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Perspective

U.S. FDA Approved Drugs from 2015−June 2020: A Perspective

Priyadeep Bhutani,[#] Gaurav Joshi,[#] Nivethitha Raja, Namrata Bachhav, Prabhakar K. Rajanna, Hemant Bhutani, Atish T. Paul,[*] and Raj Kumar[*]

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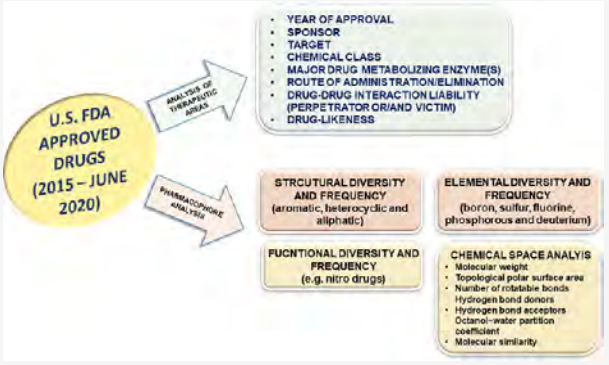
ABSTRACT: In the present work, we report compilation and analysis of 245 drugs, including small and macromolecules approved by the U.S. FDA from 2015 until June 2020. Nearly 29% of the drugs were approved for the treatment of various types of cancers. Other major therapeutic areas of focus were infectious diseases (14%); neurological conditions (12%); and genetic, metabolic, and cardiovascular disorders (7−8% each). Itemization of the approved drugs according to the year of approval, sponsor, target, chemical class, major drug-metabolizing enzyme(s), route of administration/elimination, and drug−drug interaction liability (perpetrator or/and victim) is presented and discussed. An effort has been made to analyze the pharmacophores to identify the structural (e.g., aromatic, heterocycle, and aliphatic), elemental (e.g., boron, sulfur, fluorine, phosphorus, and deuterium), and functional group (e.g., nitro drugs) diversity among the approved drugs. Further, descriptor-based chemical space analysis of FDA approved drugs and several strategies utilized for optimizing metabolism leading to their discoveries have been emphasized. Finally, an analysis of drug-likeness for the approved drugs is presented.



INTRODUCTION

Drug discovery is a complex interdisciplinary process, and it continues to pose a plethora of challenges for the pharmaceutical industry and allied fields.[1] In recent times, the expectations from new drugs to exhibit better performance over the existing ones in the market has increased tremendously.[2] The main reason attributed to this is probably the strict requirements imposed by different regulatory agencies around the world.[3,4] Considering the last five years of approvals (2015−June 2020) by the Centre for Drug Evaluation and Research (CDER) of the U.S. FDA, a total of 245 drugs were approved including small and macromolecules (Figure 1). Of these, a record number of drugs were approved in 2018 (59), and a minimum of approvals came through in 2016 (22). For all the other years of the study (i.e., 2015, 2017, and 2019), the number of new drug approvals from the agency remained in the range of 45−48. Approval of 25 drugs until June 2020 indicates that this year also might end up with a similar number of approvals.[5−7] Among the different therapeutic categories, anticancer drugs accounted for 29% of drug approvals followed by anti-infectives (14%) and drugs for neurological disorders (12%). Other major areas of focus from the pharmaceutical industry wherein approvals came through were genetic, autoimmune, cardiac, and metabolic disorders (each ranging between 6 and 8%).

Considering the drug discovery, on an average, one drug out of every 8000−10 000 compounds is approved for the market.[10] The drug-likeness for any compound is largely determined by its pharmacokinetics (PK), safety, and efficacy. The goal of PK studies is to ascertain and eventually help achieve the desired efficacy and safety profile.[11−13] Efficacy, safety, and PK are interconnected, and assigning the cause of failure of a compound to any one of these factors could be misleading. For example, extensive metabolism could be one of the reasons for not achieving the desired efficacy, and toxicity might be observed because of the formation of metabolites.[14] The benzylic C−H bond and the allylic methyl and *O*-, *N*-, *S*-methyl groups, when not sterically hindered, are ideal metabolic soft spots and substrates of cytochrome (CYP) P450 mediated oxidative and reductive metabolism reactions. Overall, CYP enzymes are responsible for the metabolism of most of the small molecules. However, the structure−metabolism relationship of drugs metabolized through CYPs is complex. Hydrophobic, steric, hydrogen bonding, or ionic interactions with specific amino acids at the active site of the enzyme determine the affinity of the substrate with the active site of an enzyme. Common methods to decrease and/or block metabolism are (1) replacing the H atom of the C−H bond with a bulky group, bioisostere, a deuterium, or a halogen atom; or (2) place a bulky group in a neighboring site to decrease or block the accessibility of the enzyme. For

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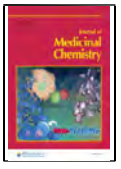

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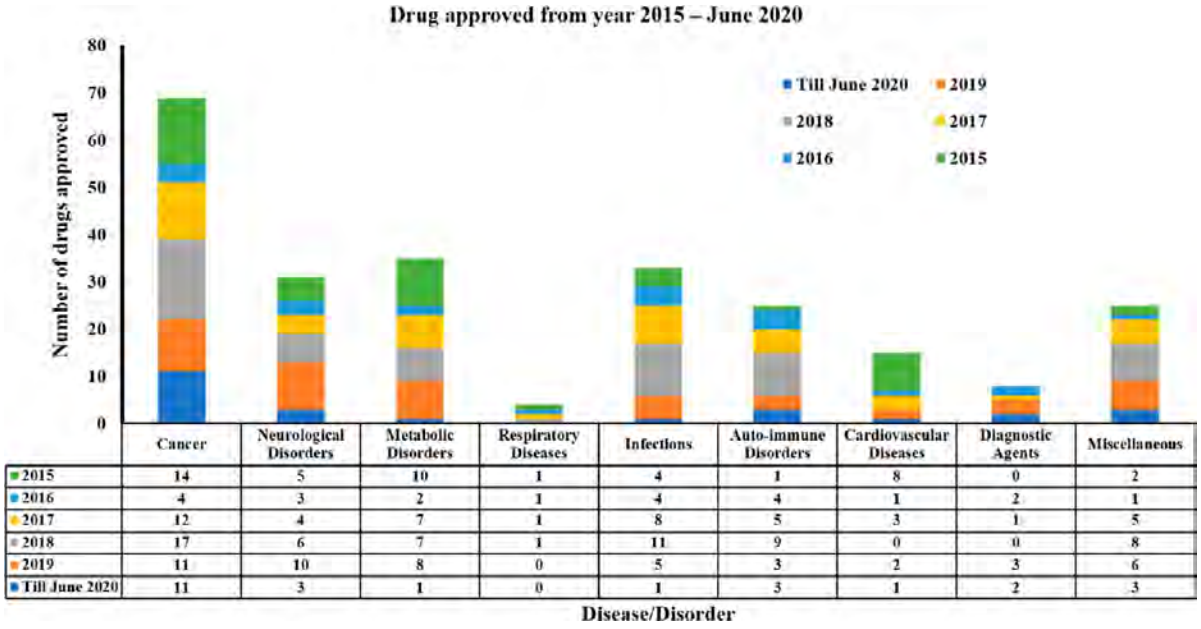

	Cancer	Neurological Disorders	Metabolic Disorders	Respiratory Diseases	Infections	Auto-immune Disorders	Cardiovascular Diseases	Diagnostic Agents	Miscellaneous
2015	14	5	10	1	4	1	8	0	2
2016	4	3	2	1	4	4	1	2	1
2017	12	4	7	1	8	5	3	1	5
2018	17	6	7	1	11	9	0	0	8
2019	11	10	8	0	5	3	2	3	6
Till June 2020	11	3	1	0	1	3	1	2	3

Figure 1. Bar graph illustration of the number of year-wise drug approvals for various diseases/disorders. The data pertains to 2015–June 2020. The source of the data is the U.S. FDA Web site[8] and DrugBank database.[9]

example, when a benzylic methyl group is identified as a metabolic soft spot, a halogen atom, or a $-CF_3$ group, could be used to replace the H atom of the benzylic methyl group.

An ideal drug candidate should be able to provide sustained exposure to have increased patient compliance due to decreased dosing frequency. It should undergo balanced clearance pathways and should not interfere with DMEs (drug-metabolizing enzymes) and transporters. In general, drugs are classified as either victims (directly affected) or perpetrators (cause interactions) in DDI (drug–drug interactions).[15] Medicinal chemists optimizing their compounds for candidate selection are often posed with the following questions: (1) What is the elimination pathway for the molecule of interest? (2) What are the metabolic liabilities of the molecule? (3) Does the compound of interest have the chance to undergo bioactivation to form a reactive metabolite? (4) Do any of the metabolites have either on- or off-target activity?[16] Two other essential parameters controlling rate and extent of absorption of drugs are solubility and permeability, and a Biopharmaceutics Classification System (BCS) for correlating *in vitro* dissolution and *in vivo* bioavailability has been proposed.[17] Several theories are available on predicting the "requisite" physicochemical properties for "drug-like" absorption potential for new chemical entities. As per Lipinski's rule, reduced intestinal permeability is reported for compounds (intended to be administered orally) with more than two out-of-range parameters from the following: more than five hydrogen-bond donors (sum of OH and NH groups), more than 10 hydrogen-bond acceptors (sum of N and O), molecular weight (MW) > 500, and log $P > 5$.[18−20]

While compiling this Perspective, we came across many worthy reviews on FDA approved drugs which are either yearly publications focusing on a particular issue[6,7,21,22] or are relatively old.[23] In this Perspective, we broadly categorized and discussed in the first section the U.S. FDA approved drug candidates of the last five years (2015–June 2020) based on their therapeutic areas, year of approval, sponsor, target, chemical class (small and macromolecules including antibody–drug conjugates), major drug-metabolizing enzyme(s), route of administration/elimination, and DDI liability (perpetrator and victim). The data was collected from the U.S. FDA Web site and the DrugBank database. In a later section, we comprehensively analyzed the structural (e.g., aromatic, heterocycle, and aliphatic), elemental (e.g., boron, sulfur, fluorine, phosphorus and deuterium), and functional (e.g., nitro drugs) diversity and frequency, and chemical space among the approved drugs and finally pharmacokinetic aspects and market outlook are discussed.

■ ANTI-CANCER DRUGS

According to the WHO, more than 100 types of cancer are currently known, and the five most common cancers in 2018 were lung, colorectal, stomach, breast, and liver.[24] Total deaths due to various types of cancer were more than 9 million in that year. Each cancer type requires a separate diagnosis and treatment strategy, which further creates an additional burden on and challenge for the discovery of anticancer drugs. Since the advent of the first anticancer therapy in the 1940s using nitrogen mustards and antifolate drugs,[25] there has been an incredible improvement in the design of new anticancer drugs.[26] The last five years have witnessed the FDA approving a total of 69 drug/drug combinations for the treatment of various types of cancers including 51 small molecules (Table 1, Figures 2 and 3) and 19 macromolecules (Table 2).

Neratinib (**15**), a kinase inhibitor, was approved for the treatment of HER2-overexpressed/amplified breast cancer. The other approved anticancer kinase inhibitor drugs included cobimetinib (**4**), copanlisib (**22**), and acalabrutib (**19**) as inhibitors of MAPK, PI3K/AKT, and BTK, respectively. Drugs targeting vascular endothelial growth factor (VEGF; lenvatinib, **7** and brolucizumab), basic fibroblast growth factor (bFGF; erdafitinib, **40** and pemigatinib, **43**), platelet-derived endothelial growth factor (PDGFR; olaratumab), and granulocyte colony-stimulating factor (CSF; pexidartinib, **37**) were approved in the study period to prevent the formation of new blood vessels and thus subsequently suppress tumor growth. There was one antiapoptotic drug; venetoclax (**12**) targeting Bcl-2 was approved in the year 2017[27] for the treatment of chronic

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Table 1. Illustrative Compilation of U.S. FDA Approved Anti-Cancer Drugs (Small Molecules) from the Year 2015 until June 2020, Featuring Their Indication, Year of Approval, Sponsor, Target, Chemical Class, Major Drug Metabolizing Enzyme(s), Route of Administration/Elimination, and Drug Interactions (Perpetrator or/and Victim)[¶]

