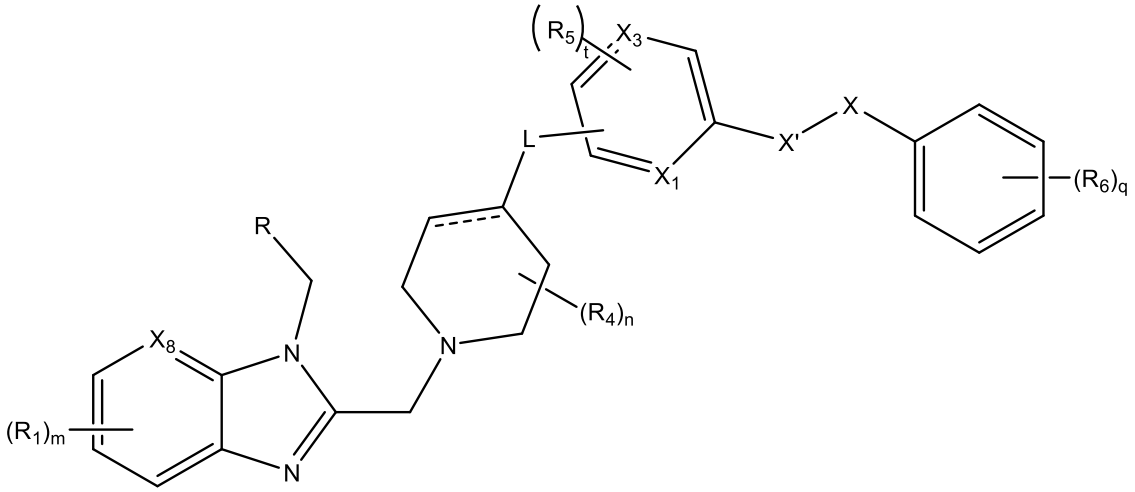
CLAIMS

1. A compound of Formula (IE):



Formula (IE)

or a pharmaceutically acceptable salt, solvate, enantiomer, or isotopic variation thereof, wherein:

⎓ is a single bond or a double bond;

X is -O-, and X' is $-C(R_{d1})(R_{d2})-$;

L is independently selected from $-OC(R_{d1})(R_{d2})-$, $-C(R_{d1})(R_{d2})O-$, -O-, -S- or $-N(R_{d4})-$;

X_1, X_3, and X_8 are independently selected from $-CR_5-$ or -N-;

R is independently selected from 6- to 10- membered aryl, 5- to 8-membered heteroaryl, 3- to 8- membered saturated or partially saturated cycloalkyl, and 3-to 8- membered saturated or partially saturated heterocyclyl, each of which is independently optionally substituted with one to multiple substituents selected from deuterium, halogen, haloalkyl, CN, cyanoethyl, O=, OH, C_{1-3} alkyl, and C_{1-3} alkoxy, and wherein the alkyl and alkoxy are optionally substituted with one to three substituent groups selected from deuterium, halogen, CN, OCH_3, and OH;

each R_1 is the same or different and is independently selected from the group consisting of deuterium, halogen, CN, OH, SH, NH_2, COOH, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, and C_{2-10} heteroalkyl, wherein the alkyl, alkenyl, alkynyl, alkoxy, and heteroalkyl are optionally substituted with one to more groups selected from hydrogen, deuterium, halogen, oxo, CN, CF_3, OH, OCH_3, OCH_2CH_3, saturated or partially saturated C_{3-6} cycloalkyl;

each R_4 is the same or different and is independently selected from deuterium, halogen, CN, OH, SH and NH_2, COOH, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, and C_{2-10} heteroalkyl, wherein the alkyl, alkynyl, alkoxy, and heteroalkyl are optionally substituted with one or more groups selected from deuterium, halogen, oxo, CN, and OH;

each R_5 is the same or different and is independently selected from hydrogen, deuterium, halogen, CN, OH, SH, NH_2, COOH, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, and C_{2-10} heteroalkyl, wherein the alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl are independently optionally substituted with one or more groups selected from deuterium, halogen, oxo, CN, CF_3, OH, OCH_3, and OCH_2CH_3;

each R_6 is the same or different and is independently selected from deuterium, halogen, CN, OH, SH, NH_2, COOH, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, and C_{2-10} heteroalkyl, wherein the alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl are independently optionally substituted with one or more groups selected from deuterium, halogen, oxo, CN, CF_3, OH, OCH_3, and OCH_2CH_3;

each R_{d1}, R_{d2} is the same or different, and is independently selected from hydrogen, deuterium, NH_2, C_{1-10} alkyl, C_{2-10} alkynyl, C_{1-10} alkoxy, C_{1-10} alkylacyl, C_{1-10} alkylsulfonyl, or C_{2-10} heteroalkyl, wherein the alkyl, alkynyl, alkylacyl, and alkylsulfonyl are optionally substituted with one to multiple groups selected from deuterium, halogen, oxo, CN, and OH;

each hetero represents a heteroatom independently selected from O, N, S, P and isotopes thereof;

each halogen is independently selected from F, Cl, Br, I and isotopes thereof;

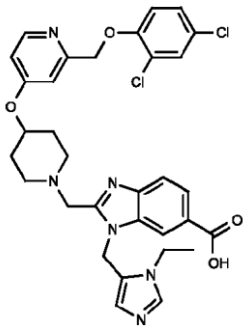
m is selected from 0, 1, 2, 3 and 4;

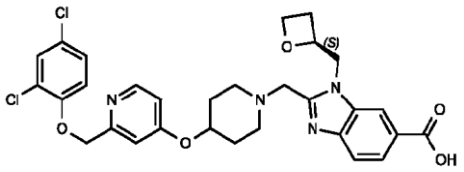
n is selected from 0, 1, 2, 3, 4 and 5;

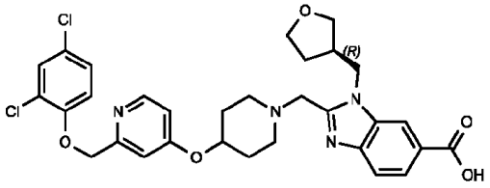
q is selected from 0, 1, 2, 3, 4 and 5; and

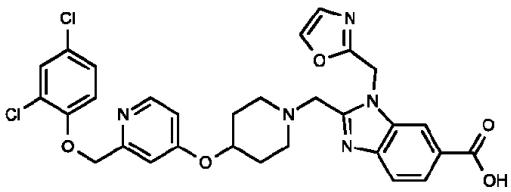
t is selected from 0, 1, 2, 3, and 4;

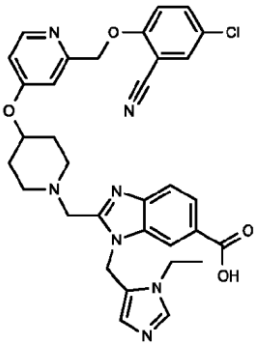
and provided that the compound is not the following compound:

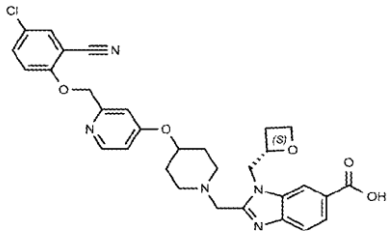


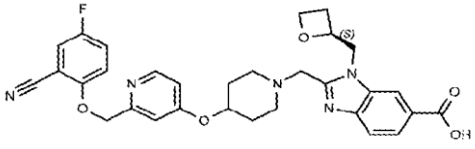






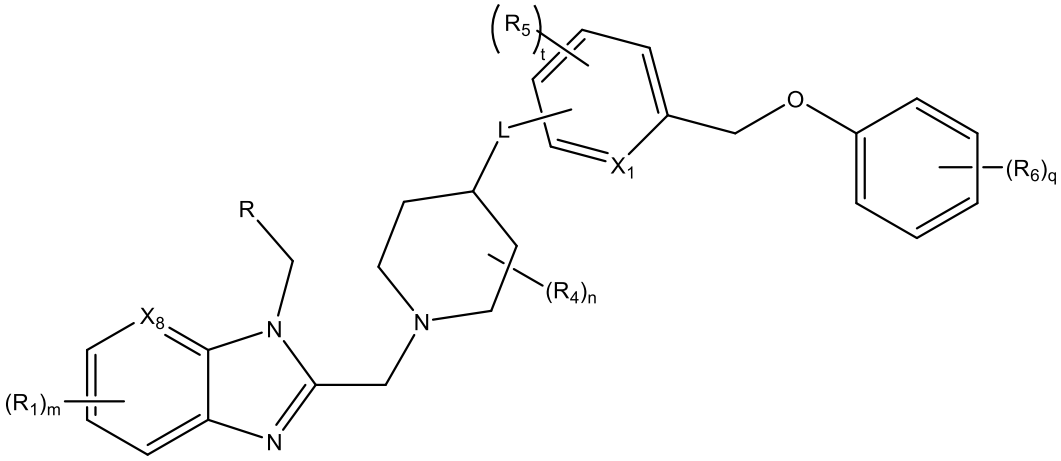






.

2. The compound according to claim 1, wherein the compound is a compound of Formula (IF-1),



Formula (IF-1)

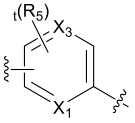
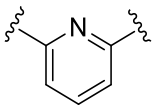
or a pharmaceutically acceptable salt, solvate, enantiomer, or isotopic variation thereof.

3. The compound according to claim 1 or 2, wherein X_1 is N.

4. The compound according to any one of claims 1-3, wherein X_3 is CH, and X_8 is CH or N.

5. The compound according to any one of claims 1-4, wherein X' is $-CH_2-$.

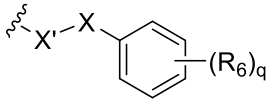
6. The compound according to any one of claims 1-5, wherein L is O.

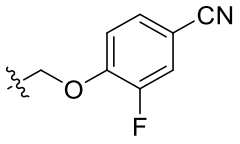
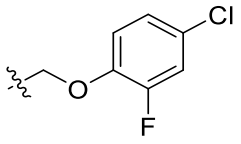
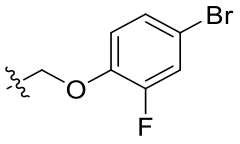
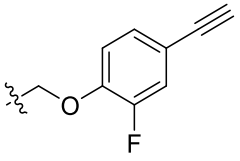
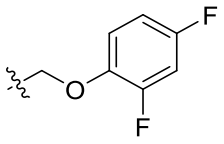
7. The compound according to any one of claims 1-6, wherein  is .

8. The compound according to any one of claims 1-7, wherein R is oxetanyl.

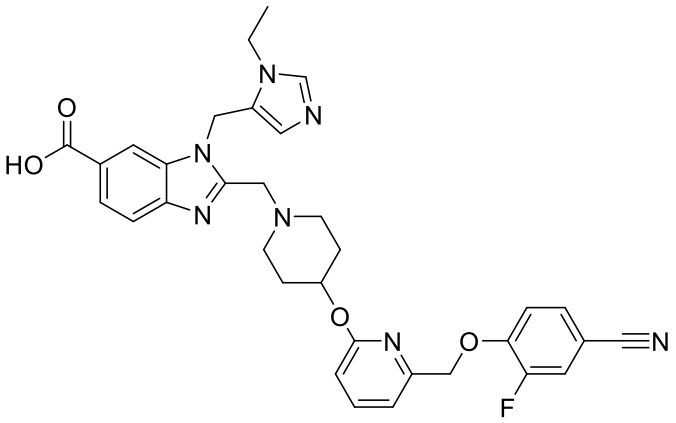
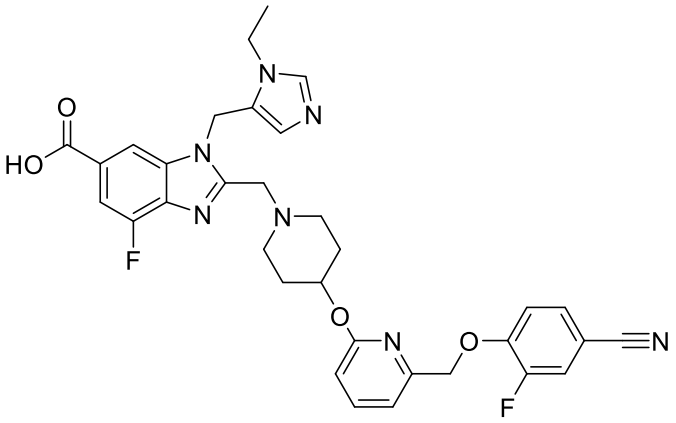
9. The compound according to any one of claims 1-8, wherein R_1 is COOH, and m is 1.

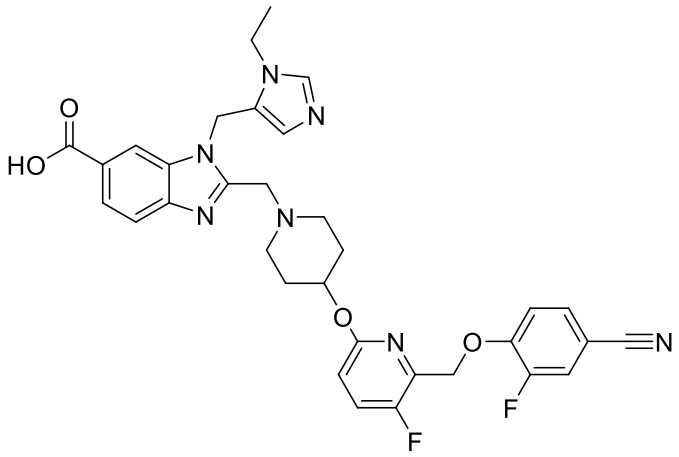
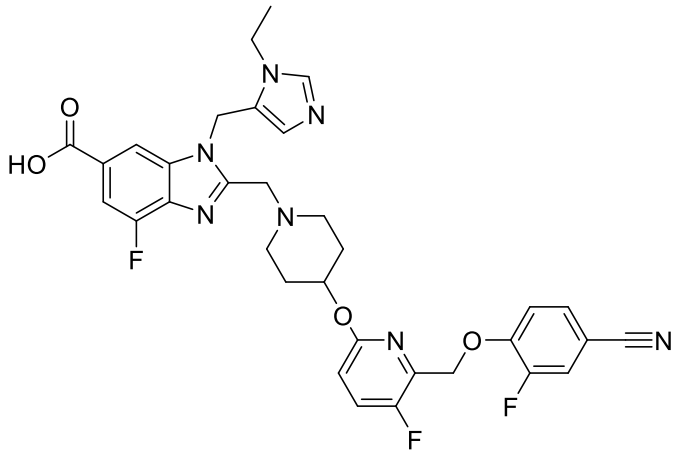
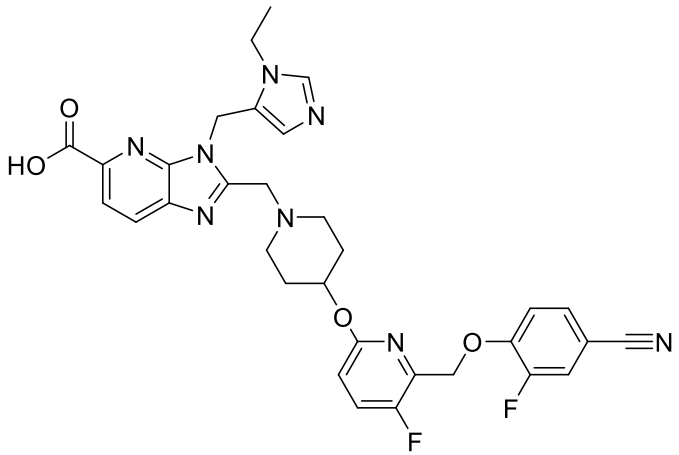
10. The compound according to any one of claims 1-9, wherein R_4 is absent or C_{1-10} alkyl.

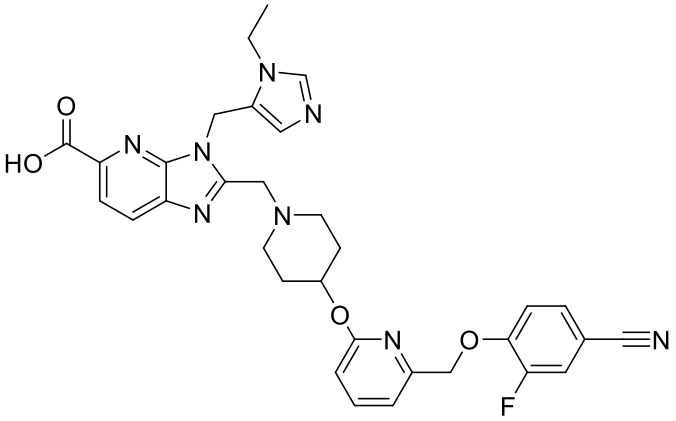
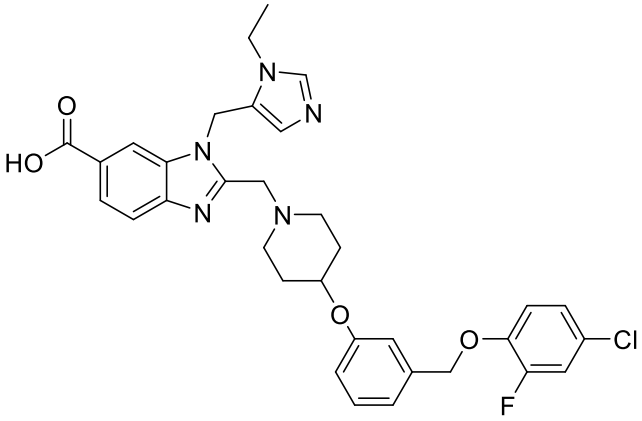
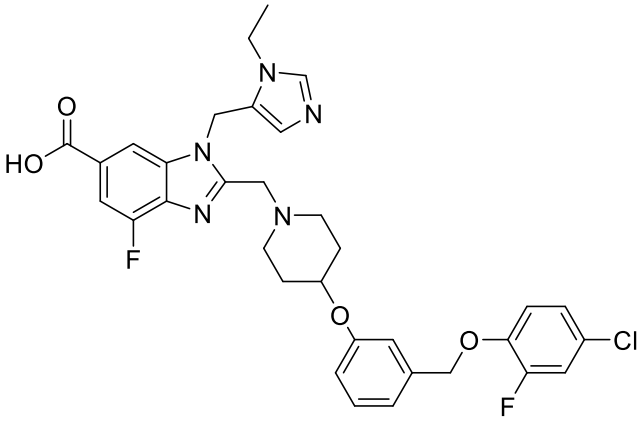
11. The compound according to any one of claims 1-3, wherein  is

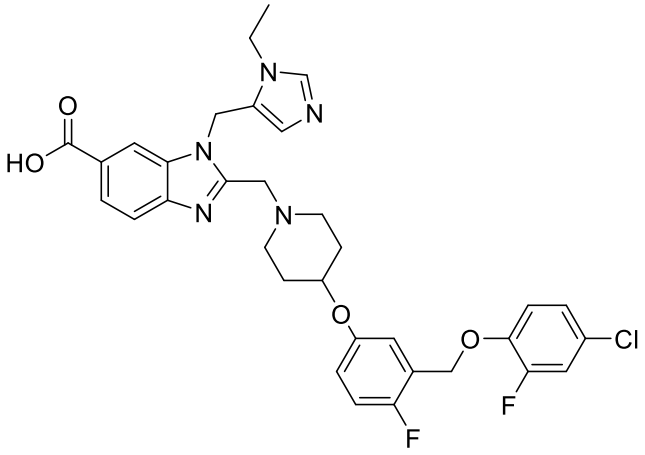
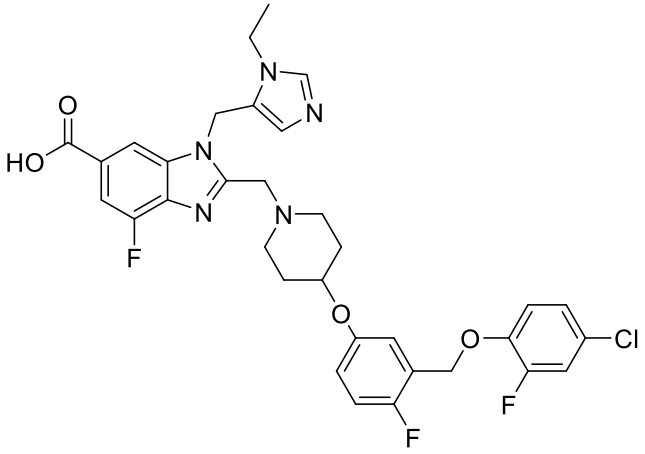
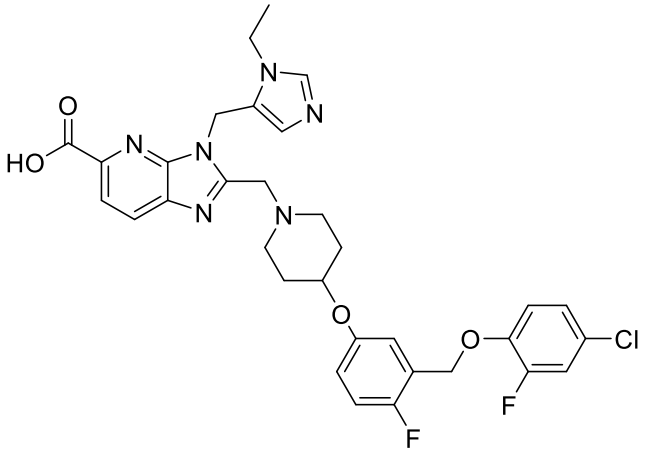
, , , , or .

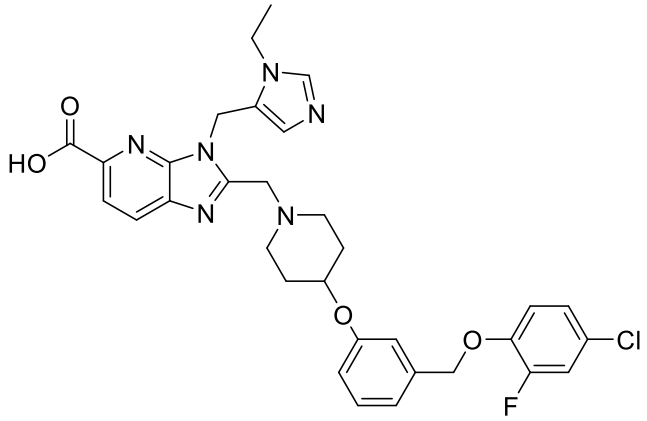
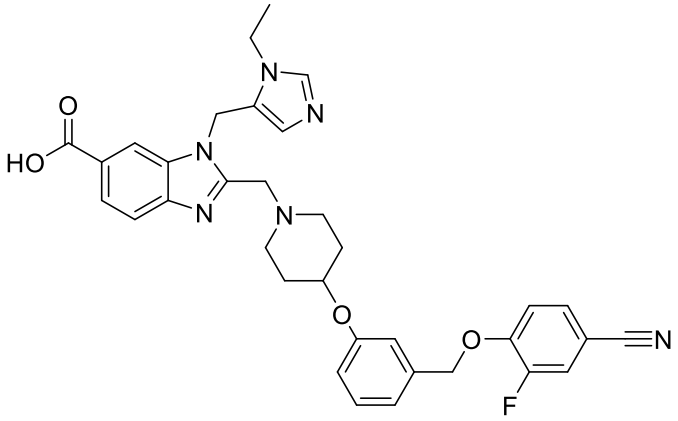
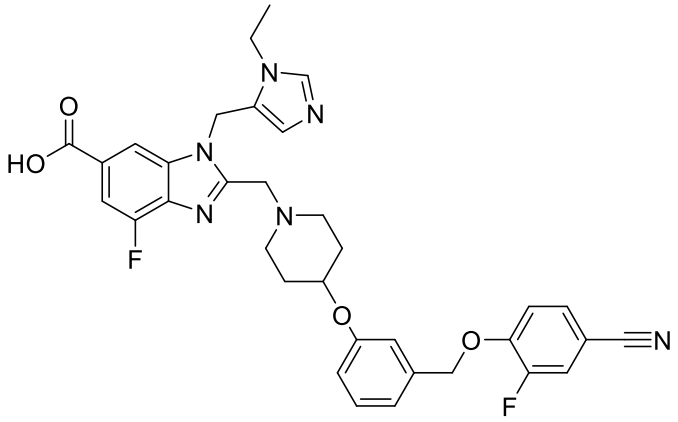
12. A compound selected from the compounds of the following structures:

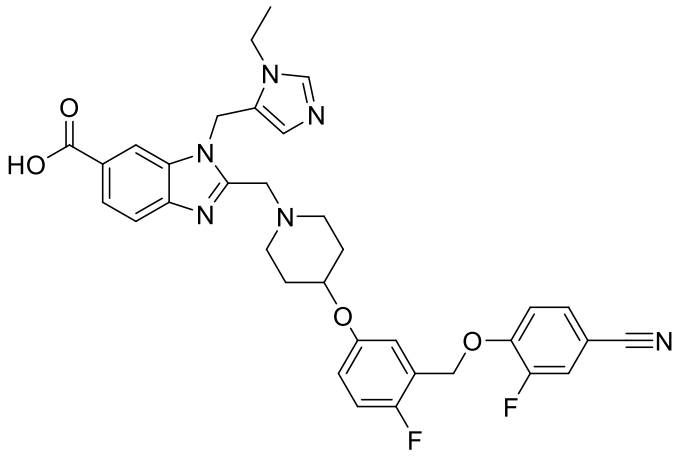
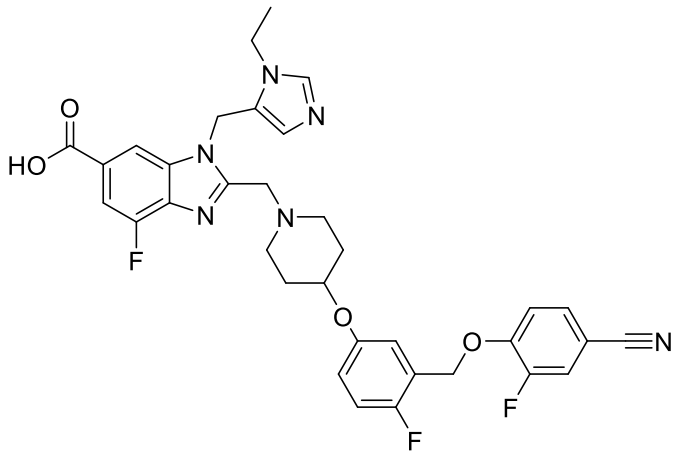
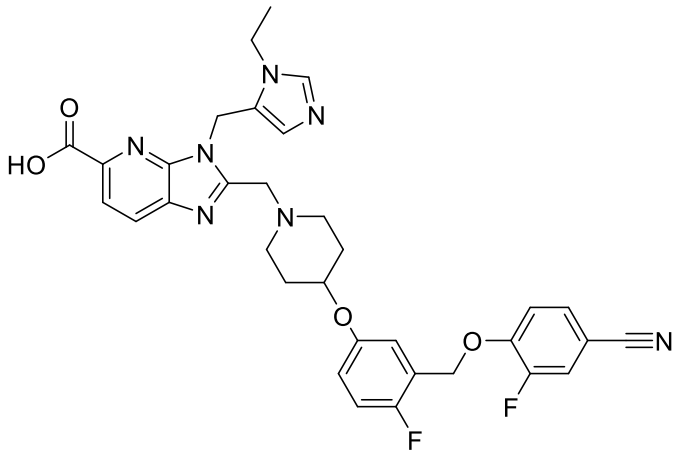
Compound NO.	**Structure**
Compound 1	
Compound 2	

