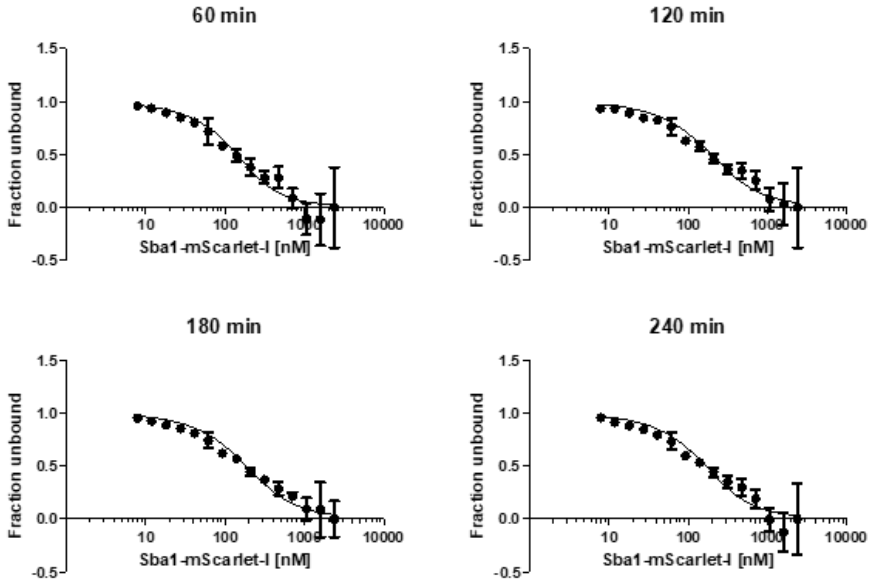
pharmaceuticals

Supplementary Materials

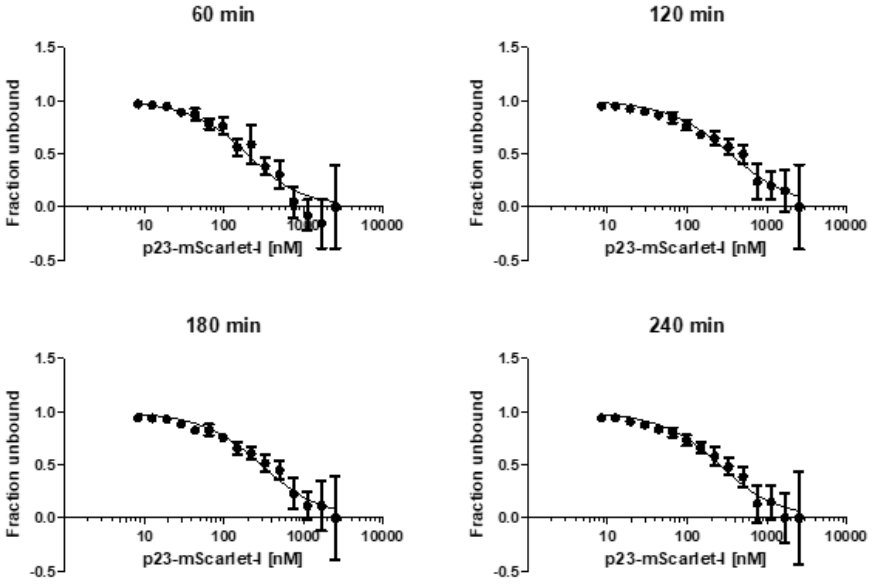
Figures

A *C. albicans*



Time point (min)	K_d (nM)	PCI 95.5% (nM)	ACI 95.5% (nM)
60	50	30-80	50-70
120	100	80-130	100-140
180	100	70-120	100-130
240	80	50-110	80-110

B *human* – HSP90α



Time point (min)	K_d (nM)	PCI 95.5% (nM)	ACI 95.5% (nM)
60	120	70-170	90-140
120	270	220-320	240-320
180	220	180-260	200-270
240	180	140-210	150-220

Figure S1. Equilibrium check of *C. albicans* HSP90 – Sba1 and *human* HSP90α – p23 binding. 200 nM donor molecule was incubated at 30 °C (*C. albicans* HSP90E36A-mNeonGreen) or 37 °C (*human* HSP90αE47A-mNeonGreen) with 0-3 000 nM (lowest non-zero concentration 10 nM) of acceptor molecule (*C. albicans* Sba1-mScarlet-I) or (*human* p23-mScarlet-I) and measured every 60 min for up to 4 h. The equilibrium dissociation constant (K_d) of the interaction was calculated for all time points with GraphPad Prism5. Precision and accuracy confidence interval (PCI and ACI, respectively) at a 95.5% confidence level were determined according to the method of Wang et al. [29].

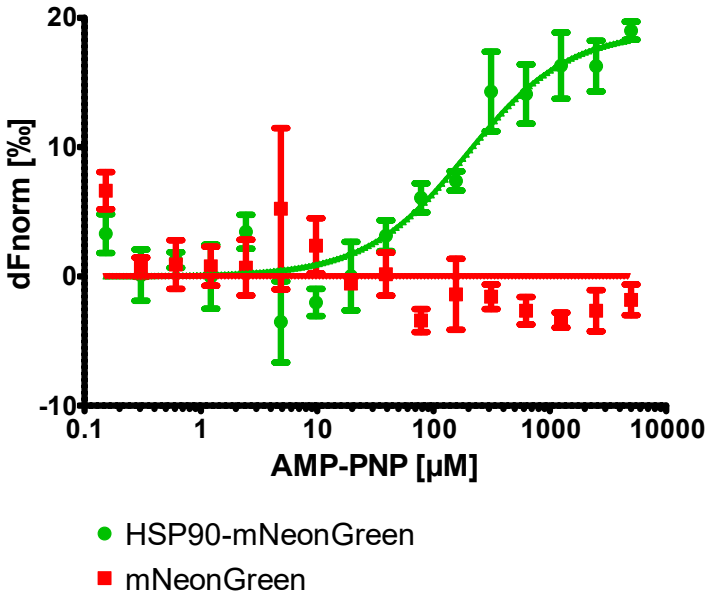


Figure S2. AMP-PNP binding affinity to *C. albicans* HSP90. In this MST experiment the concentration of HSP90-mNeonGreen (green circles) as well as for the negative control mNeonGreen (red squares) was kept constant (50 nM), while the concentration of the non-labeled ligand (AMP-PNP) was varied between 153-5 000 nM. After 5 min incubation at room temperature, the samples were loaded into Monolith NT.115 Capillaries (NanoTemper Technologies, Munich, Germany) and the MST measurement was performed at room temperature using the Monolith NT.115 (NanoTemper Technologies, Munich, Germany) at 35% LED power and high (80%) MST power. An MST-on time of 30 s was used for analysis, and a K_d of 200 ± 70 µM was derived. n = 3 independent measurements, error bars represent the standard deviation.

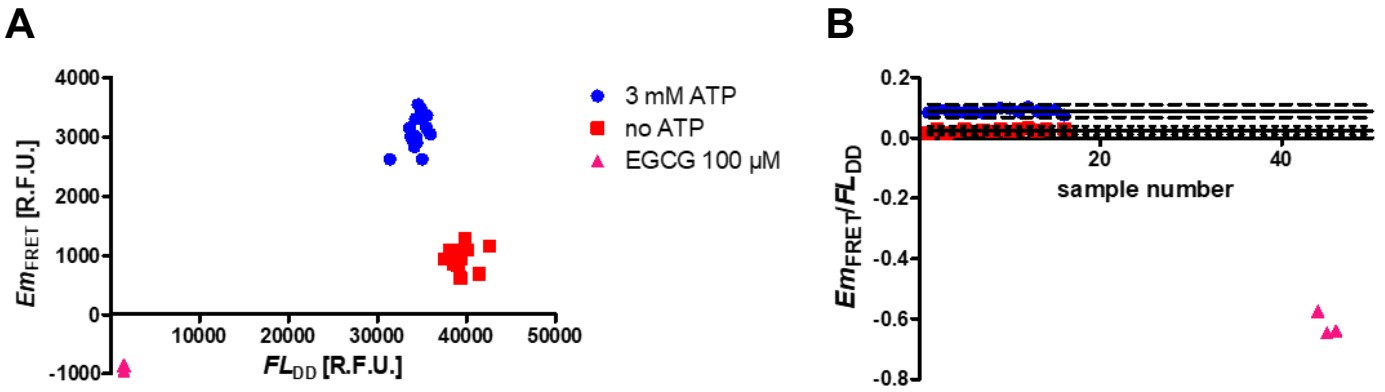


Figure S3. EGCG is a PAIN compound. **(A)** Incubation of *human* HSP90α-mNeonGreen (1 µM) and p23-mScarlet-I (2 µM) with 100 µM EGCG (pink triangles) in reaction buffer containing 3 mM ATP leads to strong decrease in FRET emission (Em_{FRET}) as well as donor emission (FL_{DD}) compared to binding control (blue circles) and non-binding control (red squares). Both binding and non-binding control contained donor and acceptor in the same concentrations with 3 mM ATP or no ATP included in the buffer. **(B)** This leads to a negative Em_{FRET}/FL_{DD} quotient. If a compound prevents binding of HSP90α and p23, both decrease in FRET emission and increase in donor emission occurs. The here observed effect of EGCG is attributed to unspecific effects such as covalent protein modifications. The same effect was observed on the binding of *C. albicans* HSP90 – Sba1 (data not shown). [R.F.U.] relative fluorescence units.

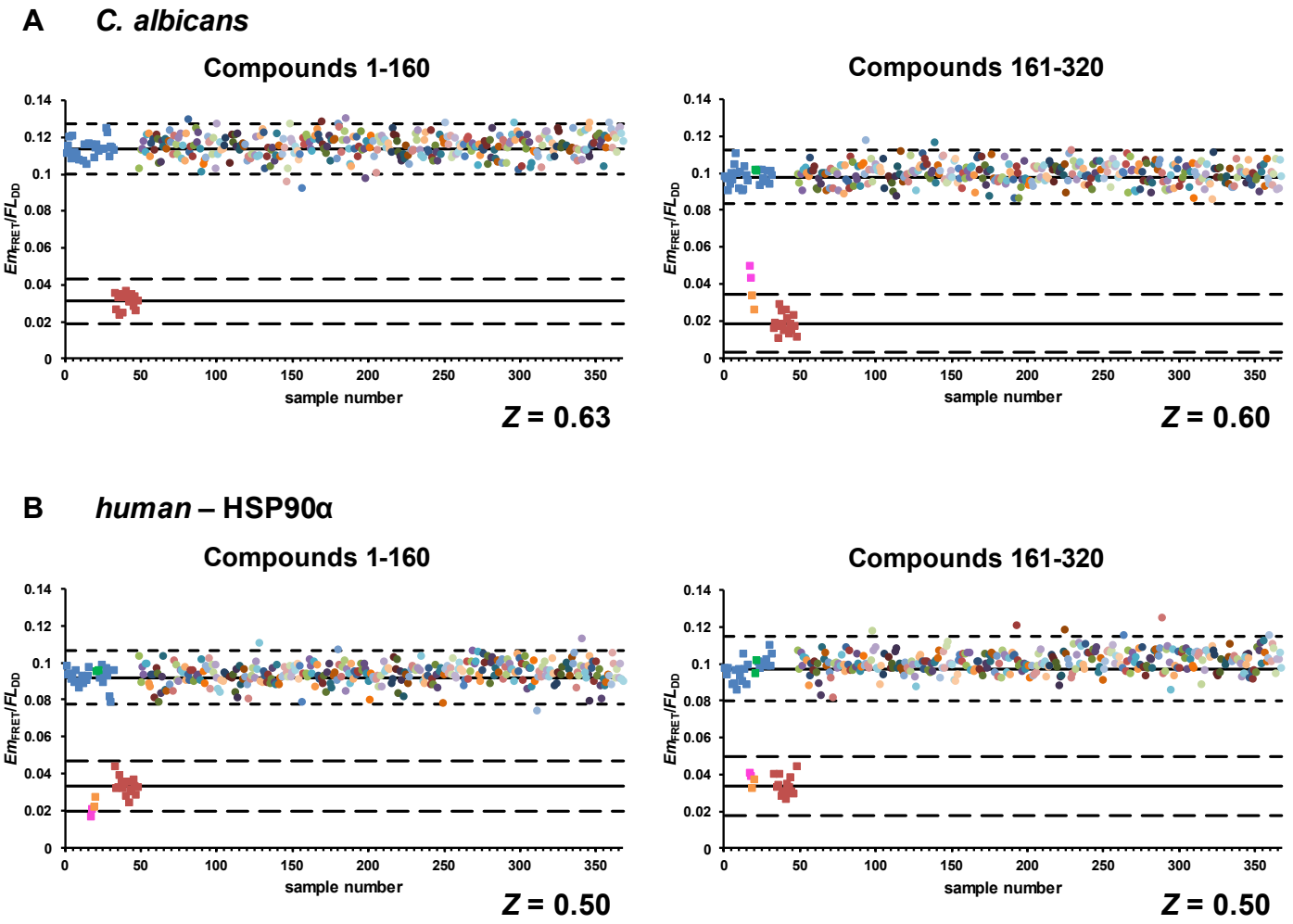


Figure S4. Screening of nucleoside-mimetics library. Individual samples. **(A)** *C. albicans* HSP90-mNeonGreen (1 μM) and Sba1-mScarlet-I (2 μM) were incubated with compounds (100 μM, colored circles) in reaction buffer 1% DMSO, 3 mM ATP for 15 min at 30 °C prior to measurement. 3 mM ATP containing samples without compound (blue squares) and no ATP samples (red squares) served as binding and non-binding controls, respectively. The inhibition controls geldanamycin (pink squares) and luminespib (orange squares) were screened at concentrations of 100 μM and 10 μM, respectively. The non-inhibition control withaferin A (green squares) was screened at 10 μM. **(B)** Screening for inhibition of *human* HSP90α-mNeonGreen – p23-mScarlet-I binding was performed analogous, except for incubating at 37 °C prior to measurement. Each color represents the signal of a compound that was screened in duplicate. The shown Z-values were calculated based on individual well signal.

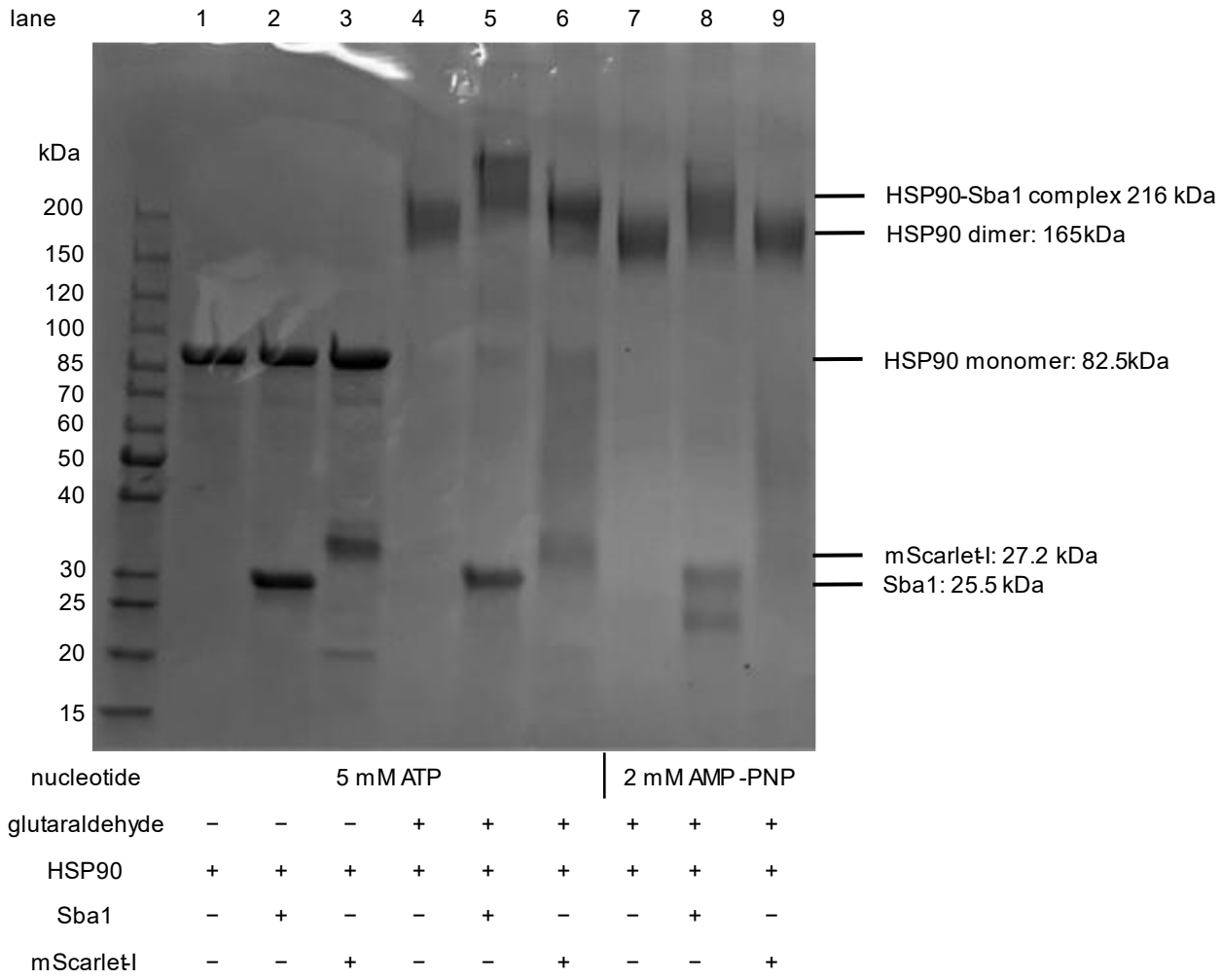


Figure S5. Confirmatory cross-linking SDS-PAGE of *C. albicans* HSP90 dimers and HSP90—Sba1 binding. The experiment was conducted analogously to Figure 6. Proteins were separated by SDS-PAGE without prior heating of samples followed by Coomassie staining. Lanes 1-3 not treated with glutaraldehyde show monomeric HSP90 (82.5 kDa) as well as Sba1 (25.5 kDa, lane 2) and mScarlet-I (27.2 kDa, lane 3). mScarlet-I was used as a negative control to show that cross-linking was specific for interacting proteins. Upon addition of glutaraldehyde higher molecular weight bands corresponding to homodimers of HSP90 (lane 4 and 7) as well as for HSP90-Sba1 complex (lane 5 and 8) could be observed, whereas no interaction between HSP90 and mScarlet-I was apparent (lane 6 and 9).

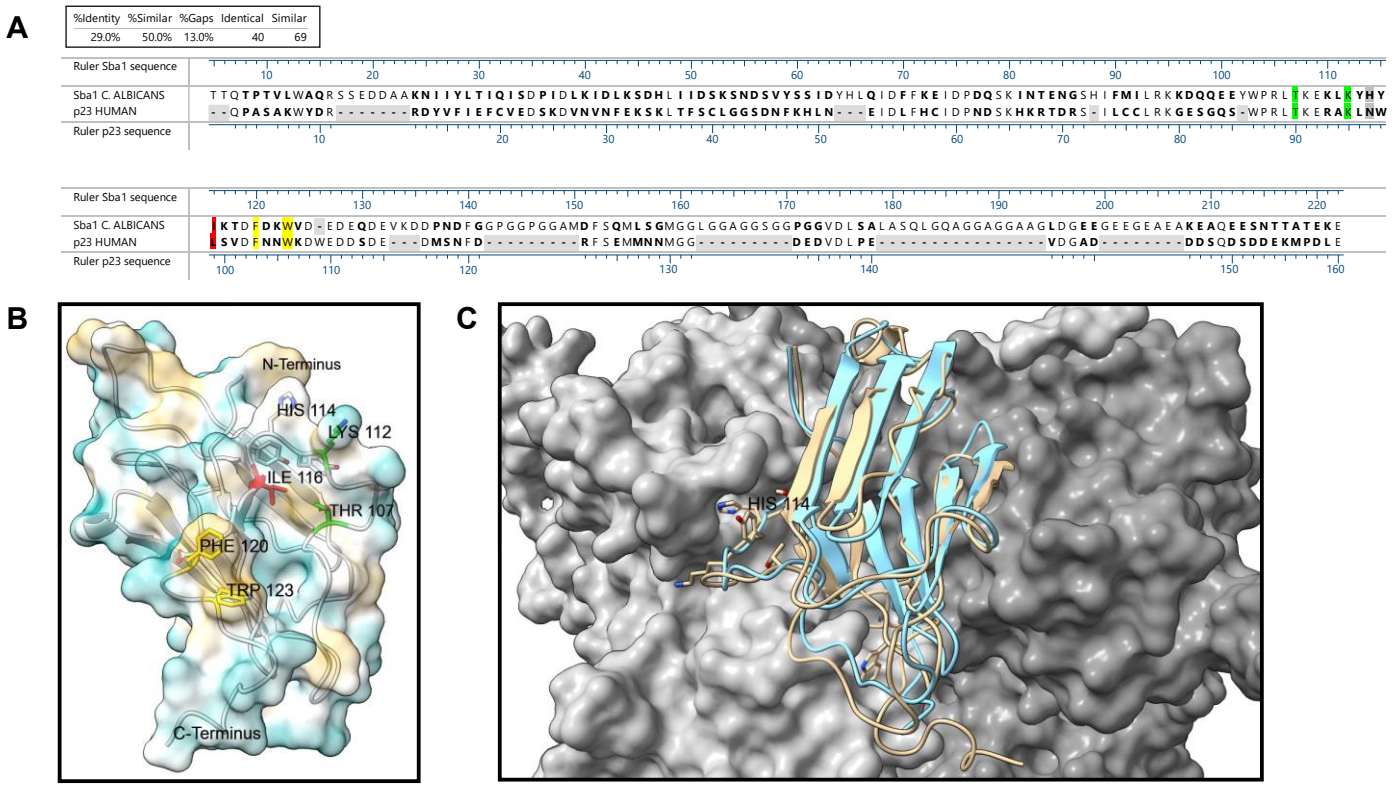


Figure S6. Potential for selective *C. albicans* Sba1 inhibitor development. **(A)** Sequence alignment of *C. albicans* Sba1 (UniProtKB: A0A1D8PQ94) with *human* p23 (Q15185). Amino acids that differ between compared sequences in bold. Sequences show low sequence identity and similarity between species. Residues important for p23/Sba1 binding to HSP90 marked yellow [55] and red [56]. Amino acids that are putatively involved in binding with the Sba1/p23 inhibitor gedunin highlighted in green [57]. **(B)** Homology model of *C. albicans* Sba1 based on crystal structure 2CG9. Hot spot amino acids involved in HSP90 or gedunin binding are colored in accordance with **(A)**. (**C)** Superimposition of homology model of *C. albicans* HSP90:Sba1 (based on 2CG9) with cryo-EM structure of *human* HSP90:p23 complex (7L7J). Whereas HSP90 sequence and structure are heavily conserved across species, Sba1 (beige) and p23 (light blue) show marked structural differences. HSP90 monomers shown in gray and dark gray. *C. albicans* His114 reaches into buried pocket of HSP90 and is not conserved, as are the amino acids in its vicinity (112-116). This could potentially be a target site for selective inhibitor development.

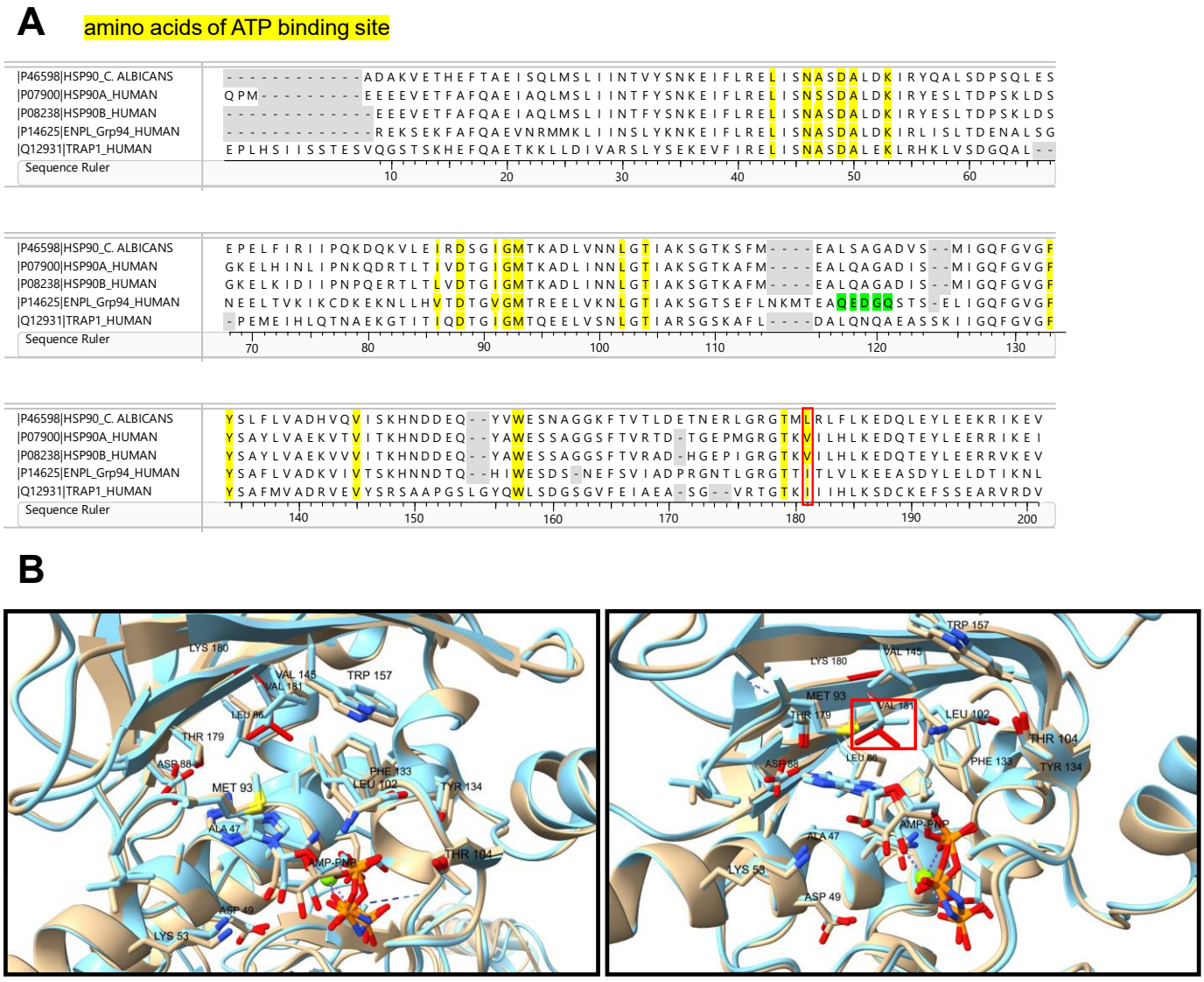


Figure S7. The nucleotide-binding site of *C. albicans* and *human* isoforms shows high degree of conservation and high structural similarity. **(A)** Sequence alignment of *C. albicans* HSP90 and the *human* isoforms of HSP90α, β, Grp94 and TRAP-1. Amino acids of the ATP binding site are highlighted in yellow according to Mishra *et al.* 2021 [71]. Only one amino acid of the binding site differs in *C. albicans* HSP90 when compared to the *human* isoforms (L176, corresponding to V181 for *human* HSP90β). This amino acid is highlighted with a red box. Five amino acid QEDGQ insertion into primary sequence of Grp94 highlighted in green. This insertion leads to a conformational change within the ATP-binding pocket of Grp94 that was exploited to develop an isoform-selective Grp94 inhibitor [72]. **(B)** Superimposition of cryo-EM structures of *S. cerevisiae* HSP90 (beige, PDB: 6XLC) and *human* HSP90β (light blue, PDB: 8EOB). Both structures were solved with HSP90 in the N-terminally dimerized conformation when bound to the non-hydrolysable ATP analogue AMP-PNP. Generally, also a high three-dimensional similarity in the conformation of involved amino acids is observed. Images show different angles of the ATP-binding site. The amino acid L176 is highlighted in red and marked with a red box in the second image. Analysis was performed with ChimeraX. **(A), (B)** Shown numeration of amino acids based on the *human* HSP90β sequence.

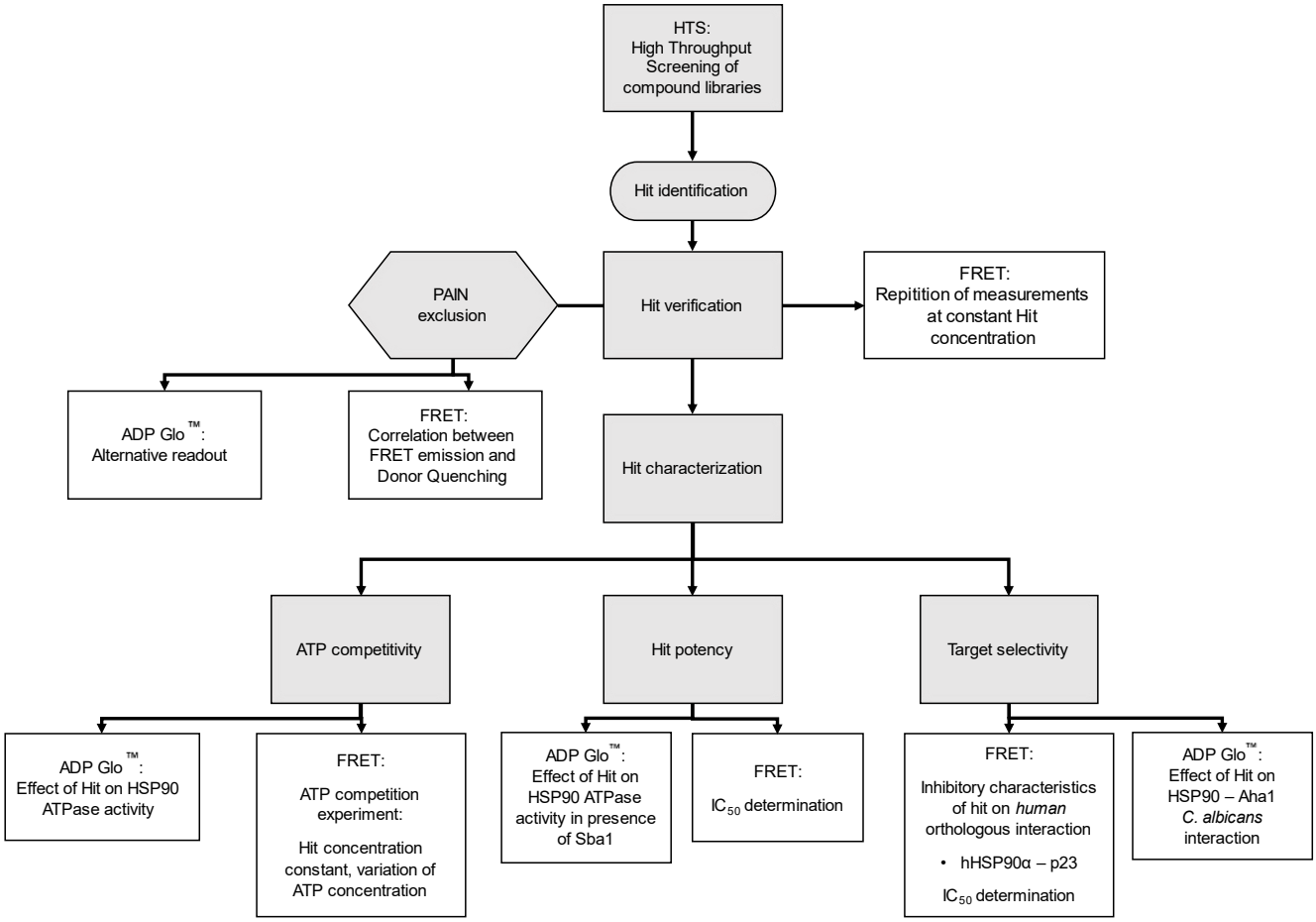


Figure S8. Workflow: Identification and profiling of inhibitors of *C. albicans* HSP90-Sba1 binding.

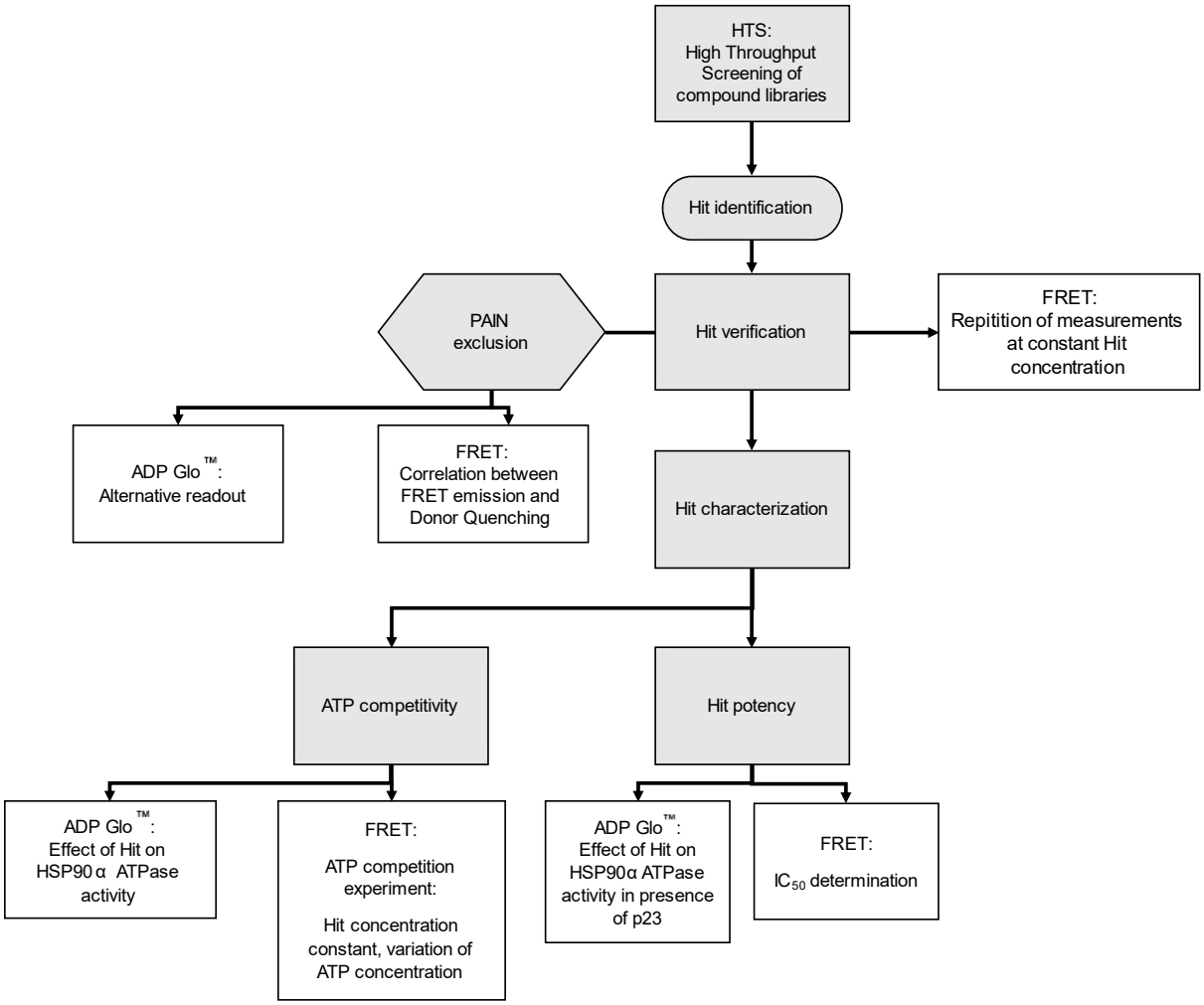


Figure S9. Workflow: Identification and profiling of inhibitors of *human* HSP90α-p23 binding.