Brand name (Active ingredient/Route of administration)	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Alecensa (Alectinib/PO)	ALK-positive lung cancer	2015/Roche /P, O, A, B	ALK	Indole and derivatives	CYP3A4	---[a]	Feces
Ninlaro (Ixazomib/PO)	Multiple myeloma	2015/Takeda/P, O	Proteasome	Hippuric acids and derivatives	3A4 (42%), 1A2 (26%), 2B6 (16%), 2C8 (6%), 2D6 (5%), 2C19 (5%) and 2C9 (< 1%)	Victim with CYP3A4 inhibitors and inducers	62% in urine and 22% in feces
Ibrance (Palbociclib/PO)	HR+ve, HER2-ve breast cancer	2015/Pfizer/P, B, A	CDK4 and CDK6	Diazinanes	CYP3A and SULT2A1	Victim with Per with CYP3A4 inhibitors and inducers	17.5% in urine and 74% in feces
Tagrisso (Osimertinib/PO)	Metastatic EGFR T790M mutation-positive NSCLC)	2015/AstraZeneca /P, O, B, A	EGFR	N-alkylindoles	CYP3A	Victim with CYP3A4 inhibitors and inducers	14% in urine and 68% in feces
Cotellic (Cobimetinib/PO)	Metastatic melanoma with a BRAF mutation (V600E or V600K)	2015/Genentech/P , O	MAPK	Benzoic acids and derivatives	CYP3A and UGT2B7	Victim with CYP3A4 inhibitors and inducers	17.8% in urine and 76% in feces
Farydak (Panobinostat/PO)	Multiple myeloma after receiving at least 2 prior regimens	2015/Novartis/P, O, A	Histone deacetylase	Tryptamines and derivatives	CYP3A, CYP2D6, CYP2C19, UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, and UGT2B4	Victim with CYP3A4 inhibitors and inducers and perpetrator on CYP2D6 substrates; Avoid concomitant use with anti-arrhythmic drugs	51% in urine and 50% in feces
Lenvima (Lenvatinib/PO)	Thyroid cancer	2015/Eisai/P, O	VEGFR1, VEGFR2 and VEGFR3 inhibitor, FGFR1,2,3,4 and PDGFRα, KIT and RET	Quinoline carboxamides	CYP3A and aldehyde oxidase	Avoid concomitant use with QT-prolonging drugs	25% in urine and 64% in feces
Lonsurf (Trifluridine/PO)	Metastatic colorectal cancer	2015/Taiho/S	Thymidylate synthetase (Antimetabolites)	Pyrimidine nucleosides	thymidine phosphorylase	---[a]	55% in urine and 3% in feces
Lonsurf (Tipiracil/PO)			Thymidine phosphorylase (Antimetabolites)	Diazinanes	enterobacterial metabolism	---[a]	27% in urine and 50% in feces
Yondelis (Trabectedin /IV)	Metastatic liposarcoma or leiomyosarcoma	2015/Johnson & Johnson/P, O	Alkylating drug	Benzene and substituted derivatives	CYP3A4	Victim with CYP3A4 inhibitors and inducers	6% in urine and 58% in feces
Odomzo (Sonidegib/PO)	Basal cell carcinoma	2015/Novartis/S	Smoothened (Smo)	Benzene and substituted derivatives	CYP3A4	Victim with CYP3A4 inhibitors and inducers	30% in urine and 70% in feces
Rubraca (Rucaparib/PO)	Advanced ovarian cancer	2016/Clovis Oncology / P, O, A, B	PARP-1,2 and 3	Indole and derivatives	CYP2D6	Perpetrator with CYP1A2, CYP3A, CYP2C9, and CYP2C19 substrates	30% in urine and 70% in feces
Venclexta (Venetoclax/PO)	CLL with 17p deletion	2016/AbbVie / P, O, A, B	BCL-2 protein	Diazinanes	CYP3A4	Victim with CYP3A4 inhibitors and inducers and P-gp inhibitors and perpetrator with P-gp substrates	0.1% in urine and 99.9% in feces
Verzenio (Abemaciclib/PO)	HR+ve, HER2-ve breast cancer	2017/Eli Lilly /P, B	CDK4 and CDK6	Benzimidazoles	CYP3A4	Victim with CYP3A4 inhibitor and inducer	33% in urine and 81% in feces
Idhifa (Enasidenib/PO)	AML with an IDH2 mutation	2017/Celgene/Agios /P, O	IDH2 enzyme	Aminotriazines	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4	Victim with CYP3A4 inhibitors and inducers	11% in urine and 89% in feces
Nerlynx (Neratinib maleate/PO)	HER2-overexpressed/amplified breast cancer	2017/Puma Biotechnology /S	EGFR	Quinolines and derivatives	CYP3A4	Victim with CYP3A4 inhibitors and inducers and perpetrator with P-gp substrates; Avoid concomitant use with proton pump inhibitors and H2-receptor antagonists	1.1% in urine and 97% in feces
Rydapt (Midostaurin/PO)	AML that has FLT3 mutation	2017/Novartis /P, O, B	Tyrosine kinases	Indole and derivatives	CYP3A4	Victim with CYP3A4 inhibitors and inducers	5% in urine and 95% in feces
Alunbrig (Brigatinib/PO)	ALK-positive lung cancer	2017/Ariad Pharmaceuticals/Takeda/ P, O, A, B	ALK, EGFR, ROS1, and IGF-1	Piperidines	CYP2C8 and CYP3A4	Victim with CYP3A4 inhibitors and inducers	25% in urine and 65% in feces
Zejula (Niraparib/PO)	The epithelial ovarian, fallopian tube, or primary peritoneal cancer	2017/Tesaro /P, O, B	PARP-1,2 and 3 enzymes	Piperidines	carboxylesterases	---[a]	47.5 % in urine and 40% in feces
Kisqali (Ribociclib/PO)	HR+ve, HER2-ve breast cancer	2017/Novartis/P, B	CDK4 and CDK6	Diazinanes	CYP3A4	Victim with CYP3A4 inhibitors and inducers and perpetrator with CYP3A4 substrate; Avoid concomitant use with anti-arrhythmic and QT-prolonging drugs	23% in urine and 69% in feces
Calquence (Acalabrutinib/PO)	Mantle cell lymphoma (MCL)	2017/AstraZeneca /Acerta Pharma /P, O, A, B	BTK	Azoles	CYP3A4	Victim with CYP3A4 inhibitors and inducers; Avoid concomitant use with proton pump inhibitors and H2-receptor antagonists	12% in urine and 84% in feces
Aliqopa (Copanlisib/IV)	Relapsed follicular lymphoma (FL)	2017/Bayer /P, O, A	PI3K- α and PI3K- δ	Diazanapthalenes	CYP3A4 and CYP1A1	Victim with CYP3A4 and P-gp inhibitors and inducers	22% in urine and 64% in feces
Xospata (Gilteritinib/PO)	AML with a FLT3 mutation	2018/Astellas /P, O, B	ITD, TKD, FLT3 , AXL and ALK Tyrosine kinase inhibitor	Piperidines	CYP3A4	Victim with CYP3A4 and P-gp inhibitors and inducers	16.4% in urine and 64.5% in feces

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Table 1. continued

Brand name (Active ingredient/Route of administration)	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Vitrakvi (Larotrectinib/PO)	Solid tumors	2018/Loxo Oncology/Bayer /P,O,A,B	Tropomyosin receptors kinase; (TRKA,B, and c) NTRK inhibitor	Hydroxypyrrolidine-1-carboxamide	CYP3A4	Victim with CYP3A4 inhibitors and inducers and perpetrator with CYP3A4 substrates	39% in urine and 58% in feces
Daurismo (Glasdegib/PO)	AML	2018/Pfizer/P, O	Smoothened (Smo) receptor inhibitor: inhibits Hedgehog signaling pathway	N-phenylureas	CYP3A4	Victim with CYP3A4 inhibitors and inducers; Avoid concomitant use with QT-prolonging drugs	42% in urine and 49% in feces
Lorbrena (Lorlatinib/PO)	ALK-positive metastatic NSCLC	2018/Pfizer/P,O, B, A	Tyrosine Kinase inhibitor	Macrolactams	CYP3A4 and UGT1A4	Victim with CYP3A4 inhibitors and inducers and perpetrator with CYP3A4 substrates	48% in urine and 41% in feces
Talzenna (Talazoparib/PO)	HER2-ve locally advanced or metastatic breast cancer	2018/Pfizer/P	PARP-1 and 2 enzymes	Quinolines and derivatives	Minimal hepatic metabolism	Victim with P-gp and BCRP inhibitors	69% in urine and 20% in feces
Copiktra (Duvelisib/PO)	CLL or SLL	2018/Verastem /P, O, A	PI3K-δ and PI3K-γ	Isoquinolines and derivatives	CYP3A4	Victim with CYP3A4 inhibitors and inducers and perpetrator with CYP3A4 substrates	14% in urine and 79% in feces
Tibsovo (Ivosidenib/PO)	AML	2018/Agios Pharmaceuticals /P, O	IDH-1	Carboxylic acid derivatives	CYP3A4	Victim with CYP3A4 inhibitors and inducers and perpetrator with CYP3A4 substrates; Avoid concomitant use with QT-prolonging drugs	17% in urine and 77% in feces
Braftovi (Encorafenib/PO)	Metastatic melanoma with a BRAF mutation (V600E or V600K)	2018/Array BioPharma /S, O	Kinase (BRAF gene)	Azoles	CYP3A4, CYP2C19 and CYP2D6	Victim with CYP3A4 inhibitors and inducers and perpetrator with CYP3A4 substrates	47% in urine and 47% in feces
Mektovi (Binimetinib/PO)	Metastatic melanoma with a BRAF mutation (V600E or V600K)	2018/Array BioPharma /S, O	MAPK 1/2	Benzene and substituted derivatives	UGT1A1	---[a]	31 % in urine and 62% in feces
Erleada (Apalutamide/PO)	Non-metastatic prostate cancer	2018/Johnson & Johnson/P	Androgen receptor (AR)	Azolidines	CYP2C8 and CYP3A4	Perpetrator with CYP3A4, CYP2C19, CYP2C9, UGT, P-gp, BCRP, or OATP1B1 substrates	65 % in urine and 24% in feces
Lutathera (Lutetium Lu 177 dotatate/IV)	Gastroenteropancreatic neuroendocrine tumors	2018/Advanced Accelerator Applications/Novartis/P, O	Somatostatin (SSRT1,2,3,4, and 5)	Somatostatin analog	No hepatic metabolism	Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of Lutathera	99% in urine
Vizimpro (Dacomitinib/PO)	Metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations	2018/Pfizer /P, O	Tyrosine kinase inhibitor (EGRF)	Diazanapthalenes	CYP2D6 and CYP3A4	Perpetrator with CYP2D6 inhibitors; Avoid concomitant use with proton pump inhibitors	3% in urine and 79% in feces
Brukinsa (Zanubrutinib/PO)	MCL	2019/Biegene/P, O	BTK inhibitor	Benzene and substituted derivatives	CYP3A4	Victim with CYP3A4 inhibitors and inducers	8% in urine and 87% in feces
Nubeqa (Darolutamide/PO)	Non-metastatic prostate cancer	2019/Bayer/P	Nonsteroidal androgen receptor	Azoles	CYP3A4, UGT1A9 and UGT1A1.	Victim with CYP3A4 inhibitors and inducers and perpetrator with BCRP substrates	63% in urine and 32% in feces
Piqray (Alpelisib/PO)	HR+ve, HER2-ve breast cancer	2019/Novartis/P	PI3K	Carboxylic acid derivatives	chemical and enzymatic hydrolysis	Victim with CYP3A4 inhibitors and inducers and BCRP inhibitors and perpetrator with CYP2C9 substrates	14% in urine and 81% in feces
Balversa (Erdafitinib/PO)	Metastatic urothelial carcinoma	2019/Janssen/P, B, A	FGFR	Organonitrogen compounds	CYP2C9 and CYP3A4	Victim with CYP3A4 and CYP2C9 inhibitors and inducer and BCRP inhibitors and perpetrator with CYP3A4, OCT2 and P-gp substrates; Avoid concomitant use with agents that can alter serum phosphate levels	19% in urine and 69% in feces
Turalio (Pexidartinib/PO)	Symptomatic tenosynovial giant cell tumor	2019/Daiichi Sankyo/P, O, B	Colony-stimulating factor (CSF1)/CSF1 receptor	Pyrrolopyridines	CYP3A4 and UGT1A4	Victim with CYP3A4 and CYP2C9 inhibitors and inducer and UGT inhibitors; Avoid concomitant use of proton pump inhibitors; Avoid co-administration of TURALIO with other products known to cause hepatotoxicity	27% in urine and 65% in feces
Xpovio (Selinexor/PO)	Relapsed or refractory multiple myeloma	2019/Karyopharm Theraps/P, O	Exportin-1 inhibitor	Azoles	CYP3A4 and UGT	---[a]	Information not available
Inrebic (Fedratinib/PO)	Myelofibrosis	2019/Celgene/BMS/P, O	Kinase inhibitor	Benzene sulfonamids	CYP3A4, CYP2C19, FMO3	Victim with CYP3A4 and CYP2C19 inhibitors and inducers	5% in urine and 77% in feces
Rozlytrek (Entrectinib/PO)	Metastatic ROS1-positive NSCLC	2019/Genentech /P, O	Kinase inhibitor	Diazinanes	CYP3A4	Victim with CYP3A4 inhibitors and inducers	3% in urine and 83% in feces
Qinlock (Ripretinib/PO)	Gastrointestinal-stromal tumors	2020/Deciphera Pharms/P, O	Protein Kinase	Phenylurea derivative	CYP3A4	Victim with CYP3A4 inhibitors and inducers	0.02% in urine and 34% in feces
Retevmo (Selpercatinib/PO)	Lung and thyroid cancers	2020/Loxo Oncology Inc/P, O	Kinase	Pyridine-3-carbonitrile derivative	CYP3A4	Victim with CYP3A4 inhibitors and inducers; Perpetrator on CYP3A4 and CYP2C8 substrates; Avoid concomitant use with proton pump inhibitors	24% in urine and 69% in feces

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Table 1. continued

Brand name (Active ingredient/Route of administration)	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Tabrecta (Capmatinib/PO)	NSCLC	2020/Novartis/P, O	Hepatocyte growth factor receptor inhibitor	Quinolines and derivatives	CYP3A4 and aldehyde oxidase	Victim with CYP3A4 inhibitors and inducers; Perpetrator with BCRP and P-gp substrates; Avoid concomitant use with agents that can alter serum phosphate levels Avoid concomitant use with proton pump inhibitors	24% in urine and 42% in feces
Pemazyre (Pemigatinib/PO)	Cholangiocarcinoma	2020/Incyte Corp/P, O	FGFR	Tetraen-12-one Derivative	CYP3A4	Victim with CYP3A4 inhibitors and inducers	12.6% in urine and 82% in feces
Tukysa (Tucatinib/PO)	Metastatic HER2-positive breast cancer	2020/Seattle Genetics/P, O	HER2	Diazanapthalenes	CYP2C8 and to a lesser extent via CYP3A	Victim with CYP3A4 inhibitors and inducers; Perpetrator with CYP3A4 and P-gp substrates	24% in urine and 42% in feces
Koselugo (Selumetinib/PO)	Neurofibromatosis type 1	2020/AstraZeneca / P, O	MAPK	Benzimidazoles	CYP3A4	Victim with CYP3A4 inhibitors and inducers	33% in urine and 59% in feces
Ayvakit (Avapritinib/PO)	Metastatic gastrointestinal stromal tumor	2020/Blueprint Medicines/P, O	Tyrosine kinase	Ethan-1-amine Derivative	CYP3A4 and to a lesser extent via CYP2C9	Victim with CYP3A4 inhibitors and inducers	18% in urine and 70% in feces
Tazverik (Tazemetostat/PO)	Epithelioid sarcoma	2020/Epizyme Inc/P, O	Methyltransferase (EZH2 and EZH1)	Benzene and substituted derivatives	CYP3A4	Victim with CYP3A4 inhibitors and inducers	15% in urine and 79% in feces
Zepzelca (Lurbinectedin/IV)	Metastatic small cell lung cancer	2020/Jazz/P, O	Alkylating drug	Aromatic heteropolycyclic compounds	CYP3A4	Victim with CYP3A4 inhibitors and inducers	6% in urine and 89% in feces

[a]No interaction reported. [g]ALK: anaplastic lymphoma kinase; HR: hormone receptor; HER: human epidermal growth factor; CDK: cyclin dependent kinase; EGFR: epidermal growth factor receptor; NSCLC: nonsmall-cell lung carcinoma; EGFR: epidermal growth factor receptor;TK: Tyrosine kinase; MAPK: mitogen-activated protein kinase; VEGFR: vascular endothelial growth factor receptor; PARP: polyadenosine 5′-diphosphoribose polymerase; CLL: chronic lymphocytic leukemia; BCL: B-cell lymphoma; AML: acute myeloid leukemia; IDH: isocitrate dehydrogenase; AR: Androgen receptor; MCL: mantle cell lymphoma; BTK: bruton tyrosine kinase; FL: follicular lymphoma; PI3K: phosphatidylinositol-3-kinase; NTRK: neurotrophin receptor kinase; SLL: small lymphocytic lymphoma; FGFR: fibroblast growth factor receptor; CSF: colony-stimulating factor; ROS: reactive oxygen species; A, accelerated; B, breakthrough; O, orphan; P, priority; S, standard CYP: cytochrome; PO: peroral; IV: intravenous.

