

Table S1. FDA approved drugs with a known covalent mechanism of action^a

Active ingredient ^b	Drug brand name	Sponsor ^c	Approval year	Target	Indication	Treatment area	Warhead ^d	Reversibility	Target Residue
Acetylsalicylic acid	Aspirin	Bayer	1900	Cyclooxygenases	Fever, pain, inflammation	Anti-inflammatory	Acetyl ester	Irreversible	Ser
Propylthiouracil	Propylthiouracil	Dava Pharms Inc	1947	Thyroxine-5-deiodinase	Hyperthyroidism	Hyperthyroidism	Thio-dihydro-pyrimidinedione	Irreversible	Sec ^e
Mechlorethamine	Mustargen	Recordati Rare	1949	DNA (alkylation)	T-cell lymphoma	Cancer	Aziridinium (prodrug)	Irreversible	Purines (N7)
Disulfiram	Antabuse	Teva	1951	Aldehyde dehydrogenase	Alcoholism	Addiction	Dithiocarbamate	Irreversible	Cys
Penicillin G	Bicillin	Wyeth Ayerst	1951	PBP	Bacterial infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Isoniazid	Nydrazid	Bristol Myers Squibb	1952	Enol-acyl carrier protein reductase	Mycobacteria	Anti-microbial	Acyl hydrazide derived radical (prodrug)	Irreversible	NADH
Phenoxybenzamine	Dibenzyline	Concordia	1953	α -adrenergic receptor	Pheochromocytoma	Cardiovascular diseases	Aziridinium (prodrug)	Irreversible	Cys
Warfarin	Coumadin	Bristol Myers Squibb	1954	Vitamin K reductase	Anti-coagulant	Cardiovascular diseases	Lactone	Irreversible	Cys
Busulfan	Myleran	Aspen Global Inc	1954	DNA (alkylation)	Chronic myelogenous leukemia	Cancer	Mesylate	Irreversible	Purines (N7)
Penicillin V	V-cillin	Lilly	1955	PBP	Bacterial infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Chlorambucil	Leukeran	Aspen Global Inc	1957	DNA (alkylation)	Lymphoma and Hodgkin's disease	Cancer	Aziridinium (prodrug)	Irreversible	Purines (N7)
Thiotepa	Thiotepa	Immunex	1959	DNA (alkylation)	Ovarian and breast adenocarcinoma	Cancer	Aziridine	Irreversible	Purines (N7)
Cyclophosphamide	Cytoxan	Baxter	1959	DNA (alkylation)	Lymphoma, multiple myeloma	Cancer	Aziridinium (prodrug)	Irreversible	Purines (N7)
Ampicillin	Penbritin	Wyeth Ayerst	1961	PBP	Bacterial infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Fluorouracil	Fluorouracil	Spetrum Pharms	1962	Thymidylate synthase	Metastatic gastrointestinal adenocarcinoma	Cancer	Dihydro-pyrimidinedione	Irreversible	Cys, Tetrahydrofolate cofactor
D-cycloserine	Seromycin	Purdue	1964	Alanine racemase, D-alanine:D-alanine ligase	Bacterial infections	Anti-microbial	Amine	Irreversible	PLP cofactor (imine intermediate)
Melphalan	Alkeran	Apotex	1964	DNA (alkylation)	Multiple myeloma	Cancer	Aziridinium (prodrug)	Irreversible	Purines (N7)
Floxuridine	Fudr	Hospira	1970	Thymidylate synthase	Metastatic gastrointestinal adenocarcinoma	Cancer	Dihydro-pyrimidinedione	Irreversible	Cys, Tetrahydrofolate cofactor
Amoxicillin	Amoxil	GSK	1974	PBP	Bacterial infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Carbidopa	Synmet	Merck	1975	PLP-dependent decarboxylases	Parkinson's disease	CNS diseases	Hydrazine	Irreversible	PLP
Dacarbazine	Dtic-dome	Bayer	1975	DNA (alkylation)	Melanoma, Hodgkin's disease	Cancer	Methyldiazonium (prodrug)	Irreversible	Purines (N7)
Lomustine	Gleostine	Corden Pharma	1976	DNA, proteins (alkylation)	Brain tumors, multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma	Cancer	Isocyanate, diazohydroxide (prodrug)	Irreversible	DNA, proteins