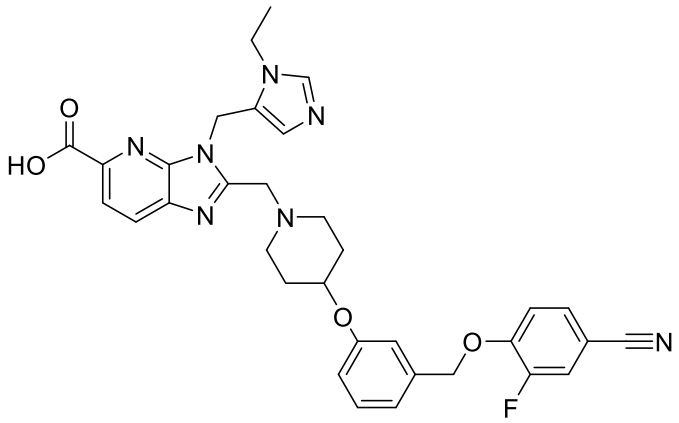
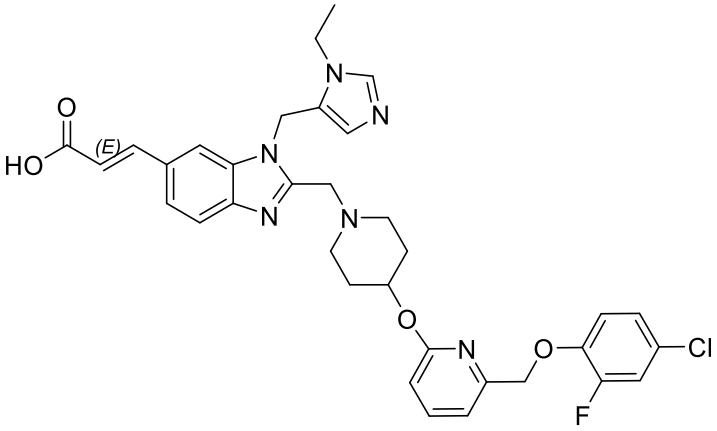
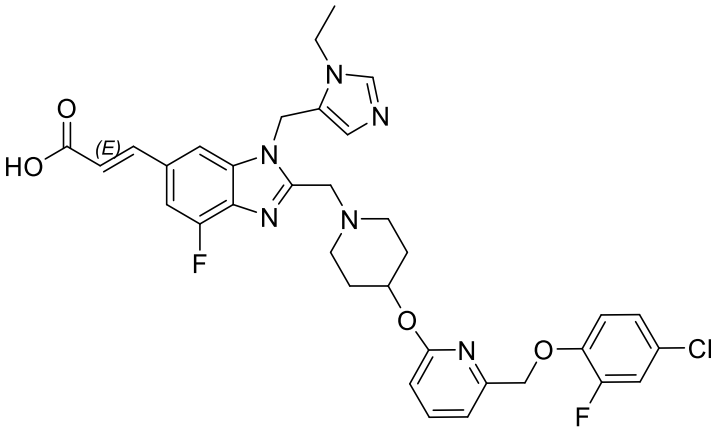
Compound 3	
Compound 4	
Compound 5	

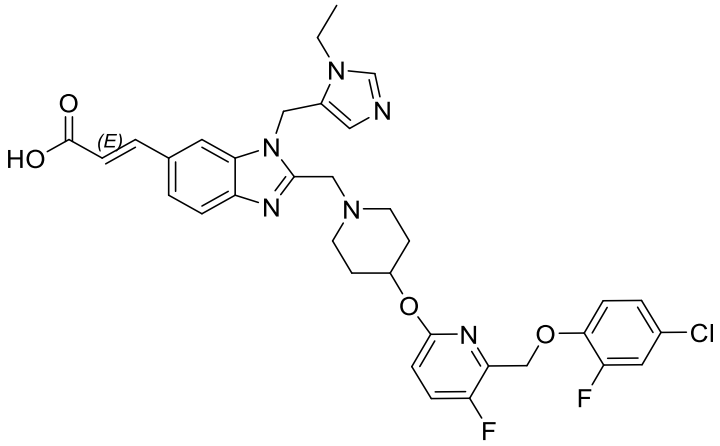
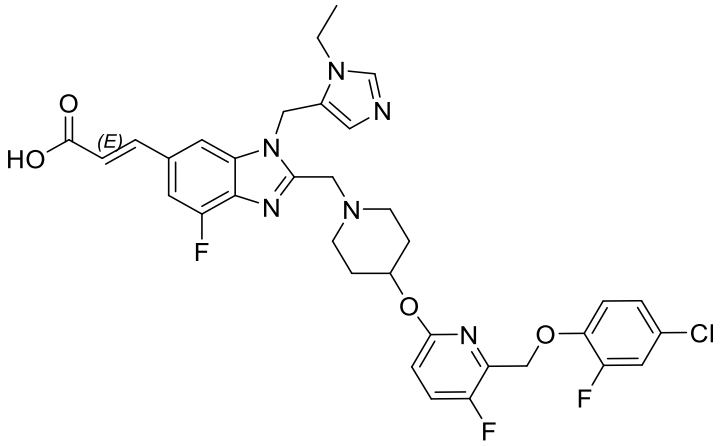
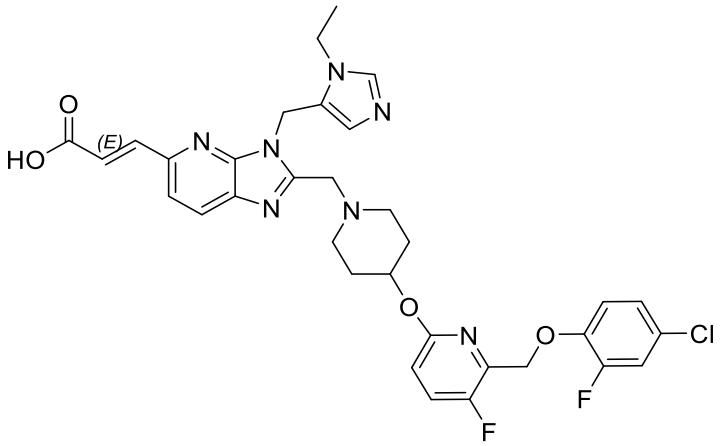
Compound 6	
Compound 7	
Compound 8	

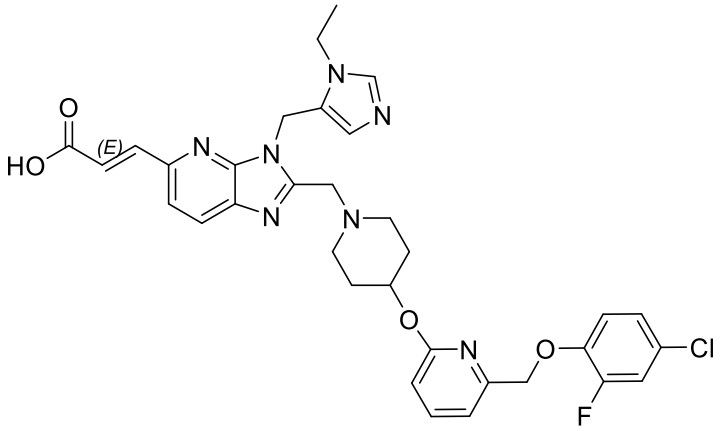
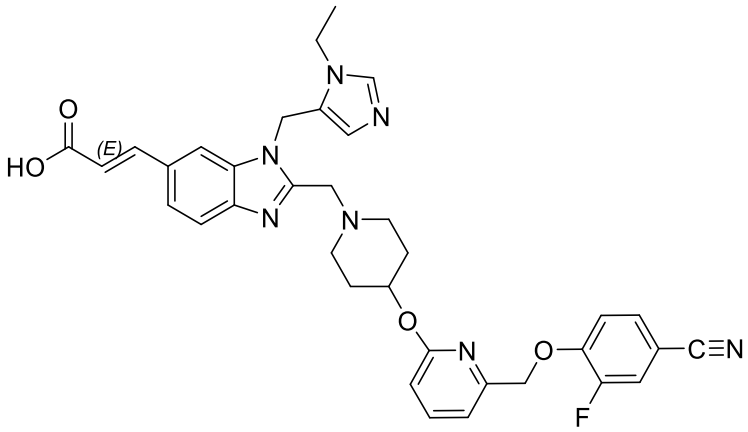
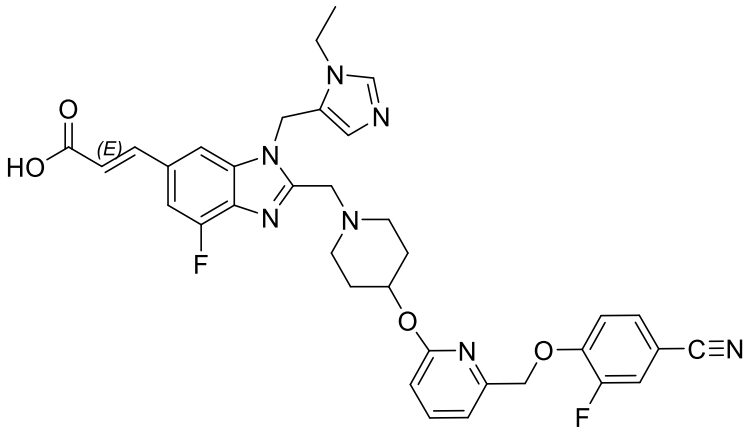
Compound 9	
Compound 10	
Compound 11	

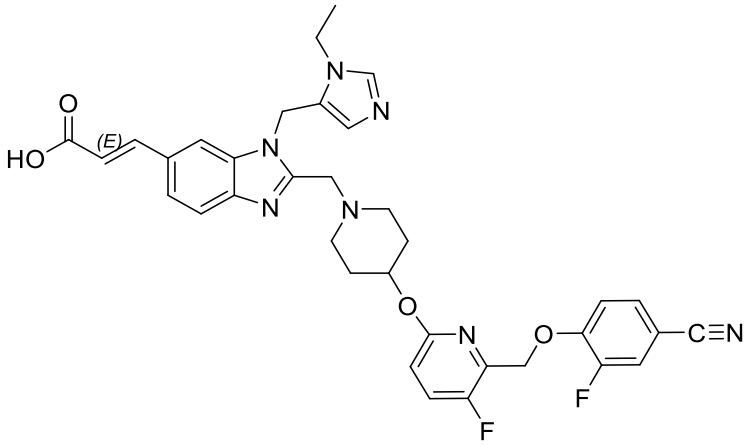
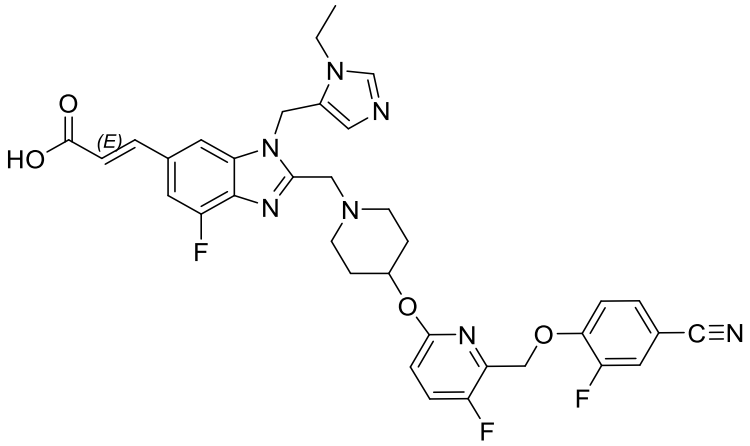
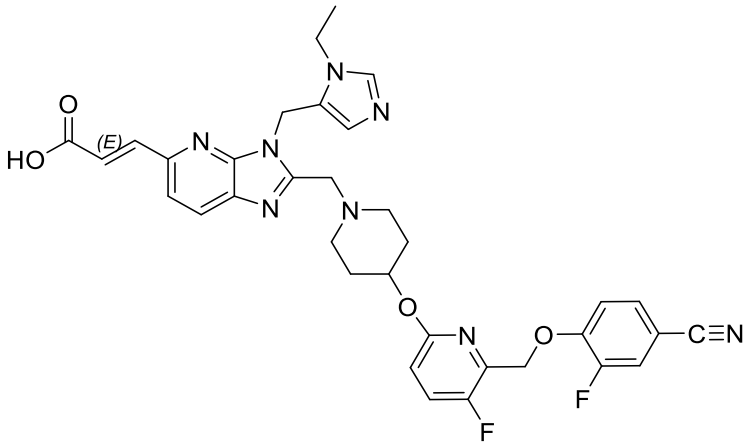
Compound 12	
Compound 13	
Compound 14	

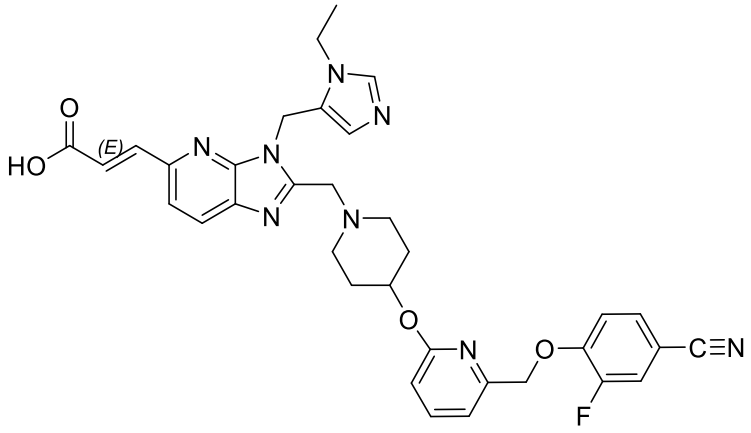
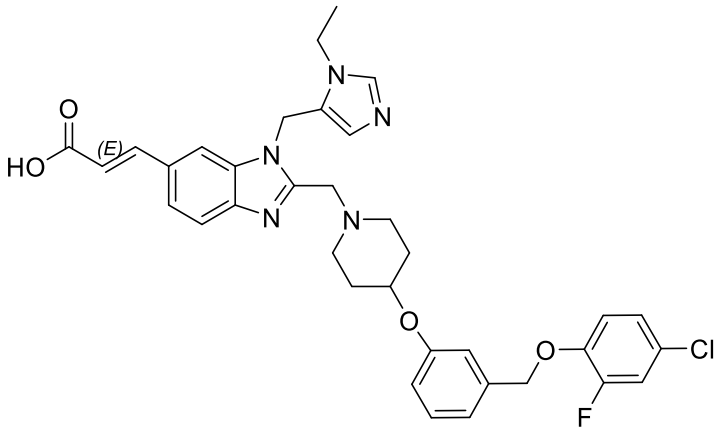
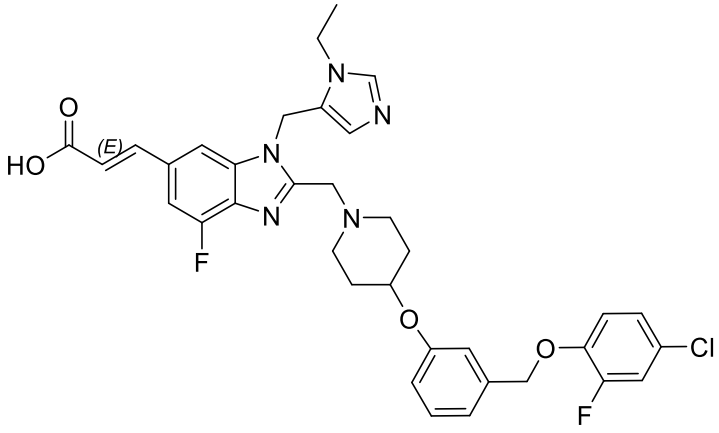
Compound 15	
Compound 16	
Compound 17	

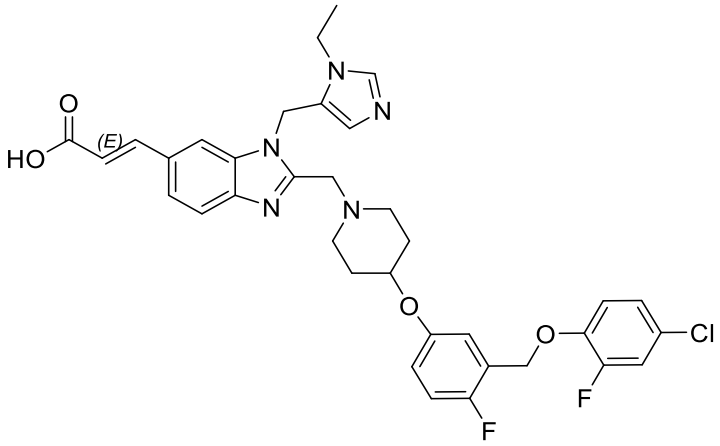
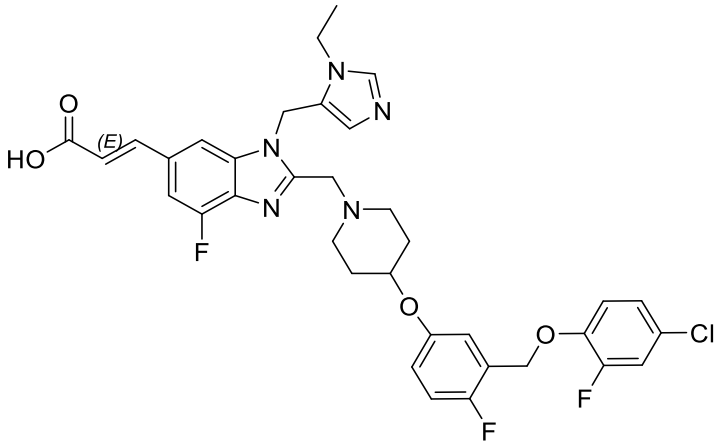
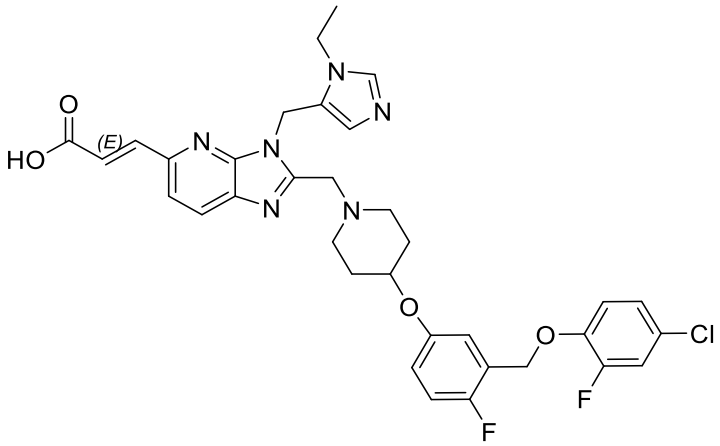
Compound 18	
Compound 19	
Compound 20	

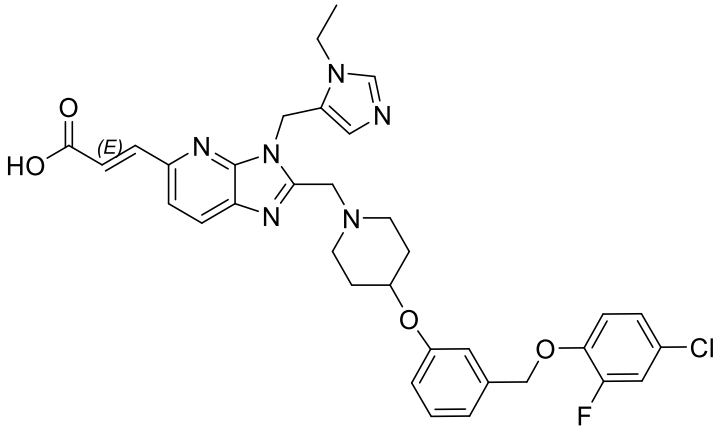
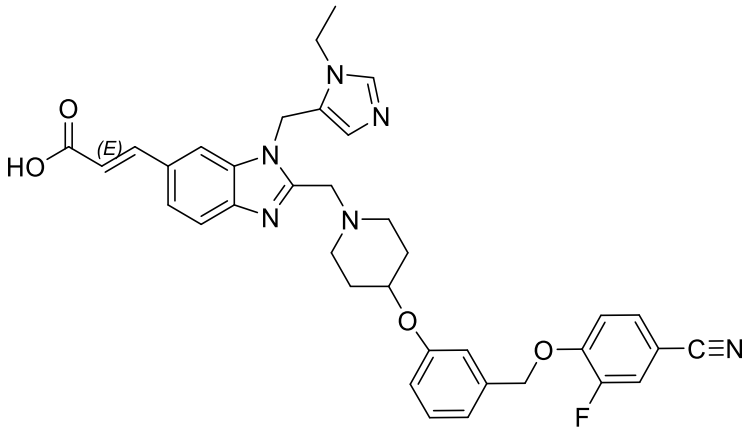
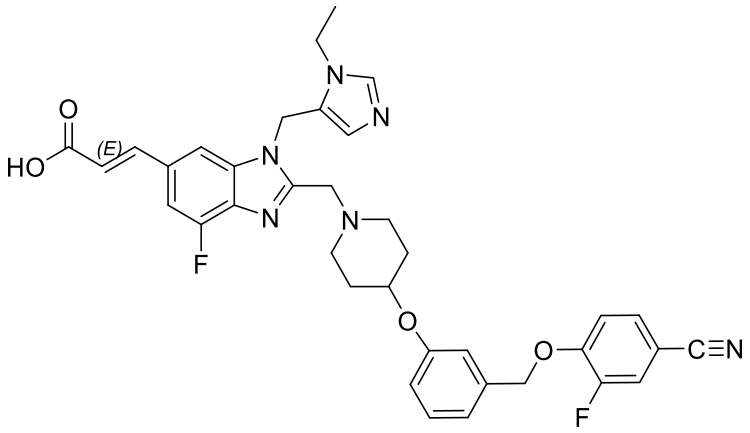
Compound 21	
Compound 22	
Compound 23	

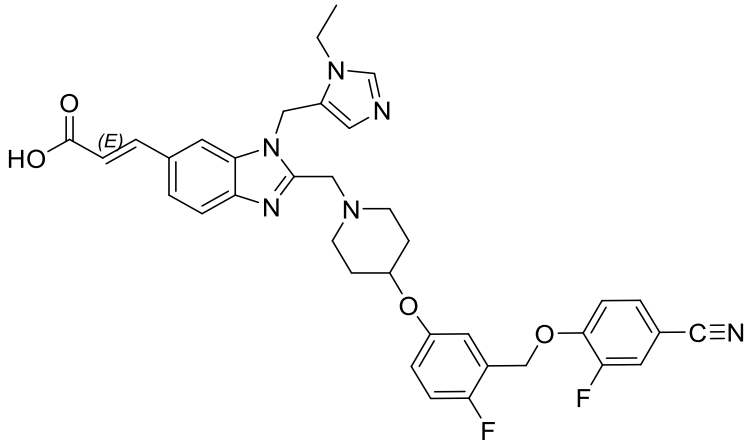
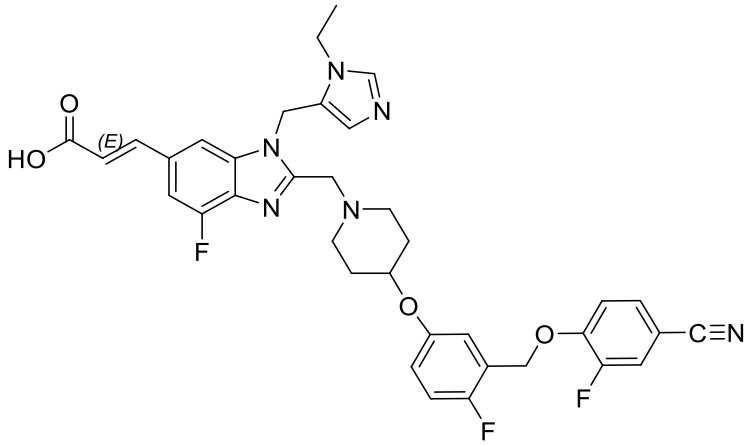
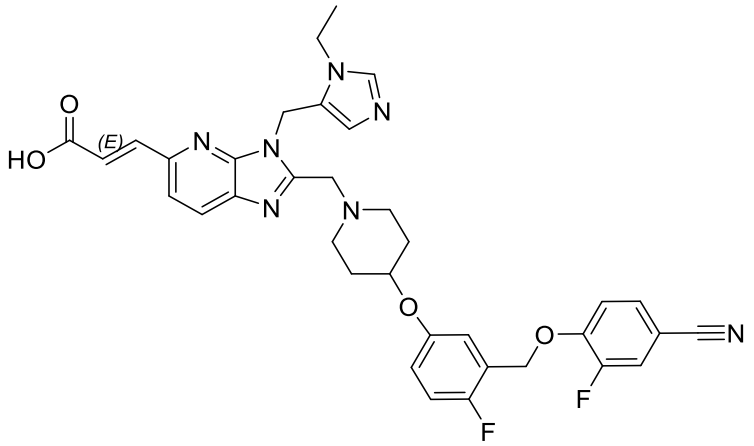
Compound 24	
Compound 25	
Compound 26	

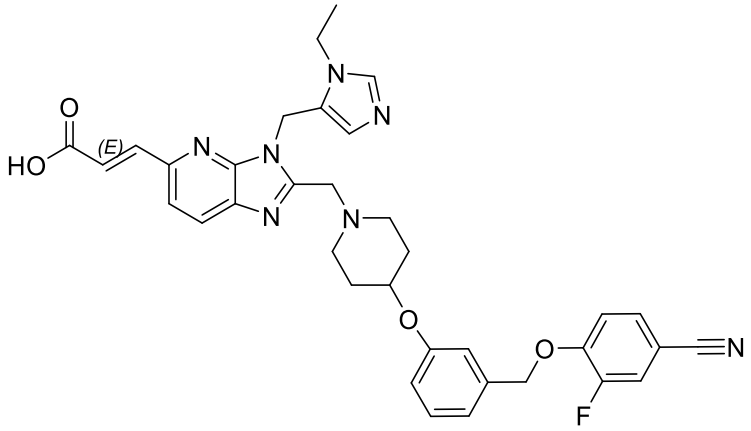
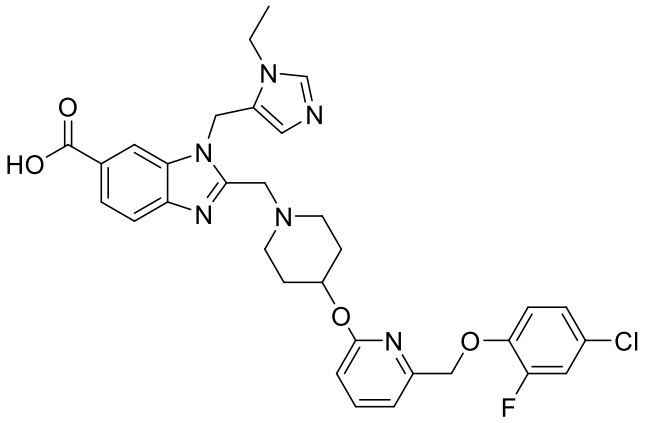
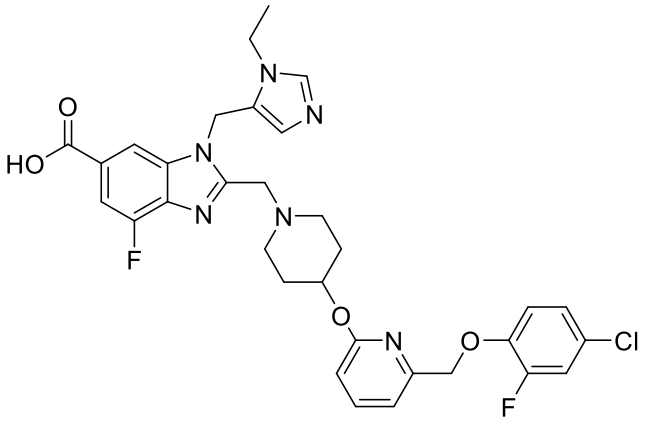
Compound 27	
Compound 28	
Compound 29	