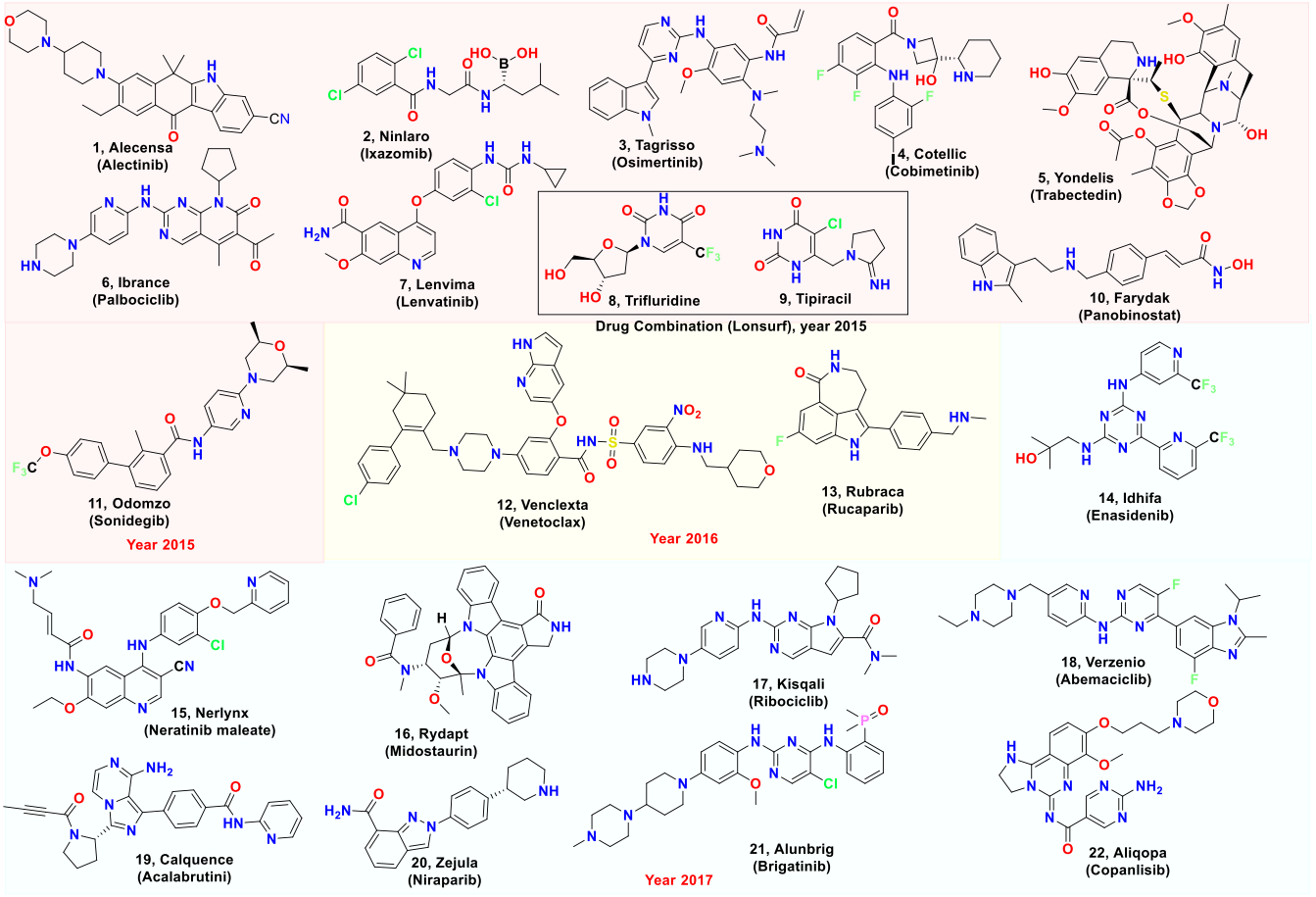

Figure 2. Chemical structures of small molecules as anticancer agents approved by FDA between 2015 and 2017 (Part-1).

lymphocytic leukemia. The agency approved first-in-class enasidenib (**14**), an inhibitor of mutated isocitrate dehydrogenase 2 (IDH2) for acute myeloid leukemia, confirming metabolism-altering drugs as a means of targeting and killing cancer cells. The agency also approved Amgen's talimogene laherparepvec, the first cancer-killing virus. Several monoclonal

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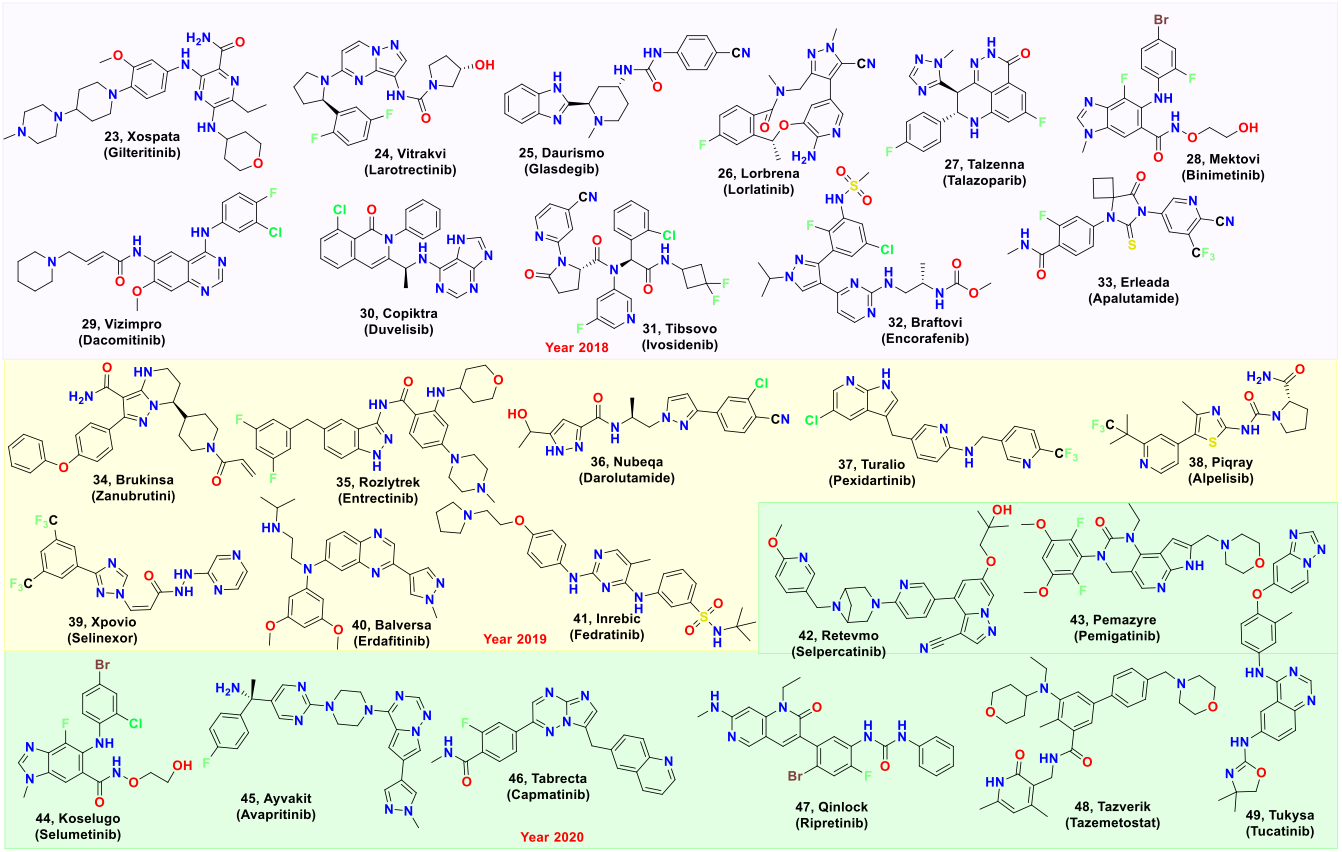

Figure 3. Chemical structures of small molecules approved as anticancer agents approved by FDA between 2018 and June 2020 (Part-2).

antibodies (mAbs) including but not limited to atezolizumab, avelumab, durvalumab, and cemiplimab targeting PD-L1 (immune checkpoints) were approved in the last five years. The approvals also include other immunotherapies and chimeric antigen receptor therapies.[28]

We noticed increased approvals for antibody−drug conjugates (ADCs) since 2015.[29] ADCs are highly selective and allow specific delivery of cytotoxic agents to the intended cancer cell target.[30,31] Their success has been marked by FDA approval of five ADCs in the last five years including inotuzumab ozogamicin for acute lymphoblastic leukemia, fam-trastuzumab deruxtecan for metastatic breast cancer, enfortumab vedotin for refractory bladder cancer, sacituzumab govitecan for metastatic triple-negative breast cancer, and polatuzumab vedotin for relapsed or refractory diffuse large B-cell lymphoma.

Typically, anticancer drugs are coadministered with other drugs and therefore have a high propensity to undergo DDI either as victim and/or perpetrator. Some of the drugs used for cancer therapy act as a victim in the presence of CYP3A4 modulators (both inhibitor as well as inducer) and P-gp (P-glycoprotein) and BCRP (breast cancer resistance protein) inhibitors, while others may be a perpetrator (impact the systemic exposure of coadministered drugs through inhibition of various enzymes like CYP3A4, CYP2C9. CYP2D6, CYP2C19 and transporters like P-gp, BCRP, OATP1B1; see Tables 1 and 2). Overall, CYPs played a significant role in the metabolism of 43 out of 51 small molecules, and for almost all the drugs (42 out of 43), the major enzyme involved is CYP3A4. Rucaparib (**13**), a first-in-class PARP inhibitor, is metabolized primarily by CYP2D6. Carboxylesterase-mediated amide hydrolysis is the major pathway for the metabolism of niraparib (**20**), leading to the formation of an inactive acid metabolite followed by glucuronidation. Aldehyde oxidase (AO) along with CYP3A4 are involved in the metabolism of capmatinib (**46**) and **7** (quinoline derivatives). Catabolism is primarily responsible for the elimination of all the macromolecules. A total of 47 out of 51 anticancer small-molecule drugs were approved for administration through the peroral route and 4 (trabectedin (**5**), copanlisib (**22**), lurbinectedin, and lutetium Lu 177 dotatate) through the intravenous route, and all the macromolecules were approved for use through the intravenous route.

Drug design for anticancer drugs has shifted from traditional cytotoxic chemotherapy to targeted cancer drugs,[32] which is further supported with increased understanding of the disease at the molecular level.[33,34] The overall success rate for the oncology drugs in the clinical development is estimated at ∼10%, while the cost of introducing a new drug to the market is estimated at greater than 1 billion US$.[35−37] Unfortunately, the major challenge is the development of drug resistance that leads to mortality and morbidity.[38] Considering the global market, it is anticipated that the targeted anticancer therapy would acquire the highest revenue contribution in cancer drug market by 2026. It is also anticipated that five regions (i.e., North America, Latin America, Europe, Asia Pacific excluding Japan, Middle East, and Africa) would drive anticancer research. AbbVie, Bayer, Pfizer, Bristol Myers Squibb, Roche, Eli Lilly, Novartis, AstraZeneca, and Johnson & Johnson will continue to be major players in the area and would contribute toward more than 2/3rd market share of anticancer drugs.[39]

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Table 2. Illustrative Compilation of U.S. FDA Approved Anti-Cancer Drugs (Macromolecules) from the Year 2015 until June 2020, Featuring Their Indication, Year of Approval, Sponsor, Target, Route of Administration, and Class[¶]

Brand name (Active ingredient/Route of administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Class
Empliciti (Elotuzumab/IV)	Monoclonal Antibody	Multiple myeloma	2015/Bristol Myers Squibb/P, O, B	SLAMF7 protein (cell surface)	Humanized IgG1
Portrazza (Necitumumab/IV)	Monoclonal Antibody	Metastatic squamous NSCLC	2015/Eli Lilly /S, O	EGFR	Humanized IgG1
Darzalex (Daratumumab/IV)	Monoclonal Antibody	Multiple myeloma	2015/Johnson & Johnson/P, O, A, B	CD38 antigen (cell surface)	Humanized IgG1
Unituxin (Dinutuximab/IV)	Monoclonal Antibody	Paediatric patients with high-risk neuroblastoma	2015/United Therapeutics/P, O	Glycolipid GD2 (cell surface)	Chimeric monoclonal antibody
Lartruvo (Olaratumab/IV)	Monoclonal Antibody	Soft tissue sarcoma	2016/Eli Lilly / P, O, A, B	PDGFR-α blocking antibody (intracellular protein kinase)	Humanized IgG1
Tecentriq (Atezolizumab/IV)	Monoclonal Antibody	Urothelial carcinoma	2016/Genentech /P, A, B	PD-L1 (immune checkpoint inhibitors)	IgG1 kappa immunoglobulin
Bavencio (Avelumab/IV)	Monoclonal Antibody	Metastatic Merkel cell carcinoma	2017/Merck KGaA/Pfizer / P, O, A, B	PD-L1 (immune checkpoint inhibitors)	Humanized IgG1
Imfinzi (Durvalumab/IV)	Monoclonal Antibody	Metastatic urothelial carcinoma	2017/AstraZeneca /P, B, A	PD-L1 (immune checkpoint inhibitors)	Human immunoglobulin G1 kappa (IgG1κ)
Besponsa (Inotuzumab ozogamicin/IV)	Antibody Drug Conjugate	ALL	2017/Pfizer /P, O, B	CD22-directed ADC	Humanized immunoglobulin class G subtype 4 (IgG4) kappa antibody +gamma-calicheamicin + an acid-cleavable linker
Elzonris (Tagraxofusp-erzs/IV)	Monoclonal Antibody	Blastic plasmacytoid dendritic cell neoplasm	2018/Stemline Therapeutics /P, O, B	IL-3 conjugated truncated diphtheria toxin	Fusion protein
Asparlas (Calaspargase pegol-mknl/IV)	Enzyme	ALL	2018/Servier/S, O	Asparagine specific enzyme	Enzyme
Libtayo (Cemiplimab-rwlc/IV)	Monoclonal Antibody	Cutaneous squamous cell carcinoma	2018/Regeneron/Sanofi /P, B	PD-L1 (immune checkpoint inhibitors)	Humanized IgG4
Lumoxiti (Moxetumomab pasudotox-tdfk/IV)	Cytotoxin	Hairy cell leukemia	2018/AstraZeneca /P, O	CD22-directed cytotoxin (cell surface)	Recombinant, murine immunoglobulin
Poteligeo (Mogamulizumab-kpkc/IV)	Monoclonal Antibody	Non-Hodgkin lymphoma	2018/Kyowa Hakko Kirin /P, O, B	CCR4- directed monoclonal antibody	Human immunoglobulin G1 kappa (IgG1κ)
Enhertu (Fam-trastuzumab deruxtecan-nxki/IV)	Antibody Drug Conjugate	Metastatic breast cancer	2019/Daiichi Sankyo/ AstraZeneca/P, B, A	HER2-directed antibody and topoisomerase inhibitor conjugate	Humanized anti-HER2 IgG1 monoclonal antibody (mAb) + a topoisomerase inhibitor + tetrapeptide-based cleavable linker.
Padcev (Enfortumab vedotin-ejfv/IV)	Antibody Drug Conjugate	Refractory bladder cancer	2019/Astellas/P, B, A	CD-30, Human IgG1 directed against Nectin-4, (cell surface)	IgG1 kappa monoclonal antibody + monomethyl auristatin E (MMAE) + a protease-cleavable maleimidocaproyl valine-citrulline (vc) linker
Polivy (Polatuzumab vedotin-piiq/IV)	Antibody Drug Conjugate	Relapsed or refractory diffuse large B-cell lymphoma	2019/Roche/P, O, A, B	CD79b-directed antibody-drug conjugate with activity against dividing B cells.	IgG1 monoclonal antibody specific for human CD79b; + the small molecule anti-mitotic agent MMAE; + a protease-cleavable linker
Trodelvy (Sacituzumab govitecan-hziy/IV)	Antibody Drug Conjugate	Metastatic triple-negative breast cancer	2020/Immunomedics Inc/NA	Trop-2-directed antibody and topoisomerase inhibitor conjugate	Humanized monoclonal antibody, hRS7 IgG1κ+ SN-38 + hydrolysable linker
Sarclisa (Isatuximab/IV)	Monoclonal Antibody	Multiple myeloma	2020/Sanofi/O	CD38-directed cytolytic antibody	Humanized IgG1

