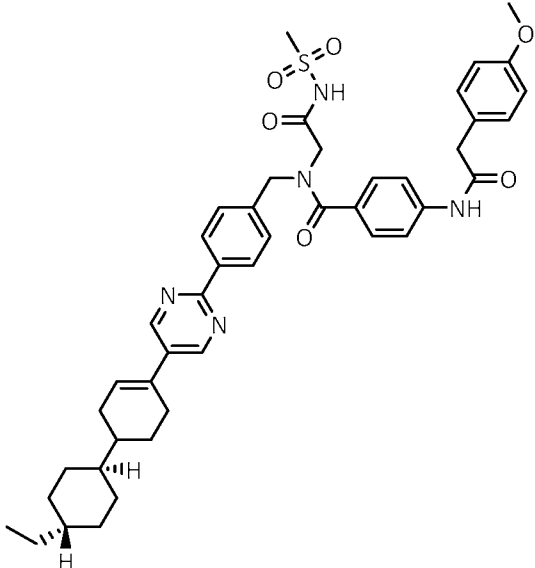
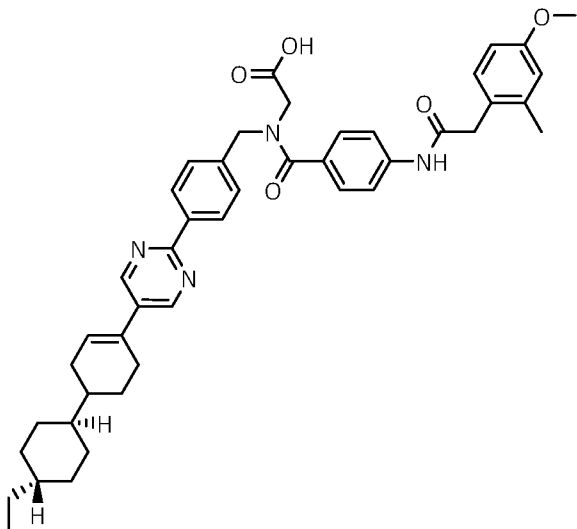
Structure	Cpd. No.
 <p>Chemical structure of compound 38. It features a bicyclic core consisting of two fused cyclohexane rings. The left ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring has a hydrogen atom on a wedged bond. This core is connected via a cyclohexane ring to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is linked to a nitrogen atom. This nitrogen atom is part of a chain: -N(CH₂)₂-C(=O)-O-CH₂-C(=O)-NH-. The nitrogen of this amide group is attached to a para-substituted benzene ring. This benzene ring is connected to another nitrogen atom, which is part of a chain: -N(CH₂)₂-C(=O)-NH-. The nitrogen of this amide group is attached to a para-substituted benzene ring. This benzene ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The other two substituents on this ring are fluorine atoms (F) and a dimethylamino group (-N(CH₃)₂).</p>	38
 <p>Chemical structure of compound 39. It features a bicyclic core consisting of two fused cyclohexane rings. The left ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring has a hydrogen atom on a wedged bond. This core is connected via a cyclohexane ring to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is linked to a nitrogen atom. This nitrogen atom is part of a chain: -N(CH₂)₂-C(=O)-O-CH₂-C(=O)-NH-. The nitrogen of this amide group is attached to a para-substituted benzene ring. This benzene ring is connected to another nitrogen atom, which is part of a chain: -N(CH₂)₂-C(=O)-NH-. The nitrogen of this amide group is attached to a para-substituted benzene ring. This benzene ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The other two substituents on this ring are chlorine atoms (Cl).</p>	39

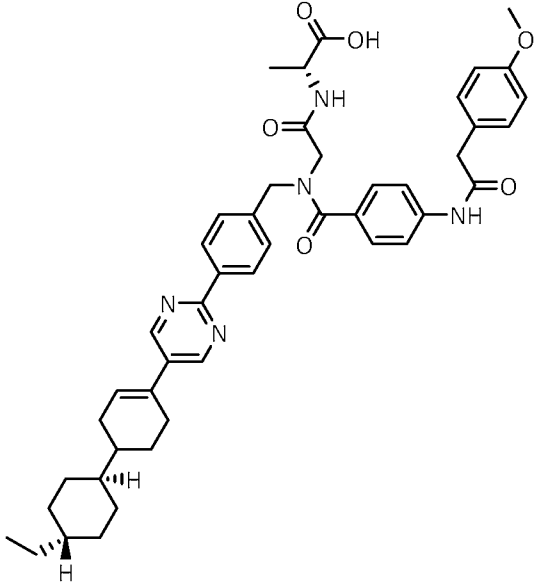
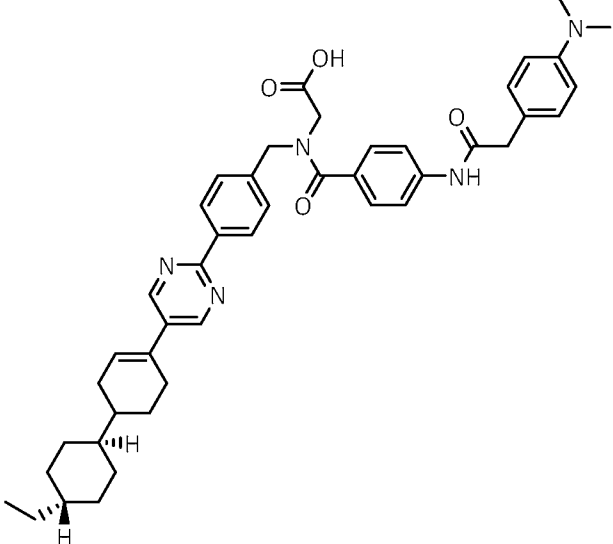
Structure	Cpd. No.
 <p>Chemical structure of compound 40: A bicyclic core consisting of two fused cyclohexane rings. The left ring has a methyl group and a hydrogen atom at the 1-position, both shown with wedged bonds. The right ring has a hydrogen atom at the 1-position, also shown with a wedged bond. This bicyclic core is connected via a methylene group to a pyrimidine ring. The pyrimidine ring is further connected to a para-substituted benzene ring. This benzene ring is linked to a nitrogen atom that is part of a chain containing a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). The carbonyl group is connected to another para-substituted benzene ring, which is in turn connected to an amide group (-NH-). This amide group is linked to a methylene group, which is connected to another para-substituted benzene ring. This final benzene ring has a cyano group (-CN) at the para position.</p>	40
 <p>Chemical structure of compound 41: Similar to compound 40, but the final para-substituted benzene ring has a methoxy group (-OCH₃) at the para position and a cyano group (-CN) at the meta position.</p>	41
 <p>Chemical structure of compound 42: Similar to compound 40, but the final para-substituted benzene ring has a trifluoromethyl group (-CF₃) at the para position.</p>	42

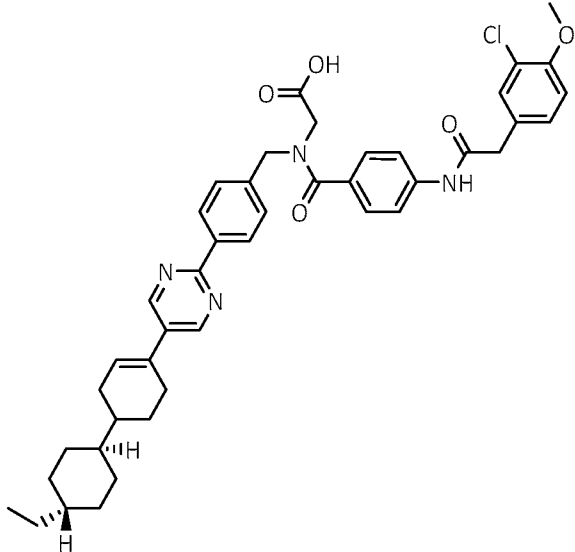
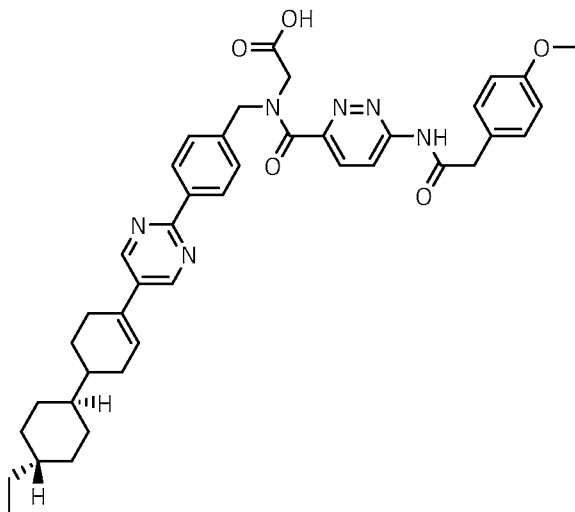
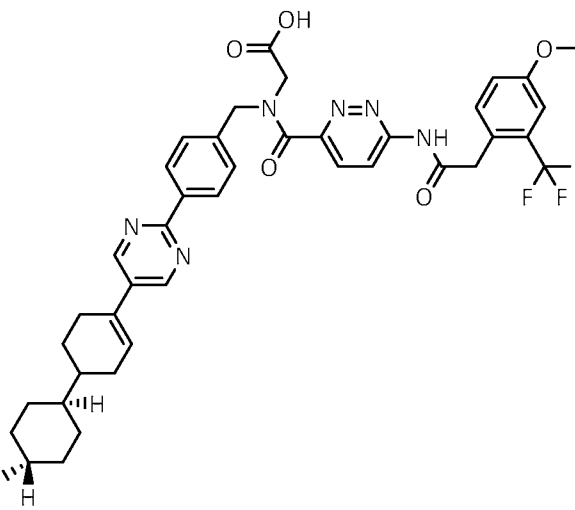
Structure	Cpd. No.
 <p>Chemical structure of compound 43: A bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group on a wedge and a hydrogen on a dash. The right ring has a hydrogen on a dash. A 1,2,4-triazole ring is attached to the right ring. The triazole ring is further substituted with a phenyl ring, which is connected via a methylene group to a nitrogen atom. This nitrogen atom is part of a chain: -N(CH₂)-C(=O)-O-CH₂-COOH. The nitrogen atom is also part of an amide linkage: -N(CH₂)-C(=O)-NH-Ph-CH₂-C(=O)-CH₂-Ph(OMe)₂, where Ph(OMe)₂ is a 1,3-dimethoxyphenyl group.</p>	43
 <p>Chemical structure of compound 44: Similar to compound 43, but the 1,3-dimethoxyphenyl group is replaced by a 2,4-dichlorophenyl group.</p>	44
 <p>Chemical structure of compound 45: Similar to compound 43, but the 1,3-dimethoxyphenyl group is replaced by a 2-cyano-5-phenylphenyl group.</p>	45

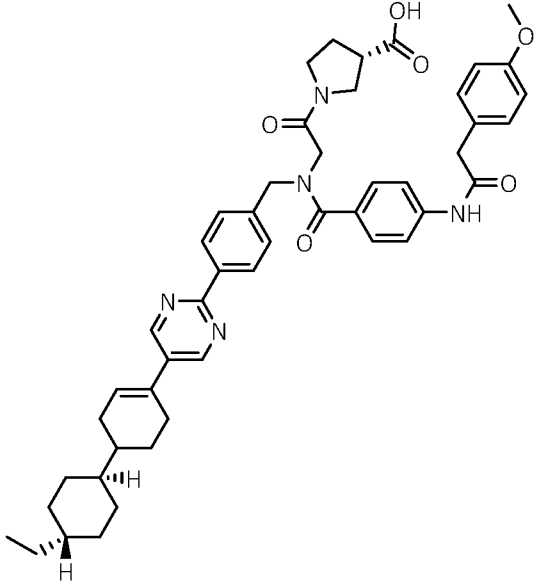
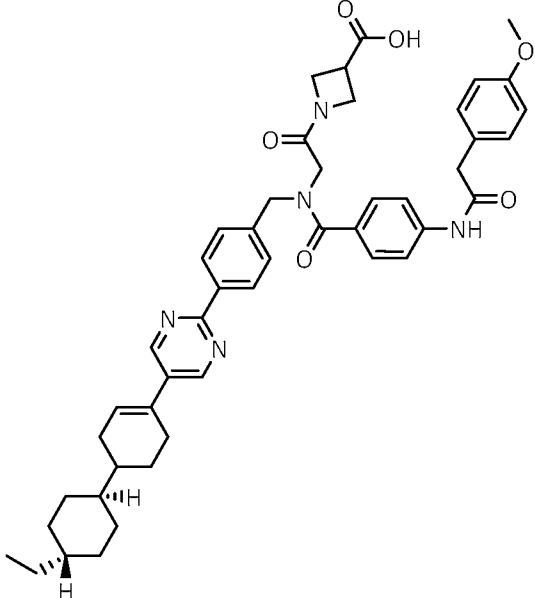
Structure	Cpd. No.
 <p>Chemical structure of compound 46: A bicyclic core consisting of two fused cyclohexane rings. The left ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring has a hydrogen atom on a wedged bond. The bicyclic system is connected via a methylene group to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring. This benzene ring is linked to a nitrogen atom, which is part of a chain containing a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). The chain continues to a pyridine ring, which is connected to an amide group (-NH-). The amide group is linked to a benzene ring substituted with a methoxy group (-OCH₃) and a trifluoromethyl group (-CF₃).</p>	46
 <p>Chemical structure of compound 47: Similar to compound 46, but the pyridine ring is substituted with a nitrile group (-CN) at the 3-position.</p>	47
 <p>Chemical structure of compound 48: Similar to compound 46, but the amide group is linked to a benzene ring substituted with an ethoxy group (-OCH₂CH₃).</p>	48

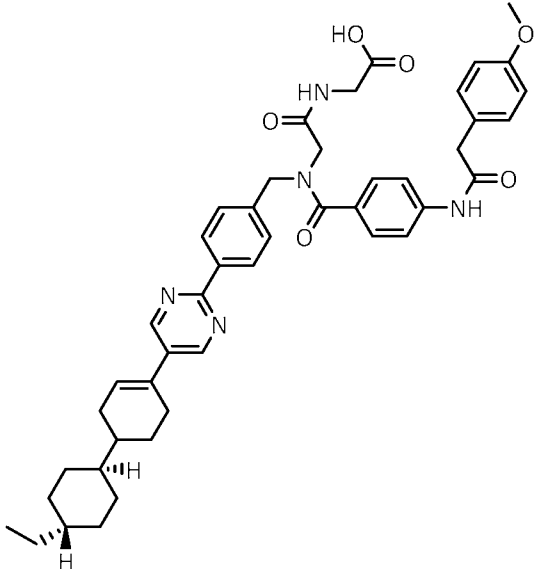
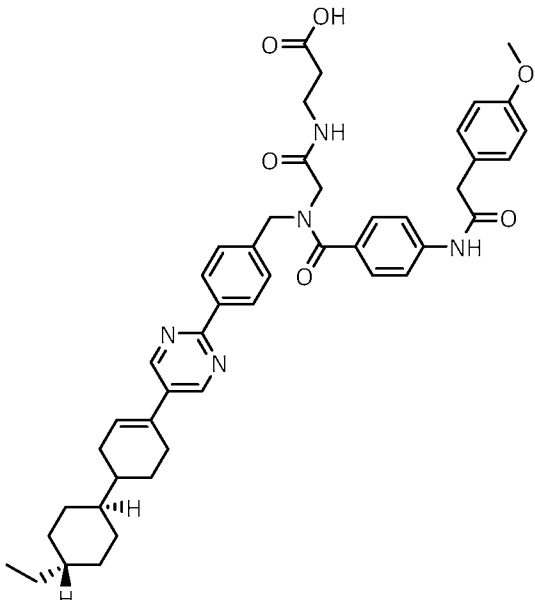
Structure	Cpd. No.
 <p>Chemical structure of compound 49: A bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring has a hydrogen atom on a dashed bond. This core is connected via a methylene group to a pyrimidine ring. The pyrimidine ring is further connected to a para-substituted benzene ring. This benzene ring is linked to a nitrogen atom, which is part of a chain containing a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). The carbonyl group is connected to another para-substituted benzene ring, which is in turn connected to an amide group (-NH-). The amide group is linked to a methylene group, which is connected to a para-substituted benzene ring with a methoxy group (-OCH₃) and a methyl group.</p>	49
 <p>Chemical structure of compound 50: Similar to compound 49, but the para-substituted benzene ring at the end of the chain has a fluorine atom (-F) and a methoxy group (-OCH₃) at the 3-position.</p>	50
 <p>Chemical structure of compound 51: Similar to compound 49, but the para-substituted benzene ring at the end of the chain has a methoxy group (-OCH₃) and a chlorine atom (-Cl) at the 3-position.</p>	51

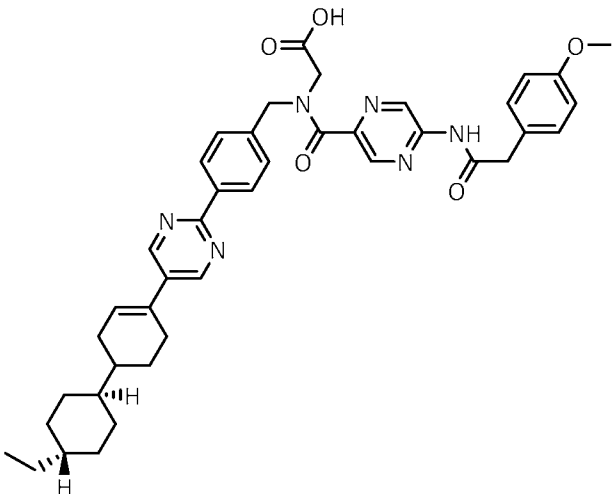
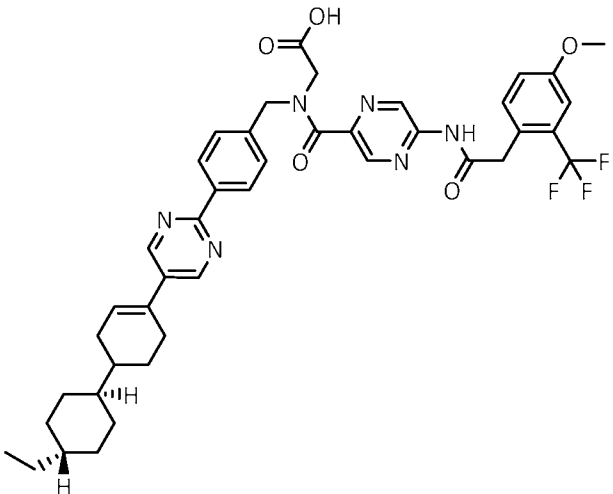
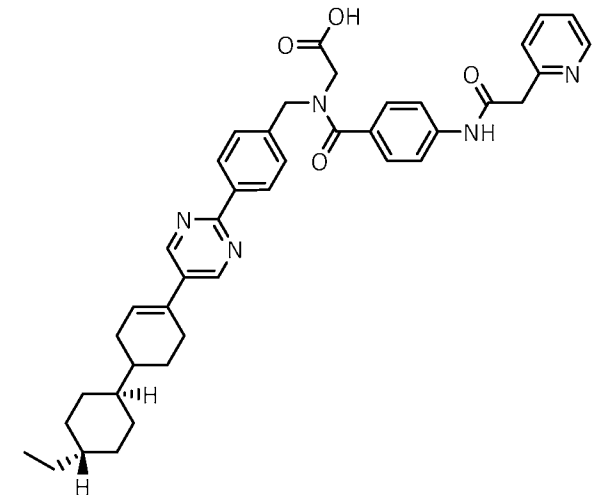
Structure	Cpd. No.
 <p>Chemical structure of compound 52. It features a bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group and a hydrogen atom on a chiral center. The right ring is substituted with a piperidine ring, which is further substituted with a pyrimidine ring. The pyrimidine ring is connected to a benzene ring, which is linked to a methylene group. This methylene group is attached to a nitrogen atom that is part of a sulfonamide group (-NH-SO₂-CH₃). The nitrogen atom is also bonded to a carbonyl group (-C(=O)-), which is connected to another benzene ring. This second benzene ring has an amide group (-NH-) and a methylene group (-CH₂-) attached to it. The methylene group is connected to a carbonyl group (-C(=O)-), which is finally attached to a benzene ring with a methoxy group (-OCH₃).</p>	52
 <p>Chemical structure of compound 53. It features a bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group and a hydrogen atom on a chiral center. The right ring is substituted with a piperidine ring, which is further substituted with a pyrimidine ring. The pyrimidine ring is connected to a benzene ring, which is linked to a methylene group. This methylene group is attached to a nitrogen atom that is part of a carboxamide group (-NH-COOH). The nitrogen atom is also bonded to a carbonyl group (-C(=O)-), which is connected to another benzene ring. This second benzene ring has an amide group (-NH-) and a methylene group (-CH₂-) attached to it. The methylene group is connected to a carbonyl group (-C(=O)-), which is finally attached to a benzene ring with a methoxy group (-OCH₃) and a methyl group (-CH₃).</p>	53

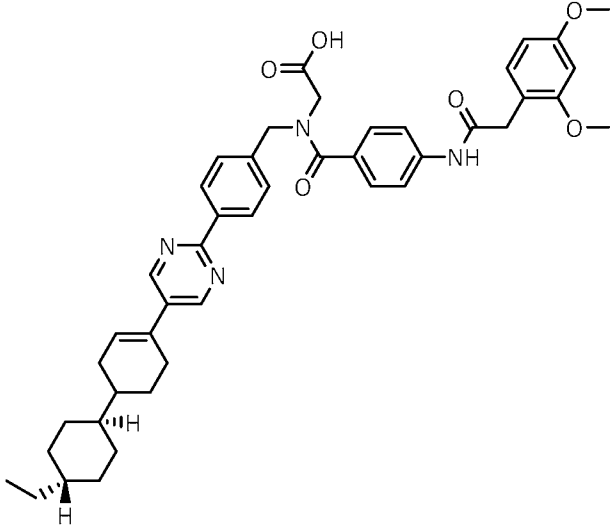
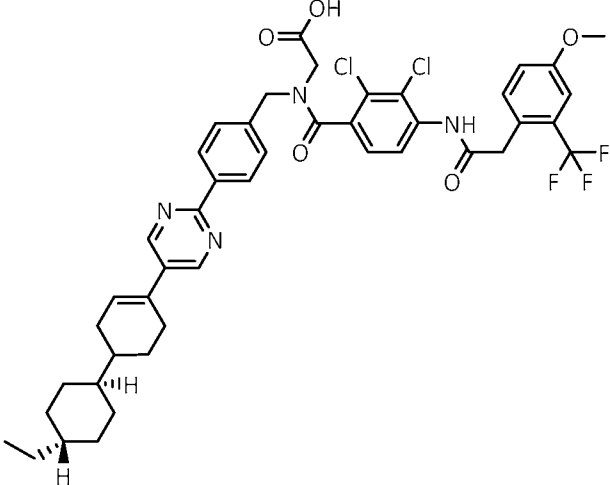
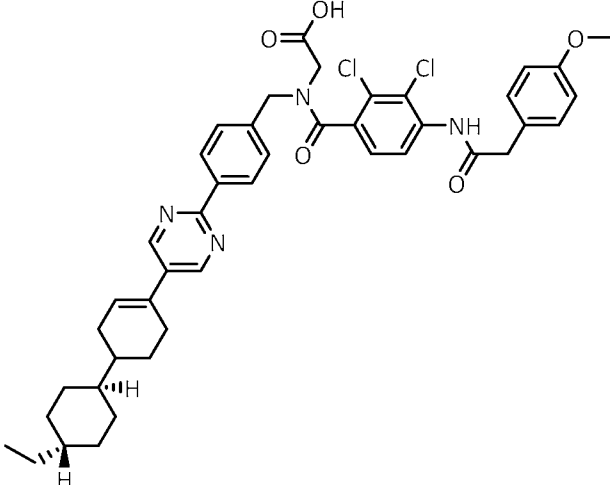
Structure	Cpd. No.
 <p>Chemical structure of compound 54. It features a bicyclic core consisting of two fused six-membered rings. The left ring is a cyclohexane with a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring is a cyclohexane with a hydrogen atom on a wedged bond. This bicyclic core is connected via a methylene group to a pyrimidine ring. The pyrimidine ring is further connected to a para-substituted benzene ring. This benzene ring is linked to a nitrogen atom, which is part of a chain containing a carboxylic acid group (COOH) and a secondary amide group (NH). The nitrogen atom is also connected to another para-substituted benzene ring. This second benzene ring is linked to a secondary amide group (NH) which is further connected to a methylene group, and finally to a para-substituted benzene ring with a methoxy group (OCH₃).</p>	54
 <p>Chemical structure of compound 55. It features a bicyclic core consisting of two fused six-membered rings. The left ring is a cyclohexane with a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring is a cyclohexane with a hydrogen atom on a wedged bond. This bicyclic core is connected via a methylene group to a pyrimidine ring. The pyrimidine ring is further connected to a para-substituted benzene ring. This benzene ring is linked to a nitrogen atom, which is part of a chain containing a carboxylic acid group (COOH) and a secondary amide group (NH). The nitrogen atom is also connected to another para-substituted benzene ring. This second benzene ring is linked to a secondary amide group (NH) which is further connected to a methylene group, and finally to a para-substituted benzene ring with a dimethylamino group (N(CH₃)₂).</p>	55

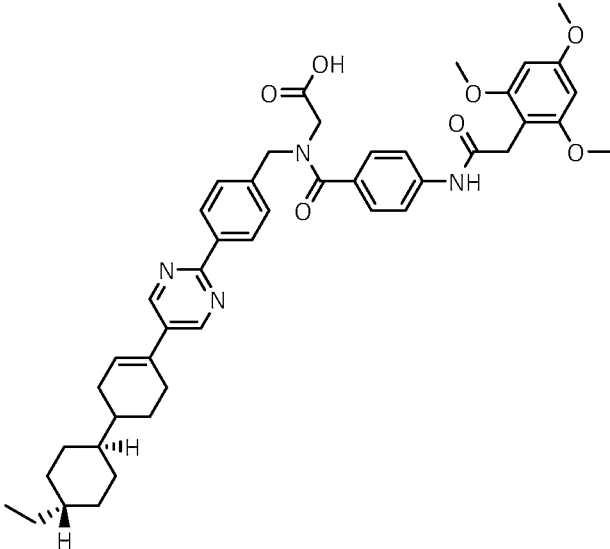
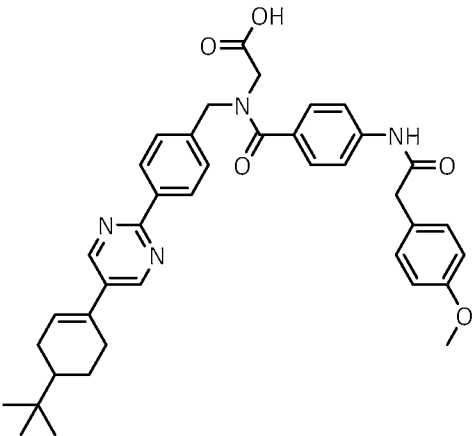
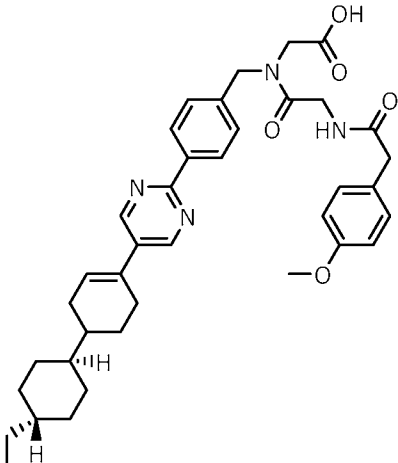
Structure	Cpd. No.
 <p>Chemical structure of compound 56: A bicyclic core consisting of two fused cyclohexane rings. The right-hand ring has a methyl group at the 1-position and a hydrogen atom at the 2-position, both shown with wedged bonds. The left-hand ring has a hydrogen atom at the 6-position, also shown with a wedged bond. A piperazine ring is attached to the 4-position of the left-hand ring. The 2-position of the piperazine ring is connected to a benzene ring. This benzene ring is further connected to a pyridine ring. The 4-position of the pyridine ring is connected to a carbonyl group (C=O). The nitrogen of this carbonyl group is bonded to a methylene group (-CH2-), which is in turn bonded to another carbonyl group (C=O). The nitrogen of this second carbonyl group is bonded to a propionic acid chain (-CH2-CH2-COOH). The 6-position of the pyridine ring is connected to an amide group (-NH-), which is bonded to a methylene group (-CH2-). This methylene group is further bonded to another carbonyl group (C=O). The nitrogen of this carbonyl group is bonded to a benzene ring. This benzene ring has a methoxy group (-OCH3) at the 3-position and a chlorine atom (-Cl) at the 4-position.</p>	56
 <p>Chemical structure of compound 57: A bicyclic core consisting of two fused cyclohexane rings. The right-hand ring has a methyl group at the 1-position and a hydrogen atom at the 2-position, both shown with wedged bonds. The left-hand ring has a hydrogen atom at the 6-position, also shown with a wedged bond. A piperazine ring is attached to the 4-position of the left-hand ring. The 2-position of the piperazine ring is connected to a benzene ring. This benzene ring is further connected to a pyridine ring. The 4-position of the pyridine ring is connected to a carbonyl group (C=O). The nitrogen of this carbonyl group is bonded to a methylene group (-CH2-), which is in turn bonded to another carbonyl group (C=O). The nitrogen of this second carbonyl group is bonded to a propionic acid chain (-CH2-CH2-COOH). The 6-position of the pyridine ring is connected to an amide group (-NH-), which is bonded to a methylene group (-CH2-). This methylene group is further bonded to another carbonyl group (C=O). The nitrogen of this carbonyl group is bonded to a benzene ring. This benzene ring has a methoxy group (-OCH3) at the 4-position.</p>	57
 <p>Chemical structure of compound 58: A bicyclic core consisting of two fused cyclohexane rings. The right-hand ring has a methyl group at the 1-position and a hydrogen atom at the 2-position, both shown with wedged bonds. The left-hand ring has a hydrogen atom at the 6-position, also shown with a wedged bond. A piperazine ring is attached to the 4-position of the left-hand ring. The 2-position of the piperazine ring is connected to a benzene ring. This benzene ring is further connected to a pyridine ring. The 4-position of the pyridine ring is connected to a carbonyl group (C=O). The nitrogen of this carbonyl group is bonded to a methylene group (-CH2-), which is in turn bonded to another carbonyl group (C=O). The nitrogen of this second carbonyl group is bonded to a propionic acid chain (-CH2-CH2-COOH). The 6-position of the pyridine ring is connected to an amide group (-NH-), which is bonded to a methylene group (-CH2-). This methylene group is further bonded to another carbonyl group (C=O). The nitrogen of this carbonyl group is bonded to a benzene ring. This benzene ring has a methoxy group (-OCH3) at the 4-position and a trifluoromethyl group (-CF3) at the 3-position.</p>	58

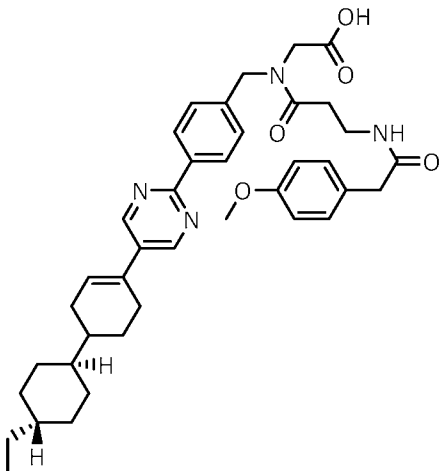
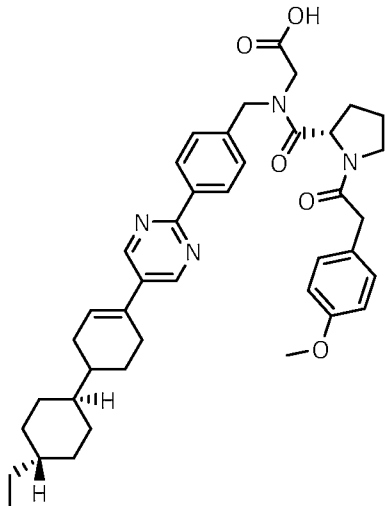
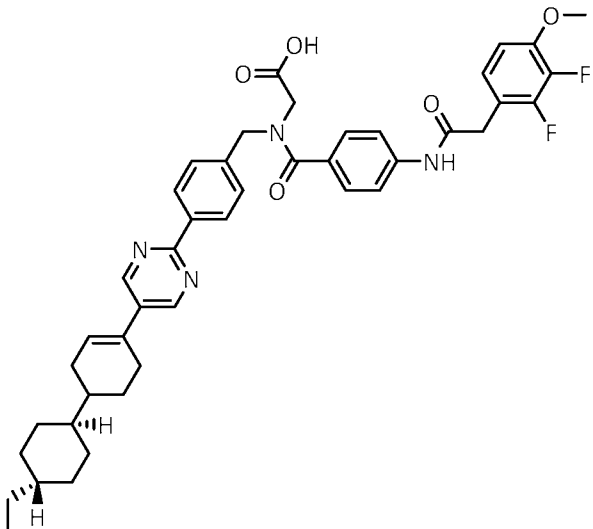
Structure	Cpd. No.
 <p>Chemical structure of compound 59. It features a bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group and a hydrogen atom at the bottom position, both shown with wedged bonds. The right ring has a hydrogen atom at the top position, also shown with a wedged bond. This core is connected via a cyclohexane ring to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is linked to a methylene group (-CH2-). This methylene group is attached to a nitrogen atom that is part of a chain: -N(CH2)-C(=O)-N(CH2)-C(=O)-. The second nitrogen in this chain is attached to a benzene ring with an amino group (-NH-) at the para position. This benzene ring is also connected to a methylene group (-CH2-), which is attached to another benzene ring. This final benzene ring has a methoxy group (-OCH3) at the para position and a -CH2-C(=O)- group at the other para position.</p>	59
 <p>Chemical structure of compound 60. It features a bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group and a hydrogen atom at the bottom position, both shown with wedged bonds. The right ring has a hydrogen atom at the top position, also shown with a wedged bond. This core is connected via a cyclohexane ring to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is linked to a methylene group (-CH2-). This methylene group is attached to a nitrogen atom that is part of a chain: -N(CH2)-C(=O)-N(CH2)-C(=O)-. The second nitrogen in this chain is attached to a five-membered ring containing a nitrogen atom and a carboxylic acid group (-COOH). This five-membered ring is also connected to a methylene group (-CH2-), which is attached to another benzene ring. This final benzene ring has a methoxy group (-OCH3) at the para position and a -CH2-C(=O)- group at the other para position.</p>	60

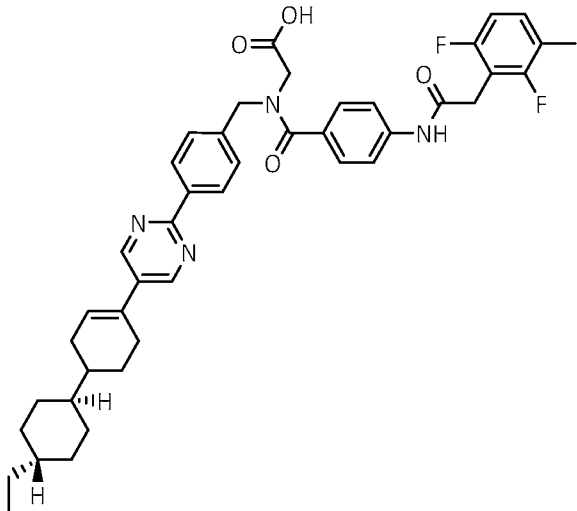
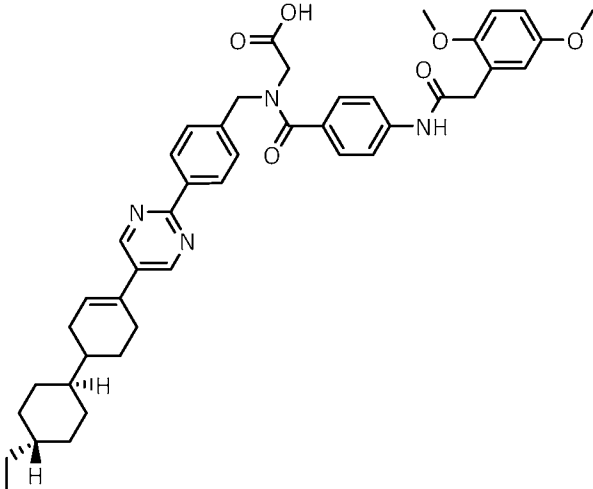
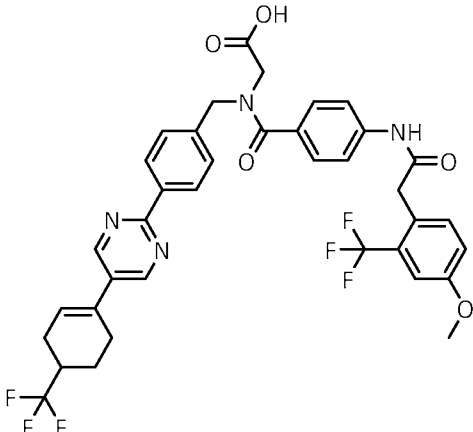
Structure	Cpd. No.
 <p>Chemical structure of compound 61. It features a bicyclic core consisting of two fused six-membered rings. The left ring is a cyclohexane with a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring is a cyclohexane with a hydrogen atom on a wedged bond. This bicyclic core is connected via a methylene group to a pyrimidine ring. The pyrimidine ring is further connected to a para-substituted benzene ring. This benzene ring is linked to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. This second carbonyl group is attached to a para-substituted benzene ring with an amino group (-NH-). This ring is further connected to a methylene group, which is attached to another para-substituted benzene ring with a methoxy group (-OCH₃). A side chain is attached to the nitrogen atom in the chain, consisting of a methylene group, a carbonyl group, and a hydroxyl group (-OH).</p>	61
 <p>Chemical structure of compound 62. It features a bicyclic core consisting of two fused six-membered rings. The left ring is a cyclohexane with a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring is a cyclohexane with a hydrogen atom on a wedged bond. This bicyclic core is connected via a methylene group to a pyrimidine ring. The pyrimidine ring is further connected to a para-substituted benzene ring. This benzene ring is linked to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. This second carbonyl group is attached to a para-substituted benzene ring with an amino group (-NH-). This ring is further connected to a methylene group, which is attached to another para-substituted benzene ring with a methoxy group (-OCH₃). A side chain is attached to the nitrogen atom in the chain, consisting of a methylene group, a carbonyl group, and a hydroxyl group (-OH).</p>	62

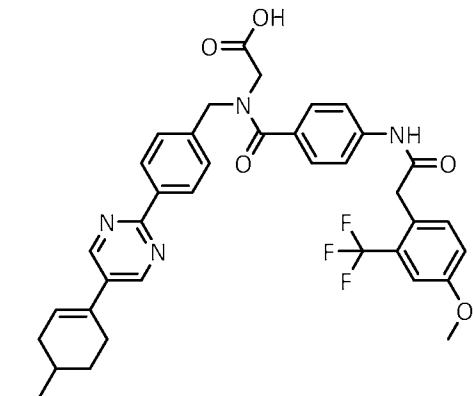
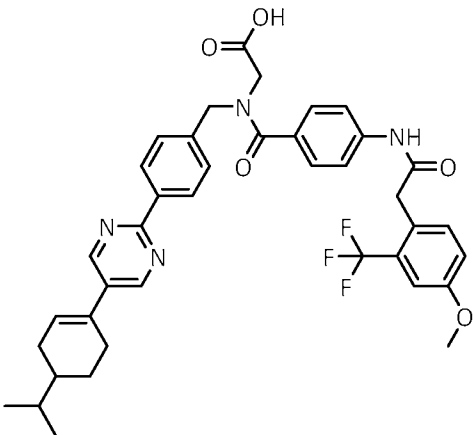
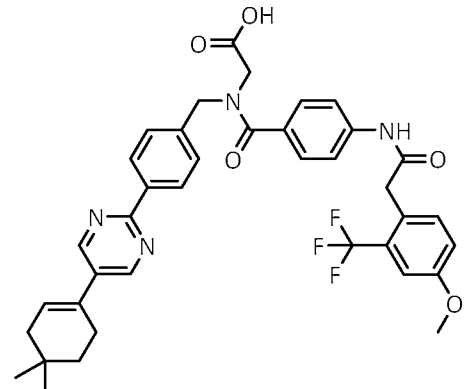
Structure	Cpd. No.
 <p>Chemical structure of compound 63: A bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group on a wedge and a hydrogen atom on a dash. The right ring has a hydrogen atom on a dash. A 1,2,4-triazole ring is attached to the right ring. This triazole is further substituted with a 4-methoxyphenyl group, a 2-hydroxyacetamido group, and a 2-((4-methoxyphenyl)amino)acetamido group.</p>	63
 <p>Chemical structure of compound 64: Similar to compound 63, but the 4-methoxyphenyl group is replaced by a 2,4-difluorophenyl group.</p>	64
 <p>Chemical structure of compound 65: Similar to compound 63, but the 4-methoxyphenyl group is replaced by a 2-pyridyl group.</p>	65

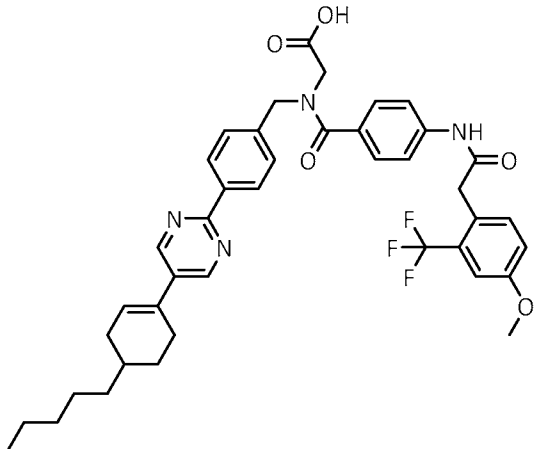
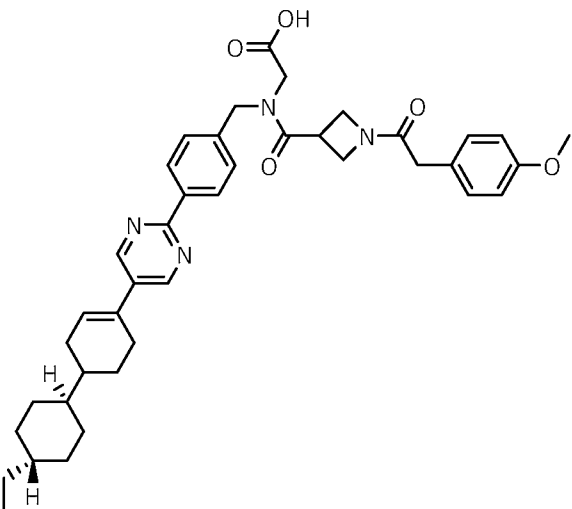
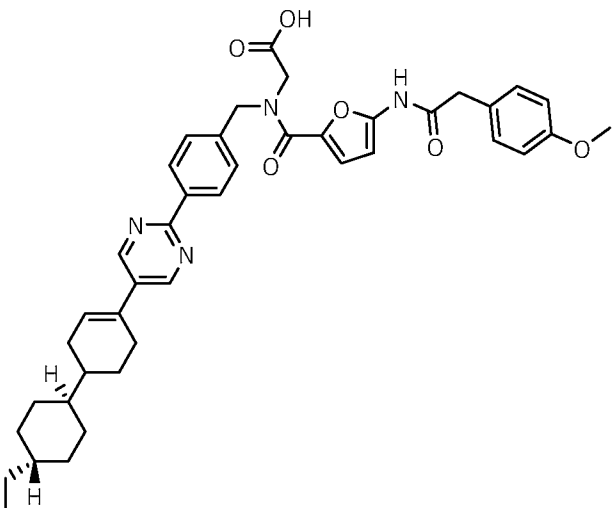
Structure	Cpd. No.
 <p>Chemical structure of compound 66: A bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group and a hydrogen atom at the bottom position. The right ring has a hydrogen atom at the top position. A benzene ring is attached to the right ring, which is further connected to a pyrimidine ring. This pyrimidine ring is linked to a para-substituted benzene ring. This benzene ring is connected to a nitrogen atom, which is part of a chain containing a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). This carbonyl group is further connected to another para-substituted benzene ring, which is linked to an amide group (-NH-). The amide group is connected to a methylene group (-CH2-), which is finally connected to a para-substituted benzene ring with two methoxy groups (-OCH3).</p>	66
 <p>Chemical structure of compound 67: Similar to compound 66, but the central benzene ring is substituted with two chlorine atoms (-Cl) and a trifluoromethyl group (-CF3) at the para position relative to the amide group.</p>	67
 <p>Chemical structure of compound 68: Similar to compound 67, but the central benzene ring is substituted with two chlorine atoms (-Cl) at the meta positions relative to the amide group.</p>	68

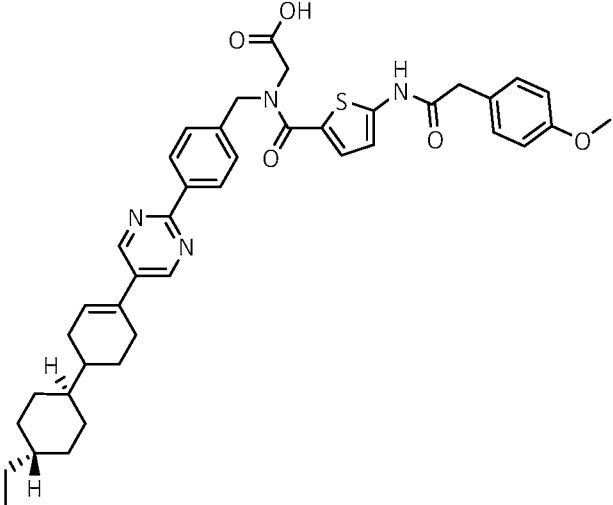
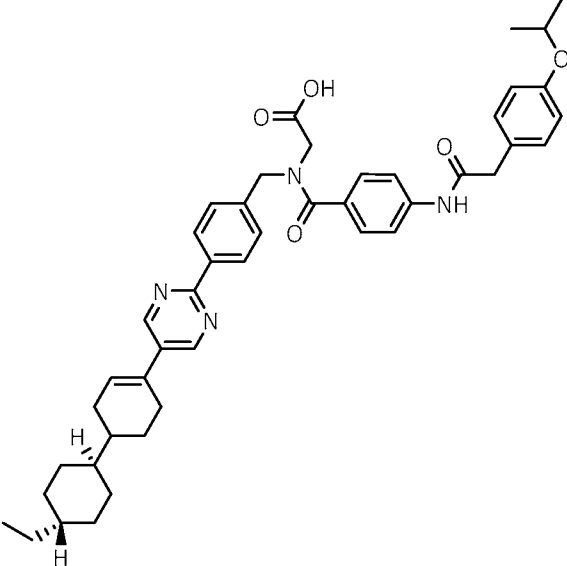
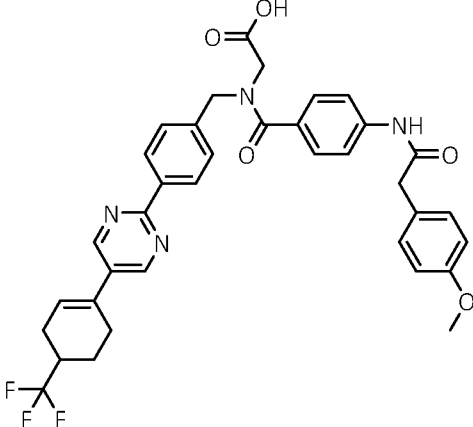
Structure	Cpd. No.
 <p>Chemical structure of compound 69: A complex molecule featuring a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. One of the cyclohexane rings is substituted with a 1,2,4-triazole ring. The triazole ring is further substituted with a phenyl ring. This phenyl ring is connected via a methylene group to a nitrogen atom, which is part of a side chain containing a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). The other end of this side chain is connected to a para-substituted benzamide group (-NH-C(=O)-C₆H₄-NH-), which is in turn connected to a 3,4,5-trimethoxyphenyl ring.</p>	69
 <p>Chemical structure of compound 70: Similar to compound 69, it features a bicyclic core with a 1,2,4-triazole ring. The triazole ring is substituted with a phenyl ring, which is connected via a methylene group to a nitrogen atom. This nitrogen is part of a side chain containing a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). The other end of this side chain is connected to a para-substituted benzamide group (-NH-C(=O)-C₆H₄-NH-), which is in turn connected to a 4-methoxyphenyl ring.</p>	70
 <p>Chemical structure of compound 71: Similar to compound 69, it features a bicyclic core with a 1,2,4-triazole ring. The triazole ring is substituted with a phenyl ring, which is connected via a methylene group to a nitrogen atom. This nitrogen is part of a side chain containing a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). The other end of this side chain is connected to a para-substituted benzamide group (-NH-C(=O)-C₆H₄-NH-), which is in turn connected to a 4-methoxyphenyl ring.</p>	71

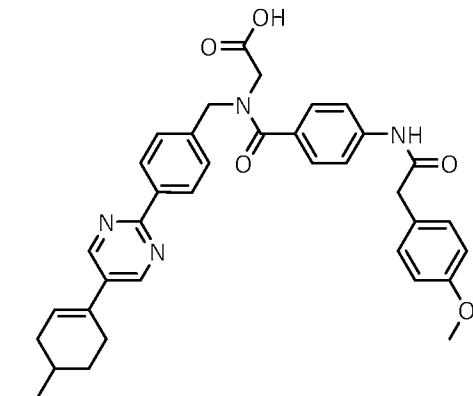
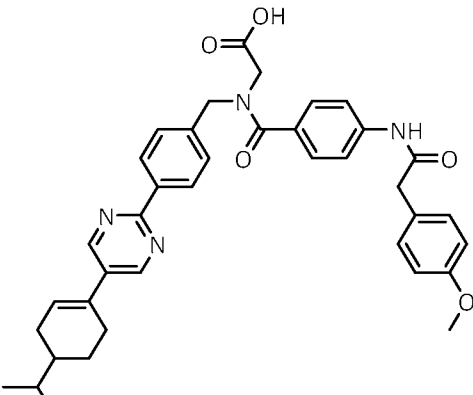
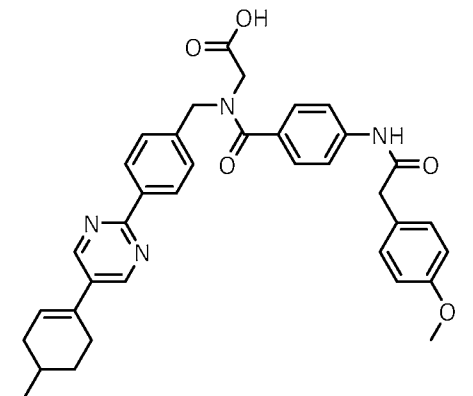
Structure	Cpd. No.
 <p>Chemical structure of compound 72. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. A 1,2,4-triazole ring is attached to the bicyclic system. The triazole ring is further substituted with a 4-methoxyphenyl group and a 4-(2-(2-hydroxyacetyl)aminoethyl)phenyl group.</p>	72
 <p>Chemical structure of compound 73. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. A 1,2,4-triazole ring is attached to the bicyclic system. The triazole ring is further substituted with a 4-methoxyphenyl group and a 4-(2-(2-(pyrrolidin-2-yl)acetyl)aminoethyl)phenyl group.</p>	73
 <p>Chemical structure of compound 74. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. A 1,2,4-triazole ring is attached to the bicyclic system. The triazole ring is further substituted with a 4-methoxyphenyl group and a 4-(2-(2-(2,4-difluorophenyl)aminoethyl)acetyl)phenyl group.</p>	74

