(12) STANDARD PATENT (11) Application No. **AU 2015321654 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Heterocyclic compounds and use thereof

(51) International Patent Classification(s)
C07D 403/14 (2006.01) ***C07D 239/70*** (2006.01)
A61K 31/506 (2006.01) ***C07D 401/14*** (2006.01)
A61K 31/517 (2006.01) ***C07D 403/12*** (2006.01)
C07D 239/24 (2006.01)

(21) Application No: **2015321654** (22) Date of Filing: **2015.09.21**

(87) WIPO No: **WO16/048861**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/053,389	**2014.09.22**	**US**

(43) Publication Date: **2016.03.31**
(44) Accepted Journal Date: **2019.10.31**

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Baldwins Intellectual Property, Level 20, Dimension Data House 157 Lambton Quay, Wellington, 6011, NZ

(56) Related Art
WO 2014074517 A1
WO 2008005538 A2
US 6156758 A
WO 1993020078 A1
BRILL, W. K. -D. et al., "Solid-phase synthesis of 2,6,8-trisubstituted purines", Tetrahedron Letters, (2001), vol. 42, no. 37, pages 6515 - 6518
POPOVA, L. M. et al., "Synthesis and properties of 2,4-disubstituted 6-fluoropyrimidines", Russian Journal of Organic Chemistry, (1996), vol. 32, no. 9, pages 1424 - 1428
CAS Registry Number 923221-53-8; STN Entry Date 26 February 2007; (4-(4-methyl-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)piperazin-1-yl)(phenyl)methanone
CAS Registry Number 747351-91-3; STN Entry Date 17 September 2004; 6-(4-formylpiperazin-1-yl)-2-(piperazin-1-yl)pyrimidine-4-carbonitrile
CAS Registry Number 744986-10-5; STN Entry Date 15 September 2004; 2,4-di(piperazin-1-yl)-6-thiomorpholinopyrimidine-5-carbonitrile
CAS Registry Number 746594-35-4; STN Entry Date 17 September 2004; 1,1'-(pyrimidine-2,4-diylbis(piperazine-4,1-diyl))bis(2-chloroethan-1-one)
CAS Registry Number 702635-05-0; STN Entry Date 2 July 2004; 1,1'-(pyrimidine-2,4-diyl)dipiperazine
JP 49-036700 A

COWDEN, W. B. et. al., "Pyrimidine N-Oxides. II* The synthesis of some amino- and imino-pyrimidine N-oxides and related compounds", Aust. J. Chem., (1979), vol. 32, pages 2049 - 2057
LEE, O et. al., "Electrophillic condensation of pyrimidines with cyclic ketones", Tetrahedron Letters, (1997), vol. 38., no. 36, pages 6401 - 6404
WO 2009123221 A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 March 2016 (31.03.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/048861 A3

(51) International Patent Classification:
C07D 403/14 (2006.01) *C07D 239/70* (2006.01)
C07D 403/12 (2006.01) *A61K 31/506* (2006.01)
C07D 401/14 (2006.01) *A61K 31/517* (2006.01)
C07D 239/24 (2006.01)

(21) International Application Number:
PCT/US2015/051143

(22) International Filing Date:
21 September 2015 (21.09.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/053,389 22 September 2014 (22.09.2014) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
15 September 2016

WO 2016/048861 A3

(54) Title: HETEROCYCLIC COMPOUNDS AND USE THEREOF

(57) Abstract: Heterocyclic compounds of Formula (I) shown herein. Also disclosed are pharmaceutical compositions containing the heterocyclic compounds and methods of using the heterocyclic compounds to mobilize hematopoietic stem cells and endothelial progenitor cells into the peripheral circulation. Further provided are methods for treating tissue injury, cancer, inflammatory disease, and autoimmune disease with the heterocyclic compounds.

HETEROCYCLIC COMPOUNDS AND USE THEREOF

BACKGROUND

Chemokines regulate the trafficking of various types of mononuclear cells. They are classified into four subfamilies of CC, CXC, CX3C, and C, based on positions of conserved cysteine residues in their N-termini.

Stromal-derived factor-1 (SDF-1), a CXC chemokine, plays key roles in homing and mobilization of hematopoietic stem cells, endothelial progenitor cells, and hematopoietic progenitor cells. The physiological function of SDF-1 is mediated by the type 4 CXC chemokine receptor (CXCR4).

The interaction between CXCR4 and SDF-1 contributes to multiple pathological conditions such as HIV, rheumatoid arthritis, asthma, and tumor metastases. For example, activation of the CXCR4/SDF-1 pathway in tumors leads to upregulation of angiogenic vascular endothelial growth factor (VEGF). On the other hand, disrupting the interaction between CXCR4 and SDF-1 by CXCR4 antagonists suppresses VEGF-dependent tumor angiogenesis and growth. Compounds that disrupt the interaction between CXCR4 and SDF-1 can be used for treating various diseases including tissue injury, cancer, inflammatory disease, and autoimmune disease.

There is a need to develop new compounds that can effectively disrupt the interaction between CXCR4 and SDF-1.

The reference to any prior art in the specification is not, and should not be taken as, an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge.

[followed by page 1a]

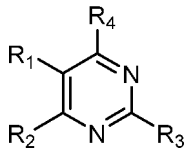
2015321654 27 Sep 2019

SUMMARY

The present invention is based on an unexpected discovery that certain heterocyclic compounds effectively bind to CXCR4 and disrupt the interaction between CXCR4 and SDF-1.

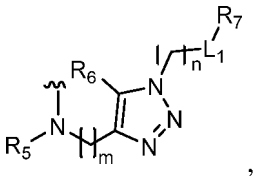
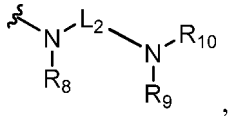
In one aspect, this invention relates to heterocyclic compounds of Formula (I):

[followed by page 2]

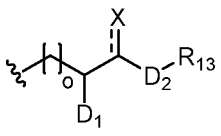


(I).

In this formula, each of R_1 and R_2, independently, is H, halo, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl; or R_1 and R_2, together with the two carbon atoms to which they are bonded, are C_{5-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, C_{5-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, and heteroaryl being optionally substituted with halo, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxyl, aryl, heteroaryl, or $C(O)OR_a$, in which R_a is H, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl; and

each of R_3 and R_4, independently, is NR_bR_c,  , or  ,

in which each of R_b and R_c, independently, is H or C_{1-6} alkyl; R_5 is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, and heteroaryl being optionally substituted with halo, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl; R_6 is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl; L_1 is heteroaryl, C_{1-10} heterocycloalkyl, NH, or NR_d, in which R_d is $C(O)(CH_2)_2CHNH_2CO_2R_e$, R_e being H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl; R_7 is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, and heteroaryl being optionally substituted with hydroxy, hydroxy C_{1-6} alkyl, halo, nitro, cyano, amino, amino C_{1-6} alkyl, amino C_{3-10}

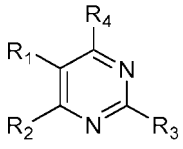
cycloalkyl, amino C_{1-10} heterocycloalkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl; m is 1-6; n is 1-6; each of R_8 and $R_{9,}$ independently, is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, and heteroaryl being optionally substituted with $C(O)OR_f$, in which R_f is H, C_{1-10} alkyl, C_{3-20} cycloalkyl, C_{3-20} heterocycloalkyl, aryl, or heteroaryl; or R_8 and $R_{9,}$ together with the nitrogen atoms to which they are bonded, are C_{3-10} heterocycloalkyl; L_2 is C_{1-6} alkyl; or L_2, together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl or heteroaryl; and R_{10} is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl, $C(O)OR_g$, $C(S)NR_hR_i$, $C(O)NR_jR_k$, or $C(O)R_p$, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, and heteroaryl alkyl being optionally substituted with hydroxy, halo, nitro, cyano, amino, $C(O)OR_{11}$, or $P(O)(OR_{12})_2$, in which each of R_{11} and R_{12}, independently, is H or C_{1-6} alkyl; or R_{10}, together with R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl or heteroaryl; each of R_g, R_h, R_i, R_j, and R_k, independently, being H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} alkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl; and R_p being H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl, or 

, in which each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl is optionally substituted with halo, $P(O)(OH)_{2,}$ or $P(O)(O\text{-}C_{1-6}\text{ alkyl})_2$; o is 0-2; D_1 is OH or $NR_{14}R_{15}$, each of R_{14} and R_{15}, independently, being H, $C(O)CH(NH_2)CH_2OH$, or $C(NH)NH_2$; D_2 is O or NR_{16}, R_{16} being H, C_{1-6} alkyl, $S(O)_2R_q$, NHR_r, or $CH_2CO_2R_s$, in which each of R_q and R_r, independently, is aryl optionally substituted with halo or alkoxyl, and R_s is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} alkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl; R_{13} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl

2015321654 27 Sep 2019

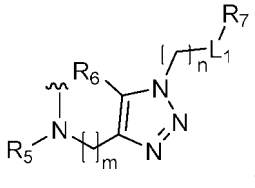
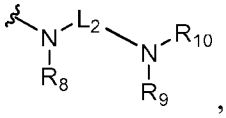
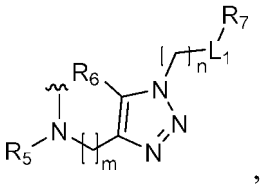
alkyl, heteroaryl alkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl being optionally substituted with hydroxy, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, heteroaryl, $P(O)(OH)_2$, $P(O)(O\text{-}C_{1-6}$ alkyl$)_2$, hydroxy, or $C(O)OR_t$, in which R_t is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} alkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl; and ═X is ═O or —aryl.

In a particular aspect, the invention relates to a compound of formula (I):


(I),

wherein

each of R_1 and R_2, independently, is H, halo, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl; or R_1 and R_2, together with the two carbon atoms to which they are bonded, are C_{5-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, C_{5-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, and heteroaryl being optionally substituted with halo, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxyl, aryl, heteroaryl, or $C(O)OR_a$, in which R_a is H, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl; and

each of R_3 and R_4, independently, is NR_bR_c,  , or  , at least one of R_3 and R_4 being  ,

2015321654 27 Sep 2019

in which

each of R_b and R_c, independently, is H or C_{1-6} alkyl;

R_5 is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, and heteroaryl being optionally substituted with halo, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl;

R_6 is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl;

L_1 is heteroaryl, C_{1-10} heterocycloalkyl, NH, or NR_d, in which R_d is $C(O)(CH_2)_2CHNH_2CO_2R_e$, R_e being H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl;

R_7 is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, and heteroaryl being optionally substituted with hydroxy, hydroxy C_{1-6} alkyl, halo, nitro, cyano, amino, amino C_{1-6} alkyl, amino C_{3-10} cycloalkyl, amino C_{1-10} heterocycloalkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl;

m is 1-6;

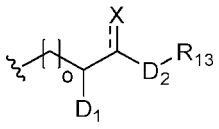
n is 1-6;

each of R_8 and R_9, independently, is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, and heteroaryl being optionally substituted with $C(O)OR_f$, in which R_f is H, C_{1-10} alkyl, C_{3-20} cycloalkyl, C_{3-20} heterocycloalkyl, aryl, or heteroaryl; or R_8 and R_9, together with the nitrogen atoms to which they are bonded, are C_{3-10} heterocycloalkyl;

2015321654 27 Sep 2019

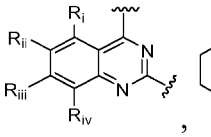
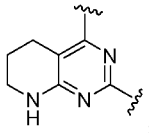
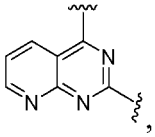
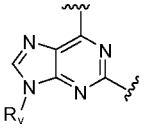
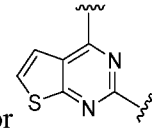
L_2 is C_{1-6} alkyl; or L_2, together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl or heteroaryl; and

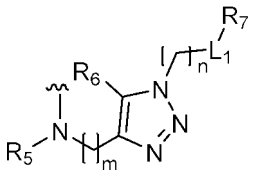
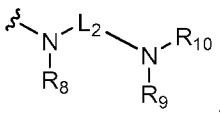
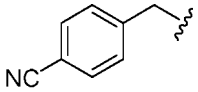
R_{10} is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl, $C(O)OR_g$, $C(S)NR_hR_i$, $C(O)NR_jR_k$, or $C(O)R_p$, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, and heteroaryl alkyl being optionally substituted with hydroxy, halo, nitro, cyano, amino, $C(O)OR_{11}$, or $P(O)(OR_{12})_2$, in which each of R_{11} and R_{12}, independently, is H or C_{1-6} alkyl; or R_{10}, together with R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl or heteroaryl; each of R_g, R_h, R_i, R_j, and R_k, independently, being H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} alkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl; and R_p being H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl, or



, in which each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl is optionally substituted with halo, $P(O)(OH)_2$, or $P(O)(O\text{-}C_{1-6}\text{ alkyl})_2$; o is 0-2; D_1 is OH or $NR_{14}R_{15}$, each of R_{14} and R_{15}, independently, being H, $C(O)CH(NH_2)CH_2OH$, or $C(NH)NH_2$; D_2 is O or NR_{16}, R_{16} being H, C_{1-6} alkyl, $S(O)_2R_q$, NHR_r, or $CH_2CO_2R_s$, in which each of R_q and R_r, independently, is aryl optionally substituted with halo or alkoxyl, and R_s is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} alkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl; R_{13} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, and heteroaryl being optionally substituted with hydroxy, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, heteroaryl, $P(O)(OH)_2$, $P(O)(O\text{-}C_{1-6}\text{ alkyl})_2$, hydroxy, or $C(O)OR_t$, in which R_t is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} alkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl; and ---X is =O or —aryl.

One subset of the above-described heterocyclic compounds includes those in which each of R_1 and R_2, independently, is H, amino, or C_{1-10} heterocycloalkyl (e.g., morpholine, piperidine, or piperazine) optionally substituted with C_{1-6} alkyl or $C(O)OR_a$, in which R_a is H or C_{1-10} alkyl.

Another subset of the heterocyclic compounds of this invention includes those in which R_1 and R_2, together with the two carbon atoms to which they are bonded, are C_{5-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl. Examples of heteroaryl include  ,  ,  ,  , or  , each of R_i, R_{ii}, R_{iii}, R_{iv}, and R_v, independently, being H, halo, C_{1-10} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl.

Still another subset of the heterocyclic compounds of this invention includes those in which each of R_3 and R_4, independently, is  or  . R_5 is preferably H, cyano substituted aryl alkyl (e.g., ), or unsubstituted heteroaryl

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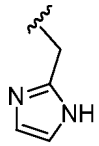
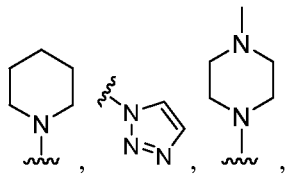
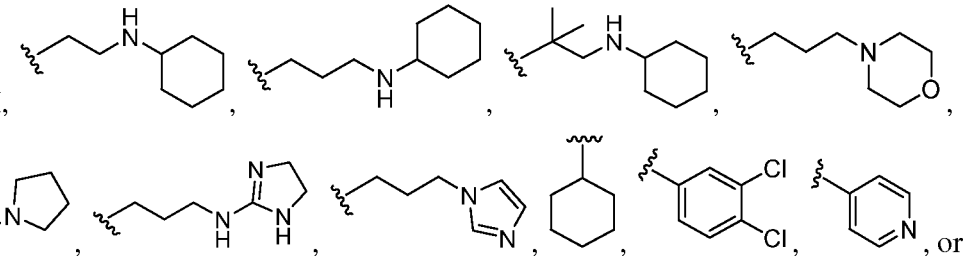
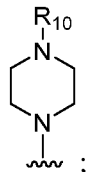
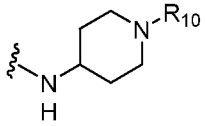
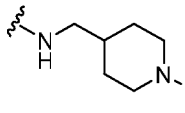
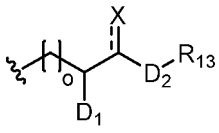
alkyl (e.g., ); R6 is preferably H, aryl (e.g., phenyl), heteroaryl (e.g., pyridinyl); L_1 is preferably NH,  , or -NC(O)$(CH_2)_2$CHNH_2CO_2H; R_7 is preferably H, CH_2OH,  ; each of R_8 and R_9, independently, is H or C_{1-6} alkyl optionally substituted with C(O)OR_f, in which R_f is H or C_{1-10} alkyl, or R_8 and R_9, together with the nitrogen atoms to which they are bonded, are preferably  ; L_2, together with R_8 or R_9 and the nitrogen atom to which they are bonded, is preferably C_{4-10} heterocycloalkyl (e.g.,  or ); R_{10} is preferably H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl, C(O)OR_g, C(S)NR_hR_i, or C(O)NR_jR_k, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, and heteroaryl alkyl being optionally substituted with hydroxy, halo, C(O)OR_{11}, or P(O)$(OR_{12})_2$; or R_{10}, together with R_9 and the nitrogen atom to which they are bonded, is preferably C_{4-10} heterocycloalkyl or heteroaryl; or R_{10} is preferably C(O)R_p, R_p being C_{1-6} alkyl, C_{3-10} cycloalkyl, aryl, heteroaryl, or



, in which each of C_{1-6} alkyl, C_{3-10} cycloalkyl, aryl, and heteroaryl C_{1-6} alkyl is optionally substituted with halo or $P(O)(OH)_2$.

The term "alkyl" herein refers to a saturated, linear or branched hydrocarbon moiety, such as $-CH_3$ or branched $-C_3H_7$. The term "cycloalkyl" refers to a non-aromatic, monocyclic, bicyclic, tricyclic, or tetracyclic hydrocarbon moiety, such as cyclohexyl, cyclohexen-3-yl, or adamantyl. The term "alkoxyl" refers to an –O-alkyl radical. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy. The term "heterocycloalkyl" refers to a non-aromatic, monocyclic, bicyclic, tricyclic, or tetracyclic moiety having one or more ring heteroatoms (e.g., N, O, or S), such as 4-tetrahydropyranyl or 4-pyranyl. The term "aryl" refers to a hydrocarbon moiety having one or more aromatic rings. Examples of aryl moieties include phenyl (Ph), phenylene, naphthyl, naphthylene, pyrenyl, anthryl, and phenanthryl. The term "heteroaryl" refers to a moiety having one or more aromatic rings that contain at least one heteroatom (e.g., N, O, or S). Examples of heteroaryl moieties include furyl, furylene, fluorenyl, pyrrolyl, thienyl, oxazolyl, imidazolyl, thiazolyl, pyridyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl and indolyl. The term "aryl alkyl" refers to an alkyl that is substituted with at least one aryl group. Examples of aryl alkyl include benzyl (Bn) and 1-naphthylmethyl. The term "heteroaryl alkyl" refers to an alkyl that is substituted with at least one heteroaryl group. Examples of heteroaryl alkyl include 2-furanyl-methyl and 2-thienylmethyl. The term "amino alkyl" refers to an alkyl that is substituted with at least one amino group. Examples of amino alkyl include aminomethyl and 2-aminoethyl. The term "amino cycloalkyl" refers to a cycloalkyl that is substituted with at least one amino group. Examples of amino cycloalkyl include amino cyclopropyl and amino cyclopentyl. The term

"hydroxyl alkyl" refers to an alkyl that is substituted with at least one hydroxyl group. Examples of hydroxyl alkyl include hydroxyl methyl and hydroxyl ethyl.

Alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aryl alkyl, and heteroaryl alkyl mentioned herein include both substituted and unsubstituted moieties, unless specified otherwise. Possible substituents on cycloalkyl, heterocycloalkyl, aryl, and heteroaryl include C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{1-20} heterocycloalkyl, C_{1-20} heterocycloalkenyl, C_{1-10} alkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, amino, C_{1-10} alkylamino, C_{1-20} dialkylamino, arylamino, diarylamino, hydroxyl, halogen, thio, C_{1-10} alkylthio, arylthio, C_{1-10} alkylsulfonyl, arylsulfonyl, acylamino, aminoacyl, aminothioacyl, amidino, guanidine, ureido, cyano, nitro, acyl, thioacyl, acyloxy, carboxyl, and carboxylic ester. On the other hand, possible substituents on alkyl include all of the above-recited substituents except C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl. Cycloalkyl, heterocycloalkyl, aryl, and heteroaryl can also be fused with each other.

The heterocyclic compounds described above include the compounds themselves, as well as their salts, prodrugs, and solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a heterocyclic compounds. Suitable anions include chloride, bromide, iodide, sulfate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, acetate, malate, tosylate, tartrate, fumurate, glutamate, glucuronate, lactate, glutarate, and maleate. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a heterocyclic compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The heterocyclic compounds also include those salts containing quaternary nitrogen atoms. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administering to a subject, are capable of providing active heterocyclic compounds. A solvate refers to a complex formed between an active heterocyclic compound and a pharmaceutically acceptable

solvent. Examples of a pharmaceutically acceptable solvent include water, ethanol, isopropanol, ethyl acetate, acetic acid, and ethanolamine.

The heterocyclic compounds may contain non-aromatic double bonds, which can occur as cis- or trans- isomeric forms. Such isomeric forms are contemplated.

Another aspect of this invention is related to a method for mobilizing hematopoietic stem cells (HSC) and endothelial progenitor cells (EPC) into the peripheral circulation. The method includes contacting HSC and EPC with an effective amount of one or more of the heterocyclic compounds of Formula (I) described above.

An additional aspect of this invention relates to a method for treating tissue injury, cancer, inflammatory disease, and autoimmune disease. The method includes administering to a subject in need thereof an effective amount of one or more of the heterocyclic compounds of Formula (I) described above. Examples of tissue injury include neurodegenerative disease, retinal pigment epithelium dysfunction, heart and myocardial infarction, ischemic disease (e.g., ischemic stroke and limb ischemia), wound, bone fracture, pancreatic injury, kidney injury, intestinal injury, and lung injury. Examples of cancer include acute myeloid leukemia, non-small cell lung cancer, multiple myeloma, and pancreatic cancer. Examples of inflammatory disease include inflammatory bowel disease, allergic asthma, and ocular uveitis. An exemplary autoimmune disease is rheumatoid arthritis.

In a particular example, the method is performed to treat a kidney injury (e.g., an acute kidney injury). The method includes administering to a subject suffering from a kidney injury an effective amount of one or more of the heterocyclic compounds described above.

Also within the scope of this invention is a pharmaceutical composition containing one or more of the above-described heterocyclic compounds of Formula (I). The pharmaceutical composition can be used for treating tissue injury (e.g., an acute kidney injury), cancer, inflammatory disease, and autoimmune disease.

This invention also features use of one or more of the above-described heterocyclic compounds of Formula (I) for the manufacture of a medicament for treating tissue injury (e.g., an acute kidney injury), cancer, inflammatory disease, and autoimmune disease.

The term "treating" or "treatment" refers to administering one or more of the heterocyclic compounds to a subject, who has an above-described disease, a symptom of such a disease, or a predisposition toward such a disease, with the purpose to confer a therapeutic effect, e.g., to cure, relieve, alter, affect, ameliorate, or prevent the above-described disease, the symptom of it, or the predisposition toward it. "An effective amount" refers to the amount of an active compound that is required to confer the therapeutic effect. Effective doses will vary, as recognized by those skilled in the art, depending on the types of disease treated, route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatment.

To practice the method of the present invention, a composition having one or more of the above-described heterocyclic compounds can be administered parenterally, orally, nasally, rectally, topically, or buccally. The term "parenteral" as used herein refers to subcutaneous, intracutaneous, intravenous, intraperitoneal, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, or intracranial injection, as well as any suitable infusion technique.

A sterile injectable composition can be a solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution, and isotonic sodium chloride solution. In addition, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or di-glycerides). Fatty acid, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil and castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long chain

alcohol diluent or dispersant, carboxymethyl cellulose, or similar dispersing agents. Other commonly used surfactants such as Tweens and Spans or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purpose of formulation.

A composition for oral administration can be any orally acceptable dosage form including capsules, tablets, emulsions and aqueous suspensions, dispersions, and solutions. In the case of tablets, commonly used carriers include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added.

A nasal aerosol or inhalation composition can be prepared according to techniques well known in the art of pharmaceutical formulation. For example, such a composition can be prepared as a solution in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

A composition having one or more of the above-described heterocyclic compounds can also be administered in the form of suppositories for rectal administration.

The carrier in the pharmaceutical composition must be “acceptable” in the sense that it is compatible with the active ingredient of the composition (and preferably, capable of stabilizing the active ingredient) and not deleterious to the subject to be treated. One or more solubilizing agents can be utilized as pharmaceutical excipients for delivery of an active 1,5-diphenyl-penta-1,4-dien-3-one compound. Examples of other carriers include colloidal silicon oxide, magnesium stearate, cellulose, sodium lauryl sulfate, and D&C Yellow # 10.

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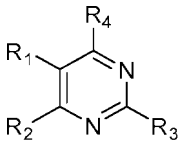
Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like, are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense, that is to say, in the sense of "including, but not limited to".

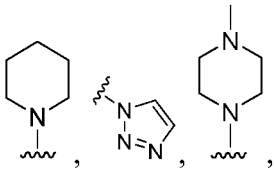
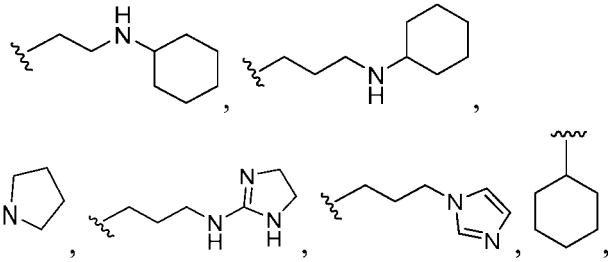
The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

Disclosed are heterocyclic compounds of Formula (I):



(I).

Referring to this formula, two sets of particularly preferred heterocyclic compounds include (i) those in which each of R_1 and R_2, independently, is H, amino, C_{1-10} heterocycloalkyl optionally substituted with C_{1-6} alkyl or $C(O)OR_a$, in which R_a is H, C_{1-10} alkyl; R_5 is H, aryl alkyl, heteroaryl alkyl, each of aryl alkyl and heteroaryl alkyl being optionally substituted with cyano; R_6 is H, aryl, or heteroaryl; L_1 is NH,  , or -$NC(O)(CH_2)_2CHNH_2CO_2H$; R_7 is H, CH_2OH, 

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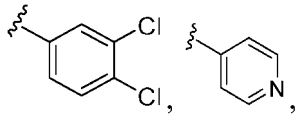

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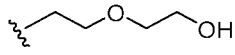
, or 

; each of R_8 and $R_{9,}$ independently, is H or C_{1-6} alkyl optionally substituted with $C(O)OR_f$, in which R_f is H or C_{1-10} alkyl, or R_8 and $R_{9,}$ together with the nitrogen atoms to which they are

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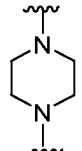
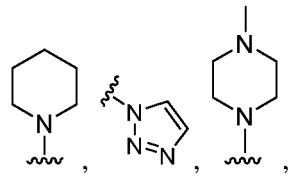
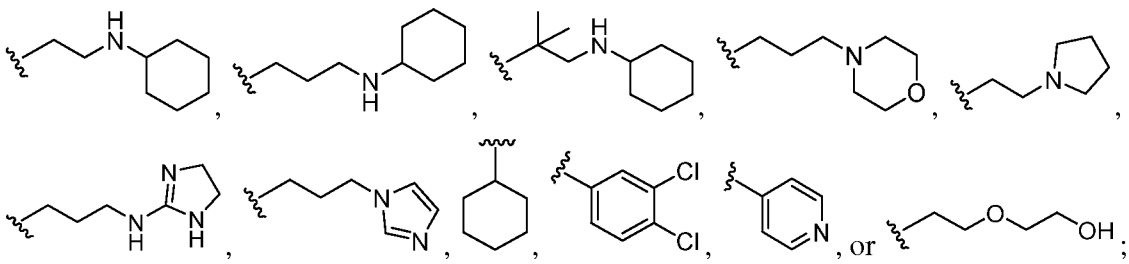


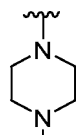
bonded, are ; and L_2 together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl; R_{10} is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl, $C(O)OR_g$, $C(S)NR_hR_i$, or $C(O)NR_jR_k$, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, and heteroaryl alkyl being optionally substituted with hydroxy, halo, $C(O)OR_{11}$, or $P(O)(OR_{12})_2$; or R_{10}, together with R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl or heteroaryl; and (ii) those in which R_1 and R_2, together with the two carbon atoms to which they are bonded, are C_{5-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl; R_5 is H, aryl alkyl, or heteroaryl alkyl, each of aryl alkyl and heteroaryl alkyl being optionally substituted with cyano; R_6 is H, aryl, or heteroaryl; L_1 is



NH, , , , or $-NC(O)(CH_2)_2CHNH_2CO_2H$; R_7 is H, CH_2OH,

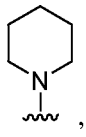
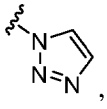
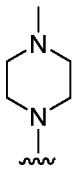
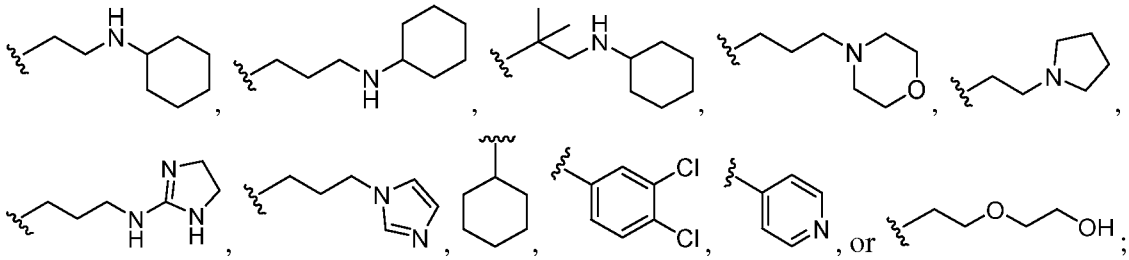
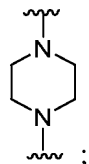
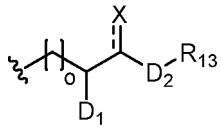


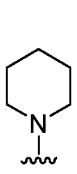
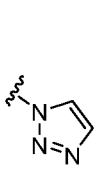
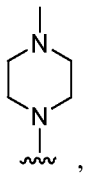
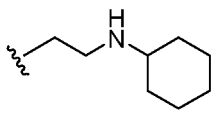
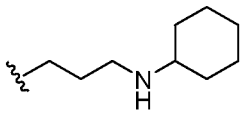
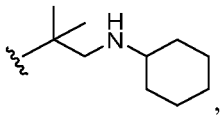
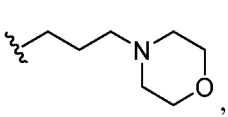
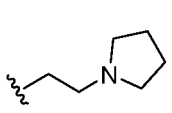
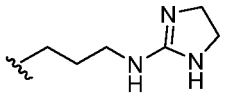
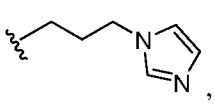
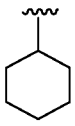
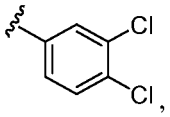
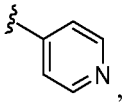
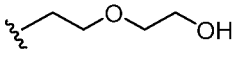
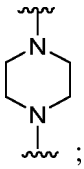
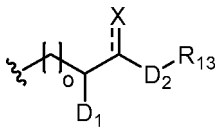
each of R_8 and R_9, independently, is H or C_{1-6} alkyl optionally substituted with $C(O)OR_f$, in which R_f is H or C_{1-10} alkyl, or R_8 and R_9, together with the nitrogen atoms to which they are



bonded, are ; and L_2 together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl; R_{10} is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl, $C(O)OR_g$, $C(S)NR_hR_i$, or $C(O)NR_jR_k$, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl,

heteroaryl, aryl alkyl, and heteroaryl alkyl being optionally substituted with hydroxy, halo, $C(O)OR_{11}$, or $P(O)(OR_{12})_2$; or R_{10}, together with R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl or heteroaryl.

Referring back to Formula (I), two more sets of particularly preferred compounds include (i) those in which each of R_1 and R_2, independently, is H, amino, C_{1-10} heterocycloalkyl optionally substituted with C_{1-6} alkyl or $C(O)OR_a$, in which R_a is H, C_{1-10} alkyl; R_5 is H, aryl alkyl, heteroaryl alkyl, each of aryl alkyl and heteroaryl alkyl being optionally substituted with cyano; R_6 is H, aryl, or heteroaryl; L_1 is NH,  ,  ,  , or -NC(O)$(CH_2)_2$CHNH_2CO_2H; R_7 is H, CH_2OH,  ; each of R_8 and R_9, independently, is H or C_{1-6} alkyl optionally substituted with $C(O)OR_f$, in which R_f is H or C_{1-10} alkyl, or R_8 and R_9, together with the nitrogen atoms to which they are bonded, are  ; and L_2 together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl; R_{10} is $C(O)R_p$, R_p being C_{1-6} alkyl, C_{3-10} cycloalkyl, aryl, heteroaryl, or  , in which each of C_{1-6} alkyl, C_{3-10} cycloalkyl, aryl, and heteroaryl C_{1-6} alkyl is optionally substituted with halo or $P(O)(OH)_2$, and ---X is =O; and (ii) those in which R_1 and R_2, together with the two carbon atoms to which they are bonded,

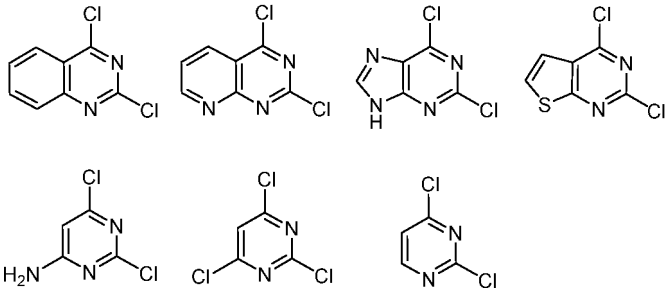
are C_{5-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl; R_5 is H, aryl alkyl, or heteroaryl alkyl, each of aryl alkyl and heteroaryl alkyl being optionally substituted with cyano; R_6 is H, aryl, or heteroaryl; L_1 is NH,  ,  ,  , or -$NC(O)(CH_2)_2CHNH_2CO_2H$; R_7 is H, CH_2OH,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; each of R_8 and $R_{9,}$ independently, is H or C_{1-6} alkyl optionally substituted with $C(O)OR_f$, in which R_f is H or C_{1-10} alkyl, or R_8 and $R_{9,}$ together with the nitrogen atoms to which they are bonded, are  ; and L_2 together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl; R_{10} is $C(O)R_p$, R_p being C_{1-6} alkyl, C_{3-10} cycloalkyl, aryl, heteroaryl, or  , in which each of C_{1-6} alkyl, C_{3-10} cycloalkyl, aryl, and heteroaryl C_{1-6} alkyl is optionally substituted with halo or $P(O)(OH)_2$, and $\overset{\cdots}{=}X$ is $=O$.

Also within this invention is a pharmaceutical composition containing one or more of the heterocyclic compounds of Formula (I) for treating tissue injury (e.g., an acute kidney injury), cancer, inflammatory disease, and autoimmune disease.

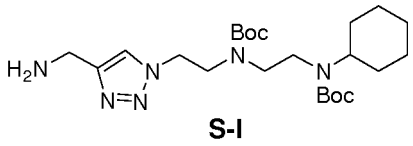
Further covered by this invention is a method for treating tissue injury (e.g., an acute kidney injury), cancer, inflammatory disease, and autoimmune disease, the method including administering to a subject in need thereof an effective amount of a compound of Formula (I).

The heterocyclic compounds of Formula (I) described above can be prepared according to well-known methods in the field. Provided below are actual examples of preparing compounds 1-273 from the following starting materials and side chain compounds.

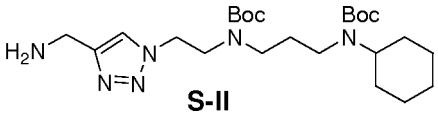
Starting materials: 2,4-dichloro heterocyclic derivatives



Side chain compounds: S-I, S-II, S-III, and S-IV



S-I



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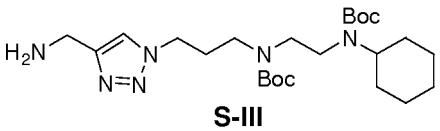
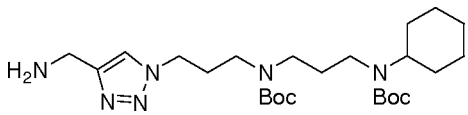
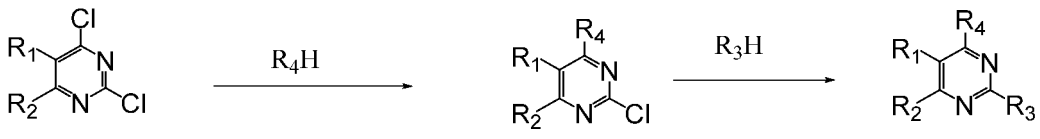


S-III



S-IV

Depicted below is a typical synthetic route for synthesizing certain compounds of Formula (I). Compound A containing two halo groups reacts with amino compound R_4-H to give compound B, which reacts with amino compound R_3-H (which can be the same as R_4-H) to give compound C, i.e., a compound of Formula (I).



A B C

The compound thus synthesized can be purified by a method such as column chromatography, high-pressure liquid chromatography, or recrystallization.

The intermediates used in the synthesis described above are either commercially available or can be prepared by methods known in the art. The methods may also include additional steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups if necessary to facilitate synthesis of the compounds. In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds.

Synthetic chemistry transformations and protecting group methodologies (protection and de-protection) used for synthesizing the compounds of Formula (I) are well known in the art. See, for example, R. Larock, Comprehensive Organic Transformations (2nd Ed., VCH Publishers 1999); P. G. M. Wuts and T. W. Greene, Greene's Protective Groups in Organic Synthesis (4th Ed., John Wiley and Sons 2007); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis (John Wiley and Sons 1994); L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis (2nd ed., John Wiley and Sons 2009); and G. J. Yu *et al.*, *J. Med. Chem.* 2008, *51*, 6044-6054.

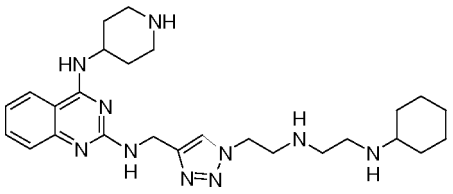
The compounds mentioned herein may contain a non-aromatic double bond and one or more asymmetric centers. Thus, they can occur as racemates or racemic mixtures, single enantiomers, individual diastereomers, diastereomeric mixtures, or cis- or trans- isomeric forms. All such isomeric forms are contemplated.

The compounds of Formula (I) thus prepared can be initially screened using *in vitro* assays, e.g., the radioligand binding assay described in Example 2 below, for their potency in inhibiting binding of SDF-1 to CXCR4. They can be subsequently evaluated using *in vivo* assays, e.g., a colony-forming assay, for their efficacy in enhancing hematopoietic stem cell mobilization in a mammal. The selected compounds can be further tested to verify their efficacy in treating tissue injury (e.g., acute kidney injury and ischemic stroke), cancer,

inflammatory disease, and autoimmune disease. For example, a compound can be administered to an animal (e.g., a mouse) having an ischemic acute kidney injury and its therapeutic effects are then assessed. Based on the results, an appropriate dosage range and administration route can be determined.

Without further elaboration, it is believed that one skilled in the art can, based on the above description, utilize the present invention to its fullest extent. The following specific examples are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All publications cited herein are incorporated by reference.

Shown below are the structures of 273 exemplary compounds of Formula (I). The methods for preparing these compounds, as well as the analytical data for the compounds thus prepared, are set forth in Example 1 below. The procedures for testing these compounds are described in Examples 2-4 also below.



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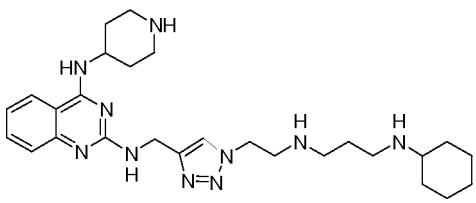

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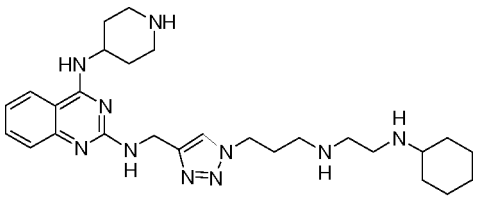

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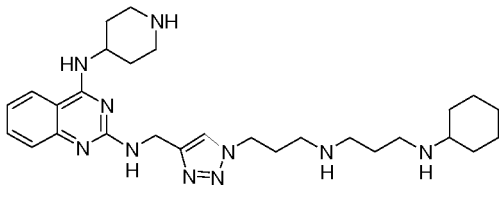

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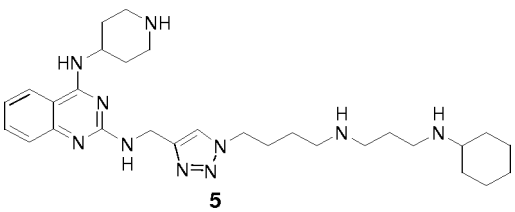

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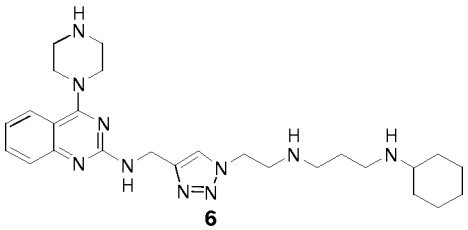

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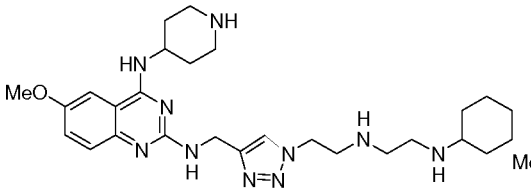

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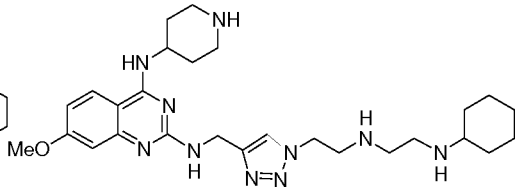

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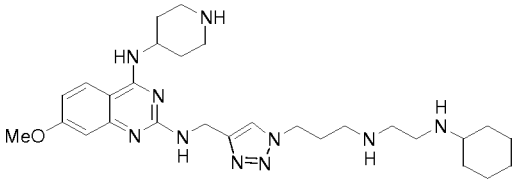

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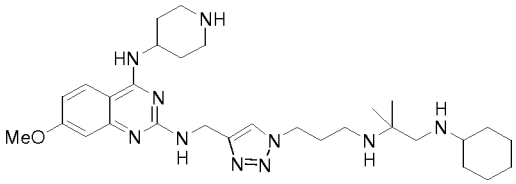

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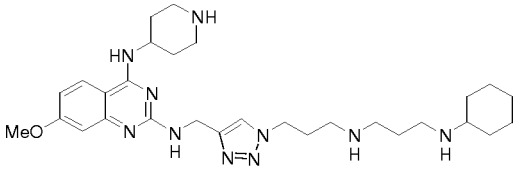

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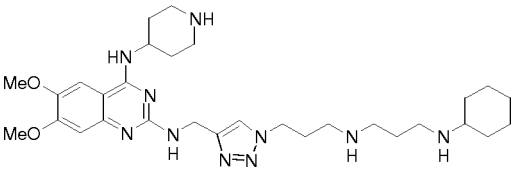

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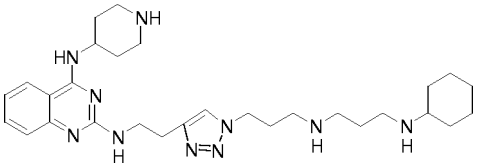

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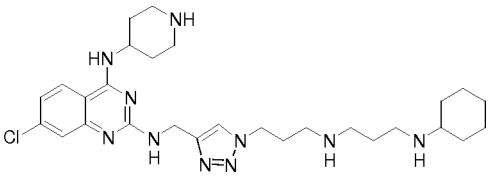

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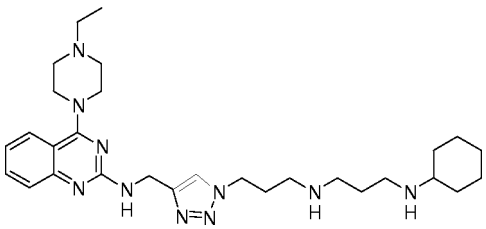

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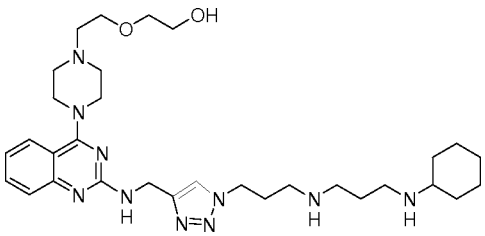

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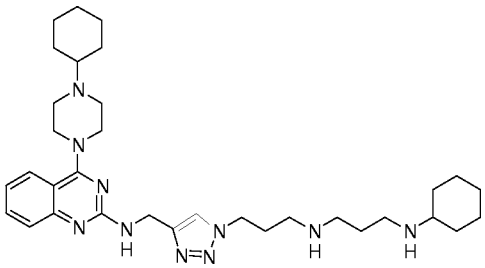

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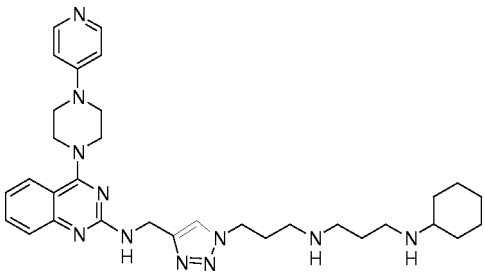

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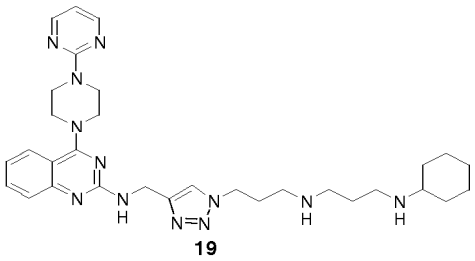

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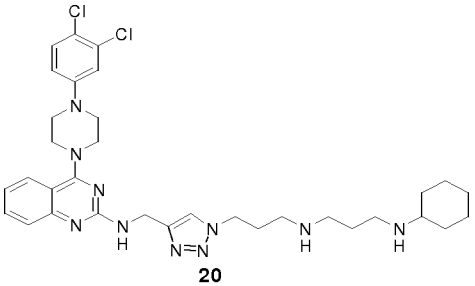

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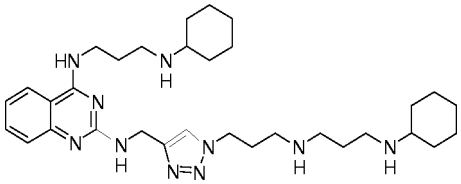

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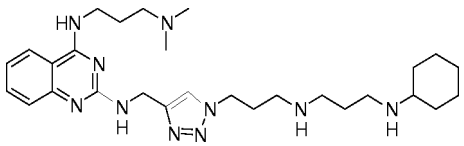

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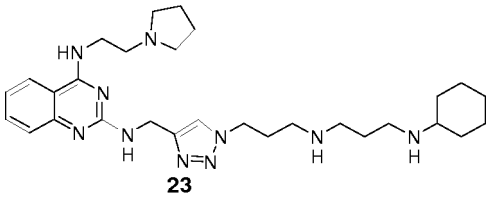

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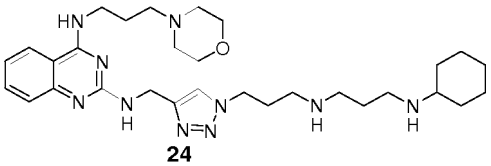

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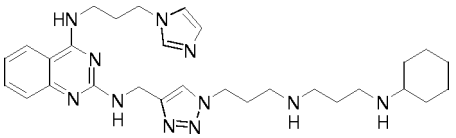

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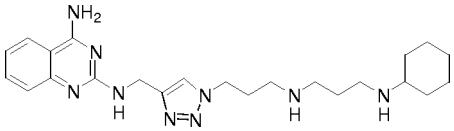

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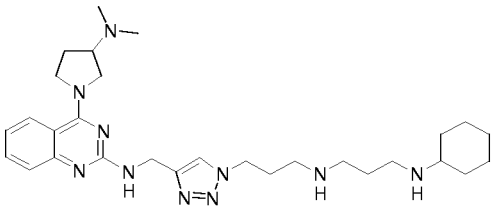

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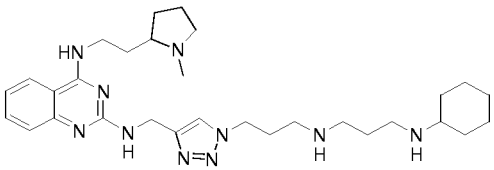

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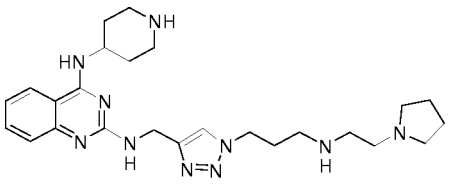

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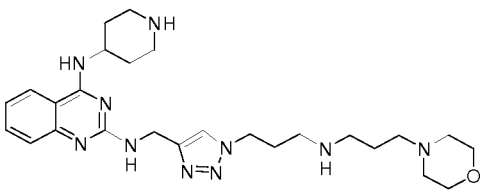

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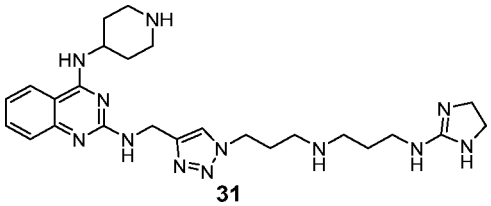

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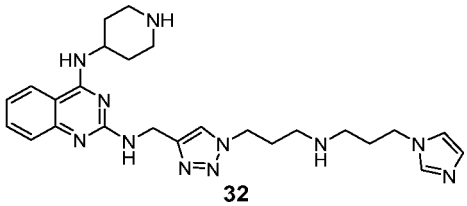

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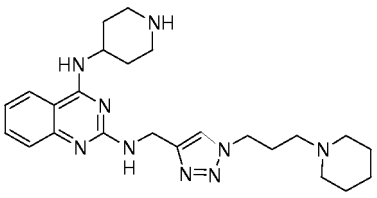

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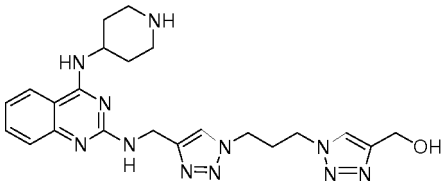

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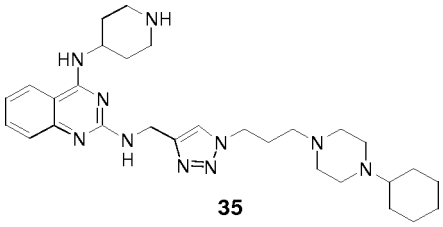

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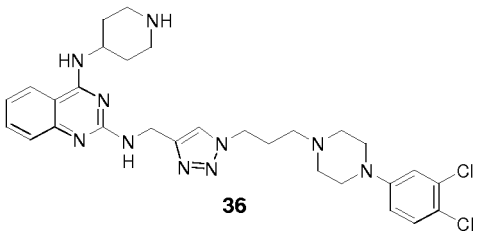

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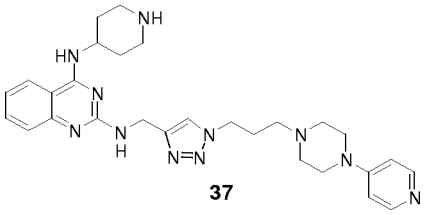

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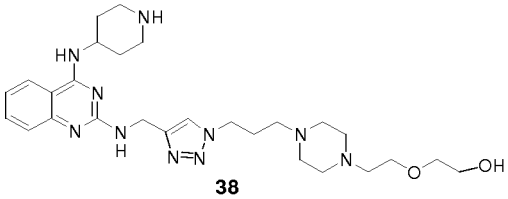

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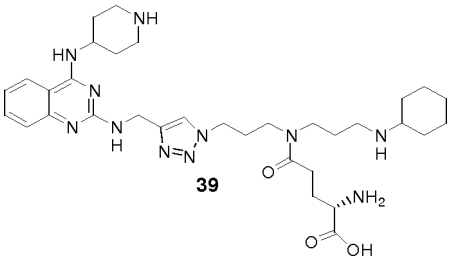

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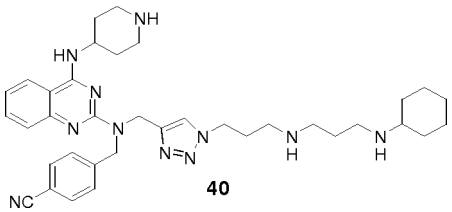

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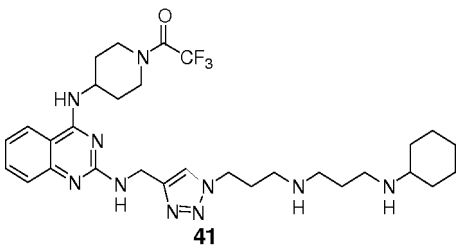

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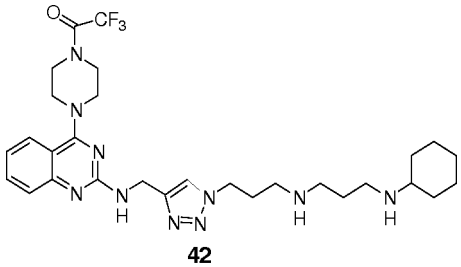

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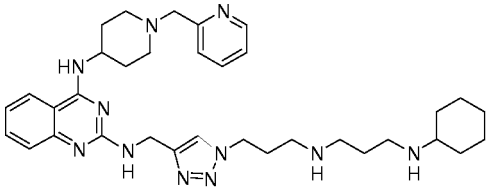

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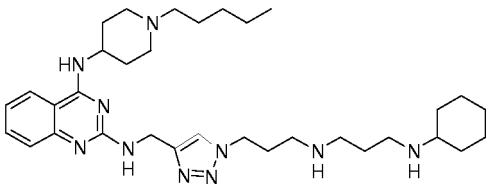

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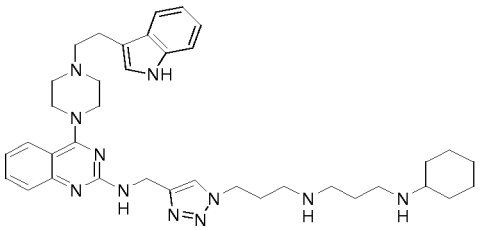

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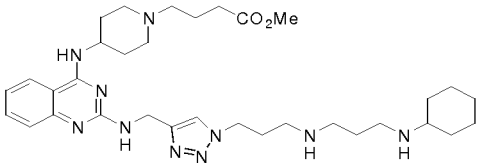

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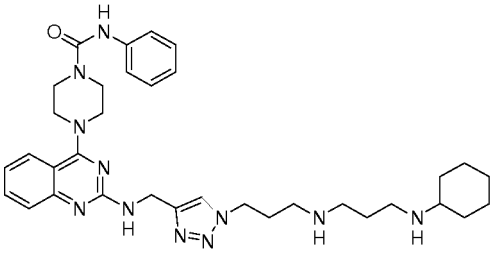

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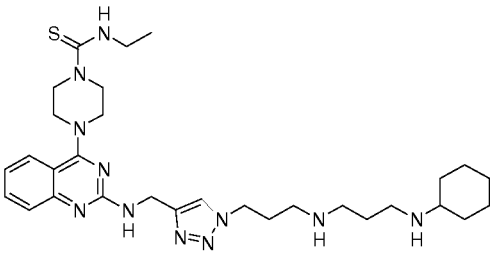

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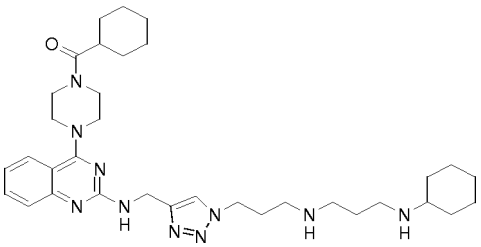

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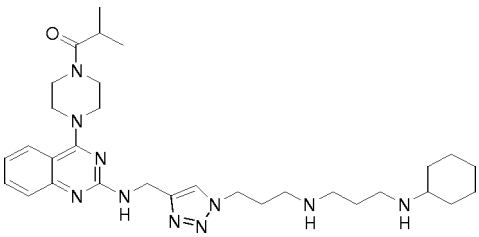

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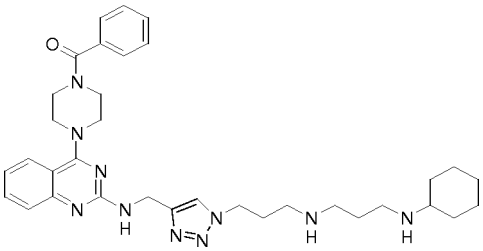

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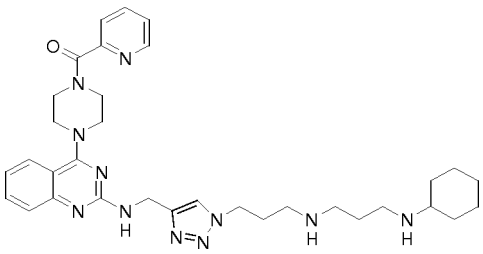

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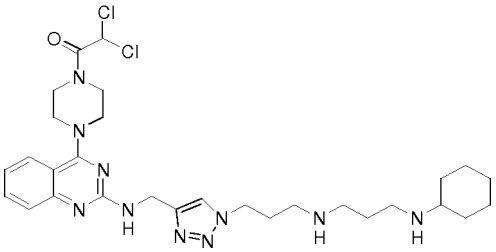

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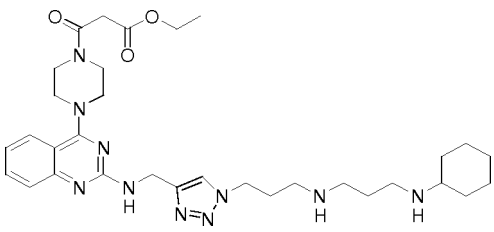

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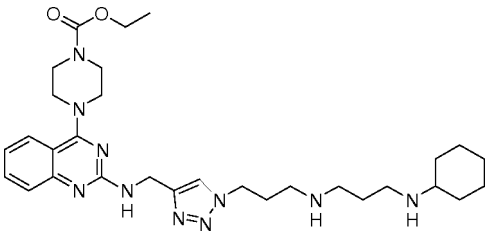

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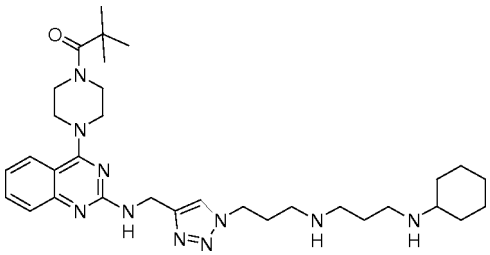

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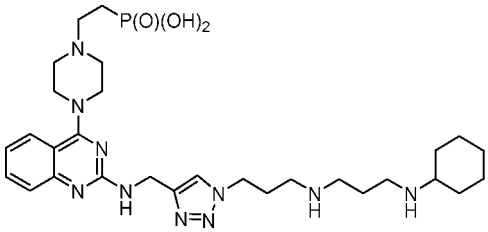

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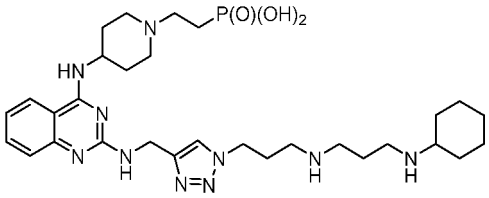

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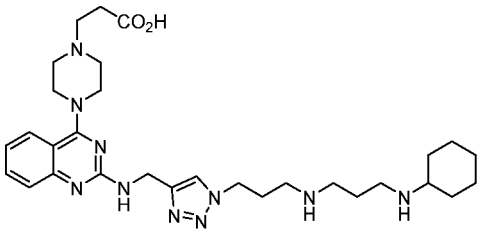

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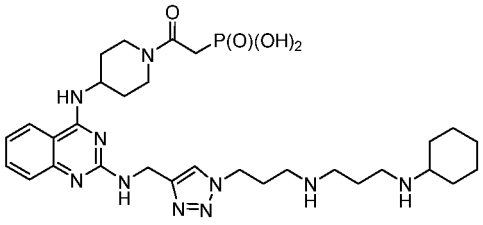

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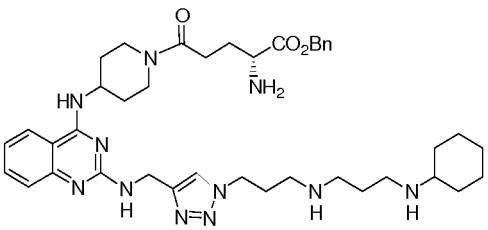

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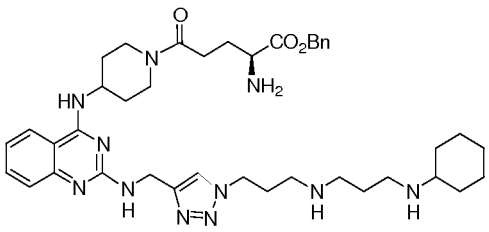

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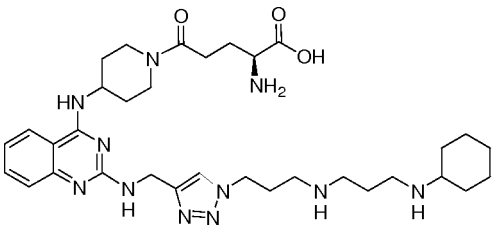

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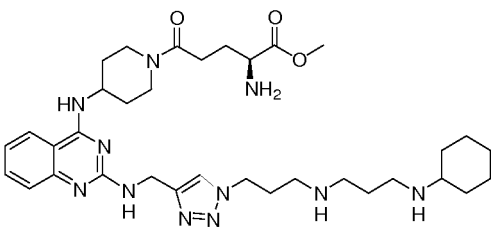

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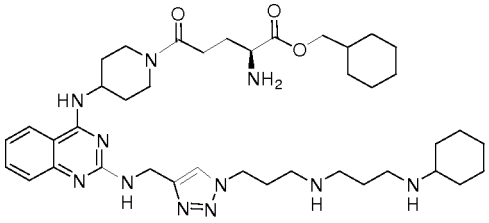

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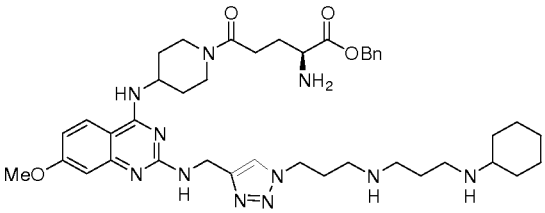

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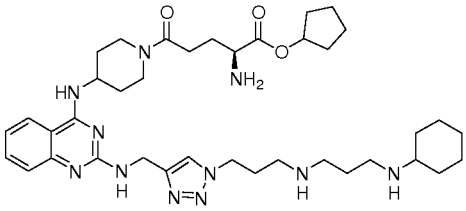

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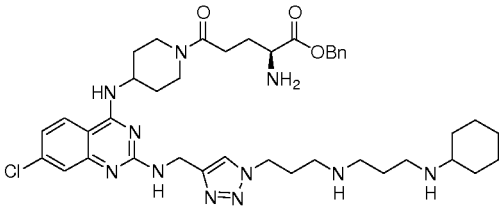

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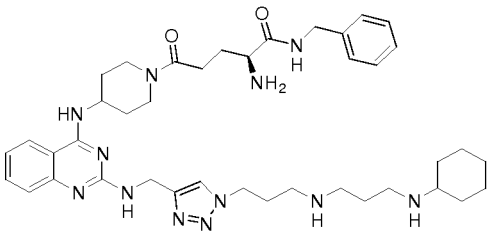

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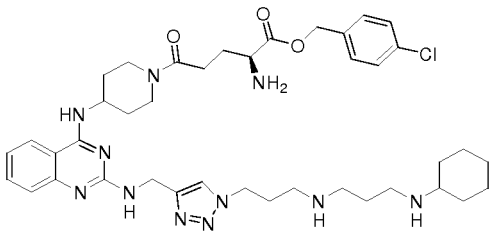

