

Supporting Information

SYNTHI: A NEW OPEN-SOURCE TOOL FOR SYNTTHON-BASED LIBRARY DESIGN

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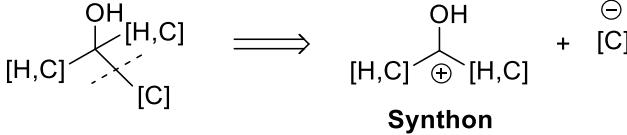
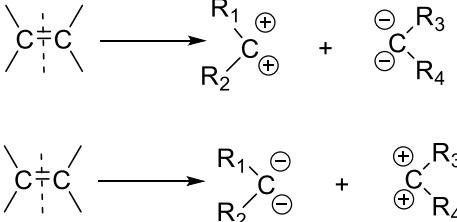
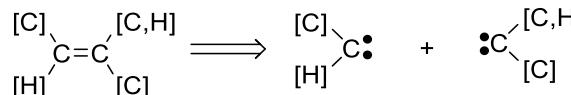
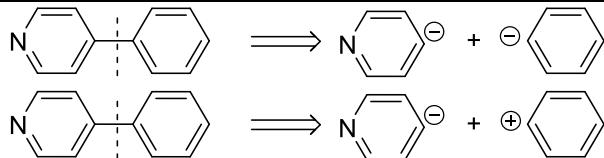
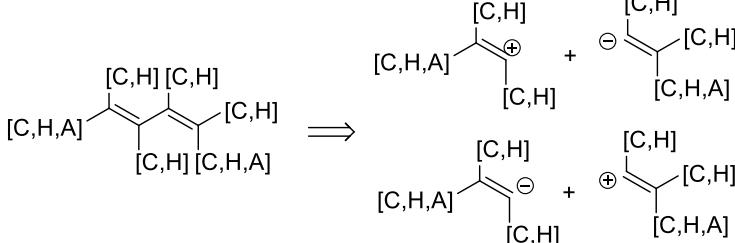
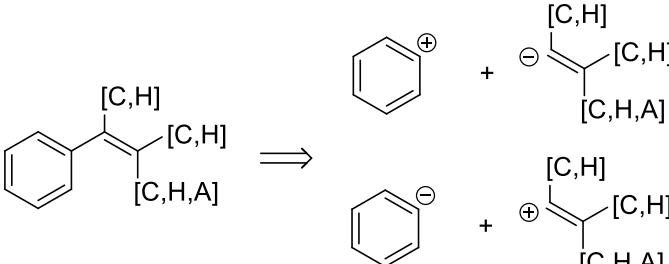
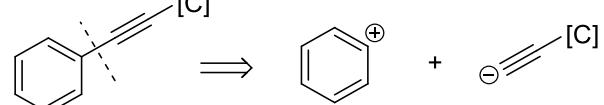
Table S3. SynthI Fragmentation Comparison with Literature Reported Synthesis..... 24

Table S1. SynthI Reaction Rules Specification

R1 – N-acylation	
R1.1 - Amine acylation	$\begin{array}{c} \text{[C]} \\ \\ \text{C} \backslash \text{N} \\ \\ \text{O} \end{array} \longrightarrow \begin{array}{c} \text{[C]} \\ \\ \text{C}^+ \\ \\ \text{O} \end{array} + \begin{array}{c} \ominus \\ \text{N} \\ \\ \text{C} \end{array}$
R1.2 – N-Acylation of RN-X compounds (<i>hydrazides, sulfonylacetamides, substituted acetyl isocyanides, N-hydroxyamides, N-Acetylguanidines</i>)	$\begin{array}{c} \text{[C]} \\ \\ \text{C} \backslash \text{N} \\ \\ \text{O} \\ \\ \text{X} \end{array} \longrightarrow \begin{array}{c} \text{[C]} \\ \\ \text{C}^+ \\ \\ \text{O} \end{array} + \begin{array}{c} \ominus \\ \text{N} \\ \\ \text{C} \\ \\ \text{X} \end{array}$
R1.3 - N-Acylation by O=C(+)-X reagents (except isocyanates - R1.4) (<i>carbamates, carbamide halogenides, substituted sulfanylformamide</i>)	$\begin{array}{c} \text{X} \\ \\ \text{C} \backslash \text{N} \\ \\ \text{O} \end{array} \longrightarrow \begin{array}{c} \text{X} \\ \\ \text{C}^+ \\ \\ \text{O} \end{array} + \begin{array}{c} \ominus \\ \text{N} \\ \\ \text{C} \end{array}$
R1.4 - Amine acylation by isocyanates or analogues (<i>ureas</i>)	$\begin{array}{c} \text{R}_1 \quad \text{R}_3 \\ \quad \\ \text{R}_2 \text{--} \text{N} \text{--} \text{C} \text{--} \text{N} \text{--} \text{R}_4 \\ \\ \text{O} \end{array} \longrightarrow \begin{array}{c} \text{R}_1 \\ \\ \text{R}_2 \text{--} \text{N}^\ominus \\ \end{array} + \begin{array}{c} \text{R}_3 \\ \\ \text{C}^+ \text{--} \text{N} \text{--} \text{R}_4 \\ \\ \text{O} \end{array}$ $\begin{array}{c} \text{R}_1 \quad \text{R}_3 \\ \quad \\ \text{R}_2 \text{--} \text{N} \text{--} \text{C} \text{--} \text{N} \text{--} \text{R}_4 \\ \\ \text{O} \end{array} \longrightarrow \begin{array}{c} \text{R}_1 \\ \\ \text{R}_2 \text{--} \text{N} \text{--} \text{C}^+ \\ \\ \text{O} \end{array} + \begin{array}{c} \text{R}_3 \\ \\ \text{N}^\ominus \text{--} \text{R}_4 \end{array}$
R2 - O-acylation	
R2.1 Alcohol/Phenol acylation	$\begin{array}{c} \text{[C]} \\ \\ \text{C} \backslash \text{O} \\ \\ \text{O} \end{array} \longrightarrow \begin{array}{c} \text{[C]} \\ \\ \text{C}^+ \\ \\ \text{O} \end{array} + \begin{array}{c} \ominus \\ \text{O} \\ \\ \text{C} \end{array}$
R2.2 O-Acylation by O=C(+)-X reagents	$\begin{array}{c} \text{X} \\ \\ \text{C} \backslash \text{O} \\ \\ \text{O} \end{array} \longrightarrow \begin{array}{c} \text{X} \\ \\ \text{C}^+ \\ \\ \text{O} \end{array} + \begin{array}{c} \ominus \\ \text{O} \\ \\ \text{C} \end{array}$

R2.3 O-Acylation of O-X compounds	$\begin{array}{c} [C] \\ \diagup \quad \diagdown \\ \text{O} \quad \text{O}-\text{X} \end{array} \longrightarrow \begin{array}{c} [C] \\ \diagup \quad \diagdown \\ \text{O} \quad \text{O}^+ \end{array} + \begin{array}{c} \ominus \\ \text{O}-\text{X} \end{array}$
R3 Amine_alkylation_arylation	
R3.1 - SN alkylation of amines;	$\begin{array}{c} \backslash \\ \text{N}-[\text{C}_{\text{sp}}^3] \end{array} \longrightarrow \begin{array}{c} \backslash \\ \text{N}^\ominus \end{array} + \begin{array}{c} \oplus \\ [\text{C}_{\text{sp}}^3] \end{array}$
R3.2 - Buchwald-Hartwig amination(BHA), Cu-mediated C-N coupling;	$\begin{array}{c} \backslash \\ \text{N}-[\text{C}_{\text{sp}}^2] \end{array} \longrightarrow \begin{array}{c} \backslash \\ \text{N}^\ominus \end{array} + \begin{array}{c} \oplus \\ [\text{C}_{\text{sp}}^2] \end{array}$ aromatic
R3.3 Umpolung cross-coupling	$\begin{array}{c} \backslash \\ \text{N}-[\text{C}_{\text{sp}}^2] \end{array} \longrightarrow \begin{array}{c} \oplus \\ \text{N} \end{array} + \begin{array}{c} \ominus \\ [\text{C}_{\text{sp}}^2] \end{array}$ aromatic
R3.4 Tertiary amines alkylation arylation	$\begin{array}{c} \oplus \\ \text{N}+[\text{C}_{\text{sp}}^3] \end{array} \longrightarrow \begin{array}{c} \backslash \\ \text{N}^\ominus \end{array} + \begin{array}{c} \oplus \\ [\text{C}_{\text{sp}}^3] \end{array}$
R4 - O-alkylation_arylation	
R4.1 - SN alkylation	$\begin{array}{c} \backslash \quad / \\ \text{[C]} \quad \text{O} \end{array} \begin{array}{c} \diagup \quad \diagdown \\ \text{[C}_{\text{sp}}^3] \end{array} \longrightarrow \begin{array}{c} \text{[C]}-\text{O}^\ominus \end{array} + \begin{array}{c} \oplus \\ [\text{C}_{\text{sp}}^3] \end{array}$
R4.2 - Cu-mediated C-O coupling	$\begin{array}{c} \backslash \quad / \\ \text{[C]} \quad \text{O} \end{array} \begin{array}{c} \diagup \quad \diagdown \\ \text{[C}_{\text{sp}}^2] \end{array} \longrightarrow \begin{array}{c} \text{[C]}-\text{O}^\ominus \end{array} + \begin{array}{c} \oplus \\ [\text{C}_{\text{sp}}^2] \end{array}$ aromatic
R4.3 - Chan-Evans-Lam coupling	$\begin{array}{c} \backslash \quad / \\ \text{[C]} \quad \text{O} \end{array} \begin{array}{c} \diagup \quad \diagdown \\ \text{[C}_{\text{sp}}^2] \end{array} \longrightarrow \begin{array}{c} \text{[C]}-\text{O}^\ominus \end{array} + \begin{array}{c} \ominus \\ [\text{C}_{\text{sp}}^2] \end{array}$ aromatic only Boron cmpds
R4.4 - N-O-alkylation	$\begin{array}{c} \text{[N]}-\text{O} \begin{array}{c} \diagup \quad \diagdown \\ \text{C(Alk)} \end{array} \end{array} \longrightarrow \begin{array}{c} \text{[N]}-\text{O}^\ominus \end{array} + \begin{array}{c} \oplus \\ \text{C(Alk)} \end{array}$
R5 - Alkylation_arylation_of_NH-heterocycles	
R5.1 - SN alkylation;	$\begin{array}{c} \text{N}=\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{N} \quad \text{N}+[\text{C}_{\text{sp}}^3] \end{array} \end{array} \longrightarrow \begin{array}{c} \text{N}=\text{N}^\ominus \end{array} + \begin{array}{c} \oplus \\ [\text{C}_{\text{sp}}^3] \end{array}$

R5.2 - Chan-Evans-Lam coupling	<p style="text-align: center;">aromatic or vinyl</p> <p style="text-align: right;">only Boron cmpds</p>
R5.3 - Cu-mediated C-N coupling	<p style="text-align: center;">aromatic or vinyl</p>
R6 - Alkylation_arylation_of_NH-lactam	
R6.1 - SN alkylation	<p style="text-align: center;">sp^3/aromatic/vinyl</p>
R6.2 - Chan-Evans-Lam coupling	<p style="text-align: center;">sp^3/aromatic/vinyl</p> <p style="text-align: right;">only Boron cmpds</p>
R6.3 - Cu-mediated C-N coupling	
R7.1- S-alkylation arylation	<p style="text-align: center;">[C]~S~[C] \longrightarrow [C]~S^- + [C]</p> <p style="text-align: center;">C(Alk, (Het)Ar)</p>
R7.2 - Simple alkylation of sulphinic acid salts; R7.3 - Cu-catalyzed arylation of sulphinic acid salts	<p style="text-align: center;">[C]~S~[C] \longrightarrow [C]~S^- + [C]</p> <p style="text-align: center;">C(Alk, (Het)Ar)</p>
R8 - Amine_sulphoacylation	
R9 - Condensation_of_Y-NH2_with_carbonyl_compounds	
R10 - Metal organics C-C bong assembling	

R10.1 - Addition of Li, Mg, Zn organics to aldehydes and ketones	
R10.2 - Acylation of Li, Mg, Zn organics	
R11.1 - Knoevenagel-, Wittig-, Julia-Kocienski- type reactions,	
R11.2 - Olefin Metathesis	
R12 - C-C couplings	
R12.1 - Suzuki cross-coupling C(Ar)- C(Ar)	
R12.2 - Suzuki coupling C(sp2) - C(sp2)	
R12.3 - Heck and Suzuki coupling C(Ar) - C(sp2)	
R12.4 - Sonogashira coupling C(Ar) - C(sp)	

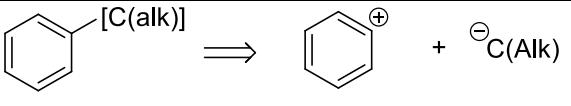
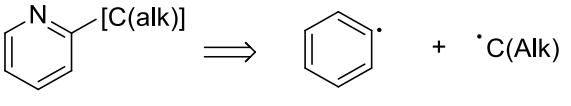
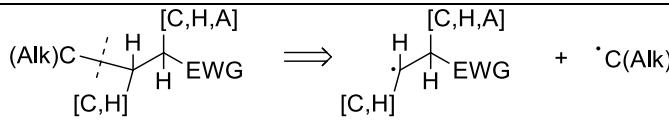
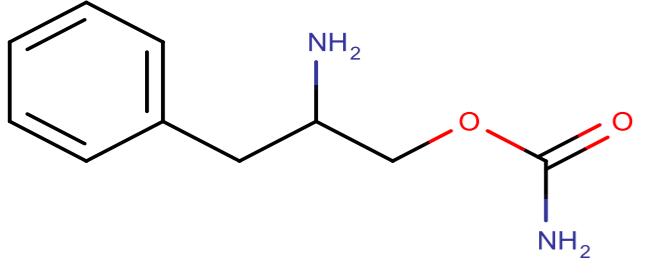
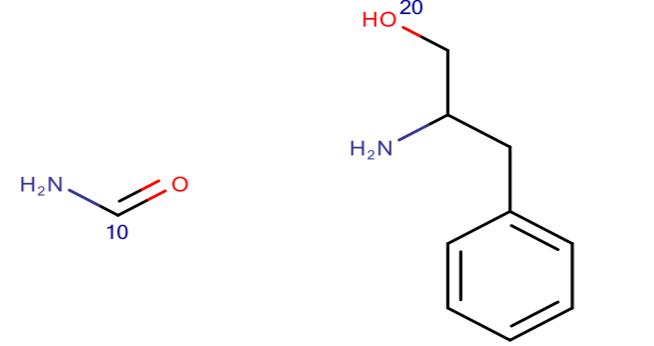
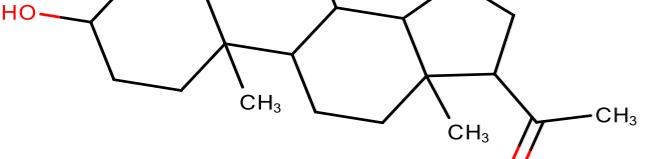
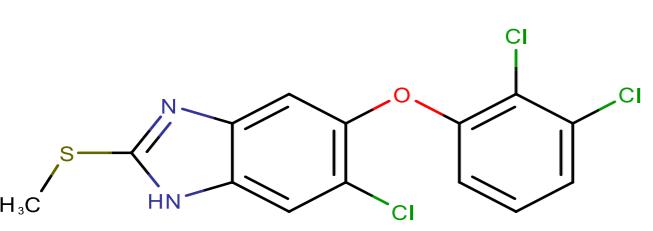
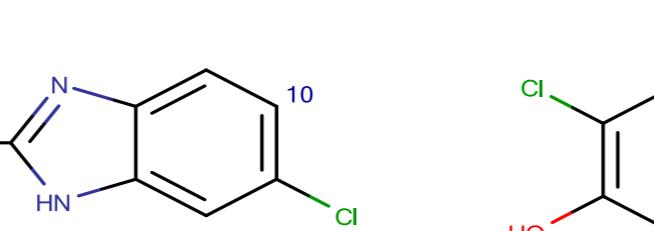
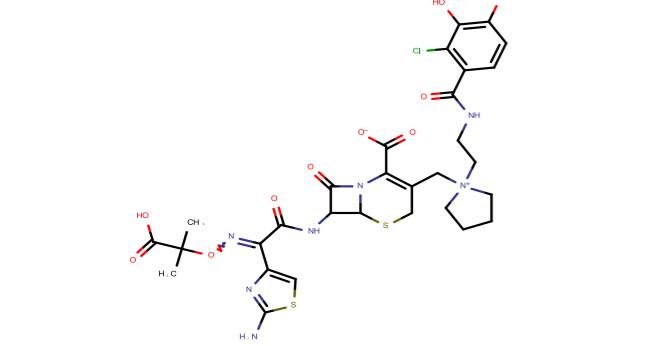
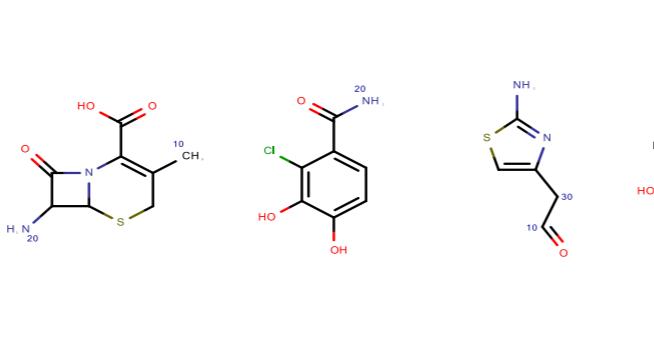
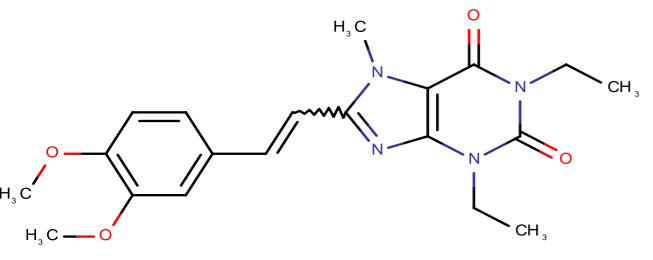
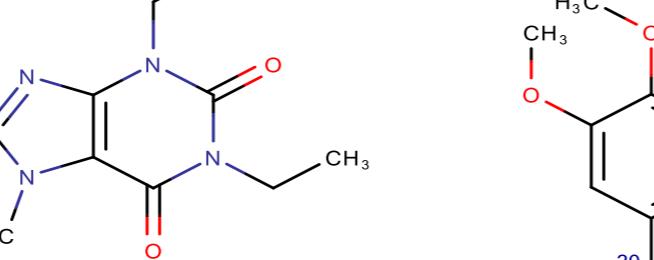
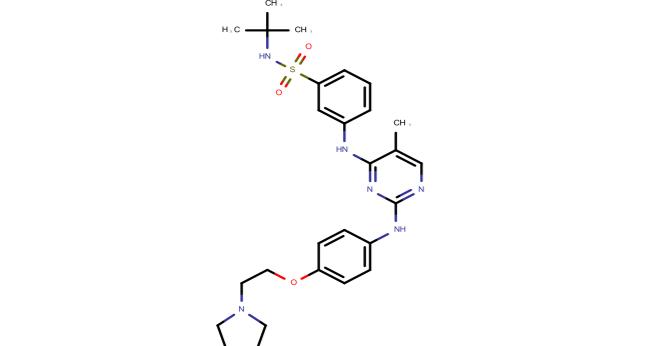
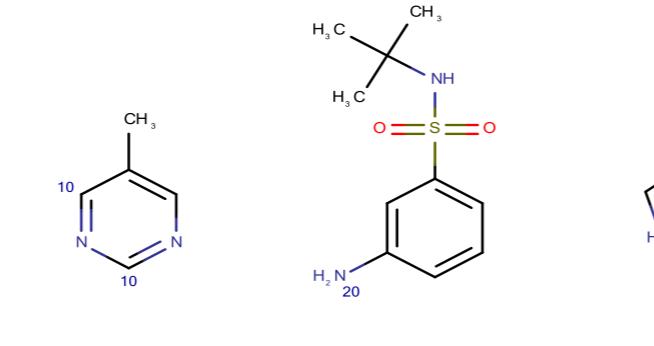
R12.5 - Novel methods for C(Ar)-C(sp ₃) coupling	
R13 - Radical_reactions	
R13.1 - Minisci reaction and Baran diversinates C(Ar)-C(sp ₃)	
R13.2 - Giese reaction C(sp ₃) - C(sp ₃)	 <p>EWG = CN, COR, CONH₂, CONHR, CONR₂, COOR, NO₂, SO₂R</p>

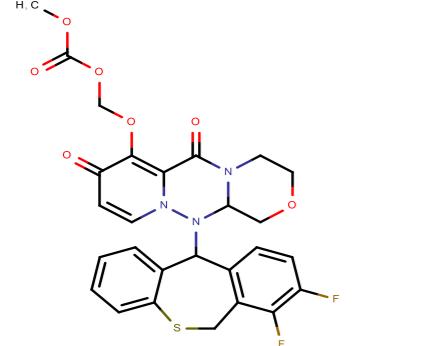
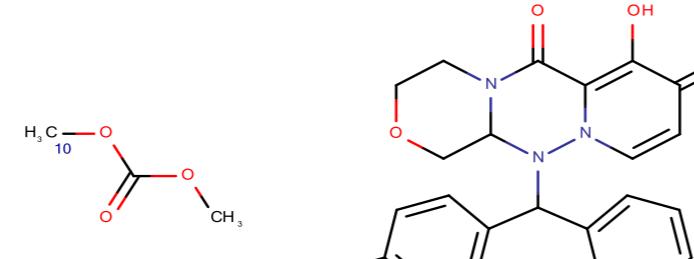
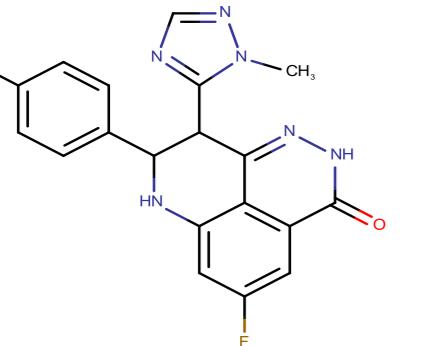
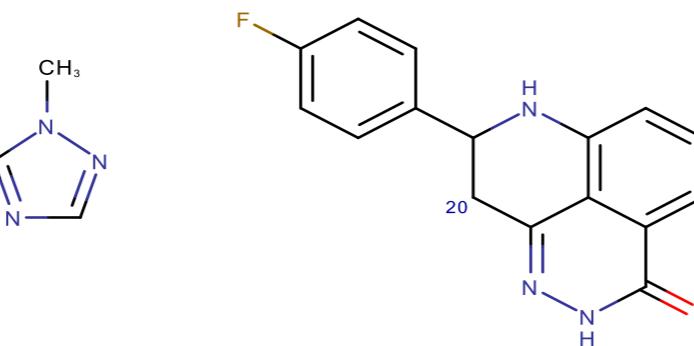
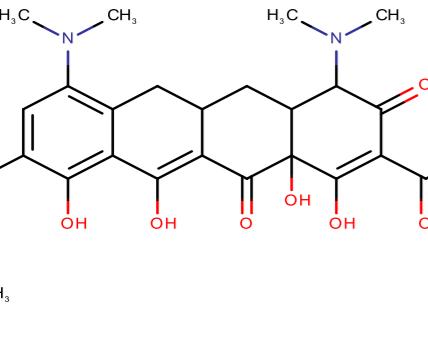
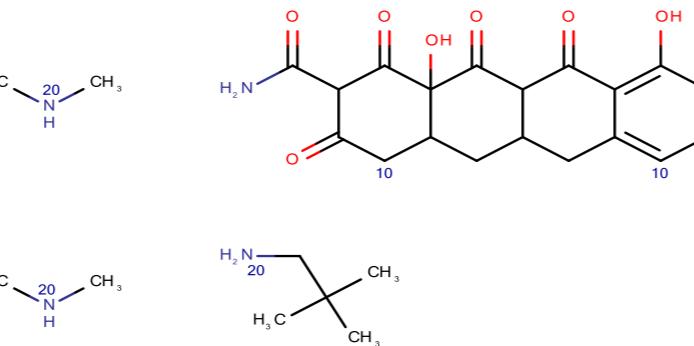
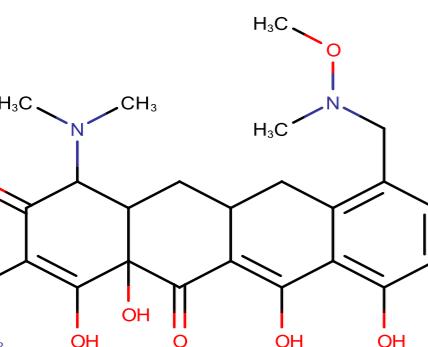
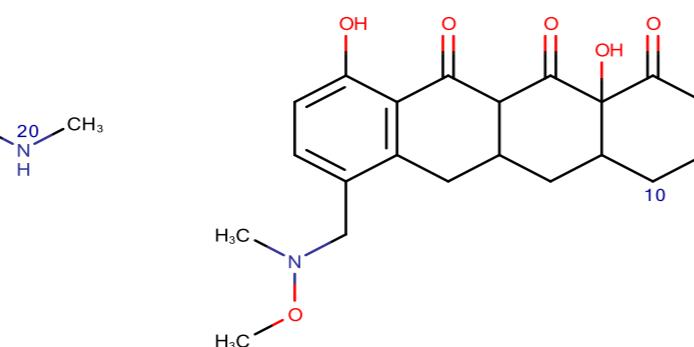
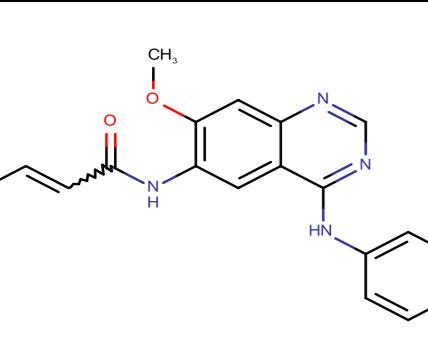
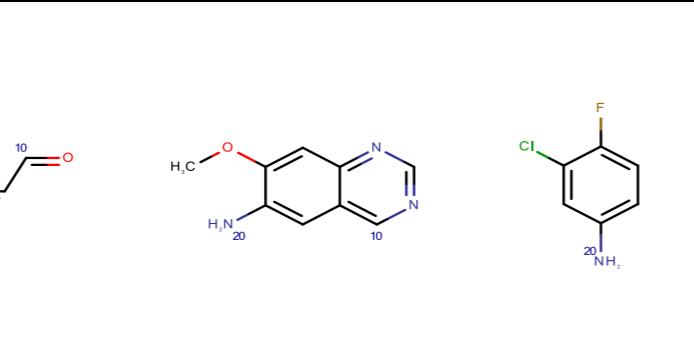
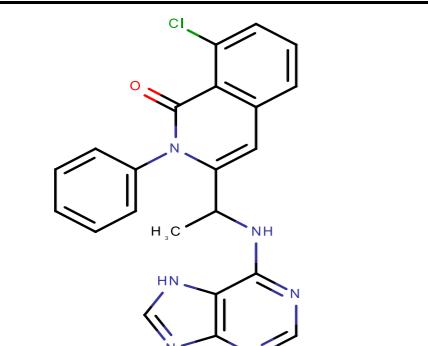
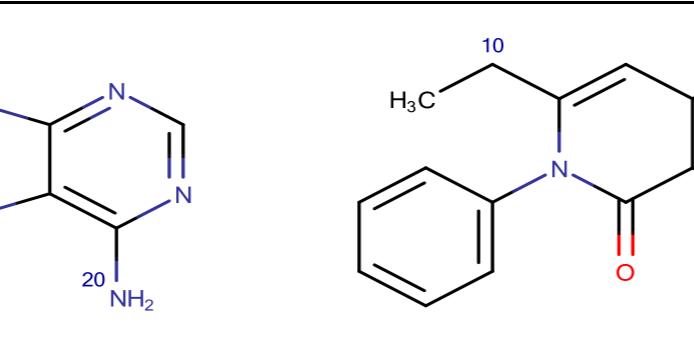
Table S2. SynthI Fragmentation Results