Carmustine	Bicnu	Emcure Pharms LTD	1977	DNA, proteins (alkylation)	Brain tumors, Hodgkin's disease	Cancer	Isocyanate, diazohydroxide (prodrug)	Irreversible	DNA, proteins
Cisplatin	Platinol	HQ SPCLT Pharma	1978	DNA (crosslinker)	Ovarian and testicular cancer, bladder carcinoma	Cancer	Pt (II)	Irreversible	Purines (N7)
Cefaclor	Ceclor	Lilly	1979	PBP	Bacterial infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Trifluridine	Viroptic	Monarch Pharms	1980	Thymidylate synthase	keratitis and keratoconjunctivitis by HPV	Anti-microbial	Dihydro-pyrimidinedione (suicidal)	Irreversible	Cys, Tyr
Estramustine	Emcyt	Pharmacia and Upjohn	1981	DNA (alkylation)	Prostate cancer	Cancer	Aziridinium (prodrug)	Irreversible	Purines (N7)
Streptozocin	Zanosar	Teva	1982	DNA, proteins (alkylation)	Pancreatic cancer	Cancer	Isocyanate, diazohydroxide (prodrug)	Irreversible	DNA, proteins

Ceftriaxone	Rocephin	Roche	1984	PBP	Bacterial infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Clavulanic acid	Augmentin	Neopharma	1984	β -lactamases	β -lactam resistant bacterial infections	Anti-microbial	β -lactam (suicidal)	Irreversible	Ser
Cephalexin	Keflex	Pragma	1986	PBP	Bacterial infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Sulbactam	Unasyn	Pfizer	1986	β -lactamases	Bacterial infections	Anti-microbial	β -lactam (suicidal)	Irreversible	Ser
Ifosfamide	Ifex	Baxter	1987	DNA (alkylation)	Testicular cancer	Cancer	Aziridinium (prodrug)	Irreversible	Purines (N7)
Cefuroxime axetil	Ceftin	GSK	1987	PBP	Bacterial infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Omeprazole	Prilosec	Astrazeneca	1989	H+/K+ ATPase	Esophageal reflux and heartburn	Gastro-intestinal diseases	Sulfenic acid (prodrug)	Irreversible	Cys
Selegiline	Selegiline hydrochloride	Somerset	1989	MAO-B	Parkinson's disease	CNS diseases	Propargylamine (suicidal)	Irreversible	FAD (N5)
Carboplatin	Paraplatin	Corden Pharma	1989	DNA (crosslinker)	Ovarian cancer	Cancer	Pt (II)	Irreversible	Purines (N7)
Eflornithine	Ornidyl	Sanofi	1990	Ornithine decarboxylase	African trypanosomiasis	Anti-microbial	Difluoromethyl group (suicidal)	Irreversible	Cys
Altretamine	Hexalen	Eisai	1990	DNA (alkylation)	Ovarian cancer	Cancer	Formimine (prodrug)	Irreversible	Purines (N7)
Cefprozil	Cefzil	Corden Pharma	1991	PBP	Bacterial infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Finasteride	Proscar	Merck	1992	5-alpha-reductase	Symptomatic benign prostatic hyperplasia	Cancer	Acrilamide	Reversible*	NADH
Tazobactam	Zosyn	Wyeth Pharms	1993	β -lactamases	Bacterial infections	Anti-microbial	β -lactam (suicidal)	Irreversible	Ser
Lansoprazole	Prevacid	Takeda	1995	H+/K+ ATPase	Esophageal reflux and heartburn	Gastro-intestinal diseases	Sulfenic acid (prodrug)	Irreversible	Cys
Gemcitabine	Gemzar	Lilly	1996	Ribonucleoside reductatase	Non-small cell lung cancer, pancreatic cancer, breast and ovarian cancer	Cancer	Geminal difluoride ^f	Irreversible	Cys
Fosfomycin	Monurol	Zambon	1996	UDP-N-acetylgluco-samine-3-enolpyruvyl-transferase	Bacterial infections	Anti-microbial	Epoxide	Irreversible	Cys