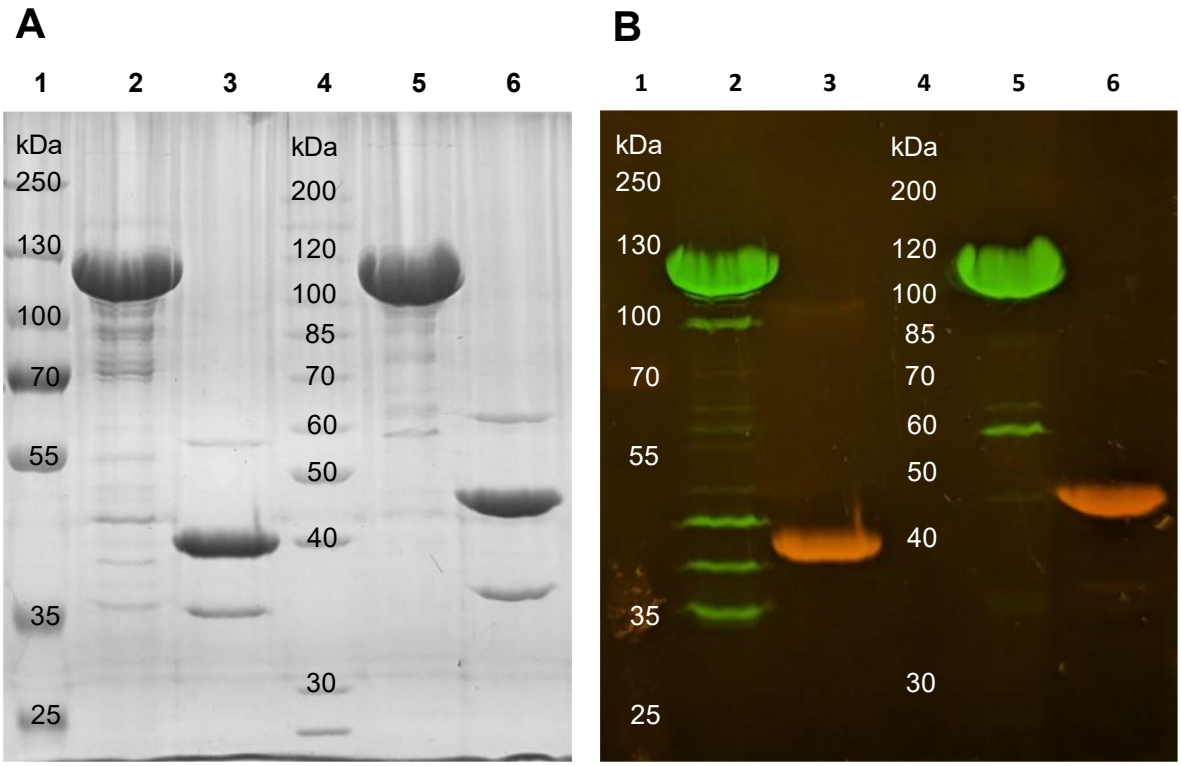


Figure S10. SDS-PAGE and purity assessment of fusion proteins for K_d experiments. Shown is the polyacrylamide gel (10%) after SDS-PAGE after Coomassie brilliant blue staining **(A)** and prior to staining under UV light **(B)** visualizing the fluorescence of the fluorescent fusion proteins. The purity of protein solutions was assessed via densitometric analysis of the Coomassie stained gel with ImageJ. The concentrations of L_0 and T_0 were corrected for the assessed purity prior to calculation of K_d. Lane 1: PAGE Ruler Prestained Plus. Lane 2: HSP90αE47A-mNeonGreen (113 kDa), purity 78.5%. Lane 3: p23-mScarlet-I (47 kDa), purity 84.1%. Lane 4: PAGE Ruler Unstained. Lane 5: HSP90E36A-mNeonGreen (109 kDa), purity 91.5%. Lane 6: Sba1-mScarlet-I (52 kDa), purity 79.5%. Due to the proteins being at least still partly folded, the migration pattern on the gel can slightly differ from their actual molecular weights.

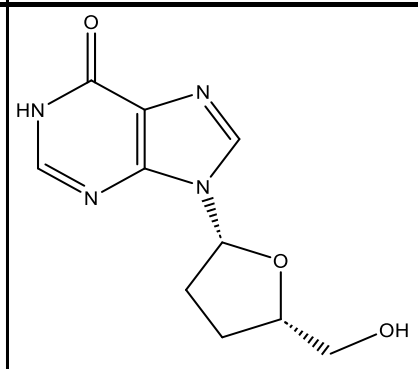
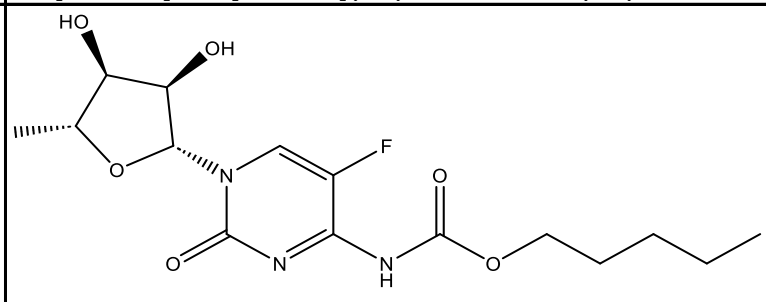
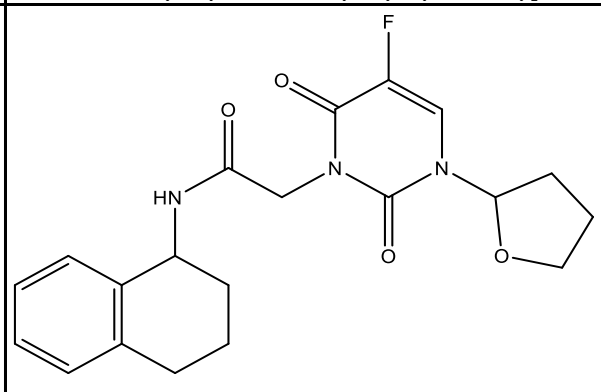
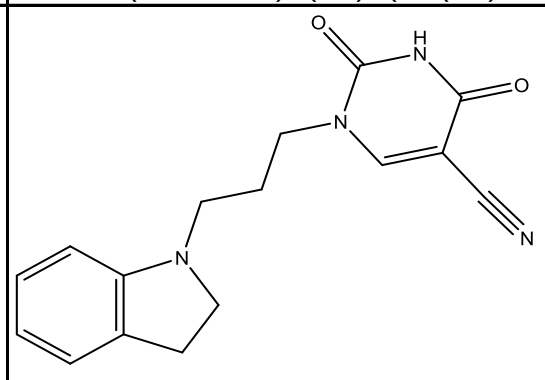
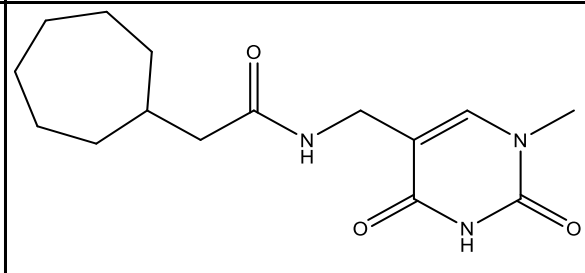
Tables

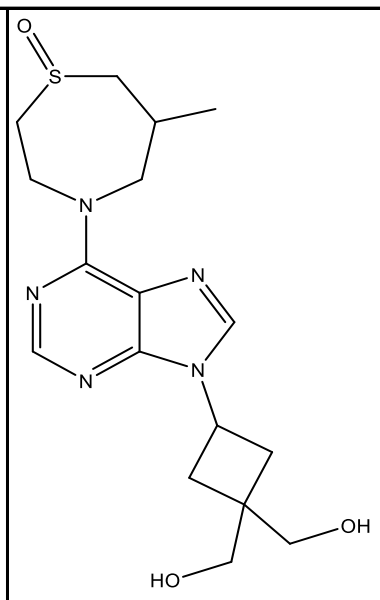
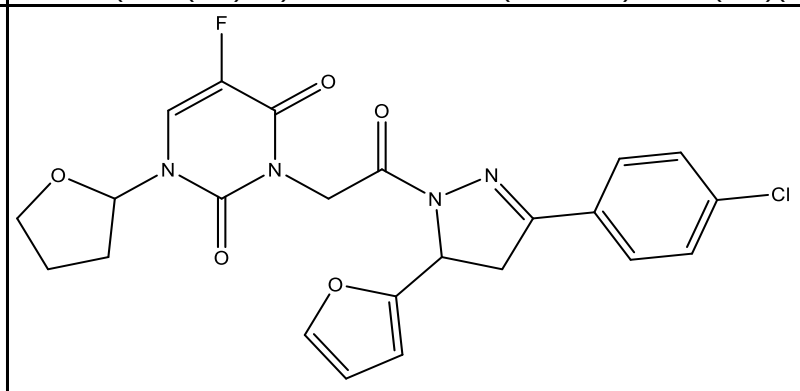
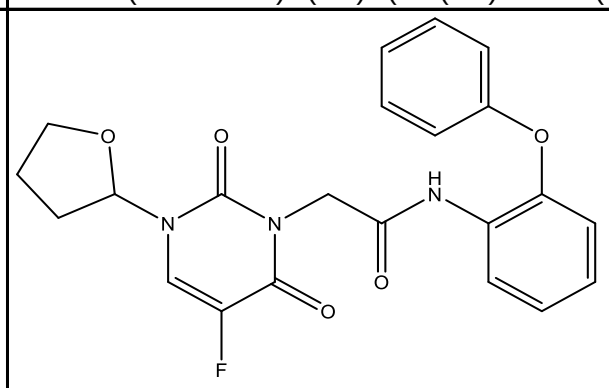
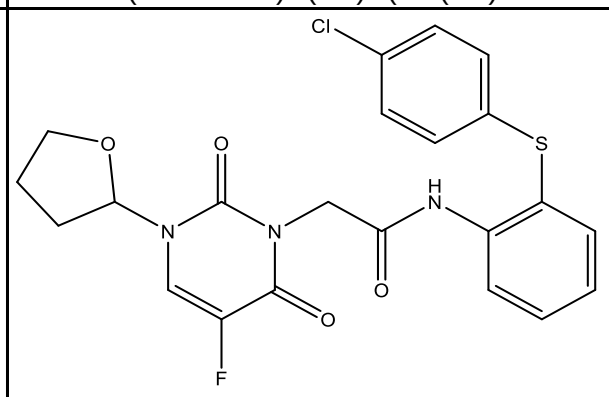
Table S1. Characteristics of screened HSP90 inhibitors and their influence on HSP90 - Sba1/p23 binding according to literature.

name	K_d value [nM]	ATP competitive	Influence on p23/Sba1 binding	HSP90 binding site (domain)	Reference(s)
Geldanamycin	1200	Yes	Yes	NTD	[82]
Celastrol	NA	No	No	CTD	[40], [83]
Radicicol	19	Yes	Yes	NTD	[82]
NVP-AUY922 (luminespib)	1.7	Yes	Yes	NTD	[76], [84]
Snx-5422	16	Yes	Yes	NTD	[78]
BIIB021	1.7 ± 0.4 (K_i)	Yes	Yes	NTD	[85]
Silibinin	NA	NA	NA	CTD	[86]
Deguelin	NA	No	NA	CTD	[87], [88]
Withaferin A	NA	No	No	CTD	[41]
(−)-Epigallocatechin-3-gallate (EGCG)	NA	No	Yes	CTD	[42], [43]

NA: not available; NTD: N-terminal domain; CTD: C-terminal domain

Table S2. Compound list of nucleoside-mimetic library

#	Structure
1	 OC[C@@H]1CC[C@@H](O1)N2C=NC=3C(=O)NC=NC23
2	 CCCCCOC(=O)NC1=NC(=O)N(C=C1F)[C@@H]2O[C@H](C)[C@@H](O)[C@H]2O
3	 FC1=CN(C2CCCO2)C(=O)N(CC(=O)NC3CCCC=4C=CC=CC34)C1=O
4	 O=C1NC(=O)N(CCCN2CCC=3C=CC=CC23)C=C1C#N
5	 CN1C=C(CNC(=O)CC2CCCCCC2)C(=O)NC1=O

	
6	CC1CN(CCS(=O)C1)C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4
	
7	FC1=CN(C2CCCO2)C(=O)N(CC(=O)N3N=C(CC3C4=CC=CO4)C=5C=CC(Cl)=CC5)C1=O
	
8	FC1=CN(C2CCCO2)C(=O)N(CC(=O)NC=3C=CC=CC3OC=4C=CC=CC4)C1=O
	
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	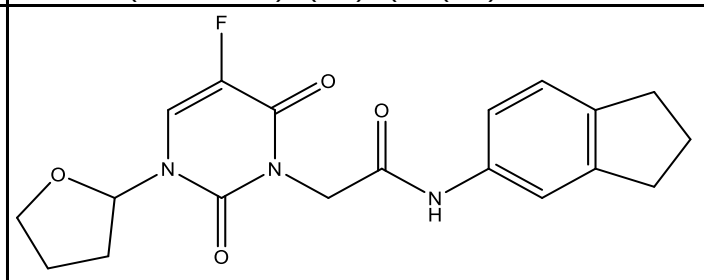
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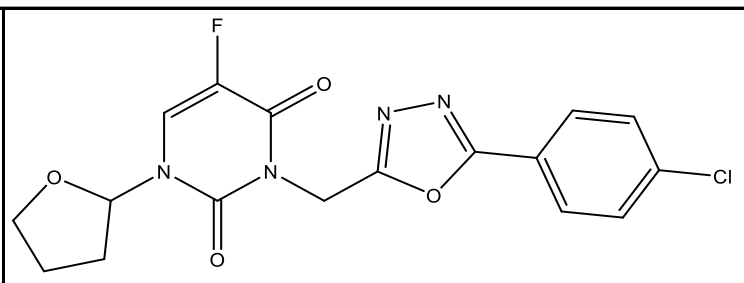
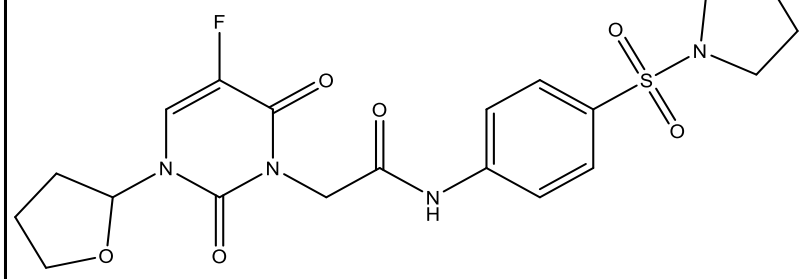
	
11	FC1=CN(C2CCCO2)C(=O)N(CC3=NN=C(O3)C=4C=CC(Cl)=CC4)C1=O
	
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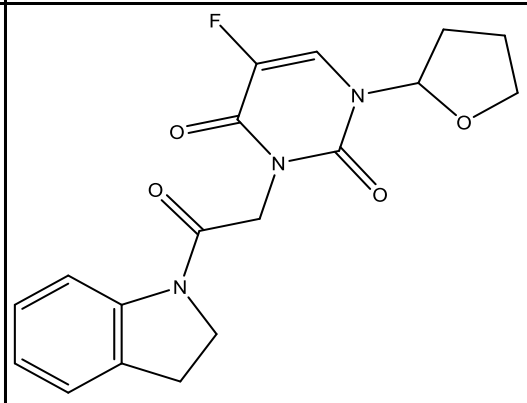
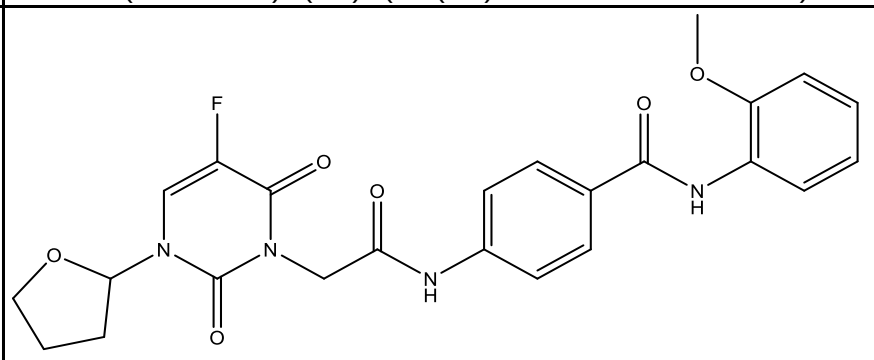
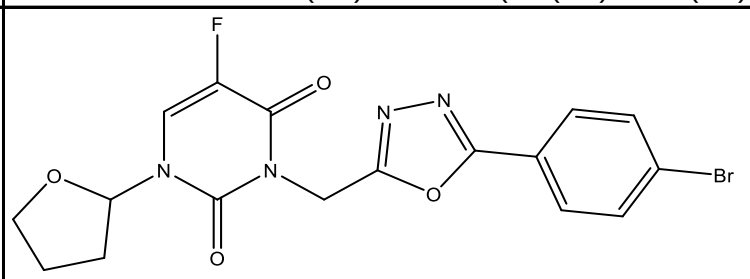
	
13	FC1=CN(C2CCCO2)C(=O)N(CC(=O)N3CCC=4C=CC=CC34)C1=O
	
14	COC=1C=CC=CC1NC(=O)C=2C=CC(NC(=O)CN3C(=O)C(F)=CN(C4CCCO4)C3=O)=CC2
	
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	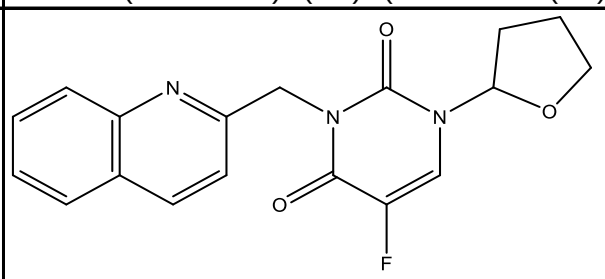
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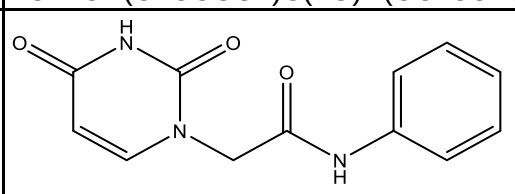
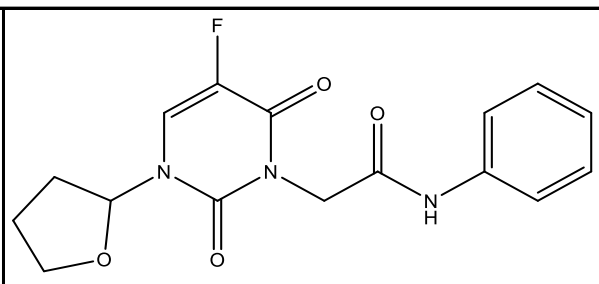
	
17	O=C(CN1C=CC(=O)NC1=O)NC=2C=CC=CC2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	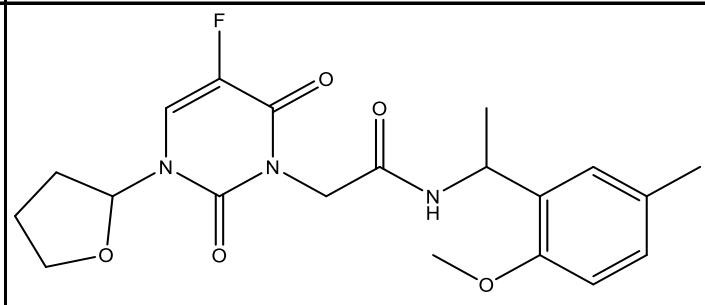
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	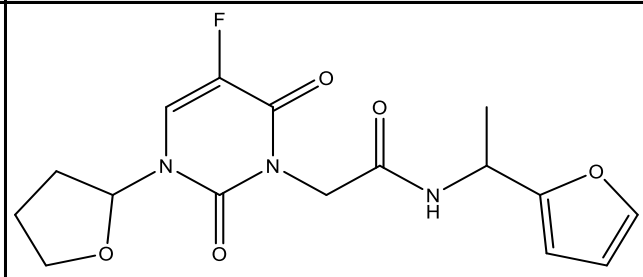
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	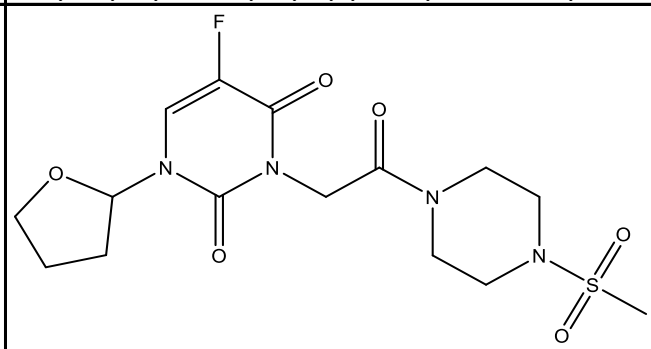
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	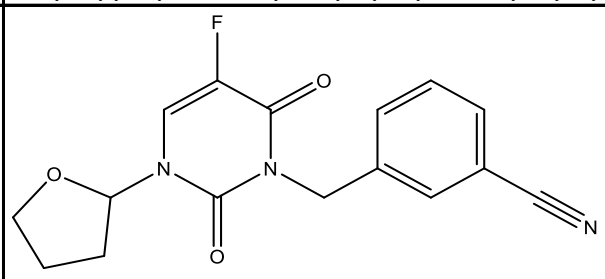
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	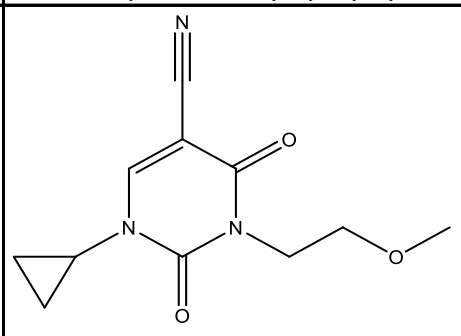
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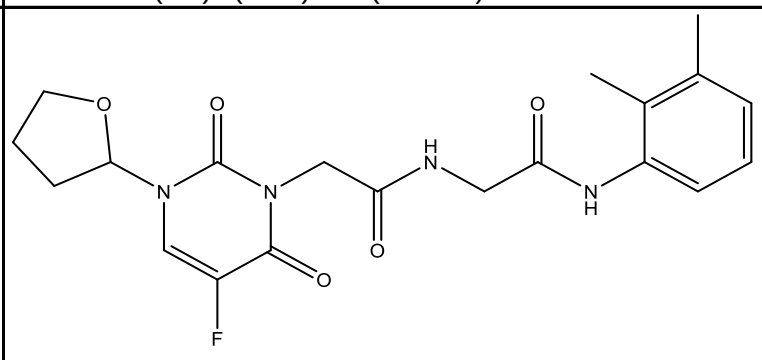
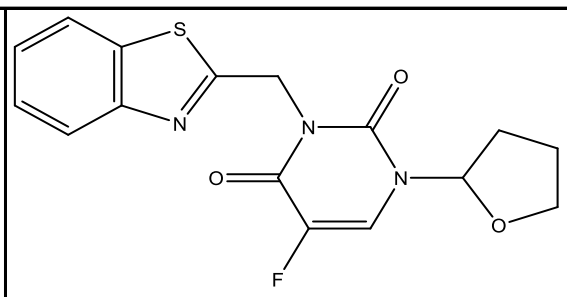
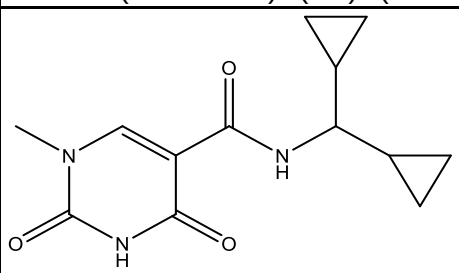
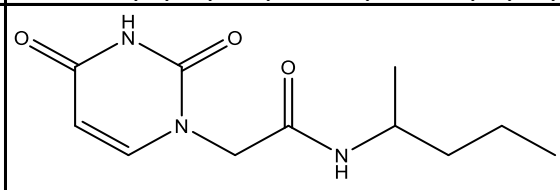
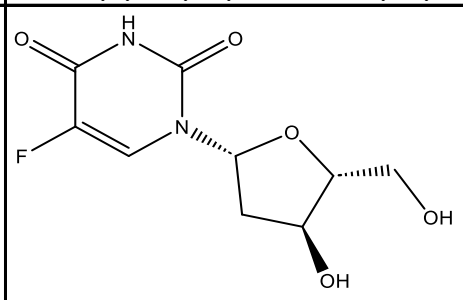
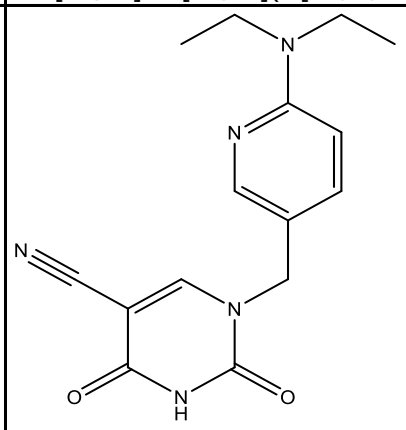
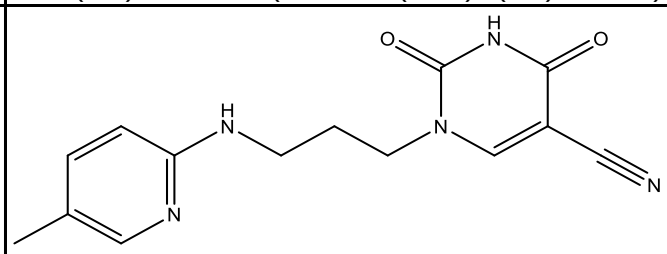
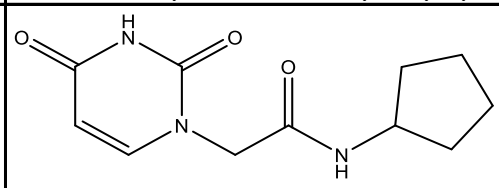
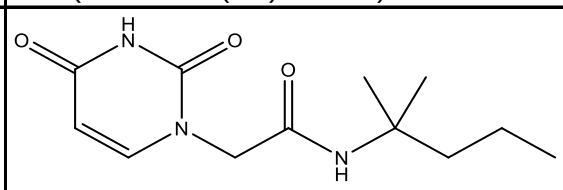
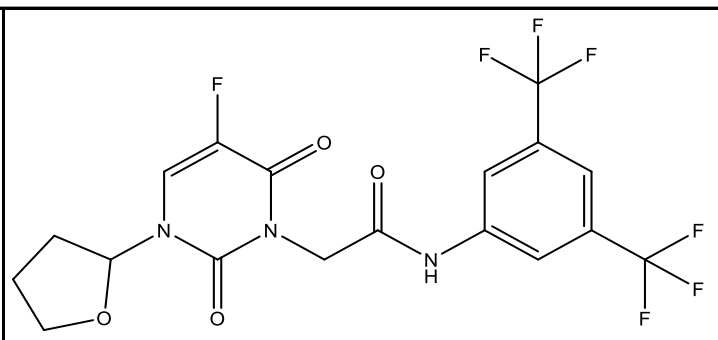
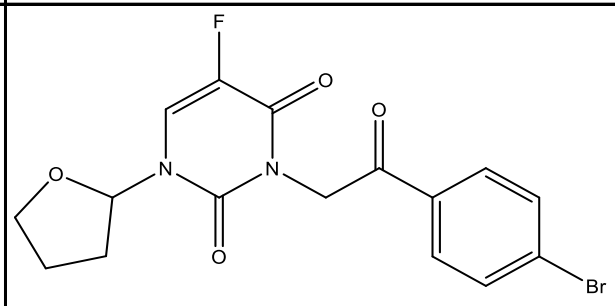
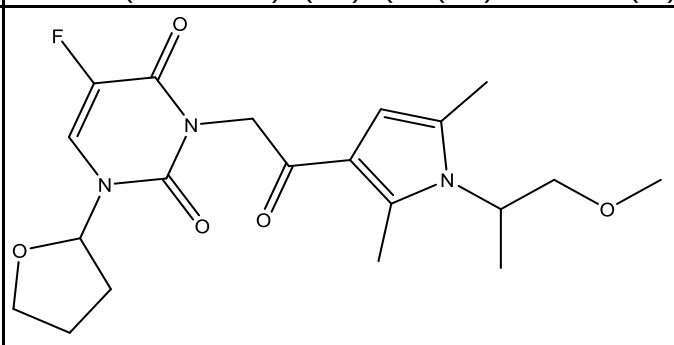
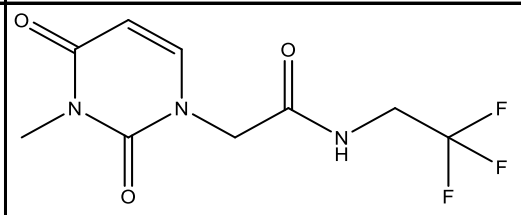
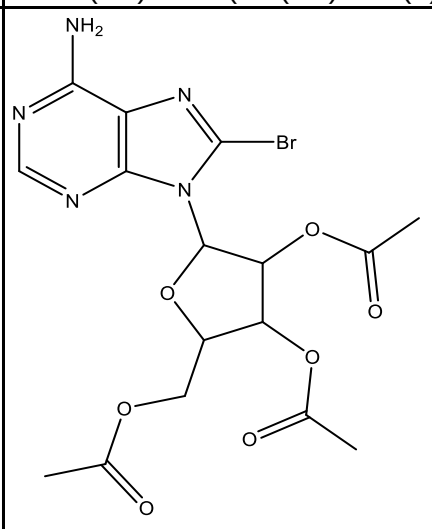
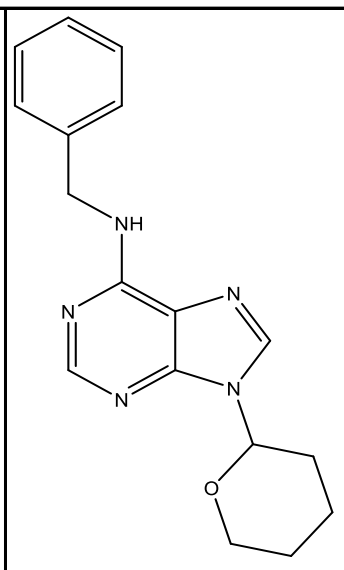
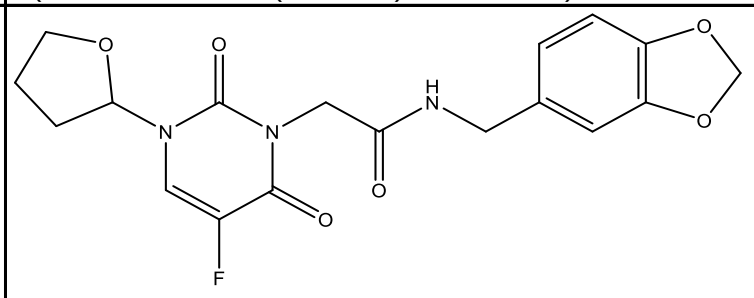
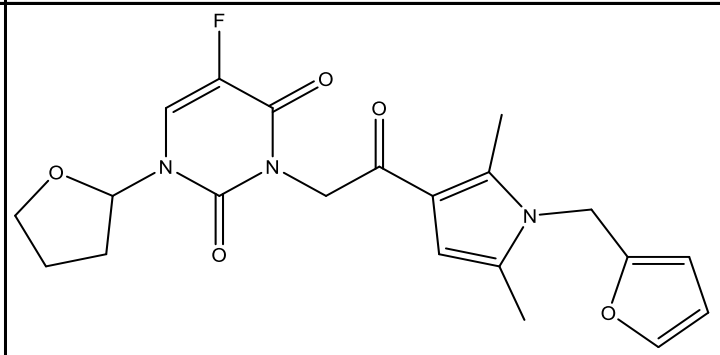
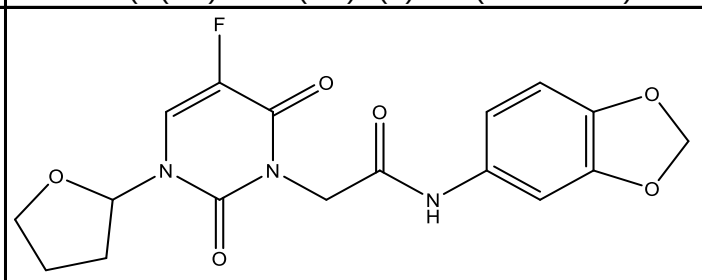
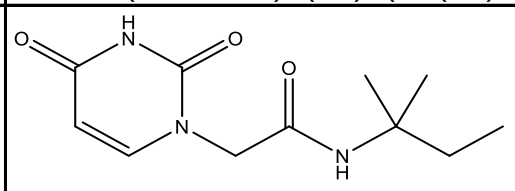
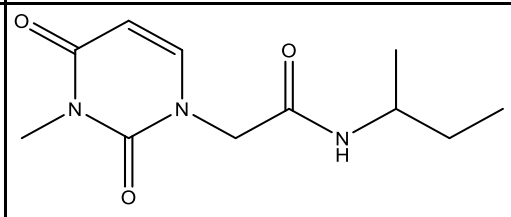
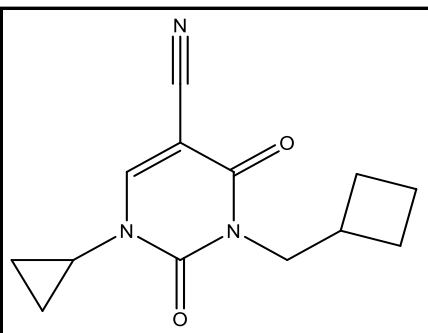
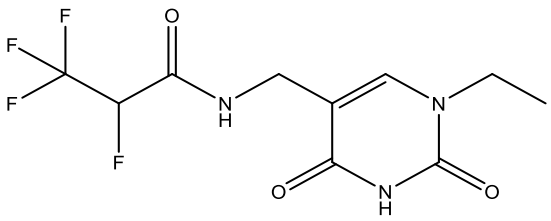
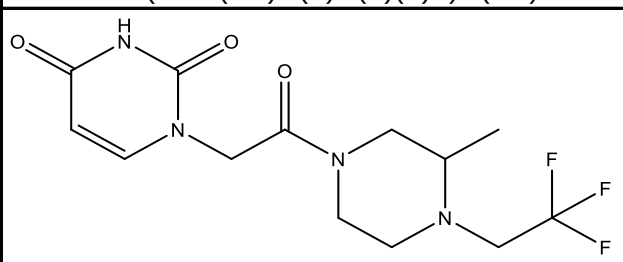
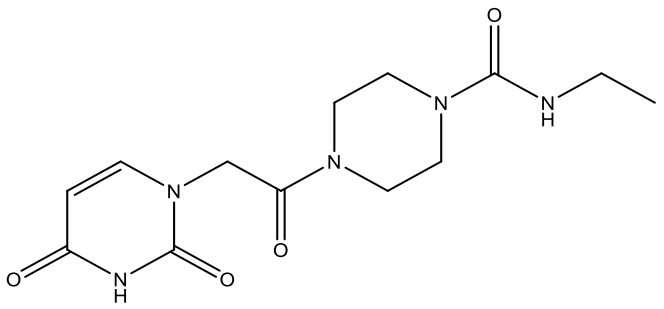
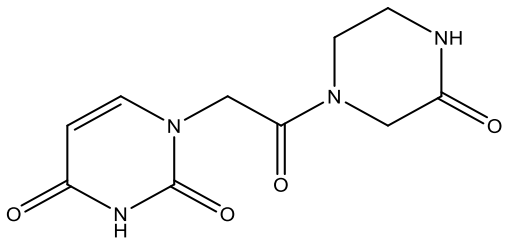
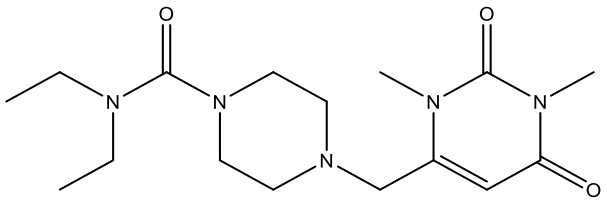
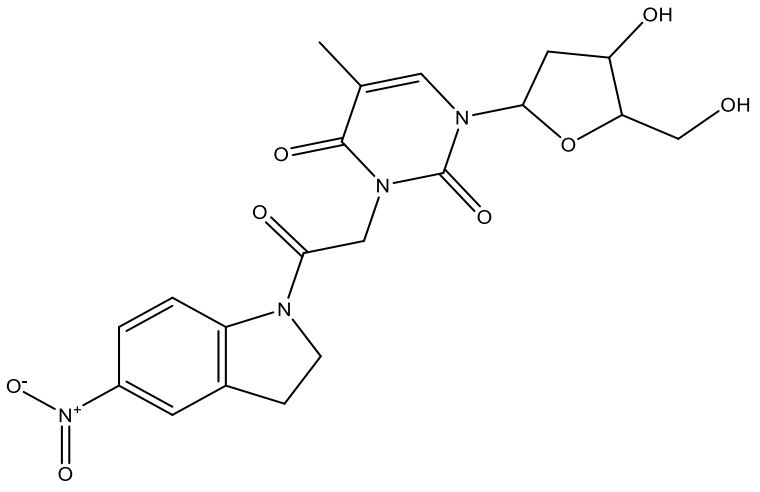
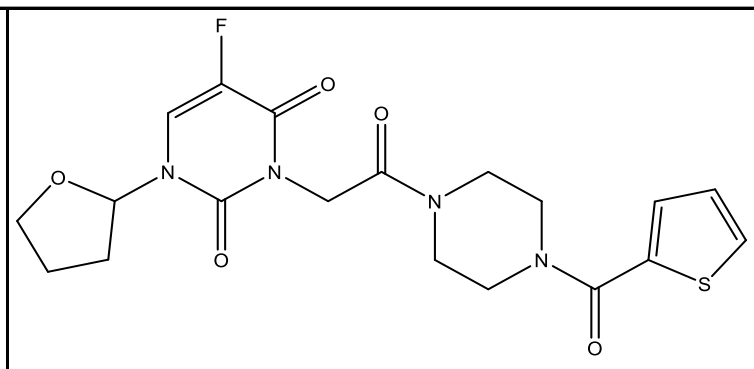
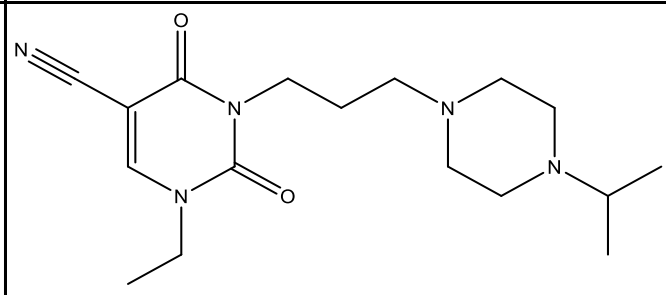
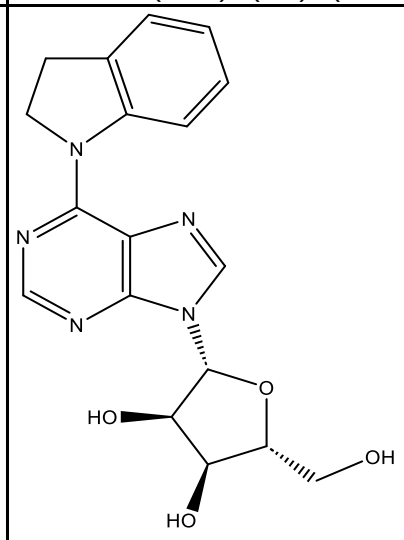
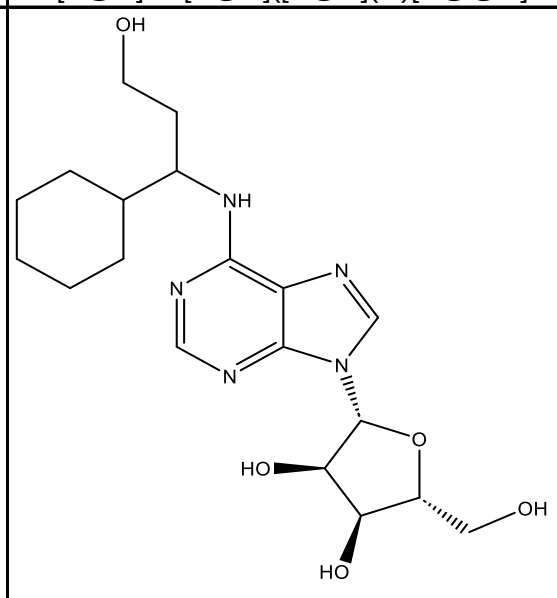
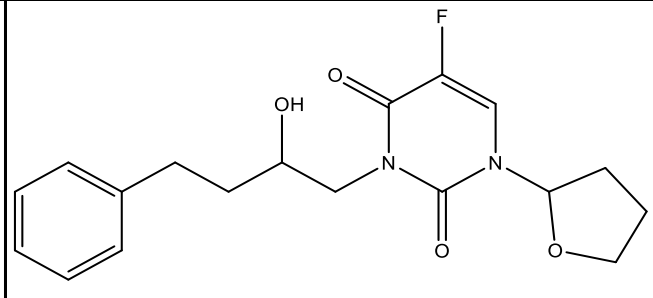
	