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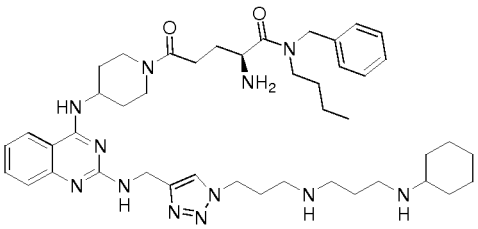

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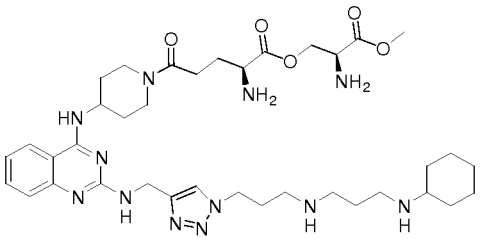

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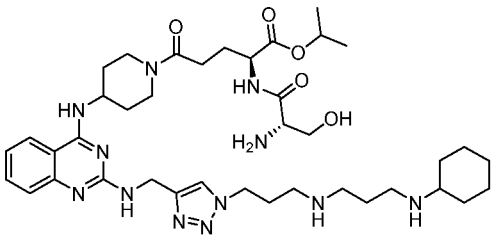

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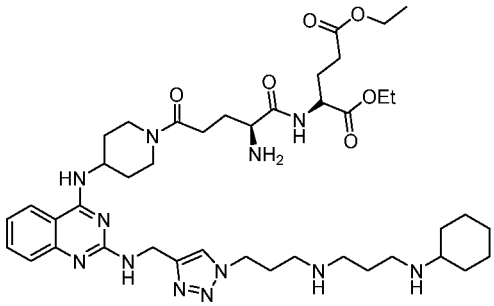

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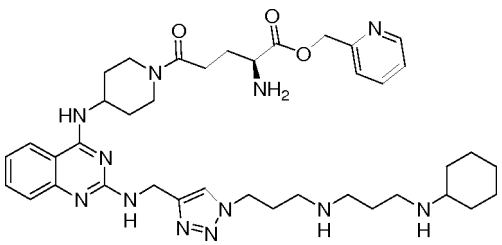

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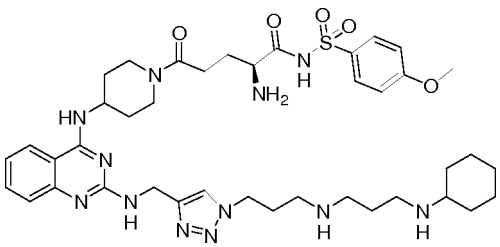

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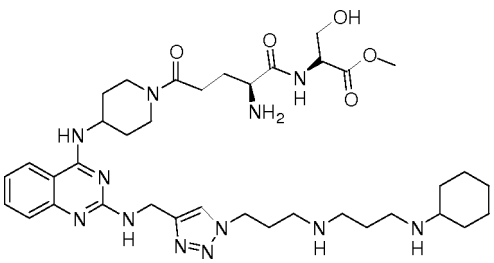

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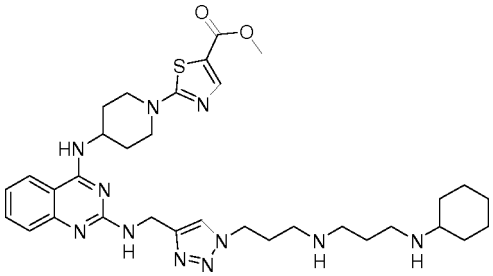

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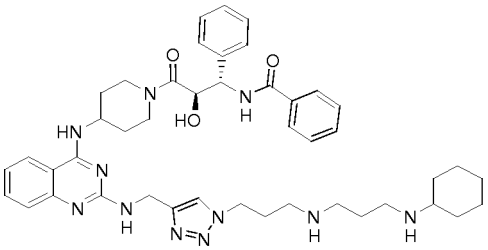

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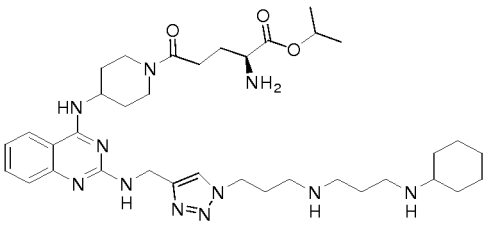

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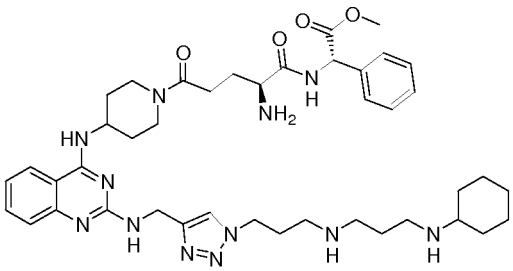

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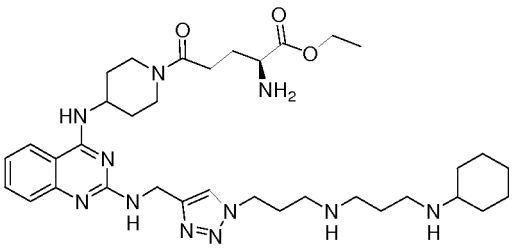

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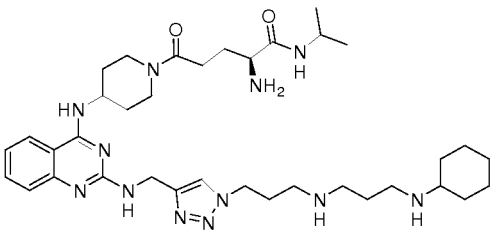

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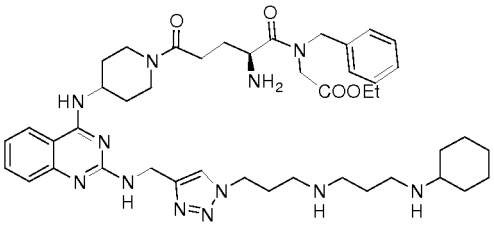

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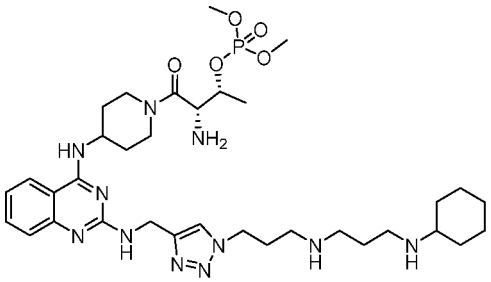

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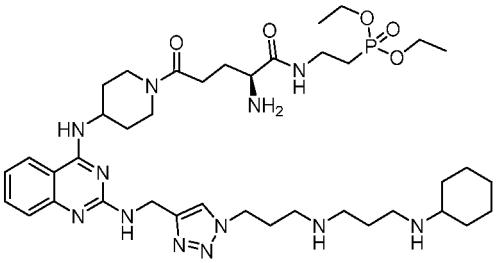

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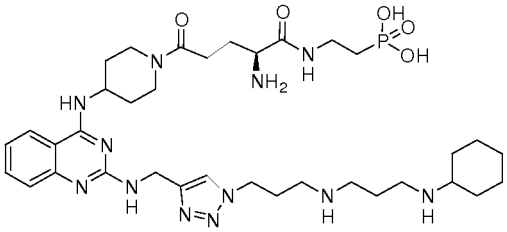

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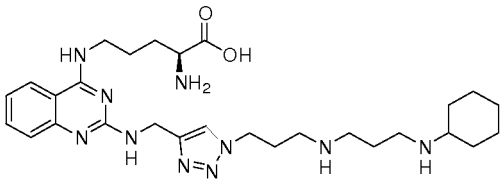

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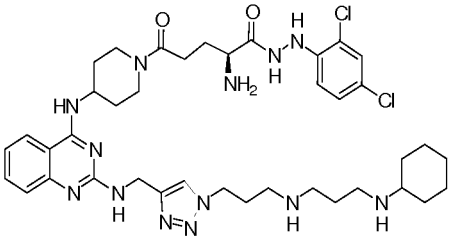

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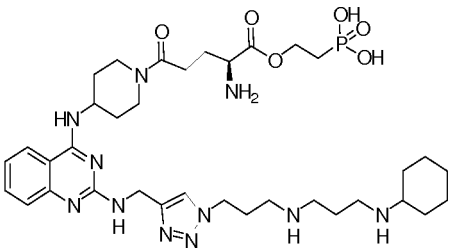

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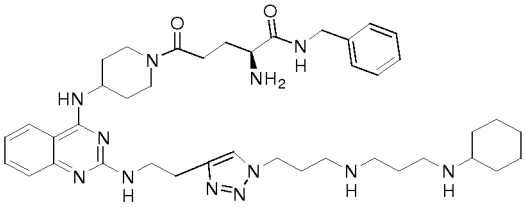

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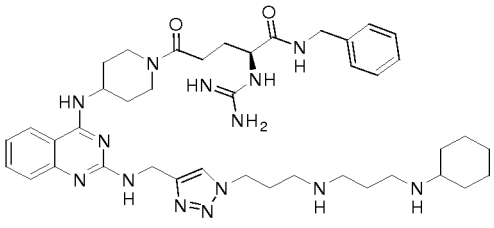

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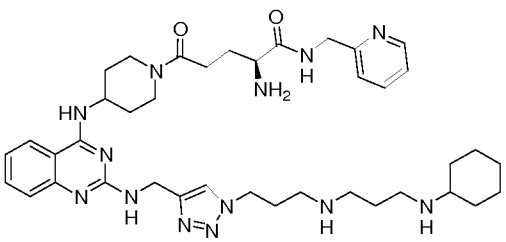

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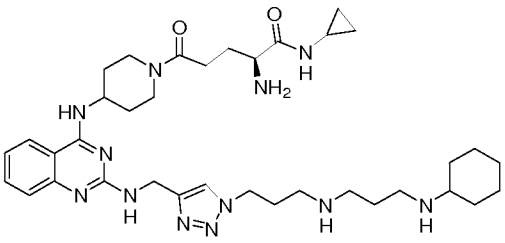

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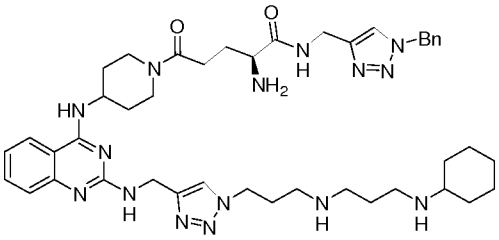

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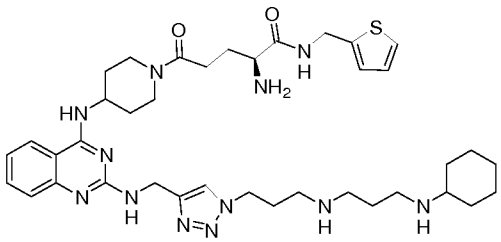

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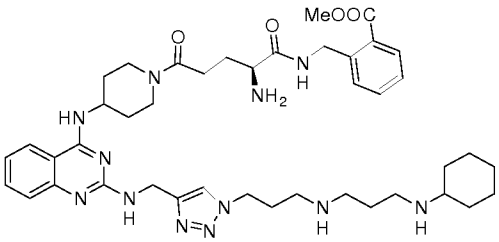

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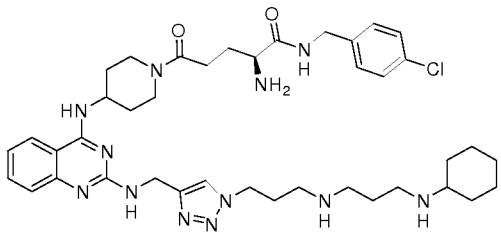

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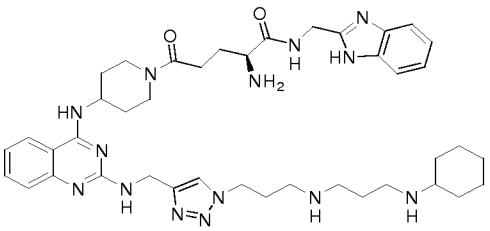

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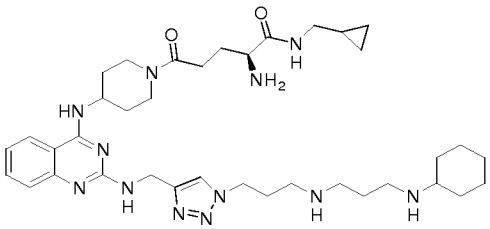

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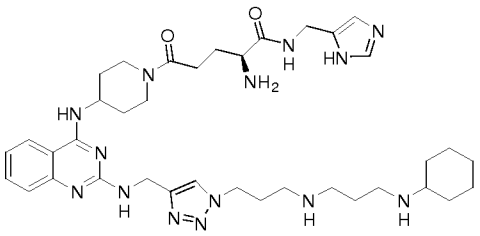

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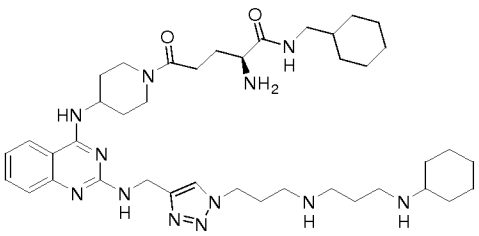

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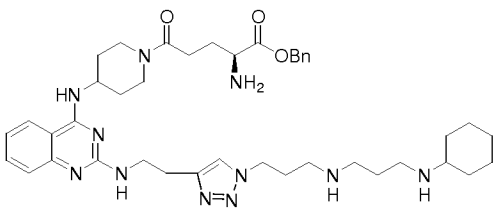

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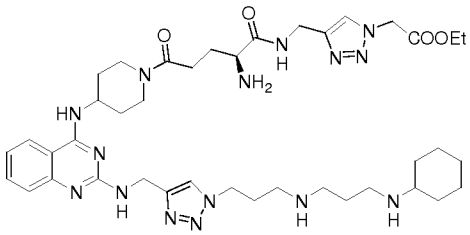

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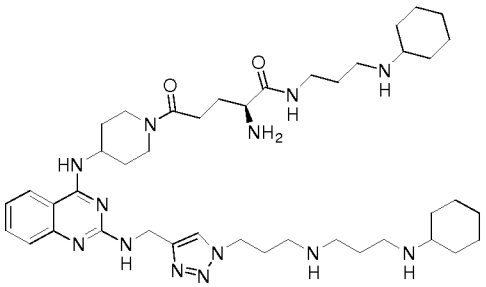

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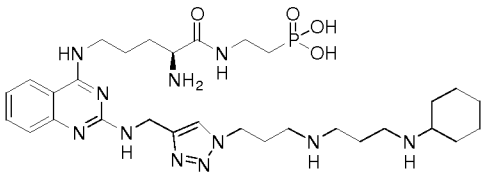

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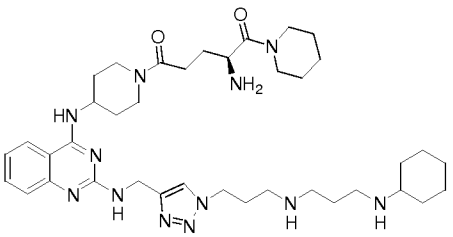

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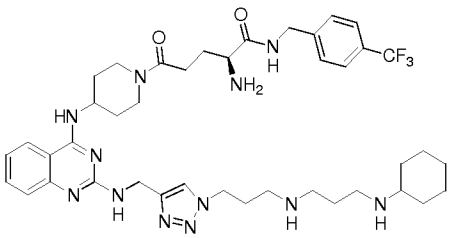

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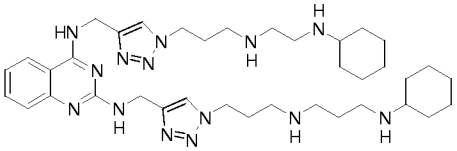

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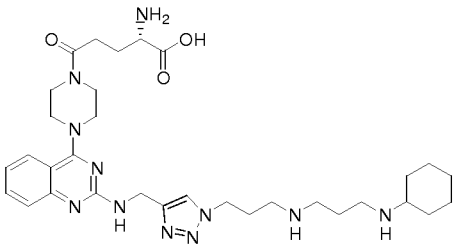

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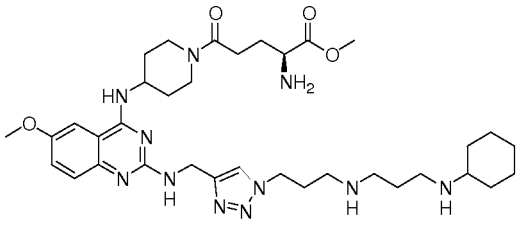

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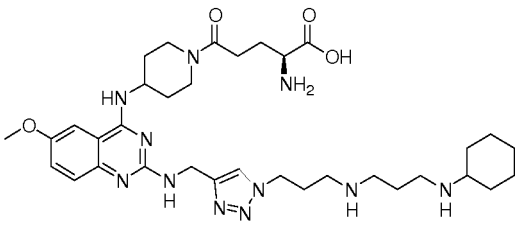

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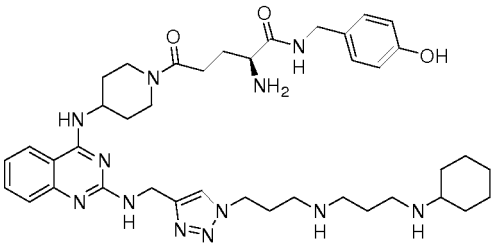

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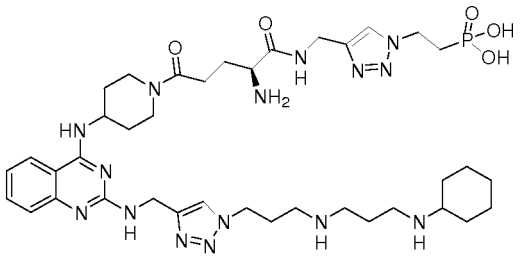

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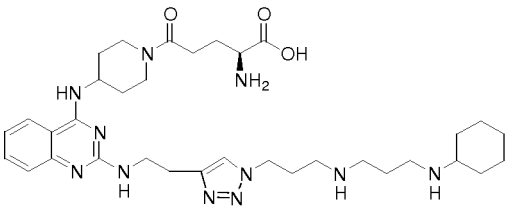

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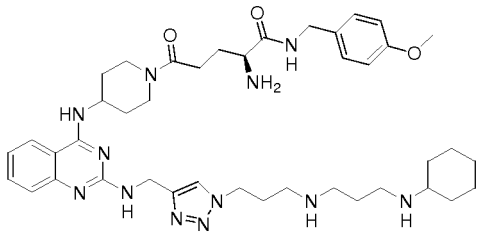

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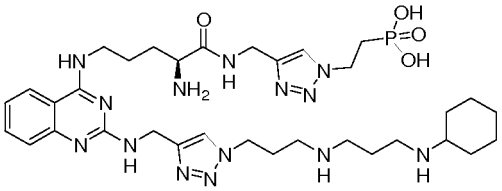

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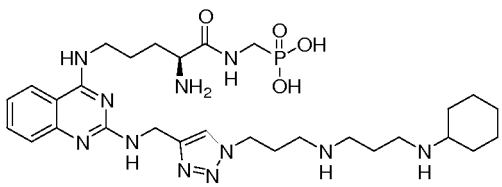

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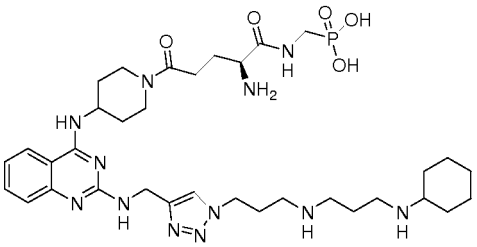

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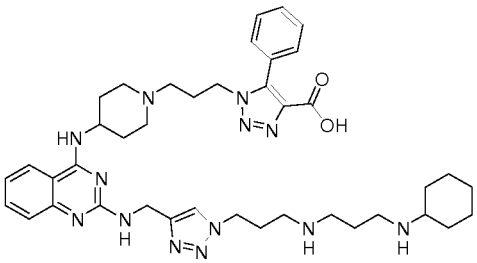

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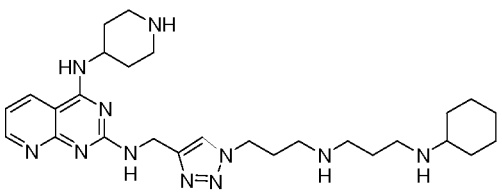

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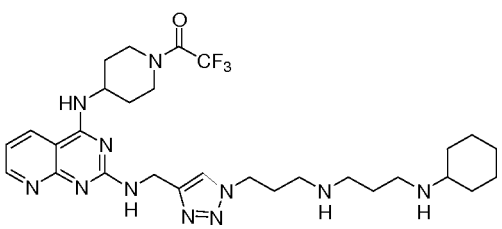

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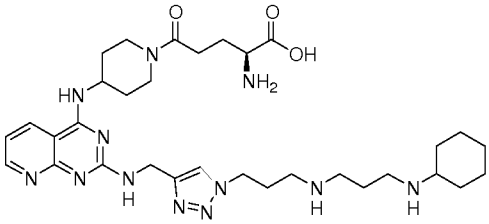

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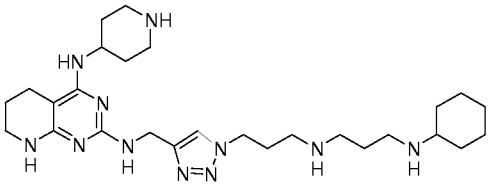

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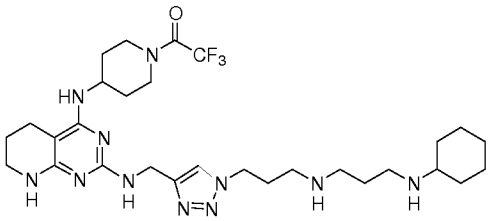

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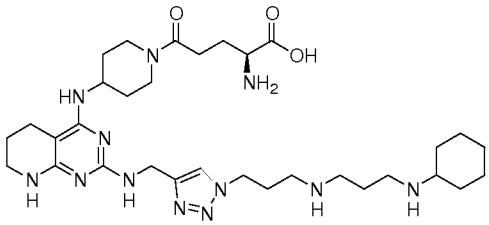

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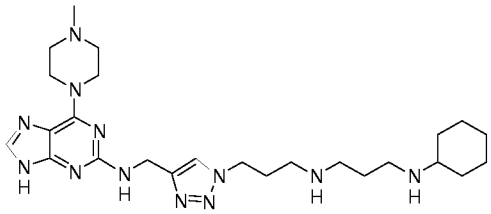

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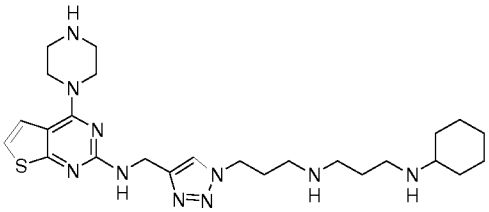

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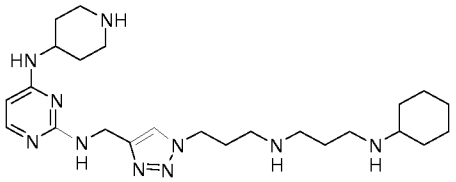

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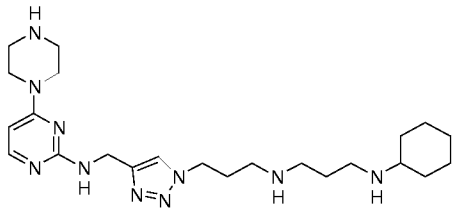

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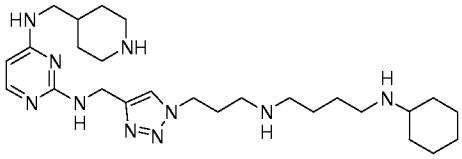

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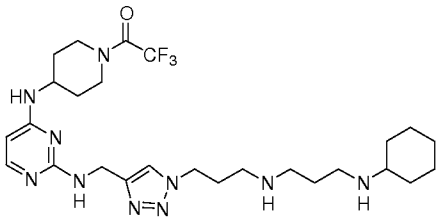

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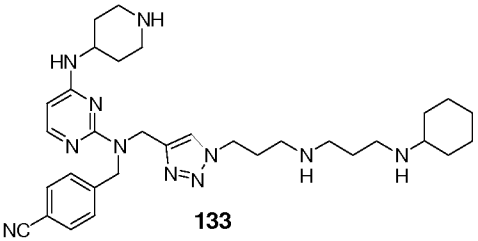

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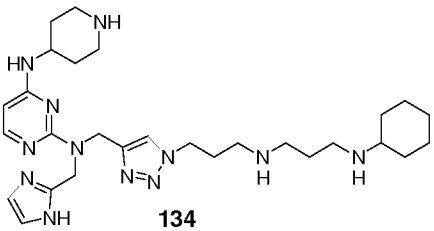

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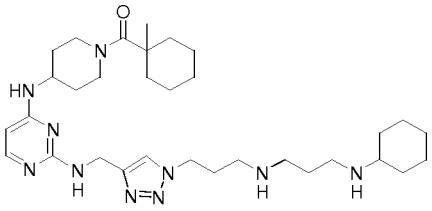

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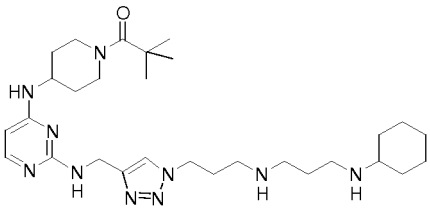

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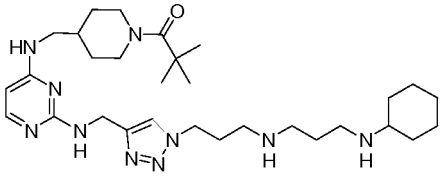

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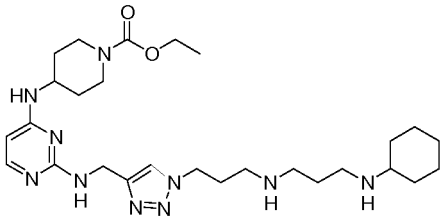

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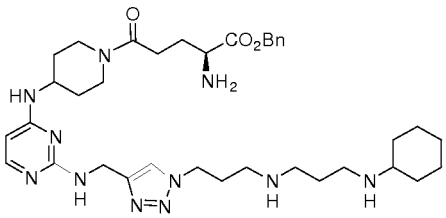

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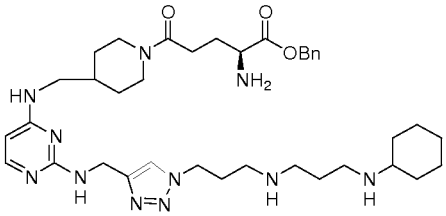

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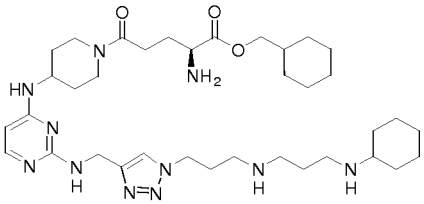

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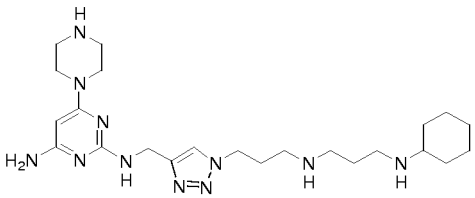

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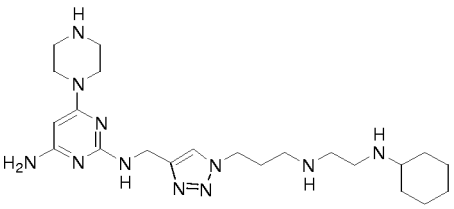

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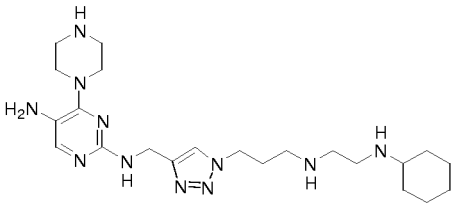

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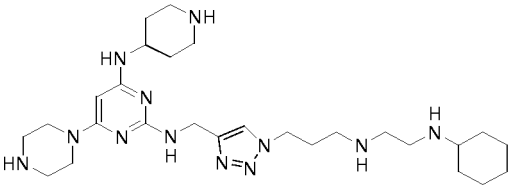

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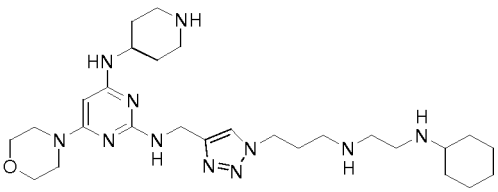

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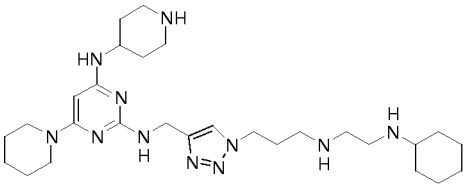

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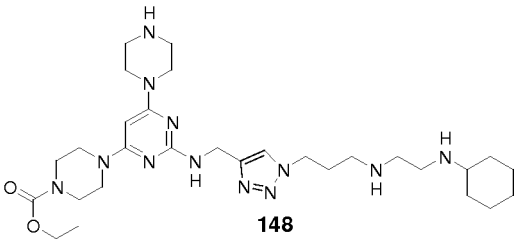

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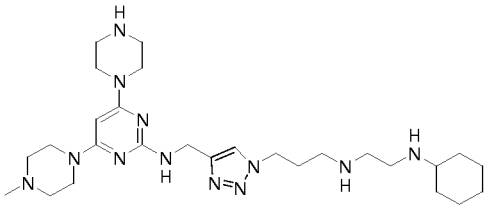

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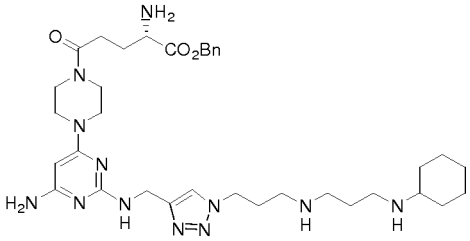

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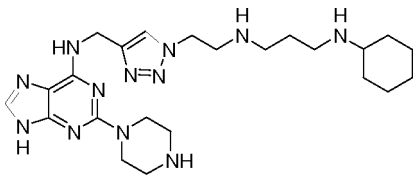

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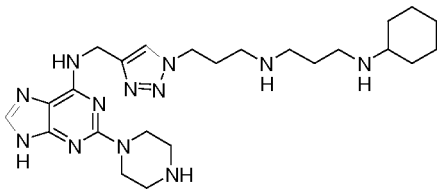

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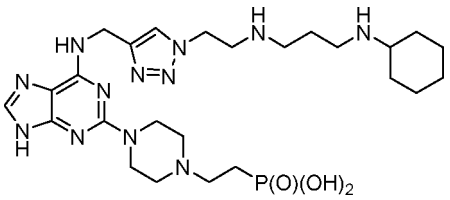

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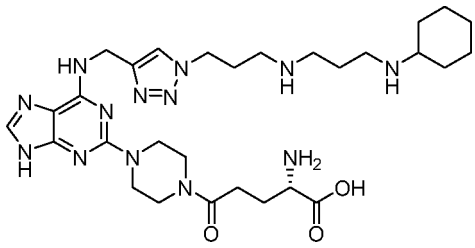

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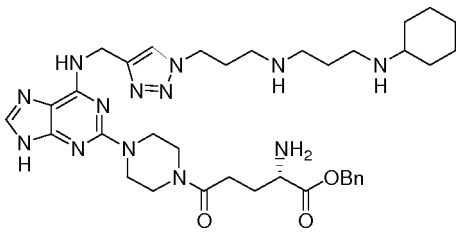

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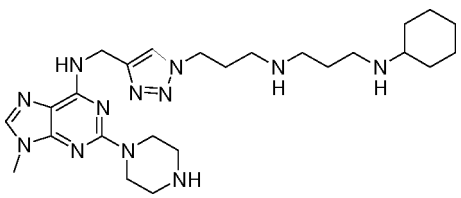

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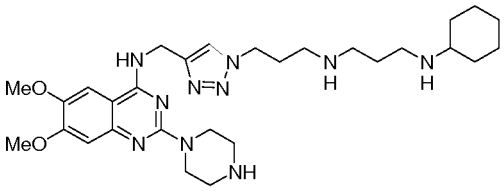

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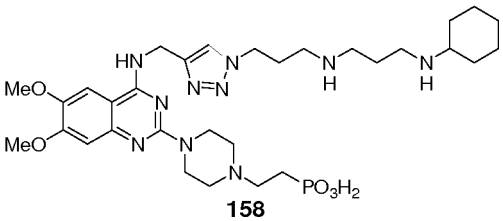

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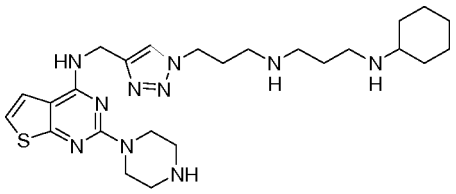

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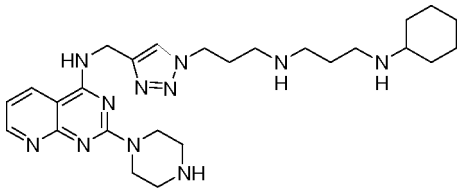

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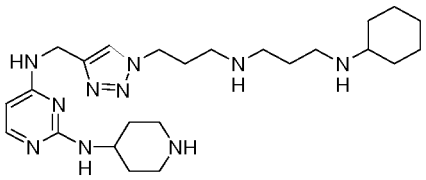

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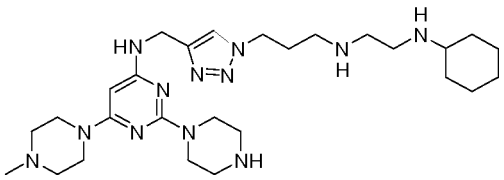

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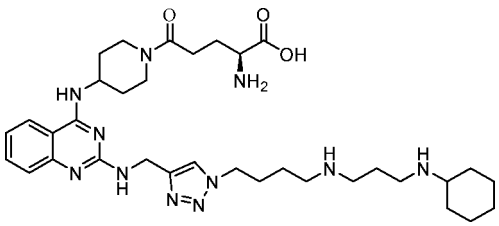

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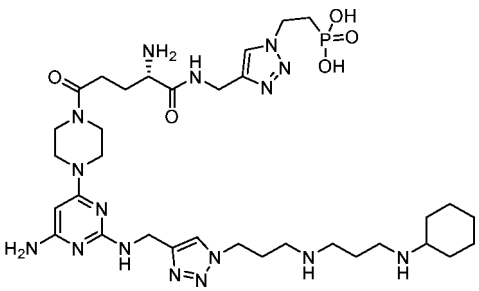

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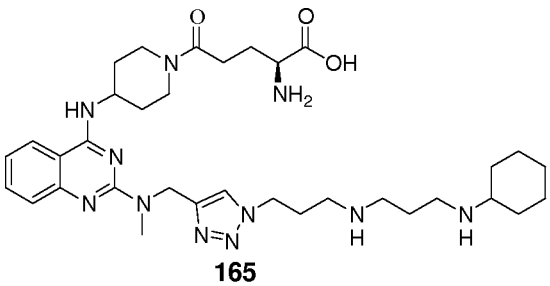

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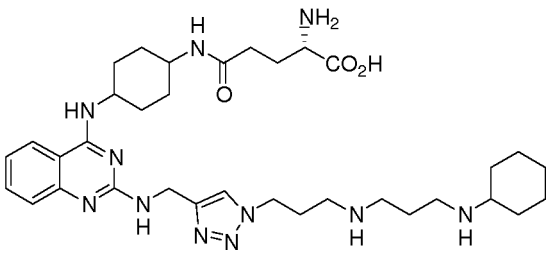

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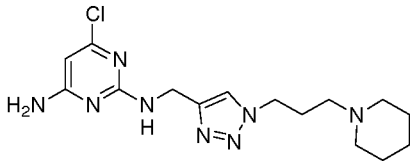

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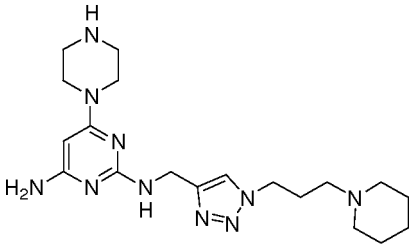

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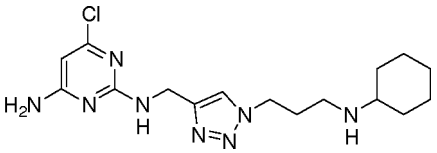

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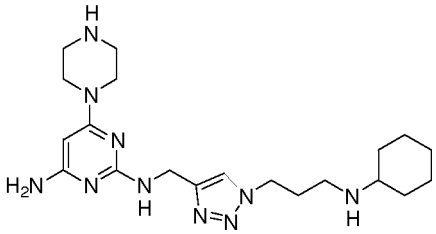

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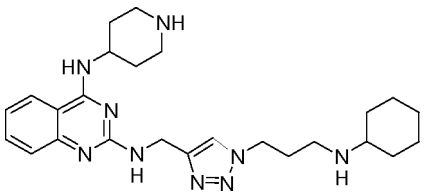

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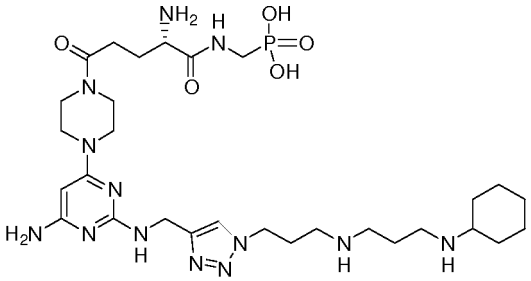

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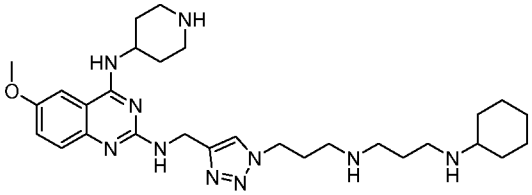

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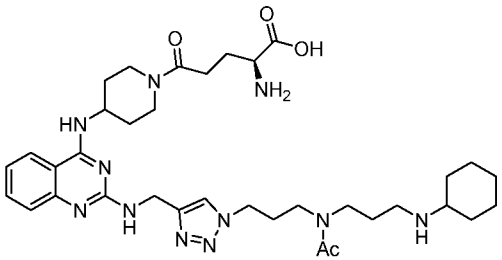

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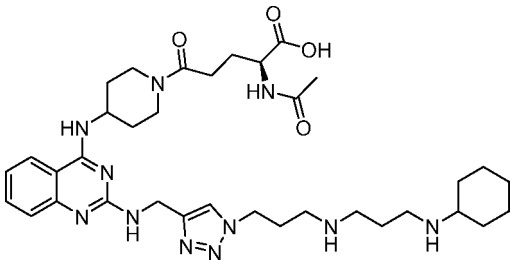

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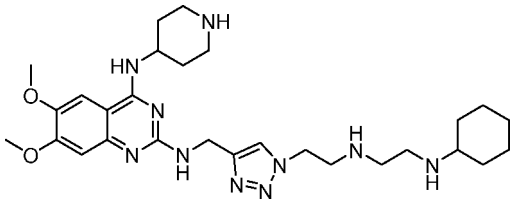

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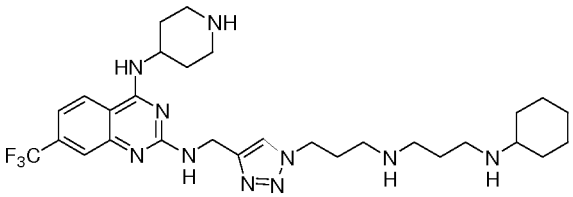

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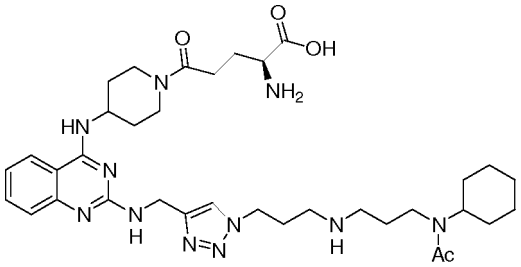

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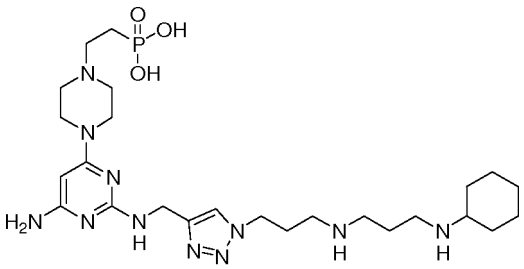

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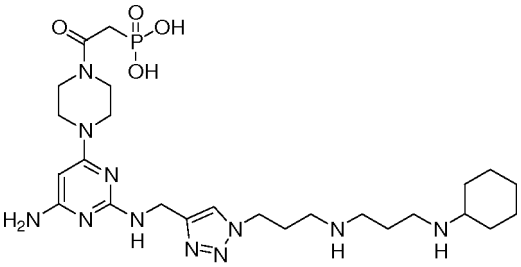

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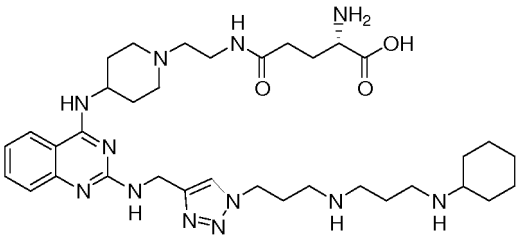

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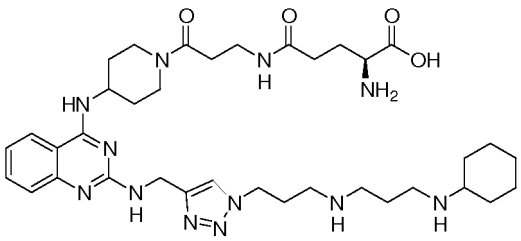

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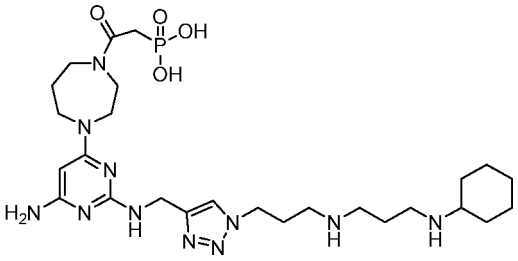

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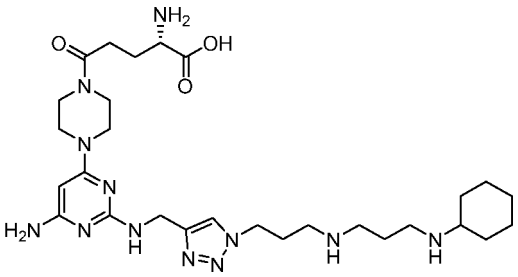

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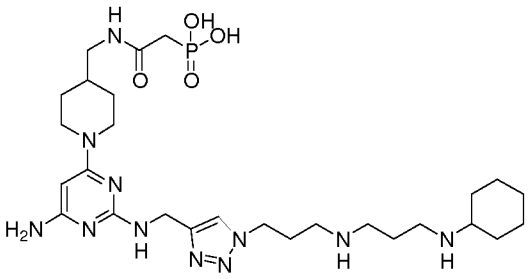

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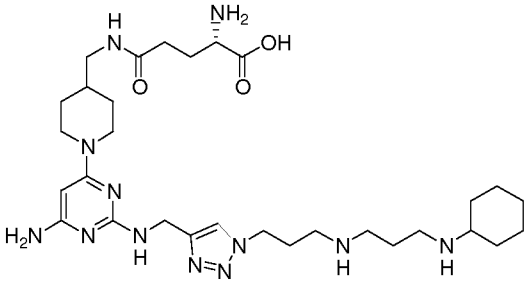

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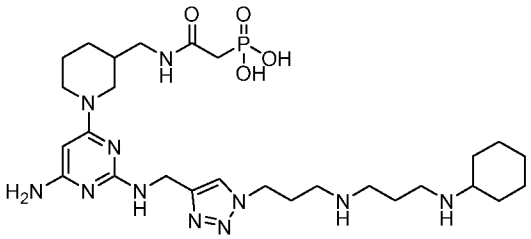

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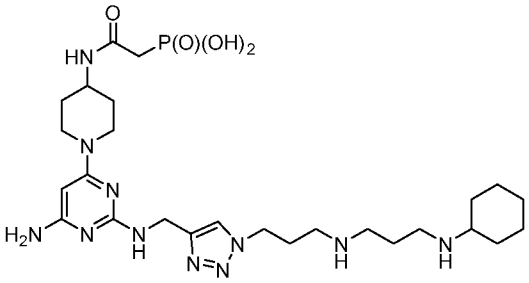

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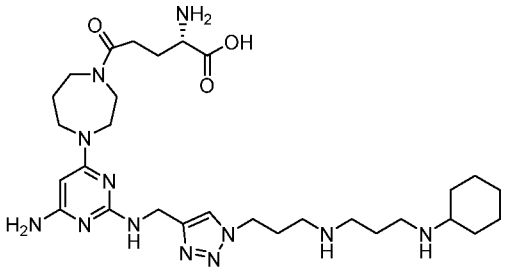

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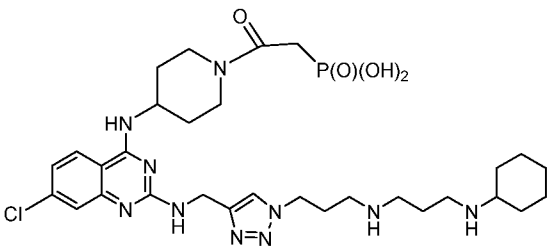

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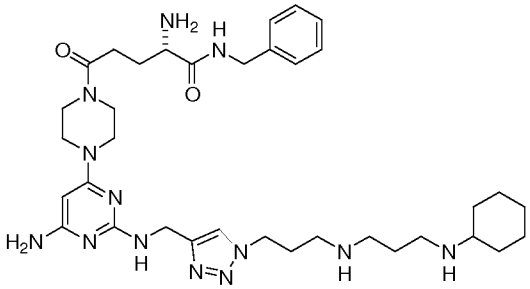

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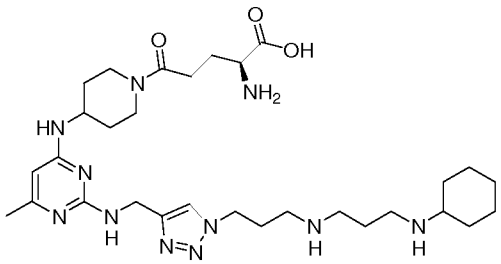

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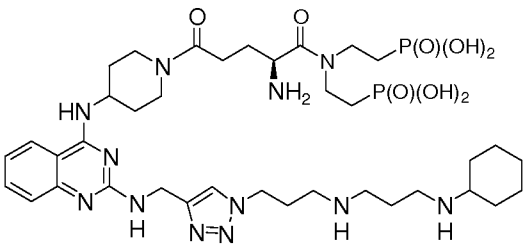

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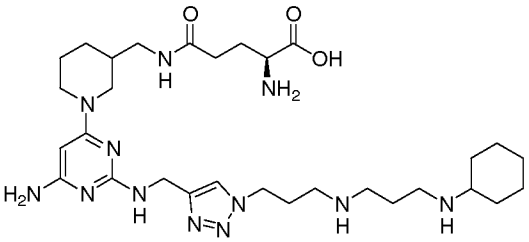

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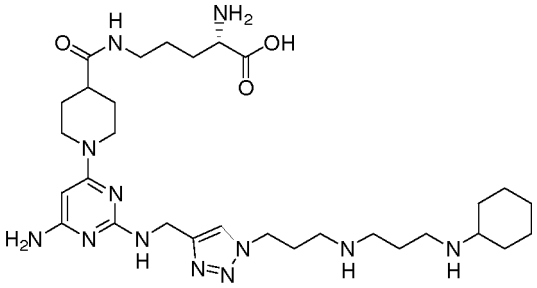

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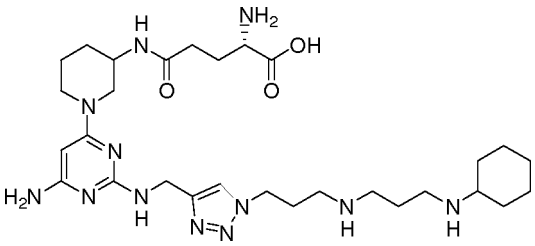

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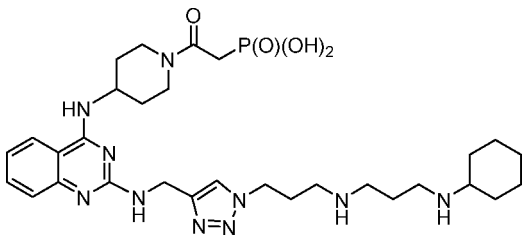

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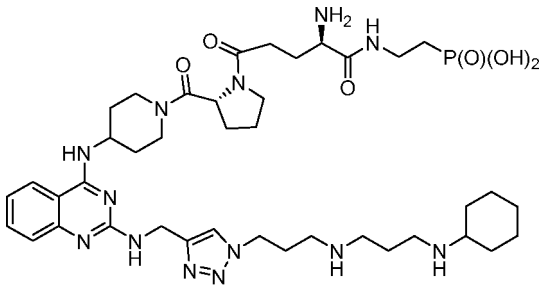

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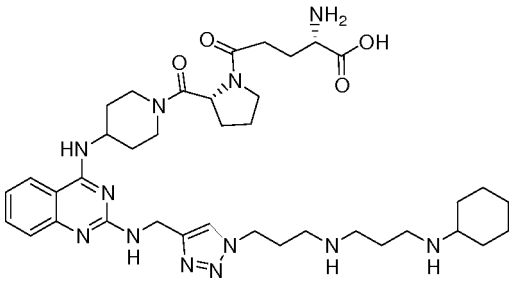

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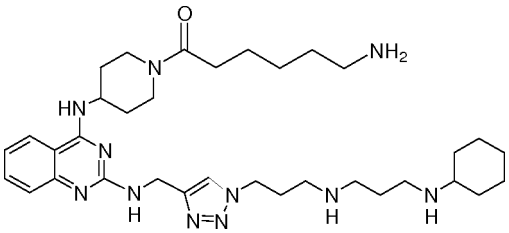

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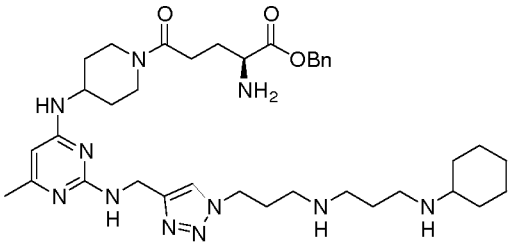

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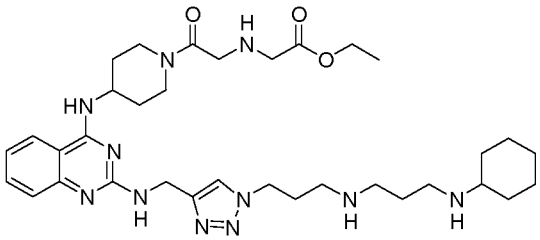

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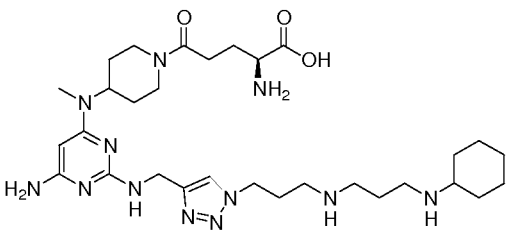

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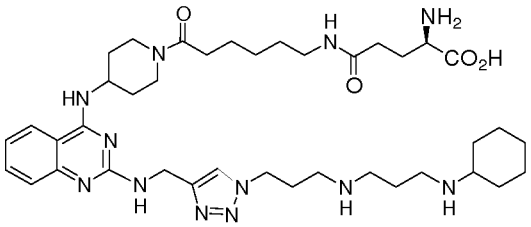

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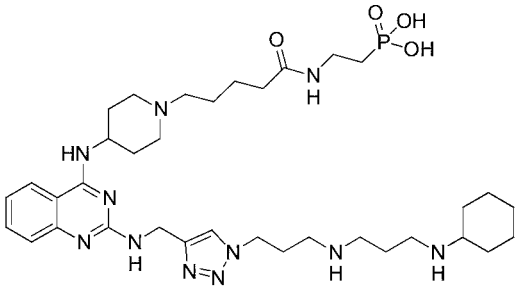

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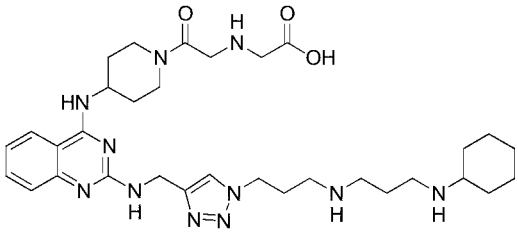

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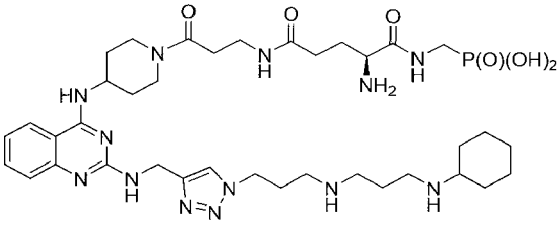

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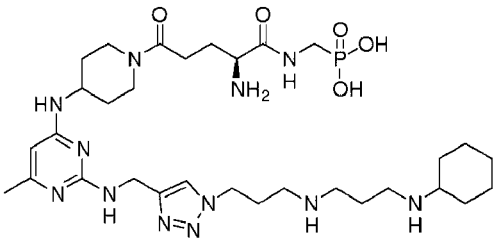

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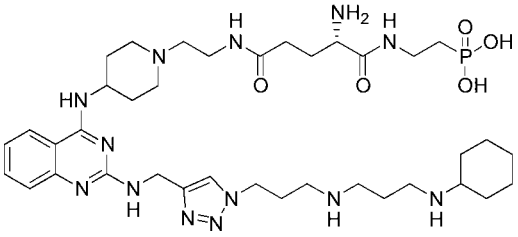

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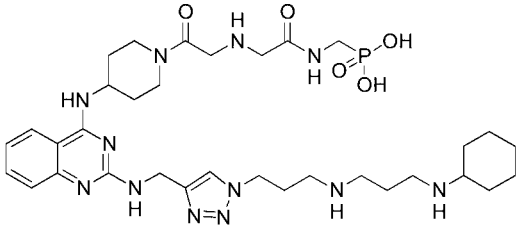

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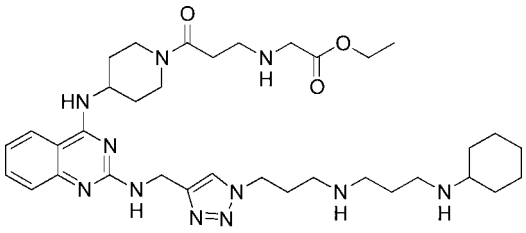

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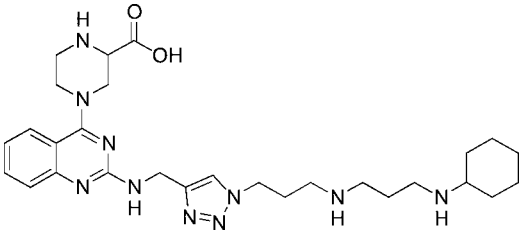

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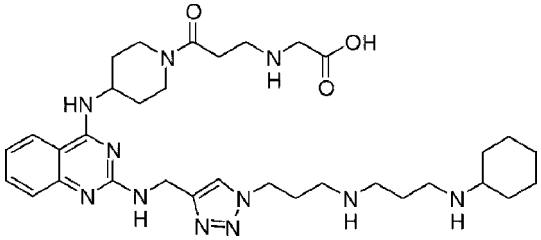

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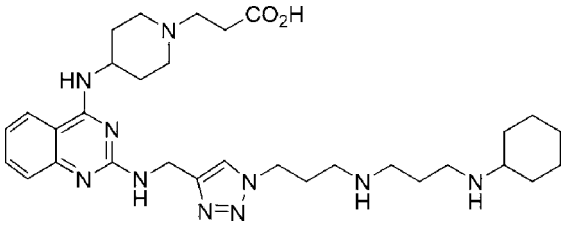

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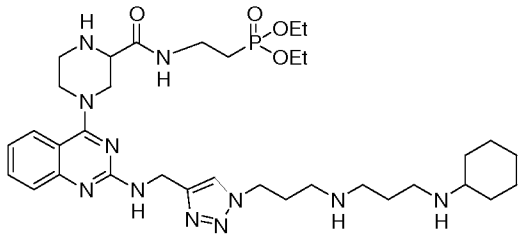

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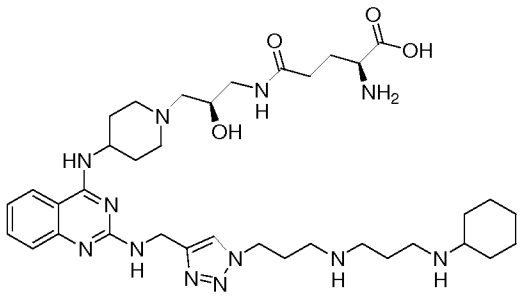

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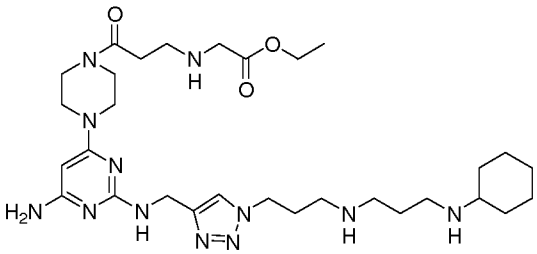

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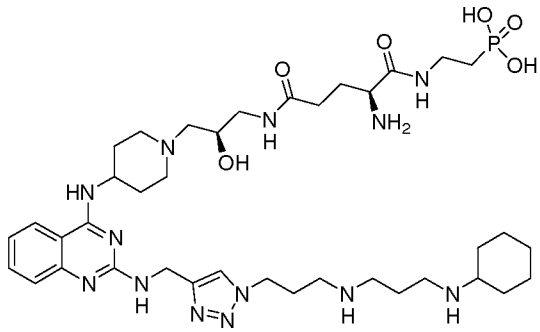

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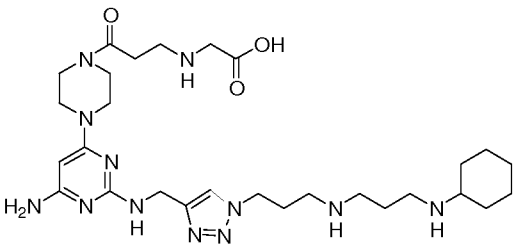

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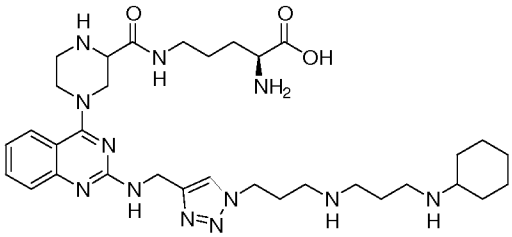

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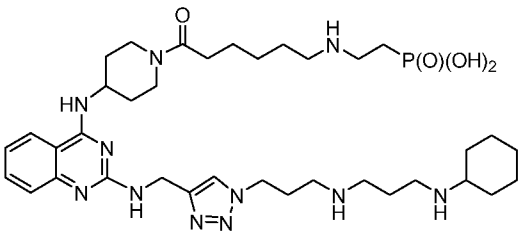

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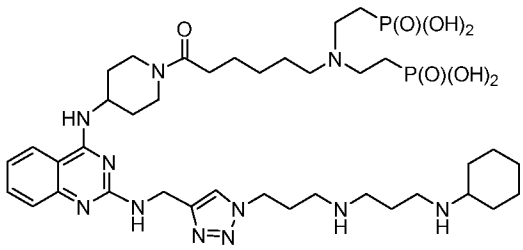

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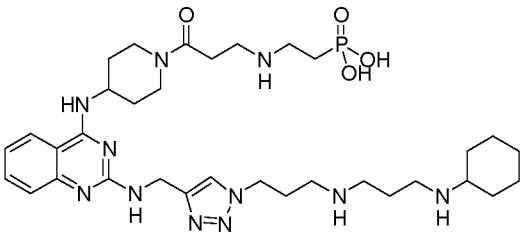

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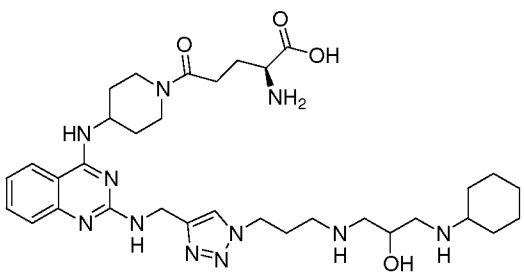

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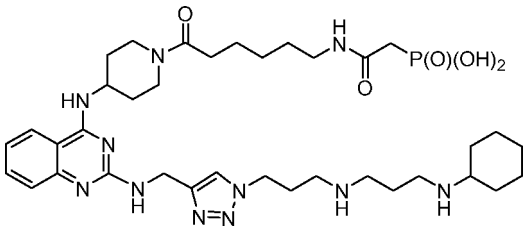

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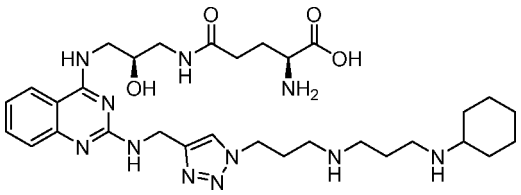

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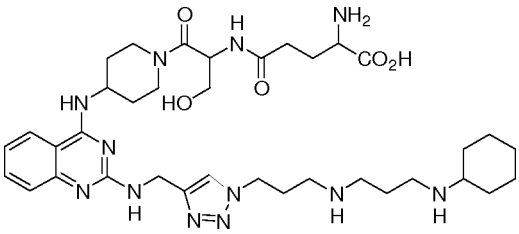

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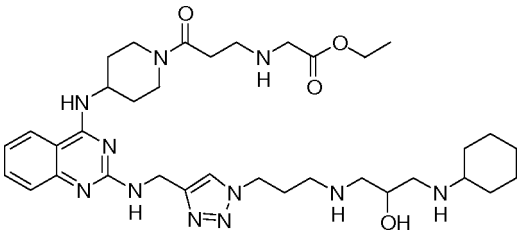

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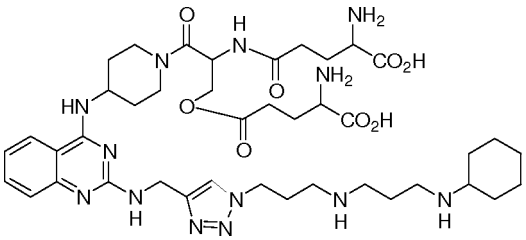

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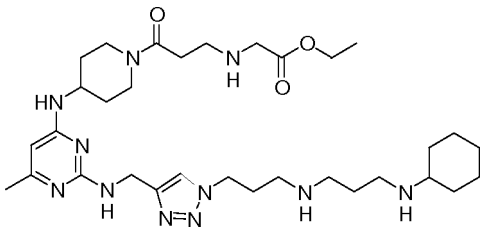

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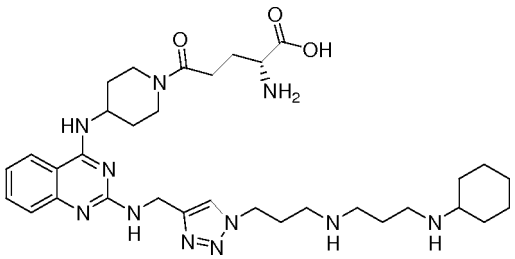

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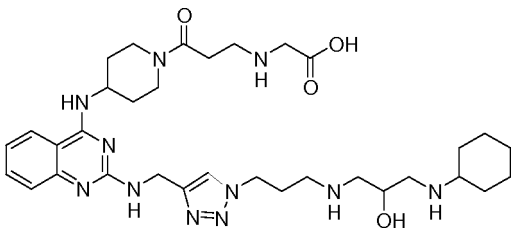

