Supplementary Materials: Potential Drugs Targeting the SARS-Coronavirus 2 RNA Cap 2′-O-Methyltransferase nsp16/nsp10 Complex

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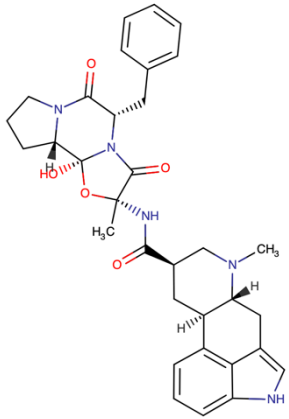
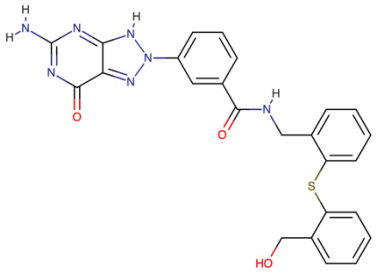
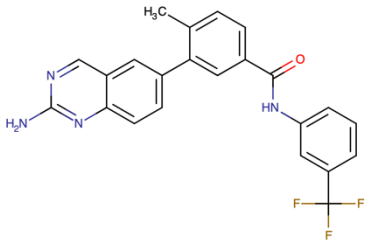
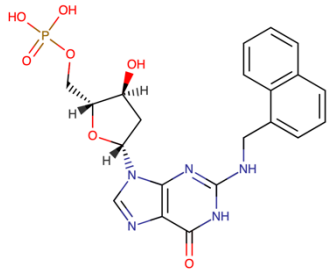
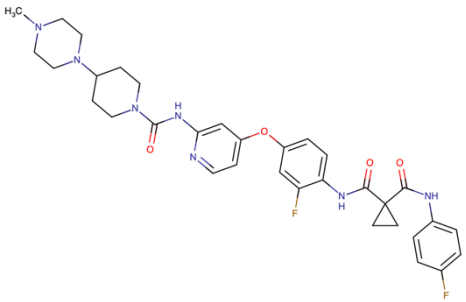
Table S1. Binding energies and dissociation constants of top-scoring nsp16/nsp10-targeting candidates.

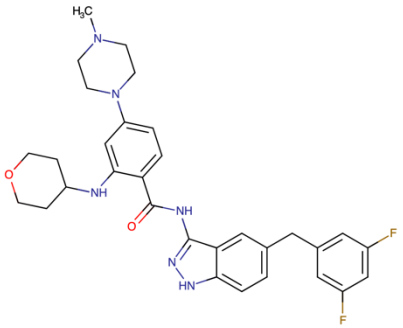
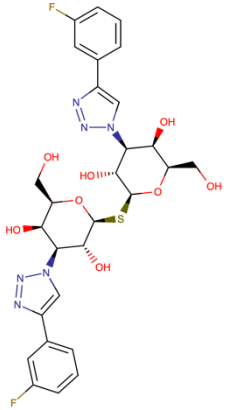
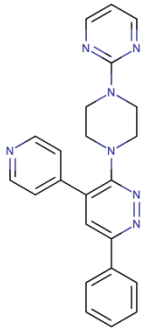
DB Code	Generic Name	SAM-Binding Site	Nsp16/nsp10 Interface	RNA-Binding Groove
		ΔG (kcal/mol)/K_D (μM)	ΔG (kcal/mol)/K_D (μM)	ΔG (kcal/mol)/K_D (μM)
DB00320	Dihydroergotamine	−10.8/0.0243		
DB03231	–	−10.3/0.0547		
DB06925	–	−10.3/0.0547		
DB08237	–	−10.3/0.0547		
DB11977	Golvatinib	−10.3/0.0547		
DB11986	Entrectinib	−10.3/0.0547		
DB12895	TD-139	−10.3/0.0547		
DB12899	TT-301	−10.3/0.0547		
DB13053	CP-195543	−10.3/0.0547		
DB14870	PF-5190457	−10.3/0.0547		
DB01897	–	−10.2/0.0643		
DB03571	–	−10.1/0.0757		
DB06638	Quarfloxin		−8.9/0.5309	
DB12799	Laniquidar		−8.9/0.5309	
DB06555	Siramesine		−8.5/1.0163	
DB05075	TG-100801		−8.4/1.1954	
DB13050	Tirilazad		−8.4/1.1954	
DB00872	Conivaptan		−8.4/1.1954	
DB14895	Vibegron		−8.4/1.1954	
DB06938	–		−8.3/1.4061	
DB11852	Tegobuvir		−8.2/1.654	
DB12341	Aticaprant		−8.2/1.654	
DB04289	Genz-10850		−8.2/1.654	
DB09143	Sonidegib		−8.1/1.9455	
DB04016	–			−9.8/0.1231
DB12457	Rimegepant			−9.7/0.1449
DB13109	PKI-179			−9.4/0.2358
DB01830	AP-22408			-9.4/0.2358
DB05678	SLx-4090			−9.3/0.2773