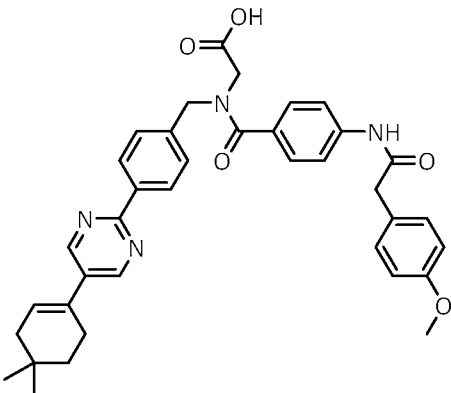
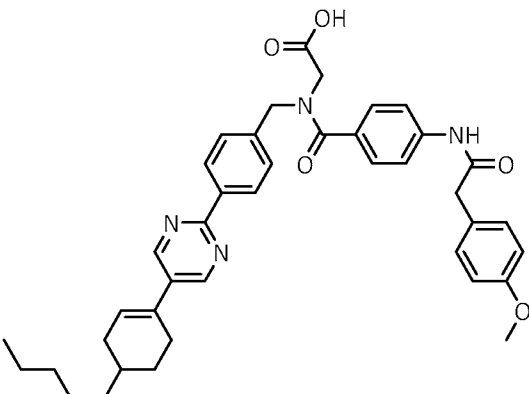
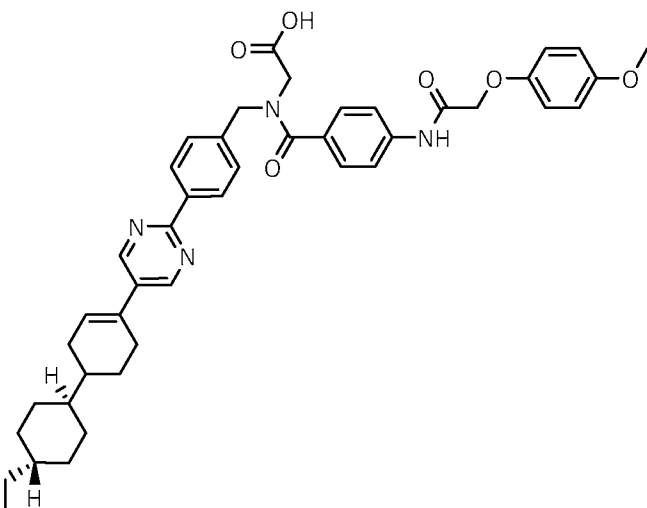
Structure	Cpd. No.
	<p>75</p>
	<p>76</p>
	<p>77</p>

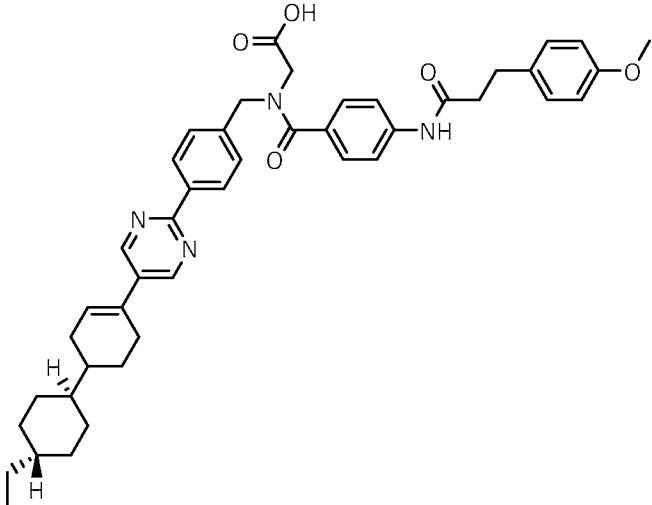
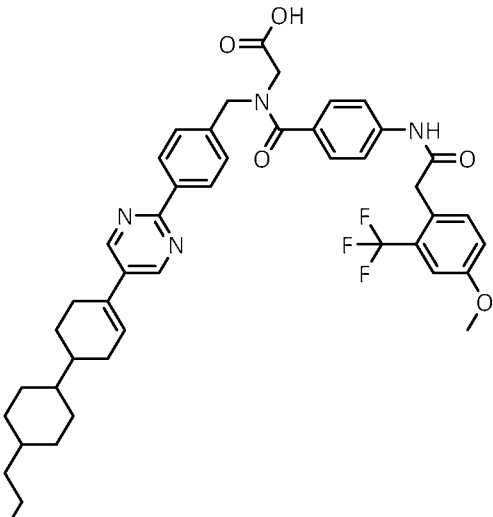
Structure	Cpd. No.
	78
	79
	80

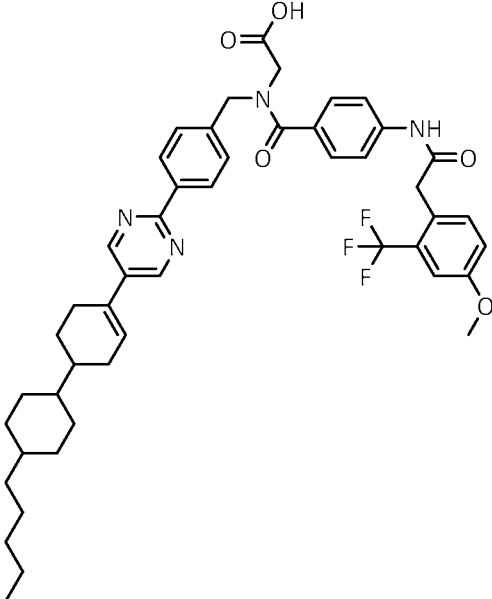
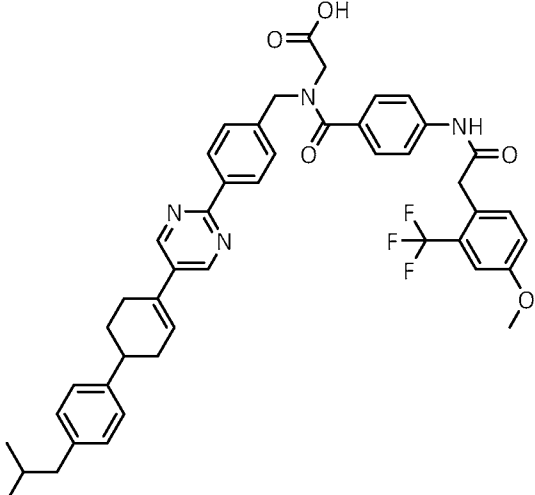
Structure	Cpd. No.
 <p>Chemical structure of compound 81: A complex molecule featuring a central benzimidazole ring system. One benzimidazole nitrogen is substituted with a propyl chain. The other benzimidazole nitrogen is substituted with a benzene ring. This benzene ring is further substituted with a methylene group, which is connected to a nitrogen atom. This nitrogen atom is part of a chain that includes a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). The carbonyl group is further substituted with a benzene ring, which is in turn substituted with a methylene group, a trifluoromethyl group (-CF₃), and a methoxy group (-OCH₃).</p>	81
 <p>Chemical structure of compound 82: A complex molecule featuring a central benzimidazole ring system. One benzimidazole nitrogen is substituted with a propyl chain. The other benzimidazole nitrogen is substituted with a benzene ring. This benzene ring is further substituted with a methylene group, which is connected to a nitrogen atom. This nitrogen atom is part of a chain that includes a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). The carbonyl group is further substituted with a five-membered ring (likely a pyrrolidine ring), which is in turn substituted with a methylene group, a carbonyl group (-C(=O)-), and a benzene ring. The benzene ring is substituted with a methoxy group (-OCH₃).</p>	82
 <p>Chemical structure of compound 83: A complex molecule featuring a central benzimidazole ring system. One benzimidazole nitrogen is substituted with a propyl chain. The other benzimidazole nitrogen is substituted with a benzene ring. This benzene ring is further substituted with a methylene group, which is connected to a nitrogen atom. This nitrogen atom is part of a chain that includes a carboxylic acid group (-COOH) and a carbonyl group (-C(=O)-). The carbonyl group is further substituted with a furan ring, which is in turn substituted with a methylene group, a carbonyl group (-C(=O)-), and a benzene ring. The benzene ring is substituted with a methoxy group (-OCH₃).</p>	83

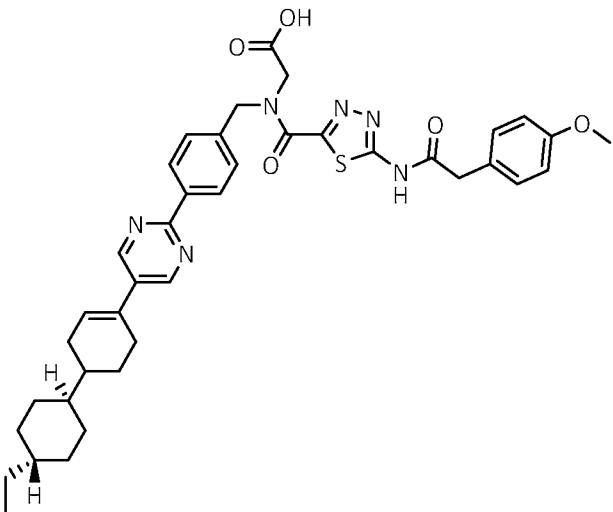
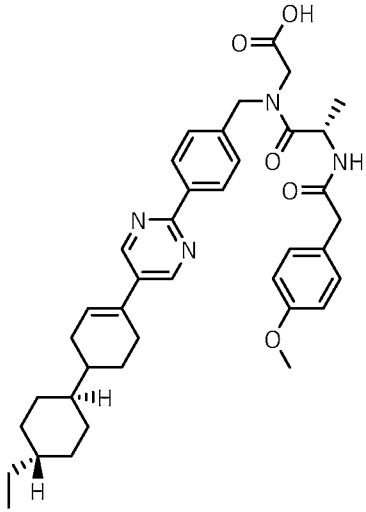
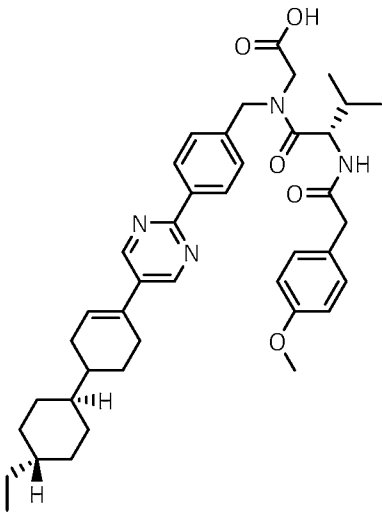
Structure	Cpd. No.
 <p>Chemical structure of compound 84: A bicyclic system consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedges and dashes. One of the cyclohexane rings is substituted with a trifluoromethyl group (-CF₃) and a 1,2,4-triazole ring. The triazole ring is further substituted with a benzene ring. This benzene ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a chain: -N(CH₂)-C(=O)-CH₂-COOH. The nitrogen atom is also bonded to a thiophene ring. The thiophene ring is substituted with an amide group (-NH-CO-CH₂-C₆H₄-OCH₃).</p>	<p>84</p>
 <p>Chemical structure of compound 85: A bicyclic system consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedges and dashes. One of the cyclohexane rings is substituted with a trifluoromethyl group (-CF₃) and a 1,2,4-triazole ring. The triazole ring is further substituted with a benzene ring. This benzene ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a chain: -N(CH₂)-C(=O)-CH₂-COOH. The nitrogen atom is also bonded to a benzene ring. This benzene ring is substituted with an amide group (-NH-CO-CH₂-C₆H₄-OCH₂CH(CH₃)₂).</p>	<p>85</p>
 <p>Chemical structure of compound 86: A bicyclic system consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedges and dashes. One of the cyclohexane rings is substituted with a trifluoromethyl group (-CF₃) and a 1,2,4-triazole ring. The triazole ring is further substituted with a benzene ring. This benzene ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a chain: -N(CH₂)-C(=O)-CH₂-COOH. The nitrogen atom is also bonded to a benzene ring. This benzene ring is substituted with an amide group (-NH-CO-CH₂-C₆H₄-OCH₃).</p>	<p>86</p>

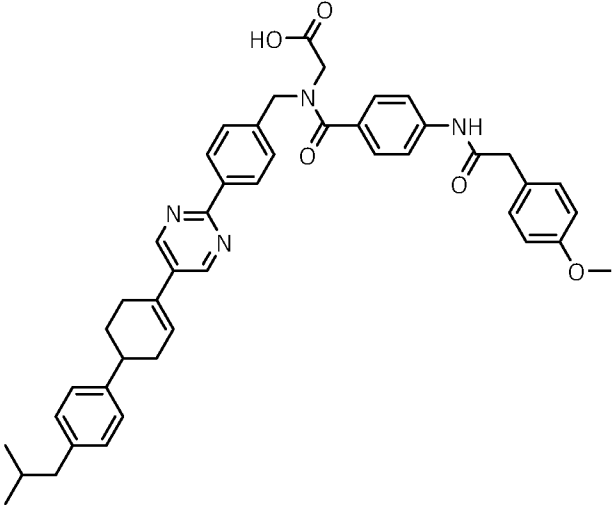
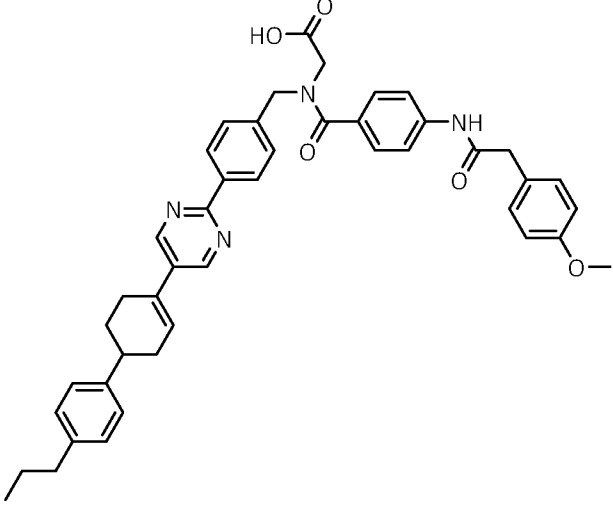
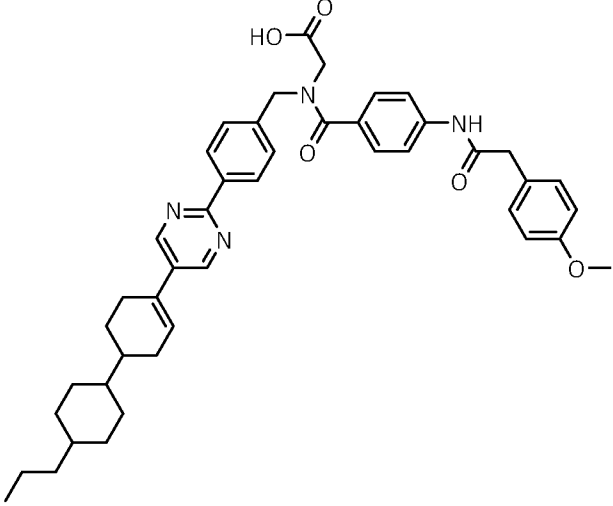
Structure	Cpd. No.
 <p>Chemical structure of compound 87: A central benzamide core (4-aminobenzamide) is substituted at the para position with a (2-ethylphenyl)pyrimidin-5-ylmethyl group and at the other para position with a (4-methoxyphenyl)methyl group. The amide nitrogen is substituted with a hydroxyethyl group (-CH₂CH₂OH).</p>	87
 <p>Chemical structure of compound 88: A central benzamide core (4-aminobenzamide) is substituted at the para position with a (2-isopropylphenyl)pyrimidin-5-ylmethyl group and at the other para position with a (4-methoxyphenyl)methyl group. The amide nitrogen is substituted with a hydroxyethyl group (-CH₂CH₂OH).</p>	88
 <p>Chemical structure of compound 89: A central benzamide core (4-aminobenzamide) is substituted at the para position with a (2-methylphenyl)pyrimidin-5-ylmethyl group and at the other para position with a (4-methoxyphenyl)methyl group. The amide nitrogen is substituted with a hydroxyethyl group (-CH₂CH₂OH).</p>	89

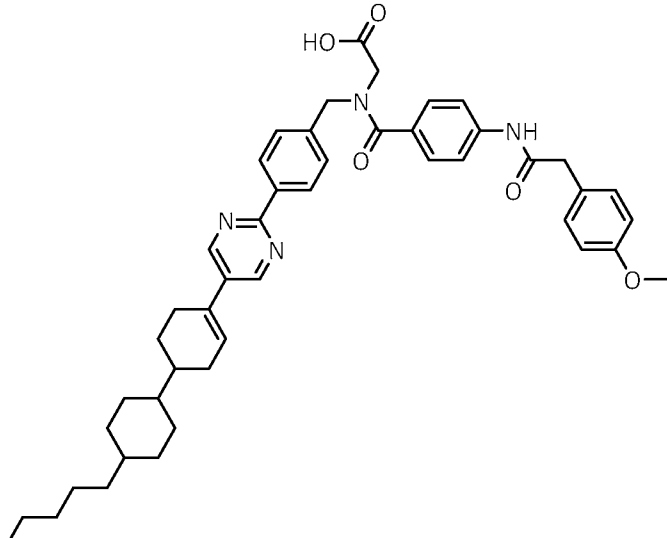
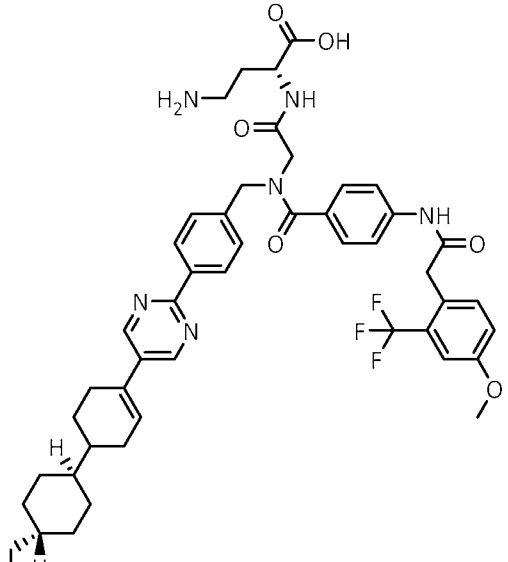
Structure	Cpd. No.
 <p>Chemical structure of compound 90: A central benzamide core is substituted at the para position with a 4-methoxybenzamide group and at the other para position with a (2-(4-(1,1-dimethyl-4-propylpiperidin-4-yl)phenyl)imidazole-5-yl)methyl group. The amide nitrogen is substituted with a 2-hydroxyethyl group.</p>	90
 <p>Chemical structure of compound 91: A central benzamide core is substituted at the para position with a 4-methoxybenzamide group and at the other para position with a (2-(4-propylphenyl)imidazole-5-yl)methyl group. The amide nitrogen is substituted with a 2-hydroxyethyl group.</p>	91
 <p>Chemical structure of compound 92: A central benzamide core is substituted at the para position with a 4-methoxybenzamide group and at the other para position with a (2-(4-(1,1-dimethyl-4-(1-methylpiperidin-4-yl)phenyl)phenyl)imidazole-5-yl)methyl group. The amide nitrogen is substituted with a 2-hydroxyethyl group. The stereochemistry of the piperidine ring is indicated with wedged and dashed bonds.</p>	92

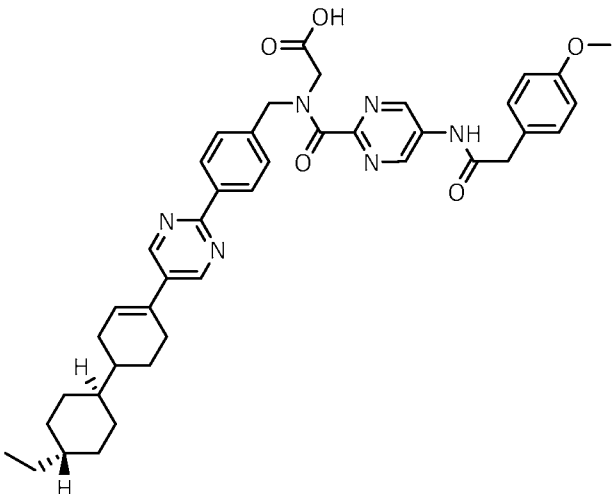
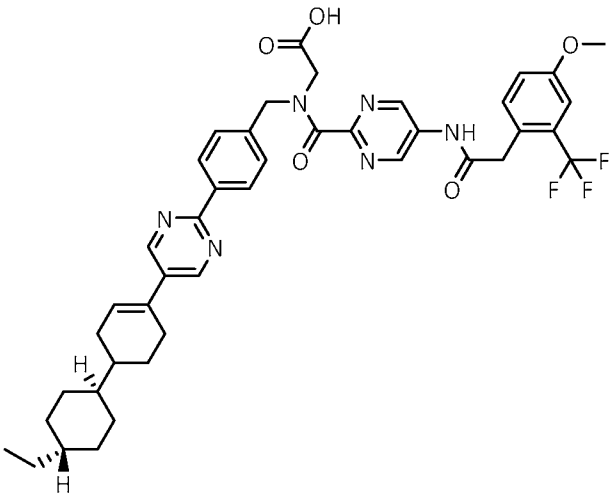
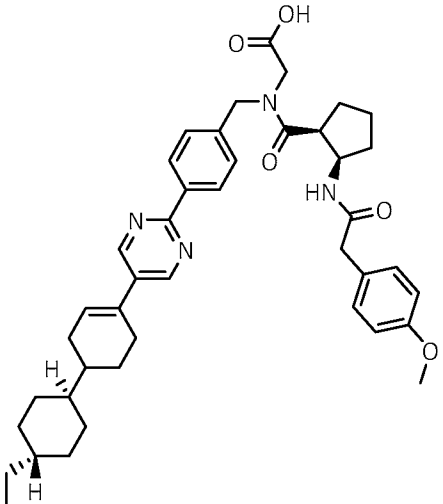
Structure	Cpd. No.
 <p>Chemical structure of compound 93: A complex molecule featuring a central benzimidazole ring system. The benzimidazole is substituted with a propyl chain at the 2-position and a 4-methoxyphenyl group at the 5-position. The 4-position of the benzimidazole is linked via a methylene group to a nitrogen atom, which is part of a succinamic acid derivative (N-(2-hydroxyethyl)acetamide). This nitrogen is also connected to a 4-methoxyphenyl group via an amide bond. The 4-position of this phenyl ring is further substituted with a propyl chain.</p>	93
 <p>Chemical structure of compound 94: A complex molecule featuring a central benzimidazole ring system. The benzimidazole is substituted with a propyl chain at the 2-position and a 4-propylphenyl group at the 5-position. The 4-position of the benzimidazole is linked via a methylene group to a nitrogen atom, which is part of a succinamic acid derivative (N-(2-hydroxyethyl)acetamide). This nitrogen is also connected to a 4-methoxyphenyl group via an amide bond. The 4-position of this phenyl ring is further substituted with a propyl chain.</p>	94

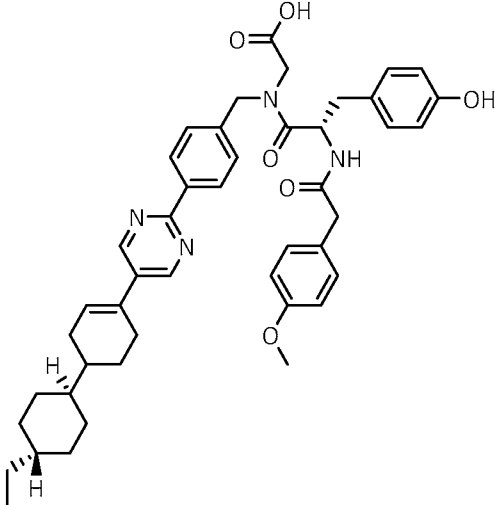
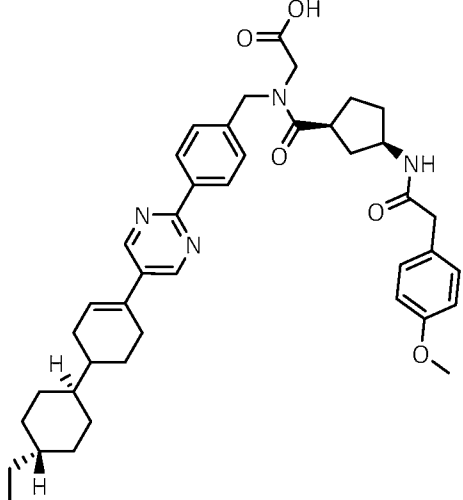
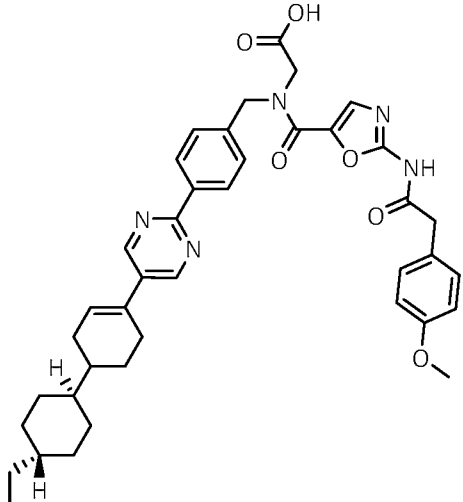
Structure	Cpd. No.
 <p>Chemical structure of compound 95: A complex molecule featuring a central benzamide core. The benzamide nitrogen is substituted with a propionic acid group (-CH2-CH2-COOH). The benzamide carbonyl is attached to a phenyl ring. This phenyl ring is further substituted with a methylene group (-CH2-) which is attached to a pyridine ring. The pyridine ring is substituted at the 2-position with a phenyl ring. This phenyl ring is further substituted with a methylene group (-CH2-) which is attached to a cyclohexane ring. The cyclohexane ring is substituted at the 1-position with a propyl chain (-CH2-CH2-CH3).</p>	95
 <p>Chemical structure of compound 96: A complex molecule featuring a central benzamide core. The benzamide nitrogen is substituted with a propionic acid group (-CH2-CH2-COOH). The benzamide carbonyl is attached to a phenyl ring. This phenyl ring is further substituted with a methylene group (-CH2-) which is attached to a pyridine ring. The pyridine ring is substituted at the 2-position with a phenyl ring. This phenyl ring is further substituted with a methylene group (-CH2-) which is attached to a cyclohexane ring. The cyclohexane ring is substituted at the 1-position with a 4-isobutylphenyl group (-CH2-CH2-C6H4-CH2-CH(CH3)2).</p>	96

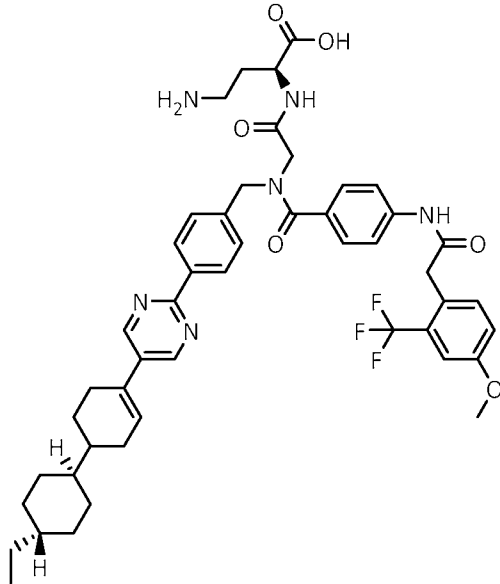
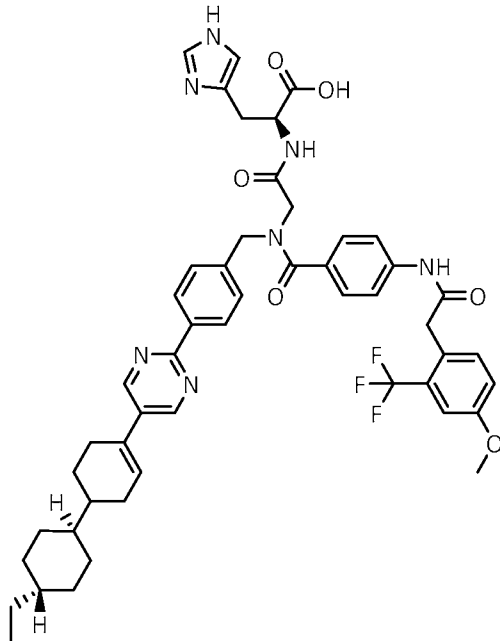
Structure	Cpd. No.
 <p>Chemical structure of compound 97. It features a bicyclic core consisting of two fused cyclohexane rings. The core is substituted with a pyrimidine ring, which is further linked to a benzene ring. This benzene ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carboxylic acid group (-COOH) and a thiazole ring. The thiazole ring is substituted with a methylene group, which is in turn connected to another benzene ring. This second benzene ring has a methoxy group (-OCH₃) at the para position.</p>	97
 <p>Chemical structure of compound 98. It features a bicyclic core consisting of two fused cyclohexane rings. The core is substituted with a pyrimidine ring, which is further linked to a benzene ring. This benzene ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carboxylic acid group (-COOH) and a secondary amide group (-NH-). The secondary amide group is further substituted with a methylene group, which is in turn connected to another benzene ring. This second benzene ring has a methoxy group (-OCH₃) at the para position.</p>	98
 <p>Chemical structure of compound 99. It features a bicyclic core consisting of two fused cyclohexane rings. The core is substituted with a pyrimidine ring, which is further linked to a benzene ring. This benzene ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carboxylic acid group (-COOH) and a secondary amide group (-NH-). The secondary amide group is further substituted with a methylene group, which is in turn connected to another benzene ring. This second benzene ring has a methoxy group (-OCH₃) at the para position.</p>	99

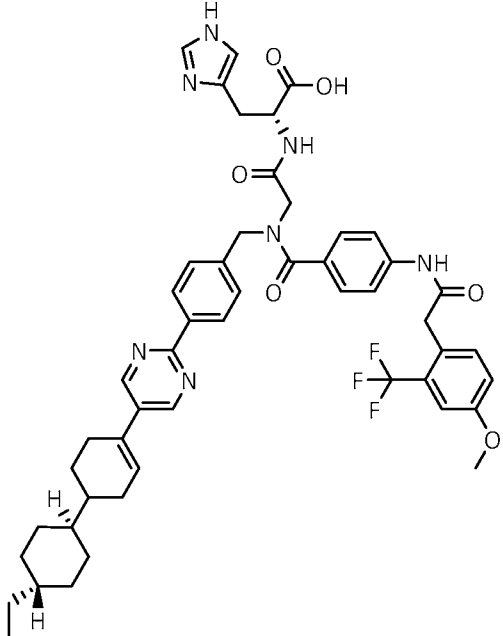
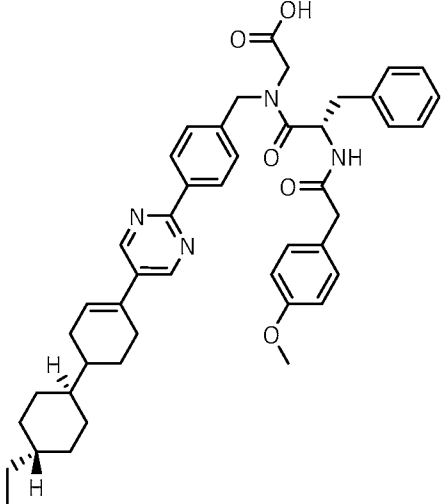
Structure	Cpd. No.
 <p>Chemical structure of compound 100: A central benzimidazole ring system is substituted at the 2-position with a 4-(4-isobutylphenyl)phenyl group. The 5-position of the benzimidazole is substituted with a 4-(2-(2-(4-methoxyphenyl)acetamido)acetyl)phenyl group. The 1-position of the benzimidazole is substituted with a 2-(2-(2-(4-methoxyphenyl)acetamido)acetyl)phenyl group.</p>	100
 <p>Chemical structure of compound 101: A central benzimidazole ring system is substituted at the 2-position with a 4-(4-propylphenyl)phenyl group. The 5-position of the benzimidazole is substituted with a 4-(2-(2-(4-methoxyphenyl)acetamido)acetyl)phenyl group. The 1-position of the benzimidazole is substituted with a 2-(2-(2-(4-methoxyphenyl)acetamido)acetyl)phenyl group.</p>	101
 <p>Chemical structure of compound 102: A central benzimidazole ring system is substituted at the 2-position with a 4-(4-propylphenyl)phenyl group. The 5-position of the benzimidazole is substituted with a 4-(2-(2-(4-methoxyphenyl)acetamido)acetyl)phenyl group. The 1-position of the benzimidazole is substituted with a 2-(2-(2-(4-methoxyphenyl)acetamido)acetyl)phenyl group.</p>	102

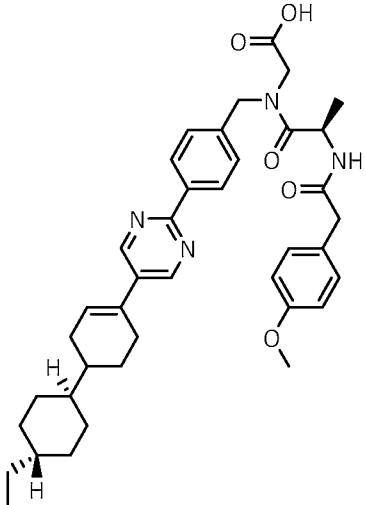
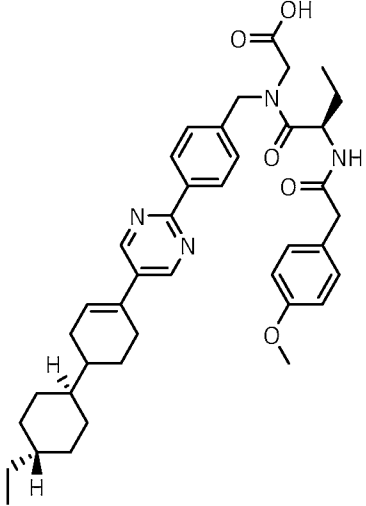
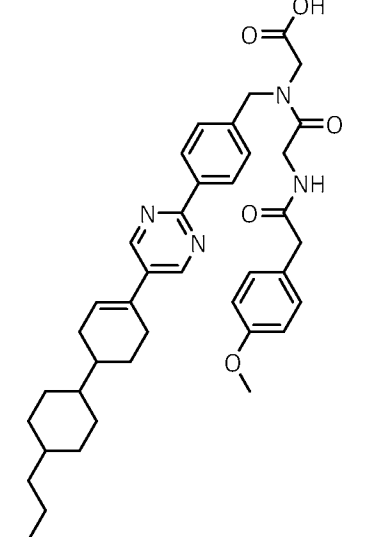
Structure	Cpd. No.
 <p>Chemical structure of compound 103: A complex molecule featuring a central benzimidazole ring system. One benzimidazole nitrogen is substituted with a propyl chain. The other benzimidazole nitrogen is substituted with a phenyl ring, which is further substituted with a propyl chain. The benzimidazole ring is connected via a methylene group to a benzene ring. This benzene ring is substituted with a propyl chain and a carboxylic acid group (-COOH). The benzimidazole ring is also connected via a methylene group to a benzene ring, which is substituted with a propyl chain and a carboxylic acid group (-COOH). The benzimidazole ring is also connected via a methylene group to a benzene ring, which is substituted with a propyl chain and a carboxylic acid group (-COOH).</p>	103
 <p>Chemical structure of compound 104: A complex molecule featuring a central benzimidazole ring system. One benzimidazole nitrogen is substituted with a propyl chain. The other benzimidazole nitrogen is substituted with a phenyl ring, which is further substituted with a propyl chain. The benzimidazole ring is connected via a methylene group to a benzene ring. This benzene ring is substituted with a propyl chain and a carboxylic acid group (-COOH). The benzimidazole ring is also connected via a methylene group to a benzene ring, which is substituted with a propyl chain and a carboxylic acid group (-COOH). The benzimidazole ring is also connected via a methylene group to a benzene ring, which is substituted with a propyl chain and a carboxylic acid group (-COOH).</p>	104

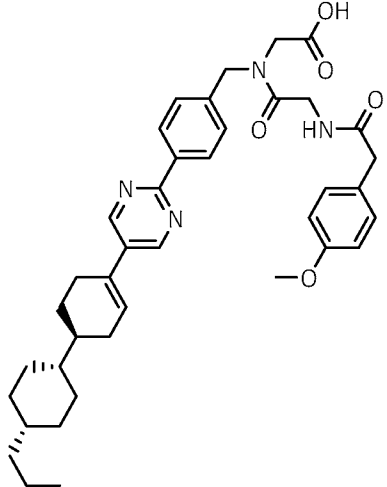
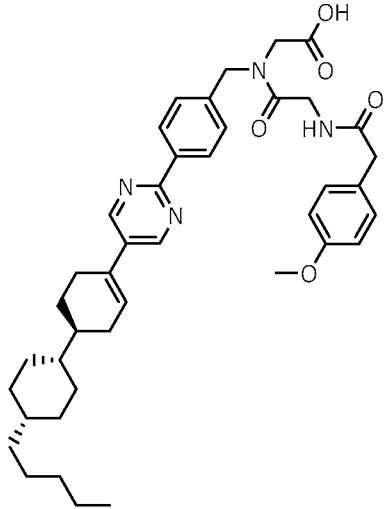
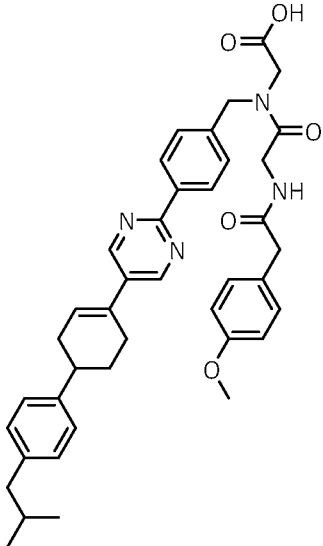
Structure	Cpd. No.
 <p>Chemical structure of compound 105: A complex molecule featuring a bicyclic core consisting of two cyclohexane rings. The core is substituted with a methyl group and a hydrogen atom. A chain of rings is attached to the core, including a pyrimidine ring, a benzene ring, and another pyrimidine ring. This chain is further substituted with a hydroxymethyl group, a carbonyl group, and a benzamide moiety with a methoxy group.</p>	105
 <p>Chemical structure of compound 106: Similar to compound 105, but the benzamide moiety is substituted with a trifluoromethyl group instead of a methoxy group.</p>	106
 <p>Chemical structure of compound 107: Similar to compound 105, but the hydroxymethyl group is replaced by a cyclopentane ring substituted with a hydrogen atom and a benzamide moiety with a methoxy group.</p>	107

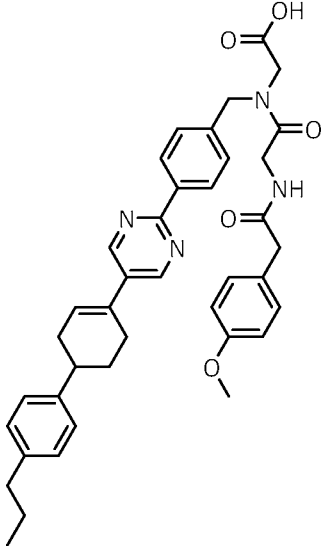
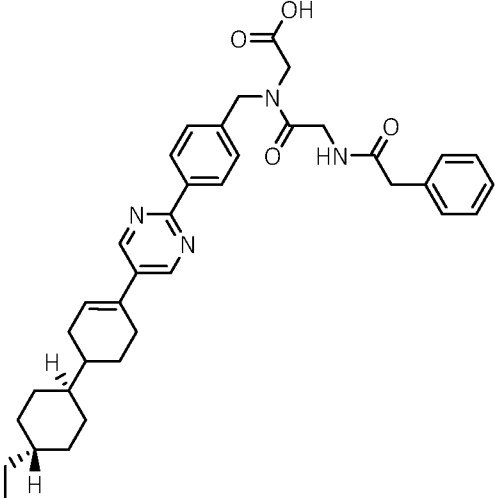
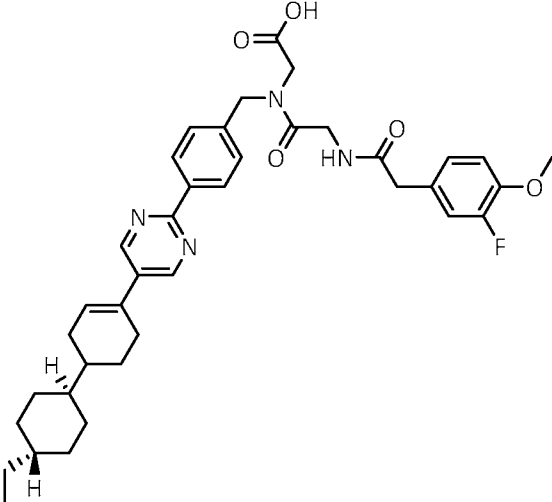
Structure	Cpd. No.
 <p>Chemical structure of compound 108. It features a bicyclic core consisting of two fused cyclohexane rings. The core is substituted with a 1,2,4-triazole ring, which is further linked to a phenyl ring. This phenyl ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carboxylic acid group (-COOH) and a 4-hydroxyphenyl group (-C₆H₄-OH). Additionally, the nitrogen atom is linked to a carbonyl group, which is connected to a methylene group, and finally to a 4-methoxyphenyl group (-C₆H₄-OCH₃).</p>	108
 <p>Chemical structure of compound 109. It features a bicyclic core consisting of two fused cyclohexane rings. The core is substituted with a 1,2,4-triazole ring, which is further linked to a phenyl ring. This phenyl ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carboxylic acid group (-COOH) and a 4-methoxyphenyl group (-C₆H₄-OCH₃). Additionally, the nitrogen atom is linked to a carbonyl group, which is connected to a methylene group, and finally to a 4-methoxyphenyl group (-C₆H₄-OCH₃).</p>	109
 <p>Chemical structure of compound 110. It features a bicyclic core consisting of two fused cyclohexane rings. The core is substituted with a 1,2,4-triazole ring, which is further linked to a phenyl ring. This phenyl ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carboxylic acid group (-COOH) and a 4-methoxyphenyl group (-C₆H₄-OCH₃). Additionally, the nitrogen atom is linked to a carbonyl group, which is connected to a methylene group, and finally to a 4-methoxyphenyl group (-C₆H₄-OCH₃).</p>	110

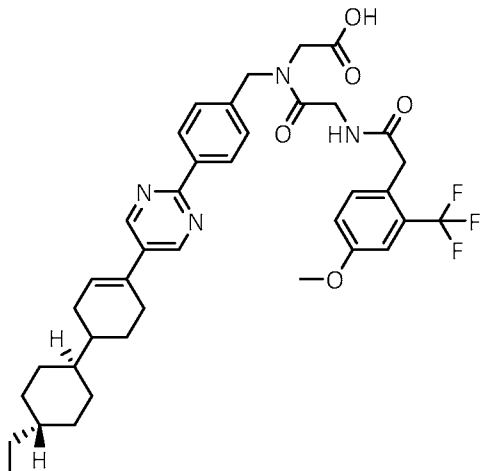
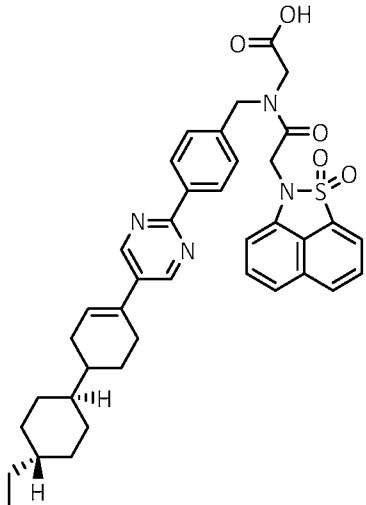
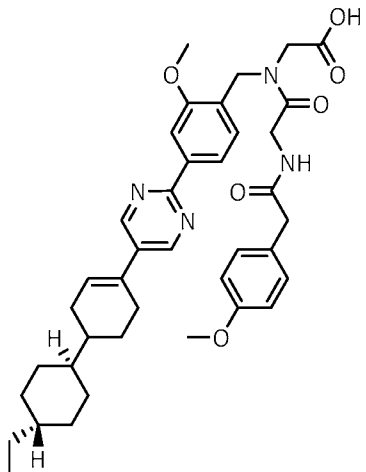
Structure	Cpd. No.
 <p>Chemical structure of compound 111. It features a bicyclic core consisting of two fused cyclohexane rings. One ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The other ring is substituted with a phenyl ring, which is further substituted with a pyrimidine ring. The pyrimidine ring is connected via a methylene group to a nitrogen atom of a secondary amide. This amide is linked to a benzamide moiety, which is in turn connected to a 4-(trifluoromethyl)-3-methoxyphenyl group. A side chain is attached to the nitrogen of the secondary amide, consisting of a methylene group, a secondary amide, and a propanoic acid moiety.</p>	111
 <p>Chemical structure of compound 112. It features a bicyclic core consisting of two fused cyclohexane rings. One ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The other ring is substituted with a phenyl ring, which is further substituted with a pyrimidine ring. The pyrimidine ring is connected via a methylene group to a nitrogen atom of a secondary amide. This amide is linked to a benzamide moiety, which is in turn connected to a 4-(trifluoromethyl)-3-methoxyphenyl group. A side chain is attached to the nitrogen of the secondary amide, consisting of a methylene group, a secondary amide, and a propanoic acid moiety with a 1H-imidazole ring attached to the alpha carbon.</p>	112

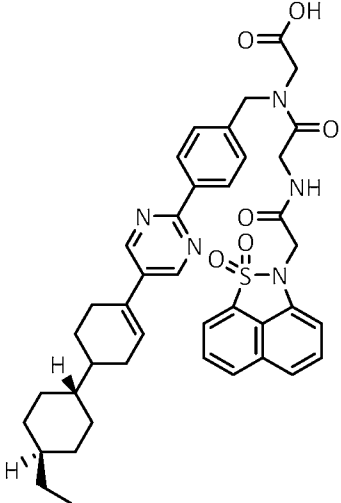
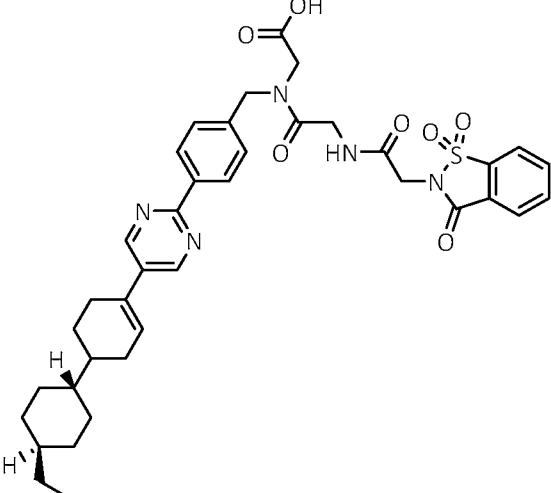
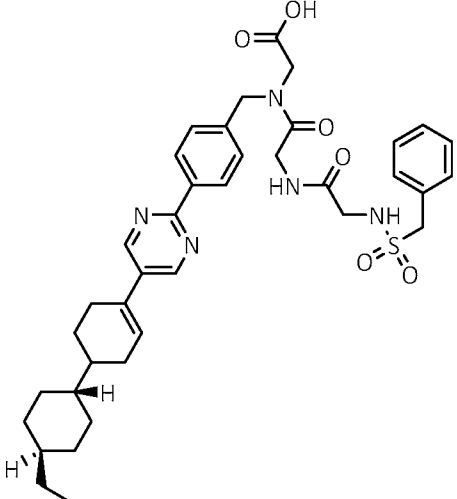
Structure	Cpd. No.
 <p>Chemical structure of compound 113: A bicyclic core consisting of two fused cyclohexane rings. The right-hand ring has a methyl group on a wedge and a hydrogen atom on a dash. The left-hand ring is connected to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is linked to a methylene group (-CH2-). This methylene group is attached to a nitrogen atom of a secondary amide (-NH-CH2-CO-). The nitrogen of this amide is also bonded to a propionic acid chain (-CH2-CH2-COOH). The carbonyl oxygen of this amide is bonded to another benzene ring. This second benzene ring has an amide group (-NH-CO-) at the para position, which is connected to a methylene group (-CH2-). This methylene group is attached to a benzene ring with a methoxy group (-OCH3) at the para position and a trifluoromethyl group (-CF3) at the meta position.</p>	<p>113</p>
 <p>Chemical structure of compound 114: A bicyclic core consisting of two fused cyclohexane rings. The right-hand ring has a methyl group on a wedge and a hydrogen atom on a dash. The left-hand ring is connected to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is linked to a methylene group (-CH2-). This methylene group is attached to a nitrogen atom of a secondary amide (-NH-CH2-CO-). The nitrogen of this amide is also bonded to a propionic acid chain (-CH2-CH2-COOH). The carbonyl oxygen of this amide is bonded to another benzene ring. This second benzene ring has an amide group (-NH-CO-) at the para position, which is connected to a methylene group (-CH2-). This methylene group is attached to a benzene ring with a methoxy group (-OCH3) at the para position.</p>	<p>114</p>