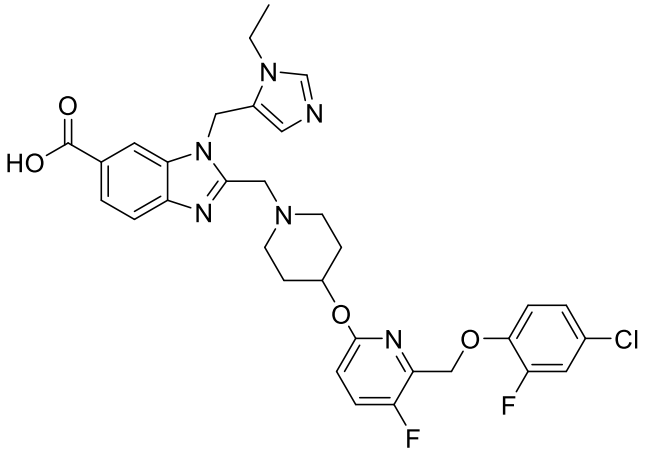
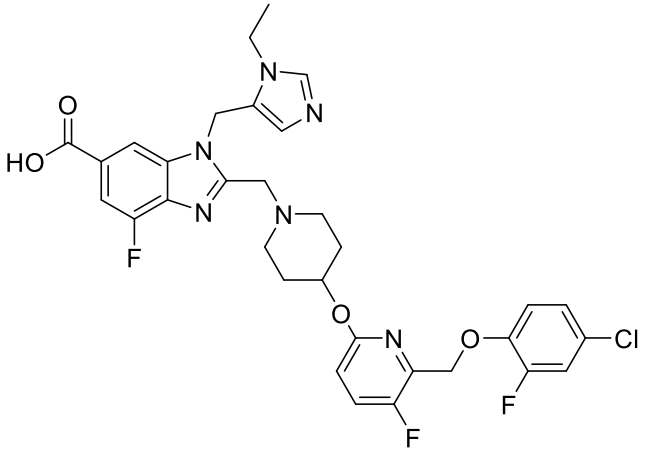
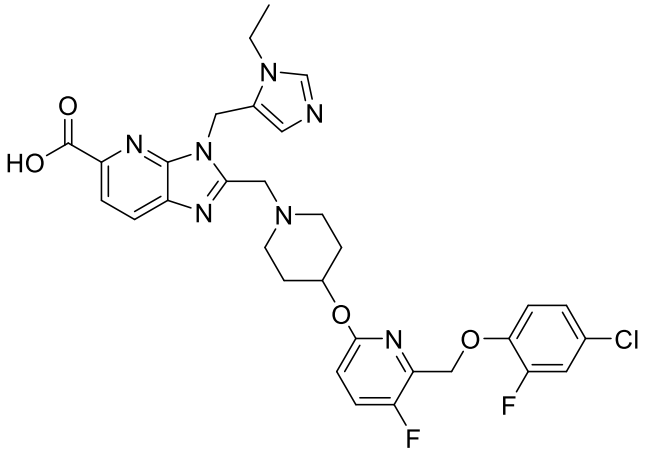
Compound 30	
Compound 31	
Compound 32	

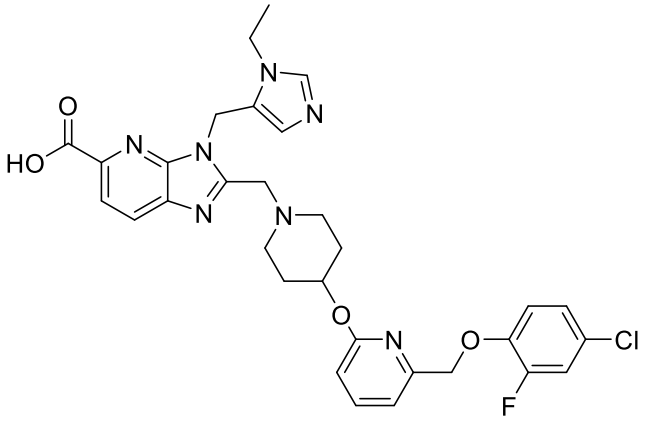
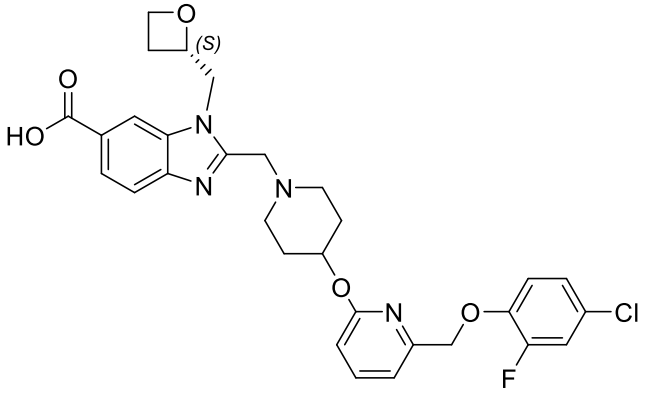
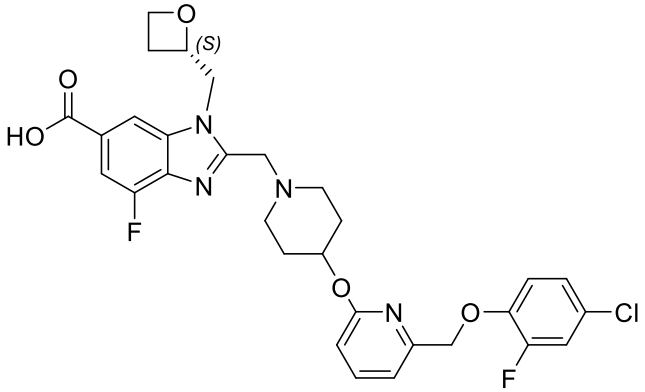
Compound 33	
Compound 34	
Compound 35	

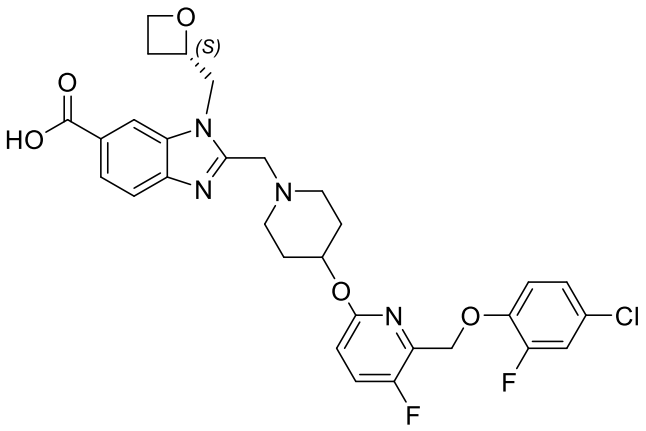
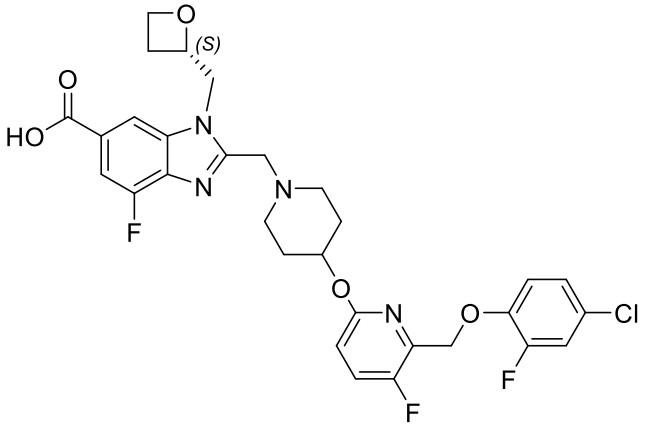
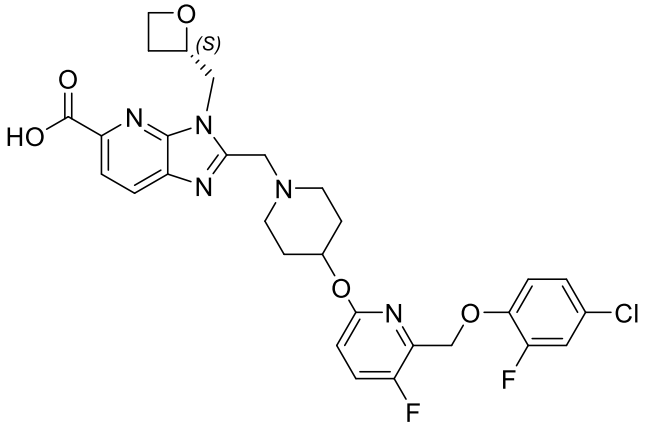
Compound 36	
Compound 37	
Compound 38	

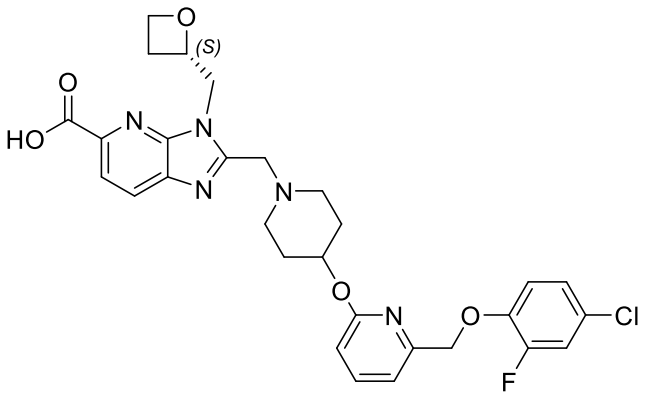
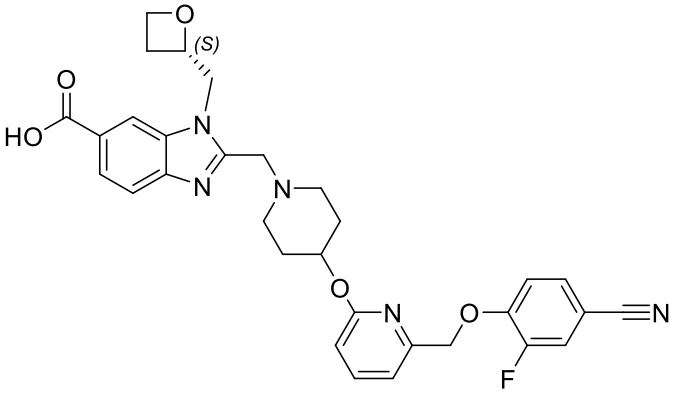
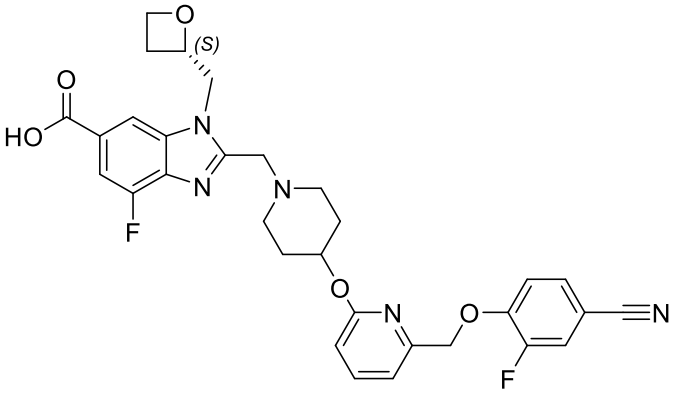
Compound 39	
Compound 40	
Compound 41	

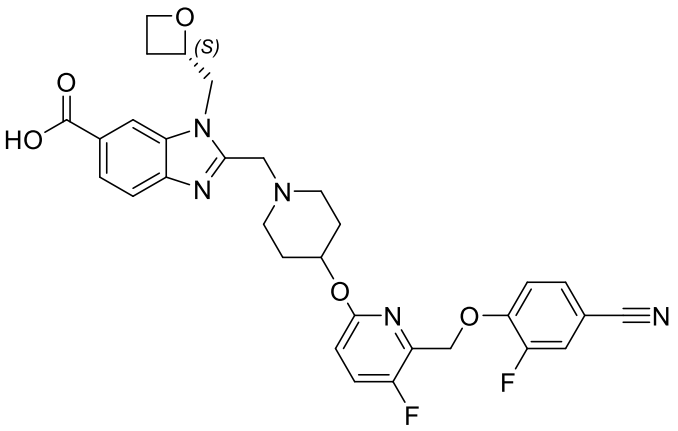
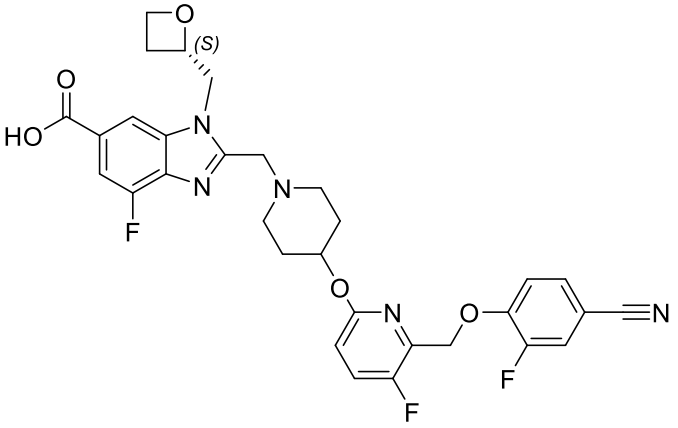
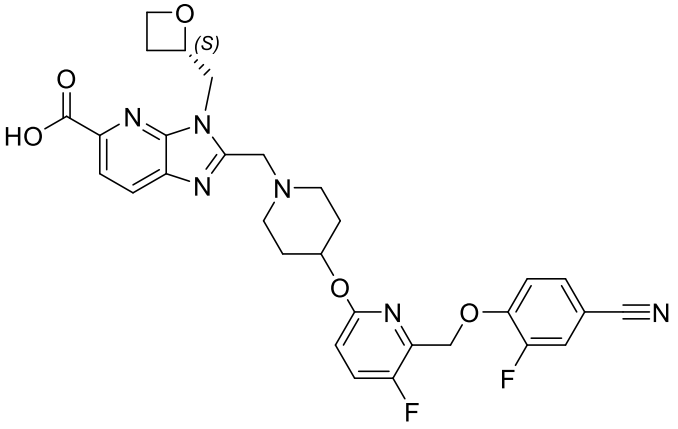
Compound 42	
Compound 43	
Compound 44	

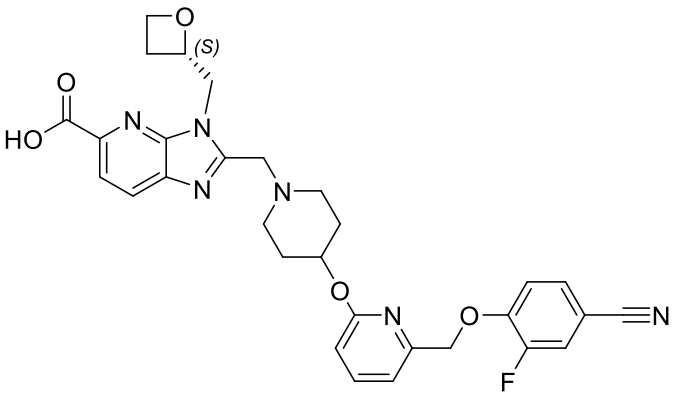
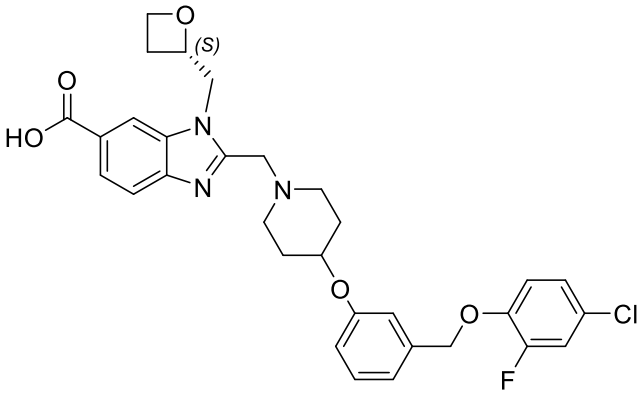
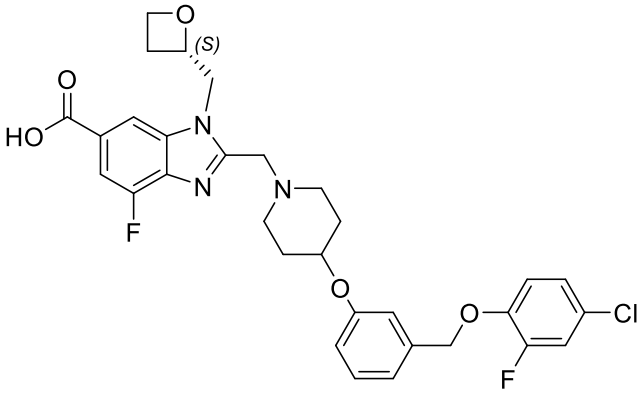
Compound 45	
Compound 46	
Compound 47	

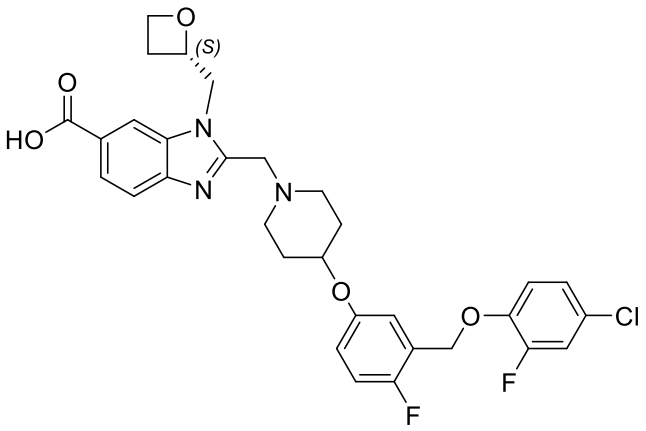
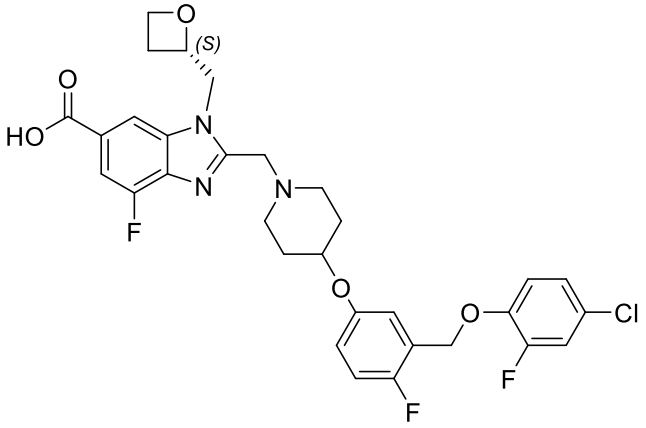
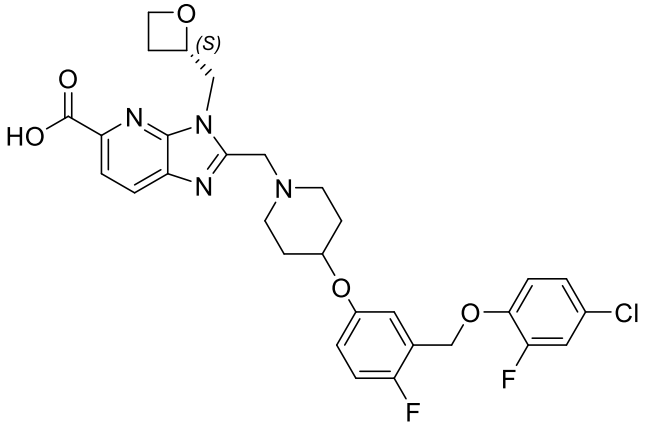
Compound 48	
Compound 49	
Compound 50	

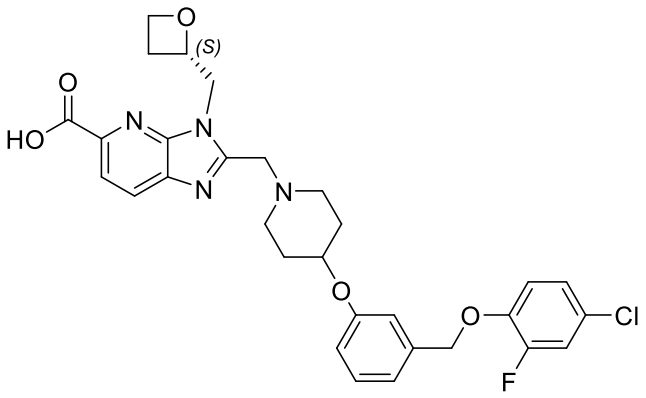
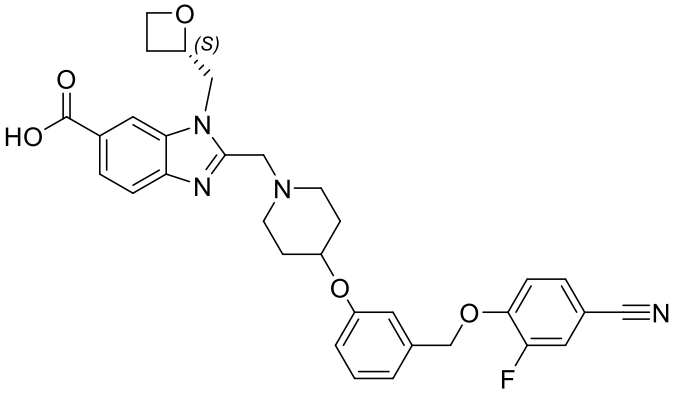
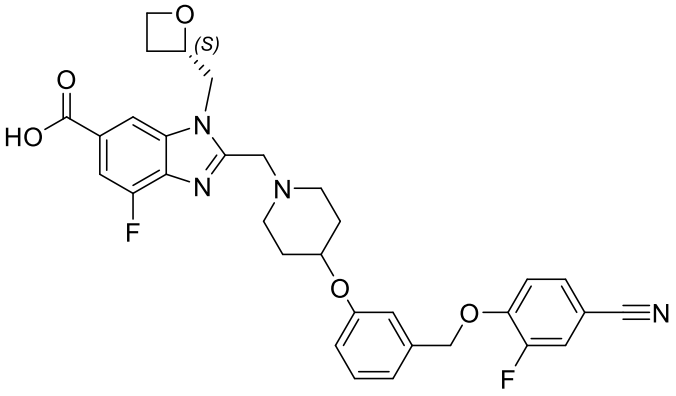
Compound 51	
Compound 52	
Compound 53	

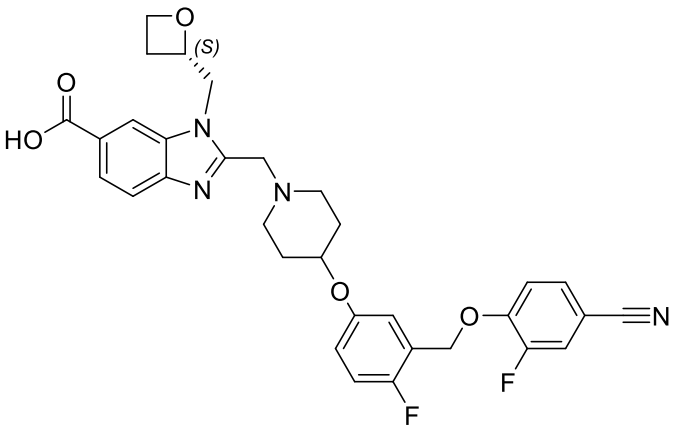
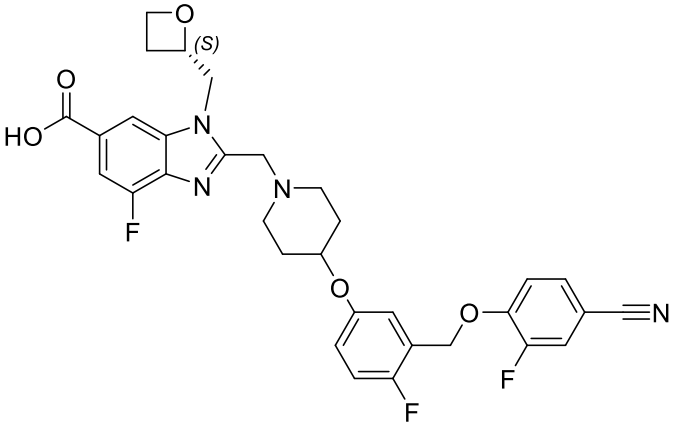
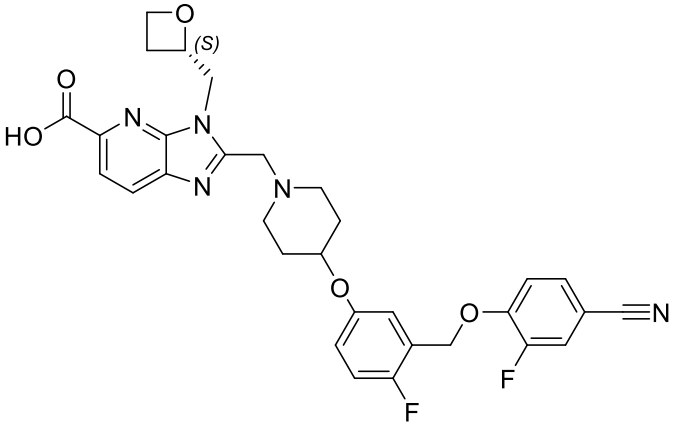
Compound 54	
Compound 55	
Compound 56	

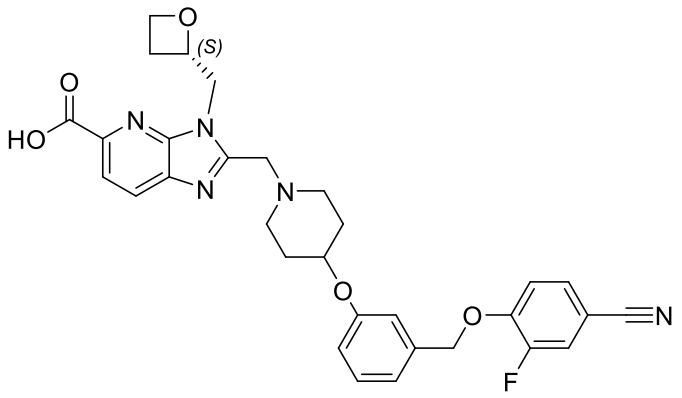
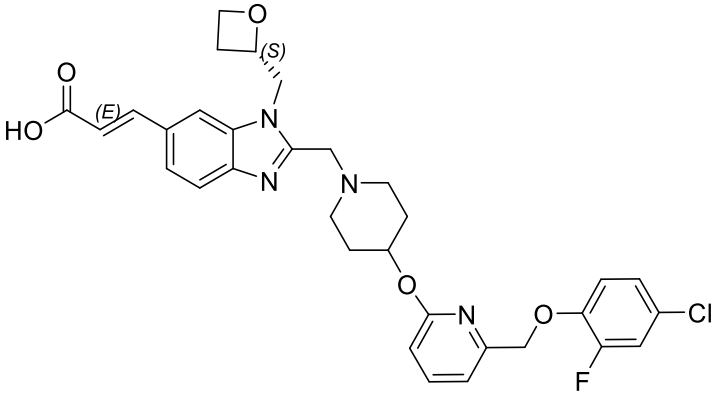
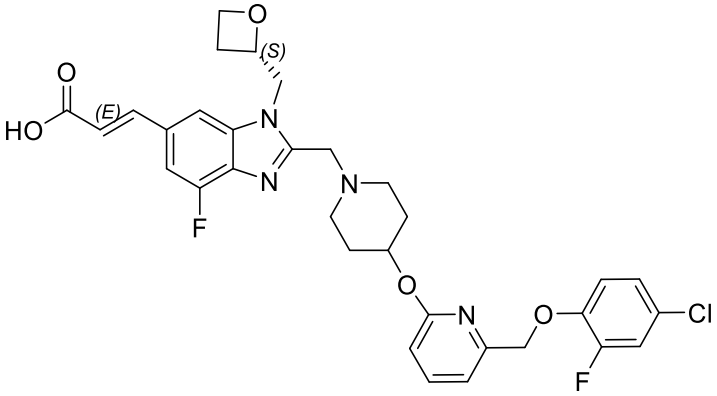
Compound 57	
Compound 58	
Compound 59	