24	CC=1C=CC=C(NC(=O)CNC(=O)CN2C(=O)C(F)=CN(C3CCCO3)C2=O)C1C

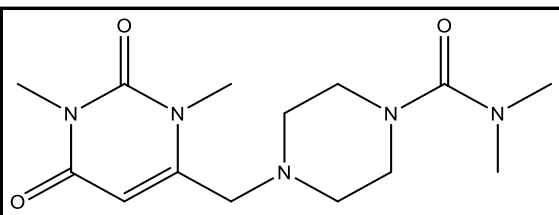
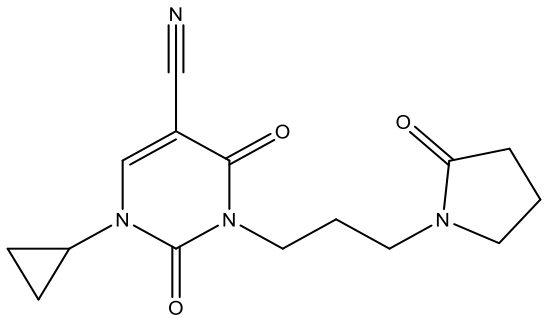
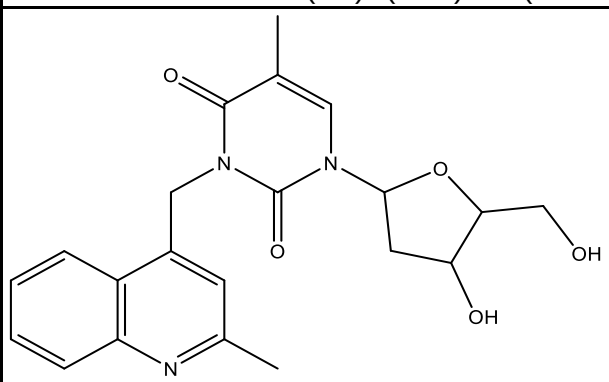
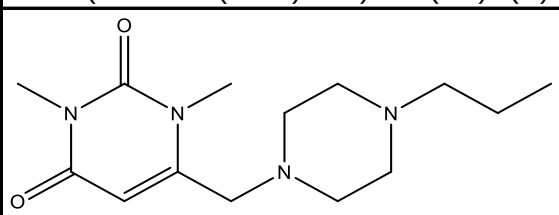
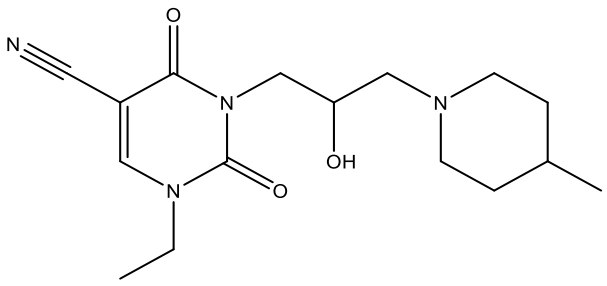
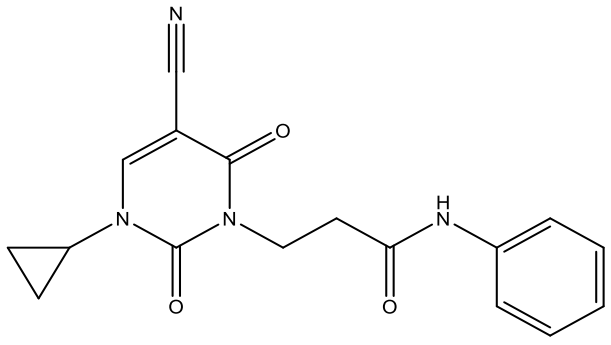
25		FC1=CN(C2CCCO2)C(=O)N(CC3=NC=4C=CC=CC4S3)C1=O
26		CN1C=C(C(=O)NC(C2CC2)C3CC3)C(=O)NC1=O
27		CCCC(C)NC(=O)CN1C=CC(=O)NC1=O
28		OC[C@H]1O[C@H](C[C@@H]1O)N2C=C(F)C(=O)NC2=O
29		CCN(CC)C=1C=CC(CN2C=C(C#N)C(=O)NC2=O)=CN1
30		CC=1C=CC(NCCCN2C=C(C#N)C(=O)NC2=O)=NC1
31		O=C(CN1C=CC(=O)NC1=O)NC2CCCC2
32		CCCC(C)(C)NC(=O)CN1C=CC(=O)NC1=O

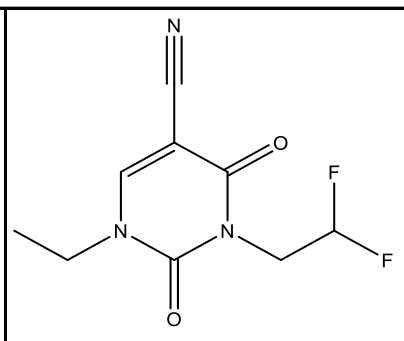
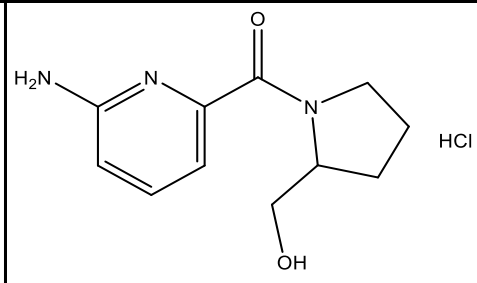
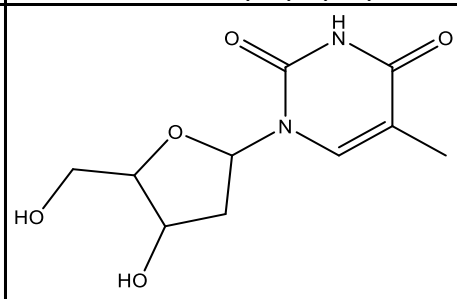
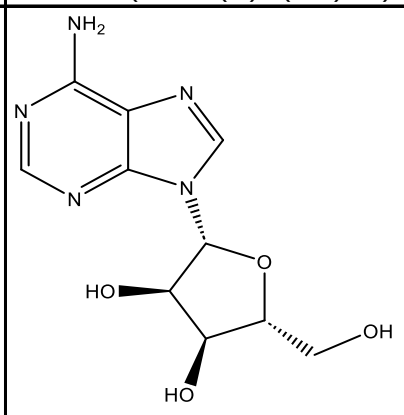
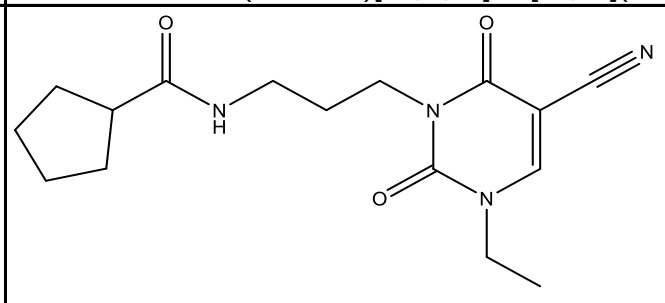
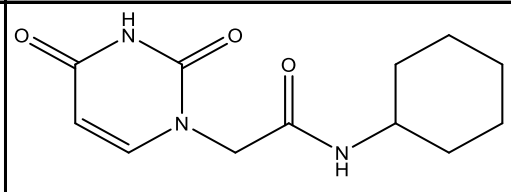
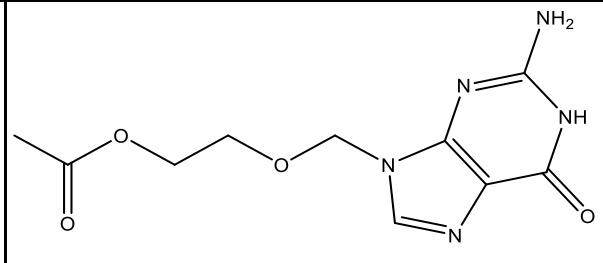
	
33	FC1=CN(C2CCCO2)C(=O)N(CC(=O)NC=3C=C(C=C(C3)C(F)(F)F)C(F)(F)F)C1=O
	
34	FC1=CN(C2CCCO2)C(=O)N(CC(=O)C=3C=CC(Br)=CC3)C1=O
	
35	COCC(C)N1C(C)=CC(C(=O)CN2C(=O)C(F)=CN(C3CCCO3)C2=O)=C1C
	
36	CN1C(=O)C=CN(CC(=O)NCC(F)(F)F)C1=O
	
37	CC(=O)OCC1OC(C(OC(=O)C)C1OC(=O)C)N2C(Br)=NC=3C(N)=NC=NC23

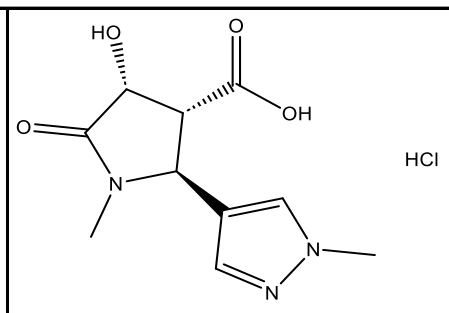
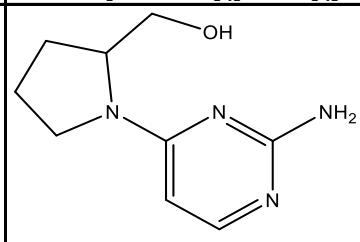
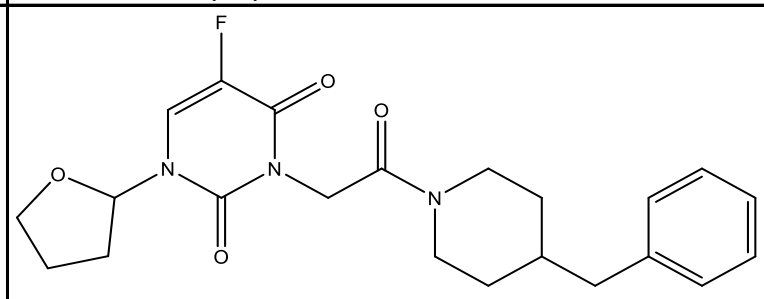
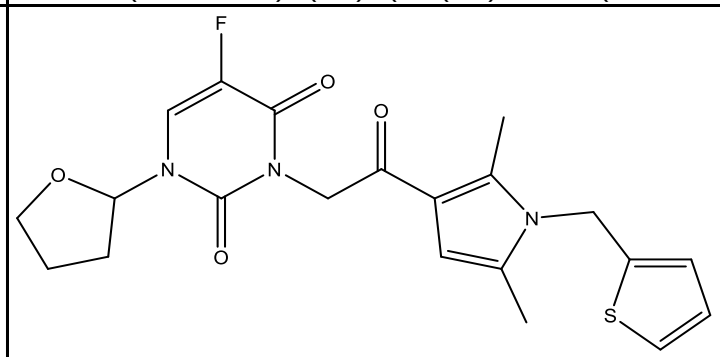
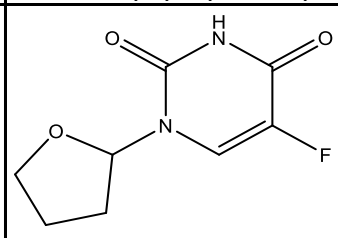
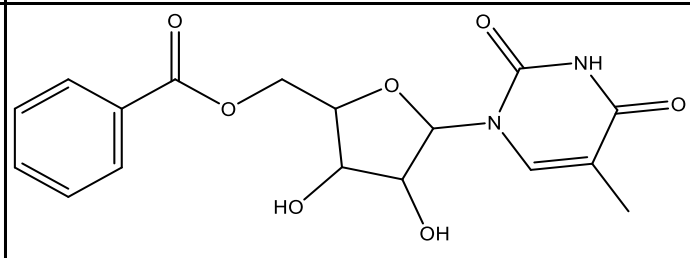
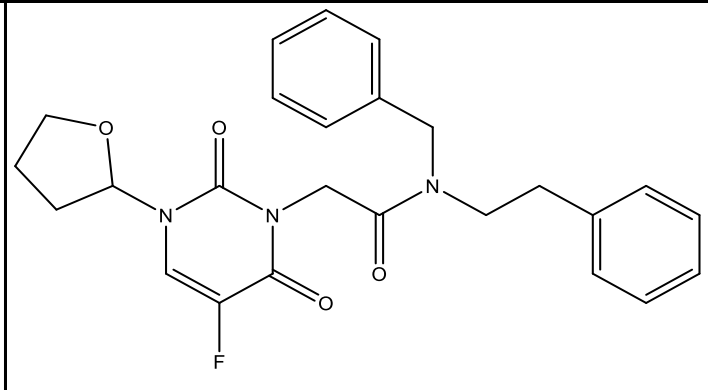
	
38	C(NC=1N=CN=C2N(C=NC12)C3CCCCO3)C=4C=CC=CC4
	
39	FC1=CN(C2CCCO2)C(=O)N(CC(=O)NCC=3C=CC=4OCOC4C3)C1=O
	
40	CC1=CC(C(=O)CN2C(=O)C(F)=CN(C3CCCO3)C2=O)=C(C)N1CC4=CC=CO4
	
41	FC1=CN(C2CCCO2)C(=O)N(CC(=O)NC=3C=CC=4OCOC4C3)C1=O
	
42	CCC(C)(C)NC(=O)CN1C=CC(=O)NC1=O
	
43	CCC(C)NC(=O)CN1C=CC(=O)N(C)C1=O

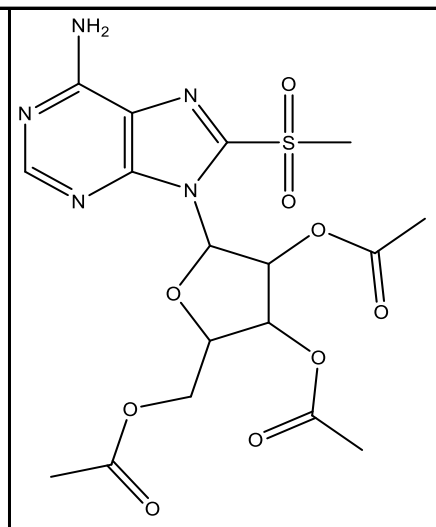
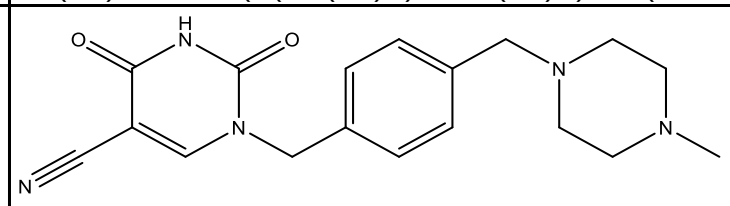
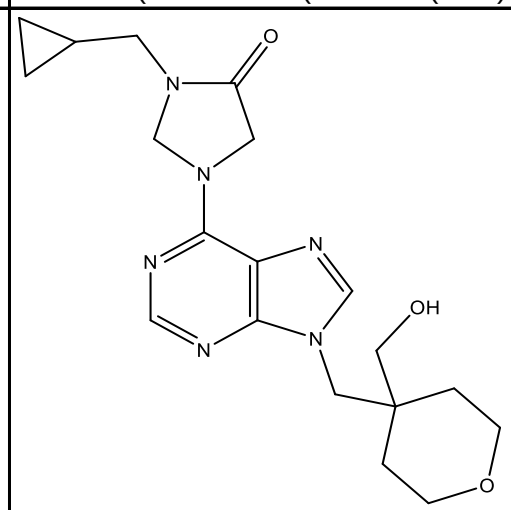
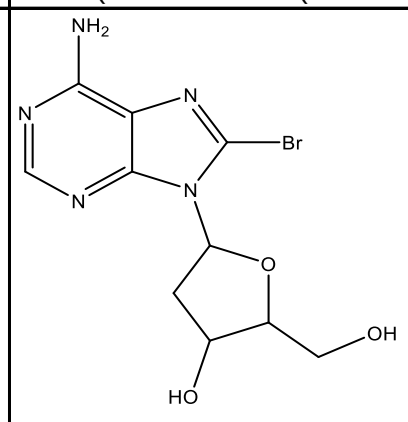
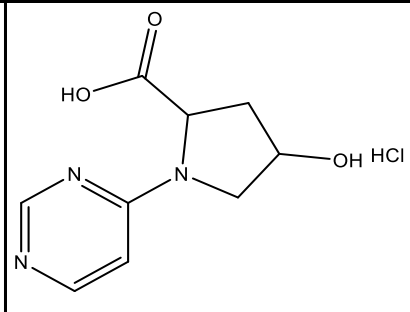
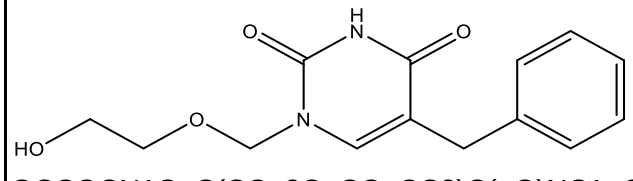
44		O=C1C(C#N)=CN(C2CC2)C(=O)N1CC3CCC3
45		CCN1C=C(CNC(=O)C(F)C(F)(F)F)C(=O)NC1=O
46		CC1CN(CCN1CC(F)(F)F)C(=O)CN2C=CC(=O)NC2=O
47		CCNC(=O)N1CCN(CC1)C(=O)CN2C=CC(=O)NC2=O
48		O=C(CN1C=CC(=O)NC1=O)N2CCNC(=O)C2
49		CCN(CC)C(=O)N1CCN(CC2=CC(=O)N(C)C(=O)N2C)CC1
50		CC1=CN(C2CC(O)C(CO)O2)C(=O)N(CC(=O)N3CCC=4C=C(C=CC34)[N+](=O)[O-])C1=O

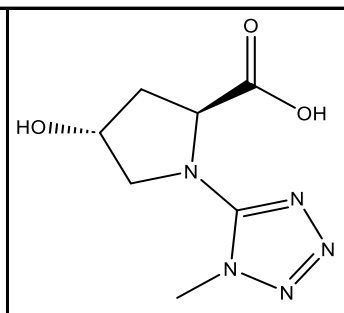
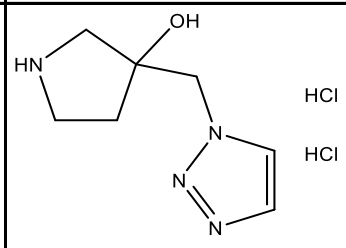
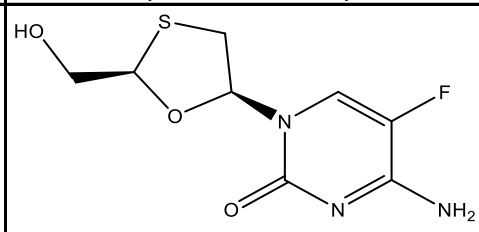
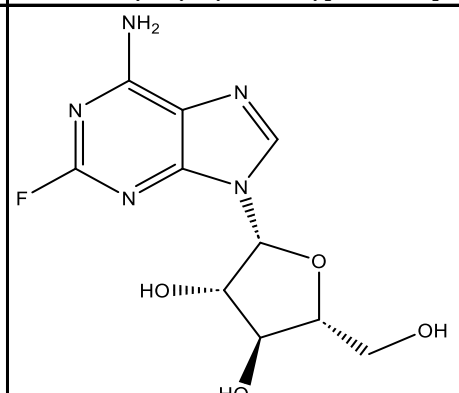
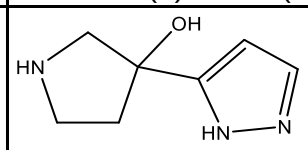
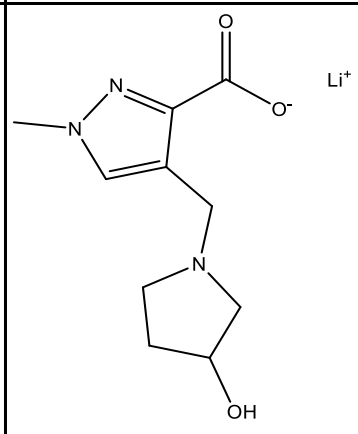
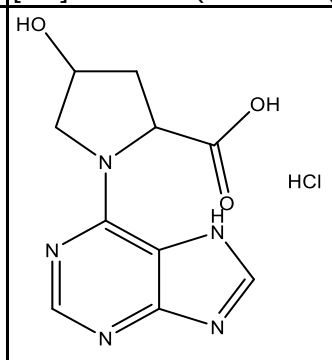
51		FC1=CN(C2CCCO2)C(=O)N(CC(=O)N3CCN(CC3)C(=O)C4=CC=CS4)C1=O
52		CCN1C=C(C#N)C(=O)N(CCCN2CCN(CC2)C(C)C)C1=O
53		OC[C@H]1O[C@H]([C@H](O)[C@@H]1O)N2C=NC=3C(=NC=NC23)N4CCC=5C=CC=CC45
54		OCCC(NC=1N=CN=C2N(C=NC12)[C@@H]3O[C@H](CO)[C@@H](O)[C@H]3O)C4CCCCC4
55		OC(CCC=1C=CC=CC1)CN2C(=O)C(F)=CN(C3CCCO3)C2=O

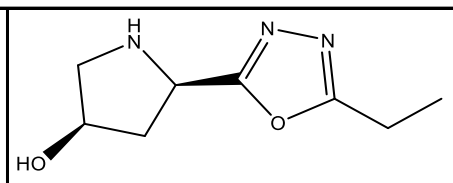
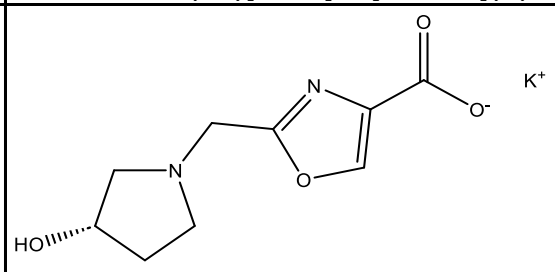
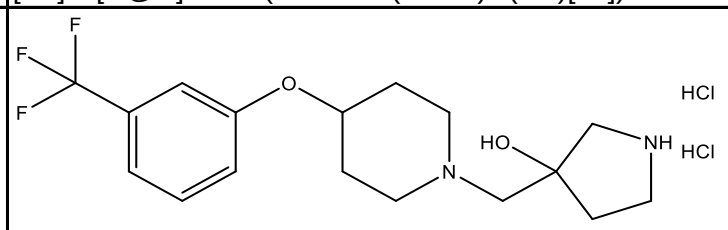
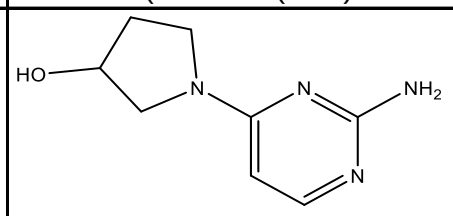
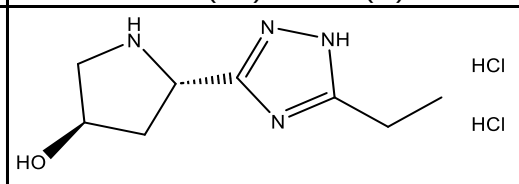
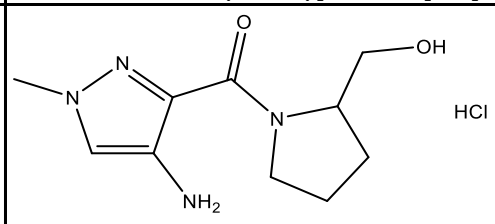
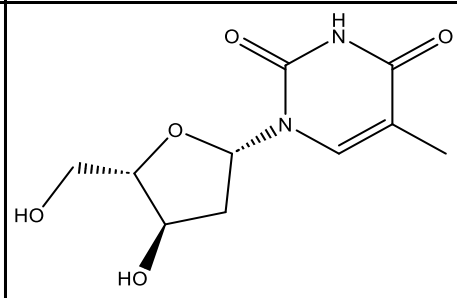
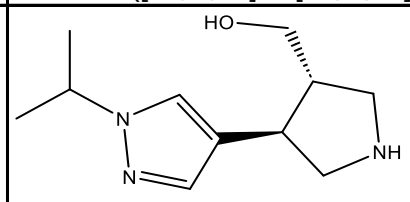
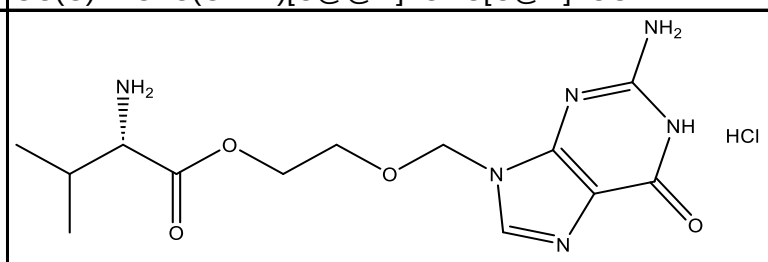
		
56	CN(C)C(=O)N1CCN(CC2=CC(=O)N(C)C(=O)N2C)CC1	
		
57	O=C1CCCN1CCCN2C(=O)C(C#N)=CN(C3CC3)C2=O	
		
58	CC=1C=C(CN2C(=O)C(C)=CN(C3CC(O)C(CO)O3)C2=O)C=4C=CC=CC4N1	
59	CN1C(CN2CCN(CCO)CC2)=CC(=O)N(C)C1=O	
		
60	CCCN1CCN(CC2=CC(=O)N(C)C(=O)N2C)CC1	
		
61	CCN1C=C(C#N)C(=O)N(CC(O)CN2CCC(C)CC2)C1=O	
		
62	O=C(CCN1C(=O)C(C#N)=CN(C2CC2)C1=O)NC=3C=CC=CC3	

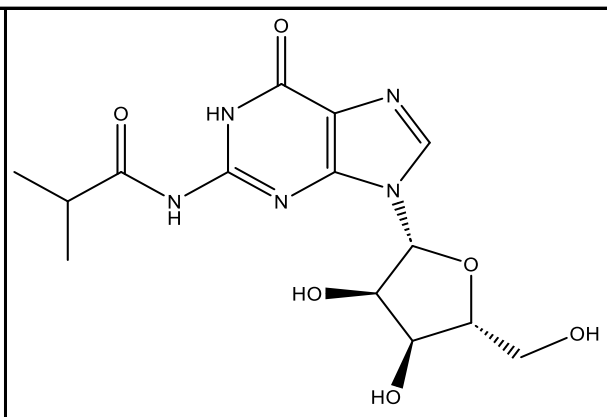
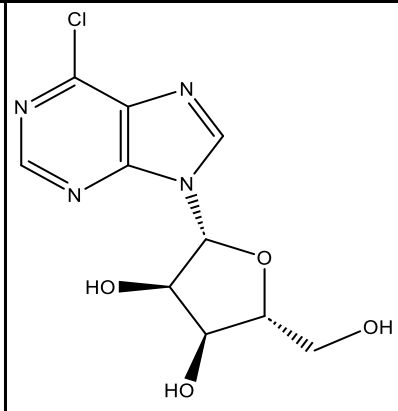
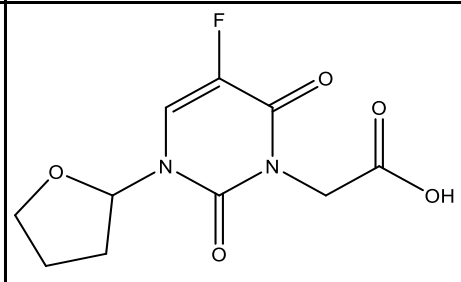
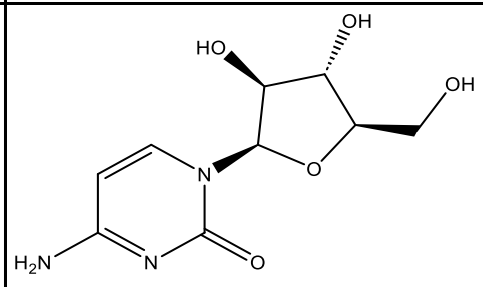
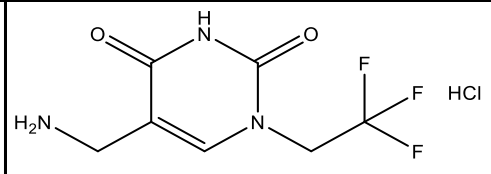
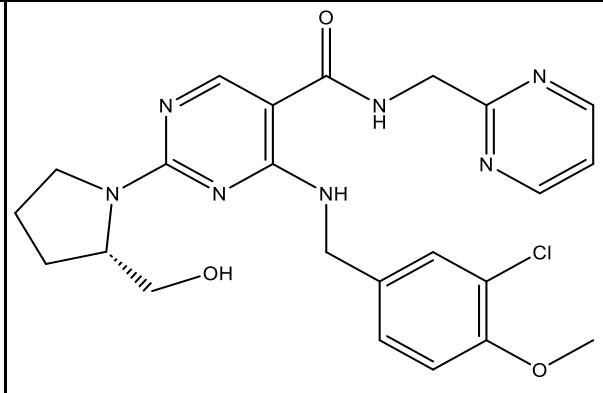
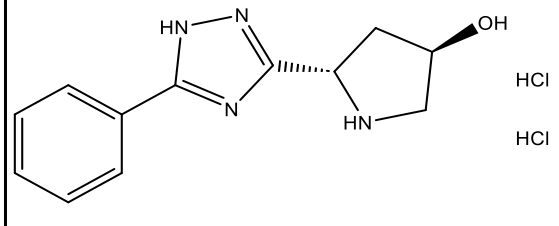
	
63	CCN1C=C(C#N)C(=O)N(CC(F)F)C1=O
	
64	Cl.NC=1C=CC=C(N1)C(=O)N2CCCC2CO
	
65	CC1=CN(C2CC(O)C(CO)O2)C(=O)NC1=O
	
66	NC=1N=CN=C2N(C=NC12)[C@@H]3O[C@H](CO)[C@@H](O)[C@H]3O
	
67	CCN1C=C(C#N)C(=O)N(CCCNC(=O)C2CCCC2)C1=O
	
68	O=C(CN1C=CC(=O)NC1=O)NC2CCCCC2
	
69	CC(=O)OCCOCN1C=NC=2C(=O)NC(N)=NC12

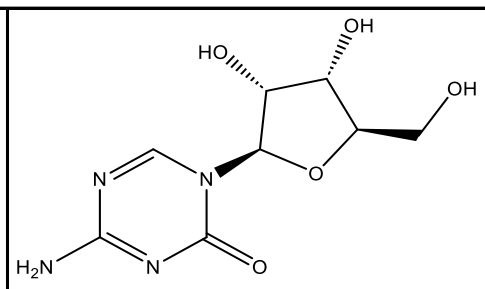
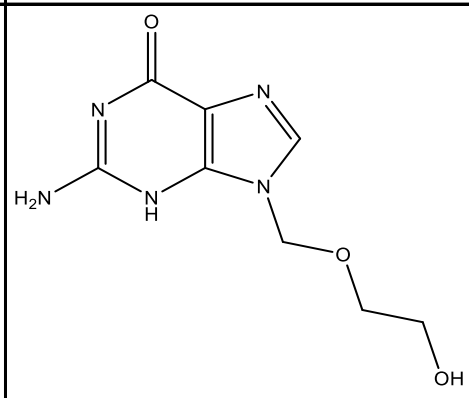
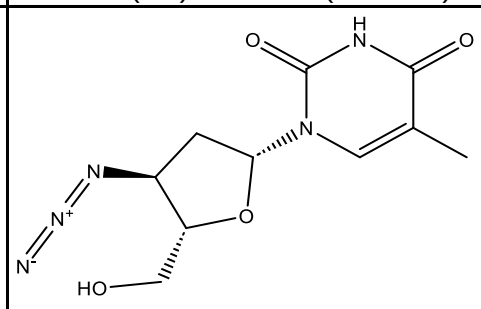
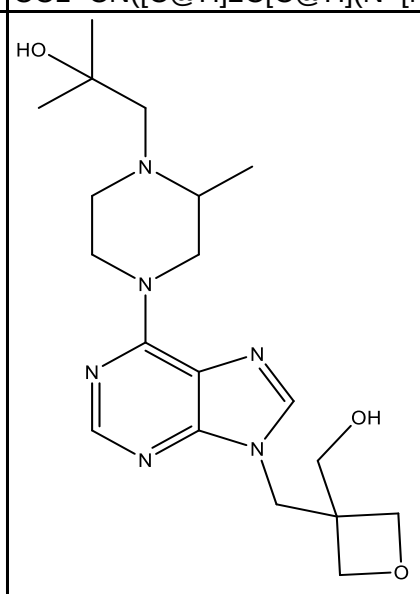
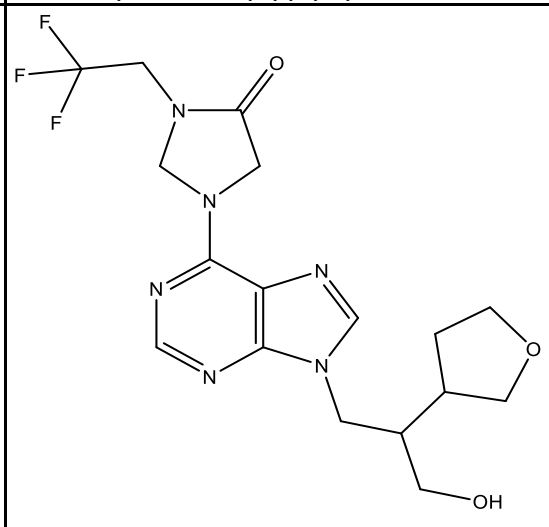
	