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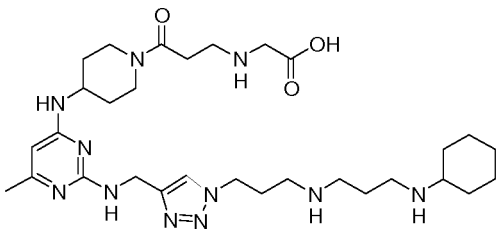

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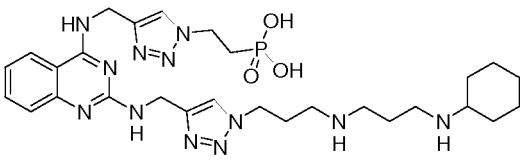

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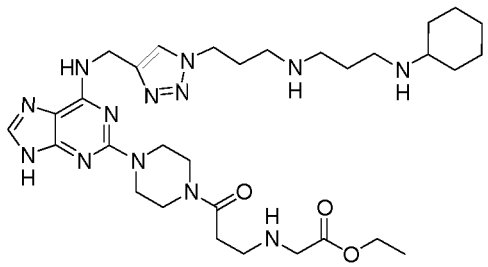

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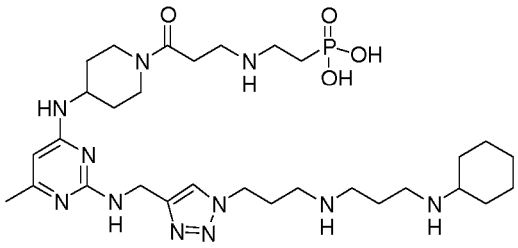

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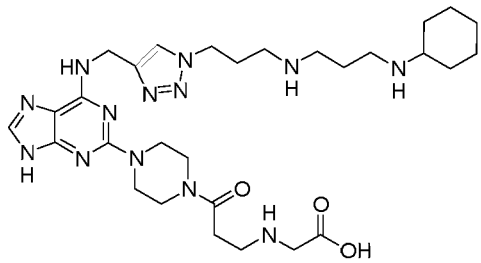

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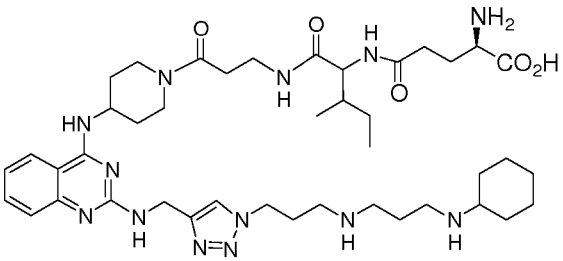

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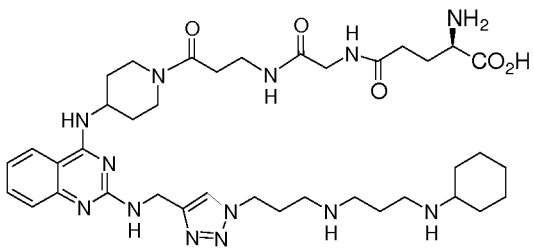

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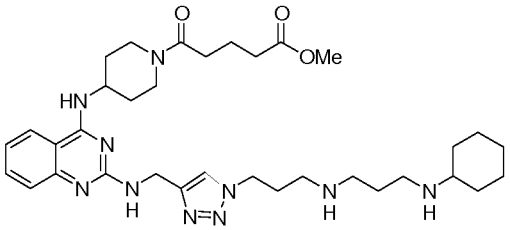

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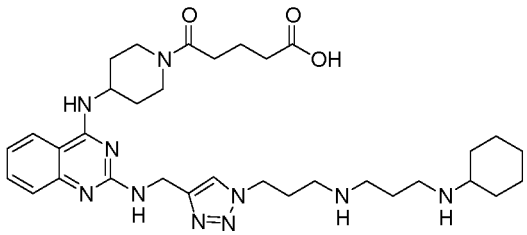

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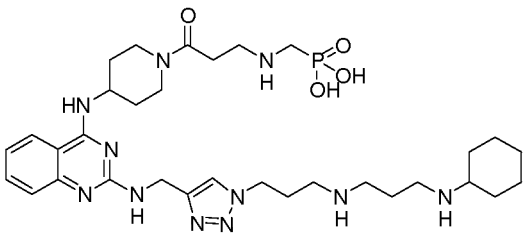

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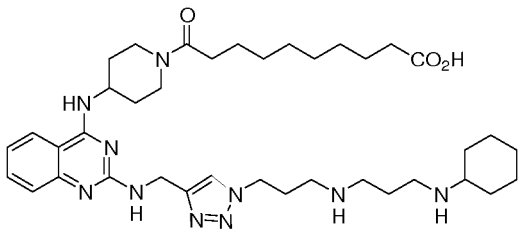

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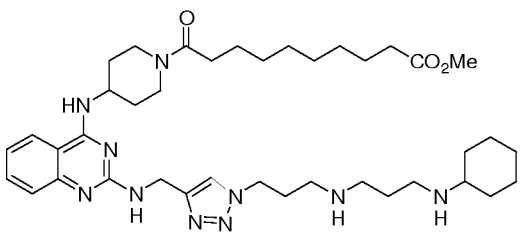

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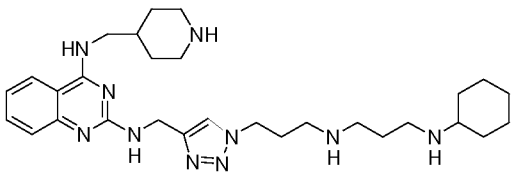

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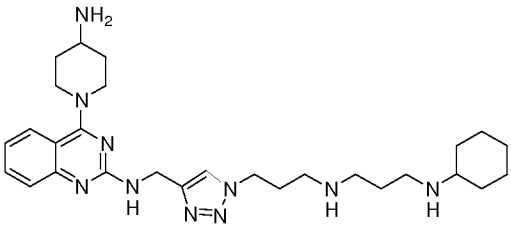

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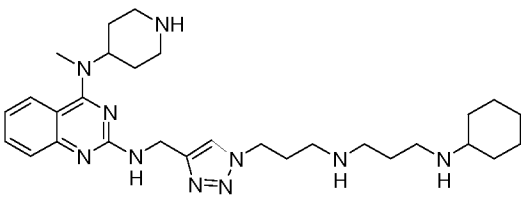

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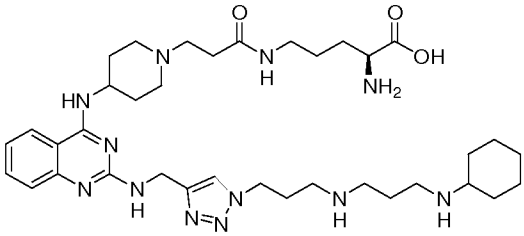

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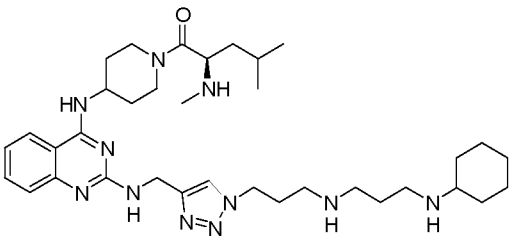

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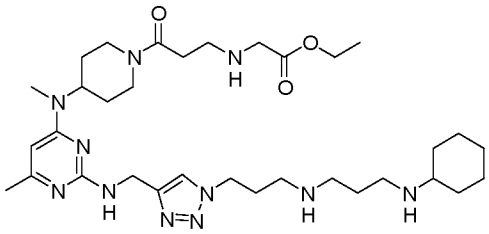

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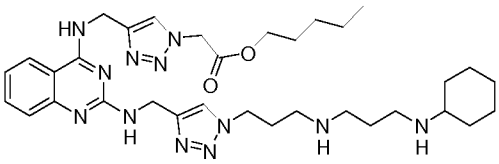

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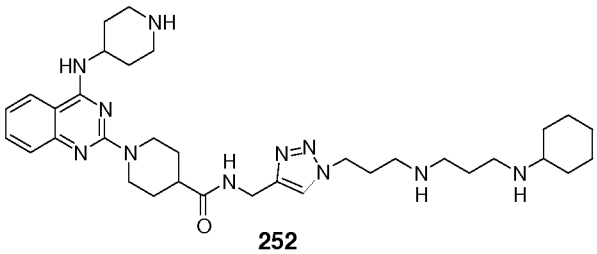

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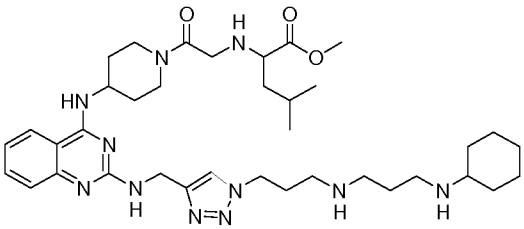

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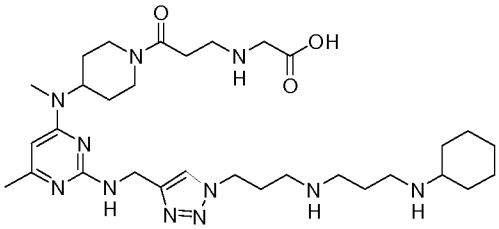

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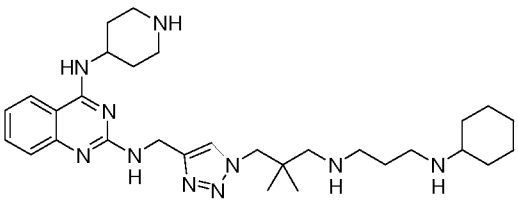

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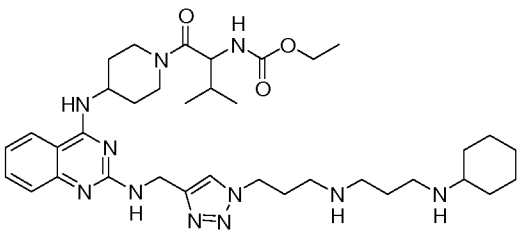

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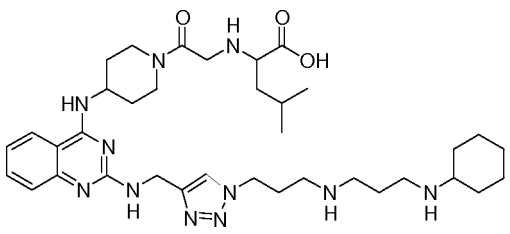

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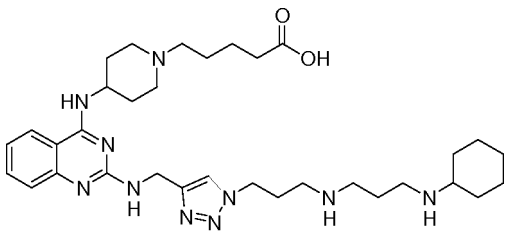

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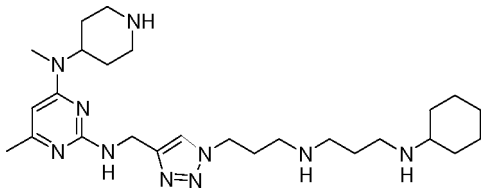

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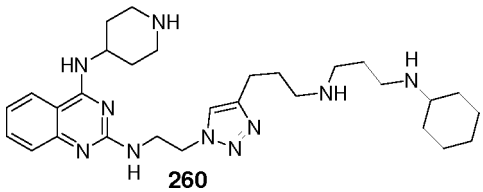

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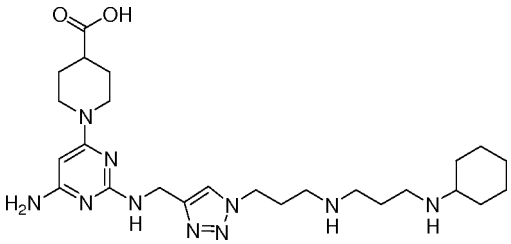

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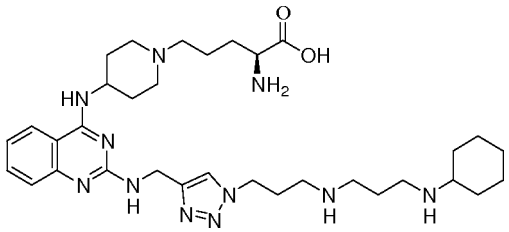

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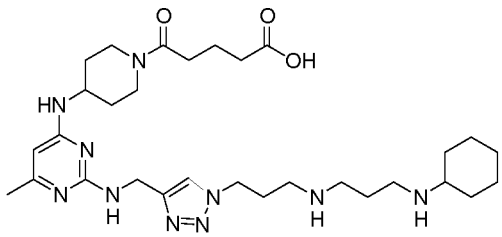

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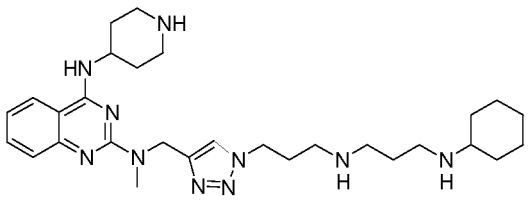

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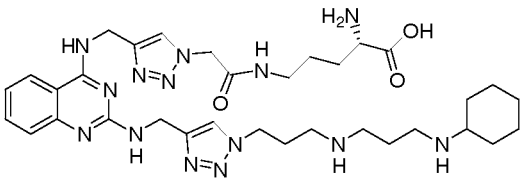

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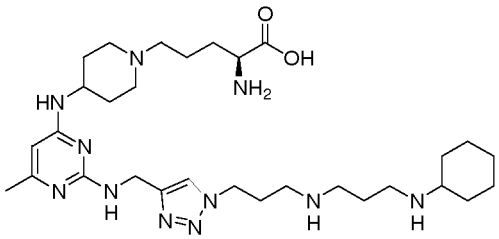

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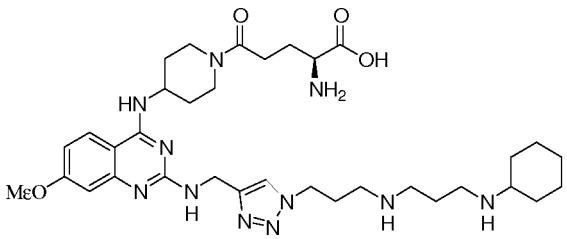

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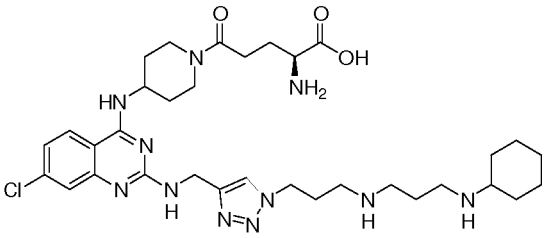

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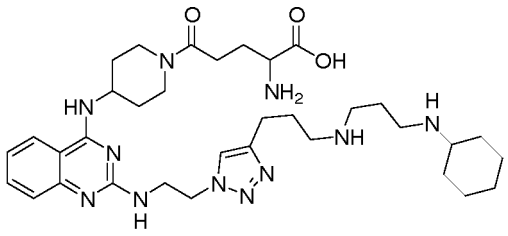

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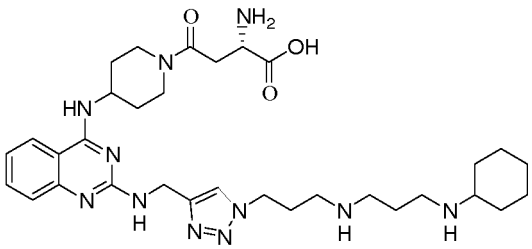

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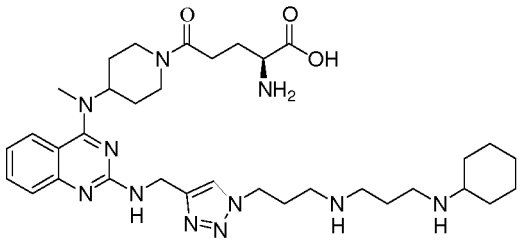

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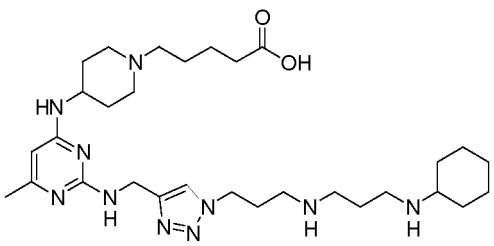

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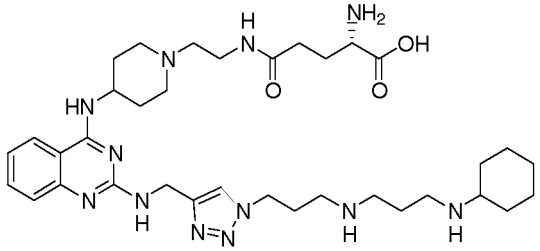


273

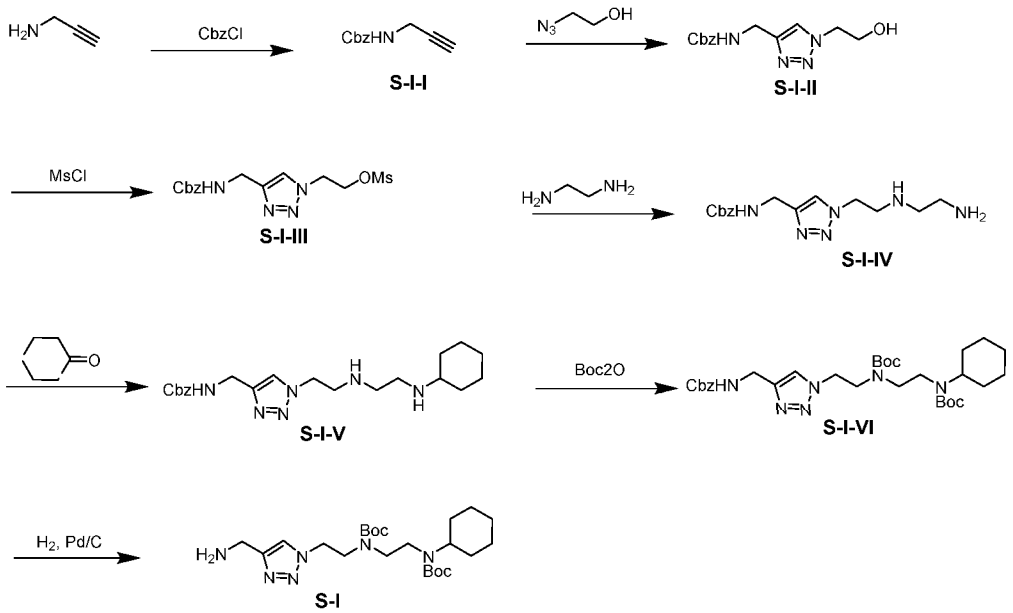
Described below are procedures for preparing four side chains, i.e., S-I, S-II, S-III and S-IV that were used to synthesize the exemplary 273 compounds. Note that side chains S-II, S-III and S-IV were prepared in a manner similar to that used to prepare side chain S-I.

All chemicals and solvents were purchased from commercial suppliers and used as received. All reactions were carried out under an atmosphere of dry nitrogen. Reactions were monitored by TLC using Merck 60 F254 silica gel glass backed plates (5 × 10 cm); and zones were detected visually under ultraviolet irradiation (254 nm) or by spraying with phosphomolybdic acid reagent (Aldrich) followed by heating at 80 °C. All flash column chromatography was performed with Merck Kieselgel 60, No. 9385, 230-400 mesh ASTM silica gel as the stationary phase. Proton (^{1}H) nuclear magnetic resonance spectra were measured on a Varian Mercury-300 or Varian Mercury-400 spectrometer. Chemical shifts

were recorded in parts per million (ppm) on the delta (δ) scale relative to the resonance of the solvent peak. The following abbreviations were used to describe coupling: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; br = broad; and m = multiplet. LCMS data were measured on an Agilent MSD-1100 ESI-MS/MS, Agilent 1200 series LC/MSD VL, and Waters Acquity UPLC-ESI-MS/MS system.

Preparation of S-I

Side chain S-I was prepared according to the scheme shown below:



Benzyl chloroformate (6.07 g, 35.47 mmole) was added at 5-10 °C to a solution of Prop-2-ynylamine (1.97 g, 35.82 mmole) and potassium carbonate (K_2CO_3; 10.11 g, 73.26 mmole) in a mixture of tetrahydrofuran and water (THF/H_2O; 20 mL/40 mL) under an atmosphere of nitrogen. The resulting mixture was warmed to room temperature for 15 h and then quenched with ammonium chloride NH_4Cl (aq) (100 mL, 2 M). The aqueous phase was extracted with ethyl acetate (3x100 mL). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get the crude residue. Crystallization of the crude residue using a solvent

mixture of n-hexane/dichloromethane at -20 oC gave the product S-I-I (6.42 g, y: 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 5H), 5.13 (s, 2H), 3.99 (m, 2H), 2.24 (dd, J = 2.8, 2.4 Hz, 1H); ESMS *m/z*: 190.1 (M+1).

To a solution of S-I-I (6.42 g, 33.97 mmole) and 2-Azido-ethanol (3.56 g, 40.88 mmole) in ethanol (EtOH; 150 mL) under an atmosphere of nitrogen was added a solution of copper sulfate ($CuSO_4$; 0.83 g, 5.18 mmole), (+) sodium L-asorbate (1.65 g, 8.34 mmole) and K_2CO_3 (3.40 g, 24.64 mmole) in H_2O (36 mL). The mixture was stirred at 25 °C for 15 h, and then concentrated under reduced pressure by removing EtOH to give the residue. The residue was extracted with dichloromethane (CH_2Cl_2; 3x100 mL) and the combined extracts were washed with brine, dried over anhydrous sodium sulfate (Na_2SO_4), and filtered, and concentrated under reduced pressure to get the crude residue. Crystallization of the crude residue by using solvent system with n-hexane gave the product S-I-II (7.79 g, y: 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (br s, 1H), 7.38-7.31 (m, 5H), 5.09 (s, 2H), 4.46-4.42 (m, 4H), 4.03 (m, 2H); ESMS *m/z*: 277.1 (M+1).

MsCl (3.40 g, 29.72 mmole) was added dropwise at 5-10 °C to a solution of S-I-II (7.79 g, 28.18 mmole) and TEA (7.92 g, 78.43 mmole) in dicloromathane (180 mL). The resulting mixture was warmed to room temperature for 15 h and then quenched with NH_4Cl (aq). The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$(aq) and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get the crude product S-I-III (7.75 g, y: 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.40-7.32 (m, 5H), 5.09 (s, 2H), 4.68-4.61 (m, 4H), 4.46 (m, 2H), 2.91 (s, 3H); ESMS *m/z*: 355.1 (M+1).

A solution of S-I-III (7.75 g, 21.89 mmole) and Ethane-1,2-diamine (9.30 g, 154.77 mmole) in THF (160 mL) was heated at 65 °C for 15 h. After the reaction was complete, the mixture was concentrated under reduced pressure by removing THF to give the residue. The residue was extracted with CH_2Cl_2 (2x150 mL) and the combined extracts were washed with

brine, dried over anhydrous Na_2SO_4, and filtered, and concentrated under reduced pressure to get the crude product S-I-IV (5.69 g, y: 82%) as a light yellow solid. A solution of linker S-I-IV (5.69 g, 17.86 mmole) and cyclohexanone (1.68 g, 17.17 mmole) in MeOH (210 mL) was heated at 60 °C for 15 h and then cooled to 5-10 °C. To the mixture was slowly added $NaBH_4$ (0.56 g, 14.85 mmole) and stirred for 1 h, and then was quenched with NH_4Cl (aq) (50 mL, 2M). The mixture was concentrated under reduced pressure by removing MeOH to give the residue. The residue was extracted with CH_2Cl_2 (2x150 mL) and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and filtered to afford the filtrate of product S-I-V. To a magnetically stirred filtrate of product S-I-V was added Boc_2O anhydride (7.09 g, 32.52 mmole) one potion. The mixture was stirred at room temperature for 15 h, and then concentrated under reduced pressure by removing CH_2Cl_2 to give the crude residue, which was purified with flash chromatography with n-hexane/ethyl acetate (1:1) to afford the product S-I-VI (6.49 g, y: 61% over 2 steps). ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (br s, 1H), 7.32-7.28 (m, 5H), 5.10 (s, 2H), 4.50 (m, 2H), 4.43 (d, J = 6.0 Hz, 1H), 3.56 (m, 2H), 3.16-2.94 (m, 4H), 1.72 (m, 2H), 1.64-1.58 (m, 3H), 1.45-1.21 (m, 23H), 1.02 (m, 1H); ESMS *m/z*: 601.4 (M+1).

A solution of S-I-VI (6.49 g, 10.81 mmole) and Pd/C (0.65 g) in methanol (65 mL) was stirred under H_2(g) at 25 °C for 6 h. After the reaction was complete, the resulting mixture was filtered and the filtrate was concentrated under reduced pressure to give the product S-I (4.5 g, y: 89%) as sticky oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (br s, 1H), 4.50 (m, 2H), 3.88-3.63 (m, 4H), 3.21-2.96 (m, 4H), 1.73 (m, 2H), 1.64-1.59 (m, 3H), 1.47-1.21 (m, 23H), 1.04 (m, 1H); ESMS *m/z*: 467.3 (M+1).

Preparation of S-II

Starting from Prop-2-ynylamine ((1.97 g, 35.82 mmole)), S-II was obtained as sticky oil (4.22 g, 25% over six steps). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (br s, 1H), 4.51 (m, 2H),

3.95 (br s, 2H), 3.61 (m, 2H), 3.15-2.91 (m, 4H), 1.73 (m, 2H), 1.65-1.59 (m, 5H), 1.46-1.22 (m, 23H), 1.03 (m, 1H); ESMS *m/z*: 481.3 (M+1)

Preparation of S-III

Starting from Prop-2-ynylamine ((1.97 g, 35.82 mmole)), S-III was obtained as sticky oil (4.16 g, 24% over six steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 4.33 (t, *J* = 6.9 Hz, 2H), 3.97 (s, 2H), 3.38-3.06 (m, 6H), 2.14 (m, 2H), 1.78-1.59 (m, 5H), 1.47-1.22 (m, 23H), 1.03 (m, 1H); ESMS *m/z*: 481.3 (M+1).

Preparation of S-IV

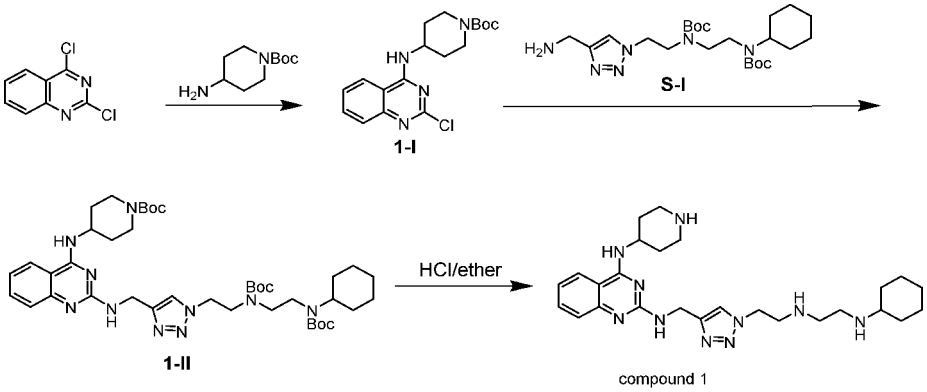
Starting from Prop-2-ynylamine ((1.97 g, 35.82 mmole)), S-IV was obtained as sticky oil (3.91 g, 22% over six steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (br s, 1H), 4.35 (t, *J* = 6.8 Hz, 2H), 4.10 (s, 2H), 3.35-3.00 (m, 6H), 2.15 (m, 2H), 1.76-1.59 (m, 7H), 1.48-1.23 (m, 23H), 1.05 (m, 1H); ESMS *m/z*: 495.3 (M+1).

EXAMPLE 1

Compounds 1-273 were synthesized by assembling starting materials and side chain compounds set forth below:

*Preparation of Compound **1***

Shown below is a scheme for synthesizing compound **1** via intermediates 1-I and 1-II.



4-amino-piperidine-1-carboxylic acid tert-butyl ester (930 mg) and triethylamine (TEA; 1.01 g) were added to a solution of 2,4-dichloro-quinazoline (1.01 g) in tetrahydrofuran (THF; 30 mL) under an atmosphere of nitrogen. The resulting reaction mixture was stirred at 25 °C for 15 h and then quenched with aqueous ammonium chloride (NH_4Cl; 50 mL, 2 M). The mixture was extracted with ethyl acetate (3x100 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with n-hexane / ethyl acetate (1:1) to afford compound 1-I (1.31 g, 71% yield) as a solid.

A solution of compound 1-I (800 mg) and intermediate S-I (1.32 g) in 1-pentanol (1.4 mL) was heated at 120 °C for 15 min using microwave radiation. The resulting mixture was concentrated. The residue thus obtained was purified with flash chromatography on silica gel with MeOH / DCM (1/32) to afford compound 1-II (960 mg, 55% yield).

A solution of 1N HCl/diethyl ether (8 mL) was added to the solution of compound 1-II (400 mg) in dichloromethane (16 mL). The reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrochloride salt of compound **1** (280 mg, 87% yield). ^{1}H NMR (400 MHz, D_2O) δ 8.15 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.68 (dd, J = 8.0, 7.6 Hz, 1H), 7.31 (dd, J = 8.4, 7.6 Hz, 1H), 7.25 (m, 1H), 4.90 (m, 2H), 4.85 (s, 2H), 4.38 (m, 1H), 3.78 (t, J = 5.2 Hz, 2H), 3.61-3.44 (m, 5H), 3.24-3.16 (m, 3H), 2.19 (m, 2H), 2.07 (m, 2H), 1.94 (m, 2H), 1.83 (m, 2H), 1.66 (m, 1H), 1.41-1.18 (m, 6H); EI-MS: 493.3 (M+1).

*Preparation of Compound **2***

Compound **2** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.12 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.73 (dd, J = 8.0, 7.6 Hz, 1H), 7.36 (dd, J = 8.4, 7.6 Hz, 1H), 7.32 (m, 1H), 4.86 (s, 2H), 4.84 (m, 2H), 4.42 (m, 1H), 3.70 (t, J = 6.0 Hz, 2H), 3.57 (m, 2H), 3.26-3.12 (m, 6H), 2.22-2.04 (m, 6H), 1.92 (m, 2H), 1.83 (m, 2H), 1.66 (m, 1H), 1.41-1.17 (m, 6H); EI-MS: 507.3 (M+1).

*Preparation of Compound **3***

Compound **3** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 8.0, 7.6 Hz, 1H), 7.36-7.2 (m, 2H), 4.83 (s, 2H), 4.57 (t, J = 6.8 Hz, 2H), 4.36 (m, 1H), 3.57 (m, 2H), 3.44-3.41 (m, 4H), 3.22-3.16 (m, 4H), 2.38 (m, 2H), 2.04-1.98 (m, 4H), 1.92 (m, 2H), 1.82 (m, 2H), 1.66 (m, 1H), 1.41-1.18 (m, 6H); EI-MS: 507.3 (M+1).

*Preparation of Compound **4***

Compound **4** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.05 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.72 (dd, J = 8.0, 7.6 Hz, 1H), 7.36-7.31 (m, 2H), 4.84 (s, 2H), 4.55 (t, J = 6.8 Hz, 2H), 4.40 (m, 1H), 3.56 (m, 2H), 3.20-3.14 (m, 8H), 2.34 (m, 2H), 2.20-2.02 (m, 6H), 1.92 (m, 2H), 1.82 (m, 2H), 1.66 (m, 1H), 1.41-1.18 (m, 6H); EI-MS: 521.3 (M+1).

*Preparation of Compound **5***

Compound **5** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.63 (dd, J = 8.0, 7.6 Hz, 1H), 7.26-7.21 (m, 2H), 4.82 (s, 2H), 4.47 (t, J = 6.8 Hz, 2H), 4.33 (m, 1H), 3.57 (m, 2H), 3.20-3.04 (m, 8H), 2.15-1.96 (m, 8H), 1.84 (m, 2H), 1.78 (m, 2H), 1.75-1.60 (m, 3H), 1.39-1.17 (m, 6H); EI-MS: 535.4 (M+1).

*Preparation of Compound **6***

Compound **6** was prepared in a manner similar to that used to prepare compound **1**. EI-MS: 493.3 (M+1).

*Preparation of Compound **7***

Compound **7** was prepared in a manner similar to that used to prepare compound **1**. EI-MS: 523.3 (M+1).

*Preparation of Compound **8***

Compound **8** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.15 (s, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 6.74 (dd, *J* = 9.0, 2.1 Hz, 1H), 6.53 (d, *J* = 2.1 Hz, 1H), 4.90 (m, 2H), 4.62 (s, 2H), 4.38 (m, 1H), 3.83 (s, 3H), 3.78 (t, *J* = 5.2 Hz, 2H), 3.62-3.45 (m, 5H), 3.24-3.16 (m, 3H), 2.18 (m, 2H), 2.06 (m, 2H), 1.92 (m, 2H), 1.82 (m, 2H), 1.63 (m, 1H), 1.38-1.17 (m, 6H); EI-MS: 523.3 (M+1).

*Preparation of Compound **9***

Compound **9** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (300 MHz, D_2O) δ 8.13 (s, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 6.75 (dd, *J* = 9.0, 2.1 Hz, 1H), 6.54 (d, *J* = 2.1 Hz, 1H), 4.83 (s, 2H), 4.59 (t, *J* = 6.8 Hz, 2H), 4.35 (m, 1H), 3.82 (s, 3H), 3.60 (m, 2H), 3.44-3.41 (m, 4H), 3.22-3.17 (m, 4H), 2.37 (m, 2H), 2.20-2.04 (m, 4H), 1.90 (m, 2H), 1.82 (m, 2H), 1.66 (m, 1H), 1.38-1.19 (m, 6H); EI-MS: 537.3 (M+1).

*Preparation of Compound **10***

Compound **10** was prepared in a manner similar to that used to prepare compound **1**. EI-MS: 565.4 (M+1).

*Preparation of Compound **11***

Compound **11** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 1H), 6.60 (s, 1H), 4.84 (s, 2H), 4.57 (t, *J* = 6.9 Hz, 2H), 4.36 (m, 1H), 3.84 (s, 3H), 3.57 (m, 2H), 3.23-3.08 (m, 8H), 2.34 (m, 2H), 2.20-2.02 (m, 6H), 1.92 (m, 2H), 1.84 (m, 2H), 1.65 (m, 1H), 1.40-1.18 (m, 6H); EI-MS: 551.4 (M+1).

*Preparation of Compound **12***

Compound **12** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 7.27 (s, 1H), 6.61 (s, 1H), 4.83 (s, 2H), 4.56 (t, *J* = 6.8 Hz, 2H), 4.38 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.57 (m, 2H), 3.23-3.08 (m, 8H), 2.34 (m, 2H), 2.18-2.00 (m, 6H), 1.94 (m, 2H), 1.82 (m, 2H), 1.64 (m, 1H), 1.38-1.18 (m, 6H); EI-MS: 581.4 (M+1).

*Preparation of Compound **13***

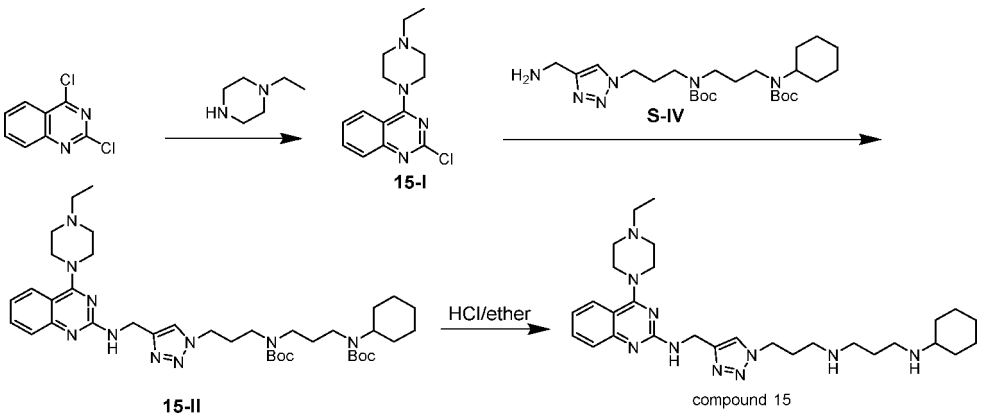
Compound **13** was prepared in a manner similar to that used to prepare compound **1**. EI-MS: 535.4 (M+1).

*Preparation of Compound **14***

Compound **14** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.12 (s, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.47 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 4.83 (s, 2H), 4.57 (t, *J* = 6.8 Hz, 2H), 4.35 (m, 1H), 3.57 (m, 2H), 3.22-3.08 (m, 8H), 2.35 (m, 2H), 2.21-2.01 (m, 6H), 1.95 (m, 2H), 1.79 (m, 2H), 1.61 (m, 1H), 1.36-1.18 (m, 6H); EI-MS: 555.3 (M+1).

*Preparation of Compound **15***

Shown below is a scheme for synthesizing compound **15** via intermediates 15-I and 15-II.



1-ethyl-piperazine (750 mg) and triethylamine (TEA) (1.01 g) were added to a solution of 2,4-dichloro-quinazoline (1.0 g) in THF (30 mL) under an atmosphere of nitrogen . The resulting mixture was stirred at 25 °C for 15 h and then quenched with aqueous NH_4Cl (50 mL, 2 M). The mixture was extracted with ethyl acetate (3x100 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash

chromatography on silica gel with n-hexane / ethyl acetate (1:1) to afford compound 15-I (1.1 g, 78% yield) as a solid.

A solution of compounds 15-I (0.5 g) and S-IV (0.8 g) in 1-pentanol (1.4 mL) was heated at 120 °C for 15 min using microwave radiation. The resulting mixture was concentrated. The residue thus obtained was purified by flash chromatography with MeOH / DCM (1/32) to afford compound 15-II (860 mg, 65% yield).

A solution of 1N HCl/diethyl ether (6 mL) was added to the solution of compound 15-II (300 mg) in dichloromethane (12 mL). The reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrochloride salt of compound **15** (224 mg, 81% yield). EI-MS: 535.4 (M+1).

*Preparation of Compound **16***

Compound **16** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 595.4 (M+1).

*Preparation of Compound **17***

Compound **17** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 589.4 (M+1).

*Preparation of Compound **18***

Compound **18** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 584.4 (M+1).

*Preparation of Compound **19***

Compound **19** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 585.4 (M+1).

*Preparation of Compound **20***

Compound **20** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 651.3 (M+1).

*Preparation of Compound **21***

Compound **21** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 577.4 (M+1).

*Preparation of Compound **22***

Compound **22** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 523.4 (M+1).

*Preparation of Compound **23***

Compound **23** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 535.4 (M+1).

*Preparation of Compound **24***

Compound **24** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 565.4 (M+1).

*Preparation of Compound **25***

Compound **25** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 546.3 (M+1).

*Preparation of Compound **26***

Compound **26** was prepared in a manner similar to that used to prepare compound **15**. ^{1}H NMR (400 MHz, D_2O) δ 8.26 (s, 1H), 8.13 (d, 1H), 7.82 (t, 1H), 7.48-7.41 (m, 2H), 4.83 (s, 2H), 4.61 (t, 2H), 3.22-3.07 (m, 8H), 2.38 (m, 2H), 2.21-2.08 (m, 4H), 1.87 (m, 2H), 1.70 (m, 1H), 1.44-1.18 (m, 6H); EI-MS: 438.3 (M+1).

*Preparation of Compound **27***

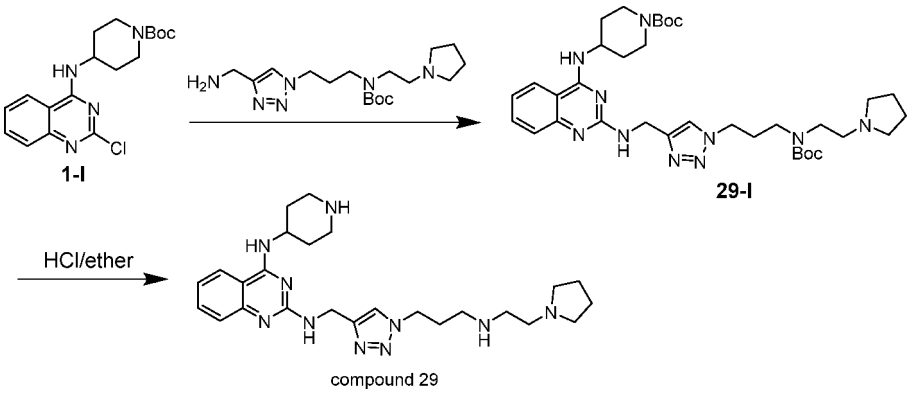
Compound **27** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 535.4 (M+1).

*Preparation of Compound **28***

Compound **28** was prepared in a manner similar to that used to prepare compound **15**. EI-MS: 549.4 (M+1).

*Preparation of Compound **29***

Shown below is a scheme for synthesizing compound **29** from compound 1-I via intermediate 29-I.



A solution of 1-I (800 mg) and [3-(4-aminomethyl-[1,2,3]triazol-1-yl)-propyl]-(2-pyrrolidin-1-yl-ethyl)-carbamic acid *tert*-butyl ester (1.0 g) in 1-pentanol (3 mL) was heated at 120 °C for 15 minutes using microwave radiation. The resulting mixture was concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1/32) to afford compound 29-I (1.0 g, 67% yield).

A solution of 1N HCl/diethyl ether (4 mL) was added to the solution of compound 29-I (200 mg) in dichloromethane (8 mL). The resulting reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrochloride salt of compound **29** (160 mg, 87% yield). EI-MS: 479.3 (M+1).

*Preparation of Compound **30***

Compound **30** was prepared in a manner similar to that used to prepare compound **29**. EI-MS: 509.3 (M+1).

*Preparation of Compound **31***

Compound **31** was prepared in a manner similar to that used to prepare compound **29**. EI-MS: 507.3 (M+1).

*Preparation of Compound **32***

Compound **32** was prepared in a manner similar to that used to prepare compound **29**. EI-MS: 490.3 (M+1).

*Preparation of Compound **33***

Compound **33** was prepared in a manner similar to that used to prepare compound **29**. EI-MS: 450.3 (M+1).

*Preparation of Compound **34***

Compound **34** was prepared in a manner similar to that used to prepare compound **29**. EI-MS: 464.2 (M+1).

*Preparation of Compound **35***

Compound **35** was prepared in a manner similar to that used to prepare compound **29**. EI-MS: 533.4 (M+1).

*Preparation of Compound **36***

Compound **36** was prepared in a manner similar to that used to prepare compound **29**. EI-MS: 595.2 (M+1).

*Preparation of Compound **37***

Compound **37** was prepared in a manner similar to that used to prepare compound **29**. EI-MS: 528.3 (M+1).

*Preparation of Compound **38***

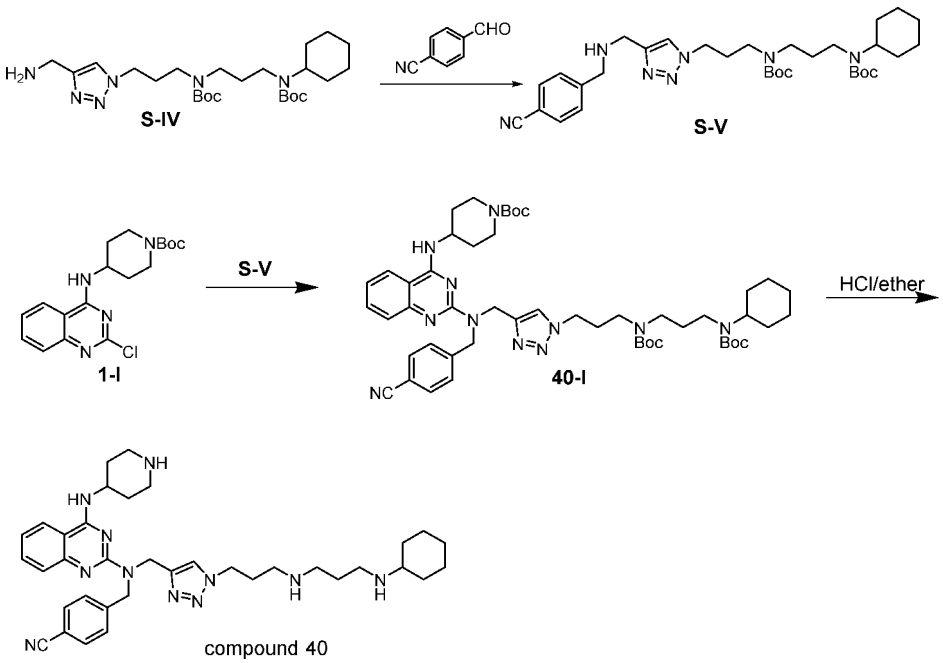
Compound **38** was prepared in a manner similar to that used to prepare compound **29**. EI-MS: 539.3 (M+1).

*Preparation of Compound **39***

Compound **39** was prepared in a manner similar to that used to prepare compound **29**. ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.03 (d, 1H), 7.81 (t, 1H), 7.48-7.40 (m, 2H), 4.86 (s, 2H), 4.52 (t, 2H), 4.45 (m, 1H), 3.98 (m, 1H), 3.57 (m, 2H), 3.45-2.96 (m, 8H), 2.59 (m, 2H), 2.31-1.80 (m, 14H), 1.68 (m, 1H), 1.41-1.16 (m, 6H); EI-MS: 650.4 (M+1).

*Preparation of Compound **40***

Shown below is a scheme for synthesizing compound **40** from compound 1-I via intermediate 40-I.



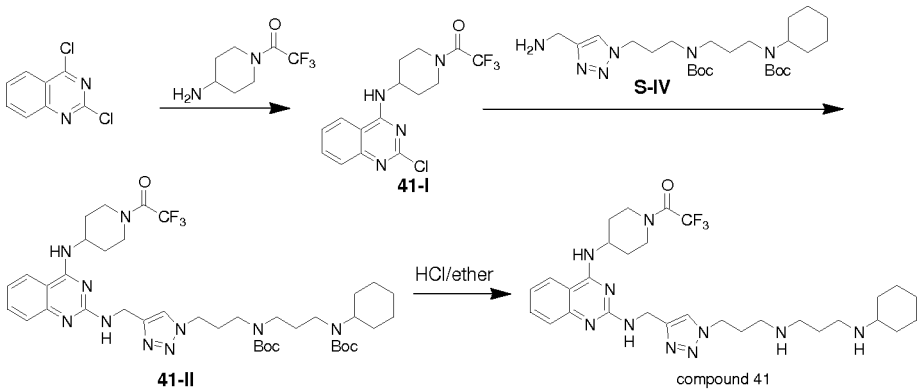
A solution of compound S-IV (494 mg) and 4-formyl-benzonitrile (157 mg) in methanol (8 mL) was heated at 60 °C for 6 h and then cooled to room temperature. To the mixture was slowly added $NaBH_4$ (60 mg). The resulting reaction mixture was stirred for 1 h, quenched with aqueous NH_4Cl (5 mL, 2 M), and concentrated. The residue thus obtained was extracted with dichloromethane (3x100 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:1) to afford compound S-V (487 mg, 80% yield) as light yellow solid.

A solution of compounds 1-I (625 mg) and S-V (1.3 g) in 1-pentanol (2 mL) was heated at 130 °C for 10 minutes using microwave radiation. The resulting mixture was concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1/32) to afford compound 40-I (806 mg, 50% yield).

A solution of 1N HCl/diethyl ether (16 mL) was added to the solution of compound 40-I (806 mg) in dichloromethane (32 mL). The reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrochloride salt of compound **40** (589 mg, 88% yield). EI-MS: 636.4 (M+1).

*Preparation of Compound **41***

Shown below is a scheme for synthesizing compound **41** via intermediates 41-I and 41-II.



A hydrochloride salt of 1-(4-Amino-piperidin-1-yl)-2,2,2-trifluoro-ethanone (1.01 g) and TEA (1.02 g) were added to a solution of 2,4-dichloro-quinazoline (1.02 g) in THF (30 mL) under an atmosphere of nitrogen. The resulting reaction mixture was stirred at 25 °C for 15 h and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with ethyl acetate (3x100 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with n-hexane / ethyl acetate (1:1) to give compound 41-I (1.37 g, 75% yield) as a solid.

A solution of compound 41-I (1.17 g) and S-IV (1.32 g) in 1-pentanol (3 mL) was heated at 120 °C for 15 minutes using microwave radiation. The resulting mixture was concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:32) to afford compound 41-II (1.43 g, 54% yield).

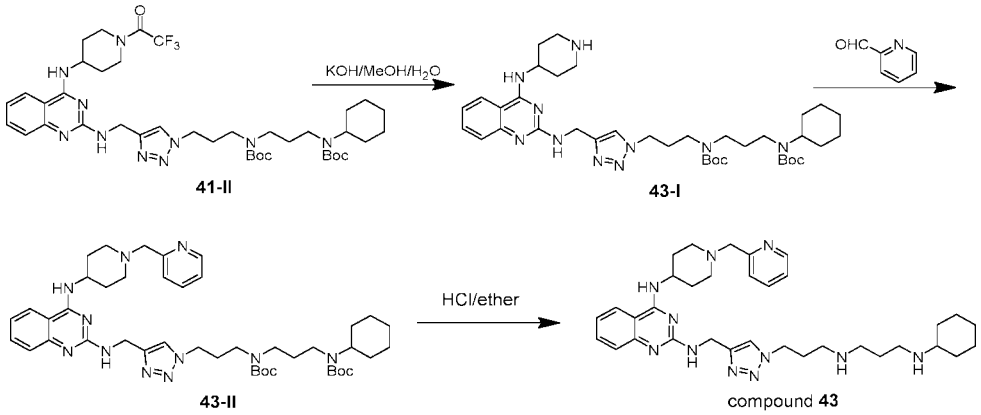
A solution of 1N HCl/diethyl ether (10 mL) was added to the solution of compound 41-II (500 mg) in dichloromethane (20 mL). The reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrochloride salt of compound **41** (402 mg, 86% yield). EI-MS: 617.3 (M+1).

*Preparation of Compound **42***

Compound **42** was prepared in a manner similar to that used to prepare compound **41**. EI-MS: 603.3 (M+1).

*Preparation of Compound **43***

Shown below is a scheme for synthesizing compound **43** from compound 41-II via intermediates 43-I and 43-II.



To a magnetically stirred solution of compound 41-II (6.5 g) in MeOH/THF (58 mL/58 mL) under an atmosphere of nitrogen was added a solution of KOH (1.3 g) in H_2O (13 mL). The mixture was stirred at 25 °C for 15 hours and then concentrated. The residue thus obtained was extracted with dichloromethane (3x650 mL). The combined extracts were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give the crude compound 43-I (5.5 g, 96% yield) as light yellow solid.

[followed by page 58a]

2015321654 27 Sep 2019

A solution of compound 43-I (300 mg), pyridine-2-carbaldehyde (67 mg), sodium triacetoxyborohydride (390 mg), and HOAc (10 mg) in dichloromethane (30 mL) was stirred at 25 °C for 15 hours. The reaction mixture was quenched with aqueous NH_4Cl (50 mL, 2 M)

[followed by page 59]

and extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:4) to afford compound 43-II (281 mg, 83% yield).

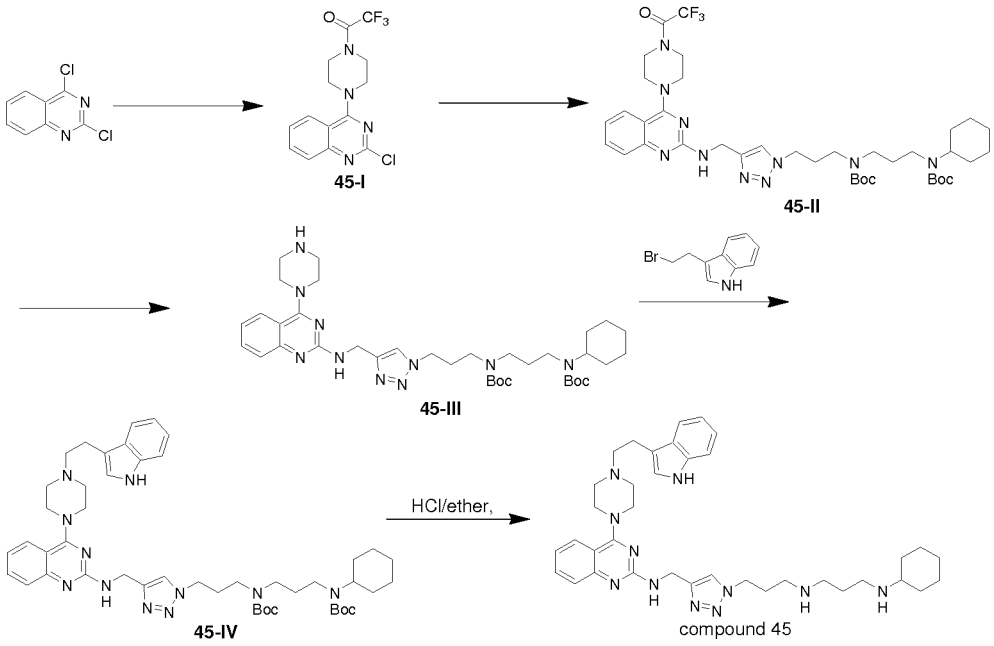
A solution of 1N HCl/diethyl ether (5.6 mL) was added to a solution of compound **43-II** (281 mg) in dichloromethane (11.2 mL). The reaction mixture was stirred for 15 h and concentrated to afford hydrochloride salt of compound **43** (225 mg, 86% yield). EI-MS: 612.4 (M+1).

*Preparation of Compound **44***

Compound **44** was prepared in a manner similar to that used to prepare compound **43**. EI-MS: 591.4 (M+1).

*Preparation of Compound **45***

Shown below is a scheme for synthesizing compound **45** via intermediates 45-I to 45-IV.



To a magnetically stirred solution of 2,4-dichloro-quinazoline (1.4 g) in THF (42 mL) under an atmosphere of nitrogen was added hydrochloride salt of 2,2,2-Trifluoro-1-piperazin-1-yl-ethanone (2.8 g). The mixture was stirred at 25 °C for 15 hours and then quenched with NH_4Cl (aq) (75 mL, 2 M). The resulting solution was extracted with ethyl acetate (3x150 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with ethyl acetate / n-hexane (1:1) to give compound 45-I (1.8 g, 74% yield).

A solution of compounds 45-I (1.8 g) and S-IV (2.0 g) in 1-pentanol (3 mL) was heated at 120 °C for 10 minutes using microwave radiation. The resulting mixture was concentrated. The residue thus obtained was purified by flash chromatography with MeOH / DCM (1/32) to afford compound 45-II (2.0 g, 48% yield).

To a magnetically stirred solution of compound 45-II (1.4 g) in EtOH (50 mL) under an atmosphere of nitrogen was added a solution of KOH (0.28 g) in H_2O (2.8 mL). The resulting mixture was stirred at 25 °C for 15 hours and then concentrated. The residue thus obtained was extracted with ethyl acetate (3x150 mL). The combined extracts were concentrated to afford compound 45-III (901 mg, 73% yield) as a solid.

To a magnetically stirred solution of compound 45-III (195 mg) in dichloromethane (10 mL) under an atmosphere of nitrogen was added side chain 3-(2-bromo-ethyl)-1H-indole (80 mg) and TEA (100 mg). The mixture was stirred at 25 °C for 15 hours and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with dichloromethane (3x50 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:4) to give compound 45-IV (183 mg, 78% yield) as a solid.

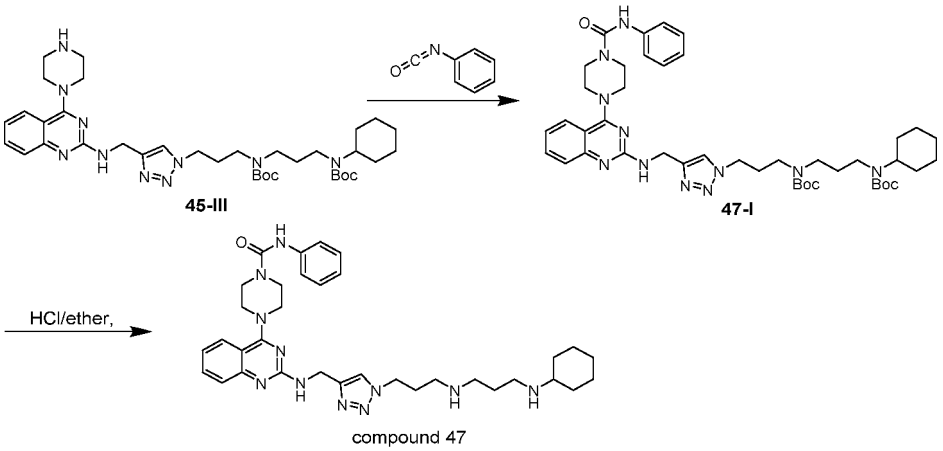
A solution of 1N HCl/diethyl ether (2 mL) was added to the solution of compound 45-IV (183 mg) in dichloromethane (4 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **45** (135 mg, 81% yield). EI-MS: 650.4 (M+1).

*Preparation of Compound **46***

Compound **46** was prepared in a manner similar to that used to prepare compound **45**. EI-MS: 621.4 (M+1).

*Preparation of Compound **47***

Shown below is a scheme for synthesizing compound **47** from compound 45-III via intermediate 47-I.



To a magnetically stirred solution of compound 45-III (200 mg) in dichloromethane (10 mL) under an atmosphere of nitrogen was added isocyanato-benzene (47 mg) and TEA (100 mg). The mixture was stirred at 25 °C for 3 hours and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with dichloromethane (3x50 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:32) to give the product 47-I (185 mg, 80% yield) as a solid.

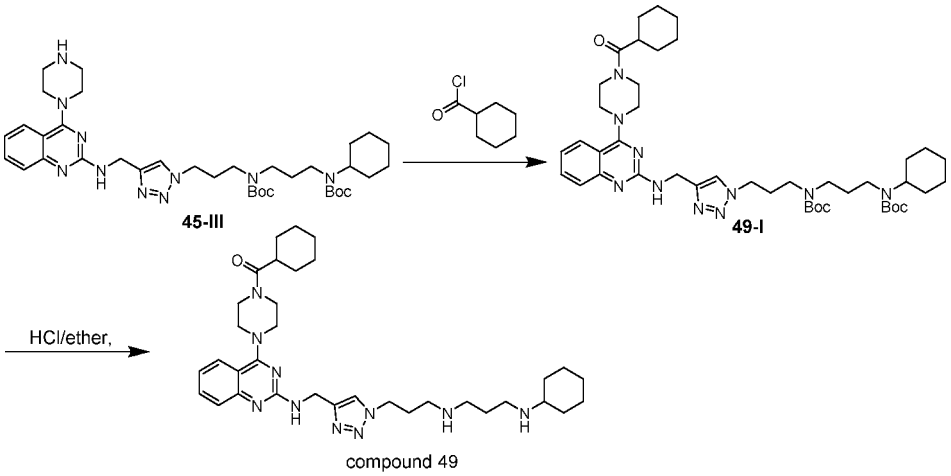
A solution of 1N HCl/diethyl ether (4 mL) was added to the solution of compound 47-I (185 mg) in dichloromethane (8 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **47** (134 mg, 81% yield). EI-MS: 626.4 (M+1).

*Preparation of Compound **48***

Compound **48** was prepared in a manner similar to that used to prepare compound **47**. EI-MS: 594.3 (M+1).

*Preparation of Compound **49***

Shown below is a scheme for synthesizing compound **49** from compound 45-III via intermediate 49-I.



To a magnetically stirred solution of compound 45-III (150 mg) in dichloromethane (5 mL) under an atmosphere of nitrogen was added cyclohexanecarbonyl chloride (35 mg) and TEA (70 mg). The resulting mixture was stirred at 25 °C for 3 hours and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with dichloromethane (3x50 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:32) to give compound 49-I (120 mg, 70% yield) as a solid.

A solution of 1N HCl/diethyl ether (2 mL) was added to the solution of compound 49-I (120 mg) in dichloromethane (4 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **49** (91 mg, 85% yield). EI-MS: 617.4 (M+1).

*Preparation of Compound **50***

Compound **50** was prepared in a manner similar to that used to prepare compound **49**. EI-MS: 577.4 (M+1).

*Preparation of Compound **51***

Compound **51** was prepared in a manner similar to that used to prepare compound **49**. EI-MS: 611.4 (M+1).

*Preparation of Compound **52***

Compound **52** was prepared in a manner similar to that used to prepare compound **49**. EI-MS: 612.4 (M+1).

*Preparation of Compound **53***

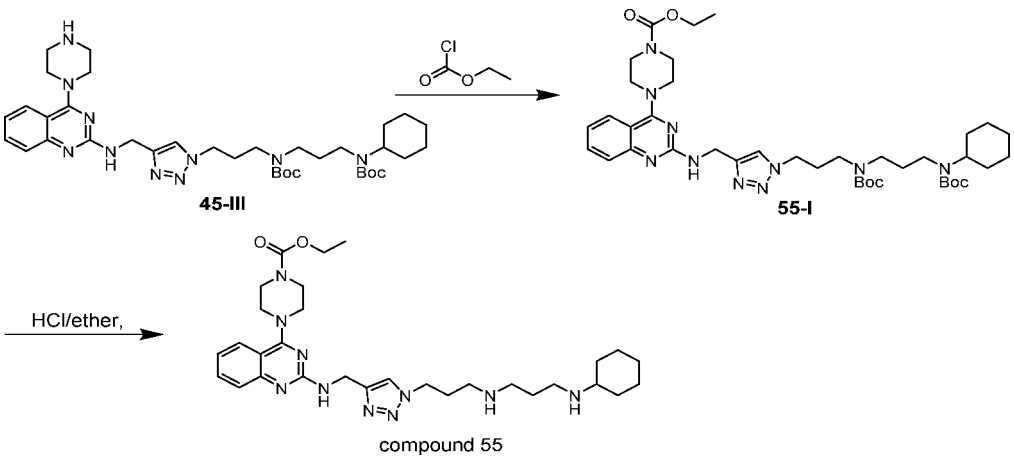
Compound **53** was prepared in a manner similar to that used to prepare compound **49**. EI-MS: 617.3 (M+1).

*Preparation of Compound **54***

Compound **54** was prepared in a manner similar to that used to prepare compound **49**. EI-MS: 621.4 (M+1).

*Preparation of Compound **55***

Shown below is a scheme for synthesizing compound **55** from compound 45-III via intermediate 55-I.

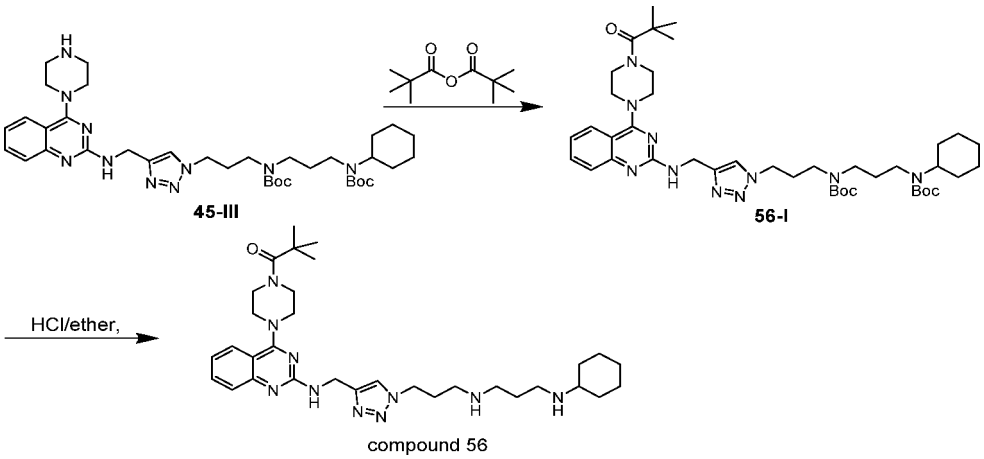


To a magnetically stirred solution of compound 45-III (268 mg) in THF (8 mL) under an atmosphere of nitrogen was added ethyl chloroformate (65 mg). The reaction mixture was stirred at 25 °C for 8 h and then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:32) to give compound 55-I (237 mg, 80% yield) as a solid.

A solution of 1N HCl/diethyl ether (5 mL) was added to the solution of compound 55-I (237 mg) in dichloromethane (10 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **55** (175 mg, 84% yield). EI-MS: 579.4 (M+1).