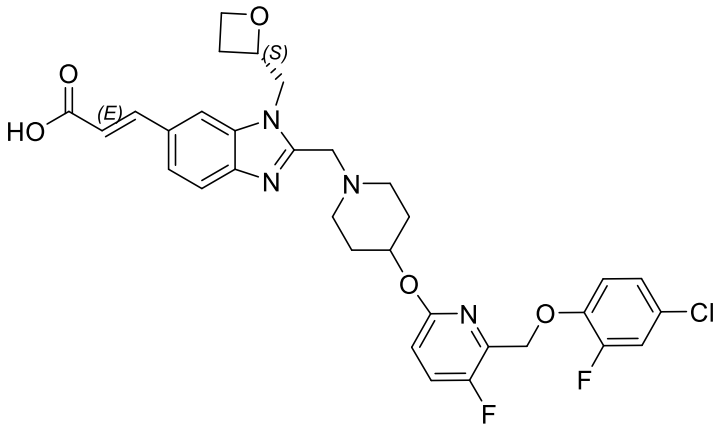
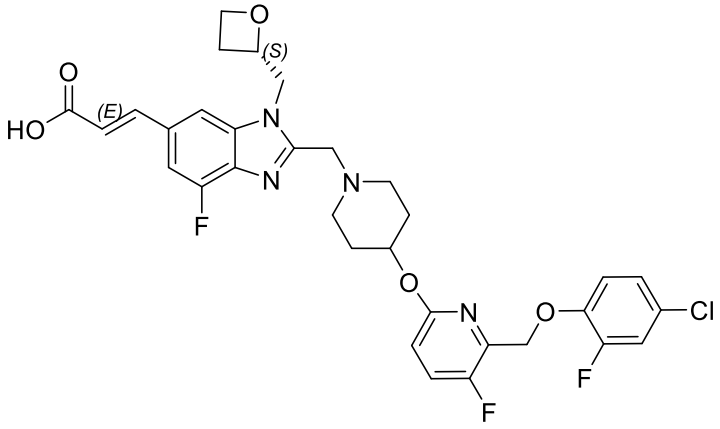
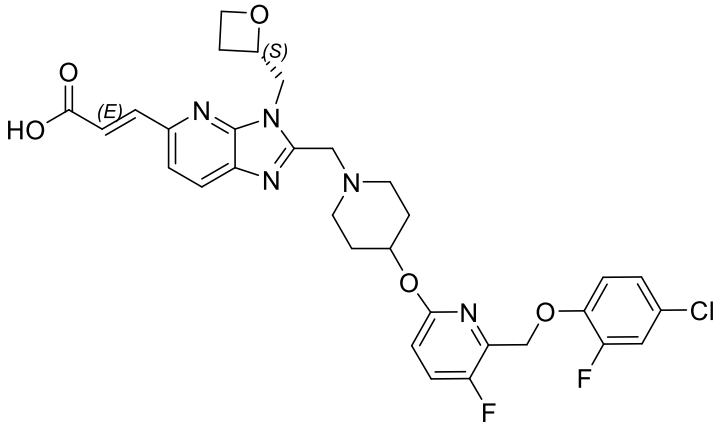
Compound 60	
Compound 61	
Compound 62	

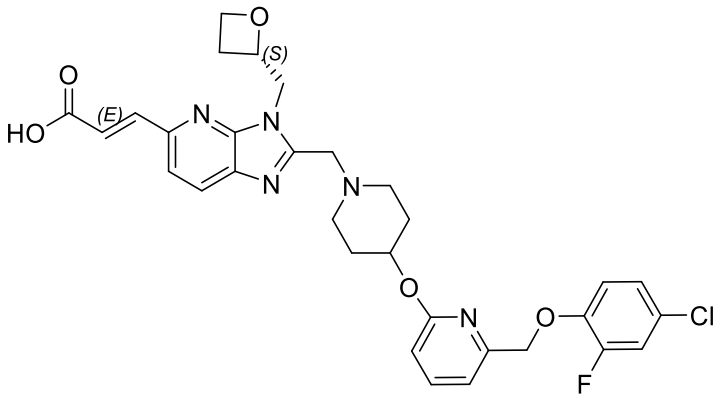
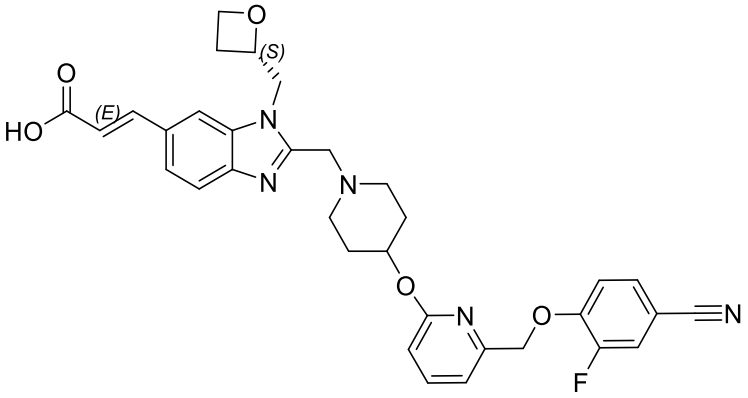
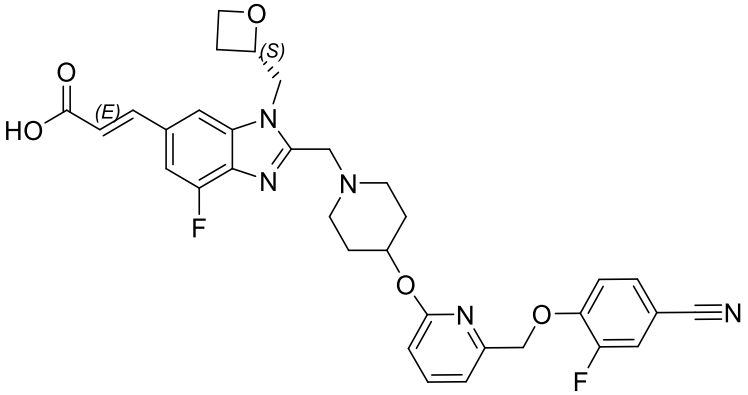
Compound 63	
Compound 64	
Compound 65	

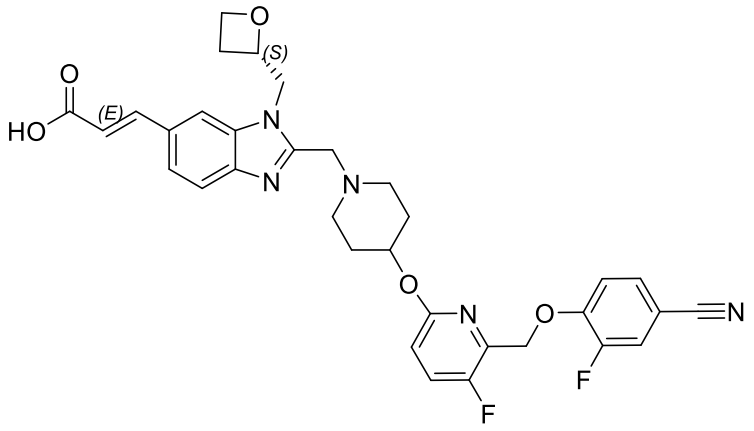
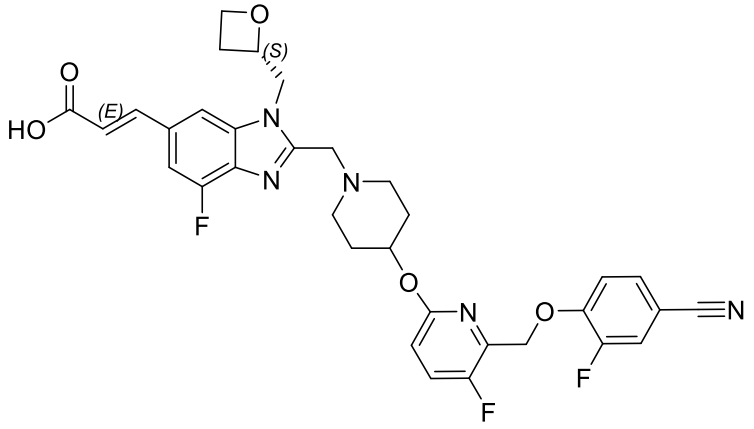
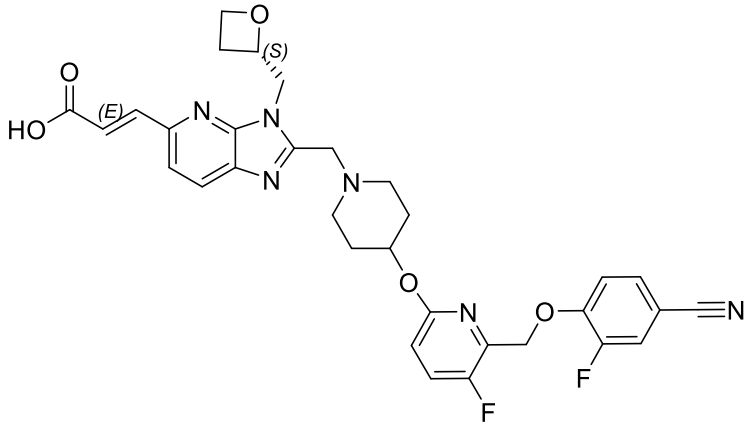
Compound 66	
Compound 67	
Compound 68	

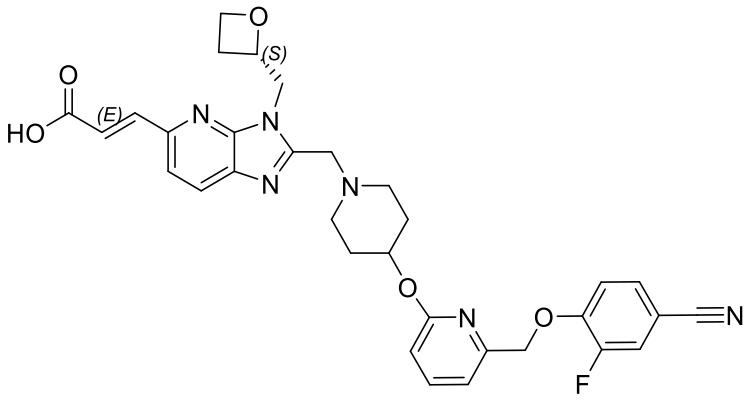
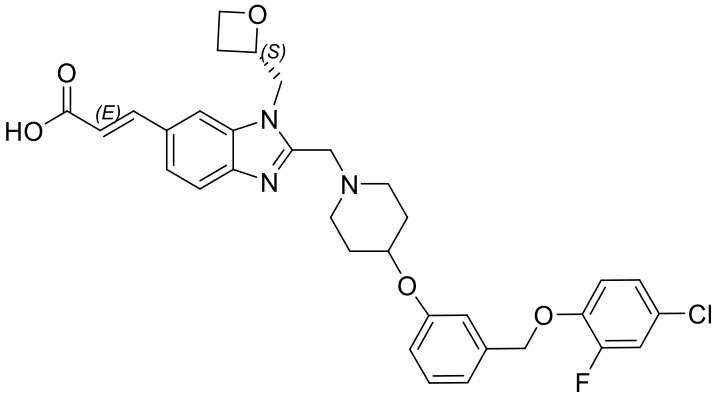
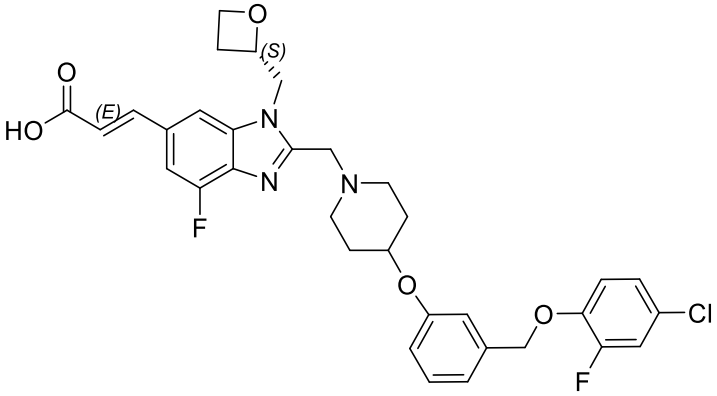
Compound 69	
Compound 70	
Compound 71	

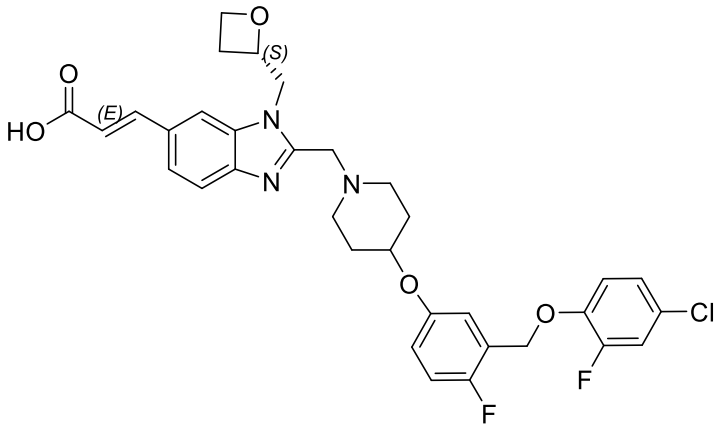
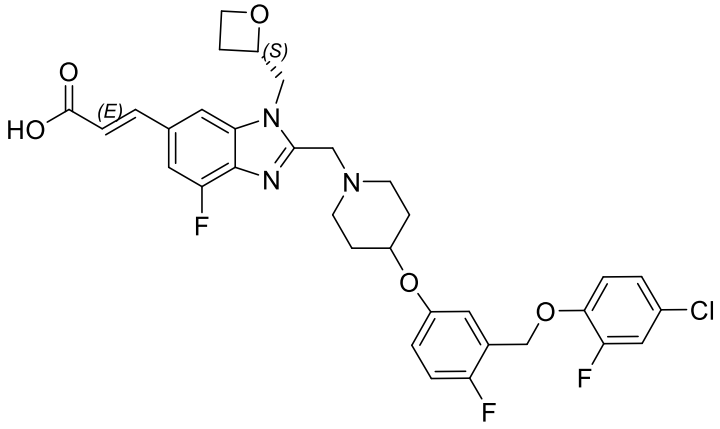
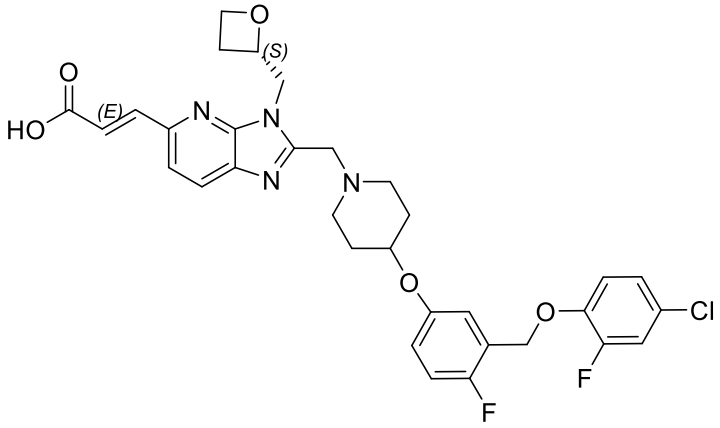
Compound 72	
Compound 73	
Compound 74	

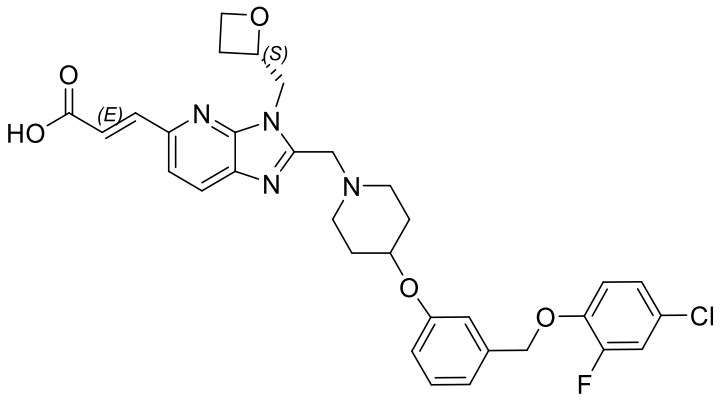
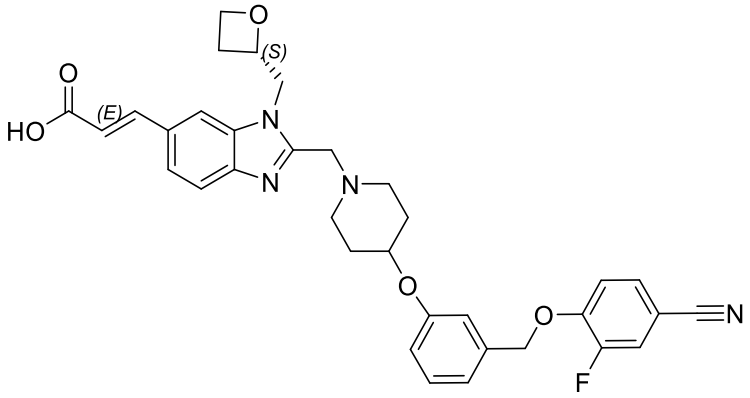
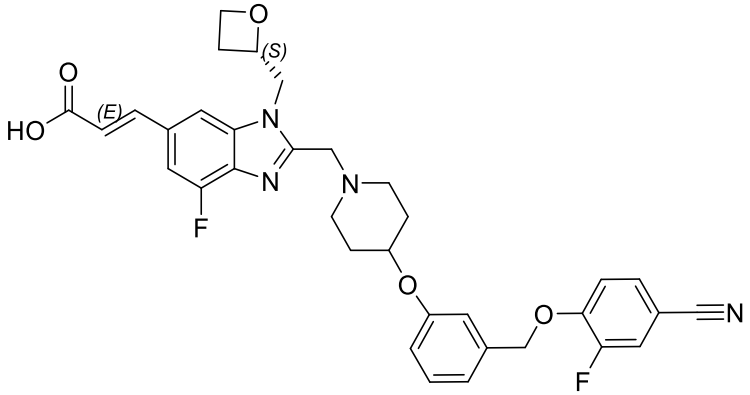
Compound 75	
Compound 76	
Compound 77	

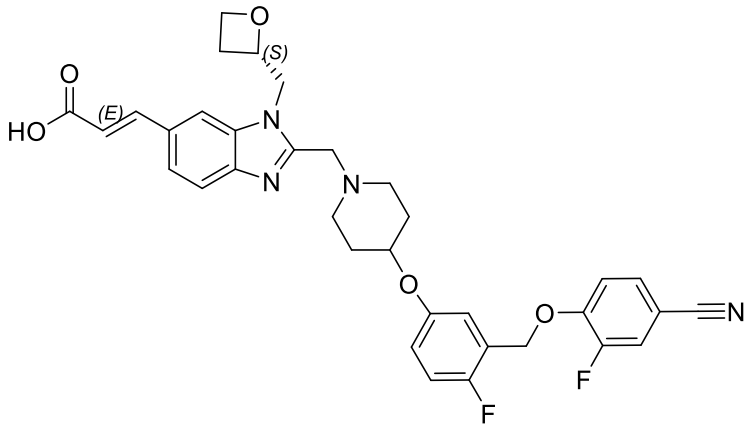
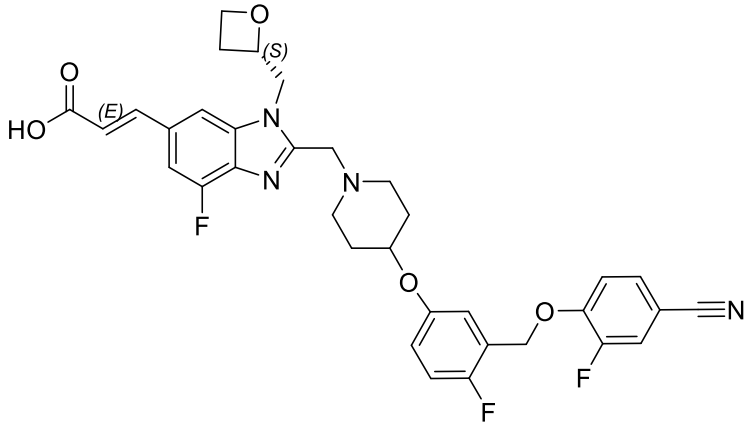
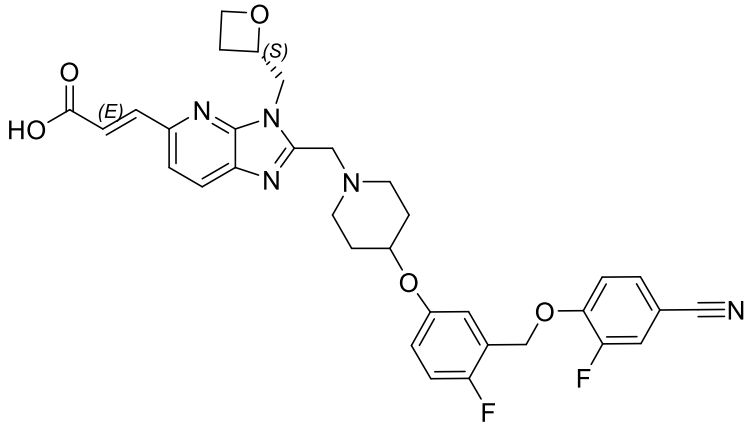
Compound 78	
Compound 79	
Compound 80	

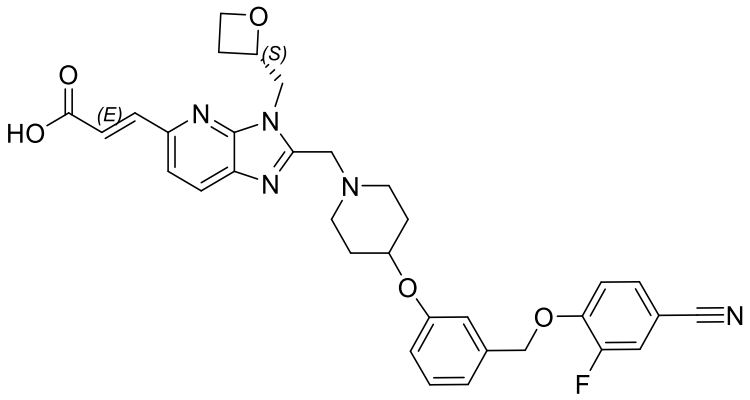
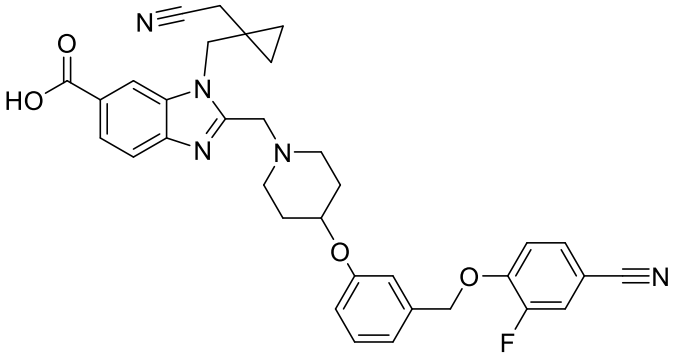
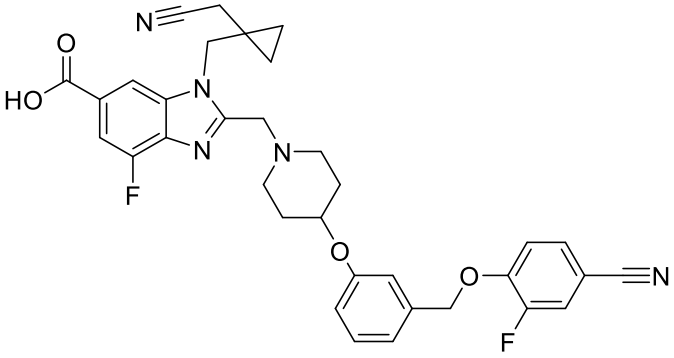
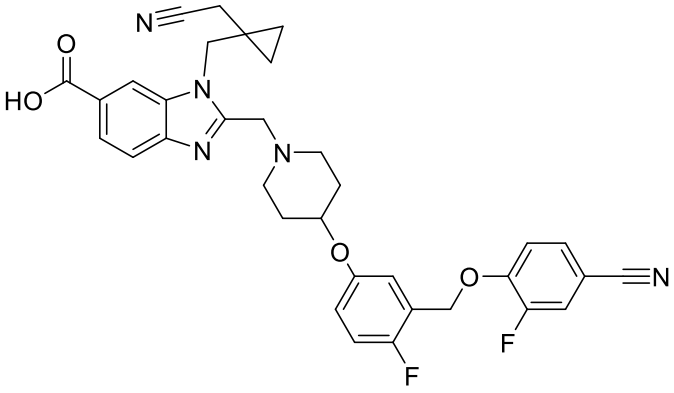
Compound 81	
Compound 82	
Compound 83	

