

Title: Pharmacokinetic Drug-Drug Interactions with Drugs Approved by the U.S. Food and Drug Administration in 2020: Mechanistic Understanding and Clinical Recommendations

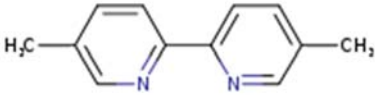
Authors: Jingjing Yu, Yan Wang, and Isabelle Ragueneau-Majlessi

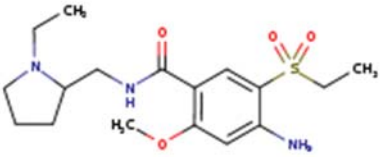
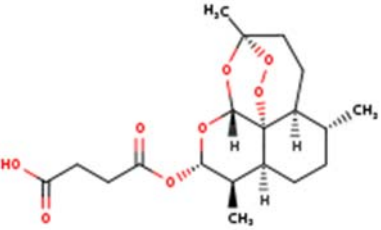
UW Drug Interaction Solutions, Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle, WA, USA (J.Y., Y.W., I.R-M.)

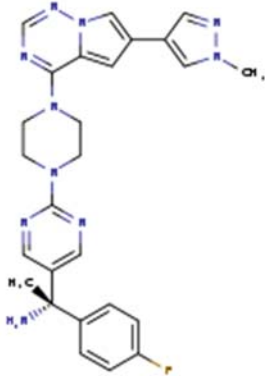
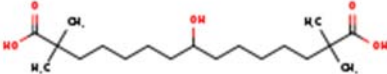
Journal: Drug Metabolism and Disposition

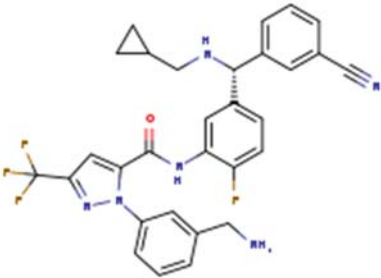
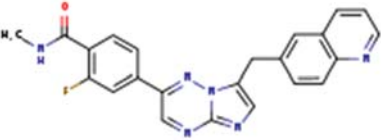
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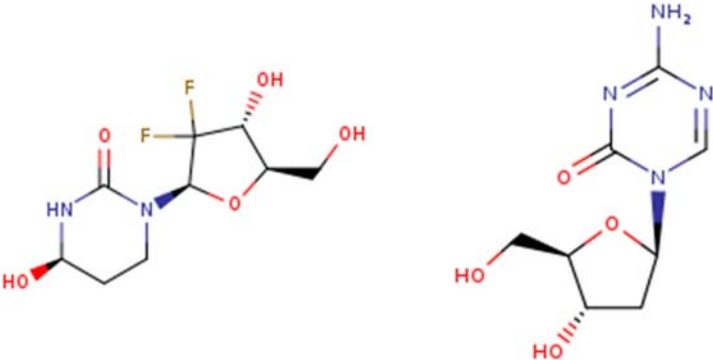
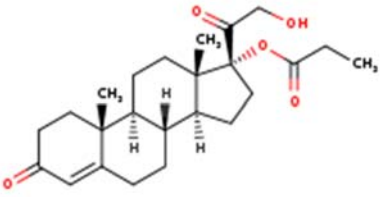
Supplemental Table 1. Clinical indications and chemical structures of small molecular drugs approved by the FDA in 2020

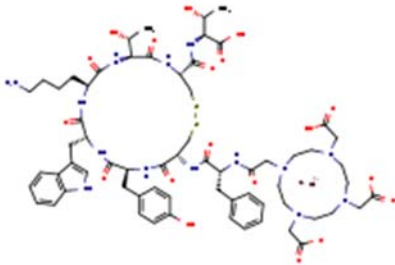
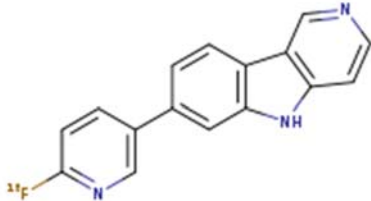
NDA Number	Drug Name (CAS Registry Number)	Clinical Indications ^a	Structure ^b
206966	abametapir (1762-34-1)	a pediculicide indicated for the topical treatment of head lice infestation in patients 6 months of age and older	 <chem>Cc1ccc2nc(C)cc2c1</chem>