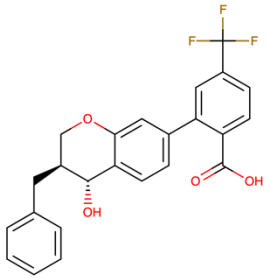
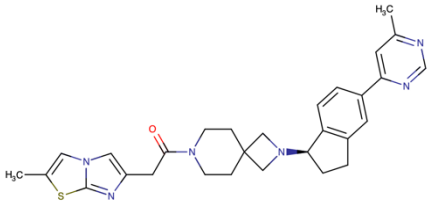
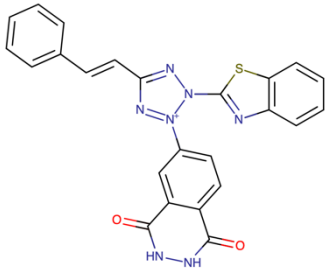
DB08233	–			−9.3/0.2773
DB08827	Lomitapide			−9.2/0.3262
DB03067	–			−9.2/0.3262
DB06896	-			−9.2/0.3262
DB15308	Ridinilazole			−9.1/0.3837
DB12154	Itacitinib			−9.1/0.3837
DB13042	Fenoverine			−9.0/0.4513
DB02449	-			−9.0/0.4513
DB15057	NUC-1031			−9.0/0.4513
DB12411	Bemcentinib	−10.9/0.0206	−8.5/1.0163	
DB05984	RAF-265	−10.2/0.0643	−8.3/1.4061	
DB01419	Antrafenine	−10.1/0.0757	−8.3/1.4061	
DB12012	PF-04457845	−10.4/0.0465		−9.1/0.3837
DB15382	SAR-125844		−8.2/1.654	−9.7/0.1449
DB12983	Phthalocyanine	−10.9/0.0206	−9.1/0.3837	−10.2/0.0643
DB12424	MK-3207	−10.9/0.0206	−8.5/1.0163	−9.7/0.1449
DB14773	Lifirafenib	−10.2/0.0643	−8.4/1.1954	−9.6/0.1704
DB11611	Lifitegrast	−10.3/0.0547	−8.3/1.4061	−9.0/0.4513

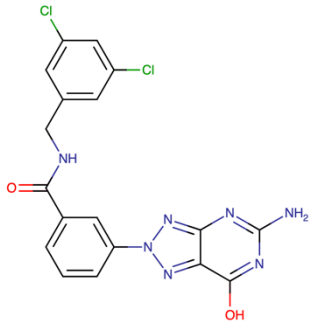
Table S2. Drug candidates targeting the SAM-binding site of the nsp16/nsp10 protein complex.

Compound Name	Compound Structure	Human Target	Drug Status
Dihydroergotamine		5-HT$_{1D}$a 5-HT$_{1D}$b receptors	Approved (migraine)
DB03231 **(EXPT02670)**		Dihydroneopterin aldolase (*Staphylococcus aureus*)	Experimental

DB06925		Tyrosine-protein kinase Lck	Experimental
DB08237		DNA polymerase kappa	Experimental
Golvatinib		c-MET/VEGFR2	Investigational

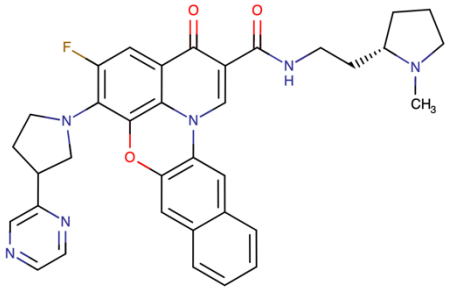
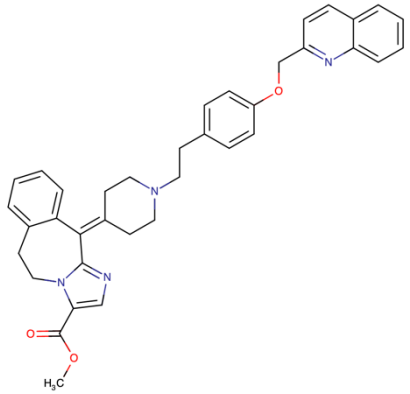
Entrectinib		Tropomyosin receptor tyrosine kinases (TRKA, TRKB, TRKC) Proto-oncogene tyrosine-protein kinase (ROS1) Anaplastic lymphoma kinase (ALK)	Approved (ROS1-positive metastatic non-small cell lung cancer and NTRK gene fusion positive solid tumors)
TD-139		Galectin-3	Investigational
TT-301		-	Investigational

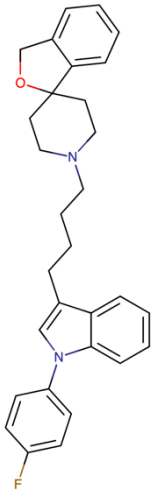
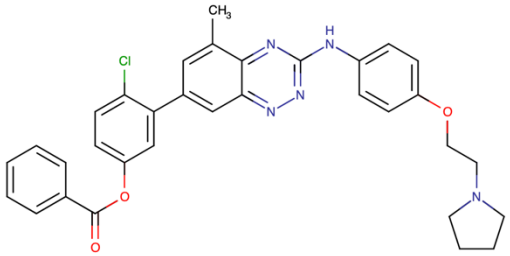
CP-195543		Leukotriene B4 receptor	Investigational
PF-5190457		GH secretagogue receptor (GHS-R1a)	Investigational
DB01897		Hematopoietic prostaglandin D synthase	Experimental

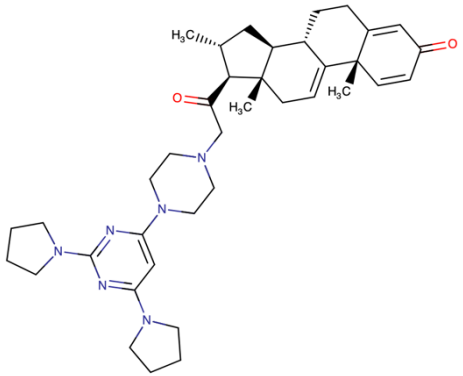
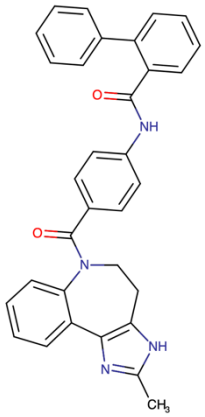
DB03571 (EXPT00198)		Dihydroneopterin aldolase (*Staphylococcus aureus*)	Experimental