*Preparation of Compound **56***

Shown below is a scheme for synthesizing compound **56** from compound 45-III via intermediate 56-I.

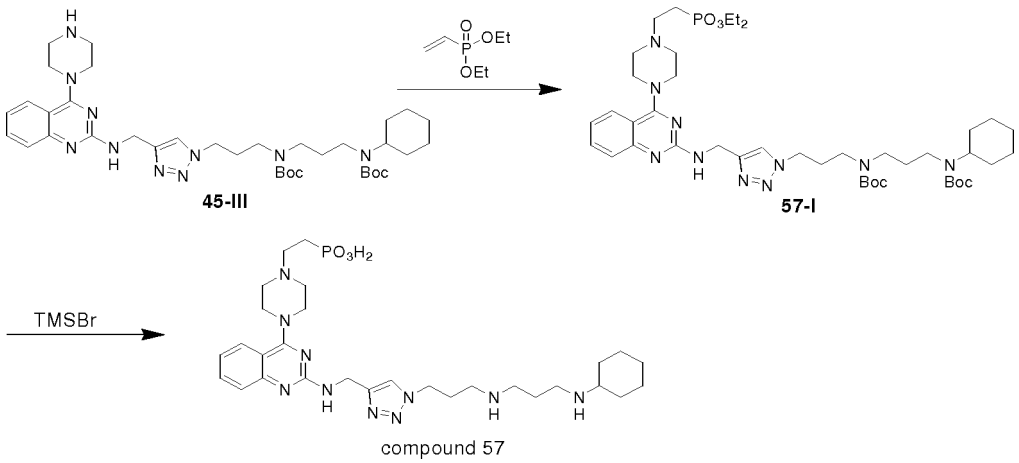


To a magnetically stirred solution of compound 45-III (203 mg) in dichloromethane (8 mL) under an atmosphere of nitrogen was added trimethylacetic anhydride (83 mg). The reaction mixture was stirred at 25 °C for 2 hours and then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:32) to give compound 56-I (170 mg, 75% yield) as a solid.

A solution of 1N HCl/diethyl ether (3 mL) was added to the solution of compound 56-I (170 mg) in dichloromethane (6 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **56** (126 mg, 84% yield). EI-MS: 591.4 (M+1).

*Preparation of Compound **57***

Shown below is a scheme for synthesizing compound **57** from compound 45-III via intermediate 57-I.



To a magnetically stirred solution of compound 45-III (350 mg) in MeOH (10 mL) under an atmosphere of nitrogen was added diethyl vinylphosphonate (224 mg). The reaction mixture was stirred at 25 °C for 15 hours and then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:32) to give compound 57-I (320 mg, 74% yield) as a solid.

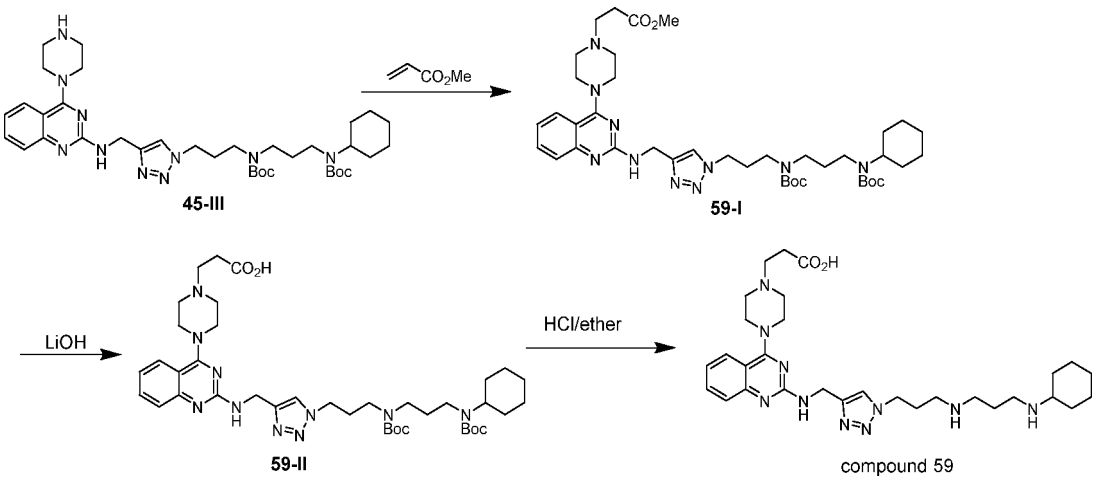
TMSBr (1 mL) was added to the solution of compound 57-I (320 mg) in dichloromethane (10 mL). The reaction mixture was stirred at 25 °C for 15 hours and then concentrated to afford hydrobromide salt of compound **57** (240 mg, 76% yield). EI-MS: 615.3 (M+1).

*Preparation of Compound **58***

Compound **58** was prepared in a manner similar to that used to prepare compound **57**. EI-MS: 628.3 (M+1).

*Preparation of Compound **59***

Shown below is a scheme for synthesizing compound **59** from compound 45-III via intermediates 59-I and 59-II.



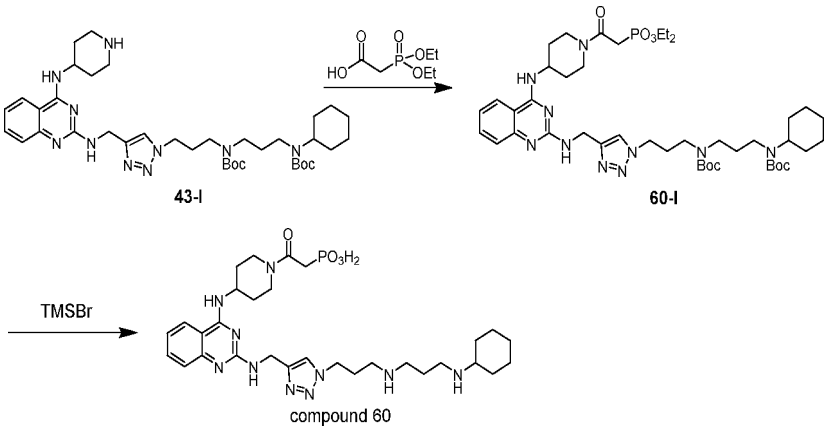
To a magnetically stirred solution of compound 45-III (200 mg) in MeOH (10 mL) under an atmosphere of nitrogen was added methylacrylate (37 mg) and TEA (100 mg). The reaction mixture was stirred at 25 °C for 15 hours and then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:9) to give compound 59-I (147 mg, 66% yield) as a solid.

To a magnetically stirred solution of compound 59-I (147 mg) in THF (5 mL) under an atmosphere of nitrogen was added aqueous LiOH (0.5 M, 5 mL). The reaction mixture was stirred at 25 °C for 15 hours and then acidified with aqueous 1N HCl (12 mL). The resulting mixture was extracted with ethyl acetate (3x50 mL). The combined extracts were concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:3) to give compound 59-II (109 mg, 72% yield) as a solid.

A solution of 1N HCl/diethyl ether (2 mL) was added to the solution of compound 59-II (109 mg) in dichloromethane (4 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **59** (74 mg, 77% yield). EI-MS: 579.4 (M+1).

*Preparation of Compound **60***

Shown below is a scheme for synthesizing compound **60** from compound 43-I via intermediate 60-I.

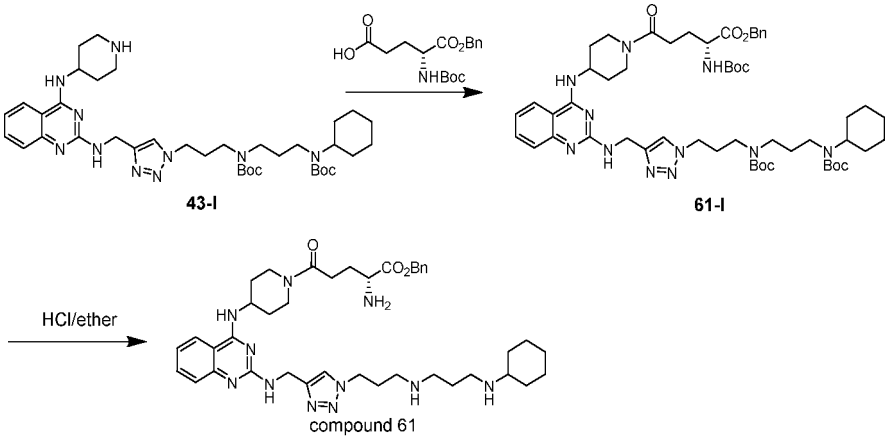


To a magnetically stirred solution of (diethoxy-phosphoryl)-acetic acid (410 mg) in dichloromethane (20 mL) under an atmosphere of nitrogen was added EDCI (680 mg) and HOBt (589 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 hour, a solution of compound 43-I (985 mg) in dichloromethane (10 mL) was added the mixture one potion. The reaction mixture was stirred for another 6 hours and then poured into water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1/32) to give compound 60-I (740 mg, 60% yield) as a solid.

TMSBr (1.5 mL) was added to the solution of compound 60-I (740 mg) in dichloromethane (15 mL). The reaction mixture was stirred at 25 °C for 15 hours and concentrated to afford hydrobromide salt of compound **60** (580 mg, 80% yield). EI-MS: 643.3 (M+1).

*Preparation of Compound **61***

Shown below is a scheme for synthesizing compound **61** from compound 43-I via intermediate 61-I.



To a magnetically stirred solution of 2-tert-Butoxycarbonylamino-pentanedioic acid monobenzyl ester (0.8 g) in dichloromethane (40 mL) under an atmosphere of nitrogen was added EDCI (450 mg) and HOBt (400 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 hour, a solution of compound 43-I (1.0 g) in DCM (10 mL) was added in one potion. The mixture was stirred for another 6 hours and then poured into water. The resulting solution was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to give compound 61-I (1.12 g, 78% yield) as a solid.

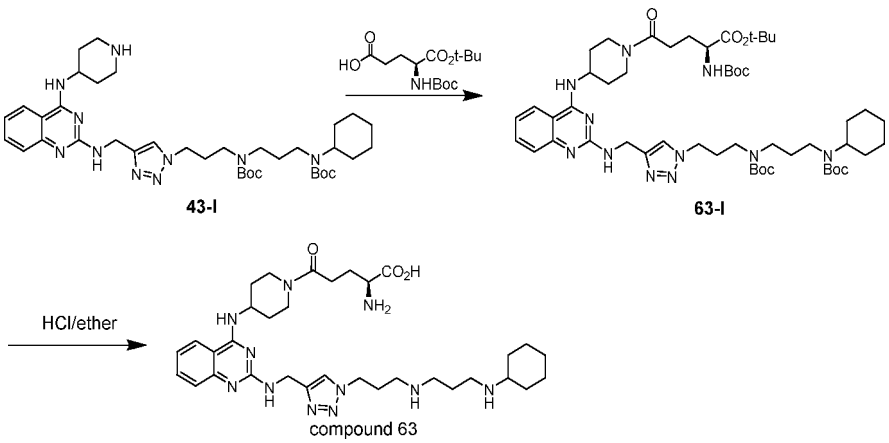
A solution of 1N HCl/diethyl ether (10 mL) was added to the solution of compound 61-I (500 mg) in dichloromethane (20 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **61** (365 mg, 86% yield). EI-MS: 740.4 (M+1).

*Preparation of Compound **62***

Compound **62** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 7.95 (d, 1H), 7.78 (t, 1H), 7.50-7.22 (m, 7H), 5.29 (m, 2H), 4.88 (s, 2H), 4.58 (t, 2H), 4.40- 4.28 (m, 3H), 3.70 (m, 1H), 3.22-3.12 (m, 8H), 3.00 (m, 1H), 2.75-2.55 (m, 3H), 2.37 (m, 2H), 2.30 (m, 2H), 2.18-2.00 (m, 5H), 1.90-1.80 (m, 3H), 1.68 (m, 2H), 1.50-1.18 (m, 7H); EI-MS:740.4 (M+1).

Preparation of Compound ***63***

Shown below is a scheme for synthesizing compound **63** from compound 43-I via intermediate 63-I.



To a magnetically stirred solution of 2-tert-Butoxycarbonylamino-pentanedioic acid 1-tert-butyl ester (300 mg) in dichloromethane (20 mL) under an atmosphere of nitrogen was added EDCI (200 mg) and HOBt (200 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 hour, a solution of compound 43-I (400 mg) in dichloromethane (10 mL) was added the mixture in one potion. The reaction mixture was stirred for another 6 hours and then poured into water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to give compound 63-I (401 mg, 72% yield) as a solid.

A solution of 4N HCl/dioxane (4 mL) was added to the solution of compound 63-I (401 mg) in dichloromethane (8 mL) and 1,4-dioxane (8 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **63** (301 mg, 88% yield). ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 7.97 (d, 1H), 7.79 (t, 1H), 7.44-7.38 (m, 2H), 4.88 (s, 2H), 4.60 (t, 2H), 4.48 (m, 1H), 4.38 (m, 1H), 4.14 (m, 1H), 4.02 (m, 1H),

3.30 (m, 1H), 3.22-3.12 (m, 6H), 2.85-2.75 (m, 3H), 2.37 (m, 2H), 2.30 (m, 2H), 2.18-1.80 (m, 8H), 1.68 (m, 2H), 1.58 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 650.4 (M+1).

*Preparation of Compound **64***

Compound **64** was prepared in a manner similar to that used to prepare compound **61**. EI-MS: 664.4 (M+1).

*Preparation of Compound **65***

Compound **65** was prepared in a manner similar to that used to prepare compound **61**. EI-MS: 746.5 (M+1).

*Preparation of Compound **66***

Compound **66** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 7.87 (d, 1H), 7.53-7.24 (m, 5H), 6.99 (m, 1H), 6.81 (m, 1H), 5.31 (m, 2H), 4.88 (s, 2H), 4.58 (m, 2H), 4.43-4.19 (m, 3H), 3.94 (s, 3H), 3.68 (m, 1H), 3.22-2.96 (m, 7H), 2.78-2.53 (m, 3H), 2.41-2.20 (m, 4H), 2.18-2.02 (m, 6H), 1.94-1.80 (m, 4H), 1.68 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 770.5 (M+1).

*Preparation of Compound **67***

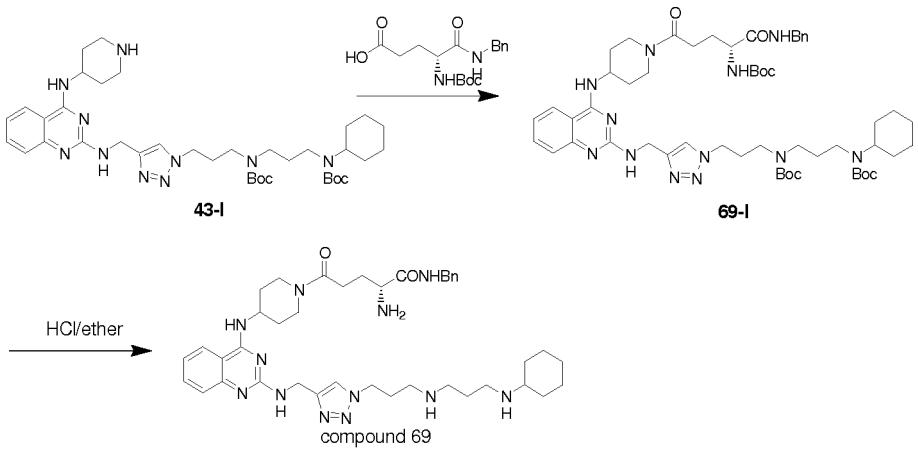
Compound 67 was prepared in a manner similar to that used to prepare compound **61**. EI-MS: 718.5 (M+1).

*Preparation of Compound **68***

Compound 68 was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 7.93 (d, 1H), 7.53-7.24 (m, 8H), 5.32 (m, 2H), 4.88 (s, 2H), 4.59 (m, 2H), 4.43-4.22 (m, 3H), 3.71 (m, 1H), 3.22-2.96 (m, 7H), 2.78-2.53 (m, 3H), 2.41-2.20 (m, 4H), 2.18-2.02 (m, 5H), 1.94-1.78 (m, 5H), 1.69 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 774.4 (M+1).

*Preparation of Compound **69***

Shown below is a scheme for synthesizing compound **69** from compound 43-I via intermediate 69-I.



To a magnetically stirred solution of 2-tert-Butoxycarbonylamino-pentanedioic acid monobenzyl ester (0.8 g) in dichloromethane (40 mL) under an atmosphere of nitrogen was added EDCI (450 mg) and HOBt (400 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 h, a solution of compound 43-I (1.0 g) in dichloromethane (10 mL) was added in one potion. The reaction mixture was stirred for another 6 h and then poured into water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to give compound 69-I (1.06 g, 74% yield) as a solid.

A solution of 1N HCl/diethyl ether (10 mL) was added to the solution of compound 69-I (500 mg) in dichloromethane (20 mL). The reaction mixture was stirred for 15 h and concentrated to afford hydrochloride salt of compound **69** (343 mg, 81% yield). ^{1}H NMR (400 MHz, D_2O) δ 8.05 (s, 1H), 8.01 (m, 2H), 7.83 (t, 1H), 7.47 (m, 2H), 7.40-7.20 (m, 5H), 4.87 (s, 2H), 4.62-4.57 (m, 3H), 4.42-4.26 (m, 3H), 4.12 (m, 1H), 3.78 (m, 1H), 3.20-3.05 (m, 7H), 2.78 (m, 1H), 2.48 (m, 2H), 2.35 (m, 2H), 2.30-2.00 (m, 7H), 1.96-1.80 (m, 4H), 1.68 (m, 1H), 1.58 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 739.5 (M+1).

*Preparation of Compound **70***

Compound **70** was prepared in a manner similar to that used to prepare compound **61**. EI-MS: 774.4 (M+1).

*Preparation of Compound **71***

Compound **71** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.02 (m, 2H), 7.83 (t, 1H), 7.47-7.22 (m, 7H), 4.88 (s, 2H), 4.62 (m, 1H), 4.60-4.57 (m, 3H), 4.48-4.30 (m, 3H), 3.73 (m, 1H), 3.53 (m, 1H), 3.35 (m, 1H), 3.25-3.05 (m, 7H), 2.78 (m, 1H), 2.58 (m, 2H), 2.40-2.20 (m, 4H), 2.18-1.80 (m, 8H), 1.78-1.58 (m, 5H), 1.42-1.18 (m, 8H), 0.95 (t, 3H); EI-MS: 795.5 (M+1).

*Preparation of Compound **72***

Compound **72** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.02 (m, 2H), 7.83 (t, 1H), 7.47-7.42 (m, 2H), 4.88 (s, 2H), 4.65 (m, 1H), 4.60-4.57 (m, 3H), 4.48-4.43 (m, 2H), 4.33 (m, 1H), 4.03 (m, 1H), 3.93 (s, 3H), 3.30 (m, 1H), 3.20-3.12 (m, 6H), 2.85-2.75 (m, 3H), 2.40-2.20 (m, 4H), 2.18-1.80 (m, 8H), 1.68 (m, 2H), 1.58 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 751.4 (M+1).

*Preparation of Compound **73***

Compound **73** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 7.93 (d, 1H), 7.76 (t, 1H), 7.42-7.33 (m, 2H), 5.08 (m, 1H), 4.86 (s, 2H), 4.57 (t, 2H), 4.52-4.30 (m, 3H), 4.28 (m, 1H), 4.12-4.00 (m, 3H), 3.30 (m, 1H), 3.20-3.12 (m, 6H), 2.82 (m, 1H), 2.72 (t, 2H), 2.38 (m, 2H), 2.30-1.81 (m, 10H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 12H); EI-MS: 779.5 (M+1).

*Preparation of Compound **74***

Compound **74** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.06-8.03 (m, 2H), 7.83 (m, 1H), 7.49-7.44 (m, 2H), 4.86 (s, 2H), 4.62-4.38 (m, 5H), 4.30-4.13 (m, 5H), 4.03(m, 1H), 3.30 (m, 1H), 3.20-3.12 (m, 6H), 2.87 (m, 1H), 2.76 (m, 2H), 2.57 (m, 2H), 2.40-1.81 (m, 14H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 12H); EI-MS: 835.5 (M+1).

*Preparation of Compound **75***

Compound **75** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.86 (s, 1H), 8.66 (m, 1H), 8.17 (br s, 1H), 8.16-7.98 (m, 3H), 7.83 (m, 1H), 7.49-7.44 (m, 2H), 5.80-5.64 (m, 2H), 4.86 (s, 2H), 4.62 (t, 2H), 4.52-4.38 (m, 3H), 4.03(m, 1H), 3.26 (m, 1H), 3.20-3.12 (m, 6H), 2.87-2.70 (m, 3H), 2.46-2.32 (m, 4H), 2.18-1.81 (m, 8H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 6H); EI-MS: 741.4 (M+1).

*Preparation of Compound **76***

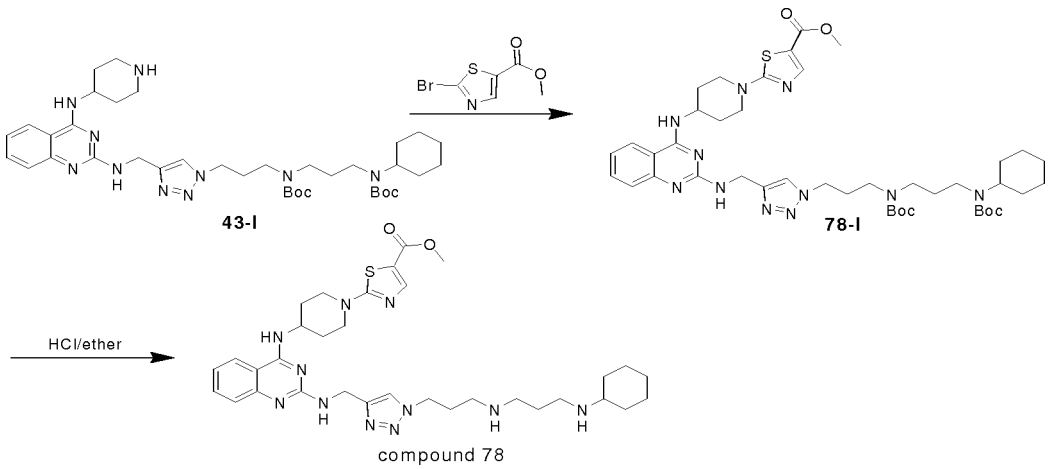
Compound **76** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.04 (d, 1H), 7.92 (d, 2H), 7.85 (t, 1H), 7.49-7.44 (m, 2H), 7.09-7.03 (m, 2H), 4.86 (s, 2H), 4.59 (t, 2H), 4.42-4.34 (m, 2H), 4.03(m, 1H), 3.80 (s, 3H), 3.64 (m, 1H), 3.20-3.12 (m, 7H), 2.81 (m, 1H), 2.42-2.36 (m, 4H), 2.34-1.81 (m, 10H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 6H); EI-MS: 819.4 (M+1).

*Preparation of Compound **77***

Compound **77** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.00 (d, 1H), 7.81 (t, 1H), 7.46-7.40 (m, 2H), 4.86 (s, 2H), 4.59 (t, 2H), 4.52-4.38 (m, 2H), 4.24(m, 1H), 4.12-3.98 (m, 3H), 3.84-3.78 (m, 4H), 3.30 (m, 1H), 3.22-3.14 (m, 6H), 2.91-2.70 (m, 3H), 2.42-2.20 (m, 4H), 2.20-1.81 (m, 8H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 6H); EI-MS: 751.4 (M+1).

*Preparation of Compound **78***

Shown below is a scheme for synthesizing compound **78** from compound 43-I via intermediate 78-I.



To a magnetically stirred solution of compound 43-I (180.5 mg) in DCM (15 mL) under an atmosphere of nitrogen was added 2-bromo-thiazole-5-carboxylic acid methyl ester (68.8 mg) and TEA (200 mg). The reaction mixture was stirred at 25 °C for 15 h and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with dichloromethane (3x50 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH/DCM = 1/19 to afford compound 78-I (161.2 mg, 75% yield) as a solid.

A solution of 1N HCl/diethyl ether (3.2 mL) was added to the solution of compound 78-I (161.2 mg) in dichloromethane (6.4 mL). The reaction mixture was stirred for 15 h and concentrated to afford hydrochloride salt of compound **78** (125 mg, 87% yield). ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.02 (d, 1H), 7.97 (s, 1H), 7.81 (t, 1H), 7.48-7.40 (m, 2H), 4.86 (s, 2H), 4.60 (t, 2H), 4.48 (m, 1H), 4.06 (m, 2H), 3.93 (s, 3H), 3.52 (m, 2H), 3.22-3.14 (m, 6H), 2.37 (m, 2H), 2.20-1.81 (m, 10H), 1.68 (m, 1H), 1.42-1.19 (m, 6H); EI-MS: 662.3 (M+1).

*Preparation of Compound **79***

Compound **79** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.02-7.90 (m, 2H), 7.84-7.71 (m, 3H), 7.70-7.38 (m, 10H), 5.23

(br s, 1H), 4.88 (s, 2H), 4.56 (m, 2H), 4.42-4.23 (m, 2H), 4.07 (m, 1H), 3.78 (m, 1H), 3.32 (m, 1H), 3.22-3.04 (m, 6H), 2.83 (m, 1H), 2.33 (m, 2H), 2.18-1.80 (m, 8H), 1.68 (m, 2H), 1.58 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 788.4 (M+1).

*Preparation of Compound **80***

Compound **80** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.05 (s, 1H), 8.00 (d, 1H), 7.81 (m, 1H), 7.46-7.40 (m, 2H), 5.17 (m, 1H), 4.86 (s, 2H), 4.58 (t, 2H), 4.52-4.38 (m, 2H), 4.20 (m, 1H), 4.03(m, 1H), 3.26 (m, 1H), 3.20-3.12 (m, 6H), 2.87-2.73 (m, 3H), 2.40-2.22 (m, 4H), 2.18-1.81 (m, 8H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 12H); EI-MS: 692.4 (M+1).

*Preparation of Compound **81***

Compound **81** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.05 (s, 1H), 8.02 (d, 1H), 7.83 (t, 1H), 7.58-7.41 (m, 7H), 5.59 (s, 1H), 4.86 (s, 2H), 4.59 (t, 2H), 4.51-4.40 (m, 2H), 4.20 (m, 1H), 4.08(m, 1H), 3.79 (s, 3H), 3.34 (m, 1H), 3.22-3.14 (m, 6H), 2.91-2.78 (m, 3H), 2.42-2.20 (m, 4H), 2.20-1.81 (m, 8H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 6H); EI-MS: 797.5 (M+1).

*Preparation of Compound **82***

Compound **82** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.04 (d, 1H), 8.03 (s, 1H), 7.84 (m, 1H), 7.50-7.44 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.52-4.38 (m, 4H), 4.20 (m, 1H), 4.03(m, 1H), 3.26 (m, 1H), 3.20-3.12 (m, 6H), 2.87-2.73 (m, 3H), 2.40-2.22 (m, 4H), 2.18-1.81 (m, 8H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 9H); EI-MS: 678.4 (M+1).

*Preparation of Compound **83***

Compound **83** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 8.02 (d, 1H), 7.83 (m, 1H), 7.49-7.42 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.50-4.40 (m, 2H), 4.05-3.98(m, 3H), 3.26 (m, 1H), 3.20-3.12 (m, 6H),

2.85 (m, 1H), 2.64 (m, 2H), 2.37 (m, 2H), 2.22 (m, 2H), 2.18-1.81 (m, 8H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 12H); EI-MS: 691.5 (M+1).

*Preparation of Compound **84***

Compound **84** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.01 (m, 2H), 7.83 (t, 1H), 7.48-7.36 (m, 7H), 4.88 (s, 2H), 4.82 (d, 1H), 4.58 (t, 2H), 4.44-4.32 (m, 3H), 4.22-4.12 (m, 3H), 3.96-3.84 (m, 2H), 3.51 (d, 1H), 3.25-3.10 (m, 8H), 2.81 (m, 1H), 2.71 (m, 1H), 2.35 (m, 2H), 2.26 (m, 2H), 2.22-2.05 (m, 5H), 1.94-1.82 (m, 3H), 1.68 (m, 2H), 1.57 (m, 1H), 1.42-1.17 (m, 9H); EI-MS: 825.5 (M+1).

*Preparation of Compound **85***

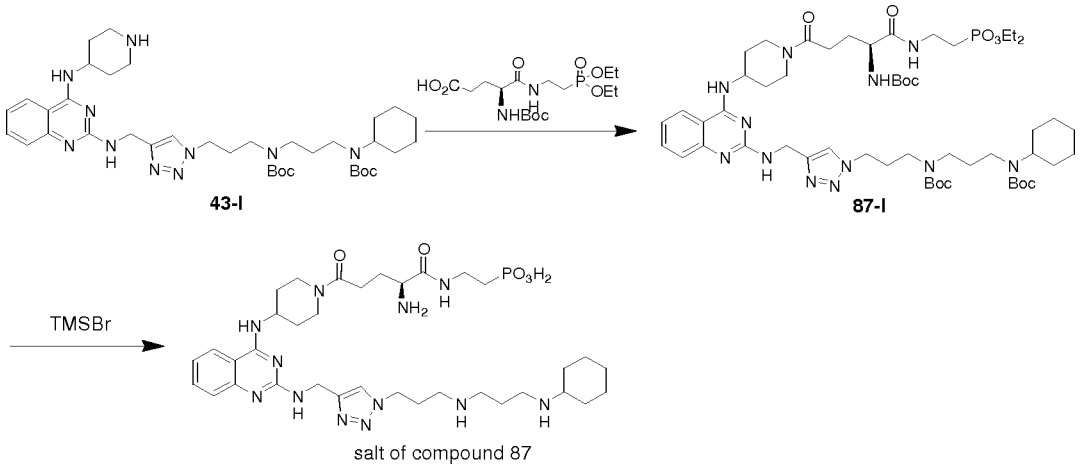
Compound **85** was prepared in a manner similar to that used to prepare compound **61**. EI-MS: 730.4 (M+1).

*Preparation of Compound **86***

Compound **86** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.04-8.02 (m, 2H), 7.83 (t, 1H), 7.50-7.44 (m, 2H), 4.88 (s, 2H), 4.58 (m, 2H), 4.52-4.42 (m, 2H), 4.22-4.01 (m, 6H), 3.51 (m, 2H), 3.32 (m, 1H), 3.22-3.04 (m, 6H), 2.85 (m, 1H), 2.68 (t, 2H), 2.36 (m, 2H), 2.30-2.20 (m, 4H), 2.18-1.80 (m, 8H), 1.68 (m, 2H), 1.58 (m, 1H), 1.42-1.18 (m, 12H); EI-MS: 813.5 (M+1).

*Preparation of Compound **87***

Shown below is a scheme for synthesizing compound **87** from compound 43-I via intermediate 87-I.



To a magnetically stirred solution of 4-tert-Butoxycarbonylamino-4-[2-(diethoxy-phosphoryl)-ethylcarbamoyl]-butyric acid (410 mg) in dichloromethane (50 mL) under an atmosphere of nitrogen was added EDCI (680 mg) and HOBt (589 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 h, a solution of compound 43-I (1000 mg) in dichloromethane (10 mL) was added to the mixture in one potion. The reaction mixture was stirred for another 6 h and then poured into water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1/19) to give compound 87-I (850 mg, 67% yield) as a solid.

TMSBr (0.6 mL) was added to the solution of compound 87-I (200 mg) in dichloromethane (15 mL). The reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrobromide salt of compound **87** (205 mg, 83% yield). ^{1}H NMR (400 MHz, D_2O) δ 8.12 (s, 1H), 7.79 (d, 1H), 7.83 (t, 1H), 7.28-7.17 (m, 2H), 4.86 (s, 2H), 4.59 (t, 2H), 4.42 (m, 1H), 4.24 (m, 1H), 4.08 (m, 1H), 3.98 (s, 1H), 3.57 (m, 2H), 3.26 (m, 1H), 3.20-3.08 (m, 6H), 2.81 (m, 1H), 2.68 (m, 2H), 2.36 (m, 2H), 2.22-1.79 (m, 12H), 1.70 (m, 2H), 1.59 (m, 1H), 1.39-1.18 (m, 6H); EI-MS: 757.4 (M+1).

*Preparation of Compound **88***

Compound **88** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.08 (s, 1H), 7.87 (d, 1H), 7.74 (t, 1H), 7.41-7.30 (m, 2H), 4.86 (s, 2H), 4.59 (t, 2H), 4.03 (t, 1H), 3.66 (t, 2H), 3.22-3.10 (m, 6H), 2.37 (m, 2H), 2.18-1.79 (m, 14H), 1.68 (m, 1H), 1.42-1.17 (m, 6H); EI-MS: 553.3 (M+1).

*Preparation of Compound **89***

Compound **89** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.10-8.00 (m, 3H), 7.86 (m, 1H), 7.52-7.41 (m, 3H), 6.95 (t, 1H), 4.87 (s, 2H), 4.62-4.40 (m, 3H), 4.40-4.26 (m, 2H), 3.78 (m, 1H), 3.20-3.10 (m, 7H), 2.81-2.67 (m, 3H), 2.40-2.26 (m, 4H), 2.20-2.00 (m, 5H), 1.96-1.80 (m, 4H), 1.68 (m, 2H), 1.42-1.18 (m, 6H); EI-MS: 808.4 (M+1).

*Preparation of Compound **90***

Compound **90** was prepared in a manner similar to that used to prepare compound **87**. ^{1}H NMR (400 MHz, D_2O) δ 8.04-8.02 (m, 2H), 7.83 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.53-4.40 (m, 4H), 4.24 (t, 1H), 4.03 (m, 1H), 3.28 (m, 1H), 3.22-3.12 (m, 8H), 2.84(m, 1H), 2.78 (t, 2H), 2.35 (t, 2H), 2.30 (m, 2H), 2.19-1.78 (m, 8H), 1.70 (m, 2H), 1.55 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 758.4 (M+1).

*Preparation of Compound **91***

Compound **91** was prepared in a manner similar to that used to prepare compound **69**. EI-MS: 753.5 (M+1).

*Preparation of Compound **92***

Compound **92** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.05 (s, 1H), 8.01 (m, 1H), 7.81 (t, 1H), 7.47-7.24 (m, 7H), 4.87 (s, 2H), 4.62-4.57 (m, 3H), 4.42-4.38 (m, 2H), 4.24 (m, 1H), 3.91-3.78 (m, 2H), 3.20-3.05 (m, 7H), 2.81 (m, 1H), 2.52 (m, 2H), 2.35 (m, 2H), 2.26-1.80 (m, 11H), 1.68 (m, 1H), 1.58 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 781.5 (M+1).

*Preparation of Compound **93***

Compound **93** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.76 (d, 1H), 8.58 (m, 1H), 8.06-7.97 (m, 4H), 7.83 (t, 1H), 7.50-7.43 (m, 2H), 4.86 (s, 2H), 4.82 (m, 2H), 4.58 (t, 2H), 4.50-4.42 (m, 2H), 4.27 (t, 1H), 3.98 (t, 1H), 3.29 (m, 1H), 3.22-3.14 (m, 6H), 2.85 (m, 1H), 2.72 (m, 2H), 2.41-2.24 (m, 4H), 2.18-2.04 (m, 5H), 1.94-1.81 (m, 3H), 1.70 (m, 2H), 1.53 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 740.5 (M+1).

*Preparation of Compound **94***

Compound 94 was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 8.01 (d, 1H), 7.82 (m, 1H), 7.49-7.42 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.50-4.40 (m, 2H), 4.05-3.98(m, 2H), 3.26 (m, 1H), 3.20-3.12 (m, 6H), 2.85 (m, 1H), 2.71 (m, 1H), 2.64 (m, 2H), 2.35 (m, 2H), 2.20 (m, 2H), 2.18-1.81 (m, 8H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 6H), 0.84 (d, 2H), 0.60 (br s, 2H); EI-MS: 689.5 (M+1).

*Preparation of Compound **95***

Compound **95** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.10 (d, 1H), 8.05-8.01 (m, 2H), 7.85 (t, 1H), 7.50-7.44 (m, 2H), 7.30-7.17 (m, 5H), 4.88 (s, 2H), 4.59-4.45 (m, 3H), 4.38-4.24 (m, 3H), 4.10 (m, 1H), 3.82 (d, 1H), 3.71 (d, 1H), 3.47 (m, 1H), 3.20-3.06 (m, 7H), 2.98-2.64 (m, 3H), 2.42-2.18 (m, 4H), 2.18-2.02 (m, 5H), 1.90-1.76 (m, 4H), 1.68-1.60 (m, 2H), 1.42-1.19 (m, 6H); EI-MS: 820.4 (M+1).

*Preparation of Compound **96***

Compound **96** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.01 (m, 2H), 7.84 (m, 1H), 7.50-7.44 (m, 2H), 7.36 (m, 1H), 7.11 (m, 1H), 6.97 (m, 1H), 4.88 (s, 2H), 4.60-4.36 (m, 6H), 4.09 (t, 1H), 3.69 (m, 1H), 3.22-3.06 (m, 9H), 2.78 (m, 1H), 2.49 (m, 2H), 2.35 (m, 2H), 2.22-2.04 (m, 5H), 1.94-1.81 (m, 4H), 1.70 (m, 1H), 1.54 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 745.4 (M+1).

*Preparation of Compound **97***

Compound **97** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.03 (d, 1H), 7.94-7.80 (m, 2H), 7.61-7.40 (m, 5H), 4.90 (s, 2H), 4.59-4.53 (m, 4H), 4.38-4.28 (m, 2H), 4.12 (m, 1H), 3.78 (s, 3H), 3.58 (m, 1H), 3.20-3.00 (m, 9H), 2.76 (m, 1H), 2.44-2.04 (m, 9H), 1.90-1.78 (m, 4H), 1.67 (m, 1H), 1.50 (m, 1H), 1.40-1.19 (m, 6H); EI-MS: 797.5 (M+1).

*Preparation of Compound **98***

Compound **98** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.08-8.04 (m, 2H), 7.86 (m, 1H), 7.54-7.48 (m, 2H), 7.35 (d, 2H), 7.21 (d, 2H), 4.86 (s, 2H), 4.65-4.53 (m, 4H), 4.42-4.26 (m, 2H), 4.18 (m, 1H), 3.51 (m, 1H), 3.22-3.03 (m, 9H), 2.78 (m, 1H), 2.48-2.22 (m, 4H), 2.18-2.02 (m, 5H), 1.93-1.81 (m, 3H), 1.68 (m, 2H), 1.56 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 773.4 (M+1).

*Preparation of Compound **99***

Compound **99** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.08 (s, 1H), 7.97 (d, 1H), 7.90-7.62 (m, 3H), 7.58-7.38 (m, 4H), 4.88 (s, 2H), 4.64-4.56 (m, 3H), 4.42-4.24 (m, 4H), 3.78 (d, 1H), 3.20-3.06 (m, 7H), 2.90-2.64 (m, 3H), 2.42-2.22 (m, 4H), 2.18-2.02 (m, 5H), 1.94-1.78 (m, 3H), 1.76-1.42 (m, 3H), 1.42-1.19 (m, 6H); EI-MS: 779.5 (M+1).

*Preparation of Compound **100***

Compound **100** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.02 (m, 2H), 7.82 (m, 1H), 7.48-7.42 (m, 2H), 4.86 (s, 2H), 4.55 (t, 2H), 4.48-4.43 (m, 2H), 4.07 (t, 1H), 4.00 (m, 1H), 3.23 (m, 1H), 3.20-3.06 (m, 8H), 2.85 (m, 1H), 2.69 (t, 2H), 2.36 (m, 2H), 2.24 (m, 2H), 2.18-2.02 (m, 5H), 1.98-1.83 (m, 3H), 1.70 (m, 2H), 1.67 (m, 1H), 1.42-1.17 (m, 6H), 1.06 (m, 1H), 0.56 (m, 2H), 0.27 (m, 2H); EI-MS: 703.5 (M+1).

*Preparation of Compound **101***

Compound **101** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.72 (s, 1H), 8.07-8.03 (m, 2H), 7.84 (m, 1H), 7.50-7.44 (m, 3H), 4.86 (s, 2H), 4.65-4.56 (m, 4H), 4.50-4.41 (m, 2H), 4.15 (t, 1H), 3.98 (m, 1H), 3.29 (m, 1H), 3.22-3.12 (m, 6H), 2.84 (m, 1H), 2.67 (m, 2H), 2.36 (m, 2H), 2.24 (m, 2H), 2.18-2.04 (m, 5H), 1.94-1.81 (m, 3H), 1.70 (m, 2H), 1.54 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 729.4 (M+1).

*Preparation of Compound **102***

Compound **102** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.03 (m, 2H), 7.84 (m, 1H), 7.50-7.42 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.52-4.41 (m, 2H), 4.08 (t, 1H), 3.98 (m, 1H), 3.31-3.29 (m, 2H), 3.22-3.11 (m, 6H), 3.03 (m, 1H), 2.84 (m, 1H), 2.65 (t, 2H), 2.37 (m, 2H), 2.24 (m, 2H), 2.18-2.02 (m, 5H), 1.93-1.84 (m, 3H), 1.78-1.50 (m, 10H), 1.42-1.17 (m, 8H), 0.98 (m, 2H); EI-MS: 745.5 (M+1).

*Preparation of Compound **103***

Compound **103** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.00-7.94 (m, 2H), 7.80 (t, 1H), 7.50-7.36 (m, 7H), 5.32 (m, 2H), 4.47 (t, 2H), 4.41 (m, 1H), 4.29 (m, 1H), 4.05-4.03 (m, 2H), 3.87 (m, 2H), 3.22-3.01 (m, 10H), 2.78 (m, 1H), 2.62 (m, 1H), 2.38-2.20 (m, 4H), 2.18-1.82 (m, 9H), 1.68 (m, 1H), 1.56 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 754.5 (M+1).

*Preparation of Compound **104***

Compound **104** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.03 (m, 3H), 7.86 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.82 (m, 2H), 4.74 (d, 1H), 4.58 (t, 2H), 4.46-4.38 (m, 3H), 4.20-4.11 (m, 3H), 3.80 (m, 1H), 3.22-3.12 (m, 7H), 2.81(m, 1H), 2.54 (t, 2H), 2.35 (t, 2H), 2.32-2.02 (m, 7H), 1.98-1.78 (m, 4H), 1.68 (m, 1H), 1.55 (m, 1H), 1.42-1.18 (m, 6H), 1.17 (t, 3H); EI-MS: 816.5 (M+1).

*Preparation of Compound **105***

Compound **105** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.03 (m, 2H), 7.83 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.51-4.40 (m, 2H), 4.09 (t, 1H), 4.01 (m, 1H), 3.40 (m, 2H), 3.30 (m, 1H), 3.20-3.06 (m, 8H), 2.85(m, 1H), 2.68 (t, 2H), 2.35 (t, 2H), 2.22 (m, 2H), 2.18-1.80 (m, 15H), 1.78-1.52 (m, 4H), 1.42-1.18 (m, 12H); EI-MS: 788.5 (M+1).

*Preparation of Compound **106***

Compound **106** was prepared in a manner similar to that used to prepare compounds **1** and **57**. ^{1}H NMR (400 MHz, D_2O) δ 8.09 (s, 1H), 7.92 (m, 1H), 7.77 (t, 1H), 7.43-7.37 (m, 2H), 4.86 (s, 2H), 4.60 (t, 2H), 4.01 (t, 1H), 3.63 (m, 2H), 3.50-3.30 (m, 4H), 3.20-3.10 (m, 6H), 2.38 (m, 2H), 2.18-1.62 (m, 11H), 1.42-1.18 (m, 6H); EI-MS: 660.3 (M+1).

*Preparation of Compound **107***

Compound **107** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.09-8.00 (m, 2H), 7.83 (t, 1H), 7.50-7.41 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.52-4.41 (m, 2H), 4.02 (t, 1H), 3.62-3.56 (m, 5H), 3.32-3.08 (m, 7H), 2.84 (m, 1H), 2.65 (t, 2H), 2.34 (m, 2H), 2.24-1.50 (m, 19H), 1.42-1.17 (m, 6H); EI-MS: 717.5 (M+1).

*Preparation of Compound **108***

Compound **108** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.03 (m, 2H), 7.85 (m, 1H), 7.58-7.46 (m, 6H), 4.86 (s, 2H), 4.56 (m, 2H), 4.42-4.10 (m, 5H), 3.53 (m, 1H), 3.20-3.03 (m, 9H), 2.75 (m, 1H), 2.50-2.22 (m, 4H), 2.18-2.02 (m, 5H), 1.93-1.81 (m, 3H), 1.68 (m, 2H), 1.56 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 807.4 (M+1).

*Preparation of Compound **109***

Compound **109** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.02-7.97 (m, 3H), 7.83 (t, 1H), 7.49-7.43 (m, 2H), 4.93 (s, 2H),

4.86 (s, 2H), 4.57-4.56 (m, 4H), 3.26-3.07 (m, 12H), 2.43-2.28 (m, 4H), 2.21-2.02 (m, 8H), 1.93-1.80 (m, 4H), 1.74-1.63 (m, 2H), 1.44-1.18 (m, 12H); EI-MS: 701.5 (M+1).

*Preparation of Compound **110***

Compound **110** was prepared in a manner similar to that used to prepare compound **63**. EI-MS: 636.4 (M+1).

*Preparation of Compound **111***

Compound **111** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 7.41-7.34 (m, 2H), 7.31 (d, 1H), 4.86 (s, 2H), 4.57 (t, 2H), 4.48 (m, 1H), 4.35 (m, 1H), 4.09 (m, 1H), 4.03(m, 1H), 3.90 (s, 6H), 3.26 (m, 1H), 3.20-3.10 (m, 6H), 2.81 (m, 1H), 2.75 (m, 2H), 2.35 (m, 2H), 2.25 (m, 2H), 2.18-1.81 (m, 8H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 6H); EI-MS: 694.4 (M+1).

*Preparation of Compound **112***

Compound **112** was prepared in a manner similar to that used to prepare compound **63**, ^{1}H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 7.41-7.30 (m, 3H), 4.86 (s, 2H), 4.57 (t, 2H), 4.47 (m, 1H), 4.40 (m, 1H), 4.09 (m, 1H), 4.03(m, 1H), 3.90 (s, 3H), 3.25 (m, 1H), 3.20-3.10 (m, 6H), 2.81 (m, 1H), 2.76 (m, 2H), 2.35 (m, 2H), 2.26 (m, 2H), 2.18-1.81 (m, 8H), 1.68 (m, 2H), 1.52 (m, 1H), 1.42-1.19 (m, 6H); EI-MS: 680.4 (M+1).

*Preparation of Compound **113***

Compound **113** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 8.00 (m, 1H), 7.82 (m, 1H), 7.47-7.42 (m, 2H), 7.28-7.22 (m, 2H), 6.83-6.73 (m, 2H), 4.86 (s, 2H), 4.82 (m, 1H), 4.57 (t, 2H), 4.41-4.24 (m, 2H), 4.18-4.04 (m, 2H), 3.56 (m, 1H), 3.22-3.01 (m, 9H), 2.78 (m, 1H), 2.48-2.18 (m, 4H), 2.18-2.02 (m,5H), 1.93-1.80 (m, 4H), 1.68 (m, 1H), 1.50 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 755.5 (M+1).

*Preparation of Compound **114***

Compound **114** was prepared in a manner similar to that used to prepare compound **87**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.03 (m, 3H), 7.82 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.70 (d, 1H), 4.62-4.56 (m, 4H), 4.46-4.40 (m, 3H), 4.11 (t, 1H), 3.80 (m, 1H), 3.22-3.12 (m, 7H), 2.81(m, 1H), 2.54 (t, 2H), 2.36 (t, 2H), 2.32-2.02 (m, 8H), 1.98-1.78 (m, 5H), 1.68 (m, 1H), 1.55 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 838.4 (M+1).

*Preparation of Compound **115***

Compound **115** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, D_2O) δ 7.97 (d, 1H), 7.93 (s, 1H), 7.78 (t, 1H), 7.44-7.37 (m, 2H), 4.54-4.42 (m, 4H), 4.14 (t, 1H), 4.08 (m, 1H), 3.87 (m, 2H), 3.31 (m, 1H), 3.22-3.01 (m, 9H), 2.92 (m, 1H), 2.77 (m, 1H), 2.36-2.20 (m, 4H), 2.18-1.80 (m, 8H), 1.68 (m, 2H), 1.61 (m, 1H), 1.42-1.18 (m, 6H) ; EI-MS: 664.4 (M+1).

*Preparation of Compound **116***

Compound **116** was prepared in a manner similar to that used to prepare compound **69**. ^{1}H NMR (400 MHz, D_2O) δ 8.07-8.04 (m, 2H), 7.86 (t, 1H), 7.54-7.48 (m, 2H), 7.38-7.35 (m, 2H), 6.88-6.80 (m, 2H), 4.86 (s, 2H), 4.80-4.76 (m, 3H), 4.22-4.06 (m, 2H), 3.51 (m, 1H), 3.22-3.00 (m, 9H), 2.78 (m, 1H), 2.48-2.22 (m, 4H), 2.18-2.02 (m, 5H), 1.93-1.81 (m, 3H), 1.68 (m, 2H), 1.56 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 769.5 (M+1).

*Preparation of Compound **117***

Compound **117** was prepared in a manner similar to that used to prepare compounds **1** and **57**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s,1H), 8.26-8.22 (m, 2H), 7.79 (t, 1H), 7.48-7.41 (m, 2H), 4.91 (s, 2H), 4.68-4.61 (m, 4H), 4.07 (t, 1H), 3.73 (m, 2H), 3.24-3.10 (m, 8H), 2.45-2.37 (m, 4H), 2.25-1.78 (m, 10H), 1.68 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 741.4 (M+1).

*Preparation of Compound **118***

Compound **118** was prepared in a manner similar to that used to prepare compounds **1** and **57**. EI-MS: 646.3 (M+1).

*Preparation of Compound **119***

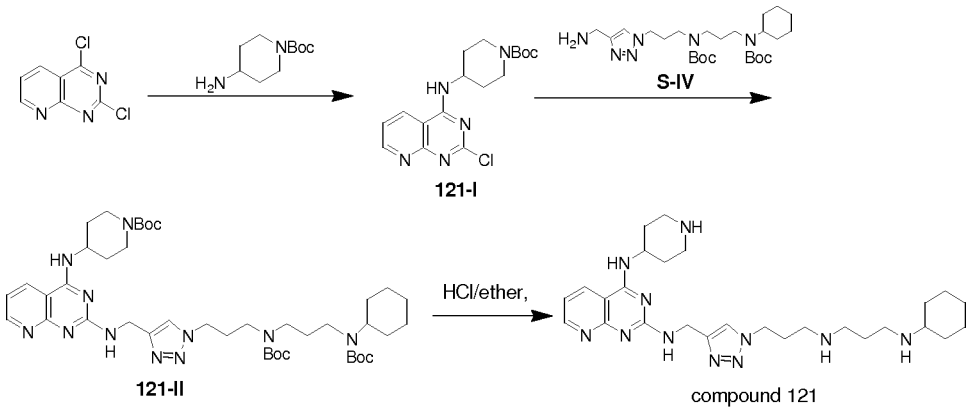
Compound **119** was prepared in a manner similar to that used to prepare compound **87**. ^{1}H NMR (400 MHz, D_2O) δ 8.03-8.00 (m, 2H), 7.82 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.46-4.43 (m, 2H), 4.14 (t, 1H), 4.01 (m, 1H), 3.53 (m, 2H), 3.23 (m, 1H), 3.22-3.14 (m, 6H), 2.84 (m, 1H), 2.70 (t, 2H), 2.36 (t, 2H), 2.23 (m, 2H), 2.19-2.02 (m, 4H), 1.99-1.81 (m, 4H), 1.68 (m, 2H), 1.58 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 743.4 (M+1).

*Preparation of Compound **120***

Compound **120** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.05 (s, 1H), 8.01 (d, 1H), 7.82 (t, 1H), 7.68-7.41 (m, 8H), 4.86 (s, 2H), 4.55 (t, 2H), 4.49 (t, 2H), 4.42 (m, 1H), 3.69 (m, 1H), 3.59 (m, 1H), 3.22-3.04 (m, 8H), 2.40-2.26 (m, 4H), 2.20-1.80 (m, 12H), 1.71 (m, 1H), 1.43-1.18 (m, 6H); EI-MS: 750.4 (M+1).

*Preparation of Compound **121***

Shown below is a scheme for synthesizing compound **121** via intermediate 121-I and 121-II.



To a magnetically stirred solution of 2,4-dichloro-pyrido[2,3-d]pyrimidine (450 mg) in THF (30 mL) under an atmosphere of nitrogen was added 4-Amino-piperidine-1-carboxylic acid tert-butyl ester (470 mg) and TEA (500 mg). The mixture was stirred at 25 ^{o}C for 15 h and then quenched with aqueous NH_4Cl (50 mL, 2 M). The mixture was

extracted with ethyl acetate (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by recrystallization from n-hexane / ethyl acetate to give compound 121-I (610 mg, 75% yield) as a light yellow solid.

A solution of compounds 121-I (610 mg) and **S-IV** (860 mg) in 1-pentanol (3 mL) was heated at 120 °C for 2 minutes using microwave radiation. The resulting mixture was concentrated. The residue thus obtained was purified by flash chromatography with MeOH / DCM (1:9) to afford compound 121-II (825 mg, 60% yield).

A solution of 1N HCl/diethyl ether (8 mL) was added to the solution of compound 121-II (400 mg) in dichloromethane (16 mL). The reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrochloride salt of compound **121** (348 mg, 93% yield). ^{1}H NMR (400 MHz, D_2O) δ 8.72 (d, 1H), 8.58 (d, 1H), 8.05 (s, 1H), 7.51 (dd, 1H), 4.91 (s, 2H), 4.57 (t, 2H), 4.51 (m, 1H), 3.56 (m, 2H), 3.22-3.08 (m, 8H), 2.36 (m, 2H), 2.22-2.04 (m, 6H),1.98-1.82 (m, 4H), 1.68 (m, 1H), 1.41-1.18 (m, 6H); EI-MS: 522.3 (M+1).

*Preparation of Compound **122***

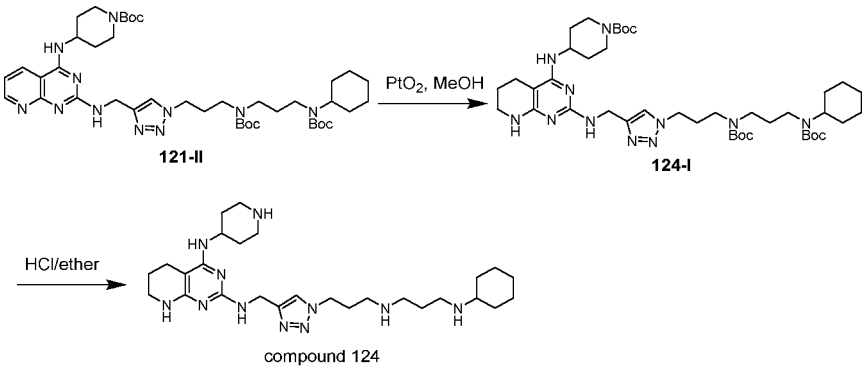
Compound **122** was prepared in a manner similar to that used to prepare compounds **121** and **45**. EI-MS: 618.3 (M+1).

*Preparation of Compound **123***

Compound **123** was prepared in a manner similar to that used to prepare compounds **121** and **63**. EI-MS: 651.4 (M+1).

*Preparation of Compound **124***

Shown below is a scheme for synthesizing compound **124** from compound 121-II via intermediate 124-I.



A solution of compound 121-II (400 mg) and PtO_2 (40 mg) in methanol (8 mL) was stirred under H_2 (1 atm) at 25 °C for 15 h. The resulting mixture was concentrated. The resulting residue was purified by flash chromatography with MeOH / DCM (1: 4) to afford compound 124-I (310 mg, 77% yield).

A solution of 1N HCl/diethyl ether (6 mL) was added to the solution of compound 124-I (310 mg) in dichloromethane (12 mL). The reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrochloride salt of compound **124** (223 mg, 88% yield). EI-MS: 526.4 (M+1).

*Preparation of Compound **125***

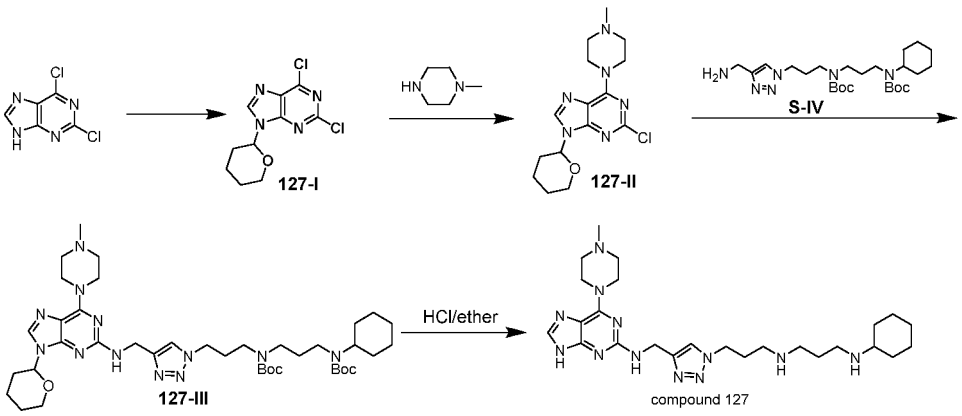
Compound **125** was prepared in a manner similar to that used to prepare compounds **122** and **124**. EI-MS: 622.4 (M+1).

*Preparation of Compound **126***

Compound **126** was prepared in a manner similar to that used to prepare compounds **63** and **124**. EI-MS: 655.4 (M+1).

*Preparation of Compound **127***

Shown below is a scheme for synthesizing compound **127** via intermediates 127-I to 127-III.



To a magnetically stirred solution of 2,6-dichloropurine (10 g) in ethyl acetate (100 mL) was added *p*-toluenesulfonic acid monohydrate (0.08 g). The resultant mixture was heated to 50 °C under an atmosphere of nitrogen and 3,4-dihydro-2*H*-pyran (7.5 mL) was added over a period of 2 h. The mixture was stirred at 25 °C for 15 h and filtrated to give crude solid. The solid was washed with n-hexane / ethyl acetate (1:1) to afford compound 127-I (14.4 g, 100% yield) as a colorless solid.

To a magnetically stirred solution of compound 127-I (1.01 g) in THF (30 mL) under an atmosphere of nitrogen was added 1-methyl-piperazine (500 mg) and TEA (1.01 g). The mixture was heated to 50 °C for 15 h and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with ethyl acetate (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with n-hexane / ethyl acetate (1:9) to give compound 127-II (0.93 g, 76% yield) as a solid.

A solution of compounds 127-II (800 mg) and S-IV (1.32 g) in 1-pentanol (3 mL) was heated at 150 °C for 180 minutes using microwave radiation. The reaction mixture was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1/9) to afford compound 127-III (322 mg, 17% yield).

A solution of 1N HCl/diethyl ether (8 mL) was added to the solution of compound 127-III (322 mg) in dichloromethane (16 mL). The reaction mixture was stirred at

25 °C for 15 h and concentrated to afford hydrochloride salt of compound **127** (248 mg, 89% yield). EI-MS: 511.3 (M+1).

*Preparation of Compound **128***

Compound **128** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 7.60 (d, 1H), 7.40 (d, 1H), 4.84 (s, 2H), 4.65 (t, 2H), 4.37 (m, 4H), 3.47 (m, 4H), 3.28-3.08 (m, 6H), 2.44 (m, 2H), 2.20-2.13 (m, 4H), 2.02 (m, 2H), 1.71 (m, 1H), 1.43-1.18 (m, 6H); EI-MS: 513.3 (M+1).

*Preparation of Compound **129***

Compound **129** was prepared in a manner similar to that used to prepare compound **1**. EI-MS: 471.3 (M+1).

*Preparation of Compound **130***

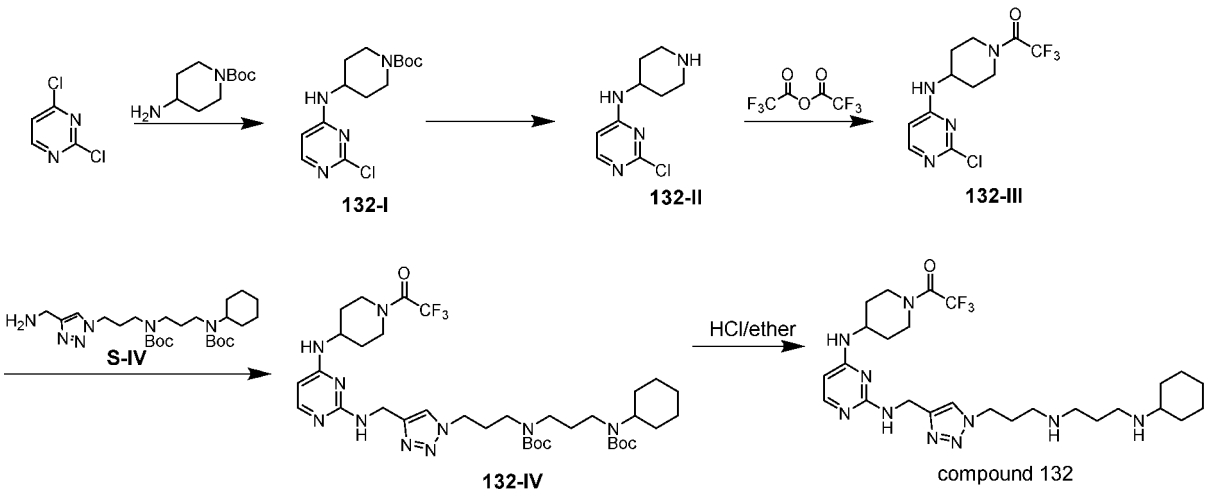
Compound **130** was prepared in a manner similar to that used to prepare compound **1**. EI-MS: 457.3 (M+1).

*Preparation of Compound **131***

Compound **131** was prepared in a manner similar to that used to prepare compound **1**. EI-MS: 499.4 (M+1).

*Preparation of Compound **132***

Shown below is a scheme for synthesizing compound **132** from 2,4-dichloropyrimidine via intermediates 132-I to 132-IV.



To a magnetically stirred solution of 2,4-dichloro-pyrimidine (4.01 g) in THF (120 mL) under an atmosphere of nitrogen was added 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester (6.42 g) and TEA (4.01 g). The mixture was stirred at 25 °C for 15 h and then quenched with aqueous NH_4Cl (200 mL, 2 M). The solution was extracted with ethyl acetate (3x400 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with n-hexane / ethyl acetate (1:1) to give compound 132-I (4.4 g, 63% yield) as a solid.

A solution of 1N HCl/diethyl ether (56 mL) was added to the solution of compound 132-I (4.4 g) in dichloromethane (112 mL). The reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrochloride salt of compound 132-II (2.8 g, 88% yield).

To a magnetically stirred solution of hydrochloride salt of compound 132-II (2.8 g) in dichloromethane (42 mL) under an atmosphere of nitrogen was added trifluoroacetic anhydride (2.8 g) and TEA (2.8 g) at 5-10 °C. The reaction mixture was stirred at 25 °C for 2 h and then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with n-hexane / ethyl acetate (1:3) to give compound 132-III (1.9 g, 55% yield).

A solution of compounds 132-III (1.2 g) and S-IV (2.0 g) in 1-pentanol (3 mL) was heated at 120 °C for 10 minutes using microwave radiation. The resulting mixture was concentrated. The residue thus obtained was purified by flash chromatography with MeOH / DCM (1/32) to afford compound 132-IV (1.8 g, 60% yield).

A solution of 1N HCl/diethyl ether (3.3 mL) was added to the solution of compound 132-IV (256 mg) in dichloromethane (6.6 mL). The reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrochloride salt of compound **132** (203 mg, 90% yield). EI-MS: 567.3 (M+1).