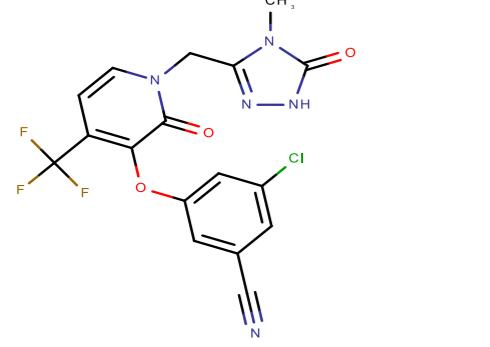
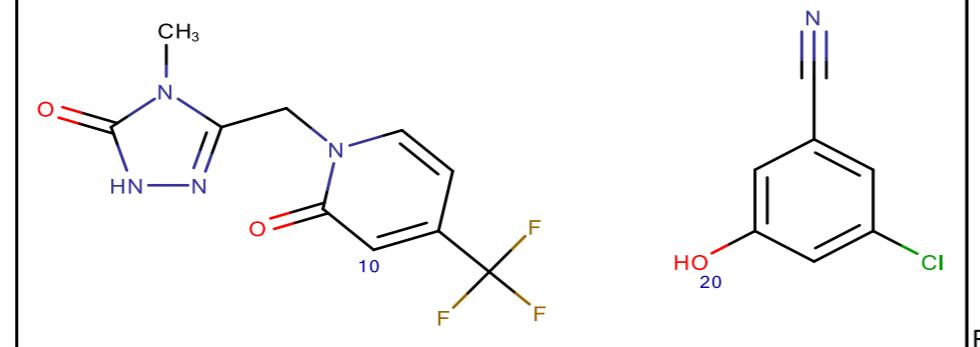
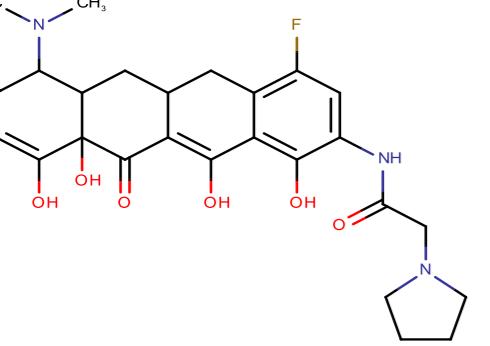
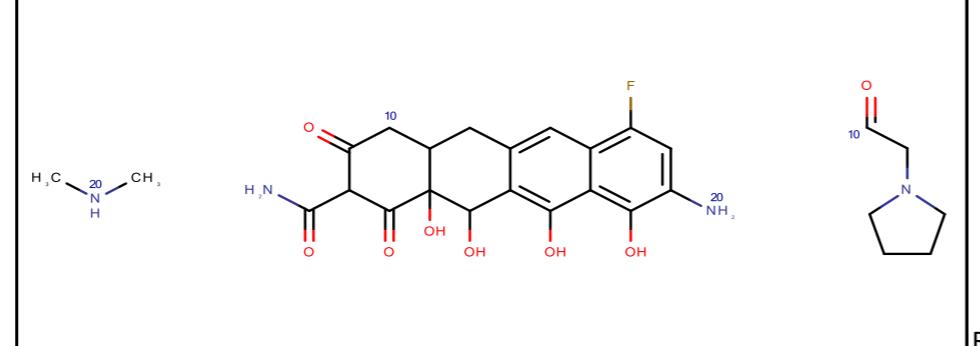
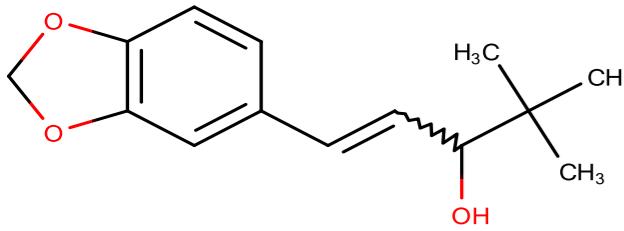
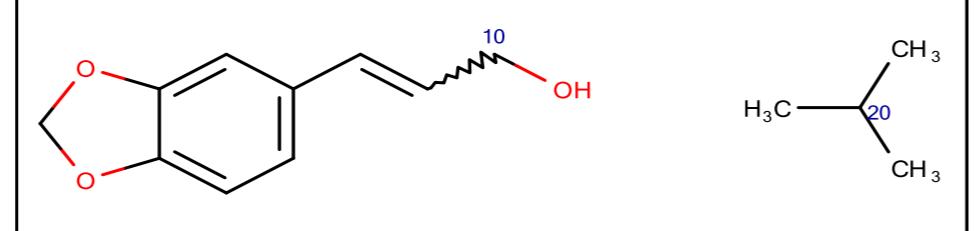
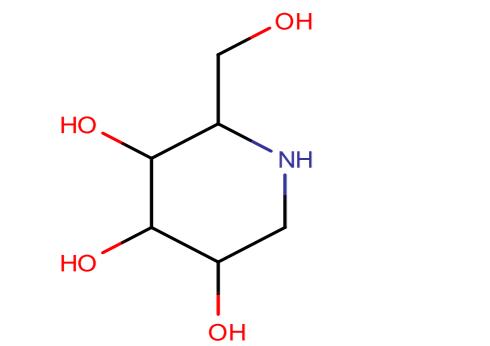
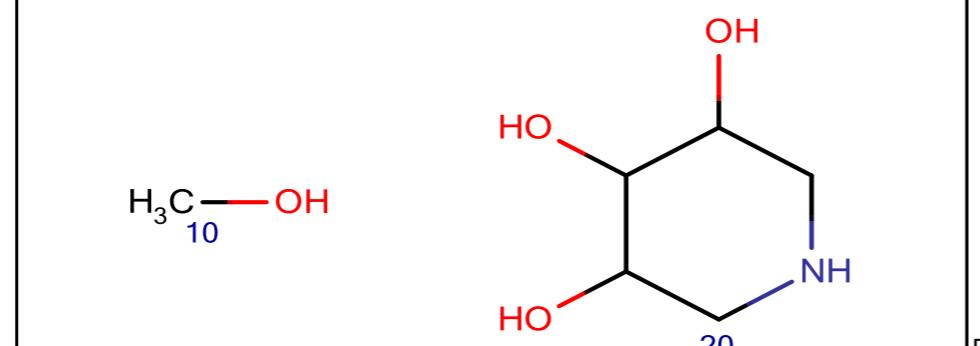
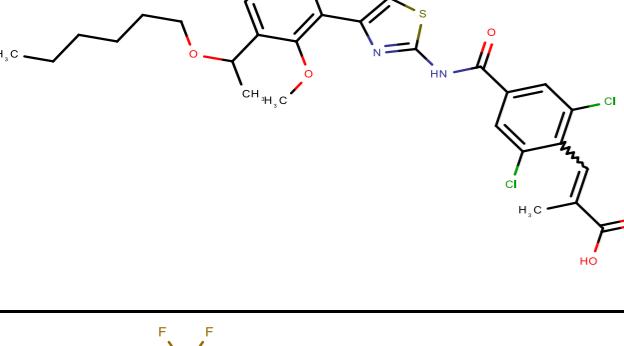
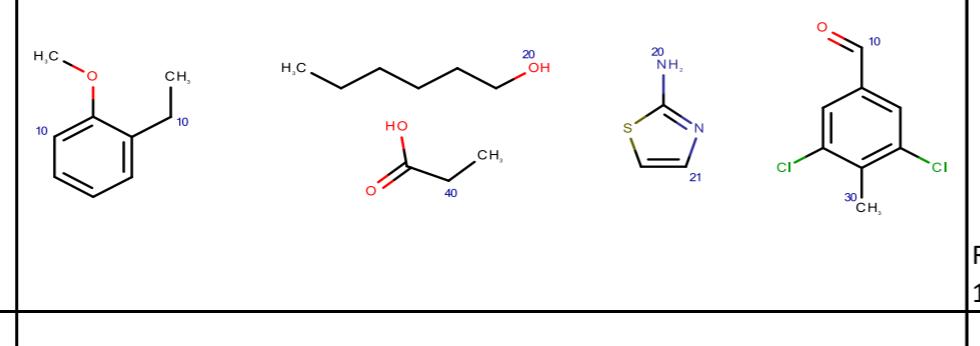
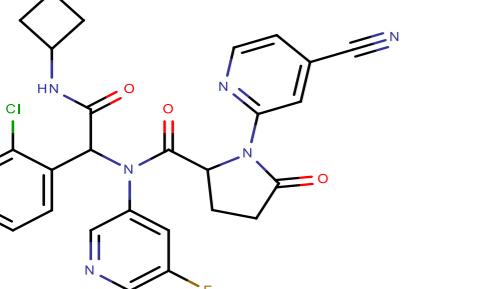
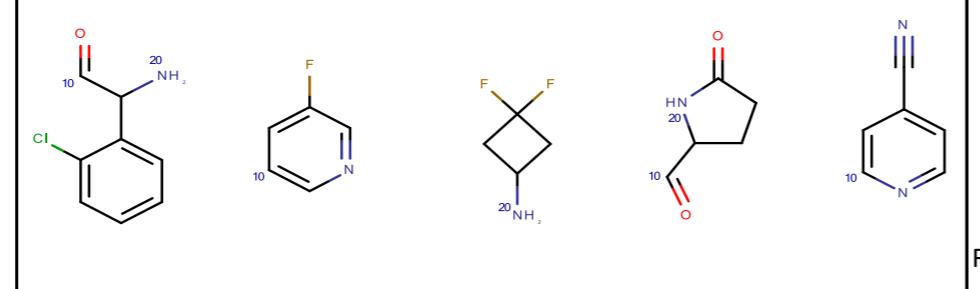
Structure	Drug Name	All Synths	Reactions	Number of Reagents	Availability	Available Synths and respective Bbids	Not available synths
	ubrogepant		R1.1_0 R12.5_0 R 6.1_0	4	0.28	AvailableSynths:FC(F)(F)[CH3:10]>EN300-91258+EN300-19568 c1cc([CH:10]cc1>EN300-120570+EN300-179189+EN300-113070+EN300-7384537+EN300-43675+EN300-7473458+EN300-19360+EN300-19359	NotAvailableSynths:CC1[CH2:20]CC([NH2:20])C(=O)[NH:20]1 O=C1Nc2ncccc2C1Cc1cc([CH:10]=O)cnc1C2
	lemborexant		R1.1_0 R12.5_0 R 4.2_0	4	0.77	AvailableSynths:Fc1ccc[cH:10]c1>EN300-39361+EN300-102338 Cc1nc[cH:10]c(C)n1>EN300-225289 Fc1ccc([NH2:20])nc1>EN300-26452	NotAvailableSynths:O=[CH:10]C1C[CH:20]1C[OH:20]
	voxelotor		R12.1_1 R4.3_0	3	1	AvailableSynths:c1cn[cH:10]c(C[OH:20])c1>EN300-179860+EN300-62117 CC(C)n1ncc[cH:21]1>EN300-1614234 O=Cc1c(O)ccc[cH:21]1>EN300-12602488	
	cenobamate		R2.2_0 R5.1_0	3	0.72	AvailableSynths:Clc1cccc1C([CH3:10])[OH:20]->EN300-43119 N[CH:10]=O->EN300-50197	NotAvailableSynths:c1nn[nH:20]n1
	zanubrutinib		R1.1_0 R12.1_1 R 4.2_0	4	0.49	AvailableSynths:c1c[cH:10]cc[cH:10]1>EN300-71276 c1ccc([OH:20])cc1>EN300-21625+EN300-17610+EN300-7470183+EN300-18348+EN300-19432+EN300-82943+EN300-18679+EN300-7464027 C=C[CH:10]=O->EN300-80741+EN300-123905+EN300-250155+EN300-7110255+EN300-380987+EN300-197151+EN300-17959+EN300-83416+EN300-19865+EN300-20010+EN300-19964+EN300-6764090+EN300-1718841+EN300-39268	NotAvailableSynths:NC(=O)c1c2n(n[cH:21]1)C(C1CC[NH:20]CC1)CCN2

	lasmiditan		R1.1_0 R10.2_0	3	0.74	AvailableSynthons:O=[CH:10]c1cccc([NH2:20])n1->EN300-160104+EN300-751120+EN300-112178 O=[CH:10]c1c(F)cc1F->EN300-67167 NotAvailableSynthons:CN1CC[CH2:20]CC1
	trifarotene		R12.1_0 R12.1_0 R12.6_0 R3.2_0 R4.3_0	6	0.65	AvailableSynthons:O=C(O)c1cc[cH:10]cc1->EN300-18213+EN300-18038+EN300-18256+EN300-19258 C[CH:21](C)C->EN300-101559+EN300-100533 OCC[OH:20]->EN300-98188+EN300-364583+EN300-97513+EN300-198934+EN300-1272986+EN300-8039691+EN300-6492170+EN300-130558 C1CC[NH:20]C1->EN300-18294 NotAvailableSynthons:c1c[cH:21][cH:21]c[cH:21]1 c1c[cH:10][cH:10]c[cH:10]1
	lefamulin		R2.1_0	2	0	AvailableSynthons: NotAvailableSynthons:C=CC1(C)CC([OH:20])C2(C)C(C)CCC3(CC(=O)C32)C(C)C1O NC1CCC(SC[CH:10]=O)C(O)C1
	upadacitinib		R1.4_0 R12.5_0	3	0.3	AvailableSynthons:O=[CH:10]NCC(F)F->EN300-95413 NotAvailableSynthons:CCC1C[NH:20]C[CH2:20]1 c1cc2c(nc3nc[cH:10]n32)[nH]1
	entrectinib		R1.1_0 R12.6_1 R3.1_1 R3.2_0	5	1	AvailableSynthons:c1c[cH:10]cc2c([NH2:20])[nH]nc12->EN300-223999 Fc1cc(F)cc([CH3:21])c1->EN300-763472 CN1CC[NH:20]CC1->EN300-18292 O=[CH:10]c1cc[cH:10]cc1[NH2:20]->EN300-177015+EN300-104066+EN300-99720+EN300-65937+EN300-225297+EN300-19595 C1C[CH2:10]CCO1->EN300-154517+EN300-104914+EN300-43315+EN300-153372+EN300-75453 R1.1_0 R12.6_1 R3.1_1 R3.2_0
	pretomanid		R4.1_0 R4.1_1	3	0.48	AvailableSynthons:F[CH:10](F)F->EN300-136055 c1cc([OH:20])ccc1[CH3:10]->EN300-21091+EN300-18030+EN300-6764090 NotAvailableSynthons:O=[N+]([O-])c1cn2c(n1)OCC([OH:20])C2

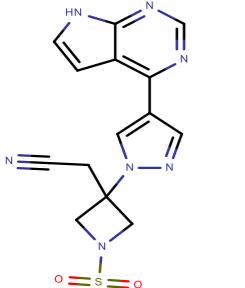
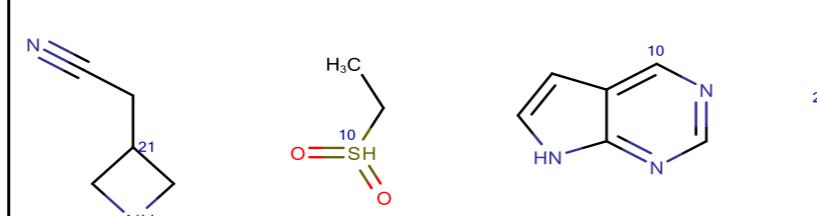
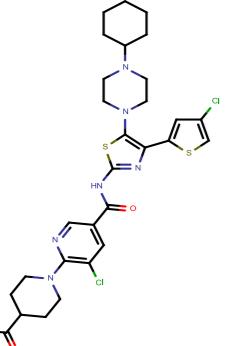
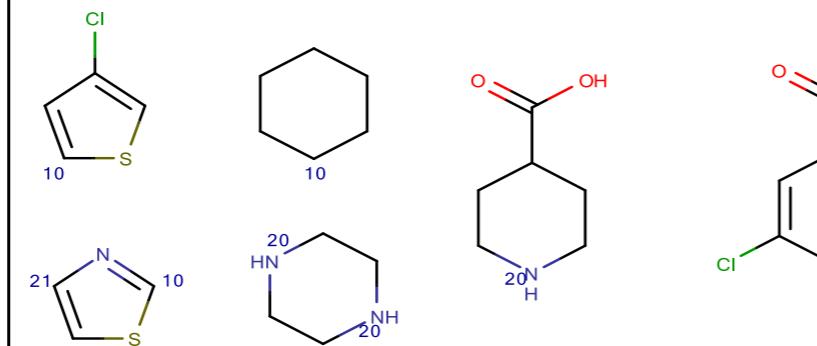
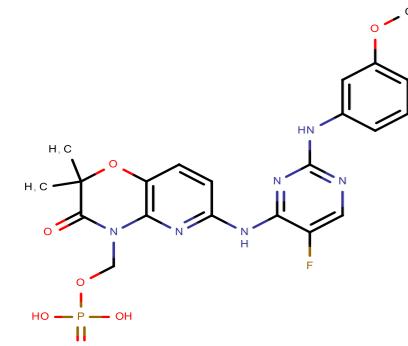
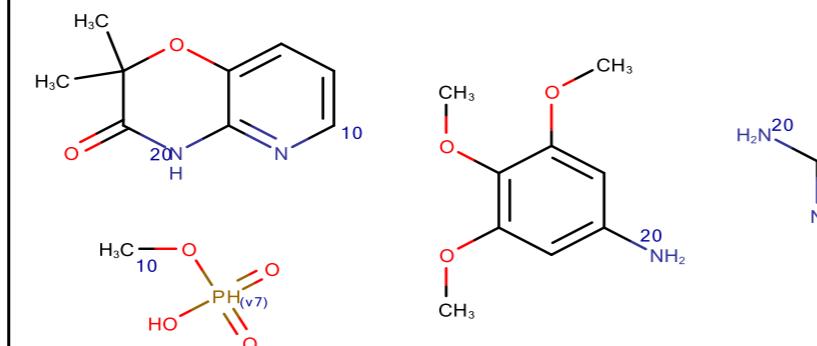
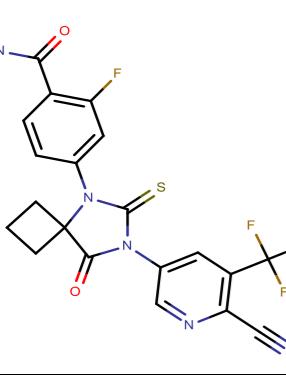
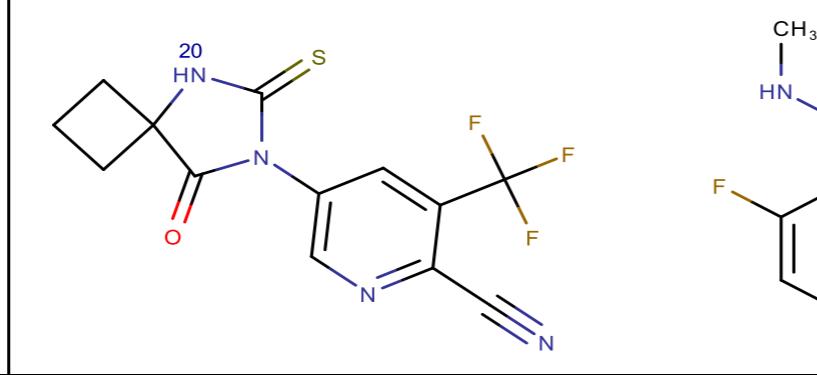
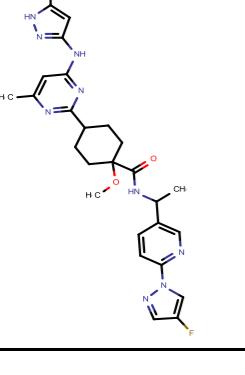
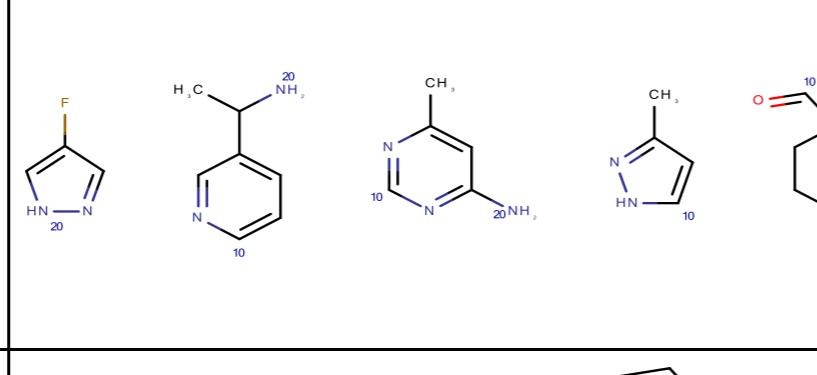
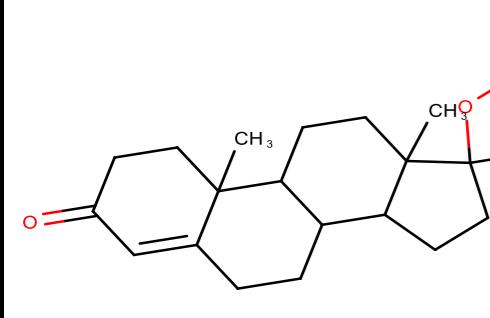
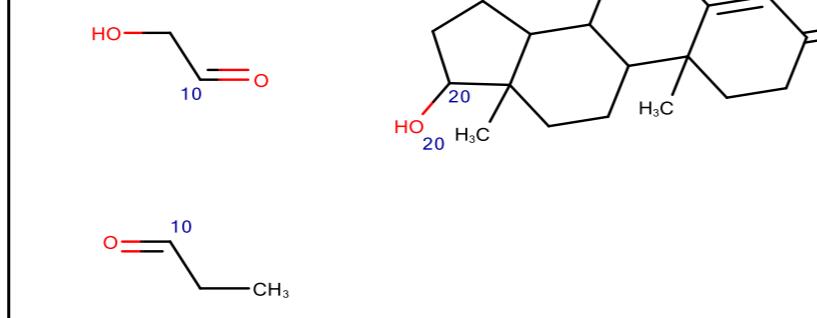
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	brexanolone		R10.2_1	2	0.13	AvailableSynthons:C[CH:10]=O->EN300-7541781+EN300-34564+EN300-244773+EN300-6759265+EN300-384728+EN300-18986+EN300-260567+EN300-26976632+EN300-264228+EN300-264363+EN300-31487+EN300-794414+EN300-21631+EN300-658987+EN300-12893+EN300-300300+EN300-6497752+EN300-172119+EN300-748873+EN300-19521+EN300-651344+EN300-6759566+EN300-1703411+EN300-726546+EN300-103034+EN300-702549+EN300-751121+EN300-7539365+EN300-	NotAvailableSynthons:CC12CCC(O)CC1CCC1C2CCC2(C)C1C[C]H2:20]2
	triclabendazole		R4.2_0	2	0.43	AvailableSynthons:Clc1cccc([OH:20])c1Cl->EN300-20355	NotAvailableSynthons:CSc1nc2c[cH:10]c(Cl)cc2[nH]1
	cefiderocol		R1.1_0 R3.1_0 R3.4_0 R9.1_0	5	0.16	AvailableSynthons:CC(C)(O[NH2:40])C(=O)O->EN300-6732766	NotAvailableSynthons:O=C(c1ccc(O)c(O)c1Cl)[NH2:20] O=C(O)C1=C([CH3:10])CSC2C([NH2:20])C(=O)N12 C1CC[NH+:20][C][CH3:10]C1 Nc1nc([CH2:30])[CH:10]=O)cs1
	istradefylline		R11.1_0	2	0.39	AvailableSynthons:COc1ccc([CH3:30])cc1OC->EN300-16145	NotAvailableSynthons:CCn1c(=O)c2c(nc([CH3:40])n2C)n(CC)c1=O
	fedratinib		R3.1_0 R3.2_0 R3.2_2	4	1	AvailableSynthons:c1cc([NH2:20])ccc1OC[CH3:10]->EN300-74137 Cc1cn[cH:10]n[ch:10]1->EN300-26623624 CC(C)(C)NS(=O)(=O)c1cccc([NH2:20])c1->EN300-11771 C1CC[NH:20]C1->EN300-18294	

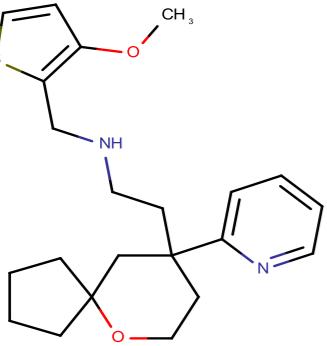
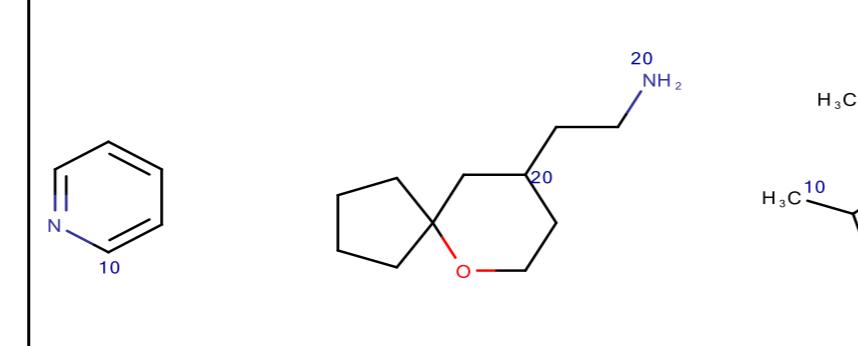
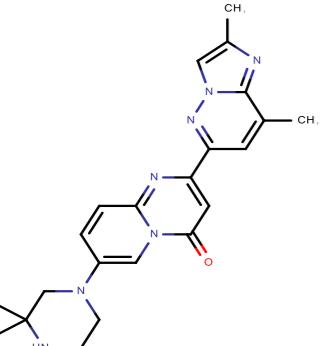
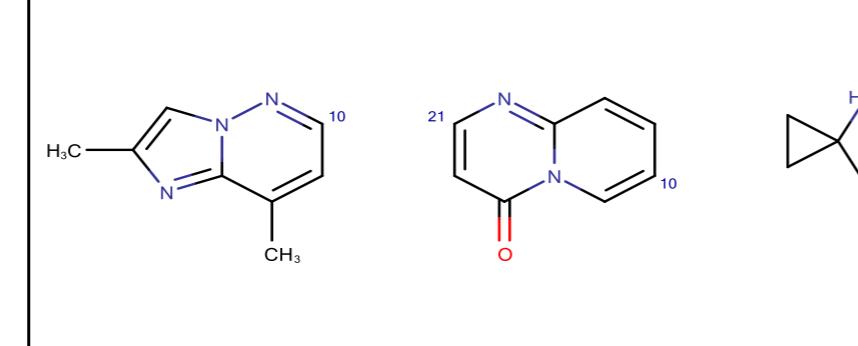
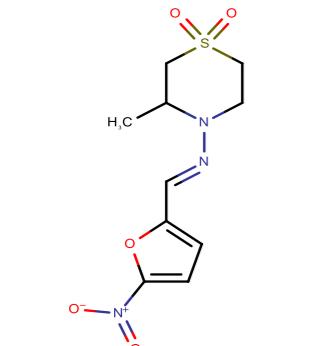
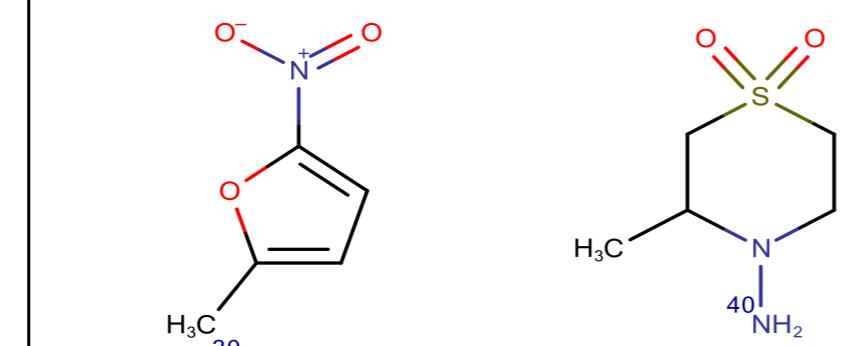
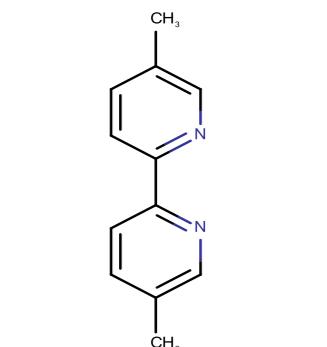
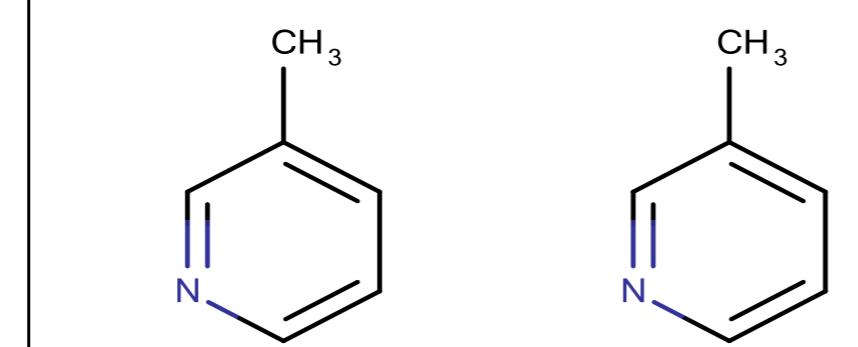
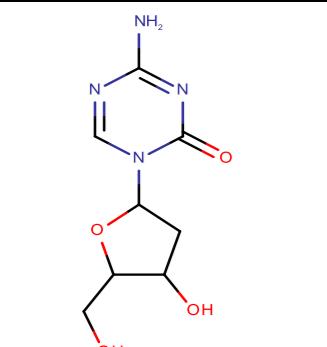
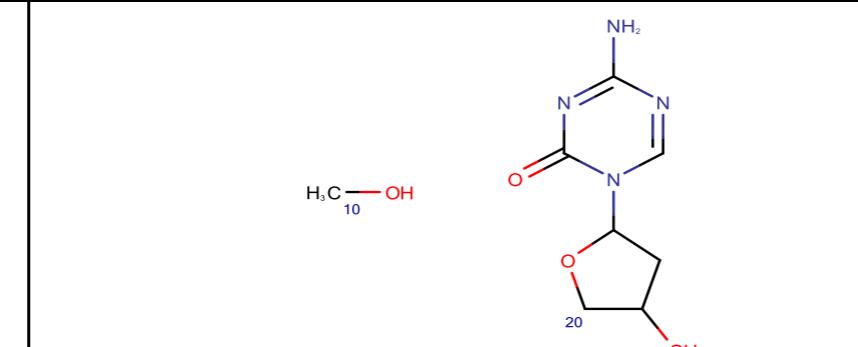
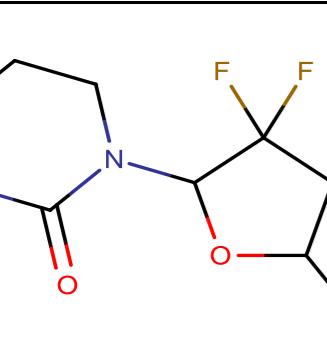
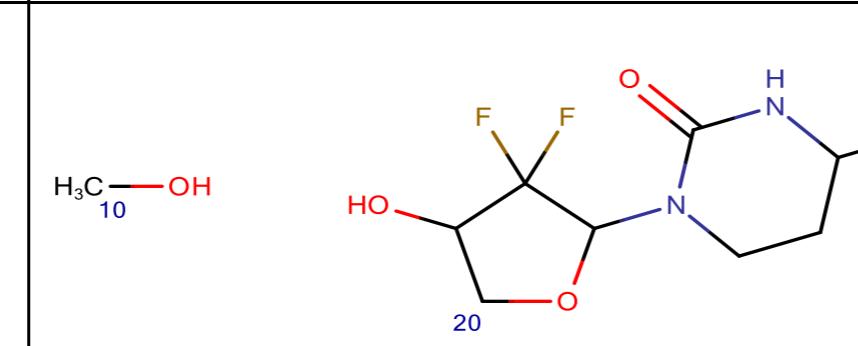
	prucalopride		R1.1_0 R3.1_0	3	0.48	AvailableSynthons:C1C[NH:20]CCC1[NH2:20]->EN300-212	NotAvailableSynthons:Nc1c(Cl)cc([CH:10]=O)c2c1CCO2
	gilteritinib		R3.1_0 R3.2_0 R3.2_2 R3.2_3	5	0.72	AvailableSynthons:OC1cc([NH2:20])cc[cH:10]1->EN300-97045 C1C[NH:20]CC[CH2:10]1->EN300-379533+EN300-16598 C1CC([NH2:20])CCO1->EN300-49115+EN300-43319 CN1CC[NH:20]CC1->EN300-18292	NotAvailableSynthons:CCc1nc(C(N)=O)[cH:10]n[cH:10]1
	larotrectinib		R1.4_0 R3.2_1	3	0.61	AvailableSynthons:Fc1ccc(F)c(C2CCC[NH:20]2)c1->EN300-1605833 OC1CC[NH:20]C1->EN300-69313+EN300-69312+EN300-295515	NotAvailableSynthons:O=[CH:10]Nc1cnn2cc[cH:10]nc12
	glasdegib		R1.4_1	2	0.39	AvailableSynthons:N#Cc1ccc(N[CH:10]=O)cc1->EN300-28749	NotAvailableSynthons:CN1CCC([NH2:20])CC1c1nc2cccc2[nH]1
	refefenacin		R2.2_0 R3.1_1 R3.1_1	4	0.8	AvailableSynthons:NC(=O)C1CC[NH:20]CC1->EN300-1265946+EN300-20201 C[NH:20]C(=O)c1ccc([CH3:10])cc1->EN300-30424 O=[CH:10]Nc1ccccc1-c1ccccc1->EN300-146798	NotAvailableSynthons:C1CN(C[CH3:10])CCC1[OH:20]
	lorlatinib		MR1.1_0 R12.1_1 R4.1_0	3	0.27	AvailableSynthons:Nc1nc[cH:10]cc1[OH:20]->EN300-128364	NotAvailableSynthons:Cn1nc(C[NH:20]C)[cH:21]c1C#N C[C:H2:10]c1cc(F)ccc1[CH:10]=O