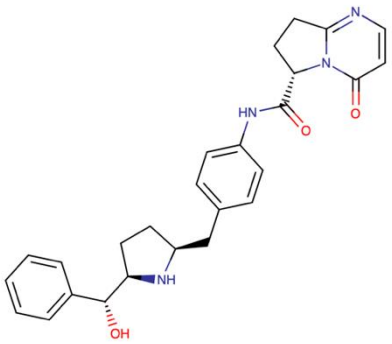
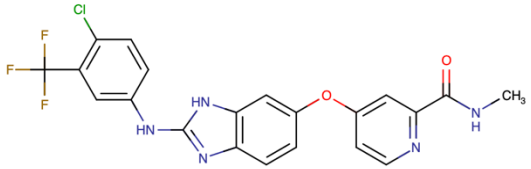
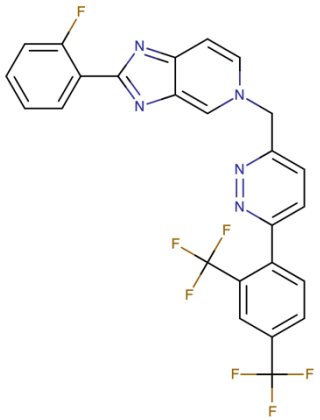
Five of the predicted drugs were experimental ones, namely: DB03231 [3-(5-Amino-7-oxo-3,7-dihydro-2H-[1,2,3]triazolo[4,5-d]pyrimidin-2-yl)-*N*-(2-{[2-(hydroxymethyl)phenyl]sulfanyl}benzyl)benzamide)], DB06925 [3-(2-aminoquinazolin-6-yl-)-4-methyl-*N*-[3-(trifluoromethyl)phenyl]benzamine], and DB08237 [2′-deoxy-*N*-(naphtalen-1-ylmethyl)guanosine 5′-(dihydrogen phosphate)], DB01897 [2-(2f-benzothiazolyl)-5-styryl-3-(4f-phthalhydrazidyl)tetrazolium chloride], and DB03571 [3-(5-amino-7-hydroxy-[1,2,3]triazolo[4,5-d]pyrimidin-2-yl)-*N*-(3,5-dichlorobenzyl)-benzamide]. DB03231 is an *N*-benzylbenzamide targeting the dehydroneopterin aldolase activity in *Staphylococcus aureus*. DB06925 is a benzalnilide targeting the Lck protein, an Src family tyrosine kinase playing a critical role in T cell maturation and activation. DB08237 is a purine 2′-deoxyribonucleoside monophosphate targeting the DNA polymerase kappa specifically involved in DNA repair. DB01897 is a phthalazinone targeting the hematopoietic prostaglandin D synthase, a bifunctional enzyme catalyzing both the conversion of PGH2 to PGD2 and the conjugation of glutathione with aryl halides and organic isothiocyanates. DB03571 is an n-benzylbenzamide dehydroneopterin targeting aldolase activity in *S. aureus*. Five of the predicted drugs were investigational ones, namely: DB11977 (golvatinib), DB12895 (TD-139), DB12899 (TT-301), DB13053 (CP-195543), and DB14870 (PF-5190457). Golvatinib (also known as E7050) is a diarylether that potently inhibits c-Met and VEGFR-2 tyrosine kinases that has been proposed as a lead compound for anti-hepatitis A drug development [1–3]. TD-139 is a disaccharide that has been investigated for the treatment of idiopathic pulmonary fibrosis [4–6]. TT-301 is a phenylpyridazine that has been used in trials studying the treatment of traumatic brain injury [7]. CP-195543 is a linear diarylhepatanoid that potent and selectively inhibits leukotriene B4 (LTB4) receptor and has been used in trials studying the treatment of arthritis rheumatoid [8,9]. PF-5190457 is an orally bioavailable, potent, and selective GHS-R1a inverse agonist trialed to treat alcohol use disorder [10–12]. Two of the predicted compounds were FDA-approved drugs, namely: DB00320 (dihydroergotamine) and DB11986 (entrectinib). Dihydroergotamine is a 9,10 alpha-dihydro derivative of ergotamine that binds with high affinity to 5-HT$_{1D}$a and 5-HT1$_{1D}$b receptors and has been used for the therapy of migraine disorders by non-oral routes including an approved nasal spray formulation [13–15]. Entrectinib is an FDA-approved phenylpiparezine that functions as a tropomyosin receptor tyrosine kinase (TRK) TRKA, TRKB, TRKC, proto-oncogene tyrosine-protein kinase ROS1, and anaplastic lymphoma kinase (ALK) inhibitor in the treatment of ROS1-positive metastatic non-small-cell lung cancer and NTRK gene fusion-positive solid tumors [16–18].

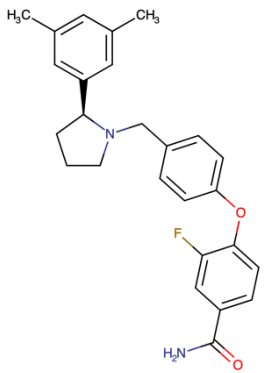
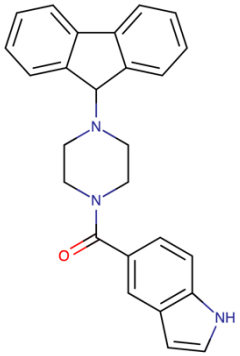
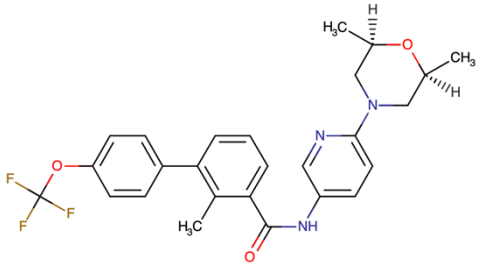
1 **Table S3.** Drug candidates targeting the nsp16/nsp10 interface of the nsp16/nsp10 protein complex.