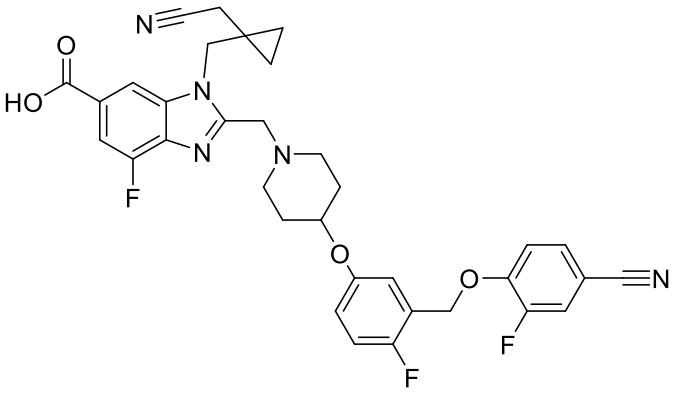
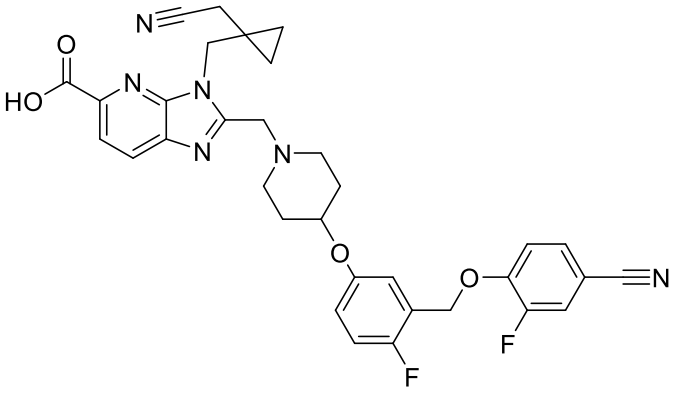
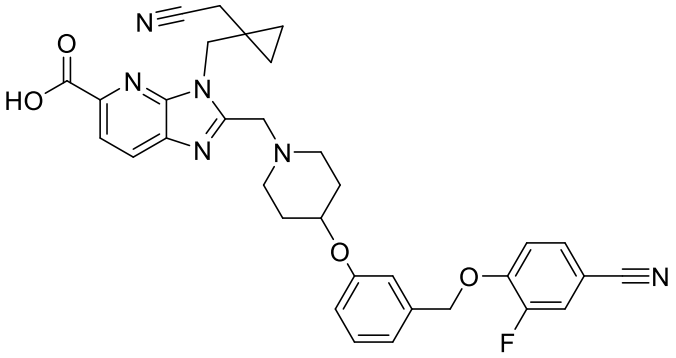
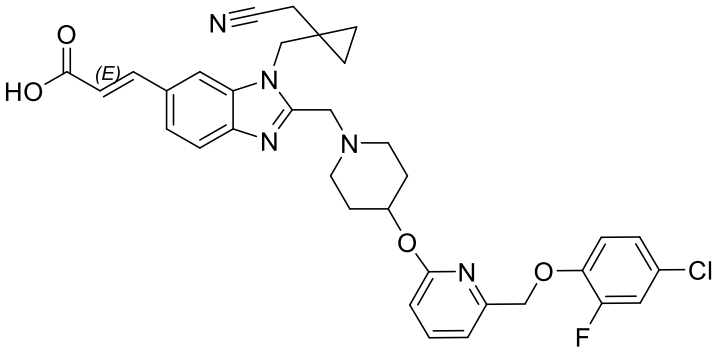
Compound 84	
Compound 85	
Compound 86	

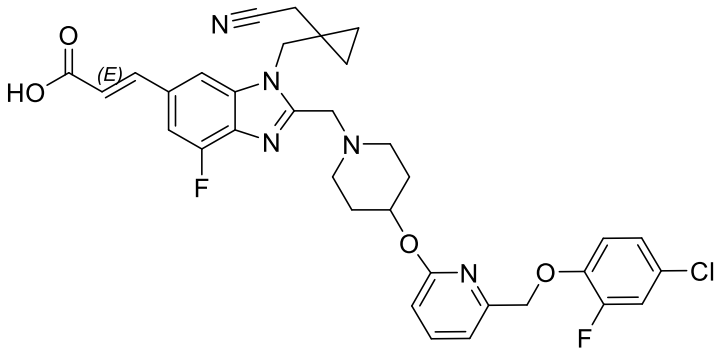
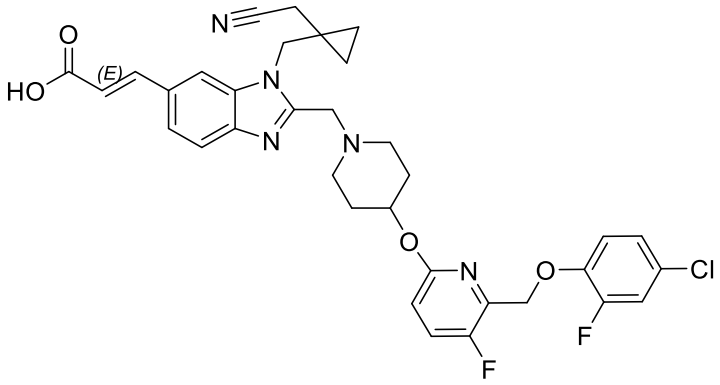
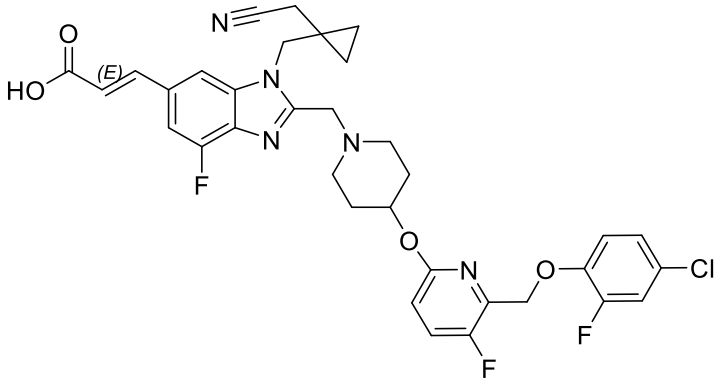
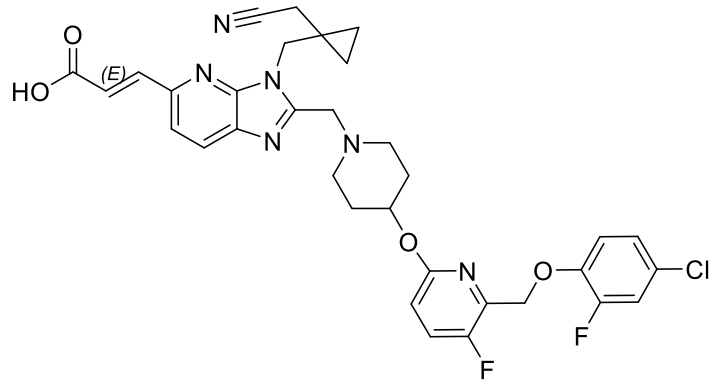
Compound 87	
Compound 88	
Compound 89	

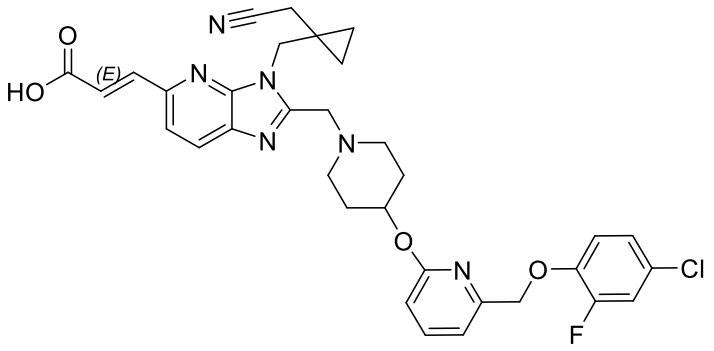
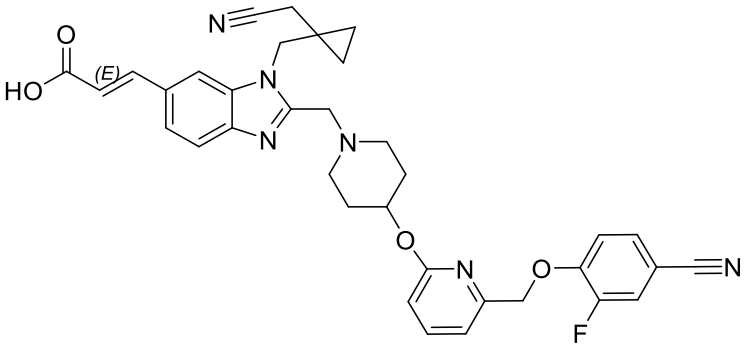
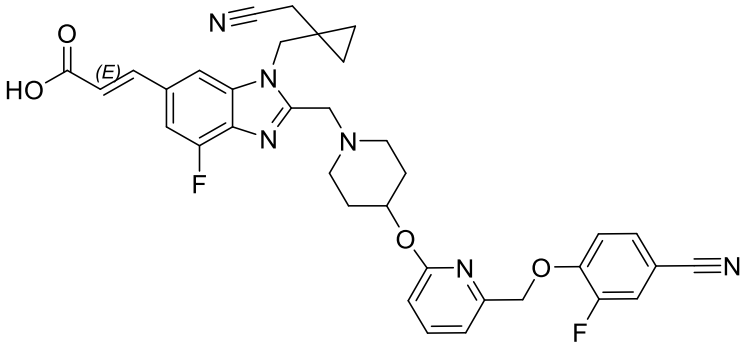
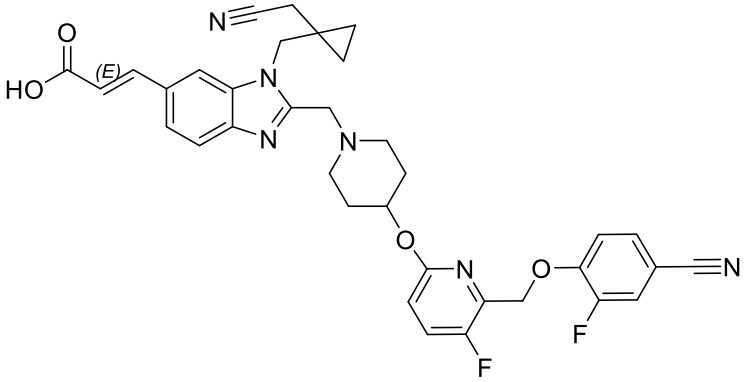
Compound 90	
Compound 91	
Compound 92	

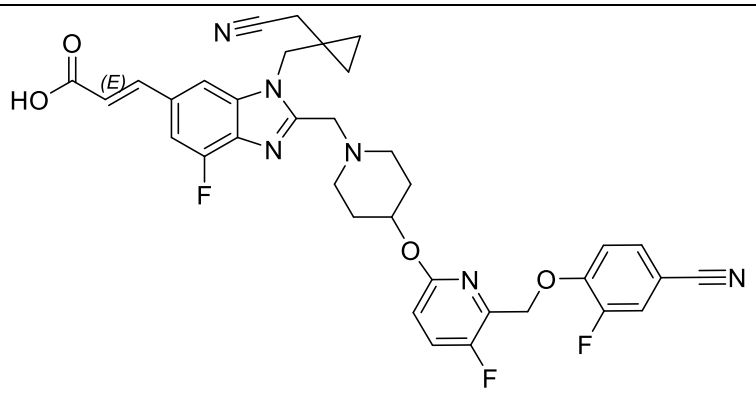
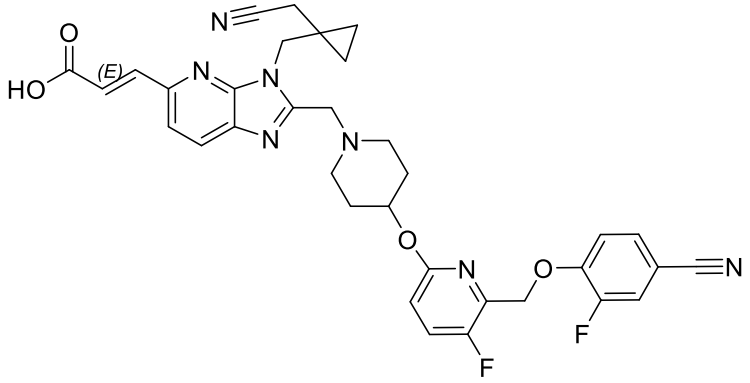
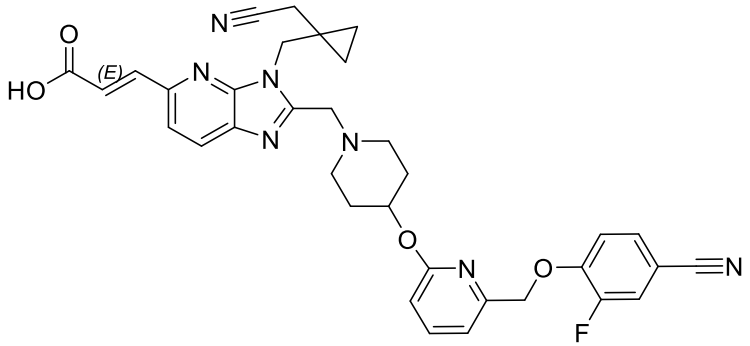
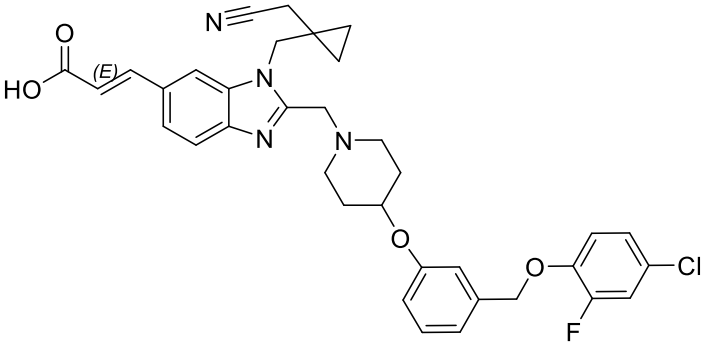
Compound 93	
Compound 94	
Compound 95	

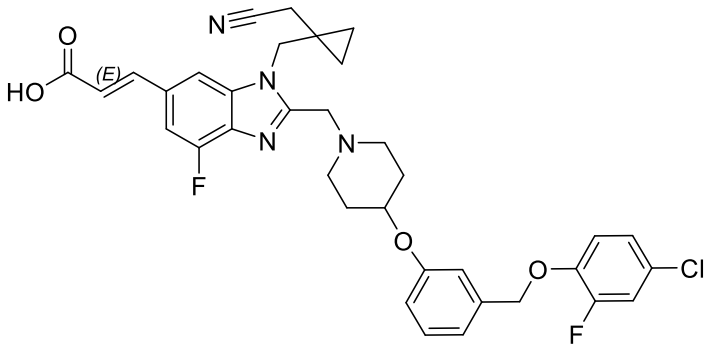
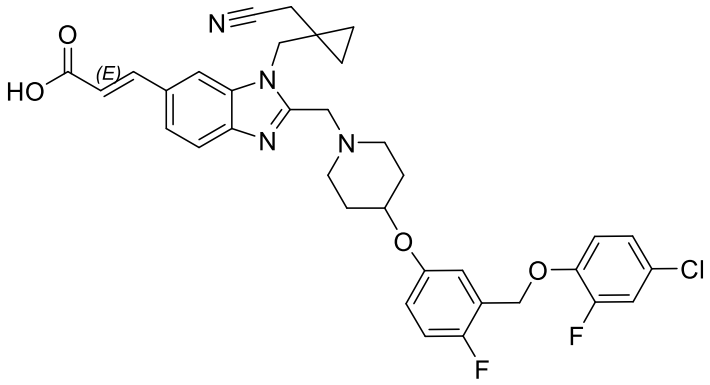
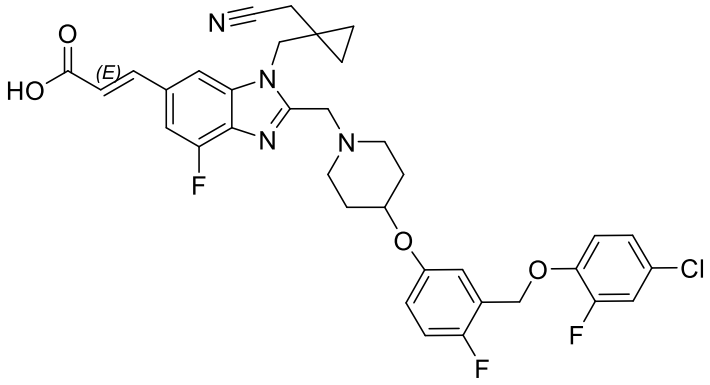
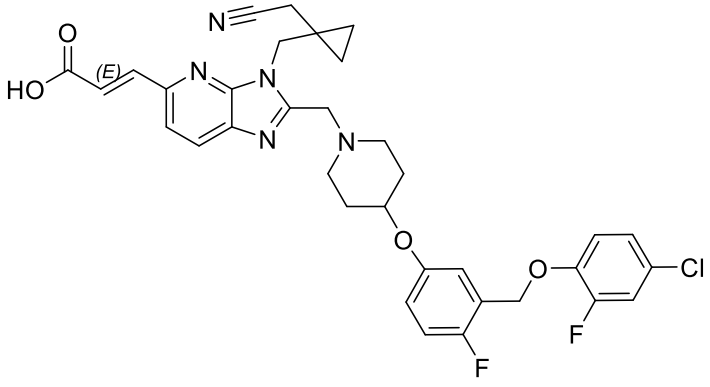
Compound 96	
Compound 97	
Compound 98	
Compound 99	

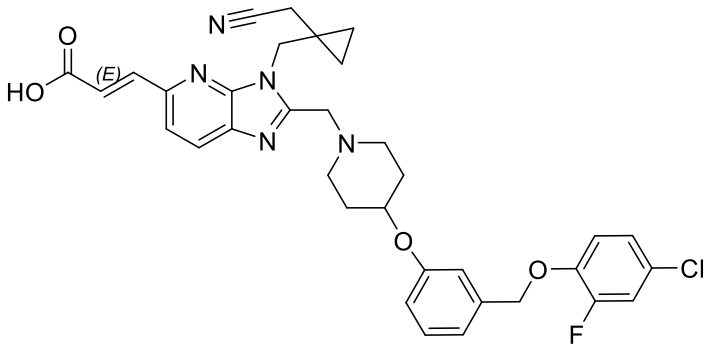
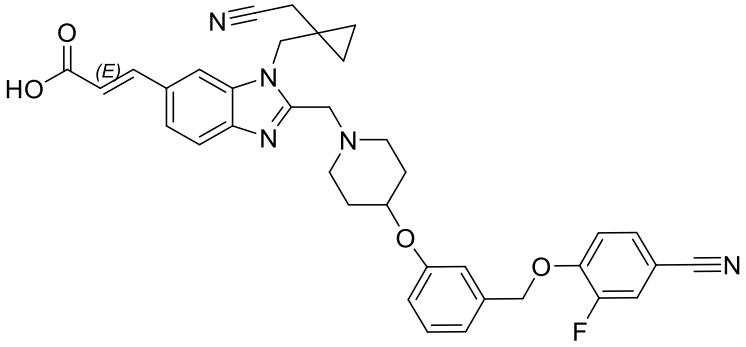
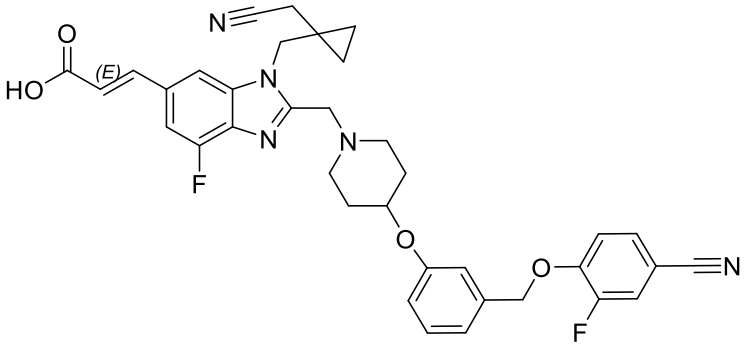
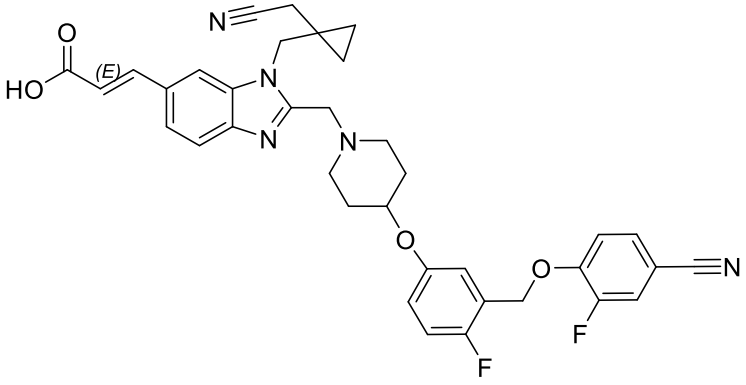
Compound 100	
Compound 101	
Compound 102	
Compound 103	

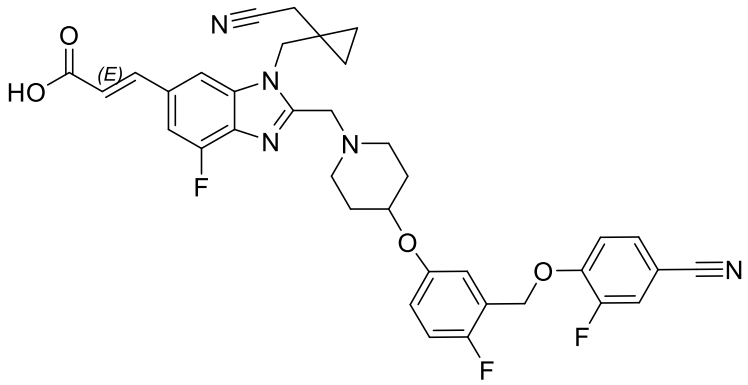
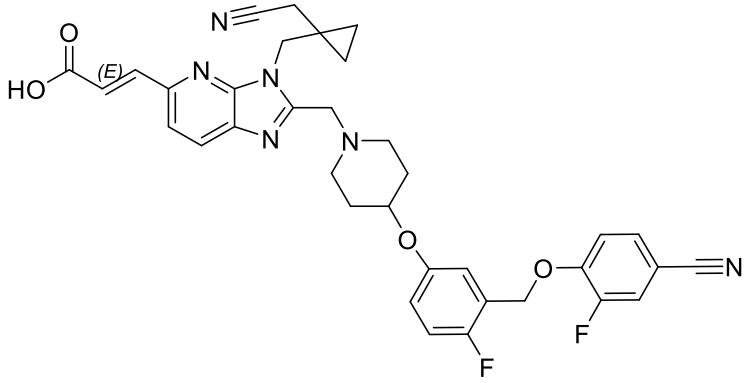
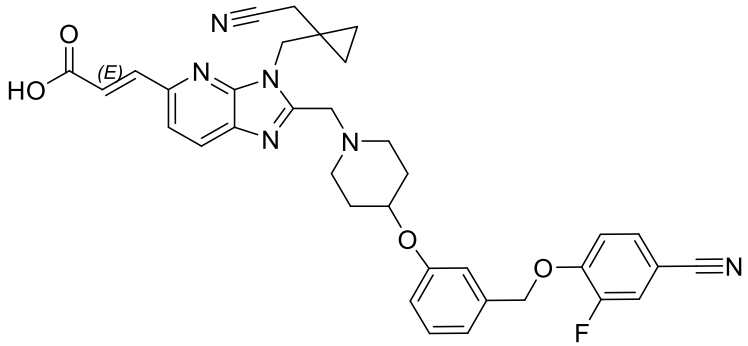
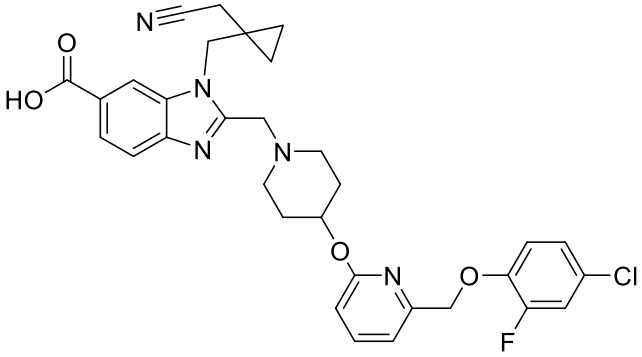
Compound 104	
Compound 105	
Compound 106	
Compound 107	

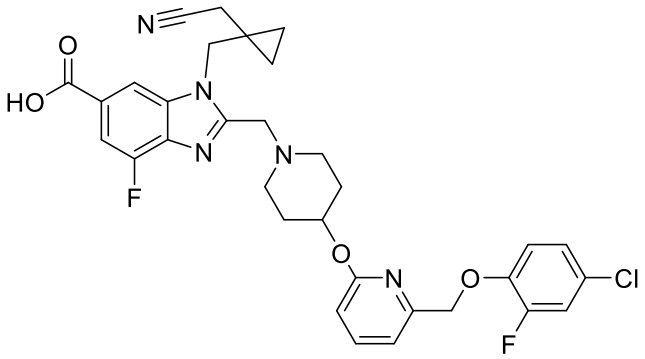
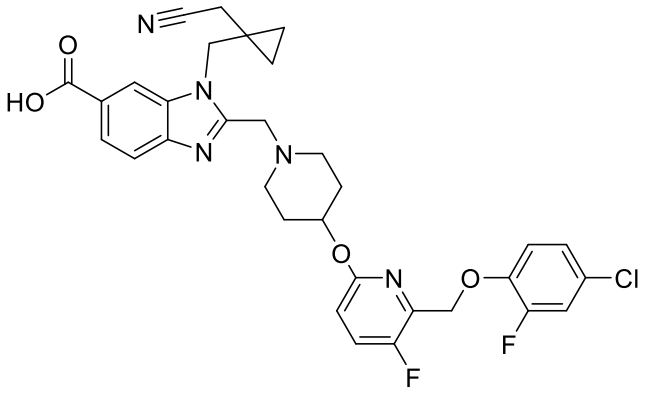
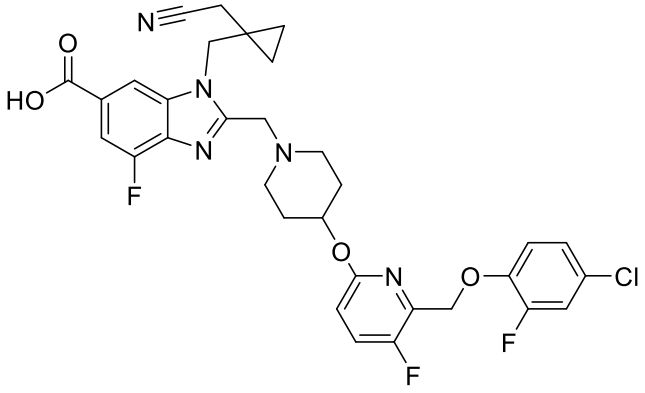
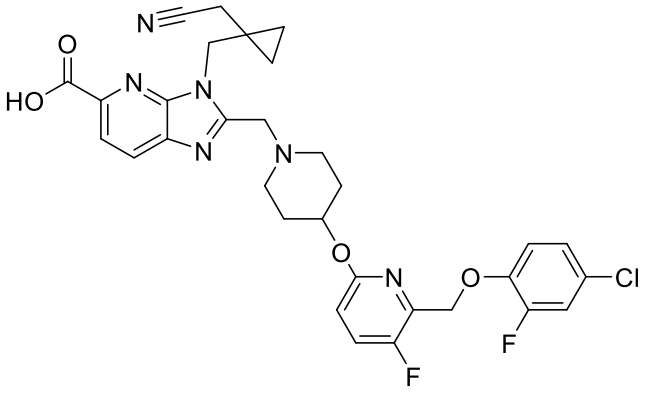
Compound 108	
Compound 109	
Compound 110	
Compound 111	