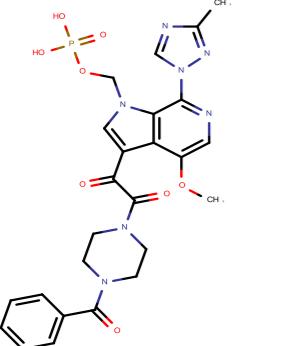
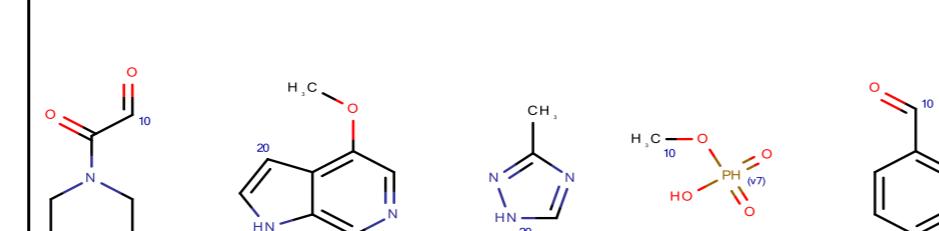
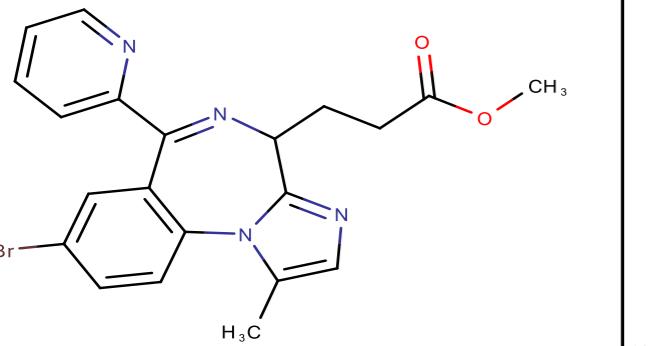
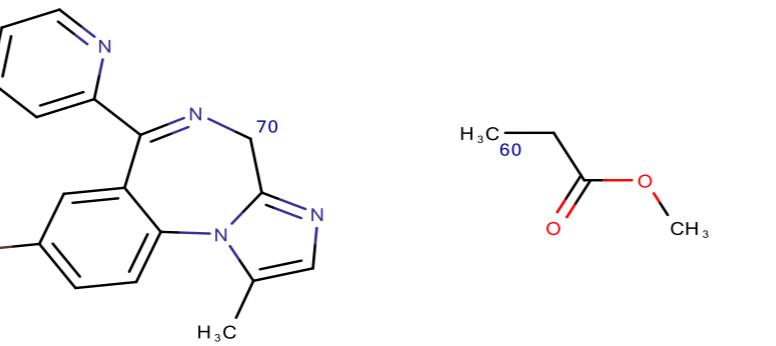
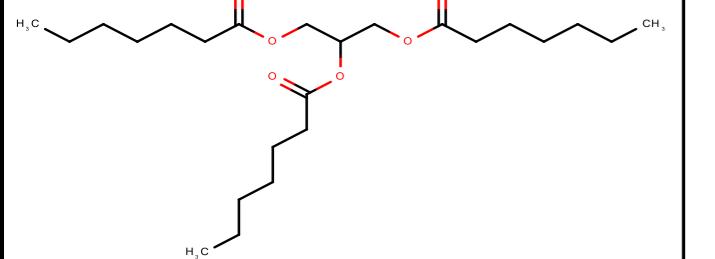
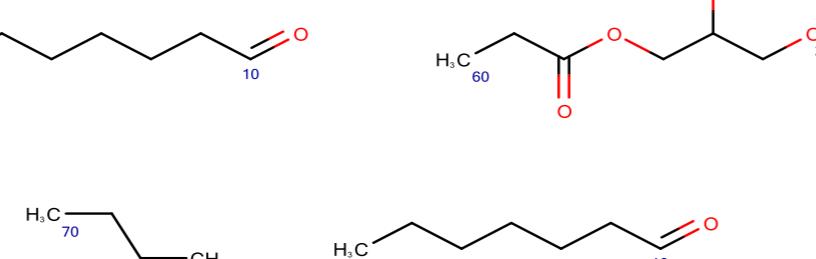
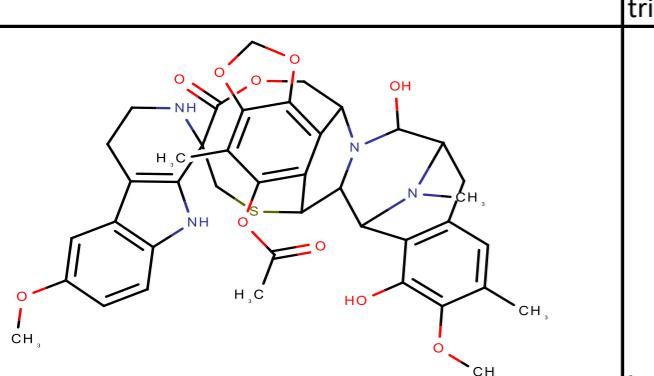
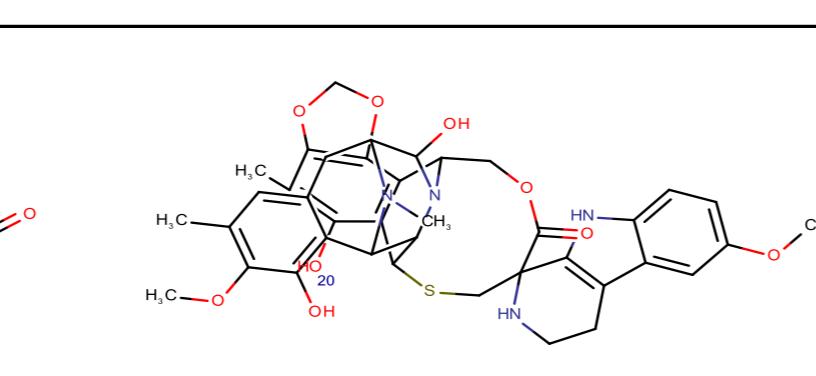
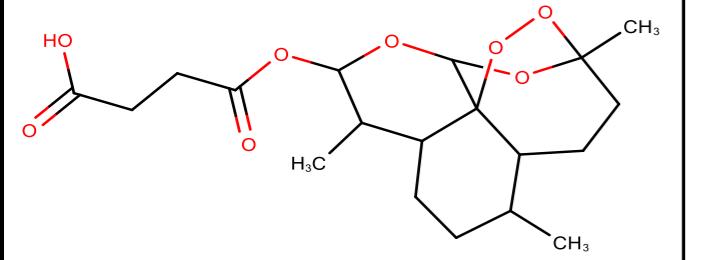
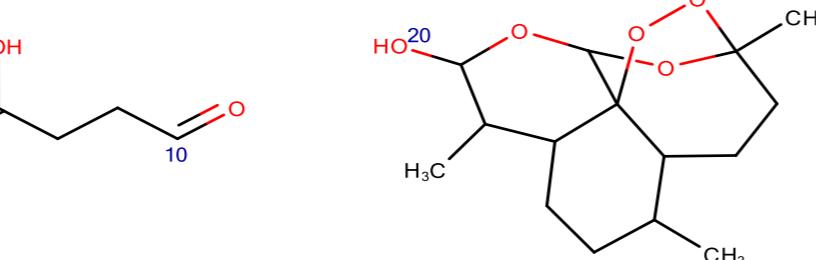
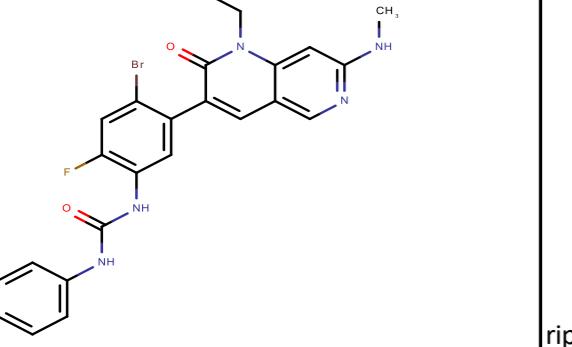
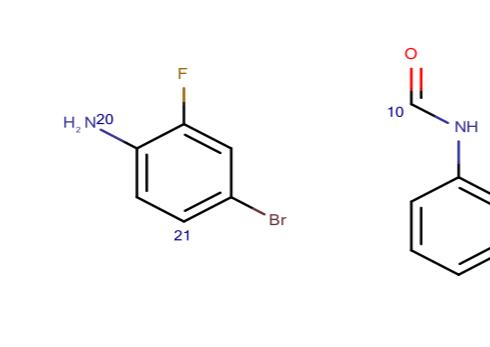
	baloxavir marboxil		R4.1_0	2	0.15	AvailableSynthons:COC(=O)O[CH3:10]>EN300-97928+EN300-6759702	NotAvailableSynthons:O=C1c2c([OH:20])c(=O)ccn2N(C2c3cccc3SCc3c2ccc(F)c3F)C2COCCN12
	talazoparib		R12.5_0	2	0.21	AvailableSynthons:Cn1ncn[cH:10]1>EN300-216044	NotAvailableSynthons:O=c1[nH]nc2c3c(cc(F)cc1)NC(c1ccc(F)cc1)[CH2:20]2
	omadacycline		R3.1_1 R3.1_2 R3.2_0	4	0.3	AvailableSynthons:C[NH:20]C>EN300-30979+EN300-30964 CC(C)(C)C[NH2:20]>EN300-52478	NotAvailableSynthons:NC(=O)C1C(=O)C2(O)C(=O)C3C(=O)c4c(O)c([CH3:10])c[cH:10]c4CC3CC2[CH2:10]C1=O
	sarecycline		R3.1_2	2	0.09	AvailableSynthons:C[NH:20]C>EN300-30979+EN300-30964	NotAvailableSynthons:CON(C)Cc1ccc(O)c2c1CC1CC3C(O)(C(=O)C(C(N)=O)C(=O)[CH2:10]3)C(=O)C1C2=O
	dacomitinib		R1.1_0 R3.1_0 R3.2_0	4	0.42	AvailableSynthons:O=[CH:10]C=C[CH3:10]>EN300-724809+EN300-258559+EN300-6740406 Fc1ccc([NH2:20])cc1Cl->EN300-20338	NotAvailableSynthons:C1CC[NH:20]CC1 COc1cc2ncn[cH:10]c2cc1[NH2:20]
	duvelisib		R3.1_0	2	0.33	AvailableSynthons:c1nc([NH2:20])c2[nH]cnc2n1>EN300-21472	NotAvailableSynthons:C[CH2:10]c1cc2cccc(Cl)c2c(=O)n1c1ccccc1

	doravirine		R4.2_0	2	0.34	AvailableSynthons:N#Cc1cc(Cl)cc([OH:20])c1->EN300-192870	NotAvailableSynthons:Cn1c(Cn2ccc(C(F)(F)[cH:10]c2=O)n[nH]c1=O
	eravacycline		R1.1_0 R3.1_2	3	0.28	AvailableSynthons:C[NH:20]C->EN300-30979+EN300-30964 O=[CH:10]CN1CCCC1->EN300-41375+EN300-43448	NotAvailableSynthons:NC(=O)C1C(=O)C2(O)C(O)c3c(cc4c(F)cc([NH2:20])c(O)c4c3O)CC2[CH2:10]C1=O
	stiripentol		R10.1_0	2	0.76	AvailableSynthons:O[CH2:10]C=Cc1ccc2c(c1)OCO2->EN300-1703969	NotAvailableSynthons:C[CH:20](C)C
	migalastat		R10.1_0	2	0	AvailableSynthons:	NotAvailableSynthons:OC1CN[CH2:20]C(O)C1O O[CH3:10]
	lusutrombopag		R1.1_0 R11.1_0 R12.1_0 R4.1_1	5	0.18	AvailableSynthons:CCCCC[OH:20]->EN300-19338	NotAvailableSynthons:OC1c(([CH2:10]C)ccc[cH:10]1 C[CH2:40]C(=O)O c1sc(([NH2:20])n[cH:21]1 O=[CH:10]c1cc(Cl)c([CH3:30])c(Cl)c1
	ivosidenib		R1.1_0 R1.1_0 R3.2_0 R6.3_0	5	1	AvailableSynthons:O=[CH:10]C(c1ccccc1Cl)[NH2:20]->EN300-306120+EN300-96012+EN300-1556164+EN300-185599 Fc1nc([cH:10]c1->EN300-52981 FC1(F)CC([NH2:20])C1->EN300-78062 O=C1CCC([CH:10]=O)[NH:20]1->EN300-1081938+EN300-185979 N#Cc1ccn[cH:10]c1->EN300-126966+EN300-1263166	

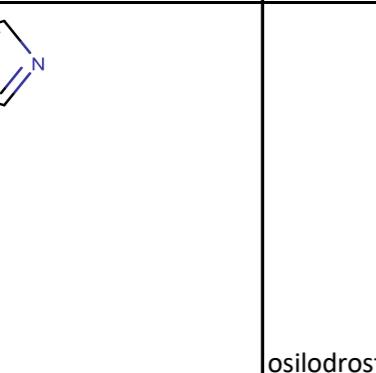
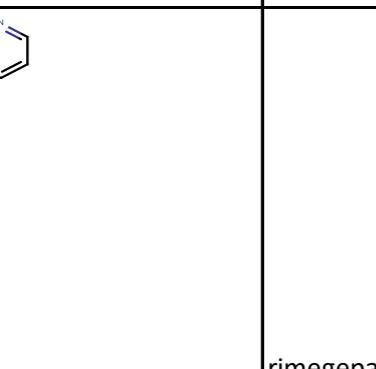
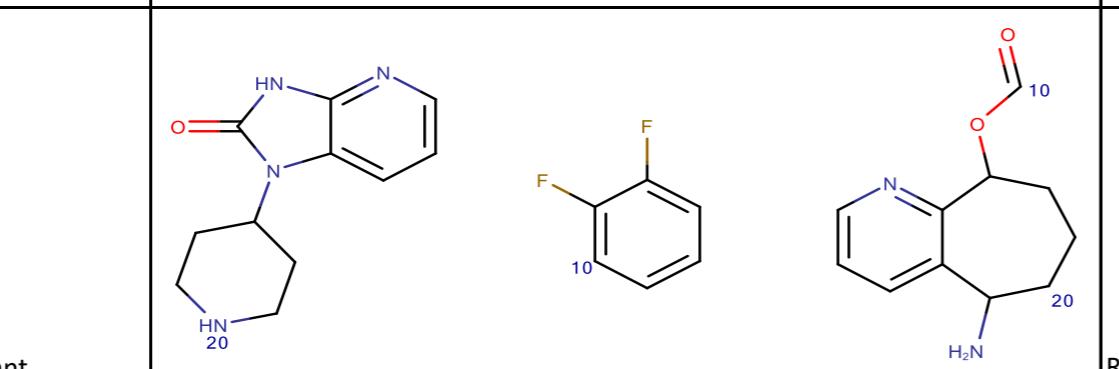
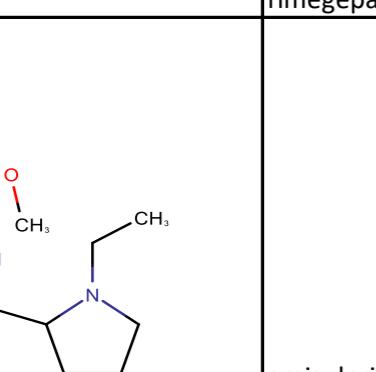
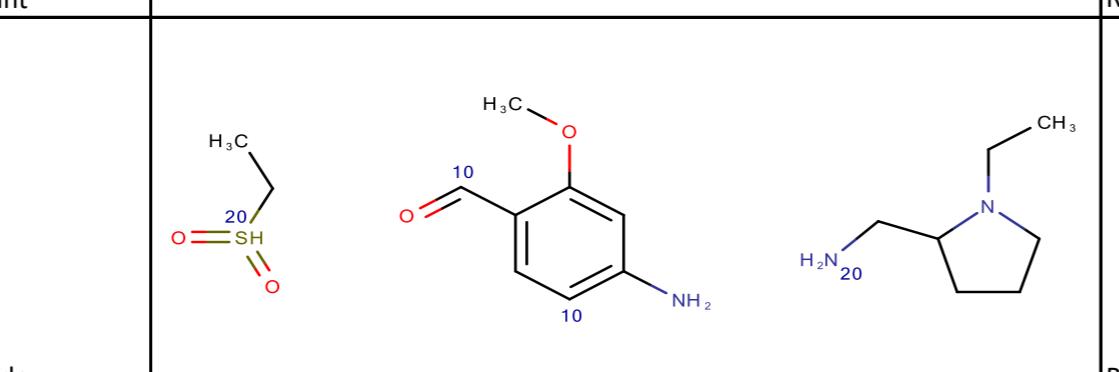
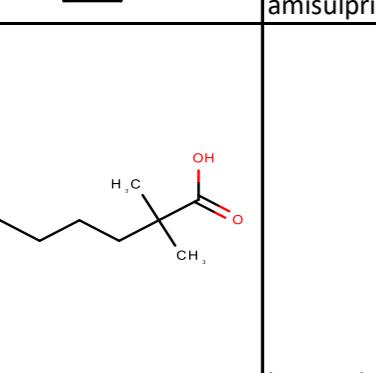
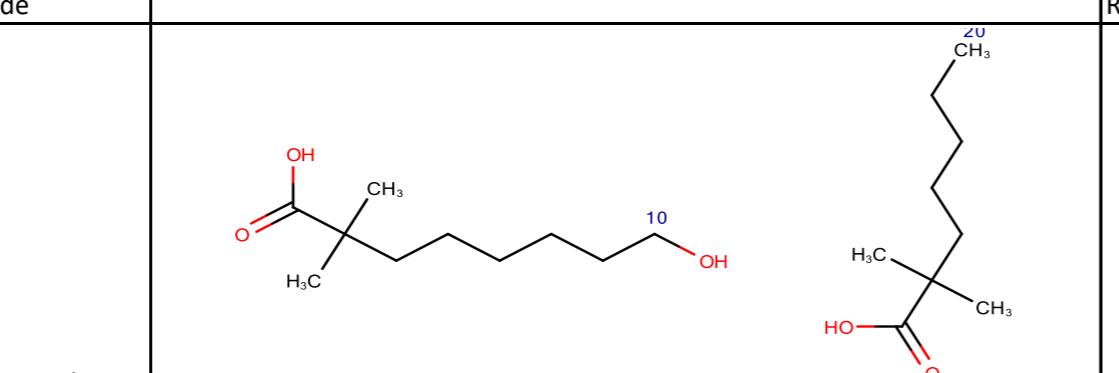
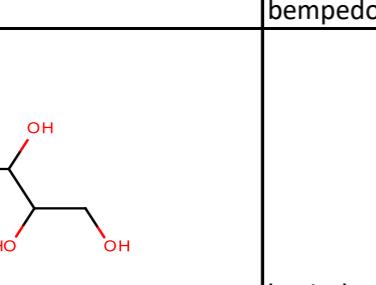
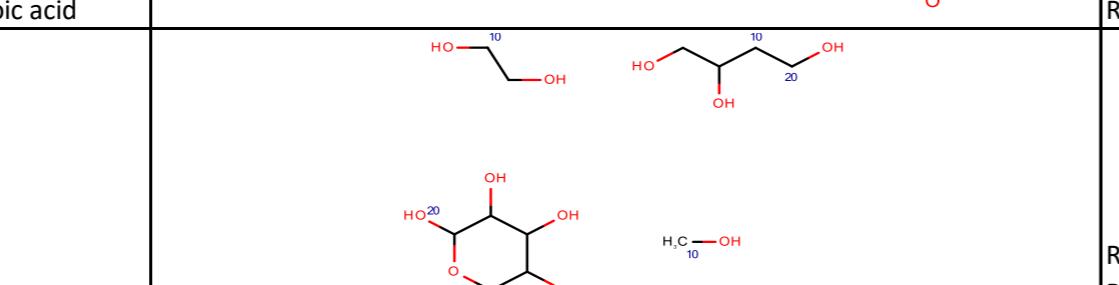
	tecovirimat		R1.2_0	2	0.44	AvailableSynthons:O=[CH:10]c1ccc(C(F)(F)F)cc1->EN300-17345+EN300-174756+EN300-21277+EN300-28647	NotAvailableSynthons:Oc1c2c(c(O)n1[NH2:20])C1C=CC2C2CC12
	encorafenib		R1.3_0 R12.1_1 R12.1_1 R3.2_0 R8.1_0	6	0.53	AvailableSynthons:C[SH:10](=O)=O->EN300-35716+EN300-227474+EN300-196868 CC(C[NH2:20])[NH2:20]->EN300-19622+EN300-1705799+EN300-178642+EN300-1703310+EN300-194309+EN300-6492099+EN300-59954+EN300-209541 c1c[cH:10]n[cH:10]n1->EN300-99945+EN300-1609154+EN300-194531+EN300-136206 CO[CH:10]=O->EN300-127538	NotAvailableSynthons:Fc1c([NH2:20])cc(Cl)c[cH:10]1 CC(C)n1c[cH:21][cH:21]n1
	binimetinib		R1.2_0 R3.2_0	3	0.52	AvailableSynthons:Fc1cc(Br)ccc1[NH2:20]->EN300-19932 OC(O)[NH2:20]->EN300-132618	NotAvailableSynthons:Cn1cnc2c(F)[cH:10]c([CH:10]=O)cc21
	plazomicin		R1.1_0 R3.1_2 R4.1_0	5	0.27	AvailableSynthons:OCC[NH2:20]->EN300-19392 NCC(O)[CH:10]=O->EN300-86223+EN300-1589650	NotAvailableSynthons:CNC1C(O)[CH2:10]OCC1(C)O NC1C=C([CH3:10])O[CH2:10]1 NC1CC([NH2:20])C([OH:20])C(O)C1[OH:20]
	cannabidiol		R12.5_0 R12.5_0	3	0.22	AvailableSynthons:CCCC[CH3:20]->EN300-19416	NotAvailableSynthons:Oc1c[cH:10]cc(O)[cH:10]1 CC(=C)C1CCC(C)=C[CH2:20]1
	moxidectin		MR2.1_0 R11.1_0 R11.1_1 R11.1_6	4	0.09	AvailableSynthons:CC(C)[CH3:30]->EN300-19563	NotAvailableSynthons:CC1C=C([CH:10]=O)C2(O)C(=C[CH3:40])COC2C1O CON=C1CC2(CC([OH:20])CC(C[CH3:40])O2)OC([CH2:40]C)C1C CC(C[CH2:30])C[CH3:30]

	baricitinib		R12.1_0 R5.2_0 R 8.1_0	4	0.73	AvailableSynthons:CC[SH:10](=O)=O->EN300-20630+EN300-53132 c1nc2[nH]ccc2[cH:10]n1->EN300-56508+EN300-6472184 c1n[nH:20]c[cH:21]1->EN300-92082+EN300-8082535+EN300-107801	NotAvailableSynthons:N#CC[CH:21]1C[NH:20]C1
	avatrombopag		R12.1_0 R3.1_0 R 3.2_0 R3.2_0 R3. 2_0	6	0.88	AvailableSynthons:Clc1cs[cH:10]c1->EN300-100283 C1C[NH:20]CC[NH:20]1->EN300-25694+EN300-749027+EN300-82962+EN300-260557+EN300-33920+EN300-50326+EN300-20101+EN300-114743 O=C(O)C1CC[NH:20]CC1->EN300-19594+EN300-66308+EN300-19517+EN300-111045+EN300-21425 O=C(c1cn[cH:10]c(Cl)c1)[NH2:20]->EN300-44287 C1CC[CH2:10]CC1->EN300-19567+EN300-19881+EN300-19310+EN300-19882	NotAvailableSynthons:n1[cH:10]s[cH:10][cH:21]1
	fostamatinib		R3.2_0 R3.2_1 R6 .1_0	4	0.53	AvailableSynthons:COc1cc([NH2:20])cc(OC)c1OC->EN300-18969 Fc1cn[cH:10]nc1[NH2:20]->EN300-220193	NotAvailableSynthons:O=[PH](=O)(O)O[CH3:10] CC1(C)Oc2cc[cH:10]nc2[NH:20]C1=O
	apalutamide		R3.2_0	2	0	AvailableSynthons:	NotAvailableSynthons:N#Cc1cc(N2C(=O)C3(CC3)[NH:20]C2=S)cc1C(F)(F)F CNC(=O)c1cc[cH:10]cc1F
	pralsetinib		R1.1_0 R12.5_0 R 3.2_1 R5.3_0	5	0.74	AvailableSynthons:Fc1cn[nH:20]c1->EN300-125422 CC(c1cc[cH:10]nc1)[NH2:20]->EN300-175268 Cc1cc([NH2:20])n[cH:10]n1->EN300-106183 Cc1c[cH:10]n1->EN300-233069	NotAvailableSynthons:COCl([CH:10]=O)CC[CH2:20]CC1
	clascoterone		R10.2_0 R2.1_0	3	0.28	AvailableSynthons:O=[CH:10]CO->EN300-42326+EN300-4632364+EN300-6476929+EN300-42539+EN300-19242+EN300-5058907+EN300-42324+EN300-5058906+EN300-103882+EN300-70749 CC[CH:10]=O->EN300-70278+EN300-175639+EN300-6494396+EN300-19539+EN300-1272986+EN300-6475364+EN300-19540+EN300-16126+EN300-206285+EN300-7460569+EN300-7655326	NotAvailableSynthons:CC12CCC(=O)C=C1CCC1C2CCC2(C)C1CC[CH:20]2[OH:20]

	oliceridine		R12.5_0 R3.1_0	3	0.52	AvailableSynthons:c1cc[cH:10]nc1->EN300-88338+EN300-18341+EN300-18089 COc1ccsc1[CH3:10]->EN300-110080	NotAvailableSynthons:C1CCC2(C1)C[CH:20](CC[NH2:20])CCO2
	risdiplam		R12.1_0 R3.2_0	3	0.63	AvailableSynthons:Cc1cn2n[cH:10]cc(C)c2n1->EN300-6739691+EN300-6759480 C1C[NH:20]CC2(CC2)N1->EN300-316657	NotAvailableSynthons:O=c1c[cH:21]nc2cc[cH:10]cn12
	nifurtimox		R9.1_0	2	0.47	AvailableSynthons:O=[N+]([O-])c1ccc([CH3:30])o1->EN300-35243	NotAvailableSynthons:CC1CS(=O)(=O)CCN1[NH2:40]
	abametapir		R12.1_0	2	1	AvailableSynthons:Cc1cc[cH:10]nc1->EN300-27031+EN300-73429+EN300-7456409 Cc1cc[cH:21]nc1->EN300-268430	
	decitabine		R10.1_0	2	0	AvailableSynthons:	NotAvailableSynthons:Nc1ncn(C2CC(O)[CH2:20]O2)c(=O)n1 O[CH3:10]
	cedazuridine		R10.1_0	2	0	AvailableSynthons:	NotAvailableSynthons:O=C1NC(O)CCN1C1O[CH2:20]C(O)C1(F)F O[CH3:10]

	fostemsavir		R1.1_1 R10.2_0 R 5.1_0 R5.2_0	5	0.59	AvailableSynthons:O=C(N1CC[NH:20]CC1)[CH:10]=O->EN300-79658+EN300-251835 Cc1nc[nH:20]n1->EN300-59689 O=[CH:10]c1ccccc1->EN300-16131+EN300-19688+EN300-19689+EN300-317668+EN300-7447932+EN300-15500+EN300-18007	NotAvailableSynthons:O=[PH](=O)(O)O[CH3:10] OCoc1cn[cH:21]c2c1[cH:20]c[nH:20]2
	remimazolam		R13.2_0	2	0.21	AvailableSynthons:COC(=O)C[CH3:60]->EN300-20010	NotAvailableSynthons:Cc1nc2n1-c1cc(Br)cc1C(c1cccn1)=N[CH2:70]2
	triheptanoin		R13.2_0 R2.1_0 R 2.1_0	4	0.67	AvailableSynthons:CCCCC[CH:10]=O->EN300-19601+EN300-19602 CCC[CH3:70]->EN300-1253016	NotAvailableSynthons:O=C(C[CH3:60])OCC(C[OH:20])[OH:20]
	lurbinectedin		R2.1_0	2	0.05	AvailableSynthons:C[CH:10]=O->EN300-7541781+EN300-34564+EN300-244773+EN300-6759265+EN300-384728+EN300-18986+EN300-260567+EN300-26976632+EN300-264228+EN300-264363+EN300-31487+EN300-794414+EN300-21631+EN300-658987+EN300-12893+EN300-300300+EN300-6497752+EN300-172119+EN300-748873+EN300-19521+EN300-651344+EN300-6759566+EN300-1703411+EN300-726546+EN300-103034+EN300-702549+EN300-751121+EN300-7539365+EN300-	NotAvailableSynthons:OC1ccc2[nH]c3c(c2c1)CCNC31CSC2c3c(c4c(c(C)c3[OH:20])OCO4)C(COC1=O)N1C(O)C3Cc4cc(C)c(OC)c(O)c4C(C21)N3C
	artesunate		R2.1_0	2	1	AvailableSynthons:O=C(O)CC[CH:10]=O->EN300-114582+EN300-24949+EN300-17161 CC1CCC2C(C)C([OH:20])OC3OC4(C)CCC1C32OO4->EN300-746891	
	ripretinib		R1.4_1 R12.1_0	3	0.27	AvailableSynthons:O=[CH:10]Nc1ccccc1->EN300-21290	NotAvailableSynthons:CCn1c(=O)[cH:10]cc2cnc(NC)cc21 Fc1cc(Br)[cH:21]cc1[NH2:20]

	selpercatinib		R12.1_1 R3.1_0 R 3.2_0 R4.1_0	5	0.69	AvailableSynthons:c1c[cH:10]nc[cH:10]1->EN300-105367+EN300-88738+EN300-100882+EN300-27448 C1C2C[NH:20]CC1[NH:20]2->EN300-190611 CC(C)(O)[CH3:10]->EN300-113587+EN300-36458+EN300-114887+EN300-93821 COc1ccc([CH3:10])cn1->EN300-91610+EN300-88128	NotAvailableSynthons:N#Cc1cnn2cc([OH:20])c[cH:21]c12
	capmatinib		R12.1_0 R12.5_0	3	0.32	AvailableSynthons:c1cnc2cc[cH:10]cc2c1->EN300-73850+EN300-51894	NotAvailableSynthons:c1nc2nc[cH:21]nn2c1[CH3:20] CNC(=O)c1cc[cH:10]cc1F
	opicapone		R12.1_0 R12.1_1	3	0	AvailableSynthons:	NotAvailableSynthons:Cc1c(Cl)c(C)[cH:10]c(Cl)[n+]1[O-] O=[N+](O-)c1c[cH:21]cc(O)c1O n1o[cH:10]n[cH:21]1
	pemigatinib		R3.1_0	2	0.17	AvailableSynthons:C1C[NH:20]CCO1->EN300-31893+EN300-30242+EN300-1709926+EN300-18064	NotAvailableSynthons:CCN1C(=O)N(c2c(F)c(OC)cc(OC)c2F)Cc2cnc3[nH]c([CH3:10])cc3c21
	tucatinib		R3.2_0 R3.2_2 R4 .2_1	4	0.53	AvailableSynthons:Cc1c[cH:10]ccc1[OH:20]->EN300-18140+EN300-152647 c1nc([NH2:20])c2c[cH:10]ccc2n1->EN300-51562	NotAvailableSynthons:c1nc2c[cH:10]ccn2n1 CC1(C)COC([NH2:20])=N1
	selumetinib		R1.2_0 R3.2_0	3	0.52	AvailableSynthons:Clc1cc(Br)ccc1[NH2:20]->EN300-20801 OC(O)[NH2:20]->EN300-132618	NotAvailableSynthons:Cn1cnc2c(F)[cH:10]c([CH:10]=O)cc21

	ozanimod			R12.1_0 R12.1_0 R3.1_0 R4.2_0	5	0.83	AvailableSynthons:c1cc2c([cH:10]c1)CC[CH2:10]2->EN300-6778226+EN300-53860+EN300-6774838 N#Cc1c[cH:10]cc[cH:10]1->EN300-244685+EN300-219973+EN300-81406 CC(C)[OH:20]->EN300-220268+EN300-395554+EN300-6487160+EN300-6733882+EN300-226213+EN300-63837+EN300-122900+EN300-135320+EN300-1697144+EN300-7440385+EN300-136738+EN300-7538370+EN300-267353+EN300-6745781+EN300-1718171+EN300-232925+EN300-88779+EN300-380987+EN300-	NotAvailableSynthons:n1o[cH:21]n[cH:21]1
	osilodrostat							
	rimegepant			R1.3_0 R12.5_0	3	0.21	AvailableSynthons:Fc1ccc[cH:10]c1F->EN300-121005	NotAvailableSynthons:O=c1[nH]c2ncccc2n1C1CC[NH:20]C C1 NC1c2cccn2C(O[CH:10]=O)CC[CH2:20]1
	amisulpride			R1.1_0 R7.3_0	3	0.36	AvailableSynthons:CCN1CCCC1C[NH2:20]->EN300-21034	NotAvailableSynthons:COc1cc(N)[cH:10]cc1[CH:10]=O CC(SH:20)(=O)=O
	bemepedoic acid			R10.1_0	2	0	AvailableSynthons:	NotAvailableSynthons:CC(C)(CCCC[CH3:20])C(=O)O CC(C)(CCCCC[CH2:10]O)C(=O)O
	lactitol			R10.1_0 R10.1_2 R4.1_0	4	0	AvailableSynthons:	NotAvailableSynthons:O[CH3:10] OC1C(O)C(O)[CH2:20]OC1[OH:20] OC[CH2:10]O OCC(O)[CH2:10][CH2:20]O

