Supporting Information for

Review

Characteristic roadmap of linker governs the rational design of PROTACs

Yawen Dong[a], Tingting Ma[a], Ting Xu[a], Zhangyan Feng[a], Yonggui Li[a], Lingling Song[a], Xiaojun Yao[c,*], Charles R. Ashby Jr.[d,*], Ge-Fei Hao[b,*]

[a] *School of Pharmaceutical Sciences, Guizhou University, Guiyang 550025, China*

[b] *State Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Center for R&D of Fine Chemicals, Guizhou University, Guiyang 550025, China*

[c] *Faculty of Applied Sciences, Macao Polytechnic University, Macao 999078, China*

[d] *Department of Pharmaceutical Sciences, St. John's University, New York, NY 11439, USA*

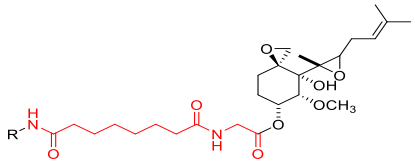
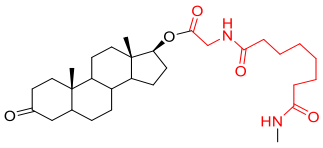
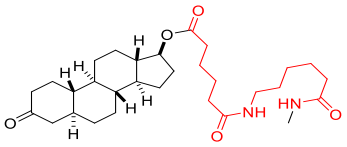
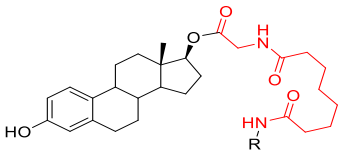
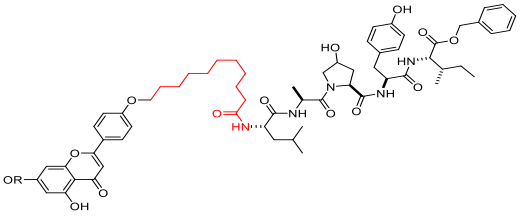
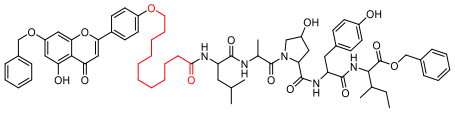
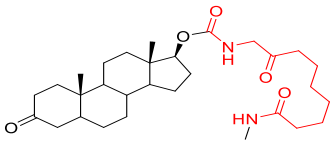
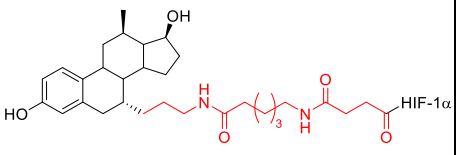
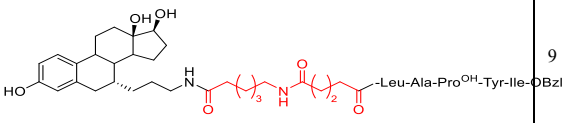
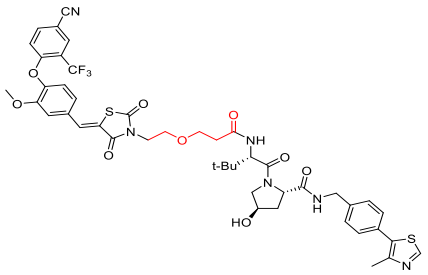
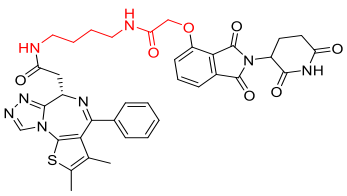
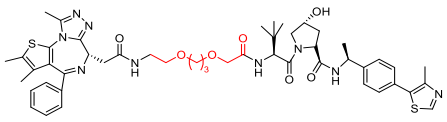
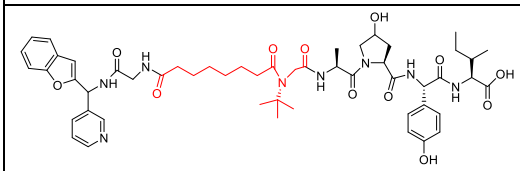
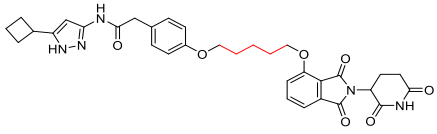
*Corresponding authors.

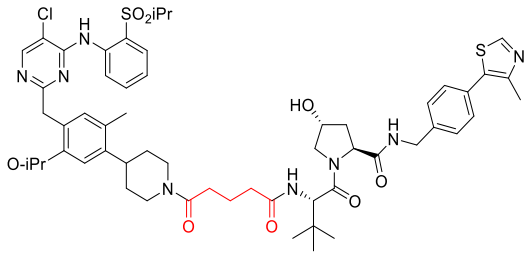
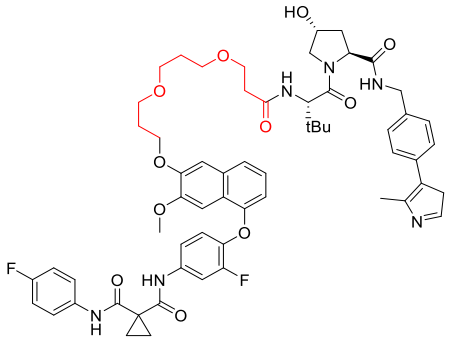
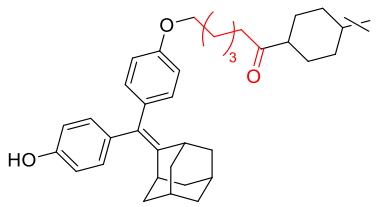
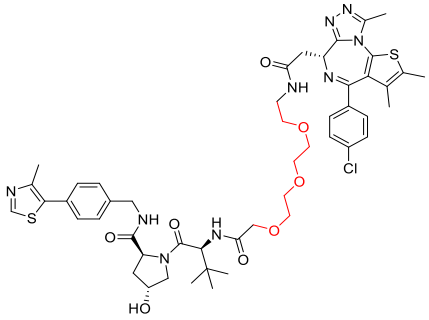
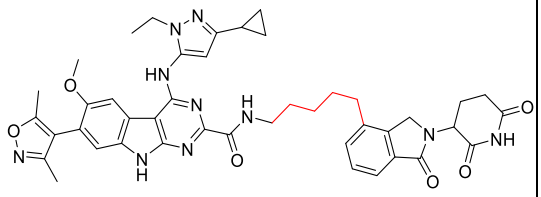
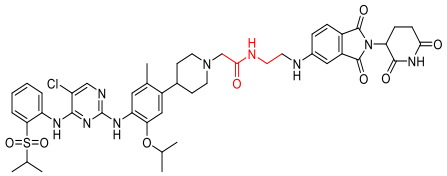
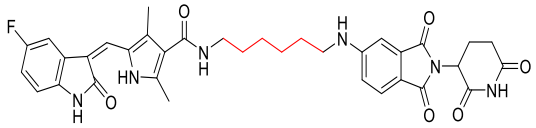
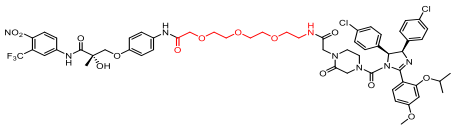
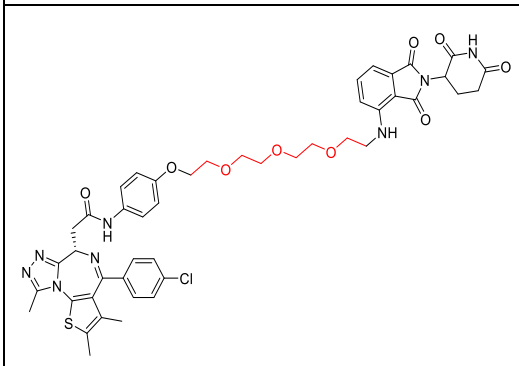
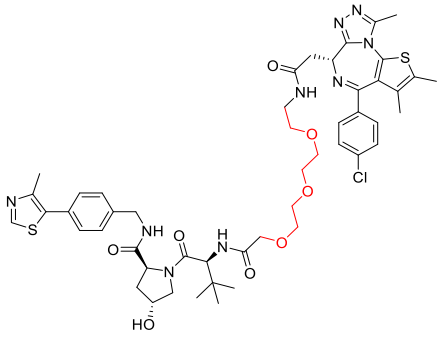
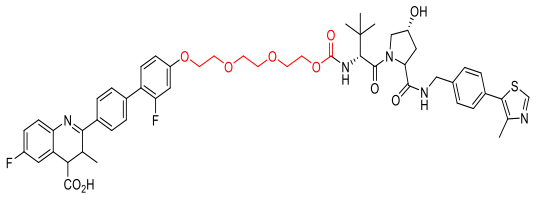
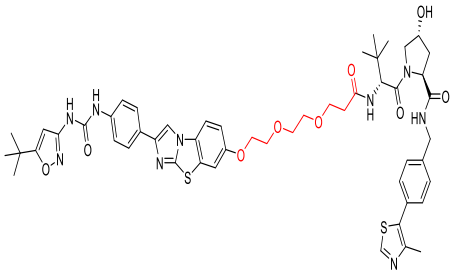
E-mail addresses: xjyao@mpu.edu.mo (Xiaojun Yao), cnsratdoc@optonline.net (Charles R. Ashby Jr.), gefei_hao@foxmail.com (Ge-Fei Hao).

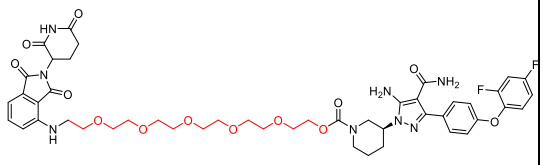
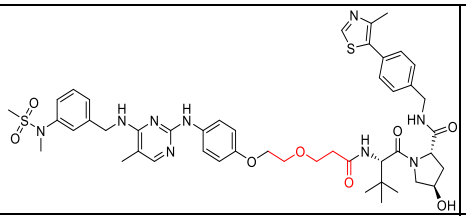
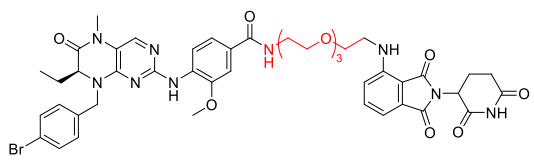
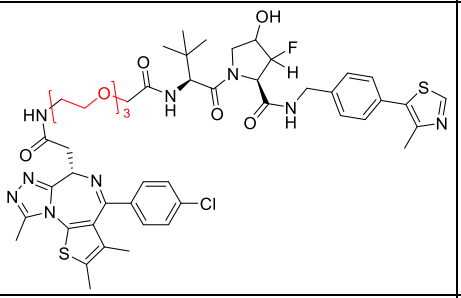
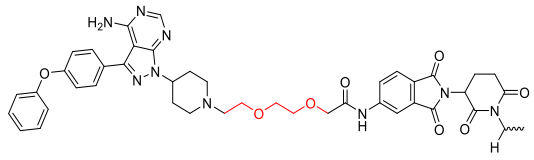
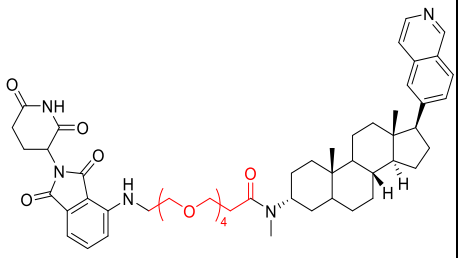
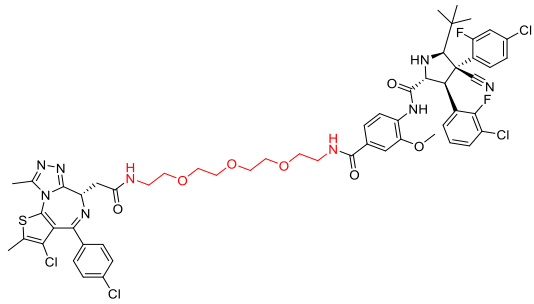
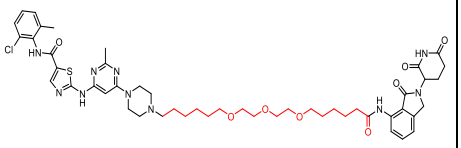
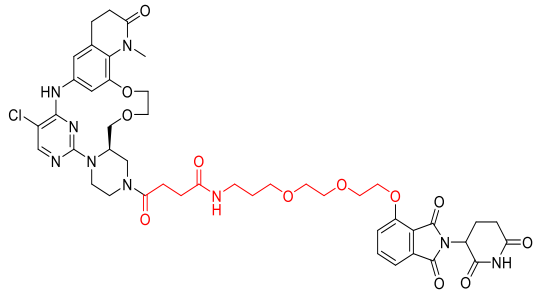
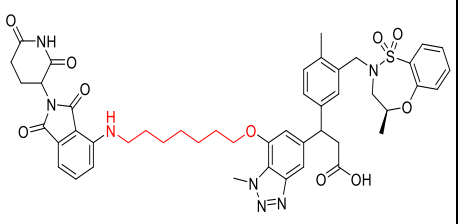
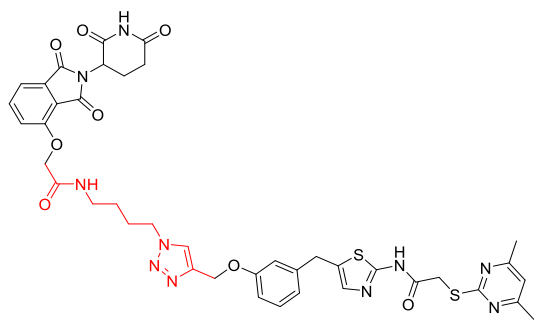
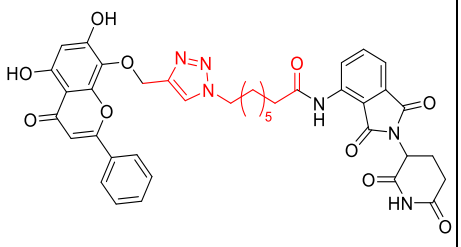
Received 6 February 2024; received in revised form 11 February 2024; accepted 2 April 2024

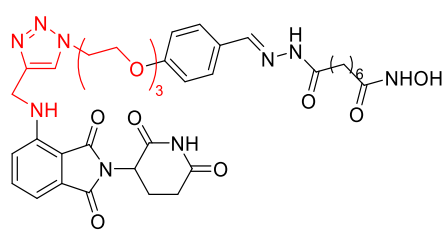
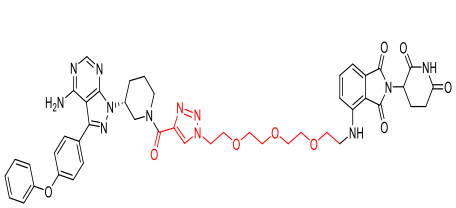
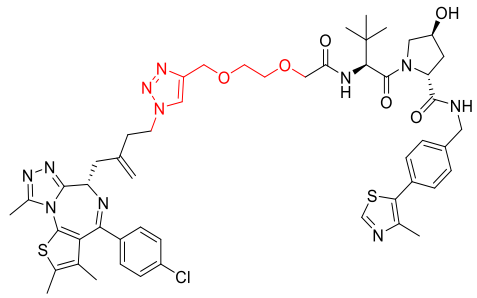
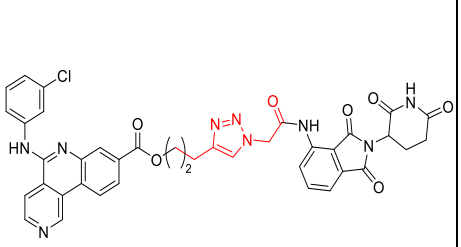
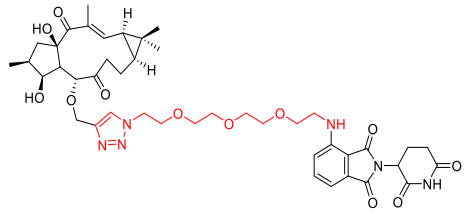
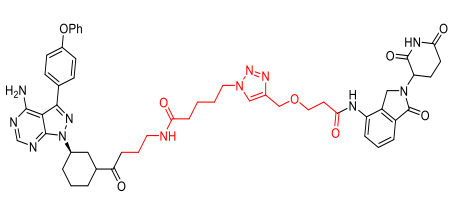
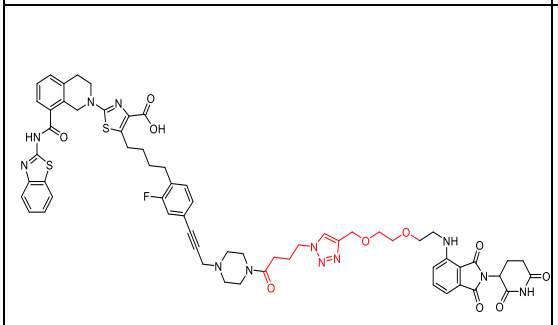
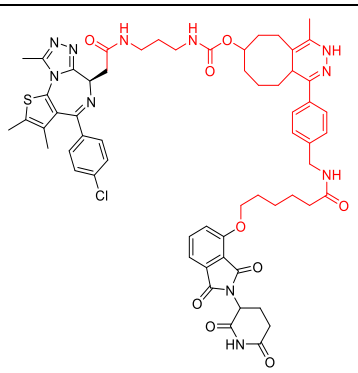
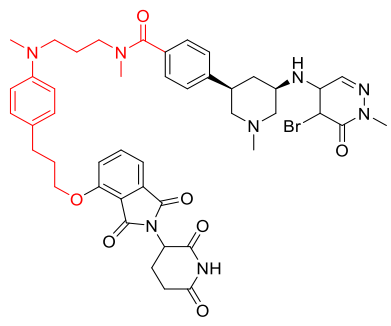
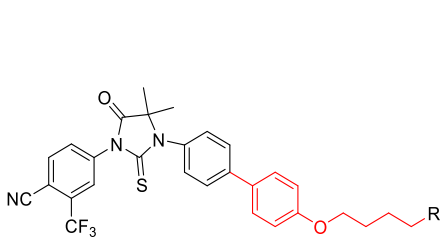
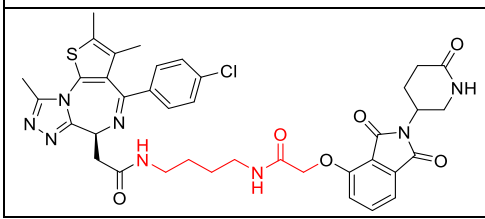
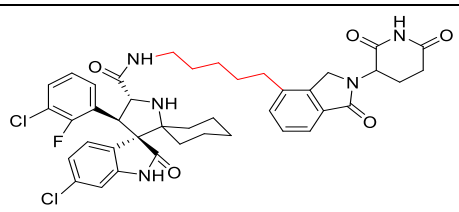
Content

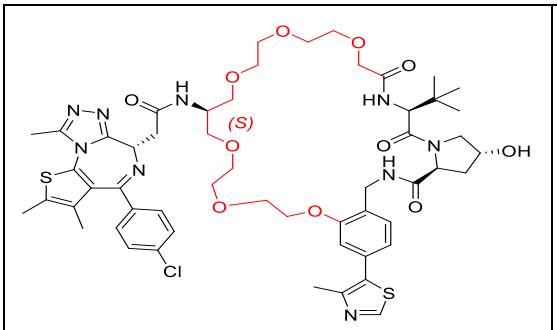
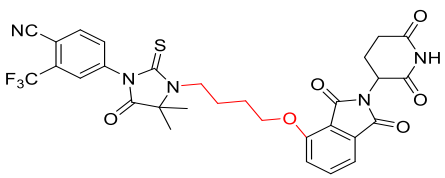
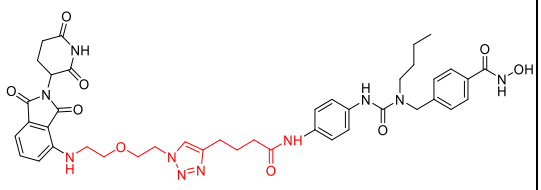
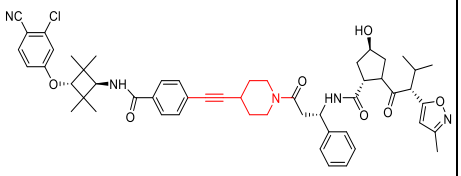
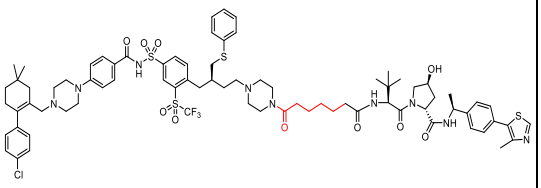
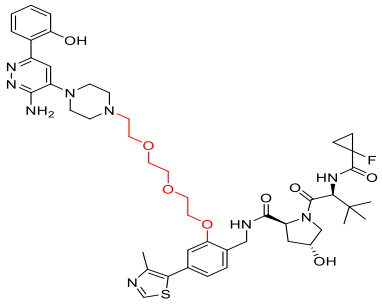
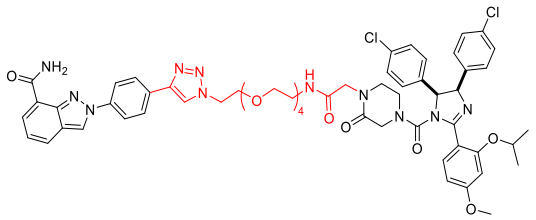
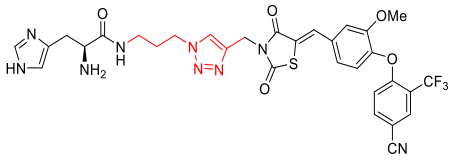
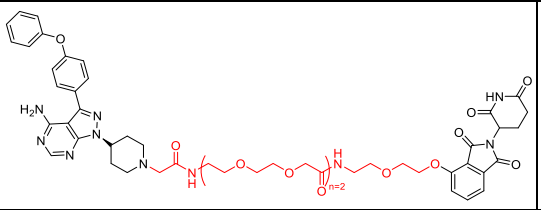
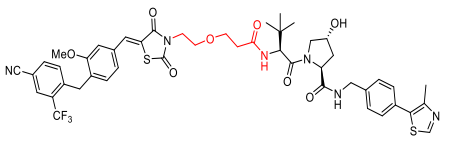
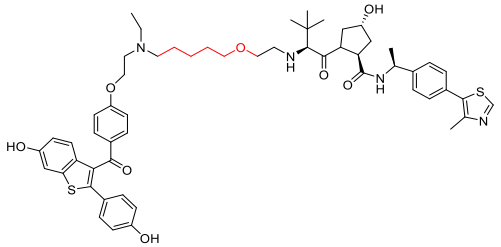
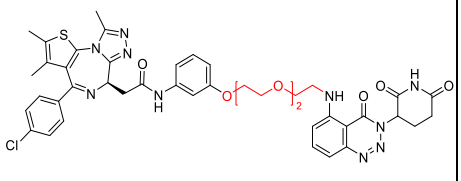
Table S1 PROTACs in the published papers (linker shown in red).