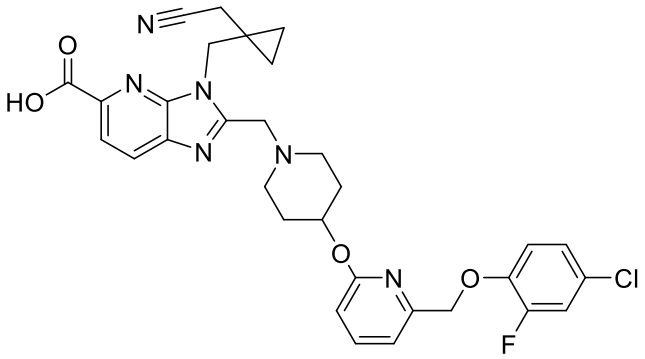
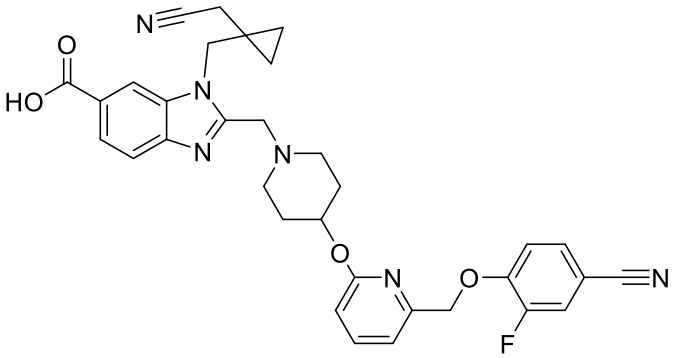
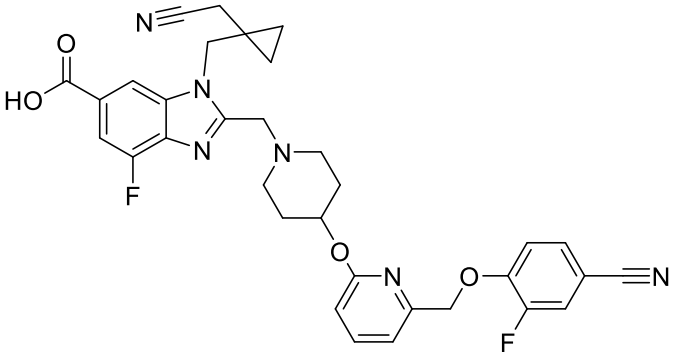
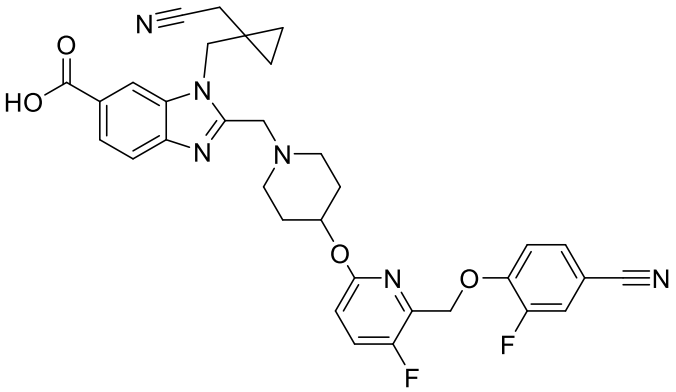
Compound 112	
Compound 113	
Compound 114	
Compound 115	

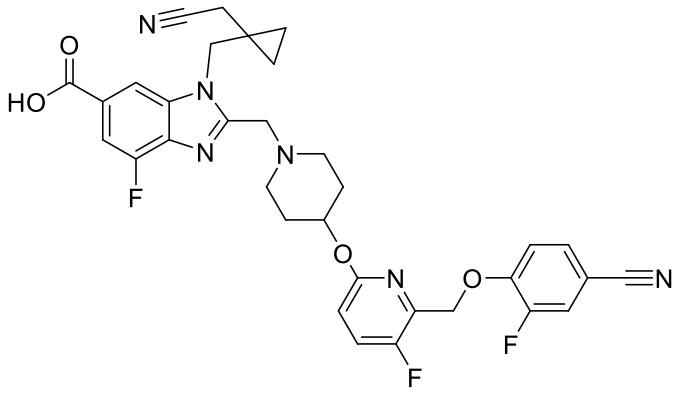
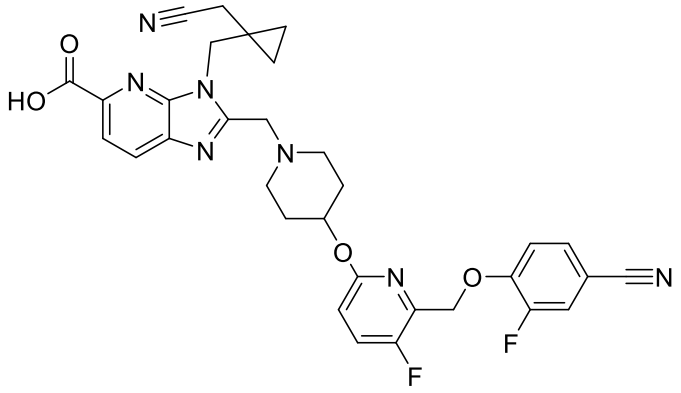
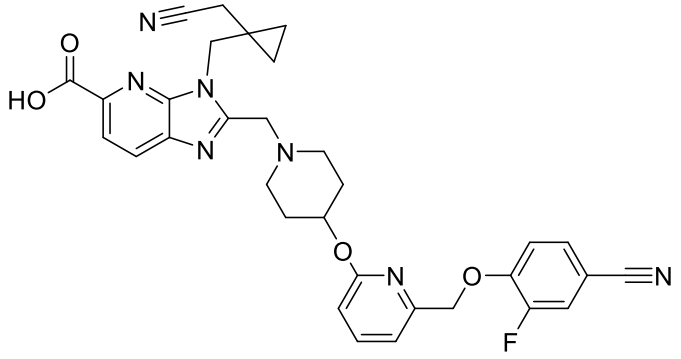
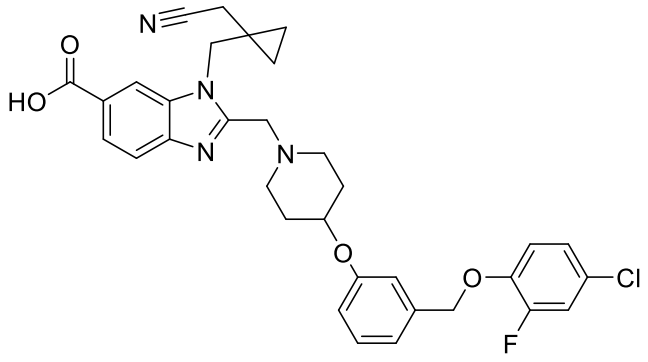
Compound 116	
Compound 117	
Compound 118	
Compound 119	

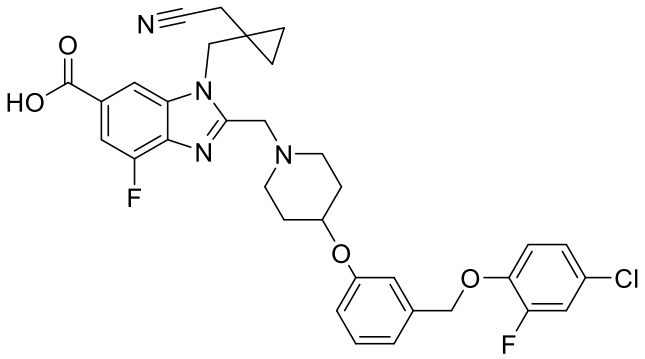
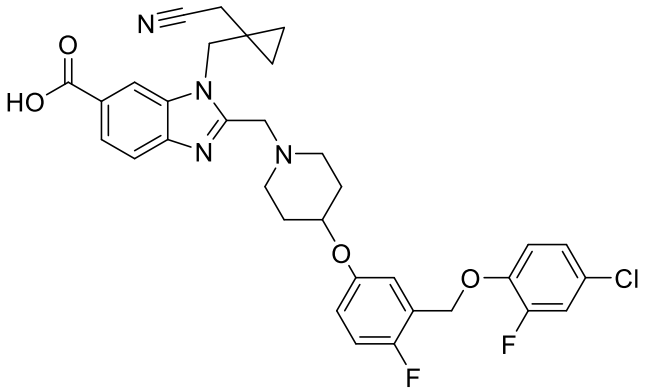
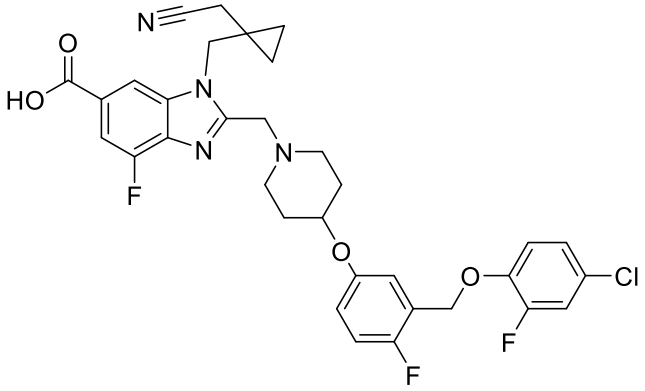
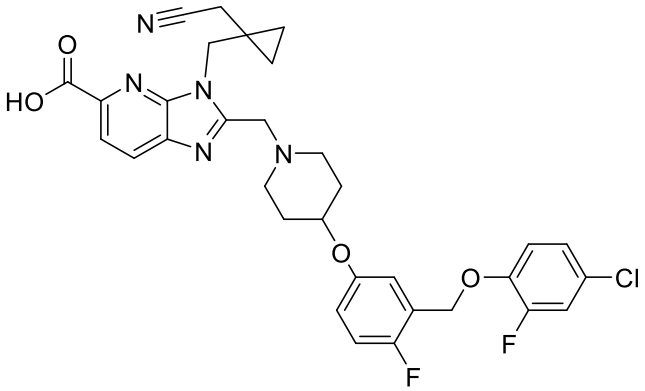
Compound 120	
Compound 121	
Compound 122	
Compound 123	

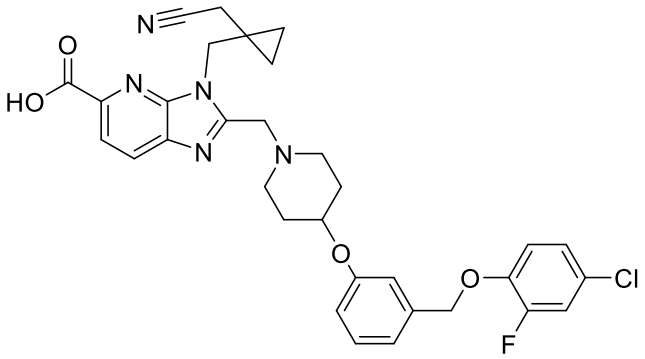
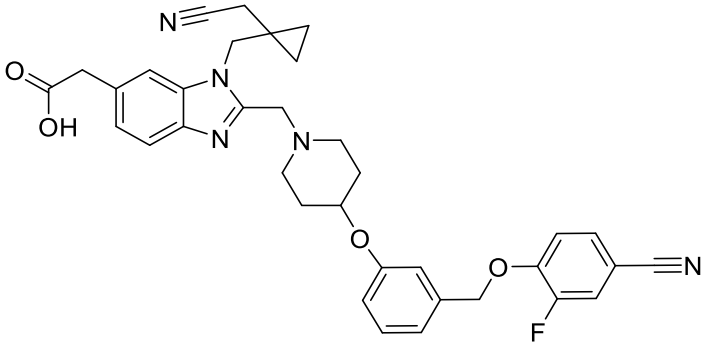
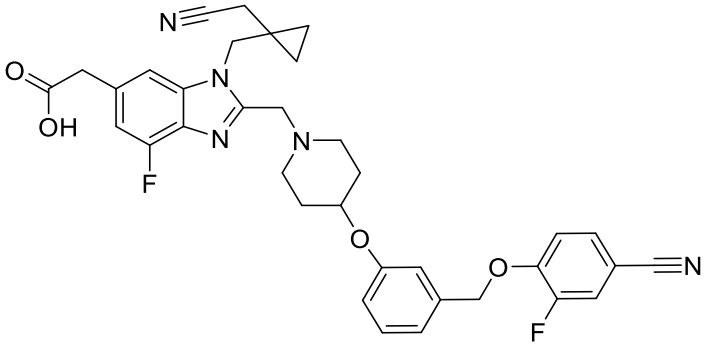
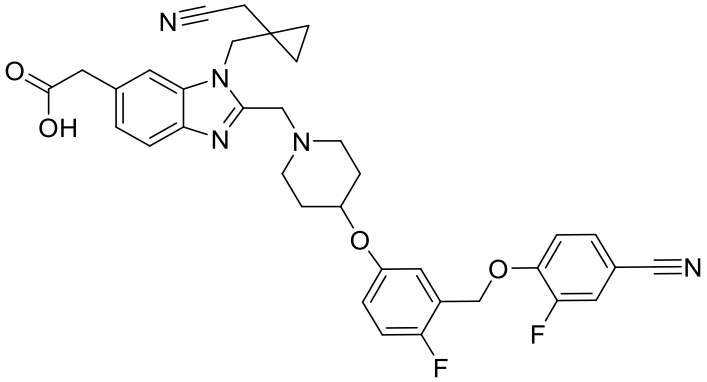
Compound 124	
Compound 125	
Compound 126	
Compound 127	

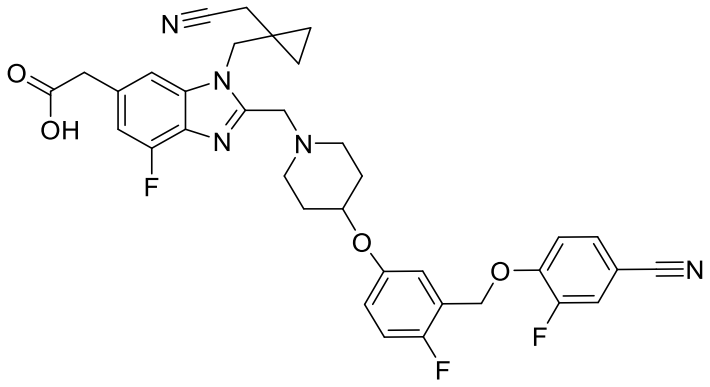
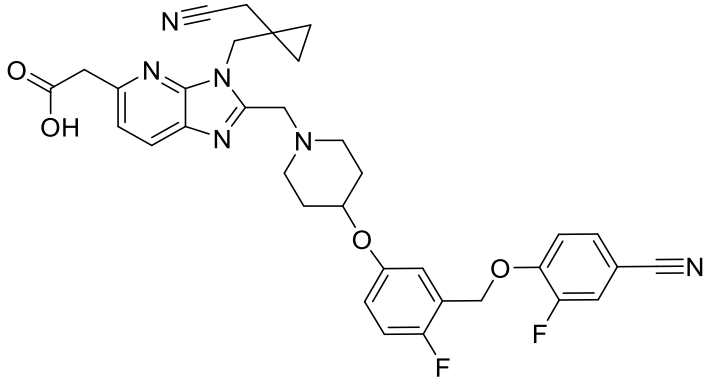
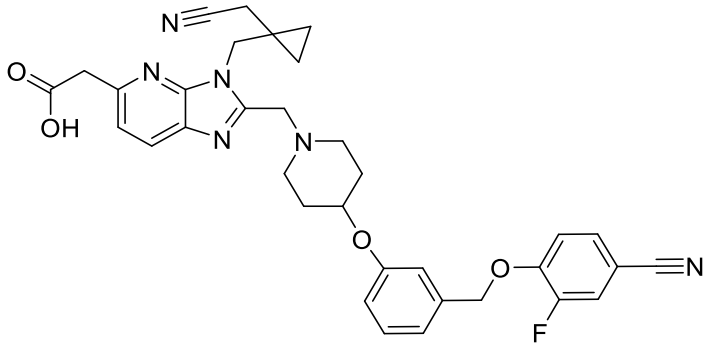
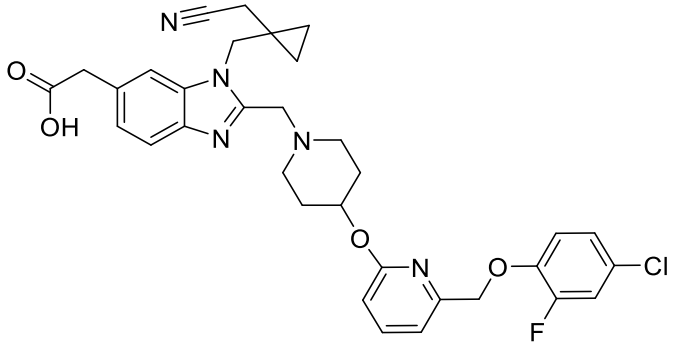
Compound 128	
Compound 129	
Compound 130	
Compound 131	

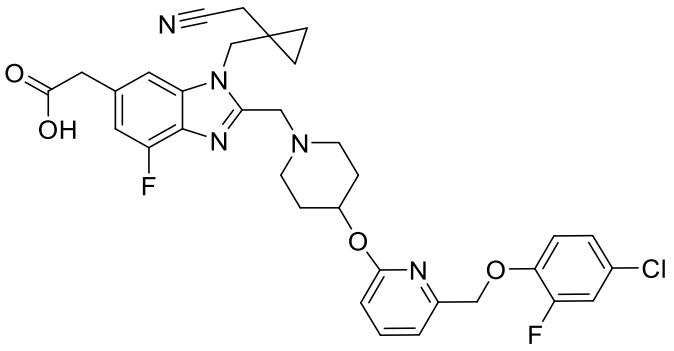
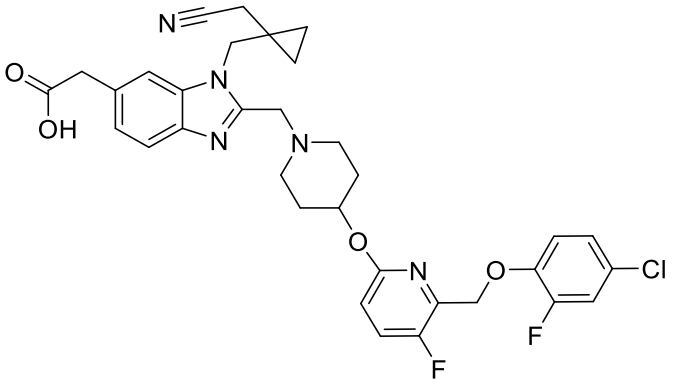
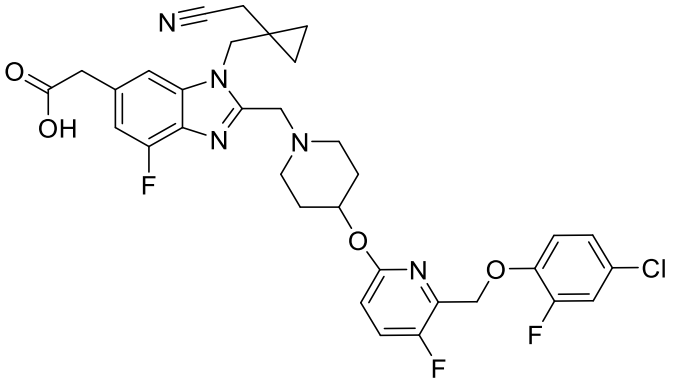
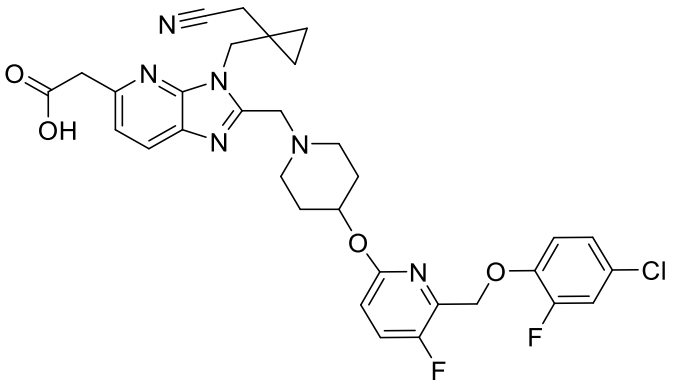
Compound 132	
Compound 133	
Compound 134	
Compound 135	

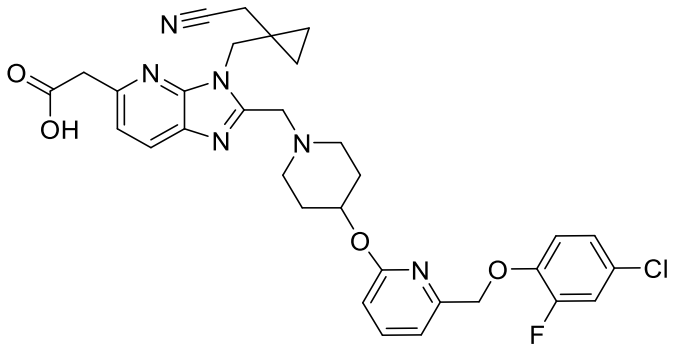
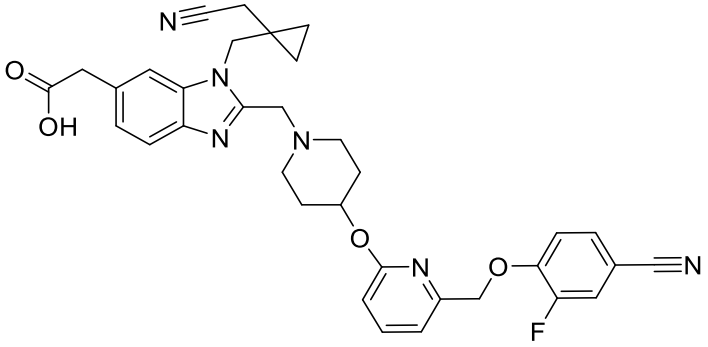
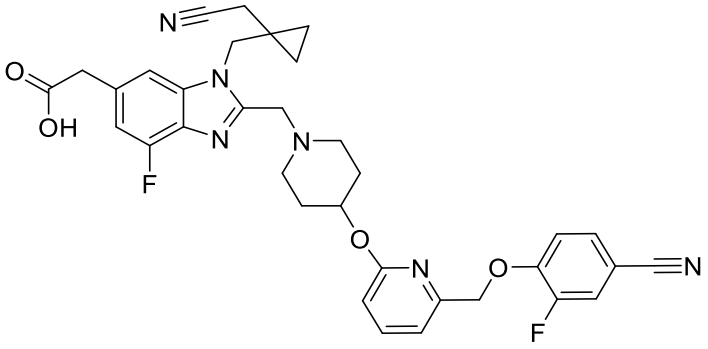
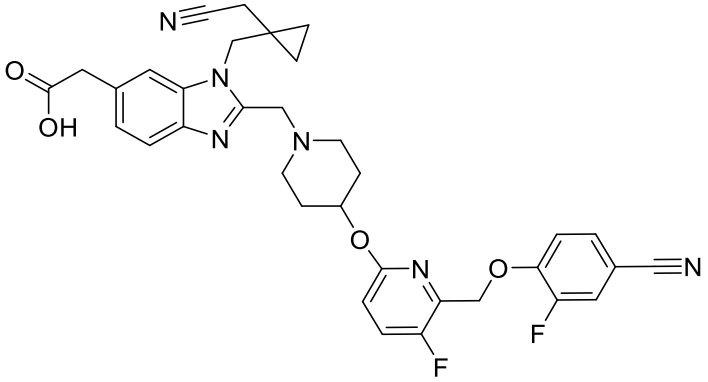
Compound 136	
Compound 137	
Compound 138	
Compound 139	

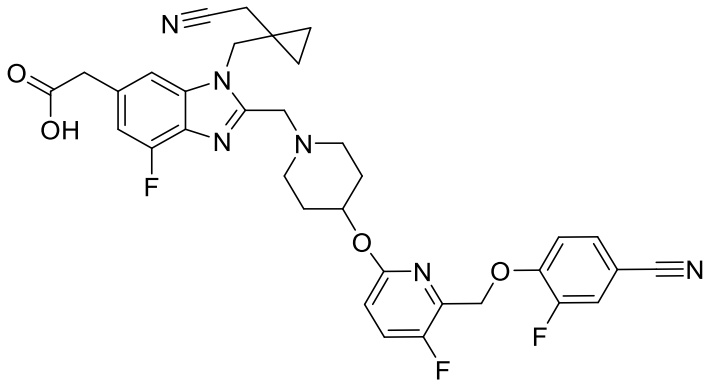
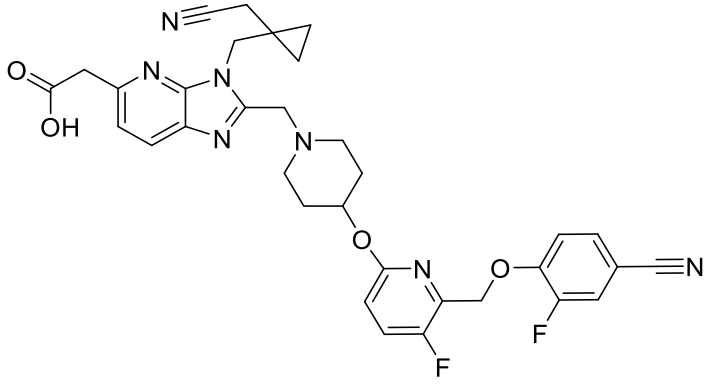
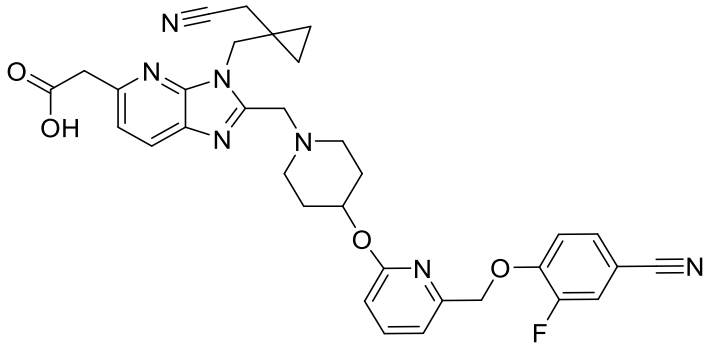
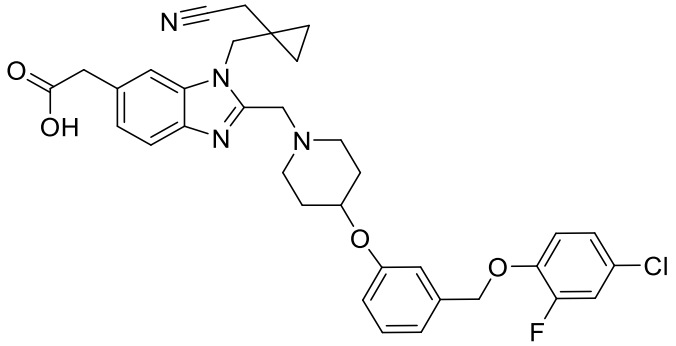
Compound 140	
Compound 141	
Compound 142	
Compound 143	