*Preparation of Compound **133***

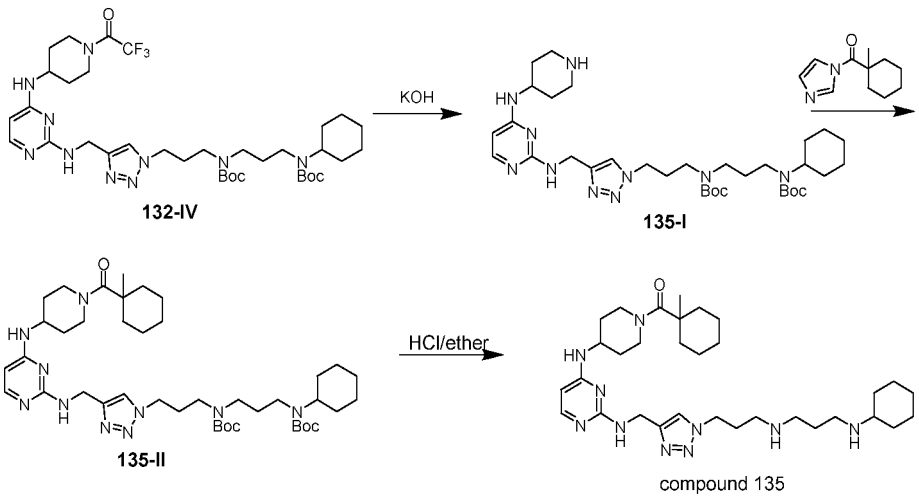
Compound **133** was prepared in a manner similar to that used to prepare compound **40**. EI-MS: 586.4 (M+1).

*Preparation of Compound **134***

Compound **134** was prepared in a manner similar to that used to prepare compound **40**. EI-MS: 551.4 (M+1).

*Preparation of Compound **135***

Shown below is a scheme for synthesizing compound **135** from compound 132-IV via intermediates 135-I and 135-II.



To a magnetically stirred solution of compound 132-IV (320 mg) in EtOH (2 mL) under an atmosphere of nitrogen was added a solution of KOH (64 mg) in H_2O (0.64 mL). The mixture was stirred at 25 °C for 15 h and then concentrated. The resulting residue was extracted with ethyl acetate (3x50 mL). The combined extracts were concentrated to give compound 135-I (250 mg, 89% yield) as a solid.

To a magnetically stirred solution of compound 135-I (250 mg) in THF (8 mL) under an atmosphere of nitrogen was added imidazol-1-yl-(1-methyl-cyclohexyl)-methanone (100 mg). The reaction mixture was stirred at 60 °C for 15 h and then concentrated. The resulting residue was purified by flash chromatography on silica gel with MeOH / DCM (1:32) to give compound 135-II (231 mg, 78% yield) as a solid.

A solution of 1N HCl/diethyl ether (4.6 mL) was added to the solution of compound 135-II (231 mg) in dichloromethane (9.2 mL). The reaction mixture was stirred for 15 h and concentrated to afford hydrochloride salt of compound **135** (168 mg, 82% yield). EI-MS: 595.4(M+1).

*Preparation of Compound **136***

Compound **136** was prepared in a manner similar to that used to prepare compounds **56** and **135**. EI-MS: 555.4 (M+1).

*Preparation of Compound **137***

Compound **137** was prepared in a manner similar to that used to prepare compounds **56** and **135**. EI-MS: 569.4 (M+1).

*Preparation of Compound **138***

Compound **138** was prepared in a manner similar to that used to prepare compounds **55** and **135**. EI-MS: 543.4 (M+1).

*Preparation of Compound **139***

Compound **139** was prepared in a manner similar to that used to prepare compounds **61** and **135**. EI-MS: 690.4 (M+1).

*Preparation of Compound **140***

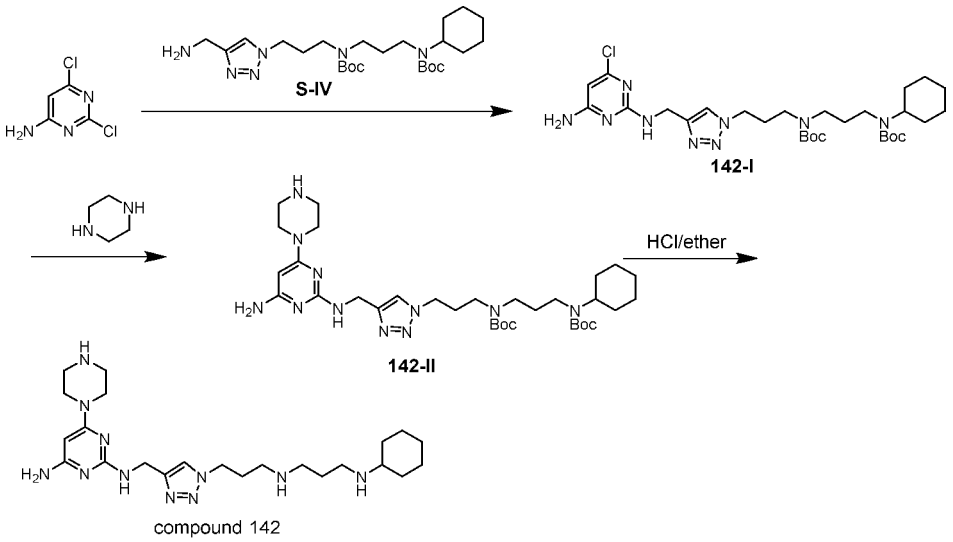
Compound **140** was prepared in a manner similar to that used to prepare compounds **61** and **135**. ^{1}H NMR (400 MHz, D_2O) δ 8.01 (s, 1H), 7.53 (d, 1H), 7.47-7.38 (m, 5H), 6.16 (d, 1H), 5.38 (d, 1H), 5.24 (d, 1H), 4.75 (s, 2H), 4.53 (t, 2H), 4.28 (m, 1H), 4.06-4.01 (m, 2H), 3.57 (m, 1H), 3.37 (m, 1H), 3.22-3.05 (m, 7H), 2.82 (t, 1H), 2.52 (m, 2H), 2.37-2.06 (m, 11H), 1.90-1.55 (m, 5H), 1.43-1.18 (m, 6H); EI-MS: 704.4 (M+1).

*Preparation of Compound **141***

Compound **141** was prepared in a manner similar to that used to prepare compounds **61** and **135**. ^{1}H NMR (400 MHz, D_2O) δ 8.02 (s, 1H), 7.55 (d, 1H), 6.09 (d, 1H), 4.83 (s, 2H), 4.58 (t, 2H), 4.36-4.02 (m, 5H), 3.92 (m, 1H), 3.28 (m, 1H), 3.22-3.06 (m, 6H), 2.92 (m, 1H), 2,74 (m, 2H), 2.40-2.22 (m, 4H), 2.18-1.80 (m, 10H), 1.77-1.45 (m, 9H), 1.42-1.18 (m, 10H); EI-MS: 696.5 (M+1).

*Preparation of Compound **142***

Shown below is a scheme for synthesizing compound **142** via intermediates 142-I and 142-II.



A solution of 2,6-dichloro-pyrimidin-4-ylamine (0.51 g) and compound S-IV (1.46 g) in 1-pentanol (2 mL) was heated at 120 °C for 15 minutes using microwave radiation. The

mixture was concentrated. The resulting residue was purified by flash chromatography with MeOH / DCM (1/32) to afford compound 142-I (0.98 g, 51% yield).

To a magnetically stirred solution of compound 142-I (0.98 g) in 1-pentanol (4 mL) under an atmosphere of nitrogen was added piperazine (2 g). The mixture was stirred at 150 °C for 4 hours and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with ethyl acetate (3X 100 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH/DCM (1:1) to give compound 142-II (0.77 g, 73% yield) as a solid.

A solution of 1N HCl/diethyl ether (6 mL) was added to the solution of compound 142-II (304 mg) in dichloromethane (12 mL). The reaction mixture was stirred at 25 °C for 15 hours and concentrated to afford hydrochloride salt of compound **142** (256 mg, 86% yield). EI-MS: 472.3 (M+1).

*Preparation of Compound **143***

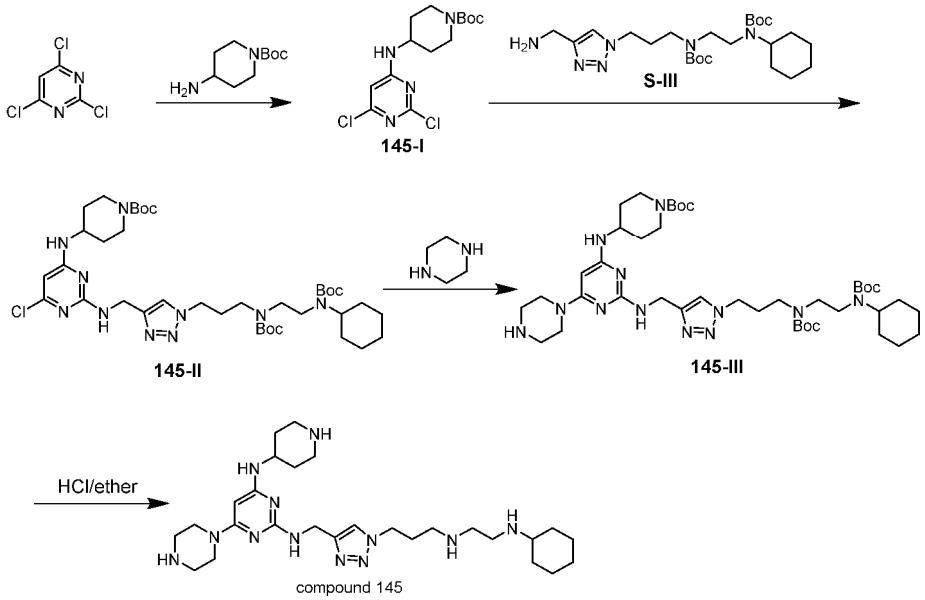
Compound **143** was prepared in a manner similar to that used to prepare compound **142**. EI-MS: 458.3 (M+1).

*Preparation of Compound **144***

Compound **144** was prepared in a manner similar to that used to prepare compound **142**. EI-MS: 458.3 (M+1).

*Preparation of Compound **145***

Shown below is a scheme for synthesizing compound **145** via intermediates 145-I to 145-III.



To a magnetically stirred solution of 2,4,6-trichloro-pyrimidine (1.02 g) in THF (50 mL) under an atmosphere of nitrogen was added 4-Amino-piperidine-1-carboxylic acid tert-butyl ester (1.01 g) and TEA (1.01 g). The mixture was stirred at 25 °C for 15 hours and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with ethyl acetate (3x100 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with n-hexane / ethyl acetate (1:1) to give compound 145-I (1.27 g, 66% yield) as a solid.

A solution of compounds 145-I (1.27 g) and S-III (1.76 g) in 1-pentanol (4 mL) was heated with at 120 °C for 15 minutes using microwave radiation. The resulting mixture was then concentrated. The residue thus obtained was purified by flash chromatography with MeOH / DCM (1:9) to afford compound 145-II (1.48 g, 51% yield).

To a magnetically stirred solution of compound 145-II (0.96 g) in 1-pentanol (4 mL) under an atmosphere of nitrogen was added piperazine (2 g). The mixture was stirred at 150 °C for 4 h and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with ethyl acetate (3x100 mL). The combined extracts were washed with

brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:1) to give compound 145-III (0.72 g, 70% yield).

A solution of 1N HCl/diethyl ether (8 mL) was added to the solution of compound 145-III (360 mg) in dichloromethane (16 mL). The reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrochloride salt of compound **145** (267 mg, 86% yield). EI-MS: 541.4 (M+1).

*Preparation of Compound **146***

Compound **146** was prepared in a manner similar to that used to prepare compound **145**. EI-MS: 542.4 (M+1).

*Preparation of Compound **147***

Compound **147** was prepared in a manner similar to that used to prepare compound **145**. EI-MS: 540.4 (M+1).

*Preparation of Compound **148***

Compound **148** was prepared in a manner similar to that used to prepare compound **145**. EI-MS: 599.4 (M+1).

*Preparation of Compound **149***

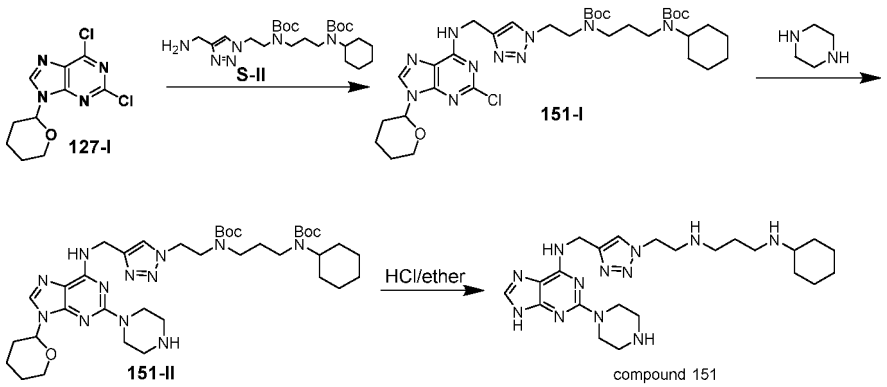
Compound **149** was prepared in a manner similar to that used to prepare compound **145**. EI-MS: 541.4 (M+1).

*Preparation of Compound **150***

Compound **150** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, D_2O) δ 8.05 (s, 1H), 7.44-7.41 (m, 3H), 7.33 (t, 2H), 7.25 (t, 1H), 5.29 (s, 2H), 4.73 (s, 2H), 4.58 (t, 2H), 4.31 (t, 1H), 3.50 (m, 4H), 3.30-3.10 (m, 10H), 2.58 (m, 2H), 2.42-2.22 (m, 4H), 2.18-2.02 (m, 4H), 1.87 (m, 2H), 1.68 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 691.4 (M+1).

*Preparation of Compound **151***

Shown below is a scheme for synthesizing compound **151** from compound 127-I via intermediates 151-I and 151-II.



To a magnetically stirred solution of compound 127-I (1.3 g) in ethyl acetate (35 mL) under an atmosphere of nitrogen was added compound S-II (2.3 g) and TEA (1.5 g). The mixture was heated to 50 °C for 4 h, cooled down to 25 °C, and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with ethyl acetate (3x100 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:9) to afford compound 151-I (2.1g, 62% yield) as a light yellow solid.

A solution of compound 151-I (2.1 g) and piperazine (2 g) in 1-pentanol (6 mL) was heated at 100 °C for 15 h. The resulting mixture was concentrated. The residue thus obtained was purified with flash chromatography on silica gel with MeOH / DCM (1:1) to afford compound 151-II (1.2 g, 53% yield).

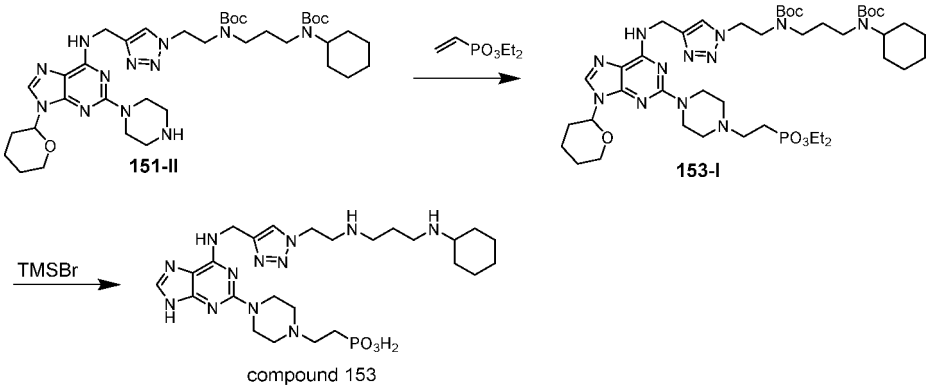
A solution of 1N HCl/diethyl ether (4.8 mL) was added to the solution of compound 151-II (240 mg) in dichloromethane (9.6 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **151** (186 mg, 89% yield). EI-MS: 483.3 (M+1).

*Preparation of Compound **152***

Compound **152** was prepared in a manner similar to that used to prepare compound **151**. EI-MS: 497.3 (M+1).

*Preparation of Compound **153***

Shown below is a scheme for synthesizing compound **153** from compound 151-II via intermediate 153-I.

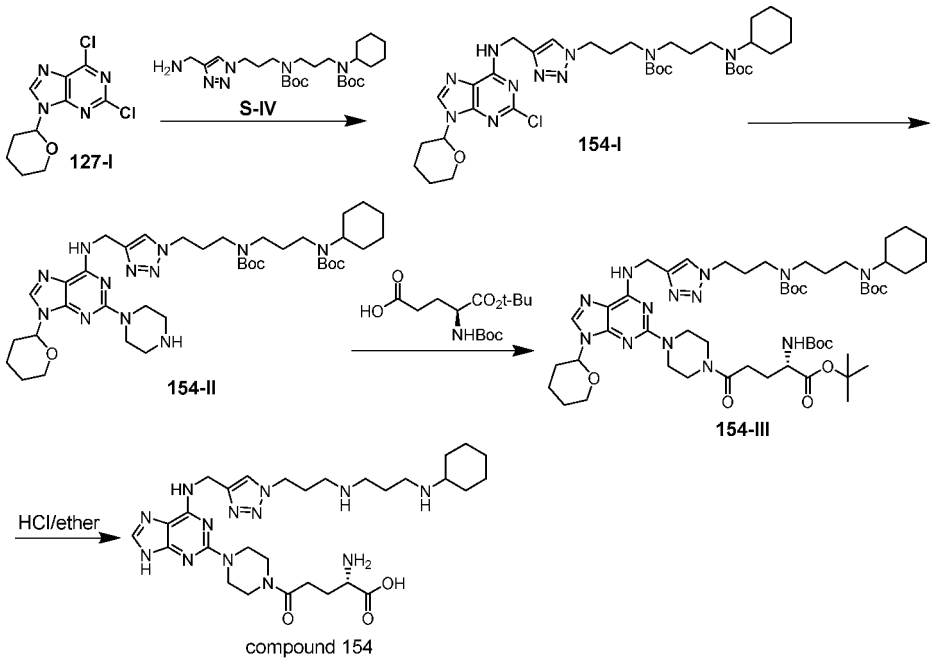


To a magnetically stirred solution of compound 151-II (350 mg) in MeOH (10 mL) under an atmosphere of nitrogen was added diethyl vinylphosphonate (224 mg). The mixture was stirred at 25 °C for 15 h and then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/9 to give compound 153-I (320 mg, 75% yield) as a solid.

TMSBr (1 mL) was added to the solution of compound 153-I (320 mg) in dichloromethane (10 mL). The reaction mixture was stirred for 15 h and concentrated to afford hydrobromide salt of compound **153** (220 mg, 92% yield). EI-MS: 591.3 (M+1).

*Preparation of Compound **154***

Shown below is a scheme for synthesizing compound **154** from compound 127-I via intermediates 154-I to 154-III.



To a magnetically stirred solution of compound 127-I (1.0 g) in ethyl acetate (35 mL) under an atmosphere of nitrogen was added compound S-IV (2.0 g) and TEA (1.2 g). The mixture was heated to 50 °C for 4 h, cooled down to 25 °C, and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with ethyl acetate (3x100 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The resulting residue was purified by flash chromatography on silica gel with MeOH / DCM (1:9) to afford compound 154-I (1.7 g, 64% yield) as a light yellow solid.

A solution of compound 154-I (1.7 g) and piperazine (2 g) in 1-pentanol (6 mL) was heated at 100 °C for 15 h. The resulting mixture was concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:1) to afford compound 154-II (1.2 g, 66% yield).

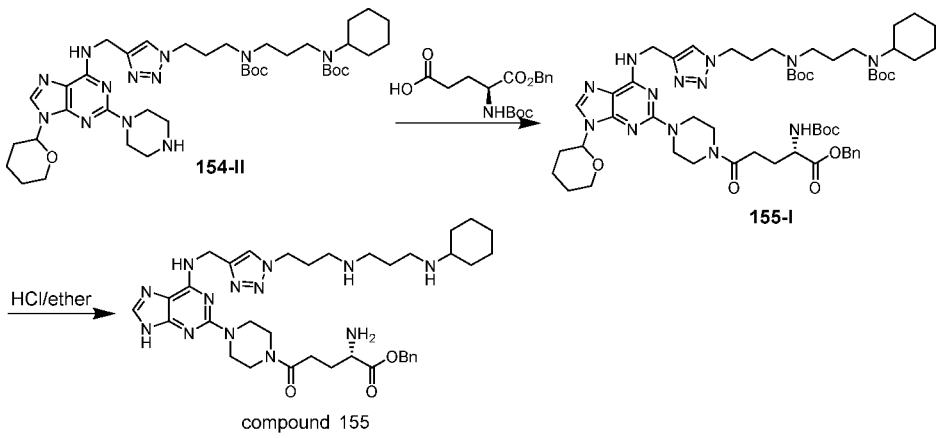
To a magnetically stirred solution of 3-tert-butoxycarbonylamino-pentanedioic acid mono-tert-butyl ester (150 mg) in dichloromethane (30 mL) under an atmosphere of nitrogen was added EDCI (100 mg) and HOBt (100 mg) at 25 °C. After the mixture was stirred at

25 °C for 1 h, a solution of compound 154-II (200 mg) in dichloromethane (10 mL) was added in one potion. The reaction mixture was stirred for another 6 h and then poured into water. The resulting solution was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/9 to give compound 154-III (185 mg, 67% yield) as a solid.

A solution of 1N HCl/diethyl ether (2 mL) was added to the solution of compound 154-III (185 mg) in dichloromethane (4 mL). The reaction mixture was stirred for 15 h and concentrated to afford hydrochloride salt of compound **154** (113 mg, 89% yield). ^{1}H NMR (400 MHz, D_2O) δ 8.21 (s, 1H), 8.05 (s, 1H), 4.95 (s, 2H), 4.57 (t, 2H), 4.11 (m, 1H), 3.90 (m, 4H), 3.78 (m, 4H), 3.22-3.10 (m, 6H), 2.76 (m, 2H), 2.35 (m, 2H), 2.28 (m, 2H), 2.20-2.02 (m, 4H), 1.86 (m, 2H), 1.67 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 626.4 (M+1).

*Preparation of Compound **155***

Shown below is a scheme for synthesizing compound **155** from compound 154-II via intermediate 155-I.



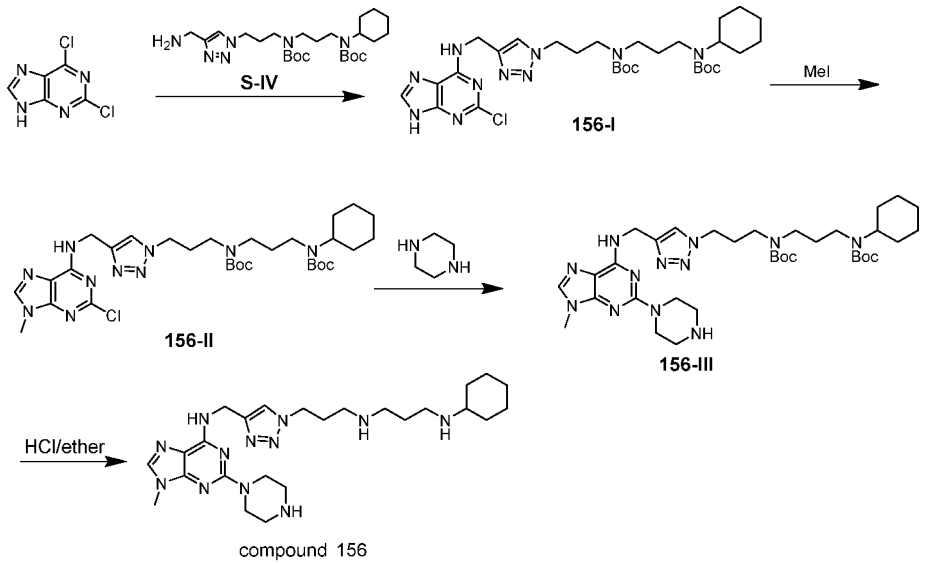
To a magnetically stirred solution of 3-tert-Butoxycarbonylamino-pentanedioic acid monobenzyl ester (0.4 g) in dichloromethane (30 mL) under an atmosphere of nitrogen was added EDCI (225 mg) and HOBt (200 mg) at 25 °C. After the mixture was stirred at 25 °C

for 1 h, a solution of compound 154-II (0.5 g) in dichloromethane was added in one potion. The reaction mixture was stirred for another 6 h and then poured into water. The resulting solution was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1/9) to give compound 155-I (570 mg, 81% yield) as a solid.

A solution of 1N HCl/diethyl ether (4 mL) was added to the solution of compound 155-I (190 mg) in dichloromethane (8 mL). The reaction mixture was stirred for 15 h and concentrated to afford hydrochloride salt of compound **155** (135 mg, 87% yield). EI-MS: 716.4 (M+1).

*Preparation of Compound **156***

Shown below is a scheme for synthesizing compound **156** via intermediates 156-I to 156-III.



To a magnetically stirred solution of 2,6-dichloropurine (0.5 g) in *t*-BuOH (30 mL) under an atmosphere of nitrogen was added compound S-IV (1.51 g) and TEA (0.5 g). The mixture was heated to 50 °C for 4 h and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with ethyl acetate (3x50 mL). The combined extracts

were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:9) to afford compound 156-I (1.52 g, 89% yield) as a solid.

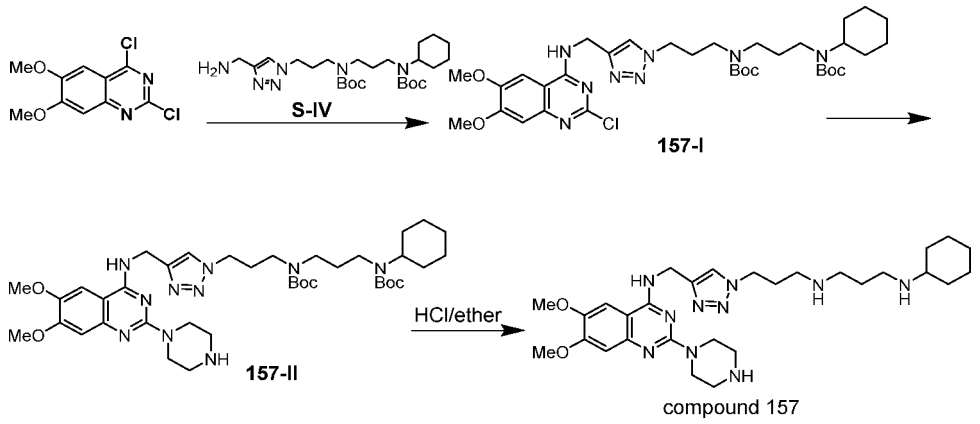
A solution of compound 156-I (300 mg), MeI (300 mg), and K_2CO_3 (72 mg) in DMF (6 mL) was stirred at 25 °C for 3 h. The reaction mixture was then poured into water. The resulting solution was extracted with ethyl acetate (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:9) to afford compound 156-II (297 mg, 97% yield).

A reaction mixture of compound 156-II (210 mg) and piperazine (87 mg) in ethylene glycol monomethyl ether (6 mL) was heated at 120 °C for 15 h. The reaction mixture was then poured into water. The resulting solution was extracted with ethyl acetate (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography with MeOH / DCM (1:1) to afford compound 156-III (156 mg, 69% yield).

A solution of 1N HCl/diethyl ether (3 mL) was added to the solution of compound 156-III (156 mg) in Dichloromethane (6 mL). The reaction mixture was stirred at 25 °C for 15 h and concentrated to afford hydrochloride salt of compound **156** (132 mg, 87% yield). EI-MS: 511.3 (M+1).

*Preparation of Compound **157***

Shown below is a scheme for synthesizing compound **157** via intermediates 157-I and 157-II.



To a magnetically stirred solution of 2,4-dichloro-6,7-dimethoxy-quinazoline (0.5 g) in THF (60 mL) under an atmosphere of nitrogen was added compound S-IV (1.2 g) and TEA (0.5 g). The reaction mixture was stirred at room temperature for 15 h and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with ethyl acetate (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with EtOAc / Hexane (9:1) to afford compound 157-I (1.15 g, 82% yield) as light yellow solid.

A solution of compound 157-I (1.15 g) and piperazine (0.6 g) in 1-pentanol (6 mL) was heated at 100 °C for 15 h. The resulting mixture was concentrated. The residue thus obtained was purified by flash chromatography with MeOH / DCM (1:3) to afford compound 157-II (0.82 g, 67% yield).

A solution of 1N HCl/diethyl ether (4.8 mL) was added to the solution of compound 157-II (250 mg) in dichloromethane (9.6 mL). The reaction mixture was stirred for 15 h and concentrated to afford hydrochloride salt of compound **157** (210 mg, 90% yield). EI-MS: 567.4 (M+1).

*Preparation of Compound **158***

Compound **158** was prepared in a manner similar to that used to prepare compounds **157** and **57**. ^1H NMR (400 MHz, D_2O) δ 8.27-8.24 (m, 2H), 7.82 (t, 1H), 7.50-7.42 (m, 2H),

4.86 (s, 2H), 4.73- 4.60 (m, 3H), 3.77 (m, 2H), 3.53-3.41 (m, 4H), 3.23-3.06 (m, 8H), 2.43-2.06 (m, 10H), 1.87 (m, 2H), 1.70 (m, 1H), 1.43-1.18 (m, 6H); EI-MS: 675.4 (M+1).

*Preparation of Compound **159***

Compound **159** was prepared in a manner similar to that used to prepare compound **157**. EI-MS: 513.3 (M+1).

*Preparation of Compound **160***

Compound **160** was prepared in a manner similar to that used to prepare compound **157**. EI-MS: 508.3 (M+1).

*Preparation of Compound **161***

Compound **161** was prepared in a manner similar to that used to prepare compound **157**. EI-MS: 471.3 (M+1).

*Preparation of Compound **162***

Compound **162** was prepared in a manner similar to that used to prepare compound **145**. EI-MS: 541.4 (M+1).

*Preparation of Compound **163***

Compound **163** was prepared in a manner similar to that used to prepare compound **63**. EI-MS: 664.4 (M+1).

*Preparation of Compound **164***

Compound **164** was prepared in a manner similar to that used to prepare compound **87**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 8.00 (s, 1H), 4.68-4.55 (m, 7H), 4.43 (d, 1H), 3.97 (t, 1H), 3.76-3.61 (m, 6H), 3.36-3.06 (m, 8H), 2.64 (t, 2H), 2.42-2.30 (m, 4H), 2.32-2.12 (m, 6H), 1.92-1.81 (m, 2H), 1.71 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 789.4 (M+1).

*Preparation of Compound **165***

Compound **165** was prepared in a manner similar to that used to prepare compound **63**. EI-MS: 664.4 (M+1).

*Preparation of Compound **166***

Compound **166** was prepared in a manner similar to that used to prepare compound **63**. EI-MS: 664.4 (M+1).

*Preparation of Compound **167***

Compound **167** was prepared in a manner similar to that used to prepare compound **142**. EI-MS: 351.1 (M+1).

*Preparation of Compound **168***

Compound **168** was prepared in a manner similar to that used to prepare compound **142**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 4.68 (s, 2H), 4.55 (t, 2H), 3.96 (m, 4H), 3.53 (m, 2H), 3.30 (m, 4H), 3.16 (m, 2H), 2.95 (m, 2H), 2.41 (m, 2H), 2.00-1.78 (m, 5H), 1.50 (m, 1H); EI-MS: 401.3 (M+1).

*Preparation of Compound **169***

Compound **169** was prepared in a manner similar to that used to prepare compound **142**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 6.22 (s, 1H), 4.71 (s, 2H), 4.56 (t, 2H), 3.08 (m, 2H), 2.31 (m, 2H), 2.09 (m, 2H), 1.85 (m, 2H), 1.71 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 365.2 (M+1).

*Preparation of Compound **170***

Compound **170** was prepared in a manner similar to that used to prepare compound **142**. ^{1}H NMR (400 MHz, D_2O) δ 8.05 (s, 1H), 4.73 (s, 2H), 4.60 (t, 2H), 3.96 (m, 4H), 3.35 (m, 4H), 3.07 (m, 2H), 2.34 (m, 2H), 2.03 (m, 2H), 1.85 (m, 2H), 1.69 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 415.3 (M+1).

*Preparation of Compound **171***

Compound **171** was prepared in a manner similar to that used to prepare compound **29**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (d, 1H), 8.14 (s, 1H), 7.82 (t, 1H), 7.48-7.42 (m, 2H), 4.86 (s, 2H), 4.62 (m, 1H), 4.56 (t, 2H), 3.52 (m, 2H), 3.24 (m, 2H), 3.07 (m, 2H), 2.31

(m, 2H), 2.22-1.98 (m, 6H), 1.85 (m, 2H), 1.68 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 464.3 (M+1).

*Preparation of Compound **172***

Compound **172** was prepared in a manner similar to that used to prepare compound **87**. ^{1}H NMR (400 MHz, D_2O) δ 8.03 (s, 1H), 4.71 (s, 2H), 4.58 (m, 2H), 4.13 (t, 1H), 3.80-3.50 (m, 9H), 3.22-3.10 (m, 7H), 2.68 (t, 2H), 2.38 (m, 2H), 2.19-2.04 (m, 4H), 1.87 (m, 2H), 1.71 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 694.4 (M+1).

*Preparation of Compound **173***

Compound **173** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H), 7.27 (s, 1H), 7.23-7.16 (m, 2H), 4.84 (s, 2H), 4.57 (t, J = 6.8 Hz, 2H), 4.38 (m, 1H), 3.81 (s, 3H), 3.57 (m, 2H), 3.23-3.09 (m, 8H), 2.33 (m, 2H), 2.20-2.02 (m, 6H), 1.92 (m, 2H), 1.82 (m, 2H), 1.65 (m, 1H), 1.38-1.16 (m, 6H); EI-MS: 551.4 (M+1).

*Preparation of Compound **174***

Compound **174** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, D_2O) δ 8.26 (d, 1H), 8.14 (br s, 1H), 7.79 (t, 1H), 7.49-7.42 (m, 2H), 4.87 (s, 2H), 4.61-4.40 (m, 4H), 4.15-4.02 (m, 2H), 3.38-2.88 (m, 8H), 2.58 (m, 2H), 2.36-1.84 (m, 17H), 1.67 (m,1H), 1.42-1.18 (m, 6H); EI-MS: 692.4 (M+1).

*Preparation of Compound **175***

Compound **175** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (d, 1H), 8.08 (br s, 1H), 7.81 (t, 1H), 7.48-7.42 (m, 2H), 4.86 (s, 2H), 4.60-4.44 (m, 5H), 4.02 (m, 1H), 3.31-3.06 (m, 7H), 2.78 (m, 1H), 2.55 (m, 2H), 2.36 (m, 2H), 2.23-1.80 (m, 13H), 1.67 (m, 2H), 1.56 (m, 1H), 1.43-1.19 (m, 6H); EI-MS: 692.4 (M+1).

*Preparation of Compound **176***

Compound **176** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 7.20 (s, 1H), 6.51 (s, 1H), 4.88 (t, *J* = 6.0 Hz, 2H), 4.83 (s, 2H), 4.38 (m, 1H), 3.78 (s, 6H), 3.76 (m, 2H), 3.61-3.43 (m, 5H), 3.24-3.15 (m, 3H), 2.20 (m, 2H), 2.06 (m, 2H), 1.94 (m, 2H), 1.83 (m, 2H), 1.67 (m, 1H), 1.41-1.19 (m, 6H); EI-MS: 553.3 (M+1).

*Preparation of Compound **177***

Compound **177** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (300 MHz, CD_3OD) δ 8.04 (d, *J* = 9.0 Hz, 1H), 7.91 (s, 1H), 7.52 (s, 1H), 7.48 (d, *J* = 9.0 Hz, 1H), 4.83 (s, 2H), 4.57 (t, *J* = 6.8 Hz, 2H), 4.38 (m, 1H), 3.57 (m, 2H), 3.22-3.08 (m, 8H), 2.34 (m, 2H), 2.21-2.01 (m, 6H), 1.95 (m, 2H), 1.79 (m, 2H), 1.61 (m, 1H), 1.36-1.18 (m, 6H); EI-MS: 589.3 (M+1).

*Preparation of Compound **178***

Compound **178** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (d, 1H), 8.11 (br s, 1H), 7.80 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.65-4.51 (m, 4H), 4.13-4.02 (m, 2H), 3.63 (m, 1H), 3.40 (t, 2H), 3.06 (m, 2H), 2.98 (m, 2H), 2.81-2.75 (m, 3H), 2.56 (m, 2H), 2.34 (m, 2H), 2.21-2.03 (m, 8H), 1.91-1.18 (m, 12H); EI-MS: 692.4 (M+1).

*Preparation of Compound **179***

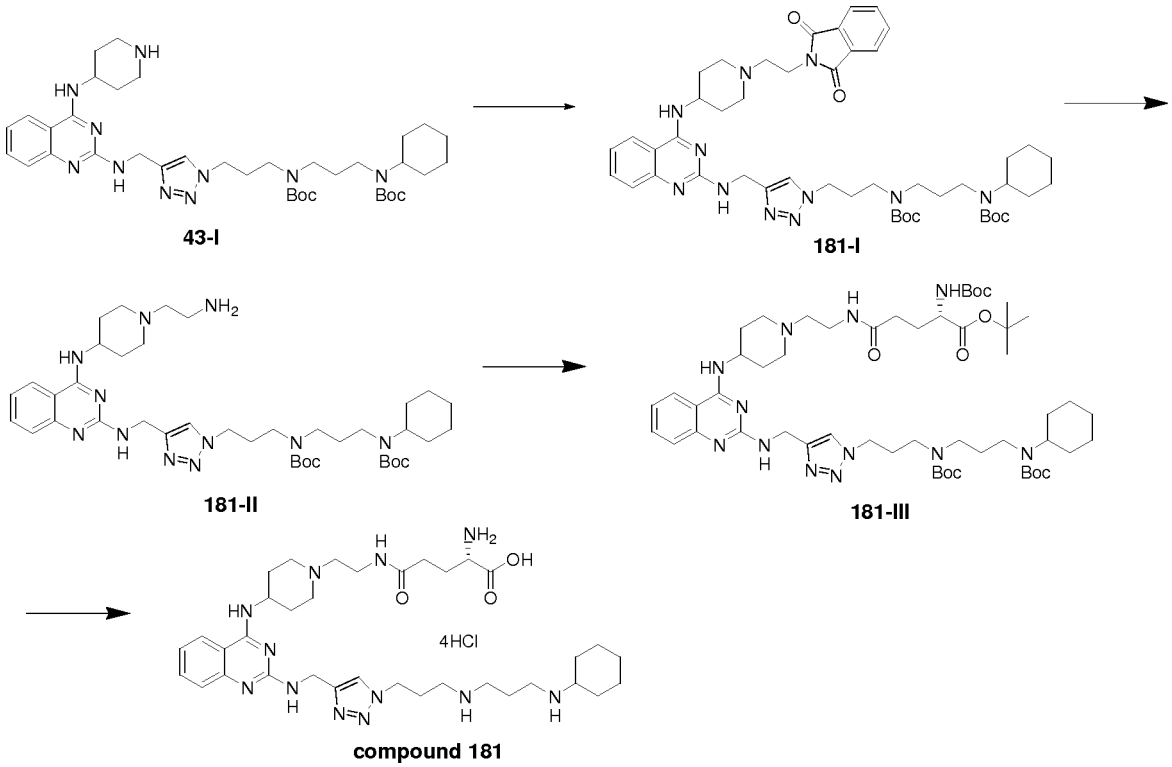
Compound **179** was prepared in a manner similar to that used to prepare compound **57**. EI-MS: 580.3 (M+1).

*Preparation of Compound **180***

Compound **180** was prepared in a manner similar to that used to prepare compound **60**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 4.69 (s, 2H), 4.62 (m, 2H), 3.80-3.62 (m, 8H), 3.26-3.10 (m, 8H), 2.39 (m, 2H), 2.19-2.10 (m, 4H), 1.87 (m, 2H), 1.71 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 594.3 (M+1).

*Preparation of Compound **181***

Shown below is a scheme for synthesizing compound **181** from compound 43-I via intermediates 181-I to 181-III.



To a magnetically stirred solution of compound 43-I (362 mg) in acetonitrile (50 mL) under an atmosphere of nitrogen was added 2-(2-bromo-ethyl)-isoindole-1,3-dione (254 mg) and K_2CO_3 (100 mg). The reaction mixture was stirred at 60 °C for 15 hours and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with dichloromethane (3x50 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH/DCM = 1/19 to afford compound 181-I (301 mg, 67% yield) as a solid.

To a stirred solution of compound 181-I (280 mg) in methanol (2.8 mL) was added 85% $NH_2NH_2 \cdot H_2O$ (200 mg) dropwise. The resulting mixture was stirred at 25 °C for 15 hours. The mixture was concentrated under reduced pressure by removing ethanol to give the

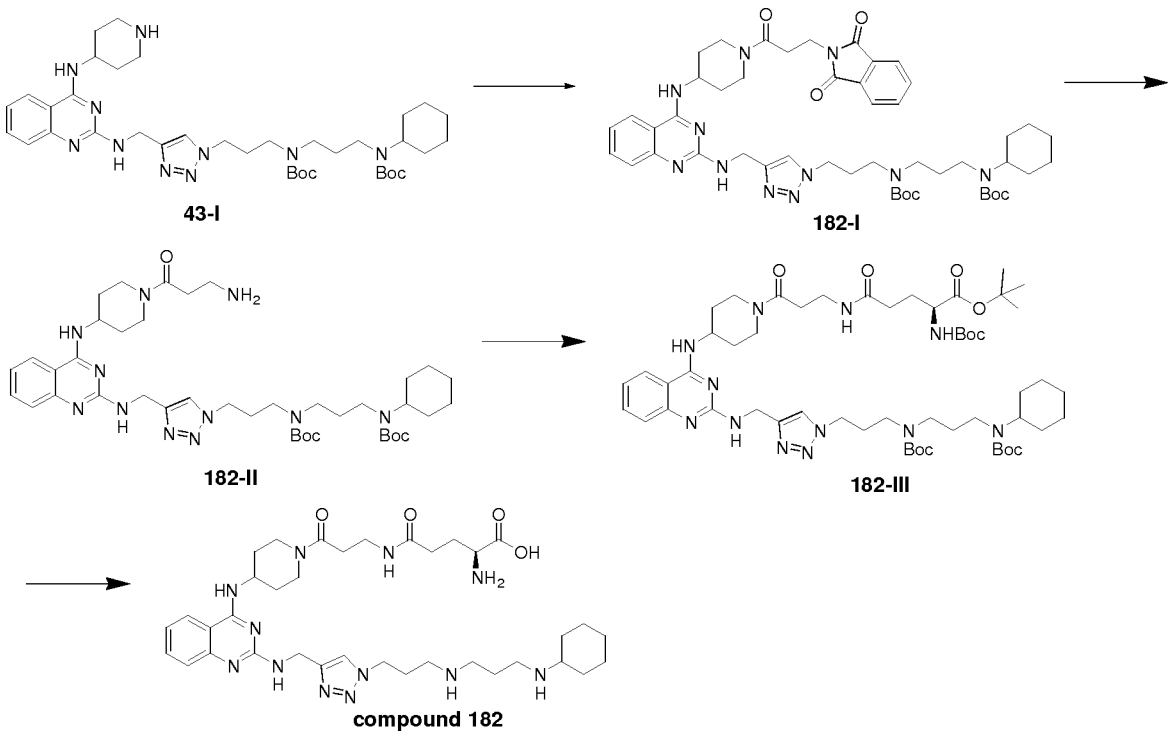
residue, which was extracted with CH_2Cl_2 (3x50 mL) and 10% K_2CO_3 (50 mL). The extracts were combined, washed with H_2O, and concentrated under reduced pressure to give the residue. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to afford compound 181-II (220 mg, 92% yield) as a solid.

To a magnetically stirred solution of 2-tert-butoxycarbonylamino-pentanedioic acid 1-tert-butyl ester (125 mg) in dichloromethane (50 mL) under an atmosphere of nitrogen was added EDCI (100 mg) and HOBt (80 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 hour, a solution of compound 181-II (210 mg) in dichloromethane (10 mL) was added the mixture in one potion. The reaction mixture was stirred for another 6 hours and then poured into water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to give compound 181-III (206 mg, 70% yield) as a solid.

A solution of 4N HCl/dioxane (1.8 mL) was added to the solution of compound 181-III (196 mg) in dichloromethane (3.6 mL) and 1,4-dioxane (3.6 mL). The reaction mixture was stirred for 15 h and concentrated to afford hydrochloride salt of compound **181** (145 mg, 92% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (d, 1H), 8.14 (s, 1H), 7.81 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.60-4.59 (m, 3H), 4.10 (t, 1H), 3.82 (m, 2H), 3.40-3.34 (m, 4H), 3.20-3.08 (m, 8H), 2.58 (m, 2H), 2.36 (m, 2H), 2.30-2.12 (m, 10H), 1.88 (m, 2H), 1.70 (m, 1H), 1.42-1.19 (m, 6H); EI-MS: 693.4 (M+1).

*Preparation of Compound **182***

Shown below is a scheme for synthesizing compound **182** from compound 43-I via intermediates 182-I to 182-III.



To a magnetically stirred solution of 3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid (160 mg) in dichloromethane (50 mL) under an atmosphere of nitrogen was added EDCI (153 mg) and HOBt (190 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 hour, a solution of compound 43-I (362 mg) in dichloromethane (10 mL) was added the mixture in one potion. The reaction mixture was stirred for another 6 hours and then poured into water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to give compound 182-II (320 mg, 69% yield) as a solid.

To a stirred solution of compound 182-II (300 mg) in methanol (3 mL) was added 85% $NH_2NH_2 \cdot H_2O$ (200 mg) dropwise. The resulting mixture was stirred at 25 °C for 15 hours. The mixture was concentrated under reduced pressure by removing ethanol to give the residue, which was extracted with CH_2Cl_2 (3x50 mL) and 10% K_2CO_3 (50 mL). The extracts

were combined, washed with H_2O, and concentrated under reduced pressure to give the residue. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to afford compound 182-II (210 mg, 81% yield) as light yellow solid.

To a magnetically stirred solution of 2-tert-Butoxycarbonylamino-pentanedioic acid 1-tert-butyl ester (115 mg) in dichloromethane (50 mL) under an atmosphere of nitrogen was added EDCI (100 mg) and HOBt (80 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 hour, a solution of compound 182-II (200 mg) in dichloromethane (10 mL) was added the mixture in one potion. The reaction mixture was stirred for another 6 hours and then poured into water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to give compound 182-III (202 mg, 74% yield) as a solid.

A solution of 4N HCl/dioxane (1.8 mL) was added to the solution of compound 182-III (190 mg) in dichloromethane (3.6 mL) and 1,4-dioxane (3.6 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **182** (130 mg, 89% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (d, 1H), 8.10 (br s, 1H), 7.81 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.61-4.48 (m, 4H), 4.06-4.02 (m, 2H), 3.47 (t, 2H), 3.29 (m, 1H), 3.20-3.11 (m, 6H), 2.81 (m, 1H), 2.67 (t, 2H), 2.49 (t, 2H), 2.36 (m, 2H), 2.23-2.03 (m, 7H), 1.92-1.82 (m, 3H), 1.73 (m, 2H), 1.55 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 721.5 (M+1).

*Preparation of Compound **183***

Compound **183** was prepared in a manner similar to that used to prepare compound **60**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.50-8.43 (m, 2H), 4.82-4.70 (m, 4H), 3.98-3.50 (m, 8H), 3.26-3.10 (m, 8H), 2.45 (m, 2H), 2.22-2.06 (m, 4H), 1.96-1.80 (m, 4H), 1.71 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 608.3 (M+1).

*Preparation of Compound **184***

Compound **184** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 4.68 (s, 2H), 4.59 (m, 2H), 4.07 (t, 1H), 3.83-3,55 (m, 6H), 3.20-3.03 (m, 8H), 2.74 (t, 2H), 2.41-2.03 (m, 8H), 1.88 (m, 2H), 1.71 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 601.4 (M+1).

*Preparation of Compound **185***

Compound **185** was prepared in a manner similar to that used to prepare compound **60**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 4.86 (s, 2H), 4.76-4.58 (m, 4H), 3.26-3.10 (m, 10H), 2.90 (d, 2H), 2.38 (m, 2H), 2.22-2.10 (m, 4H), 1.96-1.67 (m, 6H), 1.42-1.18 (m, 8H); EI-MS: 622.3 (M+1).

*Preparation of Compound **186***

Compound **186** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 4.66 (s, 2H), 4.59 (t, 2H), 4.04 (t, 1H), 3.85 (d, 1H), 3.81 (t, 1H), 3.20-2.83 (m, 10H), 2.51 (t, 2H), 2.35 (m, 2H), 2.24-2.10 (m, 7H), 1.96-1.64 (m, 6H), 1.42-1.18 (m, 7H); EI-MS: 629.4 (M+1).

*Preparation of Compound **187***

Compound **187** was prepared in a manner similar to that used to prepare compound **60**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 4.70 (s, 2H), 4.65 (t, 2H), 3.26-3.06 (m, 12H), 2.88 (m, 2H), 2.40 (m, 2H), 2.22-2.10 (m, 4H), 1.94-1.67 (m, 6H), 1.42-1.18 (m, 8H); EI-MS: 622.3 (M+1).

*Preparation of Compound **188***

Compound **188** was prepared in a manner similar to that used to prepare compound **60**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.37-8.33 (m, 2H), 4.72 (s, 2H), 4.68 (m, 2H), 3.97 (m, 1H), 3.26-3.06 (m, 10H), 2.87 (d, 2H), 2.42 (m, 2H), 2.22-2.10 (m, 4H), 1.96-1.80 (m, 4H), 1.71 (m, 1H), 1.42-1.18 (m, 8H); EI-MS: 608.3 (M+1).

*Preparation of Compound **189***

Compound **189** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 4.66 (s, 2H), 4.60 (t, 2H), 4.05 (t, 1H), 3.71-3.55 (m, 4H), 3.20-3.04 (m, 10H), 2.69 (m, 1H), 2.57 (m, 1H), 2.37 (m, 2H), 2.24-2.06 (m, 6H), 1.89-1.83 (m, 4H), 1.73 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 615.4 (M+1).

*Preparation of Compound **190***

Compound **190** was prepared in a manner similar to that used to prepare compound **60**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H), 8.17 (s, 1H), 7.49 (br s, 1H), 7.43 (d, 1H), 4.86 (s, 2H), 4.60 (t, 2H), 4.53 (m, 1H), 4.47 (m, 1H), 4.13 (m, 1H), 3.34 (m, 1H), 3.22-3.07 (m, 8H), 2.83 (m, 1H), 2.38 (m, 2H), 2.21-2.11 (m, 4H), 2.00-1.67 (m, 6H), 1.60 (m, 1H), 1.40-1.17 (m, 6H); EI-MS: 677.3 (M+1).

*Preparation of Compound **191***

Compound **191** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 7.45-7.32 (m, 4H), 7.25 (m, 1H), 4.76 (s, 2H), 4.62 (d, 1H), 4.56 (t, 2H), 4.29 (d, 1H), 4.12 (t, 1H), 3.68-3.56 (m, 4H), 3.38-3.10 (m, 10H), 2.42 (t, 2H), 2.36 (m, 2H), 2.30-2.04 (m, 6H), 1.93-1.83 (m, 2H), 1.70 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 690.4 (M+1).

*Preparation of Compound **192***

Compound **192** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, D_2O) δ 7.99 (s, 1H), 6.18 (s, 1H), 4.82 (s, 2H), 4.57 (t, 2H), 4.30 (m, 1H), 4.18-4.03 (m, 2H), 3.94 (m, 1H), 3.27 (m, 1H), 3.22-3.12 (m, 6H), 2.89 (m, 1H), 2.73 (m, 2H), 2.35 (m, 2H), 2.30-2.21 (m, 5H), 2.18-1.80 (m, 8H), 1.68 (m, 2H), 1.56 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 614.4 (M+1).

*Preparation of Compound **193***

Compound **193** was prepared in a manner similar to that used to prepare compound **87**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (d, 1H), 8.17 (s, 1H), 7.81 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.64-4.48 (m, 4H), 4.03 (m, 1H), 3.87 (m, 2H), 3.65 (m, 1H), 3.48 (m, 2H),

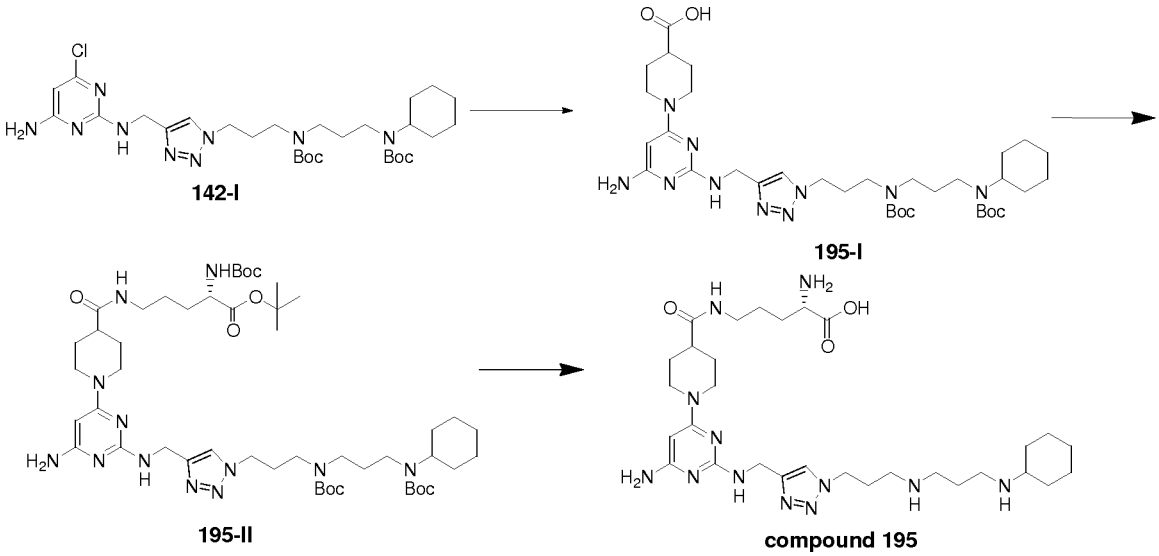
3.38-3.06 (m, 7H), 2.85 (m, 1H), 2.72 (m, 2H), 2.41 (m, 2H), 2.24-1.81 (m, 14H), 1.78-1.60 (m, 3H), 1.42-1.18 (m, 6H); EI-MS: 865.4 (M+1).

*Preparation of Compound **194***

Compound **194** was prepared in a manner similar to that used to prepare compound **63**. EI-MS: 629.4 (M+1).

*Preparation of Compound **195***

Shown below is a scheme for synthesizing compound **195** from compound 142-I via intermediates 195-I and 195-II.



To a magnetically stirred solution of compound 142-I (311 mg) in 1-pentanol (2 mL) under an atmosphere of nitrogen was added piperidine-4-carboxylic acid (129 mg). The mixture was stirred at 150 °C for 4 hours and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with ethyl acetate (3x 100 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:1) to give compound 195-I (260 mg, 73% yield) as a solid.

To a magnetically stirred solution of 195-I (240 mg) in dichloromethane (50 mL) under an atmosphere of nitrogen was added EDCI (100 mg) and HOBt (80 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 hour, a solution of compound 5-amino-2-tert-butoxycarbonylamino-pentanoic acid tert-butyl ester (140 mg) in dichloromethane (10 mL) was added the mixture in one potion. The reaction mixture was stirred for another 6 hours and then poured into water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to give compound 195-II (230 mg, 70% yield) as a solid.

A solution of 4N HCl/dioxane (2.2 mL) was added to the solution of compound 195-II (220 mg) in dichloromethane (4.4 mL) and 1,4-dioxane (4.4 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **195** (149 mg, 90% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (br s, 1H), 4.88 (s, 2H), 4.75-4.58 (m, 4H), 4.06 (m, 1H), 3.30-3.06 (m, 10H), 2.58 (m, 1H), 2.37 (m, 2H), 2.22-2.06 (m, 4H), 2.04-1.56 (m, 11H), 1.42-1.18 (m, 6H); EI-MS: 629.4 (M+1).

*Preparation of Compound **196***

Compound **194** was prepared in a manner similar to that used to prepare compounds **63** and **142**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 4.88 (s, 2H), 4.70 (d, 1H), 4.67 (d, 1H), 4.60 (t, 2H), 4.06 (m, 1H), 3.75 (m,1H), 3.30-3.06 (m, 8H), 2.50 (m, 2H), 2.38 (m, 2H), 2.18-1.80 (m, 11H), 1.69-1.61 (m, 2H), 1.42-1.18 (m, 6H); EI-MS: 615.4 (M+1).

*Preparation of Compound **197***

Compound **194** was prepared in a manner similar to that used to prepare compound **60**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (d, 1H), 8.17 (s, 1H), 7.80 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.62 (t, 2H), 4.60-4.44 (m, 2H), 4.13 (m, 1H), 3.30 (m, 1H), 3.22-3.06 (m,

8H), 2.84 (m, 1H), 2.39 (m, 2H), 2.20-2.10 (m, 4H), 2.02-1.82 (m, 4H), 1.71 (m, 2H), 1.61 (m, 1H), 1.40-1.17 (m, 6H); EI-MS: 643.3 (M+1).

*Preparation of Compound **198***

Compound **198** was prepared in a manner similar to that used to prepare compounds **87** and **182**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (d, 1H), 8.17 (s, 1H), 7.80 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.68-4.51 (m, 5H), 4.18 (m, 1H), 3.89 (m, 1H), 3.65 (m, 2H), 3.54 (m, 2H), 3.38 (m, 1H), 3.22-3.08 (m, 6H), 2.85 (m, 1H), 2.60 (t, 2H), 2.41-2.30 (m, 4H), 2.21-1.81 (m, 14H), 1.78-1.60 (m, 3H), 1.42-1.18 (m, 6H); EI-MS: 854.5 (M+1).

*Preparation of Compound **199***

Compound **199** was prepared in a manner similar to that used to prepare compounds **63 and 182**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (d, 1H), 8.11 (s, 1H), 7.81 (t, 1H), 7.48-7.41 (m, 2H), 4.86 (s, 2H), 4.61-4.52 (m, 5H), 4.16 (m, 1H), 4.06 (m, 1H), 3.38 (m, 1H), 3.20-3.07 (m, 8H), 2.88 (m, 1H), 2.68 (m, 2H), 2.41-2.22 (m, 4H), 2.21-1.82 (m, 12H), 1.78-1.60 (m, 3H), 1.42-1.18 (m, 6H); EI-MS: 747.4 (M+1).

*Preparation of Compound **200***

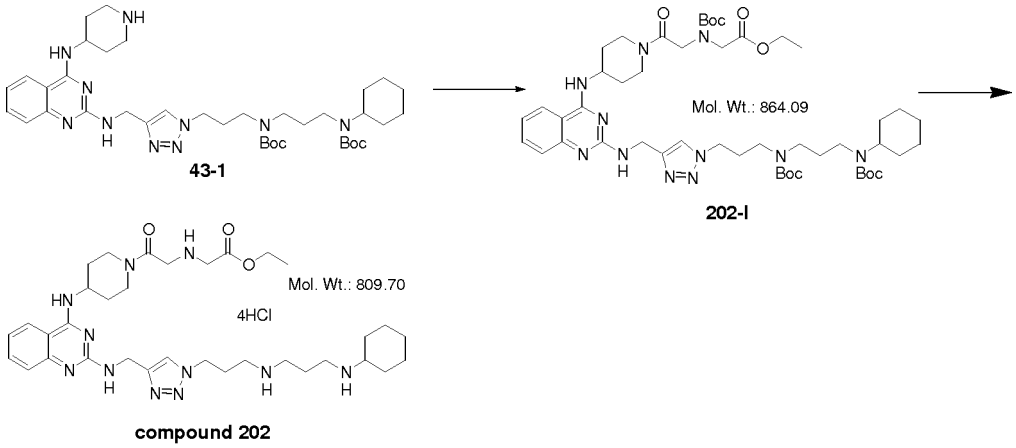
Compound **200** was prepared in a manner similar to that used to prepare compound **182**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.28-8.24 (m, 2H), 7.81 (t, 1H), 7.48-7.32 (m, 2H), 4.86 (s, 2H), 4.68-4.57 (m, 4H), 4.08 (m, 1H), 3.24-3.04 (m, 7H), 2.95 (m, 2H), 2.83 (m, 1H), 2.51 (m, 2H), 2.40 (m, 2H), 2.20-1.80 (m, 8H), 1.78-1.43 (m, 7H), 1.42-1.18 (m, 8H); EI-MS: 634.4 (M+1).

*Preparation of Compound **201***

Compound **201** was prepared in a manner similar to that used to prepare compound **61**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 7.47-7.32 (m, 5H), 6.03 (s, 1H), 5.30 (m, 2H), 4.79 (s, 2H), 4.63 (t, 2H), 4.33 (m, 1H), 4.21-4.06 (m, 2H), 3.76 (m, 1H), 3.22-3.12 (m, 9H), 2.89 (m, 1H), 2.61 (m, 2H), 2.39 (m, 2H), 2.29 (s, 3H), 2.30-1.80 (m, 11H), 1.68 (m, 1H), 1.56-1.18 (m, 7H); EI-MS: 704.4 (M+1).

*Preparation of Compound **202***

Shown below is a scheme for synthesizing compound **202** from compound 43-I via intermediate 202-I.



To a magnetically stirred solution of (ethoxycarbonylmethyl-amino)-acetic acid (161 mg) in dichloromethane (50 mL) under an atmosphere of nitrogen was added EDCI (153 mg) and HOBt (190 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 h, a solution of compound 43-I (362 mg) in dichloromethane (10 mL) was added the mixture in one potion. The reaction mixture was stirred for another 6 hours and then poured into water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to give compound 202-I (312 mg, 64% yield) as a solid.

A solution of 4N HCl/dioxane (1.8 mL) was added to the solution of compound 202-I (150 mg) in dichloromethane (3.6 mL) and 1,4-dioxane (3.6 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **202** (110 mg, 87% yield). EI-MS: 664.4 (M+1).

*Preparation of Compound **203***

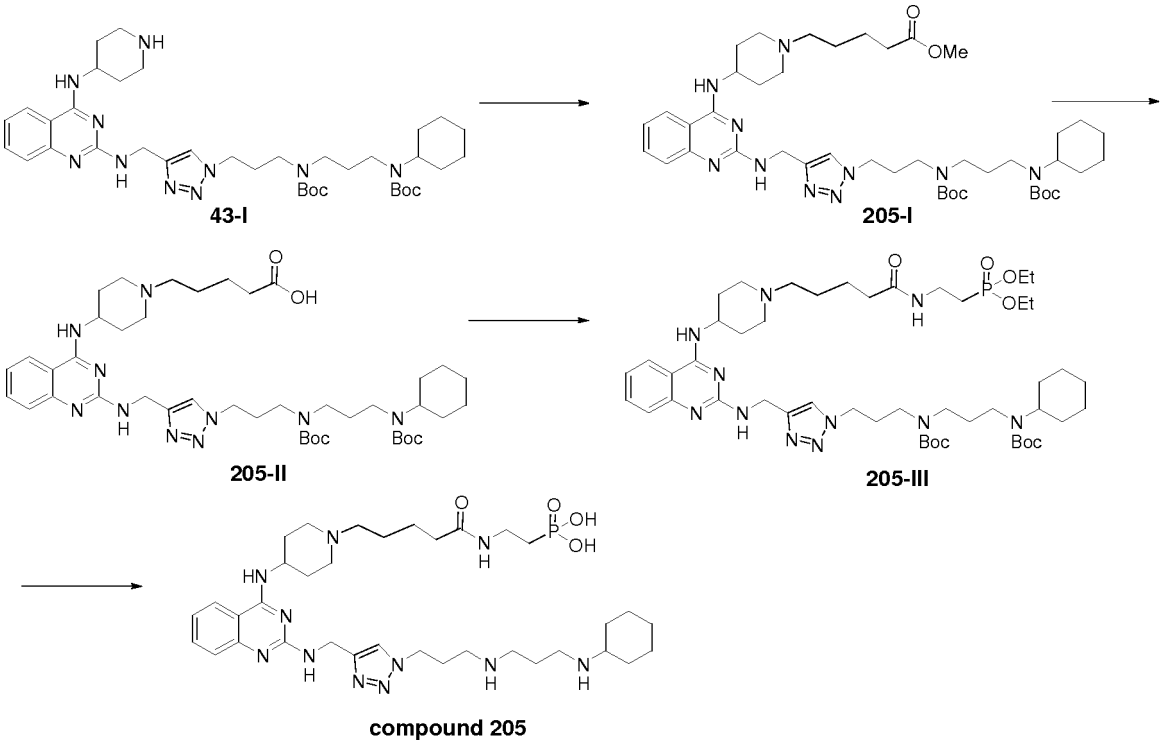
Compound **203** was prepared in a manner similar to that used to prepare compound **63**. EI-MS: 629.4 (M+1).