[¶]SLAMF: signaling lymphocytic activation molecule family member 7; EGFR: epidermal growth factor receptor; NSCLC: nonsmall cell lung cancer; CD38: cluster of differentiation 38; PDGFR-α:platelet-derived growth factor receptor alpha; PD-L1: programmed death-ligand 1; ALL: acute lymphoblastic leukemia; IL-3: Interleukin-3; CD22: cluster of differentiation-22; CCR4: CC chemokine receptor type 4; ADC: antibody drug conjugate; HER2: human epidermal growth factor receptor 2; CD79b: cluster of differentiation-79b; CD38: cluster of differentiation-38; A, accelerated; B, breakthrough; O, orphan; P, priority; S, standard; IV: intravenous.

■ DRUGS FOR NEUROLOGICAL DISORDERS

Neurological disorders can be classified into three groups: neurotraumatic diseases (strokes and epilepsy), neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), and neuropsychiatric diseases (depression, schizophrenia).[40] Neurological disorders are reported to contribute 11.6% of global disability adjusted life years (DALYs) and 16.5% (2nd leading cause) of deaths from all causes.[41]

Until 2015, there were 79 FDA approved new molecular entities for the treatment of neurological disorders.[42] Over the past five years, FDA has approved a total of 23 small molecules, one each of cyclodextrin derivative and toxin; two oligonucleotides and four monoclonal antibodies (Table 3) for the treatment of neurological disorders. Chemical structures of small molecules approved for the treatment of various neurological disorders are collated in Figure 4.

It is evident that serotonin (5-HT_{1F}) and calcitonin gene-related peptide (CGRP) targets were explored for the management of migraine in the last five years. Lasmiditan, (**64**), a 5-HT_{1F} receptor agonist, exerts effects by inhibition of trigeminal nerve firing and hyperpolarization of nerve terminals.[43] Calcitonin gene-related peptide (CGRP) release produces local vasodilation and extravasation of plasma and plasma proteins into the surrounding tissue.[44] A total of six CGRP antagonists containing two small molecules, ubrogepant (**67**) and rimegepant sulfate (**72**), and four monoclonal antibodies, namely, erenumab, fremanezumab, galcanezumab, and eptinezumab, were approved. Further, to circumvent the extrapyramidal motor side effects (EPS) due to full inhibition of dopamine D2 receptors by first-generation antipsychotics, four small molecules with serotonin 5-HT2A receptor antagonism in combination with D2 receptor partial agonism were approved by the FDA for the treatment of schizophrenia. In the antiepileptic category, targets such as gamma-aminobutyric acid (GABA) receptors and synaptic vesicle glycoprotein 2 (SV2) were explored by pharmaceutical companies in the last five years. Cannabidiol (**61**), an oral solution, was approved in 2018 for the treatment of Dravet syndrome and Lennox-Gastaut syndrome. According to the FDA, **61** does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors.[45] GABA which acts through $GABA_A$ and $GABA_B$

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Table 3. Illustrative Compilation of U.S. FDA Approved Neurological Agents, Featuring Their Indication, Year of Approval, Sponsor, Target, Chemical Class, Major Drug Metabolizing Enzyme(s), Route of Administration/Elimination, and Drug Interactions (Perpetrator or/and Victim)

Brand name (Active ingredient/Route of administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Aristada (Aripiprazole lauroxil/IM)	Small Molecule	Schizophrenia	2015/Alkermes /S	Partial agonist against D2 & 5 HT1A receptors. Antagonist at 5-HT2A receptor	Phenylpiperazines	Enzyme-mediated hydrolysis CYP3A4 & CYP2D6	Victim with CYP3A4 & CYP2D6 inhibitors	Less than 1% in the urine & 18% in the feces
Vraylar (Cariprazine/PO)	Small Molecule	Schizophrenia	2015/Forest/S	D2 and D3 receptor partial agonist, with high selectivity towards the D3 receptor	Phenylpiperazines	CYP3A4	Victim with CYP3A4 inducers & inhibitors	21% in urine
Rexulti (Brexpiprazole/PO)	Small Molecule	Schizophrenia	2015/Otsuka/S	Serotonin-dopamine activity modulator (SDAM), and a potent antagonist of serotonin 2A receptors, noradrenergic alpha 1B and 2C receptors	N-arylpiperazines	CYP3A4 & CYP2D6	Victim with CYP3A4 inducers & inhibitors and CYP2D6 inhibitors	25% in urine &46% in feces
Bridion (Sugammadex/IV)	Modified gamma cyclodextrin	Reverse effects of neuromuscular blocking drugs	2015/Merck/P	Aminosteroid neuromuscular blocking agents such as rocuronium & vecuronium	Oligosaccharides	---[b]	Contradicted to use with Toremifene & hormonal contraceptives	>90% in urine
Addyi (Flibanserin/PO)	Small Molecule	Hypoactive sexual desire disorder	2015/Sprout/S	agonist activity on 5-HTA1 and antagonist on 5-HTA2 Unknown	Phenylpiperazines	CYP3A4	Victim with CYP3A4 inducers & inhibitors; Victim with CYP2C19 inhibitors; Perpetrator when administered with Digoxin	44% in urine, & 51% in feces
Nuplazid (Pimavanserin/PO)	Small Molecule	Hallucinations & delusions associated with psychosis	2016/Acadia Pharmaceuticals /P, B	Inverse agonist on serotonin receptor subtype 5-HT2A	Phenol ethers	CYP3A4 & CYP3A5	Victim with CYP3A4 inducers & inhibitors	0.55% in urine & 1.53% in feces
Briviact (Brivaracetam/PO&IV)	Small Molecule	Epilepsy	2016/UCB/S	Affinity for synaptic vesicle protein 2A (SV2A) in the brain	Alpha amino acids derivatives	CYP2C19	Victim when co- administered with Rifampin; Perpetrator when co-administered with Carbamazepine & Phenytoin	95% in urine & < 1% in feces
Nusinersen (Spinraza/IT)	Oligonucleotide	Spinal muscular atrophy	2016/Biogen/Ionis Pharmaceuticals/P, O	Increase exon 7 inclusion in SMN2 messenger ribonucleic acid	Anti-sense oligonucleotides	Nucleases	---[a]	-
Deutetrabenazine (Austedo/PO)	Small Molecule	Chorea associated with Huntington disease	2017/Teva/S, O	VMAT2 inhibitor	Tetrahydroisoquinolines	Carbonyl reductase	Victim with CYP2D6 inhibitors	75% to 86% in urine, & 8% to 11% in feces
Ingrezza (Valbenazine/ PO)	Small Molecule	Tardive dyskinesia	2017/Neurocrine Biosciences /P, B	VMAT2 inhibitor	Alpha amino acid esters	CYP3A4/5	Victim with CYP3A4 inducers & inhibitors; Victim with CYP2D6 inhibitors; Perpetrator when co-administered with Monoamine Oxidase Inhibitors	60% in urine, & 30% in feces
Xadago (Safinamide/PO)	Small Molecule	Parkinson's Disease	2017/US WorldMeds/S	Inhibition of MAO-B with blockade of voltage-dependent Na+ and Ca2+ channels and inhibition of glutamate release	Alpha amino acid amides	Cytosolic amidases/MAO-A	Concomitant use with SNRIs, sympathomimetics & foods containing a large amount of tyramine is not recommended; Victim when co-administered with Dopamine antagonists	76% in urine
Radicava (Edaravone/IV)	Small Molecule	Amyotrophic lateral sclerosis	2017/Mitsubishi Tanabe /S, O	Decrease lipoxygenase metabolism of arachidonic acid by trapping hydroxyl radicals, and inhibit alloxan-induced lipid peroxidation and quench active oxygen species Unknown	Pyrazolones	UGT1A6, UGT1A9, UGT2B7 & UGT2B17	---[a]	Urine: Glucuronide conjugate 70-90% Sulfate conjugate 5-10%
Diacomit (Stiripentol/PO)	Small Molecule	Dravet syndrome	2018/Biocodex /P, O	Positive allosteric modulator of GABA-A receptors	Benzodioxoles	CYP1A2, CYP2C19, & CYP3A4	Perpetrator due to inhibition & induction of CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C19, P-gp & BCRP; Perpetrator when co-administered with clobazam; Victim when co-administered with CYP1A2, CYP3A4 or CYP2C19 inducers	Not available
Epidioloex (Cannabidiol/PO)	Small Molecule	Epilepsy	2018/GW Pharmaceuticals /P, O	Negative allosteric modulator of the cannabinoid CB1 receptor Unknown	Aromatic monoterpenoids	CYP2C19 & CYP3A4	Victim with CYP3A4 & CYP2C19 inducers & inhibitors; Perpetrator for UGT1A9, UGT2B7, CYP1A2, CYP2B6, CYP2C8, CYP2C9 & CYP2C19 substrates	Feces
Tegsedi (Inotersen/ SC)	Oligonucleotide	Polyneuropathy	2018/Ionis Pharmaceuticals /P, O	Degradation of TTR mRNA	Anti-sense oligonucleotides	Nucleases	---[a]	-
Emgality (Galcanezumab-gnlm/ SC)	Monoclonal Antibody	Migraine	2018/Eli Lilly /S	CGRP receptor antagonist	Humanized IgG4	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Ajovy (Fremanezumab-vfrm/ SC)	Monoclonal Antibody	Migraine	2018/Teva/P	CGRP receptor antagonist	Humanized IgG2Δa/kappa monoclonal antibody	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Erenumab (Aimovig/ SC)	Monoclonal Antibody	Migraine	2018/Amgen/Novartis/S	CGRP receptor antagonist	Humanized IgG2Δa/kappa monoclonal antibody	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG

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Table 3. continued

Brand name (Active ingredient/Route of administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Dayvigo (Lemborexant/PO)	Small Molecule	Insomnia	2019/Eisai/S	OX1 & OX2 receptors	Organonitrogen compounds	CYP3A4	Victim with CYP3A inducers & inhibitors	57.4% in the feces & 29.1% in the urine
Caplyta (Lumateperone tosylate/PO)	Small Molecule	Schizophrenia	2019/Intra-Cellular Therapies /S	5HT2A receptor antagonist	Organooxygen compounds	UDP-glucuronosyltransferase	Victim with CYP3A4 inducers & inhibitors	58% in the urine & 29% in the feces
Xcopri (Cenobamate/PO)	Small Molecule	Partial onset seizures	2019/SK Life Science/S	Positive allosteric modulator of the γ-aminobutyric acid (GABA-A) ion channel	Carbamate	UGT2B7	Perpetrator with CYP2B6, CYP3A & CYP2C19 substrates	87.8 in urine, & 5.2% in feces
Reyvow (Lasmiditan/PO)	Small Molecule	Migraine	2019/Eli Lilly/S	Serotonin (5-HT) 1F receptor agonist	Benzene and substituted derivatives	MAO-A, MAO-B, flavin monooxygenase 3	Perpetrator by inhibition of P-gp & BCRP	Parent (3%) in urine; metabolite (66%) in urine
Nourianz (Istradefylline/PO)	Small Molecule	Parkinson's disease	2019/Kyowa Kirin/S	Adenosine A2A receptor inhibitor	Imidazopyrimidines	CYP1A1 & CYP3A4	Victim with CYP3A4 inducers & inhibitors; Perpetrator with CYP3A4 & P-gp substrates	48% in the feces & 39% in the urine
Wakix (Pitolisant/PO)	Small Molecule	Narcolepsy.	2019/Harmony /P, O	Antagonist or inverse agonist of the histamine H3 receptor	Benzene and substituted derivatives	CYP2D6 & CYP3A4	Victim with CYP3A4 inducers & CYP2D6 inhibitors; Perpetrator with CYP3A4 substrates	2.3% in the feces & 90% in the urine
Sunosi (Solriamfetol/PO)	Small Molecule	Excessive sleepiness in adult patients	2019/Jazz/S, O	DNRI inhibitor	Phenylpropyl carbamate	Minimally metabolised	Do not administer with monoamine oxidase inhibitors	95% parent in the urine 1% minor metabolite in urine
Zulresso (Brexanolone/ IV)	Small Molecule	Postpartum depression in adult women	2019/Sage Therapeutics/P, B	Neuroactive steroid GABA	Steroids and steroids derivatives	Non-CYP based	---[a]	47% in feces & 42% in urine
Jeuveau (PrabotulinumtoxinA-xvfs/ IM&IV)	Toxin	Moderate to severe glabellar lines associated with corrugator &/or procerus muscle activity in adult patients	2019/Evolus/S	Acetylcholine release inhibitor	Carboxylic acids derivatives	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Ubrelvy (Ubrogepant/PO)	Small Molecule	Migraine with or without aura in adults	2019/Allergan /S	CGRP receptor antagonist	2,2,2-Trifluoroethyl-piperidin-3-yl derivative	CYP3A4	Victim with CYP3A4 inducers & inhibitors	42% in the feces & 6% in the urine
Ongentys (Opicapone/PO)	Small Molecule	Parkinson's disease	2020/Neurocrine/S	Catechol-o-methyltransferase (COMT) inhibitor	Azoles	Sulphation	---[a]	70% in feces. 20% in expired air, & 5% in urine
Nurtec ODT (Rimegepant/PO)	Small Molecule	Migraine	2020/Biohaven Pharm/P	CGRP receptor antagonist	Imidazopyridines	CYP3A4	Victim with CYP3A4 inhibitors & CYP3A inducers & inhibitors of P-gp & BCRP efflux transporters	78% in feces & 24% in urine
Vyepti (Eptinezumab-jjmr/ IV)	Monoclonal Antibody	Migraine	2020/Lundbeck /S	CGRP receptor antagonist	Humanized immunoglobulin G1	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG