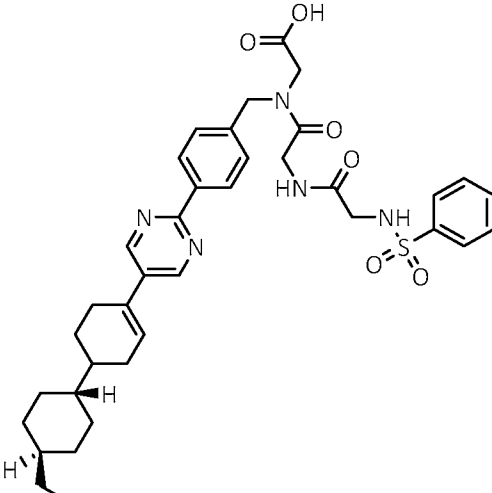
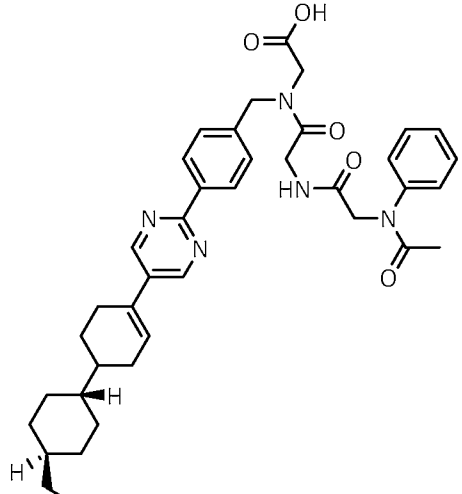
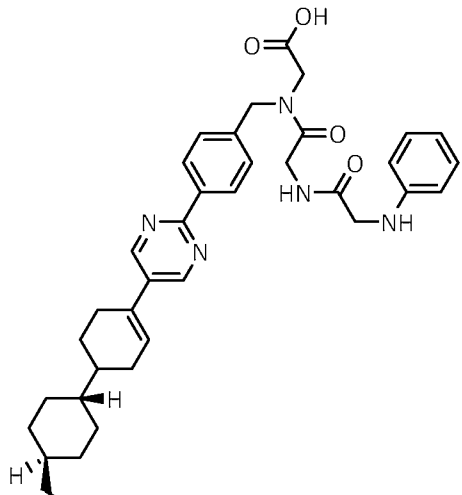
Structure	Cpd. No.
 <p>Chemical structure of compound 115. It features a bicyclic core consisting of two fused cyclohexane rings. The left ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The right ring has a hydrogen atom on a dashed bond and a methyl group on a wedged bond. This bicyclic core is connected via a piperidine ring to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is linked to a methylene group (-CH2-). This methylene group is attached to a nitrogen atom that is part of a side chain containing a carboxylic acid group (-COOH) and a secondary amide group (-NH-). The secondary amide nitrogen is bonded to a chiral center (wedged bond) which is also bonded to a methyl group (dashed bond) and a carbonyl group (-C(=O)-). This carbonyl group is connected to another methylene group (-CH2-), which is in turn connected to a benzene ring with a methoxy group (-OCH3) at the para position.</p>	115
 <p>Chemical structure of compound 116. It is identical to compound 115, but the chiral center is bonded to an ethyl group (wedged bond) instead of a methyl group (dashed bond).</p>	116
 <p>Chemical structure of compound 117. It is identical to compound 115, but the bicyclic core is substituted with a propyl group (-CH2CH2CH3) instead of a methyl group.</p>	117

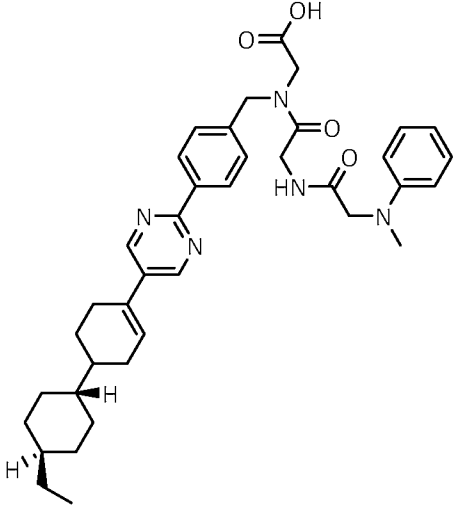
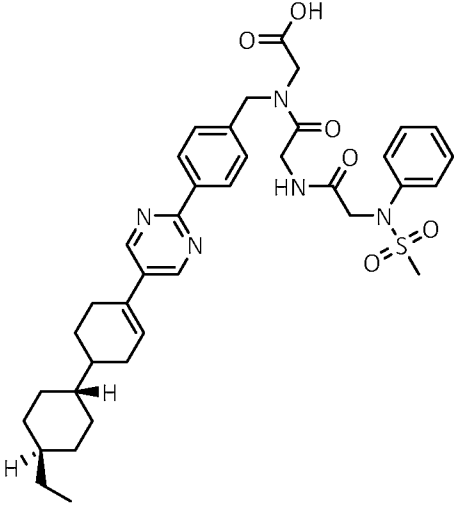
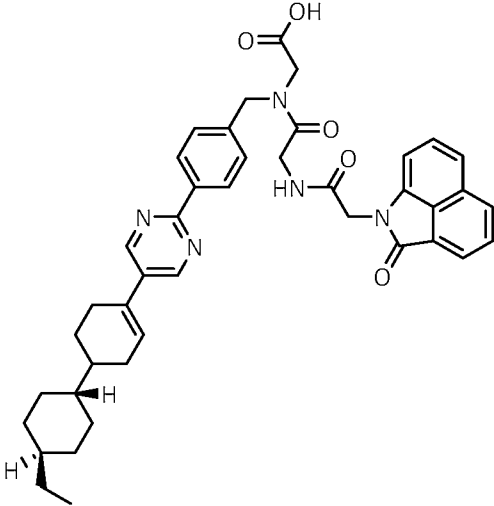
Structure	Cpd. No.
 <p>Chemical structure of compound 118. It features a central pyrimidine ring system. One side of the pyrimidine is substituted with a cyclohexane ring, which is further substituted with a propyl group. The other side of the pyrimidine is substituted with a benzene ring. This benzene ring is connected to a side chain containing a secondary amide, a primary amide, and a hydroxyl group. The primary amide is further substituted with a 4-methoxyphenyl group.</p>	118
 <p>Chemical structure of compound 119. It is similar to compound 118, but the propyl group on the cyclohexane ring is replaced by a pentyl group.</p>	119
 <p>Chemical structure of compound 120. It features a central pyrimidine ring system. One side of the pyrimidine is substituted with a cyclohexane ring, which is further substituted with a 4-isobutylphenyl group. The other side of the pyrimidine is substituted with a benzene ring. This benzene ring is connected to a side chain containing a secondary amide, a primary amide, and a hydroxyl group. The primary amide is further substituted with a 4-methoxyphenyl group.</p>	120

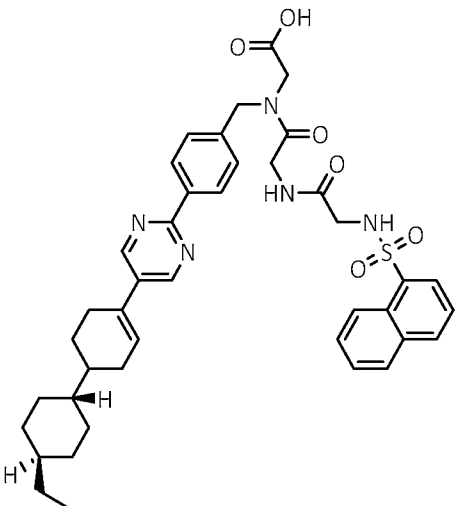
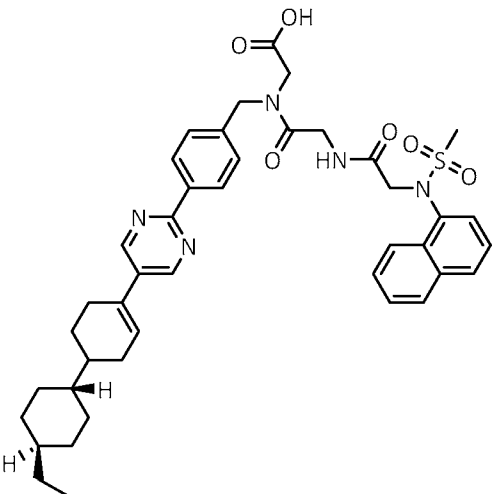
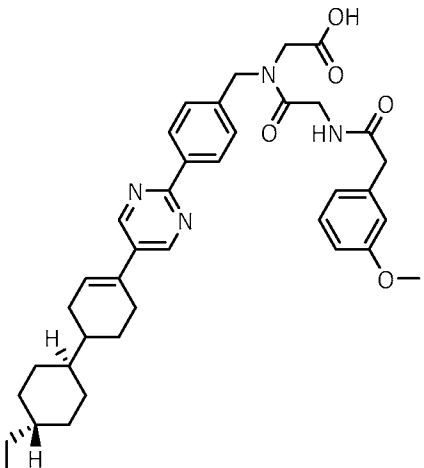
Structure	Cpd. No.
 <p>Chemical structure of compound 121: A 1,2,4-triazole ring is substituted at the 5-position with a 4-propylphenyl group and at the 3-position with a 4-(2-hydroxyacetamidoethyl)phenyl group. The 4-(2-hydroxyacetamidoethyl)phenyl group is further substituted at the para position with a 4-methoxyphenyl group.</p>	121
 <p>Chemical structure of compound 122: A 1,2,4-triazole ring is substituted at the 5-position with a 4-(1-methyl-4-iodocyclohexyl)phenyl group and at the 3-position with a 4-(2-hydroxyacetamidoethyl)phenyl group. The 4-(2-hydroxyacetamidoethyl)phenyl group is further substituted at the para position with a benzamide group.</p>	122
 <p>Chemical structure of compound 123: A 1,2,4-triazole ring is substituted at the 5-position with a 4-(1-methyl-4-iodocyclohexyl)phenyl group and at the 3-position with a 4-(2-hydroxyacetamidoethyl)phenyl group. The 4-(2-hydroxyacetamidoethyl)phenyl group is further substituted at the para position with a 4-fluoro-3-methoxyphenyl group.</p>	123

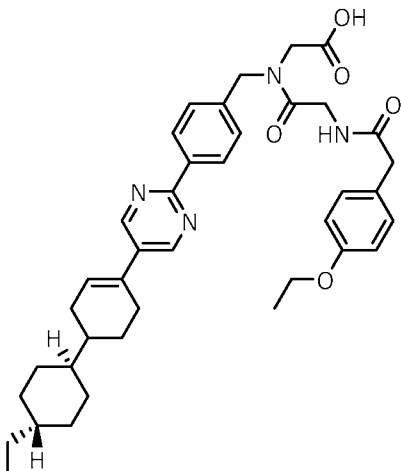
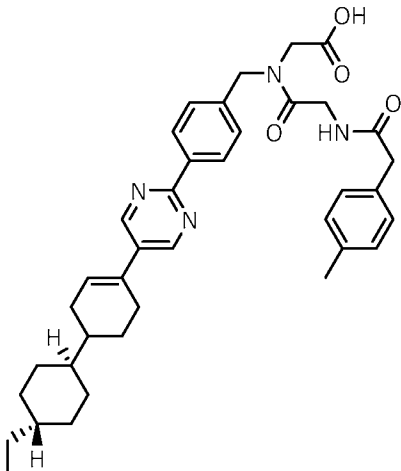
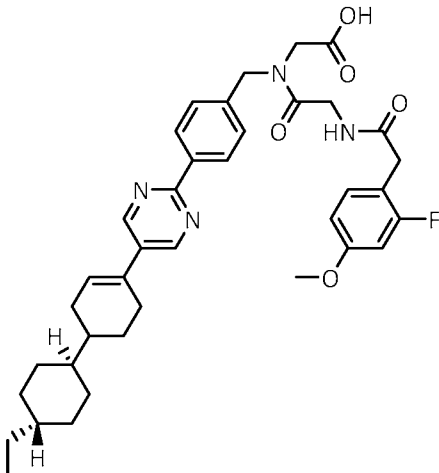
Structure	Cpd. No.
 <p>Chemical structure of compound 124. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. A 1,2,4-triazole ring is attached to the bicyclic system. The triazole ring is further substituted with a phenyl ring. This phenyl ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carbonyl group, a secondary amide group, and a carboxylic acid group. Additionally, the side chain is linked to a 4-methoxyphenyl ring, which is substituted with a trifluoromethyl group.</p>	<p>124</p>
 <p>Chemical structure of compound 125. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. A 1,2,4-triazole ring is attached to the bicyclic system. The triazole ring is further substituted with a phenyl ring. This phenyl ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carbonyl group, a secondary amide group, and a carboxylic acid group. Additionally, the side chain is linked to a benzothiazole ring system.</p>	<p>125</p>
 <p>Chemical structure of compound 126. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. A 1,2,4-triazole ring is attached to the bicyclic system. The triazole ring is further substituted with a phenyl ring. This phenyl ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carbonyl group, a secondary amide group, and a carboxylic acid group. Additionally, the side chain is linked to a 4-methoxyphenyl ring.</p>	<p>126</p>

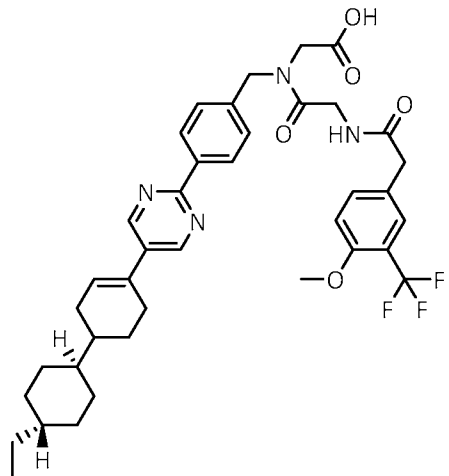
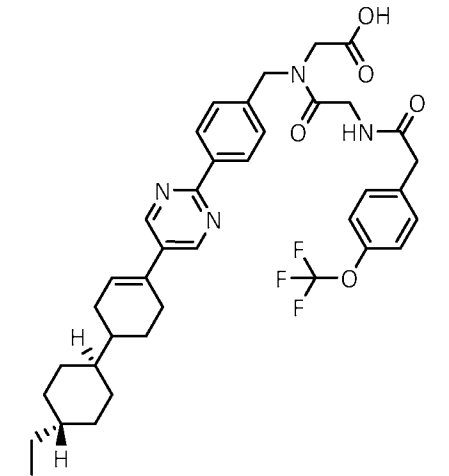
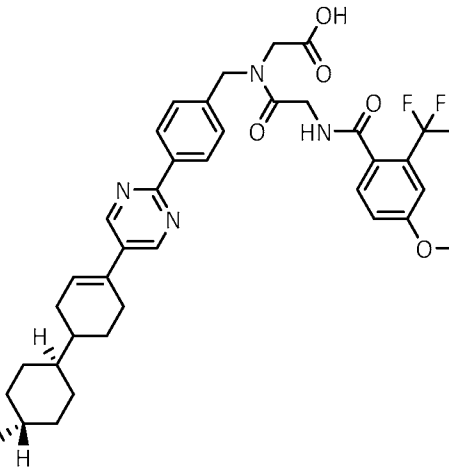
Structure	Cpd. No.
 <p>Chemical structure of compound 127. It features a bicyclic core consisting of two fused six-membered rings. One ring is substituted with a methyl group (wedge) and a hydrogen atom (dash). The other ring is substituted with a hydrogen atom (wedge). This bicyclic core is connected via a phenyl ring to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is substituted with a methyl group (wedge) and a hydrogen atom (dash). This benzene ring is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. The second carbonyl group is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. The second carbonyl group is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. The second carbonyl group is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group.</p>	127
 <p>Chemical structure of compound 128. It features a bicyclic core consisting of two fused six-membered rings. One ring is substituted with a methyl group (wedge) and a hydrogen atom (dash). The other ring is substituted with a hydrogen atom (wedge). This bicyclic core is connected via a phenyl ring to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is substituted with a methyl group (wedge) and a hydrogen atom (dash). This benzene ring is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. The second carbonyl group is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. The second carbonyl group is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. The second carbonyl group is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group.</p>	128
 <p>Chemical structure of compound 129. It features a bicyclic core consisting of two fused six-membered rings. One ring is substituted with a methyl group (wedge) and a hydrogen atom (dash). The other ring is substituted with a hydrogen atom (wedge). This bicyclic core is connected via a phenyl ring to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is substituted with a methyl group (wedge) and a hydrogen atom (dash). This benzene ring is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. The second carbonyl group is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. The second carbonyl group is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. The second carbonyl group is connected to a nitrogen atom, which is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group.</p>	129

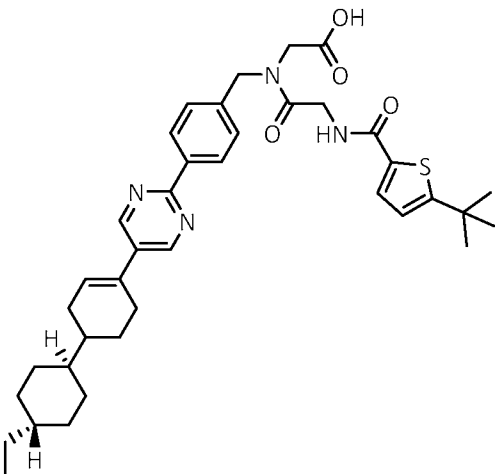
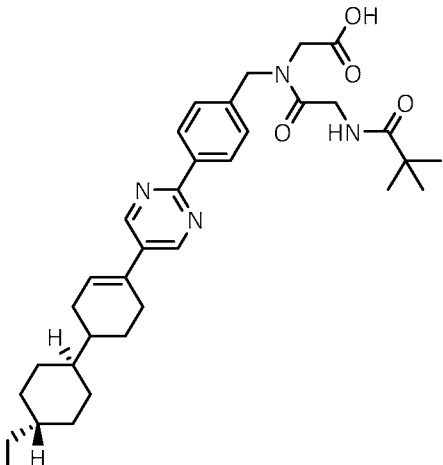
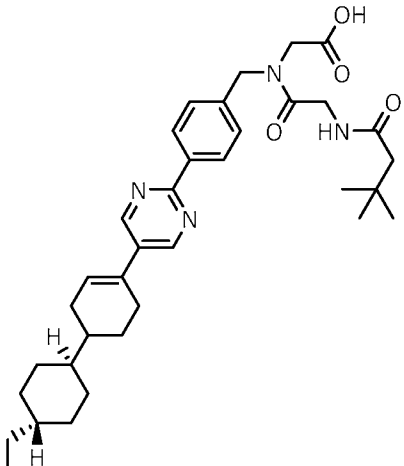
Structure	Cpd. No.
 <p>Chemical structure of compound 130: A bicyclic core consisting of two fused six-membered rings. The left ring is a cyclohexane with a methyl group at the 1-position and a hydrogen atom at the 2-position, both shown with wedged bonds. The right ring is a cyclohexane with a hydrogen atom at the 1-position, also shown with a wedged bond. A piperidine ring is attached to the 2-position of the right ring. The piperidine ring is substituted at the 4-position with a phenyl ring, which is further substituted at the para position with a pyrimidine ring. The pyrimidine ring is substituted at the 2-position with a benzyl group. The benzyl group is attached to a nitrogen atom that is also bonded to a hydroxymethyl group (-CH₂OH) and a carbonyl group (-C(=O)-). This carbonyl group is part of a secondary amide linkage (-NH-) to another carbonyl group (-C(=O)-), which is in turn bonded to a methylene group (-CH₂-) and a primary amide group (-NH-). The primary amide group is bonded to a benzene ring that has a sulfonamide group (-SO₂NH-) attached to it.</p>	<p>130</p>
 <p>Chemical structure of compound 131: Similar to compound 130, but the primary amide group (-NH-) is bonded to a methyl group (-CH₃) instead of a benzene ring.</p>	<p>131</p>
 <p>Chemical structure of compound 132: Similar to compound 130, but the primary amide group (-NH-) is bonded to a hydrogen atom (-H) instead of a benzene ring.</p>	<p>132</p>

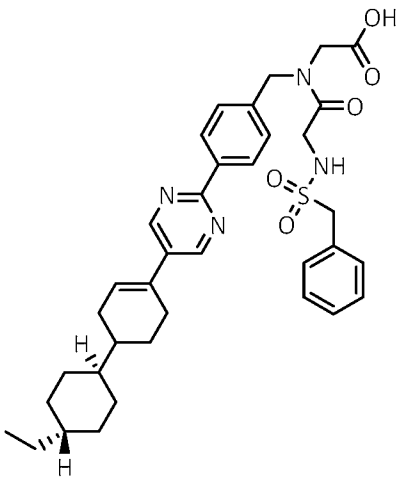
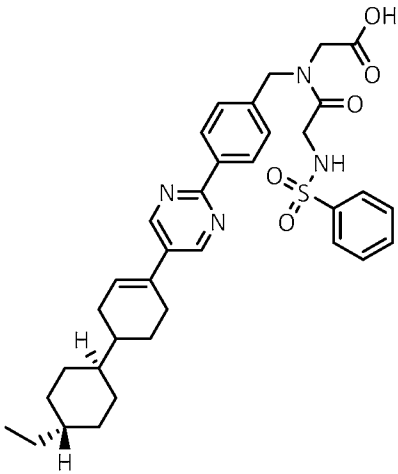
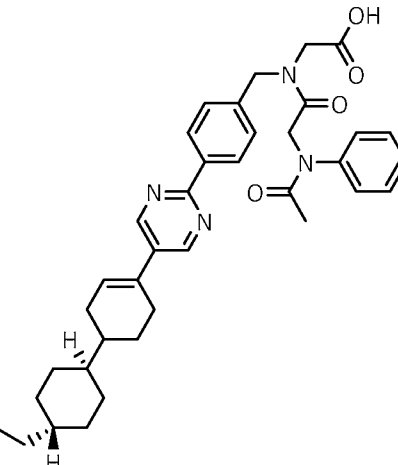
Structure	Cpd. No.
 <p>Chemical structure of compound 133. It features a bicyclic core consisting of two fused six-membered rings. One ring has a methyl group and a hydrogen atom at the 1-position, and a hydrogen atom at the 4-position. The other ring has a hydrogen atom at the 1-position. A phenyl ring is attached to the 4-position of the second ring. This phenyl ring is connected to a pyrimidine ring at its 2-position. The pyrimidine ring is further connected to a benzene ring at its 4-position. This benzene ring is connected to a methylene group, which is attached to a nitrogen atom. This nitrogen atom is part of a side chain that includes a carbonyl group, a methylene group, and a hydroxyl group. The nitrogen atom is also connected to another nitrogen atom, which is part of a side chain that includes a carbonyl group, a methylene group, and a methyl group.</p>	133
 <p>Chemical structure of compound 134. It features a bicyclic core consisting of two fused six-membered rings. One ring has a methyl group and a hydrogen atom at the 1-position, and a hydrogen atom at the 4-position. The other ring has a hydrogen atom at the 1-position. A phenyl ring is attached to the 4-position of the second ring. This phenyl ring is connected to a pyrimidine ring at its 2-position. The pyrimidine ring is further connected to a benzene ring at its 4-position. This benzene ring is connected to a methylene group, which is attached to a nitrogen atom. This nitrogen atom is part of a side chain that includes a carbonyl group, a methylene group, and a hydroxyl group. The nitrogen atom is also connected to another nitrogen atom, which is part of a side chain that includes a carbonyl group, a methylene group, and a methyl group. Additionally, the nitrogen atom is connected to a sulfur atom, which is double-bonded to two oxygen atoms.</p>	134
 <p>Chemical structure of compound 135. It features a bicyclic core consisting of two fused six-membered rings. One ring has a methyl group and a hydrogen atom at the 1-position, and a hydrogen atom at the 4-position. The other ring has a hydrogen atom at the 1-position. A phenyl ring is attached to the 4-position of the second ring. This phenyl ring is connected to a pyrimidine ring at its 2-position. The pyrimidine ring is further connected to a benzene ring at its 4-position. This benzene ring is connected to a methylene group, which is attached to a nitrogen atom. This nitrogen atom is part of a side chain that includes a carbonyl group, a methylene group, and a hydroxyl group. The nitrogen atom is also connected to another nitrogen atom, which is part of a side chain that includes a carbonyl group, a methylene group, and a methyl group. Additionally, the nitrogen atom is connected to a nitrogen atom, which is part of a side chain that includes a carbonyl group and a methyl group.</p>	135

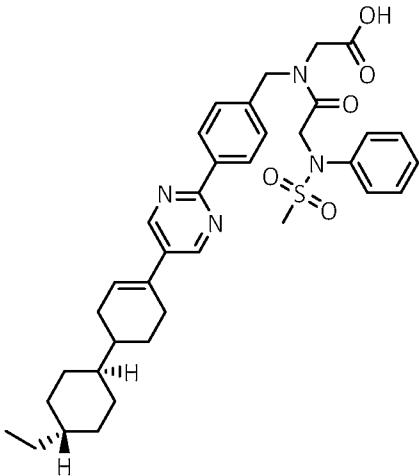
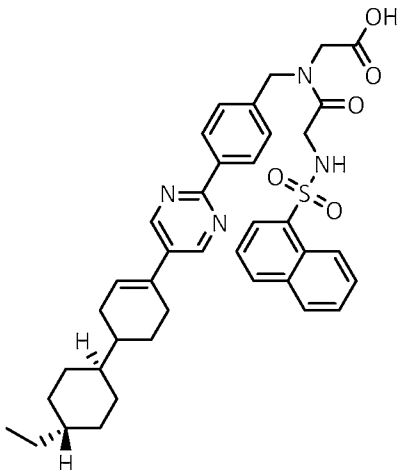
Structure	Cpd. No.
 <p>Chemical structure of compound 136. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens explicitly shown. One of the cyclohexane rings is substituted with a phenyl ring, which is further substituted with a pyrimidine ring. The pyrimidine ring is connected via a methylene group to a nitrogen atom. This nitrogen atom is part of a side chain that includes a carboxylic acid group (-COOH) and a secondary amide linkage (-NH-CO-). The secondary amide nitrogen is connected to a methylene group, which is in turn connected to another secondary amide group (-NH-CO-). This second secondary amide nitrogen is bonded to a naphthalene ring system.</p>	136
 <p>Chemical structure of compound 137. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens explicitly shown. One of the cyclohexane rings is substituted with a phenyl ring, which is further substituted with a pyrimidine ring. The pyrimidine ring is connected via a methylene group to a nitrogen atom. This nitrogen atom is part of a side chain that includes a carboxylic acid group (-COOH) and a secondary amide linkage (-NH-CO-). The secondary amide nitrogen is connected to a methylene group, which is in turn connected to another secondary amide group (-NH-CO-). This second secondary amide nitrogen is bonded to a naphthalene ring system.</p>	137
 <p>Chemical structure of compound 138. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens explicitly shown. One of the cyclohexane rings is substituted with a phenyl ring, which is further substituted with a pyrimidine ring. The pyrimidine ring is connected via a methylene group to a nitrogen atom. This nitrogen atom is part of a side chain that includes a carboxylic acid group (-COOH) and a secondary amide linkage (-NH-CO-). The secondary amide nitrogen is connected to a methylene group, which is in turn connected to another secondary amide group (-NH-CO-). This second secondary amide nitrogen is bonded to a 4-methoxyphenyl ring.</p>	138

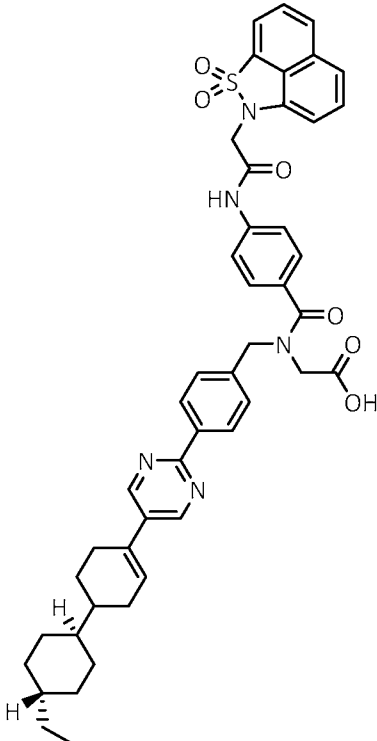
Structure	Cpd. No.
 <p>Chemical structure of compound 139. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. One of the cyclohexane rings is substituted with a 1,2,4-triazole ring. The triazole ring is further substituted with a benzene ring. This benzene ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carbonyl group, a secondary amide group, and a hydroxyl group. The side chain is also substituted with a benzene ring that has an ethoxy group at the para position.</p>	139
 <p>Chemical structure of compound 140. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. One of the cyclohexane rings is substituted with a 1,2,4-triazole ring. The triazole ring is further substituted with a benzene ring. This benzene ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carbonyl group, a secondary amide group, and a hydroxyl group. The side chain is also substituted with a benzene ring that has a methyl group at the para position.</p>	140
 <p>Chemical structure of compound 141. It features a bicyclic core consisting of two fused cyclohexane rings. The bridgehead carbons have hydrogens shown with wedged and dashed bonds. One of the cyclohexane rings is substituted with a 1,2,4-triazole ring. The triazole ring is further substituted with a benzene ring. This benzene ring is connected via a methylene group to a nitrogen atom. The nitrogen atom is part of a side chain that includes a carbonyl group, a secondary amide group, and a hydroxyl group. The side chain is also substituted with a benzene ring that has a methoxy group and a fluorine atom at the meta positions.</p>	141

Structure	Cpd. No.
 <p>Chemical structure of compound 142. It features a bicyclic system consisting of two fused cyclohexane rings. The top ring has a methyl group at the 1-position and a hydrogen atom at the 2-position, both shown with wedged bonds. The bottom ring has a hydrogen atom at the 6-position, also shown with a wedged bond. A 1,2,4-triazole ring is attached to the 4-position of the bottom ring. This triazole ring is further connected to a 4-phenyl ring, which is in turn linked via a methylene group to a nitrogen atom. This nitrogen atom is part of a 2-hydroxyethylamino group (-N(CH₂CH₂OH)). The nitrogen atom is also bonded to a carbonyl group (-C(=O)-), which is connected to a methylene group (-CH₂-). This methylene group is further connected to another carbonyl group (-C(=O)-), which is bonded to a hydrogen atom (-NH-). This hydrogen atom is connected to a methylene group (-CH₂-), which is finally connected to a 4-(2,2,2-trifluoroethoxy)phenyl ring.</p>	142
 <p>Chemical structure of compound 143. It features a bicyclic system consisting of two fused cyclohexane rings. The top ring has a methyl group at the 1-position and a hydrogen atom at the 2-position, both shown with wedged bonds. The bottom ring has a hydrogen atom at the 6-position, also shown with a wedged bond. A 1,2,4-triazole ring is attached to the 4-position of the bottom ring. This triazole ring is further connected to a 4-phenyl ring, which is in turn linked via a methylene group to a nitrogen atom. This nitrogen atom is part of a 2-hydroxyethylamino group (-N(CH₂CH₂OH)). The nitrogen atom is also bonded to a carbonyl group (-C(=O)-), which is connected to a methylene group (-CH₂-). This methylene group is further connected to another carbonyl group (-C(=O)-), which is bonded to a hydrogen atom (-NH-). This hydrogen atom is connected to a methylene group (-CH₂-), which is finally connected to a 4-(2,2,2-trifluoroethoxy)phenyl ring.</p>	143
 <p>Chemical structure of compound 144. It features a bicyclic system consisting of two fused cyclohexane rings. The top ring has a methyl group at the 1-position and a hydrogen atom at the 2-position, both shown with wedged bonds. The bottom ring has a hydrogen atom at the 6-position, also shown with a wedged bond. A 1,2,4-triazole ring is attached to the 4-position of the bottom ring. This triazole ring is further connected to a 4-phenyl ring, which is in turn linked via a methylene group to a nitrogen atom. This nitrogen atom is part of a 2-hydroxyethylamino group (-N(CH₂CH₂OH)). The nitrogen atom is also bonded to a carbonyl group (-C(=O)-), which is connected to a methylene group (-CH₂-). This methylene group is further connected to another carbonyl group (-C(=O)-), which is bonded to a hydrogen atom (-NH-). This hydrogen atom is connected to a methylene group (-CH₂-), which is finally connected to a 2-(2,2,2-trifluoroethoxy)phenyl ring.</p>	144

Structure	Cpd. No.
 <p>Chemical structure of compound 145. It features a bicyclic core consisting of two cyclohexane rings fused at the 1 and 4 positions. The core is substituted with a methyl group (wedge) and a hydrogen atom (dash) at the 1-position, and a hydrogen atom (wedge) at the 4-position. A 1,2,4-triazole ring is attached to the 1-position of the second cyclohexane ring. The triazole ring is further substituted with a 4-(benzylamino)phenyl group. The benzylamino group is part of a side chain that includes a secondary amide linkage to a 2-(tert-butyl)thiophene-5-carboxamide moiety. The side chain also contains a hydroxamic acid group (-NHOH).</p>	145
 <p>Chemical structure of compound 146. It features a bicyclic core consisting of two cyclohexane rings fused at the 1 and 4 positions. The core is substituted with a methyl group (wedge) and a hydrogen atom (dash) at the 1-position, and a hydrogen atom (wedge) at the 4-position. A 1,2,4-triazole ring is attached to the 1-position of the second cyclohexane ring. The triazole ring is further substituted with a 4-(benzylamino)phenyl group. The benzylamino group is part of a side chain that includes a secondary amide linkage to a tert-butyl amide moiety. The side chain also contains a hydroxamic acid group (-NHOH).</p>	146
 <p>Chemical structure of compound 147. It features a bicyclic core consisting of two cyclohexane rings fused at the 1 and 4 positions. The core is substituted with a methyl group (wedge) and a hydrogen atom (dash) at the 1-position, and a hydrogen atom (wedge) at the 4-position. A 1,2,4-triazole ring is attached to the 1-position of the second cyclohexane ring. The triazole ring is further substituted with a 4-(benzylamino)phenyl group. The benzylamino group is part of a side chain that includes a secondary amide linkage to a tert-butyl amide moiety. The side chain also contains a hydroxamic acid group (-NHOH).</p>	147

Structure	Cpd. No.
 <p>Chemical structure of compound 148: A bicyclic system consisting of two fused cyclohexane rings. The front ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The back ring is substituted with a 4-(4-(2-(benzenesulfonylamino)ethyl)phenyl)pyrimidin-2-yl group. The phenyl ring of the pyrimidine is further substituted with a 2-(2-(2-hydroxyacetyl)amino)ethyl group.</p>	148
 <p>Chemical structure of compound 149: Similar to compound 148, but the phenyl ring of the pyrimidine is substituted with a 2-(2-phenylamino)ethyl group instead of the 2-(2-(2-hydroxyacetyl)amino)ethyl group.</p>	149
 <p>Chemical structure of compound 150: Similar to compound 148, but the phenyl ring of the pyrimidine is substituted with a 2-(2-(2-phenylamino)ethyl)amino group instead of the 2-(2-(2-hydroxyacetyl)amino)ethyl group.</p>	150

Structure	Cpd. No.
 <p>Chemical structure of compound 151. It features a bicyclic core consisting of two fused cyclohexane rings. The front ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The back ring is substituted with a cyclohexene ring, which is further substituted with a pyrimidine ring. The pyrimidine ring is connected to a benzene ring, which is in turn connected to a nitrogen atom. This nitrogen atom is part of a side chain containing a carbonyl group, a methylene group, another nitrogen atom, and a hydroxyl group. A sulfonamide group is also attached to the side chain, consisting of a sulfur atom double-bonded to two oxygen atoms and single-bonded to a nitrogen atom, which is further bonded to a phenyl ring.</p>	151
 <p>Chemical structure of compound 152. It features a bicyclic core consisting of two fused cyclohexane rings. The front ring has a methyl group on a dashed bond and a hydrogen atom on a wedged bond. The back ring is substituted with a cyclohexene ring, which is further substituted with a pyrimidine ring. The pyrimidine ring is connected to a benzene ring, which is in turn connected to a nitrogen atom. This nitrogen atom is part of a side chain containing a carbonyl group, a methylene group, another nitrogen atom, and a hydroxyl group. A sulfonamide group is also attached to the side chain, consisting of a sulfur atom double-bonded to two oxygen atoms and single-bonded to a nitrogen atom, which is further bonded to a naphthalene ring system.</p>	152

Structure	Cpd. No.
	153

Compound Nos. 1-153 of Table 1 above include, but are not limited to, hydrates, hydrates and/or isotopes thereof, as well as pharmaceutically acceptable salts thereof.

5 A "salt" as is well known in the art includes an organic compound such as a carboxylic acid, a sulfonic acid, or an amine, in ionic form, in combination with a counter ion. For example, acids in their anionic form can form salts with cations such as metal cations, for example sodium, potassium, and the like; with ammonium salts such as NH_4^+ or the cations of various amines, including tetraalkyl ammonium salts
 10 such as tetramethylammonium, or other cations such as trimethylsulfonium, and the like.

A "pharmaceutically acceptable salt" is a salt formed from a counter ion that has been approved for human consumption and is generally non-toxic.

15 Acid addition salts of the disclosed compounds include, for example, salts prepared by adding and inorganic acid or an organic acid. Examples of inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydriodic, nitric,

carbonic, sulfuric, and phosphoric acids. Appropriate organic acids include, but are not limited to, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, representative examples of which include formic acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, 5 glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, panthothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid.

10 Base addition salts of the disclosed compounds include, but are not limited to, salts prepared by adding alkali metal, alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Representative base addition salts also include salts made from organic bases such as, for example, *N,N*-dibenzylethylenediamine, chlorprocaine, choline, 15 diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine.

A "hydrate" is a compound that exists in a composition with water molecules. The composition can include water in stoichiometric quantities, such as a monohydrate or a dihydrate, or can include water in random amounts. As the term is used herein a "hydrate" refers to a solid form (*i.e.*, a compound in water solution, while 20 it may be hydrated, is not a hydrate as the term is used herein).

A "solvate" is a similar composition except that a solvent other than water replaces the water. For example, methanol or ethanol can form an "alcoholate", which can again be stoichiometric or non-stoichiometric. As the term is used herein a "solvate" refers to a solid form (*i.e.*, a compound in solution in a solvent, while it may 25 be solvated, is not a solvate as the term is used herein).

The term "isotope" refers to atoms with the same number of protons but a different number of neutrons, and an isotope of a compound of Formula (I) includes any such compound wherein one or more atoms are replaced by an isotope of that atom. For example, carbon 12, the most common form of carbon, has six protons and six 30 neutrons, whereas carbon 13 has six protons and seven neutrons, and carbon 14 has six protons and eight neutrons. Hydrogen has two stable isotopes, deuterium (one proton

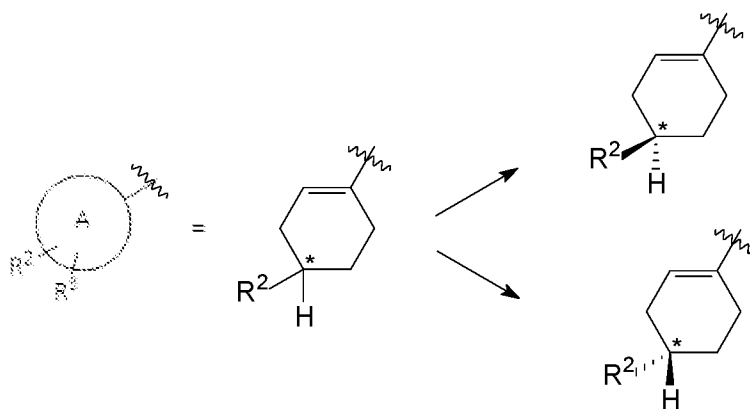
and one neutron) and tritium (one proton and two neutrons). While fluorine has a number of isotopes, fluorine 19 is longest-lived. Thus, an isotope of a compound having the structure of Formula (I) includes, but not limited to, compounds of Formula (I) wherein one or more carbon 12 atoms are replaced by carbon 13 and/or 14 atoms,
5 wherein one or more hydrogen atoms are replaced with deuterium and/or tritium, and/or wherein one or more fluorine atoms are replaced by fluorine 19.

“Stereoisomers” include all chiral, enantiomeric, diastereomeric and/or racemic forms of a compound, unless a particular stereochemistry or isomeric form is specifically indicated. Compounds of the present invention include enriched or resolved
10 optical isomers at any or all asymmetric atoms as are apparent from the depictions, at any degree of enrichment, including, for example, enrichment to a weight purity of 98%, 99%, 99.5% or 99.9%. Both racemic, enantiomeric and diastereomeric mixtures, as well as the individual optical isomers, can be synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope
15 of certain embodiments of the invention.

Enantiomers are sometimes called optical isomers because a pure enantiomer rotates plane-polarized light in a particular direction. If the light rotates clockwise, then that enantiomer is labeled “(+)” or “d” for dextrorotatory, its counterpart will rotate the light counterclockwise and is labeled “(-)” or “l” for
20 levorotatory. Stereoisomers that differ at some stereocenters but not at others are not mirror images, so they are not enantiomers. Instead, they are referred to as diastereomers. A diastereomer is any stereoisomer that is not an enantiomer.

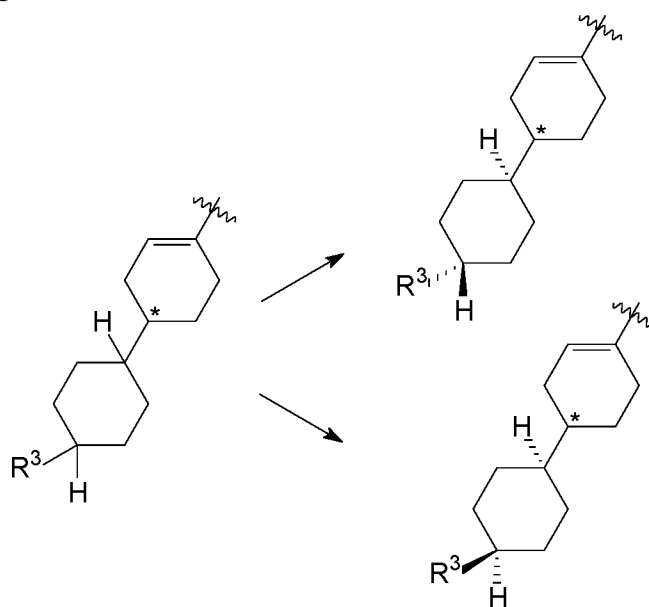
The terms “racemate” and “racemic mixture” are frequently used interchangeably. A racemate is an equal mixture of two enantiomers. A racemate is
25 labeled “(±)” because it is not optically active (*i.e.*, will not rotate plane-polarized light in either direction since its constituent enantiomers cancel each other out).

In certain representative embodiments, the “A” group of Formula (I) has the following structure, wherein the asterisk (*) denotes chiral carbon.



While the above disclosure depicts stereo confirmation at a single chiral center, it should be understood that the presence of multiple chiral centers allows for multiple combinations of stereoisomers (*e.g.*, two chiral centers will give four possible orientations, and so forth). It is intended that compounds having the structure of any one of Formulas (I)-(XII) above include all stereoisomers arising from the presence of one or more chiral centers, including any and all enantiomeric and/or diastereomeric forms, at any degree of purity, as well as racemic mixtures of the same.

In a further representative embodiment, R^2 is cyclohexyl substituted with R^3 , as illustrated below. In this embodiment, the noted hydrogen atoms can exist in a *cis*- or *trans*-configuration:



Accordingly, it is intended that compounds having the structure of any one of Formulas (I)-(XII) above also include stereoisomers involving geometric isomerism, such as the *cis*- and/or *trans*-isomers illustrated above.

It should also be understood that a prodrug is a substance that can be administered to a patient where the substance is converted *in vivo* by the action of biochemicals within the patient's body, such as enzymes, to the active pharmaceutical ingredient. Examples of prodrugs include esters of carboxylic acid groups, which can be hydrolyzed by endogenous esterases as are found in the bloodstream of humans and other mammals. In one embodiment of the present invention, substances are provided that can be administered to a patient where the substance is converted *in vivo* by the action of biochemical reactions within the patient's body, such as enzymes, to a compound having the structure of any one of Formulas (I)-(XII), or a compound of Table 1.

In one embodiment, a pharmaceutical composition is provided comprising a compound of Formula (I)-(XII), a compound of Table 1, or a pharmaceutically acceptable salt thereof, in combination with at least one pharmaceutically acceptable carrier, diluent or excipient.

As use herein, a compound that "modulates" a GLP-1 receptor means that the compound interacts with the receptor, either directly or by way of an allosteric interaction, thereby activating, potentiating and/or agonizing the GLP-1 receptor for which it modulates.

In one embodiment, the present invention encompasses compounds that modulate GLP-1 receptor, with high affinity and specificity, an agonist manner or as an activator or a potentiator. In another embodiment, a compound of the invention acts as a positive allosteric modulator of GLP-1 receptor.

In one embodiment, the present invention provides a method for agonizing a GLP-1 receptor with a compound of the invention (*i.e.*, an agonist). The method involves contacting the receptor with a suitable concentration of an inventive compound to bring about activation of the receptor. The contacting can take place *in vitro*, for example in carrying out an assay to determine the GLP-1 receptor activation activity of an inventive compound undergoing experimentation related to a submission for regulatory approval.

In one embodiment, the method for modulating a GLP-1 receptor, can also be carried out *in vivo*, that is, within the living body of a mammal, such as a human

patient or a test animal. The inventive compound can be supplied to the living organism via one of the routes as described above (*e.g.*, orally), or can be provided locally within the body tissues. In the presence of the inventive compound, activation of the receptor takes place and the effect thereof can be studied.

5 In one embodiment, a method is provided for modulation of a GLP-1 receptor by contacting the receptor with an effective amount of a compound of this invention, or a pharmaceutical composition comprising the same, wherein the GLP-1 receptor is disposed within a living mammal.

10 In one embodiment, a method is provided for treatment of a malcondition in a subject for which modulation of a GLP-1 receptor is medically indicated, by administering an effective amount of a compound of this invention to the subject at a frequency and for duration of time sufficient to provide a beneficial effect to the subject (*e.g.*, patient).

15 “Treating” or “treatment” refers to an alleviation of symptoms associated with a disorder or disease, or inhibition of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder.

20 “Effective amount” refers to an amount sufficient to produce a beneficial therapeutic effect on the patient. For example, “effective amount” or a “therapeutically effective amount” of a compound of the invention refers to an amount of the compound that alleviates, in whole or in part, symptoms associated with the disorder or condition, or halts or slows further progression or worsening of those symptoms, or prevents or provides prophylaxis for the disorder or condition. In particular, a “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result by acting as a modulator of GLP-1
25 activity. A therapeutically effective amount is also one in which any toxic or detrimental effects of compounds of the invention are outweighed by the therapeutically beneficial effects. For example, in the context of treating a malcondition mediated by activation of a GLP-1 receptor, a therapeutically effective amount of a GLP-1 receptor agonist is an amount sufficient to control the malcondition, to mitigate the progress of
30 the malcondition, or to relieve the symptoms of the malcondition. The dosages and

formulations for the other agents to be employed, where applicable, will be as set out in the latest edition of the *Physicians' Desk Reference*, incorporated herein by reference.

In one embodiment, a method is provided for treatment of a malcondition in a subject for which modulation of a GLP-1 receptor is medically indicated, by administering an effective amount of a compound of this invention to the subject at a frequency and for a duration of time sufficient to provide a beneficial effect to the subject, wherein the malcondition comprises type I diabetes, type II diabetes, gestational diabetes, obesity, excessive appetite, insufficient satiety, or metabolic disorder. In one embodiment, the subject is a patient or a human being. In certain embodiments, the human being is afflicted with, or at risk of developing, a disease or condition selected from the group consisting of type I diabetes, type II diabetes, gestational diabetes, obesity, excessive appetite, insufficient satiety, and metabolic disorder. In one embodiment, said disease is type I diabetes or type II diabetes.

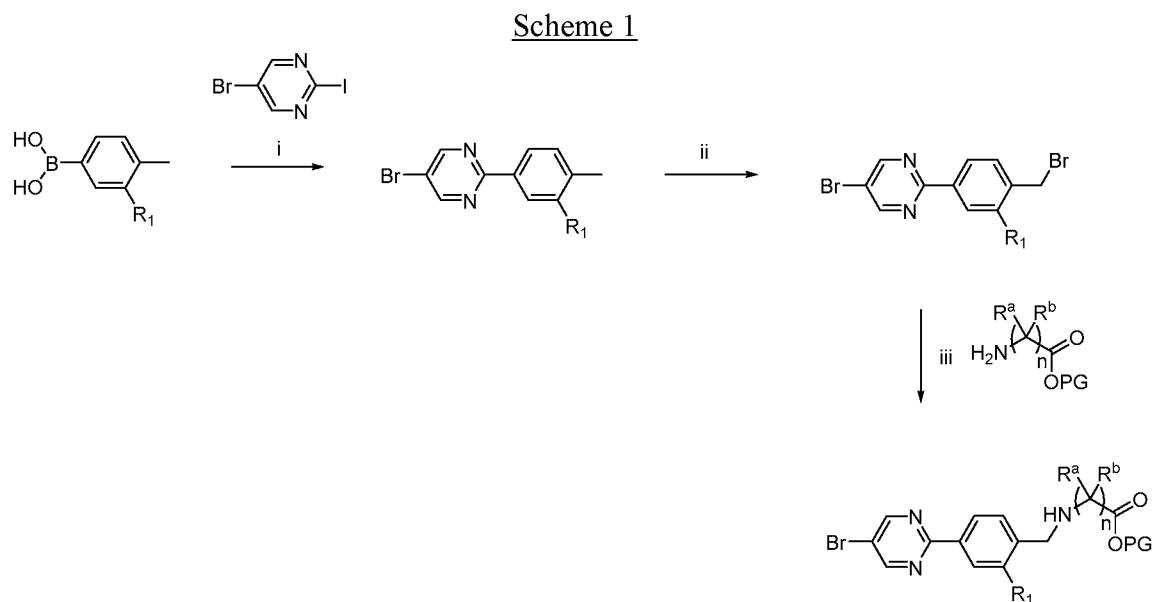
In another embodiment, methods of treatment provided by the invention include administration of a compound of the invention to a subject (*e.g.*, patient) for the treatment of non-alcoholic fatty liver disease (NAFLD) and/or non-alcoholic steatohepatitis (NASH). NAFLD is believed to be caused by the disruption of hepatic lipid homeostasis and, at least in a portion of patients, can progress to NASH. NAFLD is associated with insulin resistance in type 2 diabetes mellitus, and GLP1 increases insulin sensitivity and aids glucose metabolism. The compounds of this invention are beneficial in this context by serving to increase fatty acid oxidation, decrease lipogenesis, and/or improve hepatic glucose metabolism (*see e.g.*, Lee *et al.*, *Diabetes Metab. J.* 36:262-267, 2012; Trevaskis *et al.* *Am. J. Physiol. Gastrointest. Liver Physiol.* 302:G762-G772, 2012; Kim *et al.* *Korean J. Physiol. Pharmacol.* 18:333-339, 2014; and see: Armstrong *et al.*, *Journal of Hepatology* 62:S187-S212, 2015 for results with Liraglutide in Phase II trials).