Compound Name	Compound Structure	Human Target	Drug Status
Quarfloxin		ribosomal RNA (rRNA) biogenesis	Investigational
Laniquidar		Multidrug resistance protein 1	Investigational

Siramesine		Sigma-2 receptor	Investigational
TG-100801		VEGFR1/2/3 Tyrosine-protein kinase CSK	Investigational

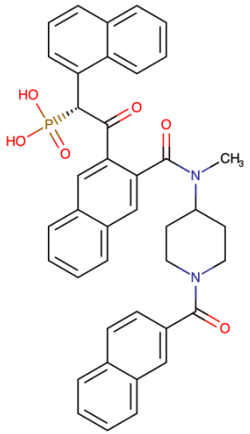
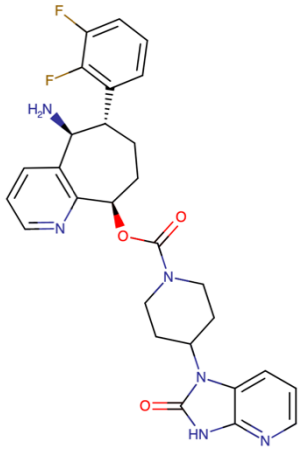
Tirilazad		Lipid peroxidation	Investigational
Conivaptan		Vasopressin receptor (V1a and V2)	Approved (Hyponatremia, syndrome of inappropriate antidiuretic hormone)

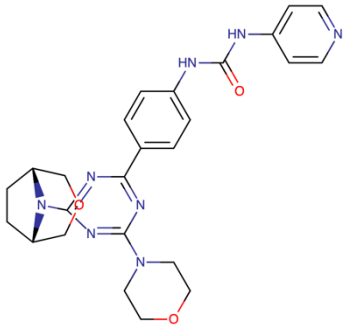
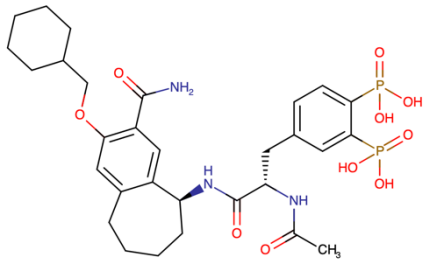
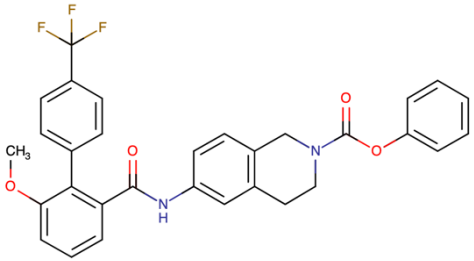
Vibegron		*Beta 3* adrenergic receptor (β3AR)	Investigational
DB06938		VEGFR2	Experimental
Tegobuvir		Hepatitis C Virus NS5B Polymerase	Investigational

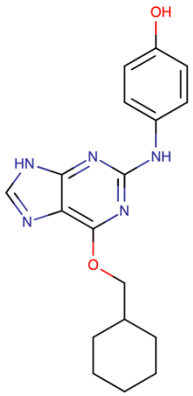
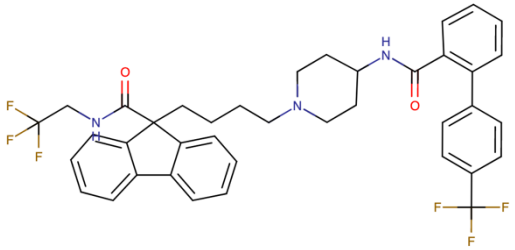
Aticaprant		κ-opioid receptor (KOR)	Investigational
Genz-10850		Enoyl-[acyl-carrier-protein] reductase (nadh) activity (*M. tuberculosis*)	Experimental
Sonidegib		Smoothened (SMO)	Approved (Basal cell carcinoma)

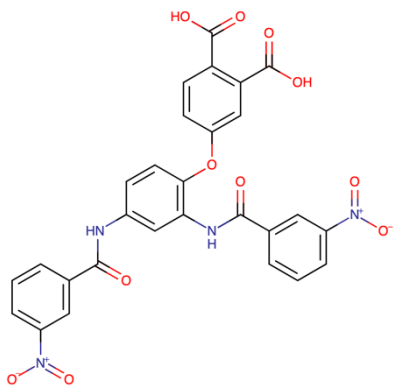
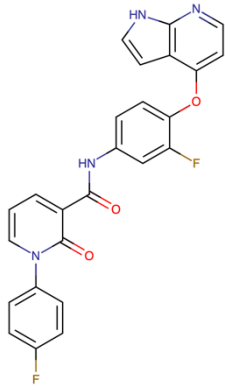
Two of the predicted compounds were experimental drugs, namely: DB06938 [4-[[2-[[4-chloro-3-(trifluoromethyl)phenyl]amino]-3H-benzimidazol-5-yl]oxy]-*N*-methyl-pyridine-2-carboxamide], and DB04289 (Genz-10850). DB06938 is a diarylether targeting vascular endothelial growth factor receptor 2 (VEGFR2). Genz-10850 is a fluorene targeting the enoyl-[acyl-carrier-protein] reductase (nadh) activity of the mycobacterial type II fatty acid synthase (FAS-II) system [19,20]. Eight of the predicted compounds were investigational drugs, namely: DB06638 (quarfloxin, CX-3543), DB12799 (laniquidar), DB06555 (siramesine), DB05075 (TG-100801), DB13050 (tirilazad), DB14895 (vibegron), DB11852 (tegobuvir), and DB12341 (LY-2456302/Aticaprant). Quarfloxin is a phenoxazine that binds and stabilizes DNA G-quadruplex (G4) sequences and operates as a direct inhibitor of ribosomal RNA biogenesis [21–25]. Laniquidar is a benzazepine belonging to the 3rd generation of highly specific and potent P-glycoprotein inhibitors [26–28]. Siramesine is a phenylpyrrole that operates as a selective sigma-2 receptor agonist to induce lysosomal leakage, cytoprotective autophagosome accumulation, and ferroptosis [29–33]. TG-100801 is a depsidone that multitargets vascular endothelial growth factor receptor (VEGFR)/Src kinases-induced viral immunopathology [34,35]. Tirilazad is a nonglucocorticoid, 21-aminosteroid (lazaroid) that potently inhibits oxygen free radical-induced, iron-catalyzed, lipid peroxidation in stroke and chronic obstructive pulmonary disease (COPD) [36,37]. Vibegron (RVT-901/MK-4618/KRP-114V) is a beta-3 adrenergic receptor beta 3 (β_3AR) agonist employed for the treatment of overactive bladder [38–40]. Tegobuvir is a non-nucleoside phenylpyridazine targeting the hepatitis C Virus RNA-dependent RNA NS5B polymerase [41–44]. LY-2456302/Aticaprant is a diphenylether targeting the κ-opioid receptor (KOR) used as a candidate to treat major depressive disorder [45,46]. Two of the predicted compounds were FDA-approved drugs, namely: DB00872 (conivaptan) and DB09143 (sonidegib). Conivaptan is a benzalnilide targeting the vasopressin receptors V1a and V2 that has been approved for hyponatremia (low blood sodium levels) caused by syndrome of inappropriate antidiuretic hormone (SIADH) [47,48]. Sonidegib (also named Odomzo) is a biphenyl derivative that antagonizes smoothened (SMO) to block the hedgehog (Hh) pathway and has been approved by the FDA to treat basal cell carcinomas [49–51].