70	Cl.CN1[C@@H]([C@H]([C@@H](O)C1=O)C(=O)O)C=2C=NN(C)C2
	
71	NC=1N=CC=C(N1)N2CCCC2CO
	
72	FC1=CN(C2CCCO2)C(=O)N(CC(=O)N3CCC(CC=4C=CC=CC4)CC3)C1=O
	
73	CC1=CC(C(=O)CN2C(=O)C(F)=CN(C3CCCO3)C2=O)=C(C)N1CC4=CC=CS4
	
74	FC1=CN(C2CCCO2)C(=O)NC1=O
	
75	CC1=CN(C2OC(COC(=O)C=3C=CC=CC3)C(O)C2O)C(=O)NC1=O
	
76	FC1=CN(C2CCCO2)C(=O)N(CC(=O)N(CCC=3C=CC=CC3)CC=4C=CC=CC4)C1=O

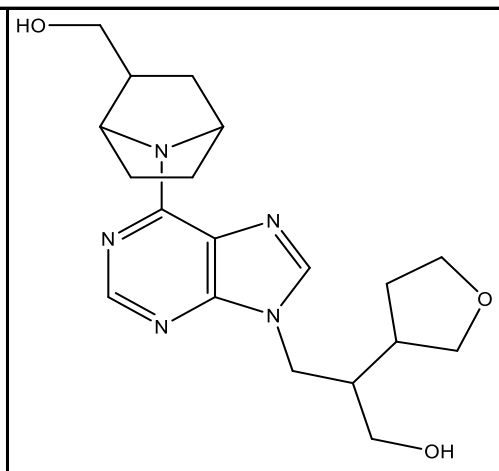
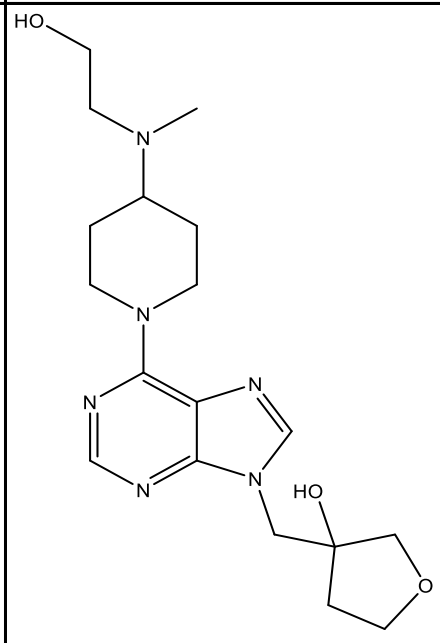
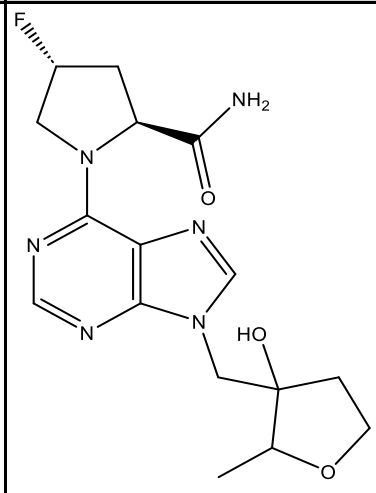
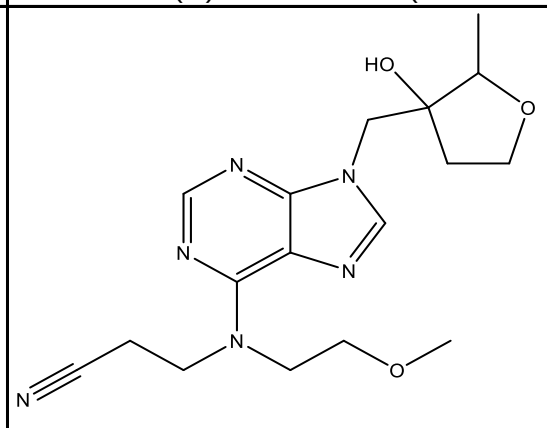
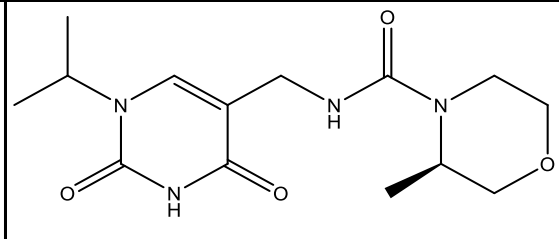
		77 CC(=O)OCC1OC(C(OC(=O)C)C1OC(=O)C)N2C(=NC=3C(N)=NC=NC23)S(=O)(=O)C
		78 CN1CCN(CC=2C=CC(CN3C=C(C#N)C(=O)NC3=O)=CC2)CC1
		79 OCC1(CN2C=NC=3C(=NC=NC23)N4CN(CC5CC5)C(=O)C4)CCOCC1
		80 NC=1N=CN=C2N(C3CC(O)C(CO)O3)C(Br)=NC12
		81 Cl.OC1CC(N(C1)C=2C=CN=CN2)C(=O)O
		82 OCCOCN1C=C(CC=2C=CC=CC2)C(=O)NC1=O

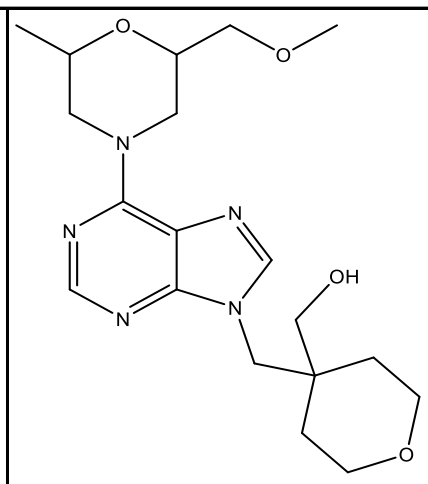
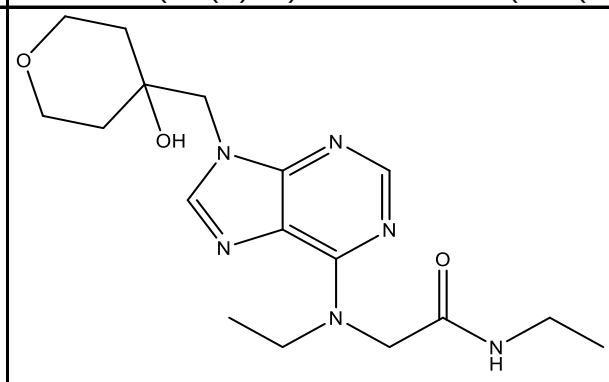
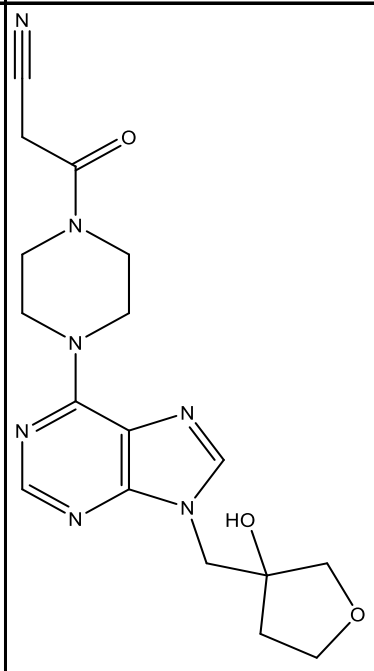
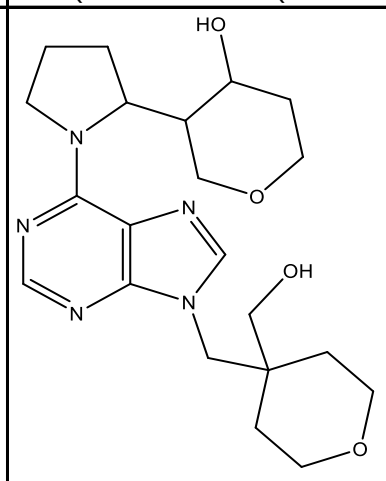
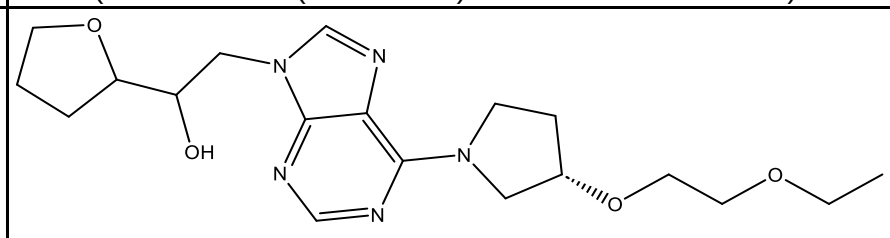
	
83	CN1N=NN=C1N2C[C@H](O)C[C@H]2C(=O)O
	
84	Cl.Cl.OC1(CN2C=CN=N2)CCNC1
	
85	NC1=NC(=O)N(C=C1F)[C@@H]2CS[C@H](CO)O2
	
86	NC=1N=C(F)N=C2N(C=NC12)[C@@H]3O[C@H](CO)[C@@H](O)[C@@H]3O
	
87	OC1(CCNC1)C2=CC=NN2
	
88	[Li+].CN1C=C(CN2CCC(O)C2)C(=N1)C(=O)[O-]
	
89	Cl.OC1CC(N(C1)C=2N=CN=C3N=CNC23)C(=O)O

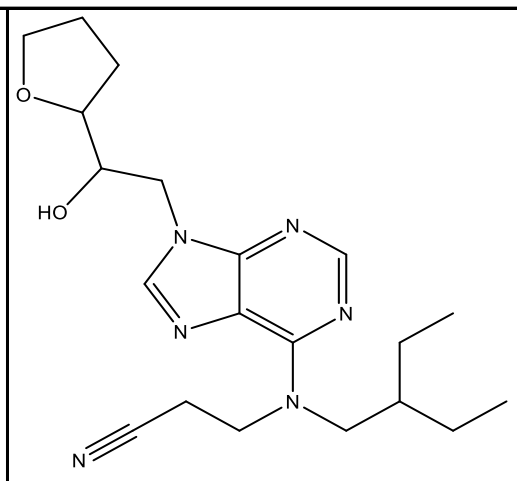
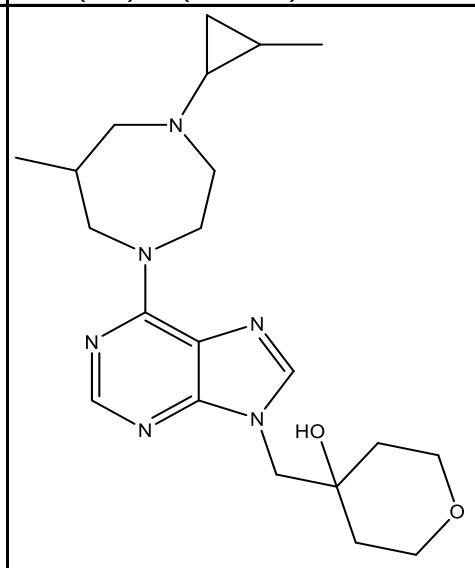
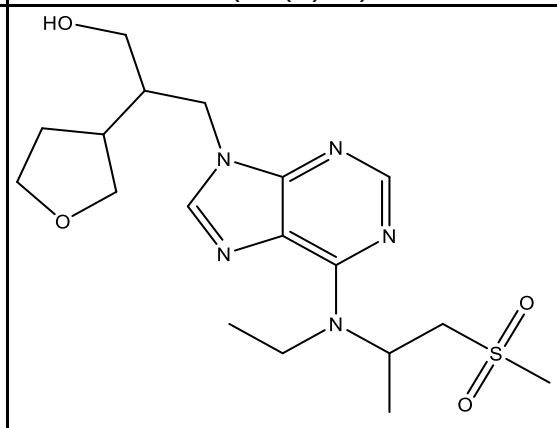
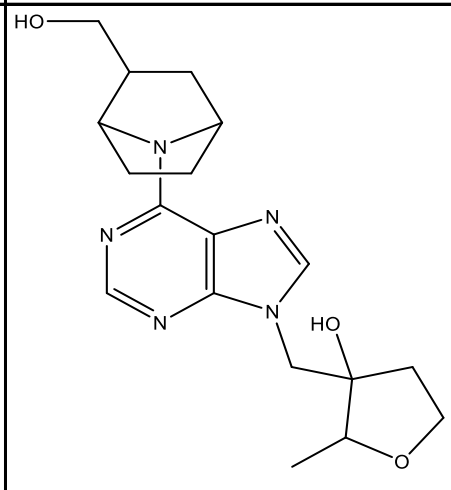
		
90	CCC1=NN=C(O1)[C@H]2C[C@@H](O)CN2	
		
91	[K+].O[C@H]1CCN(CC2=NC(=CO2)C(=O)[O-])C1	
		
92	Cl.Cl.OC1(CN2CCC(CC2)OC=3C=CC=C(C3)C(F)(F)F)CCNC1	
		
93	NC=1N=CC=C(N1)N2CCC(O)C2	
		
94	Cl.Cl.CCC1=NC(=NN1)[C@@H]2C[C@@H](O)CN2	
		
95	Cl.CN1C=C(N)C(=N1)C(=O)N2CCCC2CO	
		
96	CC1=CN([C@@H]2C[C@@H](O)[C@H](CO)O2)C(=O)NC1=O	
		
97	CC(C)N1C=C(C=N1)[C@@H]2CNC[C@H]2CO	
		
98	Cl.CC(C)[C@H](N)C(=O)OCCOCN1C=NC=2C(=O)NC(N)=NC12	

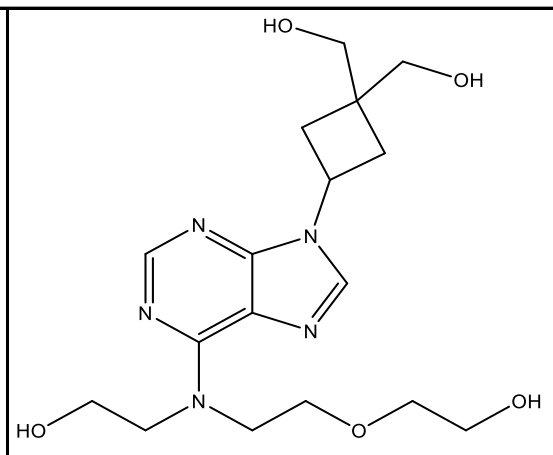
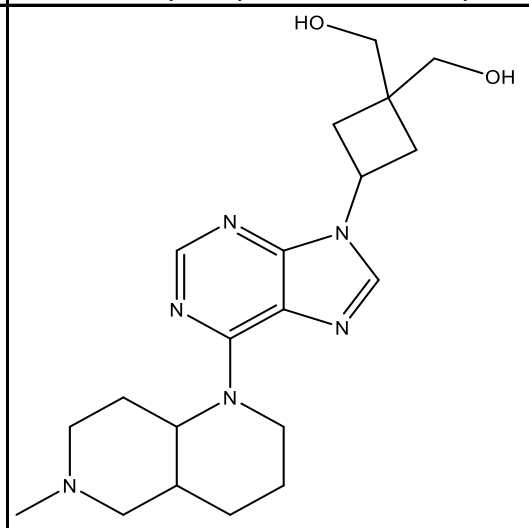
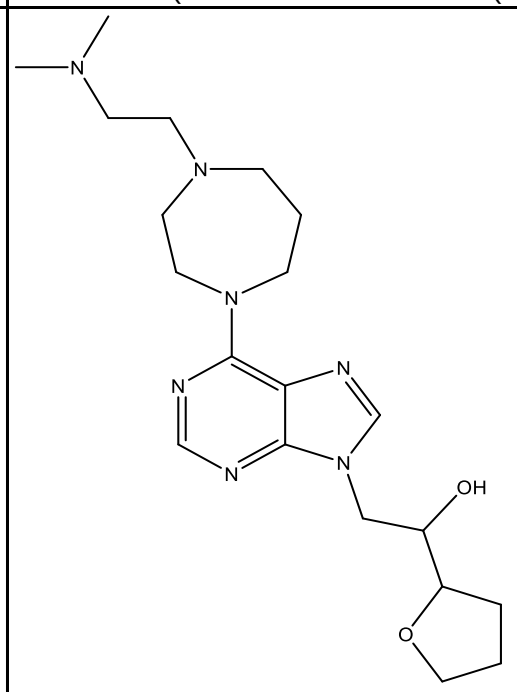
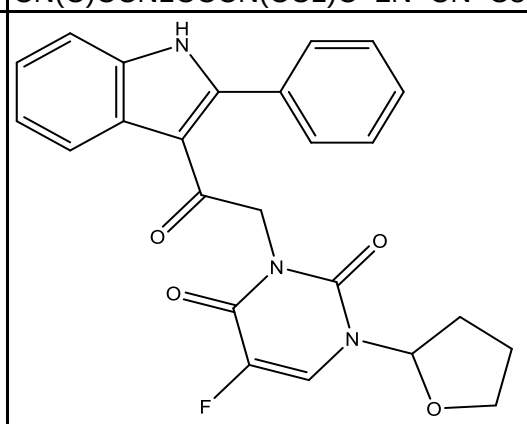
	
99	CC(C)C(=O)NC1=NC=2N(C=NC2C(=O)N1)[C@@H]3O[C@H](CO)[C@@H](O)[C@H]3O
	
100	OC[C@H]1O[C@H]([C@H](O)[C@@H]1O)N2C=NC=3C(Cl)=NC=NC23
	
101	OC(=O)CN1C(=O)C(F)=CN(C2CCCO2)C1=O
	
102	NC=1C=CN([C@@H]2O[C@H](CO)[C@@H](O)[C@@H]2O)C(=O)N1
	
103	Cl.NCC1=CN(CC(F)(F)F)C(=O)NC1=O
	
104	COC=1C=CC(CNC=2N=C(N=CC2C(=O)NCC=3N=CC=CN3)N4CCC[C@H]4CO)=CC1Cl
	
105	Cl.Cl.O[C@H]1CN[C@@H](C1)C2=NNC(=N2)C=3C=CC=CC3

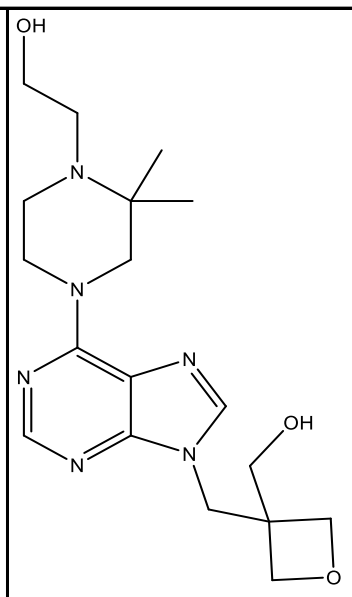
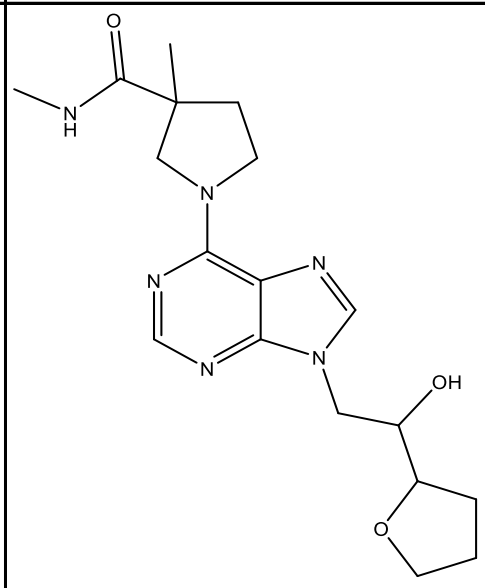
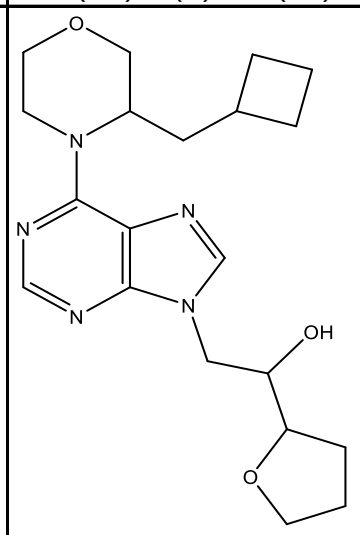
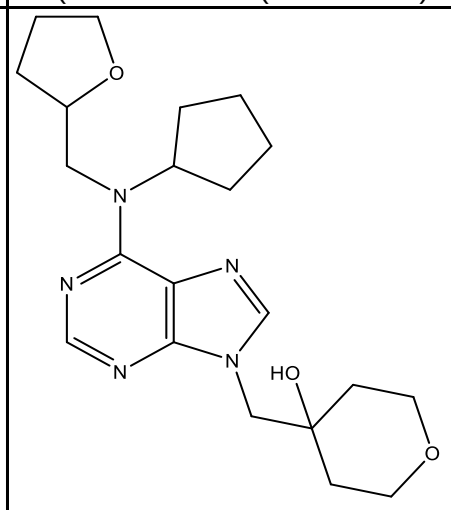
		
106	NC=1N=CN([C@@H]2O[C@H](CO)[C@@H](O)[C@H]2O)C(=O)N1	
		
107	NC1=NC(=O)C=2N=CN(COCCO)C2N1	
		
108	CC1=CN([C@H]2C[C@H](N=[N+]=[N-])[C@@H](CO)O2)C(=O)NC1=O	
		
109	CC1CN(CCN1CC(C)(C)O)C=2N=CN=C3N(CC4(CO)COC4)C=NC23	
		
110	OCC(CN1C=NC=2C(=NC=NC12)N3CN(CC(F)(F)F)C(=O)C3)C4CCOC4	

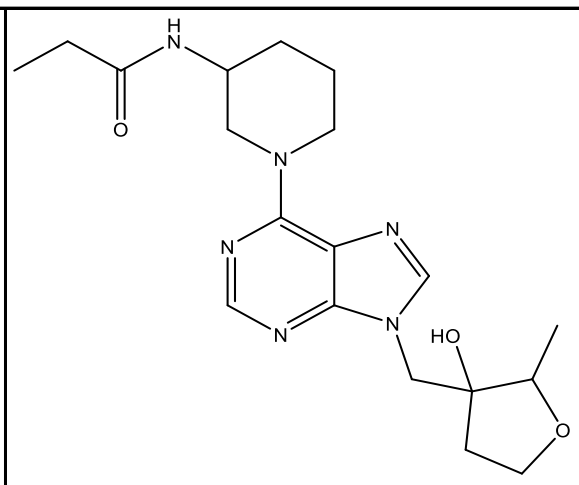
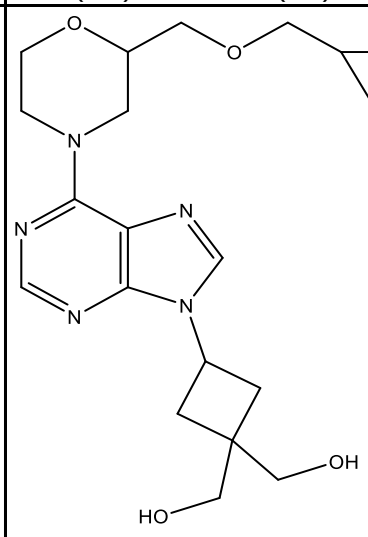
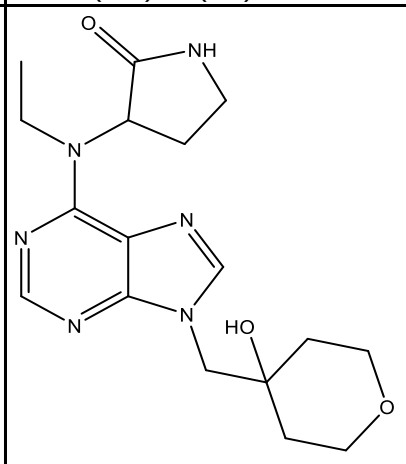
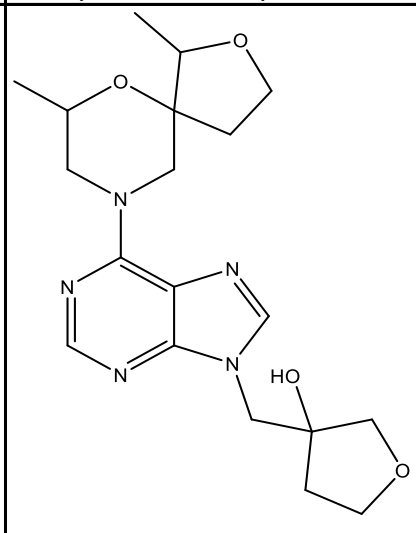
	
111	OCC(CN1C=NC=2C(=NC=NC12)N3C4CCC3C(CO)C4)C5CCOC5
	
112	CN(CCO)C1CCN(CC1)C=2N=CN=C3N(CC4(O)CCOC4)C=NC23
	
113	CC1OCCC1(O)CN2C=NC=3C(=NC=NC23)N4C[C@H](F)C[C@H]4C(=O)N
	
114	COCCN(CCC#N)C=1N=CN=C2N(CC3(O)CCOC3C)C=NC12
	
115	CC(C)N1C=C(CNC(=O)N2CCOC[C@H]2C)C(=O)NC1=O

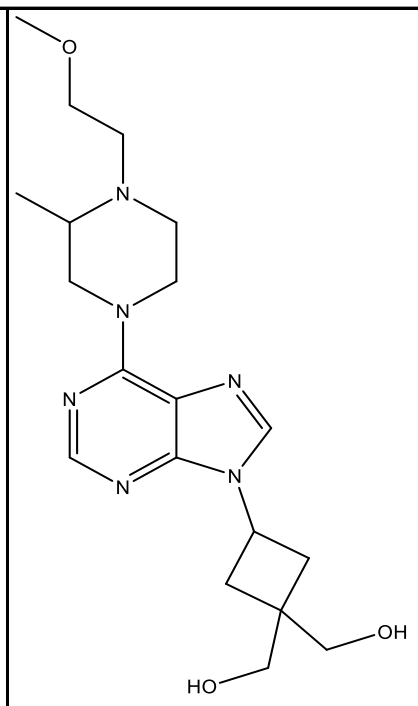
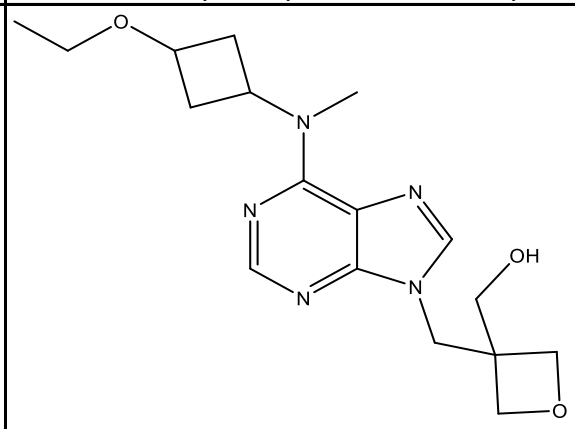
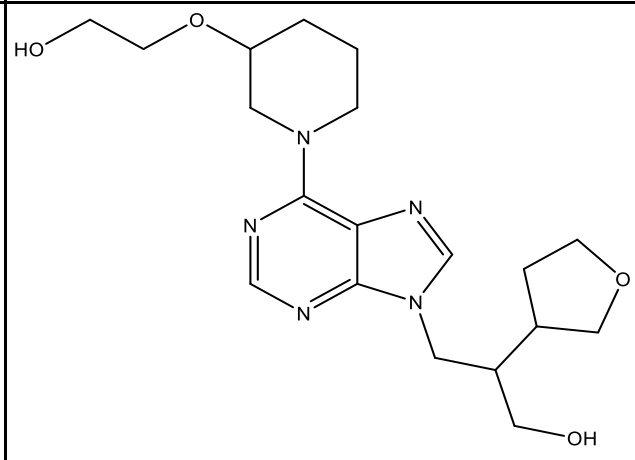
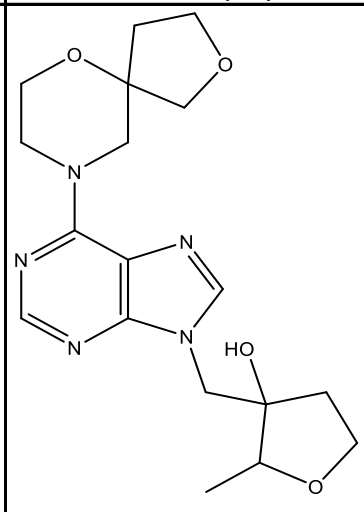
		
116	COCC1CN(CC(C)O1)C=2N=CN=C3N(CC4(CO)CCOCC4)C=NC23	
		
117	CCNC(=O)CN(CC)C=1N=CN=C2N(CC3(O)CCOCC3)C=NC12	
		
118	OC1(CN2C=NC=3C(=NC=NC23)N4CCN(CC4)C(=O)CC#N)CCOC1	
		
119	OCC1(CN2C=NC=3C(=NC=NC23)N4CCCC4C5COCCC5O)CCOCC1	
		
120	CCOCCO[C@H]1CCN(C1)C=2N=CN=C3N(CC(O)C4CCCO4)C=NC23	

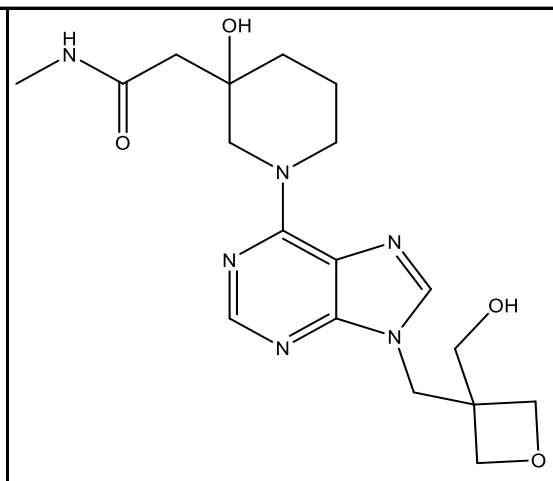
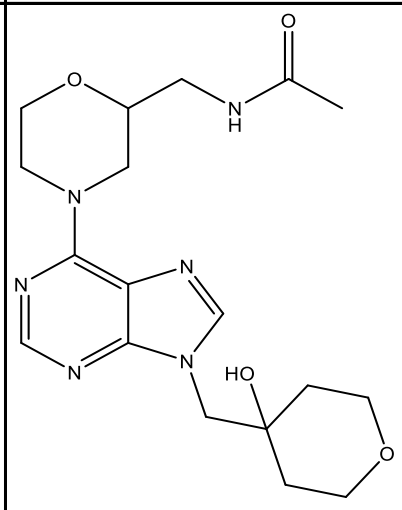
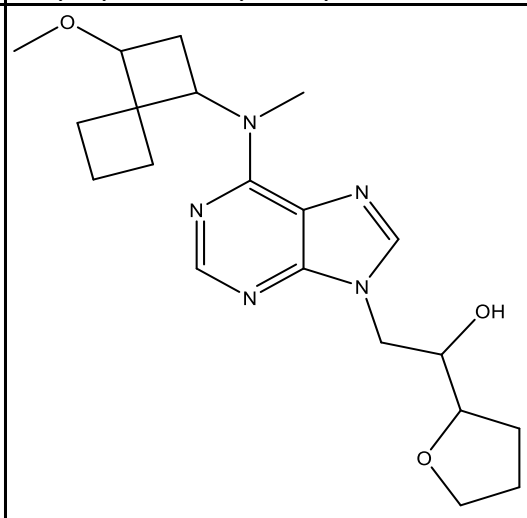
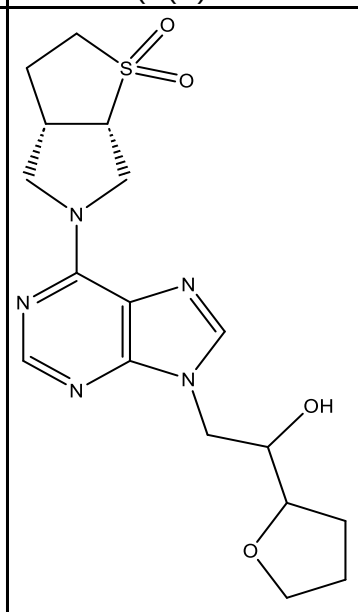
		121 CCC(CC)CN(CCC#N)C=1N=CN=C2N(CC(O)C3CCCO3)C=NC12
		122 CC1CC1N2CCN(CC(C)C2)C=3N=CN=C4N(CC5(O)CCOCC5)C=NC34
		123 CCN(C(C)CS(=O)(=O)C)C=1N=CN=C2N(CC(CO)C3CCOC3)C=NC12
		124 CC1OCCC1(O)CN2C=NC=3C(=NC=NC23)N4C5CCC4C(CO)C5

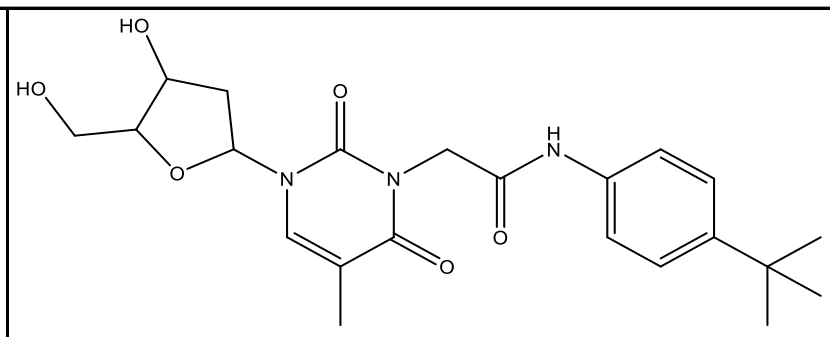
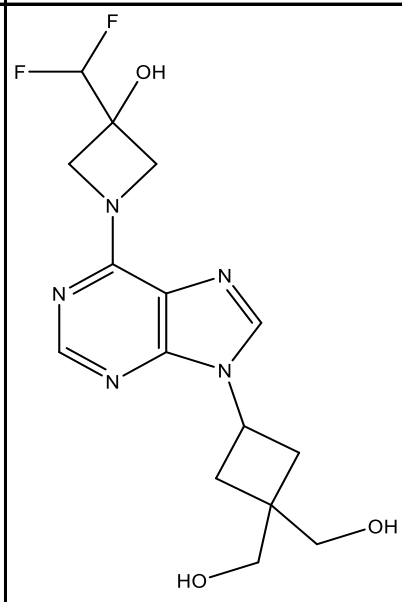
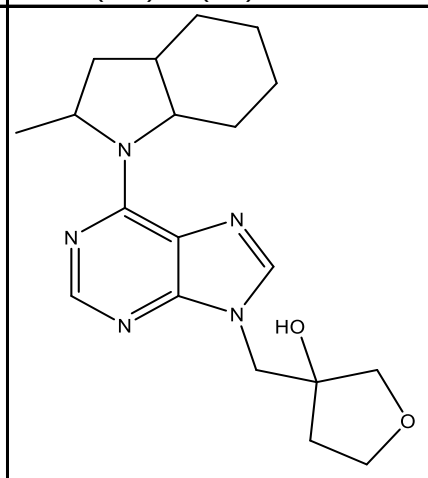
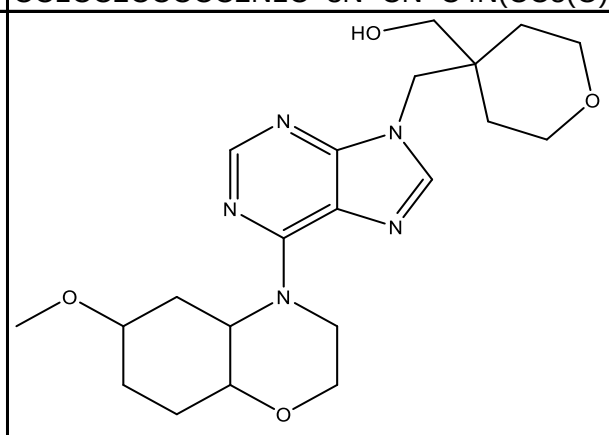
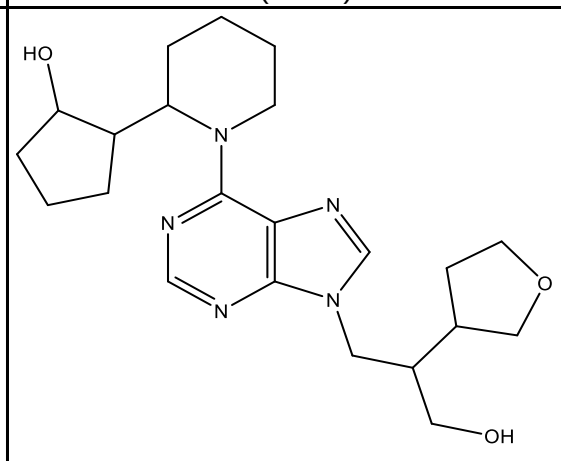
		