In one embodiment, methods are provided for use of a compound of this invention for preparation of a medicament adapted for treatment of a disorder or a malcondition wherein modulation of a GLP-1 receptor is medically indicated.

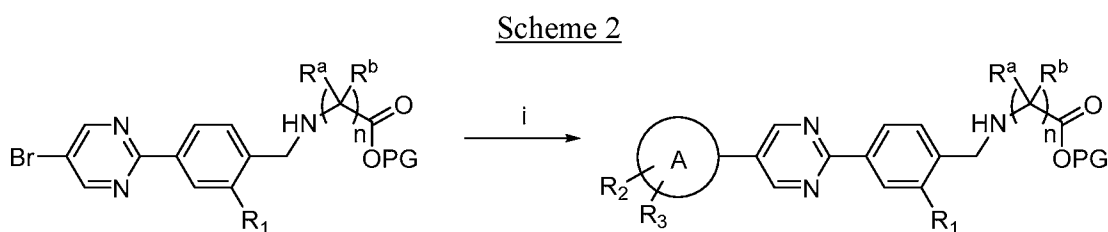
In one embodiment, the invention provides methods for synthesis of certain compounds including compounds of the invention as more fully illustrated

herein. In certain other embodiments, the invention provides certain intermediate compounds associated with such methods of synthesis as illustrated herein.

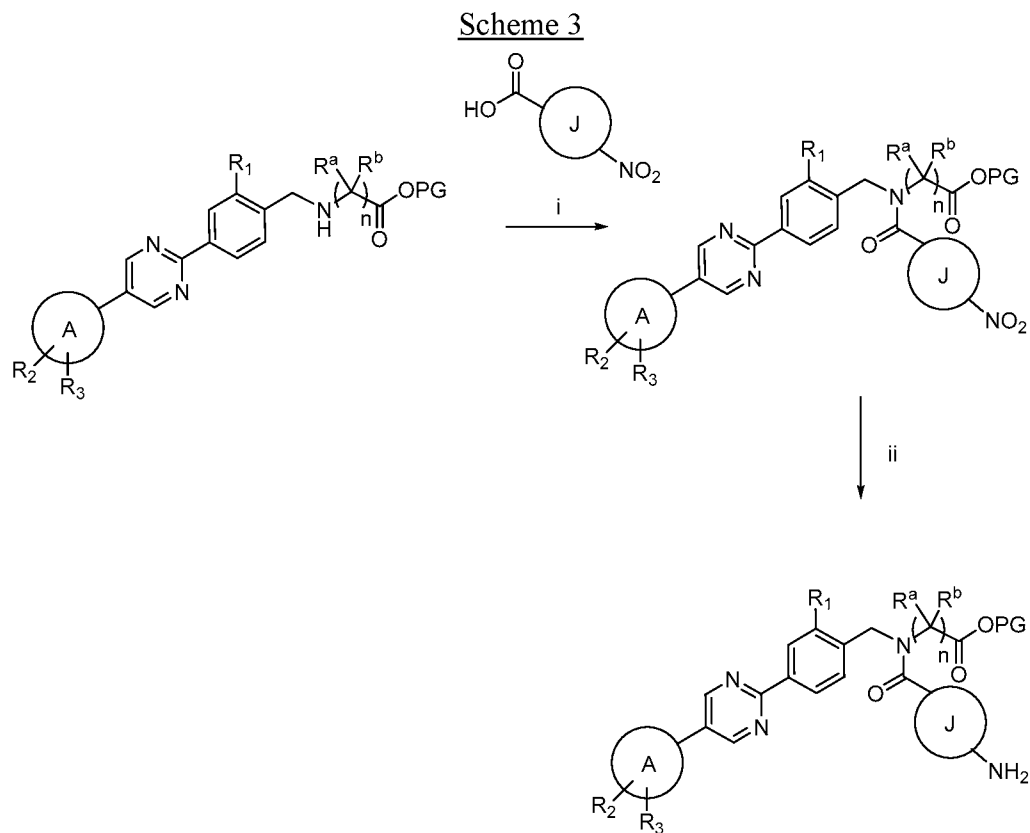
Compounds of the invention can be synthesized using standard synthetic techniques known to those of skill in the art, including the general synthetic procedures set forth in the Schemes 1-20 below.



Reagents: PG is a protecting group (i) Pd(dppf)Cl₂, Na₂CO₃ or NaHCO₃, dioxane,
 10 water; (ii) NBS, AIBN, CHCl₃; (iii) DIEA, THF.

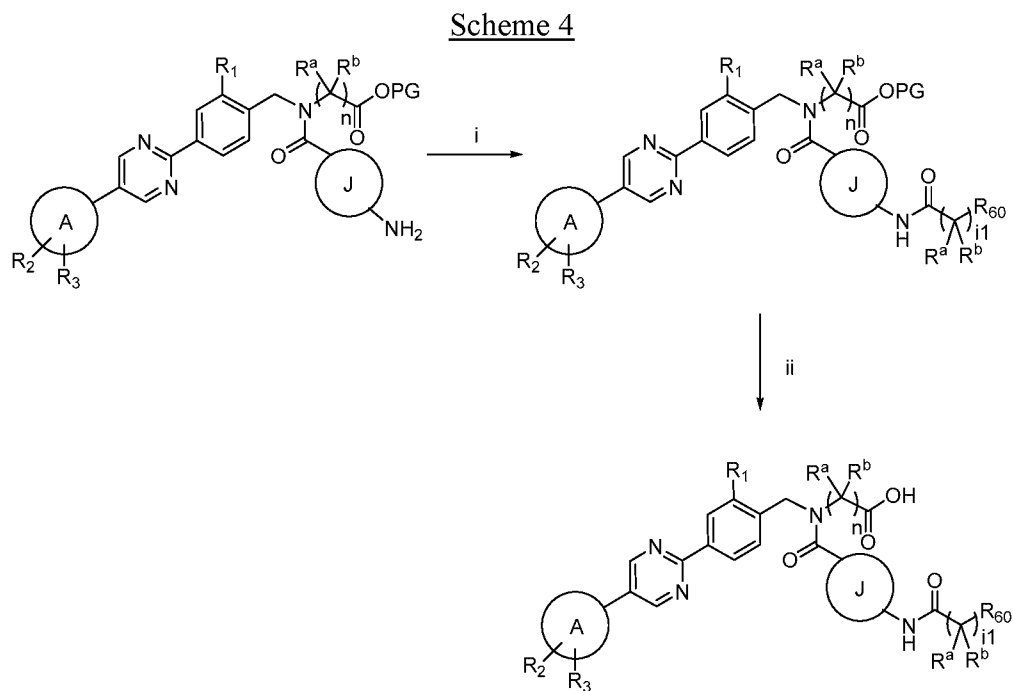


Reagents: PG is a protecting group (i) Pd(dppf)Cl₂, Na₂CO₃ or NaHCO₃, dioxane,
 water.

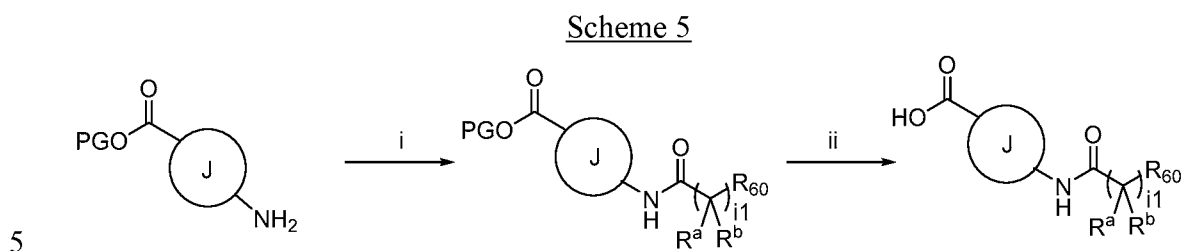


Reagents: PG is a protecting group (i) HATU, DIEA, DMF; (ii) NH_4Cl , iron, THF, EtOH, water.

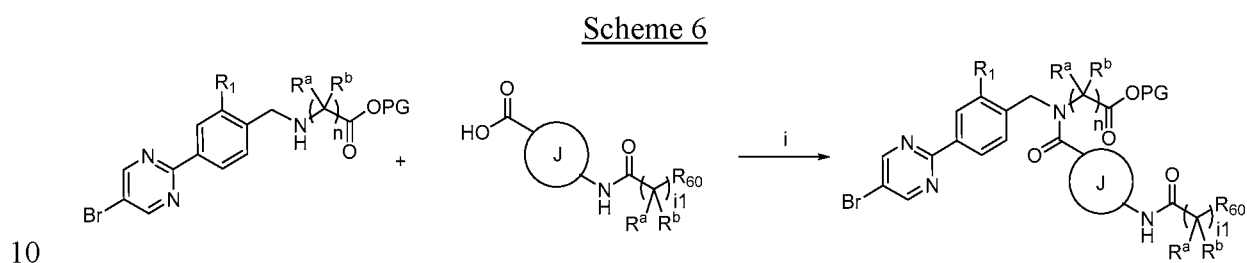
5



Reagents: PG is a protecting group (i) Coupling with acid: HATU, DIEA, DMF or coupling with acid chloride: DIEA, DCM; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.

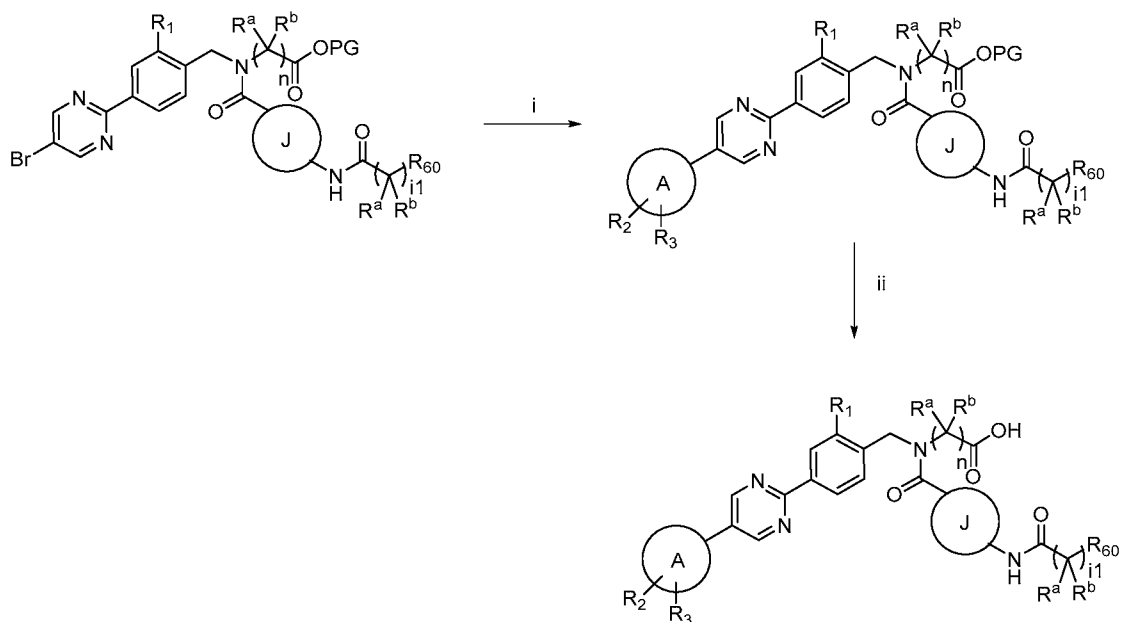


Reagents: PG is a protecting group (i) Coupling with acid: HATU, DIEA, DMF or coupling with acid chloride: DIEA, DCM; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.



Reagents: PG is a protecting group (i) Coupling with acid: HATU, DIEA, DMF or coupling with acid chloride: DIEA, DCM.

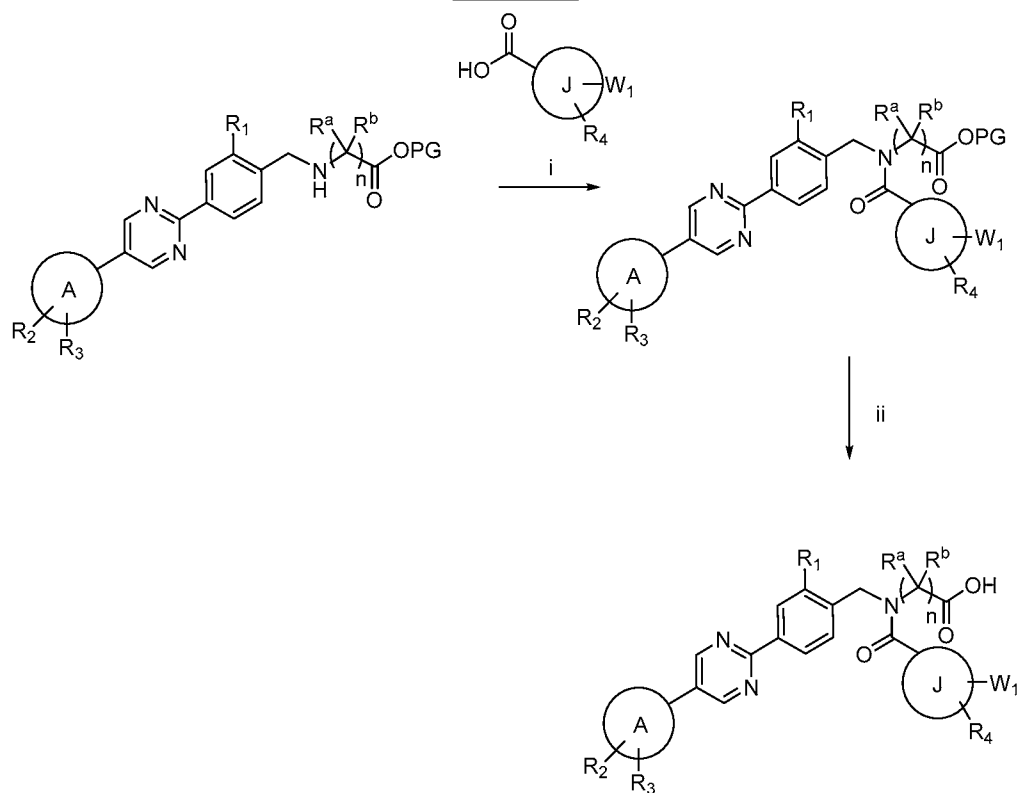
Scheme 7



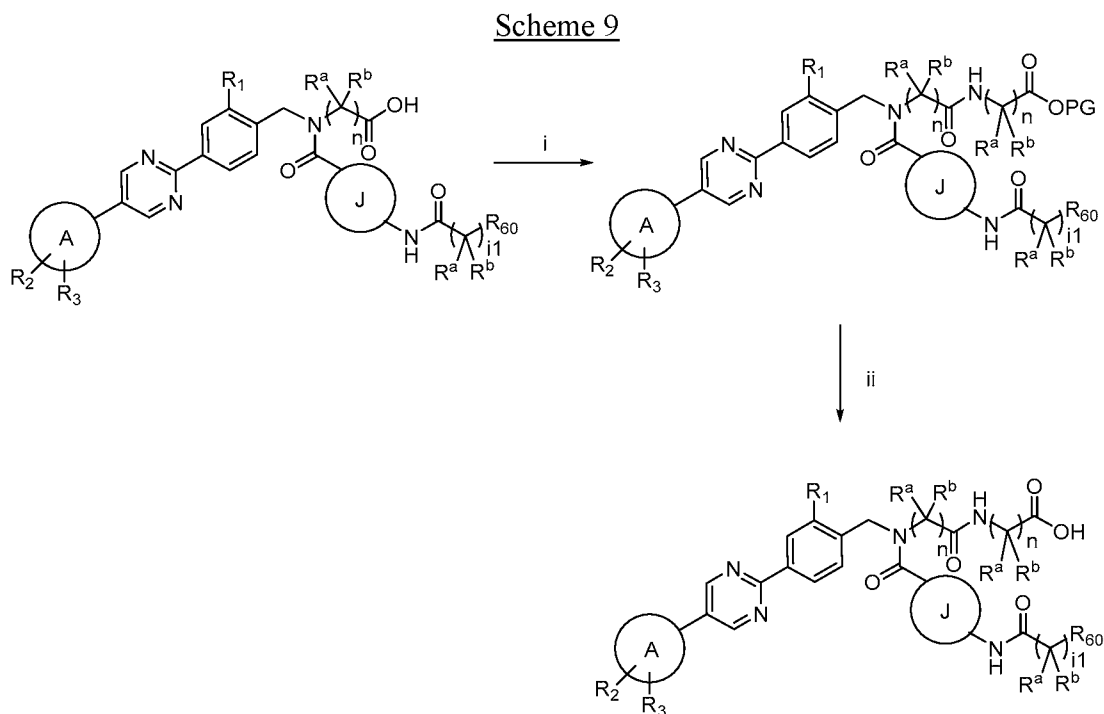
Reagents: PG is a protecting group (i) Pd(dppf)Cl₂, Na₂CO₃ or NaHCO₃, dioxane, water; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.

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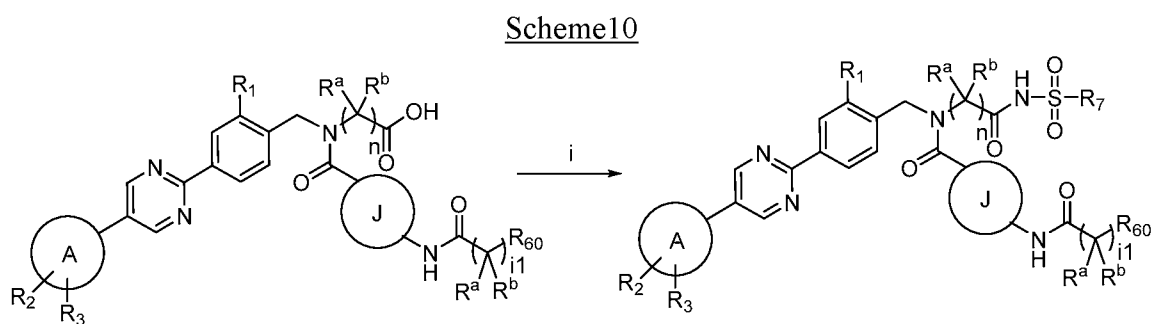
Scheme 8



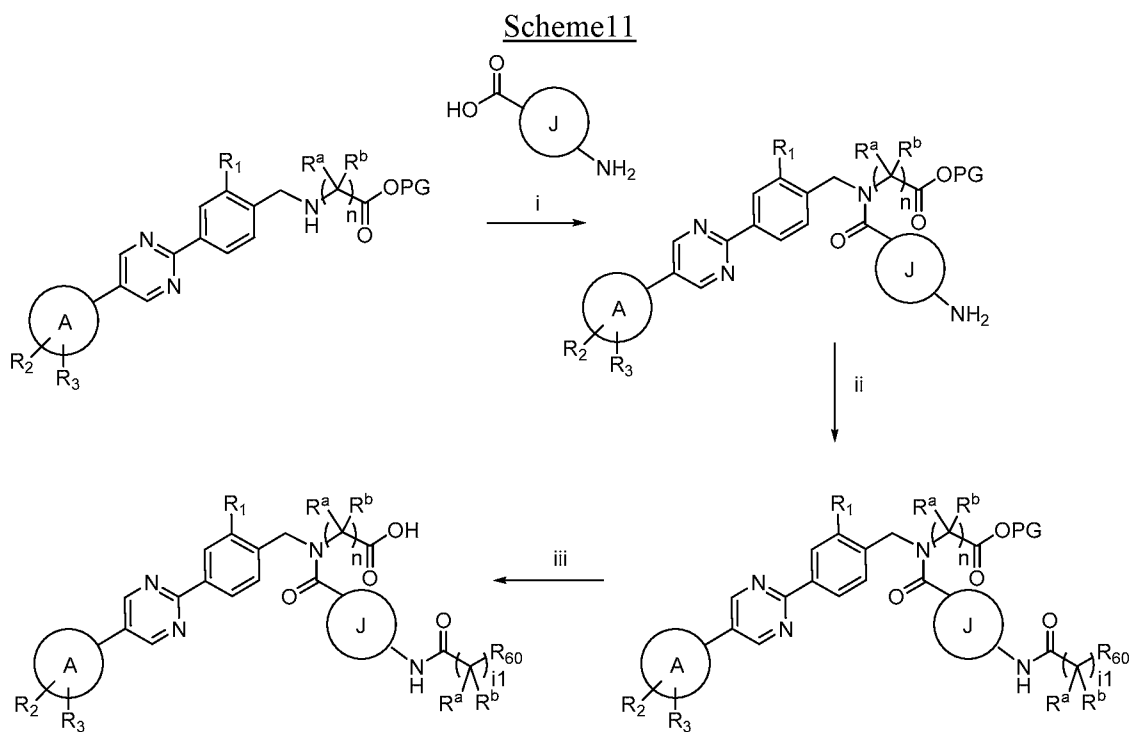
Reagents: PG is a protecting group (i) HATU, DIEA, DMF; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.



Reagents: PG is a protecting group (i) HATU, DIEA, DMF; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.

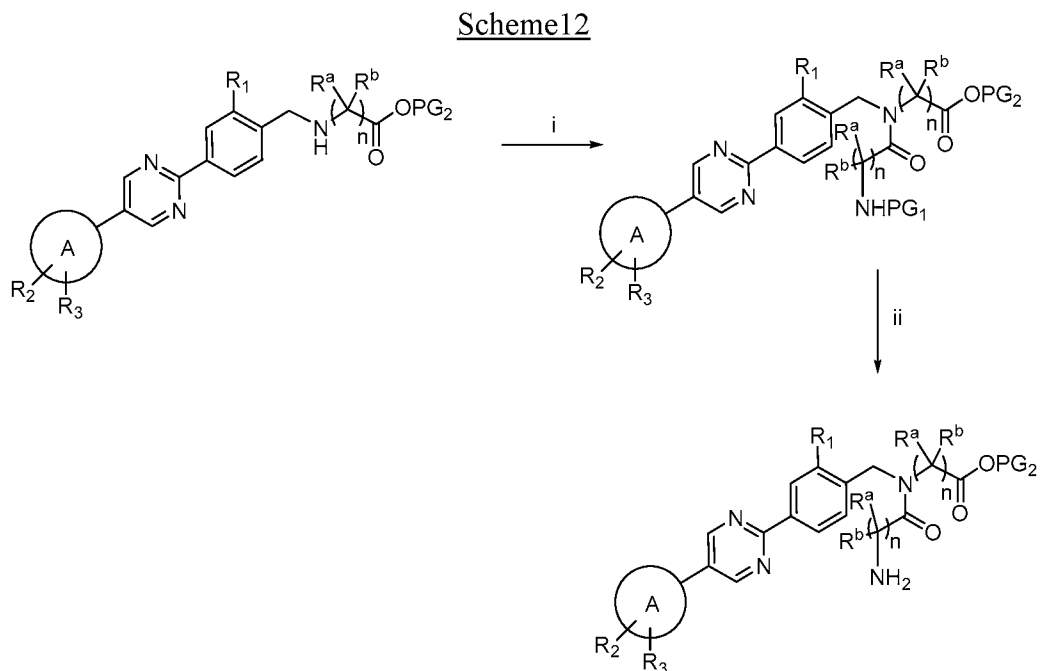


Reagents: (i) 1,1'-carbonyldiimidazole, methanesulfonamide, 1,8-diazabicyclo[5.4.0]undec-7-ene, THF.



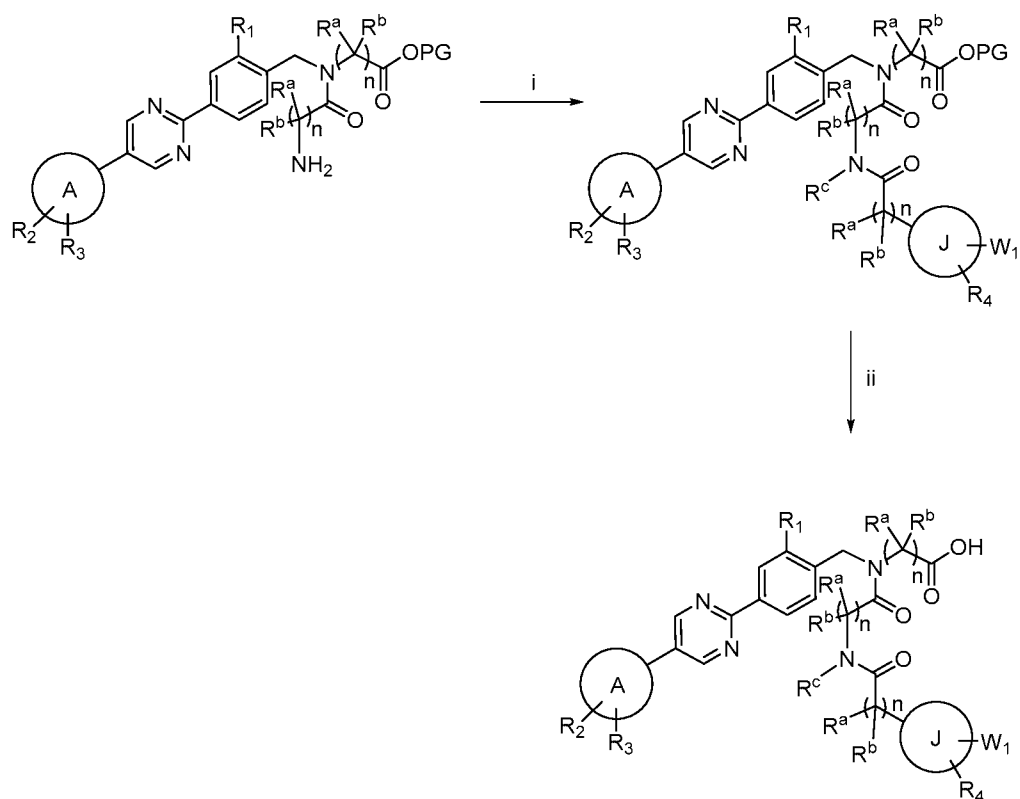
Reagents: PG is a protecting group (i) HATU, DIEA, DMF; (ii) NaH, THF; (iii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.

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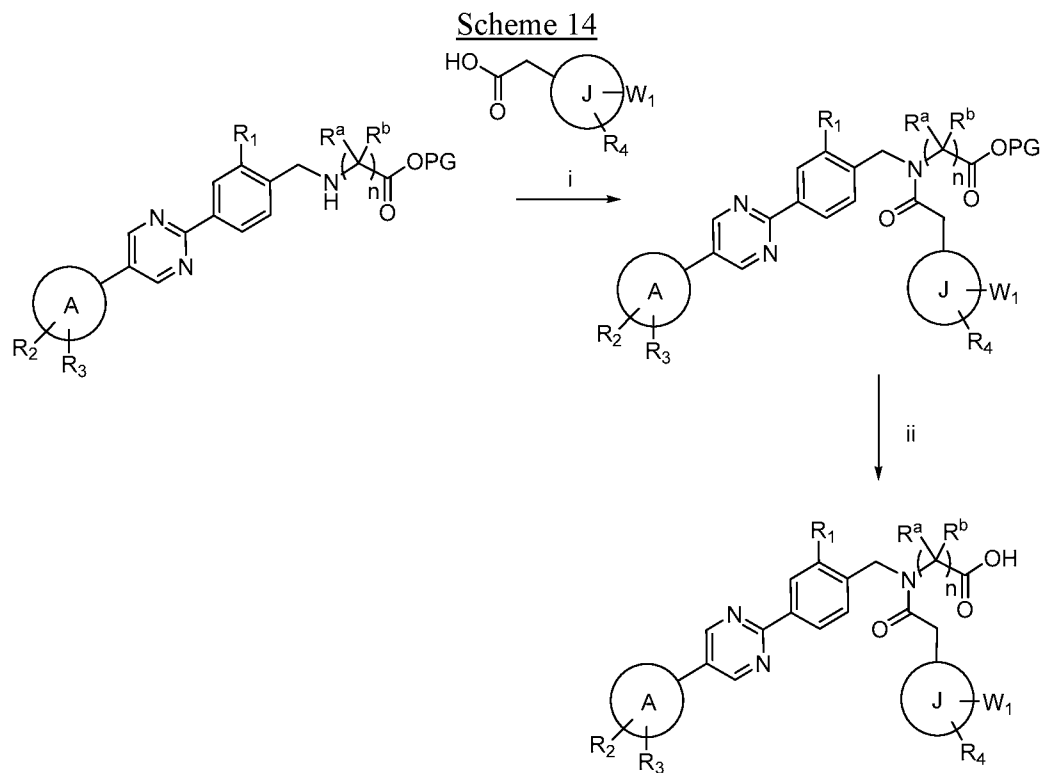


Reagents: PG₁ and PG₂ are protecting groups (i) HATU, DIEA, DMF; (ii) Deprotection of PG₁: e.g. deprotection of Boc-amine: 5-6N HCl in IPA, DCM.

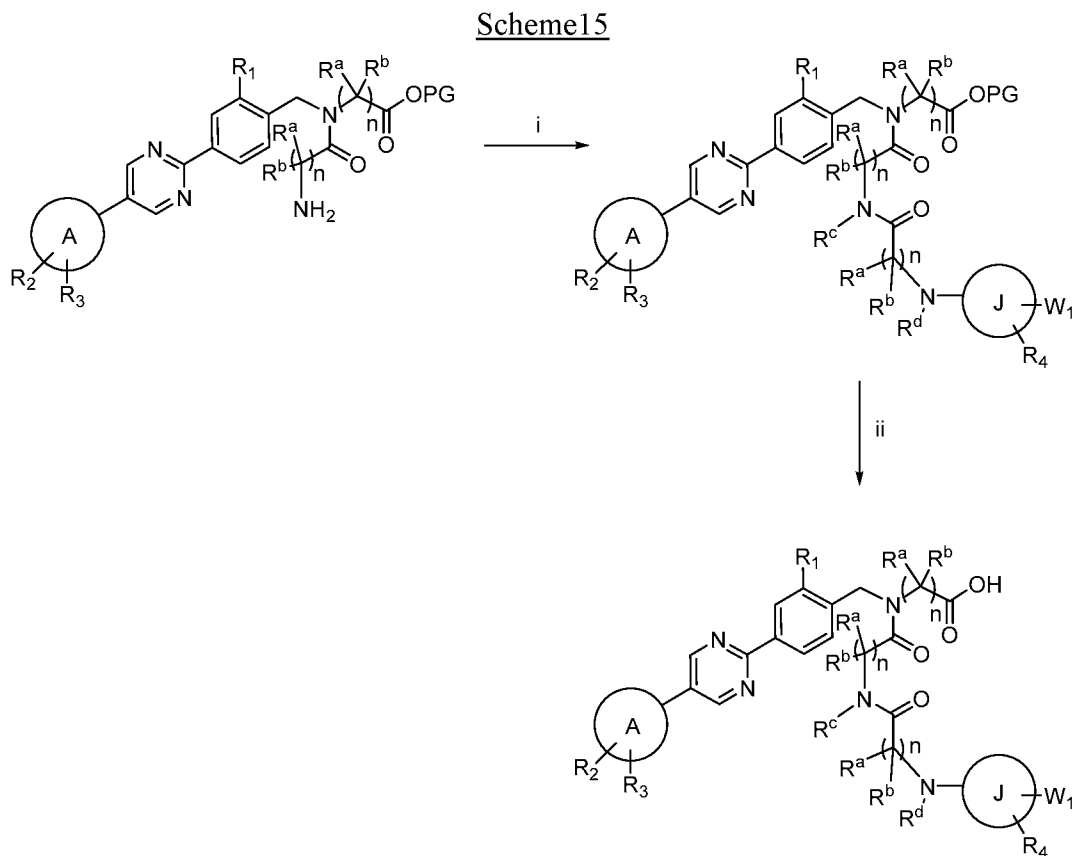
Scheme 13



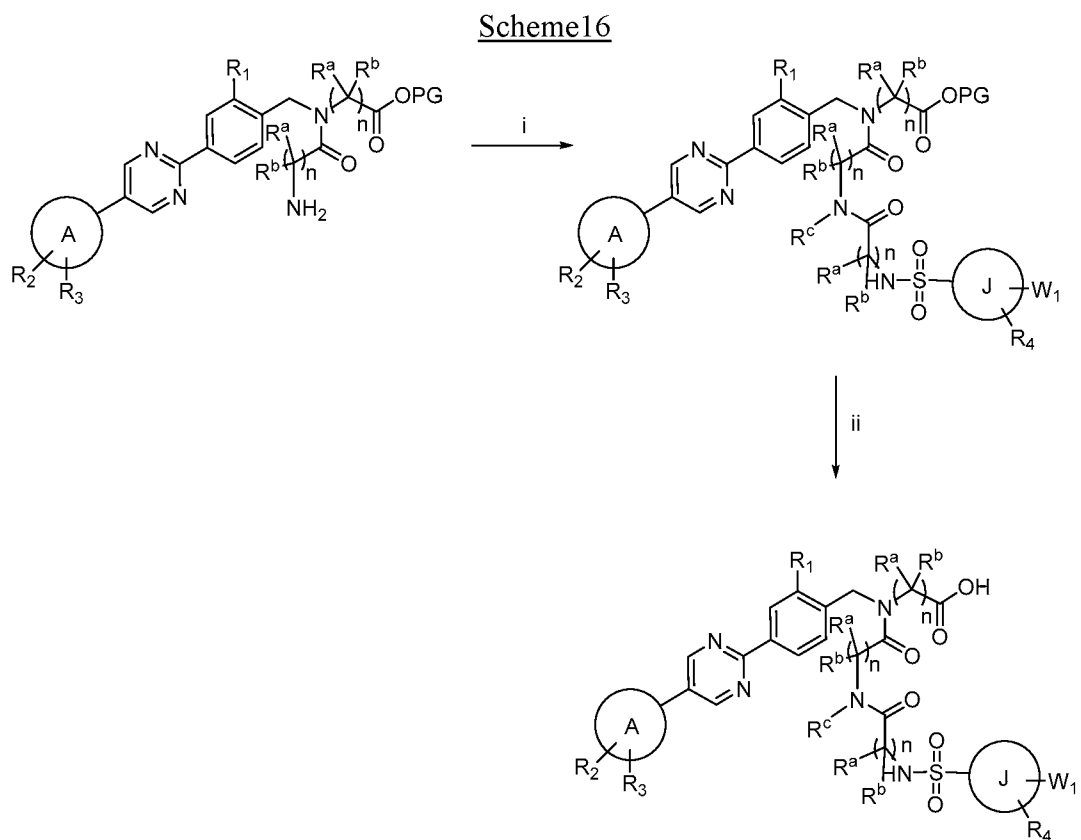
Reagents: PG is a protecting group (i) HATU, DIEA, DMF; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.



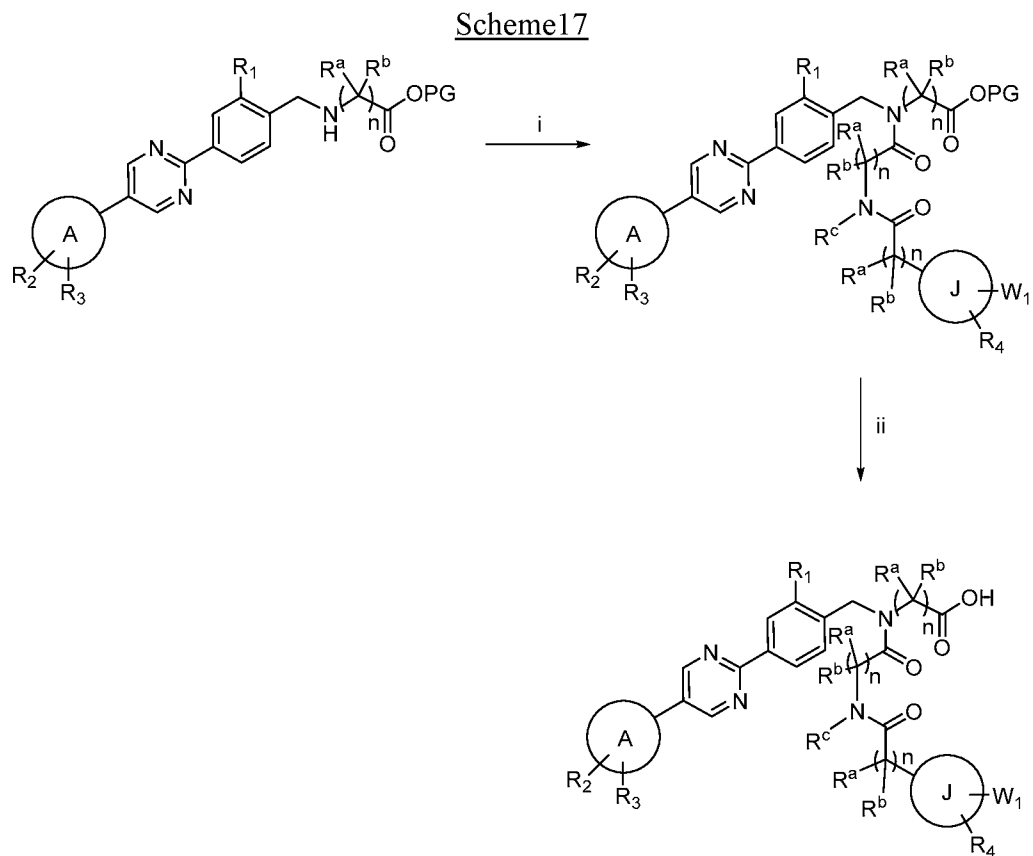
Reagents: PG is a protecting group (i) HATU, DIEA, DMF; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.



Reagents: PG is a protecting group (i) HATU, DIEA, DMF; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.

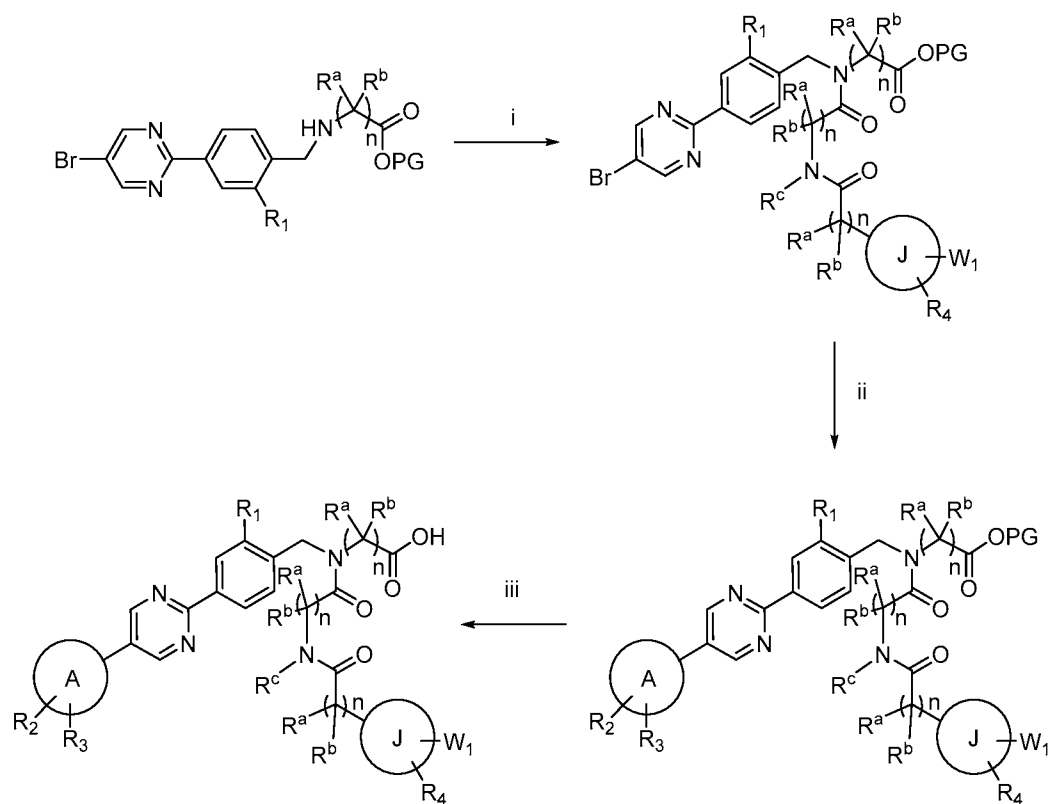


Reagents: PG is a protecting group (i) HATU, DIEA, DMF; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.



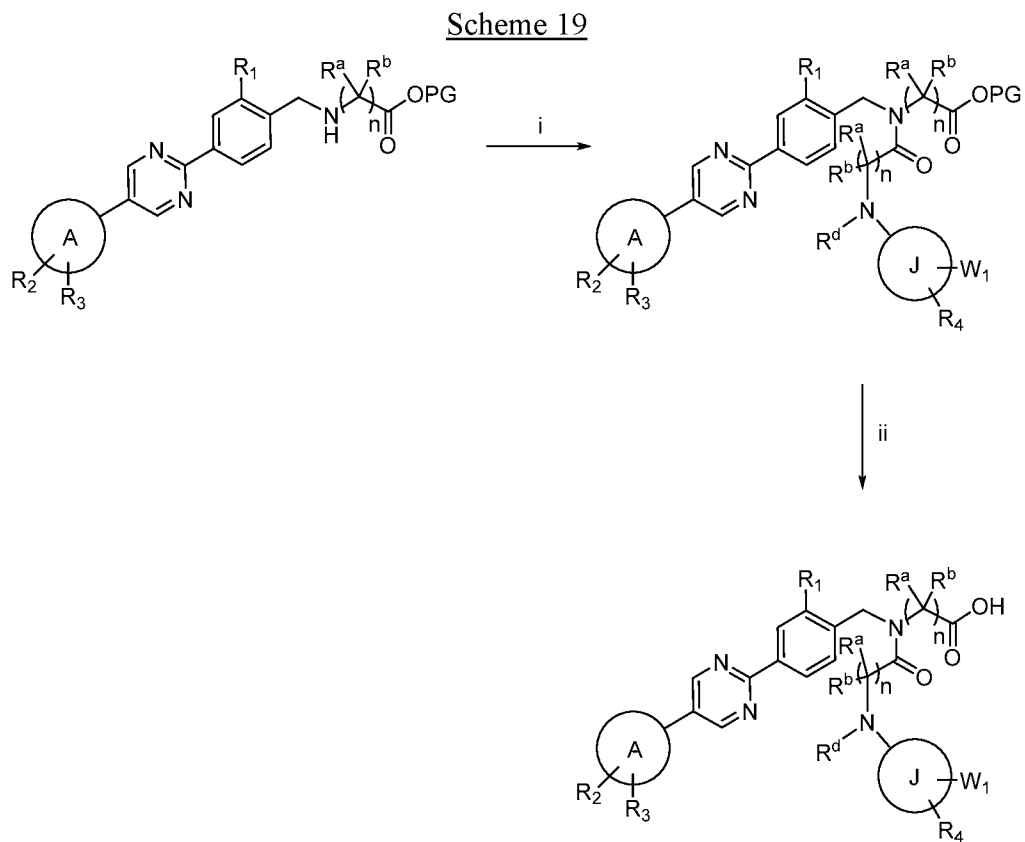
Reagents: PG is a protecting group (i) HATU, DIEA, DMF; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.

Scheme 18

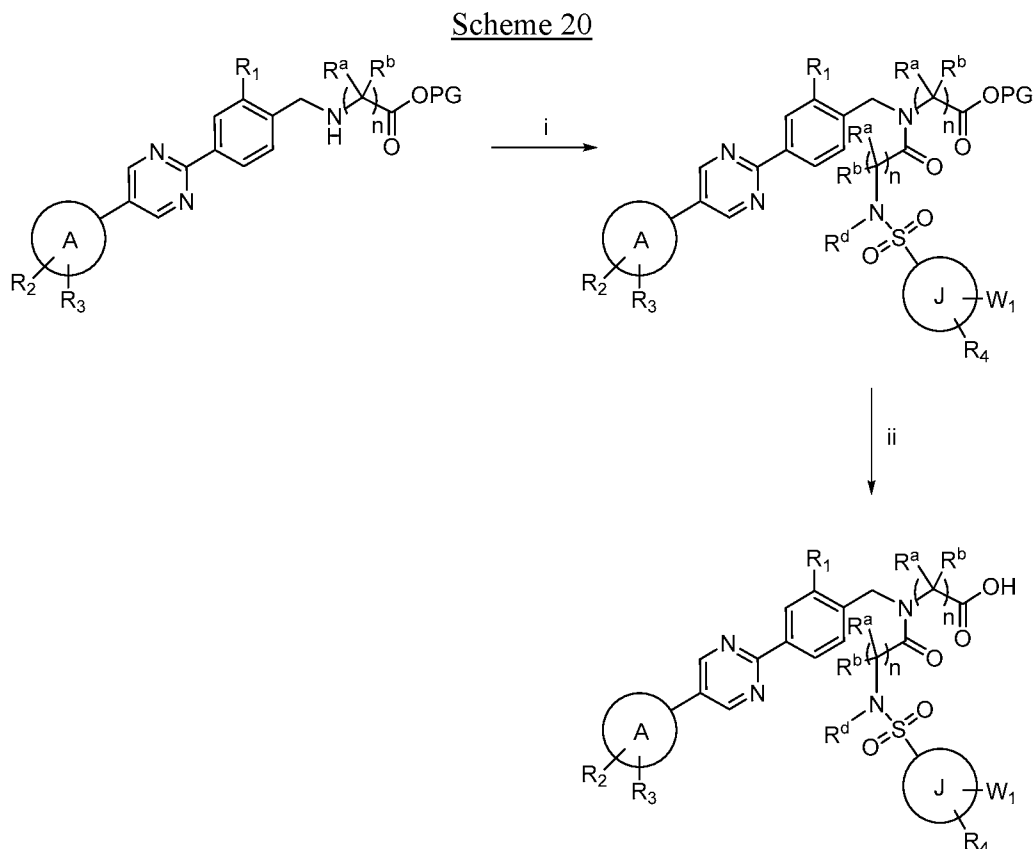


Reagents: PG is a protecting group (i) HATU, DIEA, DMF; (ii) Pd(dppf)Cl₂, Na₂CO₃ or NaHCO₃, dioxane, water; (iii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester:

5 TFA, DCM.



Reagents: PG is a protecting group (i) $HATU$, $DIEA$, DMF ; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA , DCM .



Reagents: PG is a protecting group (i) HATU, DIEA, DMF; (ii) Deprotection of PG: e.g. deprotection of *tert*-butyl ester: TFA, DCM.

5

EXAMPLES

Compound Synthesis

NMR spectra

¹H NMR (400 MHz) and ¹³C NMR (100 MHz) were obtained in solution of deuteriochloroform (CDCl₃) or dimethyl sulfoxide (d₆-DMSO). NMR spectra were processed using MestReNova 6.0.3-5604.

LCMS data

Mass spectra (LCMS) were obtained using one of 2 systems: **System 1**: Agilent 1100/6110 HPLC system equipped with a Waters X-Bridge C-8, 3.5 μ (50 x 4.6 mm) column using water with 5 mM ammonium acetate as the mobile phase C, and acetonitrile with 5 mM ammonium acetate as the mobile phase D with a flow rate of 1 mL/min. *Method 1*: 20% D (80% C) to 95% D over 12.0 min. and hold at 95% D for

2.8 min. then 20% D over 0.2 min. *Method 2*: 20% D (80% C) to 95% D over 3 min. then held at 95% D for 3.8 min. and then to 5% D over 0.2 min. **System 2**: Agilent 1260 LCMS equipped with a Waters Xselect CSH C18 3.5 μm (4.6 x 50 mm) column using water with 0.1% formic acid as mobile phase A and acetonitrile with 0.1% formic acid as mobile phase B. *Method 3*: The gradient was 5-95% mobile phase B over 13.0 min with a flow rate of 2.5 mL/min, then held at 95% for 1.0 min with a flow rate of 4.5 mL/min. *Method 4*: The gradient was 5-95% mobile phase B over 3.0 min with a flow rate of 2.5 mL/min, then held at 95% for 0.6 min with a flow rate of 4.5 mL/min.

Reaction Conditions and Abbreviations

10 Pyridine, dichloromethane (DCM), tetrahydrofuran (THF), and toluene used in the procedures were from Aldrich Sure-Seal bottles or Acros AcroSeal dry solvent and kept under nitrogen (N_2). All reactions were stirred magnetically and temperatures are external reaction temperatures. The following abbreviations are used: tetrahydrofuran (THF), ethyl acetate (EA), triethylamine (TEA), *N*-
15 hydroxybenzotriazole (HOBT), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-
b]pyridinium 3-oxide hexafluorophosphate (HATU), *N,N*-dimethylformamide (DMF), dimethyl acetamide (DMA), Di-*tert*-butyl dicarbonate (Boc_2O), *N,N*-
20 Diisopropylethylamine (DIEA), acetic acid (AcOH), hydrochloric acid (HCl), 4-
dimethylaminopyridine (DMAP), *tert*-butanol (*t*-BuOH), sodium hydride (NaH), sodium triacetoxyborohydride ($\text{Na}(\text{OAc})_3\text{BH}$), trifluoroacetic acid (TFA), room temperature (RT), dichloromethane (DCM), isopropyl alcohol (IPA), 2,2'-azobis(2-
methylpropionitrile) (AIBN).

Purifications

25 Chromatographies were carried out using a Combiflash Rf flash purification system (Teledyne Isco) equipped with Redisep (Teledyne Isco), Telos (Kinesis) or Grace Resolv (Grace Davison Discovery Sciences) silica gel (SiO_2) columns. Preparative HPLC purifications were performed using a Waters Fractionlynx system equipped with either 1) Agilent Prep-C18, 5 μm (21.2 x 50 mm) column using
30 water containing 0.1% formic acid as mobile phase A, and acetonitrile with 0.1% formic acid as mobile phase B. The gradient was 45-95% mobile phase B over 7.5 min,

held at 95% for 1 min, and then returned to 45% over 1.5 min with a flow rate of 28 mL/min or 2) Waters X-Bridge C-8, 5 μ m (19 x 150 mm) column using water containing 0.04% trifluoroacetic acid as mobile phase A, and acetonitrile with 0.04% trifluoroacetic acid as mobile phase B. The gradient was 20-95% mobile phase B over 7 min, held at 95% for 3 min, and then return to 20% over 2 min with flow rate of 28 mL/min. Fractions were collected by UV detection at 254 nm or by mass and evaporated using a Genevac EZ-2.

General Procedure 1. Palladium-Catalyzed Coupling Reactions.

A solution of boronic acid or boronate ester (1.0 – 1.3 eq), halide (1.0 – 1.3 eq), sodium bicarbonate or sodium carbonate decahydrate (2.0 – 2.5 eq), and dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II) or Pd(dppf)Cl₂ were combined in THF, acetonitrile, or dioxane (0.1 – 0.2 M) and water (0.25 – 0.50 M). The reaction was heated at 80 to 100°C until complete. The reaction was diluted with EA and washed with saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄ and concentrated. The product can be purified by chromatography, preparative HPLC, or carried on to the next step without further purification.