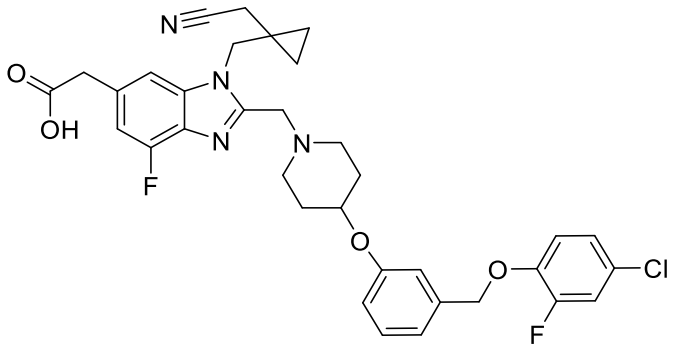
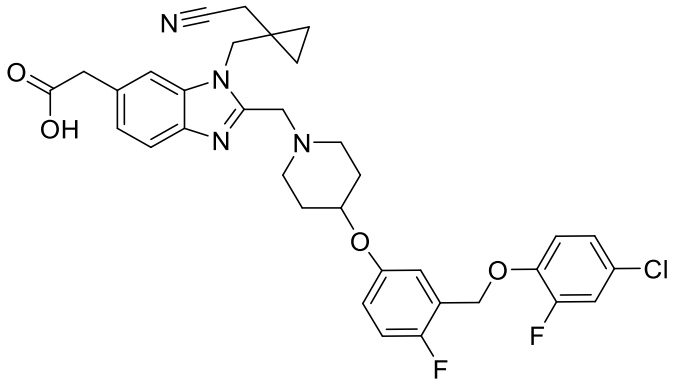
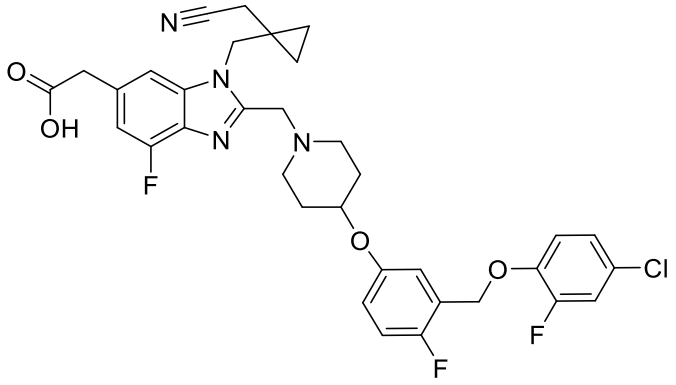
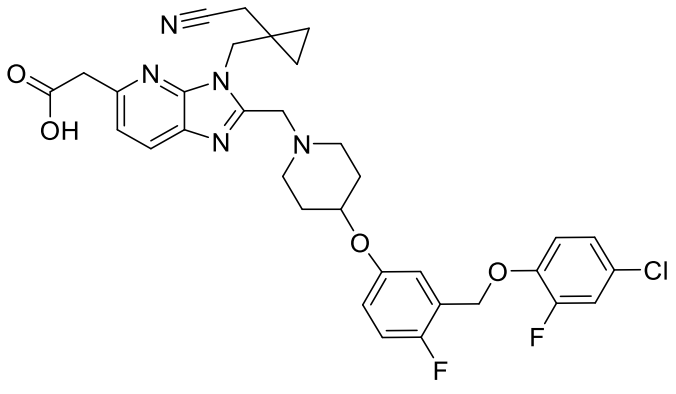
Compound 144	
Compound 145	
Compound 146	
Compound 147	

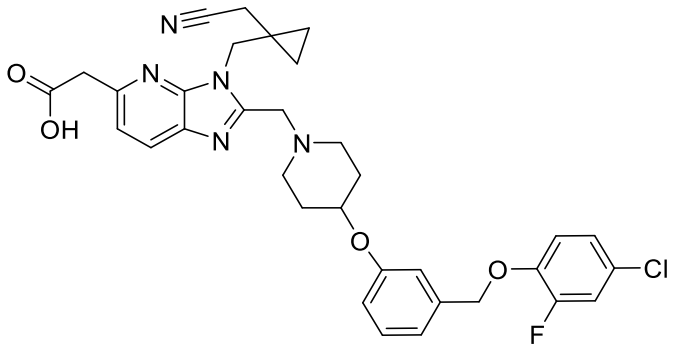
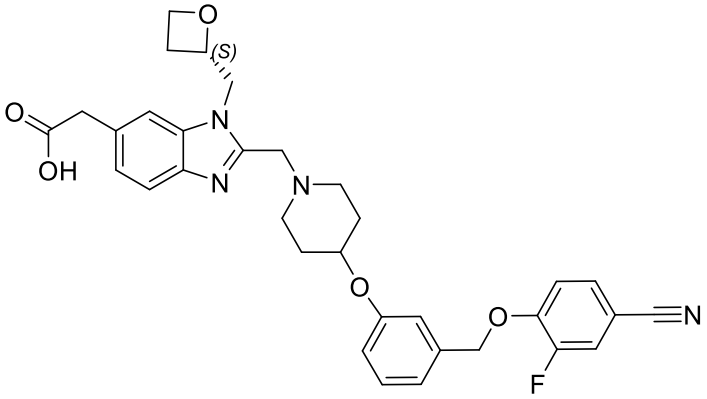
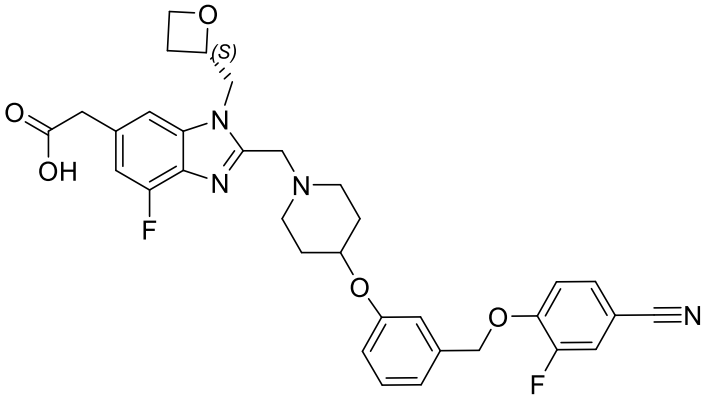
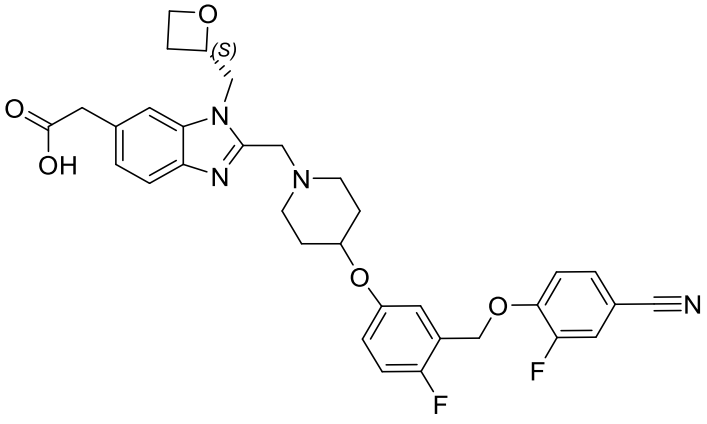
Compound 148	
Compound 149	
Compound 150	
Compound 151	

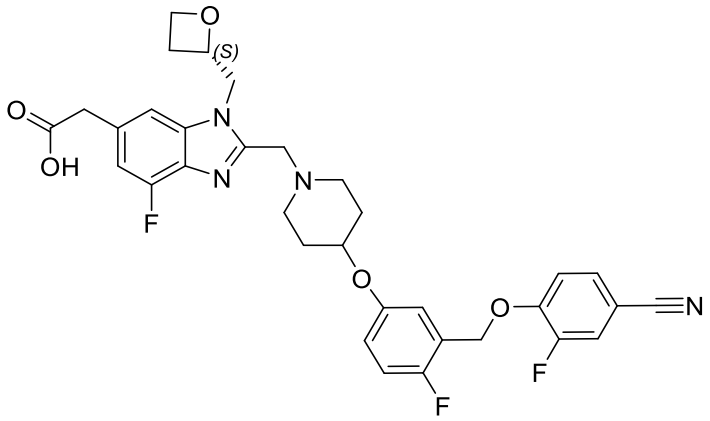
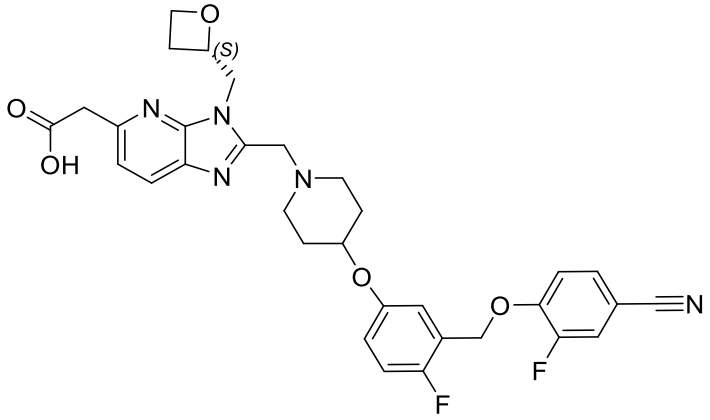
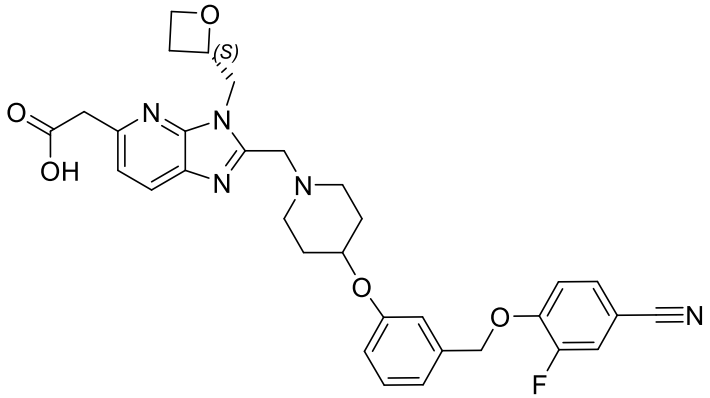
Compound 152	
Compound 153	
Compound 154	
Compound 155	

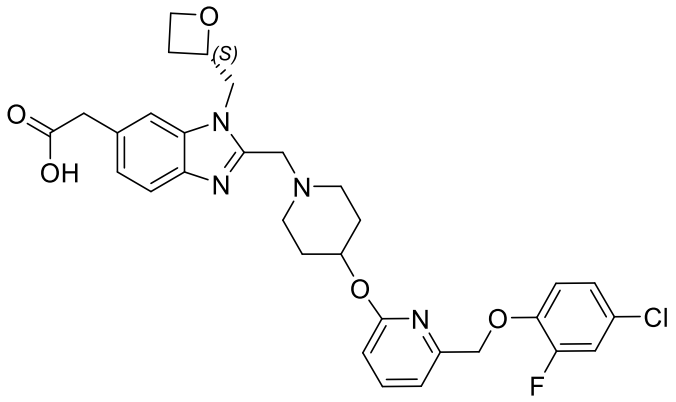
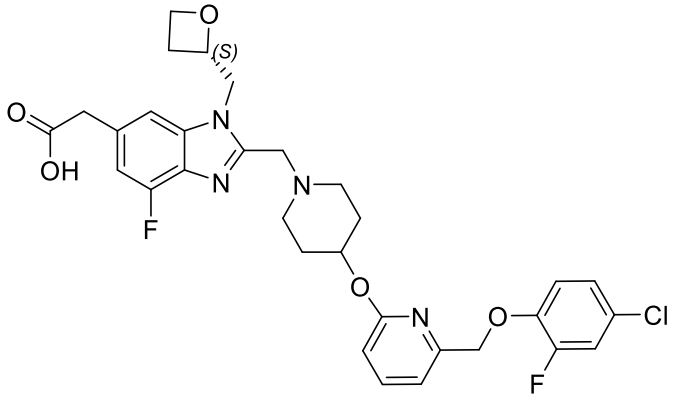
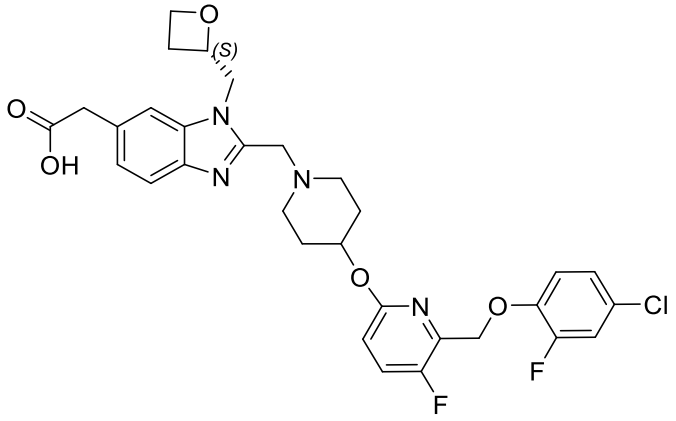
Compound 156	
Compound 157	
Compound 158	
Compound 159	

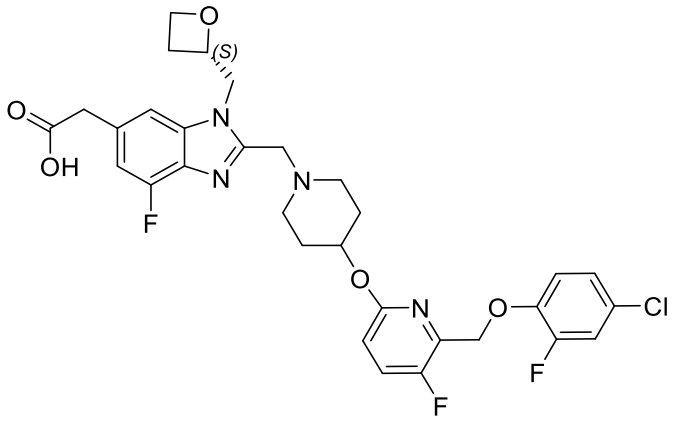
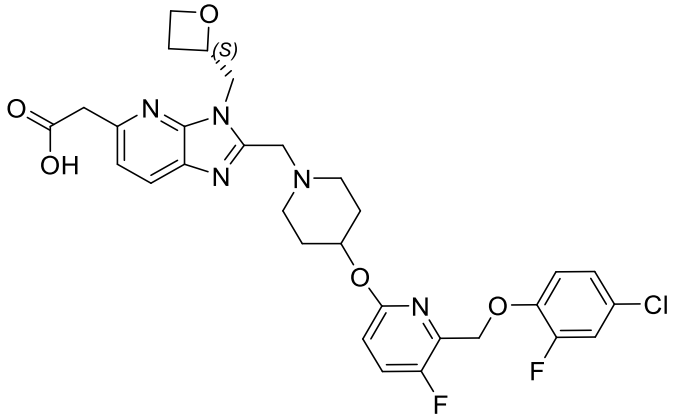
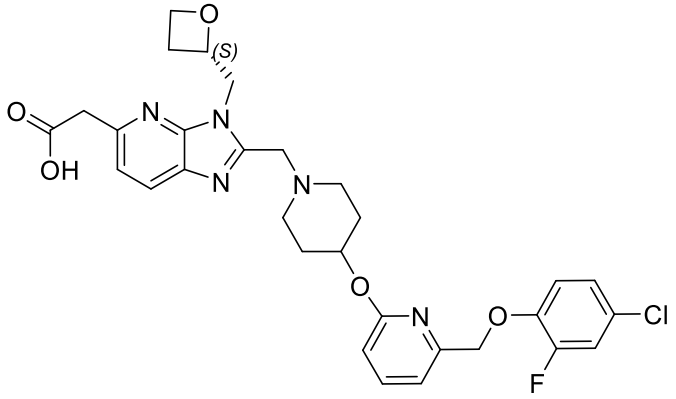
Compound 160	
Compound 161	
Compound 162	
Compound 163	

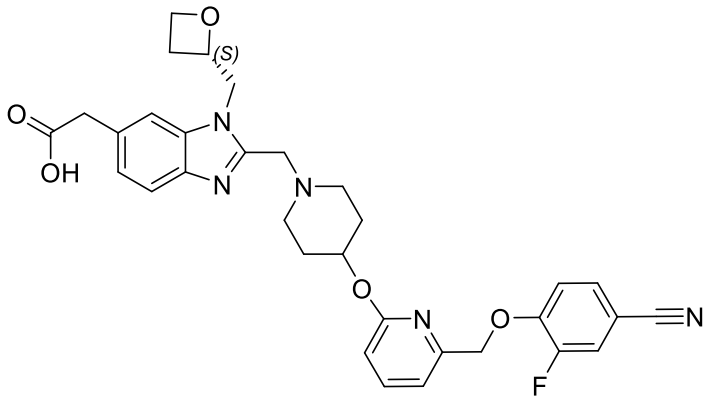
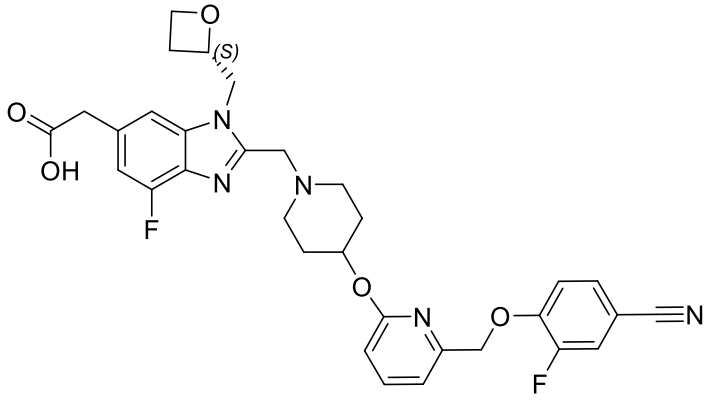
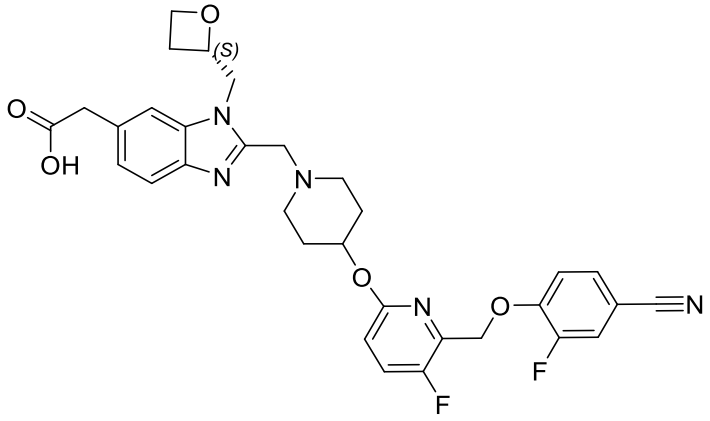
Compound 164	
Compound 165	
Compound 166	
Compound 167	

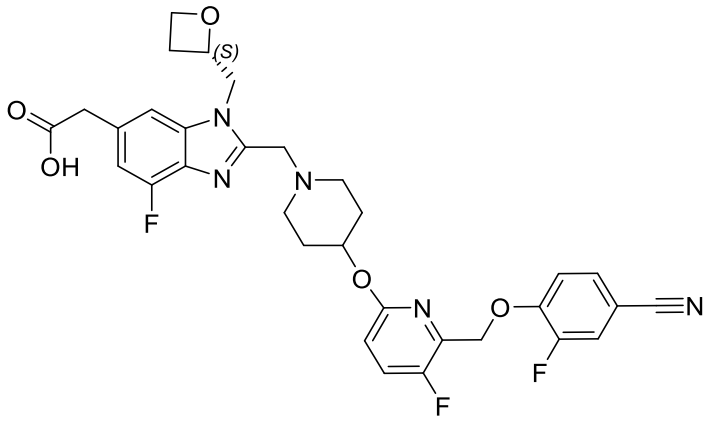
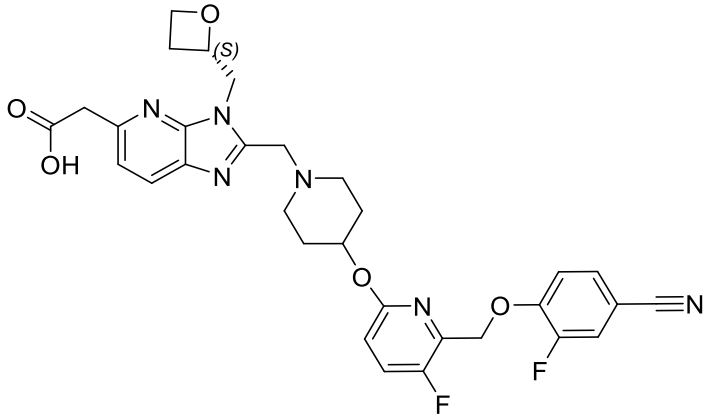
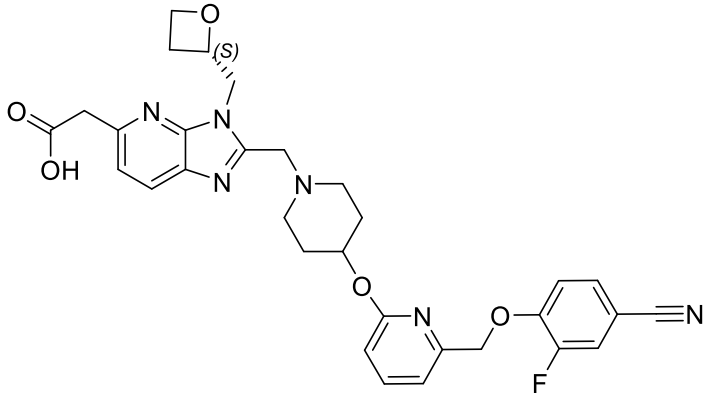
Compound 168	
Compound 169	
Compound 170	
Compound 171	

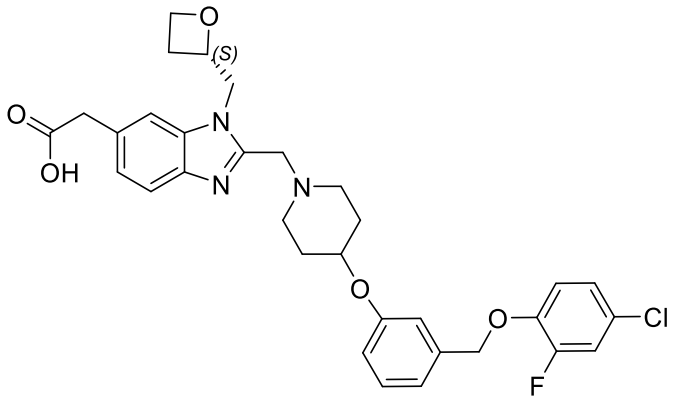
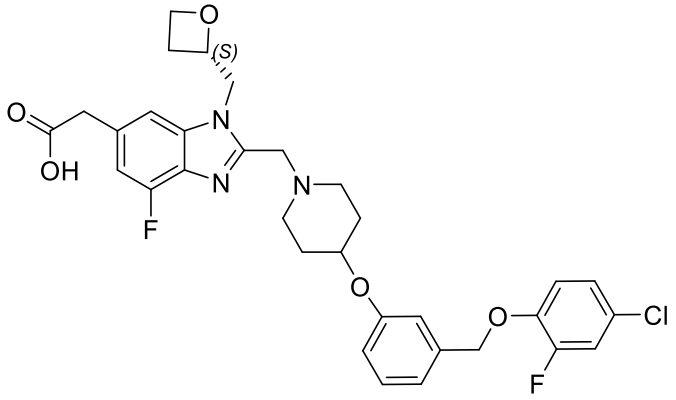
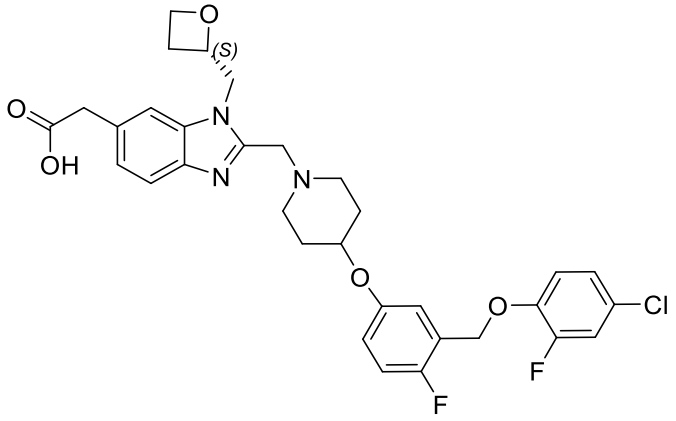
Compound 172	
Compound 173	
Compound 174	

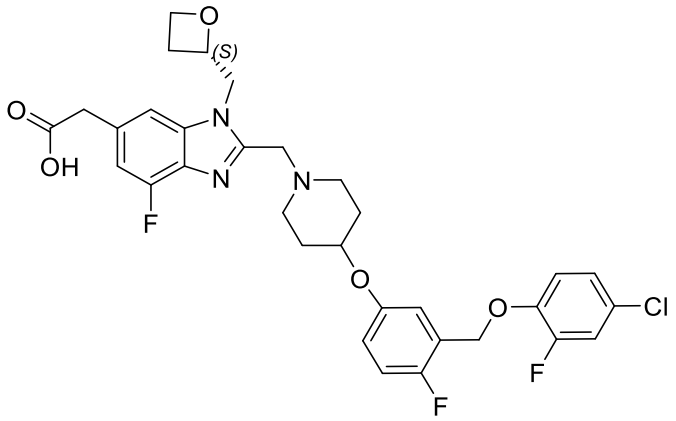
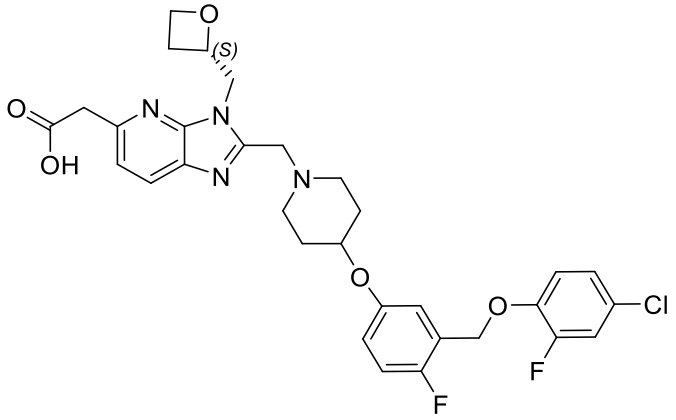
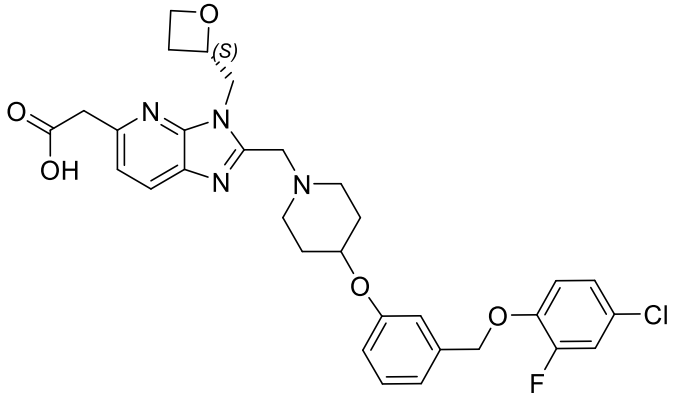
Compound 175	
Compound 176	
Compound 177	

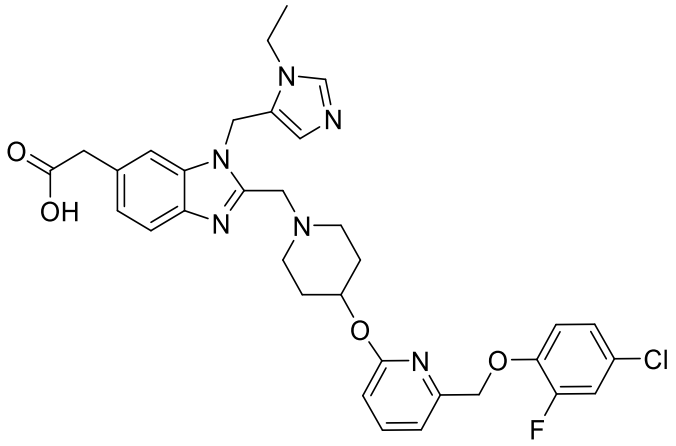
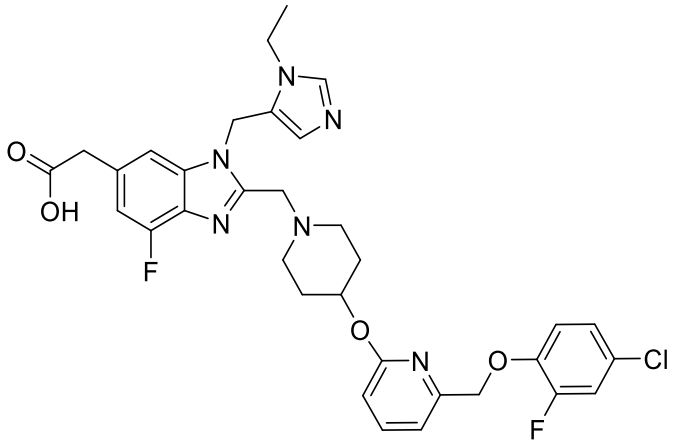
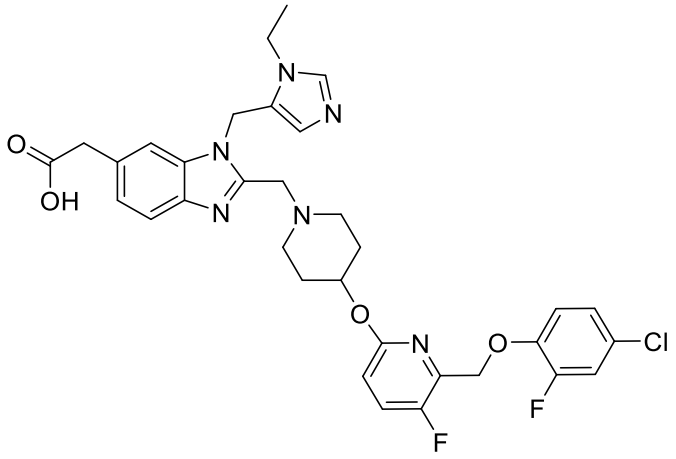
Compound 178	
Compound 179	
Compound 180	