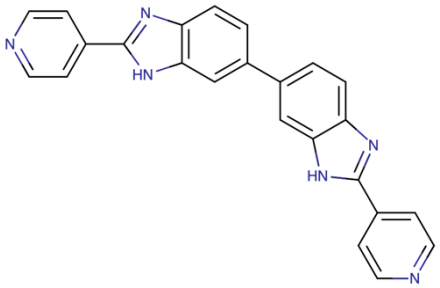
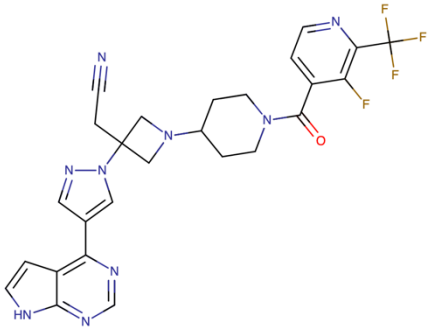
Table S4. Drug candidates targeting the RNA-binding groove of the nsp16/nsp10 protein complex.

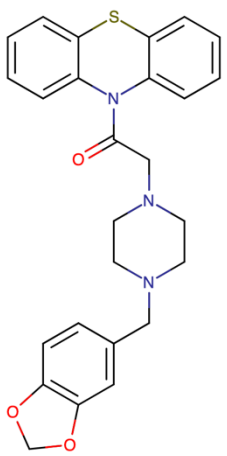
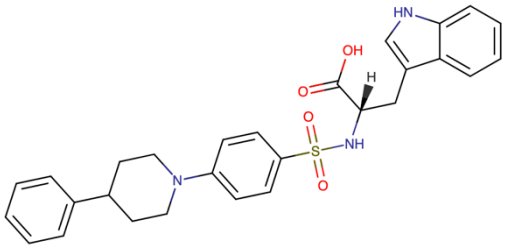
Compound Name	Compound Structure	Human Target	Drug Status
DB04016		Cathepsin G	Experimental
Rimegepant		Calcitonin gene-related peptide type 1 receptor (CGRP receptor)	Approved (Migraine headache)

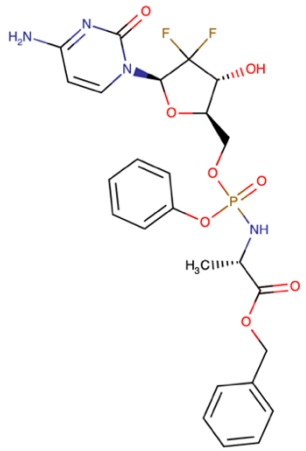
PKI-179		mTOR	Investigational
AP-22408		Tyrosine-protein kinase Lck	Experimental
SLx-4090		Microsomal triglyceride transfer protein large subunit	Investigational

DB08233		Cyclin-A2 Cyclin-dependent kinase 2	Experimental
Lomitapide		Microsomal triglyceride transfer protein large subunit	Approved (homozygous familial hypercholesterolemia)

DB03067		Glycogen phosphorylase, muscle form	Experimental
DB06896		c-MET	Experimental

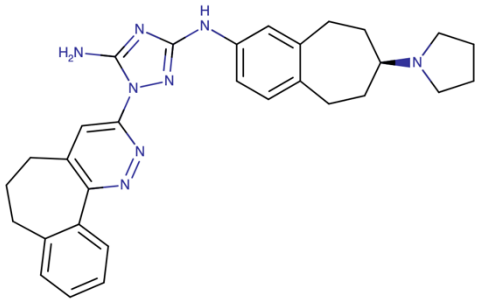
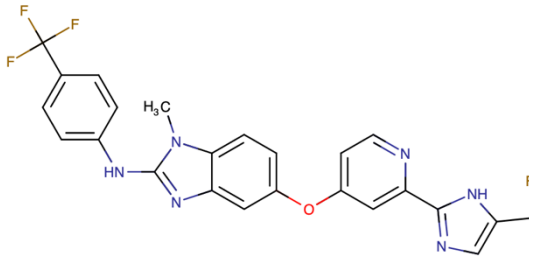
Ridinilazole		-	Investigational
Itacitinib		JAK1	Investigational

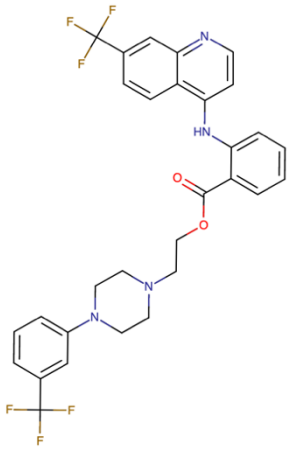
Fenoverine		Calcium ions (Ca^{2+}) channels	Investigational
DB02449		Stromelysin-1	Experimental