General Procedure 2. Preparation of Amides via Peptide Coupling.

A solution of amine (1.0 eq) and base (DIEA, TEA or NMM) (0 – 3.0 eq) in DCM or DMF (0.08 – 0.10 M) was treated with the appropriate carboxylic acid (1.0 – 1.5 eq). To this mixture was added the coupling reagent. The coupling reagent could be HATU (1.05 – 2.5 eq) optionally with DMAP (0.01 – 1 eq), EDC (1.5 eq) with HOBt (1.5 eq) or DMAP (0.01 – 1 eq), DCC (1.1 eq) with HOBt (1.1 eq) or DCC (1.5 eq) with DMAP (2.0 eq). The reaction mixture was stirred until the reaction was complete. The reaction was diluted with EA and washed with saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄ and concentrated. The product was purified by chromatography or alternatively can be carried on to the next step without further purification.

General Procedure 3. Hydrolysis of Methyl or Ethyl Esters to Acids.

To a stirring solution of ester (1 eq) in THF or dioxane and water, was added NaOH or LiOH (1 – 3 eq). The reaction mixture was stirred at up to 60 °C for up

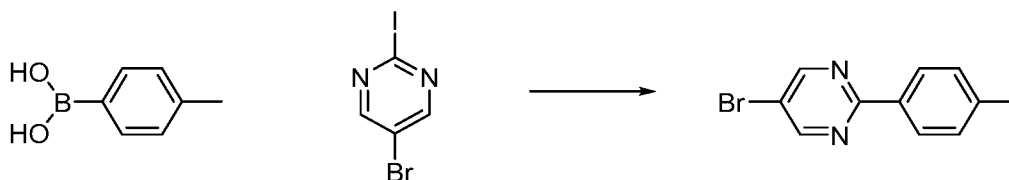
to 18 h. The reaction mixture was neutralized with AcOH or HCl and either diluted with water or concentrated. If the reaction mixture was diluted with water, then HCl was added to acidify the reaction mixture to a pH of approximately 2. The resulting precipitate was isolated by filtration to yield product which can be purified by chromatography, preparative HPLC, or used without purification. Alternatively, a solution of the ester (1 eq) in DCE was treated with trimethylstannanol (9 eq) at 80 °C for 24 to 72 h. The mixture was diluted with DCM and water and passed through a phase separator and the organics concentrated to afford product which can be purified by chromatography, preparative HPLC, or used without purification.

10 General Procedure 4. Deprotection of tert-Butyl Esters to Acids or Deprotection of Boc-Amines.

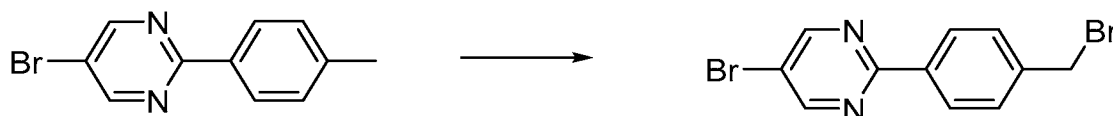
A solution of the *tert*-butyl ester or Boc-amine (1 eq) in DCM (0.06 M) was treated with TFA (0.16 – 0.33 M) or 1 - 4N HCl in ether or dioxane (10 – 2 eq). The reaction mixture was stirred at either room temperature or 30 °C until complete. The solvent was removed and the product was purified by chromatography or preparative HPLC. Alternatively, a solution of the *tert*-butyl ester (1 eq) is treated with formic acid (0.03 M) at room temperature for until the reaction is complete. The reaction was partitioned between DCM and water. The organic layer was dried and concentrated to give the free acid which could be purified by chromatography or preparative HPLC.

20 General Procedure 5. Preparation of Amides via Acid Chlorides.

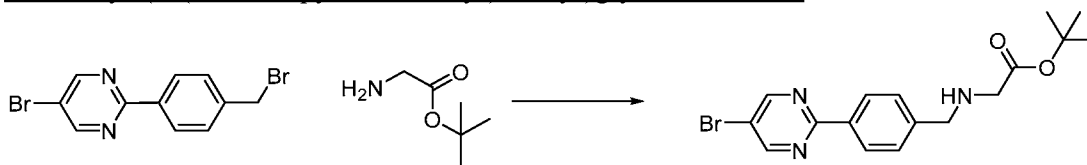
To a solution of amine (1 eq) and base (DIEA, TEA, or pyridine) (2 - 3 eq) in DCM (0.06 – 0.30 M) was treated with the appropriate acid chloride (1.0 – 1.5 eq). The reaction mixture was stirred until the reaction was complete. The reaction was diluted with DCM and washed with saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄ and concentrated. The product was purified by chromatography. Alternatively, the crude reaction mixture can be carried on to the next step without further purification.

5-Bromo-2-(p-tolyl)pyrimidine

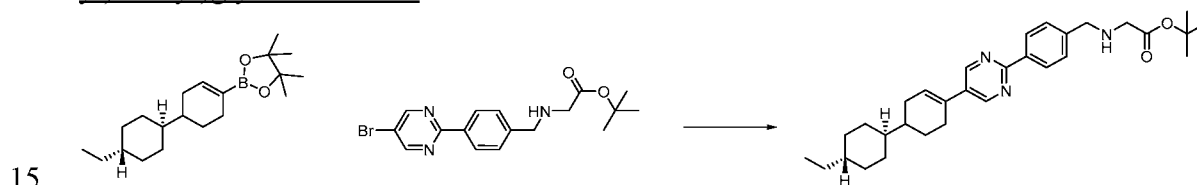
Prepared using *General Procedure 1*. To a stirring solution of *p*-tolylboronic acid (14.18 g, 104 mmol) and 5-bromo-2-iodopyrimidine (29.7 g, 104 mmol) in dioxane (140 mL) was added a solution of sodium carbonate (33.2 g, 313 mmol) in water (70 mL). The mixture was de-gassed then treated with Pd(dppf)Cl₂ (2.289 g, 3.13 mmol) and heated under reflux. After 16 h, the mixture was allowed to cool then quenched with ice-water (50 mL). 1 M HCl (350 mL) was added slowly and the product extracted with EA (2 x 350 mL). The combined organic extracts were filtered through Celite then washed successively with 1 M HCl (250 mL) and brine (300 mL), dried over MgSO₄ and solvents evaporated. Column chromatography (EA/*iso*-hexane) gave 15 g (58%) of 5-bromo-2-(*p*-tolyl)pyrimidine. LCMS-ESI (m/z) calculated for C₁₁H₉BrN₂: 248.0; found 249.1 [M+H]⁺, *t*_R = 2.60 min (*Method 4*). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.74 (s, 2H), 8.32 – 7.99 (m, 2H), 7.27 – 7.20 (m, 2H), 2.35 (s, 3H).

5-Bromo-2-(4-(bromomethyl)phenyl)pyrimidine

To a stirring solution of 5-bromo-2-(*p*-tolyl)pyrimidine (5.41 g, 21.72 mmol) in chloroform (100 mL) at reflux was added *N*-bromosuccinimide (5.08 g, 28.2 mmol) followed by 2,2'-azobis(2-methylpropionitrile) (0.535 g, 3.26 mmol). After 1.5 h, the mixture was allowed to cool and solvent evaporated. Column chromatography (EA/heptane) gave 3.9 g (55%) of 5-bromo-2-(4-(bromomethyl)phenyl)pyrimidine. LCMS-ESI (m/z) calculated for C₁₁H₈Br₂N₂: 325.9; found 327.0 [M+H]⁺, *t*_R = 2.62 min (*Method 4*). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 2H), 8.39 – 8.28 (m, 2H), 7.65 – 7.56 (m, 2H), 4.79 (s, 2H).

Tert-butyl (4-(5-bromopyrimidin-2-yl)benzyl)glycinate INT-1

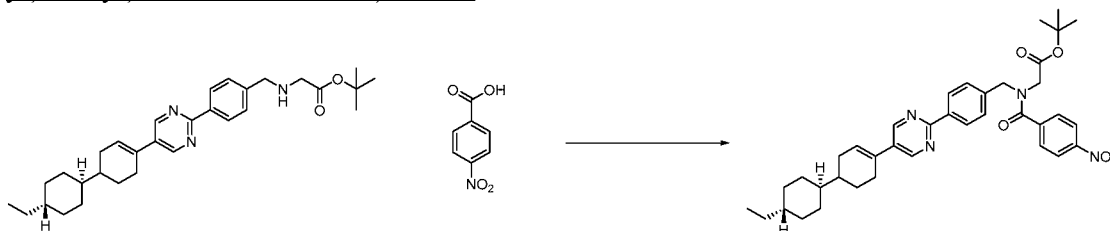
To a stirring solution of 5-bromo-2-(4-(bromomethyl)phenyl)pyrimidine
 5 (3.08 g, 9.39 mmol) in THF (100 mL) was added *tert*-butyl 2-aminoacetate (3.70 g, 28.2 mmol) added followed by DIEA (4.9 mL, 28.2 mmol). The mixture was heated under reflux for 7 h then allowed to cool overnight. The mixture was poured into water (60 mL) and extracted with EA (3 x 60 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO₄ and solvents evaporated. The residue
 10 was re-slurried from diethyl ether to afford 1.46 g (41%) of *tert*-butyl (4-(5-bromopyrimidin-2-yl)benzyl)glycinate **INT-1**. LCMS-ESI (m/z) calculated for C₁₇H₂₀BrN₃O₂: 377.1; found 378.1 [M+H]⁺, t_R = 1.42 min (*Method 4*).

Tert-butyl (4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate INT-2

Prepared using *General Procedure 1*. To a stirring solution of *tert*-butyl
 (4-(5-bromopyrimidin-2-yl)benzyl)glycinate **INT-1** (0.969 g, 2.56 mmol) and 2-
 ((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-
 20 dioxaborolane (1.06 g, 3.33 mmol) in dioxane (35 mL) was added NaHCO₃ (8.5 mL of a 0.9 M aqueous solution, 7.7 mmol). The mixture was de-gassed then treated with PdCl₂(dppf) (0.099 g, 0.128 mmol). The mixture was heated to 90°C for 3 h then allowed to cool and treated with water (30 mL). The mixture was extracted with EA (3 x 100 mL) and the combined organic extracts washed with brine (150 mL), dried over
 25 MgSO₄ and solvents evaporated. Column chromatography (EA/DCM/*iso*-hexane) gave 618 mg (49%) of *tert*-butyl (4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate **INT-2**. LCMS-ESI (m/z) calculated for

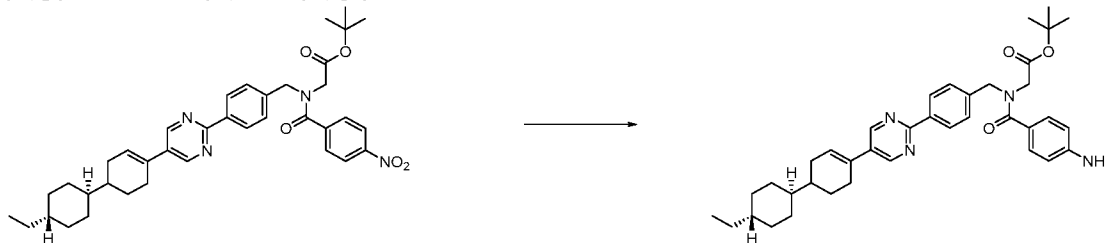
$C_{31}H_{43}N_3O_2$: 489.3; found 490.4 $[M+H]^+$, $t_R = 2.58$ min (*Method 4*). 1H NMR (400 MHz, Chloroform-*d*) δ 8.71 (s, 2H), 8.42 – 8.25 (m, 2H), 7.48 (d, $J = 8.2$ Hz, 2H), 6.36 – 6.06 (m, 1H), 4.02 (s, 2H), 3.36 (s, 2H), 2.45 – 2.23 (m, 3H), 1.95 – 1.90 (m, 2H), 1.74 (app q, $J = 12.4$ Hz, 5H), 1.40 – 1.30 (m, 10H), 1.21 – 0.85 (m, 7H), 0.83 – 0.76 (m, 5H).

Tert-butyl 2-(N-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-nitrobenzamido)acetate



Prepared using *General Procedure 2*. To a stirring suspension of *tert*-butyl (4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-glycinate **INT-2** (2 g, 4.08 mmol) and 4-nitrobenzoic acid (0.975 g, 5.72 mmol) in DMF (60 mL) was added DIEA (3.6 mL, 20.42 mmol) and HATU (2.29 g, 5.72 mmol) and the mixture heated to 80°C. After 1 h, the mixture was allowed to cool then treated with water (50 mL). The precipitate was collected by filtration, washing with toluene (50 mL) to afford 1.35 g (52%) of *tert*-butyl 2-(N-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-nitrobenzamido)acetate. LCMS-ESI (m/z) calculated for $C_{38}H_{46}N_4O_5$: 638.3; found 639.4 $[M+H]^+$, $t_R = 3.50$ min (*Method 4*). 1H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 2H), 8.36 (d, $J = 7.9$ Hz, 2H), 8.20 (app t, $J = 9.0$ Hz, 2H), 7.60 (app dd, $J = 16.6, 8.6$ Hz, 2H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 6.24 (br s, 1H), 4.81 (s, 1H), 4.53 (s, 1H), 4.06 (s, 1H), 3.62 (s, 1H), 2.46 – 2.35 (m, 2H), 2.30 – 2.23 (m, 1H), 1.98 – 1.90 (m, 2H), 1.75 (app q, $J = 12.6$ Hz, 4H), 1.44 – 1.31 (m, 10H), 1.30 – 0.90 (m, 7H), 0.87 – 0.76 (m, 5H).

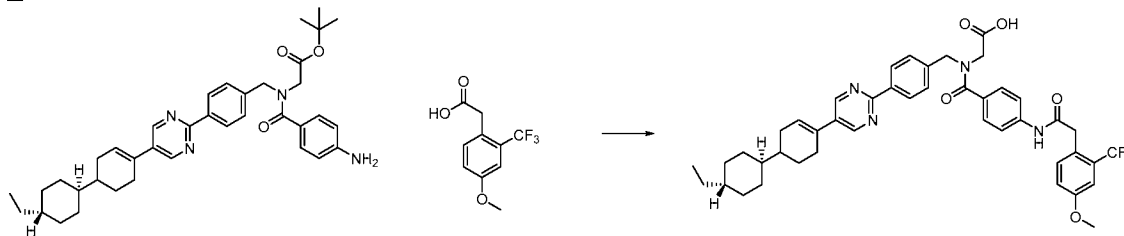
Tert-butyl N-(4-aminobenzoyl)-N-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate **INT-3**



To a stirring suspension of *tert*-butyl 2-(*N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-
 5 bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-nitrobenzamido)acetate (4.3 g, 6.73
 mmol) in THF (90 mL), EtOH (90 mL) and water (9 mL) were added a solution of
 NH₄Cl (1.837 g, 33.7 mmol) in water (2 mL) and iron (1.9 g, 33.7 mmol). The
 suspension was heated under reflux. After 3 h, the mixture was filtered hot through a
 pad of celite, washing with DCM (100 mL). The mixture was washed with 2 M NaOH
 10 (50 mL) and the aqueous further extracted with DCM (2 x 100 mL). The combined
 organic extracts were washed with brine (100 mL) and split through a hydrophobic frit.
 The solvents were evaporated to afford an off-white solid. This was taken up in DCM
 (300 mL), washed successively with water (100 mL) and brine (2 x 150 mL) then split
 through a hydrophobic frit and solvents evaporated to afford 3.72 g (91%) of *tert*-butyl
 15 *N*-(4-aminobenzoyl)-*N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-
 yl)pyrimidin-2-yl)benzyl)glycinate **INT-3**. LCMS-ESI (m/z) calculated for
 C₃₈H₄₈N₄O₃: 608.4; no mass observed, *t*_R = 3.45 min (*Method 4*).

2-(*N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-
(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)benzamido)acetic acid **Compound**

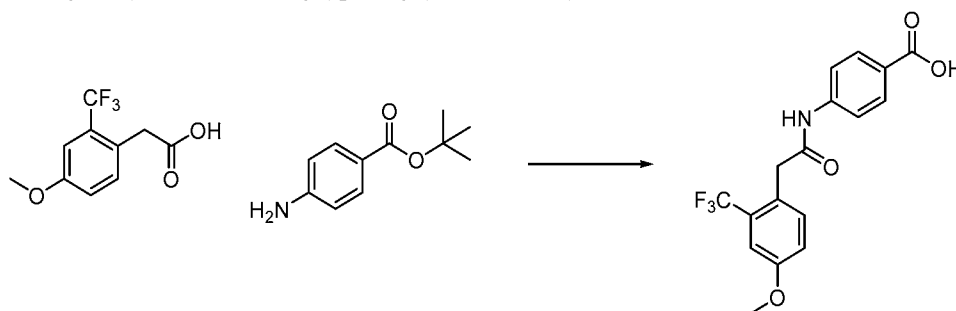
20 **1**



To a stirring solution of 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetic
 acid (0.750 g, 3.20 mmol) in DCM (10 mL) was added DMF (1 drop) and the mixture
 cooled to 0°C. Oxalyl chloride (0.22 mL, 2.56 mmol) was added. After 1 h, the cooling
 25 bath was removed. After a further 1 h, the mixture was evaporated then re-dissolved in

DCM (10 mL). The resulting solution was added dropwise to a stirring suspension of *tert*-butyl *N*-(4-aminobenzoyl)-*N*-(4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate **INT-3** (1.3 g, 2.135 mmol) and DIEA (1.2 mL, 6.41 mmol) in DCM (10 mL) at 0°C. After 10 min, the cooling bath was removed. After a
 5 further 0.5 h, the mixture was diluted with DCM (100 mL) and washed successively with 1 M HCl (100 mL) and NaHCO₃ (100 mL), dried over MgSO₄ and evaporated. The residue was taken into DCM (10 mL) and stirred with TFA (8 mL). After 2 h, the mixture was diluted with DCM (50 mL), THF (20 mL) and toluene (20 mL) and washed successively with water (100 mL) then a mixture of water (100 mL) and THF
 10 (10 mL). The organics were dried over MgSO₄ and solvents evaporated and the residue stripped with toluene (50 mL). The residue was re-crystallized from EA (40 mL) to afford crude product. This was then dissolved in DMSO (30 mL) and THF (20 mL) and treated with water (50 mL). After stirring for 1 h, the precipitate was collected by filtration to afford 1.334 g (81%) of 2-(*N*-(4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-(2-(4-methoxy-2-
 15 (trifluoromethyl)phenyl)acetamido)benzamido) acetic acid **Compound 1**. LCMS-ESI (*m/z*) calculated for C₄₄H₄₇F₃N₄O₅: 768.3; found 769.3 [M+H]⁺, *t_R* = 13.10 min (*Method 3*). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.83 (br s, 1H), 10.35 (s, 1H), 8.95 (s, 2H), 8.52 – 8.25 (m, 2H), 7.63 (app t, *J* = 10.1 Hz, 2H), 7.54 – 7.32 (m, 5H), 7.23 –
 20 7.18 (m, 2H), 6.47 (br s, 1H), 4.73 (s, 1H), 4.65 (s, 1H), 4.01 (s, 1H), 3.93 (s, 1H), 3.86 – 3.82 (m, 5H), 2.46 – 2.19 (m, 2H), 2.01 – 1.94 (m, 2H), 1.84 – 1.76 (m, 4H), 1.41 – 1.30 (m, 2H), 1.24 – 0.93 (m, 7H), 0.91 – 0.82 (m, 5H).

((4-Methoxy-2-(trifluoromethyl)phenyl)acetamido)benzoic acid



25

To a stirring solution of 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetic acid (3.25 g, 13.88 mmol) in DCM (30 mL) at 0°C was added DMF (3 drops) then

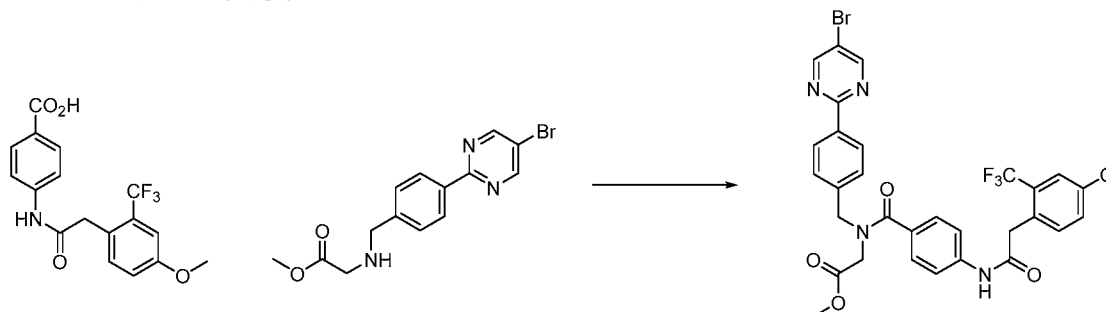
oxalyl chloride (1.5 mL, 17.4 mmol). After 10 min, the cooling bath was removed. After a further 2 h, solvents were evaporated and the residue taken into DCM (10 mL). The resulting solution was added to a stirring solution of *tert*-butyl 4-aminobenzoate (2.68 g, 13.88 mmol) and DIEA (3.8 mL, 20.8 mmol) in DCM (10 mL) at -10°C such that the internal temperature was maintained below -5°C. The mixture was allowed to warm slowly then poured into a mixture of ice-water (200 mL), 1 M HCl (50 mL) and *iso*-hexane (100 mL). After 10 min, the precipitate was collected by filtration, washing successively with water (2 x 20 mL), *iso*-hexane (2 x 20 mL), and MTBE (5 mL). The filter cake was dried in the vacuum oven then taken up in DCM (30 mL) and treated with TFA (20 mL). After 2 h, the mixture was poured into a mixture of ice-water (100 mL) and *iso*-hexane (100 mL) and the product collected by filtration washing successively with water (2 x 20 mL), *iso*-hexane (2 x 20 mL) and MTBE (5 mL). The filter cake was dried in the vacuum oven to afford 3.86 g (79%) of 4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)benzoic acid. LCMS-ESI (m/z) calculated for C₁₇H₁₄F₃NO₄: 353.1; found 354.0 [M+H]⁺, t_R = 1.94 min (*Method 4*).

Methyl 2-((4-(5-bromopyrimidin-2-yl)benzyl)amino)acetate



To a stirring mixture of 5-bromo-2-(4-(bromomethyl)phenyl)pyrimidine (1 g, 2.44 mmol) in THF (10 mL) and DMF (10 mL) was added methyl 2-aminoacetate, HCl (0.928 g, 7.32 mmol) followed by DIEA (1.3 mL, 7.32 mmol) and the reaction mixture heated to 65°C. After 1.5 h, the mixture was allowed to cool then poured into NaHCO₃ (40 mL) and extracted with EA (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO₄ and solvents evaporated. Column chromatography (EA/*iso*-hexane) gave 590 mg (72%) of methyl 2-((4-(5-bromopyrimidin-2-yl)benzyl)amino)acetate. LCMS-ESI (m/z) calculated for C₁₄H₁₄BrN₃O₂: 335.0; found 336.1 [M+H]⁺, t_R = 1.06 min (*Method 4*). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (s, 2H), 8.34 – 8.22 (m, 2H), 7.52 – 7.33 (m, 2H), 3.80 (s, 2H), 3.63 (s, 3H), 3.35 (s, 2H), 2.61 (br s, 1H).

N-(4-(5-Bromopyrimidin-2-yl)benzyl)-N-(4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)benzoyl)glycinate INT-4



5 Prepared using *General Procedure 2*. To a stirring solution of 4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)benzoic acid (410 mg, 1.16 mmol) and DIEA (0.5 mL, 2.9 mmol) in DMF (15 mL), was added HATU (455 mg, 1.16 mmol). After 15 min a solution of methyl 2-((4-(5-bromopyrimidin-2-yl)benzyl)amino)acetate (325 mg, 0.97 mmol) in DMF (15 mL) was added. After 16 h, the mixture was poured
 10 into water (50 mL) and extracted with EA (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO₄ and solvents evaporated. Column chromatography (EA/*iso*-hexane) gave 649 mg (100%) of *N*-(4-(5-bromopyrimidin-2-yl)benzyl)-*N*-(4-(2-(4-methoxy-2-(trifluoro-
 15 C₃₁H₂₆BrF₃N₄O₅: 670.1; found 671.1 [M+H]⁺, *t*_R = 2.64 min (*Method 4*).

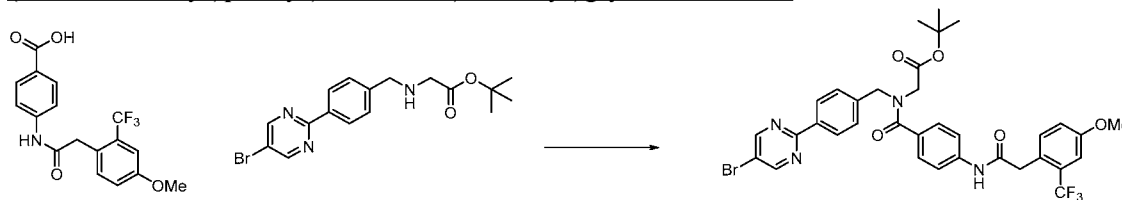
Compound 2 was prepared from methyl *N*-(4-(5-bromopyrimidin-2-yl)benzyl)-*N*-(4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)benzoyl)-glycinate **INT-4** using *General Procedures 1 then 3*.

Compounds 3-10, 125, and 148-152 were prepared from *tert*-butyl (4-
 20 (5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate **INT-2** using *General Procedures 2 then 4*.

Compounds 11 and 12 were prepared from **Compound 1** using *General Procedures 2 then 4*.

Compounds 13, 14, 15, 112, and 113 were prepared from **Compound 1**
 25 using *General Procedures 2 then 3*.

Tert-butyl N-(4-(5-bromopyrimidin-2-yl)benzyl)-N-(4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido) benzoyl)glycinate INT-5



Prepared using *General Procedure 2*. To a stirring solution of DIEA
 5 (0.97 mL, 5.55 mmol) and 4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)-
 benzoic acid (0.560 g, 1.586 mmol) in DMF (15 mL) was added HATU (0.784 g, 2.062
 mmol). After 5 min *tert*-butyl (4-(5-bromopyrimidin-2-yl)benzyl)glycinate **INT-1**
 (0.600 g, 1.586 mmol) was added. After 16 h, the mixture was poured onto 0.5 M HCl
 (50 mL) and extracted with EA (50 mL then 2 x 20 mL). The combined organic extracts
 10 were washed with brine (30 mL), dried over MgSO₄ and solvents evaporated. Column
 chromatography (EA/iso-hexane) gave 0.35 g (31%) of *tert*-butyl *N*-(4-(5-
 bromopyrimidin-2-yl)benzyl)-*N*-(4-(2-(4-methoxy-2-(trifluoromethyl)-
 phenyl)acetamido) benzoyl)glycinate **INT-5**. LCMS-ESI (m/z) calculated for
 C₃₄H₃₂BrF₃N₄O₅: 712.2; found 713.1 [M+H]⁺, *t*_R = 2.97 min (*Method 4*). ¹H NMR (400
 15 MHz, DMSO-*d*₆) δ 10.35 (s, 1H), 9.09 (s, 2H), 8.47 – 8.16 (m, 2H), 7.63 (br s, 2H),
 7.53 (d, *J* = 7.8 Hz, 1H), 7.43 (br s, 2H), 7.40 – 7.34 (m, 2H), 7.28 – 7.14 (m, 2H), 4.73
 (s, 1H), 4.63 (s, 1H), 3.99 (s, 1H), 3.95 (s, 1H), 3.85 – 3.82 (m, 5H), 1.42 (s, 5H), 1.32
 (s, 4H).

Compounds 16, 17, 77-81, and 94-96 were prepared from *tert*-butyl *N*-
 20 (4-(5-bromopyrimidin-2-yl)benzyl)-*N*-(4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)-
 acetamido) benzoyl)glycinate **INT-5** using *General Procedures 1 then 4*.

1-(3-(4-methoxy-2-(trifluoromethyl)phenyl)propanoyl)piperidine-4-
 carboxylic acid (carboxylic acid for **Compound 18**) was prepared from methyl
 piperidine-4-carboxylate and 3-(4-methoxy-2-(trifluoromethyl)phenyl)propanoic acid
 25 using *General Procedures 2 then 3*.

1-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl)piperidine-4-
 carboxylic acid (carboxylic acid for **Compound 19**) was prepared from methyl
 piperidine-4-carboxylate and 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetic acid using
General Procedures 2 then 3.

3-chloro-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)-benzoic acid (carboxylic acid for **Compound 20**) was prepared from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride and 4-amino-3-chlorobenzoic acid using *General Procedure 5*.

5 3-methoxy-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)-benzoic acid (carboxylic acid for **Compound 21**) was prepared from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride and 4-amino-3-methoxybenzoic acid using *General Procedure 5*.

10 2-methoxy-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)-benzoic acid (carboxylic acid for **Compound 22**) was prepared from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride and 4-amino-2-methoxybenzoic acid using *General Procedure 5*.

15 5-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)picolinic acid (carboxylic acid for **Compound 23**) was prepared from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride and 5-aminopicolinic acid using *General Procedure 5*.

20 2-chloro-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)-benzoic acid (carboxylic acid for **Compound 24**) was prepared from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride and 4-amino-2-chlorobenzoic acid using *General Procedure 5*.

3-cyano-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)-benzoic acid (carboxylic acid for **Compound 32**) was prepared from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride and 4-amino-3-cyanobenzoic acid using *General Procedure 5*.

25 2-bromo-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)-benzoic acid (carboxylic acid for **Compound 33**) was prepared from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride and methyl 4-amino-2-bromobenzoate using *General Procedures 5 then 3*.

30 6-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)nicotinic acid (carboxylic acid for **Compound 46**) was prepared from 2-(4-methoxy-2-

(trifluoromethyl)phenyl)acetyl chloride and methyl 6-aminonicotinate using *General Procedures 5 then 3*.

6-(2-(4-methoxyphenyl)acetamido)pyridazine-3-carboxylic acid (carboxylic acid for **Compound 57**) was prepared from 2-(4-methoxyphenyl)acetyl chloride and methyl 6-aminopyridazine-3-carboxylate using *General Procedures 5 then 3*.

6-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)pyridazine-3-carboxylic acid (carboxylic acid for **Compound 58**) was prepared from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride and methyl 6-aminopyridazine-3-carboxylate using *General Procedures 5 then 3*.

5-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)pyrazine-2-carboxylic acid (carboxylic acid for **Compound 64**) was prepared from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride and methyl 5-aminopyrazine-2-carboxylate using *General Procedures 5 then 3*.

2,3-dichloro-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)-benzoic acid (carboxylic acid for **Compound 67**) was prepared from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride and 4-amino-2,3-dichlorobenzoic acid using *General Procedure 5*.

2,3-dichloro-4-(2-(4-methoxyphenyl)acetamido)benzoic acid (carboxylic acid for **Compound 68**) was prepared from 2-(4-methoxyphenyl)acetyl chloride and 4-amino-2,3-dichlorobenzoic acid using *General Procedure 5*.

3-(2-(4-methoxyphenyl)acetamido)propanoic acid (carboxylic acid for **Compound 72**) was prepared from *tert*-butyl 3-aminopropanoate and 2-(4-methoxyphenyl)acetic acid using *General Procedures 2 then 4*.

(2-(4-methoxyphenyl)acetyl)-*L*-proline (carboxylic acid for **Compound 73**) was prepared from *tert*-butyl *L*-prolinate and 2-(4-methoxyphenyl)acetic acid using *General Procedures 2 then 4*.

1-(2-(4-methoxyphenyl)acetyl)azetidine-3-carboxylic acid (carboxylic acid for **Compound 82**) was prepared from *tert*-butyl azetidine-3-carboxylate and 2-(4-methoxyphenyl)acetic acid using *General Procedures 2 then 4*.

5-(2-(4-methoxyphenyl)acetamido)furan-2-carboxylic acid (carboxylic acid for **Compound 83**) was prepared from methyl 5-aminofuran-2-carboxylate and 2-(4-methoxyphenyl)acetyl chloride using *General Procedures 5 then 3*.

5-(2-(4-methoxyphenyl)acetamido)thiophene-2-carboxylic acid (carboxylic acid for **Compound 84**) was prepared from methyl 5-aminothiophene-2-carboxylate and 2-(4-methoxyphenyl)acetyl chloride using *General Procedures 5 then 3*.

5-(2-(4-methoxyphenyl)acetamido)-1,3,4-thiadiazole-2-carboxylic acid (carboxylic acid for **Compound 97**) was prepared from methyl 5-amino-1,3,4-thiadiazole-2-carboxylate and 2-(4-methoxyphenyl)acetyl chloride using *General Procedures 5 then 3*.

(2-(4-methoxyphenyl)acetyl)-L-alanine (carboxylic acid for **Compound 98**) was prepared from *tert*-butyl L-alaninate and 2-(4-methoxyphenyl)acetic acid using *General Procedures 2 then 4*.

(2-(4-methoxyphenyl)acetyl)-L-valine (carboxylic acid for **Compound 99**) was prepared from *tert*-butyl L-valinate and 2-(4-methoxyphenyl)acetic acid using *General Procedures 2 then 4*.

5-(2-(4-methoxy-phenyl)acetamido)pyrimidine-2-carboxylic acid (carboxylic acid for **Compound 105**) was prepared from 2-(4-methoxy-phenyl)acetyl chloride and methyl 5-aminopyrimidine-2-carboxylate using *General Procedures 5 then 3*.

5-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)pyrimidine-2-carboxylic acid (carboxylic acid for **Compound 106**) was prepared from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride and methyl 5-aminopyrimidine-2-carboxylate using *General Procedures 5 then 3*.

2-(2-(4-methoxyphenyl)acetamido)cyclopentane-1-carboxylic acid (carboxylic acid for **Compound 107**) was prepared from 2-(4-methoxyphenyl)acetyl chloride and 2-aminocyclopentane-1-carboxylic acid using *General Procedure 5*.

(2-(4-methoxyphenyl)acetyl)-L-tyrosine (carboxylic acid for **Compound 108**) was prepared from methyl L-tyrosinate and 2-(4-methoxyphenyl)acetyl chloride using *General Procedures 5 then 3*.

3-(2-(4-methoxyphenyl)acetamido)cyclopentane-1-carboxylic acid (carboxylic acid for **Compound 109**) was prepared from 2-(4-methoxyphenyl)acetyl chloride and 3-aminocyclopentane-1-carboxylic acid using *General Procedure 5*.

2-(2-(4-methoxyphenyl)acetamido)oxazole-5-carboxylic acid (carboxylic acid for **Compound 110**) was prepared from 2-(4-methoxyphenyl)acetyl chloride and 2-aminooxazole-5-carboxylic acid using *General Procedure 5*.

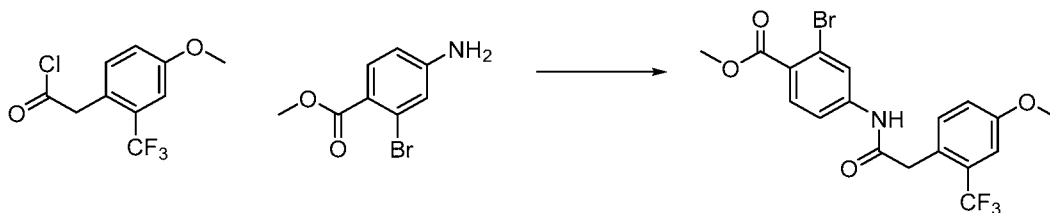
(2-(4-methoxyphenyl)acetyl)-*L*-phenylalanine (carboxylic acid for **Compound 114**) was prepared from methyl *L*-phenylalaninate and 2-(4-methoxyphenyl)acetyl chloride using *General Procedures 5 then 3*.

(2-(4-methoxyphenyl)acetyl)-*D*-alanine (carboxylic acid for **Compound 115**) was prepared from *tert*-butyl *D*-alaninate and 2-(4-methoxyphenyl)acetic acid using *General Procedures 2 then 4*.

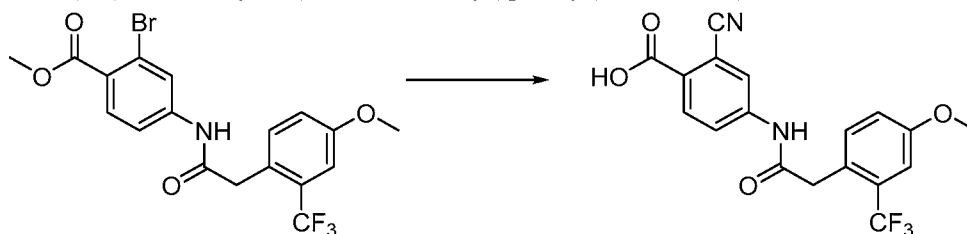
(*R*)-2-(2-(4-methoxyphenyl)acetamido)butanoic acid (carboxylic acid for **Compound 116**) was prepared from *tert*-butyl (*R*)-2-aminobutanoate and 2-(4-methoxyphenyl)acetic acid using *General Procedures 2 then 4*.

Compounds 18-24, 32, 33, 46, 57, 58, 64, 67, 68, 72, 73, 82-84, 97-99, 105-110, 114-116 were prepared from *tert*-butyl (4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate **INT-2** with the appropriate carboxylic acid using *General Procedures 2 then 4*.

20 Methyl 2-bromo-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)benzoate



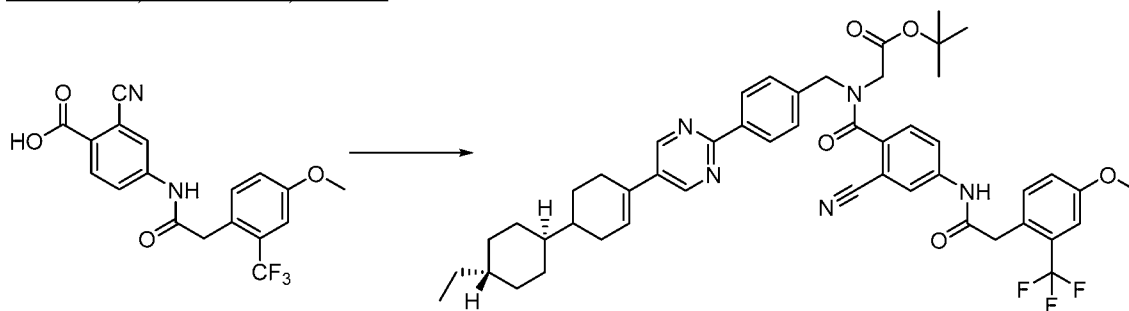
Prepared using *General Procedure 5* from 2-(4-methoxy-2-(trifluoromethyl)phenyl)acetyl chloride (800 mg, 3.17 mmol) and methyl 4-amino-2-bromobenzoate (730 mg, 3.17 mmol) to give 550 mg (33%) of methyl 2-bromo-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)benzoate. LCMS-ESI (*m/z*) calculated for $C_{18}H_{15}BrF_3NO_4$: 445.0, found 446.0 [$M+H$]⁺, t_R = 2.49 minutes (*Method 4*).

2-cyano-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)benzoic acid

Methyl 2-bromo-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)-acetamido) benzoate (290 mg, 0.65 mmol) in NMP (7.22 mL) was treated with copper cyanide (87 mg, 0.975 mmol) and heated to 150 °C for 18 hours. Water (10 mL) was added to the mixture and the layers were separated. The aqueous layer was extracted with EA (2 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated, and purified by column chromatography (0-60% EA in iso-hexanes) to give 0.140 g (52%) methyl 2-cyano-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)benzoate.

Prepared using *General Procedure 3*. To a solution of methyl 2-cyano-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)-acetamido)benzoate (0.140 g, 0.357 mmol) in THF (2.55 mL) was added 0.4 M LiOH (1.37 mL, 0.54 mmol) at 0 °C. After 4 hours, the reaction mixture was evaporated under reduced pressure to give 0.138 g (99%) of 2-cyano-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)-acetamido)benzoic acid.

Tert-butyl 2-(2-cyano-N-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)-acetamido)benzamido)acetate



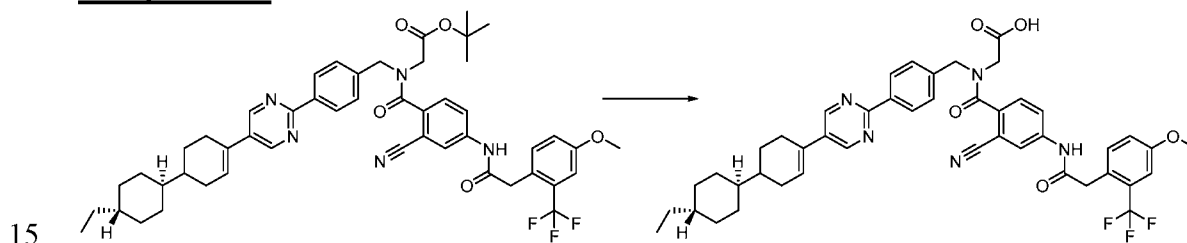
20

Prepared using *General Procedure 2*. To a stirring mixture of *tert*-butyl (4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-glycinate **INT-2** (0.117 g, 0.238 mmol) and 2-cyano-4-(2-(4-methoxy-2-

(trifluoromethyl)phenyl)acetamido) benzoic acid (0.357 g, 0.135 mmol) in DMF (3 mL) at 0 °C was added DIEA (0.246 mL, 1.43 mmol) followed by HATU (0.286 g, 0.714 mmol) and the reaction was stirred at RT for 18 h. EA (10 mL) and 1M HCl (10 mL) were added and the layers were separated. The aqueous layer was extracted with EA (10 mL) and the combined organic layers were washed with saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered, concentrated, and purified by column chromatography (0-60% EA in DCM/iso-hexanes) to give 0.109 g (50%) of *tert*-butyl 2-(2-cyano-*N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)benzamido)-acetate. LCMS-ESI (m/z) calculated for C₄₉H₅₄F₃N₅O₅: 849.4, no mass observed, *t*_R = 3.48 minutes (*Method 4*).

N-(2-cyano-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)benzoyl)-*N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycine

Compound 47

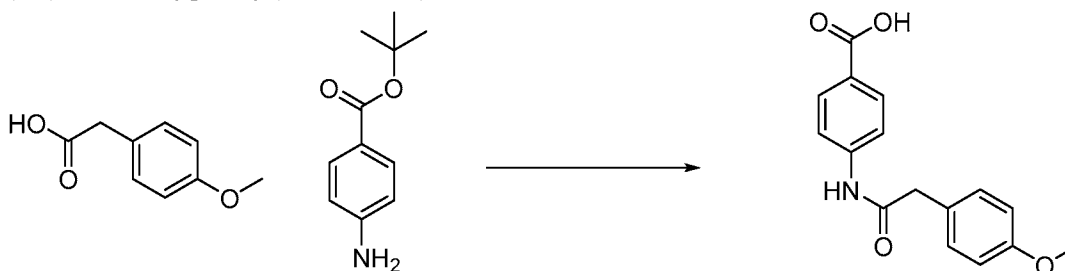


A sample of *tert*-butyl 2-(2-cyano-*N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido) benzamido)acetate (0.047 g, 0.056 mmol) was stirred in formic acid (2 mL, 0.056 mmol) for 7 h at room temperature. DCM (5 mL) and water (5 mL) were added and the layers were separated. The organic layer was collected and evaporated under reduced pressure and purified by column chromatography (0-50% EA (1% acetic) in DCM/iso-hexanes) to provide 0.006 g (13%) of *N*-(2-cyano-4-(2-(4-methoxy-2-(trifluoromethyl)phenyl)acetamido)-benzoyl)-*N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycine **Compound 47**. LCMS-ESI (m/z) calculated for C₄₅H₄₆F₃N₅O₅: 793.4, found 794 [M+H]⁺, *t*_R = 11.42 minutes (*Method 3*).

25

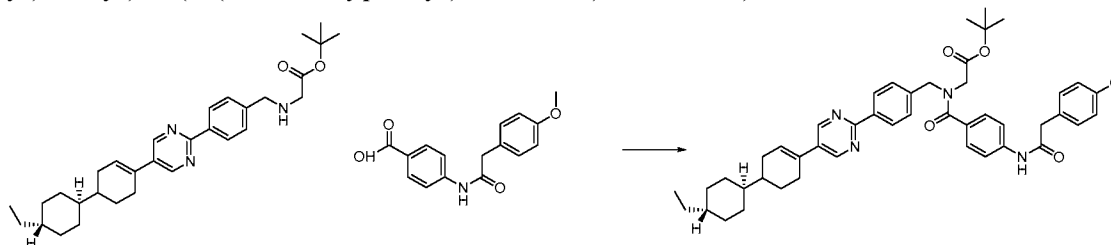
Compounds 25-28, 30, 31, 34-45, 48-51, 53, 55, 56, 65, 66, 69, 74-76, 85, 92, 93 and 153 were prepared from *tert*-butyl *N*-(4-aminobenzoyl)-*N*-(4-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate INT-3 with the appropriate carboxylic acid using *General Procedures 2 then 4*.

5 4-(2-(4-methoxyphenyl)acetamido)benzoic acid



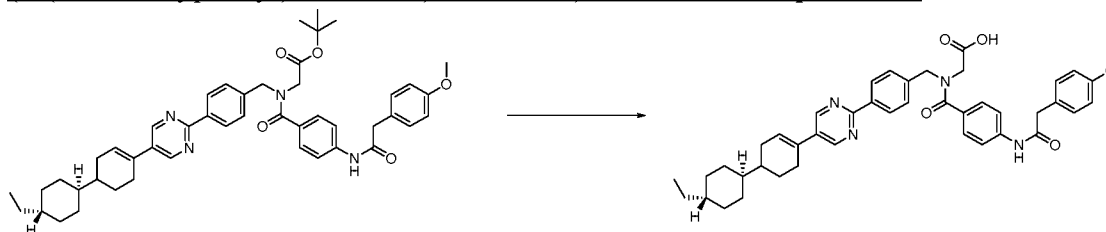
Prepared using *General Procedure 2*. To a stirring solution of 2-(4-methoxyphenyl)acetic acid (1g, 6.02 mmol), *tert*-butyl 4-aminobenzoate (1.16 g, 6.02 mmol) and triethylamine (2.2 mL, 15.04 mmol) in DMF (20 mL) was added HATU (2.477 g, 6.32 mmol). After 2 h, additional 2-(4-methoxyphenyl)acetic acid (100 mg, 0.60 mmol) and HATU (247 mg, 0.63 mmol) were added. After a further 1 h, the mixture was diluted with EA (50 mL) and washed successively with NaHCO₃ (2 x 50 mL), 1 M HCl (100 mL) and brine (50 mL), dried over MgSO₄ and solvents evaporated. The residue was taken into DCM (30 mL) and stirred with TFA (15 mL). After 4 h, the mixture was washed with water (50 mL) and split through a hydrophobic frit. Solvents were evaporated to afford 1.02 g (59%) of 4-(2-(4-methoxyphenyl)acetamido)benzoic acid. LCMS-ESI (*m/z*) calculated for C₁₆H₁₅NO₄: 285.1; found 286.0 [M+H]⁺, *t_R* = 1.70 min (*Method 4*). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.70 (s, 1H), 10.49 (s, 1H), 8.00 – 7.81 (m, 2H), 7.80 – 7.60 (m, 2H), 7.37 – 7.14 (m, 2H), 6.99 – 6.82 (m, 2H), 3.73 (s, 3H), 3.61 (s, 2H).

Tert-butyl 2-(*N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-(2-(4-methoxyphenyl)acetamido)benzamido)acetate



Prepared using *General Procedure 2*. To a stirring mixture of *tert*-butyl (4-(5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-glycinate **INT-2** (2 g, 4.08 mmol), DIEA (2.1 mL, 12.25 mmol) and 4-(2-(4-methoxyphenyl)-acetamido)benzoic acid (1.28 g, 4.49 mmol) in DMF (40 mL) and DCM (20 mL), was added HATU (1.96 g, 4.90 mmol). After 16 h, solvents were evaporated and the residue re-slurried from ACN (100 mL). Column chromatography (EA/DCM/*iso*-hexane) gave 1.905 g (62%) of *tert*-butyl 2-(*N*-(4-(5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-(2-(4-methoxyphenyl)acetamido)benzamido)acetate. LCMS-ESI (*m/z*) calculated for C₄₇H₅₆N₄O₅: 756.4; no *m/z* observed, *t_R* = 3.47 min (*Method 4*).

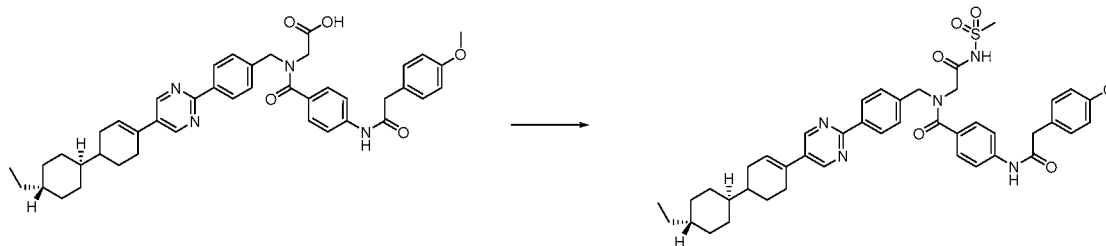
2-(*N*-(4-(5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-(2-(4-methoxyphenyl)acetamido)benzamido)acetic acid **Compound 29**



Prepared using *General Procedure 4*. To a stirring mixture of *tert*-butyl 2-(*N*-(4-(5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)-benzyl)-4-(2-(4-methoxyphenyl)acetamido)benzamido)acetate (1.9 g, 2.51 mmol) in DCM (50 mL) was added TFA (20 mL). After 2 h, solvents were evaporated and the residue re-slurried from ACN (100 mL) to afford 1.5 g (85%) of 2-(*N*-(4-(5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-(2-(4-methoxyphenyl)acetamido)benzamido)acetic acid **Compound 29**. LCMS-ESI (*m/z*) calculated for C₄₃H₄₈N₄O₅: 700.4; found 701.1 [M+H]⁺, *t_R* = 3.30 min (*Method 4*).