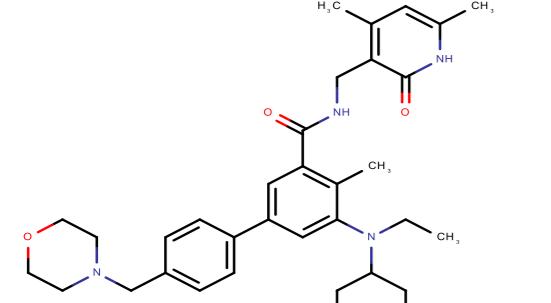
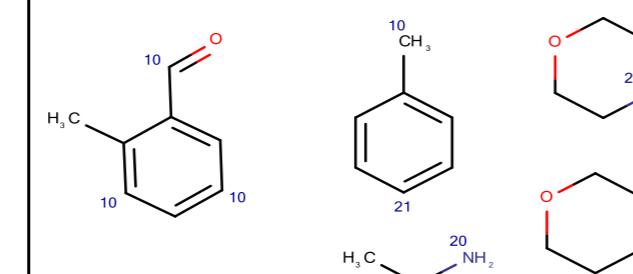
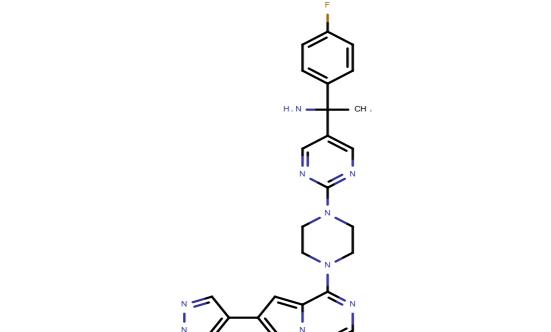
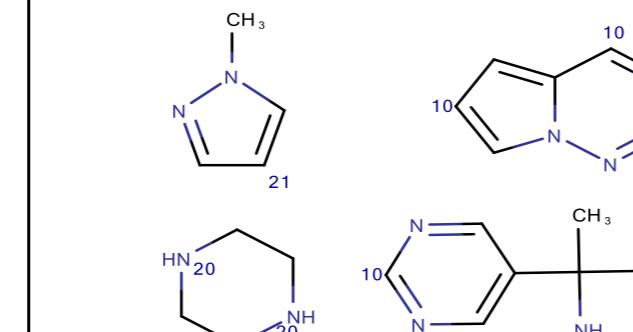
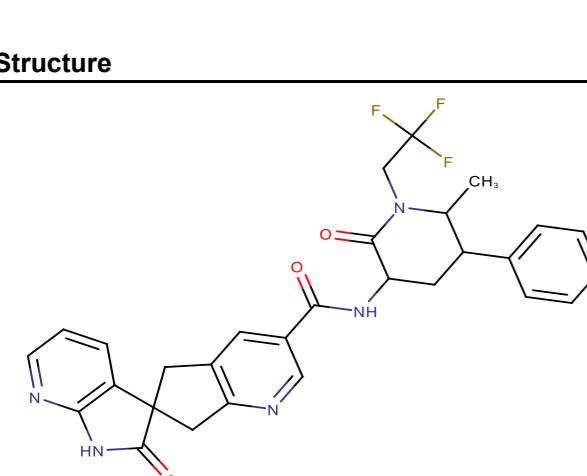
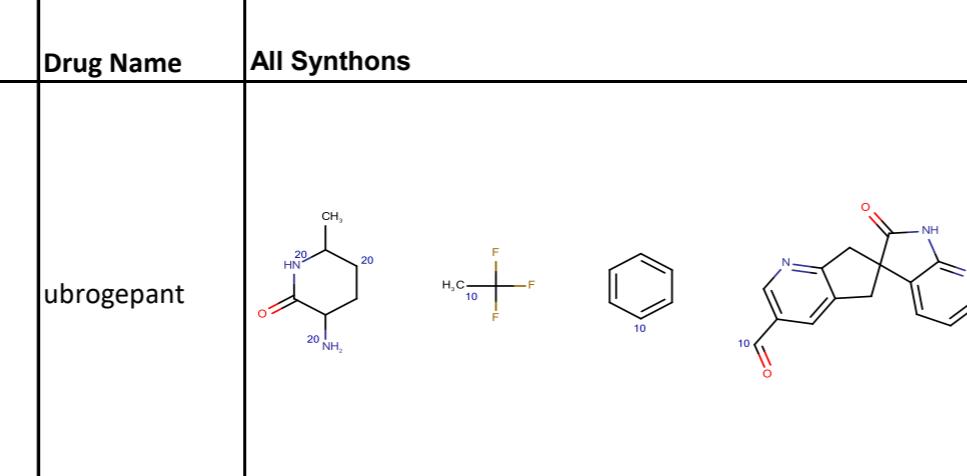
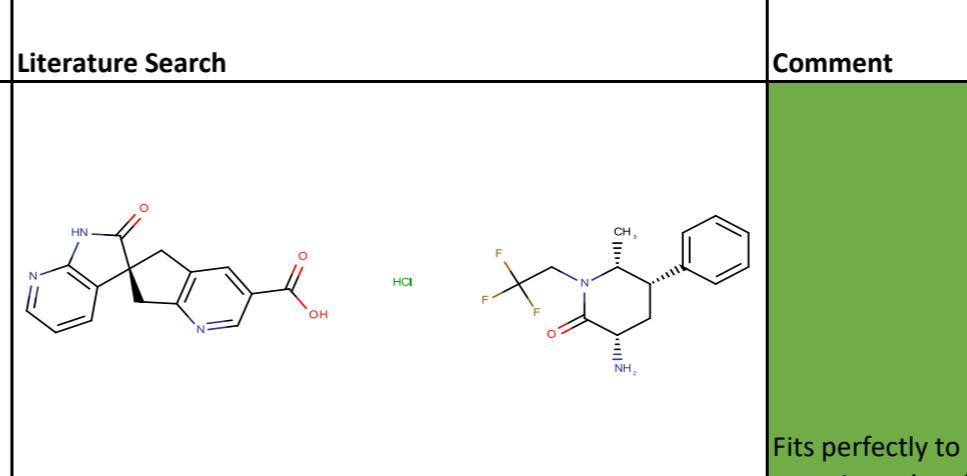
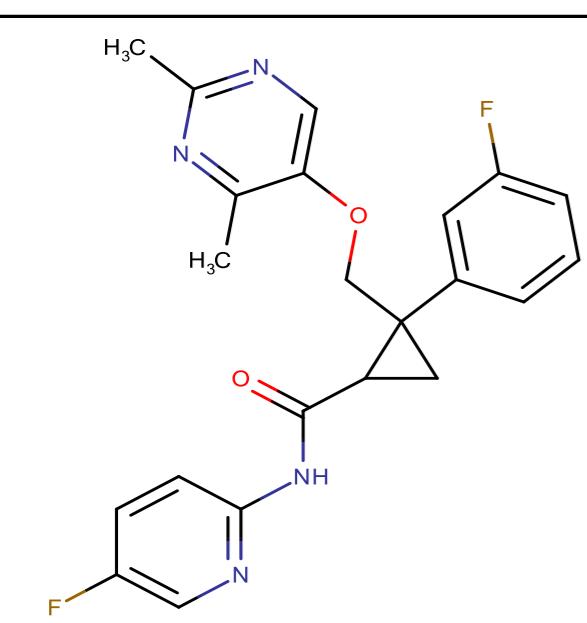
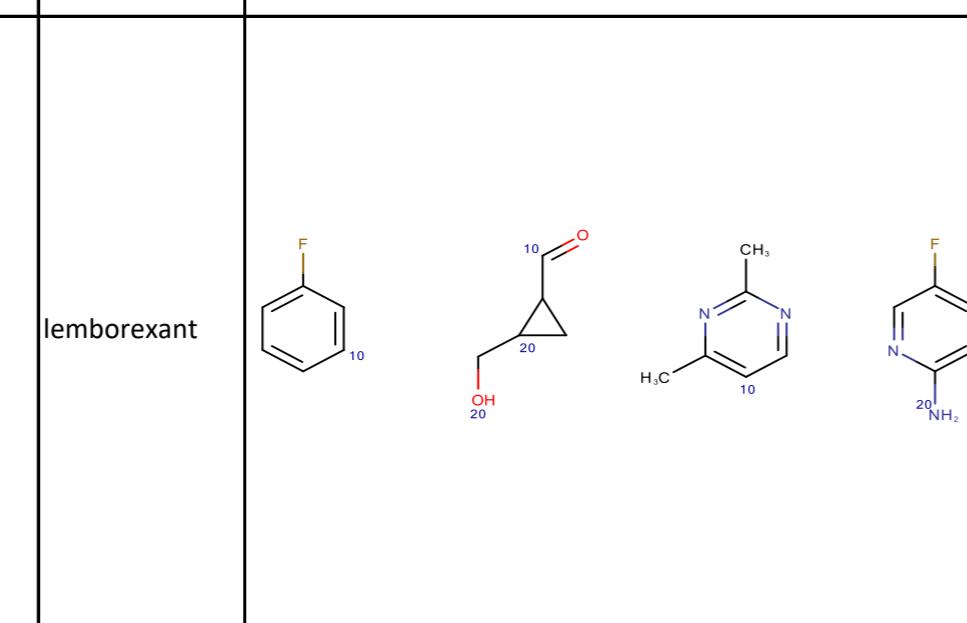
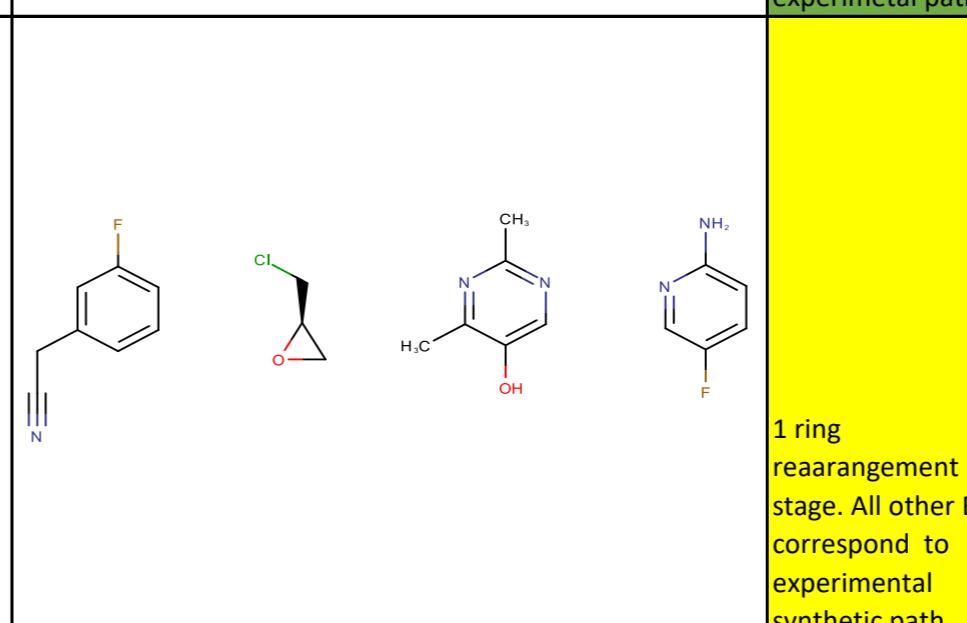
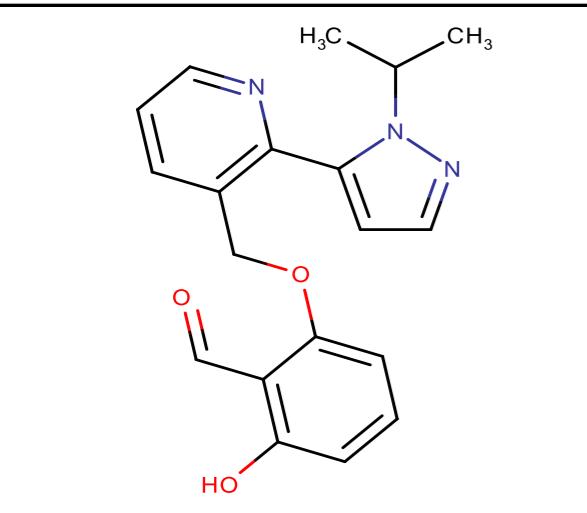
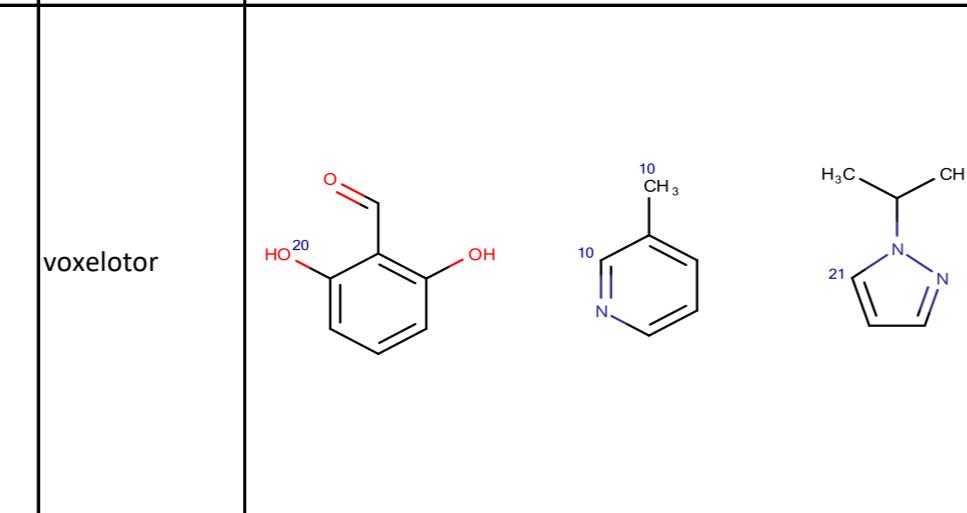
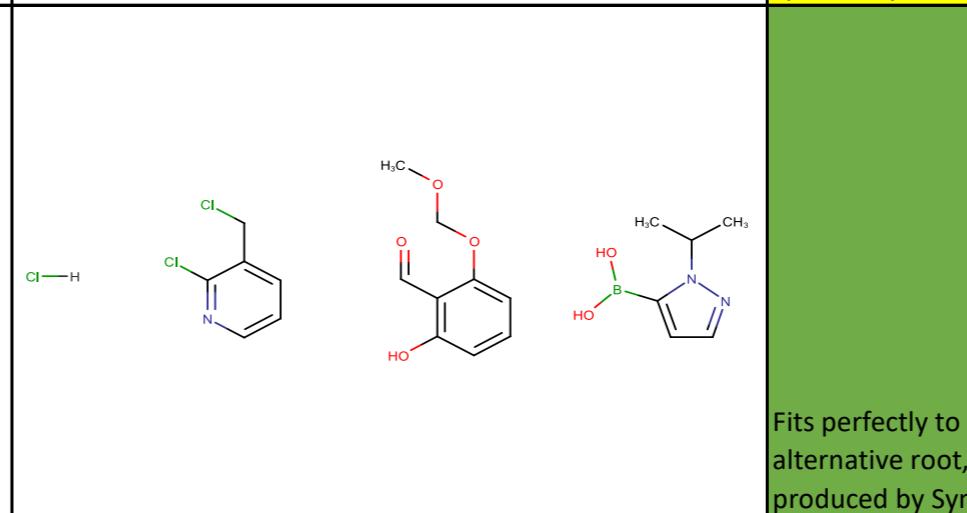
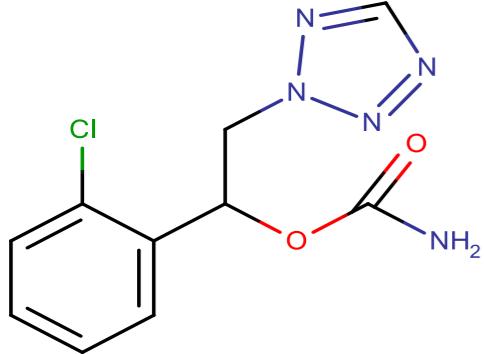
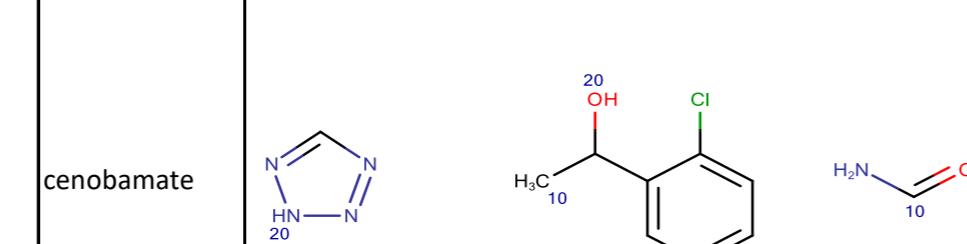
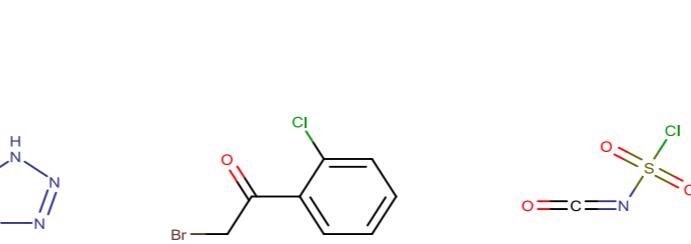
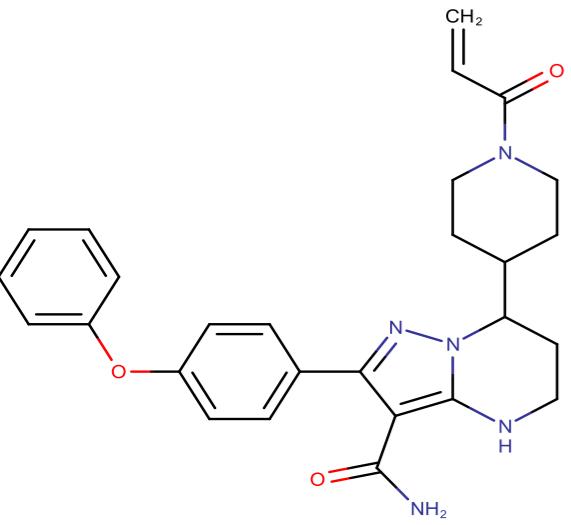
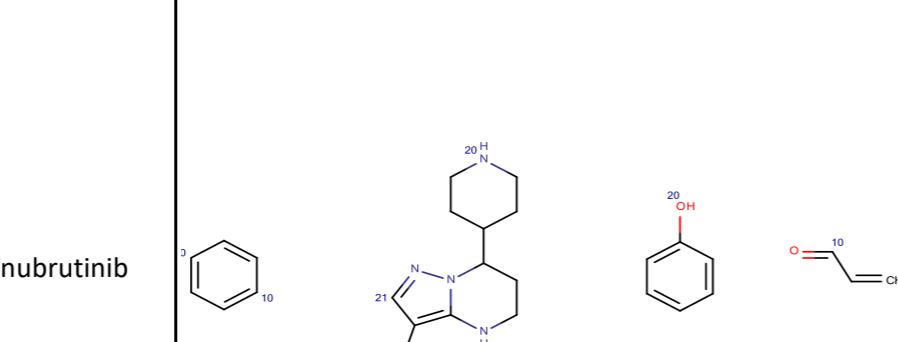
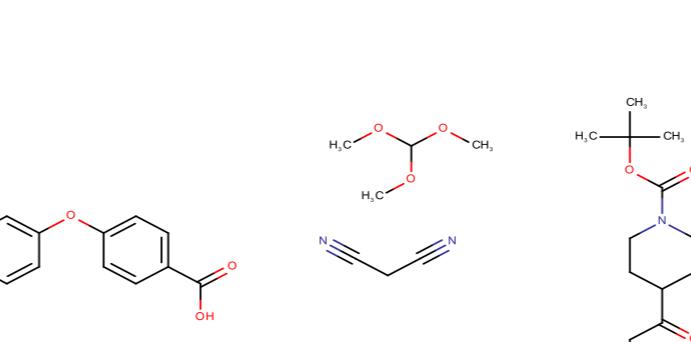
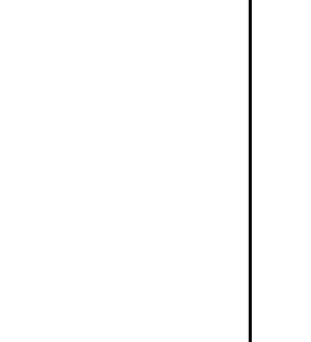
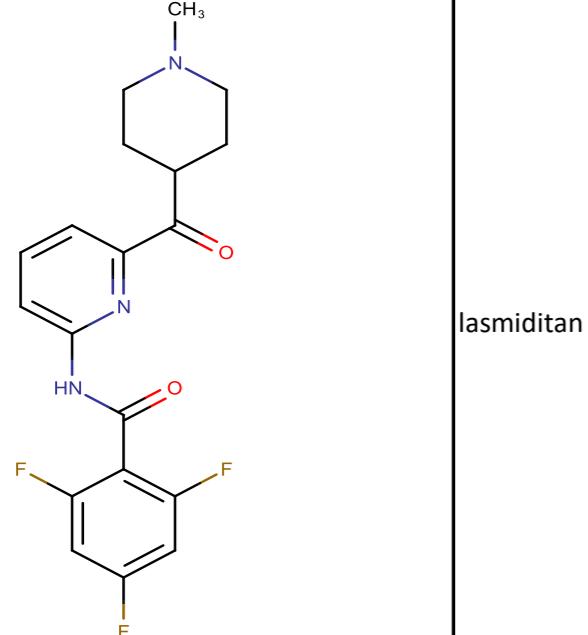
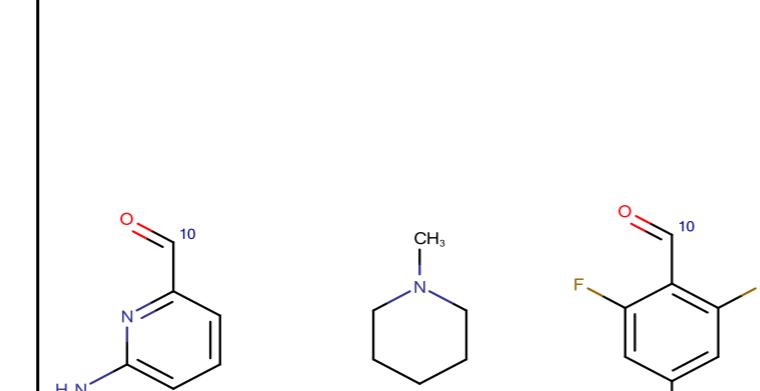
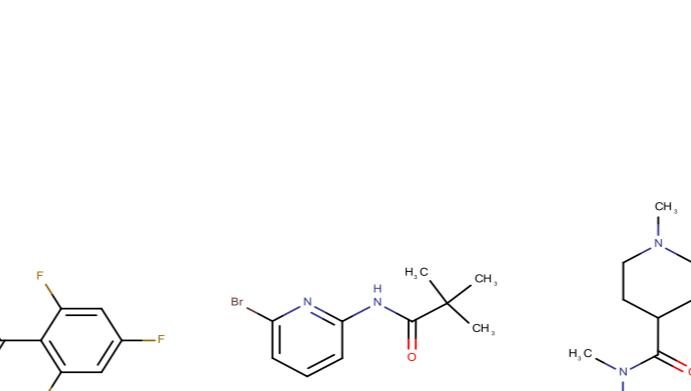
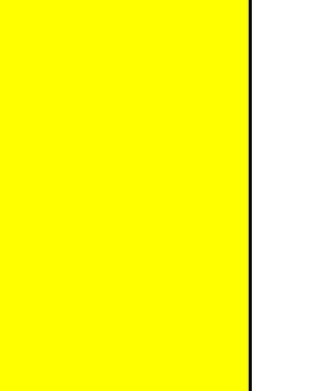
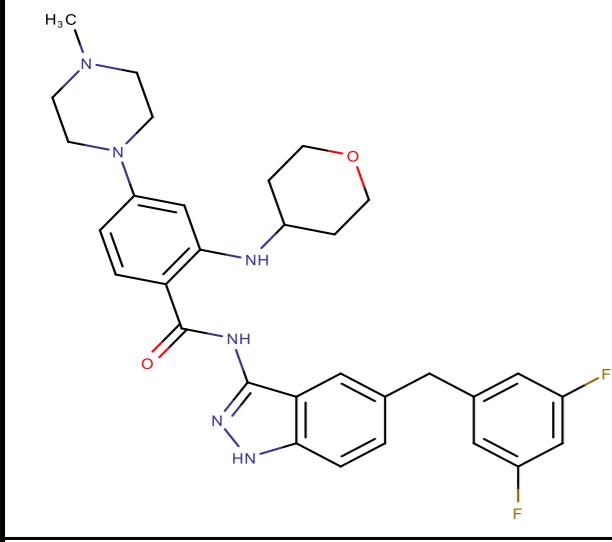
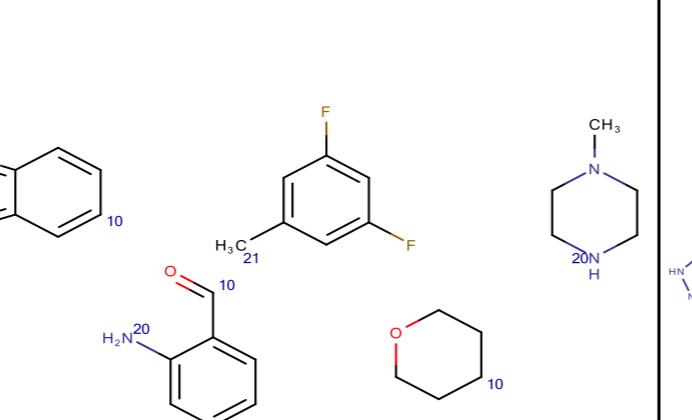
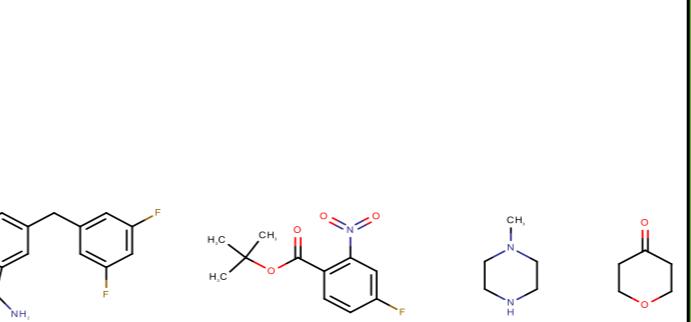
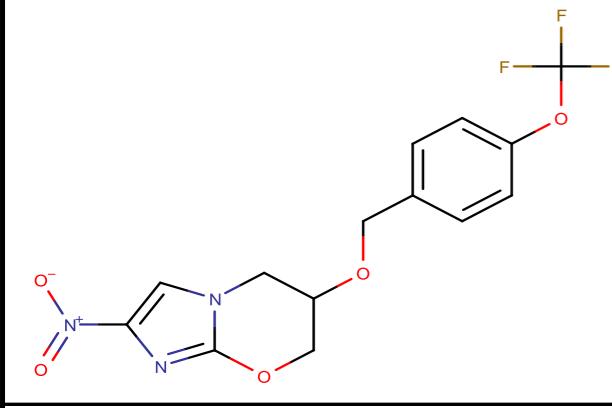
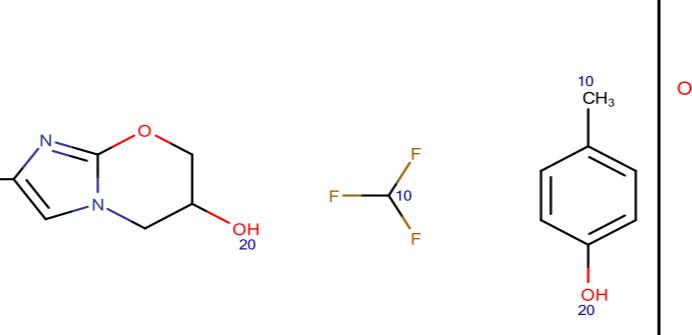
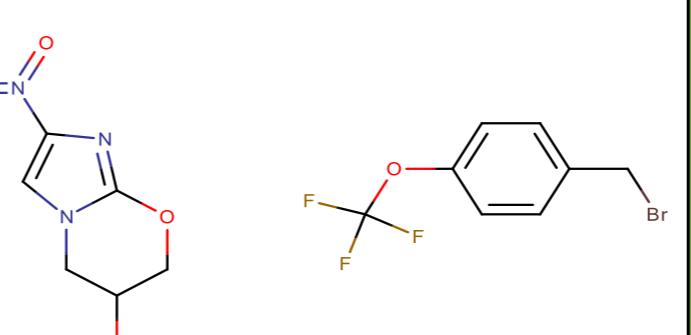
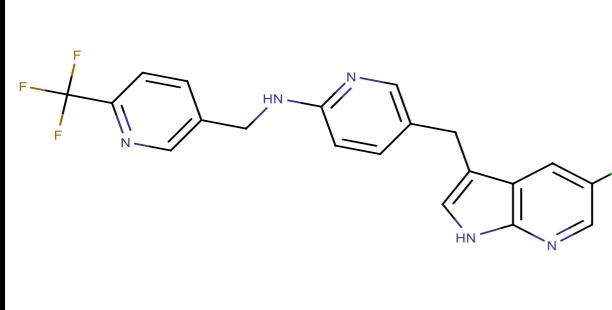
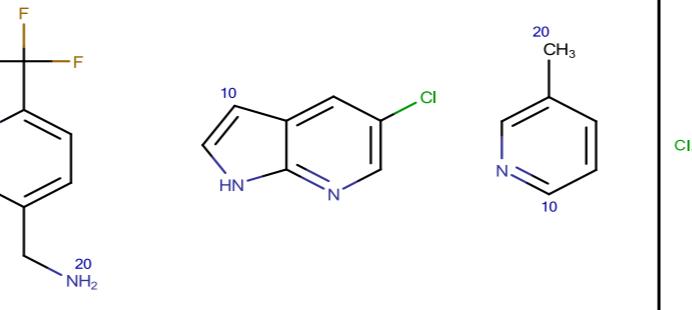
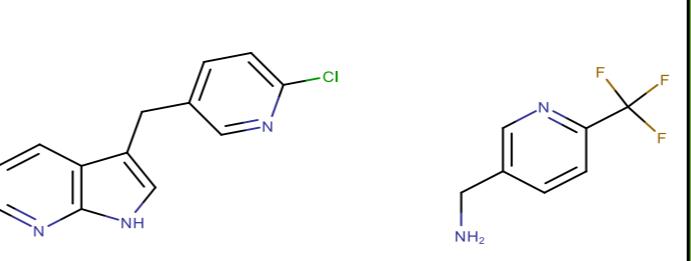
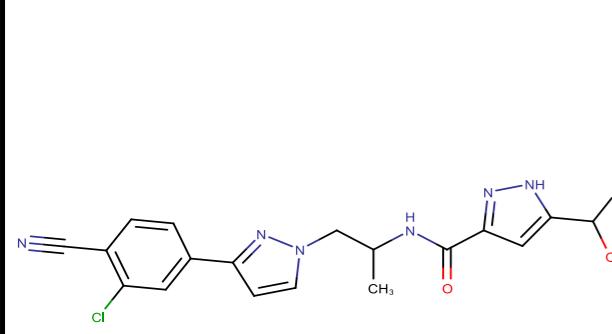
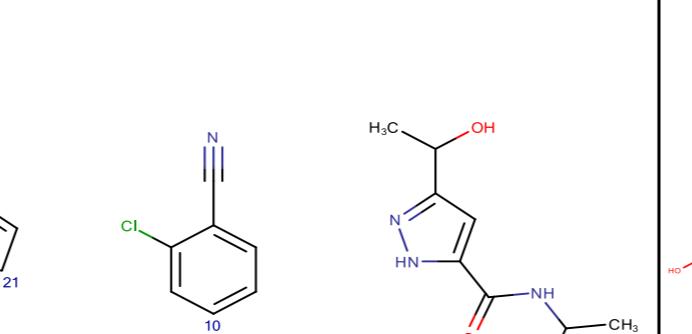
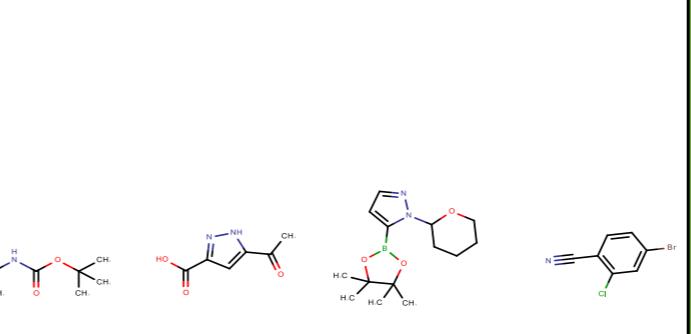
	tazemetostat		R1.1_0 R12.1_0 R 3.1_1 R3.1_2 R3. 2_0	6	0.93	AvailableSynthons:Cc1c([CH:10]=O)c[ch:10]c[ch:10]1->EN300-343096+EN300-320936 c1c[cH:21]ccc1[CH3:10]->EN300-54206+EN300-150254+EN300-124118+EN300-54979 C1C[NH:20]CCO1->EN300-31893+EN300-30242+EN300-1709926+EN300-18064 C1C[CH2:10]CCO1->EN300-154517+EN300-104914+EN300-43315+EN300-53372+EN300-75453 Cc1cc(C)c(C[NH2:20])c(=O)[nH]1->EN300-34346+EN300-14701	NotAvailableSynthons:CC[NH2:20]
	avapritinib		R12.1_1 R3.2_0 R 3.2_0	4	0.57	AvailableSynthons:C1C[NH:20]CC[NH:20]1->EN300-25694+EN300-749027+EN300-82962+EN300-260557+EN300-33920+EN300-50326+EN300-20101+EN300-114743 c1nn2c[ch:10]cc2[ch:10]n1->EN300-2279863 Cn1c[cH:21]cn1->EN300-100187+EN300-101866	NotAvailableSynthons:CC(N)(c1ccc(F)cc1)c1cn[cH:10]nc1