125	OCCOCCN(CCO)C=1N=CN=C2N(C=NC12)C3CC(CO)(CO)C3	
		
126	CN1CCC2C(CCCN2C=3N=CN=C4N(C=NC34)C5CC(CO)(CO)C5)C1	
		
127	CN(C)CCN1CCCN(CC1)C=2N=CN=C3N(CC(O)C4CCCO4)C=NC23	
		
128	FC1=CN(C2CCCO2)C(=O)N(CC(=O)C3=C(NC=4C=CC=CC34)C=5C=CC=CC5)C1=O	

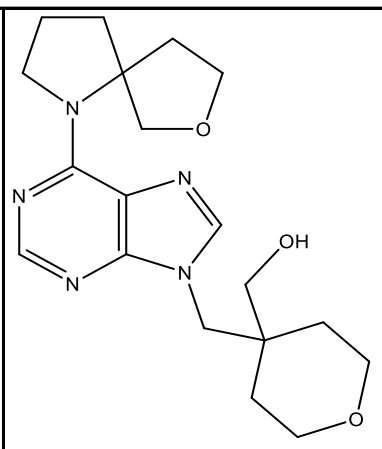
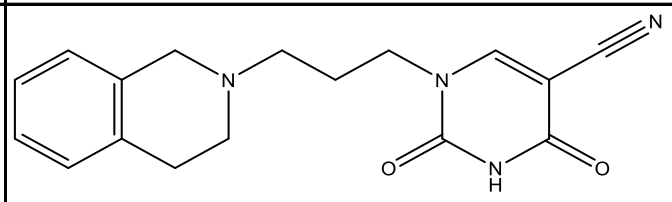
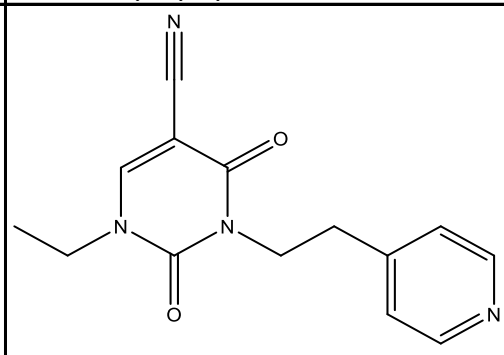
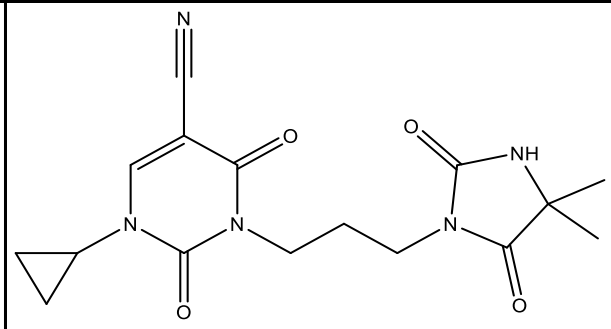
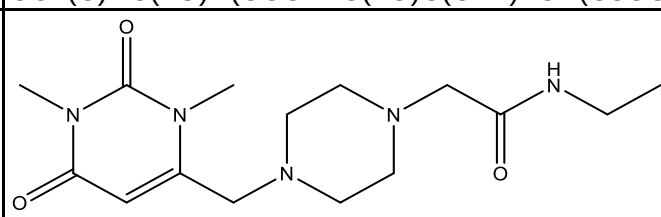
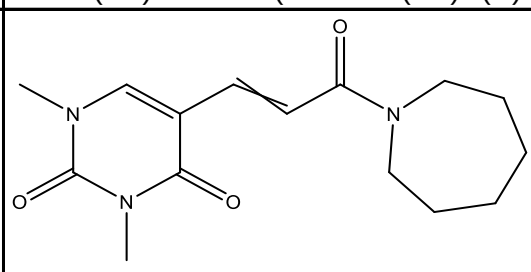
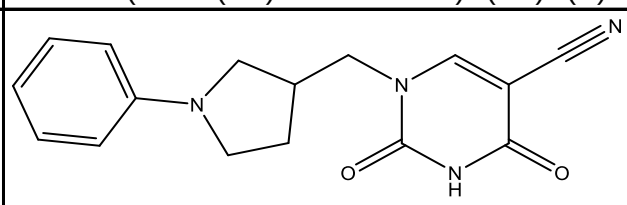
	
129	CC1(C)CN(CCN1CCO)C=2N=CN=C3N(CC4(CO)COC4)C=NC23
	
130	CNC(=O)C1(C)CCN(C1)C=2N=CN=C3N(CC(O)C4CCCO4)C=NC23
	
131	OC(CN1C=NC=2C(=NC=NC12)N3CCOCC3CC4CCC4)C5CCCO5
	
132	OC1(CN2C=NC=3C(=NC=NC23)N(CC4CCCO4)C5CCCC5)CCOCC1

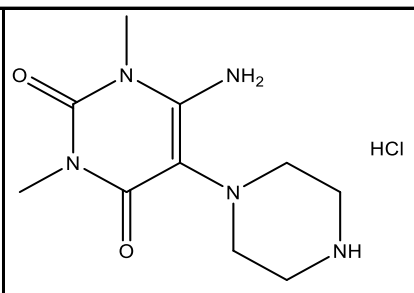
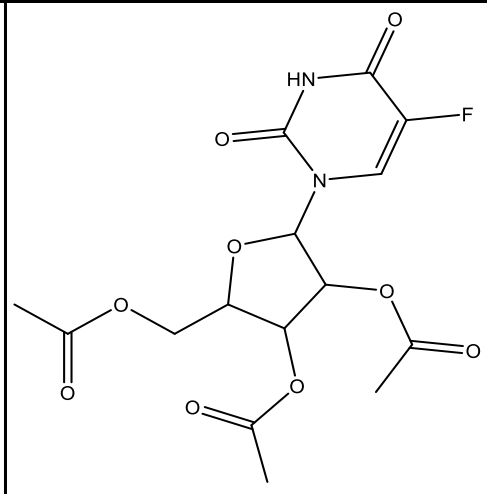
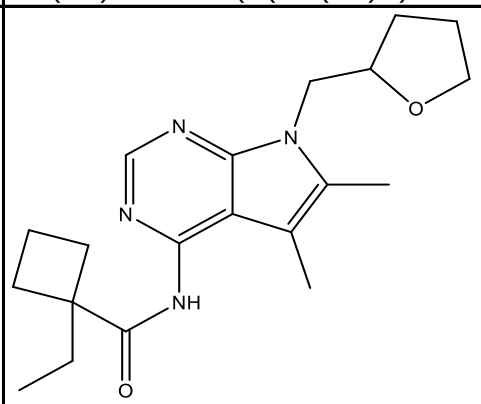
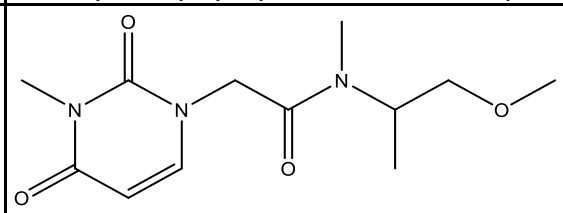
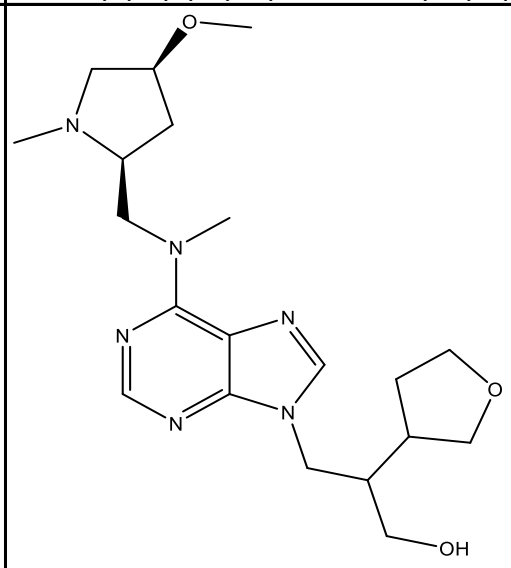
	
133	CCC(=O)NC1CCCN(C1)C=2N=CN=C3N(CC4(O)CCOC4C)C=NC23
	
134	OCC1(CO)CC(C1)N2C=NC=3C(=NC=NC23)N4CCOC(COCC5CC5)C4
	
135	CCN(C1CCNC1=O)C=2N=CN=C3N(CC4(O)CCOCC4)C=NC23
	
136	CC1OCCC21CN(CC(C)O2)C=3N=CN=C4N(CC5(O)CCOC5)C=NC34

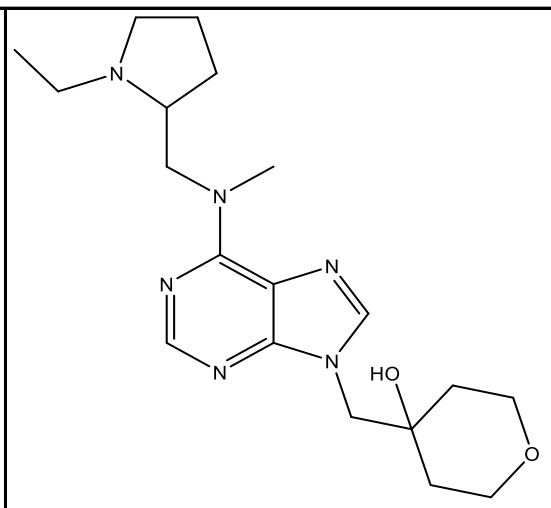
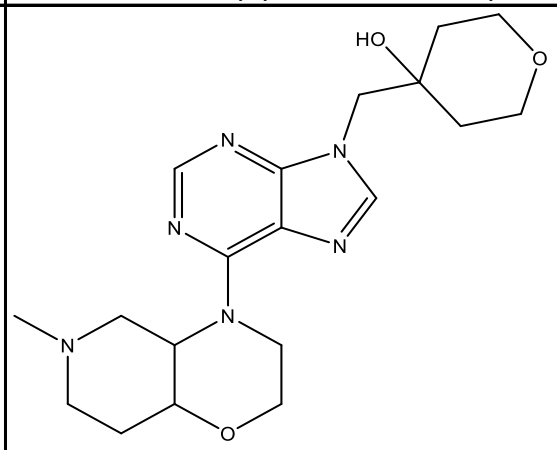
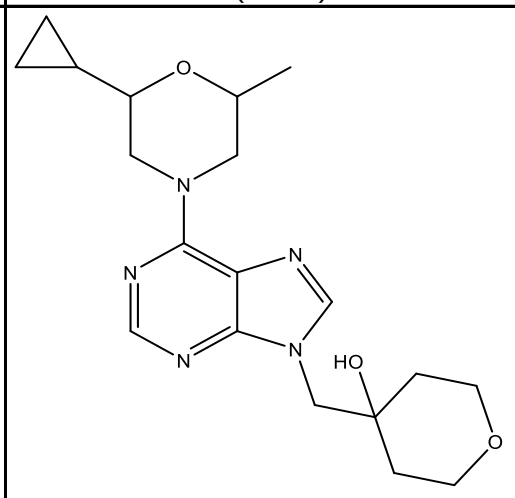
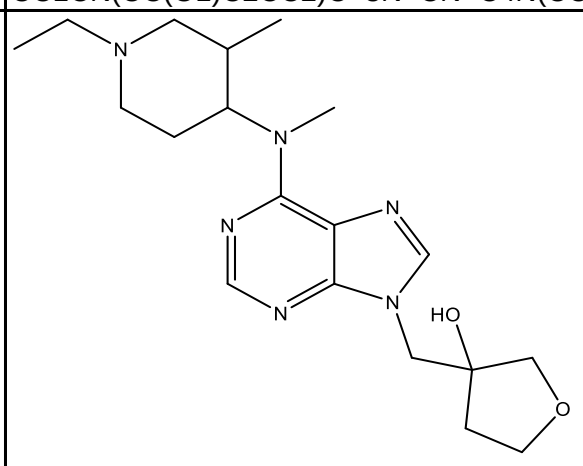
		137 COCCN1CCN(CC1C)C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4
		138 CCOC1CC(C1)N(C)C=2N=CN=C3N(CC4(CO)COC4)C=NC23
		139 OCCOC1CCCN(C1)C=2N=CN=C3N(CC(CO)C4CCOC4)C=NC23
		140 CC1OCCC1(O)CN2C=NC=3C(=NC=NC23)N4CCOC5(CCOC5)C4

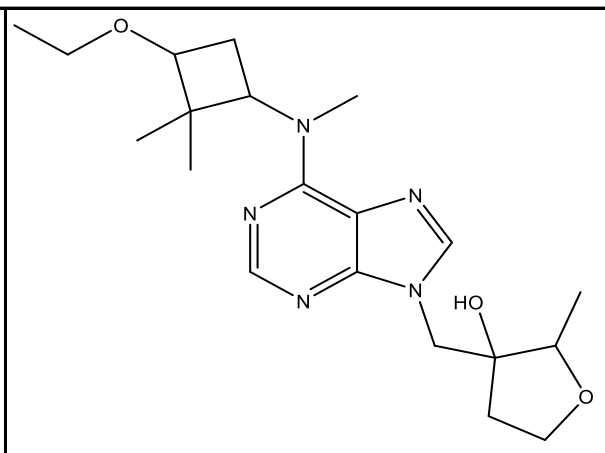
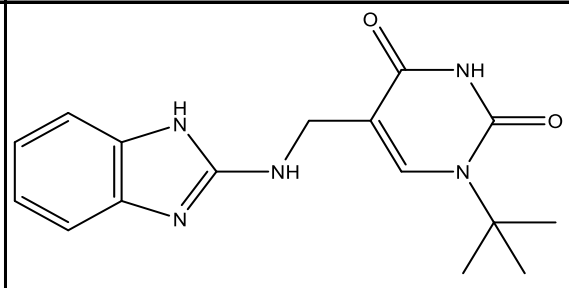
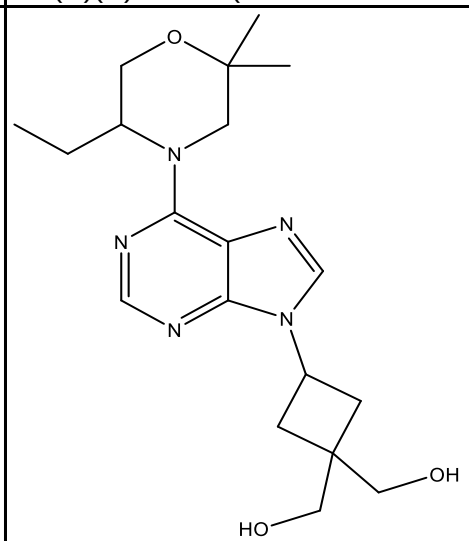
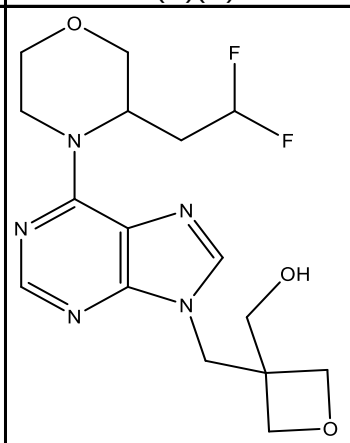
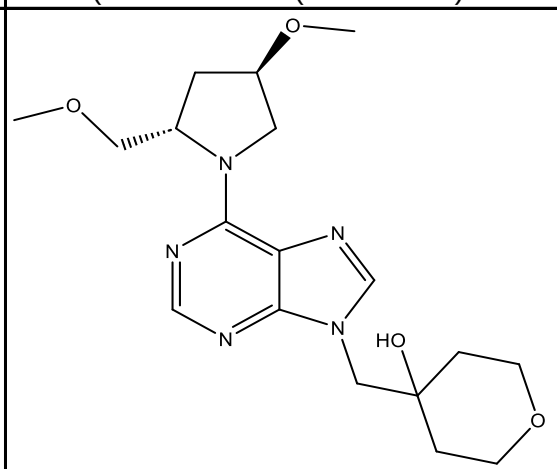
		141 CNC(=O)CC1(O)CCCN(C1)C=2N=CN=C3N(CC4(CO)COC4)C=NC23
		142 CC(=O)NCC1CN(CCO1)C=2N=CN=C3N(CC4(O)CCOCC4)C=NC23
		143 COC1CC(N(C)C=2N=CN=C3N(CC(O)C4CCCO4)C=NC23)C51CCC5
		144 OC(CN1C=NC=2C(=NC=NC12)N3C[C@@H]4CCS(=O)(=O)[C@@H]4C3)C5CCCO5

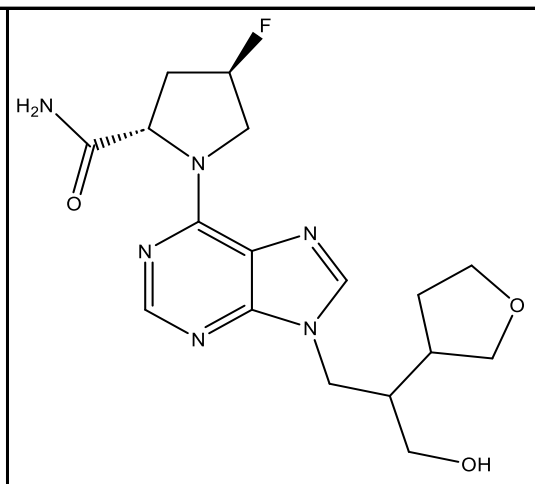
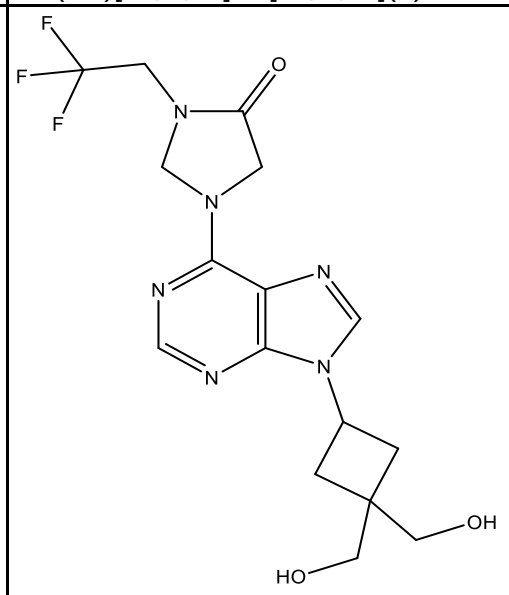
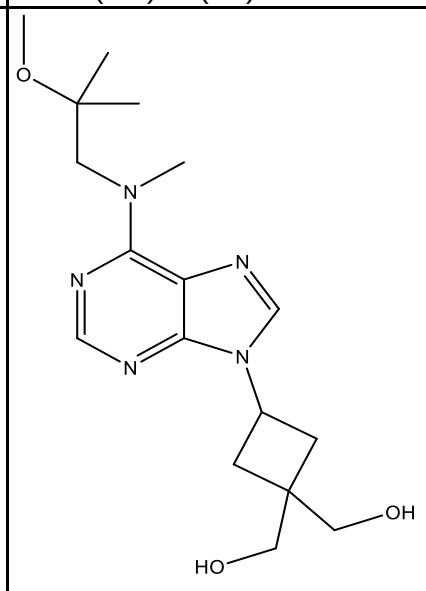
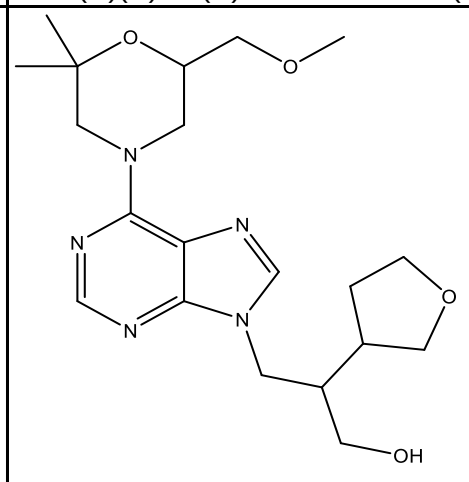
	145 CC1=CN(C2CC(O)C(CO)O2)C(=O)N(CC(=O)NC=3C=CC(=CC3)C(C)(C)C)C1=O
	146 OCC1(CO)CC(C1)N2C=NC=3C(=NC=NC23)N4CC(O)(C4)C(F)F
	147 CC1CC2CCCCC2N1C=3N=CN=C4N(CC5(O)CCOC5)C=NC34
	148 COC1CCC2OCCN(C2C1)C=3N=CN=C4N(CC5(CO)CCOCC5)C=NC34
	149 OCC(CN1C=NC=2C(=NC=NC12)N3CCCCC3C4CCCC4O)C5CCOC5

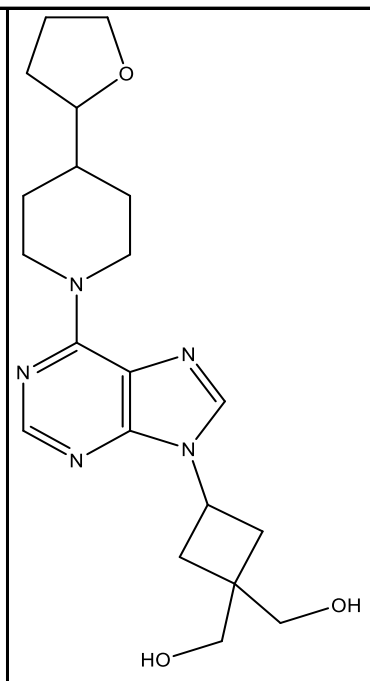
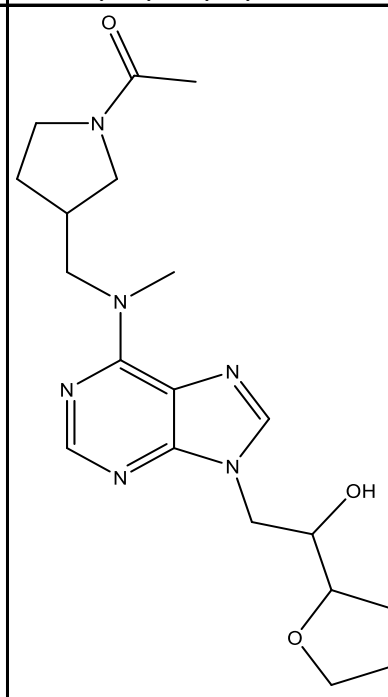
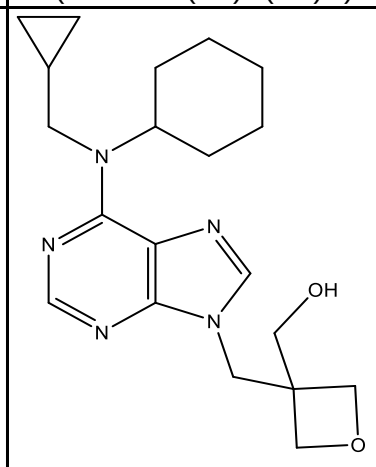
	
150	OCC1(CN2C=NC=3C(=NC=NC23)N4CCCC54CCOC5)CCOCC1
	
151	O=C1NC(=O)N(CCCN2CCC=3C=CC=CC3C2)C=C1C#N
	
152	CCN1C=C(C#N)C(=O)N(CCC=2C=CN=CC2)C1=O
	
153	CC1(C)NC(=O)N(CCCN2C(=O)C(C#N)=CN(C3CC3)C2=O)C1=O
	
154	CCNC(=O)CN1CCN(CC2=CC(=O)N(C)C(=O)N2C)CC1
	
155	CN1C=C(C=CC(=O)N2CCCCCC2)C(=O)N(C)C1=O
	
156	O=C1NC(=O)N(CC2CCN(C2)C=3C=CC=CC3)C=C1C#N

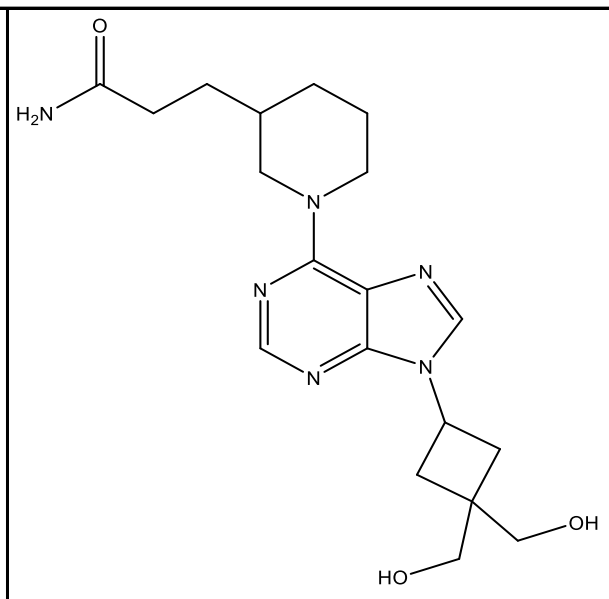
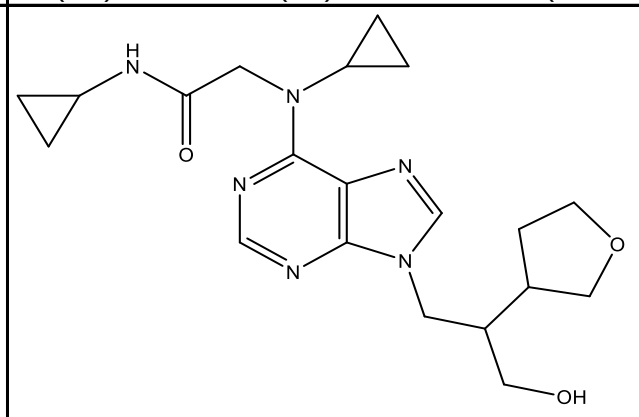
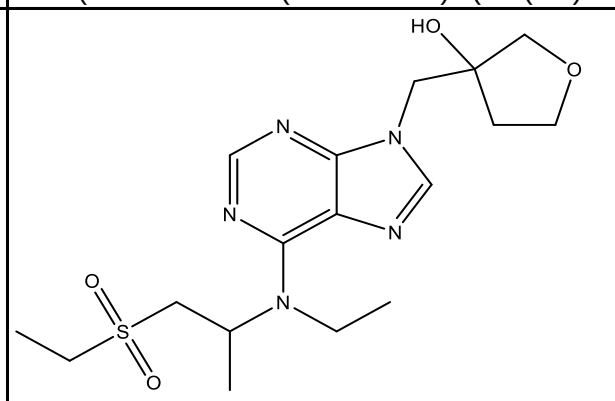
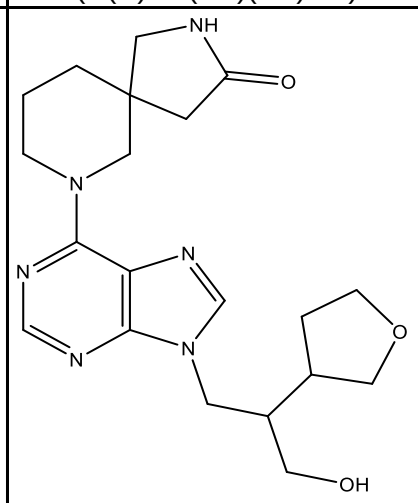
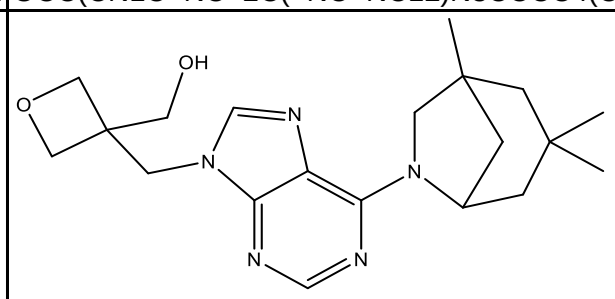
157		Cl.CN1C(N)=C(N2CCNCC2)C(=O)N(C)C1=O
158		CC(=O)OCC1OC(C(OC(=O)C)C1OC(=O)C)N2C=C(F)C(=O)NC2=O
159		CCC1(CCC1)C(=O)NC=2N=CN=C3N(CC4CCCO4)C(C)=C(C)C23
160		COCC(C)N(C)C(=O)CN1C=CC(=O)N(C)C1=O
161		CO[C@H]1C[C@@H](CN(C)C=2N=CN=C3N(CC(CO)C4CCOC4)C=NC23)N(C)C1

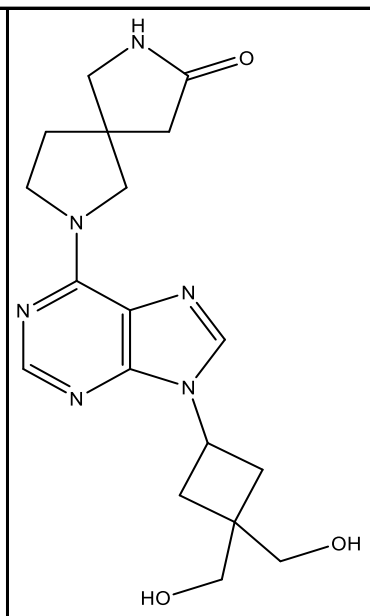
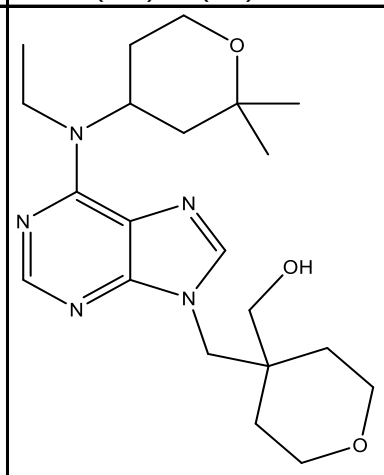
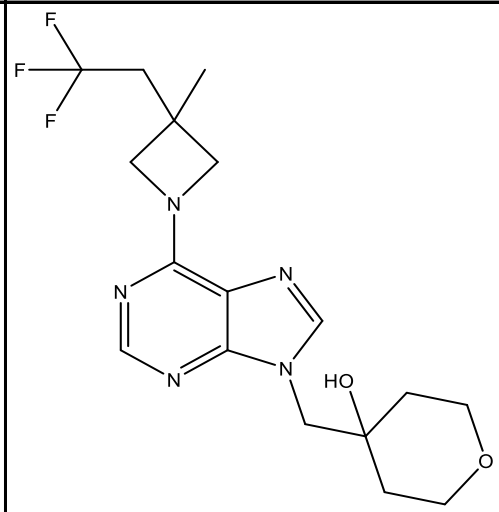
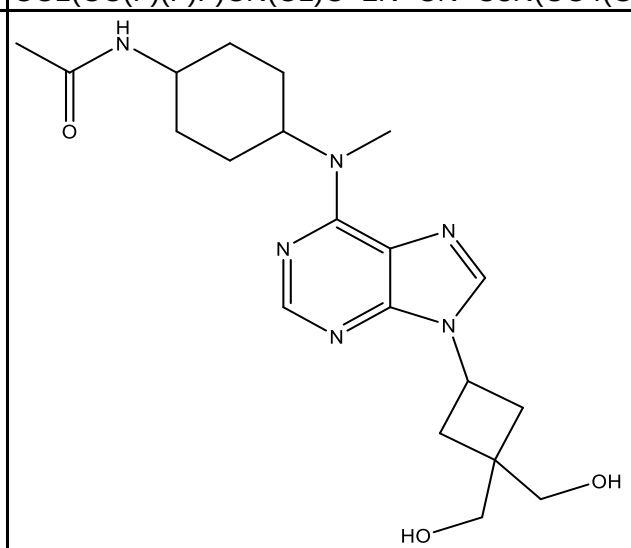
	
162	CCN1CCCC1CN(C)C=2N=CN=C3N(CC4(O)CCOCC4)C=NC23
	
163	CN1CCC2OCCN(C2C1)C=3N=CN=C4N(CC5(O)CCOCC5)C=NC34
	
164	CC1CN(CC(O1)C2CC2)C=3N=CN=C4N(CC5(O)CCOCC5)C=NC34
	
165	CCN1CCC(C(C)C1)N(C)C=2N=CN=C3N(CC4(O)CCOC4)C=NC23

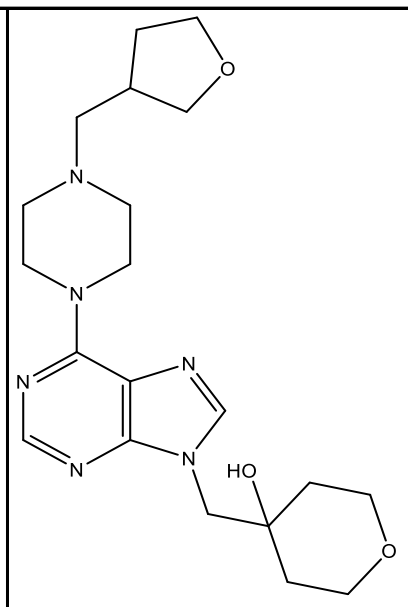
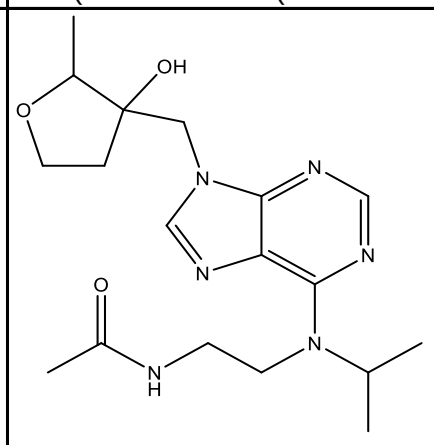
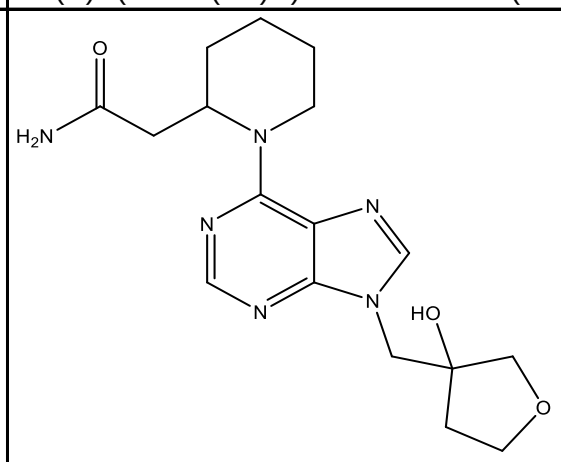
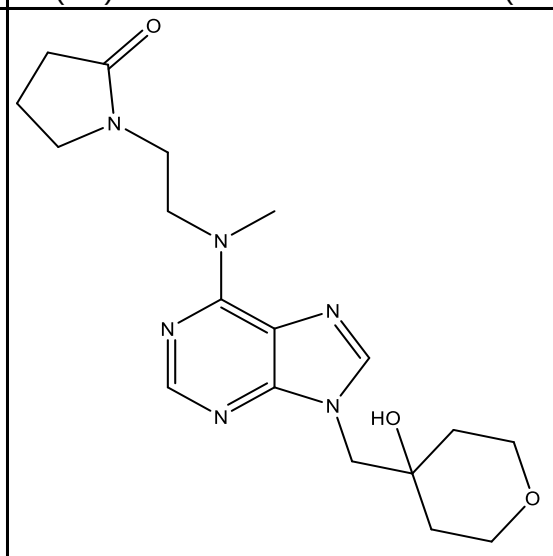
	