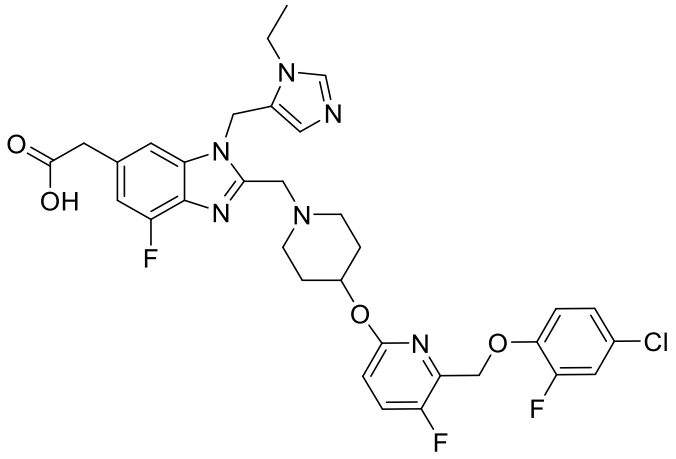
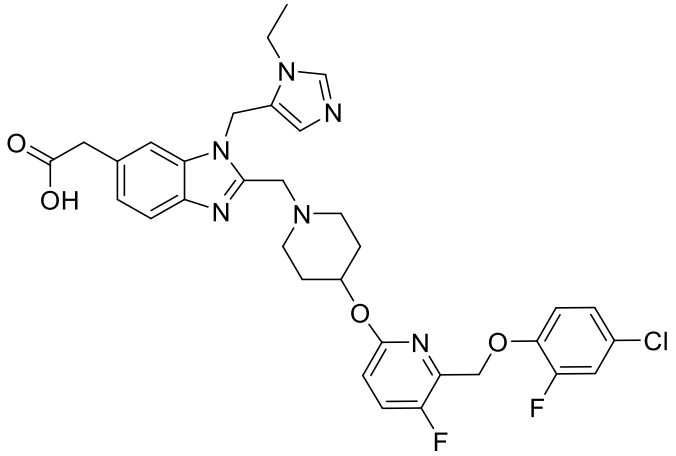
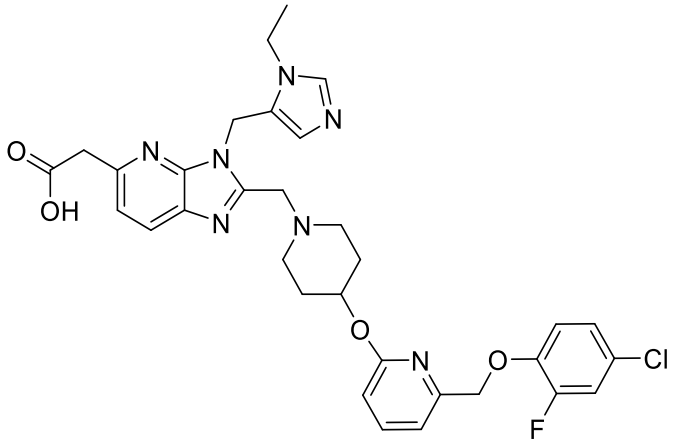
Compound 181	
Compound 182	
Compound 183	

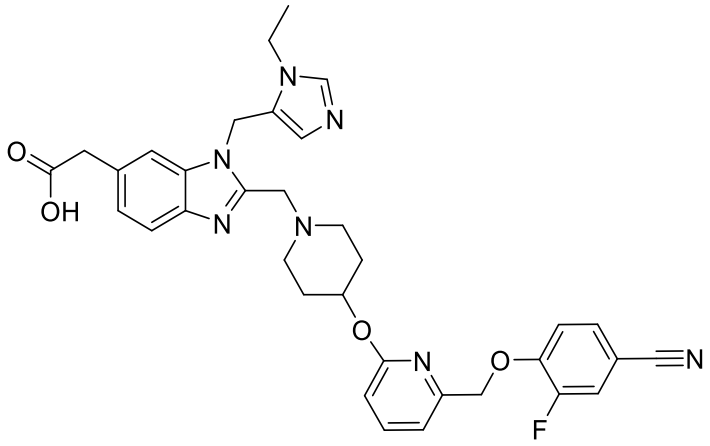
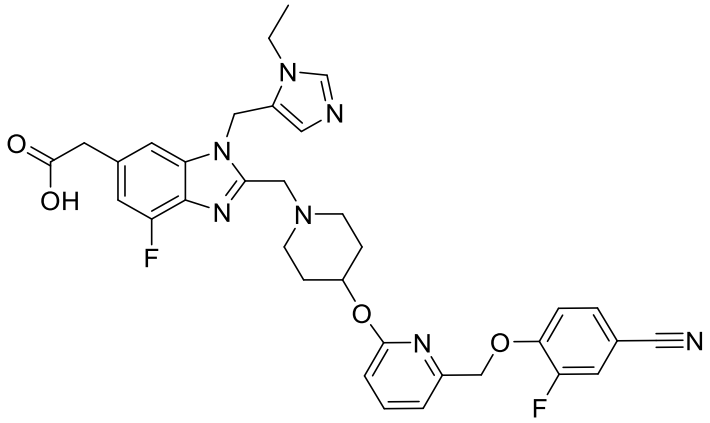
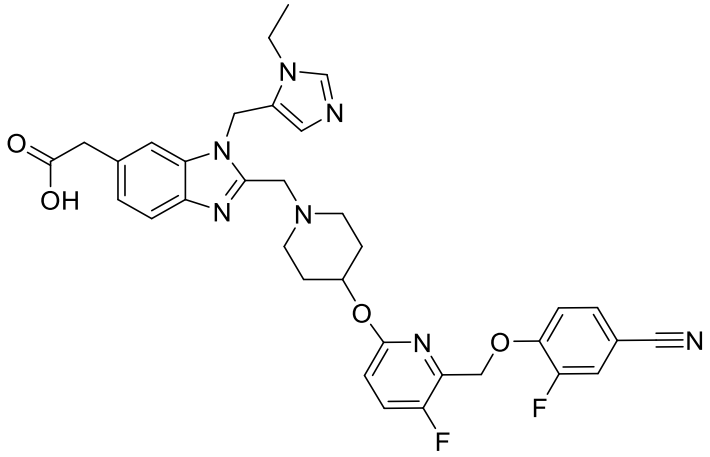
Compound 184	
Compound 185	
Compound 186	

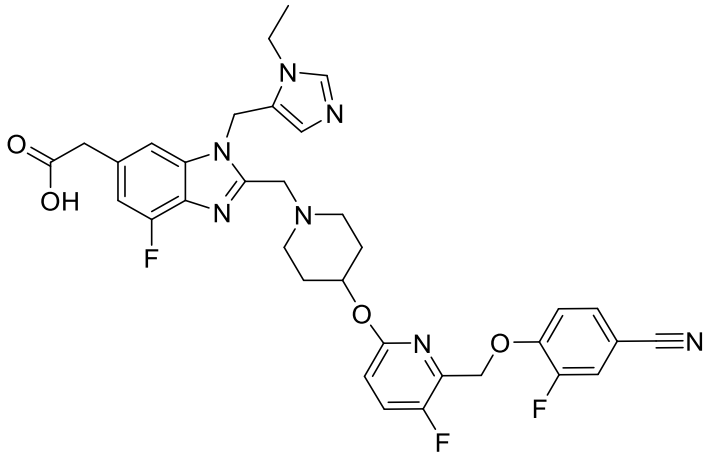
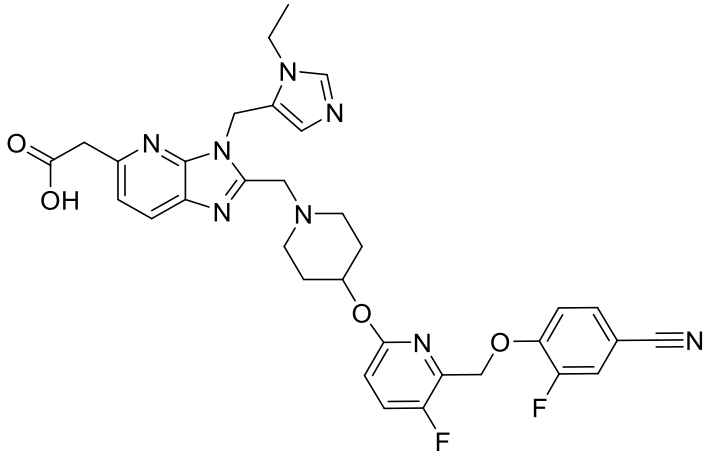
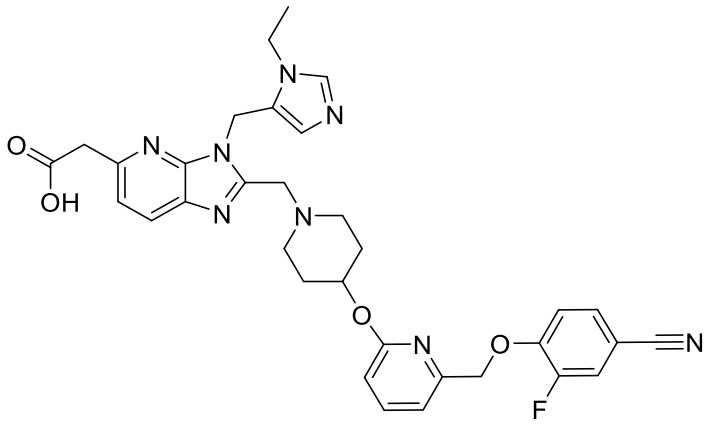
Compound 187	
Compound 188	
Compound 189	

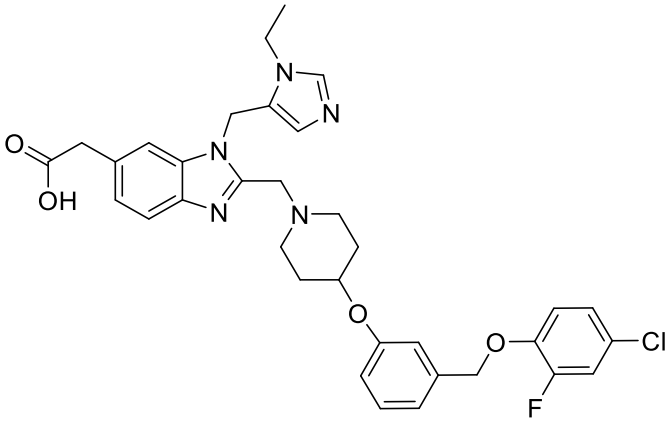
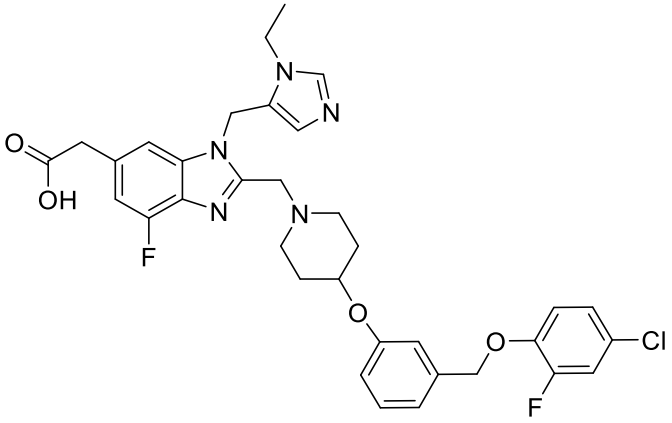
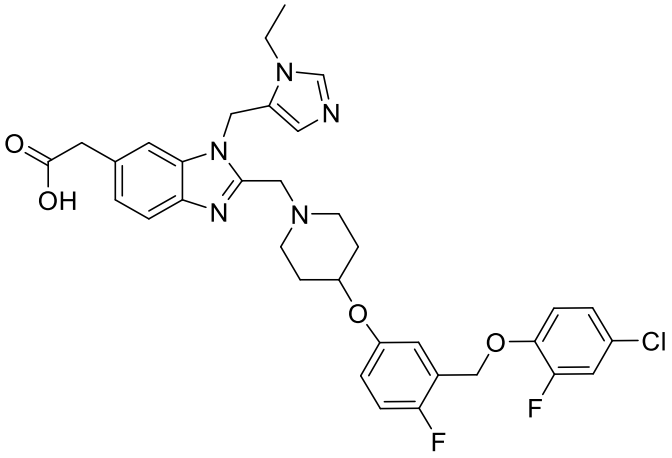
Compound 190	
Compound 191	
Compound 192	

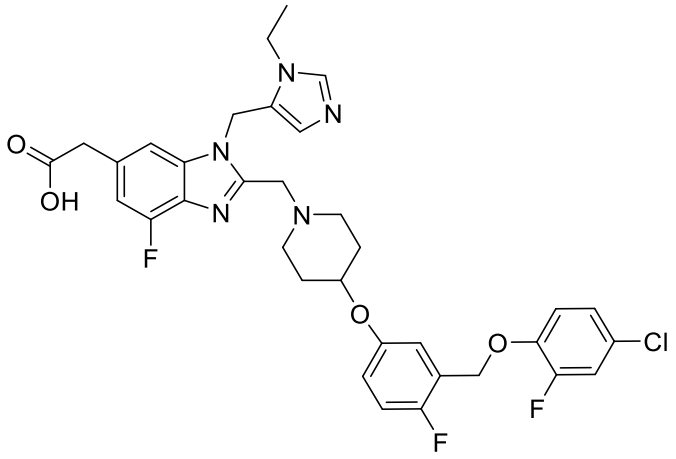
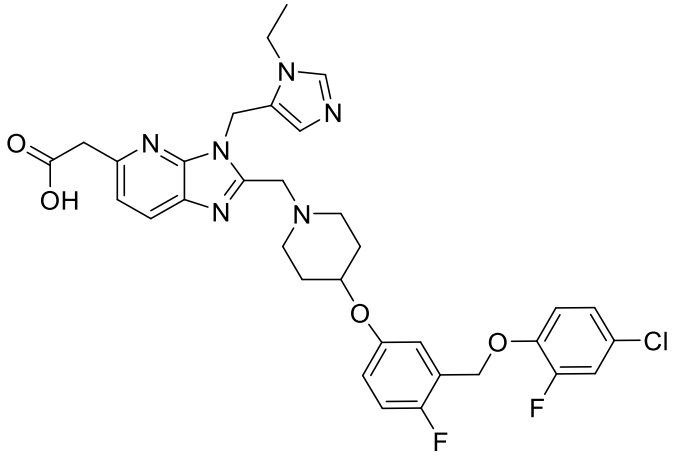
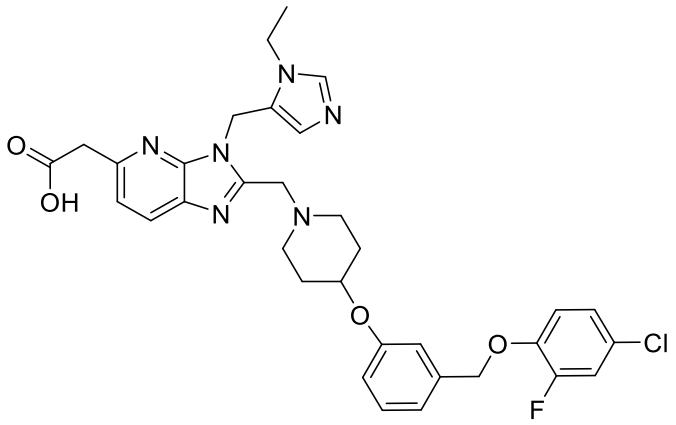
Compound 193	
Compound 194	
Compound 195	

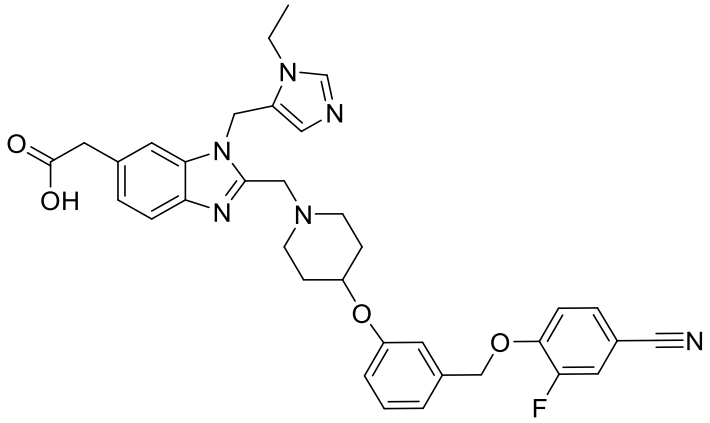
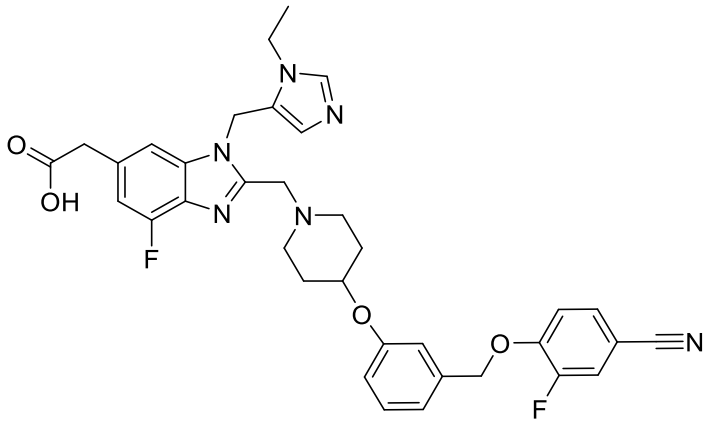
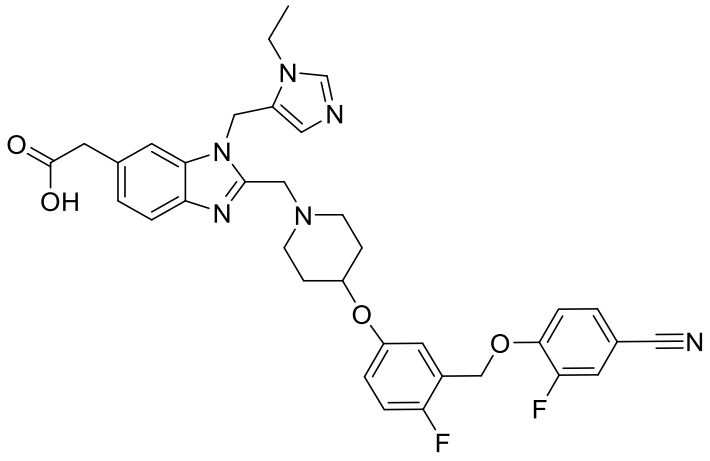
Compound 196	
Compound 197	
Compound 198	

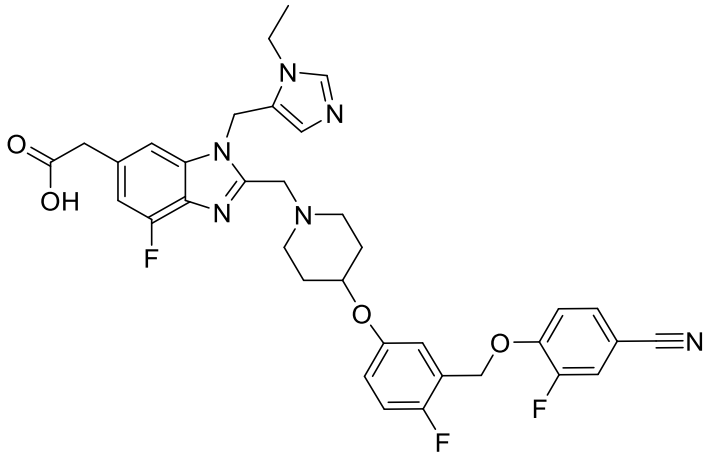
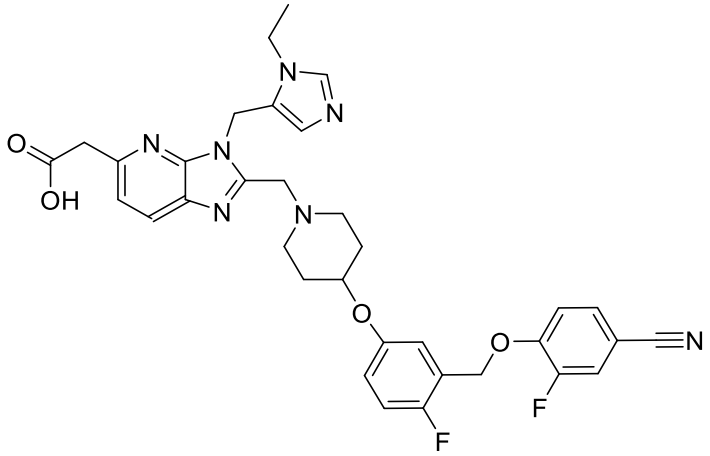
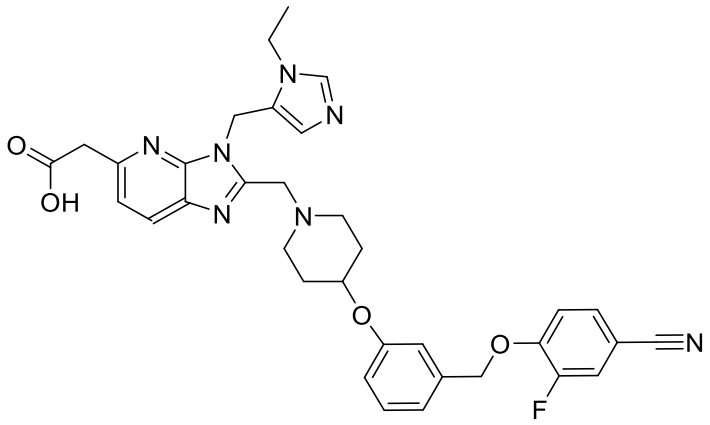
Compound 199	
Compound 200	
Compound 201	

Compound 202	
Compound 203	
Compound 204	

Compound 205	
Compound 206	
Compound 207	

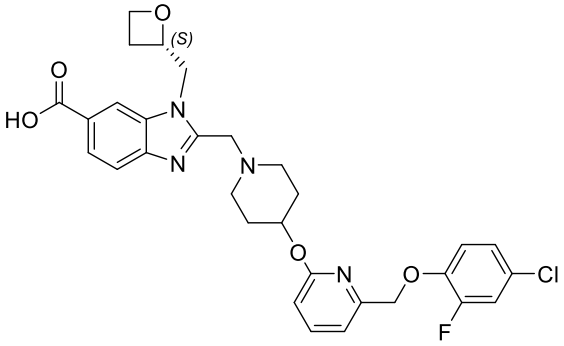
Compound 208	
Compound 209	
Compound 210	

Compound 211	
Compound 212	
Compound 213	

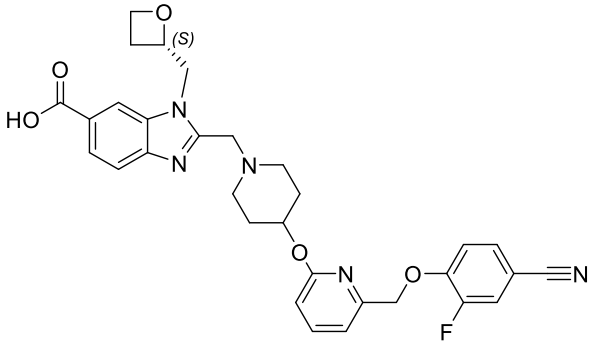
Compound 214	
Compound 215	
Compound 216	

or a pharmaceutically acceptable salt, solvate, enantiomer, or isotopic variation thereof.

13. A compound, which is:



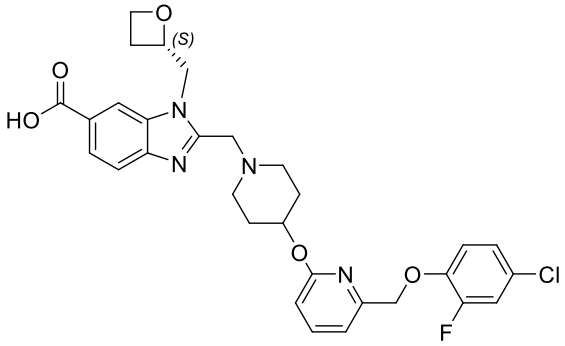
Compound 49, or



Compound 55,

or a pharmaceutically acceptable salt, solvate, or enantiomer thereof.

14. The compound of claim 13, which is a pharmaceutical acceptable salt of



Compound 49.

15. A pharmaceutical composition comprising the compound of any one of claims 1 to 14 in therapeutically effective amount.

16. Use of the compound of any one of claims 1-14 or the pharmaceutical composition of claim 15 in the manufacture of a medicament for treating a disease selected from overweight, obesity, diabetes (T1 D and/or T2DM, including pre-diabetes), idiopathic T1 D (type 1B), latent autoimmunity diabetes in adults (LADA), early-onset T2DM (EOD), atypical diabetes in youth (YOAD), diabetes in maturity of youth (MODY), malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance , impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, renal disease (e.g., acute kidney disease, renal tubular dysfunction, proinflammatory changes in proximal tubules), diabetic retinopathy, adipocyte dysfunction, visceral fat deposition, sleep apnea, obesity (including hypothalamic and monogenic obesity) and associated comorbidities (e.g., osteoarthritis and urinary incontinence), eating disorders (including binge drinking syndrome, bulimia nervosa, and syndromic obesity , such as Prader-Willi and Bardet-Biedl syndromes), weight gain due to use of other drugs (e.g., steroid and antipsychotic use), hyperglycemia, dyslipidemia (including hyperlipidemia, hypertriglyceridemia, increased total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, hyperinsulinemia, NAFLD (including steatosis, NASH, fibrosis, liver cirrhosis, hepatocellular carcinoma and other related diseases), cardiovascular disease, atherosclerosis sclerosis (including coronary artery disease), peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction (e.g., necrosis and apoptosis), stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, postprandial lipids, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, PMS, angina, thrombosis, atherosclerosis, transient ischemic attack, restenosis , impaired glucose metabolism, impaired fasting glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, psoriasis, foot ulcers, ulcerative colitis, hyperapolipoprotein B lipoproteinemia, Alzheimer's disease, schizophrenia, cognitive impairment, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome, polycystic ovary syndrome, and addiction treatment (e.g., alcohol and/or drug abuse).

17. The use according to claim 16, wherein the disease is overweight or obesity.