*Preparation of Compound **204***

Compound **204** was prepared in a manner similar to that used to prepare compound **182**. ^{1}H NMR (400 MHz, D_2O) δ 8.04-8.01 (m, 2H), 7.83 (t, 1H), 7.48-7.43 (m, 2H), 4.86 (s, 2H), 4.59 (t, 2H), 4.45-4.41 (m, 2H), 4.10 (m, 1H), 4.07 (m, 1H), 3.29-3.12 (m, 9H), 2.81 (m, 1H), 2.57-2.48 (m, 4H), 2.35 (m, 2H), 2.24 (m, 2H), 2.19-1.82 (m, 8H), 1.75-1.55 (m, 9H), 1.42-1.18 (m, 6H); EI-MS: 763.5 (M+1).

*Preparation of Compound **205***

Shown below is a scheme for synthesizing compound **205** from compound 43-I via intermediates 205-I to 205-III.



To a magnetically stirred solution of compound 43-I (362 mg) in DCM (50 mL) under an atmosphere of nitrogen was added 5-bromo-pentanoic acid methyl ester (194 mg) and TEA (200 mg). The reaction mixture was stirred at 25 °C for 15 hours and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with

dichloromethane (3x50 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to afford compound 205-I (300 mg, 71% yield) as a solid.

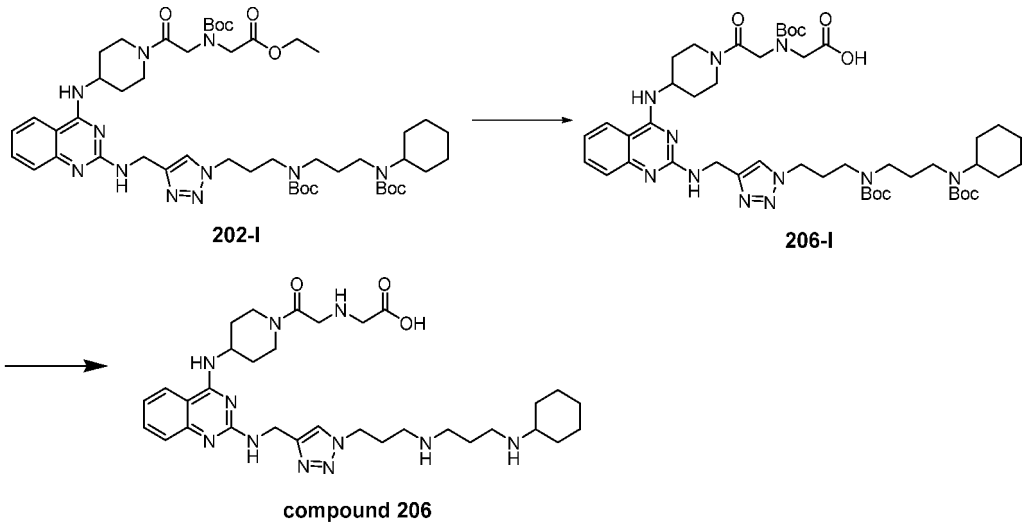
To a magnetically stirred solution of compound 205-I (280 mg) in THF (5 mL) under an atmosphere of nitrogen was added aqueous LiOH (0.5 M, 5 mL). The reaction mixture was stirred at 25 °C for 15 h and then acidified with aqueous 1N HCl (12 mL). The resulting mixture was extracted with ethyl acetate (3x50 mL). The combined extracts were concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:3) to give compound 205-II (235 mg, 87% yield) as a solid.

To a magnetically stirred solution of 205-II (220 mg) in dichloromethane (50 mL) under an atmosphere of nitrogen was added EDCI (100 mg) and HOBt (80 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 hour, a solution of compound (2-amino-ethyl)phosphonic acid diethyl ester (115 mg) in dichloromethane (10 mL) was added the mixture in one potion. The reaction mixture was stirred for another 6 hours and then poured into water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to give compound 205-III (230 mg, 76% yield) as a solid.

TMSBr (1 mL) was added to the solution of compound 205-III (220 mg) in dichloromethane (15 mL). The reaction mixture was stirred at 25 °C for 15 hours and concentrated to afford hydrobromide salt of compound **205** (186 mg, 86% yield). ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.03 (m, 2H), 7.84 (t, 1H), 7.49-7.45 (m, 2H), 4.89 (s, 2H), 4.59 (t, 2H), 4.56 (m, 1H), 3.76 (m, 2H), 3.47 (m, 2H), 3.23-3.12 (m, 10H), 2.41-2.35 (m, 4H), 2.30-2.02 (m, 7H), 1.98-1.63 (m, 10H), 1.42-1.18 (m, 6H); EI-MS: 728.5 (M+1).

Preparation of Compound ***206***

Shown below is a scheme for synthesizing compound **206** from compound 202-I via intermediate 206-I.



To a magnetically stirred solution of compound 202-I (150 mg) in THF (5 mL) under an atmosphere of nitrogen was added aqueous LiOH (0.5 M, 5 mL). The reaction mixture was stirred at 25 °C for 15 hours and then acidified with aqueous 1N HCl (12 mL). The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM (1:3) to give compound 206-I (110 mg, 76% yield) as a solid.

A solution of 4N HCl/dioxane (1.3 mL) was added to the solution of compound 206-I (150 mg) in dichloromethane (2.6 mL) and 1,4-dioxane (2.6 mL). The reaction mixture was stirred for 15 h and concentrated to afford hydrochloride salt of compound **206** (83 mg, 88% yield). ^{1}H NMR (400 MHz, D_2O) δ 8.04-8.01 (m, 2H), 7.82 (t, 1H), 7.47-7.42 (m, 2H), 4.83 (s, 2H), 4.58 (t, 2H), 4.46-4.42 (m, 2H), 4.33 (d, 1H), 4.31 (d, 1H), 4.04 (m, 2H), 3.81 (m,1H), 3.30 (m, 1H), 3.19-3.12 (m, 6H), 2.93 (m, 1H), 2.36 (m, 2H), 2.19-1.83 (m, 8H), 1.71 (m, 2H), 1.61 (m, 1H), 1.40-1.17 (m, 6H); EI-MS: 636.4 (M+1).

*Preparation of Compound **207***

Compound **207** was prepared in a manner similar to that used to prepare compounds **182** and **205**. ^{1}H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 8.02 (d, 1H), 7.83 (t, 1H), 7.46-7.42 (m, 2H), 4.84 (s, 2H), 4.59 (t, 2H), 4.46-4.42 (m, 2H), 4.10 (m, 1H), 4.03 (m, 1H), 3.58-3.50 (m, 4H), 3.29 (m, 1H), 3.20-3.12 (m, 6H), 2.83 (m, 1H), 2.76 (m, 2H), 2.46 (t, 2H), 2.36 (m, 2H), 2.22 (m, 2H), 2.19-1.96 (m, 5H), 1.90-1.86 (m, 3H), 1.69 (m, 2H), 1.58 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 814.4 (M+1).

*Preparation of Compound **208***

Compound **208** was prepared in a manner similar to that used to prepare compound **87**. ^{1}H NMR (400 MHz, D_2O) δ 8.01 (s, 1H), 4.78 (s, 2H), 4.59 (t, 2H), 4.29 (m, 1H), 4.13 (t, 1H), 4.07 (m, 1H), 3.79 (m, 1H), 3.61 (m, 2H), 3.28-3.12 (m, 7H), 2.91(m, 1H), 2.67 (t, 2H), 2.36 (t, 2H), 2.27 (s, 3H), 2.22-1.81 (m, 10H), 1.68 (m, 2H), 1.58 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 707.4 (M+1).

*Preparation of Compound **209***

Compound **209** was prepared in a manner similar to that used to prepare compound **181** and **87.** ^{1}H NMR (400 MHz, D_2O) δ 8.06-8.04 (m, 2H), 7.85 (t, 1H), 7.51-7.44 (m, 2H), 4.87 (s, 2H), 4.59 (t, 2H), 4.54 (m, 1H), 4.04 (t, 1H), 3.80 (m, 2H), 3.70 (t, 2H), 3.47 (m, 2H), 3.41 (m, 2H), 3.26-3.12 (m, 8H), 2.50 (t, 2H), 2.36 (m, 2H), 2.28-2.22 (m, 4H), 2.19-2.01 (m, 6H), 1.93 (t, 2H), 1.87 (m, 2H), 1.70 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 800.4 (M+1).

*Preparation of Compound **210***

Compound **210** was prepared in a manner similar to that used to prepare compound **87.** ^{1}H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 7.99 (d, 1H), 7.83 (t, 1H), 7.46-7.42 (m, 2H), 4.82 (s, 2H), 4.59 (t, 2H), 4.48-4.41 (m, 2H), 4.36 (d, 1H), 4.33 (d, 1H), 4.07 (s, 2H), 3.78 (m, 1H), 3.61 (d, 1H), 3.54 (d, 1H), 3.33 (m, 1H), 3.20-3.12 (m, 6H), 2.94 (m, 1H), 2.36 (m, 2H), 2.17-1.80 (m, 8H), 1.72 (m, 2H), 1.62 (m, 1H), 1.41-1.18 (m, 6H); EI-MS: 729.4 (M+1).

*Preparation of Compound **211***

Compound **211** was prepared in a manner similar to that used to prepare compound **202**. EI-MS: 678.4 (M+1).

*Preparation of Compound **212***

Compound **212** was prepared in a manner similar to that used to prepare compound **195**. EI-MS: 551.3 (M+1).

*Preparation of Compound **213***

Compound **213** was prepared in a manner similar to that used to prepare compound **206**. ^{1}H NMR (400 MHz, D_2O) δ 8.05 (s, 1H). 8.01 (d, 1H), 7.82 (t, 1H), 7.46-7.42 (m, 2H), 4.89 (s, 2H), 4.59 (t, 2H), 4.48-4.42 (m, 2H), 4.01 (m, 1H), 3.95 (s, 2H), 3.46 (t, 2H), 3.30 (m, 1H), 3.20-3.11 (m, 6H), 3.03 (t, 2H), 2.86 (m, 1H), 2.36 (m, 2H), 2.18-2.10 (m, 6H), 1.87 (m, 2H), 1.71 (m, 2H), 1.58 (m, 1H), 1.41-1.19 (m, 6H); EI-MS: 650.4 (M+1).

*Preparation of Compound **214***

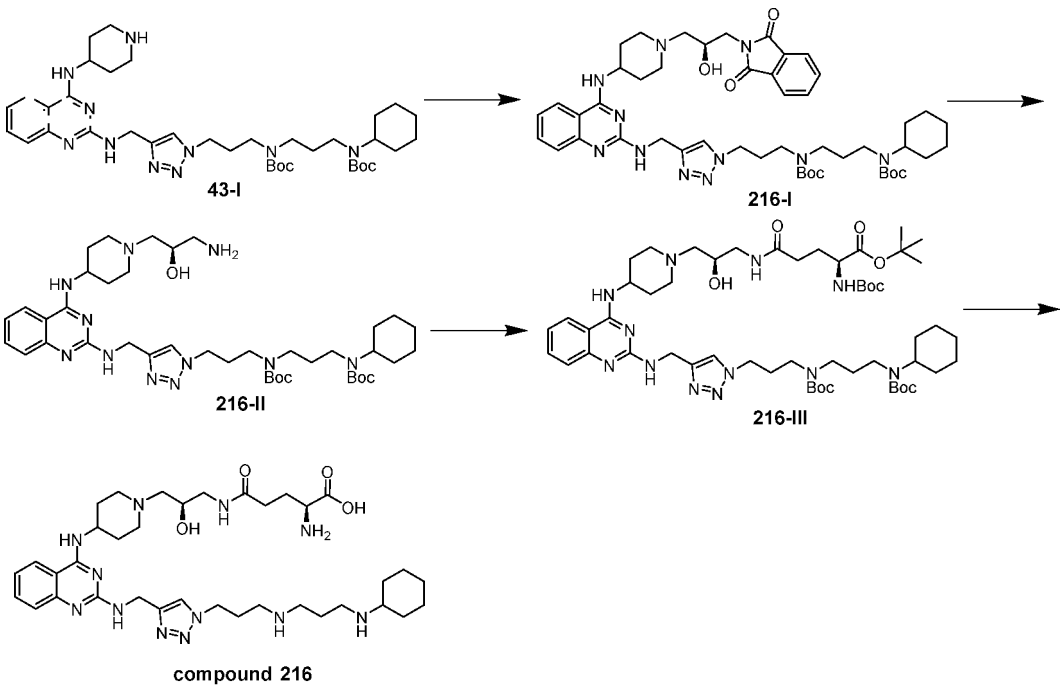
Compound **214** was prepared in a manner similar to that used to prepare compound **59**. ^{1}H NMR (400 MHz, D_2O) δ 8.07-8.04 (m, 2H), 7.84 (t, 1H), 7.52-7.44 (m, 2H), 4.89 (s, 2H), 4.60-4.42 (m, 3H), 3.78 (m, 2H), 3.51 (t, 2H), 3.22-3.08 (m, 8H), 2.89 (t, 2H), 2.38 (m, 2H), 2.26 (m, 2H), 2.20-2.09 (m, 4H), 2.00 (m, 2H), 1.88 (m, 2H), 1.71 (m, 1H), 1.43-1.18 (m, 6H); EI-MS: 593.4 (M+1).

*Preparation of Compound **215***

Compound **215** was prepared in a manner similar to that used to prepare compound **195**. EI-MS: 714.4 (M+1).

*Preparation of Compound **216***

Shown below is a scheme for synthesizing compound **216** from compound 43-I via intermediates 216-I to 216-III.



To a magnetically stirred solution of compound 43-I (362 mg) in ethanol (50 mL) under an atmosphere of nitrogen was added 2-oxiranylmethyl-isoindole-1,3-dione (203 mg). The reaction mixture was stirred at 80 °C for 15 hours and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with dichloromethane (3x50 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to afford compound 216-I (311 mg, 67% yield) as a solid.

To a stirred solution of compound 216-I (300 mg) in methanol (2.8 mL) was added 85% $NH_2NH_2 \cdot H_2O$ (200 mg) dropwise. The resulting mixture was stirred at 25 °C for 15 hours. The mixture was concentrated under reduced pressure by removing ethanol to give the residue, which was extracted with CH_2Cl_2 (3x50 mL) and 10% K_2CO_3 (50 mL). The extracts were combined, washed with H_2O, and concentrated under reduced pressure to give the residue. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to afford compound 216-II (220 mg, 86% yield) as a solid.

To a magnetically stirred solution of 2-tert-butoxycarbonylamino-pentanedioic acid 1-tert-butyl ester (120 mg) in dichloromethane (50 mL) under an atmosphere of nitrogen was added EDCI (100 mg) and HOBt (80 mg) at 25 °C. After the mixture was stirred at 25 °C for 1 hour, a solution of compound 216-II (218 mg) in dichloromethane (10 mL) was added the mixture in one potion. The reaction mixture was stirred for another 6 h and then poured into water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to give compound 216-III (202 mg, 68% yield) as a solid.

A solution of 4N HCl/dioxane (1.8 mL) was added to the solution of compound 216-III (198 mg) in dichloromethane (3.6 mL) and 1,4-dioxane (3.6 mL). The reaction mixture was stirred for 15 hours and concentrated to afford hydrochloride salt of compound **216** (145 mg, 91% yield. ^{1}H NMR (400 MHz, D_2O) δ 8.07-8.04 (m, 2H), 7.85 (t, 1H), 7.51-7.46 (m, 2H), 4.89 (s, 2H), 4.57 (t, 2H), 4.30 (m, 1H), 3.96 (m, 1H), 3.80 (m, 1H), 3.56-3.10 (m, 14H), 2.55 (m, 2H), 2.36 (m, 2H), 2.30-2.00 (m, 10H), 1.88 (m, 2H), 1.70 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 723.4 (M+1).

*Preparation of Compound **217***

Compound **217** was prepared in a manner similar to that used to prepare compound **202.** ^{1}H NMR (400 MHz, D_2O) δ 8.02 (s, 1H), 4.76 (s, 2H), 4.58 (t, 2H), 4.36 (q, 2H), 4.10 (s, 2H), 3.80-3.62 (m, 8H), 3.46 (t, 2H), 3.21-3.11 (m, 6H), 3.02 (t, 2H), 2.36 (m, 2H), 2.20-1.98 (m, 4H), 1.88 (m, 2H), 1.67 (m, 1H), 1.41-1.18 (m, 9H); EI-MS: 629.4 (M+1).

*Preparation of Compound **218***

Compound **218** was prepared in a manner similar to that used to prepare compound **216 and 87.** ^{1}H NMR (400 MHz, D_2O) δ 8.07-8.01 (m, 2H), 7.83 (t, 1H), 7.49-7.43 (m, 2H), 4.88 (s, 2H), 4.57 (t, 2H), 4.28 (m, 1H), 4.05 (m, 1H), 3.78 (m, 1H), 3.56-3.08 (m, 16H), 2.50

(m, 2H), 2.35 (m, 2H), 2.30-1.90 (m, 12H), 1.86 (m, 2H), 1.69 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 830.4 (M+1).

*Preparation of Compound **219***

Compound **219** was prepared in a manner similar to that used to prepare compound **206.** ^{1}H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 4.73 (s, 2H), 4.58 (t, 2H), 3.94 (s, 2H), 3.80-3.66 (m, 8H), 3.46 (t, 2H), 3.23-3.12 (m, 6H), 3.01 (t, 2H), 2.36 (m, 2H), 2.20-2.05 (m, 4H), 1.88 (m, 2H), 1.71 (m, 1H), 1.41-1.18 (m, 6H); EI-MS: 601.4 (M+1).

*Preparation of Compound **220***

Compound **220** was prepared in a manner similar to that used to prepare compound **195.** EI-MS: 665.4 (M+1).

*Preparation of Compound **221***

Compound **221** was prepared in a manner similar to that used to prepare compound **182.** ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 8.00 (d, 1H), 7.79 (t, 1H), 7.44-7.38 (m, 2H), 4.86 (s, 2H), 4.59 (t, 2H), 4.48-4.39 (m, 2H), 4.08 (m, 1H), 3.38-3.12 (m, 11H), 2.82 (m, 1H), 2.54 (t, 2H), 2.37 (m, 2H), 2.20-2.00 (m, 6H), 1.97-1.62 (m, 8H), 1.60-1.18 (m, 11H); EI-MS: 742.4 (M+1).

*Preparation of Compound **222***

Compound **222** was prepared in a manner similar to that used to prepare compound **182.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.01 (d, 1H), 7.80 (t, 1H), 7.44-7.40 (m, 2H), 4.86 (s, 2H), 4.59 (t, 2H), 4.48-4.39 (m, 2H), 4.07 (m, 1H), 3.45 (m, 4H), 3.34-3.26 (m, 3H), 3.20-3.12 (m, 6H), 2.82 (m, 1H), 2.55 (t, 2H), 2.36 (m, 2H), 2.20-2.00 (m, 10H), 1.92-1.78 (m, 4H), 1.77-1.64 (m, 4H), 1.58-1.42 (m, 3H), 1.42-1.18 (m, 6H); EI-MS: 850.4 (M+1).

*Preparation of Compound **223***

Compound **223** was prepared in a manner similar to that used to prepare compound **182.** ^{1}H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 7.98 (d, 1H), 7.80 (t, 1H), 7.46-7.38 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.48-4.37 (m, 2H), 3.98 (m, 1H), 3.41-3.23 (m, 5H), 3.20-3.12 (m,

6H), 2.99 (t, 2H), 2.82 (m, 1H), 2.36 (m, 2H), 2.17-1.98 (m,7H), 1.97-1.80 (m, 3H), 1.69 (m, 2H), 1.56 (m, 1H), 1.41-1.18 (m, 6H); EI-MS: 700.4 (M+1).

*Preparation of Compound **224***

Compound **224** was prepared in a manner similar to that used to prepare compound **63.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.00 (d, 1H), 7.82 (t, 1H), 7.48-7.42 (m, 2H), 4.87 (s, 2H), 4.60 (t, 2H), 4.48-4.38 (m, 2H), 4.30 (m, 1H), 4.13 (m, 1H), 4.05 (m, 1H), 3.38-3.12 (m, 7H), 2.85 (m, 1H), 2.77 (m, 2H), 2.40 (m, 2H), 2.29 (m, 2H), 2.18-1.83 (m, 6H), 1.71 (m, 2H), 1.56 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 666.4 (M+1).

*Preparation of Compound **225***

Compound **225** was prepared in a manner similar to that used to prepare compound **182** and **60.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.01 (d, 1H), 7.81 (t, 1H), 7.46-7.40 (m, 2H), 4.86 (s, 2H), 4.60 (t, 2H), 4.48-4.36 (m, 2H), 4.07 (m, 1H), 3.33-3.15 (m, 9H), 2.85-2.81 (m, 3H), 2.53 (t, 2H), 2.37 (m, 2H), 2.17-1.80 (m, 8H), 1.76-1.52 (m, 7H), 1.41-1.18 (m, 8H); EI-MS: 756.4 (M+1).

*Preparation of Compound **226***

Compound **226** was prepared in a manner similar to that used to prepare compound **216.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.03 (m, 2H), 7.83 (t, 1H), 7.51-7.42 (m, 2H), 4.88 (s, 2H), 4.57 (t, 2H), 4.07 (m, 1H), 3.95 (m, 1H), 3.74 (m, 2H), 3.38 (m, 1H), 3.30-3.06 (m, 6H), 2.93 (m, 1H), 2.47 (m, 2H), 2.34 (m, 2H), 2.20-2.00 (m, 6H), 1.84 (m, 2H), 1.67 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 640.4 (M+1).

*Preparation of Compound **227***

Compound **227** was prepared in a manner similar to that used to prepare compound **182.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.03 (d, 1H), 7.87 (t, 1H), 7.50-7.43 (m, 2H), 4.88 (s, 2H), 4.60 (t, 2H), 4.51-4.43 (m, 2H), 4.07-3.83 (m, 3H), 3.41 (m, 1H), 3.22-3.13 (m, 8H), 2.96 (m, 1H), 2.71 (m, 2H), 2.37 (m, 2H), 2.26 (m, 2H), 2.18-1.81 (m, 8H), 1.71 (m, 2H), 1.61 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 737.4 (M+1).

*Preparation of Compound **228***

Compound **228** was prepared in a manner similar to that used to prepare compound **202.** ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H). 8.01 (d, 1H), 7.84 (t, 1H), 7.49-7.41 (m, 2H), 4.86 (s, 2H), 4.61 (t, 2H), 4.50-4.30 (m, 5H), 4.12 (s, 2H), 4.03 (m, 1H), 3.50 (t, 2H), 3.36-3.13 (m, 7H), 3.05 (t, 2H), 2.87 (m, 1H), 2.42 (m, 2H), 2.20-2.02 (m,3H), 1.99-1.83 (m, 3H), 1.74 (m, 2H), 1.60 (m, 1H), 1.41-1.19 (m, 9H); EI-MS: 694.4 (M+1).

*Preparation of Compound **229***

Compound **229** was prepared in a manner similar to that used to prepare compound **182.** ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 8.03 (d, 1H), 7.83 (t, 1H), 7.50-7.41 (m, 2H), 4.88 (s, 2H), 4.60 (t, 2H), 4.51-4.44 (m, 2H), 4.19-4.16 (m, 2H), 4.07-3.78 (m, 4H), 3.43 (m, 1H), 3.22-3.11 (m, 6H), 2.96 (m, 1H), 2.73-2.65 (m, 4H), 2.40-2.21 (m, 6H), 2.18-1.80 (m, 8H), 1.71 (m, 2H), 1.62 (m, 1H), 1.42-1.19 (m, 6H); EI-MS: 866.5 (M+1).

*Preparation of Compound **230***

Compound **230** was prepared in a manner similar to that used to prepare compound **202.** ^{1}H NMR (400 MHz, D_2O) δ 8.02 (s, 1H), 4.86 (s, 2H), 4.60 (t, 2H), 4.38 (q, 2H), 4.29 (m, 1H), 4.18 (m, 1H), 4.11 (s, 2H), 3.91(m, 1H), 3.49 (t, 2H), 3.30 (m, 1H), 3.24-3.13 (m, 6H), 3.05-2.92 (m, 3H), 2.38 (m, 2H), 2.29 (s, 3H), 2.20-2.08 (m, 5H), 1.99-1.83 (m, 4H), 1.74 (m, 1H), 1.60 (m, 1H), 1.41-1.19 (m, 9H); EI-MS: 642.4 (M+1).

*Preparation of Compound **231***

Compound **231** was prepared in a manner similar to that used to prepare compound **63.** ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 7.97 (d, 1H), 7.79 (t, 1H), 7.44-7.38 (m, 2H), 4.88 (s, 2H), 4.60 (t, 2H), 4.48 (m, 1H), 4.38 (m, 1H), 4.14 (m, 1H), 4.02 (m, 1H), 3.30 (m, 1H), 3.22-3.12 (m, 6H), 2.85-2.75 (m, 3H), 2.37 (m, 2H), 2.30 (m, 2H), 2.18-1.80 (m, 8H), 1.68 (m, 2H), 1.58 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 650.4 (M+1).

*Preparation of Compound **232***

Compound **232** was prepared in a manner similar to that used to prepare compound **206.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H). 8.02 (d, 1H), 7.84 (t, 1H), 7.49-7.42 (m, 2H), 4.91 (s, 2H), 4.61 (t, 2H), 4.53-4.43 (m, 2H), 4.32 (m, 1H), 4.00 (m, 1H), 3.95 (s, 2H),3.47 (t, 2H), 3.37-3.08 (m, 7H), 3.04 (t, 2H), 2.88 (m, 1H), 2.41 (m, 2H), 2.20-2.02 (m, 3H), 1.96-1.84 (m, 3H), 1.73 (m, 2H), 1.58 (m, 1H), 1.41-1.19 (m, 6H); EI-MS: 666.4 (M+1).

*Preparation of Compound **233***

Compound **233** was prepared in a manner similar to that used to prepare compound **206.** ^{1}H NMR (400 MHz, D_2O) δ 8.02 (s, 1H), 5.94 (s, 1H), 4.86 (s, 2H), 4.60 (t, 2H), 4.30 (m, 1H), 4.17 (m, 1H), 3.99 (s, 2H), 3.91 (m, 1H), 3.46 (t, 2H), 3.30 (m, 1H), 3.23-3.12 (m, 6H), 3.01 (t, 2H), 2.94 (m, 1H), 2.36 (m, 2H), 2.28 (s, 3H), 2.20-2.08 (m, 5H), 1.99-1.81 (m, 4H), 1.73 (m, 1H), 1.57 (m, 1H), 1.41-1.19 (m, 6H); EI-MS: 614.4 (M+1).

*Preparation of Compound **234***

Compound **234** was prepared in a manner similar to that used to prepare compound **15.** ^{1}H NMR (400 MHz, D_2O) δ 8.00 (d, 1H), 7.93-7.89 (m, 2H), 7.83 (t, 1H), 7.50-7.42 (m, 2H), 4.93 (s, 2H), 4.66- 4.50 (m, 6H), 3.23-3.12 (m, 6H), 2.37 (m, 2H), 2.28 (m, 2H), 2.20-2.06 (m, 4H), 1.90-1.80 (m, 2H), 1.71 (m, 1H), 1.43-1.18 (m, 6H); EI-MS: 627.3 (M+1).

*Preparation of Compound **235***

Compound **235** was prepared in a manner similar to that used to prepare compound **151** and **202.** ^{1}H NMR (400 MHz, D_2O) δ 8.24 (s, 1H), 8.07 (s, 1H), 4.99 (s, 2H), 4.60 (t, 2H), 4.36 (q, 2H), 4.12 (s, 2H), 3.94-3.90 (m, 4H), 3.81-3.77 (m, 4H), 3.50 (t, 2H), 3.21-3.15 (m, 6H), 3.06 (t, 2H), 2.38 (m, 2H), 2.18-2.06 (m, 4H), 1.89 (m, 2H), 1.72 (m, 1H), 1.41-1.19 (m, 9H); EI-MS: 654.4 (M+1).

*Preparation of Compound **236***

Compound **236** was prepared in a manner similar to that used to prepare compound **182** and **57.** ^{1}H NMR (400 MHz, D_2O) δ 8.01 (s, 1H), 5.92 (s, 1H), 4.86 (s, 2H), 4.59 (t, 2H), 4.28 (m, 1H), 4.19 (m, 1H), 3.88 (m, 1H), 3.41-3.30 (m, 5H), 3.22-3.17 (m, 6H), 2.98 (t, 2H),

2.90 (m, 1H), 2.37 (m, 2H), 2.27 (s, 3H), 2.19-2.02 (m, 7H), 1.97-1.78 (m, 3H), 1.69 (m, 2H), 1.56 (m, 1H), 1.41-1.18 (m, 6H); EI-MS: 664.4 (M+1).

*Preparation of Compound **237***

Compound **237** was prepared in a manner similar to that used to prepare compound **151** and **206.** ^{1}H NMR (400 MHz, D_2O) δ 8.24 (s, 1H), 8.07 (s, 1H), 4.98 (s, 2H), 4.60 (t, 2H), 3.96 (s, 2H), 3.95-3.90 (m, 4H), 3.79-3.75 (m, 4H), 3.49 (t, 2H), 3.23-3.12 (m, 6H), 3.04 (t, 2H), 2.39 (m, 2H), 2.19-2.09 (m, 4H), 1.88 (m, 2H), 1.73 (m, 1H), 1.41-1.18 (m, 6H); EI-MS: 626.4 (M+1).

*Preparation of Compound **238***

Compound **238** was prepared in a manner similar to that used to prepare compound **182.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.01 (d, 1H), 7.83 (t, 1H), 7.48-7.42 (m, 2H), 4.86 (s, 2H), 4.59 (t, 2H), 4.43-4.41 (m,2H), 4.15 (m, 1H), 4.02 (m, 1H), 3.82 (m, 1H), 3.54 (m, 2H), 3.30 (m, 1H), 3.20-3.12 (m, 8H), 2.82-2.70 (m, 2H), 2.62 (m, 1H), 2.40-2.24 (m, 4H), 2.18-1.80 (m, 9H), 1.68 (m, 2H), 1.55 (m, 1H), 1.40-1.15 (m, 12H); EI-MS: 834.5

*Preparation of Compound **239***

Compound **239** was prepared in a manner similar to that used to prepare compound **182.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 8.01 (d, 1H), 7.83 (t, 1H), 7.48-7.42 (m, 2H), 4.86 (s, 2H), 4.59 (t, 2H), 4.46-4.42 (m, 2H), 4.15 (m, 1H), 4.05-4.01 (m, 2H), 3.82 (m, 1H), 3.56 (m, 2H), 3.30 (m, 1H), 3.22-3.12 (m, 8H), 2.85-2.75 (m, 2H), 2.62 (m, 1H), 2.40 (m, 2H), 2.24 (m, 2H), 2.18-1.80 (m, 8H), 1.68 (m, 2H), 1.55 (m, 1H), 1.40-1.15 (m, 6H); EI-MS: 778.5 (M+1).

*Preparation of Compound **240***

Compound **240** was prepared in a manner similar to that used to prepare compound **202.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H). 7.94 (d, 1H), 7.77 (t, 1H), 7.42-7.33 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.45 (m, 1H), 4.42 (m, 1H), 4.05 (m, 1H), 3.27 (m, 1H), 3.22-3.10

(m, 9H), 2.80 (m, 1H), 2.56 (t, 2H), 2.50 (t, 2H), 2.35 (m, 2H), 2.18-2.08 (m, 4H), 2.02-1.82 (m, 6H), 1.69 (m, 2H), 1.56 (m, 1H), 1.42-1.18 (m, 6H); EI-MS: 649.4 (M+1).

*Preparation of Compound **241***

Compound **241** was prepared in a manner similar to that used to prepare compound **206.** ^{1}H NMR (400 MHz, D_2O) δ 8.04 (s, 1H), 7.93 (d, 1H), 7.76 (t, 1H), 7.42-7.33 (m, 2H), 4.88 (s, 2H), 4.59 (t, 2H), 4.45 (m, 1H), 4.38 (m, 1H), 4.06 (m, 1H), 3.27 (m, 1H), 3.22-3.14 (m, 6H), 2.80 (m, 1H), 2.56 (t, 2H), 2.50 (t, 2H), 2.36 (m, 2H), 2.18-2.04 (m, 6H), 1.92 (t, 2H), 1.84 (m, 2H), 1.68 (m, 2H), 1.56 (m, 1H), 1.41-1.19 (m, 6H); EI-MS: 635.4 (M+1).

*Preparation of Compound **242***

Compound **242** was prepared in a manner similar to that used to prepare compound **182.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 7.97 (d, 1H), 7.79 (t, 1H), 7.46-7.38 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.48-4.37 (m, 2H), 4.01 (m, 1H), 3.50 (m, 1H), 3.36-3.12 (m, 12H), 2.84 (m, 1H), 2.36 (m, 2H), 2.19-1.80 (m, 8H), 1.69 (m, 2H), 1.58 (m, 1H), 1.41-1.18 (m, 6H); EI-MS: 686.4 (M+1).

*Preparation of Compound **243***

Compound **243** was prepared in a manner similar to that used to prepare compound **241.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H). 7.93 (d, 1H), 7.76 (t, 1H), 7.42-7.33 (m, 2H), 4.88 (s, 2H), 4.59 (t, 2H), 4.45 (m, 1H), 4.38 (m, 1H), 4.06 (m, 1H), 3.27 (m, 1H), 3.22-3.14 (m, 6H), 2.80 (m, 1H), 2.50 (t, 2H), 2.36-2.34 (m, 4H), 2.18-2.04 (m, 6H), 1.92 (m, 2H), 1.84 (m, 2H), 1.68 (m, 2H), 1.56 (m, 3H), 1.41-1.19 (m, 14H); EI-MS: 705.5 (M+1).

*Preparation of Compound **244***

Compound **244** was prepared in a manner similar to that used to prepare compound **240.** EI-MS: 719.5 (M+1).

*Preparation of Compound **245***

Compound **245** was prepared in a manner similar to that used to prepare compound **1.** ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 7.96 (d, 1H), 7.81 (t, 1H), 7.49-7.41 (m, 2H), 4.87

(s, 2H), 4.60 (t, 2H), 3.57 (m, 2H), 3.47 (m, 2H), 3.22-3.10 (m, 6H), 2.92 (t, 2H), 2.37 (m, 2H), 2.18-1.82 (m, 9H), 1.70 (m, 1H), 1.58-1.18 (m, 8H); EI-MS: 535.4 (M+1).

*Preparation of Compound **246***

Compound **246** was prepared in a manner similar to that used to prepare compound **1.** ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 7.97 (d, 1H), 7.81 (t, 1H), 7.51-7.43 (m, 2H), 4.86 (s, 2H), 4.59 (t, 2H), 3.71 (m, 2H), 3.51 (m, 2H), 3.22-3.12 (m, 7H), 2.37 (m, 2H), 2.26 (m, 2H), 2.18-2.04 (m, 5H), 1.91-1.68 (m, 4H), 1.42-1.18 (m, 6H); EI-MS: 521.4 (M+1).

*Preparation of Compound **247***

Compound **247** was prepared in a manner similar to that used to prepare compound **1.** ^{1}H NMR (400 MHz, D_2O) δ 8.11 (d, 1H), 8.05 (s, 1H), 7.81 (t, 1H), 7.50-7.40 (m, 2H), 4.86 (s, 2H), 4.82 (m, 1H), 4.57 (t, 2H), 3.61 (m, 2H), 3.44 (t, 3H), 3.22-3.10 (m, 8H), 2.36 (m, 2H), 2.20-2.00 (m, 8H), 1.88 (m, 2H), 1.70 (m, 1H), 1.42-1.19 (m, 6H); EI-MS: 499.4 (M+1).

*Preparation of Compound **248***

Compound **248** was prepared in a manner similar to that used to prepare compound **195** and **214.** EI-MS: 707.5 (M+1).

*Preparation of Compound **249***

Compound **249** was prepared in a manner similar to that used to prepare compound **202**. ^{1}H NMR (400 MHz, D_2O) δ 8.06-8.03 (m, 2H), 7.83 (t, 1H), 7.50-7.44 (m, 2H), 4.88 (s, 2H), 4.61-4.47 (m, 5H), 4.02 (m, 1H), 3.41 (m, 1H), 3.22-3.12 (m, 6H), 3.00 (m, 1H), 2.75 (d, 3H), 2.36 (m, 2H), 2.18-1.60 (m, 14H), 1.42-1.18 (m, 6H), 1.10-0.98 (m, 6H); EI-MS: 648.4 (M+1).

*Preparation of Compound **250***

Compound **250** was prepared in a manner similar to that used to prepare compound **202**. ^{1}H NMR (400 MHz, D_2O) δ 8.03 (s, 1H), 6.17 (s, 1H), 4.80 (s, 2H), 4.63-4.52 (m, 4H), 4.36 (q, 2H), 4.10 (s, 2H), 4.00(m, 1H), 3.47 (t, 2H), 3.24-3.11 (m, 7H), 3.00 (t, 2H), 2.98 (s,

3H), 2.72 (m, 1H), 2.42-2.34 (m, 5H), 2.18-2.06 (m, 5H), 1.94-1.80 (m, 3H), 1.71 (m,2H), 1.57 (m, 1H), 1.42-1.18 (m, 9H); EI-MS: 656.4 (M+1).

*Preparation of Compound **251***

Compound **251** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-7.94 (m, 3H), 7.84 (t, 1H), 7.51-7.43 (m, 2H), 5.40 (s, 2H), 4.93 (s, 2H), 4.52 (t, 2H), 4.14 (t, 2H), 3.22-3.13 (m, 8H), 2.35 (m, 2H), 2.18-2.06 (m, 4H), 1.87 (m, 2H), 1.70 (m, 1H), 1.45 (m, 2H), 1.42-1.18 (m, 6H), 1.10-0.98 (m, 4H), 0.63 (t, 3H); EI-MS: 647.4 (M+1).

*Preparation of Compound **252***

Compound **252** was prepared in a manner similar to that used to prepare compound **202**. ^{1}H NMR (400 MHz, D_2O) δ 8.06 (d, 1H), 7.97 (s, 1H), 7.83 (t, 1H), 7.57 (d, 1H), 7.48 (t, 1H), 4.86 (s, 2H), 4.62 (m, 1H), 4.59 (t, 2H), 4.52 (s, 2H), 3.62 (m, 2H), 3.36-3.10 (m, 10H), 2.79 (m, 1H), 2.42-2.36 (m, 4H), 2.18-1.97 (m, 8H), 1.88-1.70 (m, 5H), 1.42-1.19 (m, 6H); EI-MS: 632.4 (M+1).

*Preparation of Compound **253***

Compound **253** was prepared in a manner similar to that used to prepare compound **202**. ^{1}H NMR (400 MHz, D_2O) δ 8.05-8.00 (m, 2H), 7.83 (t, 1H), 7.49-7.43 (m, 2H), 4.87 (s, 2H), 4.59 (t, 2H), 4.48-4.42 (m, 2H), 4.29 (m, 2H), 4.18 (m, 1H), 3.92 (s, 3H), 3.78 (m, 1H), 3.31 (m, 1H), 3.20-3.12 (m, 6H), 2.93 (m, 1H), 2.36 (m, 2H), 2.16-2.06 (m, 6H), 2.00-1.82 (m, 5H), 1.71 (m, 2H), 1.56 (m, 1H), 1.41-1.18 (m, 6H), 1.02 (d, 6H); EI-MS: 706.5 (M+1).

*Preparation of Compound **254***

Compound **254** was prepared in a manner similar to that used to prepare compound **206**. EI-MS: 628.4 (M+1).

*Preparation of Compound **255***

Compound **255** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.07 (d, 1H), 8.05 (s, 1H), 7.83 (t, 1H), 7.51-7.44 (m, 2H), 4.91

(s, 2H), 4.52 (m, 1H), 4.47 (s, 2H), 3.56 (m, 2H), 3.26-3.10 (m, 6H), 3.05 (s, 2H), 2.26-1.82 (m, 10H), 1.70 (m, 1H), 1.42-1.19 (m, 6H), 1.13 (s, 6H); EI-MS: 549.4 (M+1).

*Preparation of Compound **256***

Compound **256** was prepared in a manner similar to that used to prepare compound **202**. EI-MS: 692.4 (M+1).

*Preparation of Compound **257***

Compound **257** was prepared in a manner similar to that used to prepare compound **206**. EI-MS: 692.4 (M+1).

*Preparation of Compound **258***

Compound **258** was prepared in a manner similar to that used to prepare compound **78** and **59.** EI-MS: 621.4 (M+1).

*Preparation of Compound **259***

Compound **259** was prepared in a manner similar to that used to prepare compound **1.** ^{1}H NMR (400 MHz, D_2O) δ 7.99 (s, 1H), 6.19 (s, 1H), 4.86 (s, 2H), 4.82 (m, 1H), 4.55 (t, 2H), 3.58 (m, 2H), 3.22-3.10 (m, 8H), 3.01 (s, 3H), 2.36-2.30 (m, 5H), 2.20-1.80 (m, 10H), 1.70 (m, 1H), 1.42-1.19 (m, 6H); EI-MS: 499.4 (M+1).

*Preparation of Compound **260***

Compound **260** was prepared in a manner similar to that used to prepare compound **1**. ^{1}H NMR (400 MHz, D_2O) δ 8.29 (d, 1H), 7.99 (s, 1H), 7.81 (t, 1H), 7.48-7.42 (m, 2H), 4.58 (m, 2H), 4.40 (m, 1H), 4.10 (m, 2H), 3.62 (m, 2H), 3.30 (m, 2H), 3.20-3.04 (m, 4H), 3.04 (m, 2H), 2.98 (m, 2H), 2.62 (t, 2H), 2.38 (m, 2H), 2.20-1.82 (m, 10H), 1.77-1.63 (m, 1H), 1.43-1.18 (m, 6H); EI-MS: 535.4 (M+1).

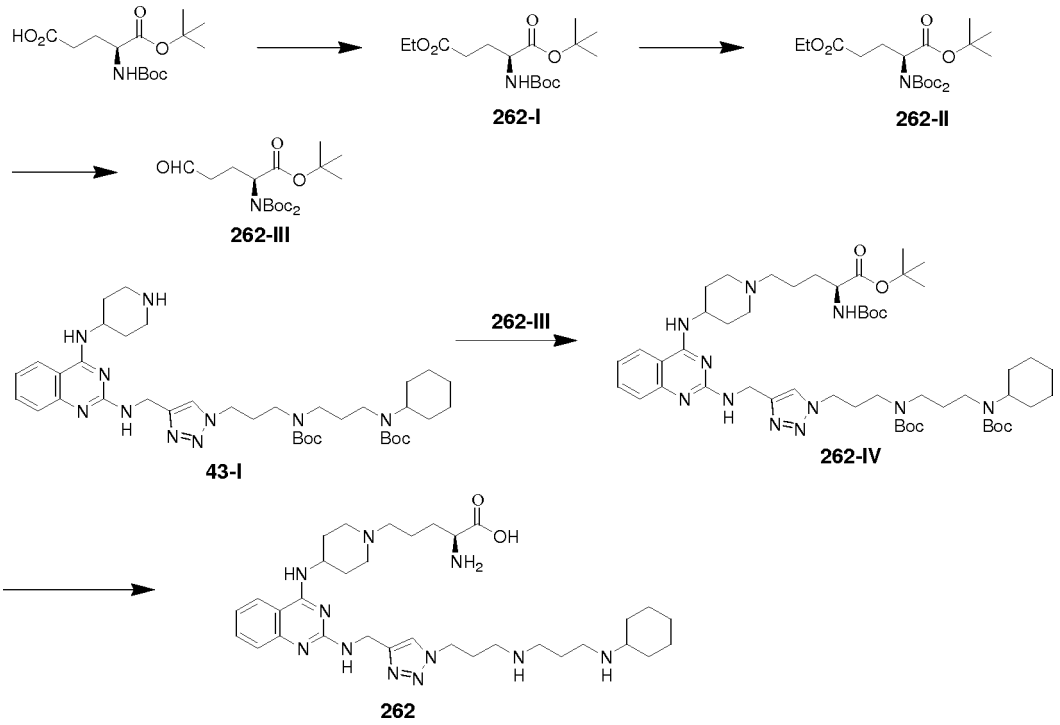
*Preparation of Compound **261***

Compound **261** was prepared in a manner similar to that used to prepare compound **142**. ^{1}H NMR (400 MHz, D_2O) δ 8.01 (s, 1H), 4.69 (s, 2H), 4.57 (t, 2H), 3.22-3.04 (m, 10H),

2.79 (m, 1H), 2.35 (m, 2H), 2.18-2.02 (m, 4H), 1.98 (m, 2H), 1.87 (m, 2H), 1.70 (m, 1H), 1.56 (m, 2H), 1.42-1.19 (m, 6H); EI-MS: 515.3 (M+1).

Preparation of Compound ***262***

Shown below is a scheme for synthesizing compound **262** from compound 43-I via intermediates 262-I to 262-IV.



EtI (936 mg) and K_2CO_3 (100 mg) were added to a solution of 2-tert-butoxycarbonylamino-pentanedioic acid 1-tert-butyl ester (909 mg) in DMF (8 mL) under an atmosphere of nitrogen. The resulting reaction mixture was stirred at 25 °C for 15 h and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with dichloromethane (3x50 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated to afford crude 262-I (712 mg, 72% yield).

Boc_2O (710 mg) , TEA (420 mg), and DMAP (122 mg) were added to a solution of 262-I (710 mg) in DCM . The mixture was stirred at 60 °C for 15 h, and then concentrated under a reduced pressure by removing CH_2Cl_2 to give the crude residue, which was purified

with flash chromatography with n-hexane / ethyl acetate (30:1) to afford the product 262-II (670 mg, 72% yield).

DIBAL (1M, 2 mL) was added at -78 °C to a solution of 262-II (650 mg) in diethyl ether (20 mL). The resulting mixture was stirred at -78 °C for 2 h, and then quenched with aqueous NH_4Cl (50 mL, 2 M). The resulting solution was extracted with dichloromethane (3x50 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with n-hexane / ethyl acetate = 19/1 to afford compound 262-III (347 mg, 59% yield).

262-III (130 mg), sodium triacetoxyborohydride (150 mg), and HOAc (60 mg) were added to a solution of 43-I (363 mg) in DCM (20 mL). The resulting mixture was stirred at 25 °C for 15 h, and then quenched with aqueous NH4Cl (50 mL, 2 M). The resulting solution was extracted with dichloromethane (3x50 mL). The extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue thus obtained was purified by flash chromatography on silica gel with MeOH / DCM = 1/19 to afford compound 262-IV (311 mg, 62% yield).

A solution of 4N HCl/dioxane (1.8 mL) was added to the solution of compound 262-IV (196 mg) in dichloromethane (3.6 mL) and 1,4-dioxane (3.6 mL). The reaction mixture was stirred for 15 h and concentrated to afford hydrochloride salt of compound **262** (135 mg, 87% yield). EI-MS: 636.4 (M+1).

*Preparation of Compound **263***

Compound **263** was prepared in a manner similar to that used to prepare compound **241**. EI-MS: 599.4 (M+1).

*Preparation of Compound **264***

Compound **264** was prepared in a manner similar to that used to prepare compound **1**. ^1H NMR (400 MHz, D_2O) δ 8.10-8.05 (m, 2H), 7.86 (t, 1H), 7.65 (d, 1H), 7.51 (t, 1H), 5.15

(s, 2H), 4.60- 4.50 (m, 3H), 3.57 (m, 2H), 3.38 (s 3H), 3.22-3.15 (m, 8H), 2.38 (m, 2H), 2.26 (m, 2H), 2.20-2.05 (m, 4H), 2.00-1.82 (m, 4H), 1.71 (m, 1H), 1.43-1.18 (m, 6H); EI-MS: 535.4 (M+1).

*Preparation of Compound **265***

Compound **265** was prepared in a manner similar to that used to prepare compound **195**. ^{1}H NMR (400 MHz, D_2O) δ 8.03-7.93 (m, 3H), 7.84 (t, 1H), 7.48 (d, 2H), 5.24 (s, 2H), 4.96 (s, 2H), 4.52 (m, 2H), 3.95 (m, 1H), 3.30 (m, 2H), 3.22-3.08 (m, 8H), 2.34 (m, 2H), 2.18-1.61 (m, 11H), 1.43-1.18 (m, 6H); EI-MS: 691.4 (M+1).

*Preparation of Compound **266***

Compound **266** was prepared in a manner similar to that used to prepare compound **262**. EI-MS: 600.4 (M+1).

*Preparation of Compound **267***

Compound **267** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, D_2O) δ8.05 (s, 1H), 7.84 (d, 1H), 6.92 (dd, 1H), 6.75 (s, 1H), 4.86 (s, 2H), 4.58 (t, 2H), 4.45 (m,1H), 4.32 (m, 1H), 4.15 (m, 1H), 4.02 (m, 1H), 3.26 (m, 1H), 3.20-3.12 (m, 6H), 2.82 (m, 1H), 2.77 (t, 2H), 2.35 (m, 2H), 2.27 (m, 2H), 2.18-1.80 (m, 8H), 1.68 (m, 2H), 1.55 (m, 1H), 1.40-1.17 (m, 6H); EI-MS: 680.4 (M+1).

*Preparation of Compound **268***

Compound **268** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, D_2O) δ 8.08 (s, 1H), 7.87 (d, 1H), 7.36-7.24 (m, 2H), 4.86 (s, 2H), 4.46 (t, 2H), 4.46 (m,1H), 4.38 (m, 1H), 4.17 (m, 1H), 4.04 (m, 1H), 3.30 (m, 1H), 3.20-3.06 (m, 6H), 2.81 (m, 1H), 2.78 (t, 2H), 2.36 (m, 2H), 2.26 (m, 2H), 2.16-1.80 (m, 8H), 1.67 (m, 2H), 1.58 (m, 1H), 1.40-1.13 (m, 6H); 684.3 (M+1).

*Preparation of Compound **269***

Compound **269** was prepared in a manner similar to that used to prepare compounds **260** and **63**. EI-MS: 664.4 (M+1).

*Preparation of Compound **270***

Compound **270** was prepared in a manner similar to that used to prepare compound **63**. ^{1}H NMR (400 MHz, D_2O) δ 8.04-8.01 (m, 2H), 7.83 (m, 1H), 7.46-7.42 (m, 2H), 4.86 (s, 2H), 4.58 (t, 2H), 4.44-4.41 (m, 2H), 4.30 (m, 1H), 4.03 (m, 1H), 3.40-3.12 (m, 9H), 2.83 (m, 1H), 2.35 (m, 2H), 2.21-1.80 (m, 8H), 1.70 (m, 2H), 1.58 (m, 1H), 1.43-1.18 (m, 6H); 636.4 (M+1).

*Preparation of Compound **271***

Compound **271** was prepared in a manner similar to that used to prepare compound **63**. EI-MS: 664.4 (M+1).

*Preparation of Compound **272***

Compound **272** was prepared in a manner similar to that used to prepare compound **258**. EI-MS: 585.4 (M+1).

*Preparation of Compound **273***

Compound **273** was prepared in a manner similar to that used to prepare compounds **181** and **63**. EI-MS: 693.4 (M+1).

EXAMPLE 2

Radioligand Binding Assay Using Membranes Prepared from Human CXCR4-transfected HEK293 Cells

Binding competition between the compounds of Formula (I) and human SDF-1 was assessed using a radioligand binding assay as described below.

Membranes (2-4 μg) prepared from human CXCR4-transfected HEK293 cells in 40 μL of assay buffer (50 mM HEPES-NaOH, pH 7.4, 100 mM NaCl, 5 mM $MgCl_2$, 1 mM $CaCl_2$, 0.5% bovine serum albumin) were incubated with 20 μL of radio-labeled ^{125}I-SDF-1 (0.16 nM) and 20 μL of a test compound in an assay plate (Costar Corning, Cambridge, MA). After 60 minutes at 30 °C, the incubation was terminated by transferring the resulting

reaction mixture to a 96-well GF/B filter plate (Millipore Corp., Billerica, MA) and filtered via a manifold. The plate was washed with 100 μL of ice-cold wash buffer (50 mM HEPES-NaOH, pH 7.4, 100 mM NaCl) four times. The radioactivity bound to the filter was measured by Topcount (PerkinElmer Inc., Waltham, MA).

It was unexpectedly observed that the concentration required to inhibit binding of ^{125}I-SDF-1 to CXCR4 by 50% (IC_{50}) of 42 tested compounds was lower than 25 nM, 97 tested compounds had IC_{50} values of 25-100 nM, and 104 tested compounds had IC_{50} values of 100-1000 nM.

The results indicate that compounds of Formula (I) have high binding affinities toward CXCR4.

Calcium Mobilization Assay Using Human CXCR4-transfected HEK293 Cells

Compounds of Formula (I) were tested for their efficacy in binding to CXCR4 using a calcium mobilization assay as follows:

Human CXCR4-transfected HEK293 cells were incubated with 50 μL Fluo-4 Dye (2X) of Fluo-4 (DIRECT™ Calcium Assay Kit, Molecular Probes; Invitrogen, Breda, The Netherlands) in 40 μL Dulbecco's modified Eagle's medium supplemented with10% fetal bovine serum in an assay plate at a density of 2×10^4 cells/well. After 60 minutes at 37 °C, the cells were treated with 10 μL of a test compound and 25 μL of SDF-1 (1 nM) at room temperature.

Unexpectedly, the concentration required to inhibit binding of SDF-1 to CXCR4 by 50% (EC_{50}) of five tested compounds was less than 100 nM and 40 tested compounds showed EC_{50} values of 100-1000 nM.

The results indicate that the compounds of Formula (I) bind strongly to CXCR4.

Chemotaxis Assay Using Lymphoblastic Leukemia (CCRF-CEM) Cells

The response of cancer cells to compounds of Formula (I) was evaluated using the chemotaxis assay as set forth below.

T-cell acute lymphoblastic leukemia (CCRF-CEM) cells in Roswell Park Memorial Institute medium (RPMI) 1640 supplemented with10% bovine serum albumin were incubated with 250 μL of a test compound. The assay was performed using Millicell Hanging Cell Culture Inserts (pore size 5 μm; 24-well plate; Millipore, Bedford, MA, USA). After 10 minutes at 37 °C, 250 μL of cells pre-incubated with a test compound were plated per well in the upper chambers of the inserts at a density of 2.5 $\times 10^5$ cells/well. 300 μL/well medium containing SDF-1 (10 nM) and a test compound were plated in the lower chamber of the insert. After 2.5 h at 37 °C, cells in both chambers of inserts were measured by flow cytometry (Guava Technologies, Hayward, CA, USA).

It was observed that 33 tested compounds unexpectedly showed concentrations required to inhibit chemotaxis by 50% (EC_{50}) with values of lower than 100 nM and 20 tested compounds showed EC_{50} values of 100-1000 nM.

The results indicate that the compounds of Formula (I) have high efficacy in inhibiting the chemotaxis of certain cancer cells.

EXAMPLE 3

Colony-Forming Assay to Evaluate Mobilization of Stem Cells in Mice

31 compounds of Formula (I) were tested to assess their efficacy in enhancing stem/progenitor cell mobilization as follows:

Each of the 31 compounds was dissolved in saline to form a solution. The solution was administered to C57BL/6 male mice (National Laboratory Animal Center, Taipei, Taiwan) subcutaneously. Mice treated with saline were used as controls. Whole blood was collected 2 h after subcutaneous injection and labeled with the following antibodies: (i) APC-conjugated anti-CXCR4 (clone 2B11; eBioscience), (ii) FITC-conjugated anti-CD34 (clone

RAM34; eBioscience), (iii) PE-conjugated anti-CD133 (clone 13A4; eBioscience), (iv) anti-c-kit (clone 2B8; eBioscience), (v) anti-Sca-1 (clone D7; eBioscience), (vi) anti-linage (Mouse Hematopoietic Lineage Biotin Panel, eBioscience), and (vii) Streptavidin PE-Cy7 (eBioscience). Hematopoietic stem cells ($CD34^+$) and endothelial progenitor cells ($CD133^+$) were quantified using antibody surface staining and flow cytometry (Guava Technologies, Hayward, CA, USA).

Unexpectedly, the test compounds significantly enhanced mobilization of $CD34^+$ hematopoietic stem cells (up to 7.8 fold) and $CD133^+$ endothelial progenitor cells (up to 5.8 fold) into peripheral blood as compared to saline controls. In addition, the tested compounds combined with G-CSF were found to unexpectedly mobilize hematopoietic stem cells synergistically as evidenced by the significant increase of CFU-GM numbers.

The results indicate that the compounds of Formula (I) have high efficacy in enhancing stem/progenitor cell mobilization.

EXAMPLE 4

Treatment of Ischemia-Reperfusion Injury in Rats

The efficacy of certain compounds of Formula (I) in treating Ischemia-Reperfusion injury was assessed using both an acute kidney injury model, an ischemic stroke model, and a limb ischemia model.

Acute Kidney Injury (AKI) model.

Each of five compounds was dissolved in saline to form a solution. The solution was administered to male Sprague-Dawley rats (National Laboratory Animal Center, Taipei, Taiwan) subcutaneously at a dosage of 6 mg/Kg. 40 minutes after the subcutaneous injection, AKI was induced in the rats by clamping their bilateral renal vein and artery for one h followed by releasing the vessel clips to allow 24-h reperfusion. Whole blood was collected 24 h after induction of AKI. Blood urea nitrogen (BUN) and serum creatinine

(SCR), two markers that increase upon kidney injury, were measured using a FUJI DRI-CHEM 3500s analyzer (Fujifilm, Tokyo, Japan). Non-AKI rats and AKI rats treated with saline were used as controls.

It was observed that the AKI rats dosed with the test compounds unexpectedly had levels of BUN and SCR, respectively, 20~71% and 20-76% of those levels induced in saline-treated AKI rats.

The results indicate that the compounds of Formula (I) have high efficacy in treating a kidney injury.

Ischemic Stroke in Rats

Adult male Sprague–Dawley rats (250-300 g) were anesthetized with chloral hydrate (400 mg/kg i.p.). The right middle cerebral artery was occluded (MCAo) and bilateral common carotids (CCAs) were clamped for 60 minutes to generate focal ischemia in the right cerebral cortex. Core body temperature was maintained at 37 °C.

Compounds **62** and **63** and a vehicle were administered to the rats at a dose of 1 mg/kg/d (i.p.) for 5 consecutive days. The first dose was given at 90 minutes after MCAo. Each animal was placed in a 42×42×31 cm activity monitor for 1 h on day 2 after MCAo. The monitor contained 16 horizontal and 8 vertical infrared sensors spaced 2.5 cm apart. Locomotor activity was calculated using the number of infrared beams broken by the animals.

TTC staining was performed on day 5 after MCAo to determine infarction size as described previously in *Brain Research*, volume 1116, issue 1, 2006, pages 159–165. Briefly, rats were decapitated and the brains were removed and sliced into 2.0-mm-thick sections. The brain slices were incubated in a 2% TTC solution (Sigma-Aldrich) for 15 minutes at room temperature and then transferred into a 4% paraformaldehyde solution for fixation. The area of infarction in each slice was measured with a digital scanner and

Imagetools programs (University of Texas Health Sciences Center). The volume of infarction in each animal was obtained from the product of average slice thickness (2 mm) and sum of infarction areas in all brain slices examined.

Unexpectedly, the rats receiving compound **62** or **63** showed a significant increase in horizontal movement number, compared with the vehicle-treated animals. Similarly, vertical movement number was significantly increased by both compounds. The volume of infarction was significantly reduced in animals treated with the tested compounds, as compared to vehicle.

The results indicate that both compounds **62** and **63** exert a protective effect in stroke animals.

Limb Ischemia in Mice

Unilateral hindlimb ischemia was induced in ICR mice by ligating and excising the right femoral artery. Briefly, animals were anesthetized by an intraperitoneal injection of Xylocaine (2 mg/kg of body weight) plus Zoletil (i.e., the dissociative anesthetic Tiletamine/Zolazepam at a ratio of 1:1; 5 mg/kg of body weight). The proximal and distal portions of the femoral artery were ligated with a silk thread, and a 0.2 centimeter section of the blood vessel was removed. Hindlimb blood perfusion was measured with a laser Doppler perfusion imager system (Moor Instruments Limited, Devon, UK) before and after the surgery and was then followed on a weekly basis. Animals were subcutaneously treated with compound **4** (6 mg/kg/d, twice a week) in saline after surgery. The animals were sacrificed by cervical dislocation without sedation at the end of the seven experimental weeks. To avoid the influence of ambient light and temperature, the results are expressed as the ratio of perfusion in the right (ischemic) versus left (non-ischemic) limb.

It was observed that compound **4** unexpectedly improved by 20-25% blood flow of mice suffering from ischemia-reperfusion injury in the ischemic hindlimb as compared with the vehicle control.

The results indicate that compound **4** is efficacious in treating limb ischemia.

OTHER EMBODIMENTS

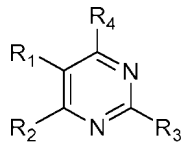
All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the scope of the following claims.

2015321654 27 Sep 2019

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

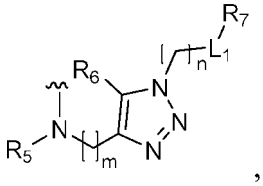
1. A compound of formula (I):

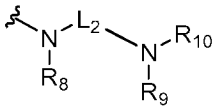
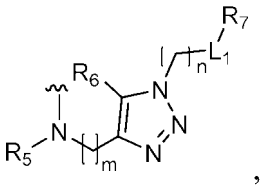


(I),

wherein

each of R_1 and R_2, independently, is H, halo, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl; or R_1 and R_2, together with the two carbon atoms to which they are bonded, are C_{5-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, C_{5-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, and heteroaryl being optionally substituted with halo, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxyl, aryl, heteroaryl, or $C(O)OR_a$, in which R_a is H, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl; and

each of R_3 and R_4, independently, is NR_bR_c,  , or

 , at least one of R_3 and R_4 being  ,

in which

each of R_b and R_c, independently, is H or C_{1-6} alkyl;

2015321654 27 Sep 2019

R_5 is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, and heteroaryl being optionally substituted with halo, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl;

R_6 is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl;

L_1 is heteroaryl, C_{1-10} heterocycloalkyl, NH, or NR_d, in which R_d is $C(O)(CH_2)_2CHNH_2CO_2R_e$, R_e being H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl;

R_7 is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, and heteroaryl being optionally substituted with hydroxy, hydroxy C_{1-6} alkyl, halo, nitro, cyano, amino, amino C_{1-6} alkyl, amino C_{3-10} cycloalkyl, amino C_{1-10} heterocycloalkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl;

m is 1-6;

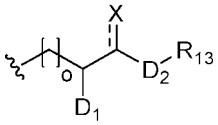
n is 1-6;

each of R_8 and R_9, independently, is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, and heteroaryl being optionally substituted with $C(O)OR_f$, in which R_f is H, C_{1-10} alkyl, C_{3-20} cycloalkyl, C_{3-20} heterocycloalkyl, aryl, or heteroaryl; or R_8 and R_9, together with the nitrogen atoms to which they are bonded, are C_{3-10} heterocycloalkyl;

2015321654 27 Sep 2019

L_2 is C_{1-6} alkyl; or L_2, together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl or heteroaryl; and

R_{10} is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl, $C(O)OR_g$, $C(S)NR_hR_i$, $C(O)NR_jR_k$, or $C(O)R_p$, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, and heteroaryl alkyl being optionally substituted with hydroxy, halo, nitro, cyano, amino, $C(O)OR_{11}$, or $P(O)(OR_{12})_2$, in which each of R_{11} and R_{12}, independently, is H or C_{1-6} alkyl; or R_{10}, together with R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl or heteroaryl; each of R_g, R_h, R_i, R_j, and R_k, independently, being H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} alkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl; and R_p being H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl, or



, in which each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl is optionally substituted with halo, $P(O)(OH)_2$, or $P(O)(O\text{-}C_{1-6}$ alkyl$)_2$; o is 0-2; D_1 is OH or $NR_{14}R_{15}$, each of R_{14} and R_{15}, independently, being H, $C(O)CH(NH_2)CH_2OH$, or $C(NH)NH_2$; D_2 is O or NR_{16}, R_{16} being H, C_{1-6} alkyl, $S(O)_2R_q$, NHR_r, or $CH_2CO_2R_s$, in which each of R_q and R_r, independently, is aryl optionally substituted with halo or alkoxyl, and R_s is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} alkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl; R_{13} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl, each of C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl, and heteroaryl being optionally substituted with hydroxy, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl alkyl, heteroaryl alkyl, aryl,

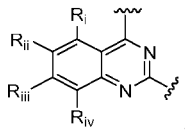
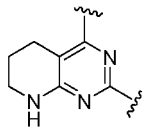
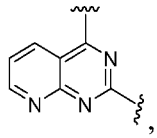
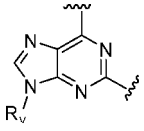
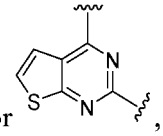
2015321654 27 Sep 2019

heteroaryl, $P(O)(OH)_2$, $P(O)(O\text{-}C_{1\text{-}6}\ alkyl)_2$, hydroxy, or $C(O)OR_t$, in which R_t is H, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxyl, $C_{1\text{-}6}$ alkyl, aryl alkyl, heteroaryl alkyl, aryl, or heteroaryl; and ---X is =O or —aryl.