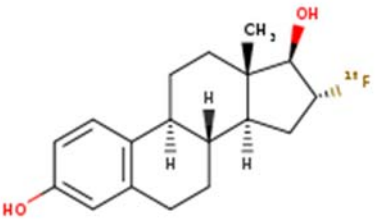
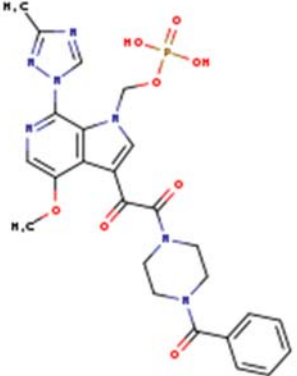
209510	amisulpride (71675-85-9)	a dopamine-2 antagonist indicated in adults for: (1) prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class; (2) treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis	 <p>The chemical structure of amisulpride consists of a central benzene ring. At the 1-position, there is a methoxy group (-OCH₃). At the 2-position, there is a primary amine group (-NH₂). At the 3-position, there is a propylsulfonamide group (-NHCH₂CH₂CH₂SO₂CH₃). At the 4-position, there is a propylpiperidine group (-CH₂CH₂CH₂N(CH₂)₃).</p>
213036	artesunate (88495-63-0)	an antimalarial indicated for the initial treatment of severe malaria in adult and pediatric patients	 <p>The chemical structure of artesunate is a complex polycyclic molecule. It features a central carbon atom bonded to a methyl group (H₃C), a hydroxyl group (HO), and a propionic acid side chain (-CH₂CH₂COOH). The molecule is highly stereocentred, with multiple chiral centers indicated by wedged and dashed bonds. It contains several oxygen atoms, some of which are part of ether linkages within the ring system.</p>

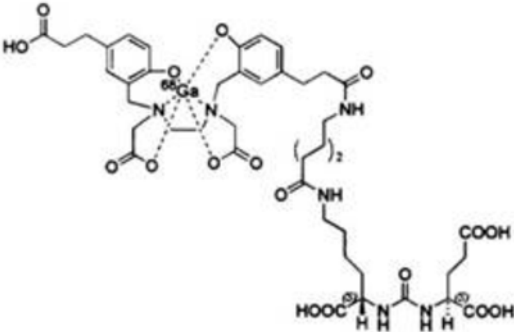
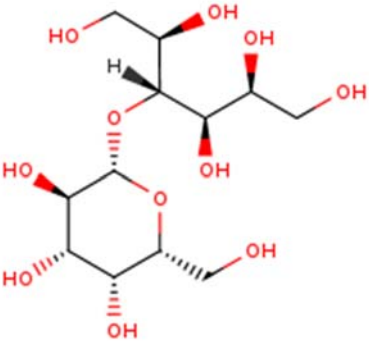
<p>212608</p>	<p>avapritinib (1703793-34-3)</p>	<p>a kinase inhibitor indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor harboring a platelet-derived growth factor receptor alpha exon 18 mutation</p>	 <p>The chemical structure of avapritinib features a central piperazine ring. One nitrogen of the piperazine is attached to a pyridine ring, which is further linked to a benzimidazole system. The other nitrogen of the piperazine is attached to a pyridine ring. This second pyridine ring is substituted at the 2-position with a chiral center (1R,2S) that has a methyl group (H3C) pointing up and a (4-fluorophenyl)amino group (NH2) pointing down. The 4-fluorophenyl group consists of a benzene ring with a fluorine atom (F) at the para position.</p>
<p>211616</p>	<p>bempedoic acid (738606-46-7)</p>	<p>an adenosine triphosphate-citrate lyase inhibitor indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C</p>	 <p>The chemical structure of bempedoic acid is a long-chain dicarboxylic acid. It consists of a central heptane chain with a hydroxyl group (OH) at the 4-position. Each end of the chain is terminated by a methyl group (H3C) and a carboxylic acid group (COOH). The methyl groups are shown with wedged bonds, and the carboxylic acid groups are shown with red oxygen atoms.</p>