N-(4-(5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-(2-(4-methoxyphenyl)acetamido)-N-(2-(methylsulfonamido)-2-oxoethyl)benzamide

Compound 52



5 To a stirring solution of 2-(N-(4-(5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-(2-(4-methoxyphenyl)-acetamido)benzamido)acetic acid **Compound 29** (1.3 g, 1.855 mmol) in THF (25 mL) at 40°C was added 1,1'-carbonyldiimidazole (1.203 g, 7.42 mmol). After 1.5 h, the mixture was treated with a solution of methanesulfonamide (1.080 g, 11.13 mmol) and

10 1,8-diazabicyclo[5.4.0]undec-7-ene (1.7 mL, 11.13 mmol) in THF (3 mL). After 4 h, the mixture was allowed to cool then diluted with DCM (50 mL), washed successively with 1 M HCl (50 mL) and brine (50 mL), dried over MgSO₄ and solvents evaporated.

15 Column chromatography (DCM/MeOH/AcOH) gave 1.05 g (73%) of N-(4-(5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-4-(2-(4-methoxyphenyl)acetamido)-N-(2-(methylsulfonamido)-2-oxoethyl)benzamide

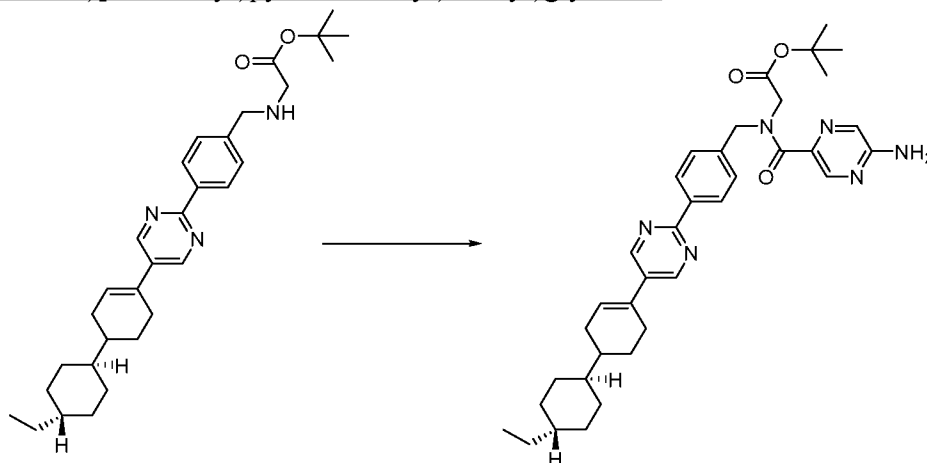
Compound 52. LCMS-ESI (m/z) calculated for C₄₄H₅₁N₅O₆S: 777.4; found 778.1 [M+H]⁺, t_R = 10.83 min (*Method 3*). ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.85 (br s, 1H), 10.31 (s, 1H), 8.95 (s, 2H), 8.51 – 8.22 (m, 2H), 7.67 – 7.63 (m, 2H), 7.56 – 7.31 (m, 4H), 7.25 – 7.22 (m, 2H), 6.93 – 6.83 (m, 2H), 6.46 (dt, *J* = 5.3, 2.4 Hz, 1H), 4.72 (s, 1H), 4.64 (s, 1H), 4.09 (s, 1H), 3.97 (s, 1H), 3.72 (s, 3H), 3.57 (s, 2H), 3.25 (s, 2H), 3.18 (s, 1H), 2.56 – 2.26 (m, 3H), 2.04 – 1.89 (m, 2H), 1.87 – 1.70 (m, 4H), 1.41 – 1.27 (m, 2H), 1.24 – 0.91 (m, 6H), 0.90 – 0.81 (m, 5H).

20

Compounds 54 and 61 were prepared from **Compound 29** using *General Procedures 2 then 4*.

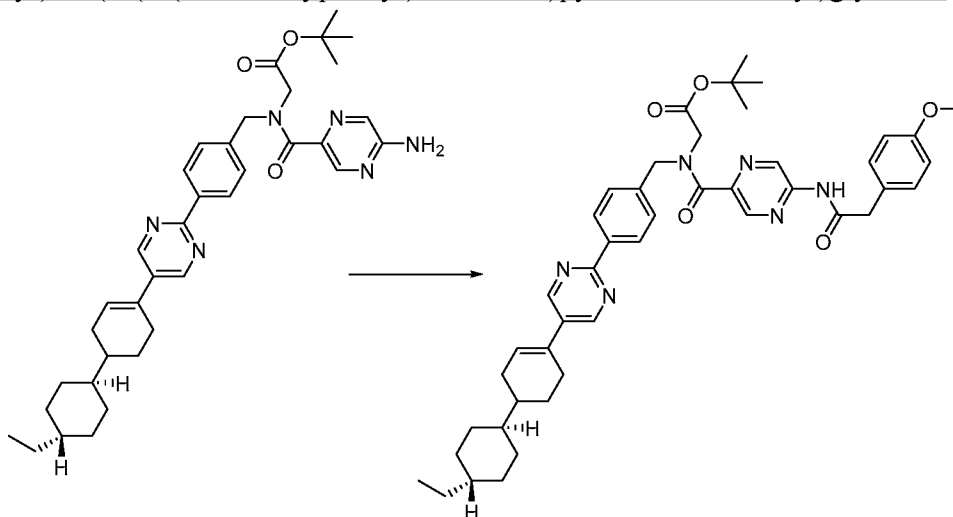
25 **Compounds 59, 60, and 62** were prepared from **Compound 29** using *General Procedures 2 then 3*.

Tert-butyl N-(5-aminopyrazine-2-carbonyl)-N-(4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate



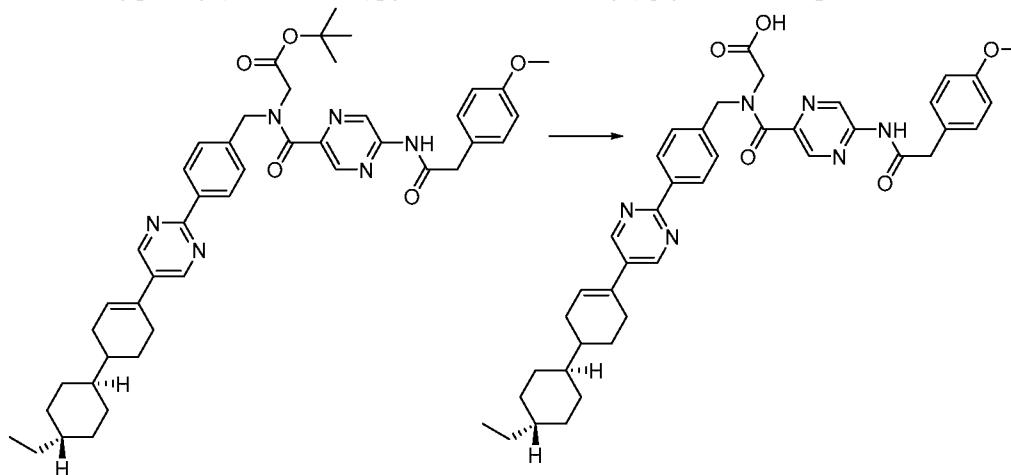
- 5 To a solution of 5-aminopyrazine-2-carboxylic acid (225.4 mg, 1.62 mmol) and DIEA (418.7 mg, 3.24 mmol) in DMF (10 mL) was added HATU (381.1 mg, 1.62 mmol). The reaction mixture was stirred 1 h at RT and *tert*-butyl (4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate **INT-2** (530.0 mg, 1.08 mmol) was added. The reaction mixture stirred at room temperature
- 10 for 3 h. The reaction mixture was diluted with EA then washed with saturated aqueous NaHCO₃ and water. The organic layer was dried over anhydrous sodium sulfate, concentrated, and purified by chromatography (EA / hexanes from 0 to 70%) to provide 628 mg (95%) of *tert*-butyl *N*-(5-aminopyrazine-2-carbonyl)-*N*-(4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate as a white solid.
- 15 LCMS-ESI (*m/z*) calculated for C₃₆H₄₆N₆O₃: 610.8; found 611.1[M+H]⁺, *t*_R = 4.873 minutes (*Method 2*).

Tert-butyl N-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-N-(5-(2-(4-methoxyphenyl)acetamido)pyrazine-2-carbonyl)glycinate



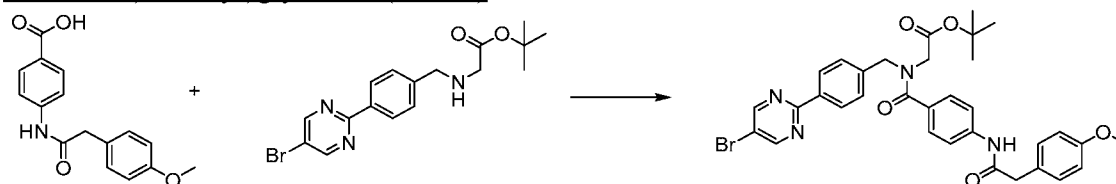
- 5 To a solution of tert-butyl *N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate (600.0 mg, 0.98 mmol) in anhydrous THF (20 mL) was added sodium hydride (47.04 mg, 1.96 mmol, 60% dispersion in mineral oil). The reaction mixture stirred at 0 °C for 2 h and then at RT for 1 h. The 2-(4-methoxyphenyl)acetyl chloride (542.78 mg, 2.94
- 10 mmol) was added to above solution at 0 °C and the reaction mixture was allowed to warm to RT. The mixture stirred was stirred for 18 h. After evaporated THF solvent, the reaction mixture was diluted with EA then washed with saturated aqueous NaHCO₃ and water. The organic layer was dried over anhydrous sodium sulfate, concentrated, and purified by chromatography (EA / hexanes from 0 to 70%) to provide 350 mg (47%) of
- 15 *tert*-butyl *N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-*N*-(5-(2-(4-methoxy-phenyl)acetamido)pyrazine-2-carbonyl)glycinate. LCMS-ESI (m/z) calculated for C₄₅H₅₄N₆O₅: 758.9; found 759.3 [M+H]⁺, *t*_R = 5.053 minutes (*Method 2*).

N-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-N-(5-(2-(4-methoxyphenyl)acetamido)pyrazine-2-carbonyl)glycine **Compound 63**



To a solution of *tert*-butyl *N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-
 5 bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-*N*-(5-(2-(4-methoxyphenyl)-
 acetamido)pyrazine-2-carbonyl)glycinate (350.0 mg, 0.461 mmol) in DCM (25 mL)
 was added TFA (1mL) at room temperature and the mixture was stirred for 4 hours. The
 solvent was removed and the residue was diluted with EA and washed with saturated
 aqueous NaHCO₃ and H₂O. The organic layer was dried over anhydrous sodium sulfate,
 10 concentrated, and purified by chromatography (DCM / MeOH from 0 to 10%) to
 provide 183 mg (57%) of *N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-
 yl)pyrimidin-2-yl)benzyl)-*N*-(5-(2-(4-methoxyphenyl)-acetamido)pyrazine-2-
 carbonyl)glycine **Compound 63**. LCMS-ESI (m/z) calculated for C₄₁H₄₆N₆O₅: 702.8;
 found 703.0 [M+H]⁺, *t*_R = 8.797 minutes (*Method 1*).

15 Tert-butyl *N*-(4-(5-bromopyrimidin-2-yl)benzyl)-*N*-(4-(2-(4-methoxyphenyl)-
 acetamido)benzoyl)glycinate (**INT-6**)

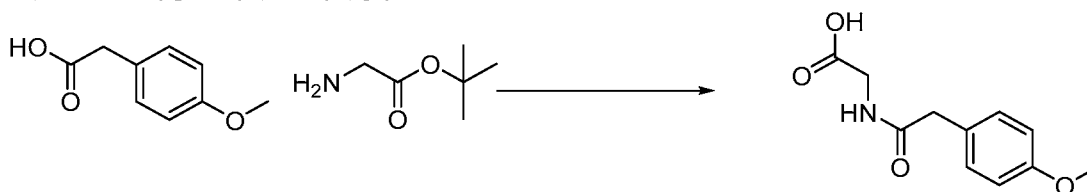


Prepared using *General Procedure 2*. A stirred solution of 4-(2-(4-
 20 methoxyphenyl)acetamido)benzoic acid (1.0 g, 3.50 mmol), *tert*-butyl (4-(5-

bromopyrimidin-2-yl)benzyl)glycinate **INT-1** (1.99 g, 80% pure, 4.2 mmol,) and DIEA (1.35g, 10.50 mmol) in DMF (20 mL) was treated with HATU (1.23 g, 5.25 mmol) added portionwise. The reaction mixture was stirred at RT for 2 h then diluted with EA (50 mL).). The combined organic layers were washed with saturated sodium bicarbonate solution (2 x 50 mL) dried over magnesium sulfate and concentrated. The crude product was purified by column chromatography (0-70% EA in Hexane) to afford 1.39 g (61.8%) of *tert*-butyl *N*-(4-(5-bromopyrimidin-2-yl)benzyl)-*N*-(4-(2-(4-methoxyphenyl)acetamido) benzoyl)-glycinate **INT-6**. LCMS-ESI (m/z) calculated for C₃₃H₃₃BrN₄O₅: 644.2, found 644.8 [M+H]⁺, t_R = 3.859 minutes (*Method 2*).

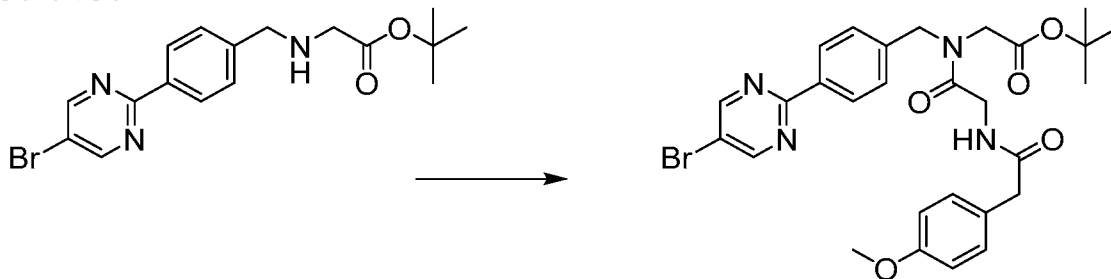
Compounds 70, 86-91, and 100-103 were prepared from *tert*-butyl *N*-(4-(5-bromopyrimidin-2-yl)benzyl)-*N*-(4-(2-(4-methoxyphenyl)acetamido)benzoyl)glycinate **INT-6** using *General Procedures 1* then 4.

(2-(4-methoxyphenyl)acetyl)glycine



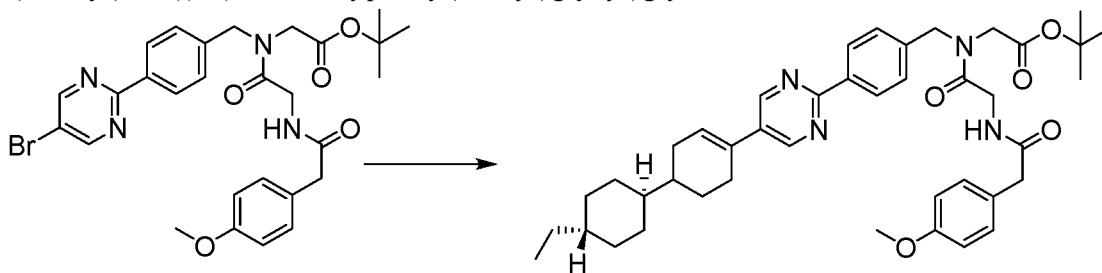
Prepared using *General Procedure 2*. To a stirring solution of 2-(4-methoxyphenyl)acetic acid (4 g, 24.1 mmol) in DMF (20 mL) was added HATU (8.50 g, 36.15 mmol) and the mixture was stirred at RT for 1 h. *Tert*-butyl glycinate hydrochloride (4.02 g, 24.1 mmol) and DIEA (9.34 g, 72.3 mmol) were added and stirred for 3 h. The mixture was diluted with EA (50 mL) and washed with NaHCO₃ (10 mL), dried over MgSO₄ and solvents evaporated. The intermediate was purified by chromatography (0-100% EA in hexane) to give 3.5 g of *tert*-butyl (2-(4-methoxyphenyl)acetyl)glycinate. This intermediate was dissolved in DCM (10 mL) and treated with TFA (2 mL) for 18 h. The solvent was removed under reduced pressure to give 2.79 g (52%) of (2-(4-methoxyphenyl)acetyl)glycine. LCMS-ESI (m/z) calculated for C₁₁H₁₃NO₄: 223.1; found 224.3 [M+H]⁺, t_R = 0.63 min (*Method 2*).

Tert-butyl N-(4-(5-bromopyrimidin-2-yl)benzyl)-N-((2-(4-methoxyphenyl)acetyl)-glycyl)glycinate



Prepared using *General Procedure 2*. To a stirring solution of (2-(4-methoxyphenyl)acetyl)glycine (2.9 g, 12.1 mmol) in DMF (20 mL) was added HATU (4.27 g, 18.15 mmol) and the mixture was stirred at RT for 1 h. *Tert*-butyl (4-(5-bromopyrimidin-2-yl)benzyl)glycinate **INT-1** (4.11 g, 10.89 mmol) and DIEA (4.69 g, 36.3 mmol) were added and stirred for 3 h. The mixture was diluted with EA (50 mL) and washed with NaHCO₃ (10 mL), dried over MgSO₄ and solvents evaporated. The intermediate was purified by chromatography (0-100% EA in hexane) to give 3.82 g (54%) of *tert*-butyl N-(4-(5-bromopyrimidin-2-yl)benzyl)-N-((2-(4-methoxyphenyl)acetyl)glycyl) glycinate. LCMS-ESI (m/z) calculated for C₂₈H₃₁BrN₄O₅: 583.5; found 584.3 [M+H]⁺, t_R = 3.82 min (*Method 2*).

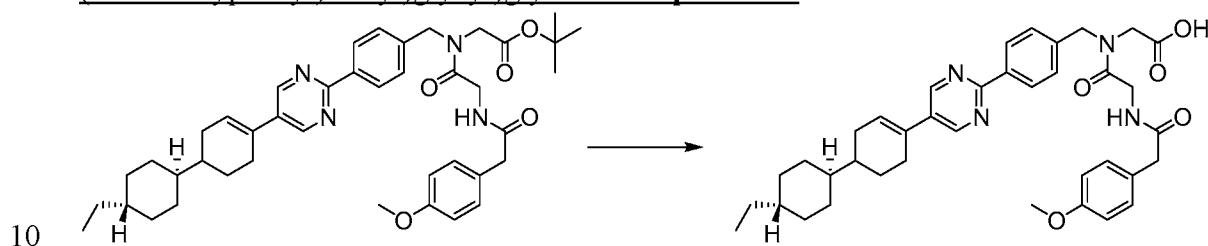
15 Tert-butyl N-(4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-N-((2-(4-methoxyphenyl)acetyl)glycyl)glycinate



Prepared using *General Procedure 1*. To a stirring solution of *tert*-butyl N-(4-(5-bromopyrimidin-2-yl)benzyl)-N-((2-(4-methoxyphenyl)acetyl)glycyl) glycinate (1.0 g, 1.71 mmol) and 2-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.82 g, 2.57 mmol) in dioxane (10.3 mL) and water (3.4 mL) was added sodium carbonate decahydrate (0.98 g, 3.43 mmol). The mixture was degassed with nitrogen for 5 min then PdCl₂(dppf) (70 mg, 0.086 mmol) was added

and the mixture was heated to 80°C for 2 h. The reaction was cooled to RT and water (100 mL) was added. The resulting precipitate was filtered and the dark brown solid was dissolved in DCM, loaded onto Celite and purified by chromatography (0-100% EA in hexane) to give 542 mg (45%) of *tert*-butyl *N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-*N*-((2-(4-methoxyphenyl)acetyl)glycyl)glycinate. LCMS-ESI (m/z) calculated for C₄₂H₅₄N₄O₅: 694.4, found 695.1 [M+H]⁺, t_R = 12.30 minutes (*Method 1*).

N-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-*N*-((2-(4-methoxyphenyl)acetyl)glycyl)glycine **Compound 71**

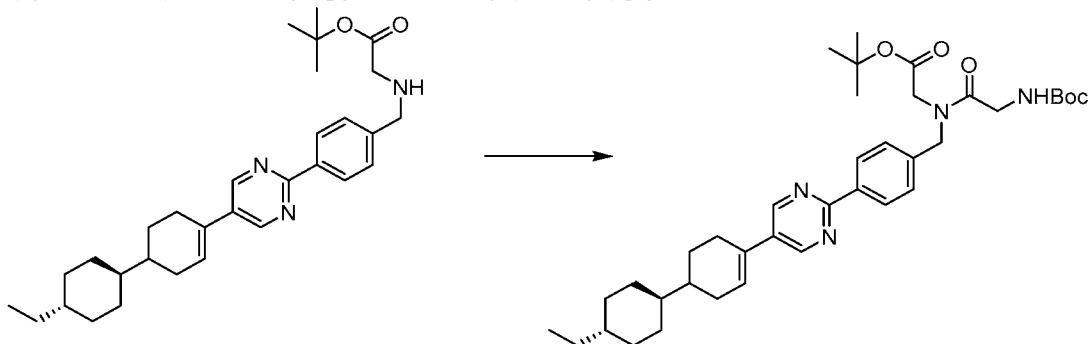


Prepared using *General Procedure 4*. To a stirring solution of *tert*-butyl *N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-*N*-((2-(4-methoxyphenyl)acetyl)glycyl)glycinate (329 mg, 0.47 mmol) in DCM (4 mL) was added TFA (1 mL). The mixture was stirred at RT for 18 h. The solvent was removed and the residue was azeotroped with acetonitrile (3 x 10 mL). The residue was dissolved in DCM (2 mL) and added dropwise to a stirring solution of acetonitrile (20 mL) and water (10 mL). The resulting precipitate was filtered and dried to give 280 mg (93%) of *N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-*N*-((2-(4-methoxyphenyl)acetyl)glycyl)glycine **Compound 71**. LCMS-ESI (m/z) calculated for C₃₈H₄₆N₄O₅: 638.4, found 639.1 [M+H]⁺, t_R = 8.09 minutes (*Method 1*).

Compounds 104 and **111** were prepared from **Compound 1** using *General Procedures 2, 3, then 4*.

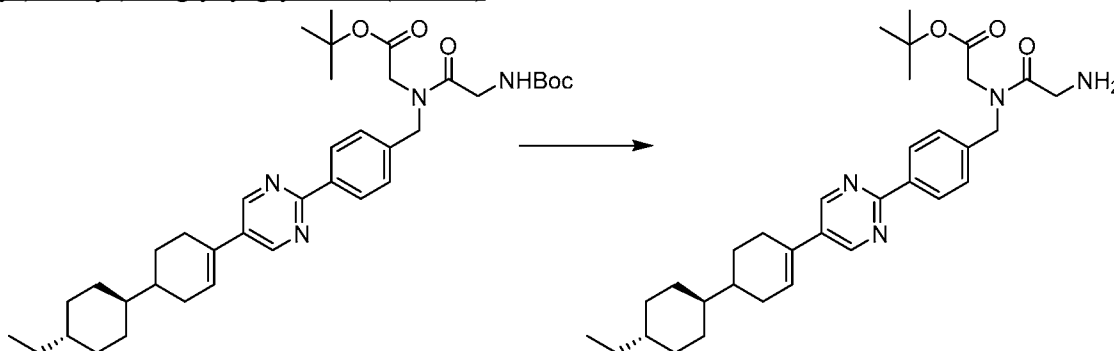
Compounds 117-121 were prepared from *tert*-butyl *N*-(4-(5-bromopyrimidin-2-yl)benzyl)-*N*-((2-(4-methoxyphenyl)acetyl)glycyl)glycinate using *General Procedures 1 then 4*.

Tert-butyl N-((tert-butoxycarbonyl)glycyl)-N-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate



Prepared using *General Procedure 2*. A stirred solution of (*tert*-butoxycarbonyl)glycine (300 mg, 1.715 mmol) and DIEA (427 μ L, 2.45 mmol) in DMF (3 mL) was treated with HATU (629 mg, 1.654 mmol) added in one portion. The reaction mixture turned yellow and was allowed to stir at RT for 5 min. *Tert*-butyl (4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-glycinate **INT-2** (600 mg, 1.225 mmol) and DMF (2 mL) was added and the reaction was allowed to stir at RT for 1 h. Water (60 mL) was added and the precipitate was filtered and washed with water (20 mL). The precipitate was dissolved in DCM, dried over magnesium sulfate and purified by chromatography (0-100% EA in hexanes) to give 583 mg (73.5%) of *tert*-butyl *N*-((*tert*-butoxycarbonyl)glycyl)-*N*-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)-pyrimidin-2-yl)benzyl)glycinate. LCMS-ESI (*m/z*) calculated for $C_{38}H_{54}N_4O_5$: 646.4, found 547.1 [*M*-Boc]⁺, t_R = 5.246 minutes (*Method 2*).

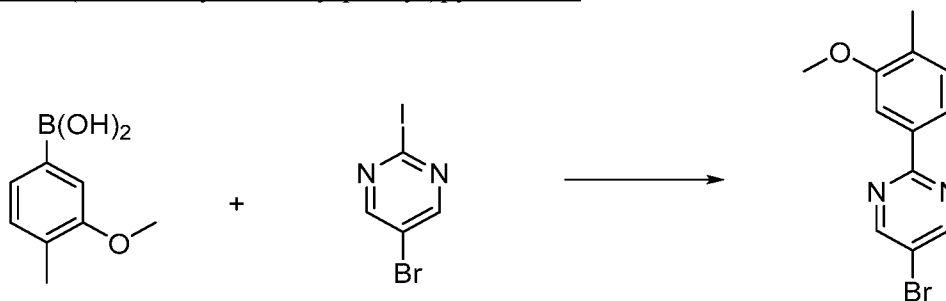
Tert-butyl N-(4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-N-glycylglycinate (**INT-7**)



Prepared using *General Procedure 4*. *Tert*-butyl *N*-((*tert*-butoxycarbonyl)glycyl)-*N*-(4-(5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate (388 mg, 0.6 mmol) in DCM (2 mL) was cooled to 0°C and treated with 5-6N hydrochloric acid in isopropanol (1.09 mL, 6 mmol). The reaction was warmed to RT and stirred for 2 h. All the solvent was removed to give 340 mg (97%) of *tert*-butyl *N*-(4-(5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-*N*-glycylglycinate **INT-7** as the hydrochloride salt which contained ~12% material where the *tert*-butyl ester was removed. LCMS-ESI (m/z) calculated for C₃₃H₄₆N₄O₃: 546.4, found 547.1 [M+H]⁺, *t*_R = 4.982 minutes (*Method 2*).

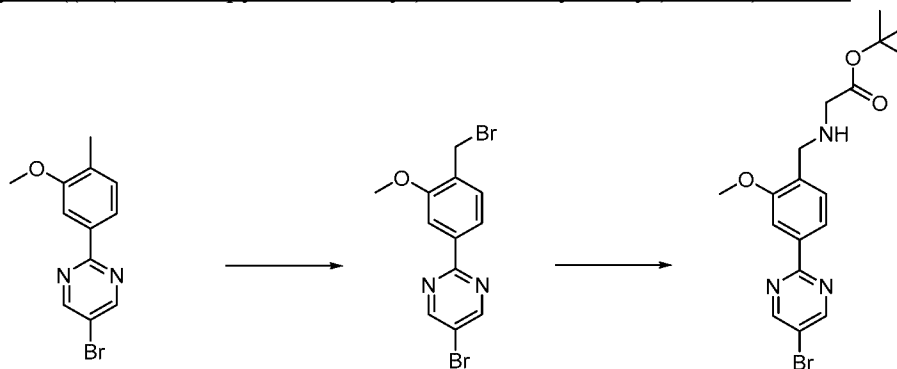
Compounds 122-124, 127, and 129-147 were prepared from *tert*-butyl *N*-(4-(5-((1*r*,4*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-*N*-glycylglycinate **INT-7** using *General Procedures 2 then 4*.

5-bromo-2-(3-methoxy-4-methylphenyl)pyrimidine



Prepared using *General Procedure 1* from (3-methoxy-4-methylphenyl)boronic acid (500 mg, 3.0 mmol) and 5-bromo-2-iodopyrimidine (858 mg, 3.0 mmol) to give 654 mg (49%) of 5-bromo-2-(3-methoxy-4-methylphenyl)pyrimidine. LCMS-ESI (m/z) calculated for C₁₂H₁₁BrN₂O: 278.01, found 278.9 [M+H]⁺, *t*_R = 2.66 minutes (*Method 4*).

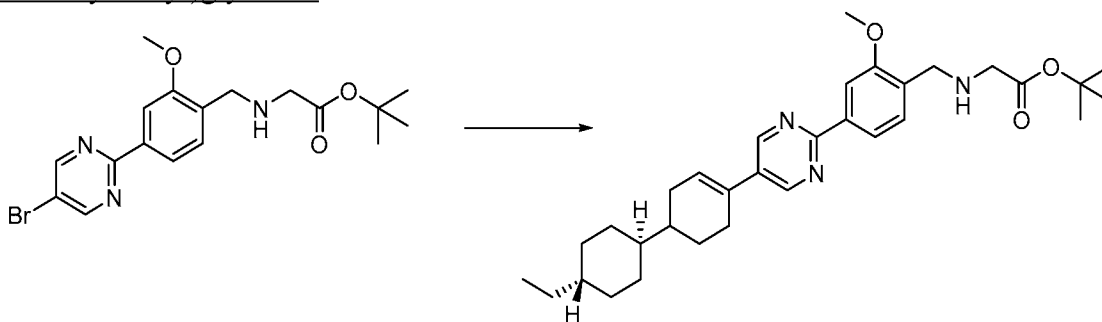
Tert-butyl 2-((4-(5-bromopyrimidin-2-yl)-2-methoxybenzyl)amino)acetate



To a round bottom flask containing 5-bromo-2-(3-methoxy-4-methylphenyl)pyrimidine (654 mg, 2.34 mmol) in chloroform (11.7 mL) was added 1-bromopyrrolidine-2,5-dione (541 mg, 3.04 mmol) and (*E*)-2,2'-(diazene-1,2-diyl)bis(2-methylpropanenitrile) (57.6 mg, 0.35 mmol). The reaction mixture was stirred and heated at reflux for 1 h. The reaction mixture was allowed to cool to RT and the solvent was removed *in vacuo* to give 838 mg of crude 5-bromo-2-(4-(bromomethyl)-3-methoxyphenyl)pyrimidine.

To a round bottom flask containing 5-bromo-2-(4-(bromomethyl)-3-methoxyphenyl)pyrimidine (838 mg, 2.34 mmol) and *tert*-butyl 2-aminoacetate hydrochloride (1177 mg, 7.02 mmol) in THF (19.51 mL) was added *N*-ethyl-*N*-isopropylpropan-2-amine (1.215 mL, 7.02 mmol). The reaction mixture was heated at 70 °C for 30 min. The reaction mixture was cooled to room temperature and diluted with water (50 mL) and EA (50 mL). The layers were partitioned and the aqueous layer was further extracted with EA (2 x 20 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed. The residue was purified by chromatography (0% to 10% THF in DCM) to afford 147 mg of *tert*-butyl 2-((4-(5-bromopyrimidin-2-yl)-2-methoxybenzyl)amino)acetate (14.61%) as a colorless solid. LCMS-ESI (*m/z*) calculated for C₁₈H₂₂BrN₃O₃: 407.08, found 407.9 [M+H]⁺, *t_R* = 1.54 minutes (*Method 4*).

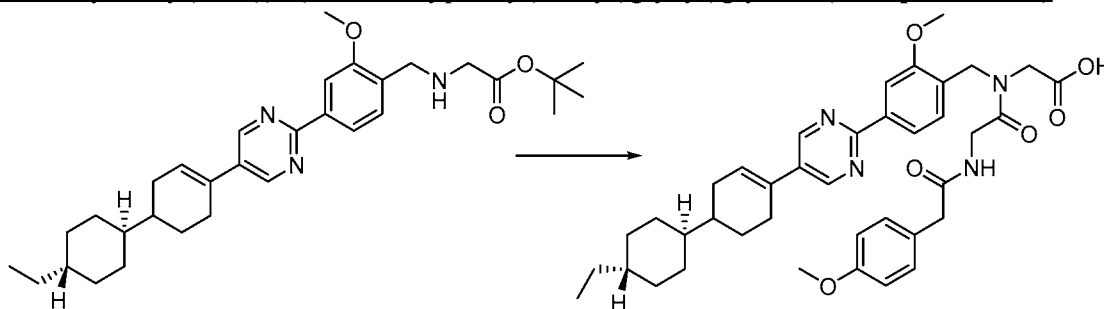
Tert-butyl (4-(5-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)-2-methoxybenzyl)glycinate



Prepared using General Procedure 1 from *tert*-butyl 2-((4-(5-bromopyrimidin-2-yl)-2-methoxybenzyl)amino)acetate (147 mg, 0.36 mmol) and 2-((1*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-

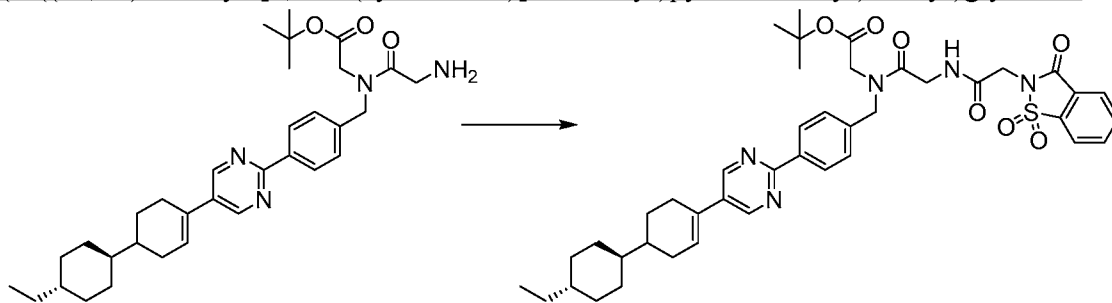
dioxaborolane (152 mg, 0.478 mmol) to give 46 mg (24%) of *tert*-butyl (4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)-2-methoxybenzyl)-glycinate. LCMS-ESI (m/z) calculated for C₃₂H₄₅N₃O₃: 519.35, found 520.2 [M+H]⁺, t_R = 2.62 minutes (*Method 4*).

- 5 N-(4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)-2-methoxybenzyl)-N-((2-(4-methoxyphenyl)acetyl)glycyl)glycine (**Compound 126**)



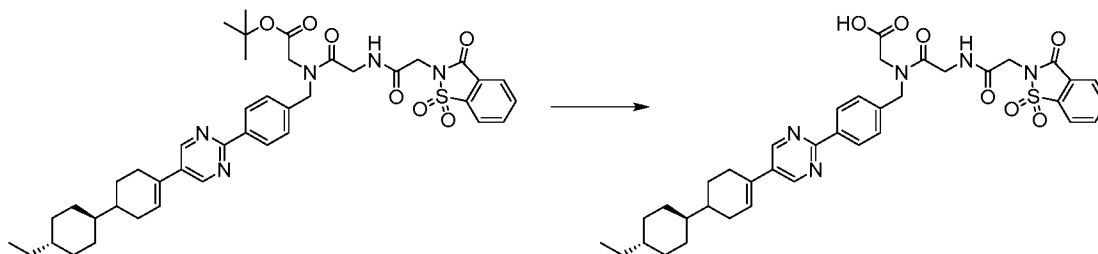
Prepared using *General Procedure 2* from *tert*-butyl (4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)-2-methoxybenzyl)glycinate (46 mg, 0.09 mmol) and 2-(2-(4-methoxyphenyl)acetamido)acetic acid (21.8 mg, 0.10 mmol) to give 50 mg (75%) of *tert*-butyl *N*-(4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)-2-methoxybenzyl)-*N*-((2-(4-methoxyphenyl)acetyl)glycyl)glycinate which was treated according to *General Procedure 4* to give 37 mg (79%) of *N*-(4-(5-((1'*r*,4'*r*)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)-2-methoxybenzyl)-*N*-((2-(4-methoxyphenyl)acetyl)glycyl)glycine (**Compound 126**). LCMS-ESI (m/z) calculated for C₃₉H₄₈N₄O₆: 668.4, found 669.1 [M+H]⁺, t_R = 10.62 minutes (*Method 3*).

Tert-butyl N-((2-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)acetyl)glycyl)-N-(4-(5-((1'r,4'r)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate



Prepared using *General Procedure 1*. To a stirring solution of 2-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)acetic acid (174 mg, 0.72 mmol) in DMF (1.2 mL) at 0 °C was added DIEA (209 μL, 0.72 mmol) and HATU (274 mg, 0.72 mmol). The mixture was stirred at 0 °C for 10 min then added to a stirring mixture of *tert*-butyl *N*-(4-(5-((1'r,4'r)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)-*N*-glycylglycinate (**INT-7**) (328 mg, 0.6 mmol) in DMF (1.2 mL). After stirring at 0 °C for 1 h, the reaction mixture was warmed to RT and stirred for 3 h. Additional DIEA (209 μL, 0.72 mmol) was added. In a separate flask, additional 2-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)acetic acid (174 mg, 0.72 mmol) in DMF (1.2 mL) at 0 °C was treated with DIEA (209 μL, 0.72 mmol) and HATU (274 mg, 0.72 mmol) and stirred at 0 °C for 10 min. This activated acid was added to the original reaction mixture and stirred at RT for 15 min. Water (40 mL) was added and the solid was filtered and dried to give crude material which was purified by chromatography (0-100% EA in DCM/hexane) to give 275 mg (60%) of *tert*-butyl *N*-((2-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)acetyl)glycyl)-*N*-(4-(5-((1'r,4'r)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate. LCMS-ESI (m/z) calculated for C₄₂H₅₁N₅O₇S: 769.4, found 770.0 [M+H]⁺, *t*_R = 4.80 minutes (*Method 2*).

N-((2-(1,1-dioxido-3-oxobenzodisothiazol-2(3H)-yl)acetyl)glycyl)-N-(4-(5-((1'r,4'r)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycine **Compound 128**



Prepared using General Procedure 4. Tert-butyl N-((2-(1,1-dioxido-3-oxobenzodisothiazol-2(3H)-yl)acetyl)glycyl)-N-(4-(5-((1'r,4'r)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycinate (275 mg, 0.357 mmol) in DCM (1 mL) was treated with TFA (1 mL) and stirred at RT for 2 h. The solvent was removed and the residue was azeotroped with DCM (3 x 5 mL) and acetonitrile (2 x 5 mL) to give 240 mg (94%) of N-((2-(1,1-dioxido-3-oxobenzodisothiazol-2(3H)-yl)acetyl)glycyl)-N-(4-(5-((1'r,4'r)-4'-ethyl-[1,1'-bi(cyclohexan)]-3-en-4-yl)pyrimidin-2-yl)benzyl)glycine **Compound 128**. LCMS-ESI (m/z) calculated for C₃₈H₄₃N₅O₇S: 713.3, found 714.0 [M+H]⁺, t_R = 7.44 minutes (Method 1).

Representative compounds and their corresponding analytical data are shown in Table 2, where the LCMS data was collected using Methods 1 and 3 (see General Methods above).

Table 2
Analytical Data for Representative Compounds

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD	CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
1	11.55	3	3	11.80	3
2	10.33	3	4	11.86	3

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
5	10.92	3
6	11.42	3
7	11.45	3
8	12.37	3
9	12.78	3
10	10.5	3
11	10.93	3
12	10.87	3
13	11.01	3
14	11.10	3
15	11.08	3
16	9.89	3
17	8.66	3

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
18	11.72	3
19	11.49	3
20	12.19	3
21	12.00	3
22	11.64	3
23	10.65	3
24	12.00	3
25	12.59	3
26	12.42	3
27	12.61	3
28	11.06	3
29	10.94	3
30	11.95	3

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
31	11.22	3
32	10.83	3
33	11.20	3
34	11.18	3
35	11.06	3
36	11.11	3
37	11.49	3
38	11.83	3
39	11.96	3
40	10.84	3
41	10.34	3
42	11.56	3
43	11.30	3

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
44	12.24	3
45	10.97	3
46	11.56	3
47	10.96	3
48	11.42	3
49	11.49	3
50	11.09	3
51	11.48	3
52	10.84	3
53	10.60	3
54	9.83	3
55	9.88	3
56	11.46	3

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
57	11.01	3
58	11.50	3
59	10.50	3
60	9.75	3
61	10.30	3
62	10.26	3
63	11.21	3
64	11.67	3
65	7.08	3
66	10.46	3
67	12.40	3
68	11.95	3
69	11.29	3

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
70	6.16	1
71	7.10	1
72	6.90	1
73	7.10	1
74	11.29	3
75	11.66	3
76	11.22	3
77	6.67	1
78	6.14	1
79	6.49	1
80	6.01	1
81	7.50	1
82	7.10	1

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
83	7.50	1
84	7.10	1
85	11.71	3
86	6.09	1
87	6.33	1
88	7.01	1
89	6.32	1
90	6.72	1
91	7.77	1
92	11.29	3
93	11.36	3
94	8.50	1
95	9.28	1

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
96	7.76	1
97	7.63	1
98	7.10	1
99	7.70	1
100	7.01	1
101	6.54	1
102	8.89	1
103	8.67	1
104	9.59	1
105	10.7	3
106	11.25	3
107	8.20	1
108	8.05	1

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
109	8.01	1
110	7.80	1
111	9.58	1
112	9.12	1
113	9.12	1
114	8.89	1
115	8.04	1
116	8.27	1
117	8.54	1
118	8.54	1
119	9.46	1
120	7.39	1
121	7.05	1

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
122	7.90	1
123	7.90	1
124	8.50	1
125	8.50	1
126	10.62	3
127	8.21	1
128	7.73	1
129	7.79	1
130	7.67	1
131	7.70	1
132	8.10	1
133	8.30	1
134	7.86	1

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
135	8.00	1
136	8.04	1
137	8.60	1
138	8.30	1
139	8.60	1
140	8.60	1
141	8.40	1
142	8.90	1
143	8.70	1
144	8.70	1

CPD. NO.	LCMS RETENTION TIME (min)	PURITY METHOD
145	8.10	1
146	8.10	1
147	8.30	1
148	8.55	1
149	8.37	1
150	8.30	1
151	8.53	1
152	8.99	1
153	8.72	1

Biological Assays

EC₂₀ GLP-1(9-36) PAM cAMP Assay: Dose Response of Compound in the Presence of Fixed Concentration of GLP-1 (9-36)

- 5 Human GLP-1R CRE-bla CHO-K1 cells were cultured in growth medium (DMEM-High glucose, 10% dialyzed FBS, 0.1 mM NEAA, 25 mM Hepes, 100 U/mL penicillin/100 µg/mL streptomycin, 5 µg/mL Blasticidin, 600 µg/mL

Hygromycin), trypsinized and plated in suspension into 384-well white flat bottom plates at 5000 cells/well in 12 μ L assay buffer (Hank's Balanced Salt Solution, 10 mM Hepes, 0.1% BSA, pH 7.4). Each compound at a 5x concentration was diluted to a final concentration range of 10 to 0.01 μ M (11 points) in assay buffer containing 1.5 mM IBMX and 4% DMSO. GLP-1(9-36) was diluted from 4.2 μ M (30x) to a final assay concentration of 60 nM in assay buffer containing 1.5 mM IBMX and 4% DMSO. Each compound concentration (5x) was added (3 μ L), followed by 0.5 μ L of GLP-1(9-36) and cells incubated for 30 minutes at 37°C. The peptide was added to the wells using siliconized tips. The reaction was stopped and levels of cAMP were quantified using the DiscoverX HitHunter cAMP kit according to the manufacturer's instructions and luminescence was detected using a SpectraMax M5 Multi-Mode Microplate reader. Luminescence was converted to total cAMP using a cAMP standard curve and data were analyzed by non-linear regression to determine the EC50 and Emax for each compound.

15 Peptide sequences:

GLP-1 (7-36): HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH₂ (SEQ ID NO: 1)

GLP-1 (9-36): EGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH₂ (SEQ ID NO: 2)

GLP-1 (7-36) was purchased from GenScript. GLP-1 (9-36) were purchased from Biopeptide Co., Inc.

20 Activity data for representative compounds is set forth in Table 3 below. In Table 3, the *EC*₂₀ *GLP-1 (9-36) PAM Activity* range is denoted as follows: "+" denotes activity < 0.8 μ M; "++" denotes activity between 0.8 μ M and 2.5 μ M; "+++" denotes activity between 2.5 to 5 μ M; and "++++" denotes activity 5 to 10 μ M.

25

Table 3

Activity of Representative Compounds

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
1	+
2	+
3	++
4	++
5	++
6	++
7	+++
8	+++
9	++
10	++
11	+
12	+
13	+
14	+

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
15	+
16	++
17	++++
18	+
19	+
20	+
21	+
22	+
23	+
24	+
25	+++
26	+
27	+
28	+

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
29	+
30	+++
31	+
32	+
33	+
34	+
35	+
36	+
37	++
38	+
39	+++
40	++
41	+
42	+

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
43	+
44	++
45	+
46	+
47	+
48	+
49	+
50	+
51	+
52	+
53	+
54	+
55	++
56	++

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
57	+
58	+
59	++
60	+
61	+
62	+
63	+
64	+
65	+
66	+
67	+
68	+
69	+
70	+++

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
71	+
72	+
73	+
74	+
75	+
76	+
77	+++
78	++++
79	+++
80	+++
81	++
82	+
83	+
84	++

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
85	+
86	+++
87	+++
88	++
89	++
90	+++
91	++
92	+
93	+
94	++
95	++
96	+
97	+
98	+

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
99	+
100	+
101	+
102	++
103	+++
104	+++
105	+
106	+
107	++
108	++
109	+
110	+
111	++
112	+

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
113	+
114	+
115	++
116	+
117	++
118	++
119	++
120	++
121	++
122	++
123	+
124	+
125	++++
126	++

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
127	+
128	+
129	++
130	+
131	+
132	++
133	+
134	+
135	++
136	+
137	+
138	+
139	++
140	++

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
141	++
142	++
143	++
144	++
145	+++
146	++
147	++

Cpd. No.	EC ₂₀ GLP-1(9-36) PAM Activity
148	++
149	+++
150	+++
151	++++
152	+
153	+

U.S. Provisional Patent Application No. 62/491,892, filed April 28, 2017, to which the present application claims priority, is hereby incorporated herein by reference in its entirety.

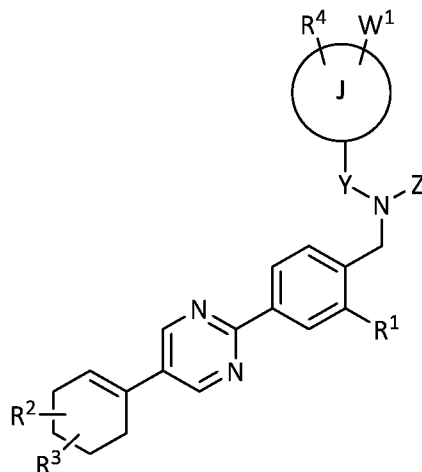
- 5 All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

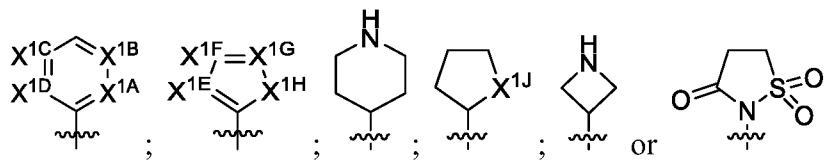
1. A compound having the structure of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

J is null or has the structure:



each of X^{1A} , X^{1B} , X^{1C} , X^{1D} , X^{1E} , X^{1F} and X^{1G} is C, CH or N;

X^{1H} is O or S;

X^{1J} is CH_2 or NH;

R^1 is H, alkyl or alkoxy;

Y is $-C(O)-$, $-CH_2-$, $-C(O)-CH_2-$, $-CH_2-C(O)-$,

$-C(O)-(CR^aR^b)_n-N(R^c)-C(O)-(CR^aR^b)_n-$, $-C(O)-(CR^aR^b)_n-N(R^d)$ where R^d may form a fused ring with J or with a fused J- R^4 - W^1 ring system,

$-C(O)-(CR^aR^b)_n-N(R^c)-C(O)-(CR^aR^b)_n-N(R^c)-S(O)_k-(CR^aR^b)_n-$,

$-C(O)-(CR^aR^b)_n-N(R^c)-C(O)-(CR^aR^b)-N(R^d)-$ where R^d may form a fused ring with J or with a fused J- R^4 - W^1 ring system, or

$-C(O)-(CR^aR^b)_n-N(R^c)-S(O)_k-(CR^aR^b)-$;

Z is $-(CR^aR^b)_n-C(O)-R^7$;

R^7 is $-OR^{30}$, $-NR^{31}R^{32}$, $-NH(CR^aR^b)_n-C(O)-R^7$, $-NHSO_2R^7$ or $-(CO)-NH-SO_2-R^7$,
or R^{31} ;

each R^{30} is independently H or alkyl;

each R^{31} and R^{32} is independently H or C_1-C_6 alkyl optionally substituted with
one or more R^{33} , or taken together with the N atom to which they are attached
can form a 3- to 7-membered heterocyclic ring;

each R^{33} is independently halo, hydroxyl, alkoxy, perhaloalkyl, perhaloalkoxy,
carboxyl, $-C(O)O-R^{30}$, $-OR^{30}$, $-N(R^{30})_2$ or heterocyclyl;

each R^4 is independently H, alkyl, alkoxy, or alkyl substituted with one or more
 R^{43} , halogen, perhaloalkyl, perhaloalkoxy, $-CN$, $-OR^{40}$ or $-NR^{41}R^{42}$;

each R^{41} and R^{42} is independently H, alkyl, $-(CH_2)_n-C(O)O-R^{40}$, $-C(O)-R^{40}$, aryl,
heteroaryl; or R^{41} and R^{42} , taken together with the N atom to which they are
attached, can form a 3- to 7-membered heterocyclic ring;

each R^{43} is independently H, halo, hydroxyl, $-NR^{41}R^{42}$, or alkoxy;

W^1 is $-(CR^aR^b)_{i1}-L^1-(CR^aR^b)_{j1}-R^{60}$ or R^4 ; or W^1 and R^4 taken together comprise a
5- or 6- membered carbocyclic or heterocyclic ring fused with the ring to
which W^1 and R^4 are attached and optionally having one, two or three
heteroatoms where each such heteroatom is independently selected from O, N,
and S, and where any ring atom of such heterocyclic ring may be optionally
substituted with one or more $-L^1-R^{13}$ or R^{13} ; or W^1 is a 5- or 6- membered
heterocyclic ring fused with a phenyl ring and having one, two or three
heteroatoms where each such heteroatom is independently selected from O, N,
and S, and where any ring atom of such fused heterocyclic ring and phenyl
ring moiety may be optionally substituted with one or more R^{14} ;

L^1 is $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-NR^{10}-$, $-C(O)NR^{10}-$,
 $-N(R^{10})-(CH_2)_n-C(O)-$, $-N(R^{10})-C(O)-N(R^{10})-$, $-N(R^{10})-S(O)_2-$,
 $-S(O)_2-NR^{10}-$, or $-N(S(O)_2)-(CH_2)_n-R^{60})_2$;

R^{60} is R^{13} , $-O-(CH_2)_n-R^{13}$, or R^{10} ;

each R^{10} , R^{11} and R^{12} is independently H or alkyl;

R^{13} is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or a fused bicycle or tricycle of any two or three of such ring moieties, or R^{13} and R^{10} taken together with the N atom to which they are attached form a heterocyclic ring, where any ring atom of R^{13} may be optionally substituted with one or more R^{14} or R^{15} ;

each R^{14} is independently H, alkyl, halo, hydroxy, cyano, alkoxy, perhaloalkyl, and perhaloalkoxy, $-OR^{10}$, $-(CH_2)_n-C(O)OR^{10}$, $-SR^{10}$, $-SO-R^{10}$, $-S(O)_2-R^{10}$, $-(CH_2)_n-NR^{11}R^{12}$, $-NH-C(O)-(CH_2)_n-R^{12}$, $-N(R^{11})-C(O)-(CH_2)_n-R^{12}$, or $-NH(CH_2)_n-R^{12}$;

R^{15} is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or a fused bicycle of any two of such ring moieties, where any ring atom of R^{15} may be optionally substituted with one or more R^{14} ;

each R^5 is independently H, alkyl, alkoxy, alkyl substituted with one or more R_{53} , halogen, perhaloalkyl, perhaloalkoxy, $-CN$, $-OR^{50}$, or $-NR^{51}R^{52}$;

each R^{40} and R^{50} is independently H or alkyl;

each R^{51} and R^{52} is independently H or alkyl, $-(CH_2)_n-C(O)O-R^{50}$, $-C(O)-R^{50}$, aryl, heteroaryl, or two taken together with the N atom to which they are attached can form a 3- to 7-membered heterocyclic ring;

each R^a and R^b is independently H, hydroxy, alkyl, or aralkyl optionally substituted with hydroxyl; or both R^a and R^b attached to the same carbon are, taken together, oxo, or cycloalkyl;

each R^c and R^d is independently H, hydroxy, alkyl, $-S(O)_k-R^7$ or $-C(O)-R^7$;

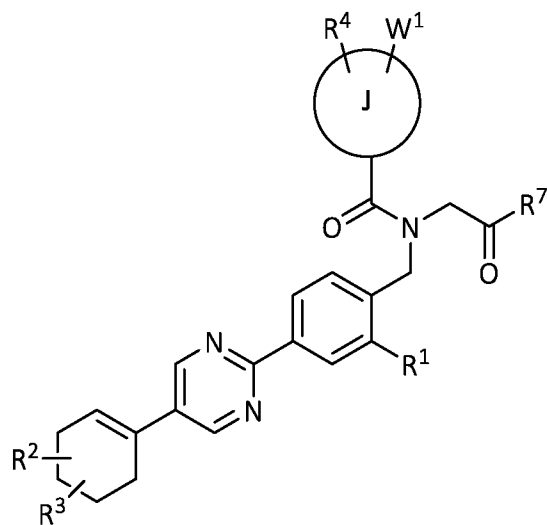
R^2 is alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or a fused bicycle of any two of such ring moieties, where any ring atom of R^2 may be optionally substituted with one or more R^3 ;

each R^3 is independently H, alkyl, or perhaloalkyl;

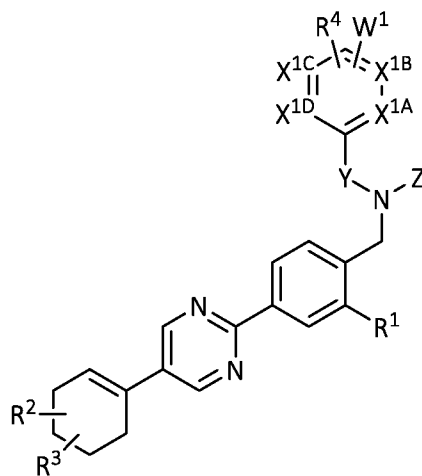
each n is independently 0, 1, 2, 3 or 4; and

each i_1 , i_2 , j_1 and j_2 is independently 0, 1, 2, 3 or 4.