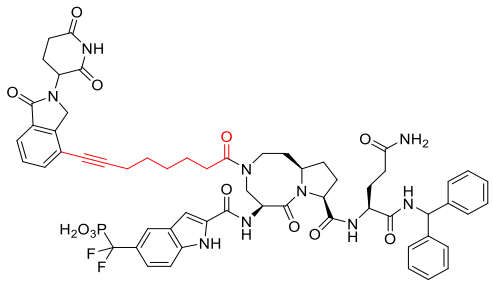
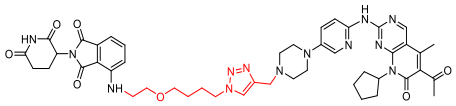
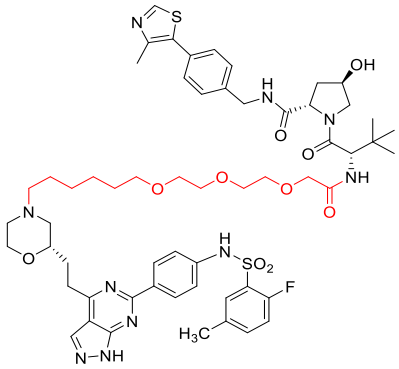
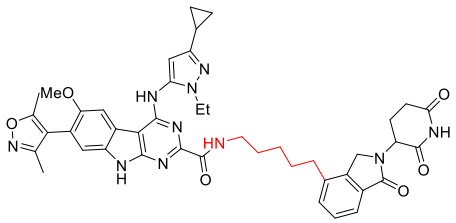
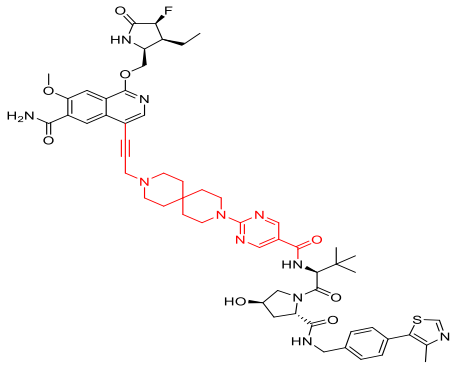
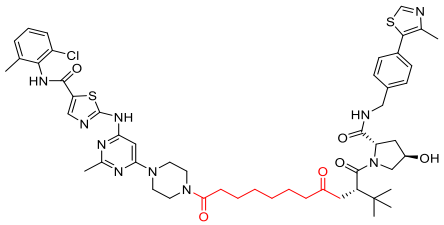
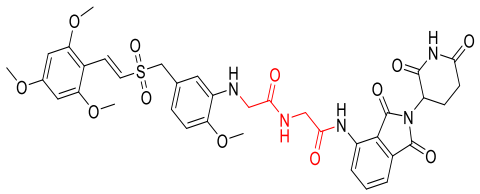
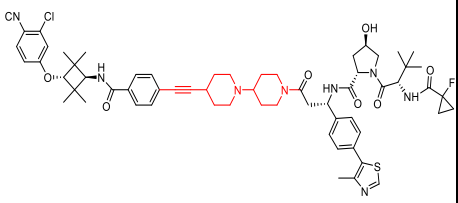
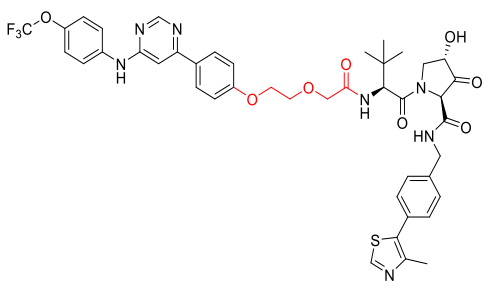
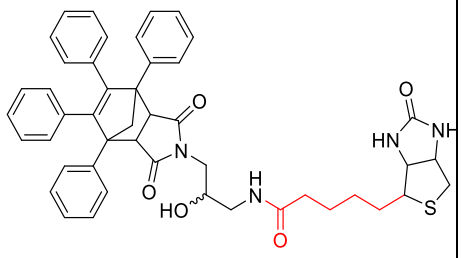
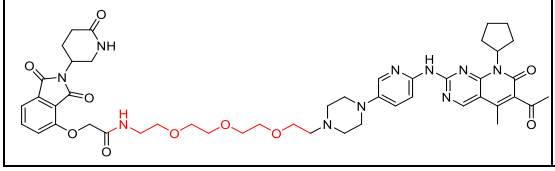
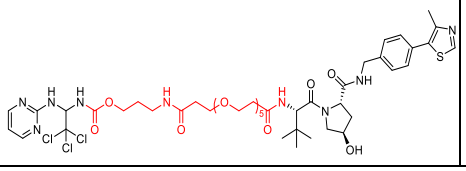
PROTACs	Ref	PROTACs	Ref
	1		2
	3		4
	5		6
	7		8
	9		10
	11		12
	13		14

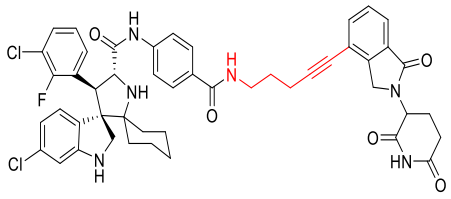
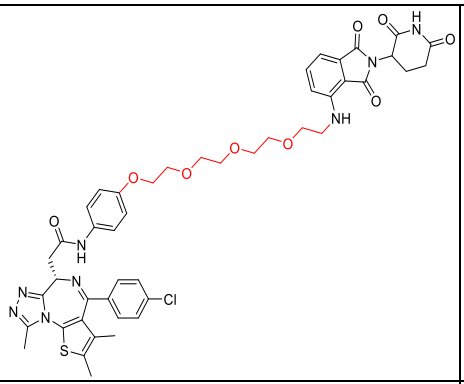
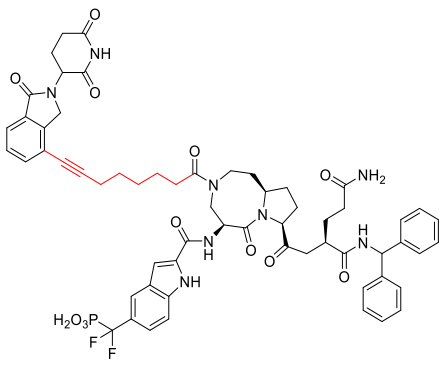
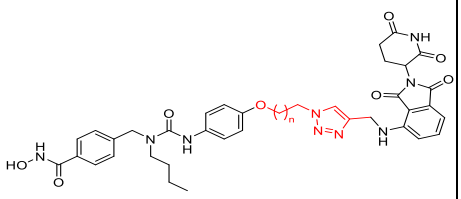
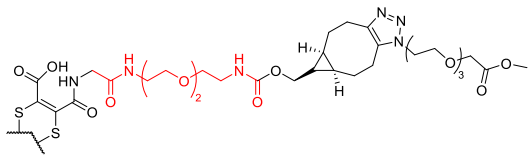
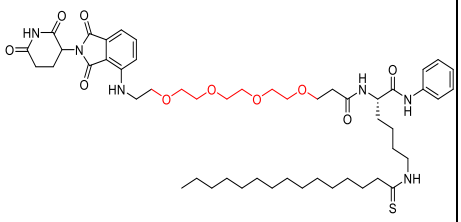
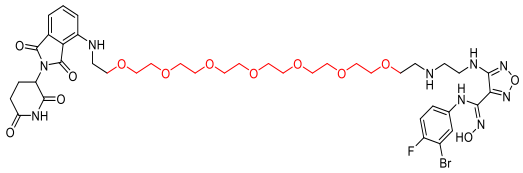
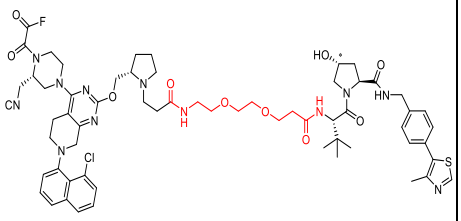
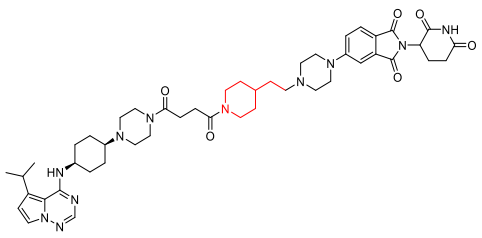
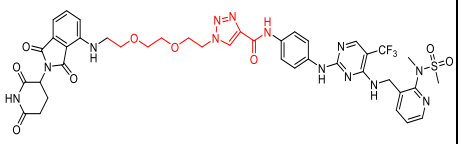
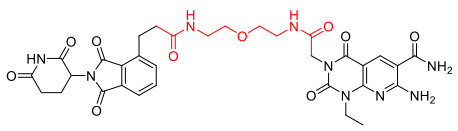
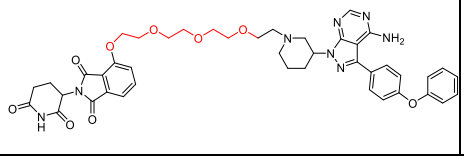
	15		16
	17		18
	19		20
	21		22
	23		24
	25		26

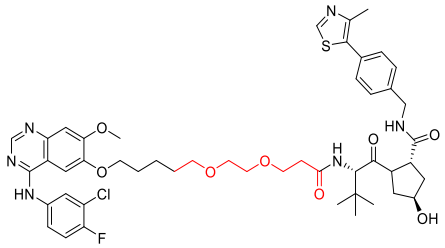
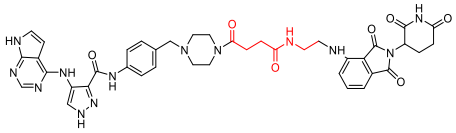
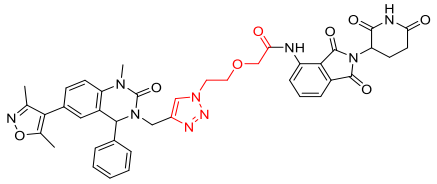
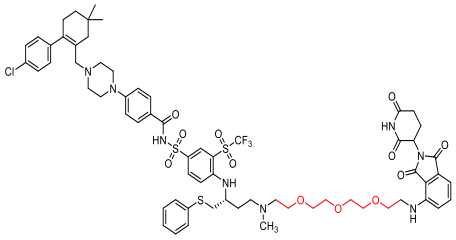
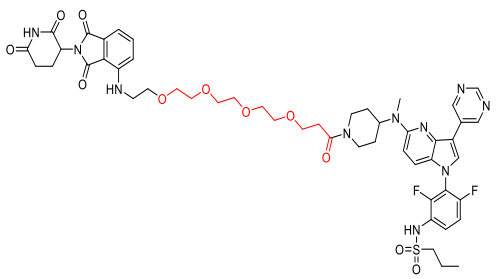
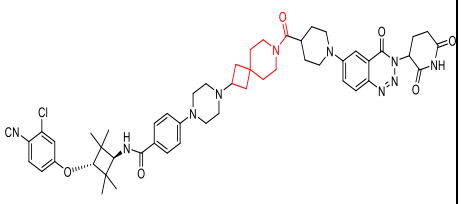
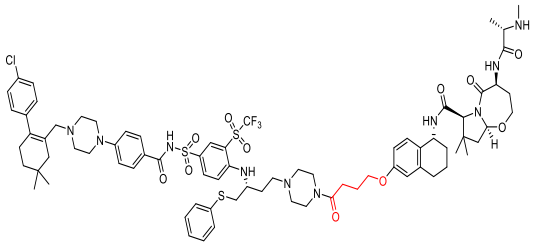
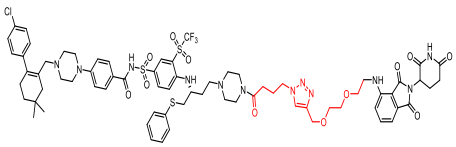
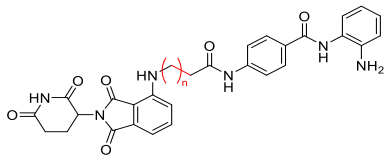
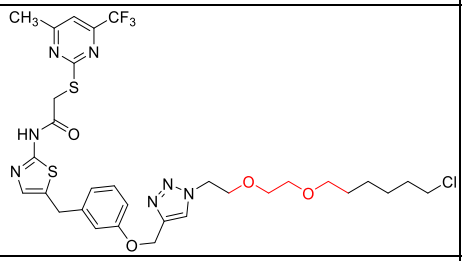
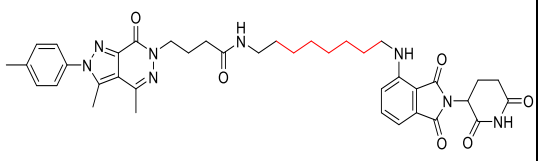
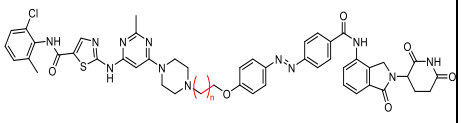
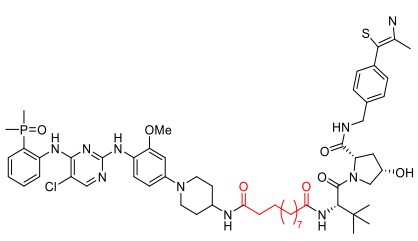
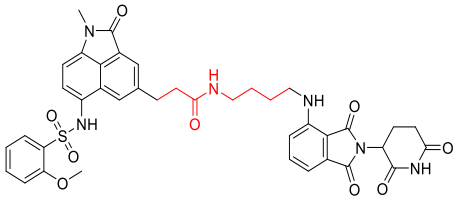
	27		28
	29		30
	31		32
	33		34
	35		36
	37		38

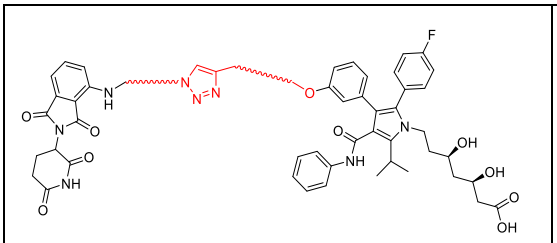
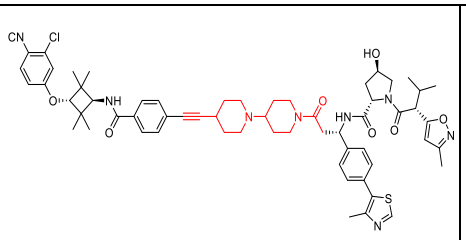
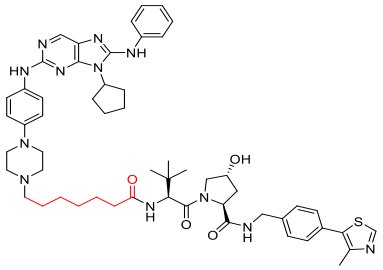
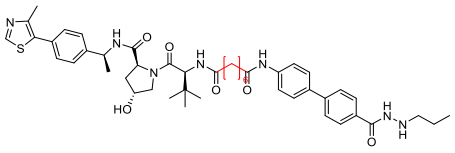
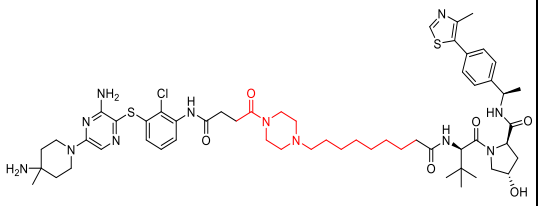
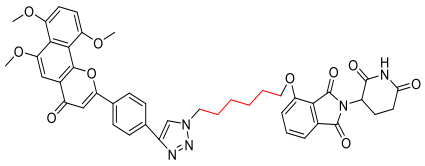
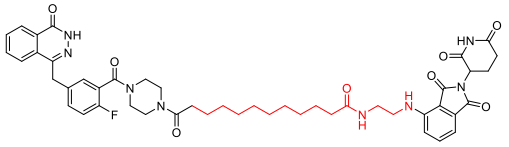
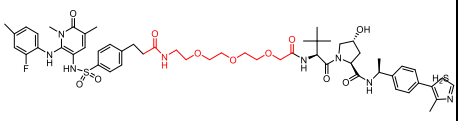
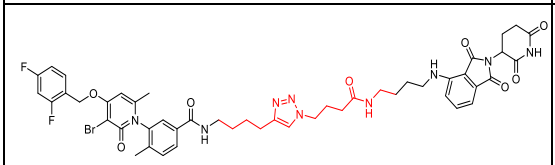
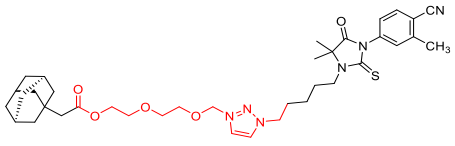
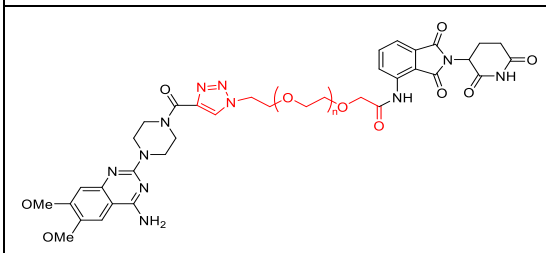
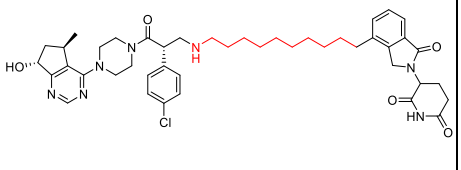
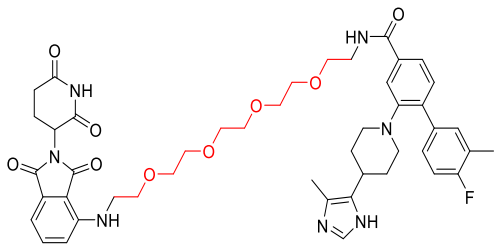
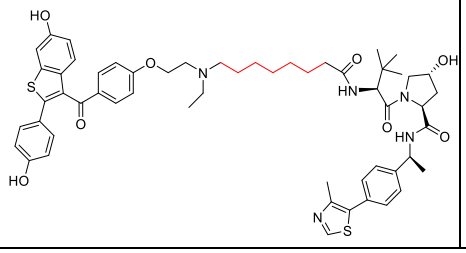
	39		40
	41		42
	43		44
	45		46
	47		48
	49		50

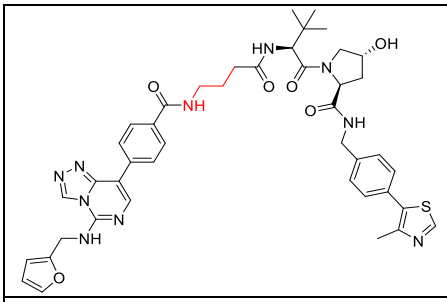
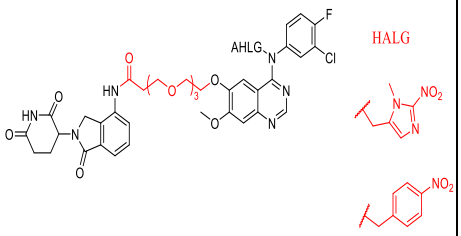
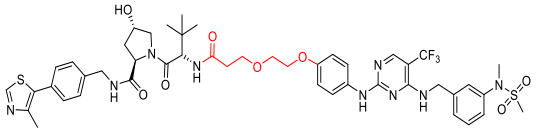
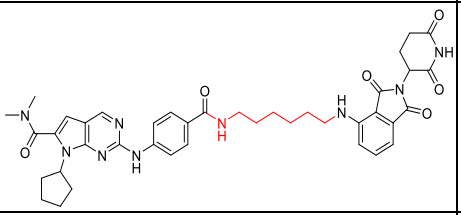
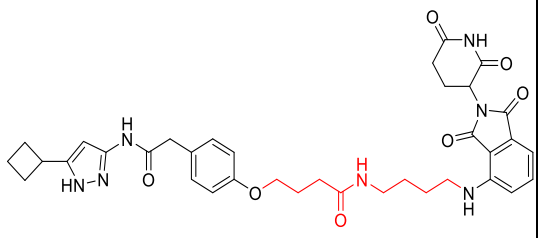
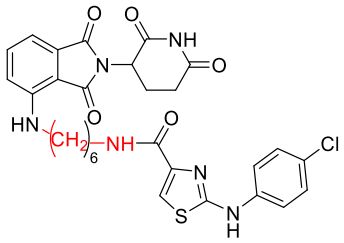
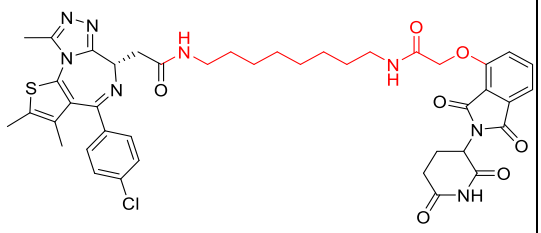
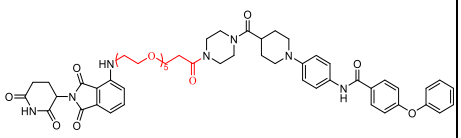
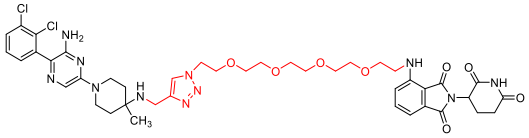
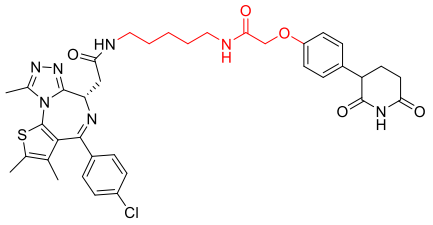
	51		52
	53		54
	55		56
	57		58
	59		60
	61		62

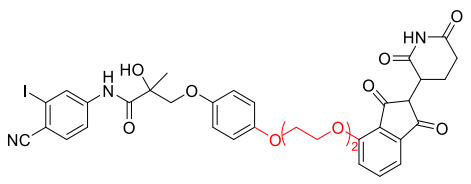
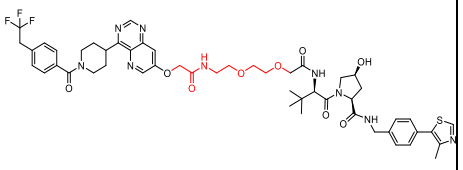
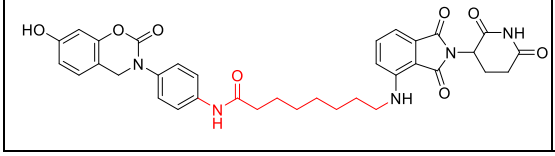
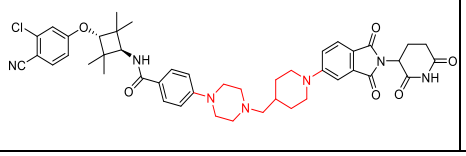
	63		64
	65		66
	67		68
	69		70
	71		72
	73		74

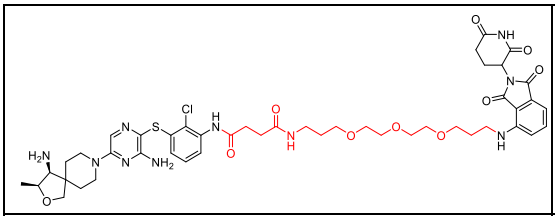
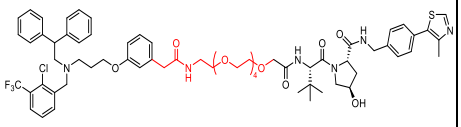
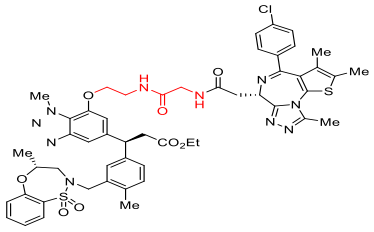
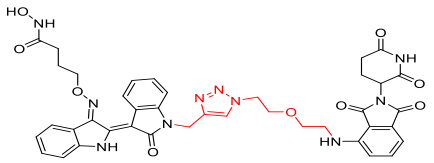
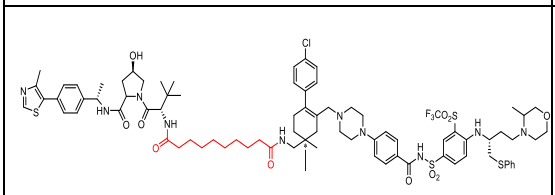
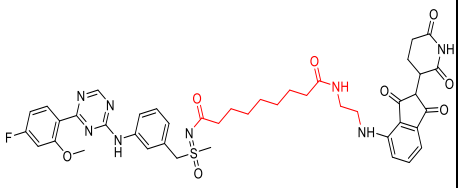
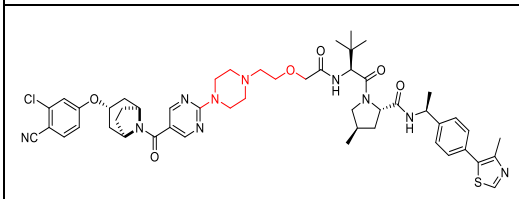
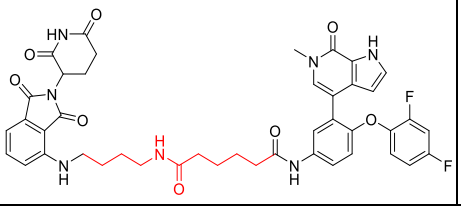
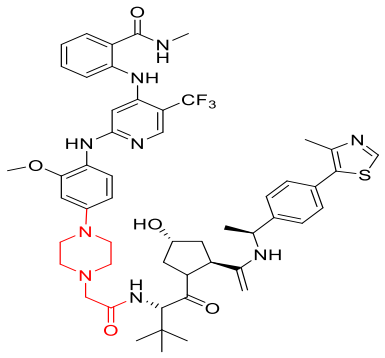
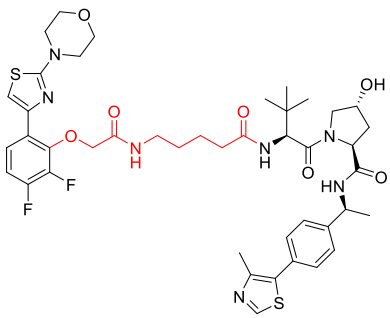
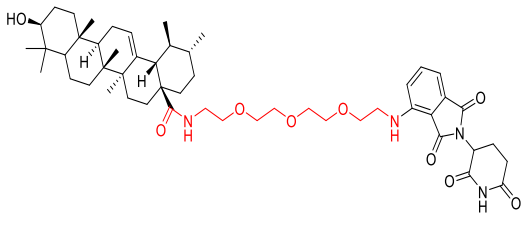
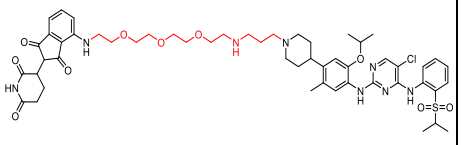
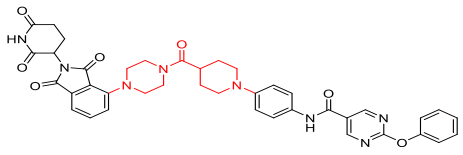
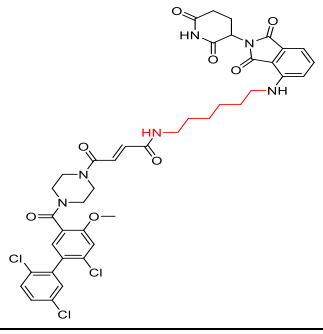
	75		76
	77		78
	79		80
	81		82
	83		84
	85		86