Table S3. SynthI Fragmentation Comparison with Literature Reported Synthesis

Structure	Drug Name	All Synthons	Literature Search	Comment	Reference
	ubrogepant			Fits perfectly to the experimental path	Yasuda, Nobuyoshi; Cleator, Ed; Kosjek, Birgit; Yin, Jianguo; Xiang, Bangping; Chen, Frank; Kuo, Shen-Chun; Belyk, Kevin; Mullens, Peter R.; Goodyear, Adrian; Edwards, John S.; Bishop, Brian; Ceglia, Scott; Belardi, Justin; Tan, Lushi; Song, Zhiguo J.; Dimichele, Lisa; Reamer, Robert; Cabirol, Fabien L.; Tang, Weng Lin; Liu, Guiquan; Organic Process Research and Development; vol. 21; 11; (2017); p. 1851 - 1858;
	lemborexant			1 ring rearrangement stage. All other BBs correspond to experimental synthetic path	Patent; EISAI R&D MANAGEMENT CO., LTD; MONIZ, George, Anthony; WILCOXEN, Annie, Zhu; BENAYOUD, Farid; LEE, Jaemoon; ZHANG, Huiming; TERAUCHI, Taro; TAKEMURA, Ayumi; YOSHIDA, Yu; TANAKA, Tosh iaki; SORIMACHI, Keiichi; NAOE, Yoshimitsu; KAZUTA, Yuji; WO2013/123240; A1; (2013);
	voxelotor			Fits perfectly to the alternative root, produced by Synthl.	Patent; BIONICE, S.L.U.; FERREIRO GIL, Juan JosÃ©; IGLESIAS RETUERTO, J esÃ©s Miguel; LORENTE BONDE-LARSEN, Antonio; WO2020/127945; A1; (2020); (33 pag.)

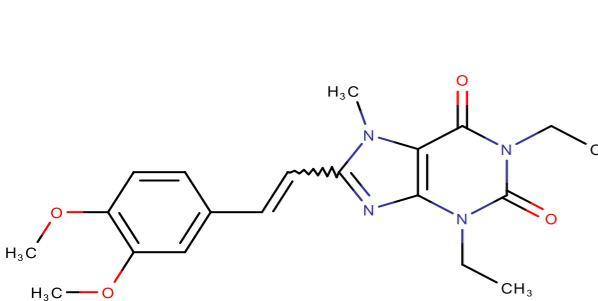
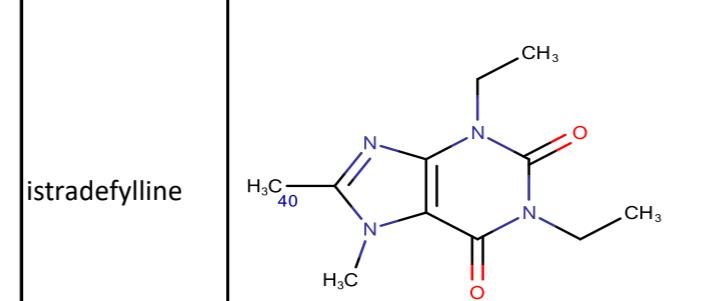
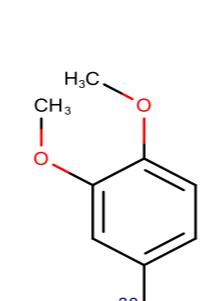
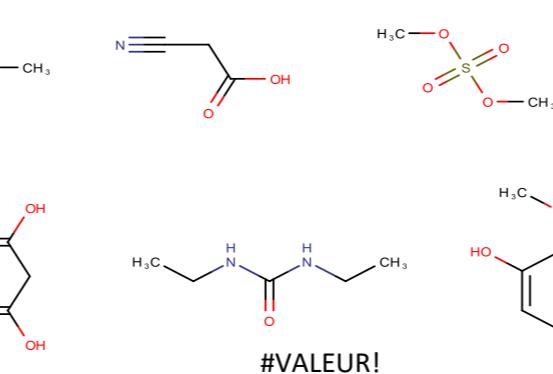
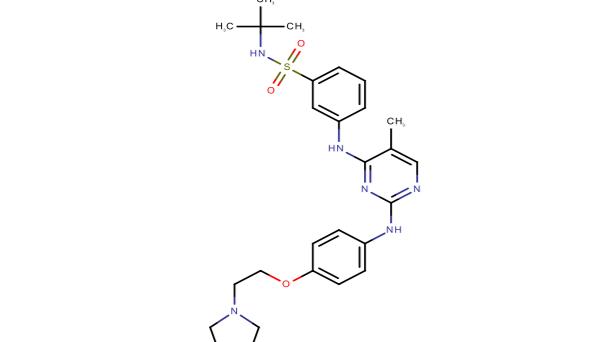
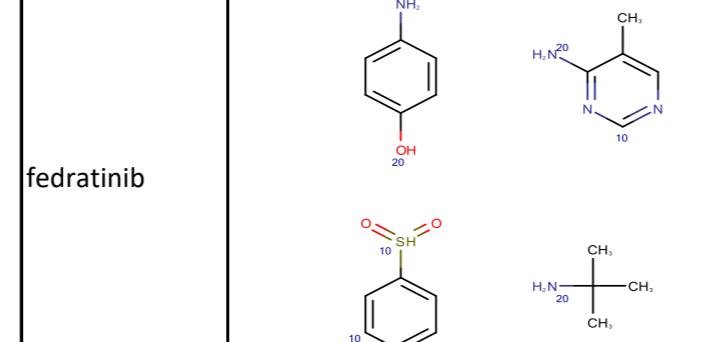
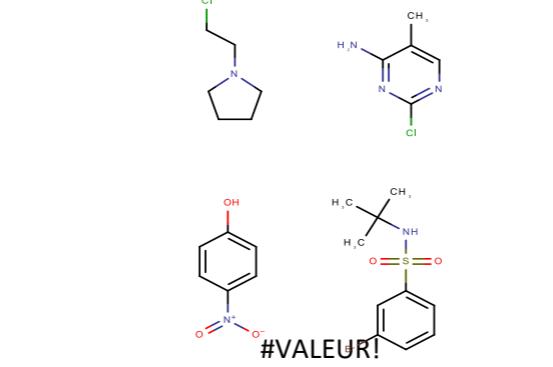
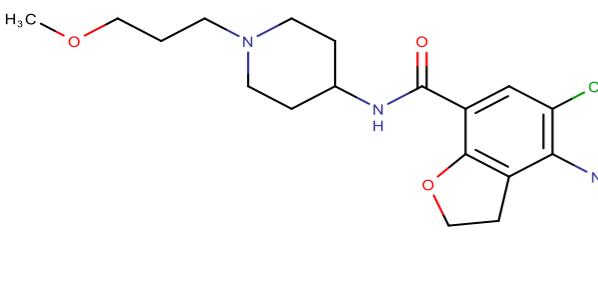
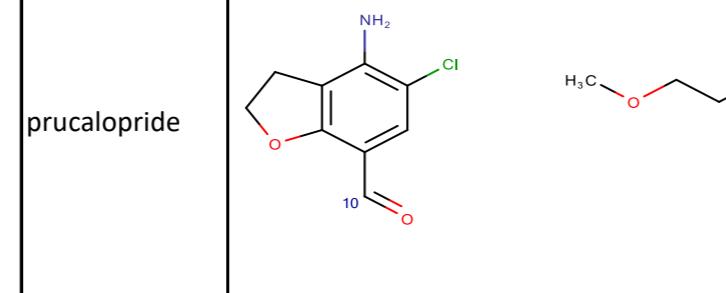
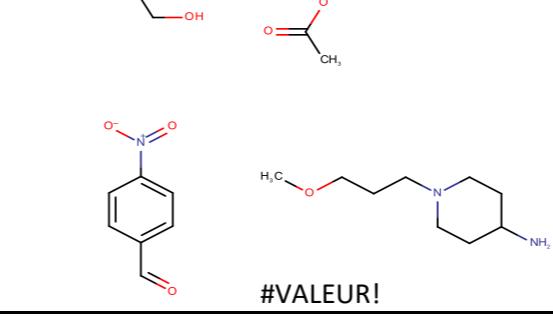
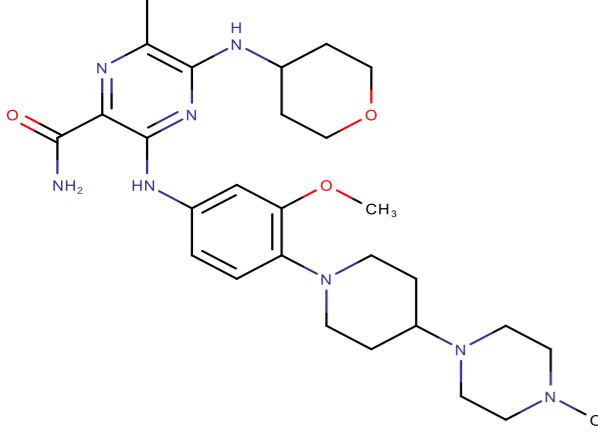
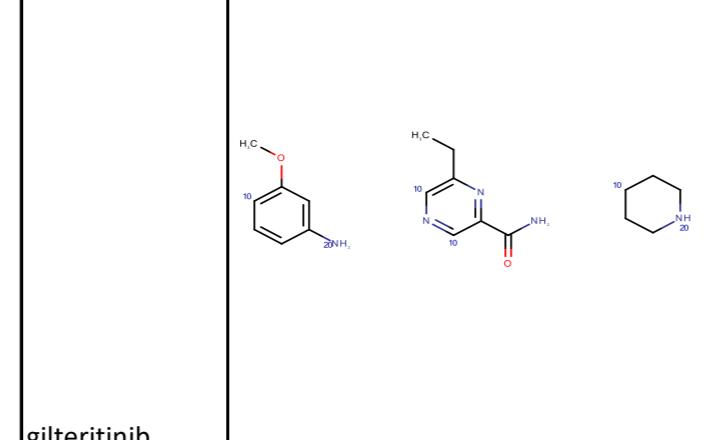
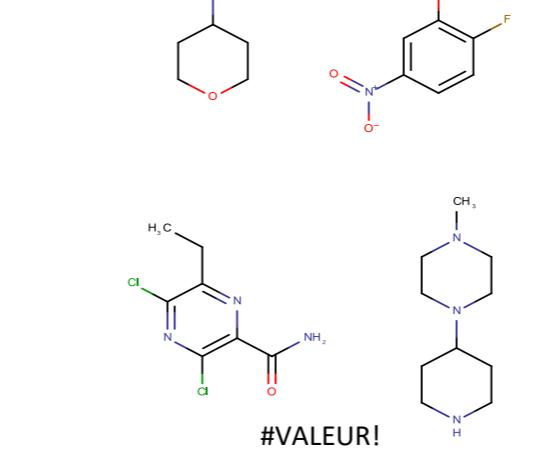
	cenobamate				Fits perfectly to the experimental path	Patent; SK CORPORATION; WO2006/112685; A1; (2006); Patent; SK HOLDINGS CO., LTD.; LIM, Sang ,Chul; UHM, Moo, Yong; CHO, Nahm, Ryune; LEE, Dae, Won; LEE, Ju, Young; KIM, Hui, Ho; LEE, Dong, Ho; WO2010/150946; A1; (2010);
	zanubrutinib				Heterocyclization reactions prevail	Patent; BEIGENE, LTD.; HU, Nan; WANG, Lai; SONG, Jing; ZHANG, Tong; Li, Kang; LUO, Lusong; WEI, Min; WANG, Zhiwei; GUO, Yunhang; WO2018/33135; A1; (2018); (69 pag.)
	lasmiditan				2/3 synthons correspond to the experimental path	Patent; GLENMARK LIFE SCIENCES LIMITED, GLENMARK PHARMACEUTICALS LIMITED; DEORE, Dinesh; BHIRUD, Shekhar Bhaskar; CHAND, Prem; NAIK, Samir; BADGUJAR, Santosh; BAVISKAR, Deepak; WO2020/95171; A1; (2020); (41 pag.)

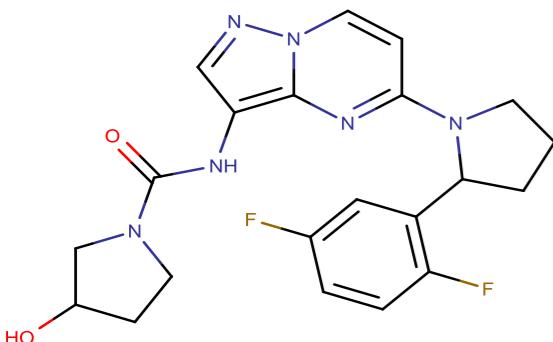
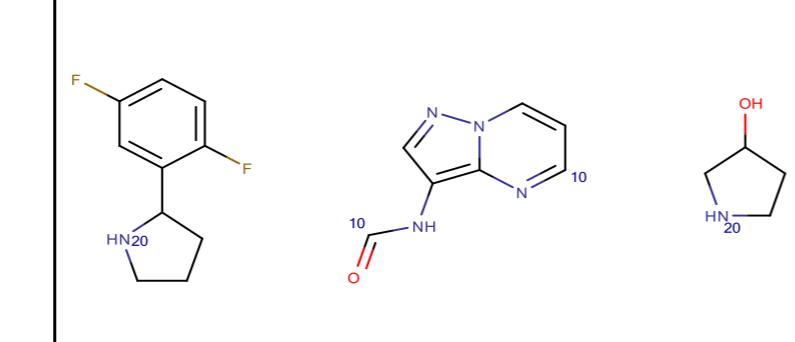
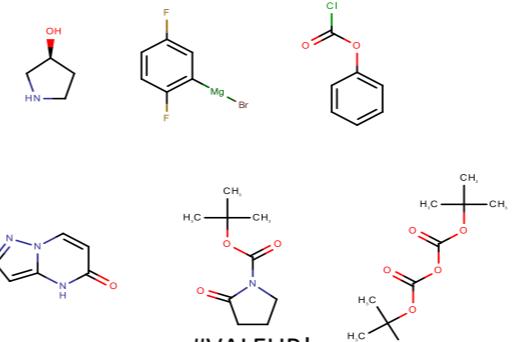
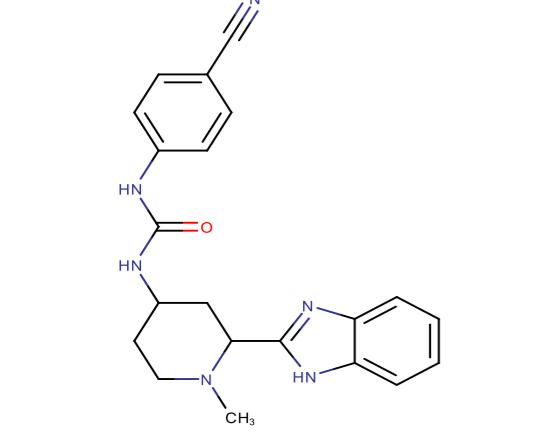
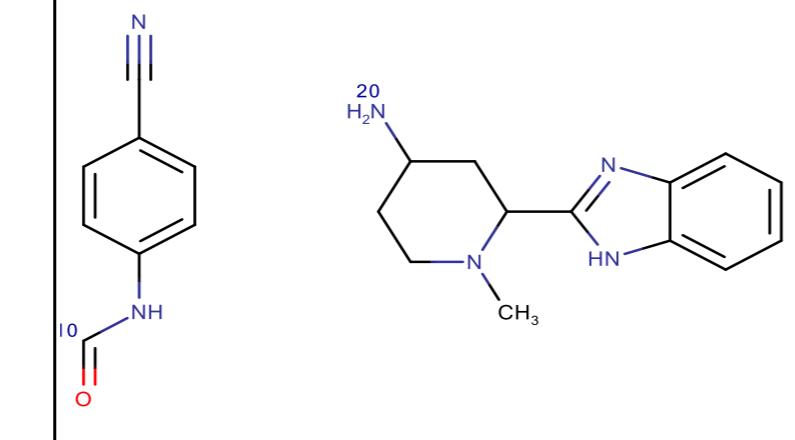
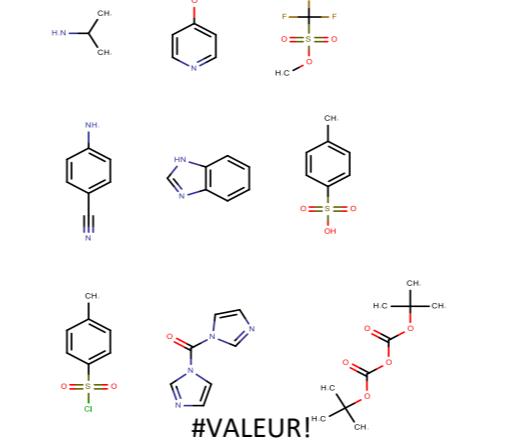
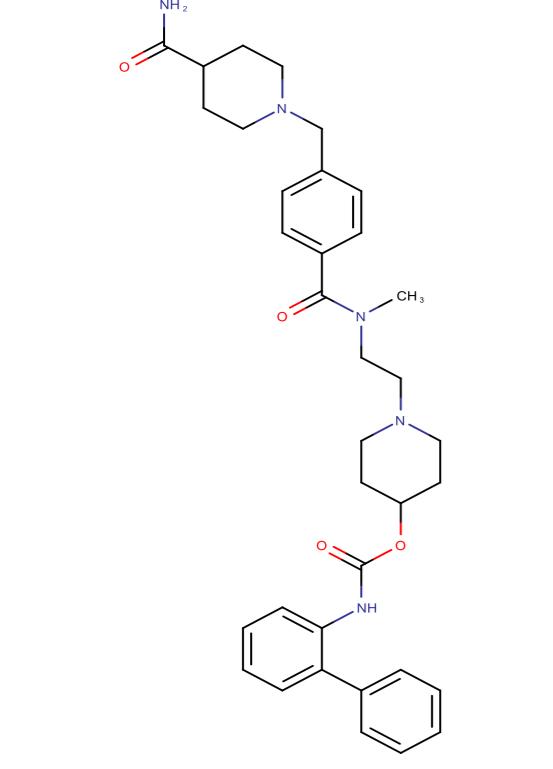
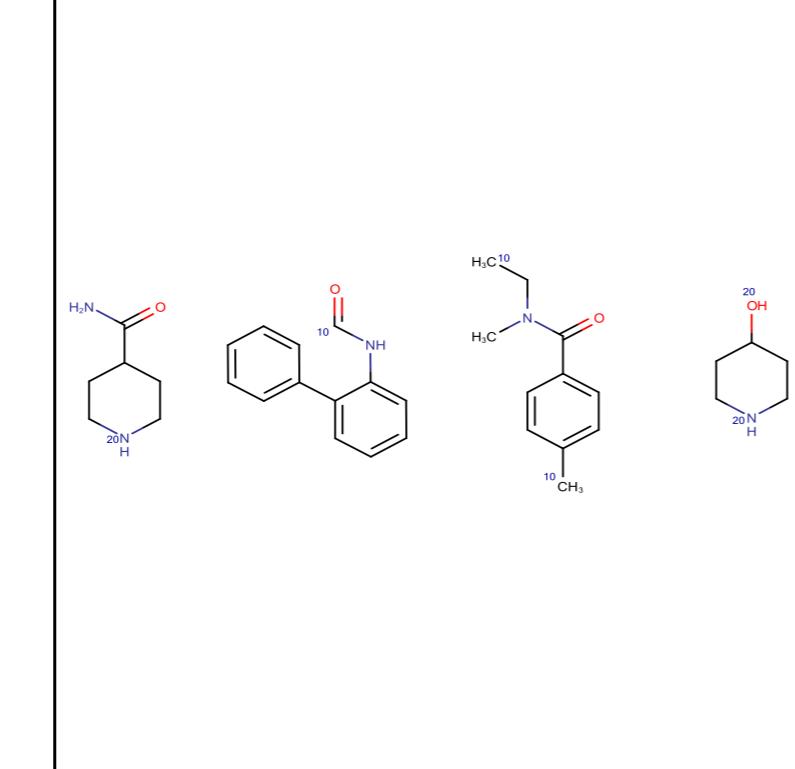
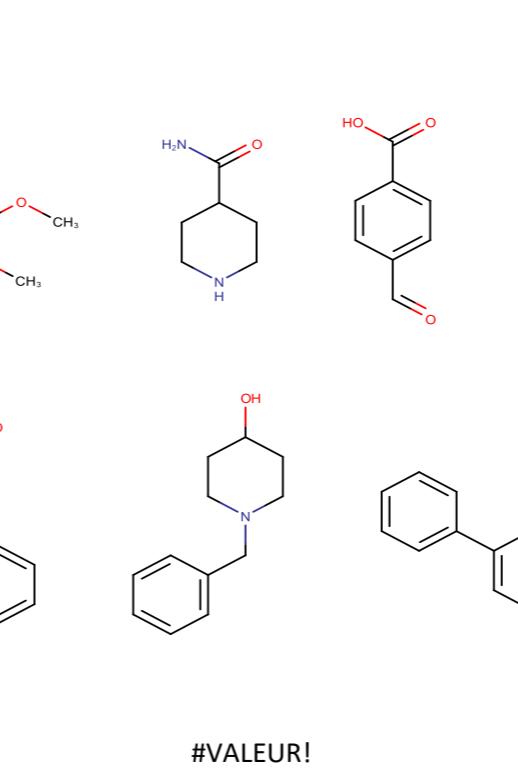
<p>trifarotene</p>	<p>trifarotene</p>	<p>trifarotene</p>	<p>Fits perfectly to the alternative root, produced by Synthl.</p> <p>GALDERMA RESEARCH & DEVELOPMENT, S.N.C.; WO2006/66978; A1; (2006);</p>
<p>lefamulin</p>	<p>lefamulin</p>	<p>lefamulin</p>	<p>Fits perfectly to the experimental path</p> <p>20045463; Patent; NABRIVA THERAPEUTICS AG; RIEDL, Rosemarie; HEILMAYER, Werner; SPENCE, Lee; WO2011/146954; A1; (2011);</p>
<p>upadacitinib</p>	<p>upadacitinib</p>	<p>upadacitinib</p>	<p>1 ring heterocyclization stage. All other BBs correspond to experimental synthetic path</p> <p>Gajdosik; Drugs of the Future; vol. 43; 10; (2018); p. 731 - 743; Patent; AbbVie Inc.; Allian, Aymen; Jayanth, Jayanthy; Mohamed, Mohamed-Eslam; Mulhern, Mathew; Nordstroem, Lars Fredrick; Othman, Ahmed; Rozema, Michael; Bhagavatula, Lakshmi; Marroum, Patr ick J.; Mayer, Peter T.; US2017/129902; A1; (2017); (275 pag.)</p>