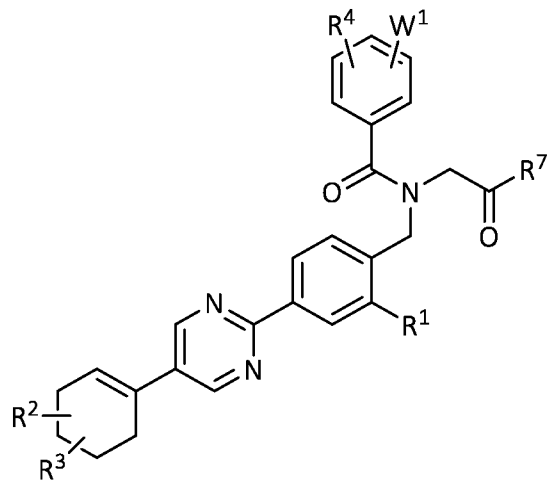
2. The compound of claim 1, wherein the compound has a structure of Formula (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII):



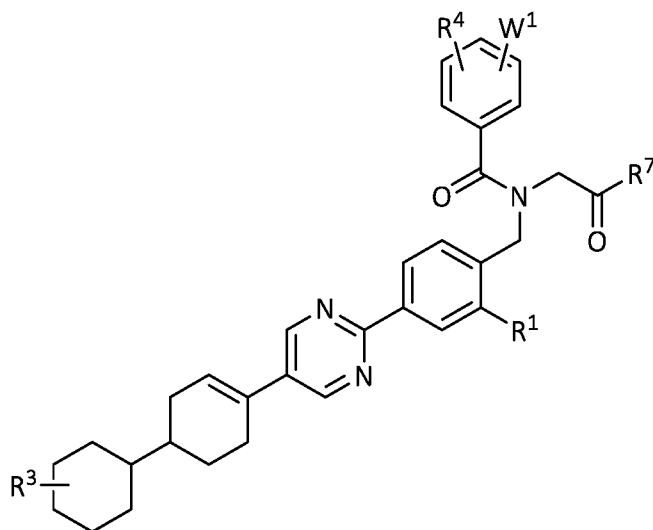
(III);



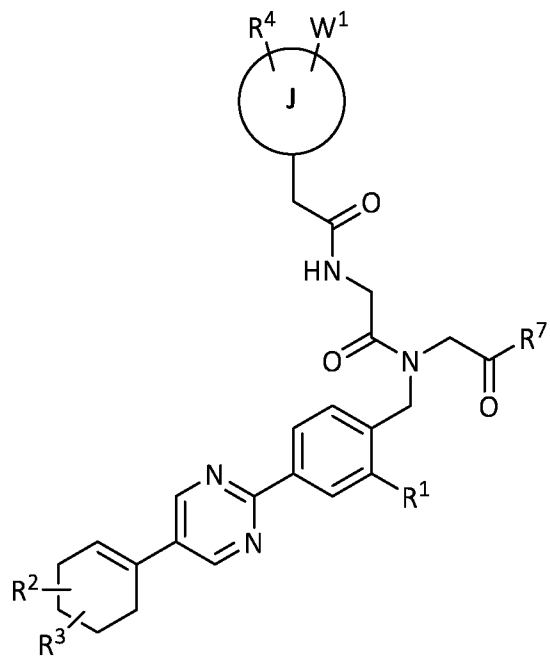
(IV);



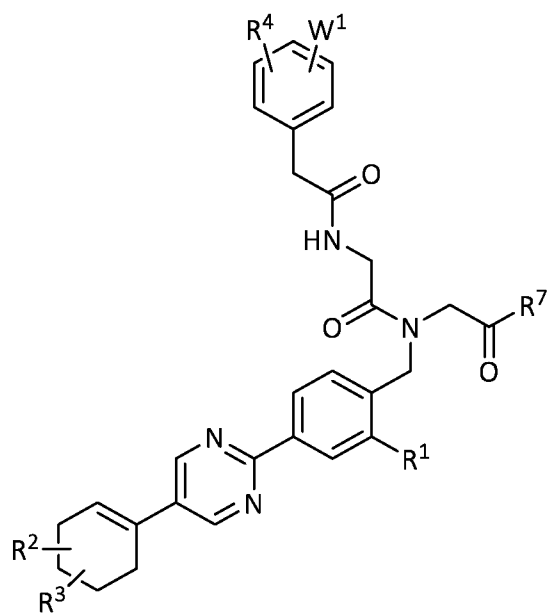
(V);



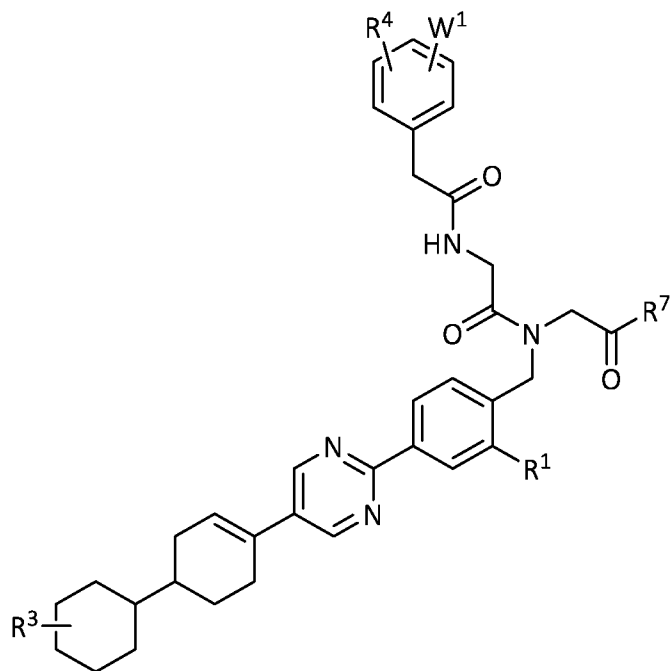
(VI);



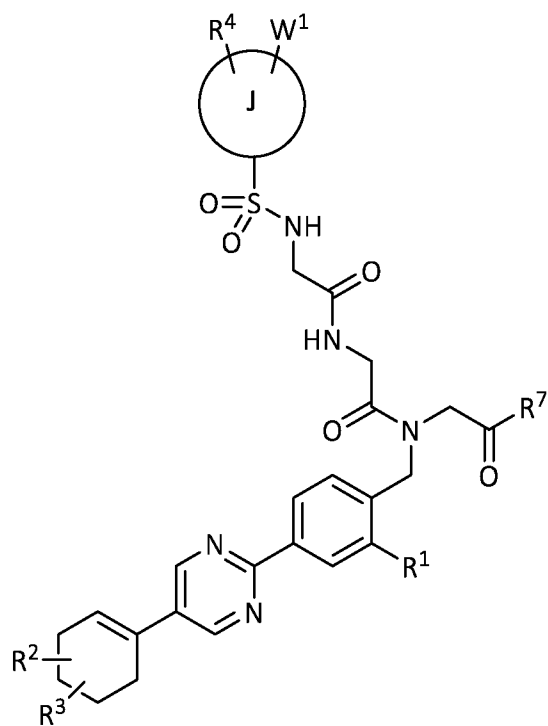
(VII);



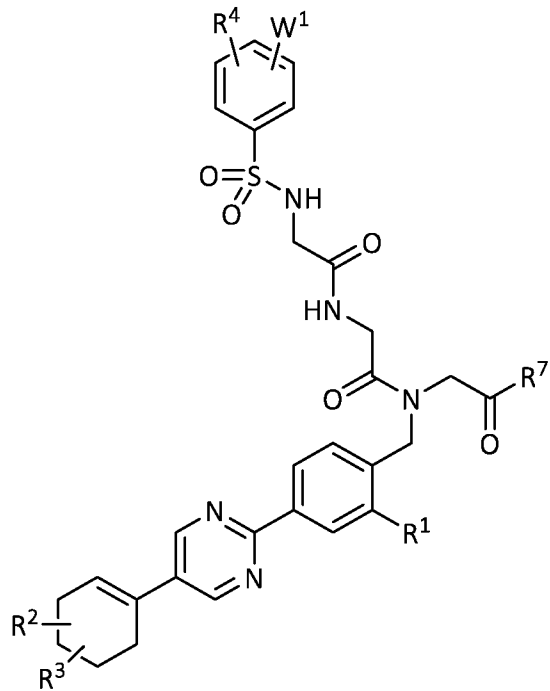
(VIII);



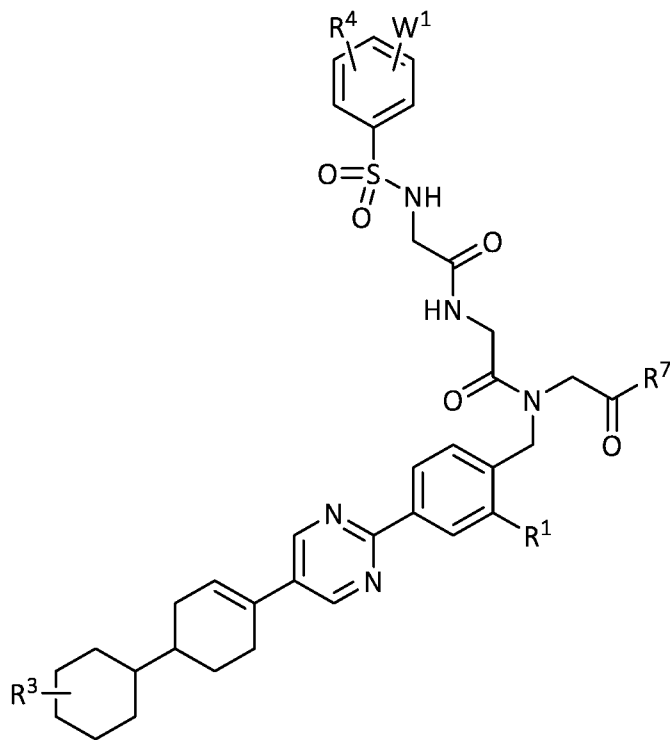
(IX);



(X);



(XI);



(XII).

3. The compound of claim 1 wherein

each of X^{1A} , X^{1B} , X^{1C} , X^{1D} is C or CH;

one of X^{1A} , X^{1B} , X^{1C} , and X^{1D} is N;

two of X^{1A} , X^{1B} , X^{1C} , and X^{1D} is N;

one of X^{1E} , X^{1F} and X^{1G} is N;

X^{1F} is N;

X^{1H} is O;

X^{1H} is S;

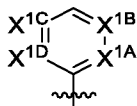
Y is $-C(O)-$, $-C(O)-CH_2-$, $-C(O)-CH_2-NH-C(O)-CH_2-$,
 $-C(O)-CH_2-NH-C(O)-CH_2-NH-S(O)_2-CH_2-$, $-C(O)-CH_2-NH-C(O)-CH_2-NH-$, or
 $-C(O)-CH_2-NH-C(O)-CH_2-NH-S(O)_2-CH_2-$; or

Z is $-CH_2C(O)OH$.

4. The compound of any one of claims 1–3 wherein

W^1 is $-(CR^aR^b)_{i1}-L^1-(CR^aR^b)_{j1}-R^{60}$, or

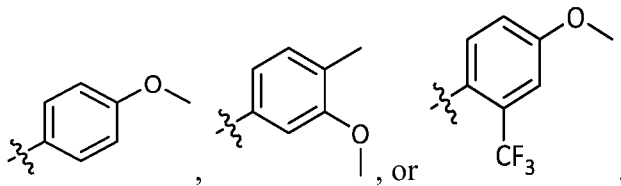
W^1 is attached at the para position of the ring moiety:



5. The compound of claim 1 wherein
- il is (a) 0, (b) 1, or (c) 2; or
- j1 is (a) 0, (b) 1, or (c) 2.
6. The compound of claim 1 wherein L^1 is (a) $-NR^{10}C(O)-$, (b) $-NR^{10}-$, or (c) $-N(R^{10})SO_2-$.
7. The compound of claim 6 wherein R^{10} is $-H$.
8. The compound of claims any one of claims 1–7 wherein R^{60} is (a) R^{13} , or (b) $-O-(CH_2)_n-R^{13}$.
9. The compound of claim 8 wherein
- (i) n in R^{60} is (a) 0 or (b) 1; and/or
- (ii) R^{13} is
- (a) phenyl, or
- (b) cycloalkyl or heterocycloalkyl; optionally wherein R^{13} is cyclopentyl, cyclohexyl, thiazolyl, tetrahydrofuranyl, oxazolyl, thiophenyl, 1,2,4-oxadiazolyl, furanyl, tetrahydro-2H-pyranyl, or piperidinyl;
- and/or wherein
- (iii) R^{13} is unsubstituted or substituted at one or more ring position with substituents selected from the group consisting of methyl, ethyl, isopropyl, t-butyl, $-CF_3$, methoxy, ethoxy, hydroxyl, $-OCF_3$, halogen, methylthio, and $-SO_2CH_3$; optionally

wherein R^{13} is substituted with one or more of methyl, methoxy, F or $-CF_3$; or

(iv) R^{60} is



10. The compound of any one of claims 4 to 9 wherein

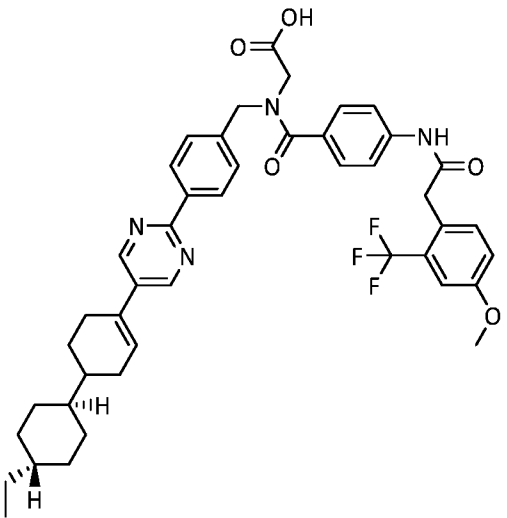
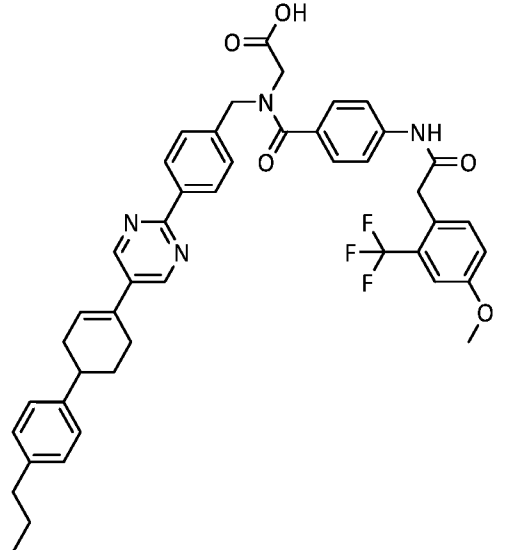
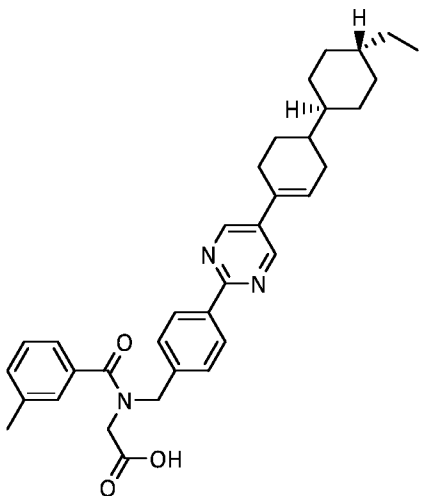
each of R^a and R^b is H;

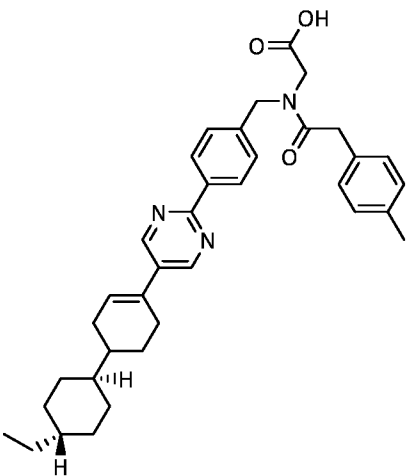
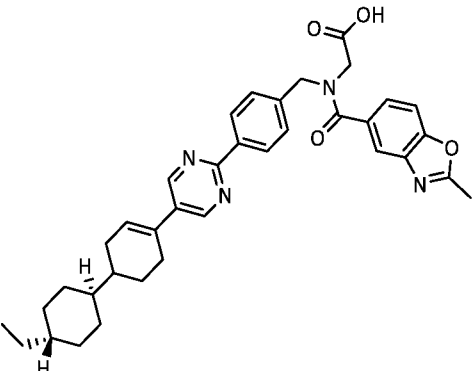
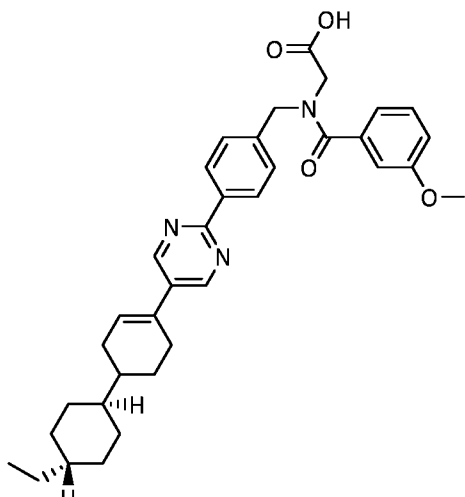
at least one of R^a and R^b and R^b is $-CH_3$; or

at least one of R^a and R^b is benzyl or hydroxybenzyl.

11. The compound of claim 1 wherein R^2 is (a) alkyl, (b) cycloalkyl, or (c) aryl, optionally wherein R^2 is substituted with at least one R^3 , further optionally wherein the at least one R^3 is (i) alkyl or (ii) perhaloalkyl.

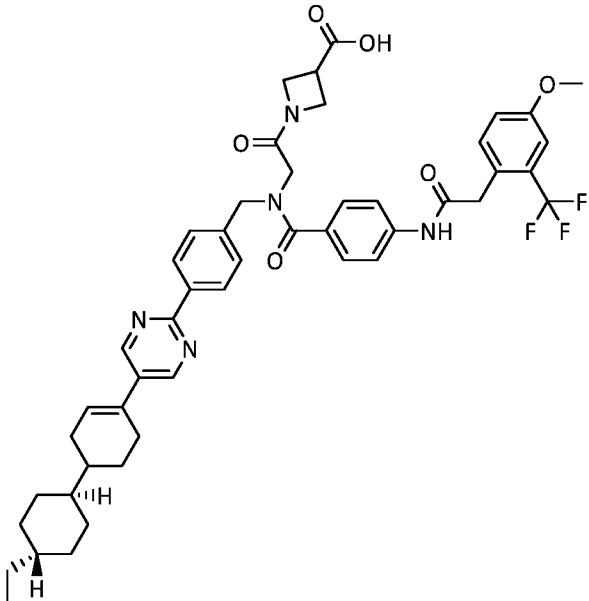
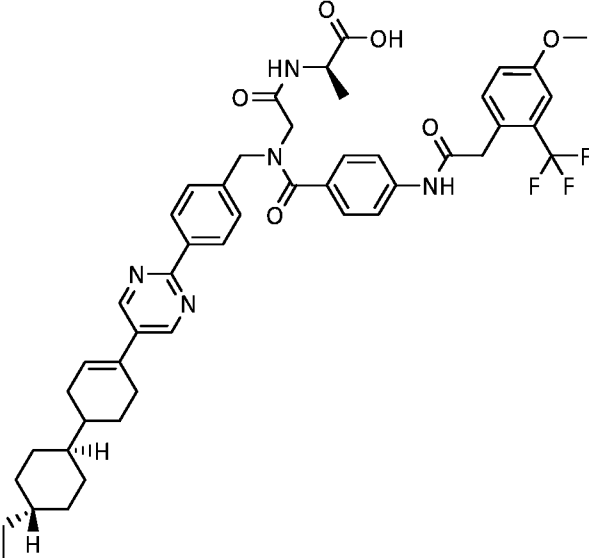
12. The compound of claim 1, wherein the compound is selected from any one of the following compounds, or any pharmaceutically acceptable salt thereof:

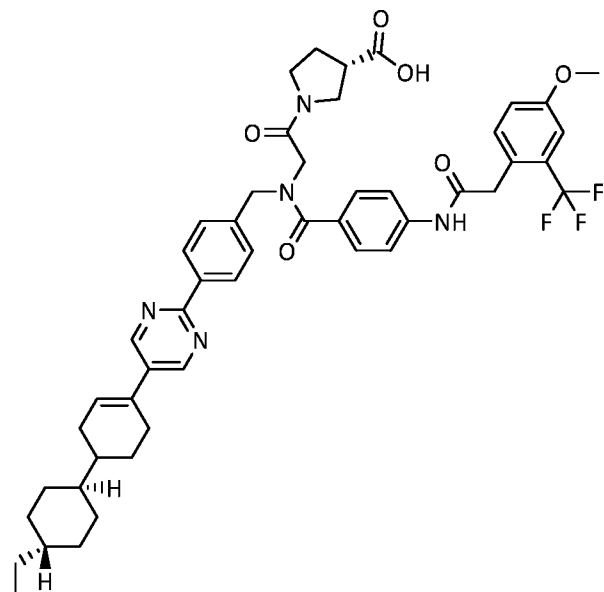
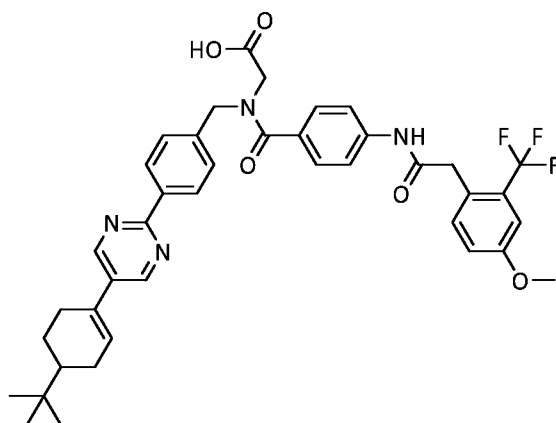
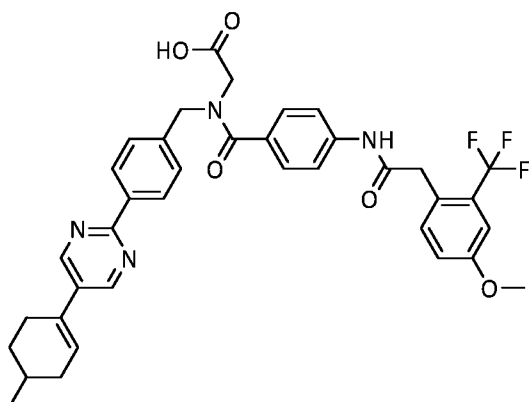
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	<p>3</p>

	<p>4</p>
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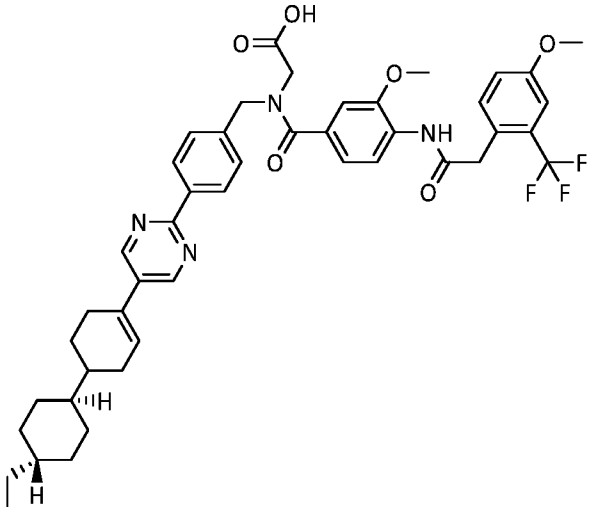
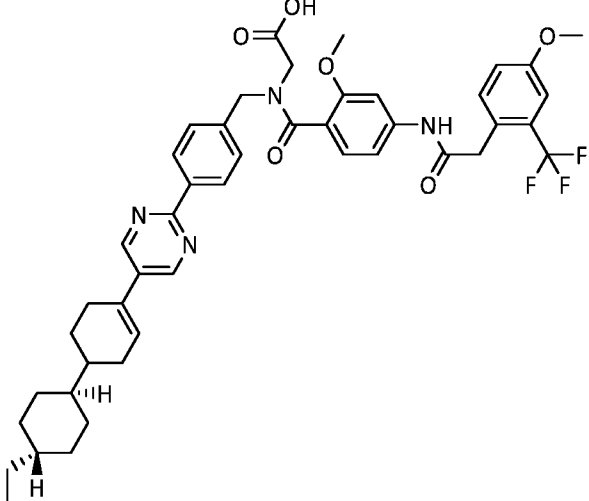
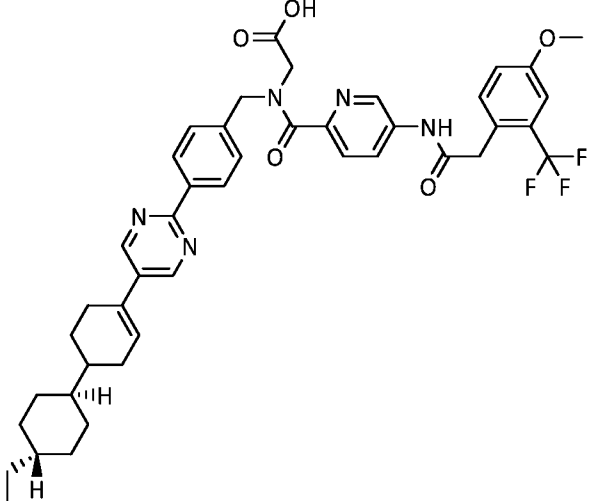
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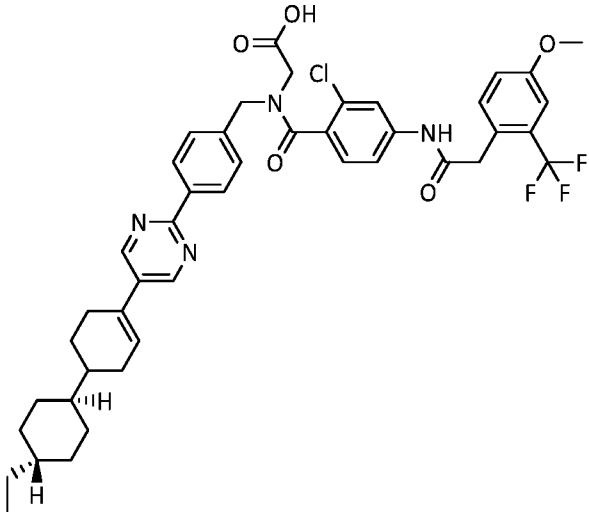
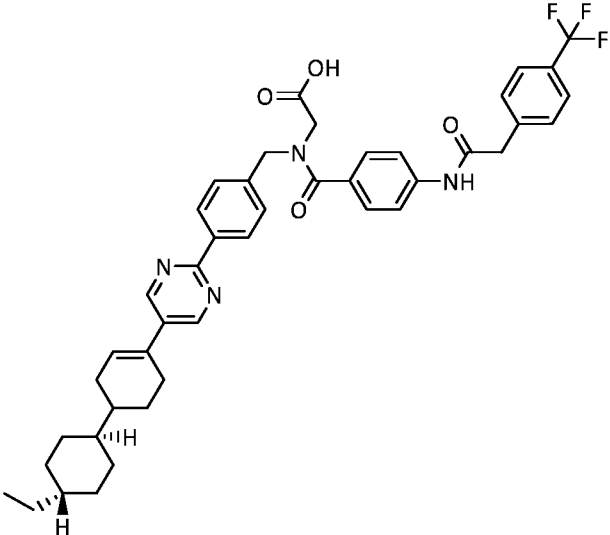
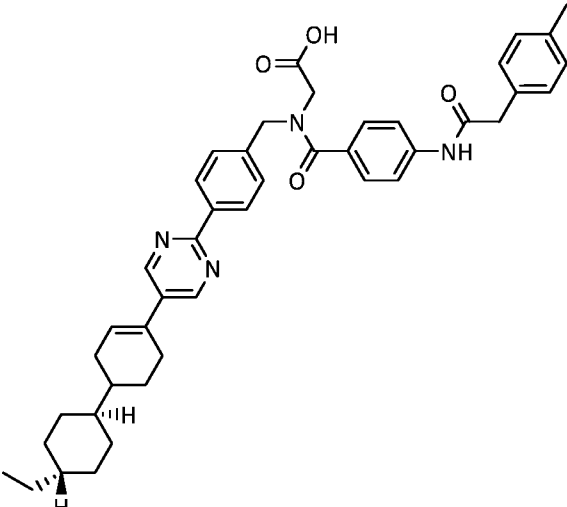
	<p>10</p>
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	<p>12</p>

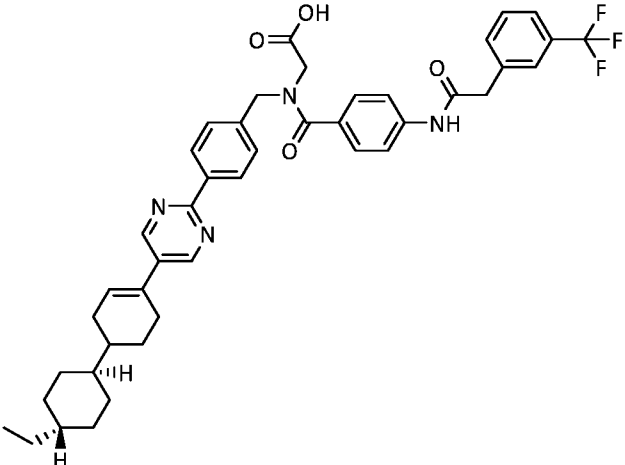
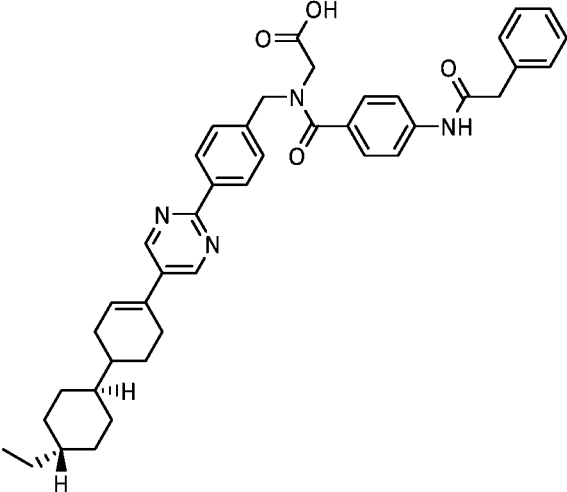
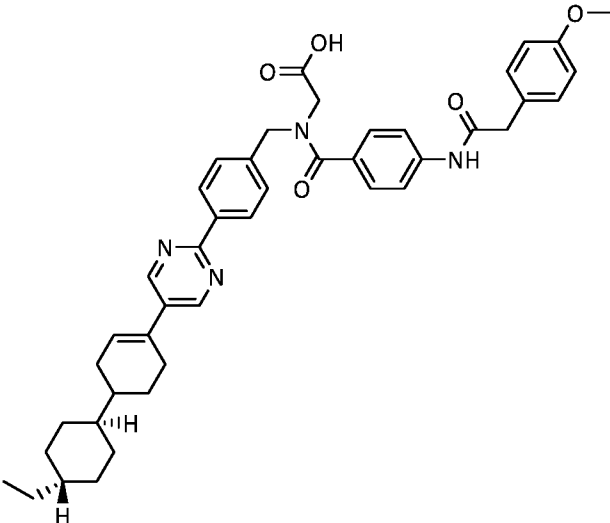
 <p>Chemical structure 13: A complex molecule featuring a bicyclic core (two fused six-membered rings) with a hydrogen atom at the bridgehead position shown with a dashed bond. This core is linked via a cyclohexene ring to a pyrimidine ring. The pyrimidine ring is further connected to a benzene ring, which is substituted with a methoxy group (-OCH₃) and a trifluoromethyl group (-CF₃). This benzene ring is part of a chain that includes a carbonyl group, a methylene group, and another carbonyl group. The second carbonyl group is attached to a nitrogen atom, which is in turn bonded to a cyclopropyl ring. The cyclopropyl ring has a carboxylic acid group (-COOH) attached to one of its carbons.</p>	<p>13</p>
 <p>Chemical structure 14: This structure is identical to structure 13, but the carboxylic acid group (-COOH) is attached to the nitrogen atom of the cyclopropyl ring instead of a carbon atom.</p>	<p>14</p>

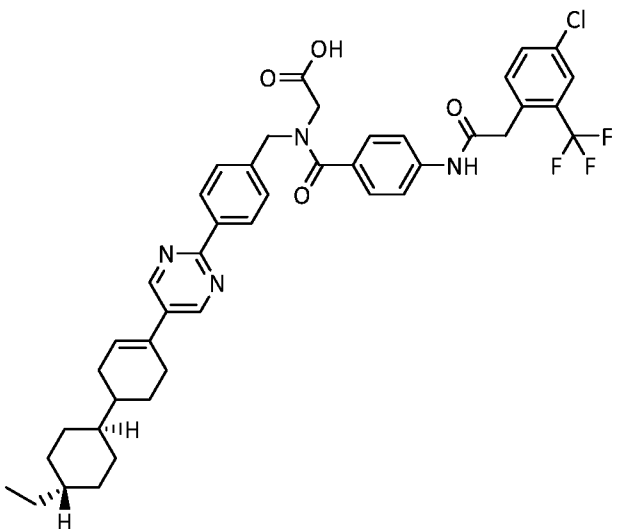
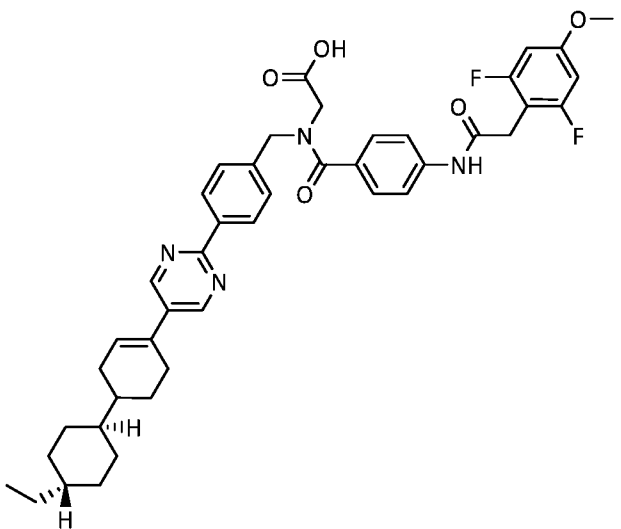
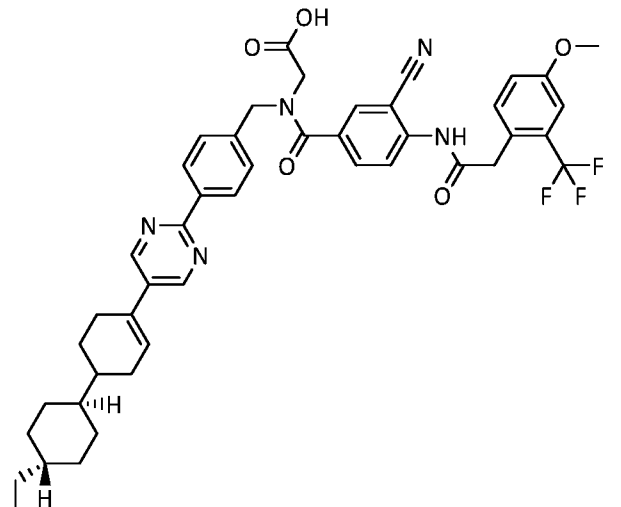
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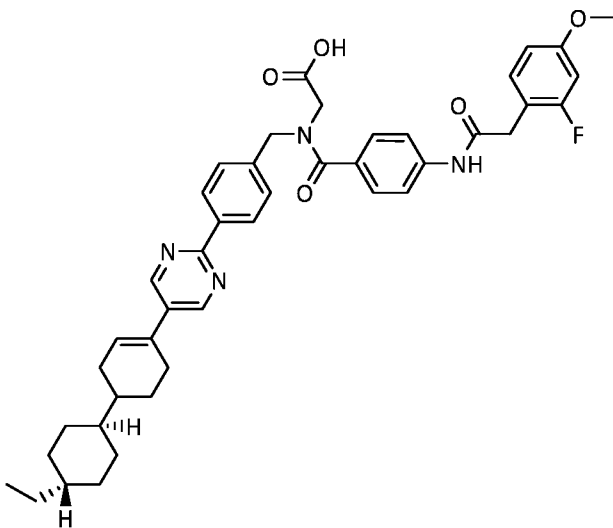
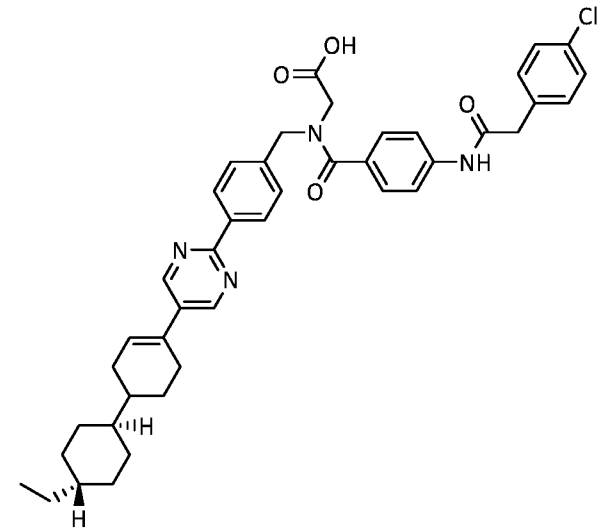
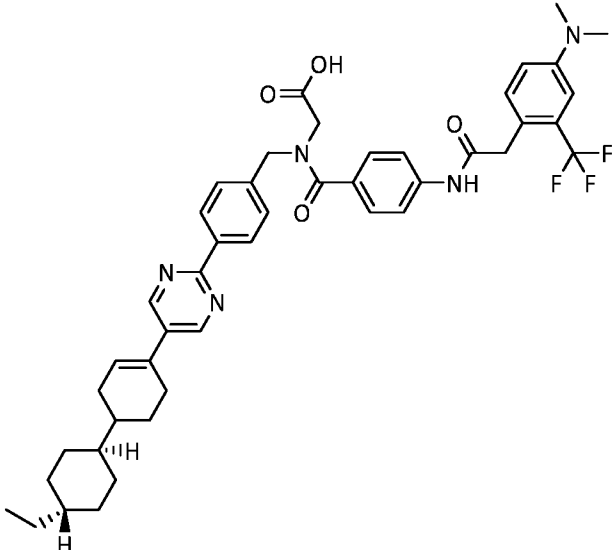
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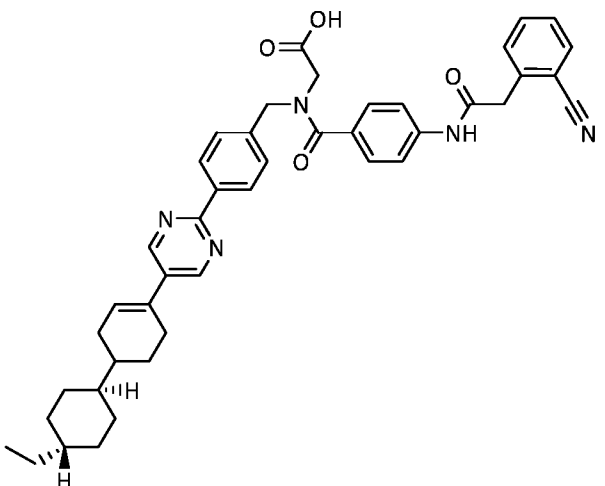
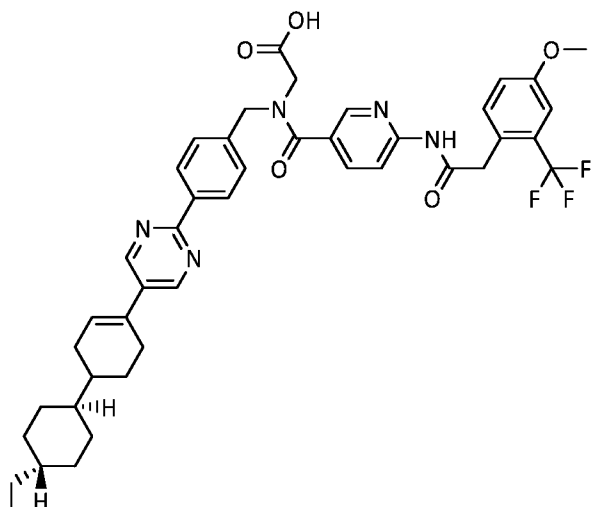
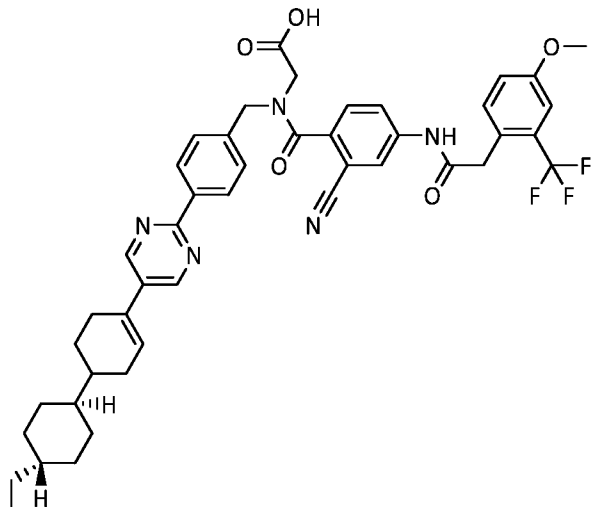
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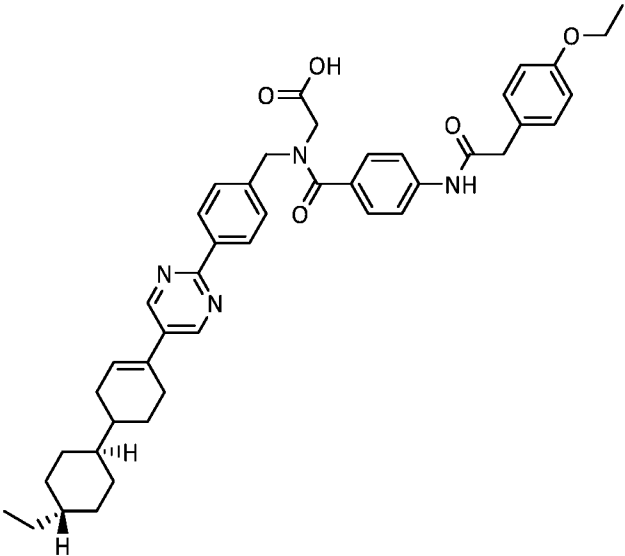
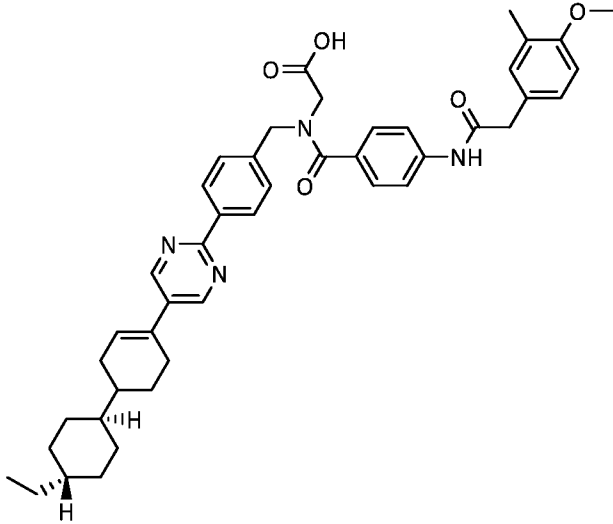
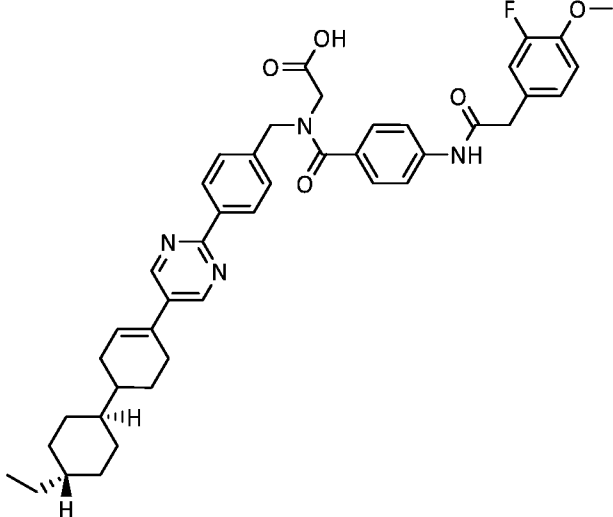
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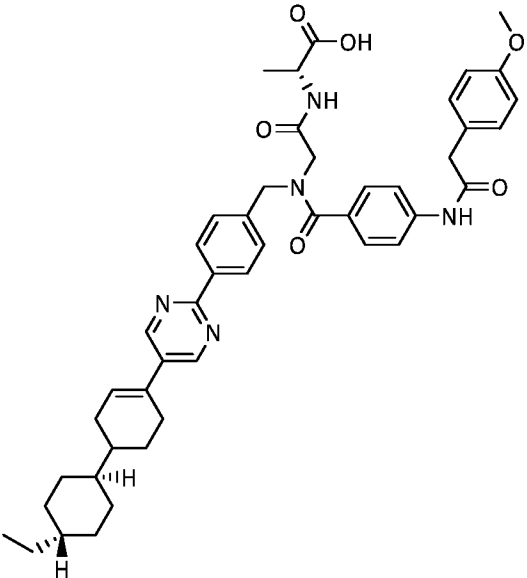
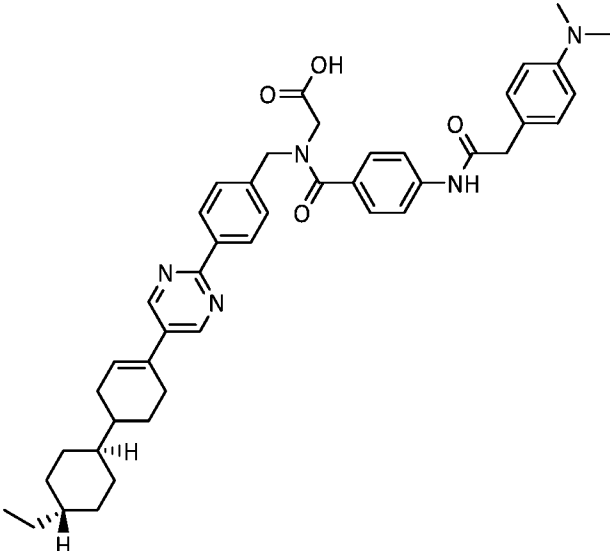
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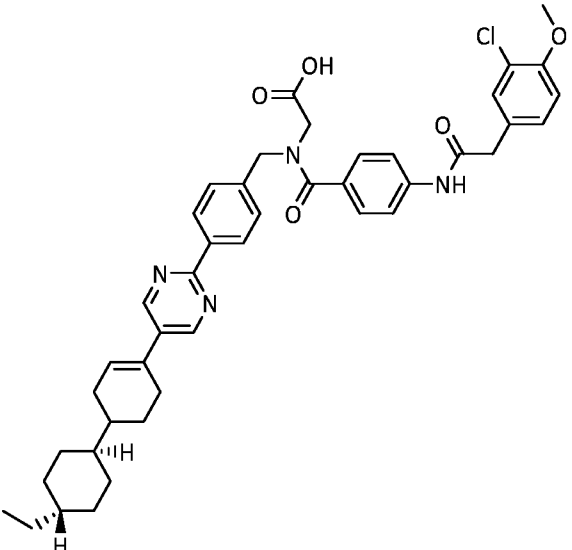
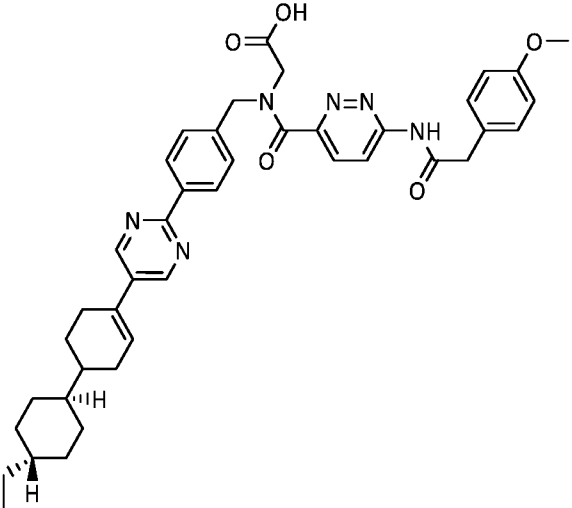
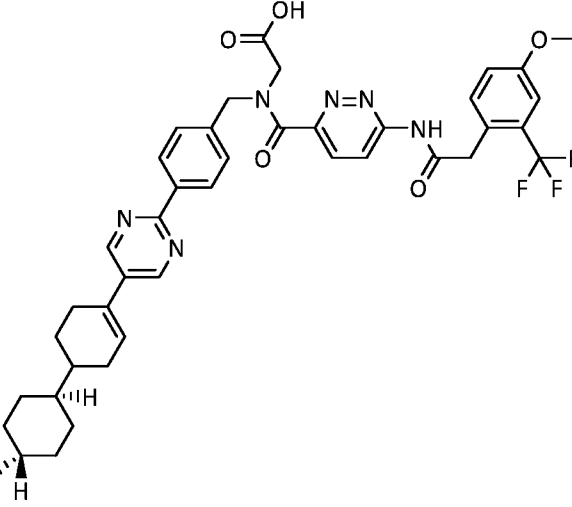
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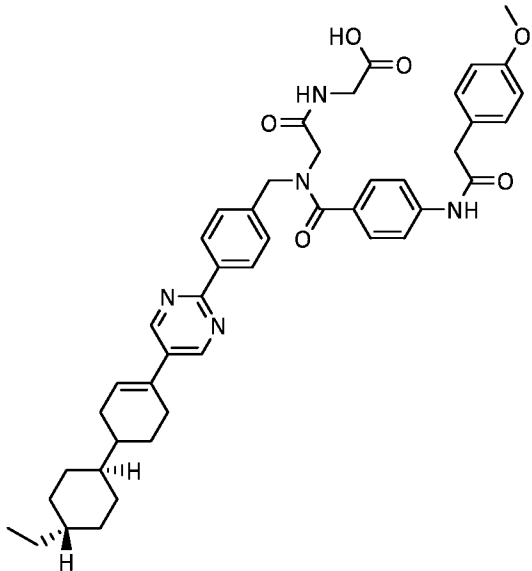
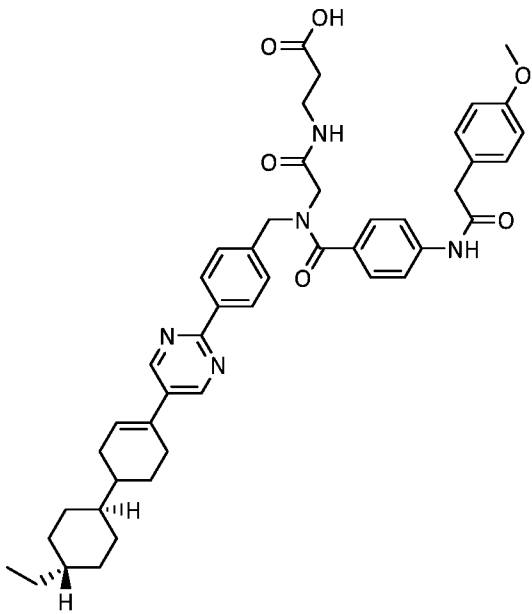
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	<p>50</p>