[a]No interaction reported. [b]No information available. [f]D2: dopamine receptor isoform 2; 5-HT: 5-hydroxytryptamine; SV2A: synaptic vesicle protein 2A; VMAT2: vesicular monoamine transporter 2; MAO: monoamine oxidase; GABA: gamma-aminobutyric acid; CGRP: calcitonin gene-related peptide; OX: orexin; DNRI: dopamine and norepinephrine reuptake inhibitor; COMT: catechol-*o*-methyltransferase; A, accelerated; B, breakthrough; O, orphan; P, priority; S, standard; PO: peroral; IV: intravenous; SC: subcutaneous; IT: intrathecal; IM: intramuscular; CYP: cytochrome P450; UGT: UDP-glucuronosyltransferase; P-gp: P-glycoprotein; BCRP: breast cancer resistance protein.

receptors is the principal inhibitory neurotransmitter in the brain.[46] Stiripentol (**60**) and cenobamate (**63**), positive allosteric modulators of $GABA_A$ receptors, were approved in 2018 and 2019, respectively, for the treatment of epilepsy. Brivaracetam (**55**), which binds SV2A with high affinity and thus induces indirect modulation of synaptic GABA release, was approved in 2016 for the treatment of partial-onset seizures. For the treatment of patients of Parkinson's disease experiencing "off" episodes, safinamide (**57**), a reversible inhibitor of MAO-B, and opicapone (**71**), a third-generation inhibitor of COMT, were approved as an add-on treatment to levodopa[47] and as an adjunctive therapy, respectively. Istradefylline (**62**), an A_{2A} receptor inhibitor, was approved in 2019 for the treatment of Parkinson's disease as an adjunct to levodopa therapy. Edaravone (**58**), a free radical scavenger which increases prostacyclin production and decreases lipoxygenase metabolism of arachidonic acid, was approved for the treatment of amyotrophic lateral sclerosis (ALS). Vesicular monoamine transporter 2 (VMAT2), which is responsible for monoamine (dopamine, norepinephrine, and serotonin) transport across synaptic vesicles, is implicated in tardive dyskinesias (TD) pathology.[48] Valbenazine (**56**), an inhibitor of VMAT2, was approved for the treatment of TD. Another VMAT2 inhibitor, deutetrabenazine (**59**), that depletes the levels of presynaptic dopamine was approved for the treatment of Huntington's disease (HD).[49] Flibanserin (**53**), an agonist of 5-HTA1 and an antagonist of 5-HTA2, and bremelanotide (2019), a melanocortin receptor agonist, were approved for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. Histaminergic neurons play a significant role in the maintenance of wakefulness.[50] Pitolisant (**66**), a histamine H3 receptor antagonist or inverse agonist, was approved for the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy in adults. Lemborexant (**69**) is a competitive antagonist of OX1 and OX2 receptors[51] and blocks the binding of neuropeptides orexin-A and -B. The drug suppresses the wake-drive, thereby promoting sleep, and is recommended for the treatment of insomnia. Nusinersen, an antisense oligonucleotide approved in 2016, increases the splicing efficiency of the

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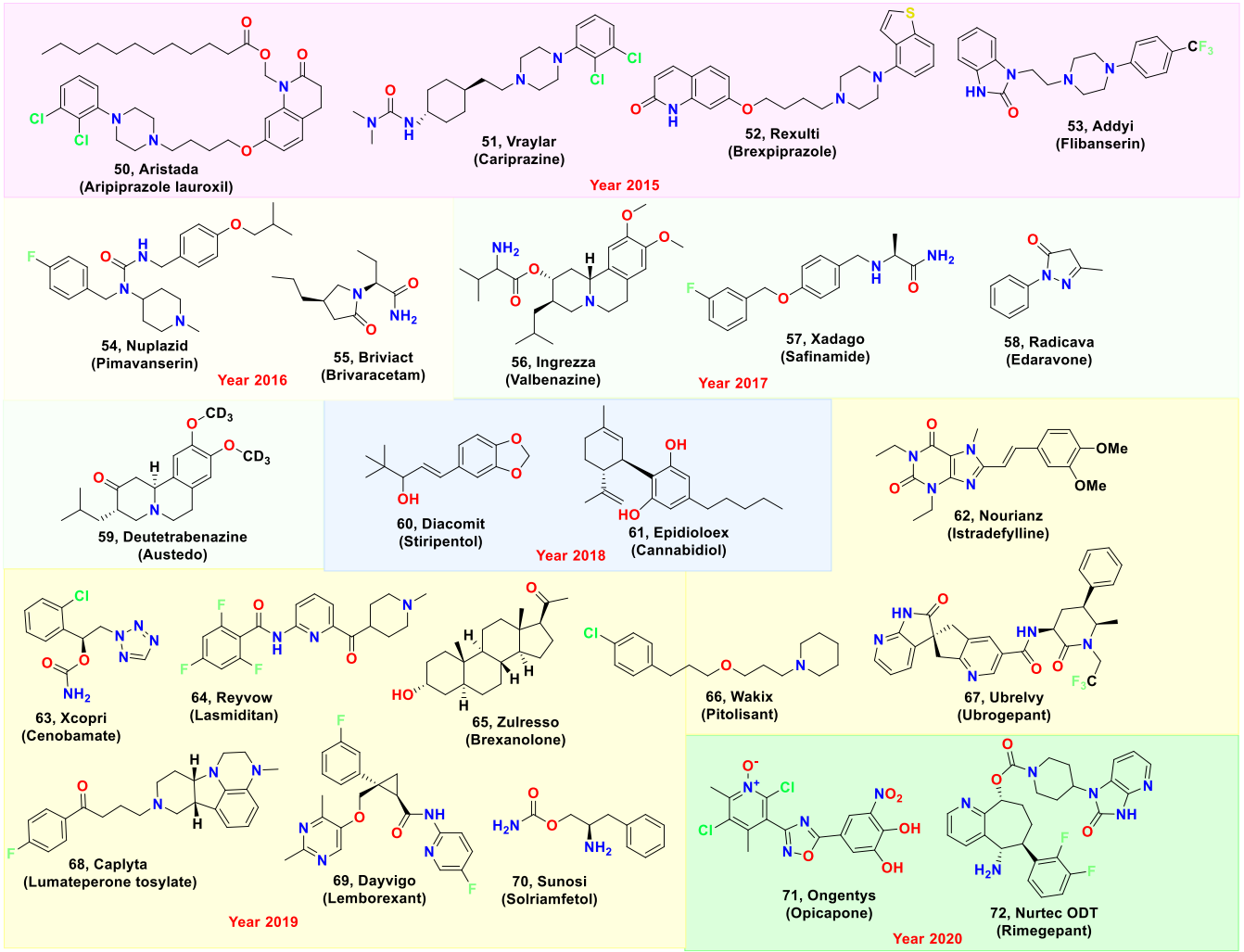

Figure 4. Chemical structures of small molecules approved for the treatment of various neurological disorders by FDA from the year 2015 until June 2020.

SMN2 pre-mRNA and corrects the SMN protein deficiency involved in spinal muscular atrophy (SMA).

A total of 21 out of 23 small molecule drugs approved for various neurological disorders are intended for administration through the peroral route and 2 through the intravenous route. Three out of 4 monoclonal antibodies are approved for the subcutaneous route, and eptinezumab (a mAb, approved for migraine) was approved for administration through the intravenous route. Approved oligonucleotides are for intrathecal and subcutaneous administration.

CYPs played significant roles in the metabolism of 14 out of 23 small molecules, wherein the major enzyme involved is CYP3A4 (for 13 out of 14 approved drugs). Nucleases are involved in the metabolism of oligonucleotides, and catabolism continues to remain the primary way for elimination of the macromolecules. Seventeen small molecules were implicated as victims during coadministration with drugs causing modulations in enzymes (CYP3A4, CYP2C19, CYP2D6, and CYP1A2) and transporters (P-gp and BCRP), details in Table 3. A majority of the approved small molecules followed the Lipinski's rule of 5. By the end of 2020, ~14% of the global population is anticipated to suffer from neurological disorders. Geographically, it is estimated that the largest market for neuro-therapeutics will be led by North America, followed by Europe and Asia-Pacific countries. The key players contributing to the market share will include Abbott, Becton and Dickinson, Novartis, Johnson & Johnson, Pfizer, Sanofi-Aventis, Biogen, GlaxoSmithKline, AstraZeneca, and Merck.[52]

DRUGS FOR THE TREATMENT OF METABOLIC/GENETIC DISORDERS

Under this category, authors have observed that a total of 35 novel therapeutic agents were approved by the U.S. FDA in the specified period, with one-third of them being small molecules (12). Antibody molecules and oligonucleotides (4 each), peptides and enzymes (5 each), polymers, hormones (2 each), and one fusion protein constituted the remaining approvals. Considering the total 76 new molecular entities approved by the FDA for the treatment of metabolic disorders until 2015, the last 5 years seem to ensure that more number of drugs are available to the patients of metabolic disorders.[53] The details of all the drugs approved for metabolic disorders during the period 2015–June 2020 are compiled in Table 4, and chemical structures of small molecules are illustrated in Figure 5. A brief overview of the compilation is presented here. In the category of antihyperuricemic/antigout drugs, lesinurad (**73**), an URAT1[54] inhibitor which causes an increase in the excretion of uric acid, was approved. Patiromer, approved in 2015 for

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Table 4. Illustrative Compilation of U.S. FDA Approved Drugs from the Year 2015 until June 2020 for Metabolic Disorders Featuring Their Indication, Year of Approval, Sponsor, Target, Chemical Class, Major Drug Metabolizing Enzyme(s), Route of Administration/Elimination, and Drug Interactions (Perpetrator or/and Victim)