Acelarin (NUC-1031)		DNA	Investigational

Six of the predicted compounds were experimental drugs, namely: DB04016 [2-[3-({methyl[1-(2-naphthoyl)piperidin-4-yl]amino}carbonyl)-2-naphthyl]-1-(1-naphthyl)-2-oxoethylphosphonic acid], DB01830 (AP-22408), DB08233 [6-cyclohexylmethyloxy-2-(4′-hydroxyanilino)purine], DB03067 [4-{2,4-Bis[(3-Nitrobenzoyl)Amino]Phenoxy}Phthalic Acid], DB06896 [1-(4-fluorophenyl)-*N*-[3-fluoro-4-(1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl]-2-oxo-1,2-dihydropyridine-3-carboxamide], DB02449 [3-(1h-indol-3-yl)-2-[4-(4-phenyl-piperidin-1-yl)-benzenesulfonylamino]-propionic acid]. DB04016 is a stilbene targeting the serine-type endopeptidase activity of cathepsin G. AP-22408 is a phenylalanine derivative targeting the Sh2 domain of the tyrosine-protein kinase Lck [52,53]. DB08233 is a hypoxanthine targeting cyclin-A2 and cyclin-dependent kinase 2. DB03067 is a benzanilide targeting pyridoxal phosphate binding of the glycogen phosphorylase. DB06896 is an aromatic anilide targeting the c-MET/hepatocyte growth factor receptor. DB02449 is a phenylpiperidine targeting stromelysin-1 (MMP3). Six of the predicted compounds were investigational drugs, namely: DB13109 (PKI-179), DB05678 (SLx-4090), DB15308 (ridinilazole), DB12154 (itacitinib), DB13042 (fenoverine), and DB15057 (acelarin/NUC-1031). PKI-179 is a *N*-phenylurea that dually targets the phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway [54,55]. SLx-4090 is a microsomal triglyceride transfer protein (MTTP) inhibitor potentially for the treatment of type 2 diabetes [56]. Ridinilazole is a targeted-spectrum antimicrobial that shows potential in treatment of *Clostridium difficile* infection [57,58]. Itacitinib is a pyridinecarboxylic acid derivative that functions as an oral, selective inhibitor of the Janus Kinase (JAK) family of protein tyrosine kinases (TYKs) with selectivity for JAK1 in the treatment of inflammatory and neoplastic diseases [59,60]. Fenoverine is an old antispasmodic phenothiazine that inhibits calcium channel currents in smooth muscle cells [61]. Acelarin/NUC-1031, also known as fosgemcitabine palabenamide, is a pre-activated nucleotide analog (gemcitabine monophosphate) that incorporates a protective phosphoramidate moiety [62,63]. Two of the predicted compounds were FDA-approved drugs, namely: DB12457 (rimegepant) and DB08827 (lomitapide). Rimegepant is an imidazopyridine that functions as an oral antagonist of the CGRP receptor and has been approved for the acute treatment of migraine headache [64,65]. Lomitapide is a fluorene that directly inhibits microsomal triglyceride transfer protein (MTP) that has been approved as an orphan drug to reduce LDL cholesterol, total cholesterol, apolipoprotein B, and non-high-density lipoprotein (non-HDL) cholesterol in patients with homozygous familial hypercholesterolemia (HoFH) [66,67].

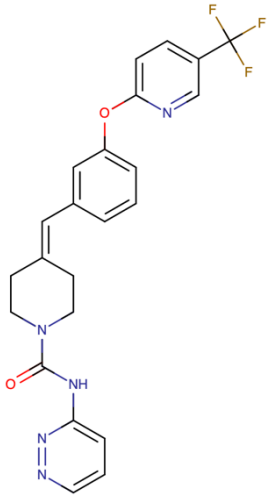
Table S5. Drug candidates targeting the SAM-binding site and nsp16/nsp10 interface of the nsp16/nsp10 protein complex.

Compound Name	Compound Structure	Human Target	Drug Status
Bemcentinib		AXL receptor tyrosine kinase	Investigational
RAF-265		VEGFR2/BRAF	Investigational

Antrafenine		Prostaglandin G/H synthase	Approved (analgesic/anti-inflammatory)

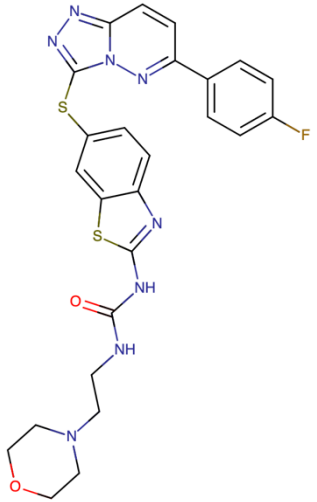
R-428 (BGB324, bemcentinib) is an aralkylamine that selectively and potentially inhibits AXL, a receptor tyrosine kinase implicated in epithelial-to-mesenchymal transition (EMT), inflammation, fibrosis, and is a key suppressor of innate immune response [68–72]. RAF-265 is a potent RAF/VEGFR2 inhibitor [73]. Antrafenine is a piperazine derivative drug that acts as an analgesic and anti-inflammatory drug with similar efficacy to naproxen via inhibition of cyclooxygenase activity [74].

Table S6. Drug candidates targeting the SAM-binding site and RNA-binding groove of the nsp16/nsp10 protein complex.