Meropenem	Merrem	Pfizer	1996	PBP	Bacterial infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Clopidogrel	Plavix	Sanofi	1997	P2Y12, platelet purinergic receptor	Reduction of risk for stroke and heart attack	Cardiovascular diseases	Thiol (prodrug)	Irreversible	Cys
Cefdinir	Omnicef	Abbvie	1997	PBP	Bacterial infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Capecitabine	Xeloda	Roche	1998	Thymidylate synthase	Dukes' C colon cancer	Cancer	Dihydro-pyrimidinedione	Irreversible	Cys, Tetrahydrofolate cofactor
Rabeprazole	Aciphex	Eisai	1999	H+/K+ ATPase	Esophageal reflux and heartburn	Gastro-intestinal diseases	Sulfenic acid (prodrug)	Irreversible	Cys
Exemestane	Aromasin	Pharmacia and Upjohn	1999	Aromatase	Breast cancer	Cancer	Cyclohexadienone (suicidal)	Irreversible	Heme-iron, nucleophilic residue
Temozolomide	Temodar	Merck	1999	DNA (alkylation)	Glioblastoma, astrocytoma	Cancer	Methyldiazonium (prodrug)	Irreversible	Purines (N7)
Orlistat	Xenical	Cheplapharm	1999	Lipases	Hyperlipidemia	Gastro-intestinal diseases	β -lactone	Reversible	Ser
Pantoprazole	Protonix	Wyeth Pharms	2000	H+/K+ ATPase	Esophageal reflux and heartburn	Gastro-intestinal diseases	Sulfenic acid (prodrug)	Irreversible	Cys
Rivastigmine	Exelon	Novartis	2000	Acetylcholinesterase, butyrylcholinesterase	Dementia/Parkinson's disease	CNS diseases	Carbamate	Slowly reversible	Ser
Esomeprazole	Nexium	Astrazeneca	2001	H+/K+ ATPase	Esophageal reflux and heartburn	Gastro-intestinal diseases	Sulfenic acid (prodrug)	Irreversible	Cys
Dutasteride	Avodart	GSK	2001	5-alpha-reductase	Symptomatic benign prostatic hyperplasia	Cancer	Acrilamide	Irreversible	NADH
Oxaliplatin	Eloxatin	Sanofi	2002	DNA (crosslinker)	Colon cancer	Cancer	Pt (II)	Irreversible	Purines (N7)
Bortezomib	Velcade	Millennium Pharms	2003	Proteasome	Multiple myeloma	Cancer	Boronic acid	Slowly reversible	Thr
Azacitidine	Vidaza	Celgene	2004	DNA methyltransferase	Myelodysplastic syndrome	Cancer	Triazinone (suicidal)	Irreversible	Cys

Decitabine	Dacogen	Otsuka Pharm Co LTD	2006	DNA methyltransferase	Myelodysplastic syndrome	Cancer	Triazinone (suicidal)	Irreversible	Cys
Rasagiline	Azilect	Teva	2006	MAO-B	Parkinson's disease	CNS diseases	Propargylamine (suicidal)	Irreversible	FAD (N5)
Bendamustine	Treanda	Cephalon	2008	DNA (alkylation)	Chronic lymphocytic leukemia (CLL), multiple myeloma, and non-Hodgkin's lymphoma	Cancer	Aziridinium (prodrug)	Irreversible	Purines (N7)
Vigabatrin	Sabril	Lundbeck Pharms LLC	2009	GABA-aminotransferase	Anti-epileptic	CNS diseases	Allylamine (suicidal)	Irreversible	PLP cofactor, Lys
Saxagliptin	Onglyza	Astrazeneca	2009	DPP4	Diabetes	Diabetes	Nitrile	Reversible	Ser
Ceftaroline fosamil	Teflaro	Cerexa	2010	PBP	Skin and skin-structure infections; community acquired pneumonia	Anti-microbial	β -lactam	Slowly reversible*	Ser
Abiraterone	Zytiga	Centocor Ortho Biotech	2011	CYP17	Metastatic castration-resistant prostate cancer	Cancer	Pyridine	Irreversible	Heme-iron (semi-covalent)
Boceprevir	Victrelis	Merck & Co.	2011	NS3/4A	HCV genotype 1	Anti-microbial	α -ketoamide	Reversible	Ser
Telaprevir	Incivek	Vertex	2011	NS3/4A	HCV genotype 2	Anti-microbial	α -ketoamide	Reversible	Ser
Carfilzomib	Kyprolis	Onyx	2012	Proteasome	Multiple myeloma	Cancer	Epoxyketone	Irreversible	Thr