Brand name (Active ingredient/Route of Administration)	Type of Molecule	Indication	Year of approval/Sponsor /Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Zurampic (Lesinurad/PO)	Small molecule	Gout	2015/AstraZeneca /S	URAT1 and OAT4	Azoles	CYP2C9	Victim with CYP2C9 inhibitors; Perpetrator with CYP3A substrates	63% in the urine & 32% in the feces
Veltassa (Patiromer for oral suspension/PO)	Polymer	Hyperkalemia	2015/Relypsa/S	Patiromer works by binding free potassium ions	Polymer	---[b]	---[a]	-
Xuriden (Uridine triacetate/PO)	Small molecule	Hereditary orotic aciduria	2015/Wellstat/P, O, B	Pyrimidine analog	Pyrimidine nucleosides	---[b]	---[a]	-
Kybella (Deoxycholic acid/ SC)	Small molecule	Fat below the chin, known as submental fat	2015/Kythera/S	Cytolytic drug	Steroids & steroid derivatives	---[b]	---[a]	-
Cholbam (Cholic acid/PO)	Small molecule	Bile acid synthesis disorders	2015/Retrophin/P, O	Bile acid synthesis disorders	Steroids & steroid derivatives	---[b]	Contradicted to co-administer with BSEP inhibitors	-
Natpara (Parathyroid hormone/ SC)	Hormone	Hypocalcemia	2015/NPS Pharma/S, O	Increase renal tubular calcium reabsorption	Carboxylic acids derivatives	Hydrolytic Enzymes	No interactions reported	-
Orkambi (Lumacaftor; ivacaftor/PO)	Small Molecule	Cystic fibrosis	2015/Vertex/P, O, B	CFTR modulator	Lumacaftor: Phenylpyridines	CYP3A	Lumacaftor- no DDI; Ivacaftor- Victim with CYP3A inhibitors & inducers	Lumacaftor- 51% in feces Ivacaftor-87.8 % in feces
Kanuma (Sebelipase alfa/IV)	Enzyme	Lysosomal Acid Lipase deficiency	2015/Alexion/P, O, B	Hydrolytic lysosomal cholesteryl ester & triacylglycerol-specific enzyme	Carboxylic acids derivatives	Hydrolytic Enzymes	---[a]	-
Tresiba (Insulin degludec injection/ SC)	Hormone	Hyperglycemia	2015/Novo Nordisk/S	Binds to Insulin receptor	Carboxylic acids derivatives	Hydrolytic Enzymes	---[a]	-
Strensiq (Asfotase alfa/SC)	Enzyme	Hypophosphatasia	2015/Alexion/S	Alkaline phosphatase	Carboxylic acids derivatives	Hydrolytic Enzymes	---[a]	-
Adlyxin (Lixisenatide/ SC)	Peptide	Type 2 diabetes mellitus	2016/Sanofi /S	GLP-1 agonist	Amino acids	Hydrolytic Enzymes	---[a]	-
Exondys 51 (Eteplirsen/IV)	Oligonucleotide	DMD	2016/Sarepta Therapeutics /P, O, A	DMD gene which is responsive to exon 51 skipping	Antisense oligonucleotide	Hydrolytic Enzymes	---[a]	-
Ozempic (Semaglutide/ SC& PO)	Peptide	Type 2 diabetes mellitus	2017/Novo Nordisk/S	GLP-1 agonist	Polypeptides	Hydrolytic Enzymes	---[a]	-
Parsabiv (Etelcalcetide/IV)	Peptide	Secondary hyperparathyroidism	2017/Amgen/Kai Pharmaceuticals /S	Calcimimetic drug	Oligopeptides	Hydrolytic Enzymes	---[a]	-
Steglatro (Ertugliflozin/PO)	Small molecule	Glycemic control patients with type 2 diabetes mellitus	2017/Merck & Co./Pfizer/S	SGLT inhibitor	Diphenylmethanes	UGT1A9 & UGT2B7	---[a]	40.9% in feces & 50.2% in urine
Emflaza (Deflazacort/PO)	Small Molecule	DMD	2017/PTC Therapeutics /P, O	Glucocorticoid receptor	Corticosteroid	CYP3A4	Victim with CYP3A4 inhibitors and inducers	Deflazacort: 68% in urine 21-desDFZ-18 % in urine
Brineura (Cerliponase alfa/ Intraventricular)	Enzyme	Batten disease	2017/BioMarin Pharmaceutical /P, O, B	Hydrolytic lysosomal N-terminal tripeptidyl peptidase	Recombinant Enzyme	Hydrolytic Enzymes	---[a]	-
Tymlos (Abaloparatide/ SC)	Peptide	Postmenopausal women with osteoporosis	2017/Radius Health Inc /S	Agonist at the PTH1 receptor (PTH1R	Peptide	Hydrolytic Enzymes	---[a]	-
Mepsevii (Vestronidase alfa-vjbk/ IV)	Enzyme	Sly syndrome	2017/BioMarin Pharmaceutical /P, O, B	Recombinant human lysosomal beta glucuronidase	Carboxylic acids and derivatives	Hydrolytic Enzymes	---[a]	-
Takhzyro (Lanadelumab/ SC)	Monoclonal Antibody	Types I & II Hereditary angioedema disorders	2018/Dyax/Shire /P, O, B	Plasma kallikrein inhibitor	Humanized IgG1/κ	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Galafold (Migalastat/ PO)	Small molecule	Fabry disease	2018/Amicus Therapeutics /P, O, A	Alpha-galactosidase A	Piperidine	Hydrolytic Enzymes	---[a]	-
Crysvita (Burosumab-twza/ SC)	Monoclonal Antibody	X-linked hypophosphatemia (XLH)	2018/Ultragenyx Pharmaceutical/Kyowa Hakko Kirin/P, O, B	Fibroblast growth factor 23	Humanized IgG1	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Onpattro (Patisiran/IV)	Oligonucleotide	Polyneuropathy of hereditary transthyretin-mediated amyloidosis	2018/Alnylam Pharmaceuticals /P, O, B	Transthyretin-directed small interfering RNA	Small interfering RNA	Hydrolytic Enzymes	---[a]	-
Symdeko (Tezacaftor; ivacaftor/PO)	Small Molecule	Cystic fibrosis	2018/Vertex Pharmaceuticals/P, O, B	CFTR modulator	Tezacaftor: Indole and derivatives; Ivacaftor: Benzene substituted derivatives	CYP3A4 & CYP3A5	Tezacaftor & ivacaftor: victim with CYP3A inhibitors and inducers	Tezacaftor- 72% in feces & 14% in urine Ivacaftor- 87.8 % in feces & 6.6% in urine
Palynziq (Pegvaliase-pqpz/ SC)	Enzyme	Phenylketonuria/BioMarin Pharmaceutical /O	2018/Biomarin Pharm/P, O	Phenylalanine-metabolizing enzyme	Carboxylic acids and derivatives	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Lokelma (Sodium zirconium cyclosilicate/PO)	Polymer	Hyperkalemia	2018/AstraZeneca/ S	Potassium binder	Polymer	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Vyondys 53 (Golodirsen/IV)	Oligonucleotide	DMD	2019/Sarepta/P, O, A	Mutation of the DMD gene that is responsive to exon 53 skipping	Oligonucleotide	Hydrolytic Enzymes	---[a]	-
Oxbryta (Voxelotor/ PO)	Small Molecule	Sickle cell disease	2019/Global Blood Therapeutics/P, O, A, B	Hemoglobin S polymerization inhibitor	Organoxygen compounds	CYP3A4	Victim with CYP3A inhibitors and inducers; Perpetrator with CYP3A4 substrates	33.3% in feces & 35.5% in urine
Adakveo (Crizanlizumab-tmca/ IV)	Monoclonal Antibody	Sickle cell disease	2019/Novartis/P, O, B	P-selectin blocker	Humanized IgG2	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG

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Table 4. continued

Br& name (Active ingredient/Route of Administration)	Type of Molecule	Indication	Year of approval/Sponsor /Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Reblozyl (Luspatercept–aamt/ SC)	Fusion protein	Thalassemia	2019/Celgene/BM S/P, O	Erythroid maturation agent	Activin receptor type IIB fused with the FC domain of human IgG1	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Evenity (Romosozumab-aqqg/ SC)	Monoclonal Antibody	Osteoporosis	2019/Amgen/S	Sclerostin inhibitor	Humanized IgG2	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Scenesse (Afamelanotide/ SC)	Peptide	Erythropoietic protoporphyria	2019/Clinuvel/P, O	Mimics endogenous alpha melanocyte-stimulating hormone	Polypeptides	Hydrolytic Enzymes	---[a]	-
Givlaari (Givosiran/ SC)	Oligonucleotide	Acute hepatic porphyria	2019/Alnylam/P, O, B	5-aminolevulinic acid synthase	Small interfering RNA	Nucleases	---[a]	-
Trikafta (Elexacaftor/Ivacaftor/Tezacaftor/PO)	Small Molecule	Cystic fibrosis	2019/Vertex/P, O, B	CFTR modulator	Elexacaftor: Pyridine-3-carboxamide; Tezacaftor: Indole derivatives; Ivacaftor: Benzene substituted derivatives	CYP3A4/5	Victim with CYP3A inhibitors and inducers; Perpetrator with CYP2C9 & P-gp substrates	Elexacaftor- Feces: 87.3% Tezacaftor - Feces: 72% Urine: 14% Ivacaftor- Feces: 87.8% & Urine: 6.6%
Isturisa (Osilodrostat/PO)	Small molecule	Cushing's disease	2020/Recordati Rare/S, O	11β-hydroxylase inhibitor (CYP11B1)	Benzene substituted derivatives	CYP3A4, CYP2B6, & CYP2D6	Victim with CYP3A4 inhibitors and inducers and CYP2B6 inducers	Feces: 1.58% & Urine: 90.6%

[a]No interaction reported. [b]No information available. [g]URAT1: uric acid transporter 1; CFTR: cystic fibrosis transmembrane conductance regulator; GLP-1: glucagon-like peptide-1; SGLT: sodium-dependent glucose cotransporters; DMD: duchenne muscular dystrophy; XLH: X-linked hypophosphatemia; FXR: farnesoid X receptor; A, accelerated; B, breakthrough; O, orphan; P, priority; S, standard; PO: peroral: IV: intravenous: SC: subcutaneous; IM: intramuscular; CYP: cytochrome P450; UGT: UDP-glucuronosyltransferase; P-gp: P-glycoprotein; BCRP: breast cancer resistance protein.

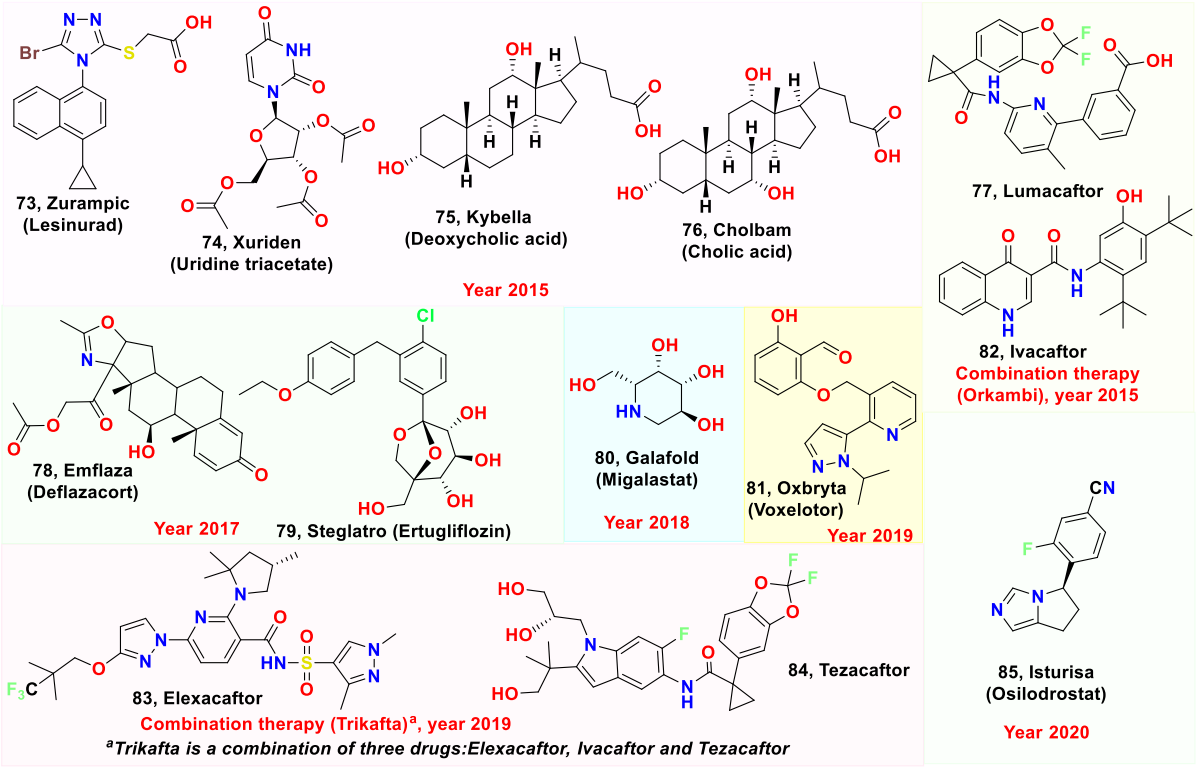

Figure 5. Chemical structures of small molecule drugs used for the treatment of various metabolic disorders approved by FDA from the year 2015 until June 2020.

hyperkalemia, is a nonabsorbed potassium-binding polymer that binds to potassium in the gastrointestinal system, resulting in excretion of potassium in feces to reduce the serum potassium levels. Natpara (2015), a parathyroid hormone involved in regulating serum calcium levels, was approved for the treatment of hypocalcemia in adults with reduced PTH (parathyroid hormone) levels.[55] Incretins (glucagon-like peptide-1; GLP-1) are the hormones produced by the intestinal mucosa which regulate the insulin secretion in response to food consumption.[56] Lixisenatide (2016), a GLP-1 receptor agonist, and semaglutide (2017), a GLP-1 analogue, were approved for the management of type 2 diabetes mellitus. Another antidiabetic drug ertugliflozin (**79**) targeting SGLT2[57] was approved in 2017. Whereas for the treatment of type 1 diabetes, insulin degludec (2018), an ultralong-acting insulin analogue, was approved. Etelcalcetide (2017), a type 2 calcimimetic, is a

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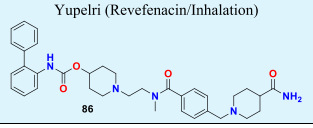
Table 5. Illustrative Compilation of U.S. FDA Approved Drugs from the Year 2015 until June 2020 for Respiratory Disease Featuring Their Indication, Year of Approval, Sponsor, Target, Chemical Class, Major Drug Metabolizing Enzyme(s), Route of Administration/Elimination, and Drug Interactions (Perpetrator or/and Victim)[¶]

Brand name (Active ingredient/Route of administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Nucala (Mepolizumab/SC)	Monoclonal Antibody	Asthma	2015/GlaxoSmithKline/S	IL-5 antagonist	Humanized IgG1	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Cinqair (Reslizumab/IV)	Monoclonal Antibody	Asthma	2016/Teva/S	IL-5 antagonist	Humanized IgG1	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Fasenra (Benralizumab/SC)	Monoclonal Antibody	Asthma	2017/AstraZeneca/S	IL-5 antagonist	Humanized IgG1 (kappa)	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Yupelri (Revefenacin/Inhalation)  86	Small Molecule	Chronic obstructive pulmonary disease	2018/Theravance Biopharma/Mylan/S	Beta-1,2, and 3 adrenergic receptor agonist (Anticholinergic)	Benzene and substituted derivatives	Amidase	Victim in the presence of OATP1B1 and OATP1B3 inhibitors	Feces (54%); urine (27%)

[a]No interaction reported. [¶]IL-5: Interleukin-5; S, standard; IV: intravenous; SC: subcutaneous; OATP: organic-anion-transporting polypeptide.

positive allosteric modulator which increases the sensitivity of the calcium-sensing receptor (CaSR) to ionized calcium and reduces PTH secretion by the negative feedback mechanism. Pegvaliase, a recombinant phenylalanine ammonia lyase (PAL) enzyme which reduces blood phenylalanine concentrations by converting phenylalanine to ammonia and *trans*-cinnamic acid, was approved in 2018. Cushing syndrome is caused by chronic elevation of circulating glucocorticoids primarily by overproduction of cortisol by the adrenals as a result of a pituitary or adrenal tumor.[58] The preferred therapeutic strategy is to reverse hypercortisolemia. Osilodrostat (**85**), approved in 2020, is an inhibitor of 11β-hydroxylase, an enzyme involved in the biosynthesis of endogenous cortisol and results in reduced cortisol concentrations. Elevated extracellular levels of inorganic pyrophosphate (PPi) results in defective mineralization and leads to bone deformation in infants. Asfotase alfa (2015) treatment replaces the level of TN-SALP (tissue nonspecific alkaline phosphatase) enzyme and reduces the PPi levels. Eteplirsen (2016), is a targeted oligonucleotide that causes exon skipping of exon 51. Deflazacort (**78**), a corticosteroid was approved for the treatment of Duchenne muscular dystrophy. Cerliponase alfa (2017) contains tripeptidyl peptidase-1 (rhTPP1), a recombinant human lysosomal exopeptidase which cleaves the N-terminal of tripeptides. The drug was approved for the treatment of ceroid lipofuscinosis type 2 (CLN2). Vestronidase alfa (2017), a recombinant human lysosomal beta-glucuronidase (GUS) acts by serving as an exogenous source of GUS enzyme through intravenous infusion.[59] Migalastat (**80**), approved for the treatment of Fabry disease, stabilizes the dysfunctional alpha-Gal A enzyme and results in the clearance of accumulated crystalline glycosphingolipids (GSLs).[60] Increased levels of fibroblast growth factor 23 (FGF23) were observed in patients with X-linked hypophosphatemia (XLH).[61] Burosumab (2018) is a monoclonal antibody that inhibits the actions of FGF23, which in turn increases the tubular reabsorption of phosphate from the kidney. Voxelotor (**81**), an HbS polymerization inhibitor prevents the formation of abnormally shaped cells and was approved for sickle cell disease. In the same category, crizanlizumab (2019), an antibody targeting P-selectin was approved for the treatment of vaso-occlusive crisis in patients with sickle cell diseases. Luspatercept (2019), a fusion protein, ameliorates ineffective erythropoiesis in patients with beta thalassemia by acting as a "ligand trap" for various members of the TGF-β superfamily. Afamelanotide (2019), a synthetic analogue of the endogenous α-MSH, was approved to prevent skin damage in people with erythropoietic protoporphyria from UV-induced damage. Cystic fibrosis (CF) is a genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which results in the production of abnormally thick mucus that builds up in the lungs, digestive tract, and other parts of the body.[62] There are more than 1700 different mutations in the CFTR gene that can cause CF, the most common one is the F508del (F: Phenylalanine) mutation. CFTR modulators are classified into potentiators (ivacaftor, **82**), correctors (lumacaftor, **77** and tezacaftor, **84**), and amplifiers (in clinical development; PTI - 428 and PTI - CH). Combination therapy is anticipated to offer better results than individual drug(s). Orkambi, symdeko, and trikafta are the three CFTR modulators approved during this period wherein orkambi and symdeko were approved for individuals with two copies of the F508del mutation (smaller CF population).[63] Trikafta (elexacaftor, tezacaftor and ivacaftor) is a triple combination therapy, which was approved for the treatment of CF patients with one or more F508del mutation in the CFTR gene (90% of the CF population). Going forward, the global CF market is expected to register a CAGR of 13.5% and is anticipated to reach USD ~ 13 000 M by 2025.[64] Drug discovery efforts for CF are spearheaded by Vertex, AbbVie, Gilead, Actavis (Allergan), Genentech (Roche), and Novartis.