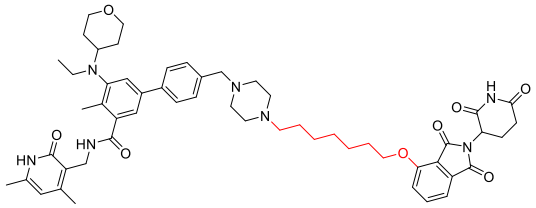
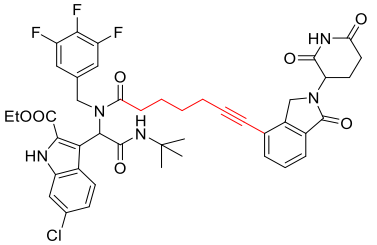
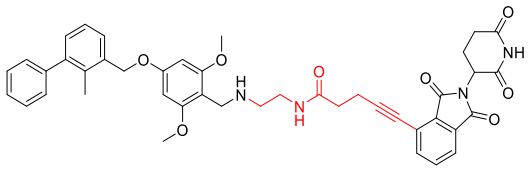
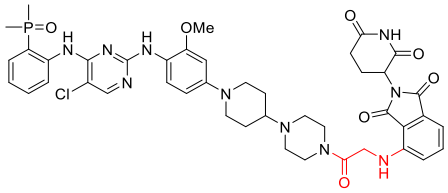
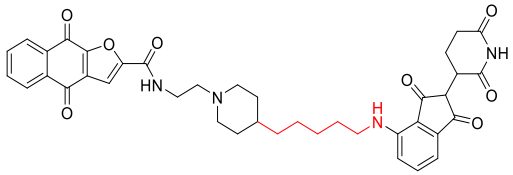
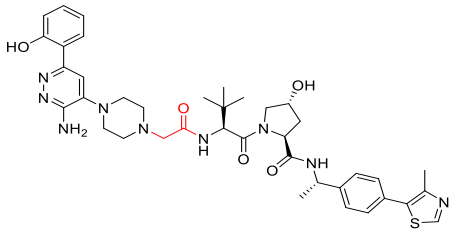
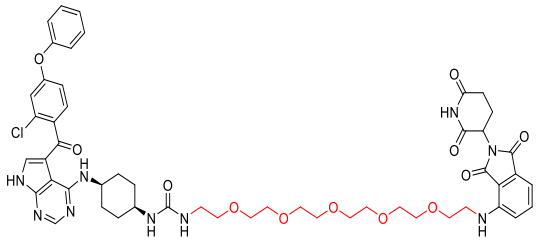
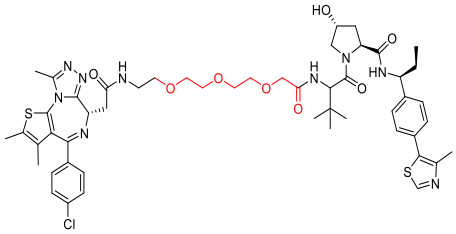
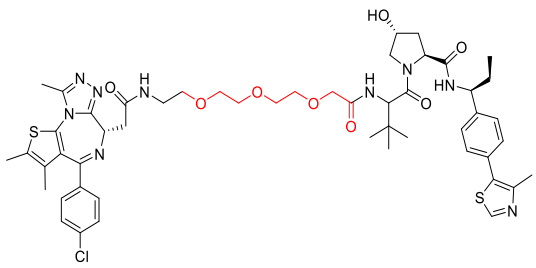
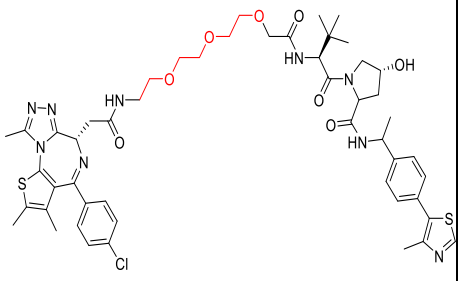
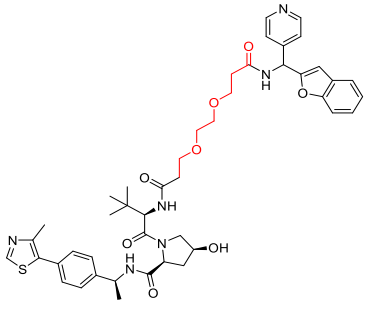
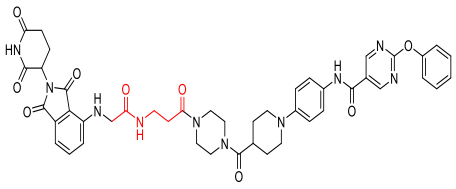
	87		88
	89		90
	91		92
	93		94
	95		96
	97		98
	99		100

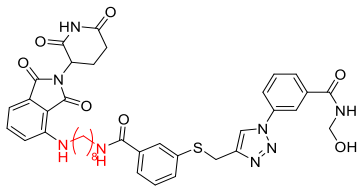
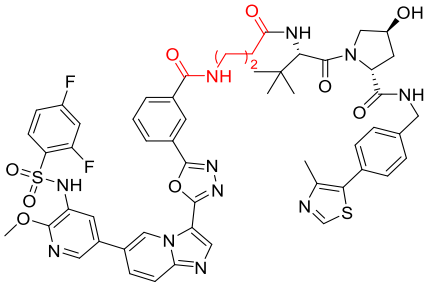
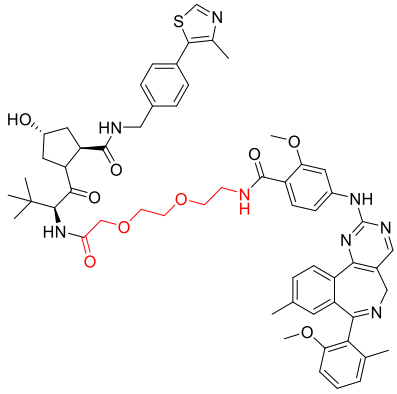
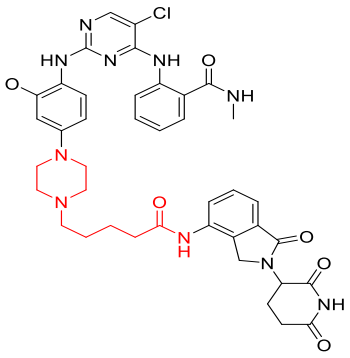
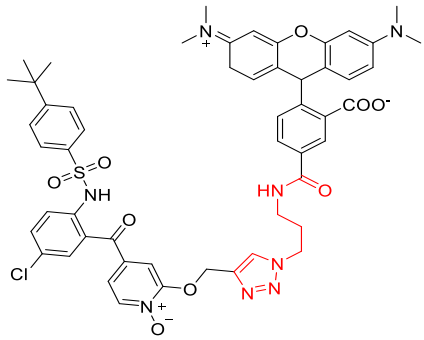
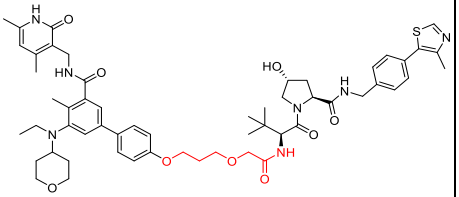
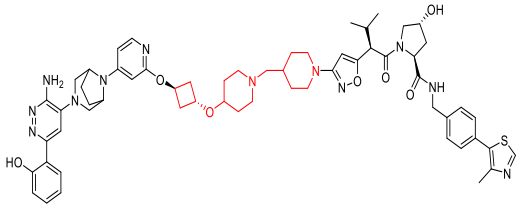
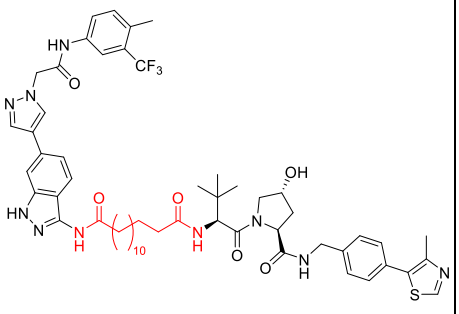
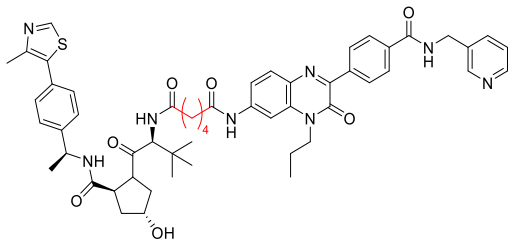
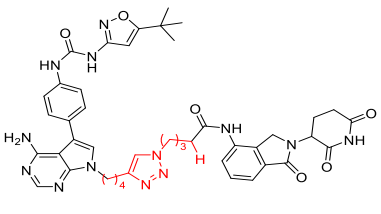
	101		102
	103		104
	105		106
	107		108
	109		110
	111		112
	113		114

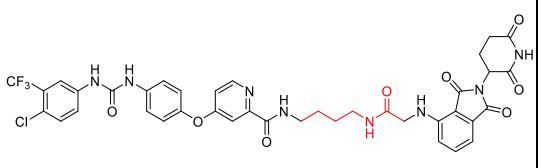
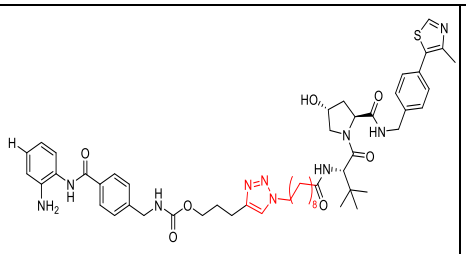
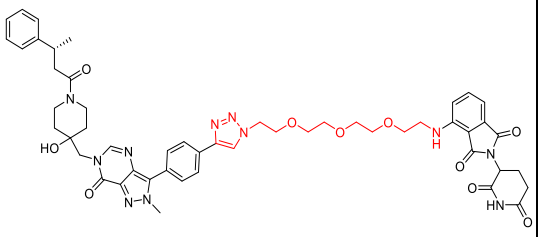
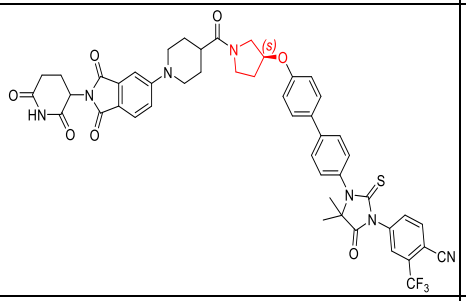
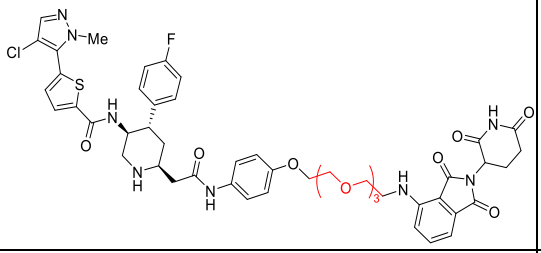
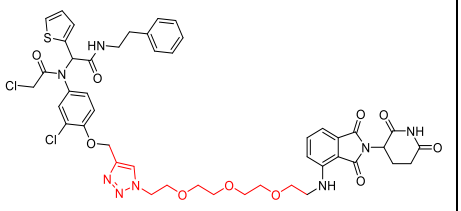
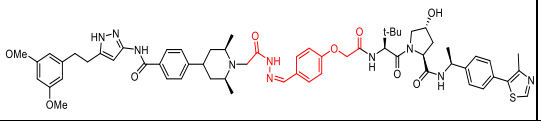
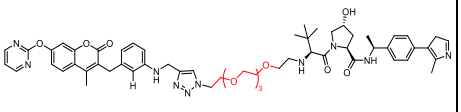
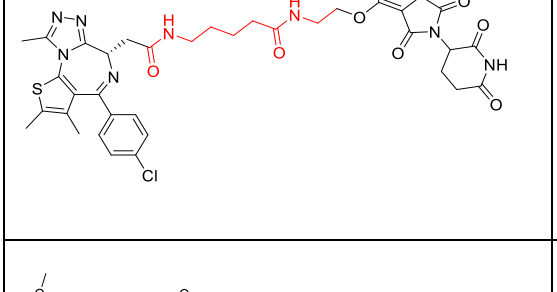
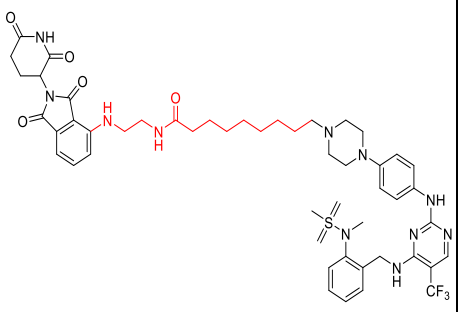
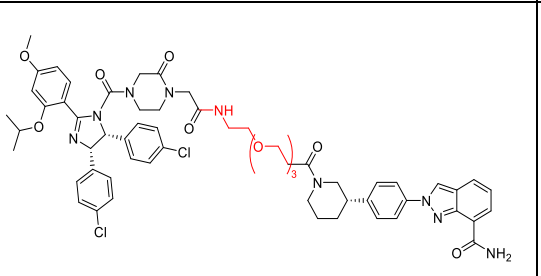
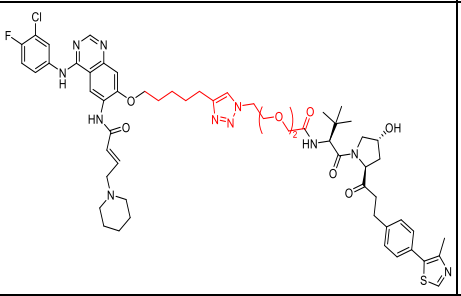
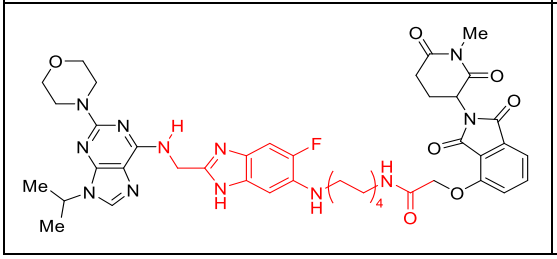
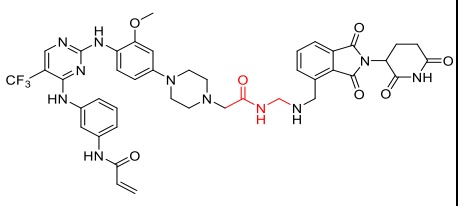
	115		116
	117		118
	119		120
	121		122
	123		124

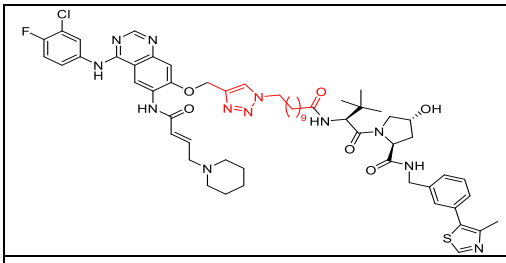
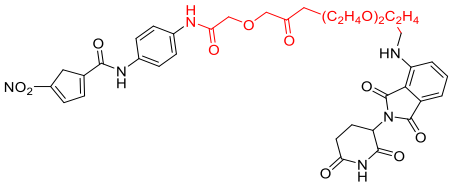
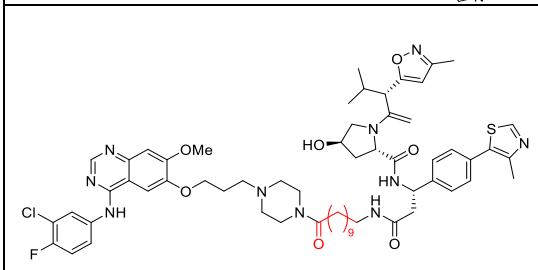
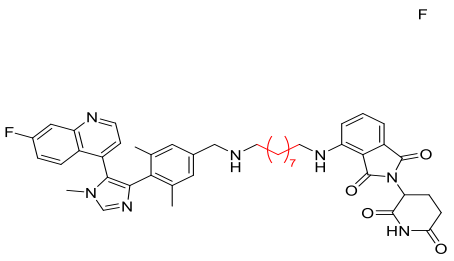
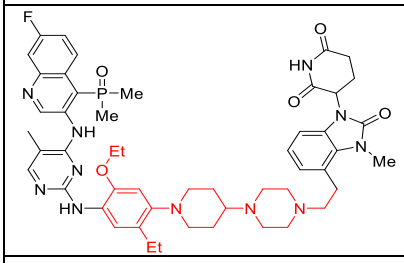
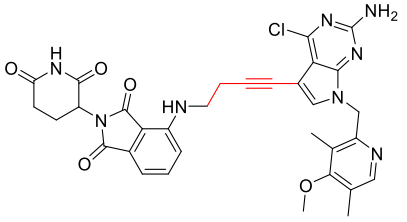
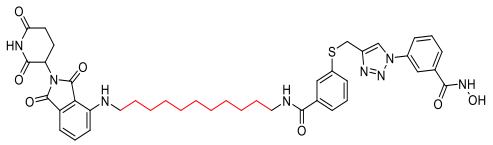
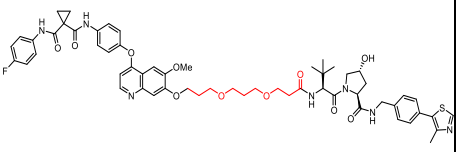
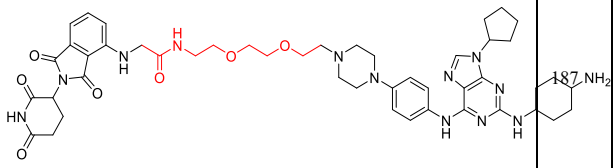
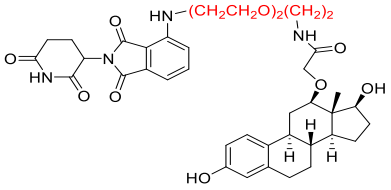
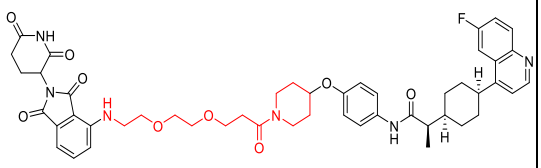
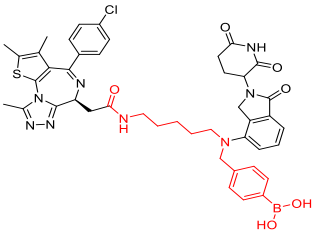
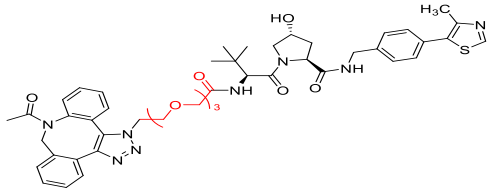
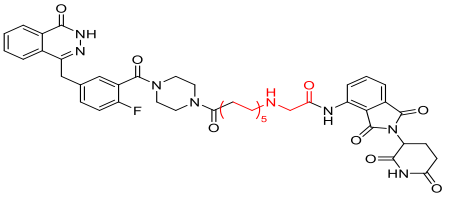
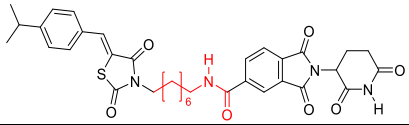
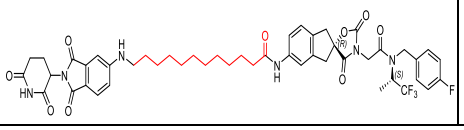
	125		126
	127		128

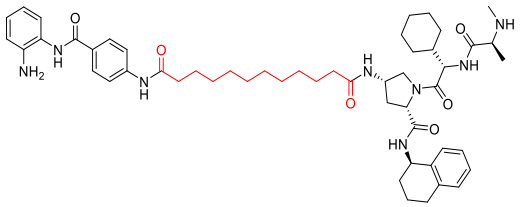
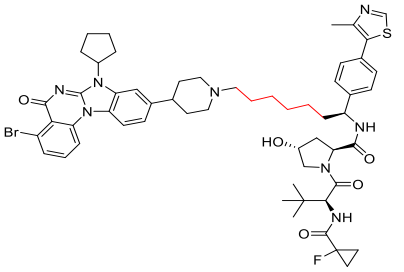
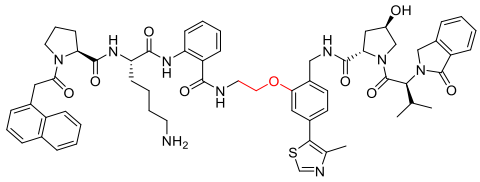
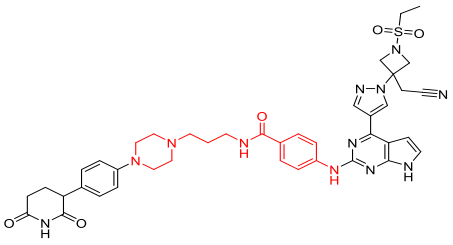
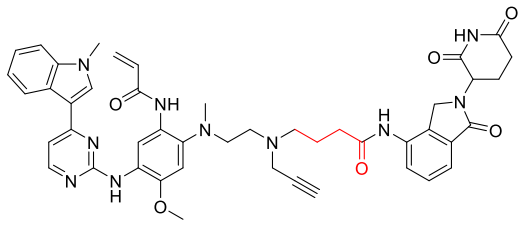
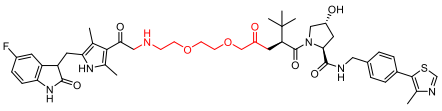
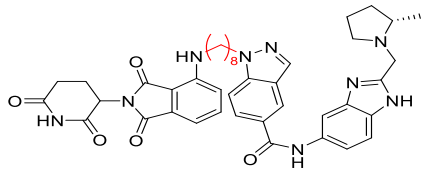
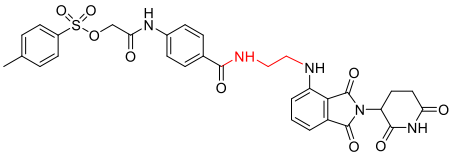
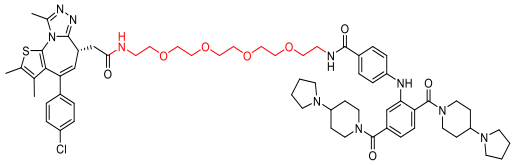
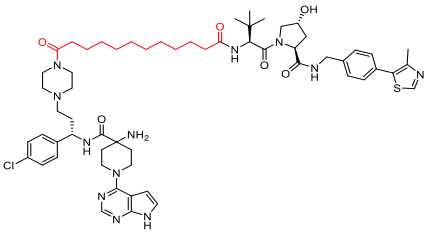
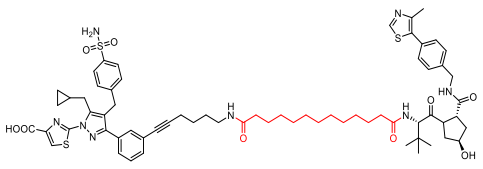
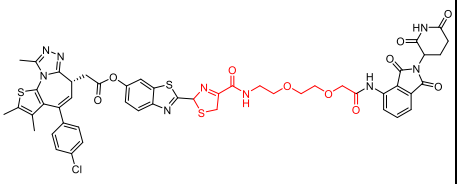
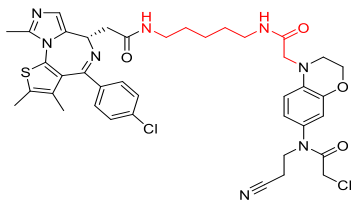
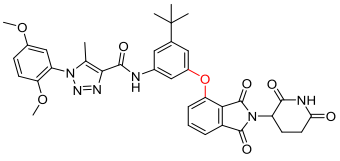
	129		130
	131		132
	133		134
	135		136
	137		138
	139		140
	141		142

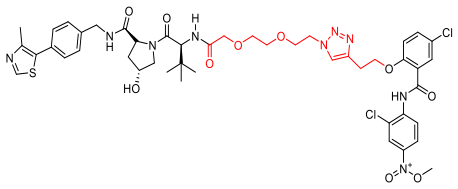
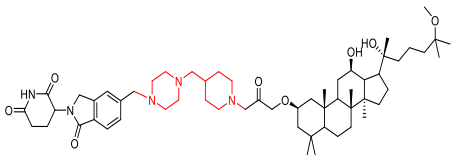
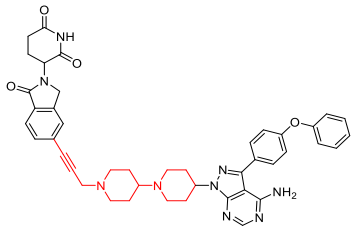
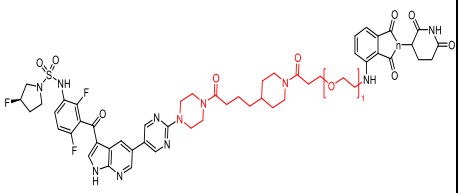
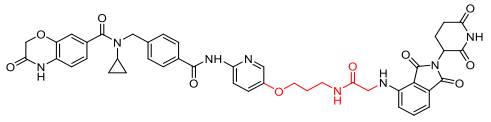
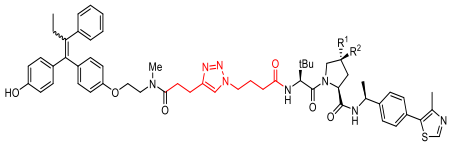
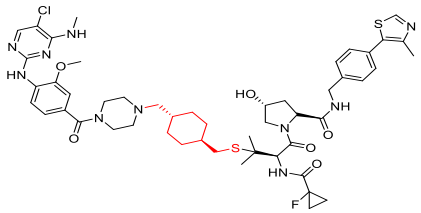
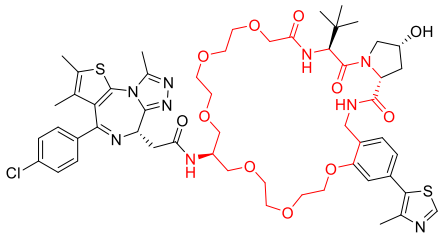
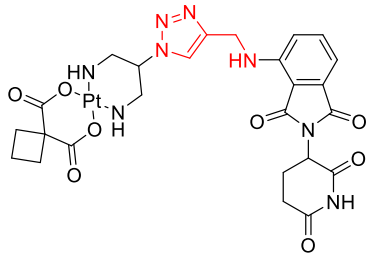
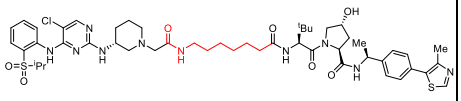
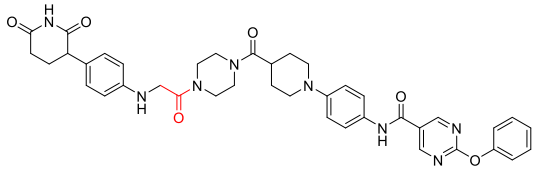
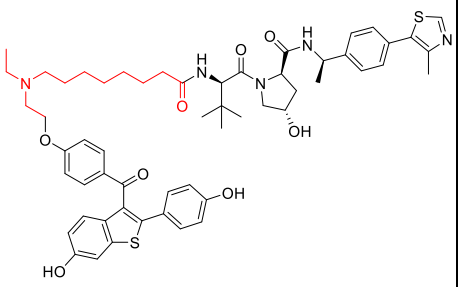
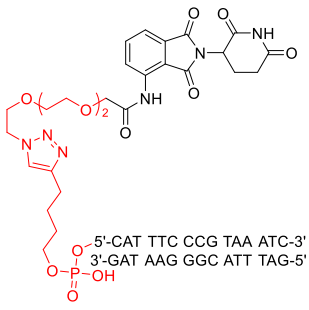
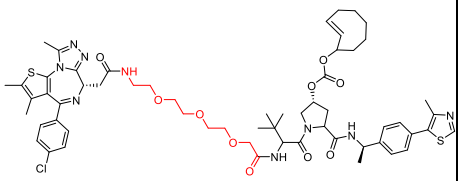
	143		144
	145		146
	147		148
	149		150
	151		152
	153		154