Ibrutinib	Imbruvica	Pharmacyclics	2013	BTK	Mantle cell lymphoma	Cancer	Acrylamide	Irreversible	Cys
Afatinib	Gilotrif	Boehringer Ingelheim	2013	EGFR, HER2 and HER4	Metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R)	Cancer	Acrylamide	Irreversible	Cys
Dimethyl fumarate	Tecfidera	Biogen Idec	2013	RSK2 (proposed) ^b	Relapsing forms of multiple sclerosis	CNS diseases	Fumarate	Irreversible	Cys
Ceftolozane	Zerbaxa	Cubist	2014	PBP	Complicated intra-abdominal infections and complicated urinary tract infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Osimertinib	Tagrisso	AstraZeneca	2015	EGFR	NSCLC with EGFR ^{T790M} mutations	Cancer	Acrylamide	Irreversible	Cys
Trabectedin	Yondelis	Johnson & Johnson	2015	DNA (alkylation)	Liposarcoma or leiomyosarcoma	Cancer	Highly reactive carbinolamine (imine intermediate)	Reversible	Guanine (N2)
Avibactam	Avycaz	Allergan	2015	β -lactamases	Complicated intra-abdominal infections and complicated urinary tract infections	Anti-microbial	(ureidooxy)sulfonic acid in diazabicyclooctanes core	Slowly reversible*	Ser
Ixazomib	Ninlaro	Takeda	2015	Proteasome	Multiple myeloma	Cancer	Boronic acid	Slowly reversible	Thr
Acalabrutinib	Calquence	AstraZeneca/Acerta Pharma	2017	BTK	Mantle cell lymphoma	Cancer	2-butynamide	Irreversible	Cys
Neratinib	Nerlynx	Puma Biotechnology	2017	EGFR, HER2 and HER4	HER2-overexpressed breast cancer	Cancer	Acrylamide	Irreversible	Cys
Vaborbactam	Vabomere	The Medicines Company/Rempex Pharmaceuticals	2017	β -lactamases	Complicated urinary tract infections	Anti-microbial	Boronic acid	Reversible	Ser
Vaborbactam	Vabomere	Rempex Pharms	2017	β -lactamases	Bacterial infections	Anti-microbial	Boronic acid	Reversible	Ser
Dacomitinib	Vizimpro	Pfizer	2018	EGFR	EGFR-mutated NSCLC	Cancer	Acrylamide	Irreversible	Cys
Zanubrutinib	Brukinsa	BeiGene	2019	BTK	Mantle cell lymphoma	Cancer	Acrylamide	Irreversible	Cys
Selinexor	Xpovio	Karyopharm Therapeutics	2019	Exportin 1 (XPO1)	Multiple myeloma	Cancer	Acrylamide	Slowly reversible	Cys
Voxelotor	Oxbryta	Global Blood Therapeutics	2019	Hemoglobin	Sickle Cell Disease	Hematologic disease	Aldehyde	Reversible	N-term Val
Cefiderocol	Fetroja	Shionogi	2019	PBP	Complicated urinary tract infections	Anti-microbial	β -lactam	Slowly reversible*	Ser
Relebactam	Recarbrio	Merck & Co.	2019	β -lactamases	Complicated urinary tract and complicated intra-abdominal infections	Anti-microbial	(ureidooxy)sulfonic acid in diazabicyclooctanes core	Reversible*	Ser

^a Data source: FDA database ^b Only the New Chemical Entity (NCE) approved in the specified year is reported for combination drugs (source: FDA database), ^c Refers to the original sponsor for FDA first approval (source: FDA database), ^d When a prodrug mechanism is entailed, the revealed warhead is reported, ^e Selenocysteine, ^f Cerqueira NMFS, Fernandes PA, Ramos MJ. Understanding ribonucleotide reductase inactivation by gemcitabine. Chem. - A Eur. J. 13(30), 8507–8515 (2007), ^g Andersen JL, Gesser B, Funder ED, et al. Dimethyl fumarate is an allosteric covalent inhibitor of the p90 ribosomal S6 kinases. Nat. Commun. 9(1), 1–8 (2018), * Inhibitor is not recovered upon release from its target.