2. The compound of claim 1, wherein each of R_1 and R_2, independently, is H, NH_2, or $C_{1\text{-}10}$ heterocycloalkyl optionally substituted with $C_{1\text{-}6}$ alkyl or $C(O)OR_a$, in which R_a is H or $C_{1\text{-}10}$ alkyl.

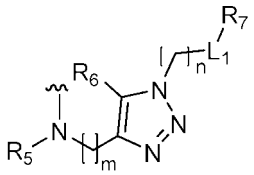
3. The compound of claim 2, wherein each of R_1 and R_2, independently, is H, NH_2, morpholine, piperidine, or piperazine substituted with $C_{1\text{-}6}$ alkyl or $C(O)OR_a$.

4. The compound of claim 1, wherein R_1 and R_2, together with the two carbon atoms to which they are bonded, are $C_{5\text{-}10}$ cycloalkyl, $C_{3\text{-}10}$ heterocycloalkyl, aryl, or heteroaryl.

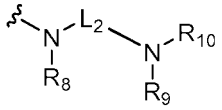
5. The compound of claim 4, wherein R_1 and R_2, together with the two carbon atoms to which they are bonded, are  ,  ,  ,  , or  , each of R_i, R_{ii}, R_{iii}, R_{iv}, and R_v, independently, being H, halo, $C_{1\text{-}10}$ alkyl, $C_{1\text{-}6}$ alkoxyl, $C_{3\text{-}10}$ cycloalkyl, $C_{3\text{-}10}$ heterocycloalkyl, aryl, or heteroaryl.

2015321654 27 Sep 2019

6. The compound of claim 1, wherein each of R_3 and R_4, independently, is

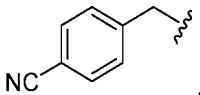


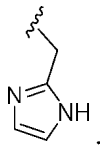
or



.

7. The compound of claim 6, wherein R_5 is H, aryl alkyl, or heteroaryl alkyl, each of aryl alkyl and heteroaryl alkyl being optionally substituted with cyano.

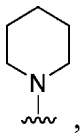
8. The compound of claim 7, wherein R_5 is H, 

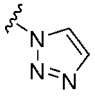
, or 

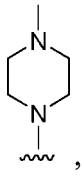
.

9. The compound of claim 6, wherein R_6 is H, aryl, or heteroaryl.

10. The compound of claim 9, wherein R_6 is H, phenyl, or pyridinyl.

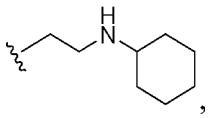
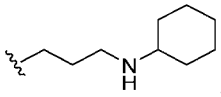
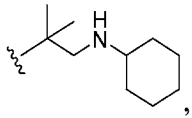
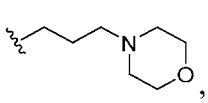
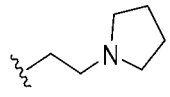
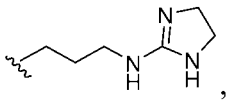
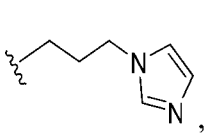
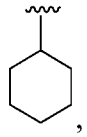
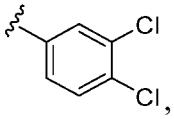
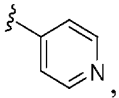
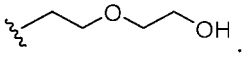
11. The compound of claim 6, wherein L_1 is NH, 

, 

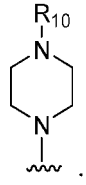
, 

, or -$NC(O)(CH_2)_2CHNH_2CO_2H$.

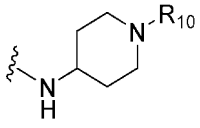
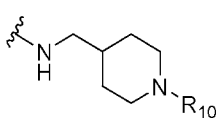
2015321654 27 Sep 2019

12. The compound of claim 6, wherein R_7 is H, CH_2OH,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

13. The compound of claim 6, wherein each of R_8 and R_9, independently, is H or C_{1-6} alkyl being optionally substituted with $C(O)OR_f$, in which R_f is H or C_{1-10} alkyl.

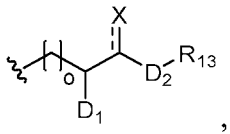
14. The compound of claim 6, wherein R_8 and R_9, together with the nitrogen atoms to which they are bonded, are  .

15. The compound of claim 6, wherein L_2, together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl.

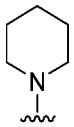
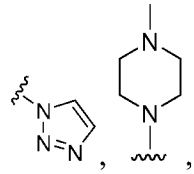
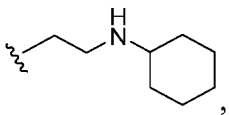
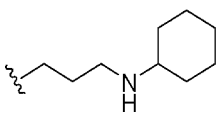
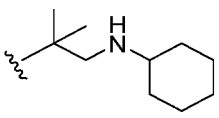
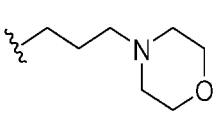
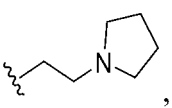
16. The compound of claim 15, wherein L_2, together with R_9 and the nitrogen atom to which they are bonded, is  or  .

2015321654 27 Sep 2019

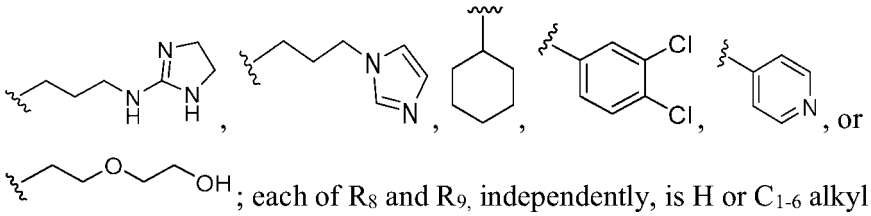
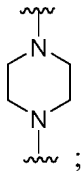
17. The compound of claim 6, wherein R_{10} is H, C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, heteroaryl alkyl, $C(O)OR_g$, $C(S)NR_hR_i$, or $C(O)NR_jR_k$, each of C_{1-6} alkyl, C_{1-6} alkoxyl, C_{3-10} cycloalkyl, C_{1-10} heterocycloalkyl, aryl, heteroaryl, aryl alkyl, and heteroaryl alkyl being optionally substituted with hydroxy, halo, $C(O)OR_{11}$, or $P(O)(OR_{12})_2$; or R_{10}, together with R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl or heteroaryl.

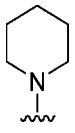
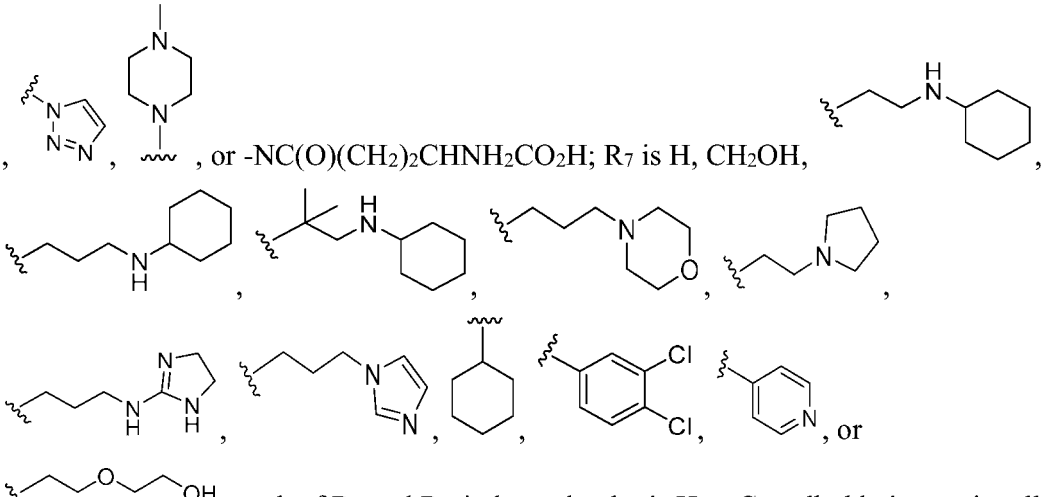
18. The compound of claim 6, wherein R_{10} is $C(O)R_p$, R_p being C_{1-6} alkyl, C_{3-10} cycloalkyl, aryl, heteroaryl, or  , in which each of C_{1-6} alkyl, C_{3-10} cycloalkyl, aryl, and heteroaryl is optionally substituted with halo or $P(O)(OH)_2$.

19. The compound of claim 18, wherein ---X is =O.

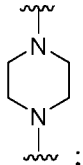
20. The compound of claim 17, wherein each of R_1 and R_2, independently, is H, amino, C_{1-10} heterocycloalkyl optionally substituted with C_{1-6} alkyl or $C(O)OR_a$, in which R_a is H, C_{1-10} alkyl; R_5 is H, aryl alkyl, heteroaryl alkyl, each of aryl alkyl and heteroaryl alkyl being optionally substituted with cyano; R_6 is H, aryl, or heteroaryl; L_1 is NH,  ,  , or $-NC(O)(CH_2)_2CHNH_2CO_2H$; R_7 is H, CH_2OH,  ,  ,  ,  ,  , .

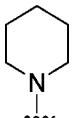
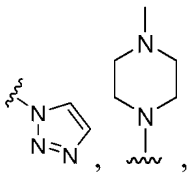
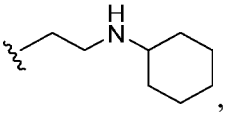
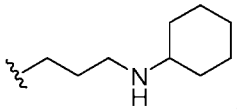
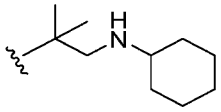
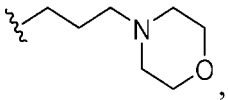
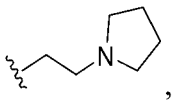
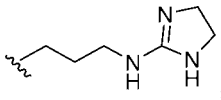
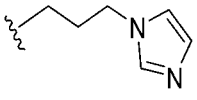
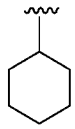
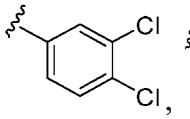
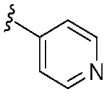
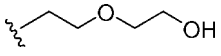
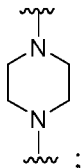
2015321654 27 Sep 2019


; each of R_8 and R_9, independently, is H or C_{1-6} alkyl being optionally substituted with $C(O)OR_f$, in which R_f is H or C_{1-10} alkyl, or R_8 and R_9, together with the nitrogen atoms to which they are bonded, are  ; or L_2, together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl.

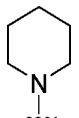
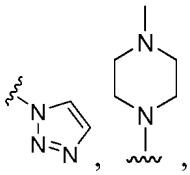
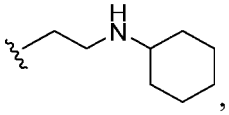
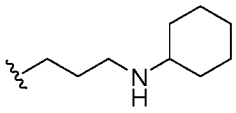
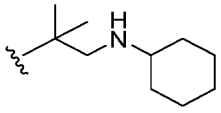
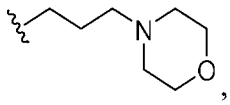
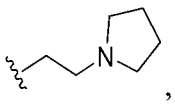
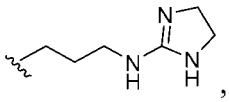
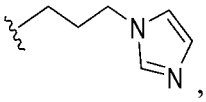
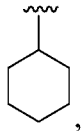
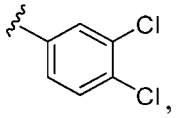
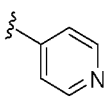
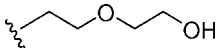
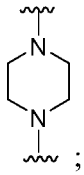
21. The compound of claim 19, wherein each of R_1 and R_2, independently, is H, amino, C_{1-10} heterocycloalkyl optionally substituted with C_{1-6} alkyl or $C(O)OR_a$, in which R_a is H, C_{1-10} alkyl; R_5 is H, aryl alkyl, heteroaryl alkyl, each of aryl alkyl and heteroaryl alkyl being optionally substituted with cyano; R_6 is H, aryl, or heteroaryl; L_1 is NH, 

; each of R_8 and R_9, independently, is H or C_{1-6} alkyl being optionally substituted with $C(O)OR_f$, in which R_f is H or C_{1-10} alkyl, or R_8 and R_9, together with the

2015321654 27 Sep 2019

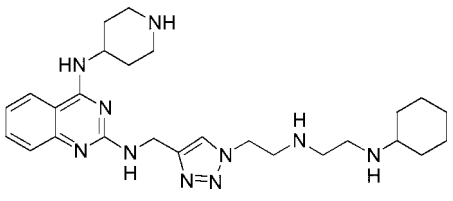
nitrogen atoms to which they are bonded, are  ; or L_2, together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl.

22. The compound of claim 17, wherein R_1 and R_2, together with the two carbon atoms to which they are bonded, are C_{5-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl; R_5 is H, aryl alkyl, heteroaryl alkyl, each of aryl alkyl and heteroaryl alkyl being optionally substituted with cyano; R_6 is H, aryl, or heteroaryl; L_1 is NH,  ,  , , or -NC(O)$(CH_2)_2$CHNH_2CO_2H; R_7 is H, CH_2OH,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; each of R_8 and R_9, independently, is H or C_{1-6} alkyl being optionally substituted with $C(O)OR_f$, in which R_f is H or C_{1-10} alkyl, or R_8 and R_9, together with the nitrogen atoms to which they are bonded, are  ; or L_2, together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl.

2015321654 27 Sep 2019

23. The compound of claim 19, wherein R_1 and R_2, together with the two carbon atoms to which they are bonded, are C_{5-10} cycloalkyl, C_{3-10} heterocycloalkyl, aryl, or heteroaryl; R_5 is H, aryl alkyl, heteroaryl alkyl, each of aryl alkyl and heteroaryl alkyl being optionally substituted with cyano; R_6 is H, aryl, or heteroaryl; L_1 is NH,  ,  , or -NC(O)$(CH_2)_2$CHNH_2CO_2H; R_7 is H, CH_2OH,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; each of R_8 and R_9, independently, is H or C_{1-6} alkyl being optionally substituted with $C(O)OR_f$, in which R_f is H or C_{1-10} alkyl, or R_8 and R_9, together with the nitrogen atoms to which they are bonded, are  ; or L_2, together with R_8 or R_9 and the nitrogen atom to which they are bonded, is C_{4-10} heterocycloalkyl.

24. A compound having one of the following structures:



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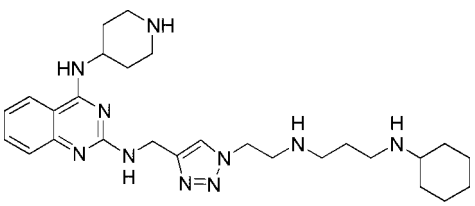

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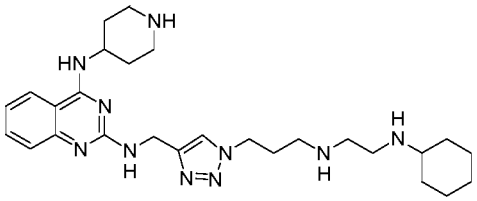
2015321654 27 Sep 2019



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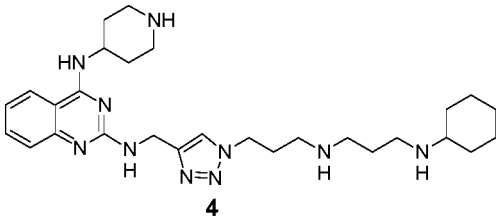

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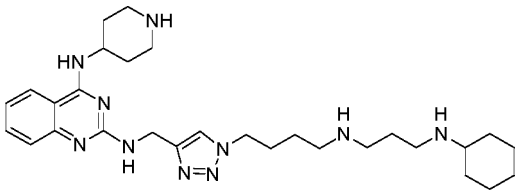

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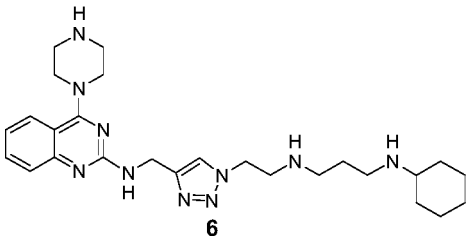

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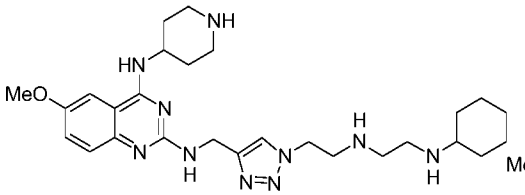

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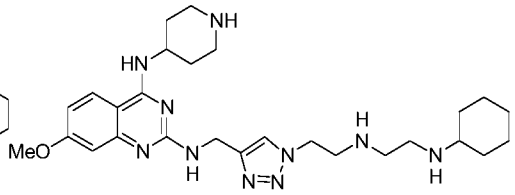

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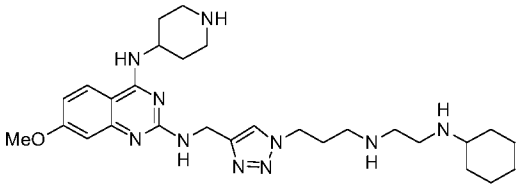

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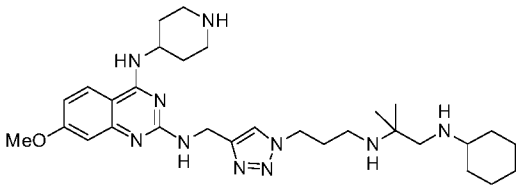

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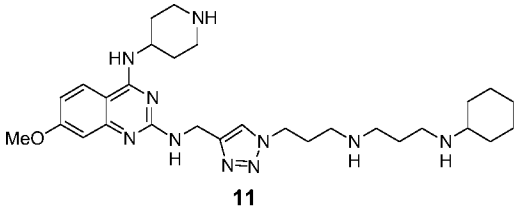

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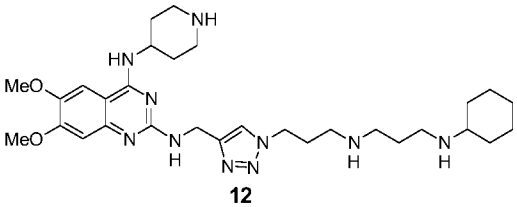

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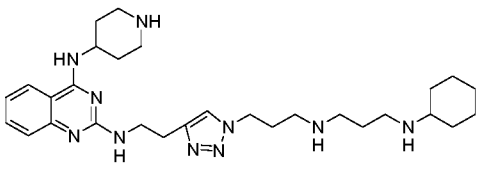
2015321654 27 Sep 2019



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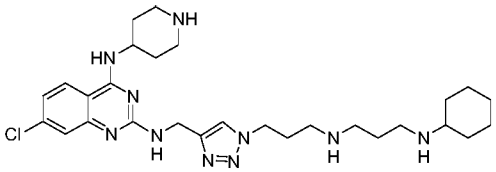

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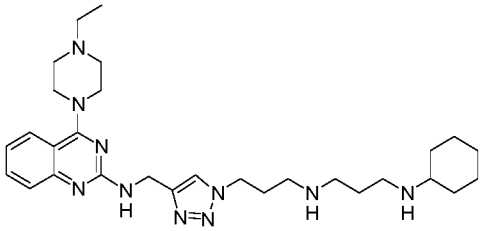

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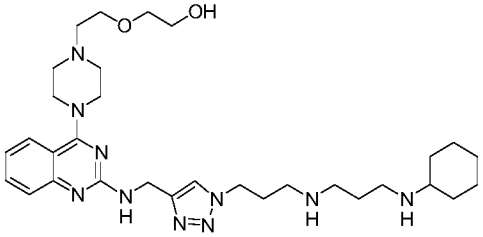

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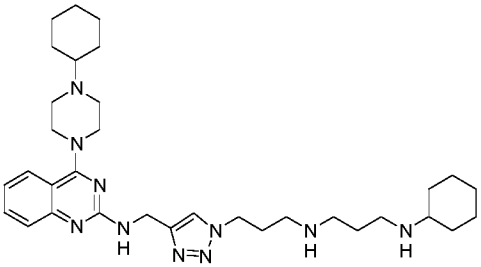

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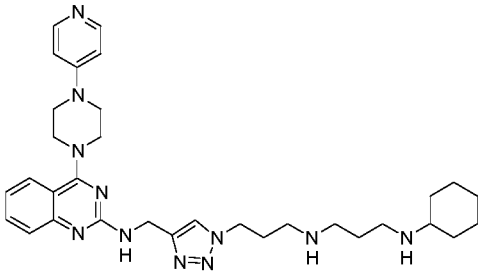

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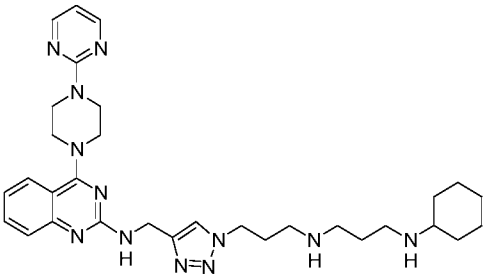

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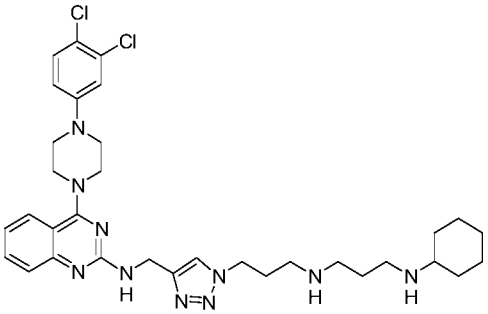

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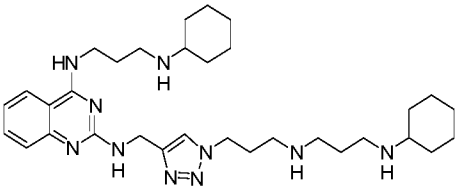

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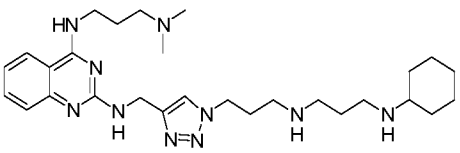

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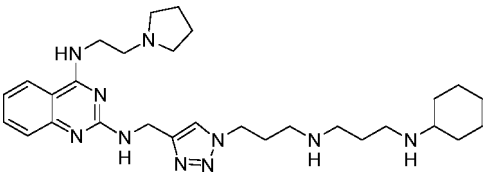

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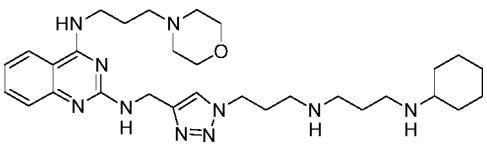

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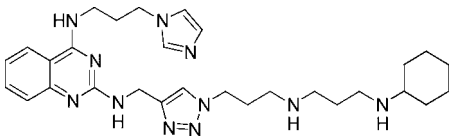
20153216654 27 Sep 2019



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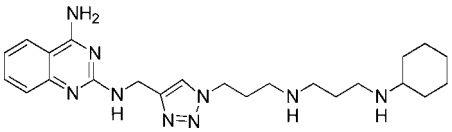

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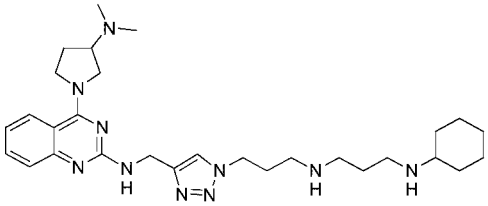

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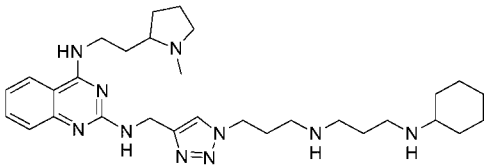

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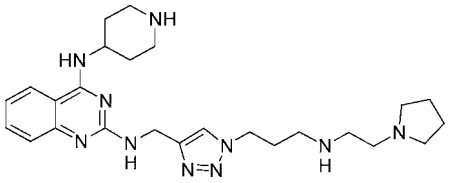

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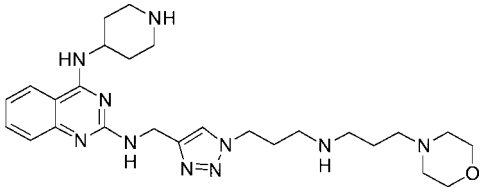

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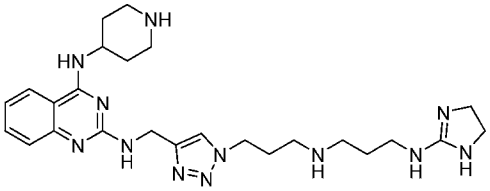

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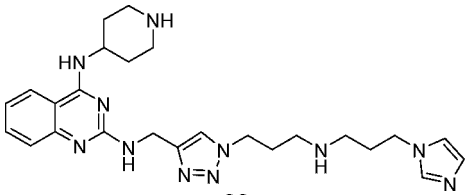

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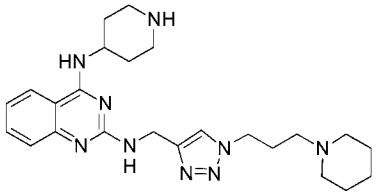

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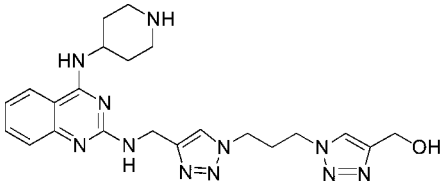

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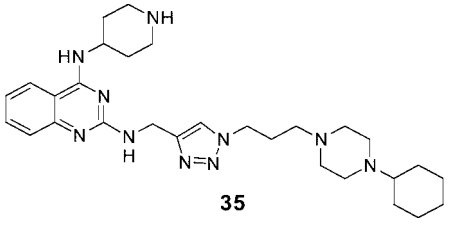

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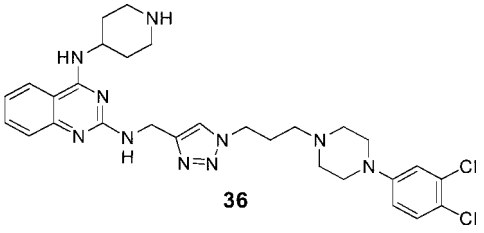

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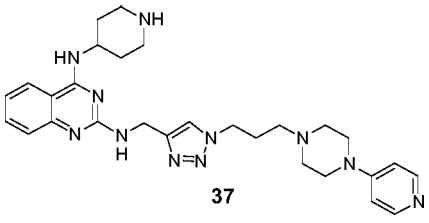
27 Sep 2019
20153216654



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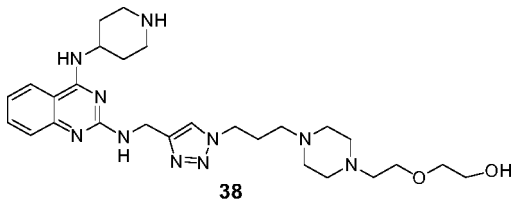

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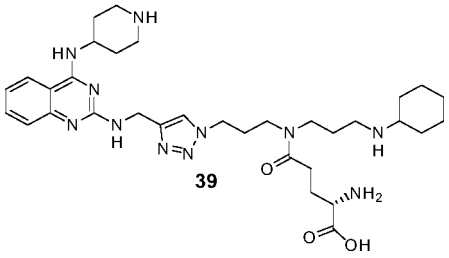

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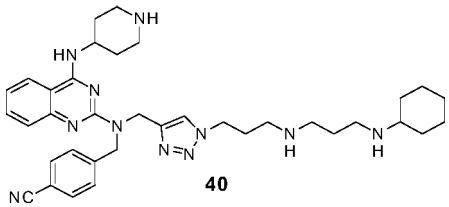

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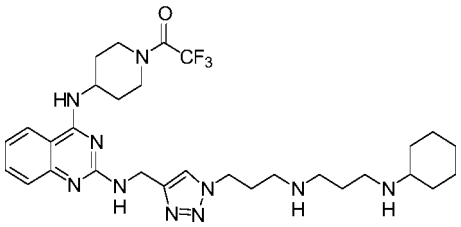

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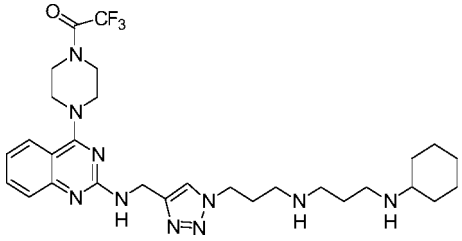

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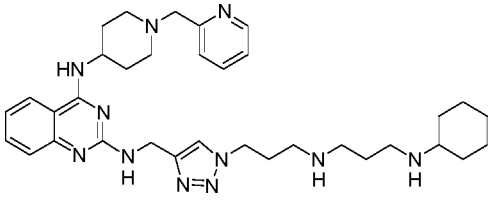

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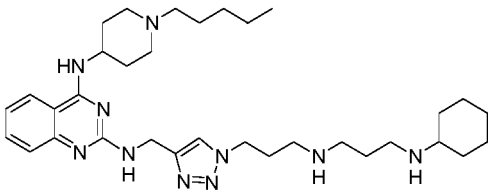

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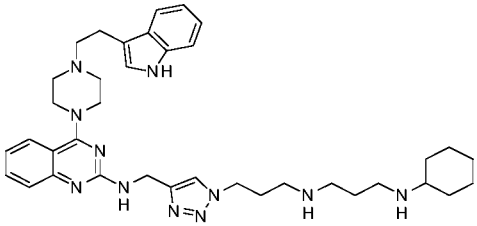

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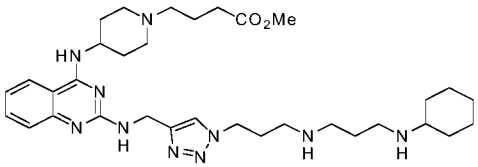

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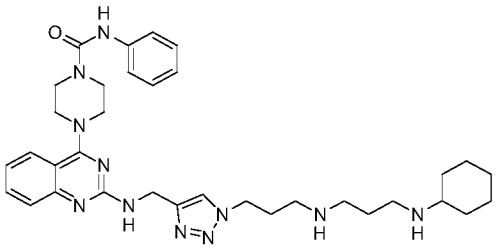

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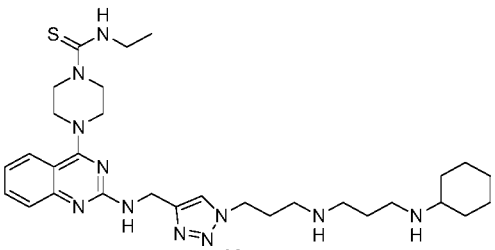

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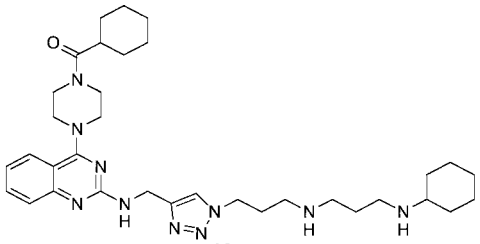
2015321654 27 Sep 2019



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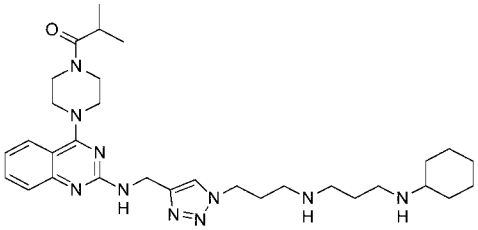

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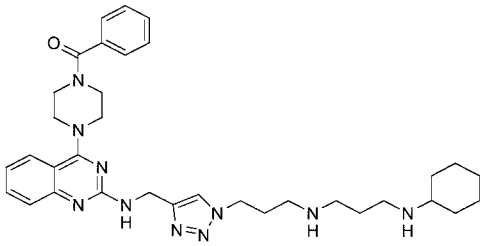

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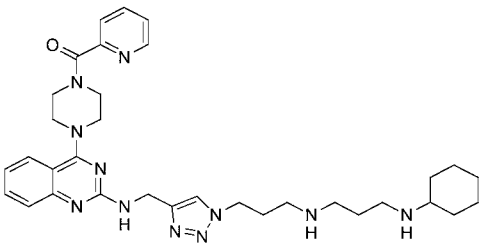

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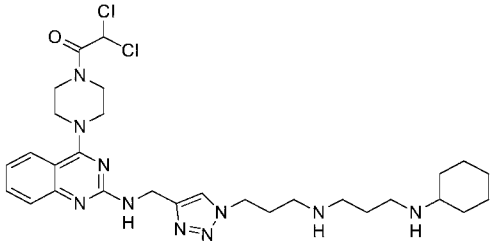

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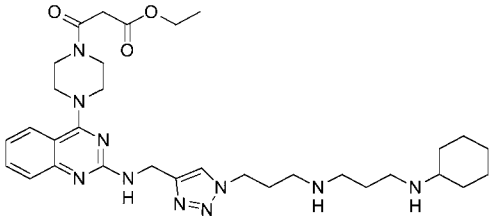

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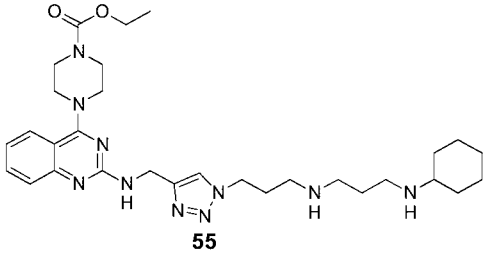

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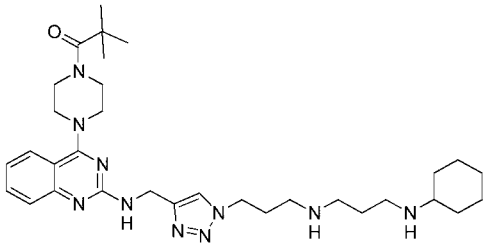

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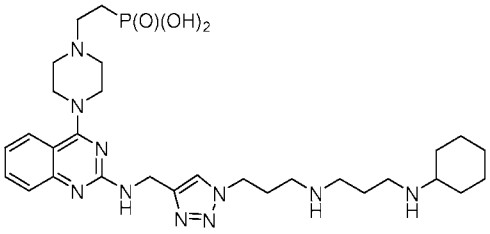

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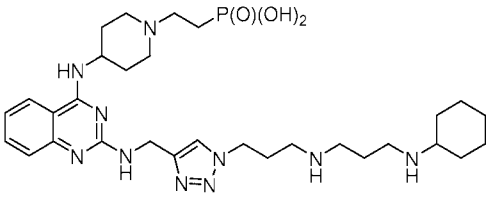
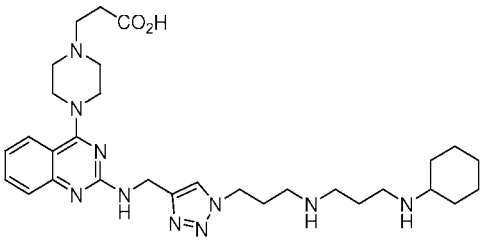


58

2015321654 27 Sep 2019



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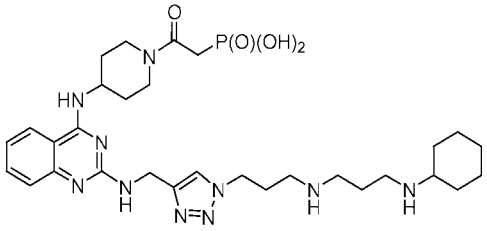

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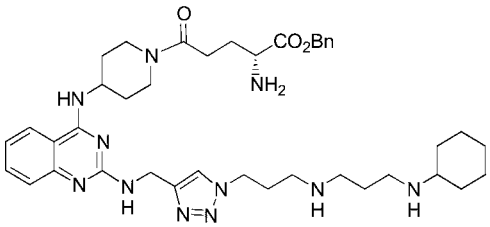

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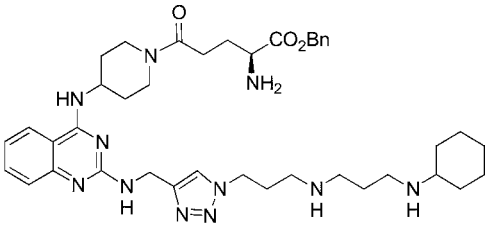

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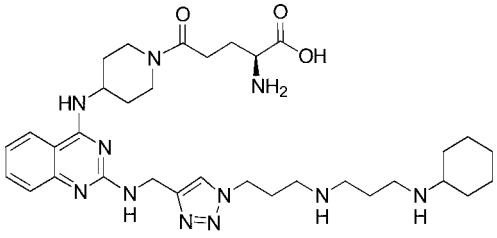

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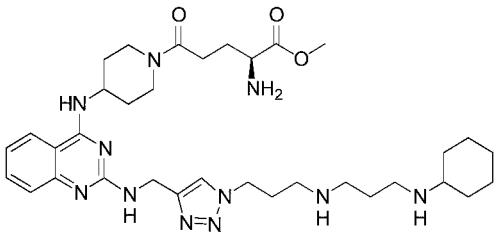

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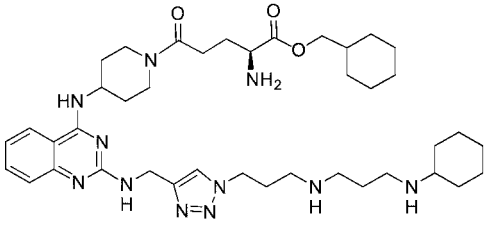

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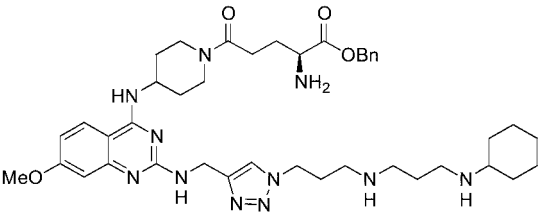

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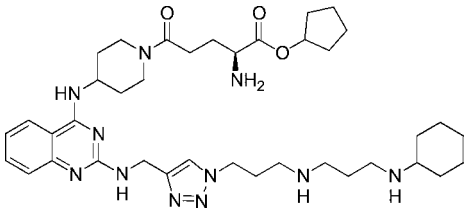

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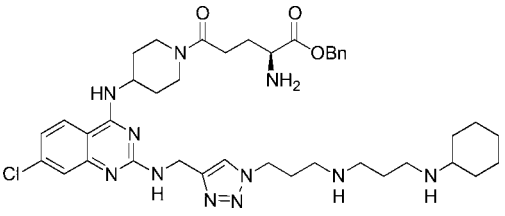
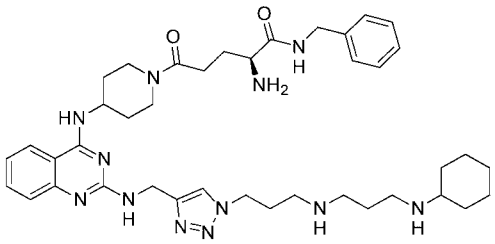


68

2015321654 27 Sep 2019



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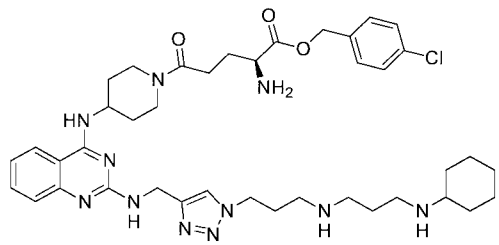

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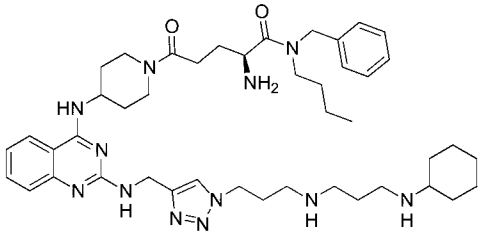

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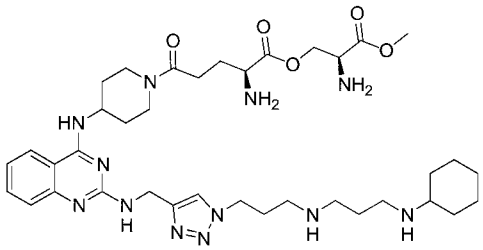

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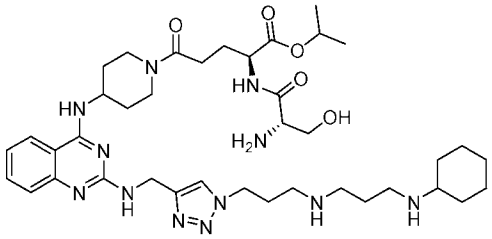

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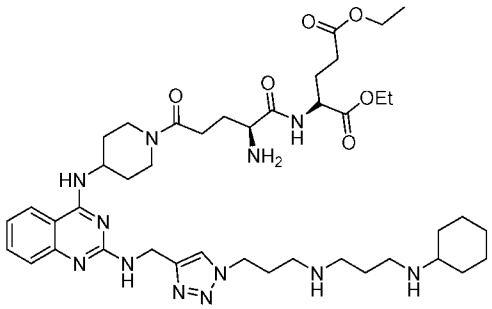

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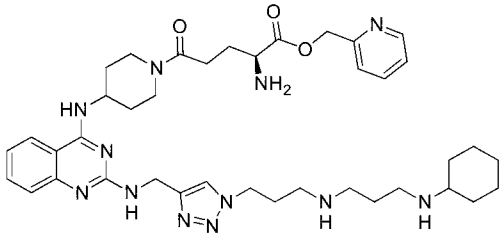

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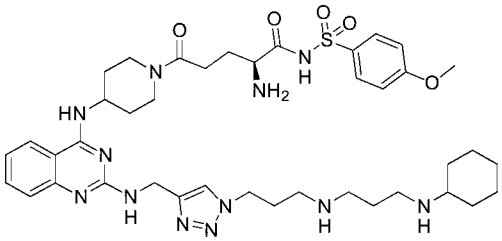

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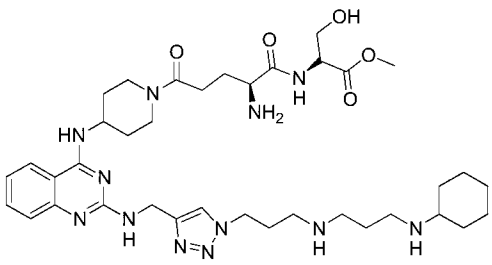

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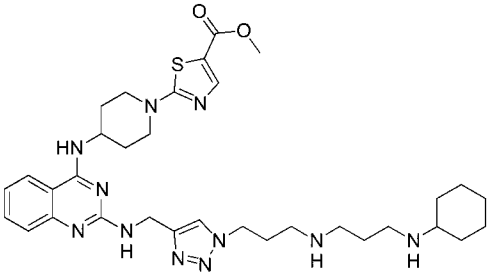
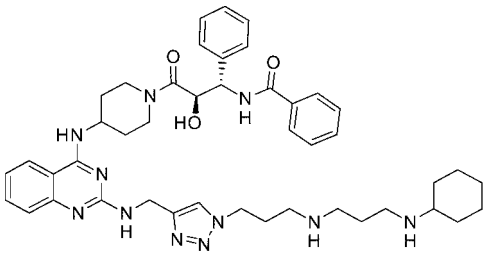


78

2015321654 27 Sep 2019



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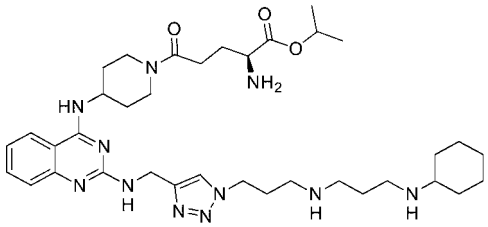

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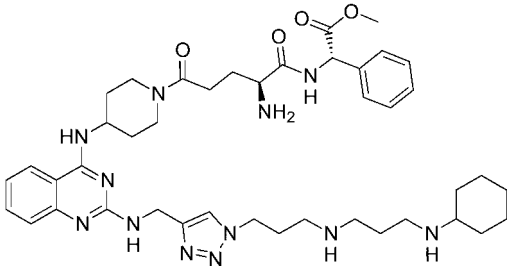

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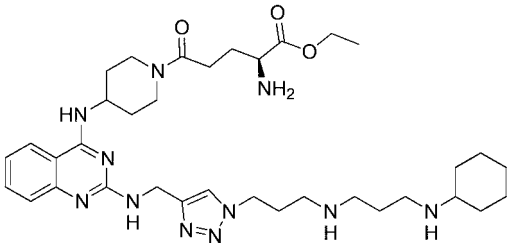

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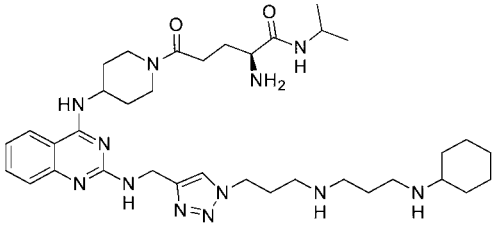

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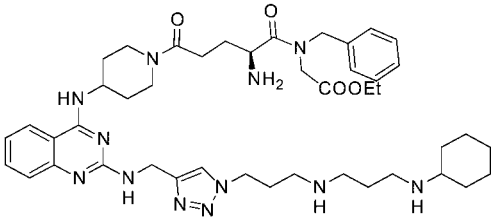

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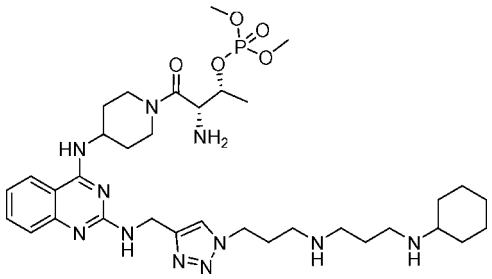

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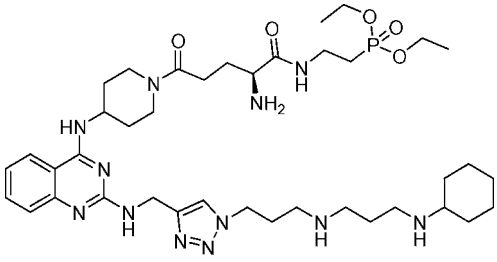
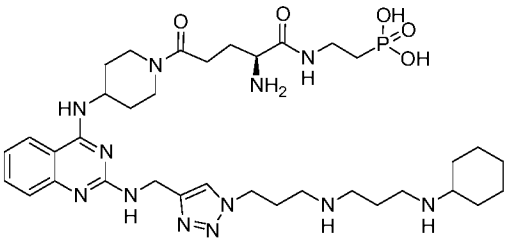
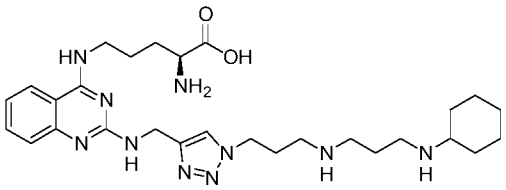


86

2015321654 27 Sep 2019



87



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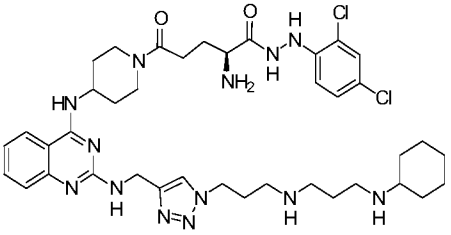

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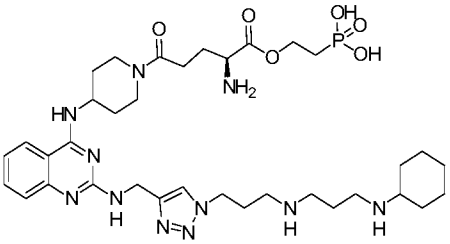

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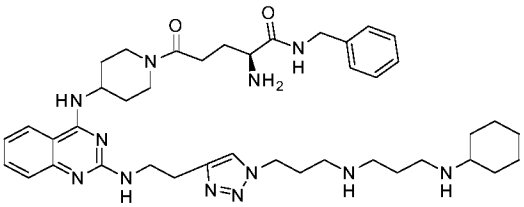

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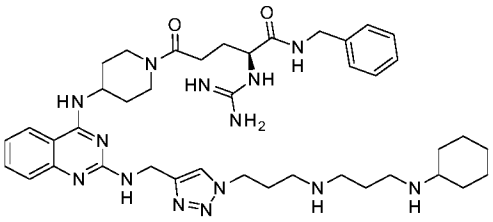

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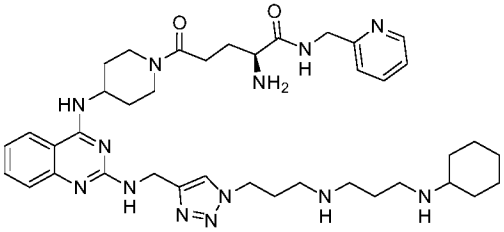

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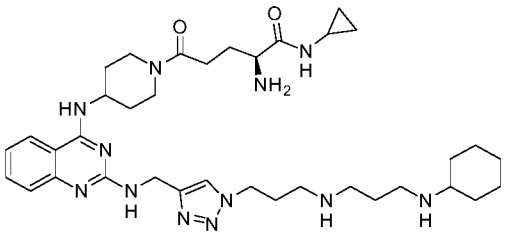

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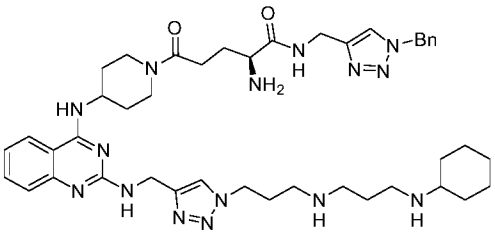

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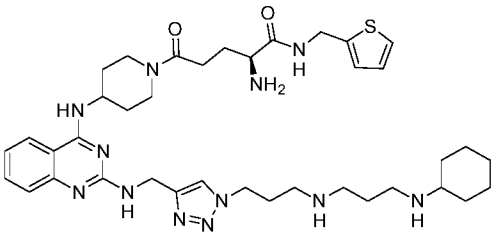

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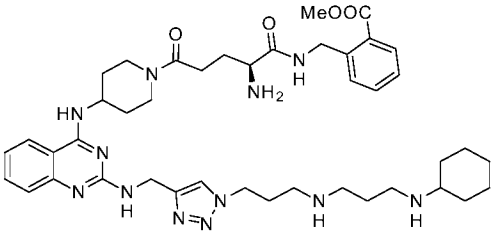

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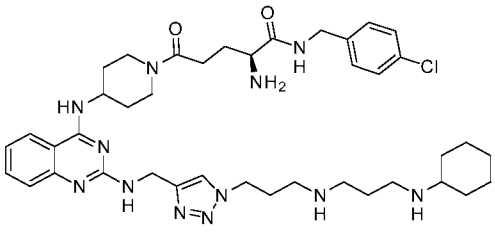
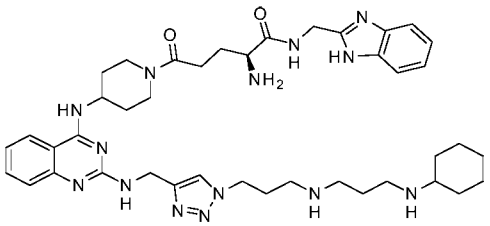


98

2015321654 27 Sep 2019



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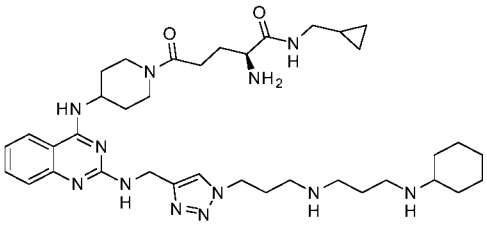

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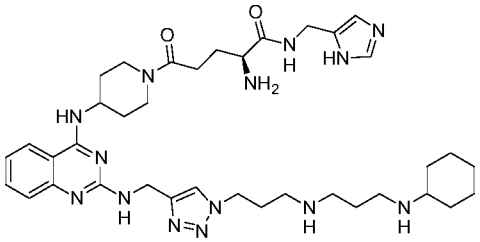

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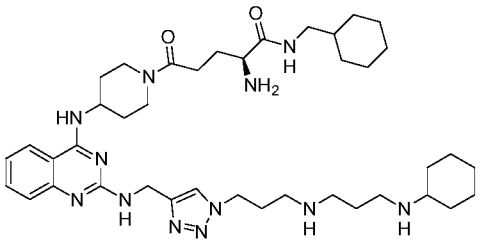

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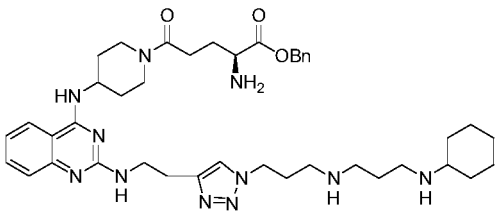

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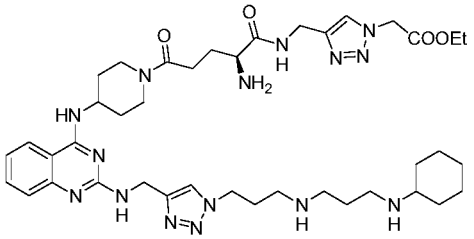

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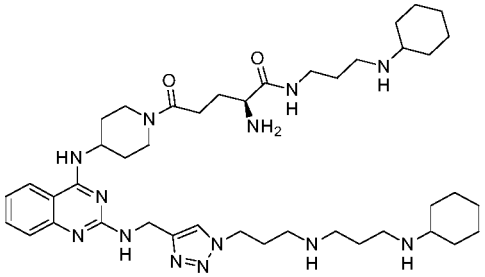

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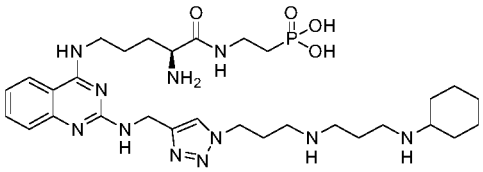

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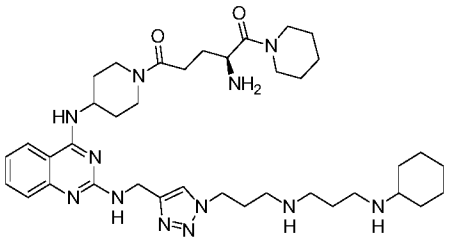
2015321654 27 Sep 2019



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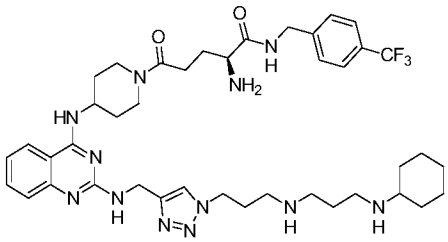

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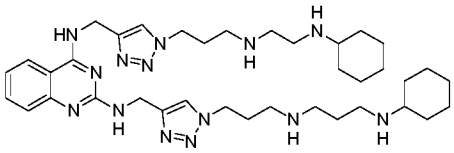

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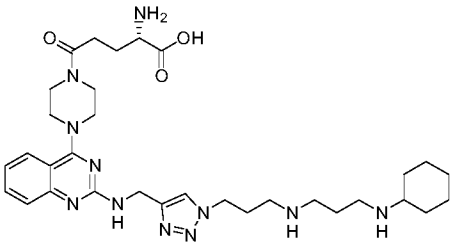

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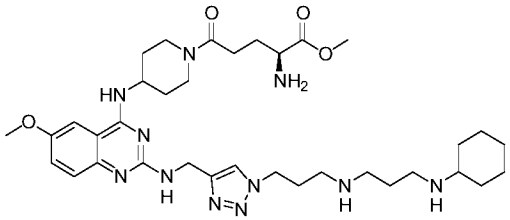

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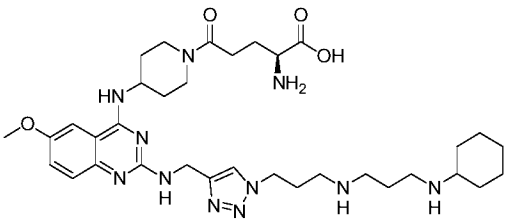

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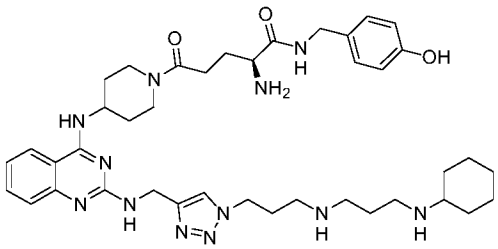

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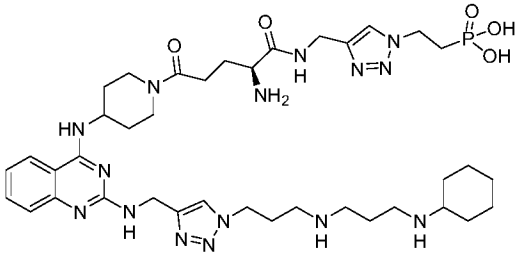

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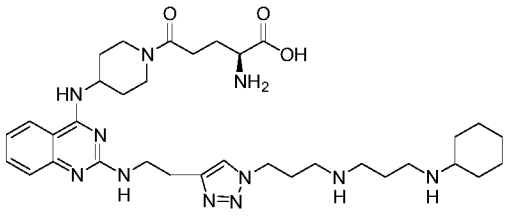

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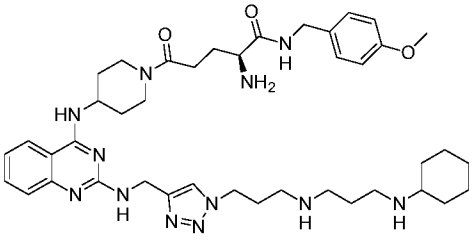

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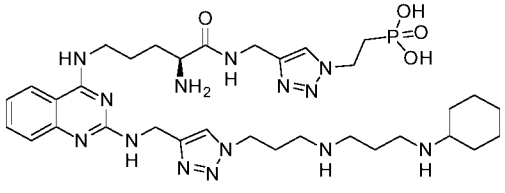

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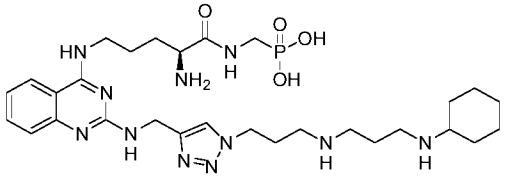
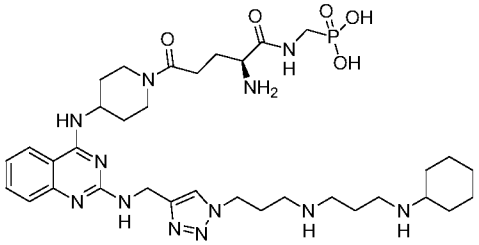


118

2015321654 27 Sep 2019



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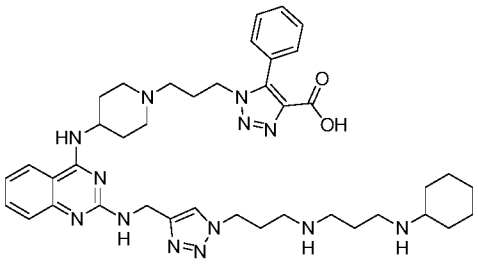

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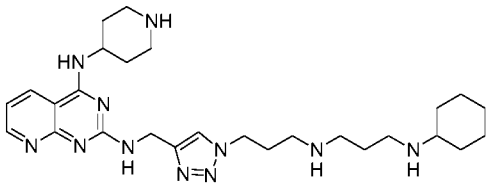

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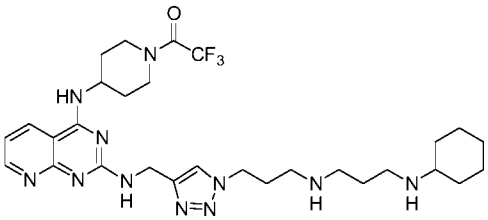

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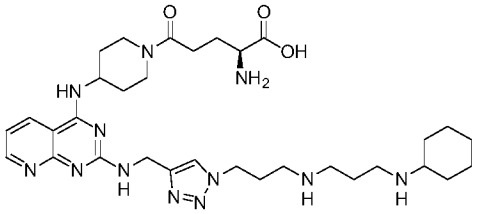

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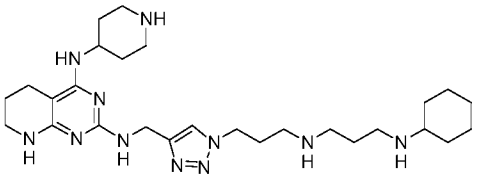

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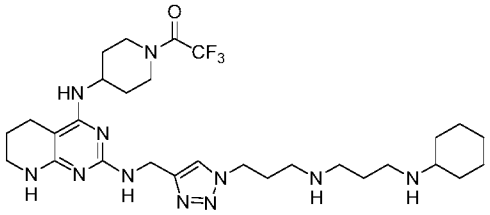

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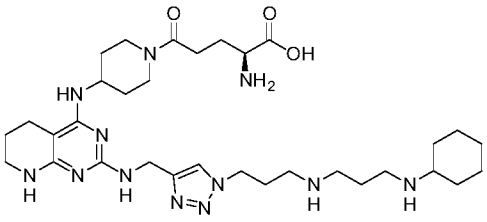

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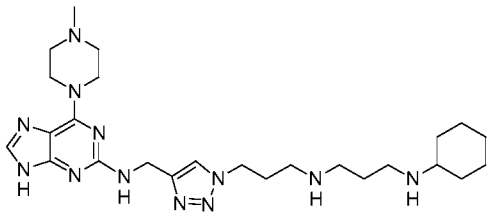

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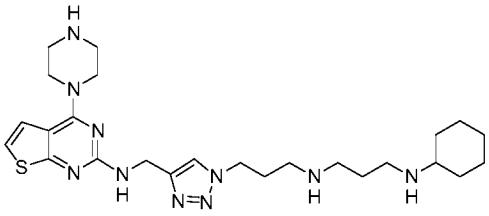
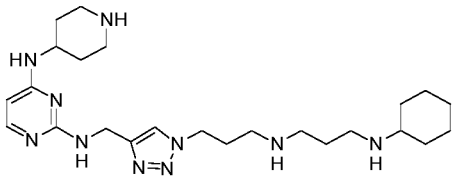


128

2015321654 27 Sep 2019



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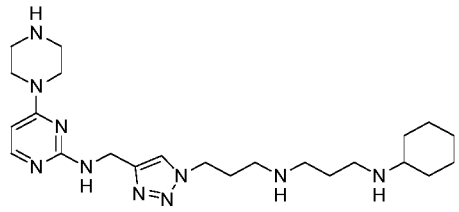

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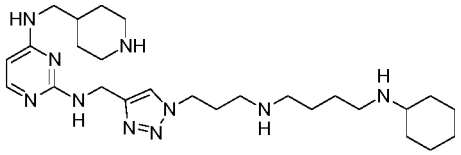

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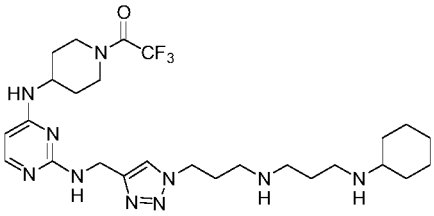

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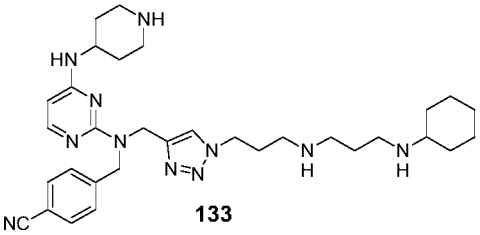

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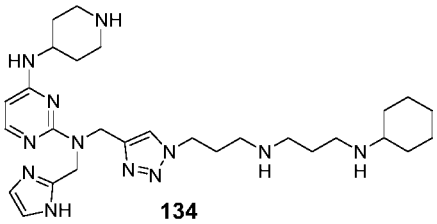