166	CCOC1CC(N(C)C=2N=CN=C3N(CC4(O)CCOC4C)C=NC23)C1(C)C
	
167	CC(C)(C)N1C=C(CNC2=NC=3C=CC=CC3N2)C(=O)NC1=O
	
168	CCC1COC(C)(C)CN1C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4
	
169	OCC1(CN2C=NC=3C(=NC=NC23)N4CCOCC4CC(F)F)COC1
	
170	COC[C@@H]1C[C@H](CN1C=2N=CN=C3N(CC4(O)CCOCC4)C=NC23)OC

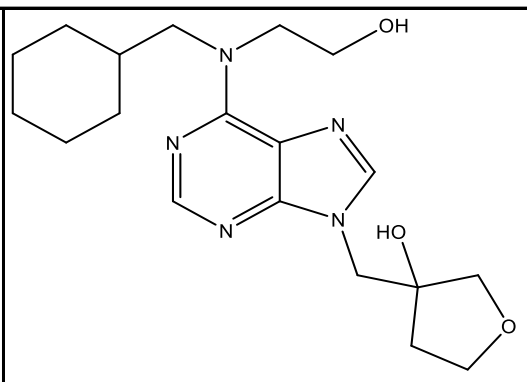
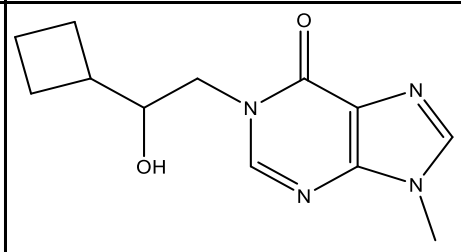
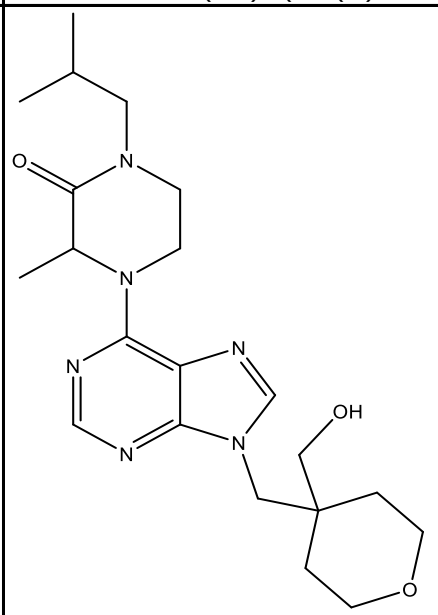
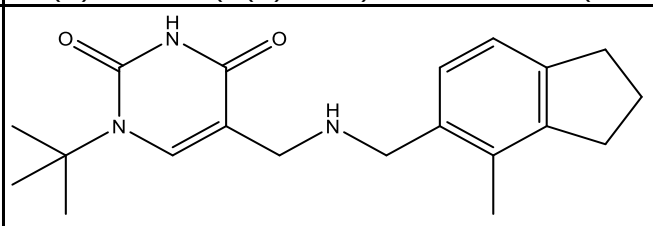
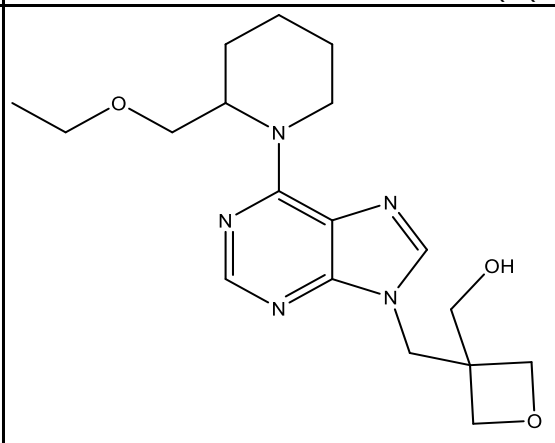
	
171	NC(=O)[C@@H]1C[C@@H](F)CN1C=2N=CN=C3N(CC(CO)C4CCOC4)C=NC23
	
172	OCC1(CO)CC(C1)N2C=NC=3C(=NC=NC23)N4CN(CC(F)(F)F)C(=O)C4
	
173	COC(C)(C)CN(C)C=1N=CN=C2N(C=NC12)C3CC(CO)(CO)C3
	
174	COCC1CN(CC(C)(C)O1)C=2N=CN=C3N(CC(CO)C4CCOC4)C=NC23

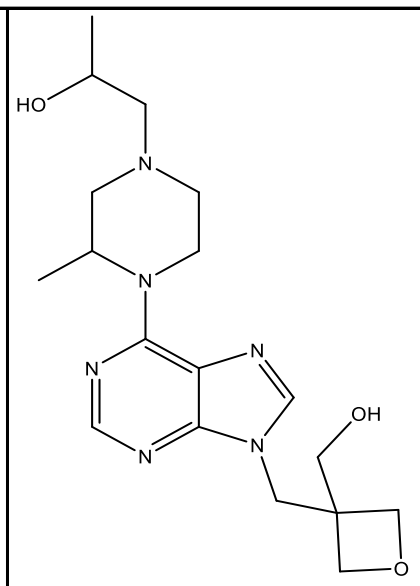
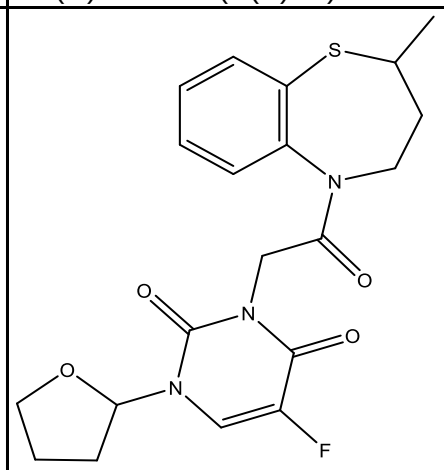
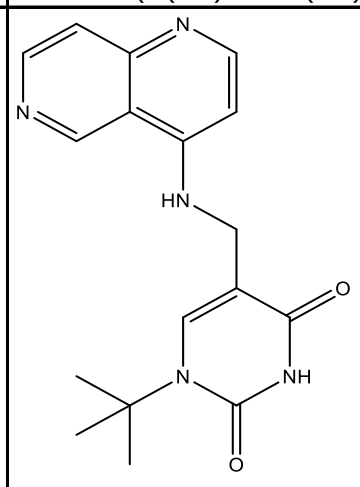
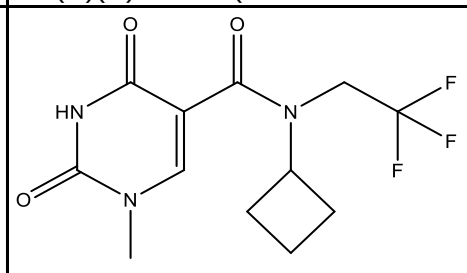
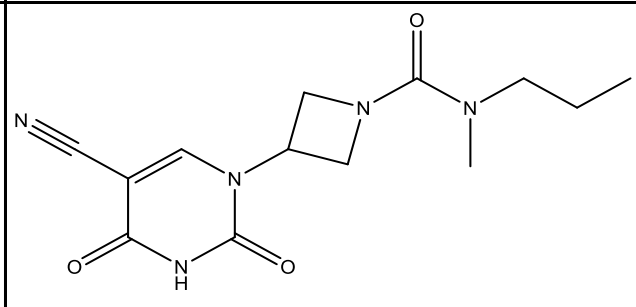
	
175	OCC1(CO)CC(C1)N2C=NC=3C(=NC=NC23)N4CCC(CC4)C5CCCO5
	
176	CN(CC1CCN(C1)C(=O)C)C=2N=CN=C3N(CC(O)C4CCCO4)C=NC23
	
177	OCC1(CN2C=NC=3C(=NC=NC23)N(CC4CC4)C5CCCCC5)COC1

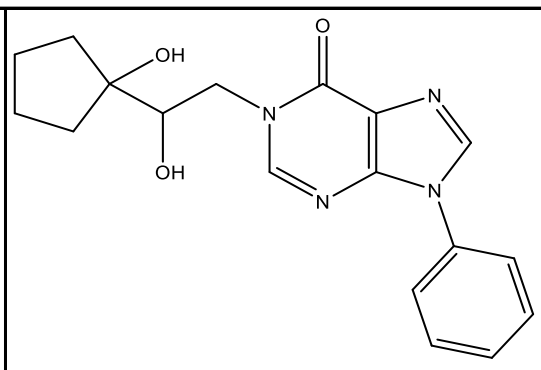
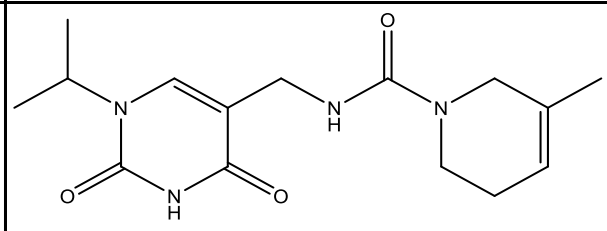
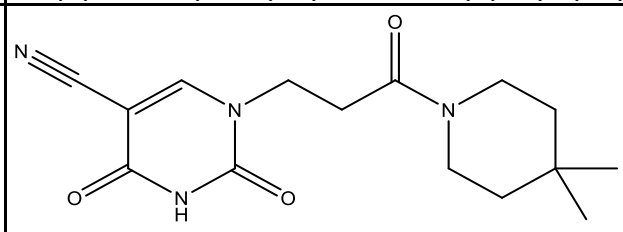
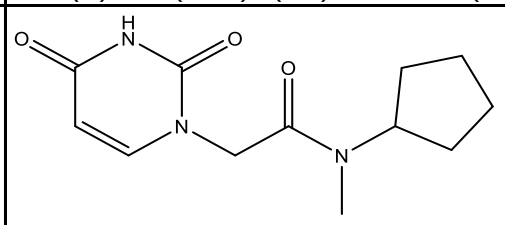
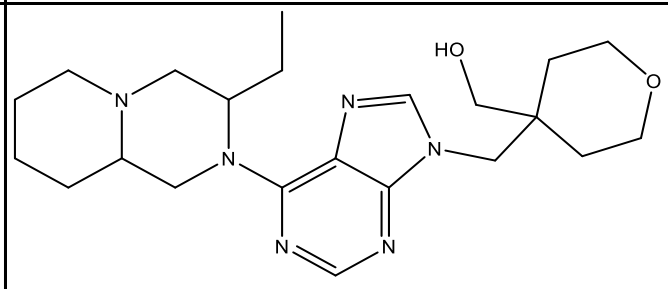
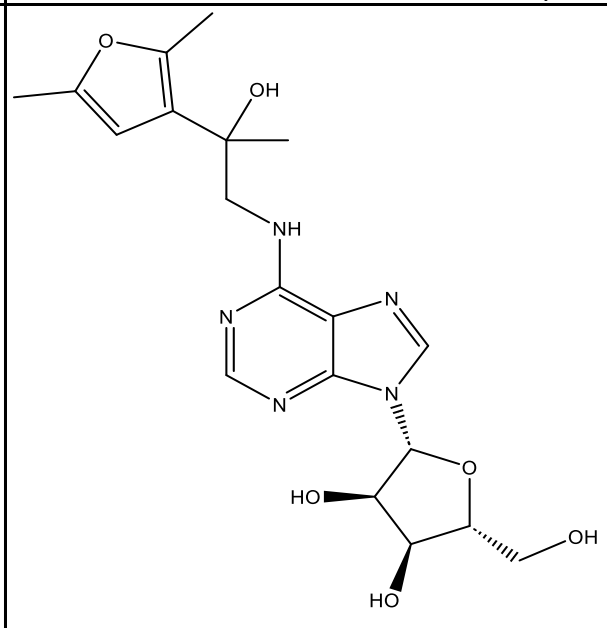
		
178	NC(=O)CCC1CCCN(C1)C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4	
		
179	OCC(CN1C=NC=2C(=NC=NC12)N(CC(=O)NC3CC3)C4CC4)C5CCOC5	
		
180	CCN(C(C)CS(=O)(=O)CC)C=1N=CN=C2N(CC3(O)CCOC3)C=NC12	
		
181	OCC(CN1C=NC=2C(=NC=NC12)N3CCCC4(CNC(=O)C4)C3)C5CCOC5	
		
182	CC1(CC2CC(C)(C)C1)CN2C=3N=CN=C4N(CC5(CO)COC5)C=NC34	

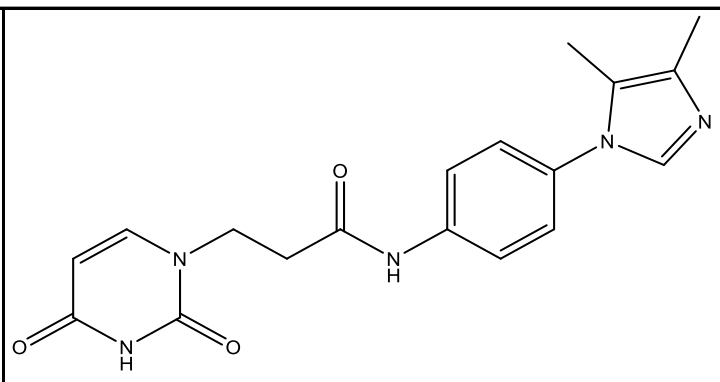
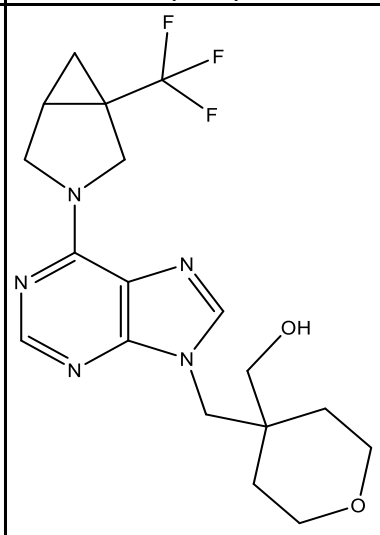
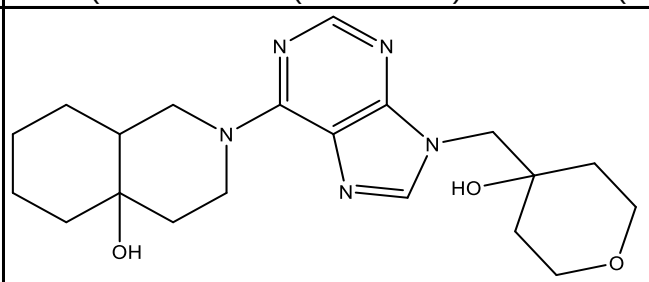
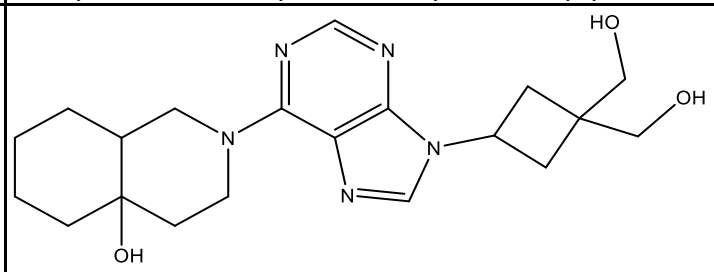
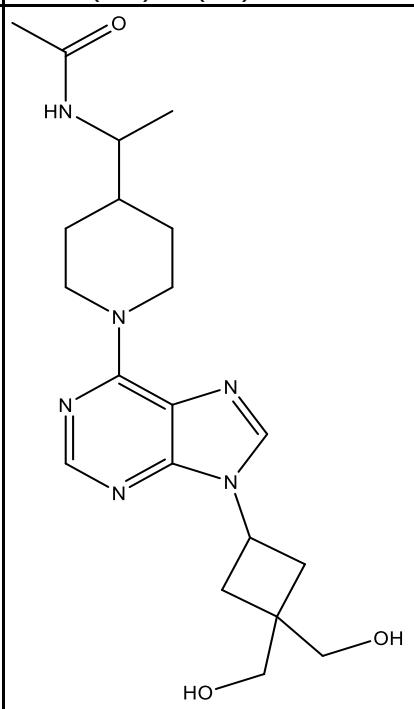
	183 OCC1(CO)CC(C1)N2C=NC=3C(=NC=NC23)N4CCC5(CNC(=O)C5)C4
	184 CCN(C1CCOC(C)(C)C1)C=2N=CN=C3N(CC4(CO)CCOCC4)C=NC23
	185 CC1(CC(F)(F)F)CN(C1)C=2N=CN=C3N(CC4(O)CCOCC4)C=NC23
	186 CN(C1CCC(CC1)NC(=O)C)C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4

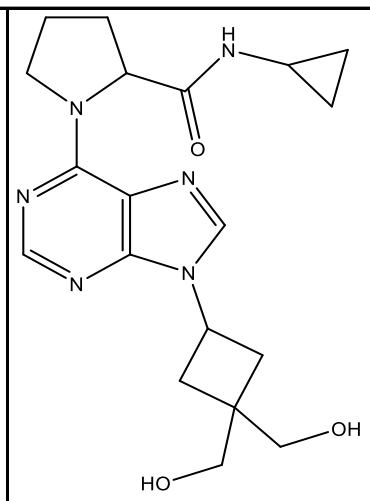
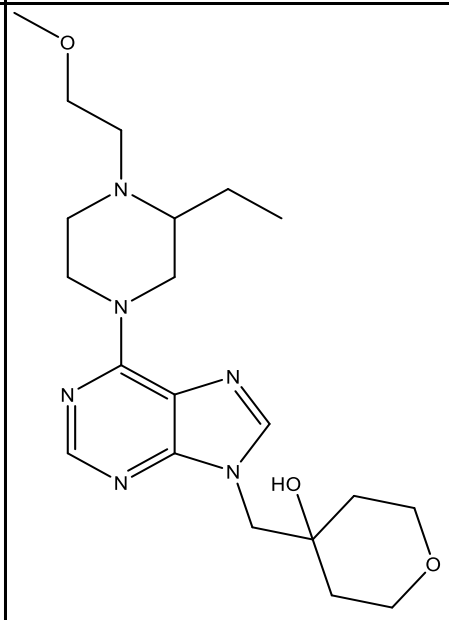
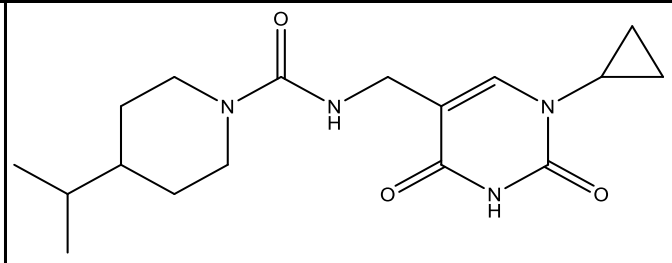
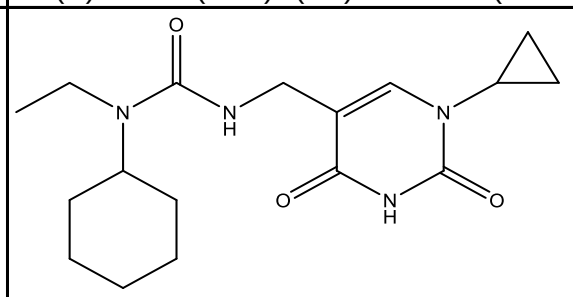
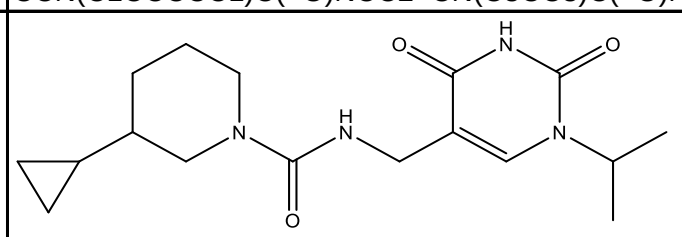
		187 OC1(CN2C=NC=3C(=NC=NC23)N4CCN(CC5CCOC5)CC4)CCOCC1
		188 CC(C)N(CCNC(=O)C)C=1N=CN=C2N(CC3(O)CCOC3C)C=NC12
		189 NC(=O)CC1CCCCN1C=2N=CN=C3N(CC4(O)CCOC4)C=NC23
		190 CN(CCN1CCCC1=O)C=2N=CN=C3N(CC4(O)CCOCC4)C=NC23

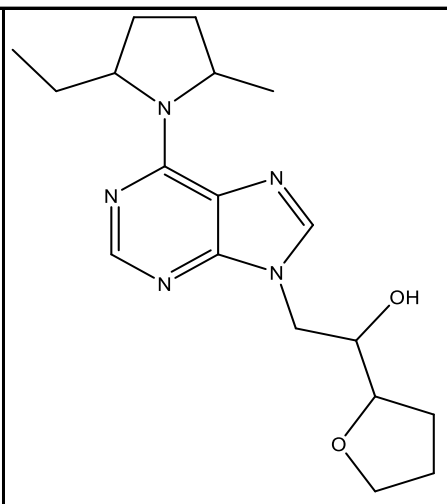
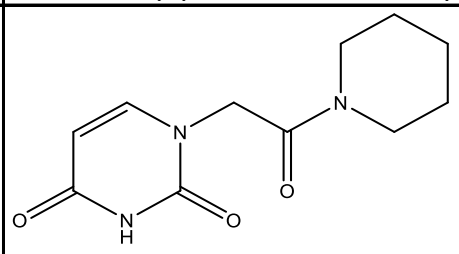
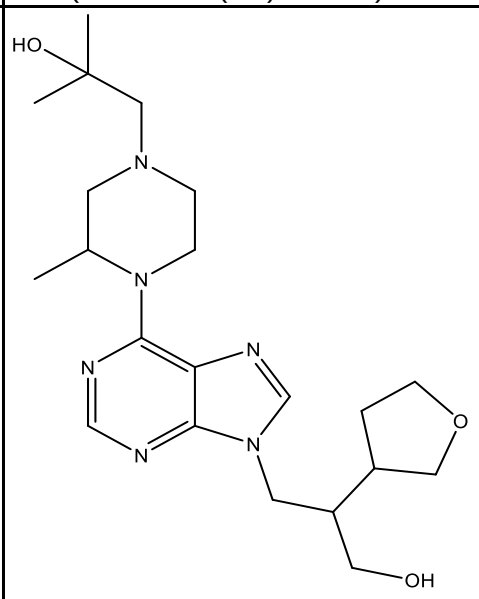
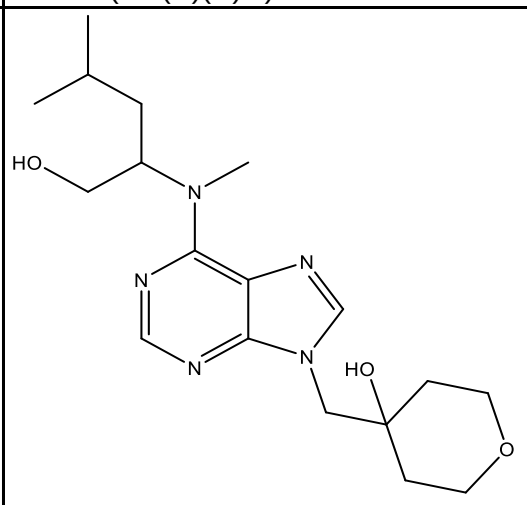
		
191	OCCN(CC1CCCCC1)C=2N=CN=C3N(CC4(O)CCOC4)C=NC23	
		
192	CN1C=NC=2C(=O)N(CC(O)C3CCC3)C=NC12	
		
193	CC(C)CN1CCN(C(C)C1=O)C=2N=CN=C3N(CC4(CO)CCOCC4)C=NC23	
		
194	CC=1C=2CCCC2C=CC1CNCC3=CN(C(=O)NC3=O)C(C)(C)C	
		
195	CCOCC1CCCCN1C=2N=CN=C3N(CC4(CO)COC4)C=NC23	

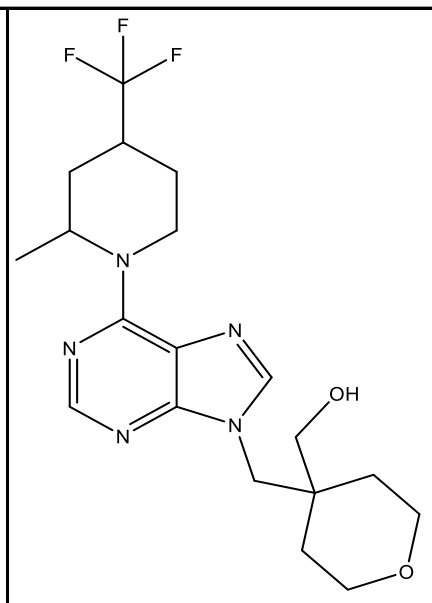
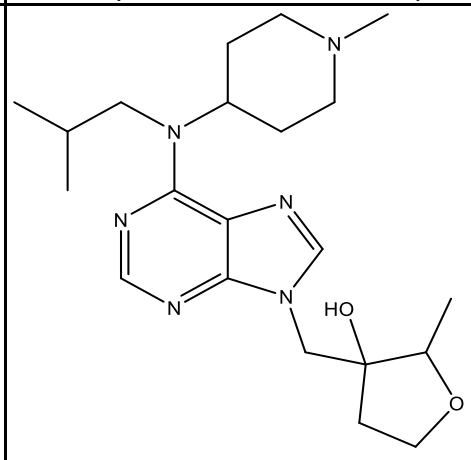
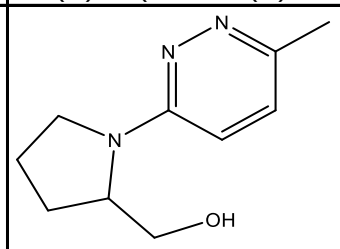
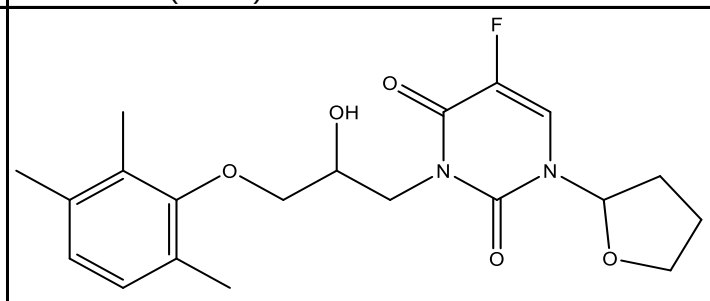
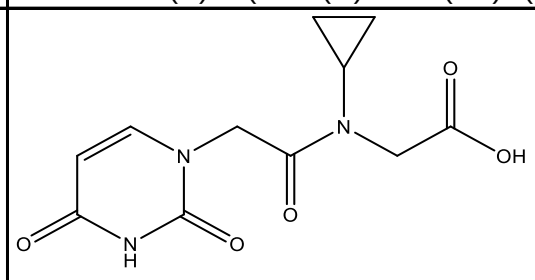
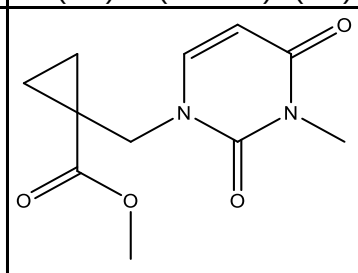
		
196	CC(O)CN1CCN(C(C)C1)C=2N=CN=C3N(CC4(CO)COC4)C=NC23	
		
197	CC1CCN(C(=O)CN2C(=O)C(F)=CN(C3CCCO3)C2=O)C=4C=CC=CC4S1	
		
198	CC(C)(C)N1C=C(CNC=2C=CN=C3C=CN=CC23)C(=O)NC1=O	
		
199	CN1C=C(C(=O)N(CC(F)(F)F)C2CCC2)C(=O)NC1=O	
		
200	CCCN(C)C(=O)N1CC(C1)N2C=C(C#N)C(=O)NC2=O	

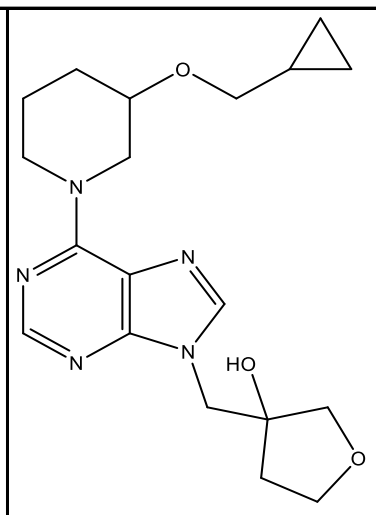
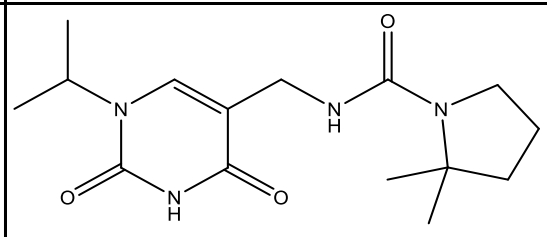
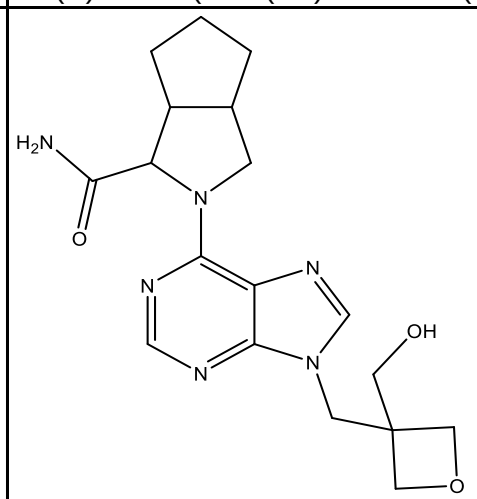
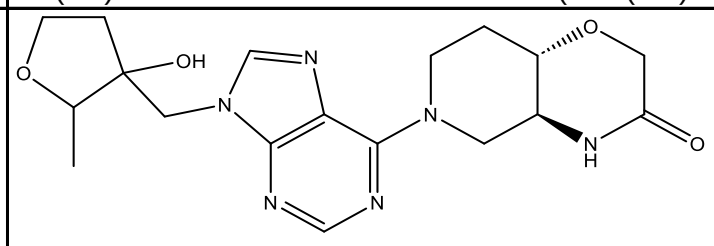
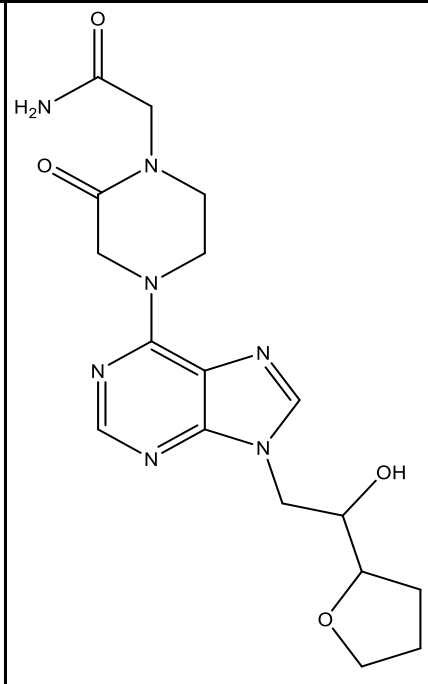
		
201	OC(CN1C=NC=2N(C=NC2C1=O)C=3C=CC=CC3)C4(O)CCCC4	
		
202	CC(C)N1C=C(CNC(=O)N2CCC=C(C)C2)C(=O)NC1=O	
		
203	CC1(C)CCN(CC1)C(=O)CCN2C=C(C#N)C(=O)NC2=O	
		
204	CN(C1CCCC1)C(=O)CN2C=CC(=O)NC2=O	
		
205	CCC1CN2CCCCC2CN1C=3N=CN=C4N(CC5(CO)CCOCC5)C=NC34	
		
206	CC1=CC(=C(C)O1)C(C)(O)CNC=2N=CN=C3N(C=NC23)[C@@H]4O[C@H](CO)[C@@H](O)[C@H]4O	

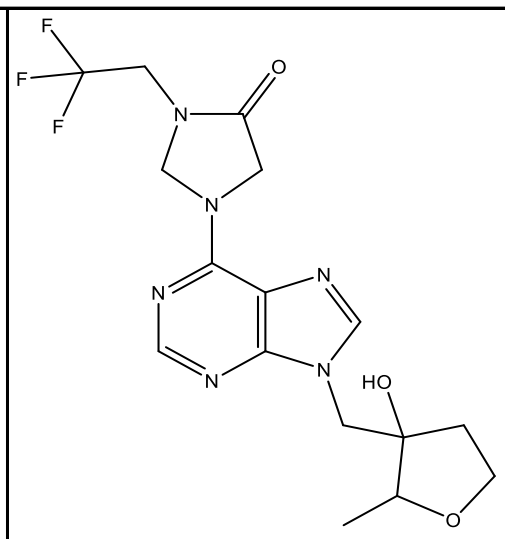
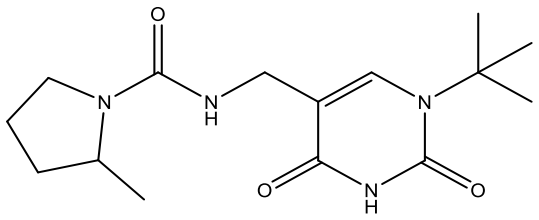
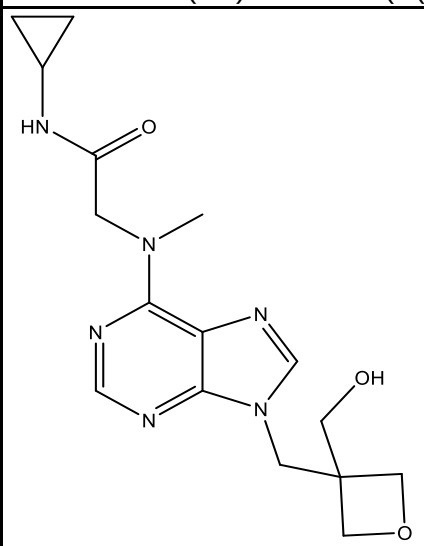
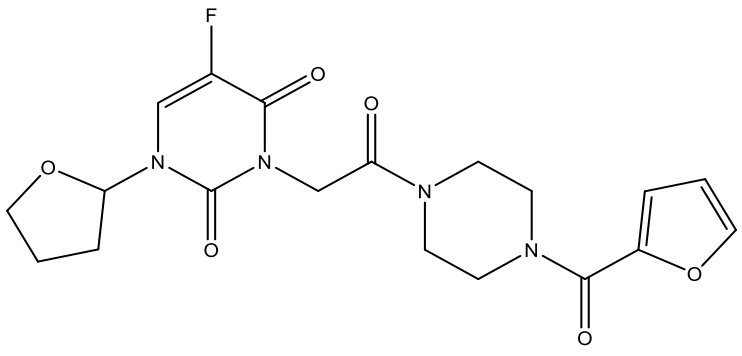
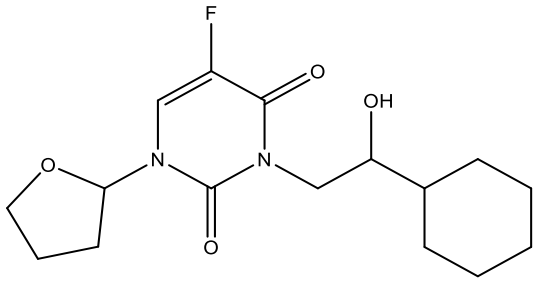
		
207	CC=1N=CN(C1C)C=2C=CC(NC(=O)CCN3C=CC(=O)NC3=O)=CC2	
		
208	OCC1(CN2C=NC=3C(=NC=NC23)N4CC5CC5(C4)C(F)(F)F)CCOCC1	
		
209	OC1(CN2C=NC=3C(=NC=NC23)N4CCC5(O)CCCCC5C4)CCOCC1	
		
210	OCC1(CO)CC(C1)N2C=NC=3C(=NC=NC23)N4CCC5(O)CCCCC5C4	
		
211	CC(NC(=O)C)C1CCN(CC1)C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4	

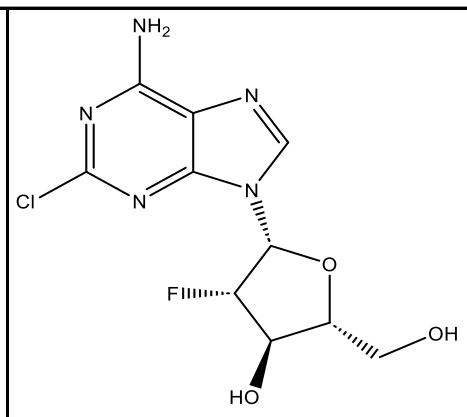
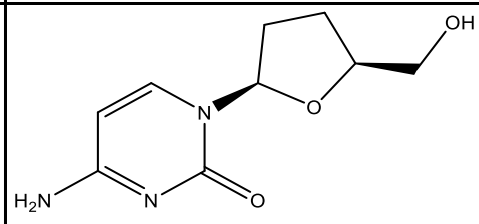
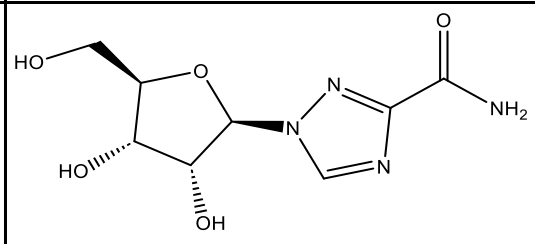
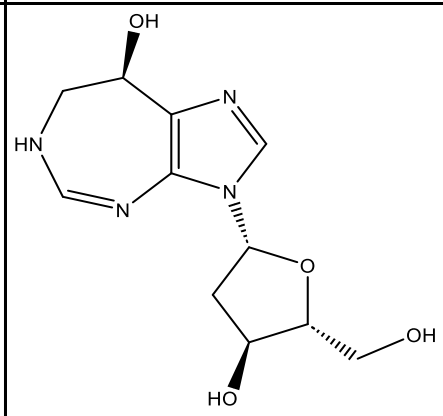
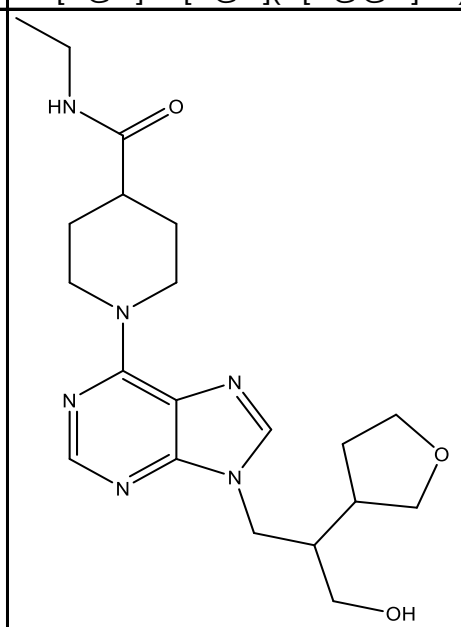
		212 OCC1(CO)CC(C1)N2C=NC=3C(=NC=NC23)N4CCCC4C(=O)NC5CC5
		213 CCC1CN(CCN1CCOC)C=2N=CN=C3N(CC4(O)CCOCC4)C=NC23
		214 CC(C)C1CCN(CC1)C(=O)NCC2=CN(C3CC3)C(=O)NC2=O
		215 CCN(C1CCCCC1)C(=O)NCC2=CN(C3CC3)C(=O)NC2=O
		216 CC(C)N1C=C(CNC(=O)N2CCCC(C2)C3CC3)C(=O)NC1=O