Except for **77** and **83**, all the approved small molecules under this category followed the Lipinski's rule. As indicated in Table 4, some of the approved small molecules were implicated as victims during coadministration with drugs causing modulations in enzymes (CYP2C9, CYP2B6, and CYP3A4) and transporters (BSEP).[65] Eleven out of 12 small molecule drugs approved for various metabolic disorders are approved for administration through the peroral route and one through the subcutaneous route. Three out of 4 monoclonal antibodies are approved for use through the subcutaneous route, and crizanlizumab (monoclonal antibody, approved for sickle cell anemia to Novartis) was approved for the intravenous route. Oligonucleotides were approved through intravenous (3) and subcutaneous (1) administration. Two polymers are approved through peroral administration during this period for the treatment of hyperkalemia. Only 7 small molecules are metabolized through CYPs, wherein again the major enzyme involved is CYP3A4 (6 out of 7), and all these molecules behave as victims when codosed with CYP3A inducer/inhibitor. Dose adjustment is required for the drugs that are eliminated through the renal pathway (e.g., **78**).

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Table 6. Illustrative Compilation of U.S. FDA Approved Drugs from the Year 2015 until June 2020 for Infectious and Parasitic Diseases Featuring Their Indication, Year of Approval, Sponsor, Target, Chemical Class, Major Drug Metabolizing Enzyme(s), Route of Administration/Elimination, and Drug Interactions (Perpetrator or/and Victim)

Brand name (Active ingredient/Route of Administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Cresemba (Isavuconazonium sulfate/IV, PO)	Small Molecule	Invasive aspergillosis and mucormycosis	2015/Astellas/P, O	Sterol 14α-demethylase	Alpha amino acid esters	CYP3A4 and CYP3A5	Victim with CYP3A4 inhibitors and strong CYP3A4 inducers	Both via urine and Feces
Avycaz (Ceftazidime-avibactam/IV)	Small Molecule	Intra-abdominal infections (cIAI), UTI	2015/Allergan /P	Ceftazidime: Cell wall inhibition; avibactam: non beta-lactamase inhibitor	Ceftazidime: cephalosporin ; avibactam: Carboxylic acids derivatives	---[b]	Victim with probenecid	Via urine
Genvoya (Elvitegravir, cobicistat, Emtricitabine, and Tenofovir alafenamide/PO)	Small Molecule	HIV-1 infection	2015/Gilead/S	HIV-1 integrase strand transfer inhibitor-Elvitegravir, a CYP3A inhibitor-Cobicistat, and Emtricitabine and Tenofovir alafenamide: both HIV1 NRTI	3'-thia pyrimidine nucleosides, Amino acids, peptides, and analogues	Elvitegravir: CYP3A (major) UGT1A1/3 (minor); Cobicistat: CYP3A (major) CYP2D6 (minor); Emtricitabine: Not significantly metabolized; Tenofovir alafenamide: Cathepsin A (PBMCs) CES1 (hepatocytes) CYP3A (minimal)	Avoid with other anti-retroviral medications for treatment of HIV-1 infection; Perpetrator with CYP3A or CYP2D6 substrates	Elvitegravir: Urine: 6% Feces: 94% Cobicistat: Urine: 8%; Feces: 86% Emtricitabine: Urine:70%; Feces: 13% Tenofovir alafenamide: Urine: <1% Feces: 31%
Daklinza (Daclatasvir/PO)	Small Molecule	Hepatitis C virus genotype 3 infections	2015/Bristol Myers Squibb/P	NS5A inhibitor	Carbamic acid derivative	CYP3A4 isoform	Victim, avoid taking with CYP3A4 inducers	88% in feces and 6.6% via urine
Zinplava (Bezlotoxumab/IV, PO)	Monoclonal Antibody	*Clostridium difficile* infection	2016/Merck & Co /P	Binds to *C. difficile* toxin B	Humanized IgG1	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Anthim (Obiltoxaximab/IV)	Monoclonal Antibody	Anthrax	2016/Elusys Therapeutics /S,O	*B. anthracis*	Humanized IgG1 kappa	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Epclusa (Sofosbuvir and Velpatasvir/PO)	Small Molecule	Hepatitis C virus infection	2016/Gilead Sciences /P, B	Sofosbuvir: HCV NS5B polymerase inhibitor; Velpatasvir: NS5A inhibitor.	Pyrimidine 2'-deoxyribonucleosides and Velpatasvir: Naphthopyrans	Sofosbuvir: Cathepsin A CES1 HINT1; Velpatasvir: CYP2B6 CYP2C8 CYP3A4	Victim with inducers and inhibitors of P-gp and CYP2B6, CYP2C8, or CYP3A4	Sofosbuvir: Urine: 80% Feces: 14%; Velpatasvir: Urine: 0.4% Feces: 94%.
Zepatier (Elbasvir and Grazoprevir/PO)	Small Molecule	Hepatitis C virus infection	2016/Merck & Co. /P, B	Elbasvir- NS5A inhibitor: Grazoprevir, NS3/4A protease inhibitor	Elbasvir: Carboxylic acids derivatives Grazoprevir: Carboxylic acids derivatives	Elbasvir: CYP3A; Grazoprevir: CYP3A	Victim with OATP1A1 and 1A3 inhibitors	Elbasvir: Urine: <1% Feces: >90%. Grazoprevir: Urine: <1% Feces: >90%.
Baxdela (Delafloxacin/IV, PO)	Small Molecule	Acute bacterial skin infections	2017/Melinta Therapeutics /P	DNA Topomerase IV and DNA gyrase inhibitors Fluoroquinolone anti-bacterial	Quinoline and derivatives	Metabolized via glucuronidation	Victim, avoid with oral quinolones/strontium gluconate and ranelate antimicrobials/live typhoid vaccine	65% via urine either unchanged or as glucuronide metabolites and 28% in feces
Vabomere (Meropenem and Vaborbactam/IV)	Small Molecule	Urinary tract infections	2017/The Medicines Company/Rempex Pharmaceuticals/P	Meropenem, D-alanyl-d-alanine carboxypeptidase DacB inhibitor (inhibits cell wall synthesis), and Vaborbactam, a beta-lactamase inhibitor	Meropenem: Beta lactams and Vaborbactam: Metalloheterocyclic compounds	Meropenem: Hydrolysis Vaborbactam: No metabolism	---[a]	Meropenem: ~2% excreted through feces Vaborbactam: 75-95% excreted through urine
Benznidazole (Benznidazole/PO)	Small Molecule	Chagas disease	2017/Chemo Research/P, O, A	Nitroimidazole anti-microbial	Organic nitro compounds	CYP450 enzymes	Victim, avoid with amprenavir, disulfiram, alcohol, and vaccines of BCG and Cholera	Via urine
Solosec (Secnidazole/IV, PO)	Small Molecule	Bacterial vaginosis	2017/Lupin/P	Nitroimidazole anti-microbial	Azoles	CYP450 enzyme	---[a]	Via urine
Xepi (Ozenoxacin/Topical)	Small Molecule	Impetigo	2017/Ferrer Internacional /S	DNA gyrase A and Topoisomerase IV	Quinoline and derivatives	---[b]	---[a]	-
Vosevi (Sofosbuvir, Velpatasvir and Voxilaprevir/PO)	Small Molecule	Hepatitis C virus infection	2017/Gilead Sciences /P, B	Sofosbuvir, NS5B polymerase inhibitor; Velpatasvir: NS5A inhibitor; Voxilaprevir: NS3/4A protease inhibitor	Sofosbuvir, Pyrimidinenucleosides; Velpatasvir: Naphthopyrans and Voxilaprevir: Carboxylic acids derivatives	Sofosbuvir: Cathepsin A CES1 HINT1; Velpatasvir: CYP2B6 CYP2C8 CYP3A4; Voxilaprevir: CYP3A4	Victim with inducers and inhibitors of P-gp and CYP2B6, CYP2C8, or CYP3A4	Sofosbuvir: Urine: 80% Feces: 14%; Velpatasvir: Urine: 0.4% Feces: 94%.; Voxilaprevir: Urine: 0% Feces: 94%.;

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Table 6. continued

Brand name (Active ingredient/Route of Administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Mavyret (Glecaprevir and Pibrentasvir/PO)	Small Molecule	Hepatitis C virus infection	2017/AbbVie/P, B	Glecaprevir: NS3/4A protease inhibitor; Pibrentasvir: NS5A inhibitor	Pibrentasvir: Piperidine and Glecaprevir: Carboxylic acids derivatives	Glecaprevir: CYP3A; Pibrentasvir: No metabolism	Victim with Carbamazepine, Efavirenz, and St. John's wort	Glecaprevir: Urine: 0.7% Feces: 92%.; Pibrentasvir: Urine: 0% Feces: 96.6%.;
Prevymis (Letermovir/IV, PO)	Small Molecule	Prophylaxis of cytomegalovirus infection	2017/Merck & Co/P, O, B	CMV DNA terminase complex inhibitor	Diazinanes	Minor metabolism via UGT1A1/1A3	Victim for OATP1B1/3 transporters inhibitors, cyclosporine	93% is excreted in the feces <2% via urine
Moxidectin (Moxidectin/PO)	Small Molecule	Onchocerciasis	2018/Medicines Development for Global Health /P,O	Inhibits parasite's GABA-A and glutamate-gated chloride ion channels	Macrolides and analogues	CYP3A and CYP2B	Victim with ivermectin	Via feces
Zemdri (Plazomicin/IV)	Small Molecule	Complicated Urinary tract infections (cUTI)	2018/Achaogen /P	Aminoglycoside antibacteria (binds 30s ribosomal subunit)	Carboxylic acids derivatives	Hydrolytic Enzymes	---[a]	-
Krintafel (Tafenoquine/PO)	Small Molecule	Plasmodium vivax malaria	2018/GlaxoSmithKline /P, O	radicals produce leads to the parasite death	8-aminoquinoline analogue of primaquine	CYP 2D6, followed by O-demethylation, N-dealkylation, N-oxidation, oxidative deamination and C-hydroxylation	Victim, avoid with OCT2 and MATE substrates	Via urine and Faeces
Aemcolo (Rifamycin/PO)	Small Molecule	Travelers' diarrhea	2018/Cosmo Technologies /P	Anti-bacterial; inhibition of RNA synthesis	Macrolactams	---[b]	---[a]	90% via feces while the urinary secretion is negligible
Nuzyra (Omadacycline/PO)	Small Molecule	Bacterial pneumonia and skin infections	2018/Paratek Pharmaceuticals /P	Inhibits bacterial 30s ribosomal subunit	Tetracyclines	---[b]	Victim, avoid with antacids and iron preparations	14.4% via urine and 81.1% in the feces
Xerava (Eravacycline/IV)	Small Molecule	Abdominal infection	2018/Tetraphase Pharmaceuticals /P	Fluorocycline anti-bacterial	Tetracyclines	CYP3A4- and FMO-mediated oxidation	Victim, avoid with CYP3A inducers	34% of the dose is excreted in urine and 47% in feces
Biktarvy (Bictegravir, Emtricitabine, Tenofovir alafenamide/PO)	Small Molecule	To treat infection in adults who have no anti-retroviral treatment history or to replace the current anti-retroviral regimen	2018/Gilead Sciences/P	Bictegravir: inhibits the strand transfer of viral DNA into the human genome, preventing HIV-1 virus replication and propagation, Emtricitabine: NRTI, Tenofovir alafenamide: potent inhibitor of hepatitis B viral replication	Bictegravir: Pyridine and derivatives, Emtricitabine: Nucleoside and nucleotide analogues, Tenofovir alafenamide: Carboxylic acids derivatives	Bictegravir: CYP3A UGT1A1; Emtricitabine: Not significantly metabolized; Tenofovir alafenamide: Cathepsin A (PBMCs) CES1 (hepatocytes) CYP3A (minimal)	Avoid with other anti-retroviral medications for treatment of HIV-1 infection; Perpetrator with CYP3A or CYP2D6 substrates	Bictegravir: Urine: 35% Feces: 60% Emtricitabine: Urine:70%; Feces: 13% Tenofovir alafenamide: Urine: <1% Feces: 31%
Trogarzo (Ibalizumab-uiyk/IV)	Monoclonal Antibody	HIV patients	2018/TaiMed Biologics/Theratechnologies /P, O, B	CD4 domain 2-directed humanized monoclonal antibody	Humanized IgG4	Hydrolytic Enzymess	---[a]	Similar to endogenous IgG
Tpoxx (Tecovirimat/PO)	Small Molecule	Smallpox	2018/SIGA Technologies /P, O	Inhibitor of the orthopoxvirus VP37 envelope wrapping protein	Isoindole derivatives	UGTs (UGT1A1 and 1A4)	Victim and perpetrator, inducer of cytochrome P450 (CYP)3A and a weak inhibitor of CYP2C8 and CYP2C19	Urine and feces
Xofluza (Baloxavir marboxil/PO)	Small Molecule	Influenza	2018/Shionogi /Roche /P	CAP-endonuclease inhibitor	Dibenzothiepins	UGT1A3, CYP3A4	Victim, avoid co-administration with polyvalent cation-containing laxatives, antacids, or oral supplements	14.7% of a single dose is excreted in the urine, and 80.1% excreted in the feces
Pifeltro (Doravirine/PO)	Small Molecule	HIV-1 infection	2018/Merck /S	Pyridinone non-nucleoside reverse transcriptase inhibitor	Organooxygen compounds	CYP3A	Victim, avoid with CYP3A inducers	Urine and feces
Fetroja (Cefiderocol/IV)	Small Molecule	Urinary tract infections	2019/Shionogi /P	Cephalosporin anti-bacterial (inhibits cell wall synthesis)	Cephalosporin	---[b]	---[a]	Urine
Xenleta (Lefamulin/IV)	Small Molecule	Bacterial pneumonia	2019/Nabriva/P	Anti-bacterial drug (binds 50s ribosomal subunit)	Pleuromutilin derivative	CYP3A4	Victim with strong and moderate CYP3A Inducers or P-gp Inducers	Majorly via feces
Pretomanid (Pretomanid/PO)	Small Molecule	Tuberculosis that affects the lungs	2019/Pfizer/Mylan/P, O	Anti-mycobacterial drug(inhibits mycloic acid biosynthesis)	nitroimidazooxazine	CYP3A4	Victim, avoid with CYP3A4 Inducers	Urine and feces