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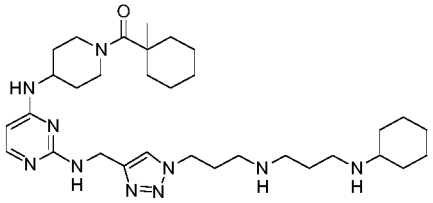

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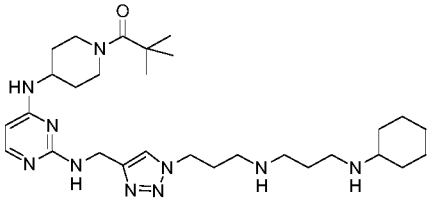

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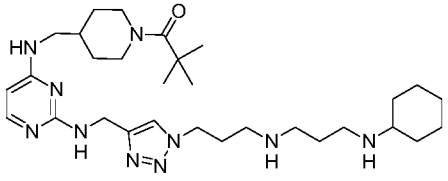

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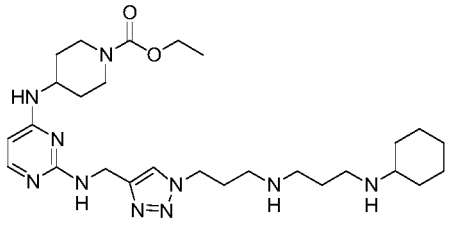

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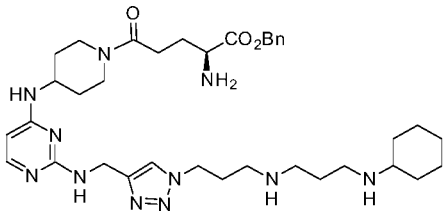

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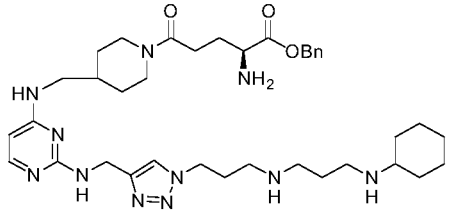

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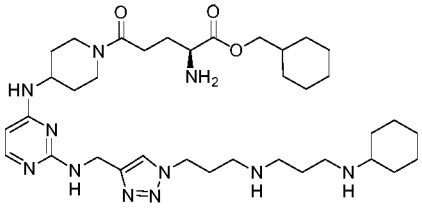
2015321654 27 Sep 2019



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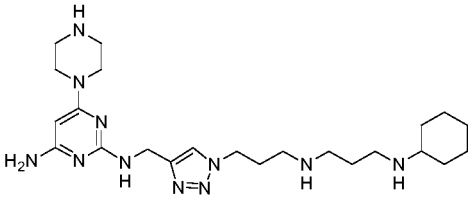

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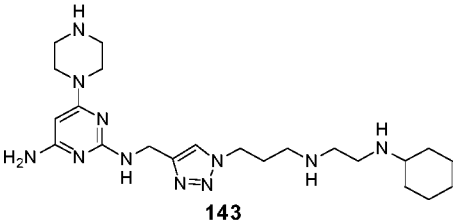

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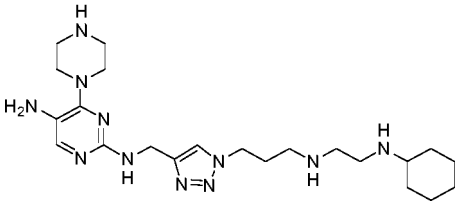

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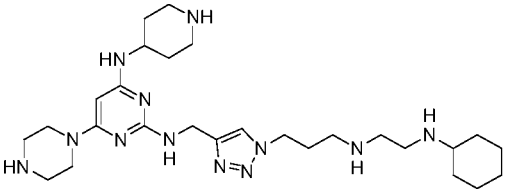

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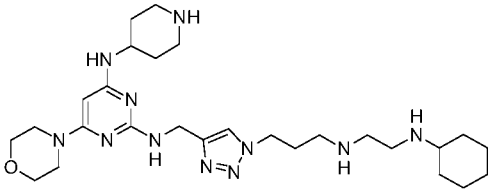
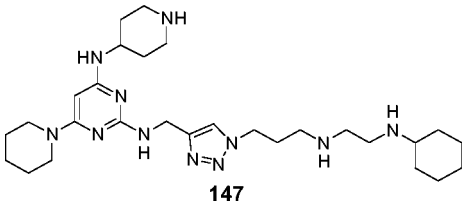


146



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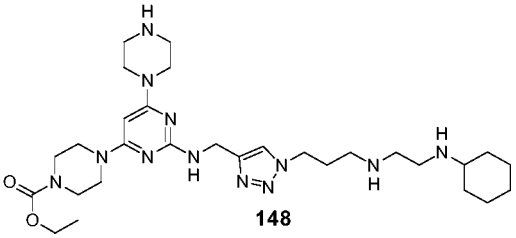

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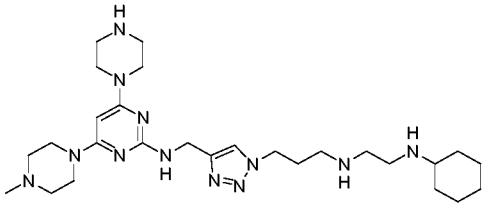

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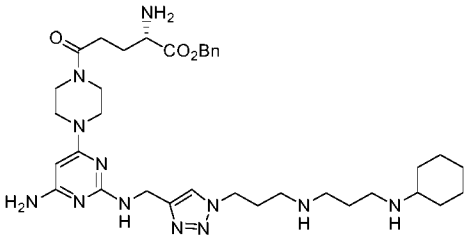

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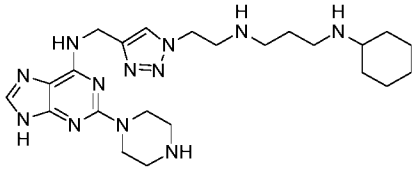

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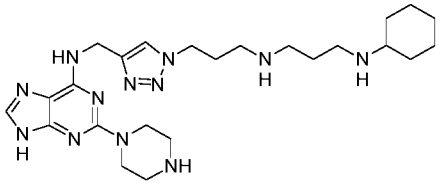

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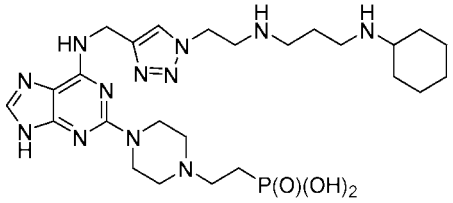
2015321654 27 Sep 2019



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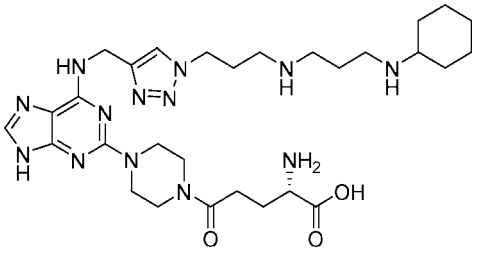

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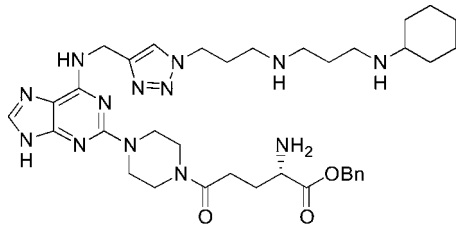

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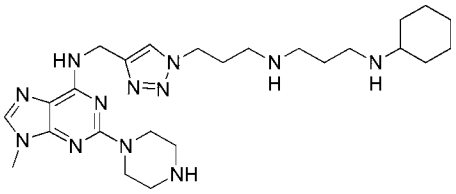

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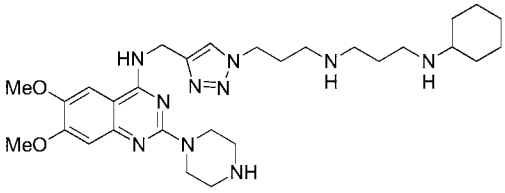

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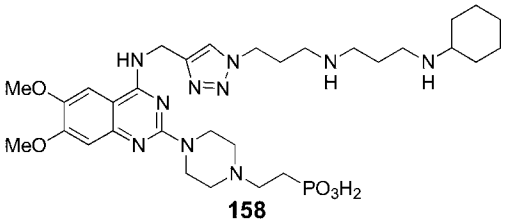

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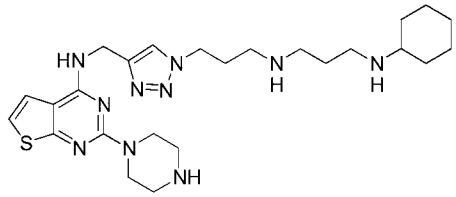

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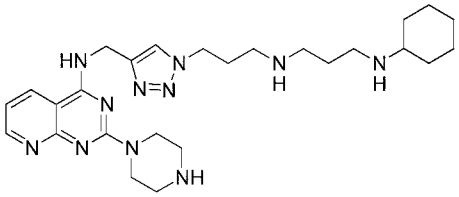

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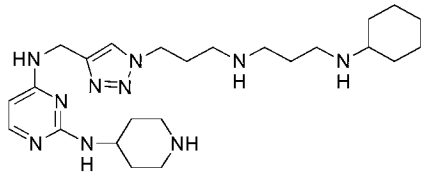

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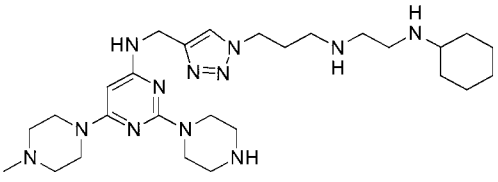

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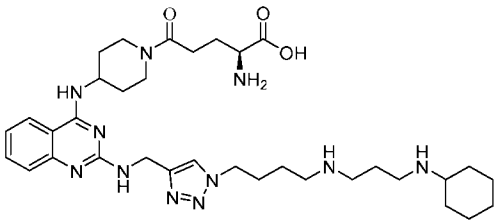
2015321654 27 Sep 2019



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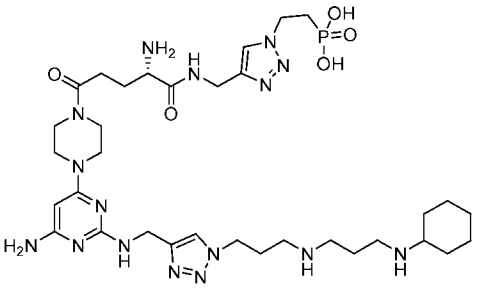

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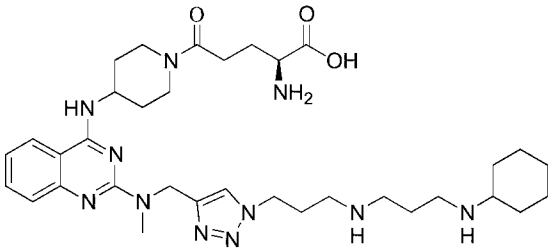

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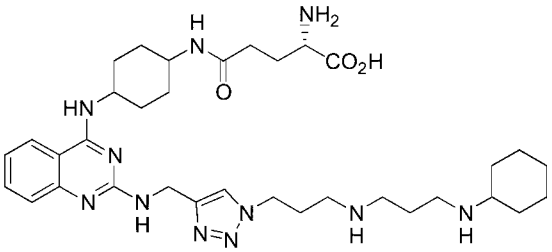

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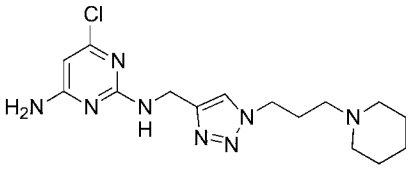

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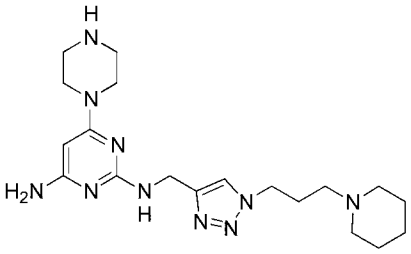

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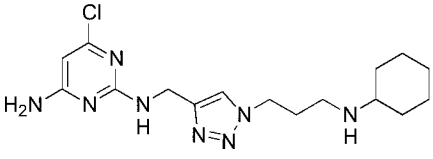

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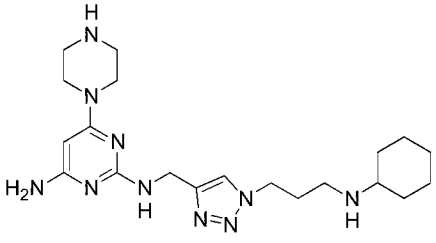

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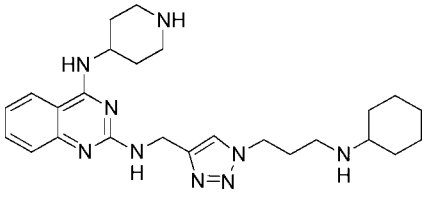
20153216654 27 Sep 2019



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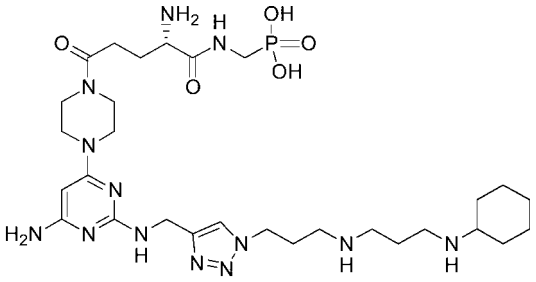

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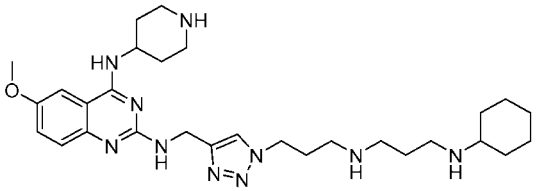

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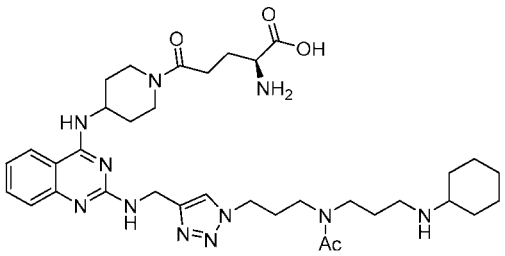

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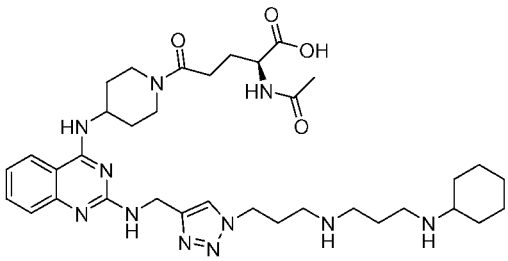

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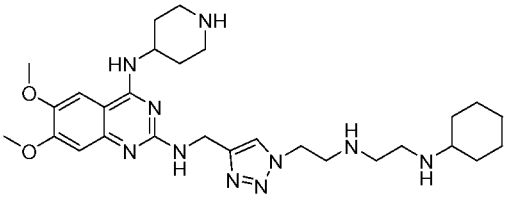

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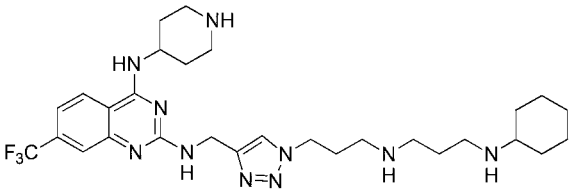

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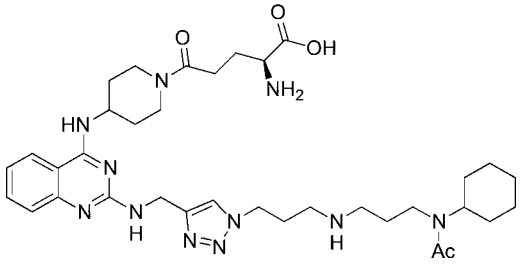

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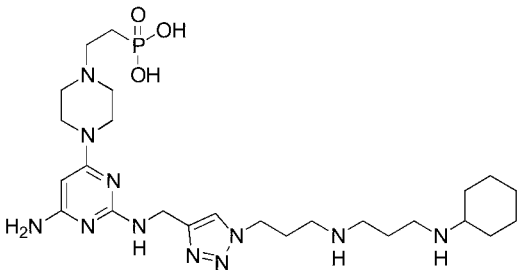

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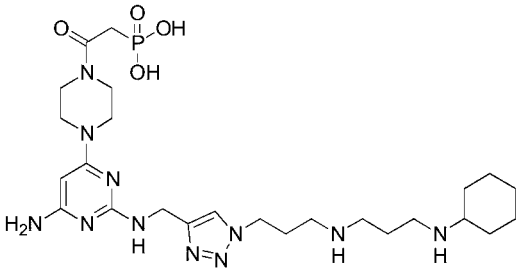

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27 Sep 2019
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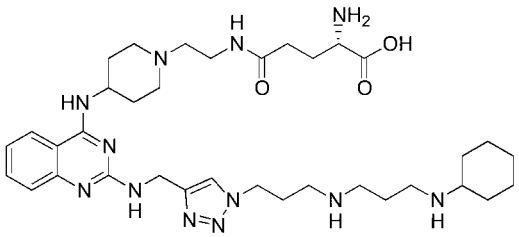

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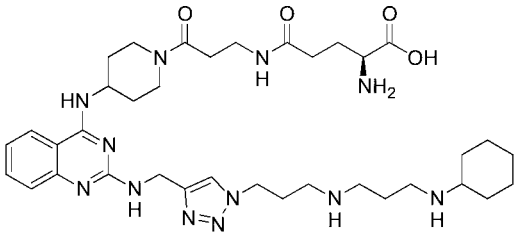

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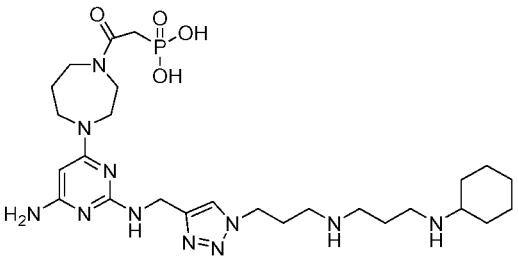

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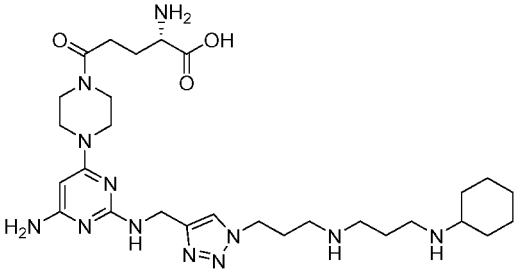

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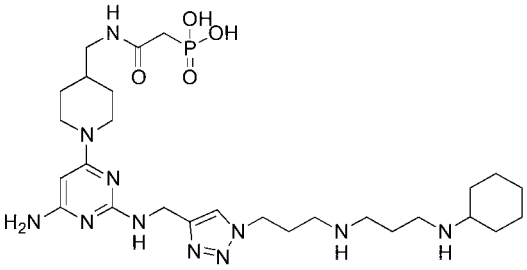

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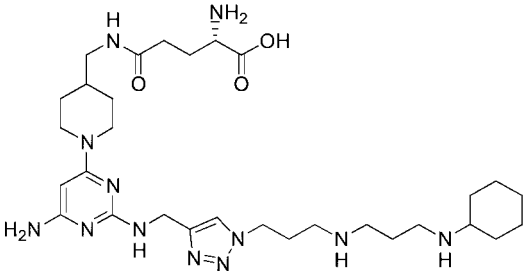

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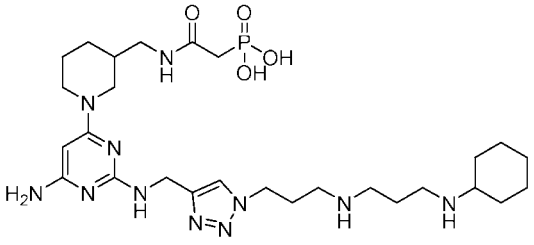

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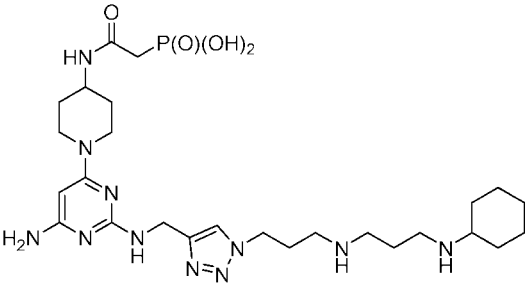

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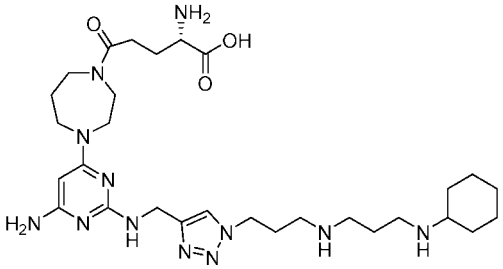

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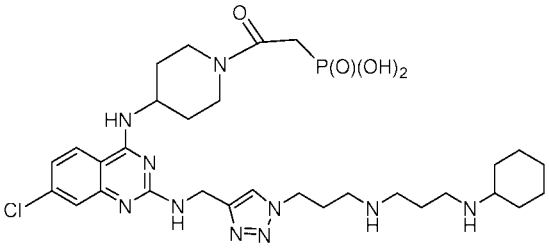

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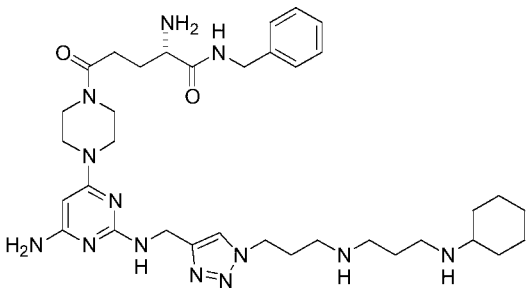
2015321654 27 Sep 2019



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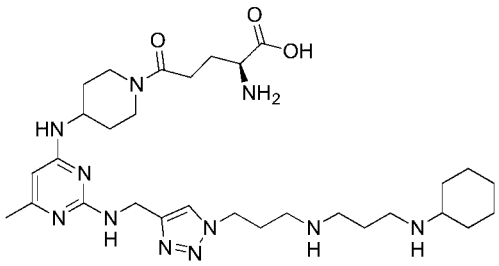

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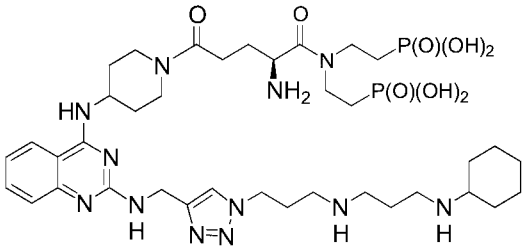

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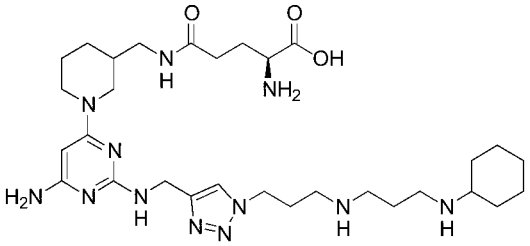

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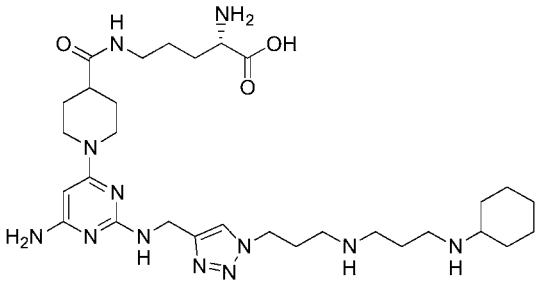

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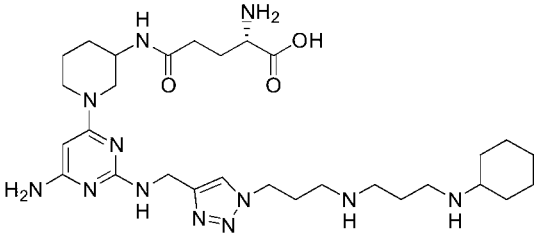

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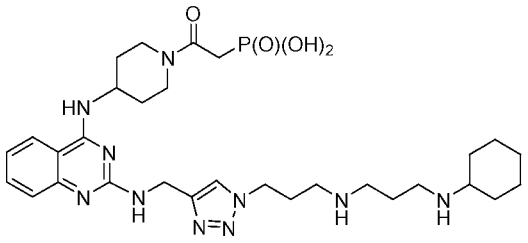

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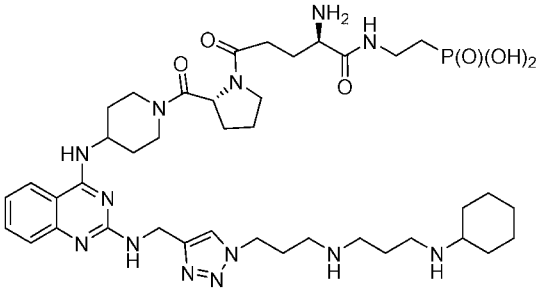

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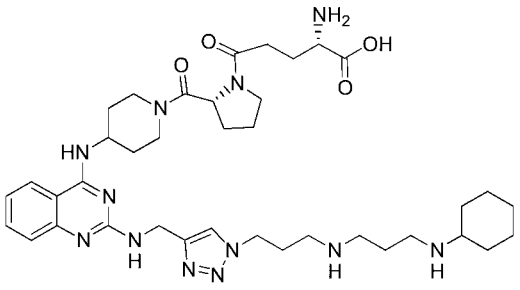
2015321654 27 Sep 2019



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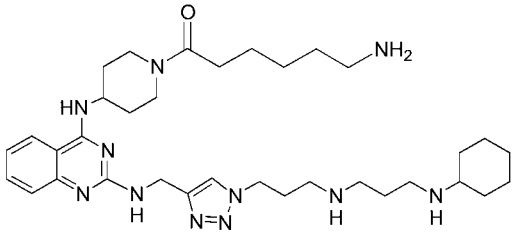

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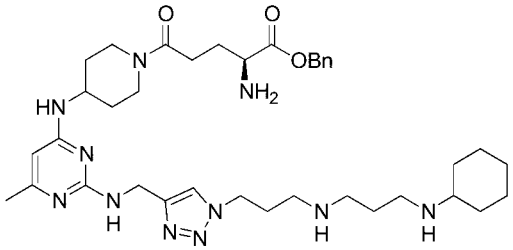

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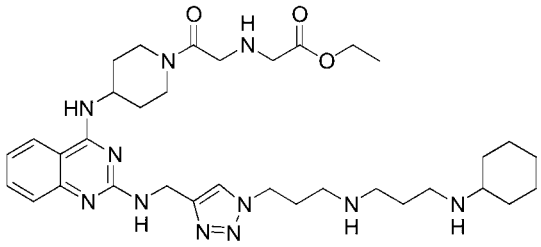

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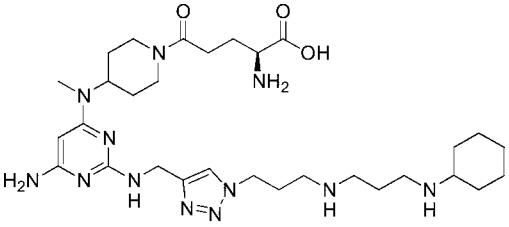

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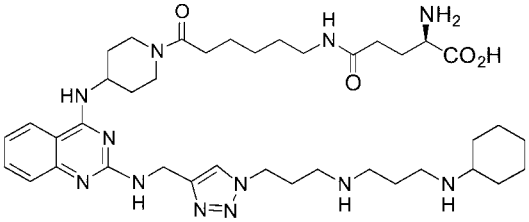

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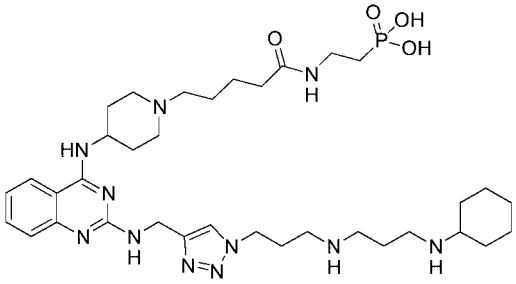

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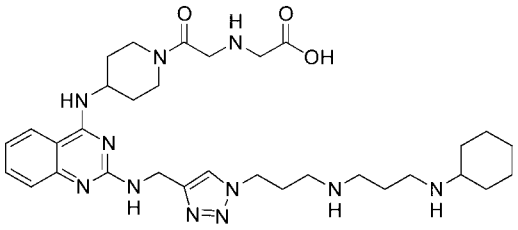

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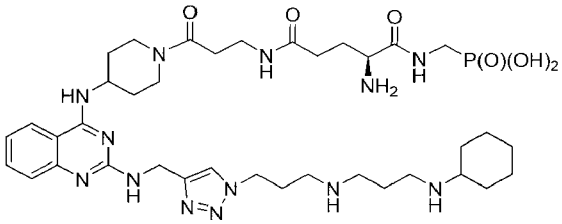

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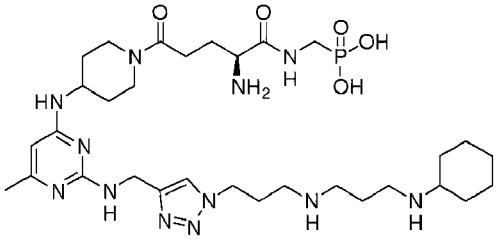
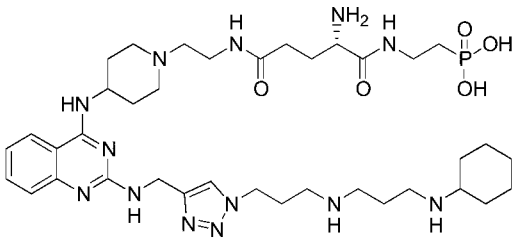


208

2015321654 27 Sep 2019



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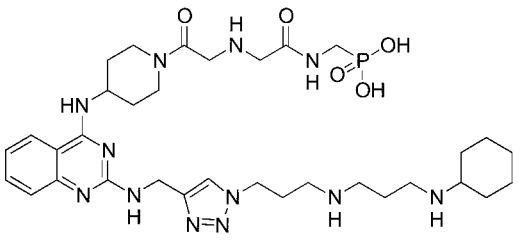

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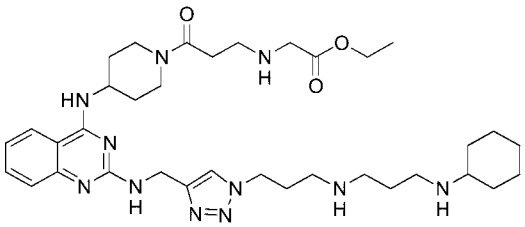

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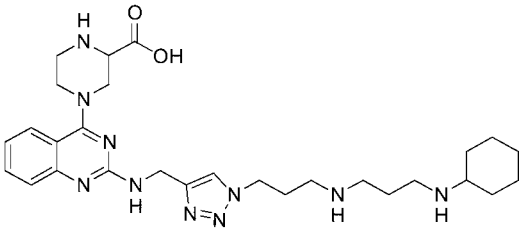

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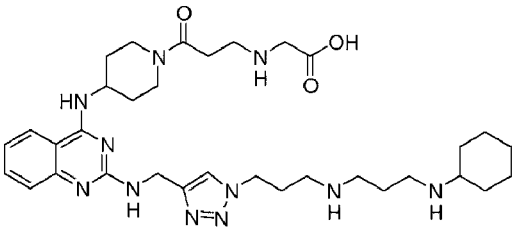

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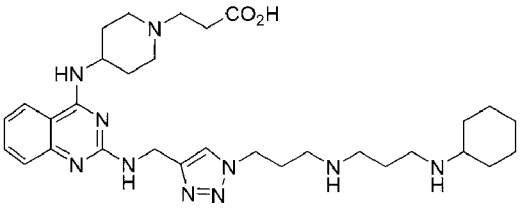

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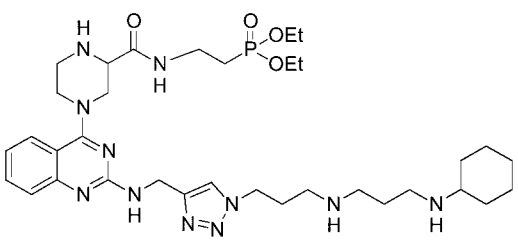
2015321654 27 Sep 2019



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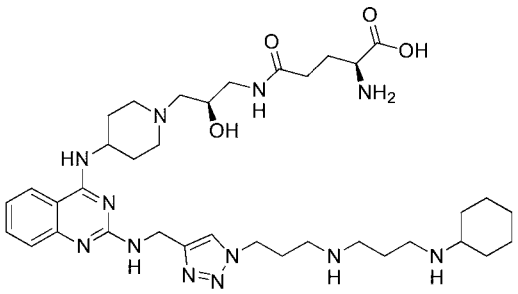

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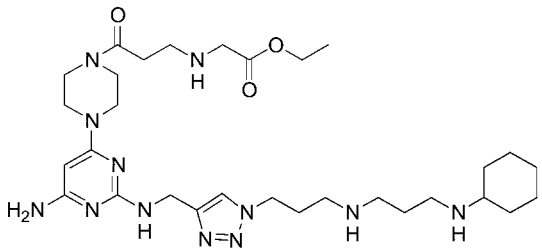

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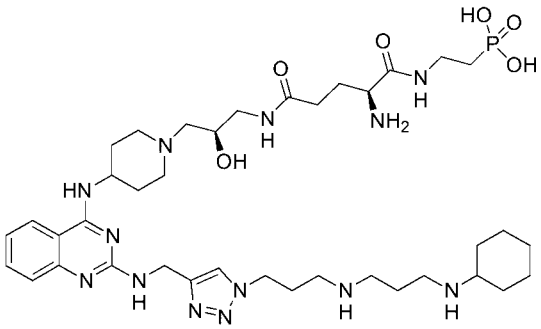

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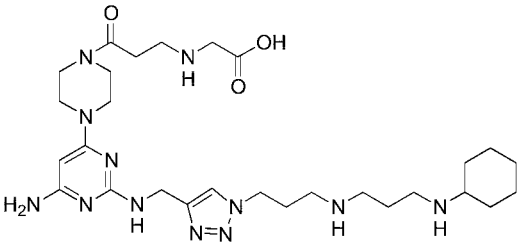

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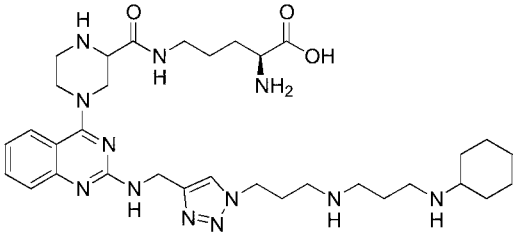

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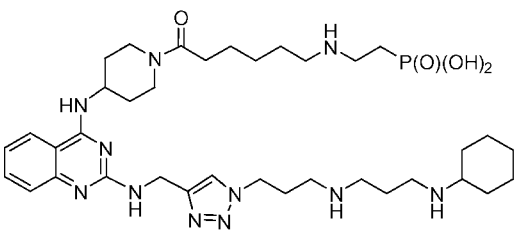

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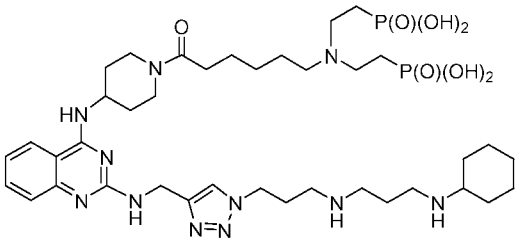

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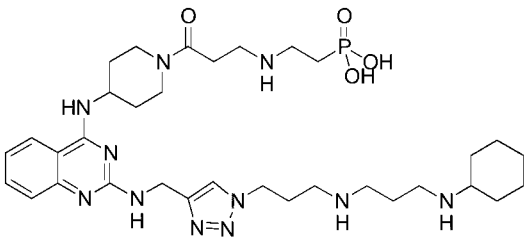
2015321654 27 Sep 2019



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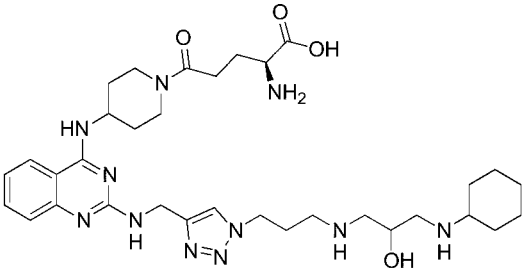

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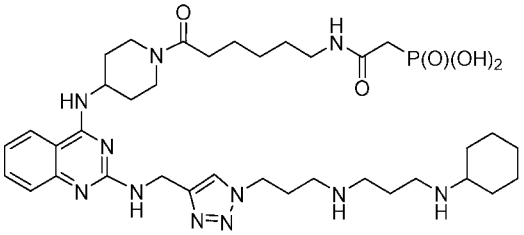

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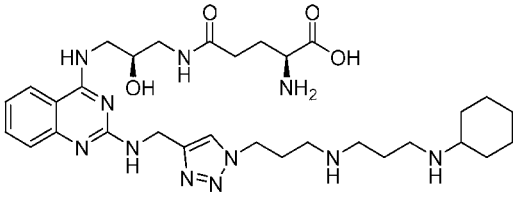

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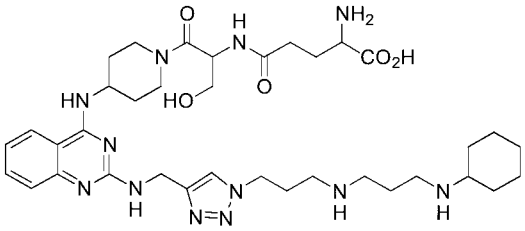

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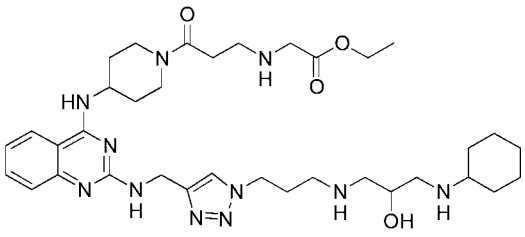

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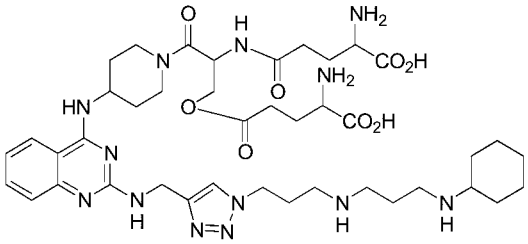

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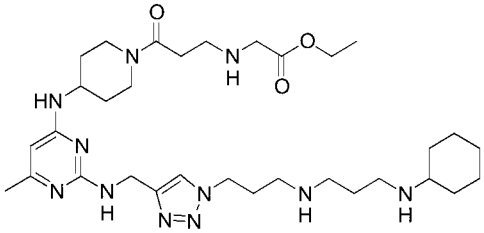

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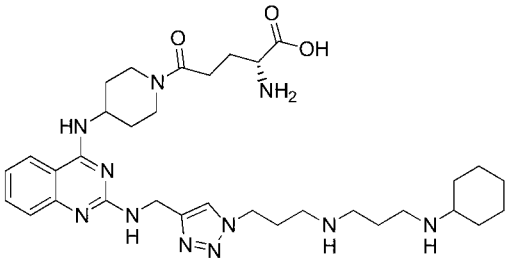

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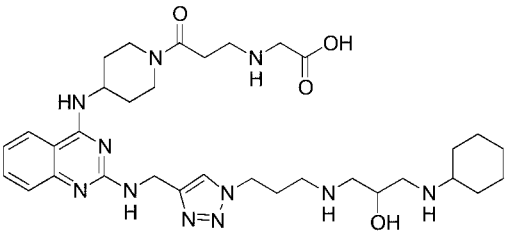

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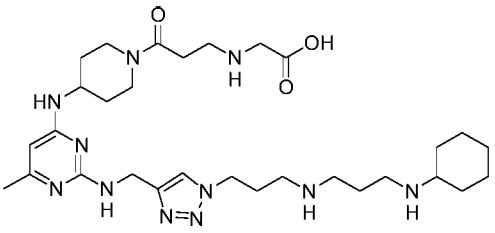
2015321654 27 Sep 2019



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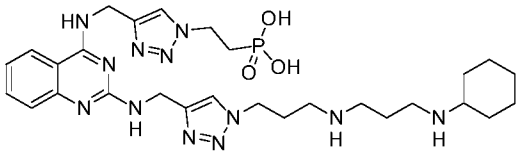

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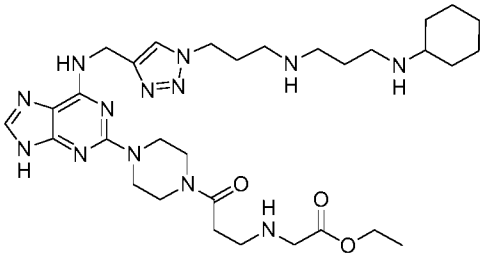

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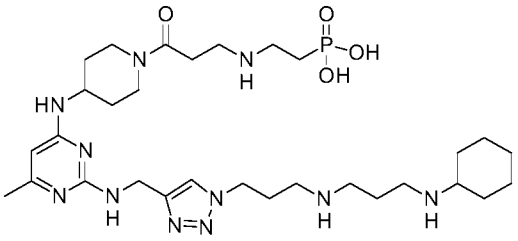

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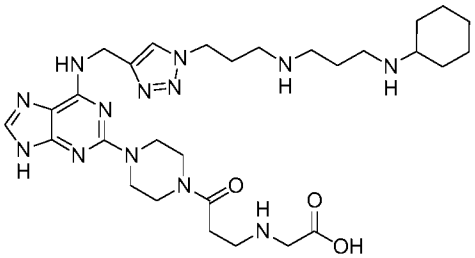

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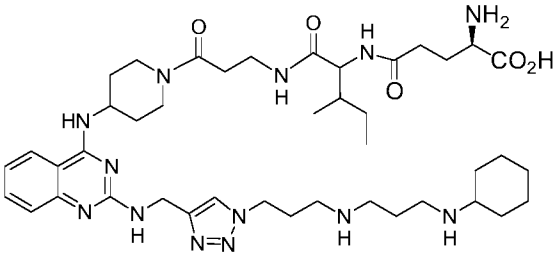

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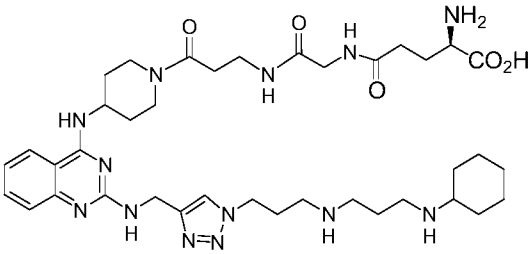

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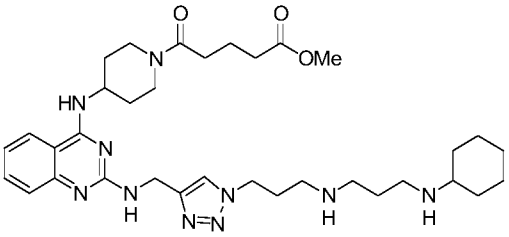

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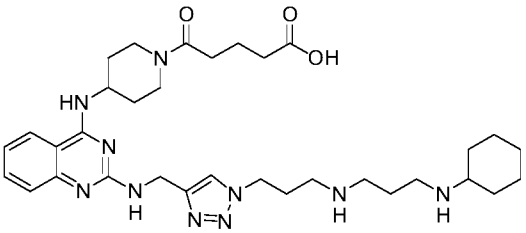

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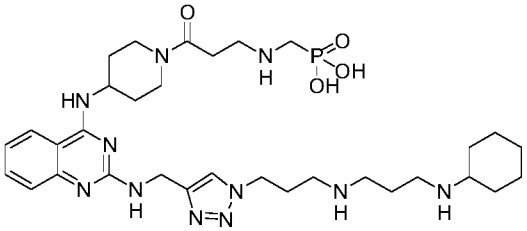

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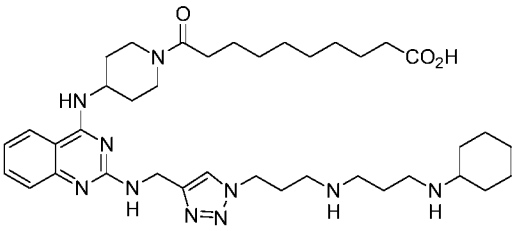
2015321654 27 Sep 2019



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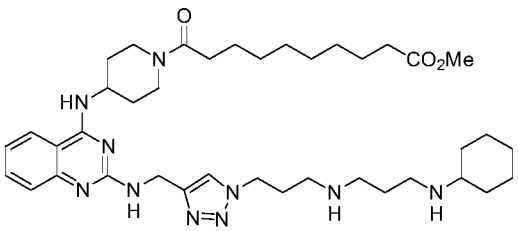

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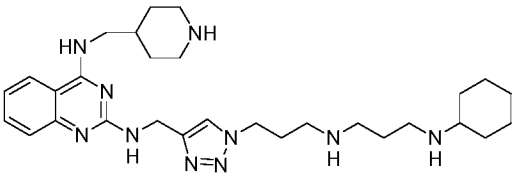

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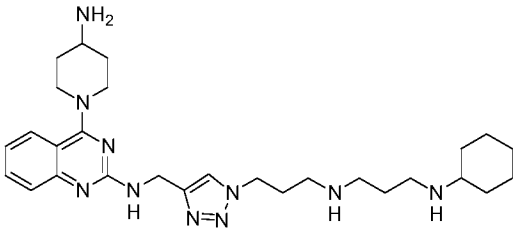

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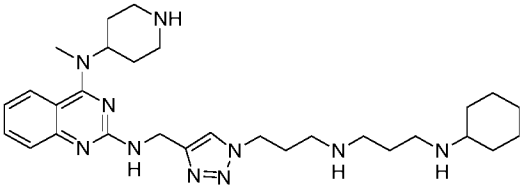

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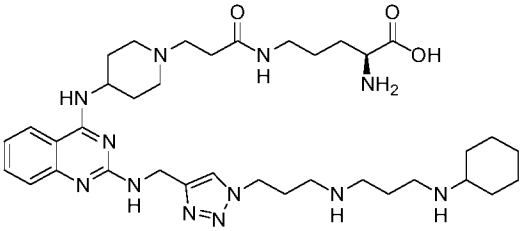

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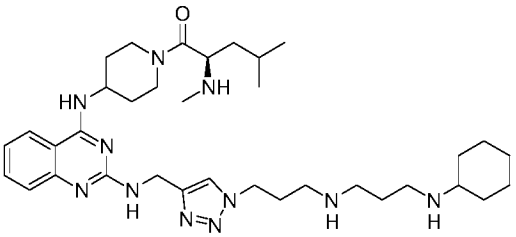

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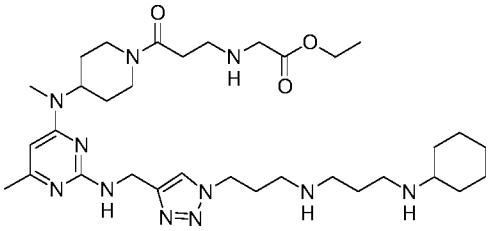

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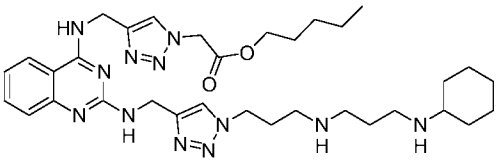

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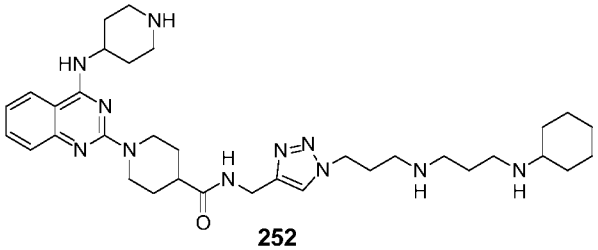

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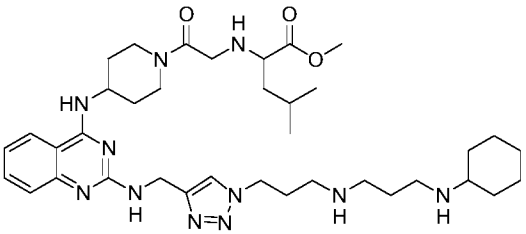

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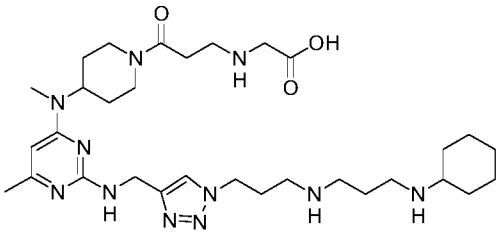

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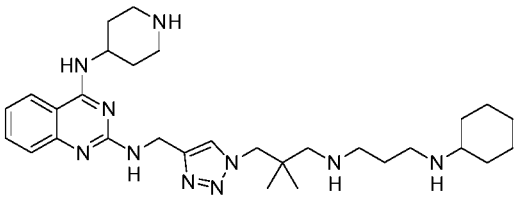
2015321654 27 Sep 2019



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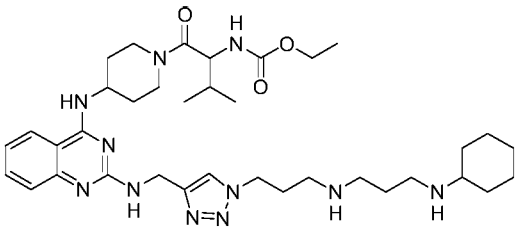

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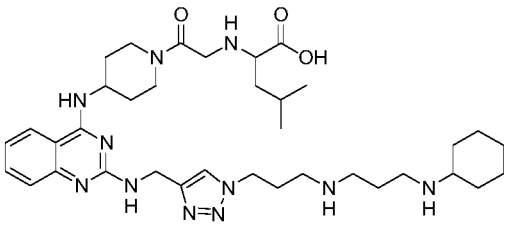

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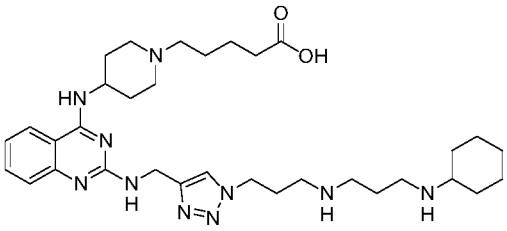

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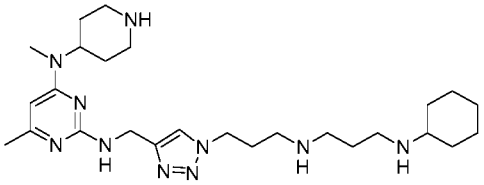

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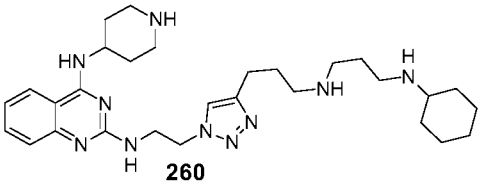

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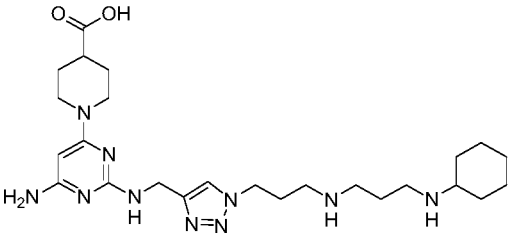

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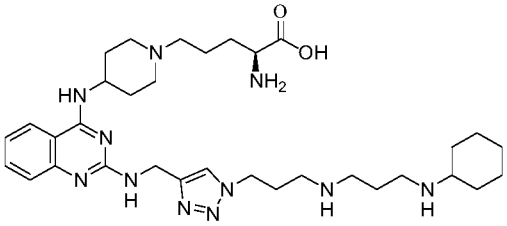

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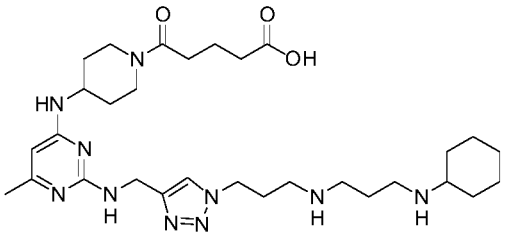

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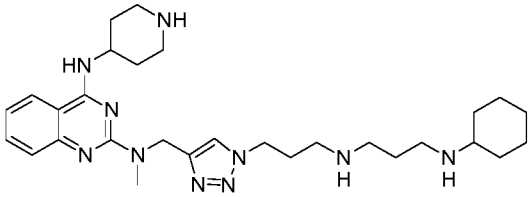

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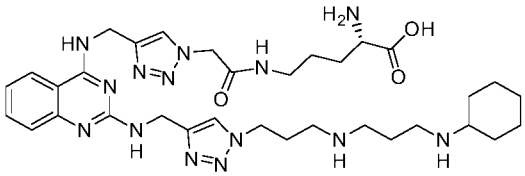

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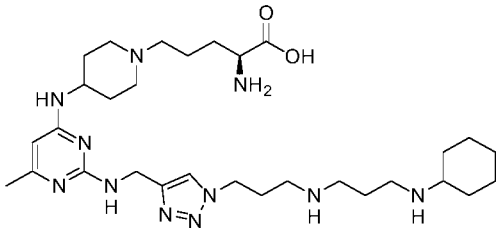
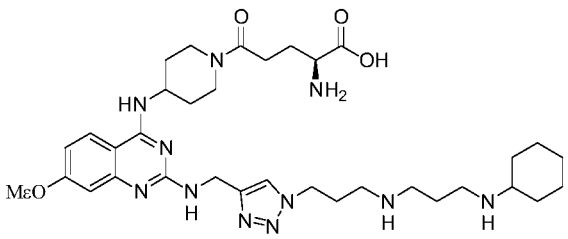


266

2015321654 27 Sep 2019



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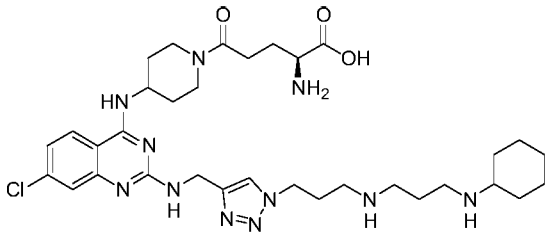

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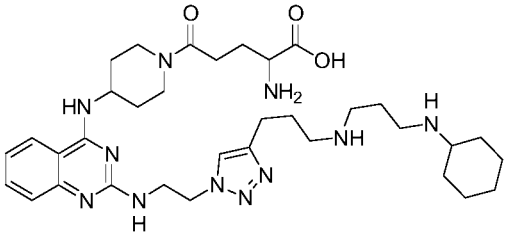

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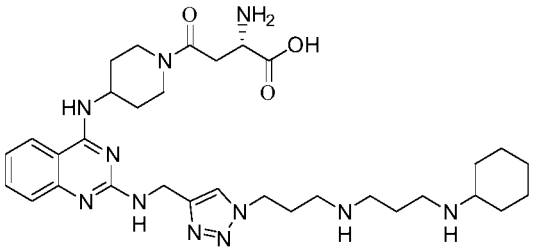

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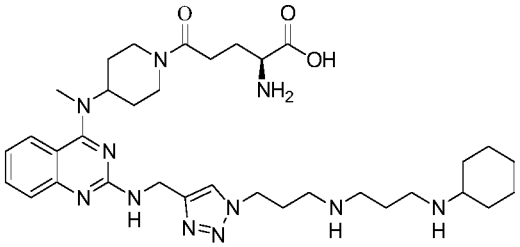

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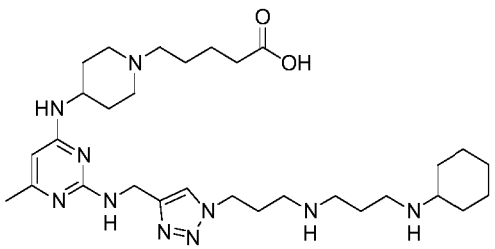

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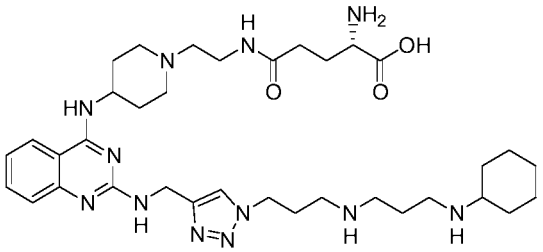
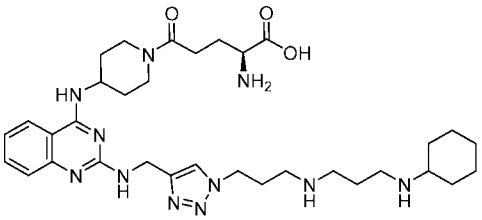


273

.

25. The compound of claim 24, wherein the compound is one of the following compounds:

2015321654 27 Sep 2019



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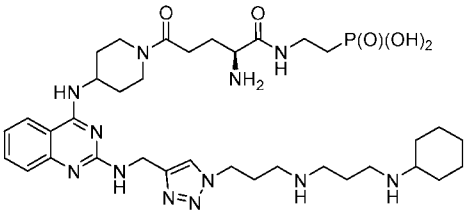

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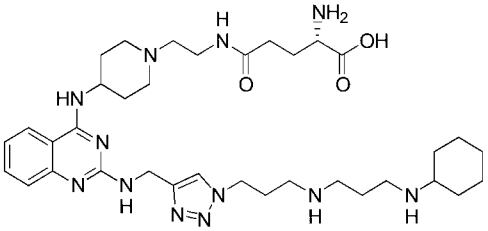

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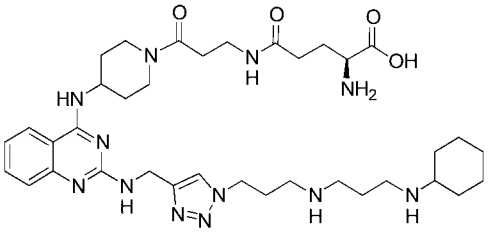

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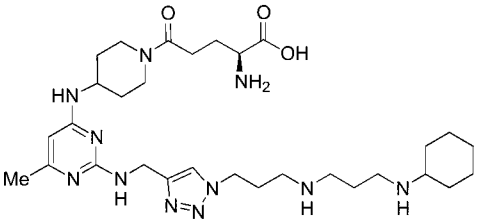

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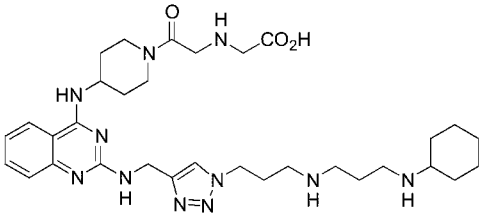

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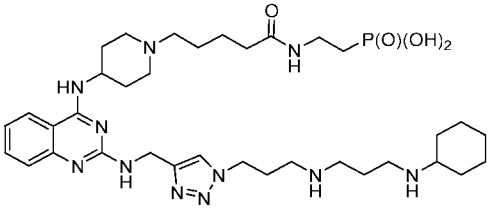

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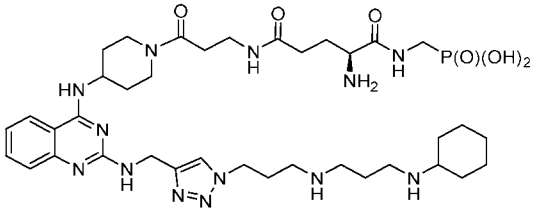

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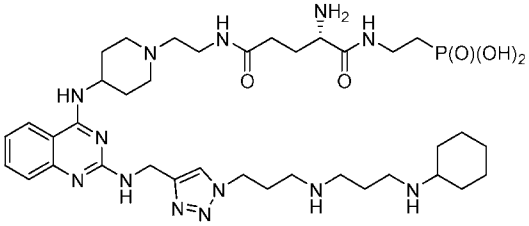

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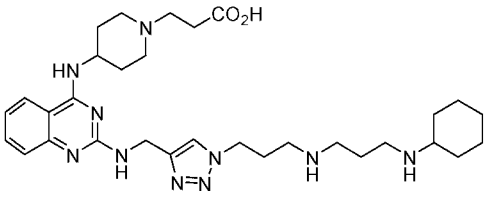
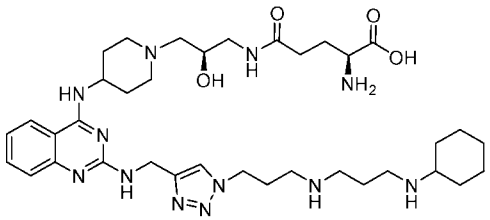


214

2015321654 27 Sep 2019



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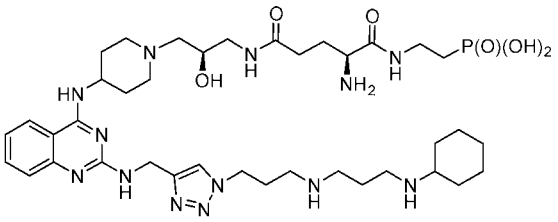

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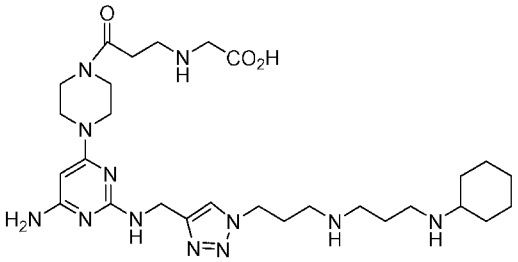

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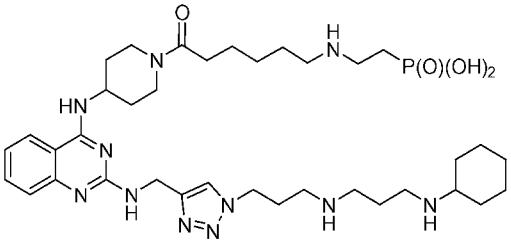

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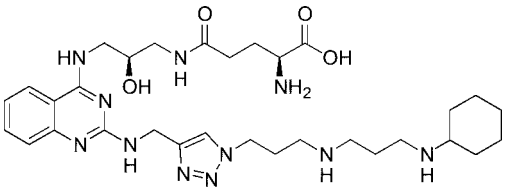

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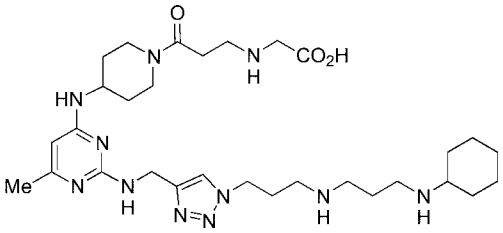

233

26. A method of mobilizing hematopoietic stem cells (HSC) and endothelial progenitor cells (EPC) into the peripheral circulation, the method comprising contacting HSC and EPC with an effective amount of a compound of claim 1.

27. A method of treating a disease mediated by the interaction between type 4 CXC chemokine receptor and stromal-derived factor-1, the method comprising administering to a subject in need thereof an effective amount of a compound of claim 1, wherein the disease is tissue injury, cancer, inflammatory disease, or autoimmune disease.

2015321654 27 Sep 2019

28. The method of claim 27, wherein the method is performed to treat tissue injury, the tissue injury being neurodegenerative disease, retinal pigment epithelium dysfunction, heart and myocardial infarction, ischemic disease, wound, bone fracture, pancreatic injury, kidney injury, intestinal injury, or lung injury.

29. The method of claim 27, wherein the method is performed to treat cancer, the cancer being acute myeloid leukemia, non-small cell lung cancer, multiple myeloma, or pancreatic cancer.

30. The method of claim 27, wherein the method is performed to treat inflammatory disease, the inflammatory disease being inflammatory bowel disease, allergic asthma, or ocular uveitis.

31. The method of claim 27, wherein the method is performed to treat autoimmune disease, the autoimmune disease being rheumatoid arthritis.

32. The method of claim 28, wherein the tissue injury is kidney injury.

33. The method of claim 28, wherein the tissue injury is an ischemic disease, the ischemic disease being ischemic stroke or limb ischemia.

34. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically acceptable carrier thereof.