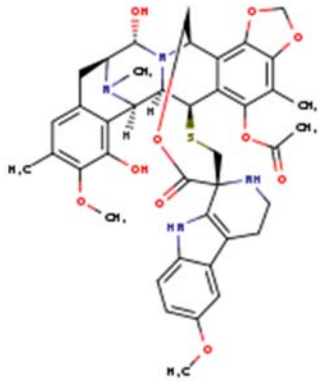
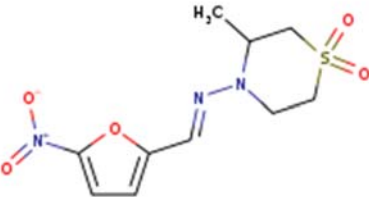
214094	berotralstat (1809010-50-1)	a kallikrein inhibitor indicated for prophylaxis to prevent attacks of hereditary angioedema in adults and pediatric patients 12 years and older	 <p>The chemical structure of berotralstat is a complex molecule. It features a central benzimidazole ring system. One of the nitrogen atoms in the benzimidazole is substituted with a 4-aminophenyl group. The other nitrogen atom is part of a fused ring system that includes a 4-cyano-2-(cyclopropylamino)phenyl group. Additionally, there is a 2-(4-fluorophenyl)acetamide group attached to the benzimidazole ring. The structure is drawn with blue lines for the carbon and nitrogen atoms, and red for the oxygen and fluorine atoms.</p>
213591	capmatinib (1029712-80-8)	a kinase inhibitor indicated for the treatment of patients with metastatic non-small cell lung cancer whose tumors have a mutation that leads to mesenchymal-epithelial transition exon 14 skipping	 <p>The chemical structure of capmatinib is a complex molecule. It features a central benzimidazole ring system. One of the nitrogen atoms in the benzimidazole is substituted with a 4-(methylamino)phenyl group. The other nitrogen atom is part of a fused ring system that includes a 4-(pyridin-2-ylmethyl)phenyl group. Additionally, there is a 2-(4-fluorophenyl)acetamide group attached to the benzimidazole ring. The structure is drawn with blue lines for the carbon and nitrogen atoms, and red for the oxygen and fluorine atoms.</p>

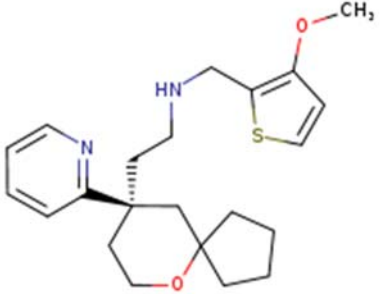
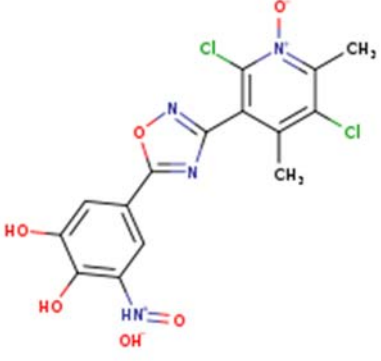
212576	cedazuridine and decitabine (1141397-80-9 and 2353-33-5)	cedazuridine, a cytidine deaminase inhibitor, co-packaged with decitabine, a nucleoside metabolic inhibitor, indicated for treatment of adult patients with myelodysplastic syndromes	 <p>The image displays two chemical structures. On the left is cedazuridine, a nucleoside with a piperidine ring attached to the 5' carbon of a ribose sugar, which is substituted with two fluorine atoms and a hydroxyl group. On the right is decitabine, a nucleoside with an amino group at the 6-position of a pyrimidine ring attached to the 5' carbon of a ribose sugar.</p>
213433	clascoterone (19608-29-8)	an androgen receptor inhibitor indicated for the topical treatment of acne vulgaris in patients 12 years of age or older	 <p>The image shows the chemical structure of clascoterone, a steroid with a ketone group at C3, a double bond at C4, and a propionic acid ester at C17. It also features methyl groups at C10 and C13, and hydrogens at C14 and C15.</p>