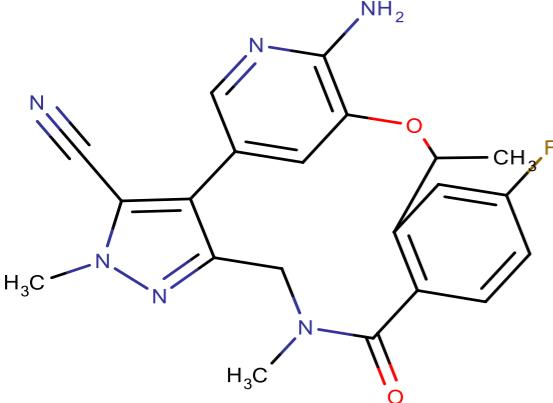
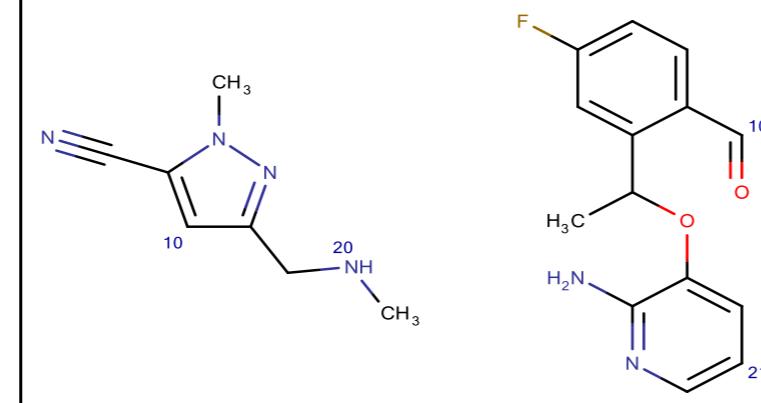
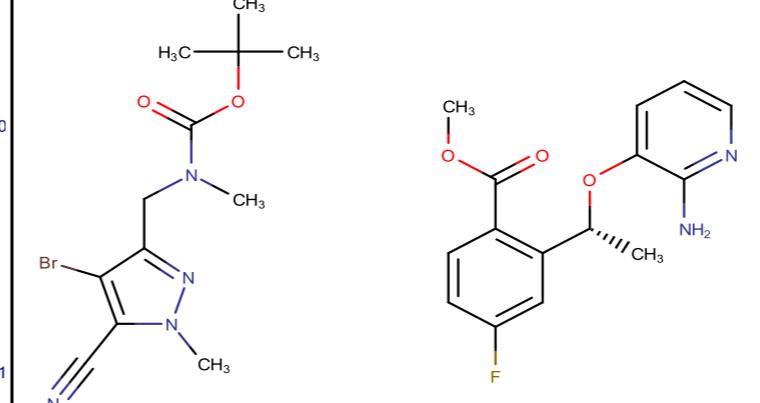
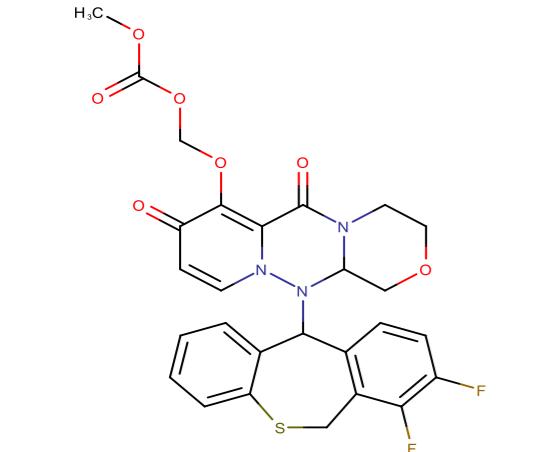
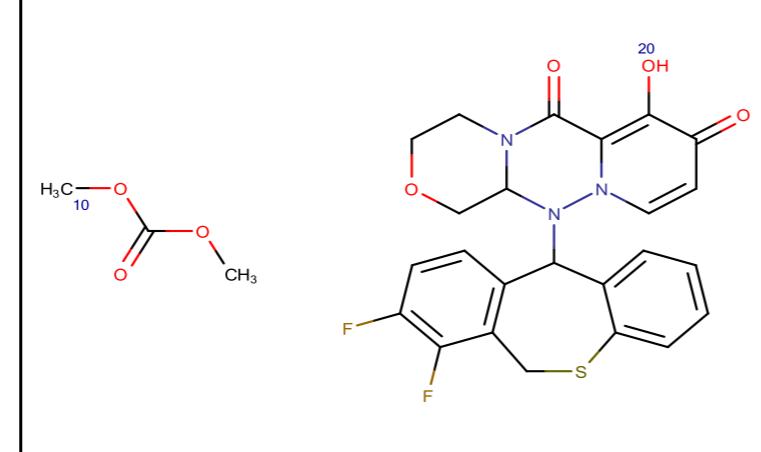
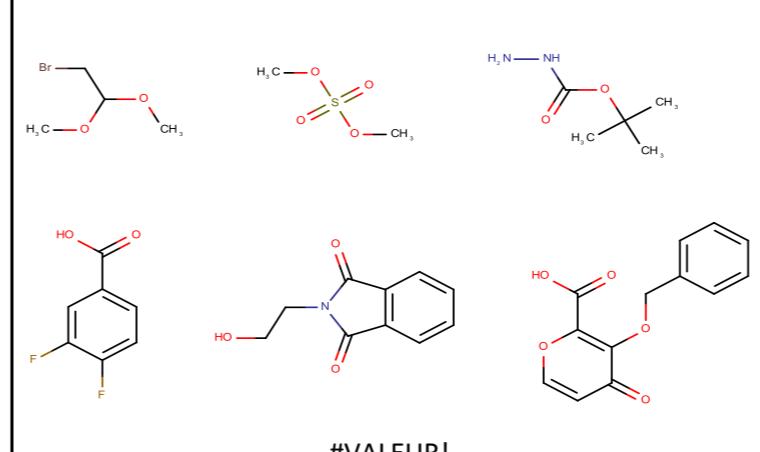
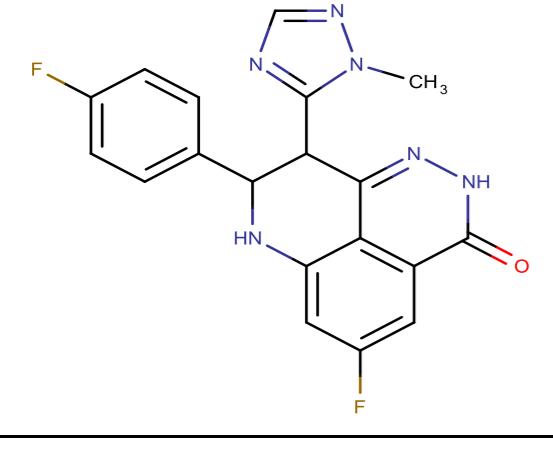
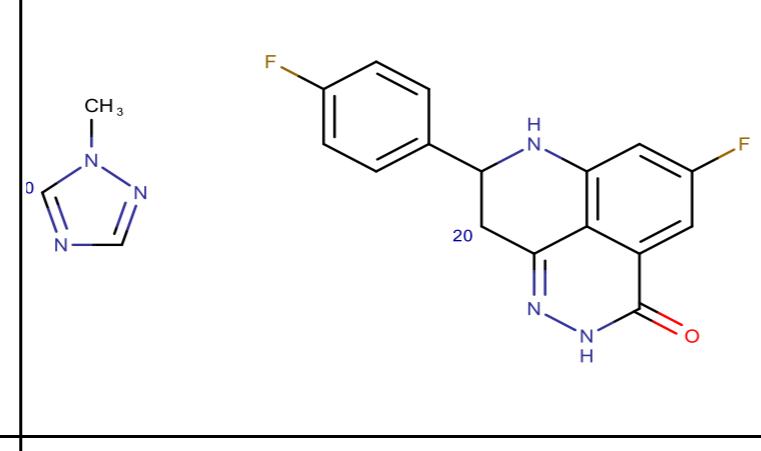
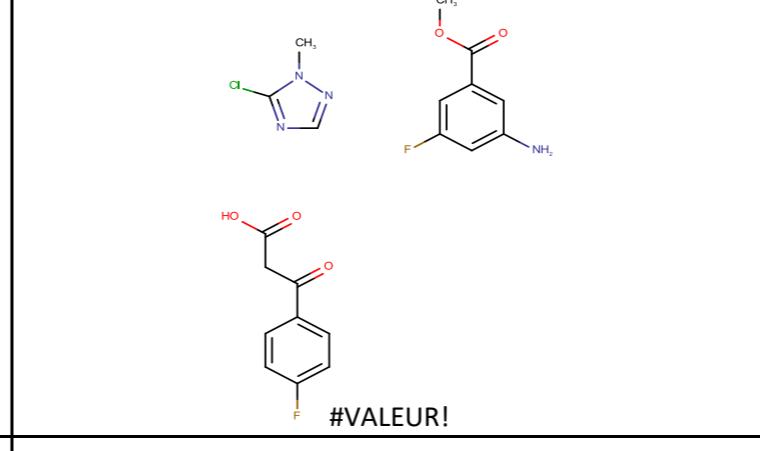
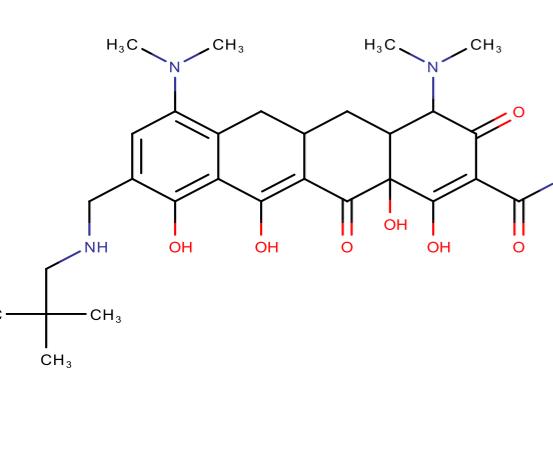
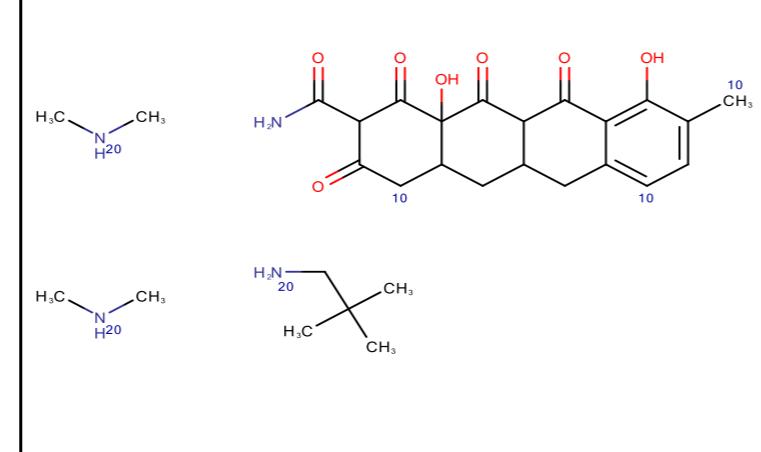
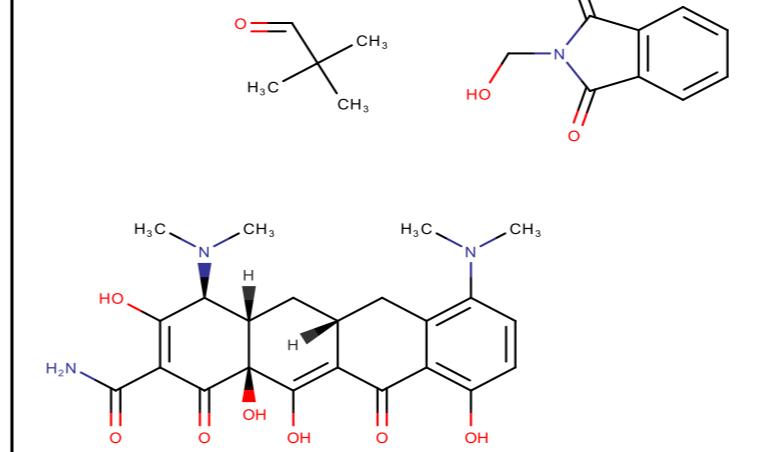
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	pretomanid			Fits perfectly to the experimental path	Thompson, Andrew M.; Blaser, Adrian; Anderson, Robert F.; Shinde, Sujata S.; Franzblau, Scott G.; Ma, Zhenkun; Denny, William A.; Palmer, Brian D.; Journal of Medicinal Chemistry; vo. I. 52; 3; (2009); p. 637 - 645;
	pexidartinib			Fits perfectly to the alternative root, produced by Synthl.	Patent; Henan Applied Technology Profession College; Liu Jiayan; Ren Yupeng; CN111233857; A; (2020); (10 pag.)
	darolutamide			Fits perfectly to the alternative root, produced by Synthl.	Patent; TÖRMÄKANGAS, Olli HEIKKINEN, Terhi; WO2016120530; (2016)

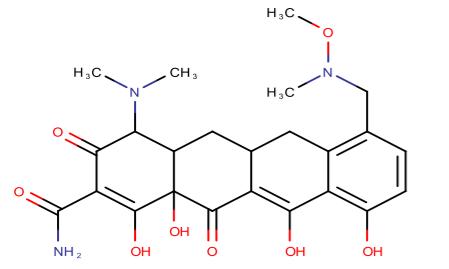
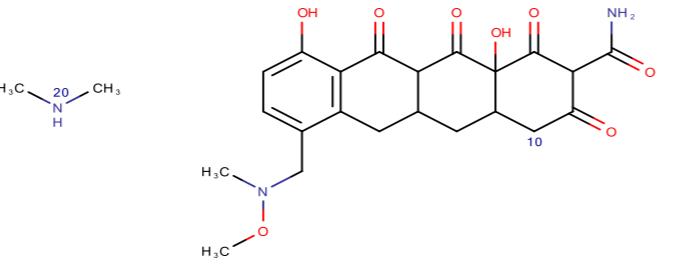
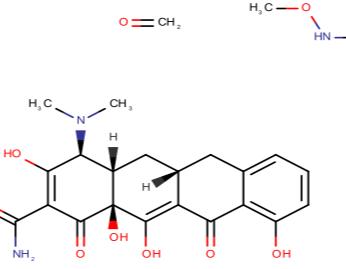
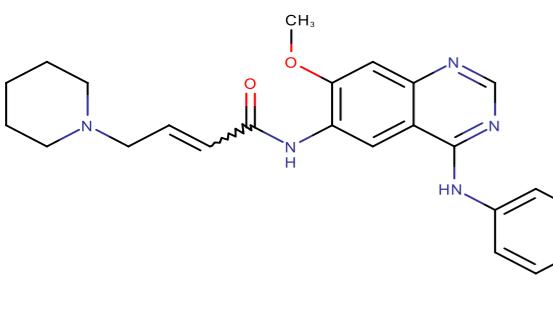
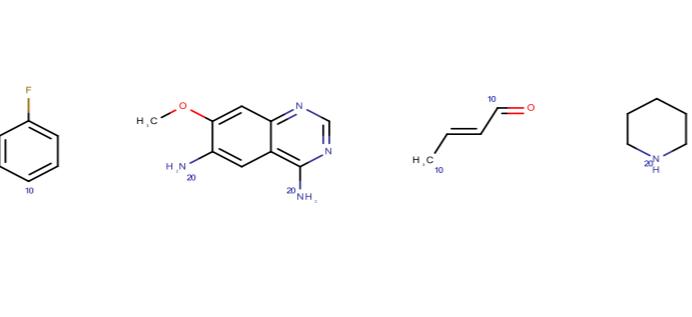
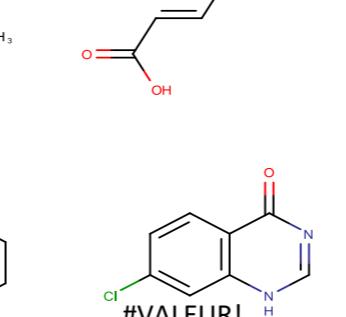
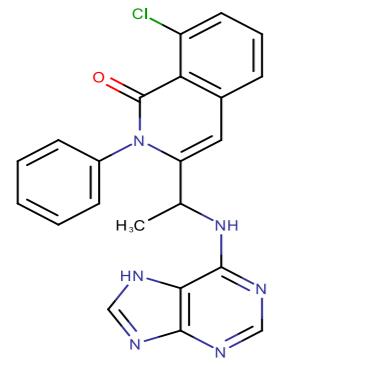
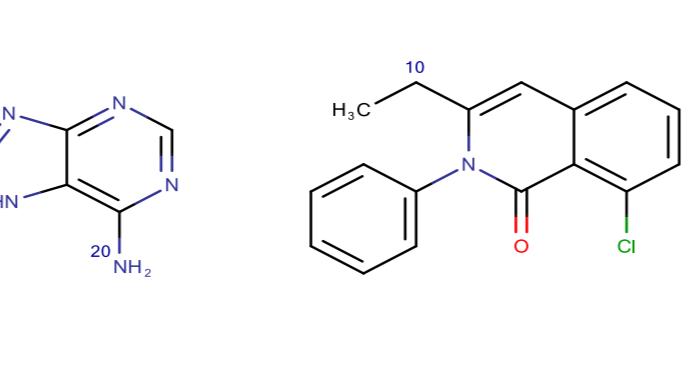
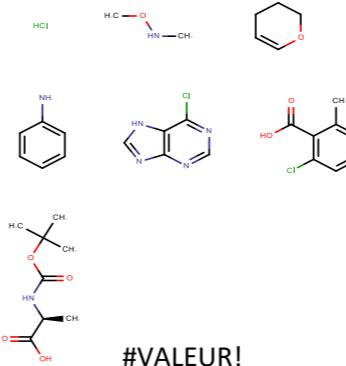
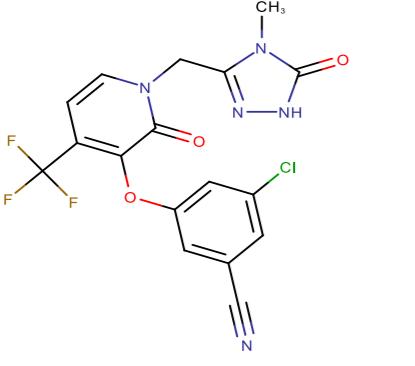
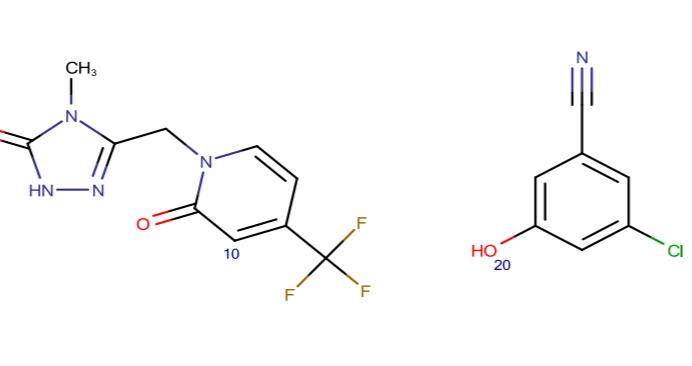
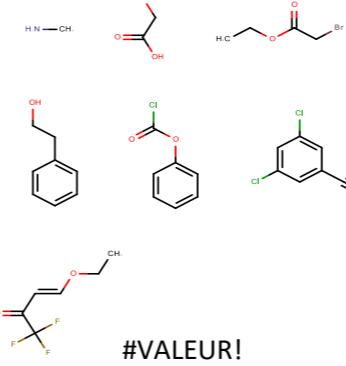
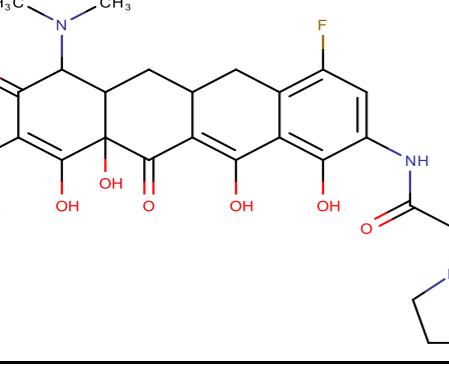
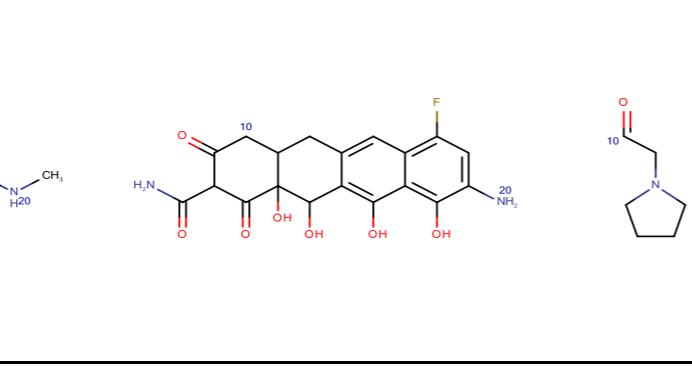
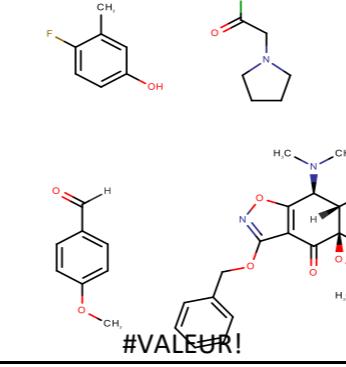
<p>selinexor</p>	<p>selinexor</p>	<p>#VALEUR!</p>	<p>Heterocyclization reactions prevail</p> <p>Preparation of hydrazide containing nuclear transport modulators and uses thereof By Sandanayaka, Vincent P. et al From PCT Int. Appl., 2013019548, 07 Feb 2013</p>
<p>alpelisib</p>		<p>#VALEUR!</p>	<p>1 ring is obtained via heterocyclization. 2/4 synthons correspond to the experimental path</p> <p>Polymorphs of (S)-pyrrolidine-1,2-dicarboxylic acid 2-amide 1-(4-methyl-5-[2-(2,2,2-trifluoro1,1-dimethylethyl)pyridin-4-yl]thiazol-2-yl)amide By Gallou, Isabelle Sylvie et al From PCT Int. Appl., 2012175522, 27 Dec 2012</p>
<p>erdafitinib</p>		<p>#VALEUR!</p>	<p>Heterocyclization reactions prevail</p> <p>Preparation method of 3-(1-methyl-1Hpyrazol-4-yl)-6-quinoxalinamine, an erdafitinib intermediate By Xu, Xuenong From Faming Zhanli Shenqing, 112125888, 25 Dec 2020</p>

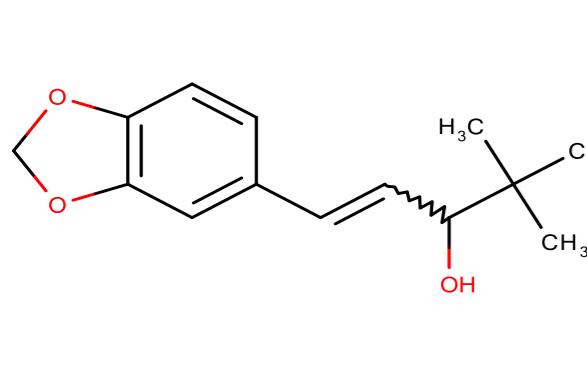
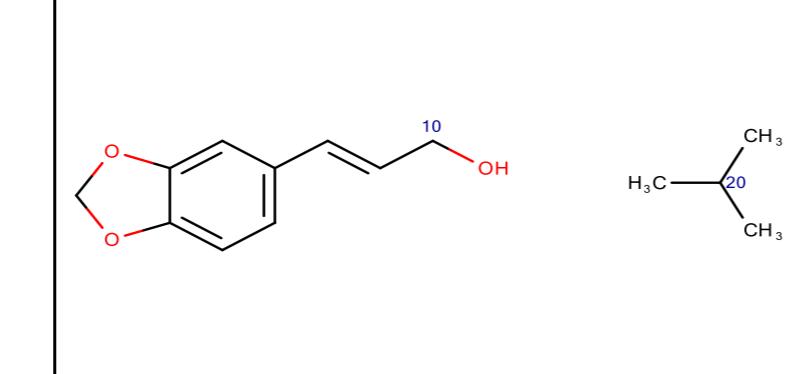
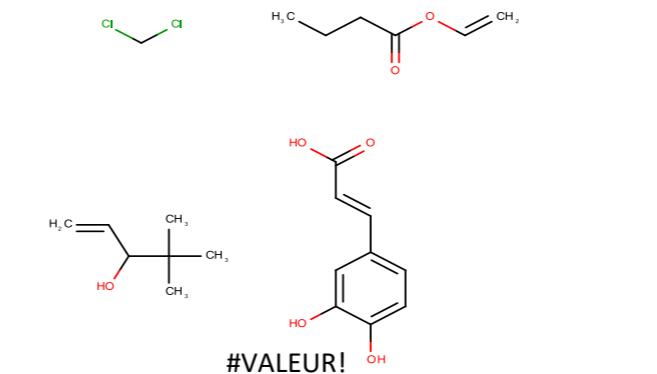
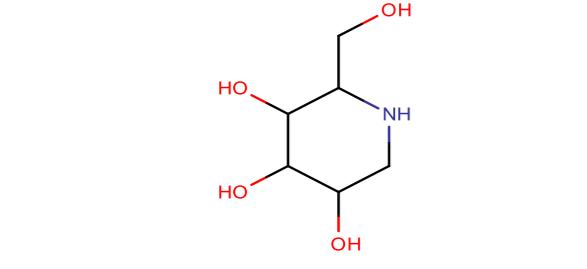
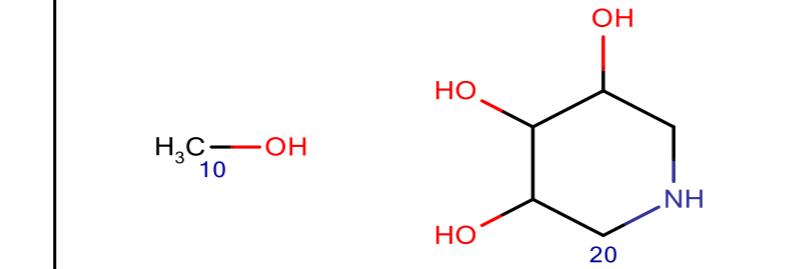
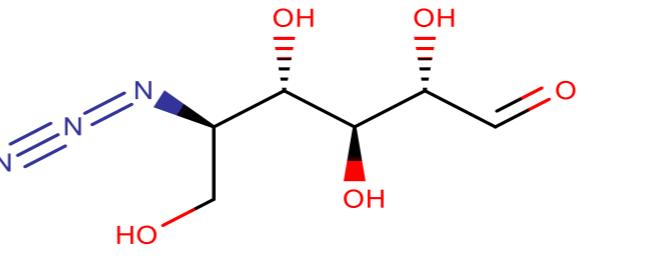
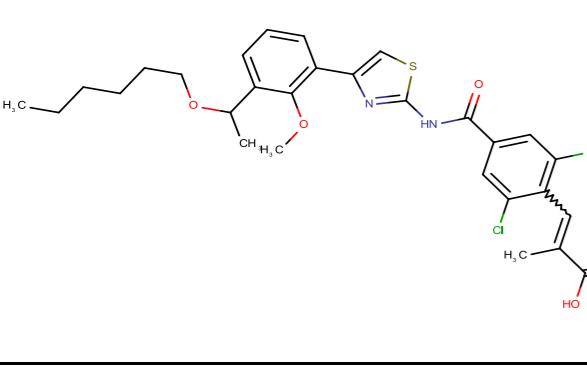
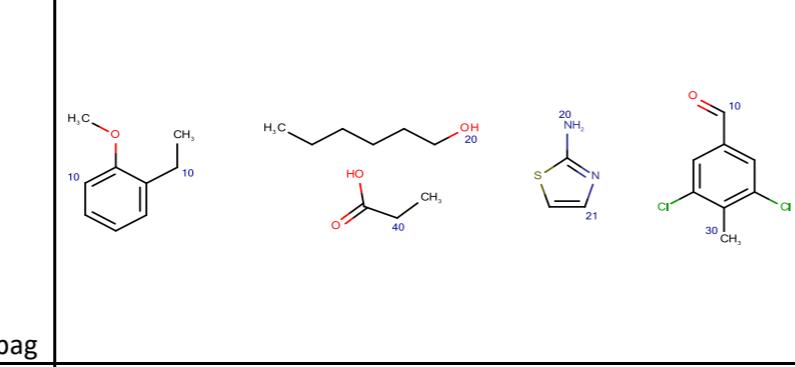
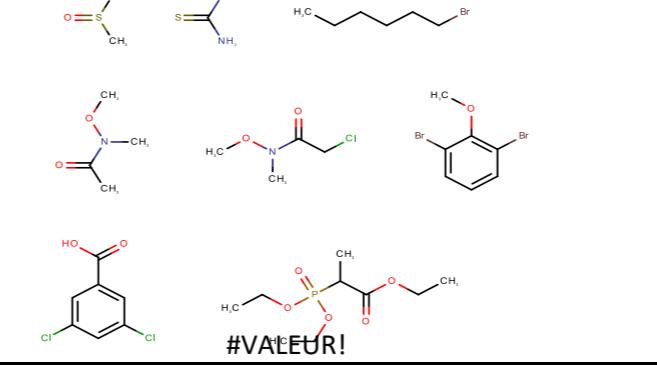
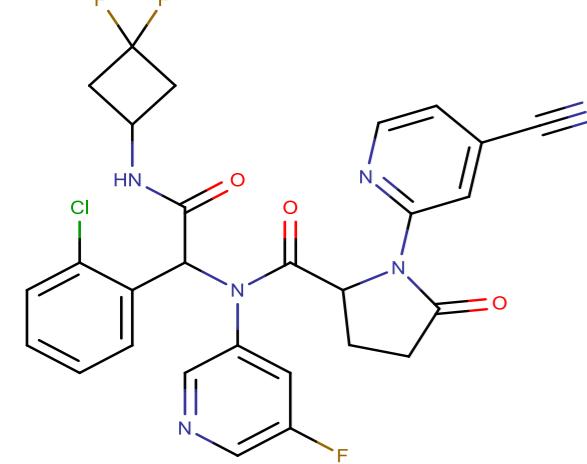
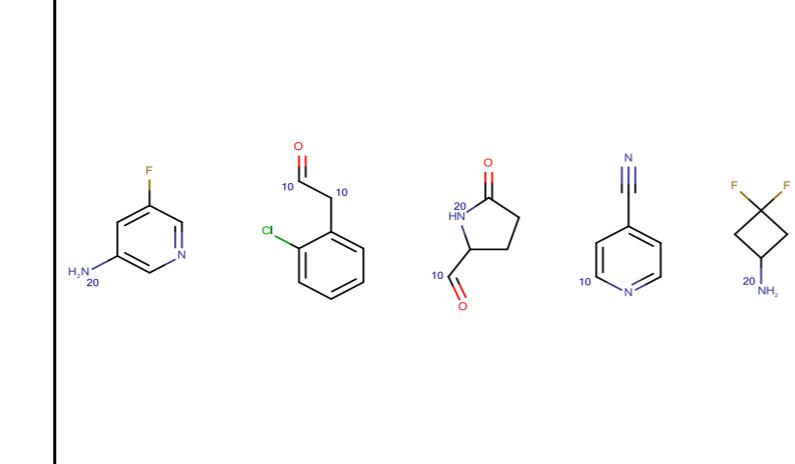
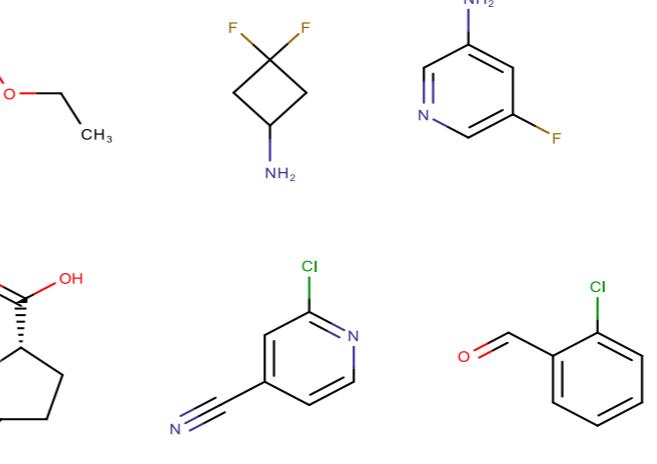
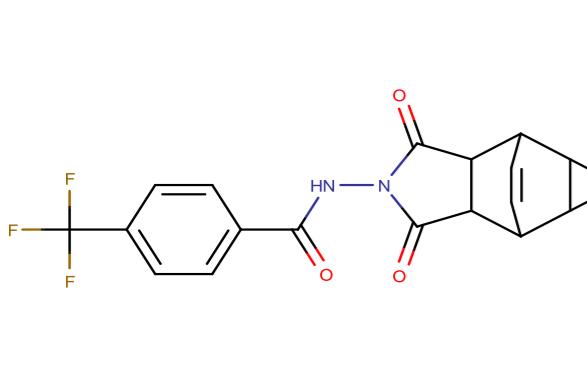
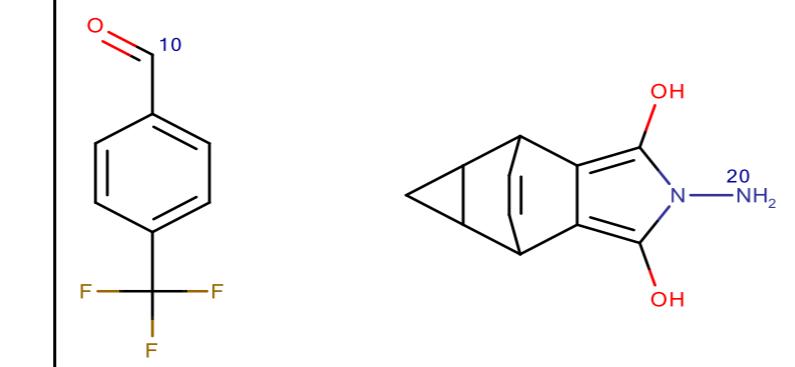
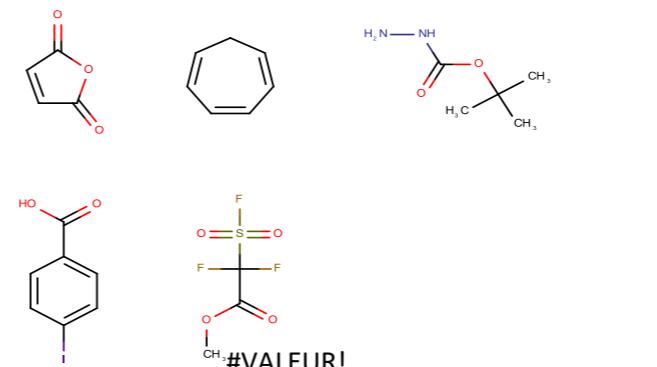
	siponimod			#VALEUR! 2/4 synthons correspond to the experimental path	Process for preparation of Siponimod, its intermediates and salts thereof By Oruganti, Srinivas et al From Indian Pat. Appl., 201741034238, 29 Mar 2019
	solriamfetol			#VALEUR! 1/2 synthons correspond to the experimental path	Process for the preparation of solriamfetol and its salts, particularly its dibenzoyl-Dtartrate and di-p-toluoyl-D-tartrate used as precursors for solriamfetol hydrochloride By Bhirud, Shekhar Bhaskar et al From PCT Int. Appl., 2020035769, 20 Feb 2020
	brexanolone			#VALEUR! Reduction of carbonyl compounds (reaction absent in Synthil 1.0)	Synthesis of deuterium labeled NMDA receptor inhibitor - 20-oxo-5β-[9,12,12-2H3]pregnan-3α-yl-L-glutamyl 1-ester By Kapras, Vojtech et al From Steroids, 77(3), 282-287; 2012
	triclabendazole			#VALEUR! Heterocyclization reactions prevail	Preparation method of triclabendazole as medicine for treating fascioliasis By Xu, Yong et al From Faming Zhuanli Shenqing, 111072570, 28 Apr 2020
	cefiderocol			Synthil produce smaller fragments, that correspond to the experimental procedure.	Cefiderocol (S-649266), A new siderophore cephalosporin exhibiting potent activities against <i>Pseudomonas aeruginosa</i> and other gram-negative pathogens including multi-drug resistant bacteria: Structure activity relationship By Aoki, Toshiaki et al From European Journal of Medicinal Chemistry, 155, 847-868; 2018