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	<p>52</p>
	<p>53</p>

 <p>Chemical structure 54: A complex molecule featuring a bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group and a hydrogen atom on a dashed bond. The right ring has a hydrogen atom on a dashed bond. This core is connected to a pyrimidine ring, which is further linked to a benzene ring. This benzene ring is connected to a nitrogen atom that is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. This second carbonyl group is attached to a benzene ring, which is in turn connected to an amide group (-NH-). The amide group is further connected to a methylene group, which is attached to a benzene ring with a methoxy group (-OCH₃) at the para position.</p>	<p>54</p>
 <p>Chemical structure 55: A complex molecule featuring a bicyclic core consisting of two fused six-membered rings. The left ring has a methyl group and a hydrogen atom on a dashed bond. The right ring has a hydrogen atom on a dashed bond. This core is connected to a pyrimidine ring, which is further linked to a benzene ring. This benzene ring is connected to a nitrogen atom that is part of a chain containing a carbonyl group, a methylene group, and another carbonyl group. This second carbonyl group is attached to a benzene ring, which is in turn connected to an amide group (-NH-). The amide group is further connected to a methylene group, which is attached to a benzene ring with a dimethylamino group (-N(CH₃)₂) at the para position.</p>	<p>55</p>

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	<p>57</p>
	<p>58</p>

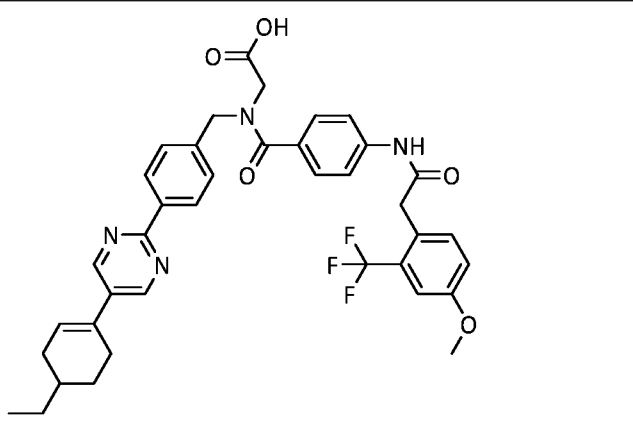
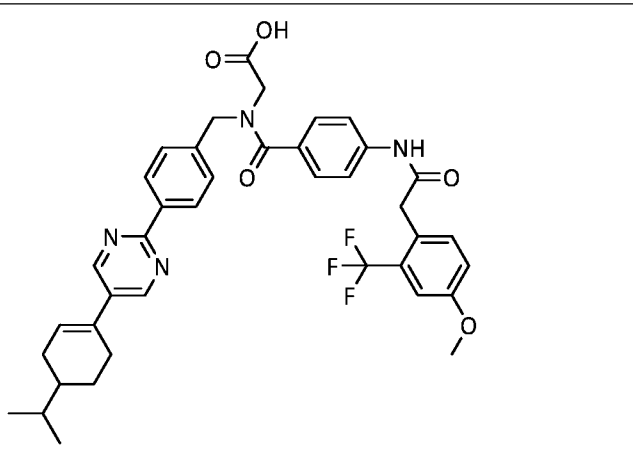
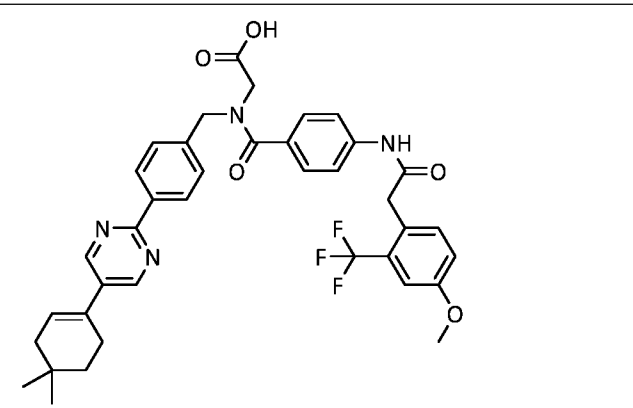
 <chem>CC[C@H]1CC[C@@H]2CC[C@H]1CC[C@@H]2C1CCN1C2=CN=CN=C2C3=CC=C(C=C3)CN(C4=CC=C(C=C4)C(=O)NCC(=O)O)C5=CC=C(C=C5)NC(=O)CC6=CC=C(OC)C=C6</chem>	<p>61</p>
 <chem>CC[C@H]1CC[C@@H]2CC[C@H]1CC[C@@H]2C1CCN1C2=CN=CN=C2C3=CC=C(C=C3)CN(C4=CC=C(C=C4)C(=O)NCC(=O)[O-])C5=CC=C(C=C5)NCC(=O)[NH3+]</chem>	<p>62</p>

	<p>63</p>
	<p>64</p>
	<p>65</p>

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	<p>67</p>
	<p>68</p>

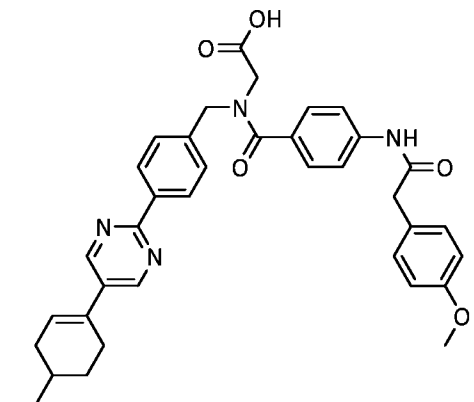
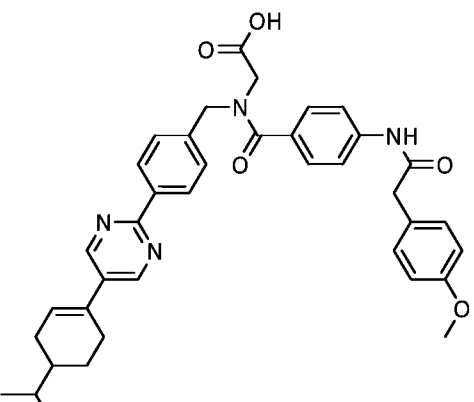
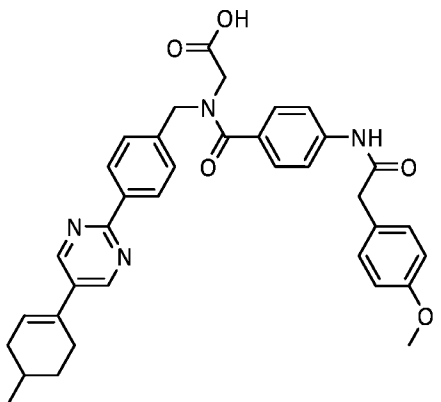
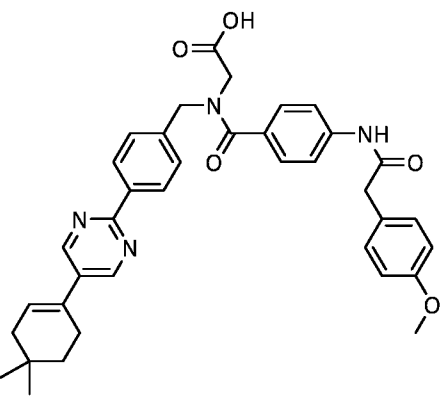
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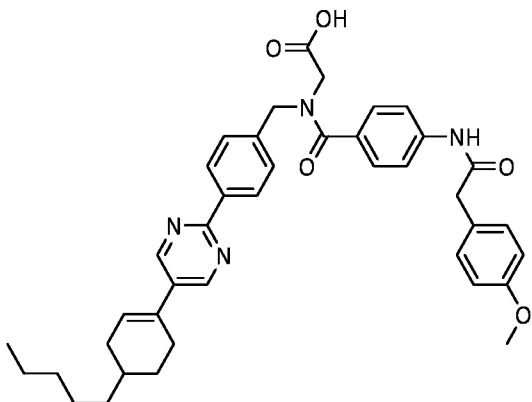
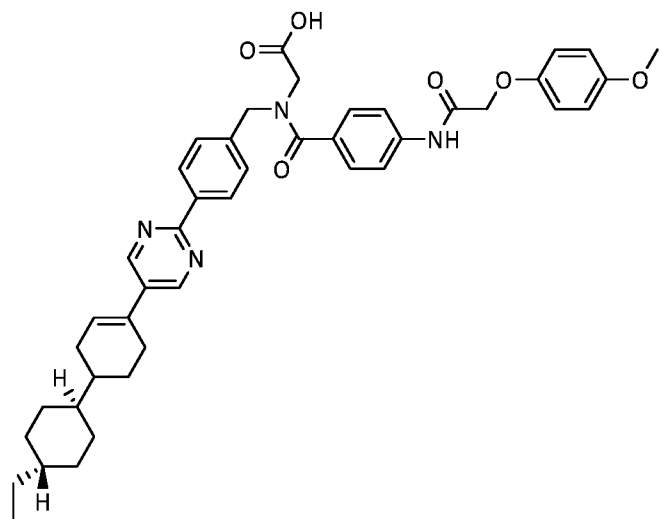
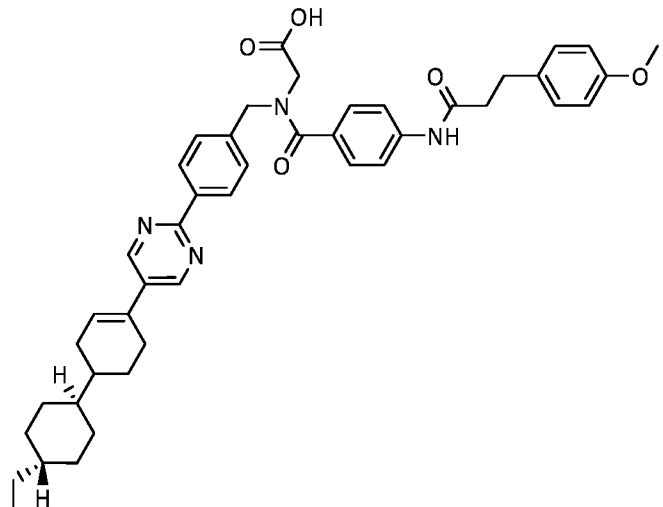
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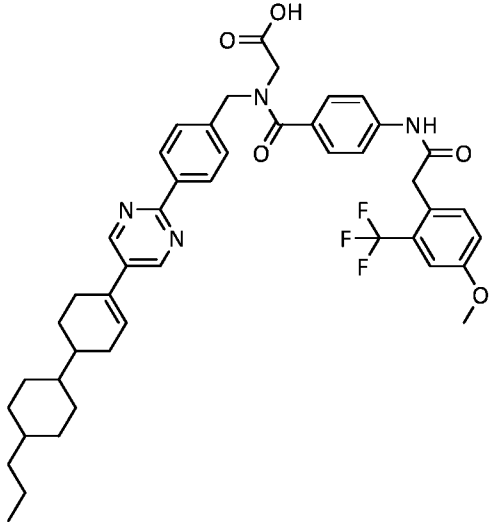
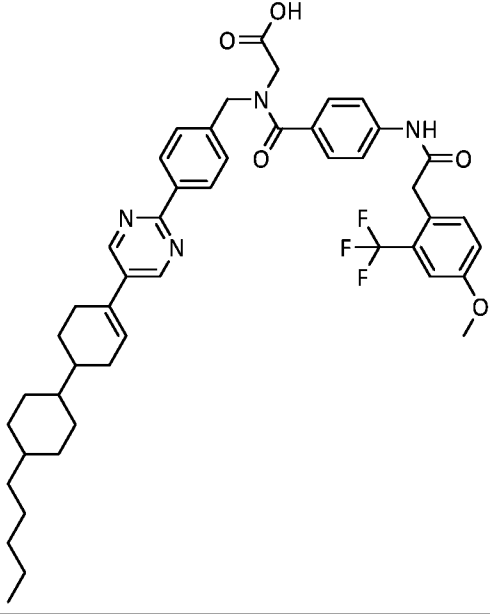
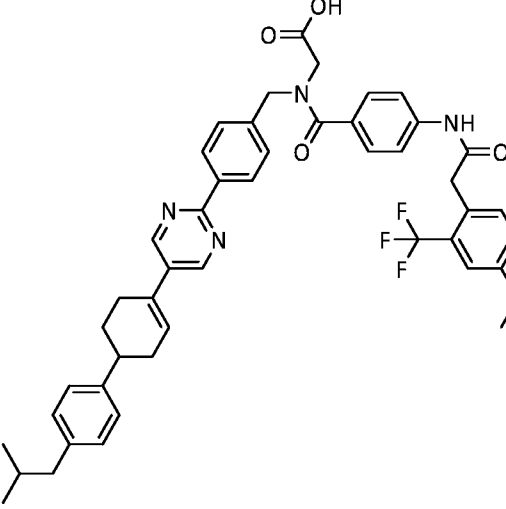
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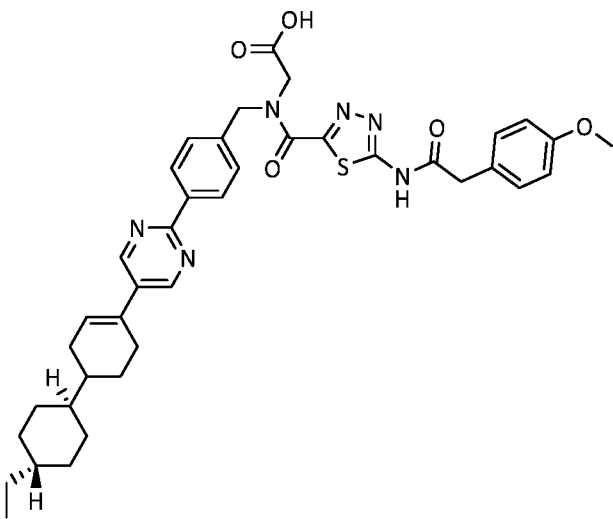
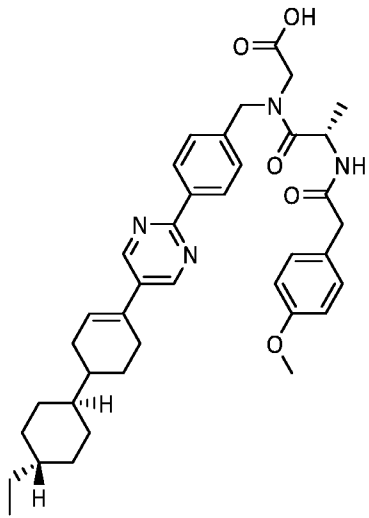
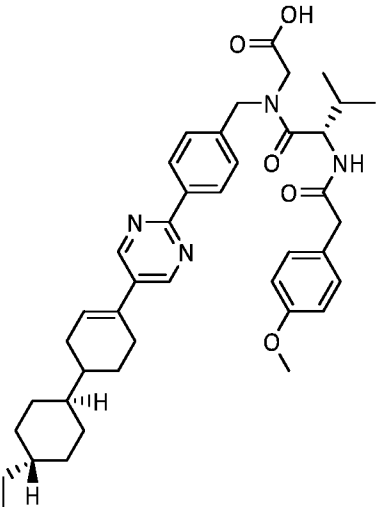
<p>Chemical structure 81: A complex molecule featuring a decyl chain, a piperidine ring, a pyrimidine ring, a benzamide group, and a 4-methoxy-2-(trifluoromethyl)phenyl group.</p>	<p>81</p>
<p>Chemical structure 82: A complex molecule featuring a decyl chain, a piperidine ring, a pyrimidine ring, a benzamide group, and a 4-methoxyphenyl group.</p>	<p>82</p>
<p>Chemical structure 83: A complex molecule featuring a decyl chain, a piperidine ring, a pyrimidine ring, a benzamide group, and a 4-methoxyphenyl group.</p>	<p>83</p>

	<p>84</p>
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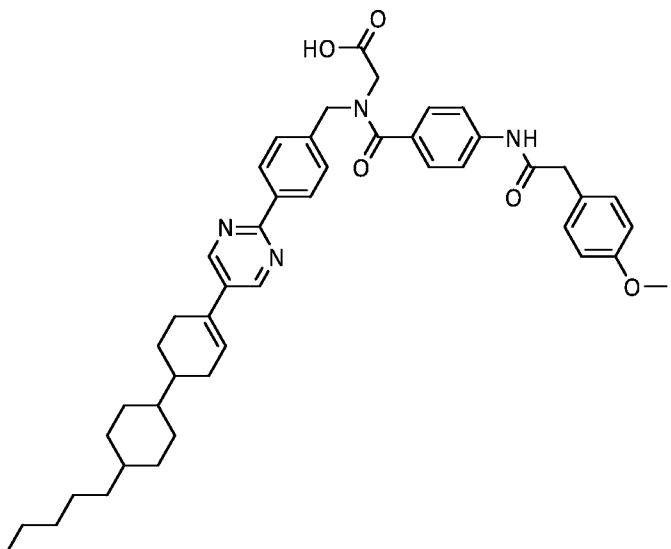
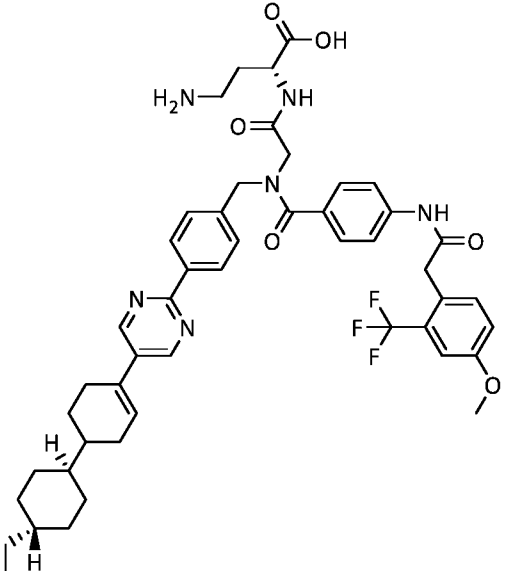
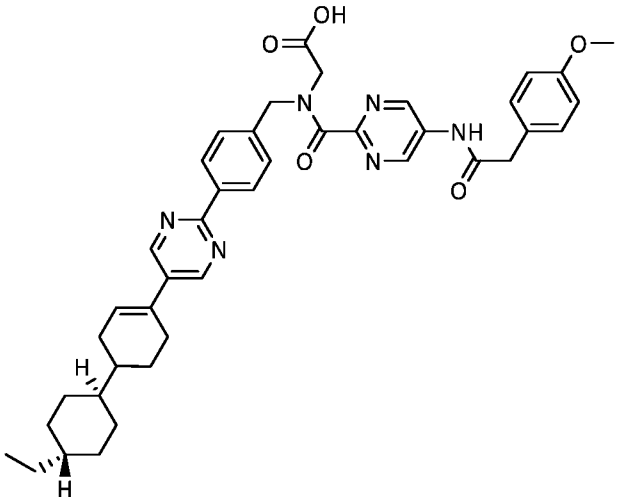
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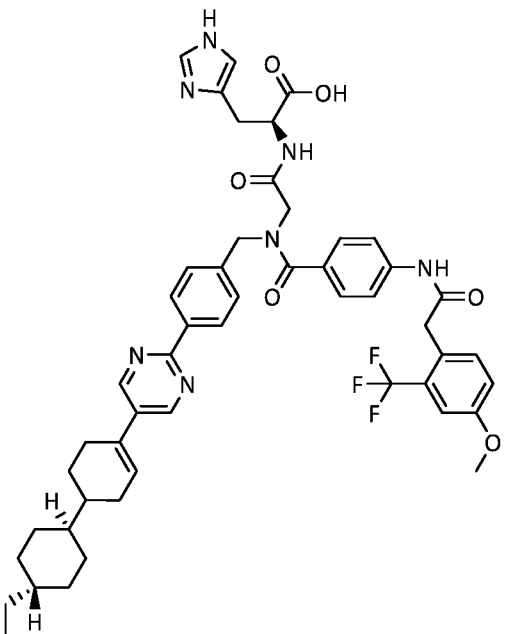
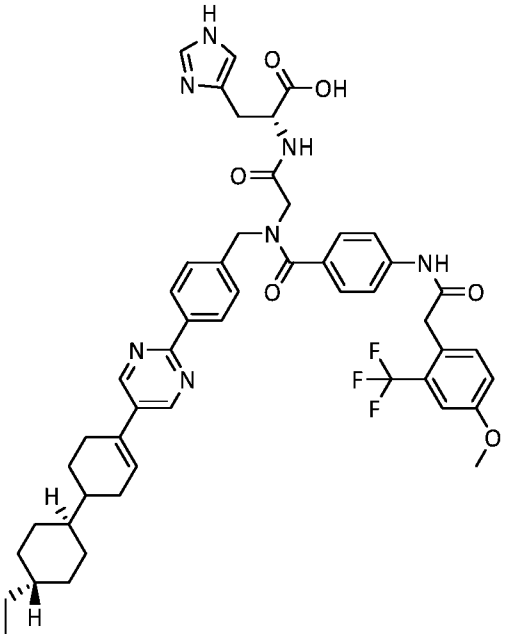
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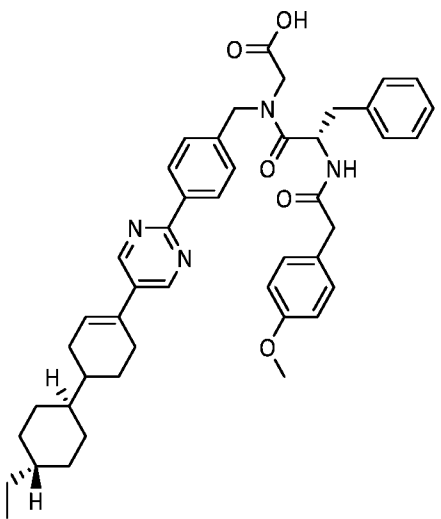
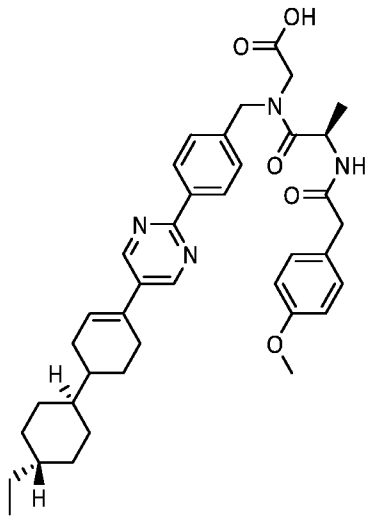
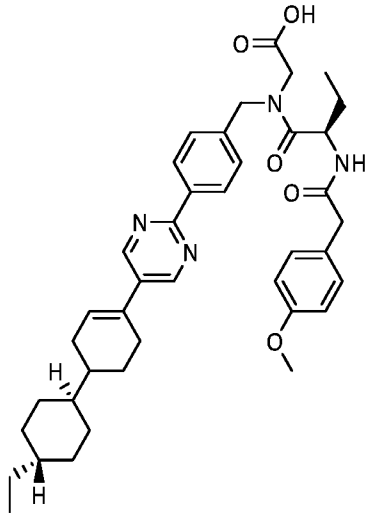
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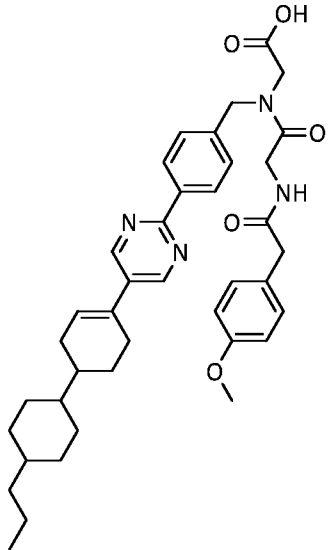
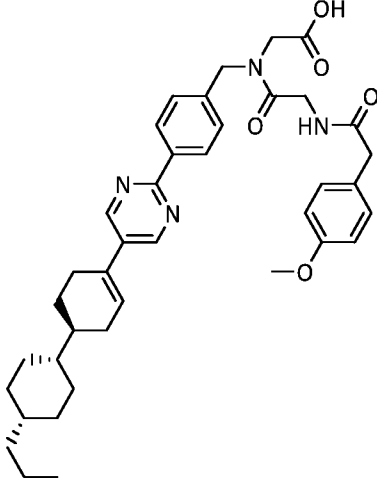
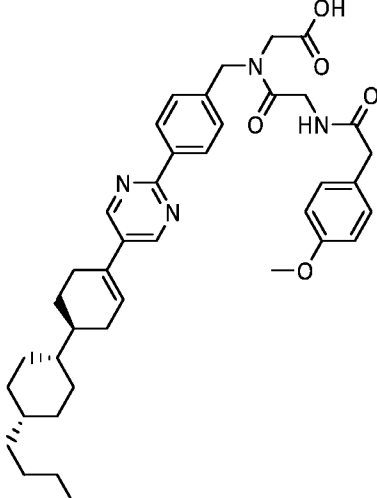
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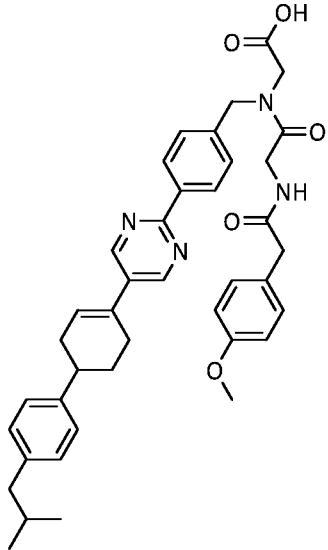
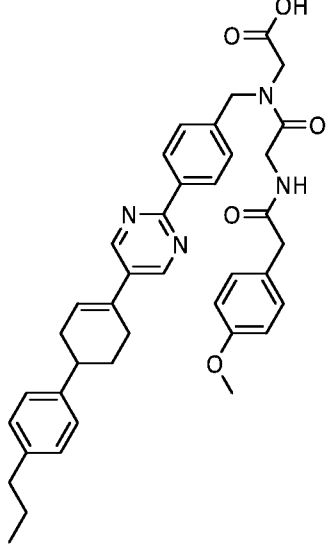
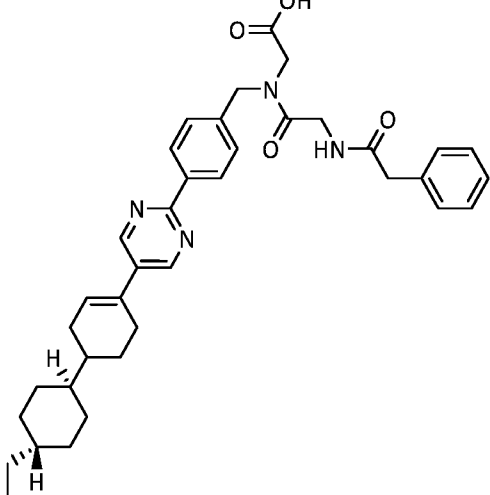
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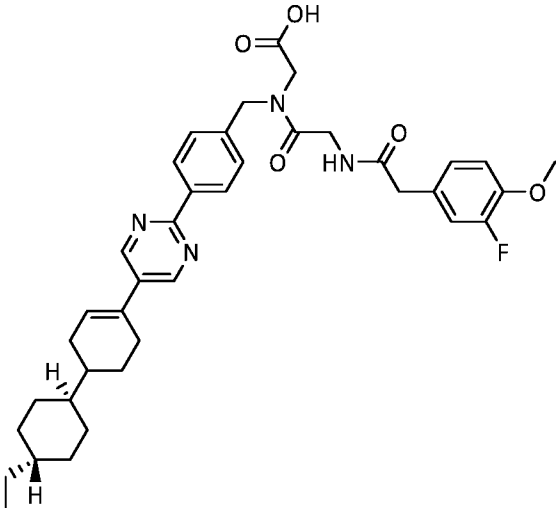
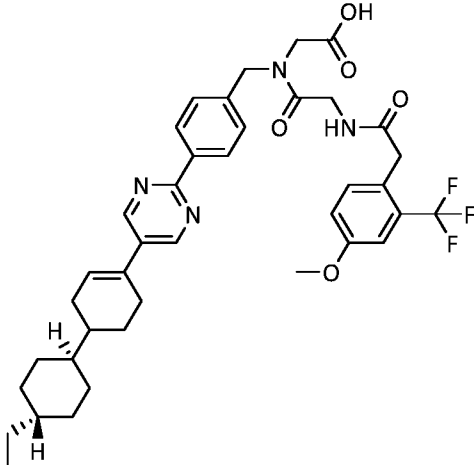
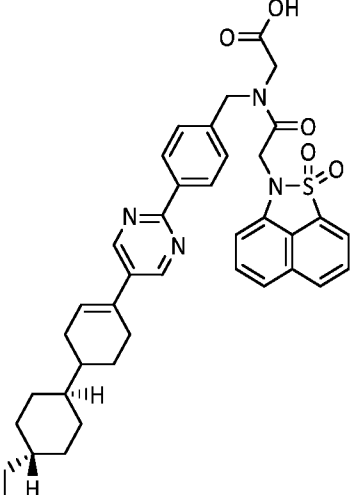
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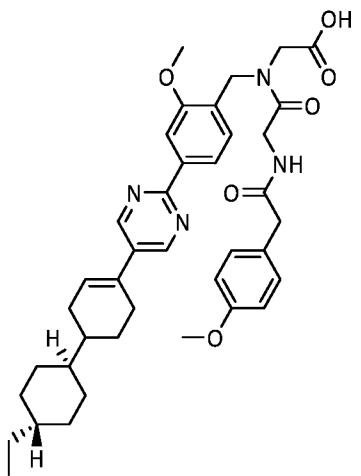
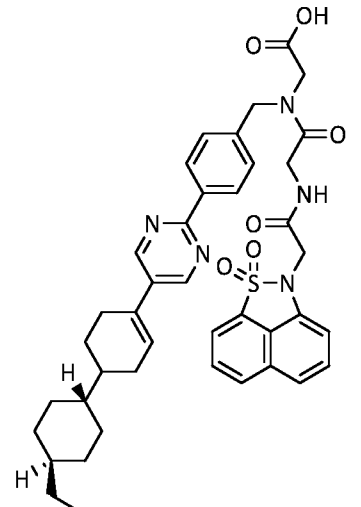
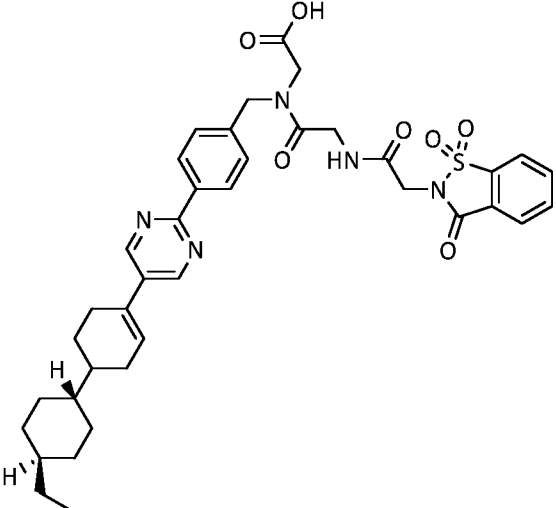
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 <chem>C[C@H]1CC[C@@H]2CC[C@H]1CC2c1ccc2nc3ccccc3n2c1Cc1ccc(cc1)C(=O)N[C@H](Cc1ccc(cc1)C(F)(F)F)C(=O)O</chem>	<p>113</p>

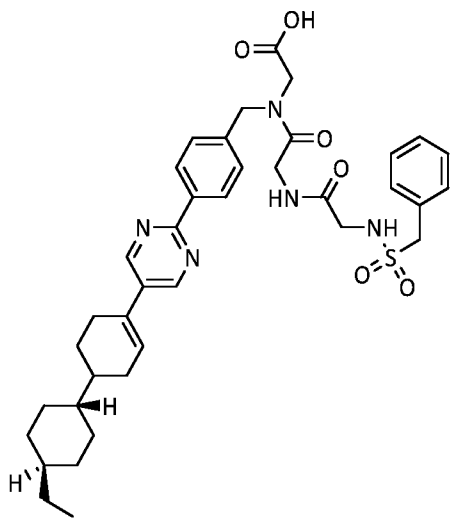
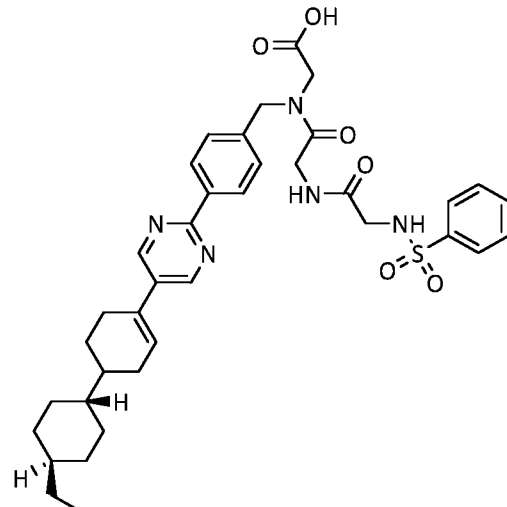
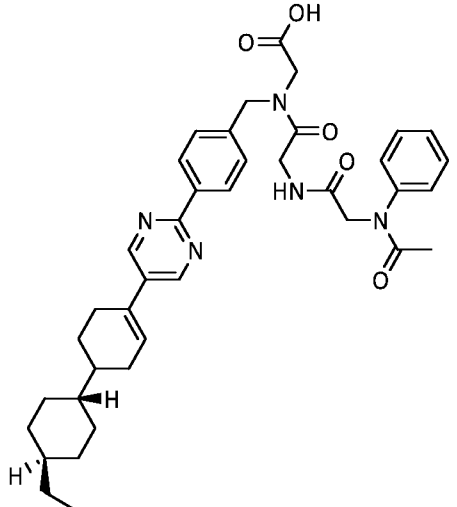
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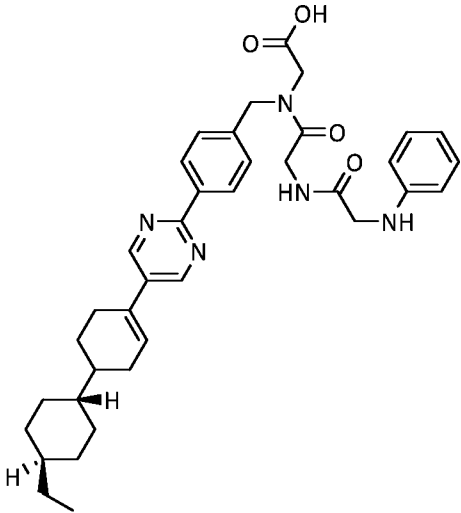
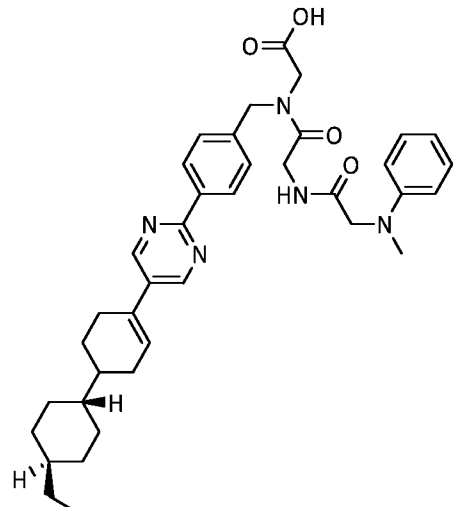
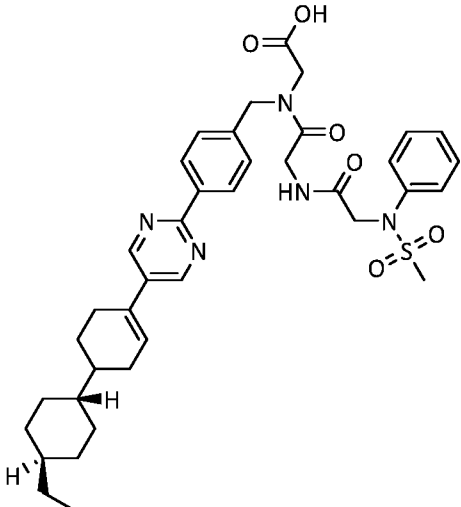
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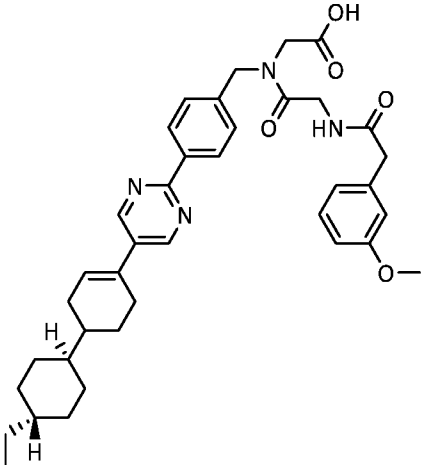
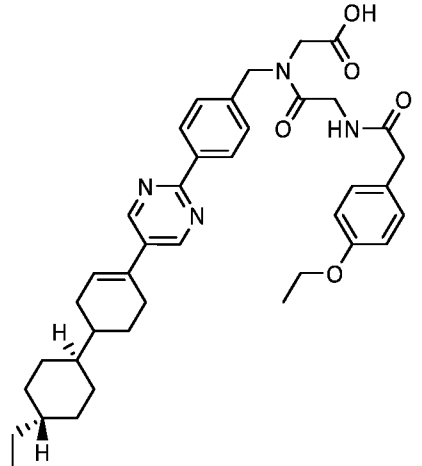
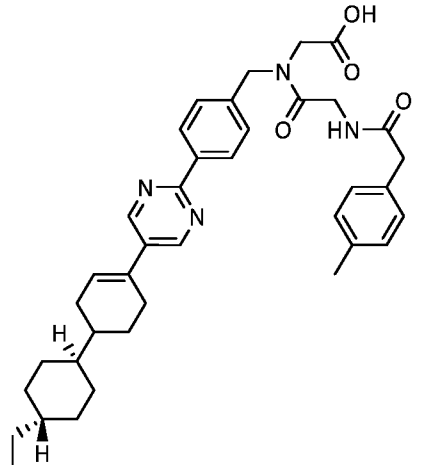
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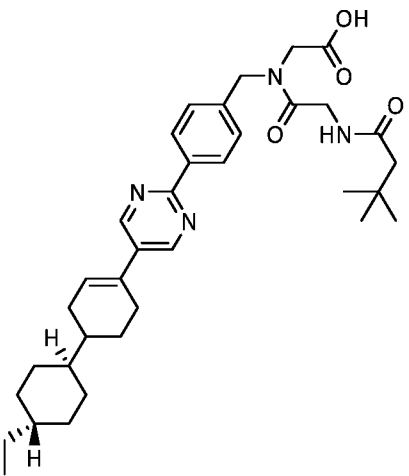
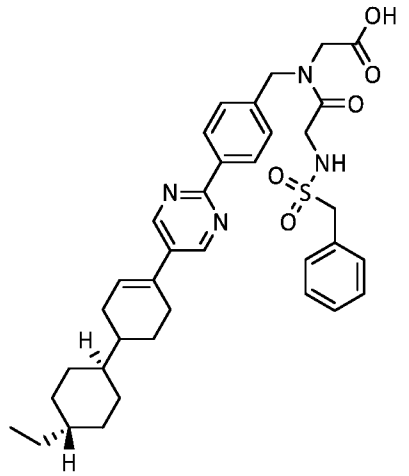
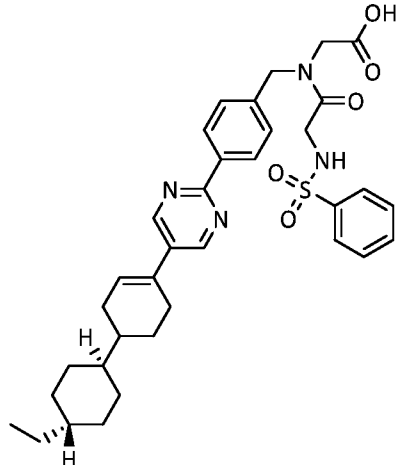
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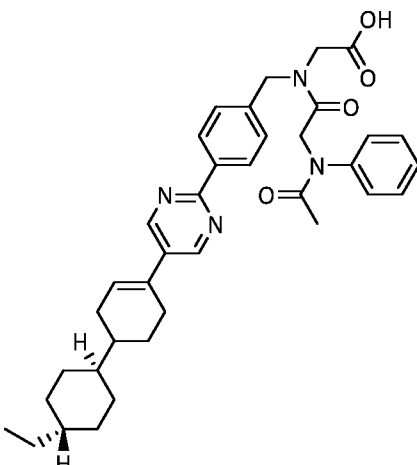
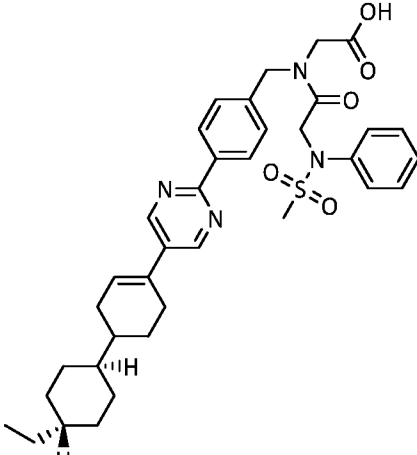
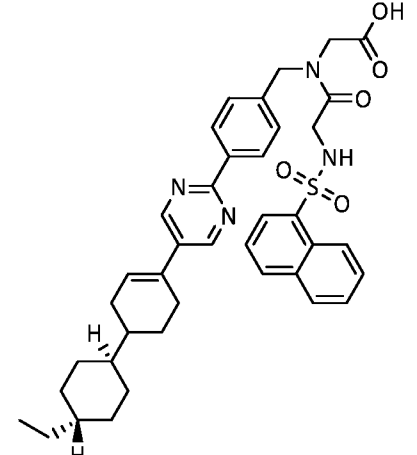
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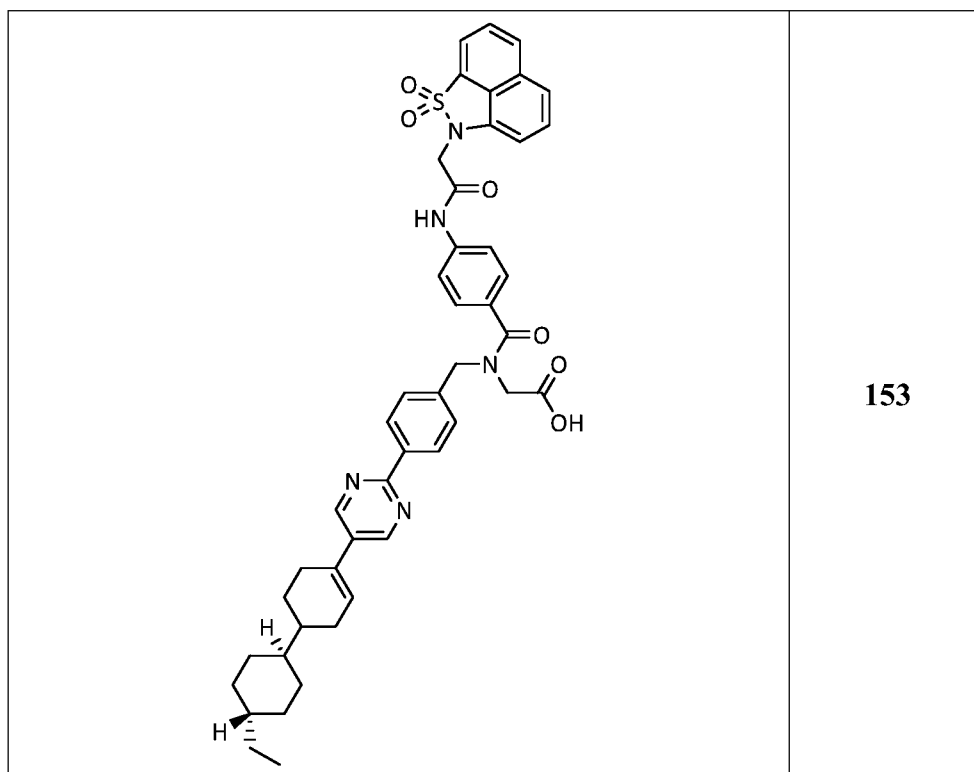
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13. A pharmaceutical composition comprising a compound any one of claims 1–12 or a pharmaceutically acceptable salt thereof together with at least one pharmaceutically acceptable carrier, diluent or excipient.

14. Use of a compound of any one of claims 1–12 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a malcondition in a patient for which modulation of a glucagon-like peptide 1 receptor is medically indicated, wherein the malcondition is selected from:

- (i) type I diabetes, type II diabetes, gestational diabetes, obesity, excessive appetite, insufficient satiety, and metabolic disorder; or
- (ii) non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

15. A method for treating a malcondition in a patient for which modulation of a glucagon-like peptide 1 receptor is medically indicated, comprising administering an effective amount of a compound of any one of claims 1–12 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 13, to the patient at a frequency and for a duration of time sufficient to provide a beneficial effect to the patient, wherein the malcondition is selected from:

- (i) type I diabetes, type II diabetes, gestational diabetes, obesity, excessive appetite, insufficient satiety, and metabolic disorder; or
- (ii) non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).