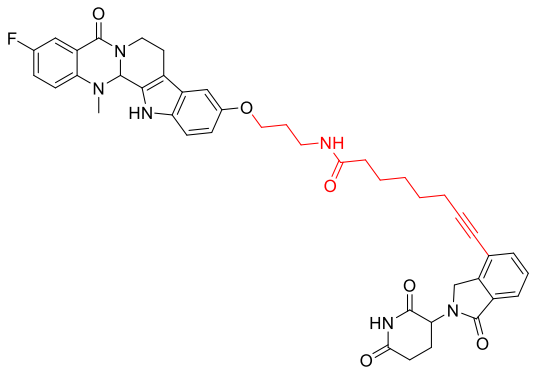
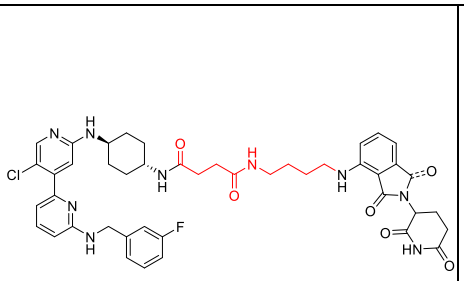
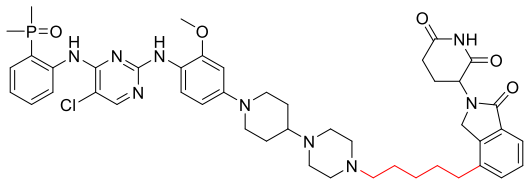
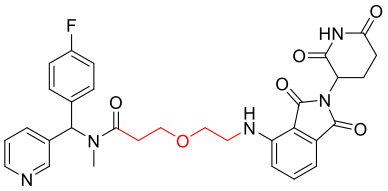
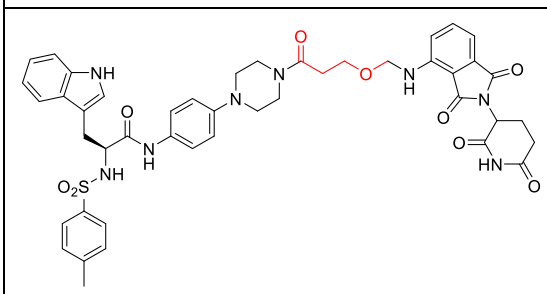
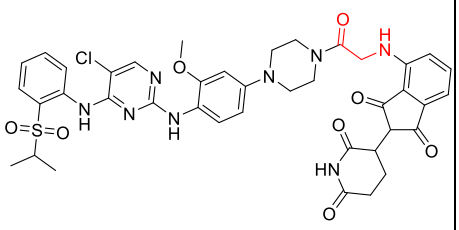
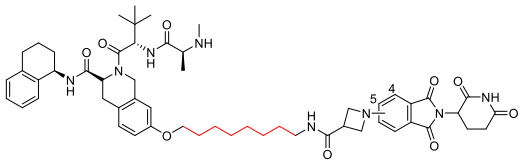
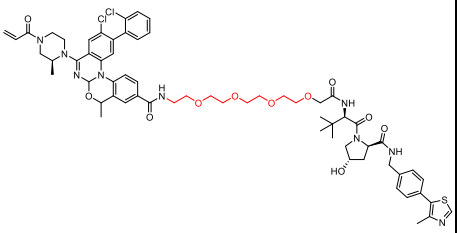
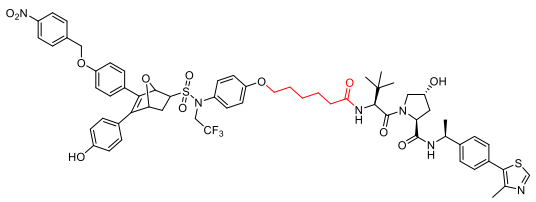
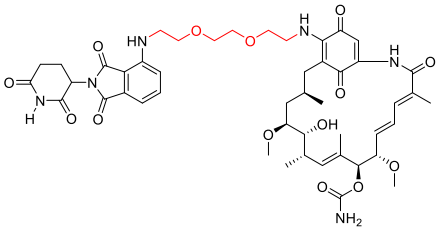
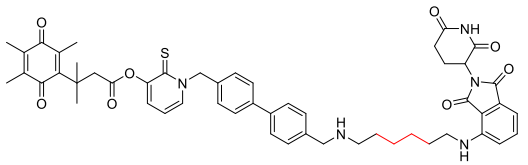
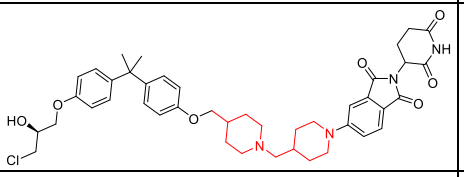
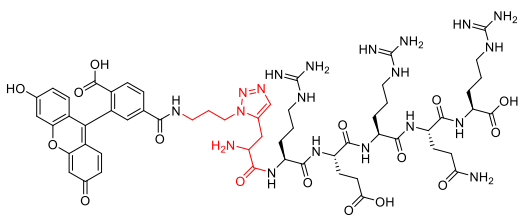
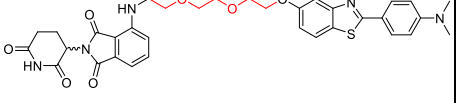
	155		156
	157		158
	159		160
	161		162
	163		164

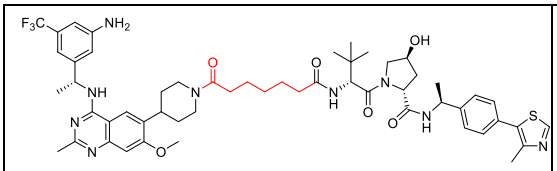
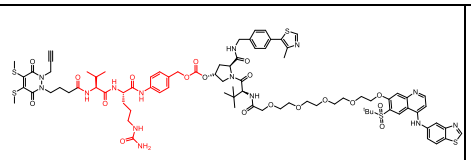
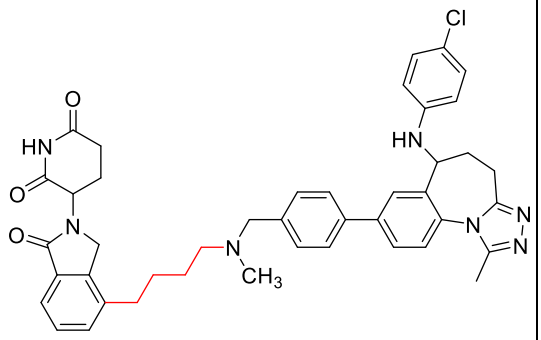
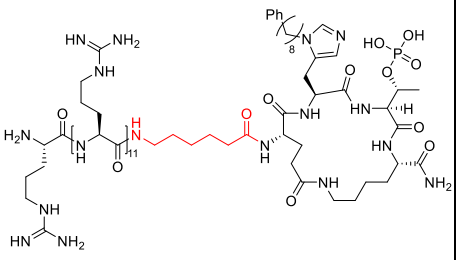
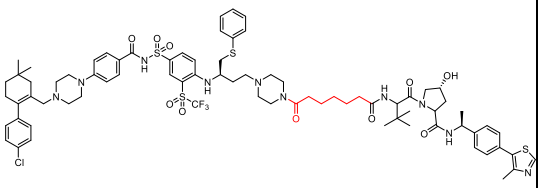
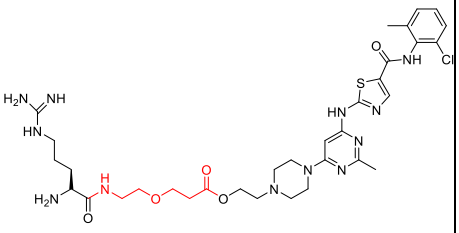
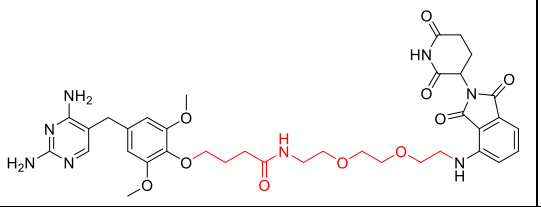
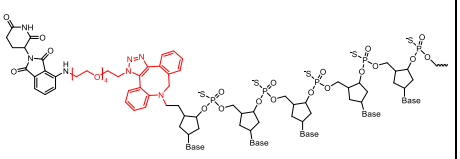
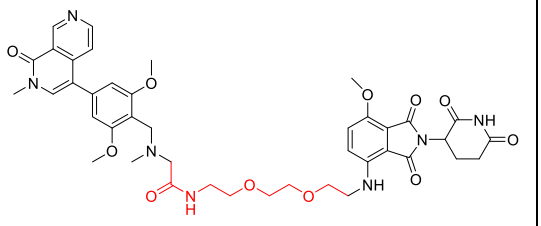
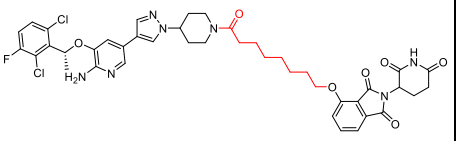
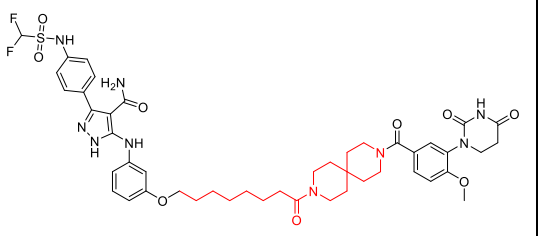
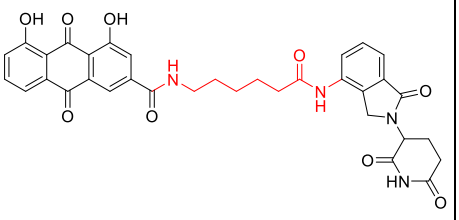
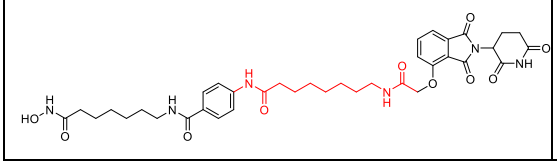
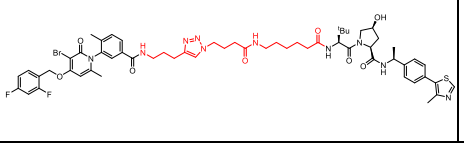
	165		166
	167		168
	169		170
	171		172
	173		174
	175		176
	177		178

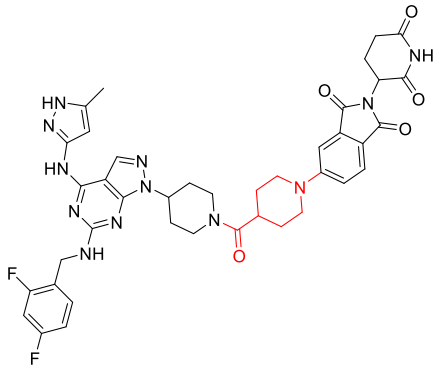
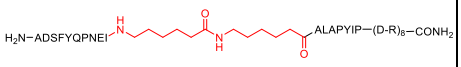
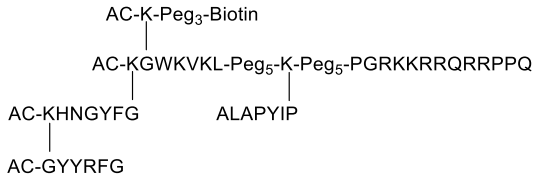
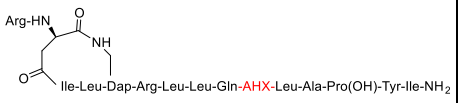
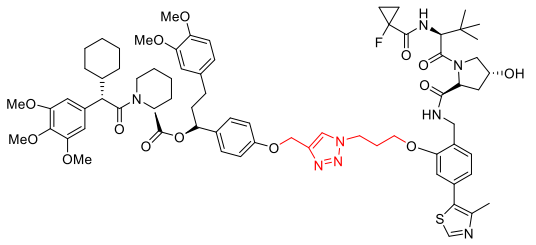
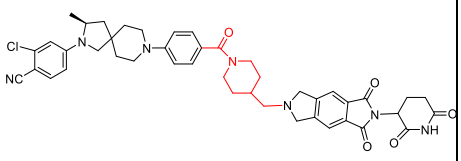
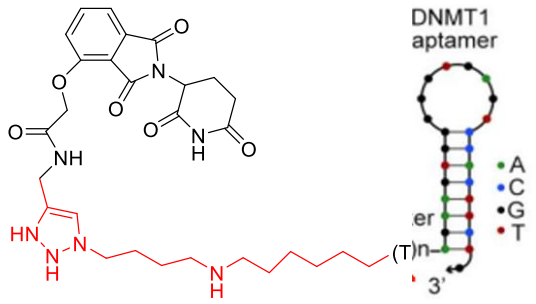
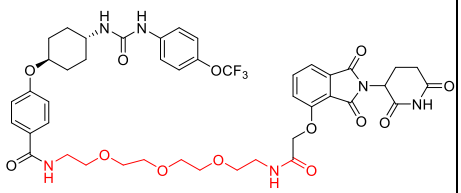
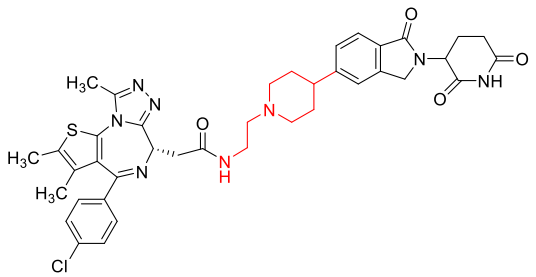
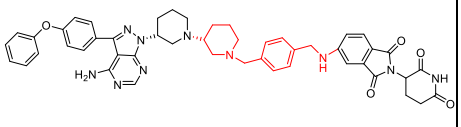
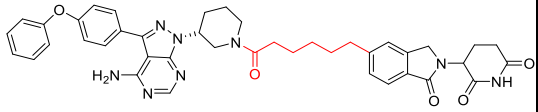
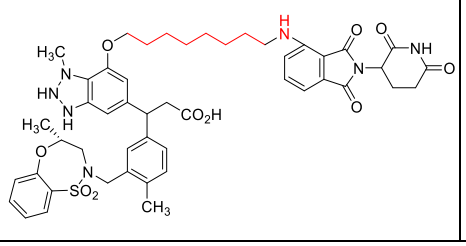
	179		180
	181		182
	183		184
	185		186
	187		188
	189		190
	191		192
	193		194

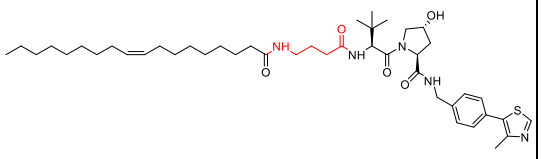
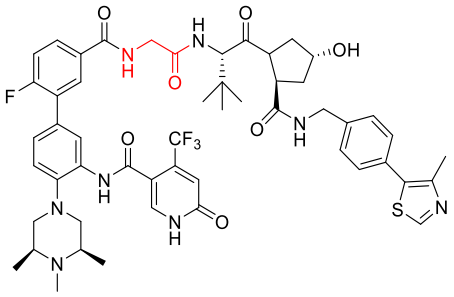
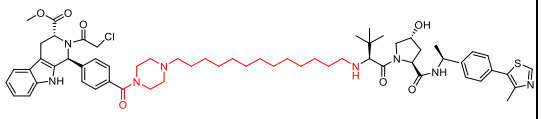
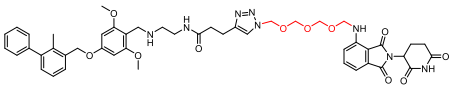
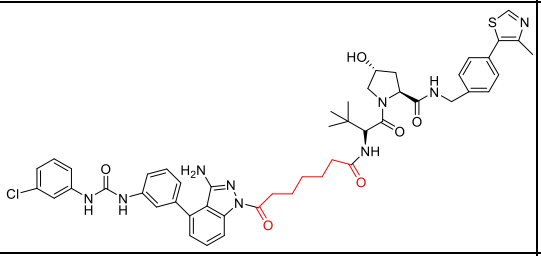
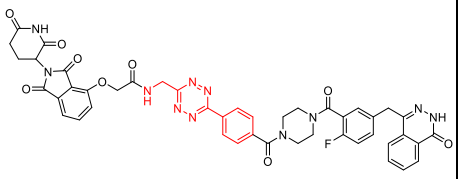
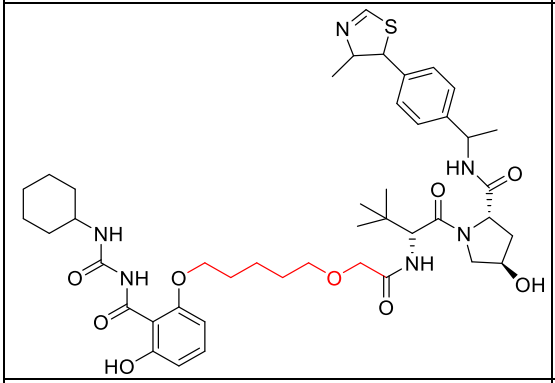
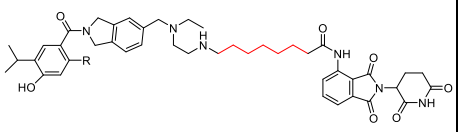
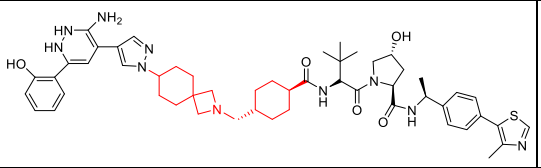
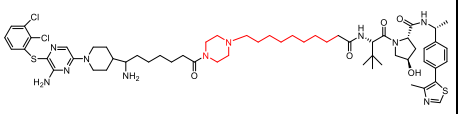
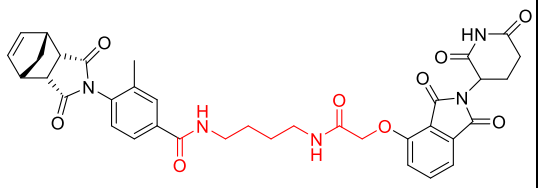
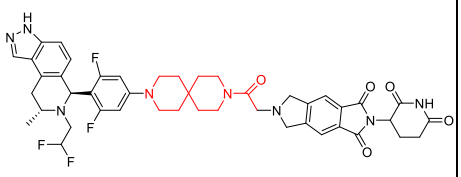
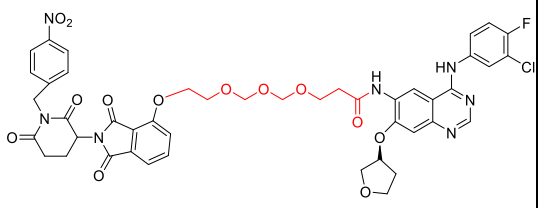
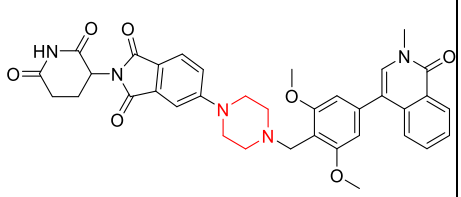
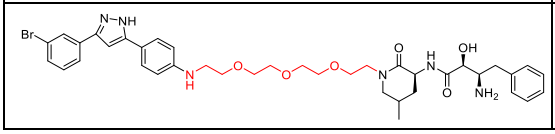
	195		196
	197		198
	199		200
	201		202
	203		204
	205		206
	207		208

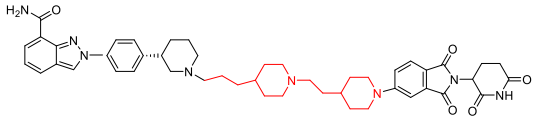
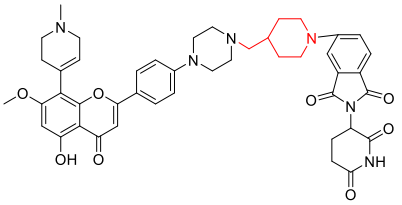
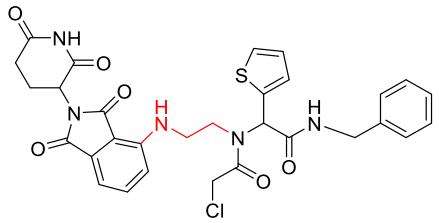
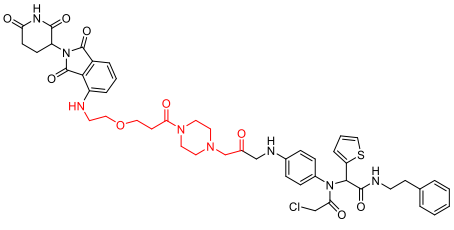
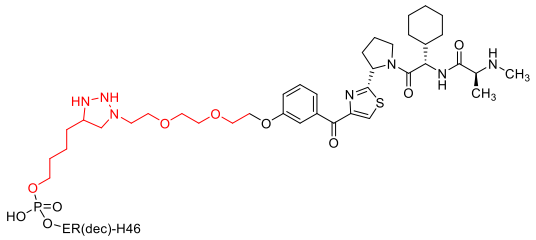
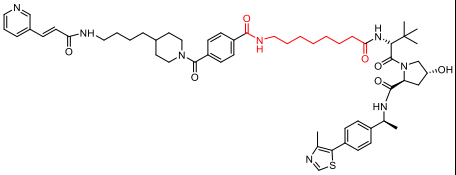
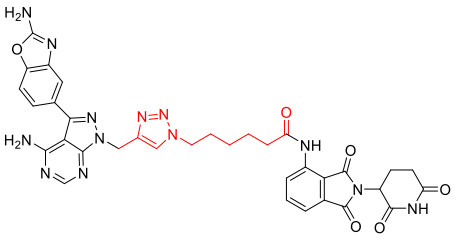
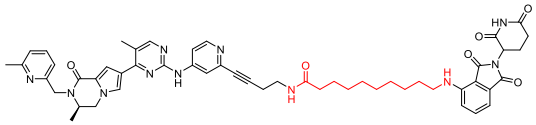
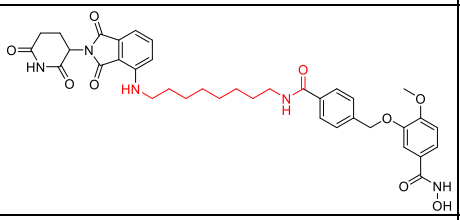
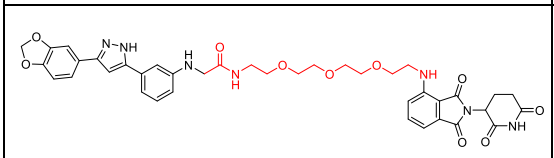
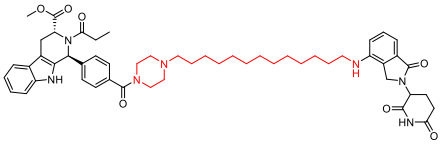
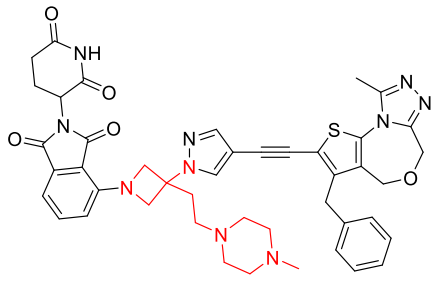
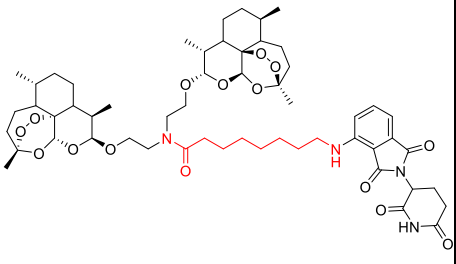
	209		210
	211		212
	213		214
	215		216
	127		218
	219		220
	221		222