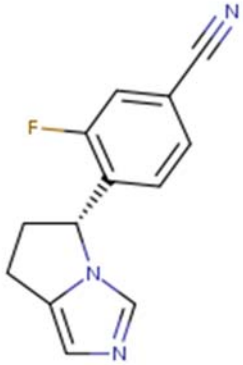
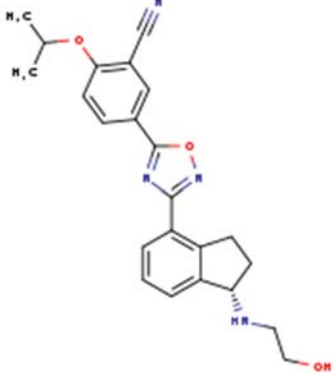
213227	copper Cu-64 dotatate (1426155-87-4)	a radioactive diagnostic agent indicated for use with positron emission tomography for localization of somatostatin receptor positive neuroendocrine tumors in patients	 The image shows the chemical structure of copper Cu-64 dotatate. It features a central copper atom (Cu) coordinated by a large, complex, multi-ring chelator molecule. The chelator has several nitrogen and oxygen donor atoms that surround the copper atom, forming a stable complex. The structure is highly branched and includes various functional groups like amides and carboxylates.
212123	flortaucipir F 18 (1522051-90-6)	a radioactive diagnostic agent containing the isotope fluorine 18. It is indicated for the evaluation of suspected Alzheimer's disease via positron emission tomography imaging of the brain	 The image shows the chemical structure of flortaucipir F 18. It consists of a central benzene ring fused to an indole ring system. A pyridine ring is attached to the benzene ring at the para position. A fluorine-18 isotope (¹⁸ F) is attached to the pyridine ring at the 3-position. The structure is shown in a simplified, skeletal representation.

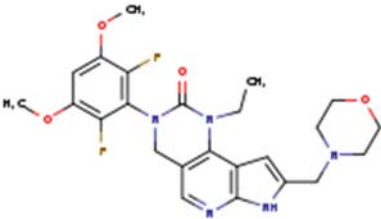
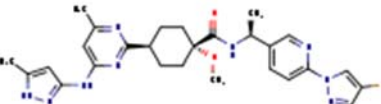
212155	fluoroestradiol F-18 (94153-53-4)	a radioactive diagnostic agent indicated for use with positron emission tomography imaging for the detection of estrogen receptor-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer	 <p>The image shows the chemical structure of fluoroestradiol F-18, a steroid hormone derivative. It features a four-ring steroid nucleus with a hydroxyl group at C3, a methyl group at C13, and a hydroxyl group at C17. A fluorine-18 atom is attached to the C16 position via a dashed bond, indicating its stereochemistry. The fluorine atom is labeled with ¹⁸F.</p>
212950	fostemsavir (864953-29-7)	a human immunodeficiency virus type 1 (HIV-1) gp120-directed attachment inhibitor, in combination with other antiretroviral(s), indicated for the treatment of HIV-1 infection in heavily treatment-experienced patients with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations	 <p>The image shows the chemical structure of fostemsavir, a HIV-1 attachment inhibitor. It consists of a central pyrazole ring system substituted with a methyl group, a methoxy group, and a phosphonate group. The phosphonate group is linked to a piperidine ring, which is further substituted with a benzoyl group. The structure is shown in a 3D perspective with various atoms colored (blue for nitrogen, red for oxygen, black for carbon, and grey for phosphorus).</p>