Compound Name	Compound Structure	Human Target	Drug Status
PF-04457845		Fatty acid amide hydrolase (FAAH)	Investigational

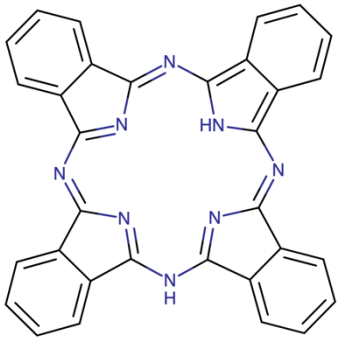
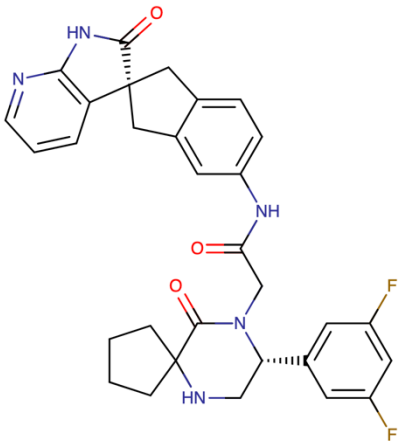
PF-04457845 is a diarylether that targets the fatty acid amide hydrolase (FAAH) that has been investigated for the treatment of Tourette Syndrome and cannabis dependence and is under investigation in fear conditioning [75–77].

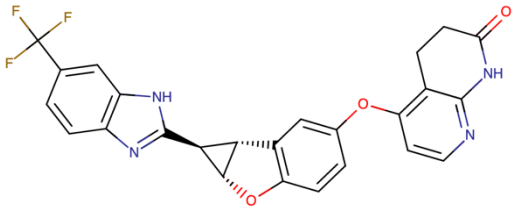
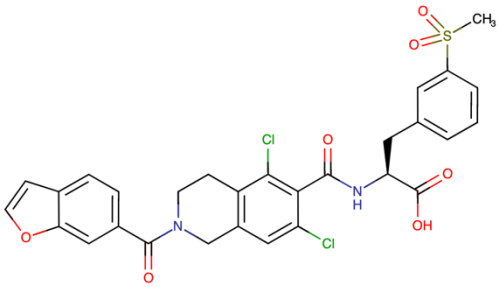
Table S7. Drug candidates targeting the nsp16/nsp10 interface and RNA-binding groove of the nsp16/nsp10 protein complex.

Compound Name	Compound Structure	Human Target	Drug Status
SAR-125844		MET receptor tyrosine kinase	Investigational

SAR-125844 is a potent intravenously active and highly selective MET tyrosine kinase inhibitor with potential antineoplastic activity [78].

Table S8. Drug candidates targeting the SAM-binding site, nsp16/nsp10 interface, and RNA-binding groove of the nsp16/nsp10 protein complex.

Compound Name	Compound Structure	Human Target	Drug Status
Phthalocyanine		-	Investigational
MK-3207		Calcitonin gene-related peptide type 1 receptor (CGRP receptor)	Investigational

Lifirafenib (BGB-283)		RAF/EGFR	Investigational
Lifitegrast		Integrin alpha-L	Approved (keratoconjunctivitis sicca)

Phthalocyanine is a cyclic tetrapyrrole that contains a phthalocyanine skeleton, which consists of four isoindole-type units, with the connecting carbon atoms in the macrocycle replaced by nitrogen. Metal derivatives of phthalocyanine have been studied for their photodynamic biocidal capacity against enveloped viruses [79–82]. MK-3207 is a potent and orally active CGRP receptor antagonists that has been used in trials studying the treatment of migraine and migraine disorders [83–85]. Lifirafenib (BGB-283) selectively binds to and inhibits the activity of wild-type BRAF and certain BRAF mutant forms, and EGFR [86]. Lifitegrast is a tetrahydroisoquinoline derivative that binds to the integrin lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes and blocks the interaction of LFA-1 with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). Lifitegrast is a FDA approved drug for the treatment of keratoconjunctivitis sicca (dry eye syndrome) [87–89].

1

Table S9. Filtering of nsp16/nsp10-targeting candidate drugs based on MD simulations for drug-protein complexes.

Drug Name	Score	Target Site	MM|PBSA (0–100 ns)	MM|PBSA (last 30 ns)
DB06638/Quarfloxin	Weak	interface	9.102	9.568
DB06555/Siramesine	Strong	interface	39.69	48.014
DB05075/TG-100801	Strong	interface	61.668	69.891
DB13050/Tirilazad	Strong	interface	48.234	40.536
DB14895/Vibegron	Diminished	interface	−1.081	−5.227
DB05984/RAF-265	Diminished	interface	29.497	24.329
DB01419/Antrafenine	Strong	interface	40.95	44.568
DB12411/R-248/BGB-324	Strong	interface	24.997	27.923
DB12411/R-248/BGB-324	Diminished	SAM site	−3.615	4.448
DB11611/Lifitegrast	Diminished	interface	20.631	4.487
DB11611/Lifitegrast	Strong	SAM site	17.475	35.27
DB14773/Lifirafenib/BGB-283	Strong	interface	41.142	45.654
DB14773/Lifirafenib/BGB-283	Weak	RNA groove	7.821	13.649
DB00872/Conivaptan	Strong	interface	37.337	36.79
DB00872/Conivaptan	Diminished	RNA groove	7.314	17.604
DB12983/Phthalocyanine	Strong	interface	26.945	27.097
DB12983/Phthalocyanine	Weak	SAM site	9.904	14.088
DB12983/Phthalocyanine	Weak	RNA groove	0.823	7.984
DB12424/MK-3207	Strong	interface	30.874	20.984
DB12424/MK-3207	Weak	SAM site	17.778	26.56
DB12424/MK-3207	Diminished	RNA groove	5.05	13.097
DB00320/Dihydroergotamine	Weak	SAM site	7.543	12.095
DB12012/PF-04457845	Diminished	SAM site	24.106	31.865
DB03231	Weak	SAM site	1.923	11.759
DB06925	Weak	SAM site	6.514	10.686
DB08237	Diminished	SAM site	−42.994	−38.728
DB11977/Golvatinib	Diminished	SAM site	−5.329	6.381
DB11986/Entrectinib	Strong	SAM site	72.21	125.784
DB12895/TD-139	Diminished	SAM site	−16.553	−10.838
DB12899/TT-301	Diminished	SAM site	2.758	8.633
DB13053/CP-195543	Diminished	SAM site	18.46	20.945