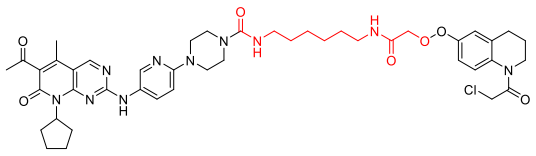
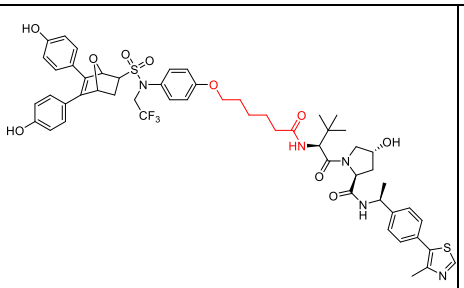
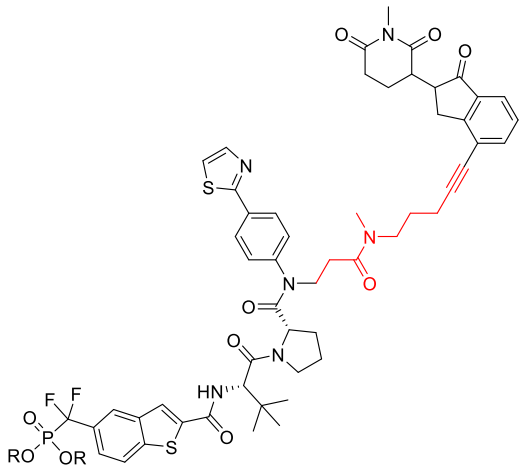
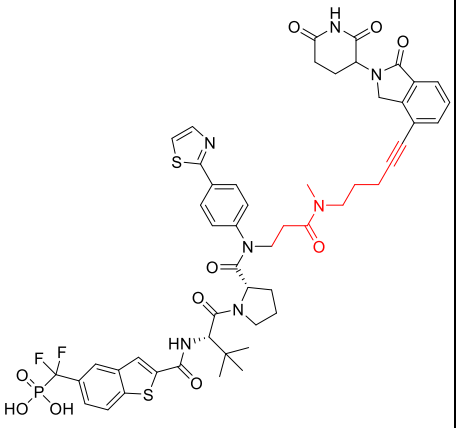
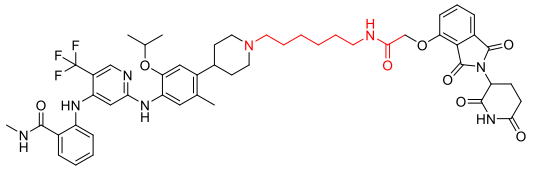
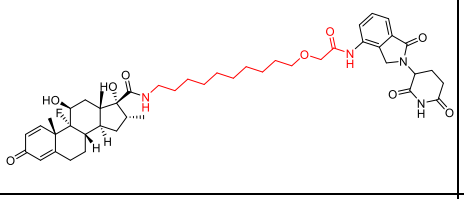
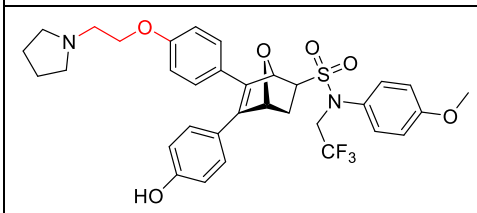
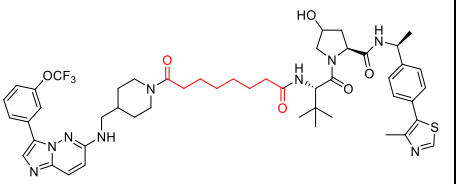
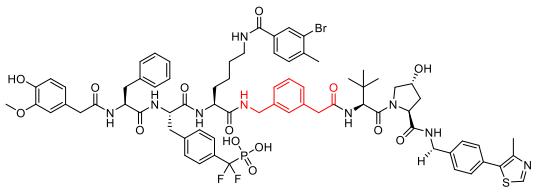
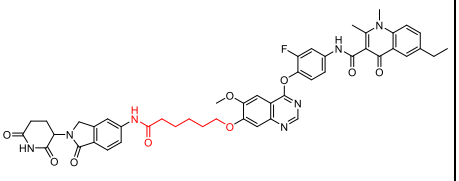
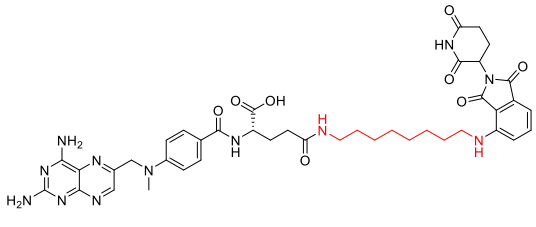
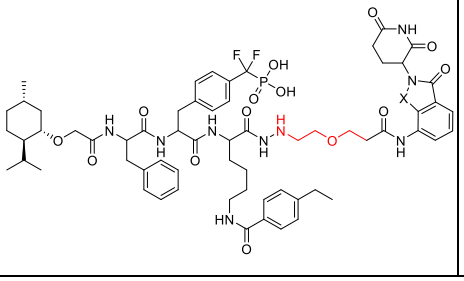
	223		224
	225		226
	227		228
	229		230
	231		232
	233		234
	235		236

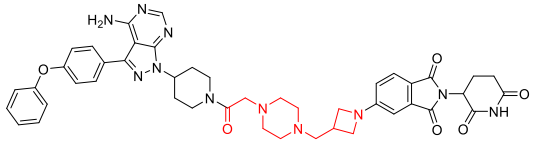
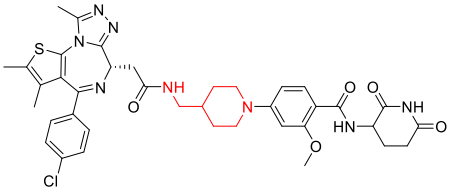
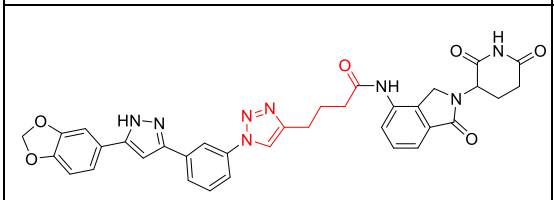
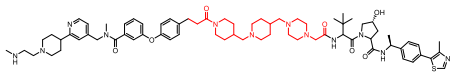
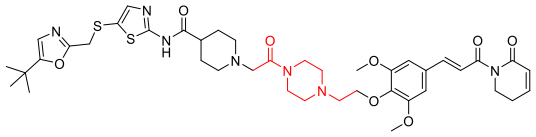
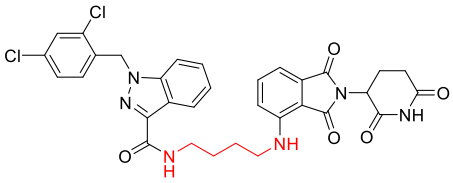
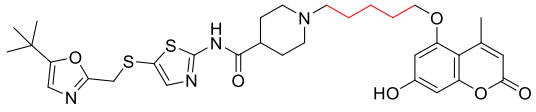
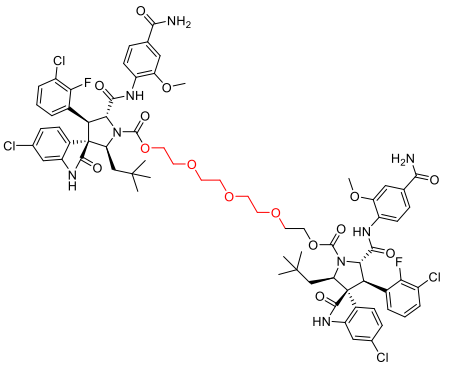
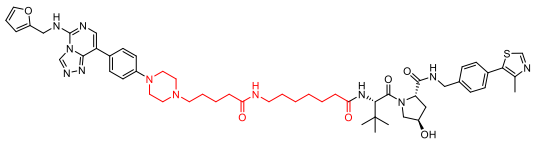
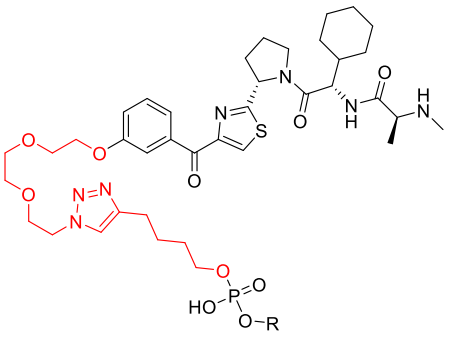
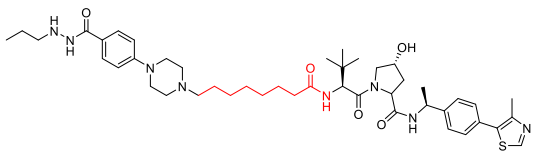
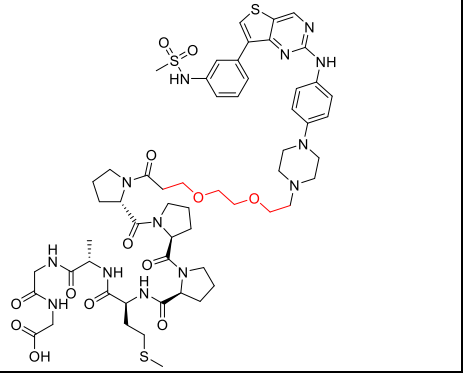
	237		238
	239		240
	241		242
	243		244
	245		246
	247		248
	249		250

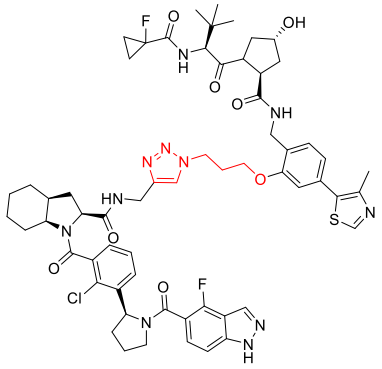
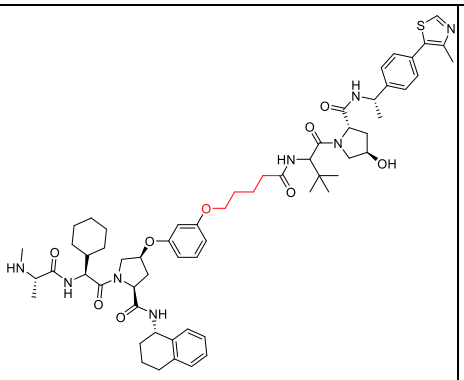
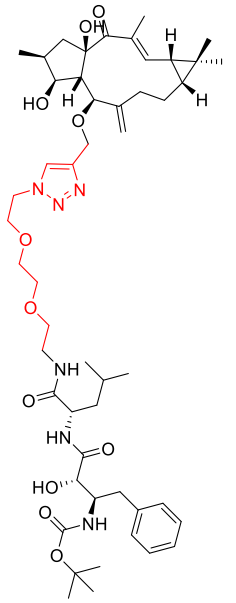
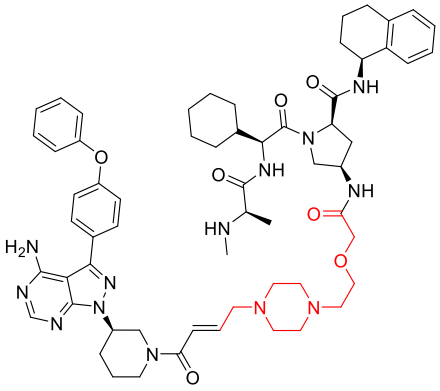
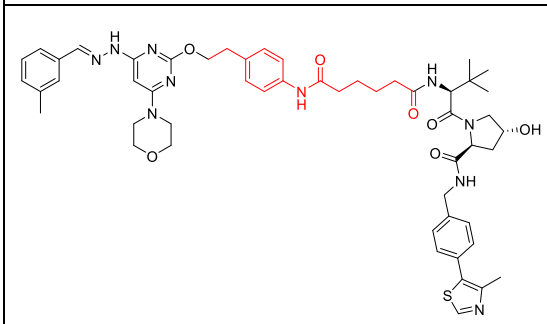
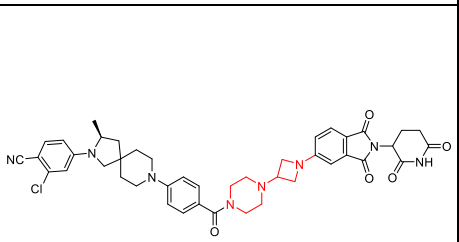
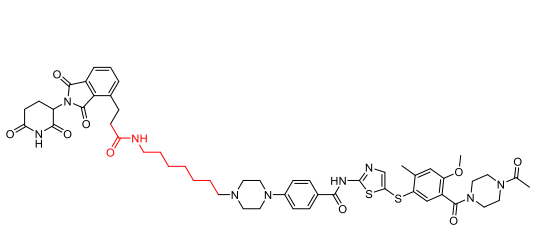
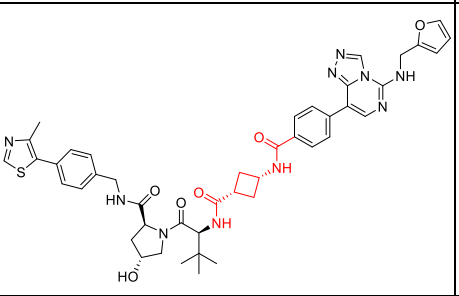
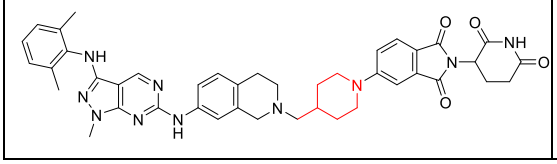
	251		252
	253		254
Rhodamine —YRCMISYGGADYKCIT —GSGS —ALAPYIP —RRRRRRRR	255	Rhodamine —GIQDT(R8)NSKKQS(S5)DTH —GSGS —ALAPYIP	256
	257		258
	259		260
	261		262
	263		264

	265		266
	267		268
	269		270
	271		272
	273		274
	275		276
	277		278
	279		280

	281		282
	283		284
	285		286
	287		288
	289		290
	291		292
	293		294

	295		296
	297		298
	299		300
	301		302
	303		304
	305		306

	307		308
	309		310
	311		312
	313		314
	315	 R=CCC GGC ATG GTT GCG GAG CAG GAG TAT AAC ACT ACC ATT G-3'	316
	317		318

	319		320
	321		322
	323		324
	325		326
	327		

Reference

1. Sakamoto KM, Kim KB, Kumagai A, Mercurio F, Crews CM, Deshaies RJ. Protacs: chimeric molecules that target proteins to the Skp1–Cullin–F box complex for ubiquitination and degradation. *Proc Natl Acad Sci USA* 2001;**98**:8554–8559.

2. Sakamoto KM, Kim KB, Verma R, Ransick A, Stein B, Crews CM, et al. Development of Protacs to target cancer–promoting proteins for ubiquitination and degradation. *Mol Cell Proteomics* 2003;**2**:1350–1358.

3. Schneekloth Jr JS, Fonseca FN, Koldobskiy M, Mandal A, Deshaies R, Sakamoto K, et al. Chemical genetic control of protein levels: selective in vivo targeted degradation. *J Am Chem Soc* 2004;**126**:3748–754.

4. Zhang D, Baek SH, Ho A, Lee H, Jeong YS, Kim K. Targeted degradation of proteins by small molecules: a novel tool for functional proteomics. *Comb Chem High T SCR* 2004;**7**:689–697.

5. Lee H, Puppala D, Choi EY, Swanson H, Kim KB. Targeted degradation of the aryl hydrocarbon receptor by the PROTAC approach: a useful chemical genetic tool. *Chembiochem* 2007;**8**:2058–2062.

6. Puppala D, Lee H, Kim KB, Swanson HI. Development of an aryl hydrocarbon receptor antagonist using the proteolysis–targeting chimeric molecules approach: a potential tool for chemoprevention. *Mol Pharmacol* 2008;**73**:1064–1071.

7. Rodriguez–Gonzalez A, Cyrus K, Salcius M, Kim K, Crews CM, Deshaies RJ, et al. Targeting steroid hormone receptors for ubiquitination and degradation in breast and prostate cancer. *Oncogene* 2008;**27**:7201–7211.

8. Cyrus K, Wehenkel M, Choi EY, Lee H, Swanson H, Kim KB. Jostling for position: optimizing linker location in the design of estrogen receptor–targeting PROTACs. *ChemMedChem* 2010;**5**:979–985.

9. Cyrus K, Wehenkel M, Choi EY, Han HJ, Lee H, Swanson H, et al. Impact of linker length on the activity of PROTACs. *Mol bioSyst* 2011;**7**:359–64.

10. Bondeson DP, Mares A, Smith IE, Ko E, Campos S, Miah AH, et al. Catalytic in vivo protein knockdown by small–molecule PROTACs. *Nat Chem Biol* 2015;**11**:611–7.

11. Winter GE, Buckley DL, Paulk J, Roberts JM, Souza A, Dhe–Paganon S, et al. DRUG DEVELOPMENT. Phthalimide conjugation as a strategy for *in vivo* target

protein degradation. *Science* 2015;**348**:1376–81.
12. Raina K, Lu J, Qian Y, Altieri M, Gordon D, Rossi AM, et al. PROTAC–induced BET protein degradation as a therapy for castration–resistant prostate cancer. *Proc Natl Acad Sci USA* 2016;**113**:7124–7129.
13. Wang X, Feng S, Fan J, Li X, Wen Q, Luo N. New strategy for renal fibrosis: Targeting Smad3 proteins for ubiquitination and degradation. *Biochem Pharmacol* 2016;**116**:200–209.
14. Robb CM, Contreras JI, Kour S, Taylor MA, Abid M, Sonawane YA, et al. Chemically induced degradation of CDK9 by a proteolysis targeting chimera (PROTAC). *Chem Commun* 2017;**53**:7577–7580.
15. Kang CH, Lee DH, Lee CO, Du Ha J, Park CH, Hwang JY. Induced protein degradation of anaplastic lymphoma kinase (ALK) by proteolysis targeting chimera (PROTAC). *Biochem Biophys Res Commun* 2018;**505**:542–547.
16. Bondeson DP, Smith BE, Burslem GM, Buhimschi AD, Hines J, Jaime–Figueroa S, et al. Lessons in PROTAC design from selective degradation with a promiscuous warhead. *Cell Chem Biol* 2018;**25**:78–87.e5.
17. Wang L, Guillen VS, Sharma N, Flessa K, Min J, Carlson KE, et al. New class of selective estrogen receptor degraders (SERDs): expanding the toolbox of PROTAC degrons. *ACS Med Chem Lett* 2018;**9**:803–808.
18. Qin C, Hu Y, Zhou B, Fernandez–Salas E, Yang CY, Liu L, et al. Discovery of QCA570 as an exceptionally potent and efficacious proteolysis targeting chimera (PROTAC). *J Med Chem* 2018;**61**:6685–6704.
19. Zhou B, Hu J, Xu F, Chen Z, Bai L, Fernandez–Salas E, et al. Discovery of a small–molecule degrader of bromodomain and extra–terminal (BET) proteins with picomolar cellular potencies and capable of achieving tumor regression. *J Med Chem* 2018;**61**:462–481.
20. Zhang C, Han XR, Yang X, Jiang B, Liu J, Xiong Y, et al. Proteolysis targeting chimeras (PROTACs) of anaplastic lymphoma kinase (ALK). *Eur J Med Chem*2018;**151**:304–314.
21. Ishoey M, Chorn S, Singh N, Jaeger MG, Brand M, Paulk J, et al. Translation termination factor GSPT1 is a phenotypically relevant off–target of heterobifunctional phthalimide degraders. *ACS Chem Biol* 2018;**13**:553–560.
22. Schneekloth AR, Pucheault M, Tae HS, Crews CM. Targeted intracellular protein degradation induced by a small molecule: En route to chemical proteomics. *Bioorg*

Med Chem Lett 2008;**18**:5904–5908.
23. Lu J, Qian Y, Altieri M, Dong H, Wang J, Raina K, et al. Hijacking the E3 ubiquitin ligase cereblon to efficiently target BRD4. *Chem Biol* 2015;**22**:755–763.
24. Gadd MS, Testa A, Lucas X, Chan KH, Chen W, Lamont DJ, et al. Structural basis of PROTAC cooperative recognition for selective protein degradation. *Nat Chem Biol* 2017;**13**:514–521.
25. Madak JT, Cuthbertson CR, Chen W, Showalter HD, Neamati N. Design, synthesis, and characterization of brequinar conjugates as probes to study DHODH inhibition. *Chemistry* 2017;**23**:13875–13878.
26. Burslem GM, Song J, Chen X, Hines J, Crews CM. Enhancing antiproliferative activity and selectivity of a FLT–3 inhibitor by proteolysis targeting chimera conversion. *J Am Chem Soc* 2018;**140**:16428–16432.
27. Zorba A, Nguyen C, Xu Y, Starr J, Borzilleri K, Smith J, et al. Delineating the role of cooperativity in the design of potent PROTACs for BTK. *Proc Natl Acad Sci USA* 2018;**115**:E7285–E7292.
28. Cromm PM, Samarasinghe KTG, Hines J, Crews CM. Addressing kinase–independent functions of fak via PROTAC–mediated degradation. *J Am Chem Soc* 2018;**140**:17019–17026.
29. Wang S, Song Y, Wang Y, Gao Y, Yu S, Zhao Q, et al. Design and synthesis of novel bispecific molecules for inducing BRD4 protein degradation. *Chem Res Chin Univ* 2018;**34**:67–74.
30. Testa A, Lucas X, Castro GV, Chan K–H, Wright JE, Runcie AC, et al. 3–Fluoro–4–hydroxyprolines: synthesis, conformational analysis, and stereoselective recognition by the VHL E3 ubiquitin ligase for targeted protein degradation. *J Am Chem Soc* 2018;**140**:9299–9313.
31. Buhimschi AD, Armstrong HA, Toure M, Jaime–Figueroa S, Chen TL, Lehman AM, et al. Targeting the C481S ibrutinib–resistance mutation in bruton's tyrosine kinase using PROTAC–mediated degradation. *Biochemistry* 2018;**57**:3564–3575.
32. Hatcher JM, Wang ES, Johannessen L, Kwiatkowski N, Sim T, Gray NS, et al. Development of highly potent and selective steroidal inhibitors and degraders of CDK8. *ACS Med Chem Lett* 2018;**9**:540–545.
33. Hines J, Lartigue S, Dong H, Qian Y, Crews CM. MDM2–recruiting PROTAC offers superior, synergistic antiproliferative activity via simultaneous degradation of BRD4 and stabilization of p53.Cancer Res 2019;**79**:251–262.

34. Lai AC, Toure M, Hellerschmied D, Salami J, Jaime–Figueroa S, Ko E, et al. Modular PROTAC design for the degradation of oncogenic BCR–ABL. *Angew Chem Int Ed* 2016;**55**:807–810.
35. McCoull W, Cheung T, Anderson E, Barton P, Burgess J, Byth K, et al. Development of a novel B–cell lymphoma 6 (BCL6) PROTAC to provide insight into small molecule targeting of BCL6. *ACS Chem Biol* 2018;**13**:3131–3141.
36. Chen H, Nguyen NH, Magtoto CM, Cobbold SA, Bidgood GM, Meza Guzman LG, et al. Design and characterization of a heterobifunctional degrader of KEAP1. *Redox Biol* 2023;**59**:102552.
37. Schiedel M, Herp D, Hammelmann S, Swyter S, Lehotzky A, Robaa D, et al. Chemically induced degradation of sirtuin 2 (Sirt2) by a proteolysis targeting chimera (PROTAC) based on sirtuin rearranging ligands (SirReals). *J Med Chem* 2018;**61**:482–491.
38. Bian J, Ren J, Li Y, Wang J, Xu X, Feng Y, et al. Discovery of Wogonin–based PROTACs against CDK9 and capable of achieving antitumor activity. *Bioorg Chem* 2018;**81**:373–381.
39. Yang K, Song Y, Xie H, Wu H, Wu YT, Leisten ED, et al. Development of the first small molecule histone deacetylase 6 (HDAC6) degraders. *Bioorg Med Chem Lett* 2018;**28**:2493–2497.
40. Sun Y, Zhao X, Ding N, Gao H, Wu Y, Yang Y, et al. PROTAC–induced BTK degradation as a novel therapy for mutated BTK C481S induced ibrutinib–resistant B–cell malignancies. *Cell Res* 2018;**28**:779–781.
41. Wurz RP, Dellamaggiore K, Dou H, Javier N, Lo MC, McCarter JD, et al. A "click chemistry platform" for the rapid synthesis of bispecific molecules for inducing protein degradation. *J Med Chem* 2018;**61**:453–461.
42. Chen H, Chen F, Liu N, Wang X, Gou S. Chemically induced degradation of CK2 by proteolysis targeting chimeras based on a ubiquitin–proteasome pathway. *Bioorg Chem* 2018;**81**:536–544.
43. Wu Y, Yang Y, Wang W, Sun D, Liang J, Zhu M, et al. PROTAC technology as a novel tool to identify the target of lathyrane diterpenoids. *Acta Pharm Sin B* 2022;**12**:4262–4265.
44. Tinworth CP, Lithgow H, Dittus L, Bassi ZI, Hughes SE, Muelbaier M, et al. PROTAC–mediated degradation of bruton's tyrosine kinase is inhibited by covalent binding. *ACS Chem Biol* 2019;**14**:342–347.