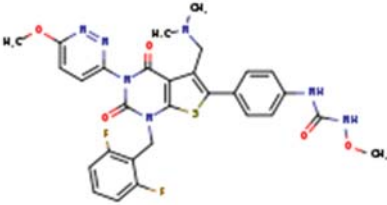
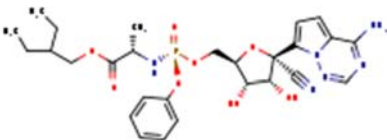
212642	gallium GA 68 PSMA-11 (1906894-20-9)	a peptide-based radioactive diagnostic agent indicated for positron emission tomography imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer meeting certain criteria	
211281	lactitol (585-86-4)	an osmotic laxative indicated for the treatment of chronic idiopathic constipation in adults	

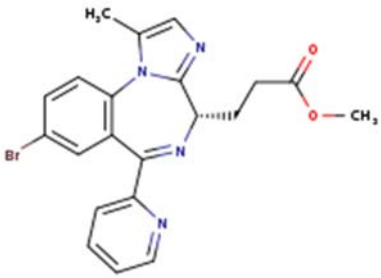
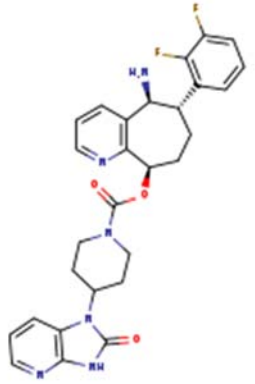
213702	lurbinectedin (497871-47-3)	an alkylating drug indicated for the treatment of adult patients with metastatic small cell lung cancer with disease progression on or after platinum-based chemotherapy	 <p>The image shows the chemical structure of lurbinectedin, a complex polycyclic molecule. It features a central core with multiple fused rings, including a benzene ring, a pyridine ring, and a piperidine ring. The structure is highly substituted with various functional groups, including hydroxyl groups, methyl groups, and a chlorine atom. The molecule is shown in a 3D perspective view.</p>
213464	nifurtimox (23256-30-6)	a nitrofuran antiprotozoal indicated in pediatric patients (birth to less than 18 years of age) for the treatment of Chagas disease (American Trypanosomiasis) caused by Trypanosoma cruzi	 <p>The image shows the chemical structure of nifurtimox, a nitrofurantoin derivative. It consists of a furan ring substituted with a nitro group (NO2) and a methylene group (-CH2-). The methylene group is connected to a piperazine ring, which is further substituted with a methyl group (H3C) and a sulfonamide group (-SO2NH2).</p>

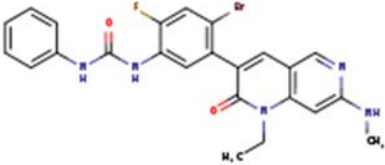
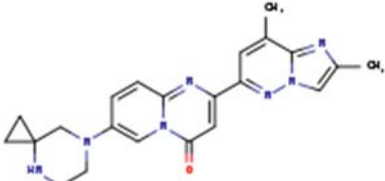
210730	oliceridine (1401028-24-7)	an opioid agonist indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate	 <p>The chemical structure of oliceridine features a central bicyclic core consisting of a piperidine ring fused to a cyclopentane ring. A pyridine ring is attached to the piperidine ring at the 2-position. A propyl chain is attached to the piperidine ring at the 4-position, with a secondary amine group (NH) at the end. This secondary amine is further connected to a 2-methoxyphenyl group.</p>
212489	opicapone (923287-50-7)	a catechol-O-methyltransferase inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes	 <p>The chemical structure of opicapone consists of a central benzimidazole ring system. One of the benzimidazole nitrogens is linked to a 3,4-dihydroquinolin-2(1H)-one ring. The other benzimidazole nitrogen is linked to a 2,4-dichloro-6-methyl-5-nitrophenyl ring. The quinolinone ring has two hydroxyl groups (HO) at the 6 and 7 positions and a hydroxyl group (OH) at the 4 position.</p>