DB14870/PF-5190457	Diminished	SAM site	28.169	80.869
DB14883/Lorecivivint	Diminished	RNA groove	46.902	21.97
DB13109/PKI-179	Diminished	RNA groove	12.456	17.272
DB11913/LY-2090314	Diminished	RNA groove	5.886	13.979
DB04016	Diminished	RNA groove	−24.172	−25.95
DB04739	Diminished	RNA groove	8.834	6.933
DB12154/Itacitinib	Strong	RNA groove	13.693	23.338
DB14859/Fosifloxouridine nafalbenamide	Diminished	RNA groove	−14.878	−17.657
DB06976	Strong	RNA groove	57.909	149.99
DB06844	Diminished	RNA groove	3,298	11,678
DB06938	Diminished	interface	18,613	10,329
DB11852/Tegobuvir	Strong	interface	55,989	56,05
DB12341/LY-2456302	Strong	interface	63.729	65.275
DB04289/Genz-10850	Strong	interface	27.67	28.451
DB09143/Sonidegib	Strong	interface	45.066	50.818
DB01897	Diminished	SAM site	24.505	28.252
DB03571	Strong	SAM site	16.184	23.292
DB12457/Rimegepant	Weak	RNA groove	5.958	18.991
DB01830/AP-22408	Diminished	RNA groove	−6.86	6.74
DB05678/SLx-4090	Diminished	RNA groove	17.443	9.449
DB08233	Diminished	RNA groove	12.558	19.145
DB08827/Lomitapide	Diminished	RNA groove	7.442	5.842
DB03067	Strong	RNA groove	72.626	72.934
DB15308/Ridinilazole	Strong	RNA groove	19.615	28.397
DB13042/Fenoverine	Diminished	RNA groove	6.763	16.032
DB02449 -9.0 kcal/mol	Strong	RNA groove	77.708	108.207
DB15057/Gemcitabine-phosphoramidate	Diminished	RNA groove	−15.739	3.958
DB05984/RAF-265	Diminished	SAM site	−3.582	−7.312
DB01419/Antrafenine	Strong	SAM site	83.067	162.432
DB15382/SAR-125844	Strong	interface	38.082	35.447
DB15382/SAR-125844	Weak	RNA groove	−0.584	12.192
DB12012/PF-04457845	Strong	RNA groove	30.717	68.413
DB14773/Lifirafenib/BGB-283	Weak	RNA groove	12.094	10.759
DB11611/Lifitegrast	Weak	RNA groove	12.339	19.104

DB11852/Tegobuvir	Strong	SAM site	34.551	44.181
DB11852/Tegobuvir	Diminished	RNA groove	25.524	30.613

2

Table S10. Selection of nsp16/nsp10-targeting candidate drugs based on MD simulations for drug-protein complexes.

Drug	Score	Target Site	MM|PBSA 0–100 ns (kcal/mol)	MM|PBSA last 30 ns (kcal/mol)
DB01419/Antrafenine	Strong	SAM-binding site	83.067	162.432
DB11986/Entrectinib	Strong	SAM-binding site	72.21	125.784
DB02449	Strong	RNA-binding groove	77.708	108.207
DB03067	Strong	RNA-binding groove	72.626	72.934
DB12012/PF-04457845	Strong	RNA-binding groove	30.717	68.413
DB05075/TG-100801	Strong	nsp10-nsp16 interface	61.668	69.891
DB12341/Aticaprant	Strong	nsp10-nsp16 interface	63.729	65.275
DB11852/Tegobuvir	Strong	nsp10-nsp16 interface	55.989	56.05
DB09143/Sonidegib	Strong	nsp10-nsp16 interface	45.066	50.818
DB06555/Siramesine	Strong	nsp10-nsp16 interface	39.69	48.014
DB14773/Lifirafenib/BGB-283	Strong	nsp10-nsp16 interface	41.142	45.654
DB01419/Antrafenine	Strong	nsp10-nsp16 interface	40.95	44.568
DB13050/Tirilazad	Strong	nsp10-nsp16 interface	48.234	40.536
DB00872/Conivaptan	Strong	nsp10-nsp16 interface	37.337	36.79
DB15382/SAR-125844	Strong	nsp10-nsp16 interface	38.082	35.447
DB04289/Genz-10850	Strong	nsp10-nsp16 interface	27.67	28.451
DB12411/Bemcentinib	Strong	nsp10-nsp16 interface	24.997	27.923
DB12983/Phthalocyanine	Strong	nsp10-nsp16 interface	26.945	27.097
DB15308/Ridinilazole	Strong	RNA-binding groove	19.615	28.397
DB11611/Lifitegrast	Strong	SAM-binding site	17.475	35.27
DB12424/MK-3207	Strong	nsp10-nsp16 interface	30.874	20.984
DB12154/Itacitinib	Strong	RNA-binding groove	13.693	23.338
DB06638/Quarfloxin	Weak	nsp10-nsp16 interface	9.102	9.568
DB11611/Lifitegrast	Weak	RNA-binding groove	12.339	19.104
DB12457/Rimegepant	Weak	RNA-binding groove	5.958	18.991
DB14773/Lifirafenib/BGB-283	Weak	RNA-binding groove	12.094	10.759
DB15382/SAR-125844	Weak	RNA-binding groove	-0.584	12.192
DB12983/Phthalocyanine	Weak	RNA-binding groove	0.823	7.984
DB12424/MK-3207	Weak	SAM-binding site	17.778	26.56

DB03571	Weak	SAM-binding site	16.184	23.292
DB12983/Phthalocyanine	Weak	SAM-binding site	9.904	14.088
DB00320/Dihydroergotamine	Weak	SAM-binding site	7.543	12.095
DB03231	Weak	SAM-binding site	1.923	11.759

3

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