45. Zhang X, Thummuri D, He Y, Liu X, Zhang P, Zhou D, et al. Utilizing PROTAC technology to address the on–target platelet toxicity associated with inhibition of BCL–X(L). *Chem Commun* 2019;**55**:14765–14768.
46. Lebraud H, Wright DJ, Johnson CN, Heightman TD. Protein degradation by in–cell self–assembly of proteolysis targeting chimeras. *ACS Cent Sci* 2016;**2**:927–934.
47. Bassi ZI, Fillmore MC, Miah AH, Chapman TD, Maller C, Roberts EJ, et al. Modulating PCAF/GCN5 immune cell function through a PROTAC approach. *ACS Chem Biol* 2018;**13**:2862–2867.
48. Salami J, Alabi S, Willard RR, Vitale NJ, Wang J, Dong H, et al. Androgen receptor degradation by the proteolysis–targeting chimera ARCC–4 outperforms enzalutamide in cellular models of prostate cancer drug resistance. *Commun Biol* 2018;**1**:100.
49. Qiu X, Sun N, Kong Y, Li Y, Yang X, Jiang B. Chemoselective synthesis of lenalidomide–based PROTAC library using alkylation reaction. *Org Lett* 2019;**21**:3838–3841.
50. Yang J, Li Y, Aguilar A, Liu Z, Yang CY, Wang S. Simple structural modifications converting a bona fide MDM2 PROTAC degrader into a molecular glue molecule: a cautionary tale in the design of PROTAC degraders. *J Med Chem* 2019;**62**:9471–9487.
51. Testa A, Hughes SJ, Lucas X, Wright JE, Ciulli A. Structure–based design of a macrocyclic PROTAC. *Angew Chem Int Ed* 2020;**59**:1727–1734.
52. Da Y, Liu S, Lin P, Wang F, Yan R, Shu Y, et al. Design, synthesis, and biological evaluation of small molecule PROTACs for potential anticancer effects. *Med Chem Res* 2020;**29**:334–340.
53. Yang H, Lv W, He M, Deng H, Li H, Wu W, et al. Plasticity in designing PROTACs for selective and potent degradation of HDAC6. *Chem Commun* 2019;**55**:14848–14851.
54. Han X, Zhao L, Xiang W, Qin C, Miao B, Xu T, et al. Discovery of highly potent and efficient PROTAC degraders of androgen receptor (AR) by employing weak binding affinity VHL E3 ligase ligands. *J Med Chem* 2019;**62**:11218–11231.
55. Khan S, Zhang X, Lv D, Zhang Q, He Y, Zhang P, et al. A selective BCL–X(L) PROTAC degrader achieves safe and potent antitumor activity. *Nat Med* 2019;**25**:1938–1947.
56. Farnaby W, Koegl M, Roy MJ, Whitworth C, Diers E, Trainor N, et al. BAF

complex vulnerabilities in cancer demonstrated via structure–based PROTAC design. *Nat Chem Biol* 2019;**15**:672–680.
57. Zhao Q, Lan T, Su S, Rao Y. Induction of apoptosis in MDA–MB–231 breast Cancer Cells by a PARP1–targeting PROTAC small molecule. *Chem Commun* 2019;**55**:369–372.
58. Shanmugasundaram K, Shao P, Chen H, Campos B, McHardy SF, Luo T, et al. A modular PROTAC design for target destruction using a degradation signal based on a single amino acid. *J Biol Chem* 2019;**294**:15172–15175.
59. Krajcovicova S, Jorda R, Hendrychova D, Krystof V, Soural M. Solid–phase synthesis for thalidomide–based proteolysis–targeting chimeras (PROTAC). *Chem Commun* 2019;**55**:929–932.
60. Peng L, Zhang Z, Lei C, Li S, Zhang Z, Ren X, et al. Identification of new small–molecule inducers of estrogen–related receptor α (ERRα) degradation. *ACS Med Chem Lett* 2019;**10**:767–772.
61. Hu J, Hu B, Wang M, Xu F, Miao B, Yang CY, et al. Discovery of ERD–308 as a highly potent proteolysis targeting chimera (PROTAC) degrader of estrogen receptor (ER). *J Med Chem* 2019;**62**:1420–1442.
62. Kim SA, Go A, Jo SH, Park SJ, Jeon YU, Kim JE, et al. A novel cereblon modulator for targeted protein degradation. *Eur J Med Chem*2019;**166**:65–74.
63. Zhou H, Bai L, Xu R, Zhao Y, Chen J, McEachern D, et al. Structure–based discovery of SD–36 as a potent, selective, and efficacious PROTAC degrader of STAT3 protein. *J Med Chem* 2019;**62**:11280–112300.
64. Su S, Yang Z, Gao H, Yang H, Zhu S, An Z, et al. Potent and preferential degradation of CDK6 via proteolysis targeting chimera degraders. *J Med Chem* 2019;**62**:7575–7582.
65. Tovell H, Testa A, Zhou H, Shpiro N, Crafter C, Ciulli A, et al. Design and characterization of SGK3–PROTAC1, an isoform specific SGK3 kinase PROTAC degrader. *ACS Chem Biol* 2019;**14**:2024–2034.
66. Shi C, Zhang H, Wang P, Wang K, Xu D, Wang H, et al. PROTAC induced–BET protein degradation exhibits potent anti–osteosarcoma activity by triggering apoptosis. *Cell Death Dis* 2019;**10**:815.
67. Nunes J, McGonagle GA, Eden J, Kiritharan G, Touzet M, Lewell X, et al. Targeting IRAK4 for degradation with PROTACs. *ACS Med Chem Lett* 2019;**10**:1081–1085.

68. Zhao Q, Ren C, Liu L, Chen J, Shao Y, Sun N, et al. Discovery of SIAIS178 as an effective BCR–ABL degrader by recruiting von Hippel–Lindau (VHL) E3 ubiquitin ligase. *J Med Chem* 2019;**62**:9281–9298.
69. Chen H, Chen F, Pei S, Gou S. Pomalidomide hybrids act as proteolysis targeting chimeras: Synthesis, anticancer activity and B–Raf degradation. *Bioorg Chem* 2019;**87**:191–199.
70. Han X, Wang C, Qin C, Xiang W, Fernandez–Salas E, Yang CY, et al. Discovery of ARD–69 as a highly potent proteolysis targeting chimera (PROTAC) degrader of androgen receptor (AR) for the treatment of prostate cancer. *J Med Chem* 2019;**62**:941–964.
71. Burslem GM, Schultz AR, Bondeson DP, Eide CA, Savage Stevens SL, Druker BJ, et al. Targeting BCR–ABL1 in chronic myeloid leukemia by PROTAC–mediated targeted protein degradation. *Cancer Res* 2019;**79**:4744–4753.
72. Cieślak M, Kaźmierczak–Barańska J, Królewska–Golińska K, Napiórkowska M, Stukan I, Wojda U, et al. New thalidomide–resembling dicarboximides target ABC50 protein and show antileukemic and immunomodulatory activities. *Biomolecules* 2019;**9**.
73. Brand M, Jiang B, Bauer S, Donovan KA, Liang Y, Wang ES, et al. Homolog–selective degradation as a strategy to probe the function of CDK6 in AML. *Cell Chem Biol* 2019;**26**:300–306.e9.
74. Chi JJ, Li H, Zhou Z, Izquierdo–Ferrer J, Xue Y, Wavelet CM, et al. A novel strategy to block mitotic progression for targeted therapy. *EBioMedicine* 2019;**49**:40–54.
75. Li Y, Yang J, Aguilar A, McEachern D, Przybranowski S, Liu L, et al. Discovery of MD–224 as a first–in–class, highly potent, and efficacious proteolysis targeting chimera murine double minute 2 degrader capable of achieving complete and durable tumor regression. *J Med Chem* 2019;**62**:448–466.
76. Piya S, Mu H, Bhattacharya S, Lorenzi PL, Davis RE, McQueen T, et al. BETP degradation simultaneously targets acute myelogenous leukemia stem cells and the microenvironment. *J Clin Investig* 2019;**129**:1878–1894.
77. Bai L, Zhou H, Xu R, Zhao Y, Chinnaswamy K, McEachern D, et al. A potent and selective small–molecule degrader of STAT3 achieves complete tumor regression *in vivo*. *Cancer Cell* 2019;**36**:498–511.e17.
78. Wu H, Yang K, Zhang Z, Leisten ED, Li Z, Xie H, et al. Development of

multifunctional histone deacetylase 6 degraders with potent antimyeloma activity. *J Med Chem* 2019;**62**:7042–7057.
79. Maneiro MA, Forte N, Shchepinova MM, Kounde CS, Chudasama V, Baker JR, et al. Antibody–PROTAC conjugates enable HER2–dependent targeted protein degradation of BRD4. *ACS Chem Biol* 2020;**15**:1306–1312.
80. Hong JY, Jing H, Price IR, Cao J, Bai JJ, Lin H, et al. Simultaneous inhibition of SIRT2 deacetylase and defatty–acylase activities via a PROTAC Strategy. *ACS Med Chem Lett* 2020;**11**:2305–2311.
81. Hu M, Zhou W, Wang Y, Yao D, Ye T, Yao Y, et al. Discovery of the first potent proteolysis targeting chimera (PROTAC) degrader of indoleamine 2,3–dioxygenase 1. *Acta Pharm Sin B* 2020;**10**:1943–1953.
82. Bond MJ, Chu L, Nalawansha DA, Li K, Crews CM, Zhao HY, et al. Targeted degradation of oncogenic KRAS(G12C) by VHL–recruiting PROTACs. *ACS Cent Sci* 2020;**6**:1367–1375.
83. Degorce SL, Tavana O, Banks E, Crafter C, Gingipalli L, Kouvchinov D, et al. Discovery of proteolysis–targeting chimera molecules that selectively degrade the IRAK3 pseudokinase. *J Med Chem* 2020;**63**:10460–10473.
84. Gao H, Wu Y, Sun Y, Yang Y, Zhou G, Rao Y. Design, synthesis, and evaluation of highly potent FAK–targeting PROTACs. *ACS Med Chem Lett* 2020;**11**:1855–1862.
85. Liu Y, Zhen Y, Wang G, Yang G, Fu L, Liu B, et al. Designing an eEF2K–Targeting PROTAC small molecule that induces apoptosis in MDA–MB–231 cells. *Eur J Med Chem*2020;**204**:112505.
86. Liu S, Da Y, Wang F, Yan R, Shu Y, Lin P, et al. Targeted selective degradation of Bruton's tyrosine kinase by PROTACs. *Med Chem Res* 2020;**29**:802–808.
87. Wang K, Zhou H. Proteolysis targeting chimera (PROTAC) for epidermal growth factor receptor enhances anti–tumor immunity in non–small cell lung cancer. *Drug Dev Res* 2021;**82**:422–429.
88. Zhou F, Chen L, Cao C, Yu J, Luo X, Zhou P, et al. Development of selective mono or dual PROTAC degrader probe of CDK isoforms. *Eur J Med Chem*2020;**187**:111952.
89. Zhang F, Wu Z, Chen P, Zhang J, Wang T, Zhou J, et al. Discovery of a new class of PROTAC BRD4 degraders based on a dihydroquinazolinone derivative and lenalidomide/pomalidomide. *Bioorg Med Chem* 2020;**28**:115228.
90. Zhang X, Thummuri D, Liu X, Hu W, Zhang P, Khan S, et al. Discovery of

PROTAC BCL–X(L) degraders as potent anticancer agents with low on–target platelet toxicity. *Eur J Med Chem*2020;**192**:112186.
91. Posternak G, Tang X, Maisonneuve P, Jin T, Lavoie H, Daou S, et al. Functional characterization of a PROTAC directed against BRAF mutant V600E. *Nat Chem Biol* 2020;**16**:1170–1178.
92. Takwale AD, Jo SH, Jeon YU, Kim HS, Shin CH, Lee HK, et al. Design and characterization of cereblon–mediated androgen receptor proteolysis–targeting chimeras. *Eur J Med Chem*2020;**208**:112769.
93. Zhang X, He Y, Zhang P, Budamagunta V, Lv D, Thummuri D, et al. Discovery of IAP–recruiting BCL–X(L) PROTACs as potent degraders across multiple cancer cell lines. *Eur J Med Chem*2020;**199**:112397.
94. He Y, Zhang X, Chang J, Kim HN, Zhang P, Wang Y, et al. Using proteolysis–targeting chimera technology to reduce navitoclax platelet toxicity and improve its senolytic activity. *Nat Commun* 2020;**11**:1996.
95. Cao F, de Weerd S, Chen D, Zwinderman MRH, van der Wouden PE, Dekker FJ. Induced protein degradation of histone deacetylases 3 (HDAC3) by proteolysis targeting chimera (PROTAC). *Eur J Med Chem*2020;**208**:112800.
96. Schiedel M, Lehotzky A, Szunyogh S, Oláh J, Hammelmann S, Wössner N, et al. HaloTag–targeted sirtuin–rearranging ligand (SirReal) for the development of proteolysis–targeting chimeras (PROTACs) against the lysine deacetylase sirtuin 2 (Sirt2)*. *Chembiochem* 2020;**21**:3371–3376.
97. Cheng J, Li Y, Wang X, Dong G, Sheng C. Discovery of novel PDEδ degraders for the treatment of KRAS mutant colorectal cancer. *J Med Chem* 2020;**63**:7892–7905.
98. Jin YH, Lu MC, Wang Y, Shan WX, Wang XY, You QD, et al. Azo–PROTAC: novel light–controlled small–molecule tool for protein knockdown. *J Med Chem* 2020;**63**:4644–4654.
99. Sun N, Ren C, Kong Y, Zhong H, Chen J, Li Y, et al. Development of a brigatinib degrader (SIAIS117) as a potential treatment for ALK positive cancer resistance. *Eur J Med Chem*2020;**193**:112190.
100. Jiang F, Wei Q, Li H, Li H, Cui Y, Ma Y, et al. Discovery of novel small molecule induced selective degradation of the bromodomain and extra–terminal (BET) bromodomain protein BRD4 and BRD2 with cellular potencies. *Bioorg Med Chem* 2020;**28**:115181.

101. Li MX, Yang Y, Zhao Q, Wu Y, Song L, Yang H, et al. Degradation versus inhibition: development of proteolysis–targeting chimeras for overcoming statin–induced compensatory upregulation of 3–hydroxy–3–methylglutaryl coenzyme a reductase. *J Med Chem* 2020;**63**:4908–4928.
102. Zhao L, Han X, Lu J, McEachern D, Wang S. A highly potent PROTAC androgen receptor (AR) degrader ARD–61 effectively inhibits AR–positive breast cancer cell growth in vitro and tumor growth *in vivo*. *Neoplasia* 2020;**22**:522–532.
103. Zhao HY, Yang XY, Lei H, Xi XX, Lu SM, Zhang JJ, et al. Discovery of potent small molecule PROTACs targeting mutant EGFR. *Eur J Med Chem*2020;**208**:112781.
104. Xiao Y, Wang J, Zhao LY, Chen X, Zheng G, Zhang X, et al. Discovery of histone deacetylase 3 (HDAC3)–specific PROTACs. *Chem Commun* 2020;**56**:9866–9869.
105. Wang M, Lu J, Wang M, Yang CY, Wang S, Yan G, et al. Correction to "discovery of SHP2–D26 as a first, potent, and effective PROTAC degrader of SHP2 protein". *J Med Chem* 2021;**64**:906–908.
106. Zhou L, Chen W, Cao C, Shi Y, Ye W, Hu J, et al. Design and synthesis of α–naphthoflavone chimera derivatives able to eliminate cytochrome P450 (CYP)1B1–mediated drug resistance via targeted CYP1B1 degradation. *Eur J Med Chem*2020;**189**:112028.
107. Cao C, Yang J, Chen Y, Zhou P, Wang Y, Du W, et al. Discovery of SK–575 as a highly potent and efficacious proteolysis–targeting chimera degrader of PARP1 for treating cancers. *J Med Chem* 2020;**63**:11012–11033.
108. Vollmer S, Cunoosamy D, Lv H, Feng H, Li X, Nan Z, et al. Design, synthesis, and biological evaluation of MEK PROTACs. *J Med Chem* 2020;**63**:157–162.
109. Donoghue C, Cubillos–Rojas M, Gutierrez–Prat N, Sanchez–Zarzalejo C, Verdaguer X, Riera A, et al. Optimal linker length for small molecule PROTACs that selectively target p38α and p38β for degradation. *Eur J Med Chem*2020;**201**:112451.
110. Xie H, Liang JJ, Wang YL, Hu TX, Wang JY, Yang RH, et al. The design, synthesis and anti–tumor mechanism study of new androgen receptor degrader. *Eur J Med Chem*2020;**204**:112512.
111. Li Z, Lin Y, Song H, Qin X, Yu Z, Zhang Z, et al. First small–molecule PROTACs for G protein–coupled receptors: inducing α (1A)–adrenergic receptor degradation. *Acta Pharm Sin B* 2020;**10**:1669–1679.

112. You I, Erickson EC, Donovan KA, Eleuteri NA, Fischer ES, Gray NS, et al. Discovery of an AKT Degrader with prolonged inhibition of downstream signaling. *Cell Chem Biol* 2020;**27**:66–73.e7.
113. Bensimon A, Pizzagalli MD, Kartnig F, Dvorak V, Essletzbichler P, Winter GE, et al. Targeted degradation of SLC transporters reveals amenability of multi–pass transmembrane proteins to ligand–induced proteolysis. *Cell Chem Biol* 2020;**27**:728–739.e9.
114. Gonzalez TL, Hancock M, Sun S, Gersch CL, Larios JM, David W, et al. Targeted degradation of activating estrogen receptor α ligand–binding domain mutations in human breast cancer. *Breast Cancer Res Treat* 2020;**180**:611–622.
115. Potjewyd F, Turner AW, Beri J, Rectenwald JM, Norris–Drouin JL, Cholensky SH, et al. Degradation of polycomb repressive complex 2 with an EED–targeted bivalent chemical degrader. *Cell Chem Biol* 2020;**27**:47–56.e15.
116. Cheng W, Li S, Wen X, Han S, Wang S, Wei H, et al. Development of hypoxia–activated PROTAC exerting a more potent effect in tumor hypoxia than in normoxia. *Chem Commun* 2021;**57**:12852–12855.
117. Liu J, Xue L, Xu X, Luo J, Zhang S. FAK–targeting PROTAC demonstrates enhanced antitumor activity against KRAS mutant non–small cell lung cancer. *Experimental Cell Res* 2021;**408**:112868.
118. Wei M, Zhao R, Cao Y, Wei Y, Li M, Dong Z, et al. First orally bioavailable prodrug of proteolysis targeting chimera (PROTAC) degrades cyclin–dependent kinases 2/4/6 in vivo. *Eur J Med Chem*2021;**209**:112903.
119. King HM, Rana S, Kubica SP, Mallareddy JR, Kizhake S, Ezell EL, et al. Aminopyrazole based CDK9 PROTAC sensitizes pancreatic cancer cells to venetoclax. *Bioorg Med Chem Lett* 2021;**43**:128061.
120. Gama–Brambila RA, Chen J, Zhou J, Tascher G, Münch C, Cheng X. A PROTAC targets splicing factor 3B1. *Cell Chem Biol* 2021;**28**:1616–1627.e8.
121. Weng G, Shen C, Cao D, Gao J, Dong X, He Q, et al. PROTAC–DB: an online database of PROTACs. *Nucleic acids research* 2021;**49**:D1381–D1387.
122. Yokoo H, Shibata N, Naganuma M, Murakami Y, Fujii K, Ito T, et al. Development of a hematopoietic prostaglandin D synthase–degradation inducer. *ACS Med Chem Lett* 2021;**12**:236–241.
123. Zheng M, Liu Y, Wu C, Yang K, Wang Q, Zhou Y, et al. Novel PROTACs for degradation of SHP2 protein. *Bioorg Chem* 2021;**110**:104788.

124. Min J, Mayasundari A, Keramatnia F, Jonchere B, Yang SW, Jarusiewicz J, et al. Phenyl–glutarimides: alternative cereblon binders for the design of PROTACs. *Angew Chem Int Ed* 2021;**60**:26663–26670.
125. Kim GY, Song CW, Yang YS, Lee NR, Yoo HS, Son SH, et al. Chemical degradation of androgen receptor (AR) using bicalutamide analog–thalidomide PROTACs. *Molecules* 2021;**26**.
126. Atilaw Y, Poongavanam V, Svensson Nilsson C, Nguyen D, Giese A, Meibom D, et al. Solution conformations shed light on PROTAC cell permeability. *ACS Med Chem Lett* 2021;**12**:107–114.
127. Xiao Z, Song S, Chen D, van Merkerk R, van der Wouden PE, Cool RH, et al. Proteolysis targeting chimera (PROTAC) for macrophage migration inhibitory factor (MIF) has anti–proliferative activity in lung cancer cells. *Angew Chem Int Ed* 2021;**60**:17514–17521.
128. Han X, Zhao L, Xiang W, Qin C, Miao B, McEachern D, et al. Strategies toward discovery of potent and orally bioavailable proteolysis targeting chimera degraders of androgen receptor for the treatment of prostate cancer. *J Med Chem* 2021;**64**:12831–12854.
129. Yang X, Wang Z, Pei Y, Song N, Xu L, Feng B, et al. Discovery of thalidomide–based PROTAC small molecules as the highly efficient SHP2 degraders. *Eur J Med Chem*2021;**218**:113341.
130. Xu H, Ohoka N, Yokoo H, Nemoto K, Ohtsuki T, Matsufuji H, et al. Development of agonist–based PROTACs targeting liver X receptor. *Front Chem* 2021;**9**:674967.
131. Wei J, Meng F, Park KS, Yim H, Velez J, Kumar P, et al. Harnessing the E3 ligase KEAP1 for targeted protein degradation. *J Am Chem Soc* 2021;**143**:15073–15083.
132. Cao Z, Gu Z, Lin S, Chen D, Wang J, Zhao Y, et al. Attenuation of NLRP3 inflammasome activation by indirubin–derived PROTAC targeting HDAC6. *ACS Chem Biol* 2021;**16**:2746–2751.
133. Pal P, Thummuri D, Lv D, Liu X, Zhang P, Hu W, et al. Discovery of a novel BCL–X(L) PROTAC degrader with enhanced BCL–2 inhibition. *J Med Chem* 2021;**64**:14230–1446.
134. Qiu X, Li Y, Yu B, Ren J, Huang H, Wang M, et al. Discovery of selective CDK9 degraders with enhancing antiproliferative activity through PROTAC conversion. *Eur*

*J Med Chem*2021;**211**:113091.
135. Chen L, Han L, Mao S, Xu P, Xu X, Zhao R, et al. Discovery of A031 as effective proteolysis targeting chimera (PROTAC) androgen receptor (AR) degrader for the treatment of prostate cancer. *Eur J Med Chem*2021;**216**:113307.
136. Xiang W, Wang Q, Ran K, Ren J, Shi Y, Yu L. Structure–guided discovery of novel potent and efficacious proteolysis targeting chimera (PROTAC) degrader of BRD4. *Bioorg Chem* 2021;**115**:105238.
137. Law RP, Nunes J, Chung CW, Bantscheff M, Buda K, Dai H, et al. Discovery and Characterisation of Highly Cooperative FAK–Degrading PROTACs. *Angew Chem Int Ed* 2021;**60**:23327–23334.
138. Lee GT, Nagaya N, Desantis J, Madura K, Sabaawy HE, Kim WJ, et al. Effects of MTX–23, a novel PROTAC of androgen receptor splice variant–7 and androgen receptor, on crpc resistant to second–line antiandrogen therapy. *Mol Cancer Ther* 2021;**20**:490–499.
139. Qi Z, Yang G, Deng T, Wang J, Zhou H, Popov SA, et al. Design and linkage optimization of ursane–thalidomide–based PROTACs and identification of their targeted–degradation properties to MDM2 protein. *Bioorg Chem* 2021;**111**:104901.
140. Yan G, Zhong X, Yue L, Pu C, Shan H, Lan S, et al. Discovery of a PROTAC targeting ALK with in vivo activity. *Eur J Med Chem*2021;**212**:113150.
141. Yokoo H, Shibata N, Endo A, Ito T, Yanase Y, Murakami Y, et al. Discovery of a highly potent and selective degrader targeting hematopoietic prostaglandin D synthase via in silico design. *J Med Chem* 2021;**64**:15868–15882.
142. Li L, Wu Y, Yang Z, Xu C, Zhao H, Liu J, et al. Discovery of KRas G12C–IN–3 and pomalidomide–based PROTACs as degraders of endogenous KRAS G12C with potent anticancer activity. *Bioorg Chem* 2021;**117**:105447.
143. Liu Z, Hu X, Wang Q, Wu X, Zhang Q, Wei W, et al. Design and synthesis of EZH2–based PROTACs to degrade the PRC2 complex for targeting the noncatalytic activity of EZH2. *J Med Chem* 2021;**64**:2829–2848.
144. Wang B, Liu J, Tandon I, Wu S, Teng P, Liao J, et al. Development of MDM2 degraders based on ligands derived from Ugi reactions: Lessons and discoveries. *Eur J Med Chem*2021;**219**:113425.
145. Wang Y, Zhou Y, Cao S, Sun Y, Dong Z, Li C, et al. *In vitro* and *in vivo* degradation of programmed cell death ligand 1 (PD–L1) by a proteolysis targeting chimera (PROTAC). *Bioorg Chem* 2021;**111**:104833.