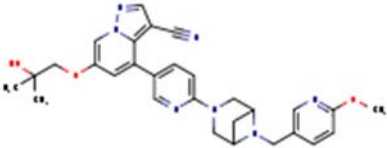
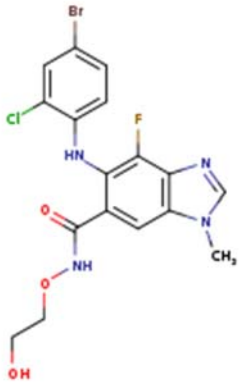
212801	osilodrostat (928134-65-0)	a cortisol synthesis inhibitor indicated for Cushing's disease for whom pituitary surgery is not an option or has not been curative	 <p>The chemical structure of osilodrostat consists of a central benzene ring. At the 1-position of the benzene ring, there is a cyano group (-C≡N). At the 2-position, there is a fluorine atom (F). At the 4-position, there is a 1,2,3,4-tetrahydro-1H-indazole ring system attached via a dashed bond, indicating stereochemistry.</p>
209899	ozanimod (1306760-87-1)	a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis	 <p>The chemical structure of ozanimod is a complex molecule. It features a central benzimidazole ring system. One of the benzimidazole nitrogens is substituted with a 2-hydroxyethylamino group (-NH-CH2-CH2-OH). The benzimidazole ring is further substituted with a 4-cyano-2-isopropoxyphenyl group. The cyano group (-C≡N) is at the 4-position of the phenyl ring, and the isopropoxy group (-O-CH(CH3)2) is at the 2-position. The benzimidazole ring is also substituted with a 2,3-dihydro-1H-indole-5-yl group.</p>

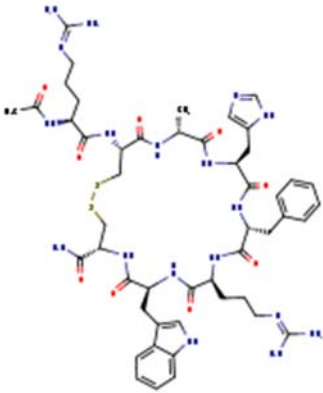
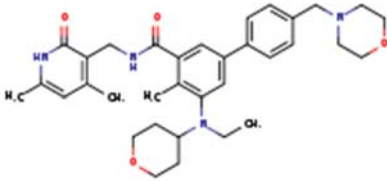
213736	pemigatinib (1513857-77-6)	a kinase inhibitor indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 fusion or other rearrangement	 <p>The chemical structure of pemigatinib features a central benzimidazole ring system. It is substituted with a morpholine ring at the 2-position, a methyl group at the 4-position, and a 2,4-difluoro-3,5-dimethoxyphenyl group at the 5-position. The benzimidazole ring also has a methyl group at the 2-position and a methyl group at the 4-position.</p>
213721	pralsetinib (2097132-94-8)	a kinase inhibitor indicated for the treatment of metastatic non-small cell lung cancer harboring the rearranged during transfection fusion-positive gene	 <p>The chemical structure of pralsetinib consists of a central piperidine ring. It is substituted with a methyl group at the 2-position, a methyl group at the 3-position, and a 4-(4-methyl-1H-imidazol-2-yl)phenyl group at the 4-position. The piperidine ring also has a methyl group at the 2-position and a methyl group at the 3-position.</p>