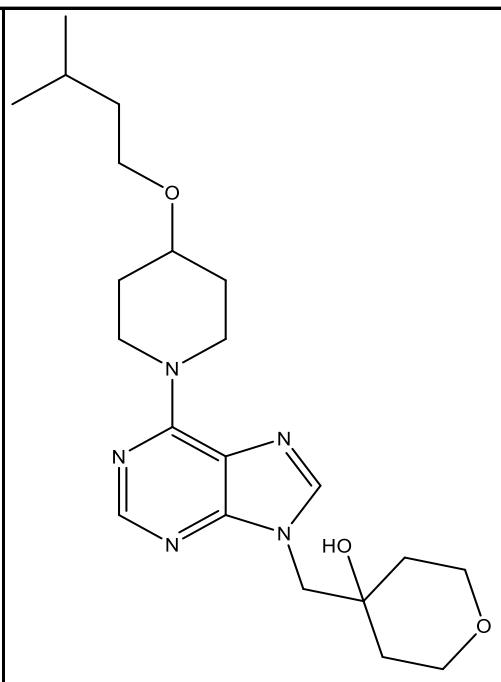
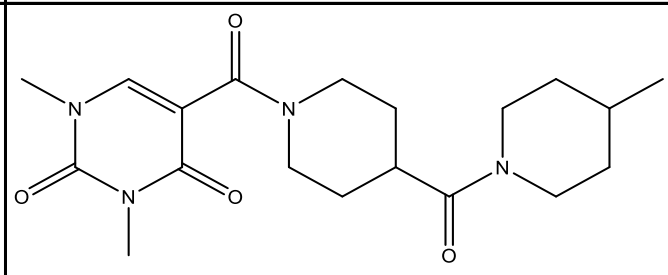
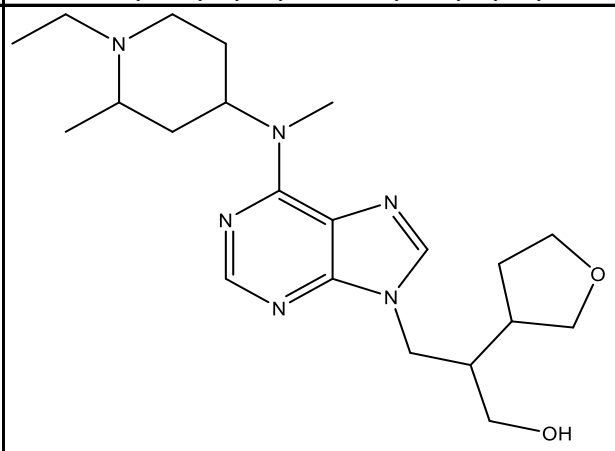
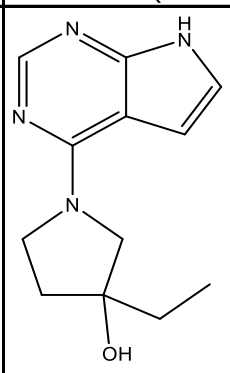
		
217	CCC1CCC(C)N1C=2N=CN=C3N(CC(O)C4CCCO4)C=NC23	
		
218	O=C(CN1C=CC(=O)NC1=O)N2CCCCC2	
		
219	CC1CN(CC(C)(C)O)CCN1C=2N=CN=C3N(CC(CO)C4CCOC4)C=NC23	
		
220	CC(C)CC(CO)N(C)C=1N=CN=C2N(CC3(O)CCOCC3)C=NC12	

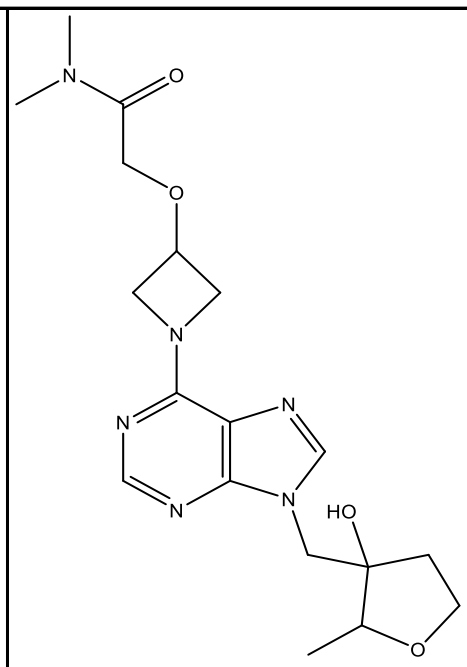
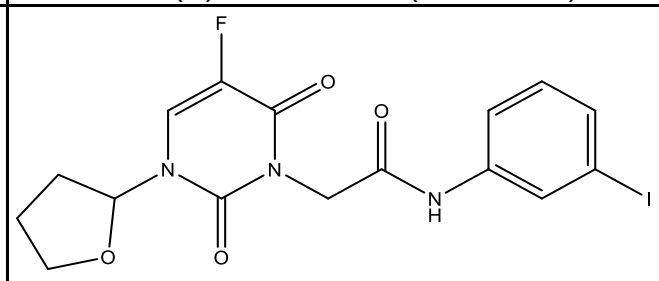
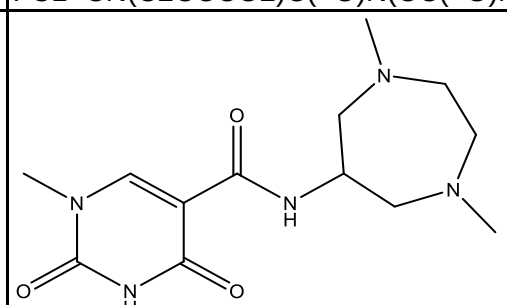
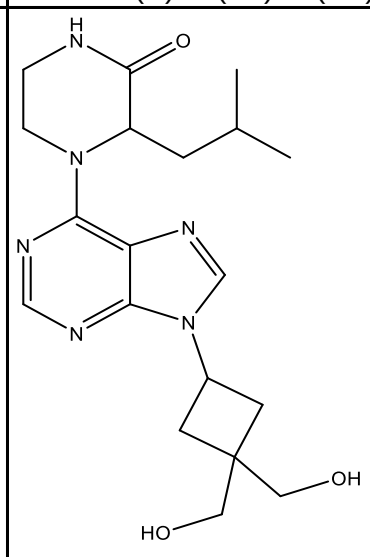
		221 CC1CC(CCN1C=2N=CN=C3N(CC4(CO)CCOCC4)C=NC23)C(F)(F)F
		222 CC(C)CN(C1CCN(C)CC1)C=2N=CN=C3N(CC4(O)CCOC4C)C=NC23
		223 CC=1C=CC(=NN1)N2CCCC2CO
		224 CC=1C=CC(C)=C(OCC(O)CN2C(=O)C(F)=CN(C3CCCO3)C2=O)C1C
		225 OC(=O)CN(C1CC1)C(=O)CN2C=CC(=O)NC2=O
		226 COC(=O)C1(CN2C=CC(=O)N(C)C2=O)CC1

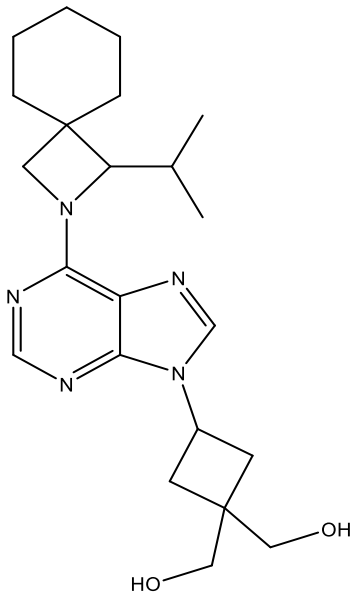
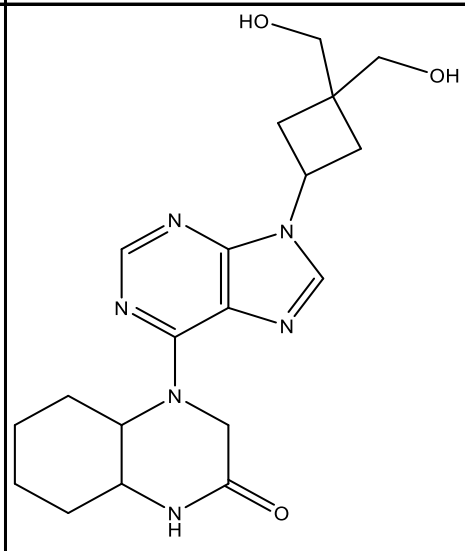
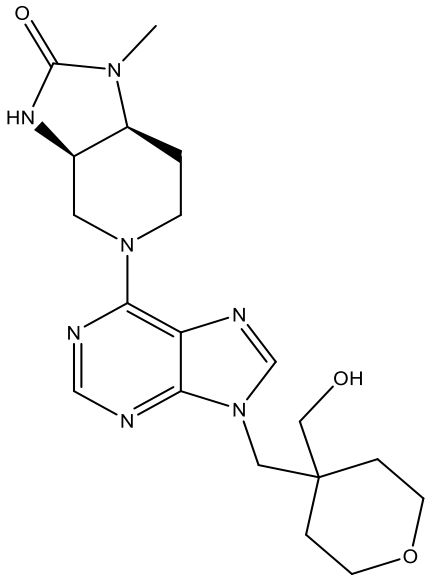
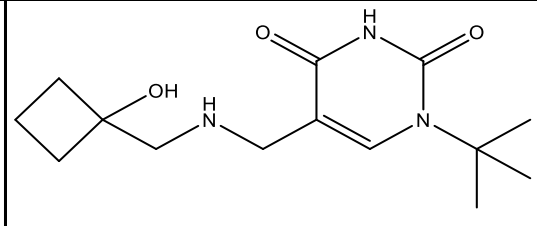
227		OC1(CN2C=NC=3C(=NC=NC23)N4CCCC(C4)OCC5CC5)CCOC1
228		CC(C)N1C=C(CNC(=O)N2CCCC2(C)C)C(=O)NC1=O
229		NC(=O)C1C2CCCC2CN1C=3N=CN=C4N(CC5(CO)COC5)C=NC34
230		CC1OCCC1(O)CN2C=NC=3C(=NC=NC23)N4CC[C@@H]5OCC(=O)N[C@H]5C4
231		NC(=O)CN1CCN(CC1=O)C=2N=CN=C3N(CC(O)C4CCCO4)C=NC23

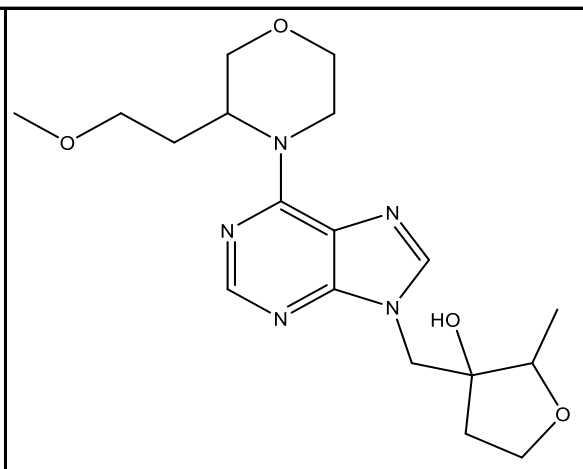
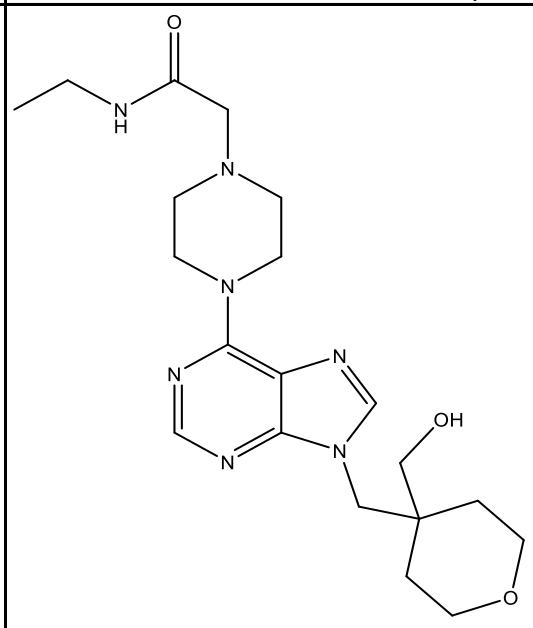
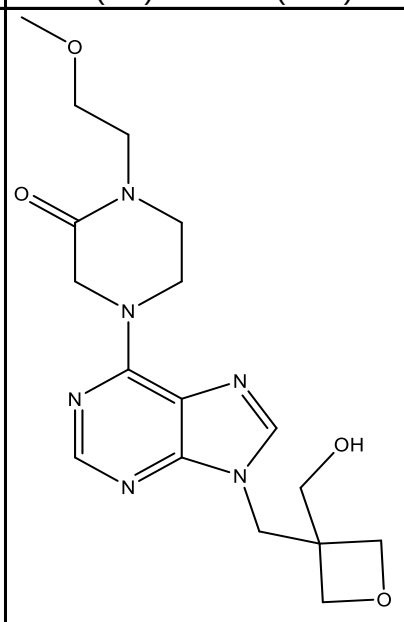
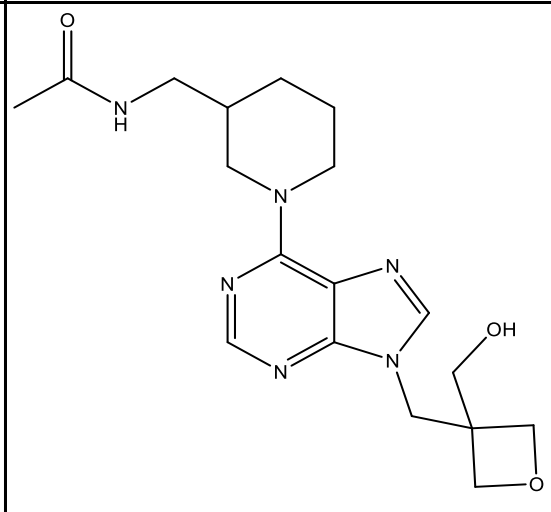
	
232	CC1OCCC1(O)CN2C=NC=3C(=NC=NC23)N4CN(CC(F)(F)F)C(=O)C4
	
233	CC1CCCN1C(=O)NCC2=CN(C(=O)NC2=O)C(C)(C)C
	
234	CN(CC(=O)NC1CC1)C=2N=CN=C3N(CC4(CO)COC4)C=NC23
	
235	FC1=CN(C2CCCO2)C(=O)N(CC(=O)N3CCN(CC3)C(=O)C4=CC=CO4)C1=O
	
236	OC(CN1C(=O)C(F)=CN(C2CCCO2)C1=O)C3CCCCC3

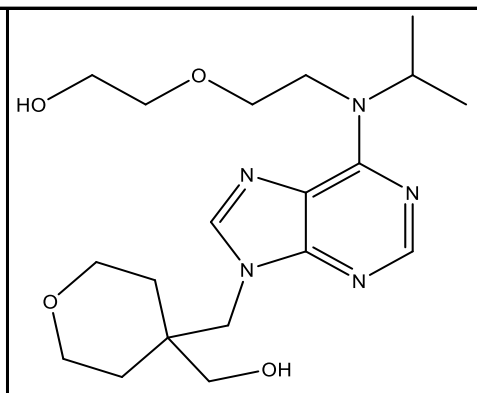
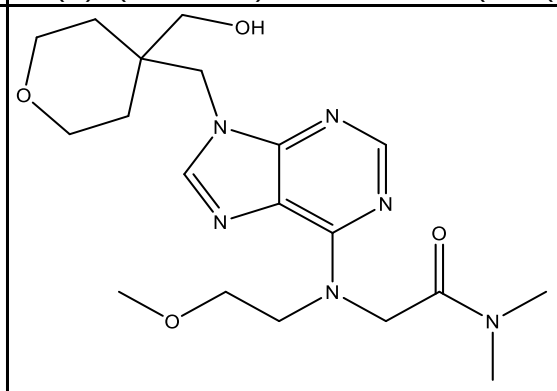
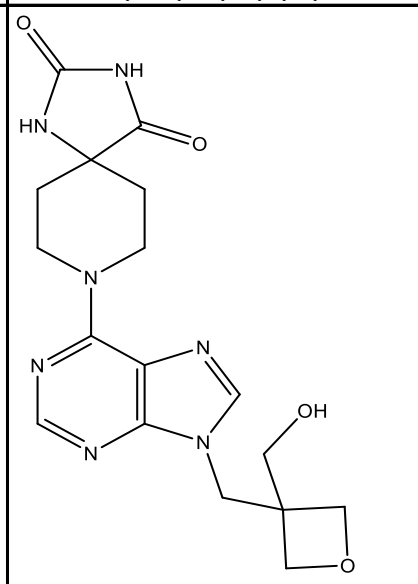
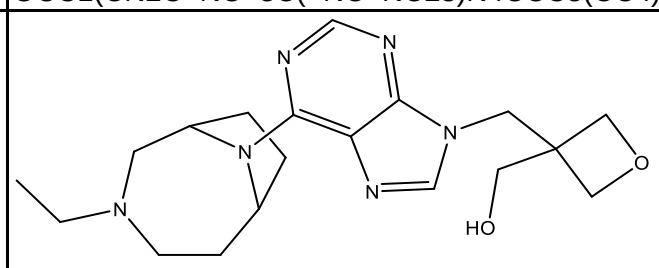
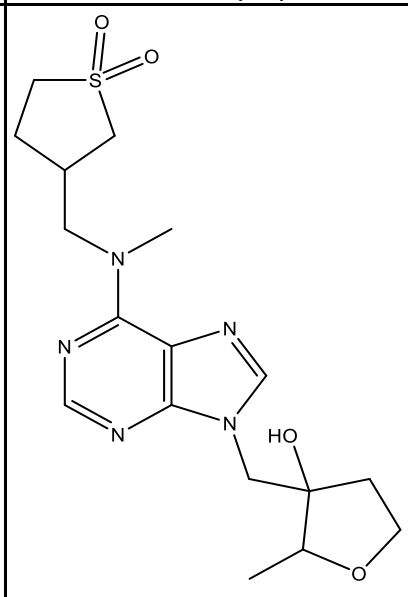
	
237	NC=1N=C(Cl)N=C2N(C=NC12)[C@@H]3O[C@H](CO)[C@@H](O)[C@@H]3F
	
238	NC=1C=CN([C@H]2CC[C@@H](CO)O2)C(=O)N1
	
239	NC(=O)C=1N=CN(N1)[C@@H]2O[C@H](CO)[C@@H](O)[C@H]2O
	
240	OC[C@H]1O[C@H](C[C@@H]1O)N2C=NC=3[C@H](O)CNC=NC32
	
241	CCNC(=O)C1CCN(CC1)C=2N=CN=C3N(CC(CO)C4CCOC4)C=NC23

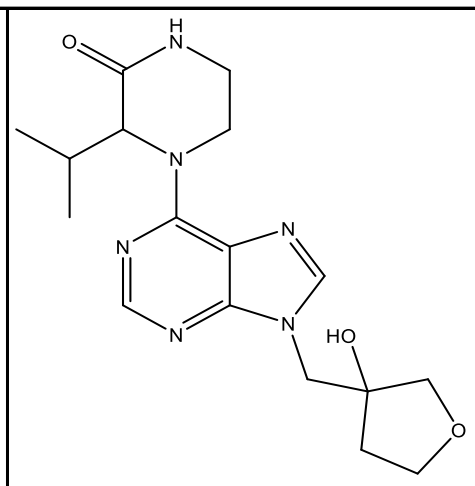
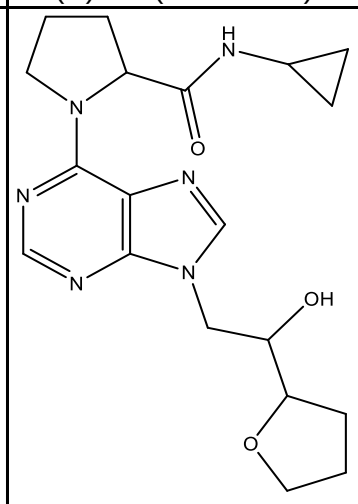
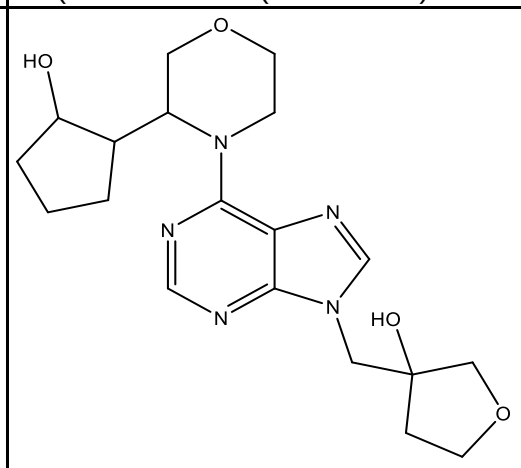
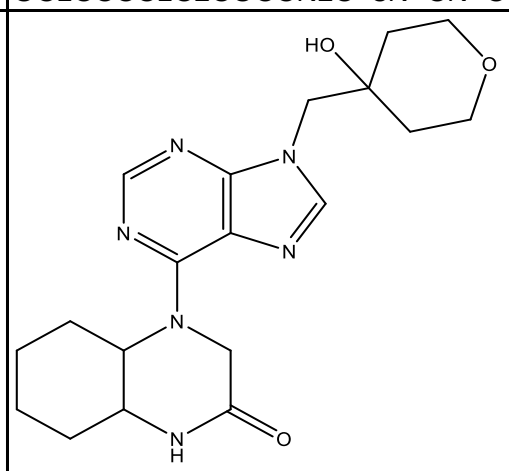
		242 CC(C)CCOC1CCN(CC1)C=2N=CN=C3N(CC4(O)CCOCC4)C=NC23
		243 CC1CCN(CC1)C(=O)C2CCN(CC2)C(=O)C3=CN(C)C(=O)N(C)C3=O
		244 CCN1CCC(CC1C)N(C)C=2N=CN=C3N(CC(CO)C4CCOC4)C=NC23
		245 CCC1(O)CCN(C1)C=2N=CN=C3NC=CC23

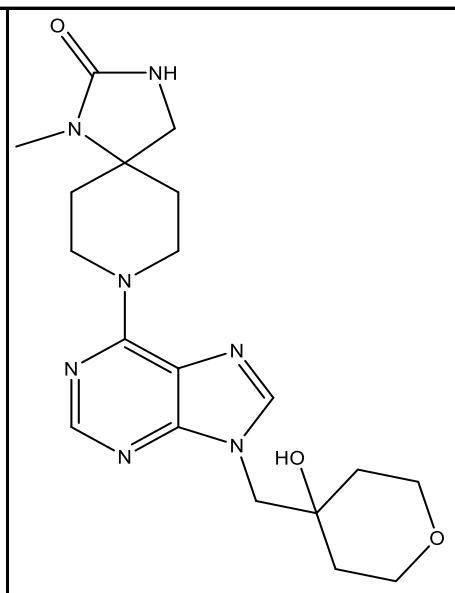
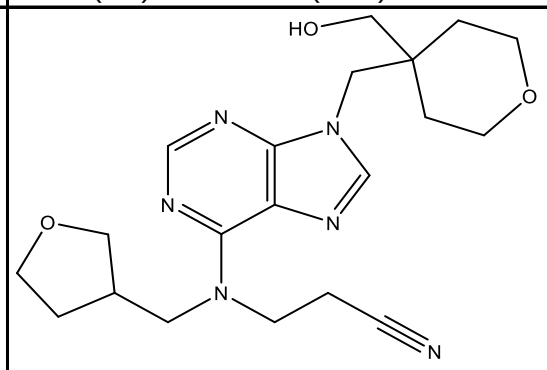
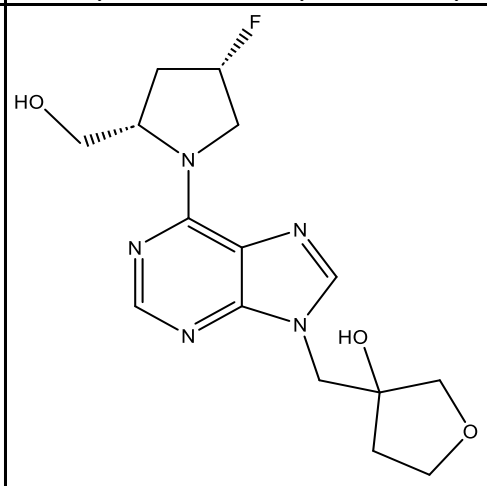
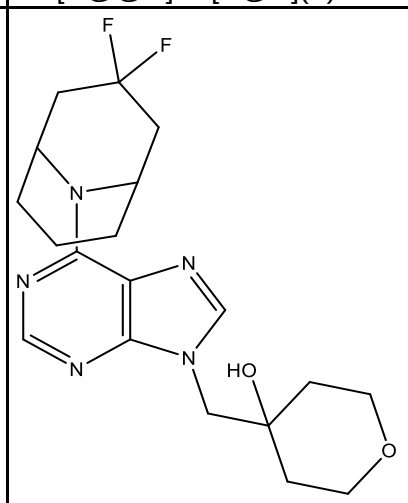
	
246	CC1OCCC1(O)CN2C=NC=3C(=NC=NC23)N4CC(C4)OCC(=O)N(C)C
	
247	FC1=CN(C2CCCO2)C(=O)N(CC(=O)NC=3C=CC=C(I)C3)C1=O
	
248	CN1CCN(C)CC(C1)NC(=O)C2=CN(C)C(=O)NC2=O
	
249	CC(C)CC1N(CCNC1=O)C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4

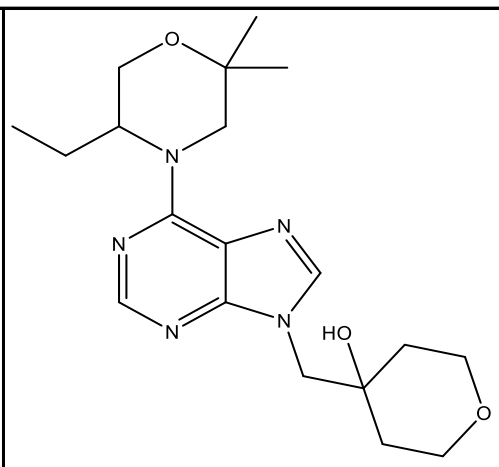
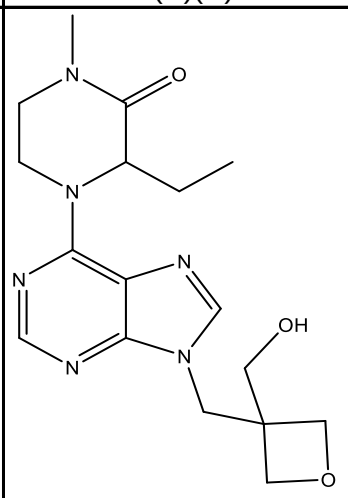
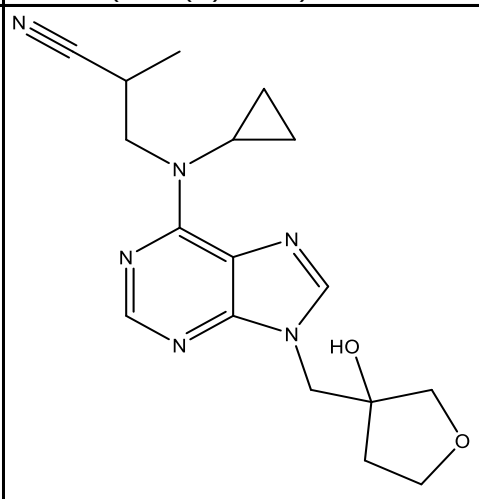
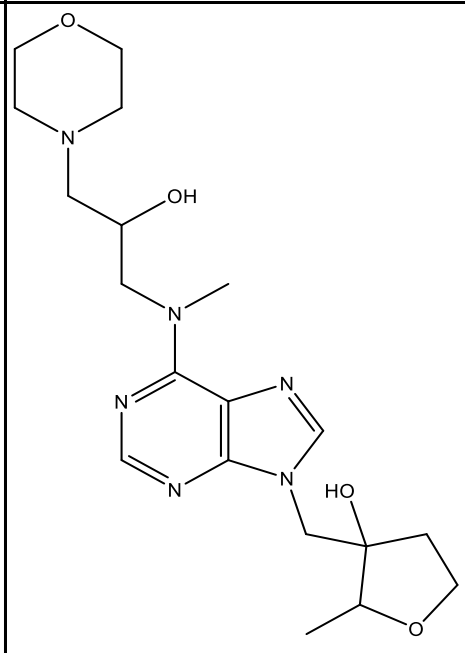
		
250	CC(C)C1N(CC21CCCCC2)C=3N=CN=C4N(C=NC34)C5CC(CO)(CO)C5	
		
251	OCC1(CO)CC(C1)N2C=NC=3C(=NC=NC23)N4CC(=O)NC5CCCCC54	
		
252	CN1[C@H]2CCN(C[C@H]2NC1=O)C=3N=CN=C4N(CC5(CO)CCOCC5)C=NC34	
		
253	CC(C)(C)N1C=C(CNCC2(O)CCC2)C(=O)NC1=O	

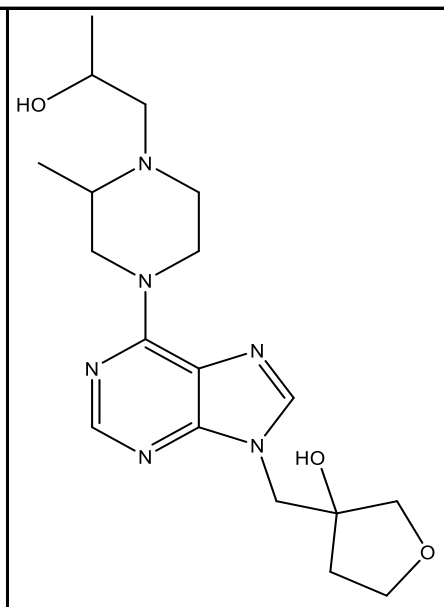
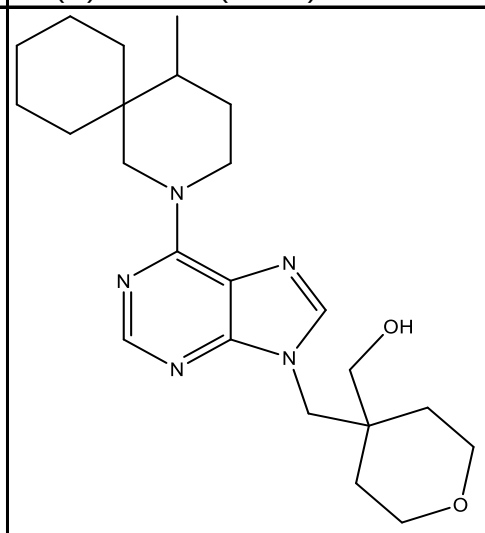
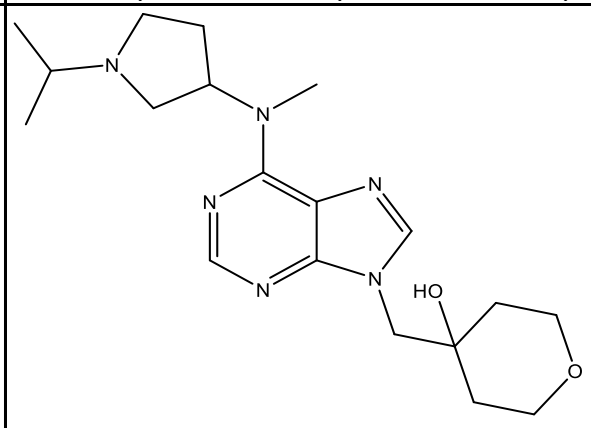
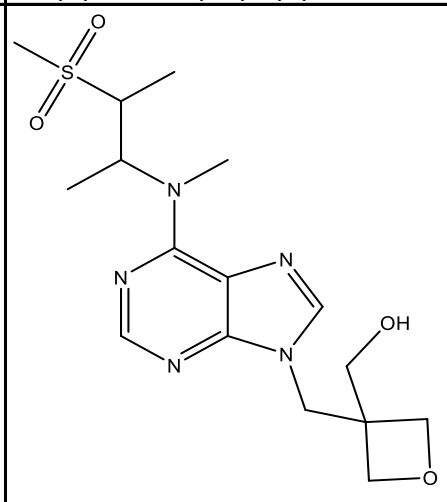
		
254	COCCC1COCCN1C=2N=CN=C3N(CC4(O)CCOC4C)C=NC23	
		
255	CCNC(=O)CN1CCN(CC1)C=2N=CN=C3N(CC4(CO)CCOCC4)C=NC23	
		
256	COCCN1CCN(CC1=O)C=2N=CN=C3N(CC4(CO)COC4)C=NC23	
		
257	CC(=O)NCC1CCCN(C1)C=2N=CN=C3N(CC4(CO)COC4)C=NC23	

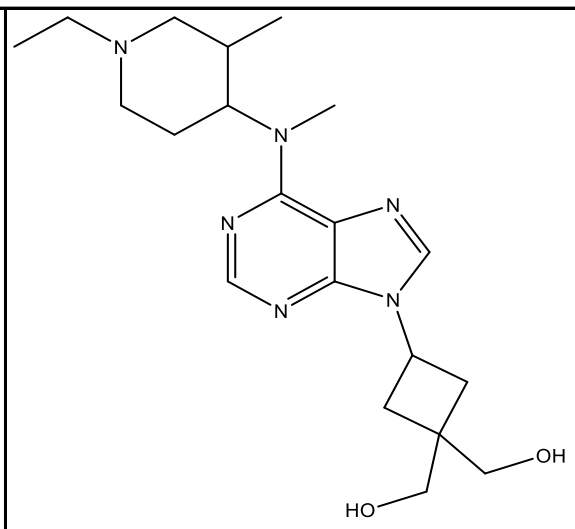
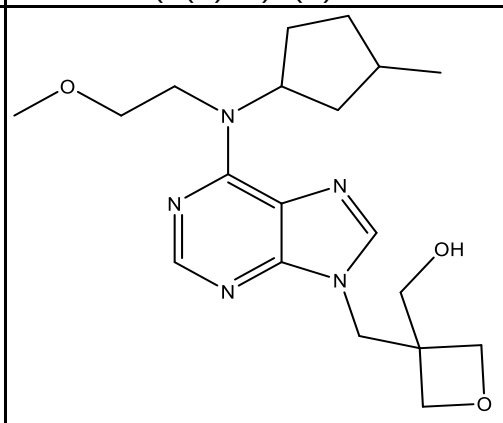
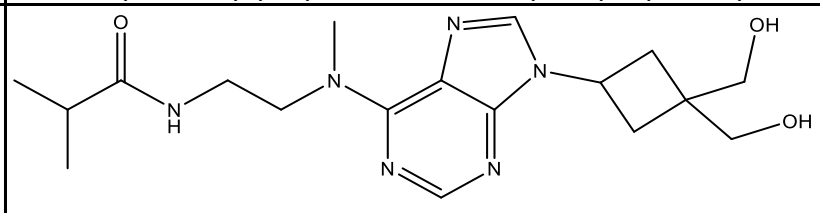
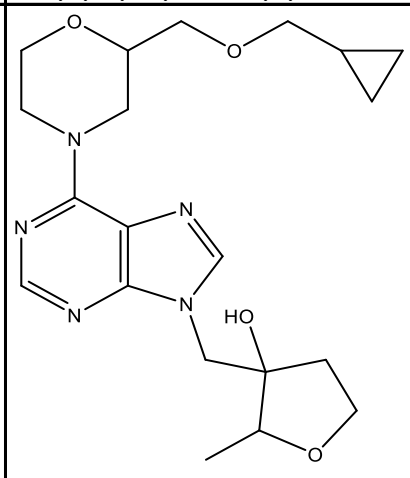
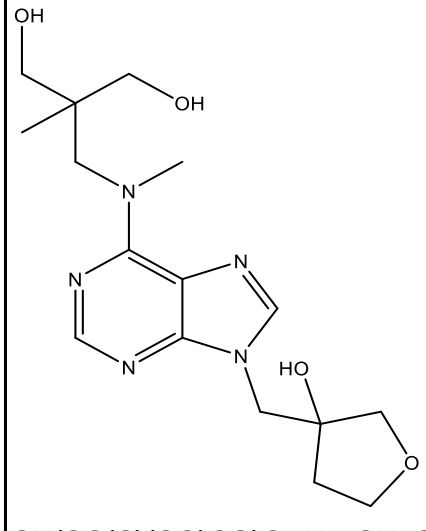
		