146. Ren C, Sun N, Liu H, Kong Y, Sun R, Qiu X, et al. Discovery of a brigatinib degrader SIAIS164018 with destroying metastasis–related oncoproteins and a reshuffling kinome profile. *J Med Chem* 2021;**64**:9152–9165.
147. Hanafi M, Chen X, Neamati N. Discovery of a napabucasin PROTAC as an effective degrader of the E3 ligase ZFP91. *J Med Chem* 2021;**64**:1626–1648.
148. Xiao L, Parolia A, Qiao Y, Bawa P, Eyunni S, Mannan R, et al. Targeting SWI/SNF ATPases in enhancer–addicted prostate cancer. *Nature* 2022;**601**:434–439.
149. Zhao Y, Shu Y, Lin J, Chen Z, Xie Q, Bao Y, et al. Discovery of novel BTK PROTACs for B–Cell lymphomas. *Eur J Med Chem*2021;**225**:113820.
150. Yang C, Yang Y, Li Y, Ni Q, Li J. Radiotherapy–triggered proteolysis targeting chimera prodrug activation in tumors. *J Am Chem Soc* 2023;**145**:385–391.
151. Xiong Y, Zhong Y, Yim H, Yang X, Park KS, Xie L, et al. Bridged proteolysis targeting chimera (PROTAC) enables degradation of undruggable targets. *J Am Chem Soc* 2022;**144**:22622–22632.
152. Gao J, Hou B, Zhu Q, Yang L, Jiang X, Zou Z, et al. Engineered bioorthogonal POLY–PROTAC nanoparticles for tumour–specific protein degradation and precise cancer therapy. *Nat Commun* 2022;**13**:4318.
153. Yang J, Ruan Y, Wang D, Fan J, Luo N, Chen H, et al. VHL–recruiting PROTAC attenuates renal fibrosis and preserves renal function via simultaneous degradation of Smad3 and stabilization of HIF–2α. *Cell Biosci* 2022;**12**:203.
154. Xu H, Kurohara T, Takano R, Yokoo H, Shibata N, Ohoka N, et al. Development of rapid and facile solid–phase synthesis of PROTACs via a variety of binding styles. *ChemistryOpen* 2022;**11**:e202200131.
155. Chotitumnavee J, Yamashita Y, Takahashi Y, Takada Y, Iida T, Oba M, et al. Selective degradation of histone deacetylase 8 mediated by a proteolysis targeting chimera (PROTAC). *Chem Commun* 2022;**58**:4635–4638.
156. Wang H, Li C, Liu X, Ma M. Design, synthesis and activity study of a novel PI3K degradation by hijacking VHL E3 ubiquitin ligase. *Bioorg Med Chem* 2022;**61**:116707.
157. Liu F, Wang X, Duan J, Hou Z, Wu Z, Liu L, et al. A temporal PROTAC cocktail–mediated sequential degradation of AURKA abrogates acute myeloid leukemia stem cells. *Adv Sci* 2022;**9**:e2104823.
158. Sun Y, Wang R, Sun Y, Wang L, Xue Y, Wang J, et al. Identification of novel and potent PROTACs targeting FAK for non–small cell lung cancer: design, synthesis,

and biological study. *Eur J Med Chem*2022;**237**:114373.
159. Huber ME, Toy L, Schmidt MF, Vogt H, Budzinski J, Wiefhoff MFJ, et al. A chemical biology toolbox targeting the intracellular binding site of CCR9: fluorescent ligands, new drug leads and PROTACs. *Angew Chem Int Ed* 2022;**61**:e202116782.
160. Dale B, Anderson C, Park KS, Kaniskan H, Ma A, Shen Y, et al. Targeting triple–negative breast cancer by a novel proteolysis targeting chimera degrader of enhancer of zeste homolog 2. *ACS Pharmacol Transl Sci* 2022;**5**:491–507.
161. Cantley J, Ye X, Rousseau E, Januario T, Hamman BD, Rose CM, et al. Selective PROTAC–mediated degradation of SMARCA2 is efficacious in SMARCA4 mutant cancers. *Nat Commun* 2022;**13**:6814.
162. Wang XR, Wang S, Mu HX, Xu KY, Wang XT, Shi JT, et al. Discovery of novel VEGFR–2–PROTAC degraders based on the localization of lysine residues via recruiting VHL for the treatment of gastric cancer. *Eur J Med Chem*2022;**244**:114821.
163. Cheng J, He S, Xu J, Huang M, Dong G, Sheng C. Making protein degradation visible: discovery of theranostic PROTACs for detecting and degrading NAMPT. *J Med Chem* 2022;**65**:15725–15737.
164. Chen Y, Yuan X, Tang M, Shi M, Yang T, Liu K, et al. Degrading FLT3–ITD protein by proteolysis targeting chimera (PROTAC). *Bioorg Chem* 2022;**119**:105508.
165. Si R, Liu N, Wang J, Zhang Q, Li Y, Pan X, et al. Discovery of selective platelet–derived growth factor receptor–beta (PDGFR–β) bifunctional small–molecule degraders. *Bioorg Med Chem* 2023;**77**:117115.
166. Cross JM, Coulson ME, Smalley JP, Pytel WA, Ismail O, Trory JS, et al. A 'click' chemistry approach to novel entinostat (MS–275) based class I histone deacetylase proteolysis targeting chimeras. *RSC Med Chem* 2022;**13**:1634–1639.
167. Pei Y, Fu J, Shi Y, Zhang M, Luo G, Luo X, et al. Discovery of a potent and selective degrader for USP7. *Angew Chem Int Ed* 2022;**61**:e202204395.
168. Gockel LM, Pfeifer V, Baltes F, Bachmaier RD, Wagner KG, Bendas G, et al. Design, synthesis, and characterization of PROTACs targeting the androgen receptor in prostate and lung cancer models. *Arch Pharm* 2022;**355**:e2100467.
169. Zhu CL, Luo X, Tian T, Rao Z, Wang H, Zhou Z, et al. Structure–based rational design enables efficient discovery of a new selective and potent AKT PROTAC degrader. *Eur J Med Chem*2022;**238**:114459.
170. Luo T, Zheng Q, Shao L, Ma T, Mao L, Wang M. Intracellular delivery of glutathione peroxidase degrader induces ferroptosis *in vivo*. *Angew Chem Int Ed*

2022;**61**:e202206277.
171. Guo L, Liu J, Nie X, Wang T, Ma ZX, Yin D, et al. Development of selective FGFR1 degraders using a rapid synthesis of proteolysis targeting chimera (Rapid–TAC) platform. *Bioorg Med Chem Lett* 2022;**75**:128982.
172. Wang C, Wang H, Zheng C, Li B, Liu Z, Zhang L, et al. Discovery of coumarin–based MEK1/2 PROTAC effective in human cancer cells. *ACS Med Chem Lett* 2023;**14**:92–102.
173. Ding M, Shao Y, Sun D, Meng S, Zang Y, Zhou Y, et al. Design, synthesis, and biological evaluation of BRD4 degraders. *Bioorg Med Chem* 2023;**78**:117134.
174. Qin Q, Wang R, Fu Q, Zhang G, Wu T, Liu N, et al. Design, synthesis, and biological evaluation of potent FAK–degrading PROTACs. *J Enzyme Inhib Med Chem* 2022;**37**:2241–2255.
175. Li G, Lin SS, Yu ZL, Wu XH, Liu JW, Tu GH, et al. A PARP1 PROTAC as a novel strategy against PARP inhibitor resistance via promotion of ferroptosis in p53–positive breast cancer. *Biochem Pharmacol* 2022;**206**:115329.
176. Shi S, Du Y, Zou Y, Niu J, Cai Z, Wang X, et al. Rational design for nitroreductase (NTR)–responsive proteolysis targeting chimeras (PROTACs) selectively targeting tumor tissues. *J Med Chem* 2022;**65**:5057–5071.
177. Niu T, Li K, Jiang L, Zhou Z, Hong J, Chen X, et al. Noncovalent CDK12/13 dual inhibitors–based PROTACs degrade CDK12–Cyclin K complex and induce synthetic lethality with PARP inhibitor. *Eur J Med Chem*2022;**228**:114012.
178. Li Q, Guo Q, Wang S, Wan S, Li Z, Zhang J, et al. Design and synthesis of proteolysis targeting chimeras (PROTACs) as an EGFR degrader based on CO–1686. *Eur J Med Chem*2022;**238**:114455.
179. Shi S, Du Y, Huang L, Cui J, Niu J, Xu Y, et al. Discovery of novel potent covalent inhibitor–based EGFR degrader with excellent in vivo efficacy. *Bioorg Chem* 2022;**120**:105605.
180. Liu J, Yuan L, Ruan Y, Deng B, Yang Z, Ren Y, et al. Novel CRBN–recruiting proteolysis–targeting chimeras as degraders of stimulator of interferon genes with *in vivo* anti–inflammatory efficacy. *J Med Chem* 2022;**65**:6593–6611.
181. Yu X, Cheng M, Lu K, Shen Y, Zhong Y, Liu J, et al. Exploring degradation of mutant and wild–type epidermal growth factor receptors induced by proteolysis–targeting chimeras. *J Med Chem* 2022;**65**:8416–8443.
182. Sun Y, Zhang Y, Chen X, Yu A, Du W, Huang Y, et al. Discovery of a potent and

selective proteolysis targeting chimera (PROTAC) degrader of NSD3 histone methyltransferase. *Eur J Med Chem*2022;**239**:114528.
183. Kargbo RB. Potent PROTACs targeting EGFR mutants in drug discovery. *ACS Med Chem Lett* 2022;**13**:1835–1836.
184. Liu Q, Tu G, Hu Y, Jiang Q, Liu J, Lin S, et al. Discovery of BP3 as an efficacious proteolysis targeting chimera (PROTAC) degrader of HSP90 for treating breast cancer. *Eur J Med Chem*2022;**228**:114013.
185. Darwish S, Ghazy E, Heimburg T, Herp D, Zeyen P, Salem–Altintas R, et al. Design, synthesis and biological characterization of histone deacetylase 8 (HDAC8) proteolysis targeting chimeras (PROTACs) with anti–neuroblastoma activity. *Int J Mol Sci* 2022;**23**.
186. Sachkova AA, Andreeva DV, Tikhomirov AS, Scherbakov AM, Salnikova DI, Sorokin DV, et al. Design, synthesis and *in vitro* investigation of cabozantinib–based PROTACs to target c–Met kinase. *Pharmaceutics* 2022;**14**.
187. Řezníčková E, Krajčovičová S, Peřina M, Kovalová M, Soural M, Kryštof V. Modulation of FLT3–ITD and CDK9 in acute myeloid leukaemia cells by novel proteolysis targeting chimera (PROTAC). *Eur J Med Chem*2022;**243**:114792.
188. Luo G, Li X, Lin X, Lu X, Li Z, Xiang H. Novel 11β–substituted estradiol conjugates: transition from ERα agonizts to effective PROTAC degraders. *J Steroid Biochem Mol Biol* 2022;**223**:106154.
189. Bollu LR, Bommi PV, Monsen PJ, Zhai L, Lauing KL, Bell A, et al. Identification and characterization of a novel indoleamine 2,3–dioxygenase 1 protein degrader for glioblastoma. *J Med Chem* 2022;**65**:15642–15662.
190. Liu H, Ren C, Sun R, Wang H, Zhan Y, Yang X, et al. Reactive oxygen species–responsive Pre–PROTAC for tumor–specific protein degradation. *Chem Commun* 2022;**58**:10072–10075.
191. Zhang L, Li L, Wang X, Liu H, Zhang Y, Xie T, et al. Development of a novel PROTAC using the nucleic acid aptamer as a targeting ligand for tumor selective degradation of nucleolin. *Mol Ther Nucleic Acids* 2022;**30**:66–79.
192. Pu C, Wang S, Luo D, Liu Y, Ma X, Zhang H, et al. Synthesis and biological evaluation of a tumor–selective degrader of PARP1. *Bioorg Med Chem* 2022;**69**:116908.
193. Lier S, Sellmer A, Orben F, Heinzlmeir S, Krauß L, Schneeweis C, et al. A novel cereblon E3 ligase modulator with antitumor activity in gastrointestinal cancer.

Bioorg Chem 2022;**119**:105505.
194. Durbin AD, Wang T, Wimalasena VK, Zimmerman MW, Li D, Dharia NV, et al. EP300 selectively controls the enhancer landscape of MYCN–amplified neuroblastoma. *Cancer Discov* 2022;**12**:730–751.
195. Baker IM, Smalley JP, Sabat KA, Hodgkinson JT, Cowley SM. Comprehensive transcriptomic analysis of novel class I HDAC proteolysis targeting chimeras (PROTACs). *Biochemistry* 2023;**62**:645–656.
196. Kofink C, Trainor N, Mair B, Wöhrle S, Wurm M, Mischerikow N, et al. A selective and orally bioavailable VHL–recruiting PROTAC achieves SMARCA2 degradation in vivo. *Nat Commun* 2022;**13**:5969.
197. Zhou Q, Wu W, Jia K, Qi G, Sun XS, Li P. Design and characterization of PROTAC degraders specific to protein N–terminal methyltransferase 1. *Eur J Med Chem*2022;**244**:114830.
198. Alcock LJ, Chang Y, Jarusiewicz JA, Actis M, Nithianantham S, Mayasundari A, et al. Development of potent and selective janus kinase 2/3 directing PG–PROTACs. *ACS Med Chem Lett* 2022;**13**:475–482.
199. Zhang W, Li P, Sun S, Jia C, Yang N, Zhuang X, et al. Discovery of highly potent and selective CRBN–recruiting EGFR(L858R/T790M) degraders in vivo. *Eur J Med Chem*2022;**238**:114509.
200. Zhai J, Li C, Sun B, Wang S, Cui Y, Gao Q, et al. Sunitinib–based proteolysis targeting chimeras (PROTACs) reduced the protein levels of FLT–3 and c–KIT in leukemia cell lines. *Bioorg Med Chem Lett* 2022;**78**:129041.
201. Li X, Yao Y, Wu F, Song Y. A proteolysis–targeting chimera molecule selectively degrades ENL and inhibits malignant gene expression and tumor growth. *J Hematol Oncol* 2022;**15**:41.
202. Li H, Wang L, Cao F, Yu D, Yang J, Yu X, et al. Design, synthesis, and biological characterization of a potent STAT3 degrader for the treatment of gastric cancer. *Front Pharmacol* 2022;**13**:944455.
203. Nalawansha DA, Li K, Hines J, Crews CM. Hijacking methyl reader proteins for nuclear–specific protein degradation. *J Am Chem Soc* 2022;**144**:5594–605.
204. Yu X, Xu J, Shen Y, Cahuzac KM, Park KS, Dale B, et al. Discovery of potent, selective, and *in vivo* efficacious AKT kinase protein degraders via structure–activity relationship studies. *J Med Chem* 2022;**65**:3644–3666.
205. Sun N, Kabir M, Lee Y, Xie L, Hu X, Velez J, et al. Discovery of the first lactate

dehydrogenase proteolysis targeting chimera degrader for the treatment of pancreatic cancer. *J Med Chem* 2023;**66**:596–610.
206. Do TC, Lau JW, Sun C, Liu S, Kha KT, Lim ST, et al. Hypoxia deactivates epigenetic feedbacks via enzyme–derived clicking proteolysis–targeting chimeras. *Sci Adv* 2022;**8**:eabq2216.
207. Henning NJ, Manford AG, Spradlin JN, Brittain SM, Zhang E, McKenna JM, et al. Discovery of a covalent FEM1B recruiter for targeted protein degradation applications. *J Am Chem Soc* 2022;**144**:701–708.
208. Huber AD, Li Y, Lin W, Galbraith AN, Mishra A, Porter SN, et al. SJPYT–195: A designed nuclear receptor degrader that functions as a molecular glue degrader of GSPT1. *ACS Med Chem Lett* 2022;**13**:1311–1320.
209. Munoz E, Chen G, Hossain A, Wu S, Oceguera Nava E, Hang J, et al. Synthesis and biological evaluation of niclosamide PROTACs. *Bioorg Med Chem Lett* 2022;**72**:128870.
210. Wang P, Zhu H, Liu J, Xie S, Xu S, Chen Y, et al. Design, synthesis, and biological evaluation of novel protopanoxadiol derivatives based PROTACs technology for the treatment of lung cancer. *Bioorg Chem* 2023;**131**:106327.
211. Zhang J, Che J, Luo X, Wu M, Kan W, Jin Y, et al. Structural feature analyzation strategies toward discovery of orally bioavailable PROTACs of bruton's tyrosine kinase for the treatment of lymphoma. *J Med Chem* 2022;**65**:9096–9125.
212. Ohoka N, Suzuki M, Uchida T, Tsukumo Y, Yoshida M, Inoue T, et al. Development of a potent small–molecule degrader against oncogenic BRAF(V600E) protein that evades paradoxical MAPK activation. *Cancer Sci* 2022;**113**:2828–2838.
213. Meng F, Xu C, Park KS, Kaniskan H, Wang GG, Jin J. Discovery of a first–in–class degrader for nuclear receptor binding SET domain protein 2 (NSD2) and ikaros/aiolos. *J Med Chem* 2022;**65**:10611–10625.
214. Loren G, Espuny I, Llorente A, Donoghue C, Verdaguer X, Gomis RR, et al. Design and optimization of oestrogen receptor PROTACs based on 4–hydroxytamoxifen. *Eur J Med Chem*2022;**243**:114770.
215. Liu X, Kalogeropulou AF, Domingos S, Makukhin N, Nirujogi RS, Singh F, et al. Discovery of XL01126: a potent, fast, cooperative, selective, orally bioavailable, and blood–brain barrier penetrant PROTAC degrader of leucine–rich repeat kinase 2. *J Am Chem Soc* 2022;**144**:16930–16952.
216. Testa A, Hughes SJ, Lucas X, Wright JE, Ciulli A. Structure-based design of a

macrocyclic PROTAC. *Angew Chem Int Ed Engl* 2020;**59**:1727–1734.
217. O'Dowd PD, Sullivan GP, Rodrigues DA, Chonghaile TN, Griffith DM. First-in-class metallo-PROTAC as an effective degrader of select Pt-binding proteins. *Chem Commun (Camb)* 2023;**59**:12641-12644.
218. Rao Z, Li K, Hong J, Chen D, Ding B, Jiang L, Qi X, Hu J, Yang B, He Q, Dong X, Cao J, Zhu CL. A practical "preTACs-cytoblot" platform accelerates the streamlined development of PROTAC-based protein degraders. *Eur J Med Chem* 2023;**251**:115248.
219. Osawa H, Kurohara T, Ito T, Shibata N, Demizu Y. CRBN ligand expansion for hematopoietic prostaglandin D2 synthase (H-PGDS) targeting PROTAC design and their in vitro ADME profiles. *Bioorg Med Chem* 2023;**84**:117259.
220. Hu B, Hu J. Complete elimination of estrogen receptor α by PROTAC estrogen receptor α degrader ERD-148 in breast cancer cells. *Breast Cancer Res Treat* 2024;**203**:383-396.
221. Shih PC, Naganuma M, Tsuji G, Demizu Y, Naito M. Development of decoy oligonucleotide-warheaded chimeric molecules targeting STAT3. *Bioorg Med Chem* 2023;**95**:117507.
222. Bi T, Liang P, Zhou Y, Wang H, Huang R, Sun Q, et al. Rational Design of Bioorthogonally Activatable PROTAC for Tumor-Targeted Protein Degradation. *J Med Chem* 2023;**66**:14843-14852.
223. Chen S, Bi K, Liang H, Wu Z, Huang M, Chen X, et al. PROTAC derivatization of natural products for target identification and drug discovery: Design of evodiamine-based PROTACs as novel REXO4 degraders. *J Adv Res* 2023:S2090-1232(23)00318-1.
224. Ao M, Wu J, Cao Y, He Y, Zhang Y, Gao X, et al The synthesis of PROTAC molecule and new target KAT6A identification of CDK9 inhibitor iCDK9. *Chinese Chemical Letters* 2023;**34**:107741.
225. Zhang Y, Xiong X, Sun R, Zhu X, Wang C, Jiang B, et al. Development of the nonreceptor tyrosine kinase FER-targeting PROTACs as a potential strategy for antagonizing ovarian cancer cell motility and invasiveness. *J Biol Chem* 2023;**299**:104825.
226. Lee H, Lee JY, Jang H, Cho HY, Kang M, Bae SH, et al. Discovery of proteolysis-targeting chimera targeting undruggable proteins using a covalent ligand screening approach. *Eur J Med Chem* 2024;**263**:115929.

227. Lee B, Kim DG, Lee A, Kim YM, Cui L, Kim S, et al. Synthesis and discovery of the first potent proteolysis targeting chimaera (PROTAC) degrader of AIMP2-DX2 as a lung cancer drug. *J Enzyme Inhib Med Chem* 2023;**38**:51-66.
228. Gong L, Li R, Gong J, Ning X, Sun J, Ma Q, et al. Discovery of a miniaturized PROTAC with potent activity and high selectivity. *Bioorg Chem* 2023;**136**:106556.
229. Park S, Kim D, Lee W, Cho JH, Kim S, Lee GS, et al. Discovery of pan-IAP degraders via a CRBN recruiting mechanism. *Eur J Med Chem* 2023;**245**:114910.
230. Zhang X, Zhao T, Sun M, Li P, Lai M, Xie L, et al. Design, synthesis and biological evaluation of KRASG12C-PROTACs. *Bioorg Med Chem* 2023;**78**:117153.
231. Xie B, Xu B, Xin L, Wei Y, Guo X, Dong C. Discovery of estrogen receptor α targeting caged hypoxia-responsive PROTACs with an inherent bicyclic skeleton for breast cancer treatment. *Bioorg Med Chem* 2023;**137**:106590.
232. Wurnig S, Vogt M, Hogenkamp J, Dienstbier N, Borkhardt A, Bhatia S, et al. Development of the first geldanamycin-based HSP90 degraders. *Front Chem* 2023;**11**:1219883.
233. Jia Q, Zhang Y, Liu F, Dong W, Zhu L, Wang F, et al. Cell-specific degradation of histone deacetylase using warhead-caged proteolysis targeting chimeras. *Anal Chem* 2023;**95**:16474-16480.
234. Zhang B, Liu C, Yang Z. Discovery of BWA-522, a first-in-class and orally bioavailable protac degrader of the androgen receptor targeting n-terminal domain for the treatment of prostate cance. *J Med Chem* 2023;**66**: 11158-11186.
235. Seipp EK, Huang R. Design and synthesis of a fluorescent probe to develop a fluorescence polarization assay for the E3 ligase FEM1C. *Bioorg Med Chem* 2023;**90**:117371.
236. Tseng YL, Lu PC, Lee CC, He RY, Huang YA, Tseng YC, Cheng TR, Huang JJ, Fang JM. Degradation of neurodegenerative disease-associated TDP-43 aggregates and oligomers via a proteolysis-targeting chimera. *J Biomed Sci* 2023;**30**:27.
237. Zhou Z, Zhou G, Zhou C, Fan Z, Cui R, Li Y, Li R, et al. Discovery of a potent, cooperative, and selective SOS1 PROTAC ZZ151 with in vivo antitumor efficacy in KRAS-mutant cancers. *J Med Chem* 2023;**66**:4197-4214.
238. Chan K , Sathyamurthi P S , Queisser M A ,et al.Antibody-proteolysis targeting chimera conjugate enables selective degradation of receptor-interacting serine/threonine-protein kinase 2 in HER2+ Cell Lines. *Burley Bioconjugate Chemistry* 2023;**34**:2049-2054.

239. Yan Z, Lyu X, Lin D, Wu G, Gong Y, Ren X, et al. Selective degradation of cellular BRD3 and BRD4-L promoted by PROTAC molecules in six cancer cell lines. *Eur J Med Chem* 2023;**254**:115381.
240. Gunasekaran P, Hwang YS, Lee GH, Park J, Kim JG, La YK, et al. Degradation of polo-like kinase 1 by the novel poly-arginine n-degron pathway PROTAC regulates tumor growth in nonsmall cell lung cancer. *J Med Chem* 2023.
241. Khan S, Zhang X, Lv D, Zhang Q, He Y, Zhang P, et al. A selective BCL-XL PROTAC degrader achieves safe and potent antitumor activity. *Nat Med* 2019;**25**:1938-1947.
242. Zhang J, Ma C, Yu Y, Liu C, Fang L, Rao H. Single amino acid-based PROTACs trigger degradation of the oncogenic kinase BCR-ABL in chronic myeloid leukemia (CML). *J Biol Chem* 2023;**299**:104994.
243. Etersque JM, Lee IK, Sharma N, Xu K, Ruff A, Northrup JD, et al. Regulation of eDHFR-tagged proteins with trimethoprim PROTACs. *Nat Commun* 2023;**14**:7071.
244. Liu R, Liu Z, Chen M, Xing H, Zhang P, Zhang J. Cooperatively designed aptamer-PROTACs for spatioselective degradation of nucleocytoplasmic shuttling protein for enhanced combinational therapy. *Chem Sci* 2023;**15**:134-145.
245. Bouguenina H, Scarpino A, O'Hanlon JA, Warne J, Wang HZ, Wah Hak LC, et al. A Degron blocking strategy towards improved CRL4CRBN recruiting PROTAC selectivity. *Chembiochem* 2023;**24**:e202300351.
246. Chen JJ, Jin JM, Gu WJ, Zhao Z, Yuan H, Zhou YD, et al. Crizotinib-based proteolysis targeting chimera suppresses gastric cancer by promoting MET degradation. *Cancer Sci* 2023;**114**:1958-1971.
247. Rathje OH, Perryman L, Payne RJ, Hamprecht DW. PROTACs targeting MLKL protect cells from necroptosis. *J Med Chem* 2023;**66**:11216-11236.
248. Xu M, Zhang Z, Zhang P, Wang Q, Xia Y, Lian C, et al. Beyond traditional methods: unveiling the skin whitening properties of Rhein-Embedded PROTACs. *Bioorg Med Chem* 2023;**96**:117537.
249. Bockstiegel J, Wurnig SL, Engelhardt J, Enns J, Hansen FK, Weindl G. Pharmacological inhibition of HDAC6 suppresses NLRP3 inflammasome-mediated IL-1β release. *Biochem Pharmacol* 2023;**215**:115693.
250. Cubillos-Rojas M, Loren G, Hakim YZ, Verdaguer X, Riera A, Nebreda AR. Synthesis and biological activity of a VHL-based PROTAC specific for p38α. *Cancers (Basel)*. 2023;**15**:611.