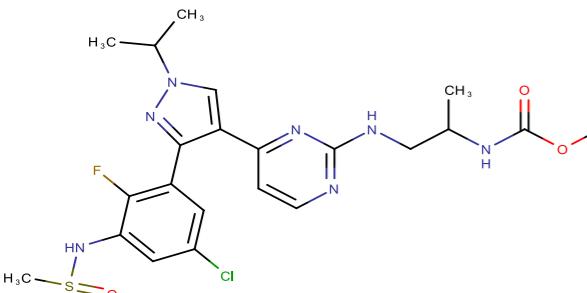
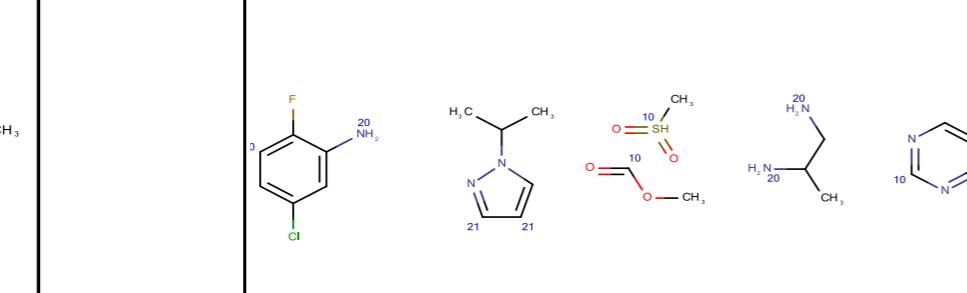
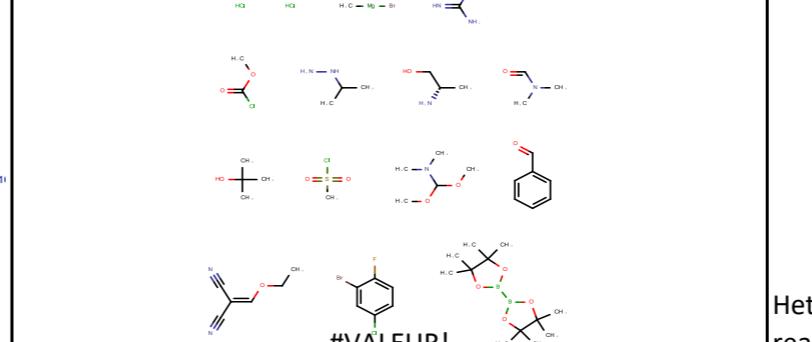
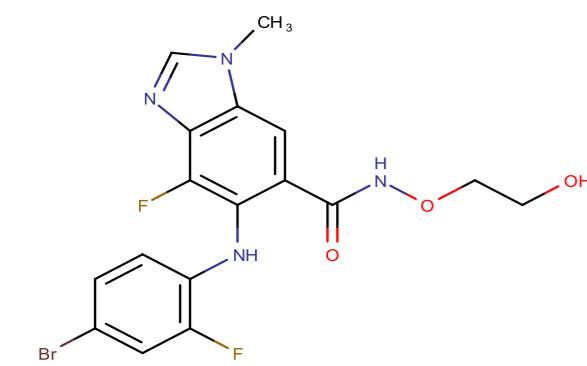
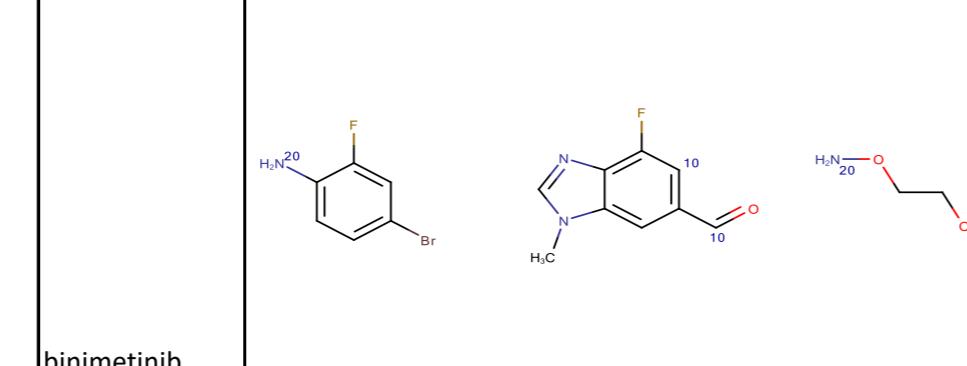
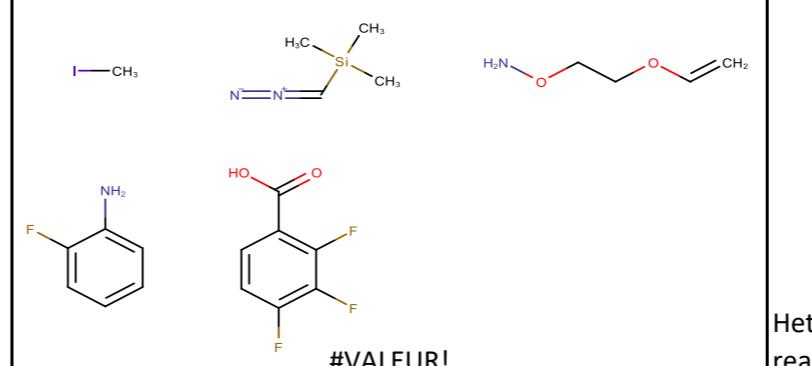
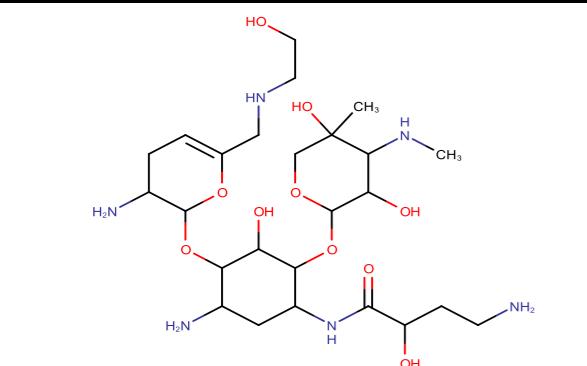
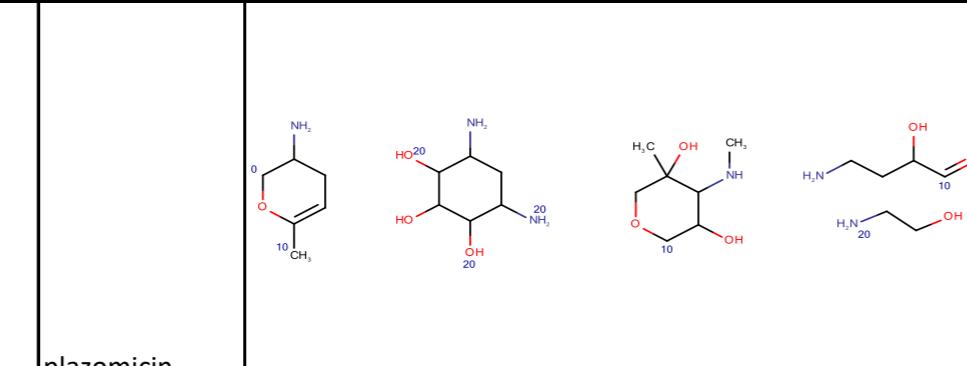
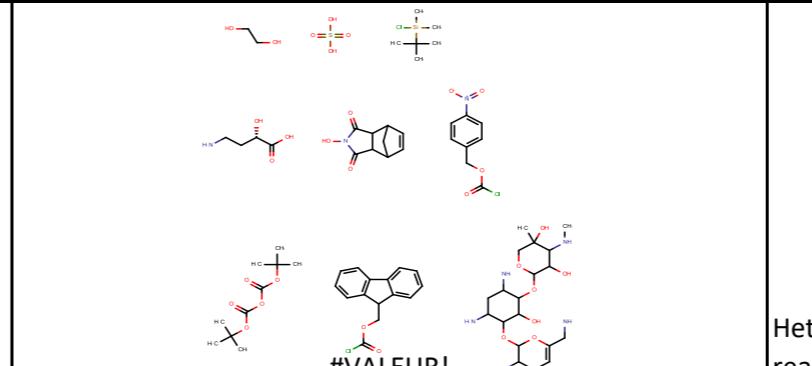
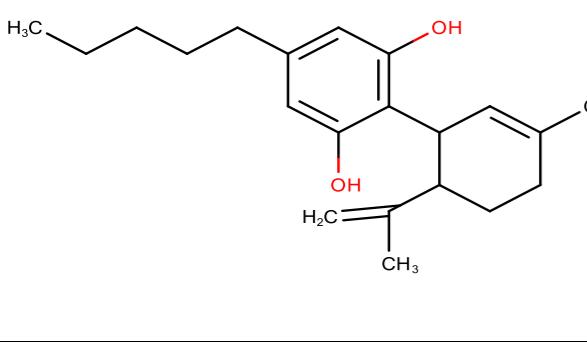
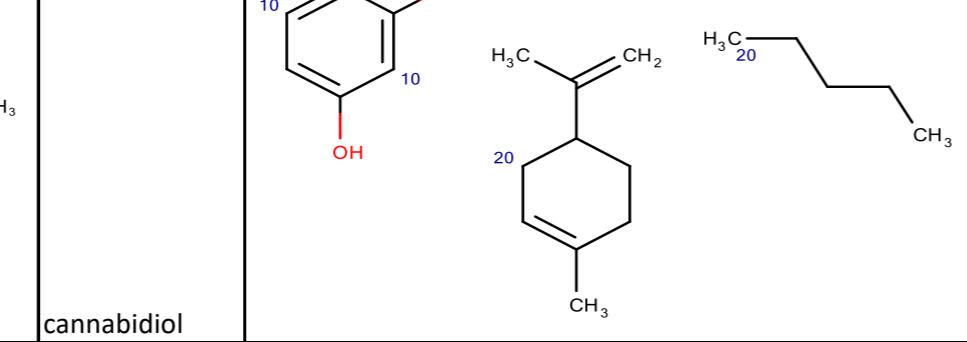
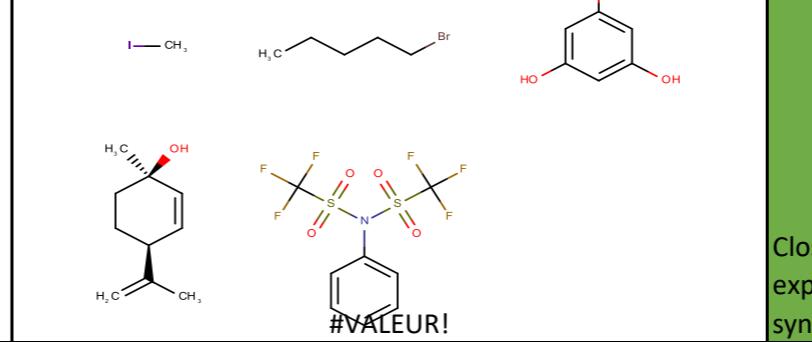
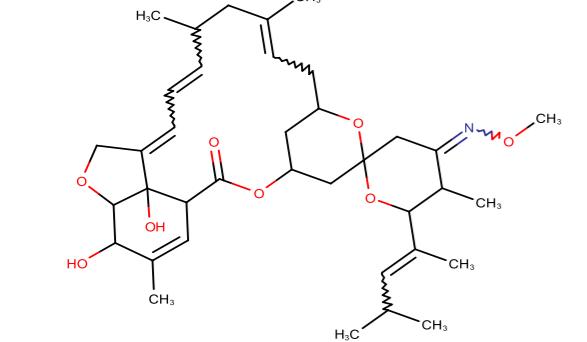
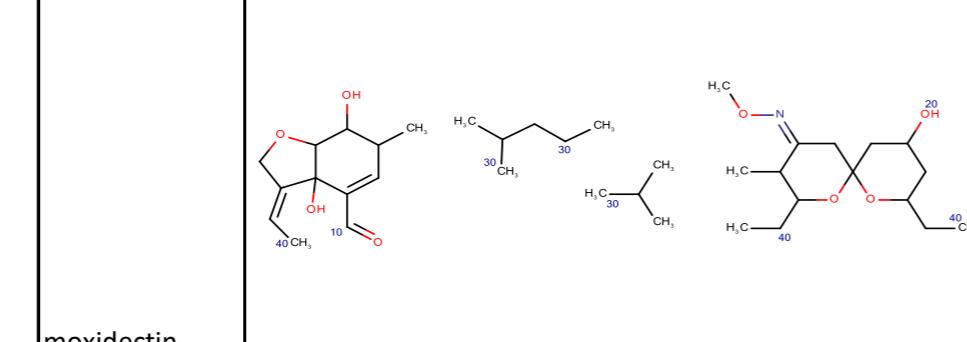
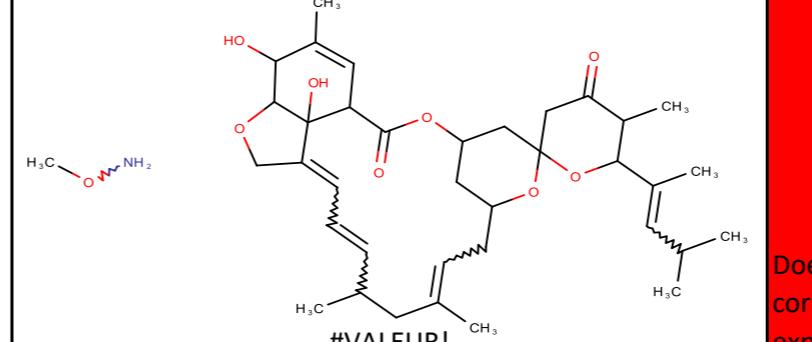
	istradefylline	 	 #VALEUR!	Heterocyclization reactions prevail	Synthesis of antiparkinsonian agent istradefylline By Li, Fan et al From Zhongguo Yiyao Gongye Zazhi, 41(4), 241-243; 2010
	fedratinib		 #VALEUR!	Fits perfectly to the alternative root, produced by Synthl.	Preparation of bi-aryl 2,4-pyrimidinediamines as inhibitors of kinases By Hood, John D. and Noronha, Glenn From U.S. Pat. Appl. Publ., 20090286789, 19 Nov 2009
	prucalopride		 #VALEUR!	Heterocyclization reaction. Remaining stages match	Preparation method of prucalopride By Feng, Chengliang et al From Faming Zuanli Shengqing, 108976216, 11 Dec 2018
	gilteritinib		 #VALEUR!	Synthl produce smaller fragments, that correspond to the experimental procedure.	Preparation of diamino heterocyclecarboxamide compounds as EML4-ALK fusion protein kinase inhibitors By Shimada, Itsuro et al From PCT Int. Appl., 2010128659, 11 Nov 2010

	larotrectinib			Fits 2/3 synthons produced by SynthI correspond to the experimental path	Method for synthesizing larotrectinib useful as Trk inhibitors By Li, Xinsheng et al From Faming Zuanli Shenqing, 109354578, 19 Feb 2019
	glasdegib			Heterocyclization reactions prevail	Development of a Concise, Asymmetric Synthesis of a Smoothed Receptor (SMO) Inhibitor: Enzymatic Transamination of a 4-Piperidinone with Dynamic Kinetic Resolution By Peng, Zhiwei et al From Organic Letters, 16(3), 860-863; 2014
	refezenacin			Fits 3/4 synthons of the alternative root produced by SynthI correspond to the experimental path	Process for preparing a biphenyl-2-ylcarbamic acid 1-(2-[[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino]ethyl)piperidin-4-yl ester By Colson, Pierre-Jean From PCT Int. Appl., 2012009166, 19 Jan 2012

	lorlatinib			Experimental pathway is very similar to the alternative route, produced by Synthl.	MACROCYCLIC DERIVATIVES FOR THE TREATMENT OF PROLIFERATIVE DISEASES. PFIZER INC.; BAILEY, Simon; BURKE, Benjamin, Joseph; COLLINS, Michael, Raymond; CUI, Jingrong, Jean; DEAL, Judith, Gail; HOFFMAN, Robert, Louis; HUANG, Qinhua; JOHNSON, Ted, William; KANIA, Robert, Steven; KATH, John, Charles; LE, Phuong, Thi, Quy; MCTIGUE, Michele, Ann; PALMER, Cynthia, Louise; RICHARDSON, Paul, Francis; SACH, Neal, WilliamWO2013/132376, 2013, A1
	baloxavir marboxil			Heterocyclization reactions prevail	Preparation of sulfur-containing heterocyclic compound By Liu, Xuejun et al From Faming Zhanli Shenqing, 111825699, 27 Oct 2020
	talazoparib			Heterocyclization reactions prevail	Preparation of PARP inhibitor talazoparib and intermediates thereof By Xu, Yong et al From U.S., 9708319, 18 Jul 2017
	omadacycline			Does not correspond to the experimental path	Process Research and Development of TP808: A Key Intermediate for the Manufacture of Synthetic Tetracyclines By Zhang, Wu-Yan et al From Organic Process Research & Development, 21(3), 377-386; 2017; PARATEK PHARMACEUTICALS, INC.; DRAPER, Michael, P.; TANAKA, S., KenWO2016/154332, 2016, A1 Location in patent: Page/Page column 49

	sarecycline			Does not correspond to the experimental path	A novel synthetic approach for the synthesis of pyridocarbazole alkaloids By: Erguen, Yavuz; et al Journal of Heterocyclic Chemistry (2003), 40(6), 1005-1010.; PARATEK PHARMACEUTICALS, INC.; ALMIRALL, LLC; GIOVANNI, Palombi; EUGENIO, Castelli; GIUSEPPE, Motta; BRENNER, Meinrad; LU, Ruiliang; (...) SEYEDI, Faye; JOHNSTON,
	dacomitinib			Fits perfectly to the alternative root, produced by Synthl.	Preparation method of dacomitinib for treating non-small cell lung cancer By Sun, Tingting From Faming Zhanli Shenqing, 107698524, 16 Feb 2018
	duvelisib			Heterocyclization reactions prevail	Processes for preparing isoquinolinones and solid forms of isoquinolinones By Ren, Pingda et al From PCT Int. Appl., 2012097000, 19 Jul 2012
	doravirine			Heterocyclization reactions prevail	Process for preparing pyridin-2(1H)-one derivatives as reverse transcriptase inhibitors By Cao, Yang et al From PCT Int. Appl., 2015084763, 11 Jun 2015
	eravacycline			Heterocyclization reactions prevail	A Divergent Route to Eravacycline By Zhang, Wu-Yan et al From Journal of Organic Chemistry, 82(2), 936-943; 2017

	stiripentol			Heterocyclization reactions prevail	Synthesis of the antiepileptic (R)-Stiripentol by a combination of lipase catalyzed resolution and alkene metathesis By El-Behairy, Mohammed Farrag and Sundby, Eirik From Tetrahedron: Asymmetry, 24(5-6), 285- 289; 2013
	migalastat			Heterocyclization reactions prevail	Kato, Atsushi; Hirokami, Yuki; Kinami, Kyoko; Tsuji, Yutaro; Miyawaki, Shota; Adachi, Isao; Hollinshead, Jackie; Nash, Robert J.; Kiappes; Zitzmann, Nicole; Cha, Jin K.; Molyneux, Russell J.; Fleet, George W.J.; Asano, Naoki[Phytochemistry, 2015, vol. 111, p. 124 - 131]
	lusutrombopag			Heterocyclization reactions prevail	Preparation of high-purity crystals of optically active compounds as thrombopoietin receptor agonists and their intermediates By Fukui, Yuuki et al From PCT Int. Appl., 2015093586, 25 Jun 2015
	ivosidenib			Experimental pathway is very similar to the alternative route, produced by Synthl.	TEVA PHARMACEUTICALS USA, INC.; ASSIA CHEMICAL INDUSTRIES LTD; MUTHUSAMY, Anantha Rajmohan; SINGH, Amit; YAZALI, Venkata Subbarao; LUTHRA, Parven Kumar; VASOYA, Sanjay Lakhbhai; PATIL, Bhatu Tumba; TANEJA, Amit Kumar; SRIVASTAV, Naveen Chandra; SINGH, Rinku; RENGASAMY, Vadivelan; TYAGI, AbhilashWO2019/104318, 2019, A1 Location in patent: Paragraph 00202; 00205
	tecovirimat			Heterocyclization reactions prevail	Process for the preparation of tecovirimat By Dai, Dongcheng From PCT Int. Appl., 2014028545, 20 Feb 2014

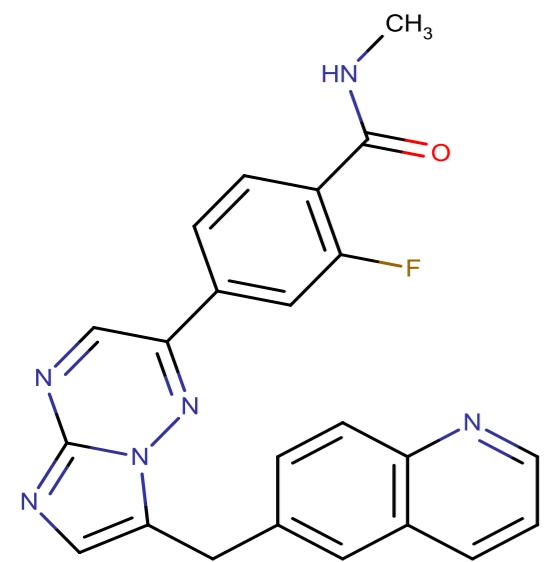
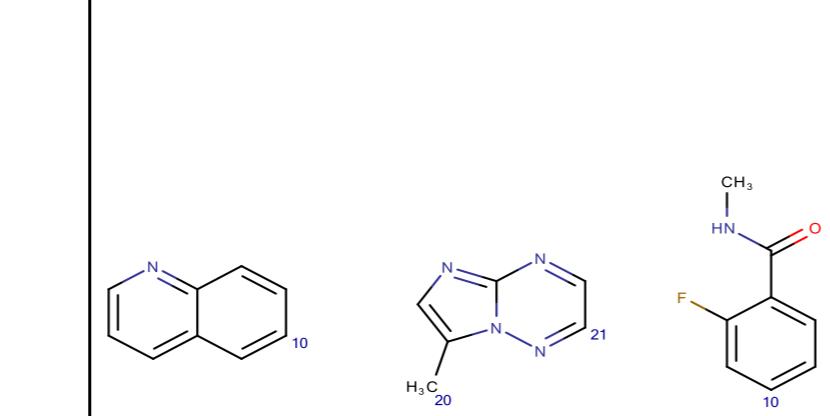
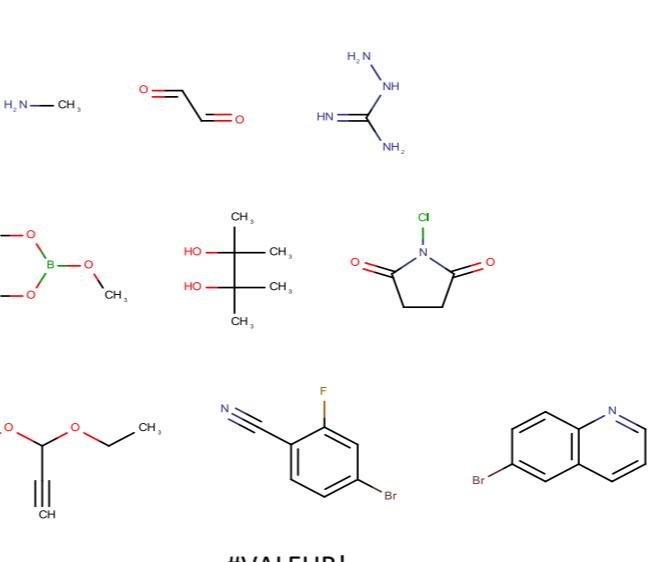
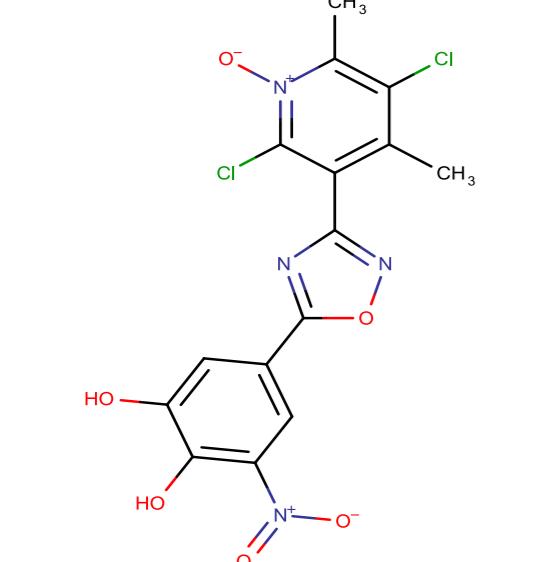
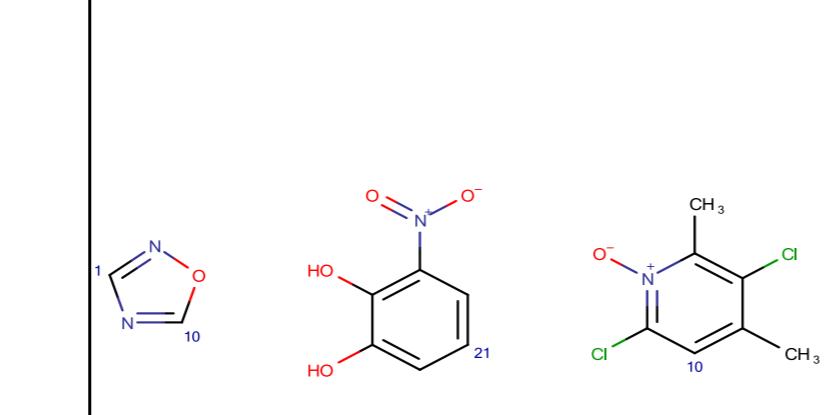
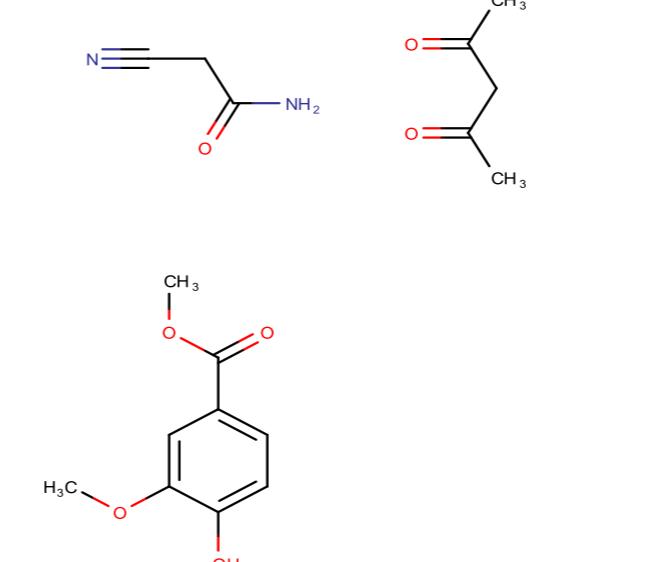
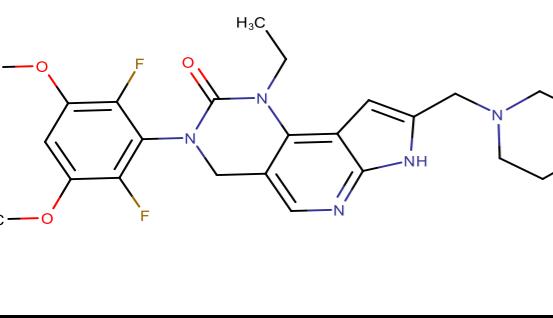
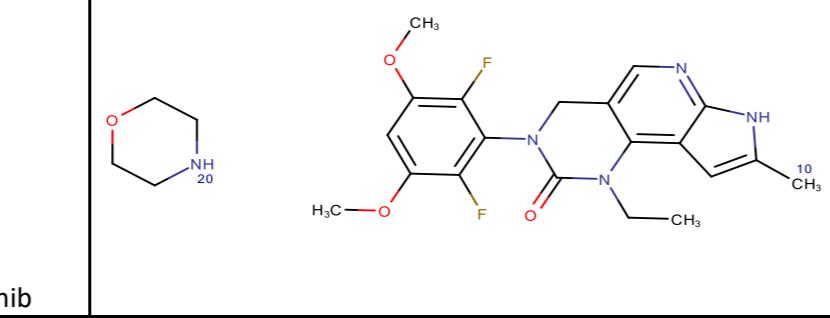
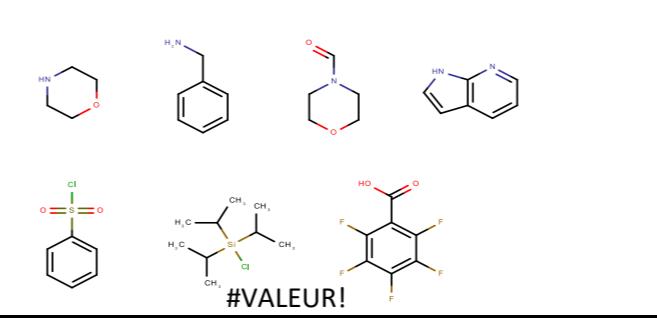
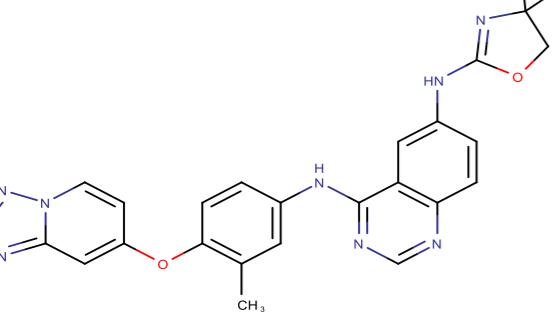
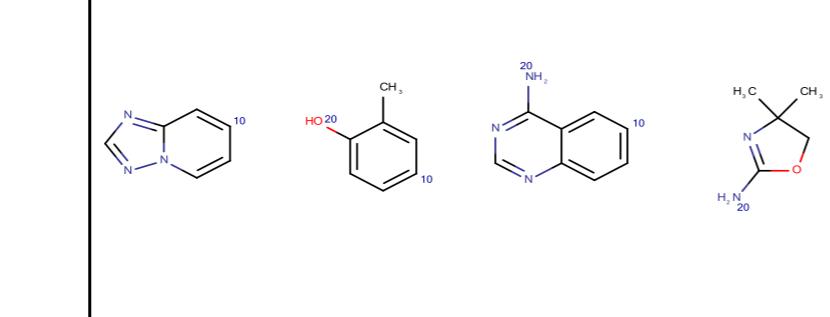
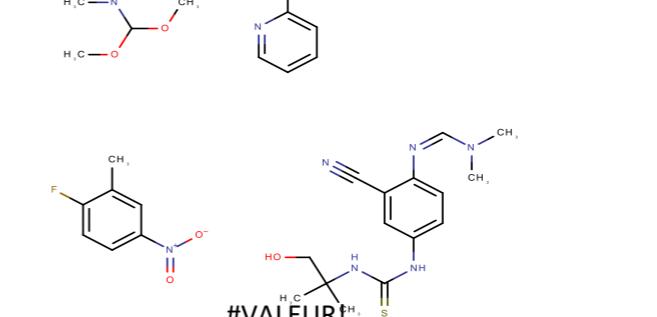
	encorafenib		 #VALEUR!	Heterocyclization reactions prevail	Preparation of sulfonamidophenylimidazopyrimidine derivatives and analogs for use as protein kinase inhibitors By Huang, Shenlin et al From PCT Int. Appl., 2011025927, 03 Mar 2011
	binimetinib		 #VALEUR!	Heterocyclization reactions prevail	Combination therapy By Huang, Xizhong et al From PCT Int. Appl., 2013142182, 26 Sep 2013
	plazomicin		 #VALEUR!	Heterocyclization reactions prevail	Method for preparing plazomicin antibiotic for bacterial infection By Ma, Shutao and Cai, Xiaokang From Faming Zhuanli Shenqing, 108948107, 07 Dec 2018
	cannabidiol		 #VALEUR!	Close to the experimental synthesis	Catalytic cannabinoid processes and precursors By Abdur-Rashid, Kamaluddin et al From PCT Int. Appl., 2020232545, 26 Nov 2020
	moxidectin		 #VALEUR!	Does not correspond to the experimental path	Dalian Join King Biochemical Tech Co., Ltd; Dai, Yao; Du, Zhibo; Wang, Rongliang CN104017001, 2016, B Location in patent: Paragraph 0018; 0049; 0050