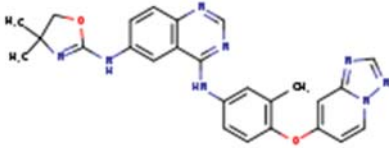
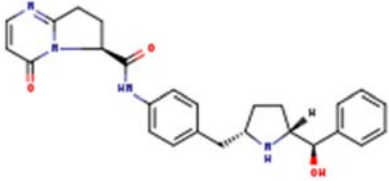
214621	relugolix (737789-87-6)	a gonadotropin-releasing hormone antagonist indicated for the treatment of patients with advanced prostate cancer	 <p>The chemical structure of relugolix is a complex molecule. It features a central thiazolidine ring system. Attached to this ring are a pyridine ring with a methoxy group, a thiazole ring with a methyl group, and a benzamide ring with a hydroxyl group. There are also two fluorine atoms on a phenyl ring attached to the thiazolidine ring.</p>
214787	remdesivir (1809249-37-3)	a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for adults and pediatrics (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 requiring hospitalization	 <p>The chemical structure of remdesivir is a nucleotide analog. It consists of a ribose sugar attached to a pyrophosphate group, which is further attached to a nucleoside. The nucleoside has a pyrimidine base (cytosine) and a hydroxyl group. There is also a phenyl ring attached to the pyrophosphate group.</p>

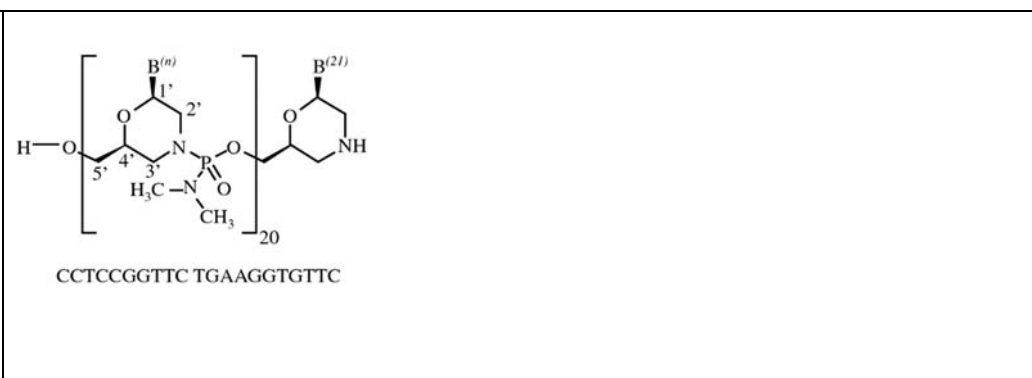
212295	remimazolam (308242-62-8)	a benzodiazepine indicated for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 min or less. It is recommended to individualize and titrate dosing to desired clinical effect	 <p>The chemical structure of remimazolam is a benzodiazepine derivative. It features a central seven-membered diazepine ring fused to a benzene ring. The benzene ring has a bromine atom (Br) at the 5-position and a methyl group (H₃C) at the 2-position. The diazepine ring has a methyl group (H₃C) at the 2-position and a pyridine ring at the 5-position. A propyl chain is attached to the diazepine ring at the 3-position, ending in a methyl ester group (-COOCH₃).</p>
212728	rimegepant (1289023-67-1)	a calcitonin gene-related peptide receptor antagonist indicated for the treatment of acute migraine in adults	 <p>The chemical structure of rimegepant is a calcitonin gene-related peptide receptor antagonist. It features a central seven-membered diazepine ring fused to a benzene ring. The benzene ring has a fluorine atom (F) at the 5-position. The diazepine ring has a methyl group (H₃C) at the 2-position and a pyridine ring at the 5-position. A propyl chain is attached to the diazepine ring at the 3-position, ending in a methyl ester group (-COOCH₃).</p>