251. Sun Y , Xue Y , Sun P ,et al.Discovery of the first potent, selective, and in vivo efficacious polo-like kinase 4 proteolysis targeting chimera degrader for the treatment of TRIM37-amplified breast cancer. *J Med Chem* 2023;**66**:8200-8221.
252. Hines J, Gough JD, Corson TW, Crews CM. Posttranslational protein knockdown coupled to receptor tyrosine kinase activation with phosphoPROTACs. *Proc Natl Acad Sci USA*. 2013;**110**:8942-7.
253. Henning RK, Varghese JO, Das S, Nag A, Tang G, Tang K, et al. Degradation of Akt using protein-catalyzed capture agents. *J Pept Sci* 2016;**22**:196-200.
254. Jiang Y, Deng Q, Zhao H, Xie M, Chen L, Yin F, et al. Development of stabilized peptide-based PROTACs against estrogen receptor α. *ACS Chem Biol* 2018;**13**:628-635.
255. Dai MY, Shi YY, Wang AJ, Liu XL, Liu M, Cai HB. High-potency PD-1/PD-L1 degradation induced by peptide-PROTAC in human cancer cells. *Cell Death Dis* 2022 ;**13**:924.
256. Lu M, Liu T, Jiao Q, Ji J, Tao M, Liu Y, et al. Discovery of a Keap1-dependent peptide PROTAC to knockdown Tau by ubiquitination-proteasome degradation pathway. *Eur J Med Chem* 2018;**146**:251-259.
257. Geiger TM, Walz M, Meyners C, Kuehn A, Dreizler JK, et al. Discovery of a potent proteolysis targeting chimera enables targeting the scaffolding functions of FK506-binding protein 51 (FKBP51). *Angew Chem Int Ed Engl* 2024;**63**:e202309706.
258. Xiang W, Zhao L, Han X, Xu T, Kregel S, et al. Discovery of ARD-1676 as a highly potent and orally efficacious AR PROTAC degrader with a broad activity against AR mutants for the treatment of AR + human prostate cancer. *J Med Chem* 2023;**66**:13280-13303.
259. Chen M, Zhou P, Kong Y, Li J, Li Y, Zhang Y, et al. Inducible degradation of oncogenic nucleolin using an aptamer-based PROTAC. *J Med Chem* 2023;**66**:1339-1348.
260. Peyman M, Barroso E, Turcu AL, Estrany F Jr, Smith D, et al. Soluble epoxide hydrolase-targeting PROTAC activates AMPK and inhibits endoplasmic reticulum stress. *Biomed Pharmacother* 2023;**168**:115667.
261. Arndt CM, Bitai J, Brunner J, Opatz T, Martinelli P, Gollner A, et al. One-Pot synthesis of cereblon proteolysis targeting chimeras via photoinduced $C(sp^2)$-$C(sp^3)$ cross coupling and amide formation for proteolysis targeting chimera library synthesis. *J Med Chem* 2023;**66**:16939-16952.

262. Sun Y, Yang Z, Zhang Z, Li Z, Guo L, Pan H, et al. Design, synthesis, and evaluation of BTK-targeting PROTACs with optimized bioavailability in vitro and in vivo. *RSC Med Chem* 2023;**14**:1562-1566.
263. Sun Y, Luo X, Yang Z, Lv W, Chen L, Li H, Rao Y. Developing potent BTK^{C481S} PROTACs for ibrutinib-resistant malignant lymphoma. *Chin Chem Lett* 2023;**34**: 107924.
264. Park SY, Gurung R, Hwang JH, Kang JH, Jung HJ, et al. Development of KEAP1-targeting PROTAC and its antioxidant properties: In vitro and in vivo. *Redox Biol* 2023;**64**:102783.
265. Chen Y, Li W, Kwon S, Wang Y, Li Z, Hu Q. Small-molecule ferritin degrader as a pyroptosis inducer. *J Am Chem Soc* 2023;**145**:9815-9824.
266. Yu X, Li D, Kottur J, Kim HS, Herring LE, Yu Y, et al. Discovery of potent and selective WDR5 proteolysis targeting chimeras as potential therapeutics for pancreatic cancer. *J Med Chem* 2023;**66**:16168-16186.
267. Wang C, Zheng C, Wang H, et al. Dual degradation mechanism of GPX_4 degrader in induction of ferroptosis exerting anti-resistant tumor effect. *Eur J Med Chem* 2023;**247**:115072.
268. Yang Liu, Mengzhu Zheng, Zhilu Ma, Yirong Zhou, et al. Design, synthesis, and evaluation of PD-L1 degraders to enhance T cell killing activity against melanoma, *Chinese Chemical Letters* 2023;**34**:107762.
269. Si R, Hai P, Zheng Y, Liu N, Wang J, Zhang Q, et al. Discovery of novel PROTACs based on multi-targeted angiogenesis inhibitors. *Bioorg Med Chem Lett* 2023;**87**:129275.
270. Jin Y, Fan J, Wang R, Wang X, Li N, You Q, Jiang Z. Ligation to scavenging strategy enables on-demand termination of targeted protein degradation. *J Am Chem Soc* 2023;**145**:7218-7229.
271. Li H, Yang W, Li H, Bai X, Zhang H, Fan W, Liu W, Sun L. PROTAC targeting cyclophilin A controls virus-induced cytokine storm. *iScience* 2023;**26**:107535.
272. Jiang Q, Fu M, Tang Y, Li G, Tu G, Wu X, et al. Discovery of X10g as a selective PROTAC degrader of Hsp90α protein for treating breast cancer. *Eur J Med Chem* 2023;**260**:115690.
273. Yang L, Tu W, Huang L, Miao B, Kaneshige A, et al. Discovery of SMD-3040 as a potent and selective SMARCA2 PROTAC degrader with strong in vivo antitumor activity. *J Med Chem* 2023;**66**:10761-10781.

274. Miao J, Bai Y, Miao Y, Qu Z, Dong J, et al. Discovery of a SHP2 Degrader with In Vivo Anti-Tumor Activity. *Molecules* 2023;**28**:6947.
275. Ismail TM, Crick RG, Du M, Shivkumar U, Carnell A, et al. Targeted Destruction of S100A4 Inhibits Metastasis of Triple Negative Breast Cancer Cells. *Biomolecules* 2023;**13**:1099.
276. Chen Z, Hu B, Rej RK, Wu D, Acharyya RK, et al. Discovery of ERD-3111 as a Potent and Orally Efficacious Estrogen Receptor PROTAC Degrader with Strong Antitumor Activity. *J Med Chem* 2023;**66**:12559-12585.
277. Cheng W, Li S, Han S, Miao R, Wang S, et al. Design, synthesis and biological evaluation of the tumor hypoxia-activated PROTACs bearing caged CRBN E3 ligase ligands. *Bioorg Med Chem* 2023;**82**:117237.
278. Zhang J, Duan H, Gui R, Wu M, Shen L, et al. Structure-based identification of new orally bioavailable BRD9-PROTACs for treating acute myelocytic leukemia. *Eur J Med Chem* 2023; **262**: 115872.
279. Wen T, Chen J, Zhang W, Pang J. Design, synthesis and biological evaluation of α-synuclein proteolysis-targeting chimeras. *Molecules* 2023;**28**:4458.
280. Xie H, Xu W, Liang J, Liu Y, Zhuo C, Zou X, Luo W, Xiao J, Lin Y, Chen L, Li H. Design, synthesis and evaluation of EZH2-based PROTACs targeting PRC2 complex in lymphoma. *Bioorg Chem* 2023;**140**:106762.
281. Wu Y, Wu M, Zheng X, Yu H, Mao X, et al. Discovery of a potent and selective PARP1 degrader promoting cell cycle arrest via intercepting CDC25C-CDK1 axis for treating triple-negative breast cancer. *Bioorg Chem* 2024;**142**:106952.
282. Wu T, Zhang Z, Gong G, Du Z, Xu Y, et al. Discovery of novel flavonoid-based CDK9 degraders for prostate cancer treatment via a PROTAC strategy. *Eur J Med Chem* 2023;**260**:115774.
283. Zhu L, Hu S, Yan X, Zeng Q, Zhang B, Jiang L, Yao SQ, Ge J. Ugi reaction-assisted assembly of covalent PROTACs against glutathione peroxidase 4. *Bioorg Chem* 2023;**134**:106461.
284. Cai M, Ma F, Hu C, Li H, Cao F, Li Y, Dong J, Qin JJ. Design and synthesis of proteolysis-targeting chimeras (PROTACs) as degraders of glutathione peroxidase 4. *Bioorg Med Chem* 2023;**90**:117352.
285. Naganuma M, Ohoka N, Tsuji G, Inoue T, Naito M, Demizu Y. Structural Optimization of decoy oligonucleotide-based PROTAC That degrades the estrogen receptor. *Bioconjug Chem* 2023;**34**:1780-1788.

286. Zhang P, Wang W, Guo M, Zhou L, Dong G, Xu D, Sheng C. Discovery of potent NAMPT-Targeting PROTACs using FK866 as the warhead. Bioorg *Med Chem Lett* 2023;**92**:129393.
287. Hatcher JM, Zwirek M, Sarhan AR, Vatsan PS, et al. Development of a highly potent and selective degrader of LRRK2. *Bioorg Med Chem Lett*. 2023;**94**:129449.
288. Zhang Q, Yan P, Zhao P, et al. Design, Synthesis, and biological evaluation of mtor-targeting protacs based on MLN0128 and pomalidomide. *Chem Pharm Bull (Tokyo)* 2023;**71**:120-128.
289. Pan P, He Y, Geng T, Li Z, Li Z, Meng X. Design, synthesis, and antitumor activity evaluation of proteolysis-targeting chimeras as degraders of extracellular signal-regulated kinases 1/2. *Int J Mol Sci* 2023;**24**:16290.
290. Zhao C, Chen D, Suo F, Setroikromo R, Quax WJ, Dekker FJ. Discovery of highly potent HDAC8 PROTACs with anti-tumor activity. *Bioorg Chem* 2023;**136**:106546.
291. Tong Y, Zhu W, Chen J, Wen T, Xu F, Pang J. Discovery of small-molecule degraders for alpha-synuclein aggregates. *J Med Chem* 2023;**66**:7926-42.
292. Zheng C, Wang C, Sun D, Wang H, Li B, Liu G, Liu Z, Zhang L, Xu P. Structure-activity relationship study of RSL3-based GPX4 degraders and its potential noncovalent optimization. *Eur J Med Chem* 2023;**255**:115393.
293. Hu J, Hu B, Xu F, Wang M, Qin C, McEachern D, et al. Precise conformational control yielding highly potent and exceptionally selective BRD4 degraders with strong antitumor activity. *J Med Chem* 2023;**66**:8222-8237.
294. Li Y, Zeng ZW, Chen D, Gu ZC, Yan WL, Yue LY, et al. Facilitated drug repurposing with artemisinin-derived PROTACs: Unveiling PCLAF as a therapeutic target. *J Med Chem* 2023;**66**:11335-11350.
295. Pu C, Liu Y, Deng R, Xu Q, Wang S, et al. Development of PROTAC degrader probe of CDK4/6 based on DCAF16. *Bioorg Chem* 2023;**138**:106637.
296. Xie B, Yin Z, Hu Z, Lv J, Du C, et al. Discovery of a novel class of PROTACs as potent and selective estrogen receptor α degraders to overcome endocrine-resistant breast cancer in vitro and in vivo. *J Med Chem* 2023;**66**:6631-6651.
297. Kaneshige A, Bai L, Wang M, McEachern D, Meagher JL, et al. Discovery of a potent and selective STAT5 PROTAC degrader with strong antitumor activity in vivo in acute myeloid leukemia. *J Med Chem* 2023;**66**:2717-2743.
298. Kaneshige A, Bai L, Wang M, McEachern D, Meagher JL, et al. A selective

small-molecule STAT5 PROTAC degrader capable of achieving tumor regression in vivo. *Nat Chem Biol* 2023;**19**:703-711.
299. Koide E, Mohardt ML, Doctor ZM, Yang A, Hao M, et al. Development and characterization of Selective FAK Inhibitors and PROTACs with in vivo activity. *Chembiochem* 2023;**24**:e202300141.
300. Gazorpak M, Hugentobler KM, Paul D, Germain PL, Kretschmer M, et al. Harnessing PROTAC technology to combat stress hormone receptor activation. *Nat Commun* 2023;**14**:8177.
301. Zhou J, Shen R, Liu J, Deng X, Xin L, Zhou HB, Huang J. A novel selective estrogen receptor degrader induces cell cycle arrest in breast cancer via ERα degradation and the autophagy-lysosome pathway. *Bioorg Med Chem* 2023;**82**:117235.
302. Torres-Ayuso P, Katerji M, Mehlich D, Lookingbill SA, Sabbasani VR, et al. PIM1 targeted degradation prevents the emergence of chemoresistance in prostate cancer. *Cell Chem Biol* 2023:S2451-9456(23)00384-7.
303. Dong J, Miao J, Miao Y, Qu Z, Zhang S, et al. Small Molecule Degraders of protein tyrosine phosphatase 1B and T-cell protein tyrosine phosphatase for cancer immunotherapy. *Angew Chem Int Ed Engl* 2023;**62**:e202303818.
304. He R, Song Z, Bai Y, He S, Huang J, et al. Discovery of AXL degraders with improved potencies in triple-negative breast cancer (TNBC) cells. *J Med Chem* 2023;**66**:1873-1891.
305. Rana S, Dranchak P, Dahlin JL, Lamy L, Li W, et al. Methotrexate-based PROTACs as DHFR-specific chemical probes. *Cell Chem Biol* 2023:S2451-9456(23)00333-1.
306. Miao J, Dong J, Miao Y, Bai Y, Qu Z, et al. Discovery of a selective TC-PTP degrader for cancer immunotherapy. *Chem Sci* 2023;**14**:12606-12614.
307. Huang J, Ma Z, Yang Z, He Z, Bao J, Peng X, Liu Y, Chen T, Cai S, Chen J, Zeng Z. Discovery of ibrutinib-based BTK PROTACs with in vivo anti-inflammatory efficacy by inhibiting NF-κB activation. *Eur J Med Chem* 2023;**259**:115664.
308. Steinebach C, Bricelj A, Murgai A, Sosič I, Bischof L, Ng YLD, et al. Leveraging ligand affinity and properties: discovery of novel benzamide-type cereblon binders for the design of PROTACs. *J Med Chem* 2023;**66**:14513-14543.
309. Pedrini M, Iannielli A, Meneghelli L, Passarella D, Broccoli V, Seneci P. Synthesis and preliminary characterization of putative anle138b-centered PROTACs

against α-synuclein aggregation. *Pharmaceutics* 2023;**15**:1467.
310. Xie H, Bacabac MS, Ma M, Kim EJ, Wang Y, Wu W, et al. Development of potent and selective coactivator-associated arginine methyltransferase 1 (CARM1) Degraders. *J Med Chem* 202;**66**:13028-13042.
311. Pei J, Xiao Y, Liu X, Hu W, Sobh A, Yuan Y, et al. Piperlongumine conjugates induce targeted protein degradation. *Cell Chem Biol* 2023;**30**:203-213.e17.
312. Sang R, Fan R, Deng A, Gou J, Lin R, Zhao T, et al. Degradation of hexokinase 2 blocks glycolysis and induces GSDME-dependent pyroptosis to amplify immunogenic cell death for breast cancer therapy. *J Med Chem* 2023;**66**:8464-8483.
313. Zeng Y, Xiao J, Xu Y, Wei F, Tian L, Gao Y, et al. Degradation of cyclin-dependent kinase 9/Cyclin T1 by optimized microtubule-associated protein 1 light chain 3 beta-recruiting coumarin analogs. *J Med Chem* 2023;**66**:12877-12893.
314. Cui J, Wang Y, Li X, Xiao F, Ren H, Wu M. Synthesis and antineoplastic activity of a dimer, spiroindolinone pyrrolidinecarboxamide. *Molecules* 2023;**28**:3912.
315. Park KS, Qin L, Kabir M, Luo K, Dale B, Zhong Y, et al. Targeted degradation of PRC1 components, BMI1 and RING1B, via a novel protein complex degrader strategy. *Adv Sci (Weinh)* 202;**10**:e2205573.
316. Tsujimura H, Naganuma M, Ohoka N, Inoue T, Naito M, Tsuji G, Demizu Y. Development of DNA aptamer-based PROTACs that degrade the estrogen receptor. *ACS Med Chem Lett* 2023;**14**:827-832.
317. Xiao Y, Hale S, Awasthee N, Meng C, Zhang X, Liu Y, et al. HDAC3 and HDAC8 PROTAC dual degrader reveals roles of histone acetylation in gene regulation. *Cell Chem Biol* 2023;**30**:1421-1435.e12.
318. Kim Y, Seo P, Jeon E, You I, Hwang K, Kim N, et al. Targeted kinase degradation via the KLHDC2 ubiquitin E3 ligase. *Cell Chem Biol* 2023;**30**:1414-1420.e5.
319. Legaard AJ, Christensen J, Kleine-Kohlbrecher D, Vacher Comet I, Fullerton Støier J, Antoku Y, et al. Discovery of NSD2-degraders from novel and selective DEL hits. *Chembiochem* 2023;**24**:e202300515.
320. Ng YLD, Bricelj A, Jansen JA, Murgai A, Peter K, Donovan KA, et al. Heterobifunctional ligase recruiters enable pan-degradation of inhibitor of apoptosis proteins. *J Med Chem* 2023;**66**:4703-4733.
321. Wang W, Liu Y, Xiong L, Sun D, Wang H, Song Z, et al. Synthesis of lathyrol PROTACs and evaluation of their anti-inflammatory activities. *J Nat Prod*

2023;**86**:767-781.
322. Schiemer J, Maxwell A, Horst R, Liu S, Uccello DP, Borzilleri K, et al. A covalent BTK ternary complex compatible with targeted protein degradation. *Nat Commun* 2023;**14**:1189.
323. Li C, Qiao Y, Jiang X, Liu L, Zheng Y, Qiu Y, et al. Discovery of a first-in-class degrader for the lipid kinase PIKfyve. *J Med Chem* 2023;**66**:12432-12445.
324. Han X, Zhao L, Xiang W, Miao B, Qin C, Wang M, et al. Discovery of ARD-2051 as a potent and orally efficacious proteolysis targeting chimera (PROTAC) degrader of androgen receptor for the treatment of advanced prostate cancer. *J Med Chem* 2023;**66**:8822-8843.
325. Jiang B, Weinstock DM, Donovan KA, Sun HW, Wolfe A, et al. ITK degradation to block T cell receptor signaling and overcome therapeutic resistance in T cell lymphomas. *Cell Chem Biol* 2023;**30**:383-393.e6.
236. Bashore FM, Foley CA, Ong HW, Rectenwald JM, Hanley RP, et al. PROTAC linkerology leads to an optimized bivalent chemical degrader of polycomb repressive complex 2 (PRC2) components. *ACS Chem Biol* 2023;**18**:494-507.
327. Lim YS, Yoo SM, Patil V, Kim HW, Kim HH, et al. Orally bioavailable BTK PROTAC active against wild-type and C481 mutant BTKs in human lymphoma CDX mouse models. *Blood Adv* 2023;**7**:92-105.

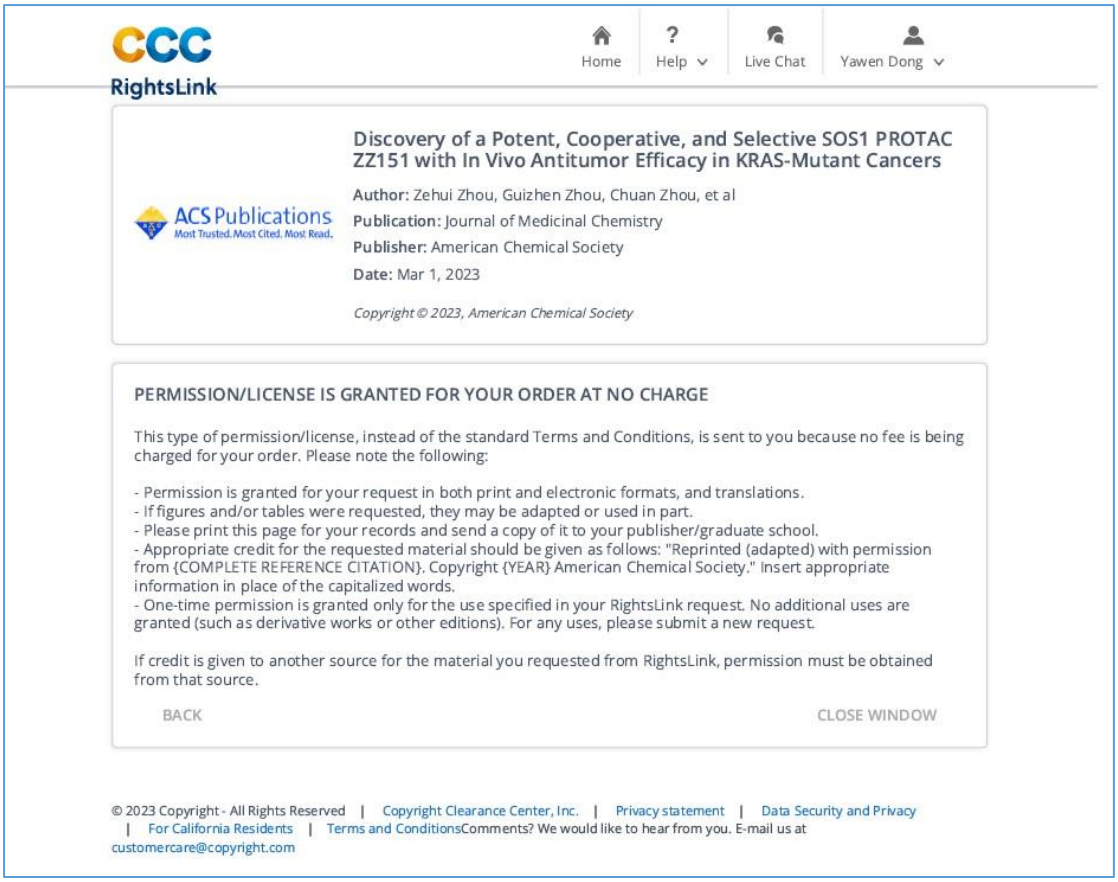


Figure S1. Copy right for Figures 4C to 4F.

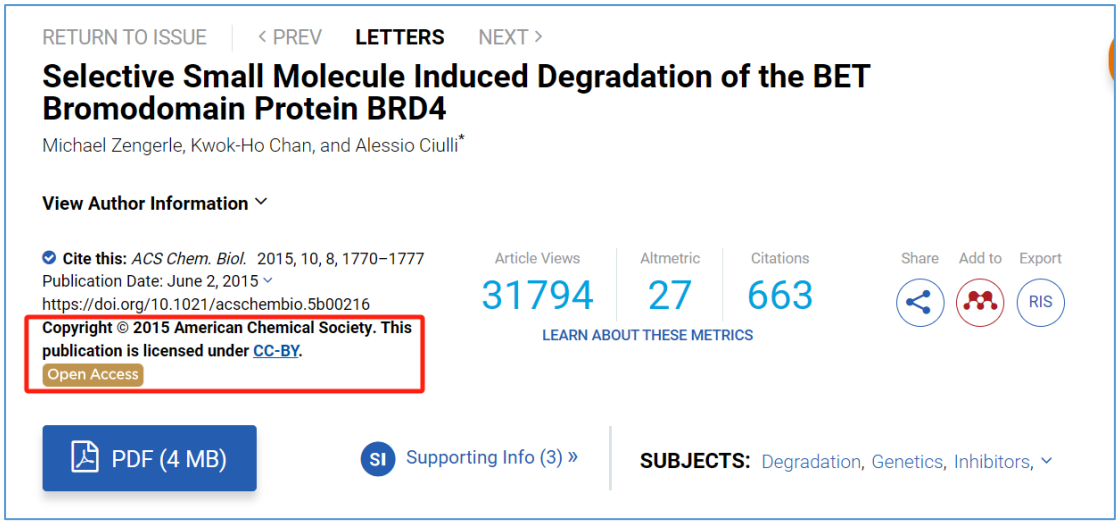


Figure S2. Copy right for Figure 5C.

Differential PROTAC substrate specificity dictated by orientation of recruited E3 ligase

Rights and permissions

Figure S3. Copy right for Figures 7C and 7D.