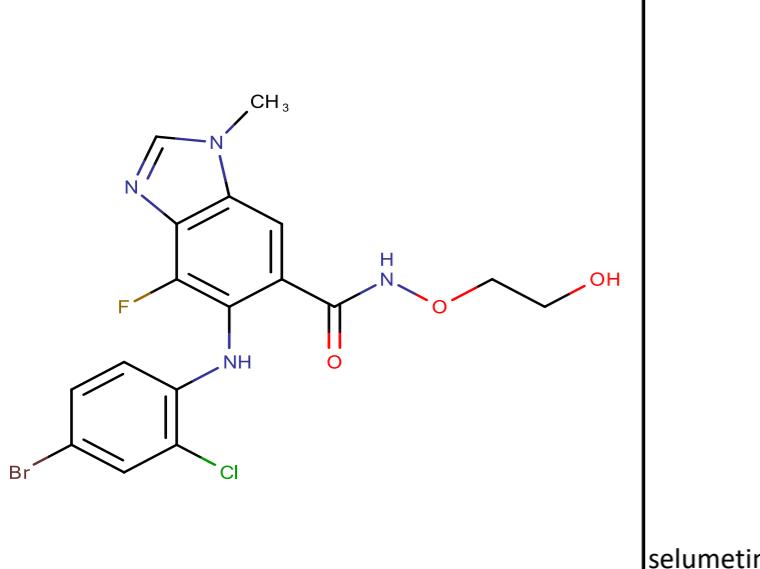
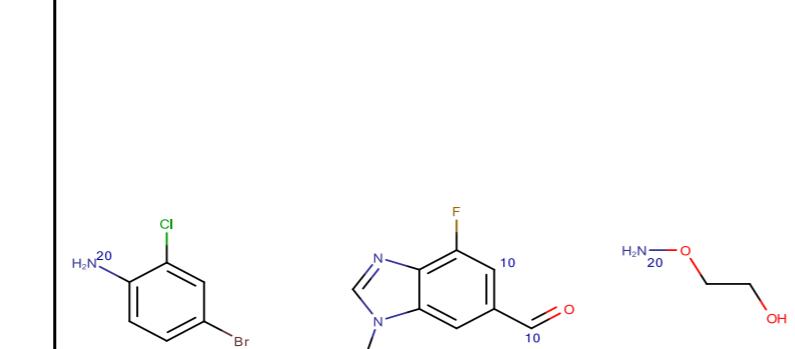
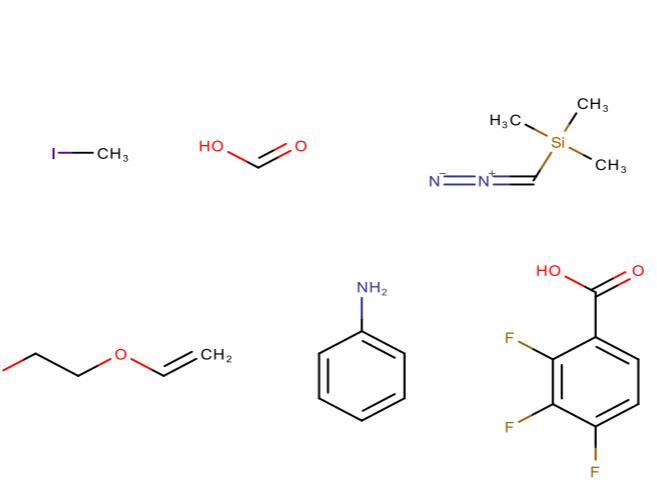
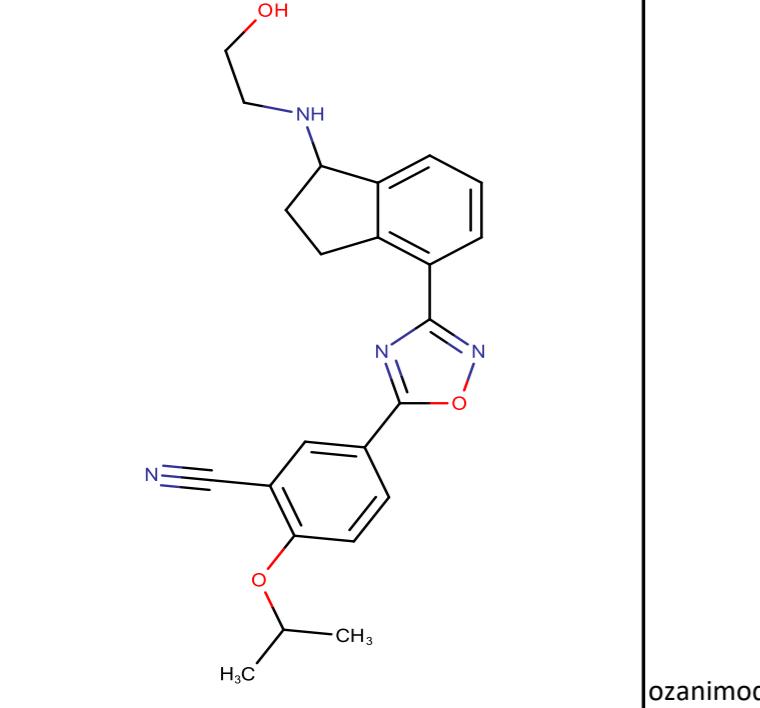
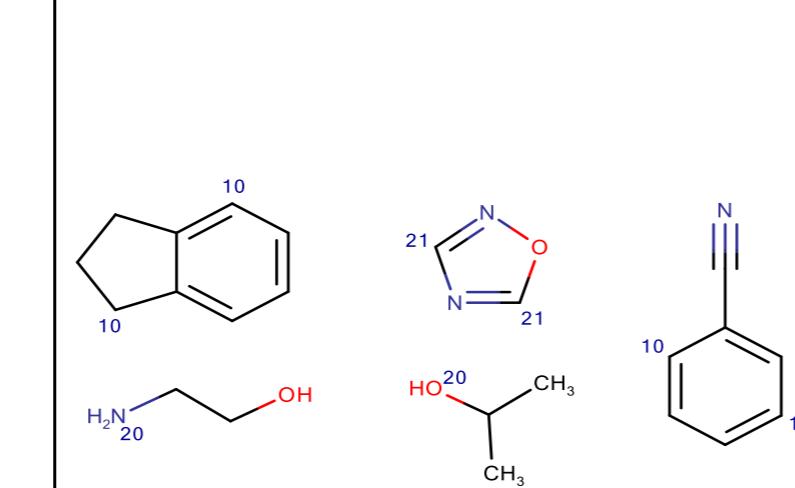
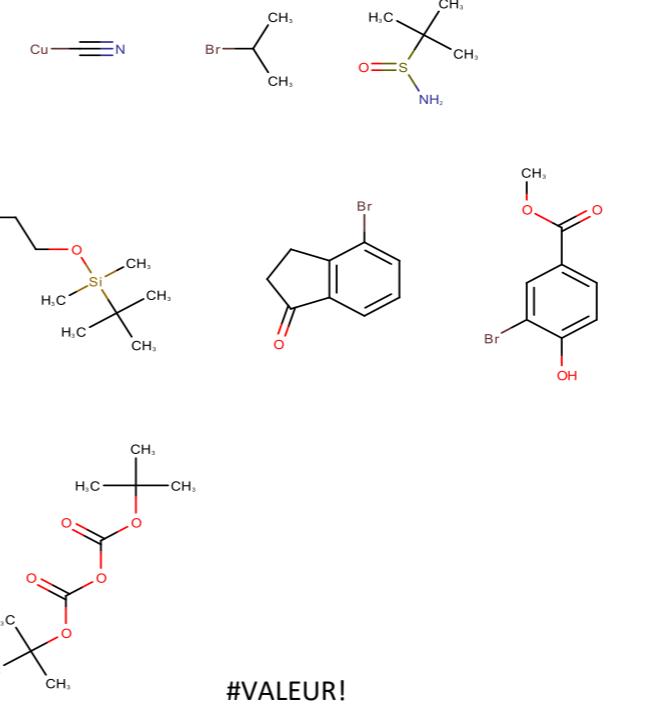
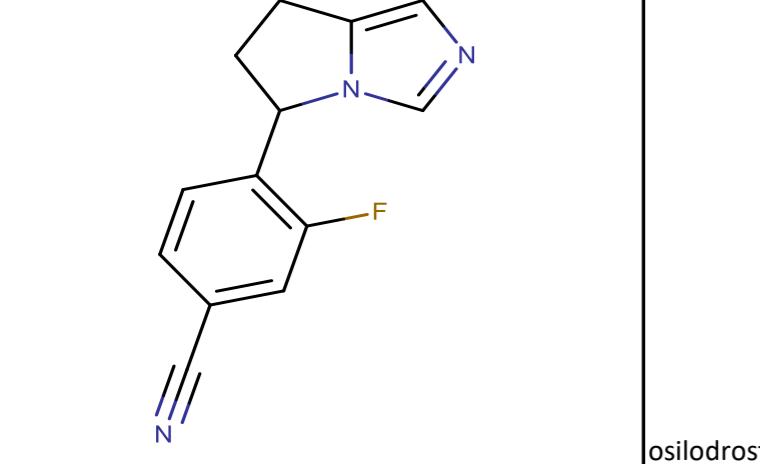
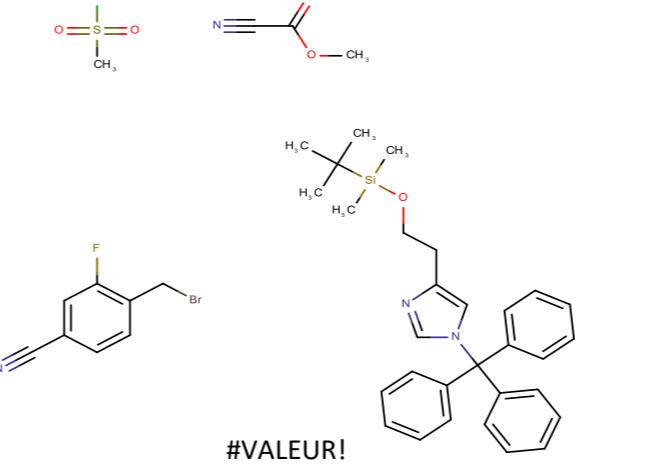
	baricitinib			1 heterocyclization stage. All other BBs correspond perfectly to Synthl results #VALEUR!	Preparation of azetidine and cyclobutane derivatives as JAK inhibitors By Rodgers, James D. et al From PCT Int. Appl., 2009114512, 17 Sep 2009
	avatrombopag			1 heterocyclization stage. All other BBs correspond perfectly to Synthl results #VALEUR!	Method of producing avatrombopag By Fazylov, Marat Felixovich et al From PCT Int. Appl., 2021021000, 04 Feb 2021
	fostamatinib			Fits perfectly to the alternative root, produced by Synthl. #VALEUR!	Preparation of pharmaceutical 2,4-pyrimidinediamines in large scale By Mckeever, Benedict et al From PCT Int. Appl., 2015095765, 25 Jun 2015
	apalutamide			Heterocyclization reactions prevail #VALEUR!	Preparation of hydantoins as androgen receptor modulators for the treatment of prostate cancer and other androgen receptorassociated diseases. By Jung, Michael E. et al From PCT Int. Appl., 2007126765, 08 Nov 2007
	pralsetinib			Fits perfectly to the alternative root, produced by Synthl. #VALEUR!	Preparation of heterocycl aminopyrazoles as inhibitors of RET kinase for the treatment of cancer By Brubaker, Jason D. et al From U.S. Pat. Appl. Publ., 20170121312, 04 May 2017; Preparation of N-containing heteroaryl derivative as protein kinase inhibitors and anticancer By Jo, Seo Hyun et al From PCT Int. Appl., 2020175968, 03 Sep 2020

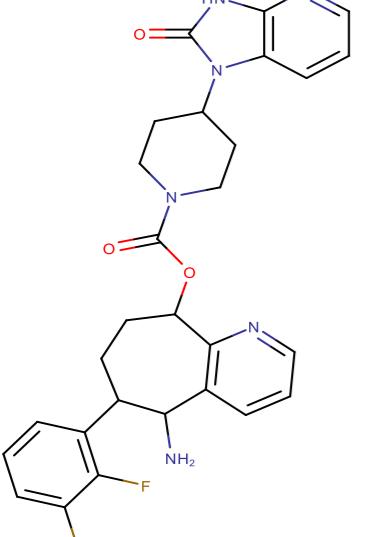
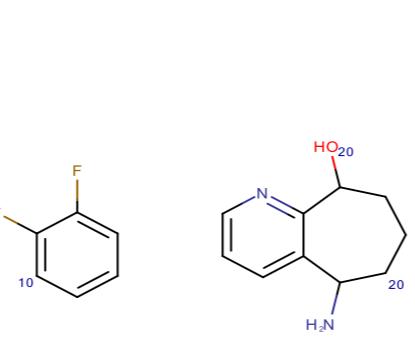
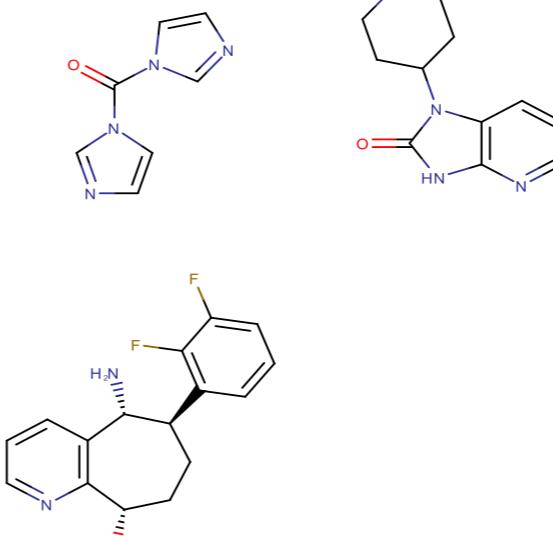
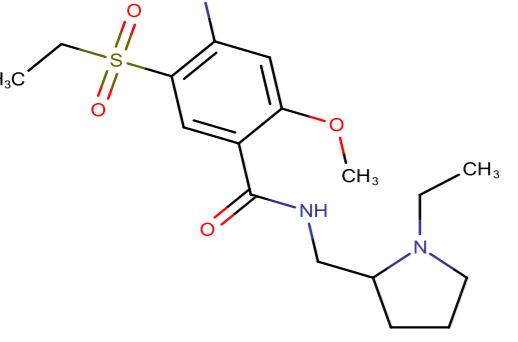
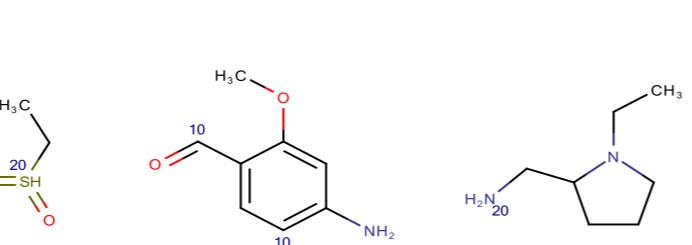
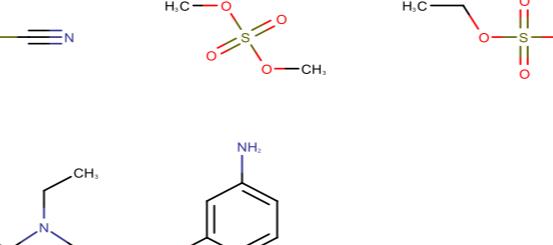
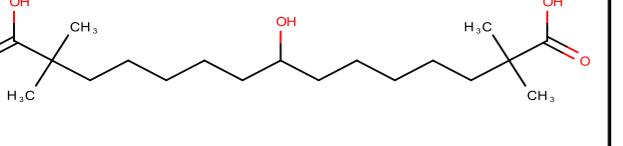
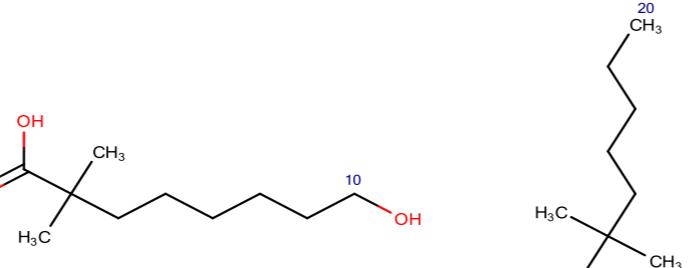
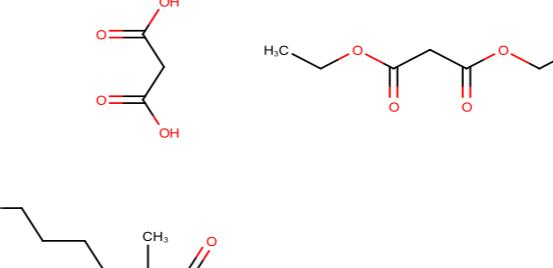
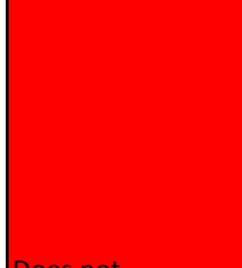
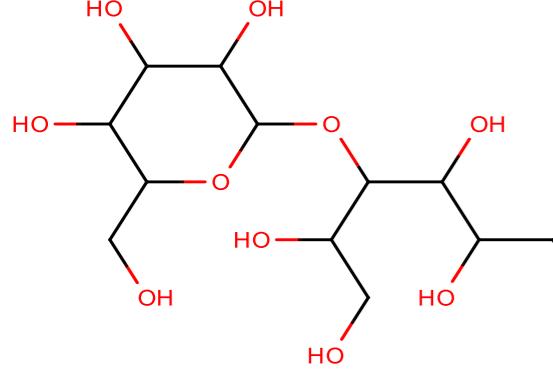
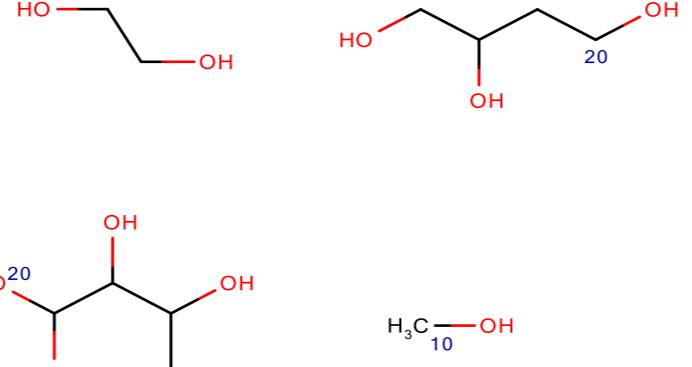
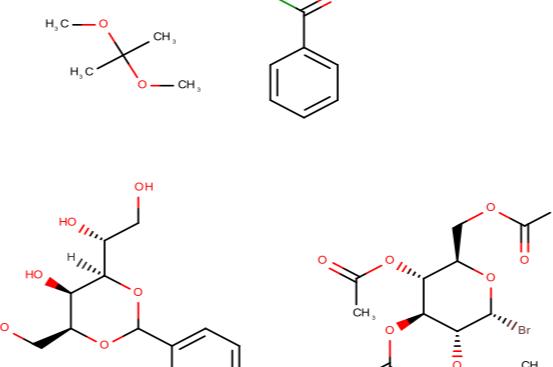
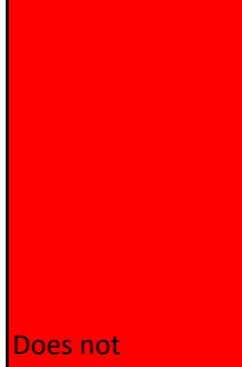
	clascoterone				Fits perfectly to the alternative root, produced by Synth!	COSMO SPA US2011/92472, 2011, A1 Location in patent: Page/Page column 5
	oliceridine				Heterocyclization reactions prevail	Preparation of deuterated compounds for treating pain By Huang, Chaoran and Cheng, Changfu From PCT Int. Appl., 2018006077, 04 Jan 2018
	risdiplam				Heterocyclization reactions prevail	Process for the preparation of 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one derivatives By Adam, Jean-Michel et al From PCT Int. Appl., 2019057740, 28 Mar 2019
	nifurtimox				Fits perfectly to the experimental path	Knowledge on the reactivity of thiomorpholine and alkyl-substituted thiomorpholines. Part 4. Joint effect of elementary sulfur and gaseous ammonia on ketones. Part 94 By: Asinger, Friedrich; et al Monatshefte fuer Chemie (1980), 111(2), 385-98.
	abametapir				No Phosphine-Free Nickel-Catalyzed Reductive Couplings in Synth!	Liao, Lian-Yan; Kong, Xing-Rui; Duan, Xin-Fang[Journal of Organic Chemistry, 2014, vol. 79, # 2, p. 777 - 782]

	decitabine				Does not correspond to the experimental path #VALEUR!	Chemi SPA EP2371825, 2011, A1 Location in patent: Page/Page column 9
	cedazuridine				Reduction (reaction absent in Synthl 1.0) #VALEUR!	Design, Synthesis, and Pharmacological Evaluation of Fluorinated Tetrahydouridine Derivatives as Inhibitors of Cytidine Deaminase By Ferraris, Dana et al From Journal of Medicinal Chemistry, 57(6), 2582-2588; 2014
	fostemsavir				1 heterocyclization stage. All other BBs correspond perfectly to Synthl results #VALEUR!	Preparation of the HIV Attachment Inhibitor BMS-663068. Part 1. Evolution of Enabling Strategies By Fox, Richard J. et al From Organic Process Research & Development, 21(8), 1095-1109; 2017
	remimazolam				Heterocyclization reactions prevail. #VALEUR!	Process for preparation of benzodiazepine derivative By Tilbrook, Stuart Gary et al From PCT Int. Appl., 2011032692, 24 Mar 2011
	triheptanoin				2/3 reaction steps correspond to experimental path #VALEUR!	Catalyst-controlled polycondensation of glycerol with diacyl chlorides: linear polyesters from a trifunctional monomer By Slavko, Ekaterina and Taylor, Mark S. From Chemical Science, 8(10), 7106-7111; 2017

	lurbinectedin			Heterocyclization reactions prevail.	A Scalable Total Synthesis of the Antitumor Agents Et-743 and Lurbinectedin By He, Weiming et al From Angewandte Chemie, International Edition, 58(12), 3972-3975; 2019
	artesunate			Fits perfectly to the experimental path	Gotsbacher, Michael P.; Cho, Sung Min; Kim, Nam Hee; Liu, Fei; Kwon, Ho Jeong; Karuso, Peter[ACS Chemical Biology, 2019, vol. 14, # 4, p. 636 - 643]
	ripretinib			1 heterocyclization stage. All other BBs correspond to experimental synthetic path	Preparation of dihydronaphthyridines and related compounds useful as kinase inhibitors for the treatment of proliferative diseases By Flynn, Daniel L. et al From U.S., 8461179, 11 Jun 2013
	selpcatinib			1 heterocyclization stage. All other BBs correspond to alternative SynthI path	Formulations comprising 6-(2-hydroxy-2-methylpropoxy)-4-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile By Reynolds, Mark and Eary, Charles Todd From PCT Int. Appl., 2019075114, 18 Apr 2019

	capmatinib		 #VALEUR!	1 heterocyclization stage. All other BBs correspond to experimental synthetic path Salts of 2-fluoro-N-methyl-4-[7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl]benzamide and processes related to preparing the same By Weng, Lingkai et al From PCT Int. Appl., 2009143211, 26 Nov 2009
	opicapone		 #VALEUR!	A [1,2,4]oxadiazole derivative as an intermediate for preparation of a catechol-Omethyltransferase inhibitor useful in treatment of Parkinson's disease via demethylation and its preparation By Russo, Domenico et al From PCT Int. Appl., 2013089573, 20 Jun 2013
	pemigatinib		 #VALEUR!	Heterocyclization reactions prevail. Solid forms of a pyrrolopyridopyrimidine, an FGFR inhibitor and processes for preparing the same By Burn, Timothy C. et al From PCT Int. Appl., 2019213544, 07 Nov 2019
	tucatinib		 #VALEUR!	Heterocyclization reactions prevail. Preparation of tucatinib and its intermediate products By Wang, Yuxuan et al From Faming Zhanli Shenqing, 111825604, 27 Oct 2020

	selumetinib		 #VALEUR!	1 heterocyclization stage. All other BBs correspond to experimental synthetic path	Preparation of phenylaminobenzimidazolecarboxylates as mitogen activated protein kinase kinase (MEK) inhibitors By Wallace, Eli M. et al From U.S. Pat. Appl. Publ., 20040116710, 17 Jun 2004
	ozanimod		 #VALEUR!	Heterocyclization reactions prevail.	Deuterium-substituted oxadiazoles as S1P1 modulators and their preparation By Zhang, Chengzhi and Chakma, Justin From PCT Int. Appl., 2016164180, 13 Oct 2016
	osilodrostat		 #VALEUR!	Not fragmented with SynthI	Meredith, Erik L.; Ksander, Gary; Monovich, Lauren G.; Papillon, Julien P. N.; Liu, Qian; Miranda, Karl; Morris, Patrick; Rao, Chang; Burgis, Robin; Capparelli, Michael; Hu, Qi-Ying; Singh, Alok; Rigel, Dean F.; Jeng, Arco Y.; Beil, Michael; Fu, Fumin; Hu, Chii-Whei; Lasala, Daniel[ACS Medicinal Chemistry Letters, 2013, vol. 4, # 12, p. 1203 - 1207]

	rimegepant		 #VALEUR!		Process for the preparation of cycloheptapyridine CGRP receptor antagonists By Leahy, David K. et al From PCT Int. Appl., 2012050764, 19 Apr 2012
	amisulpride		 #VALEUR!		An improved process for preparation of amisulpride By Paghdar, Dinesh Jayntibhai et al From Indian Pat. Appl., 2010KO00648, 02 Sep 2016
	bemedoic acid		 #VALEUR!		Preparation of novel salts and a polymorphic form of bemedoic acid By Kadam, Navnath Ambadas et al From PCT Int. Appl., 2020141419, 09 Jul 2020
	lactitol		 #VALEUR!		Preparation of polysulfated glycosides and oligosaccharides for use as anti-inflammatory agents related to disorders in the airways of mammals By Kuszmann, Janos et al From PCT Int. Appl., 2006017726, 16 Feb 2006

<p>tazemetostat</p>	<p>#VALEUR!</p>	<p>#VALEUR!</p>	<p>Fits perfectly to the experimental path</p> <p>Preparation of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide monohydrobromide polymorph as an EZH2 inhibitor for cancer treatment By Kuntz, Kevin Wayne et al From PCT Int. Appl., 2013155317, 17 Oct 2013</p>
<p>avapritinib</p>	<p>#VALEUR!</p>	<p>#VALEUR!</p>	<p>1 heterocyclization stage. All other BBs correspond to experimental synthetic path</p> <p>Compositions containing substituted pyrrolotriazines useful for treating disorders related to KIT and PDGF-R By Zhang, Yulian et al From PCT Int. Appl., 2015057873, 23 Apr 2015</p>