213973	ripretinib (1442472-39-0)	a kinase inhibitor indicated for the treatment of advanced gastrointestinal stromal tumor in patients who have received prior treatment with 3 or more kinase inhibitors, including imatinib	 <p>The chemical structure of ripretinib is a complex molecule. It features a central benzimidazole ring system. One of the benzimidazole nitrogens is substituted with a methyl group (H₃C). The other benzimidazole nitrogen is part of a fused ring system that includes a pyridine ring. This pyridine ring is further substituted with a methylamino group (NH-CH₃) and a benzamide group (-NH-C(=O)-NH-phenyl). The benzimidazole ring is also substituted with a bromine atom (Br) and a fluorine atom (F) on the benzene ring, and a methylamino group (NH-CH₃) on the imidazole ring.</p>
213535	risdiplam (1825352-65-5)	a survival of motor neuron 2 splicing modifier indicated for the treatment of spinal muscular atrophy	 <p>The chemical structure of risdiplam consists of a central benzimidazole ring system. One of the benzimidazole nitrogens is substituted with a methylamino group (NH-CH₃). The other benzimidazole nitrogen is part of a fused ring system that includes a pyridine ring. This pyridine ring is further substituted with a methylamino group (NH-CH₃) and a benzamide group (-NH-C(=O)-NH-phenyl). The benzimidazole ring is also substituted with a bromine atom (Br) and a fluorine atom (F) on the benzene ring, and a methylamino group (NH-CH₃) on the imidazole ring.</p>

213246	selpercatinib (2152628-33-4)	a kinase inhibitor indicated for the treatment of non-small cell lung cancer and thyroid cancer with specific RET gene mutations	 <p>The chemical structure of selpercatinib features a central benzimidazole ring system. One of the benzimidazole nitrogens is substituted with a propyl chain that has a hydroxyl group on the terminal carbon. The benzimidazole ring is fused to a benzene ring, which is further substituted with a cyano group and a propyl chain. This propyl chain is connected via a methylene bridge to a piperidine ring, which is in turn connected to another benzimidazole ring. The second benzimidazole ring is also substituted with a propyl chain ending in a hydroxyl group.</p>
213756	selumetinib (606143-52-6)	a kinase inhibitor indicated for the treatment of pediatric patients (2 years and older) with neurofibromatosis type 1 who have symptomatic, inoperable plexiform neurofibromas	 <p>The chemical structure of selumetinib consists of a central benzimidazole ring system. One of the benzimidazole nitrogens is substituted with a methyl group. The benzimidazole ring is fused to a benzene ring, which is substituted with a fluorine atom and a propyl chain. This propyl chain is connected via a methylene bridge to a piperidine ring, which is in turn connected to another benzimidazole ring. The second benzimidazole ring is also substituted with a propyl chain ending in a hydroxyl group.</p>

213793	setmelanotide (920014-72-8)	a melanocortin 4 receptor agonist indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance	
211723	tazemetostat (1403254-99-8)	a methyltransferase inhibitor indicated for the treatment of patients 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection	

213411	tucatinib (937263-43-9)	a kinase inhibitor indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer	 <p>The chemical structure of Tucatinib is a complex molecule. It features a central benzimidazole ring system. One of the benzimidazole nitrogens is substituted with a 2,2-dimethyl-1,3-dioxolane ring. The other benzimidazole nitrogen is linked via an amine group to a benzene ring. This benzene ring is further substituted with a hydroxyl group and a 2,3-dihydro-1H-imidazo[4,5-b]pyridine ring system.</p>
213006	vibegron (1190389-15-1)	a beta-3 adrenergic agonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults	 <p>The chemical structure of Vibegron consists of a 2,3,4,5-tetrahydroquinoline-2(1H)-one ring system. The nitrogen atom of this ring is substituted with a 4-(2-phenylpyrrolidin-1-yl)phenyl group. The pyrrolidine ring is further substituted with a hydroxyl group and a phenyl ring.</p>

212154	viltolarsen (2055732-84-6)	an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping	 <p style="text-align: center;">CCTCCGGTTC TGAAGGTGTTC</p>
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^a Clinical indications were obtained from each drug's Product Label available at Drugs@FDA, accessed in September 2021.

^b Chemical structure was obtained from <https://chem.nlm.nih.gov/chemidplus/> accessed August 2021, except gallium GA 68 PSMA-11, lumasiran, and viltolarsen whose structures were obtained from the Gallium GA 68 PSMA-11, OXLUMO, and VILTEPSO Product Label, respectively.