258	CC(C)N(CCOCCO)C=1N=CN=C2N(CC3(CO)CCOCC3)C=NC12	
		
259	COCCN(CC(=O)N(C)C)C=1N=CN=C2N(CC3(CO)CCOCC3)C=NC12	
		
260	OCC1(CN2C=NC=3C(=NC=NC23)N4CCC5(CC4)NC(=O)NC5=O)COC1	
		
261	CCN1CCC2CCC(C1)N2C=3N=CN=C4N(CC5(CO)COC5)C=NC34	
		
262	CC1OCCC1(O)CN2C=NC=3C(=NC=NC23)N(C)CC4CCS(=O)(=O)C4	

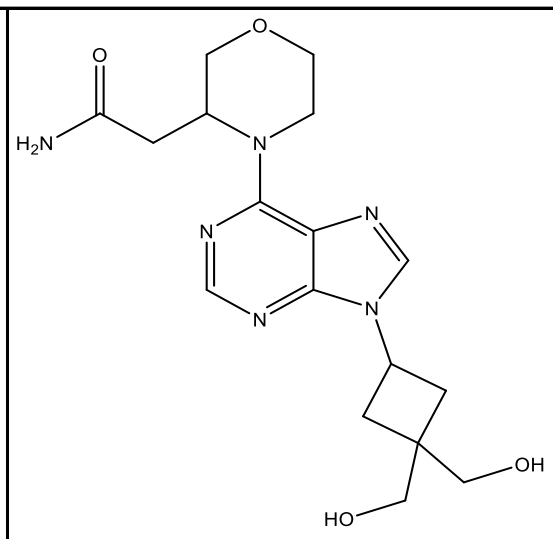
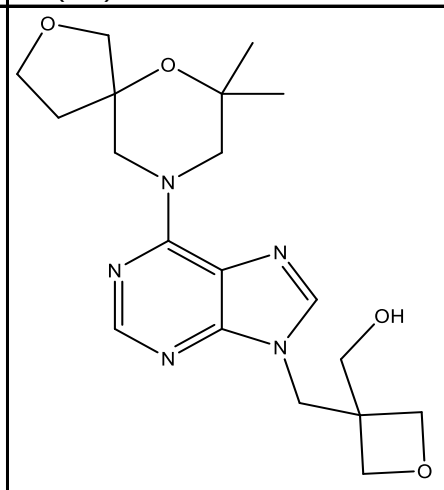
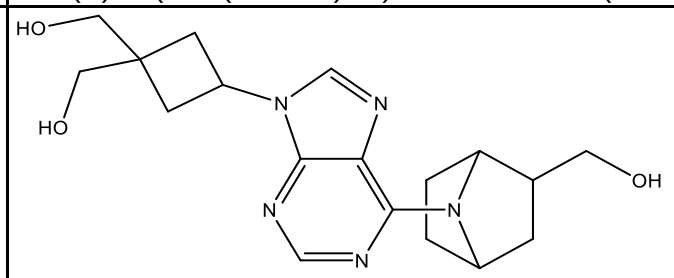
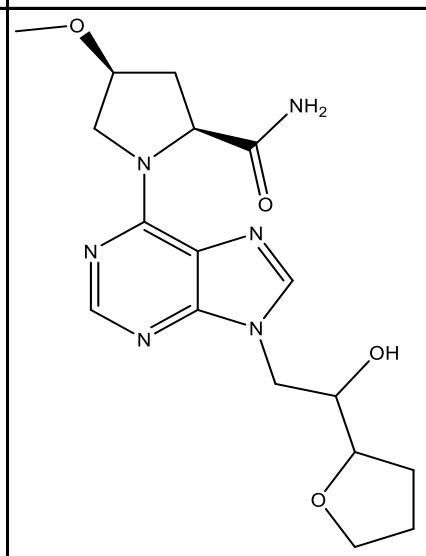
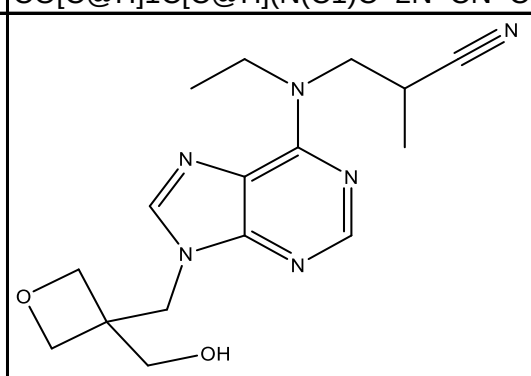
	263 CC(C)C1N(CCNC1=O)C=2N=CN=C3N(CC4(O)CCOC4)C=NC23
	264 OC(CN1C=NC=2C(=NC=NC12)N3CCCC3C(=O)NC4CC4)C5CCCO5
	265 OC1CCCC1C2COCCN2C=3N=CN=C4N(CC5(O)CCOC5)C=NC34
	266 OC1(CN2C=NC=3C(=NC=NC23)N4CC(=O)NC5CCCCC54)CCOCC1

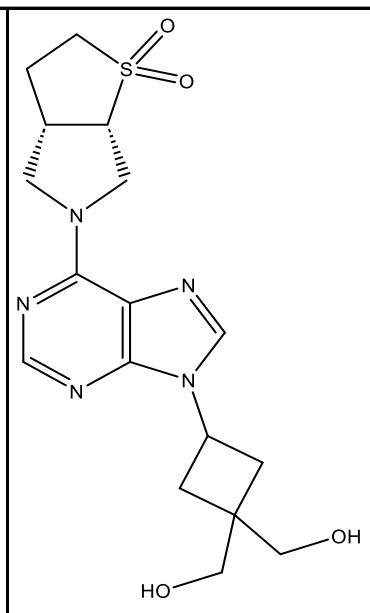
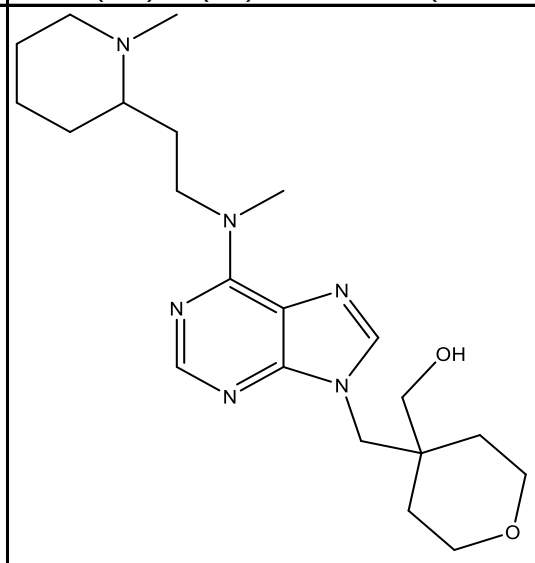
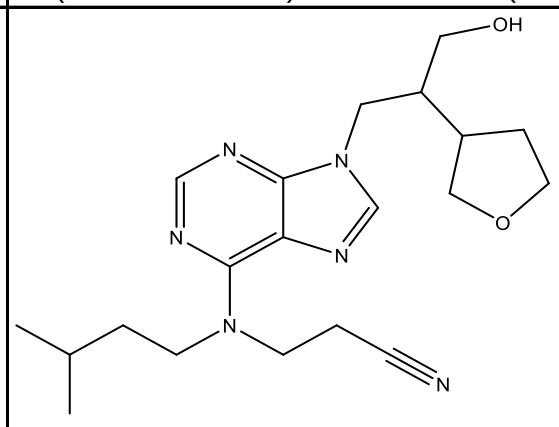
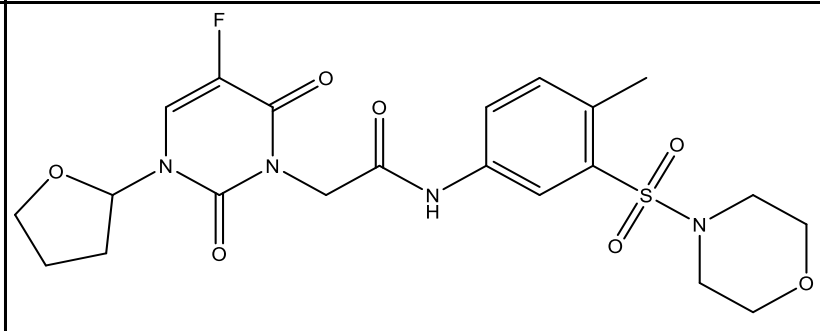
	267 CN1C(=O)NCC21CCN(CC2)C=3N=CN=C4N(CC5(O)CCOCC5)C=NC34
	268 OCC1(CN2C=NC=3C(=NC=NC23)N(CCC#N)CC4CCOC4)CCOCC1
	269 OC[C@@H]1C[C@H](F)CN1C=2N=CN=C3N(CC4(O)CCOC4)C=NC23
	270 OC1(CN2C=NC=3C(=NC=NC23)N4C5CCCC4CC(F)(F)C5)CCOCC1

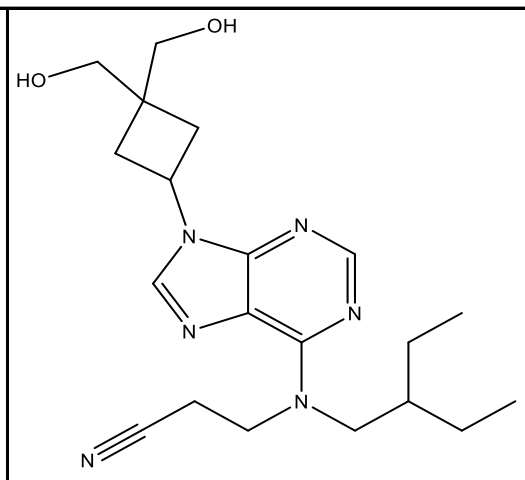
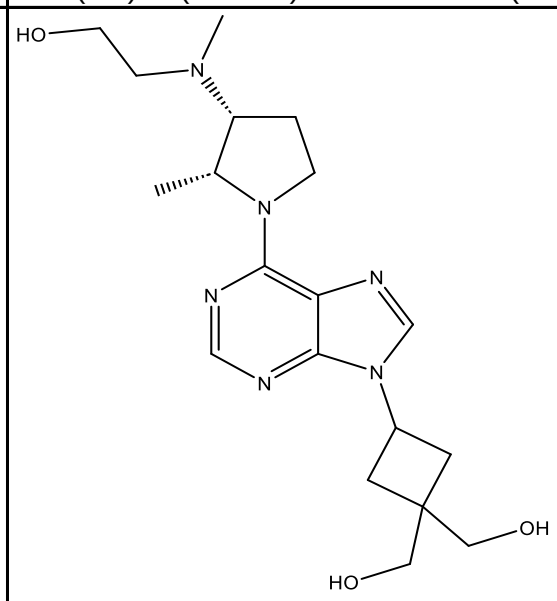
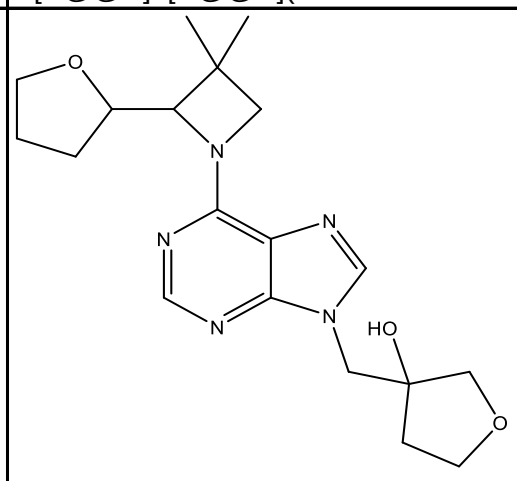
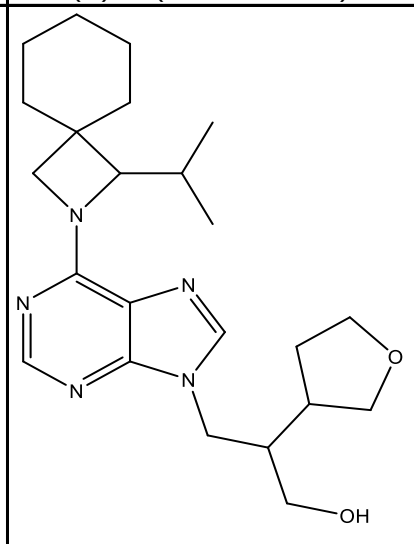
	271 CCC1COC(C)(C)CN1C=2N=CN=C3N(CC4(O)CCOCC4)C=NC23
	272 CCC1N(CCN(C)C1=O)C=2N=CN=C3N(CC4(CO)COC4)C=NC23
	273 CC(CN(C1CC1)C=2N=CN=C3N(CC4(O)CCOC4)C=NC23)C#N
	274 CC1OCCC1(O)CN2C=NC=3C(=NC=NC23)N(C)CC(O)CN4CCOCC4

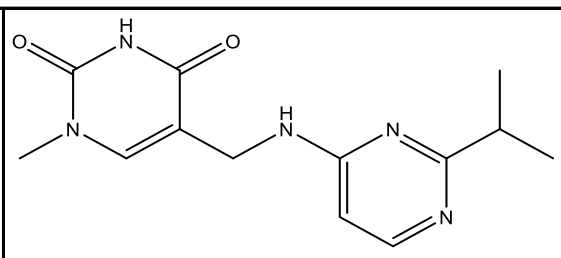
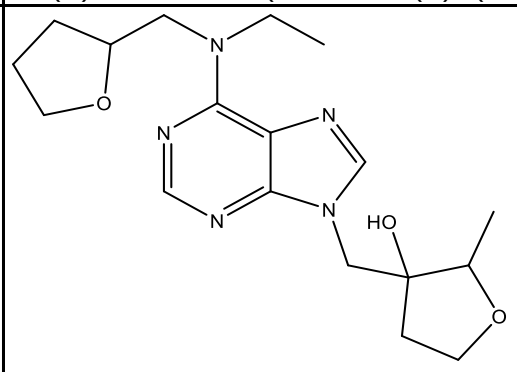
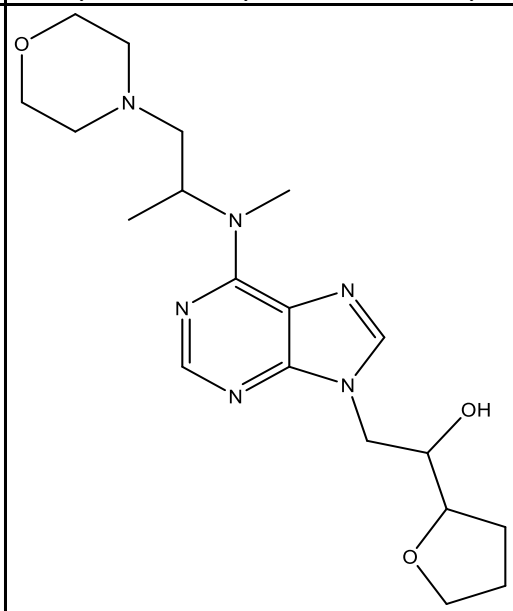
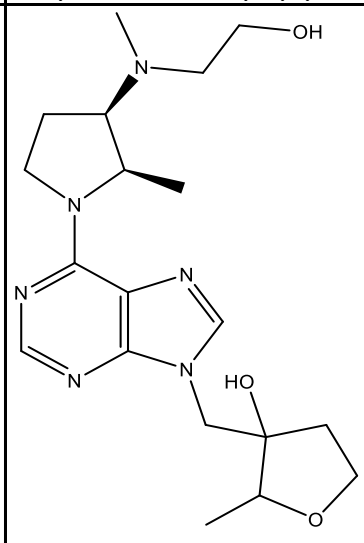
		275 CC(O)CN1CCN(CC1C)C=2N=CN=C3N(CC4(O)CCOC4)C=NC23
		276 CC1CCN(CC21CCCCC2)C=3N=CN=C4N(CC5(CO)CCOCC5)C=NC34
		277 CC(C)N1CCC(C1)N(C)C=2N=CN=C3N(CC4(O)CCOCC4)C=NC23
		278 CC(C(C)S(=O)(=O)C)N(C)C=1N=CN=C2N(CC3(CO)COC3)C=NC12

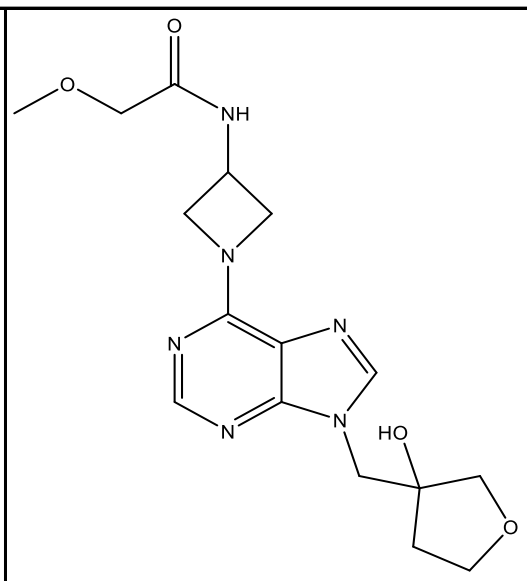
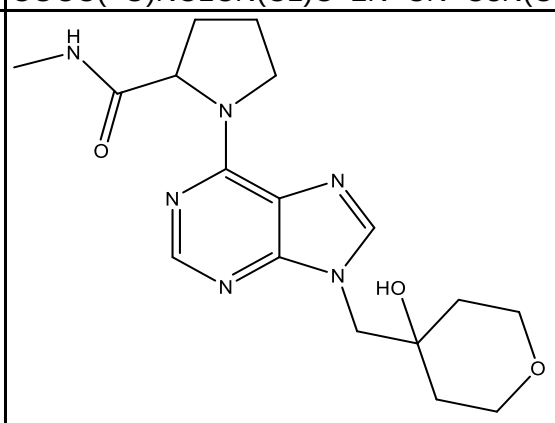
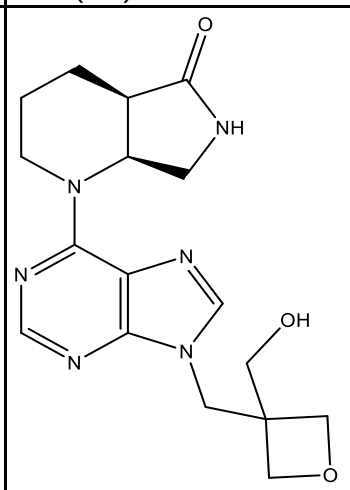
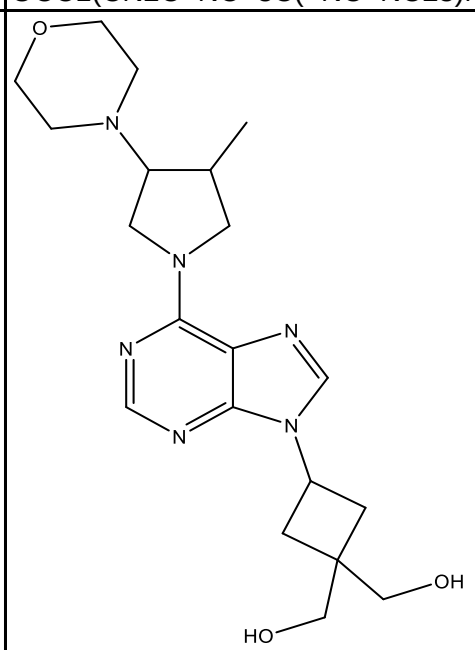
		
279	CCN1CCC(C(C)C1)N(C)C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4	
		
280	COCCN(C1CCC(C)C1)C=2N=CN=C3N(CC4(CO)COC4)C=NC23	
		
281	CC(C)C(=O)NCCN(C)C=1N=CN=C2N(C=NC12)C3CC(CO)(CO)C3	
		
282	CC1OCCC1(O)CN2C=NC=3C(=NC=NC23)N4CCOC(COCC5CC5)C4	
		
283	CN(CC(C)(CO)CO)C=1N=CN=C2N(CC3(O)CCOC3)C=NC12	

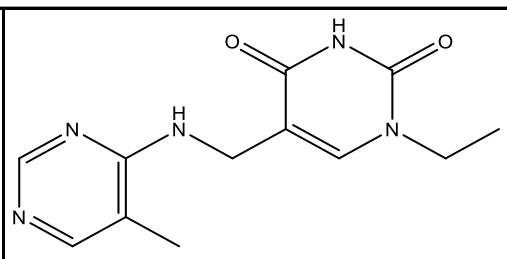
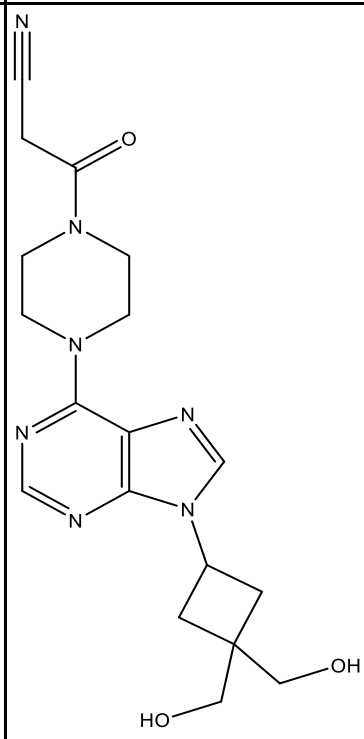
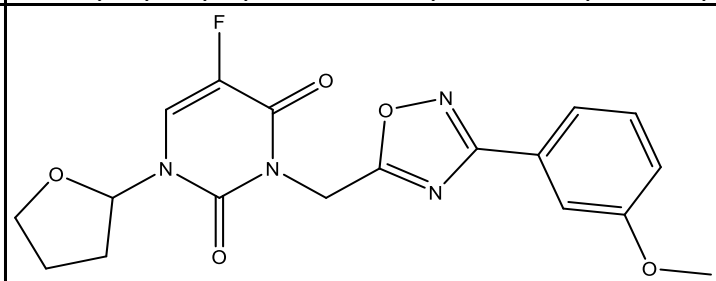
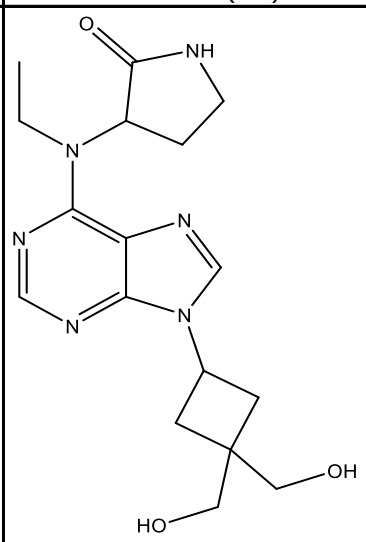
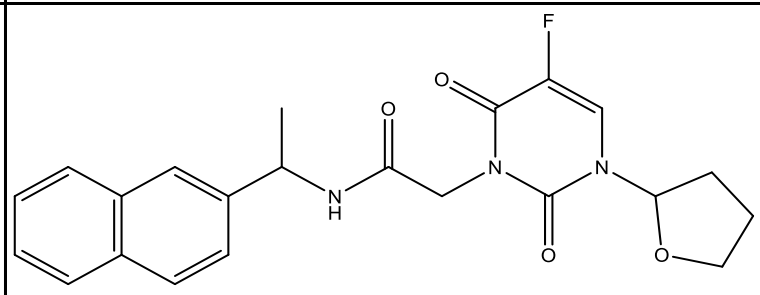
		284 NC(=O)CC1COCCN1C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4
		285 CC1(C)CN(CC2(CCOC2)O1)C=3N=CN=C4N(CC5(CO)COC5)C=NC34
		286 OCC1CC2CCC1N2C=3N=CN=C4N(C=NC34)C5CC(CO)(CO)C5
		287 CO[C@H]1C[C@H](N(C1)C=2N=CN=C3N(CC(O)C4CCCO4)C=NC23)C(=O)N
		288 CCN(CC(C)C#N)C=1N=CN=C2N(CC3(CO)COC3)C=NC12

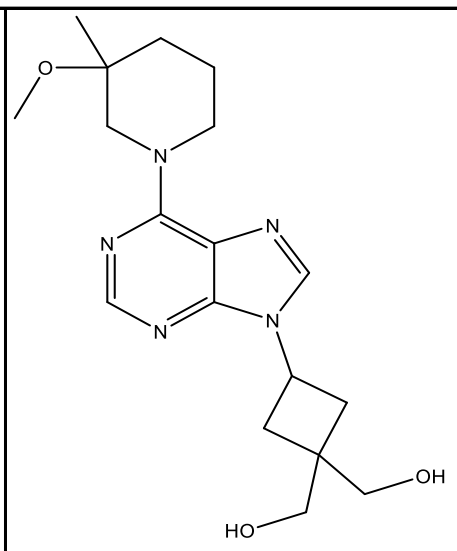
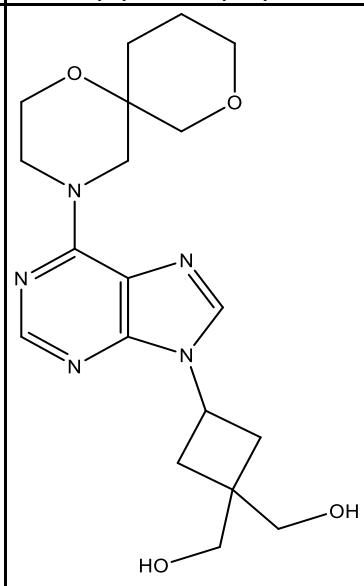
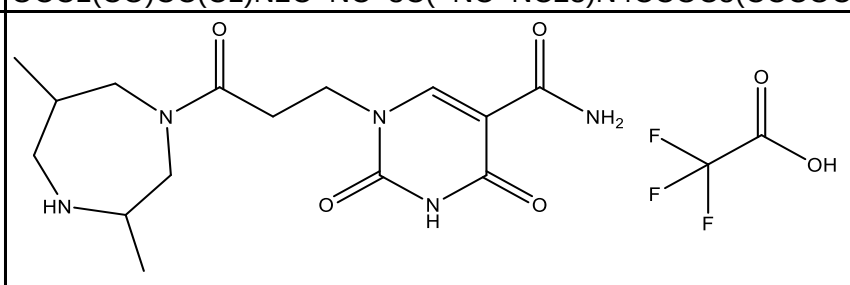
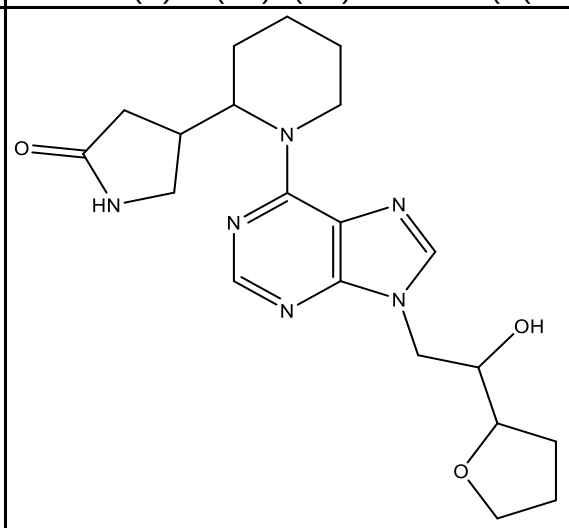
	
289	OCC1(CO)CC(C1)N2C=NC=3C(=NC=NC23)N4C[C@@H]5CCS(=O)(=O)[C@@H]5C4
	
290	CN(CCC1CCCCN1C)C=2N=CN=C3N(CC4(CO)CCOCC4)C=NC23
	
291	CC(C)CCN(CCC#N)C=1N=CN=C2N(CC(CO)C3CCOC3)C=NC12
	
292	CC=1C=CC(NC(=O)CN2C(=O)C(F)=CN(C3CCCO3)C2=O)=CC1S(=O)(=O)N4CCOCC4

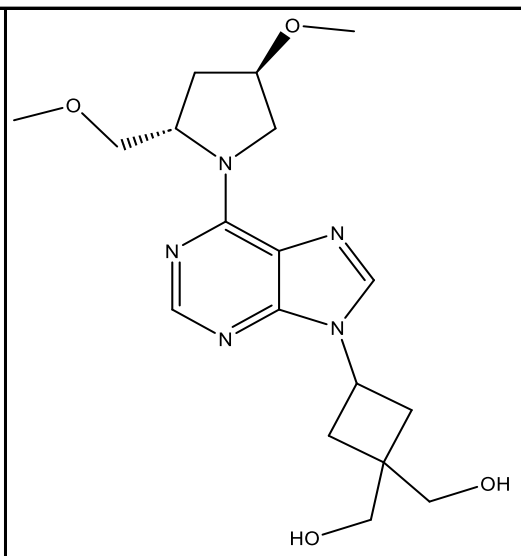
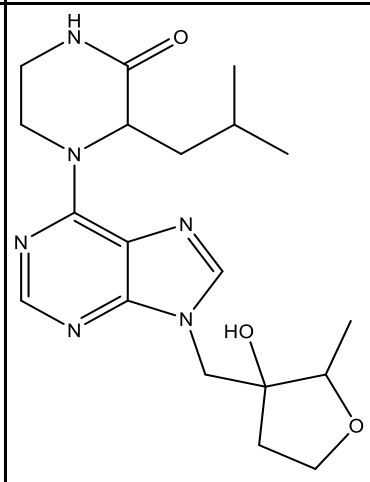
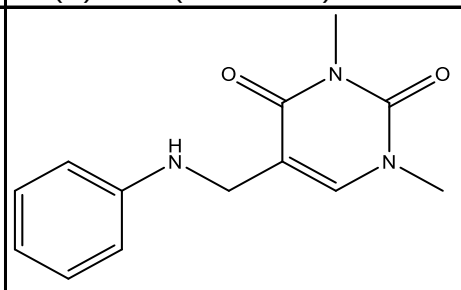
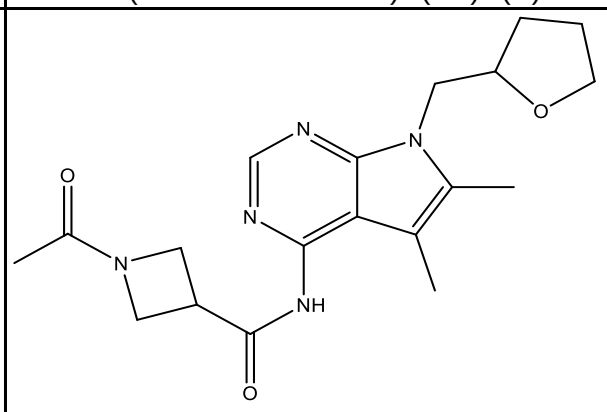
		293 CCC(CC)CN(CCC#N)C=1N=CN=C2N(C=NC12)C3CC(CO)(CO)C3
		294 C[C@@H]1[C@@H](CCN1C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4)N(C)CCO
		295 CC1(C)CN(C1C2CCCO2)C=3N=CN=C4N(CC5(O)CCOC5)C=NC34
		296 CC(C)C1N(CC21CCCCC2)C=3N=CN=C4N(CC(CO)C5CCOC5)C=NC34

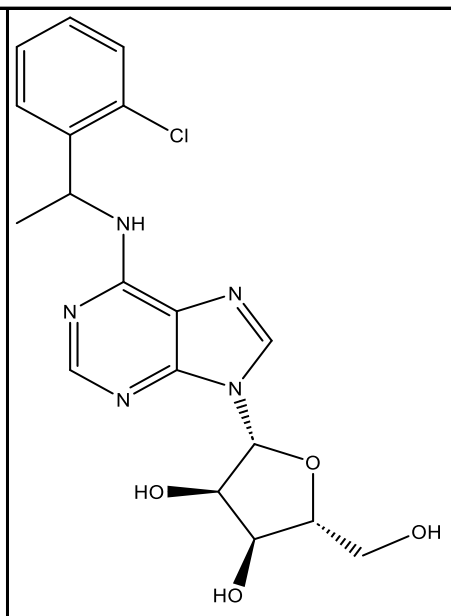
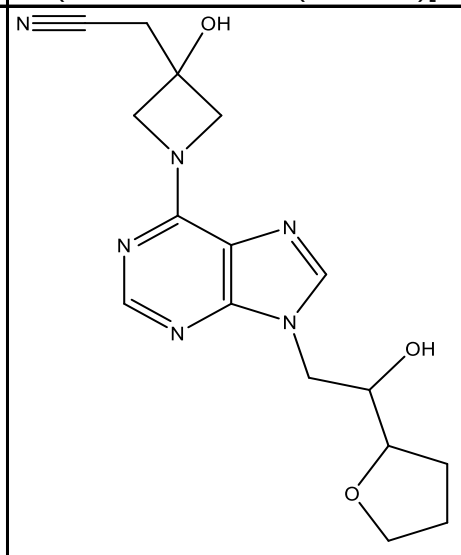
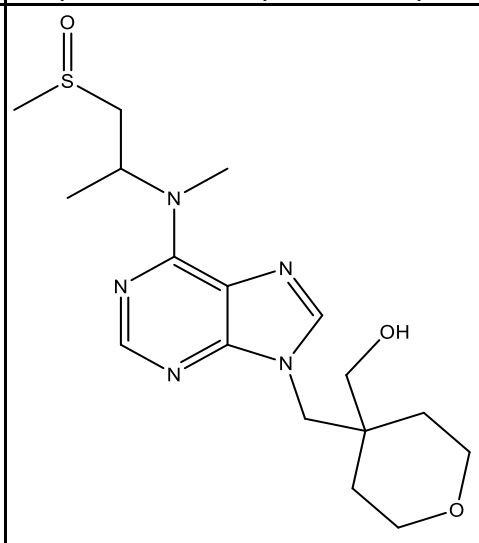
297		CC(C)C=1N=CC=C(NCC2=CN(C)C(=O)NC2=O)N1
298		CCN(CC1CCCO1)C=2N=CN=C3N(CC4(O)CCOC4C)C=NC23
299		CC(CN1CCOCC1)N(C)C=2N=CN=C3N(CC(O)C4CCCO4)C=NC23
300		CC1OCCC1(O)CN2C=NC=3C(=NC=NC23)N4CC[C@H]([C@H]4C)N(C)CCO

		301 COCC(=O)NC1CN(C1)C=2N=CN=C3N(CC4(O)CCOC4)C=NC23
		302 CNC(=O)C1CCCN1C=2N=CN=C3N(CC4(O)CCOCC4)C=NC23
		303 OCC1(CN2C=NC=3C(=NC=NC23)N4CCC[C@@H]5[C@H]4CNC5=O)COC1
		304 CC1CN(CC1N2CCOCC2)C=3N=CN=C4N(C=NC34)C5CC(CO)(CO)C5

305		CCN1C=C(CNC=2N=CN=CC2C)C(=O)NC1=O
306		OCC1(CO)CC(C1)N2C=NC=3C(=NC=NC23)N4CCN(CC4)C(=O)CC#N
307		COC=1C=CC=C(C1)C2=NOC(CN3C(=O)C(F)=CN(C4CCCO4)C3=O)=N2
308		CCN(C1CCNC1=O)C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4
309		CC(NC(=O)CN1C(=O)C(F)=CN(C2CCCO2)C1=O)C=3C=CC=4C=CC=CC4C3

	
310	COC1(C)CCCN(C1)C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4
	
311	OCC1(CO)CC(C1)N2C=NC=3C(=NC=NC23)N4CCOC5(CCCOC5)C4
	
312	CC1CNC(C)CN(C1)C(=O)CCN2C=C(C(=O)N)C(=O)NC2=O.OC(=O)C(F)(F)F
	
313	OC(CN1C=NC=2C(=NC=NC12)N3CCCCC3C4CNC(=O)C4)C5CCCO5

	314 COC[C@@H]1C[C@H](CN1C=2N=CN=C3N(C=NC23)C4CC(CO)(CO)C4)OC
	315 CC(C)CC1N(CCNC1=O)C=2N=CN=C3N(CC4(O)CCOC4C)C=NC23
	316 CN1C=C(CNC=2C=CC=CC2)C(=O)N(C)C1=O
	317 CC(=O)N1CC(C1)C(=O)NC=2N=CN=C3N(CC4CCCO4)C(C)=C(C)C23

	
318	CC(NC=1N=CN=C2N(C=NC12)[C@@H]3O[C@H](CO)[C@@H](O)[C@H]3O)C=4C=CC=CC4Cl
	
319	OC(CN1C=NC=2C(=NC=NC12)N3CC(O)(CC#N)C3)C4CCCO4
	
320	CC(CS(=O)C)N(C)C=1N=CN=C2N(CC3(CO)CCOCC3)C=NC12