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Table 6. continued

Brand name (Active ingredient/Route of Administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Recarbrio (Imipenem, cilastatin and relebactam/IV)	Small Molecule	Urinary tract and abdominal infections	2019/Merck & Co./S	Imipenem; inhibit cell wall synthesis,,Cilastatin: inhibitor of renal dehydropeptidase and Relebactam: beta-lactamase inhibitor	Imipenem: Lactam, cilastatin: Carboxylic acids derivatives and relebactam: Carboxylic acids derivatives	Imipenem: dehydropeptidase; relebactam: minimally metabolized	Avoid concomitant use with Ganciclovir and Valproic Acid	Mainly excreted by the kidneys
Egaten (Triclabendazole/PO)	Small Molecule	Fascioliasis	2019/Novartis /P, O	Anthelminthic drug (inhibits Fasciola species)	Organooxygen Compounds	CYP1A2, CYP2C9 (*in vitro*)	---[a]	-
Artesunate (Artesunate/IV)	Small Molecule	Malaria	2020/Amivas/ P, O	Endoperoxide bridge of DHA	Artemisinins	Blood Esterases (*In vitro*)	Victim, avoid with Ritonavir, Nevirapine or Strong UDP/UGT inducers	-

[a]No interaction reported. [b]No information available. [¶]UTI: urinary tract infections; HIV: human immunodeficiency virus; NRTI: nucleoside reverse transcriptase inhibitor; NS: nonstructural protein; PA: polymerase acidic; CMV: cytomegalovirus; RNA: ribonucleic acid; CD: cluster of differentiation; DHA: dihydroartemisinin; PA: polymerase acidic; A, accelerated; B, breakthrough; O, orphan; P, priority; S, standard; PO: peroral: IV: intravenous: SC: subcutaneous; BCG: Bacillus Calmette-Guérin; HINT1: histidine triad nucleotide-binding protein 1; CYP: cytochrome P450; UGT: UDP-glucuronosyltransferase; P-gp: p-glycoprotein; CES: carboxylesterases.

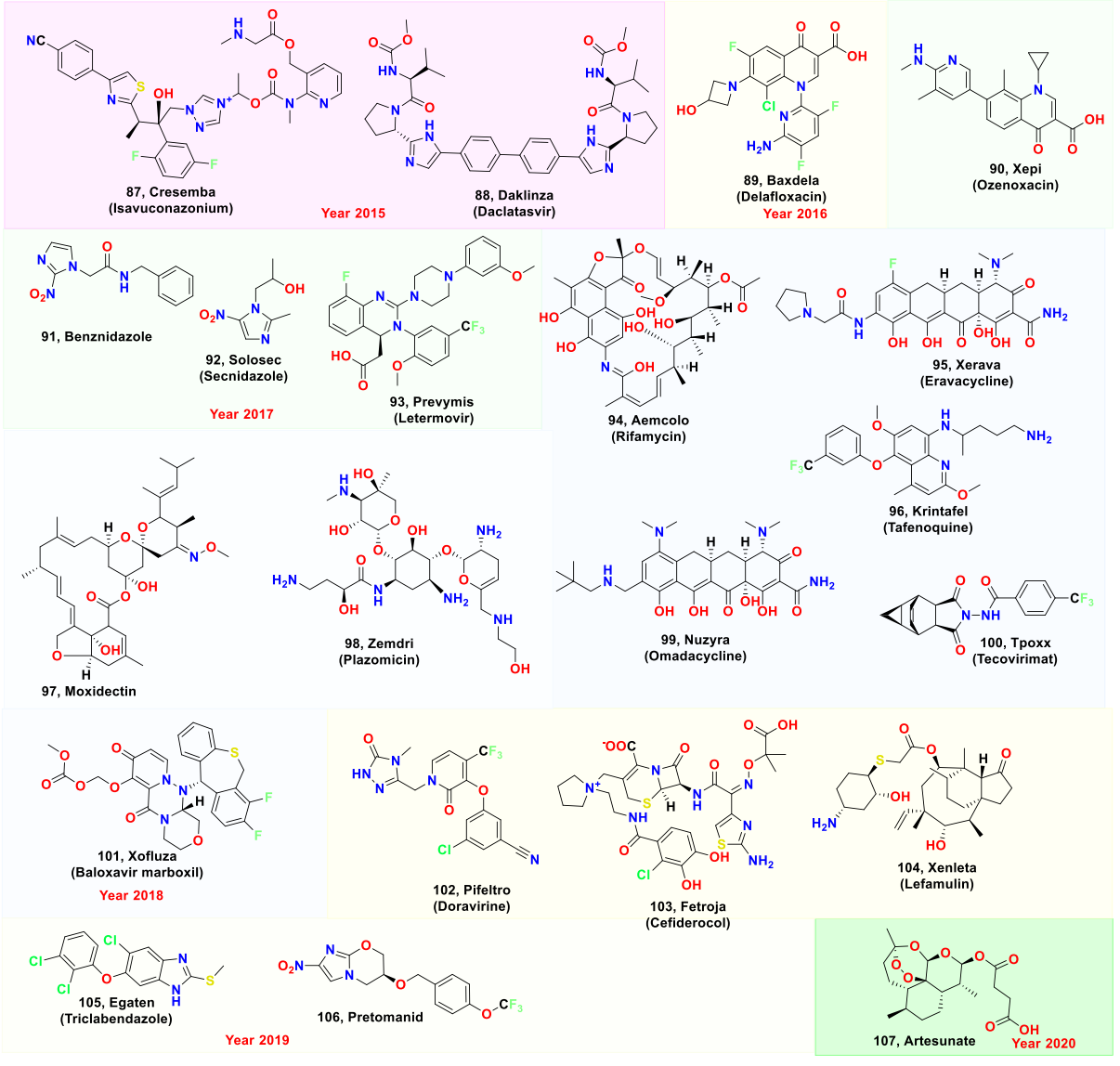

Figure 6. Chemical structures of small molecules as anti-infective agents approved by FDA from the year 2015 until June 2020 (Part 1).

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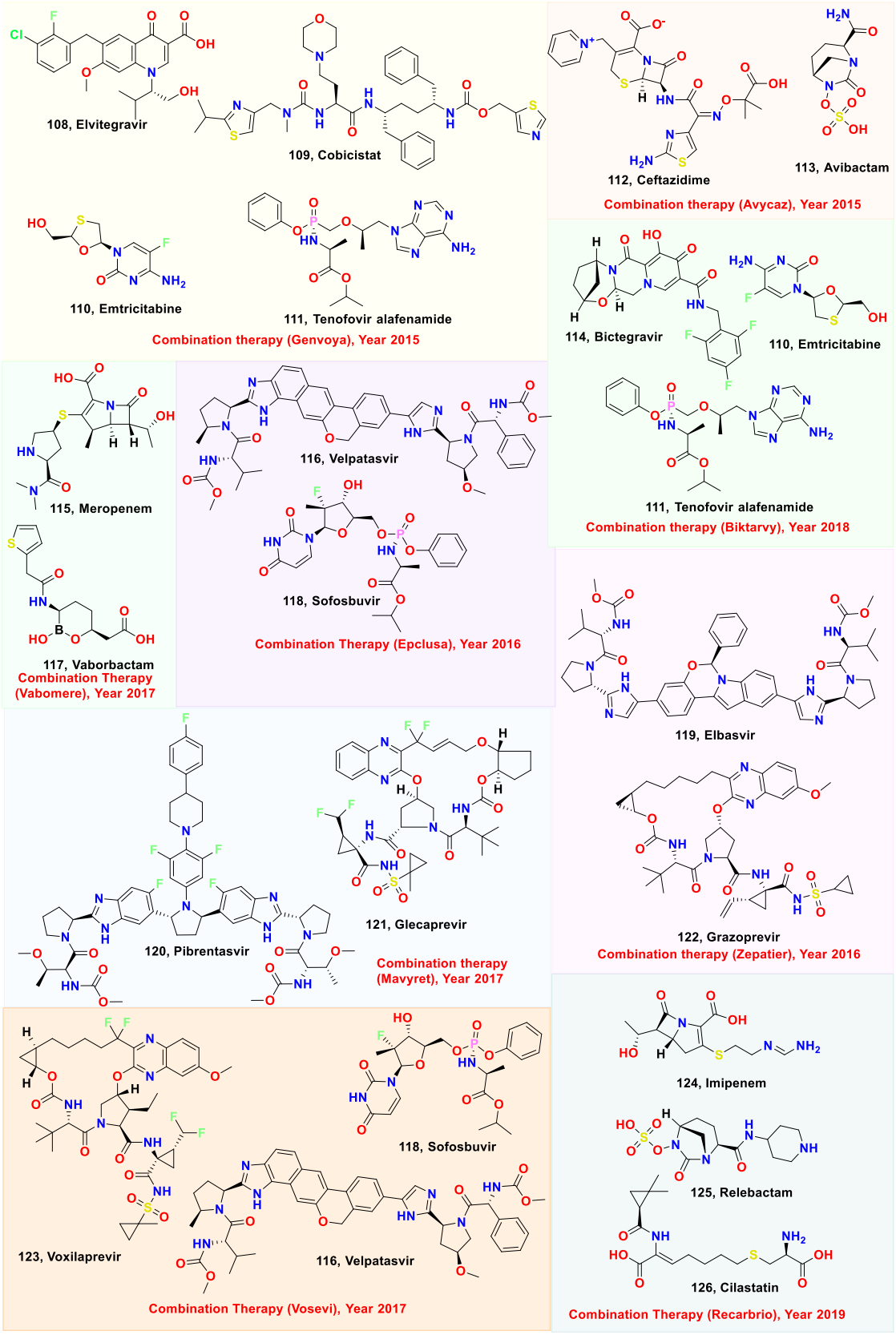

Figure 7. Chemical structures of small molecules used in combination therapy as anti-infective agents approved by the FDA from the year 2015 until June 2020 (Part 2).

In 2017, the metabolic diseases market size was valued at ~USD $50 billion, which is expected to rise at 7.6% of CAGR by 2024. Major contributing regions to research in this area and market for the therapies include Africa, North America, Asia

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Pacific, Latin America, the Middle East, and Europe. The notable companies involved in this area of research are GlaxoSmithKline, Merck, Amicus, Sanofi, Genzyme, AstraZeneca, and Horizon Pharma.[66] For genetic disorders, the market is expected to rise from USD $45 billion in 2017 to USD $86 billion by 2025. Important countries that will drive drug discovery in the area of genetic disorders are North America and the Asia Pacific region.

DRUGS FOR RESPIRATORY DISORDERS

Respiratory diseases including chronic obstructive pulmonary diseases (COPD), asthma, interstitial lung diseases, and pulmonary sarcoidosis[67] are the third leading cause of worldwide death.[68]

The U.S. FDA approved a total of just four drugs in the last five years for the treatment of asthma (3 mAbs) and chronic obstructive pulmonary disease (revefenacin **86**, a small molecule). The details of the approved drugs for respiratory diseases are compiled in Table 5. The mAbs bind to the interleukin 5 receptor, a key cytokine responsible for the differentiation, maturation, recruitment, and activation of human eosinophils which plays a key role in inflammation associated with asthma. Mepolizumab and benralizumab have been approved by the FDA for administration through subcutaneous route, while reslizumab has been approved for use via the intravenous route. **86** is a bronchodilator, long acting muscarinic antagonist (LAMA), approved for dosing through the inhalation route. After inhalation, **86** rapidly undergoes hepatic metabolism to a major active metabolite (THRX-195518), with its systemic exposure being 4- to 6-fold greater than **86**.[69] OATP1B1/1B3 inhibitors may increase serum concentrations of the active metabolite(s) of **86**.[70]

There has been a recent upsurge in research in respiratory diseases' drugs because of the Covid-19 pandemic, which primarily affects the respiratory system. The global market for drugs for respiratory diseases was estimated at $65 billion in 2019 and is expected to rise to $93 billion by end of 2020. North America accounted for 49% of the global market, followed by Western Europe (19%). Mylan, GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Merck, Roche, Novartis, and Teva are considered to be key players that will drive the market for respiratory drugs.[71]

ANTI-INFECTIVE DRUGS

Infectious diseases are caused by pathogens, which include bacteria, fungi, protozoa, worms and viruses. There were 292 approved new molecular entities until late 2013 for the treatment of infectious diseases.[72] A total of 33 anti-infective drug/drug combinations were approved by US FDA in the last five years (Table 6 and Figure 6 and 7), with 90% being small molecules (30 drug/drug combinations) and 3 mAbs. The drugs approved for the various infectious diseases are briefly discussed with their targets in this section. Complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) are caused by multidrug-resistant bacteria.[73] Eravacycline **95**,(2018), a synthetic fluorocycline antibiotic of the tetracycline, which binds to the 30S ribosomal subunit and disrupts bacterial protein synthesis was approved for the treatment of cIAI. Avycaz (the combination of ceftazidime **112**, a cephalosporin antibiotic, and avibactam **113**, a β-lactamase inhibitor, 2019), plazomicin **98**, an aminoglycoside which targets bacterial 30S ribosomal subunit and cefiderocol **103**, an inhibitor of penicillin-binding proteins (PBPs) were approved for treatment of cUTI. Vabomere, is a combination of Meropenem **115**, a penam antibacterial, and vaborbactam **117**, a beta-lactamase inhibitor was approved in 2017 for the treatment of patients with cUTI. Recarbio is a combination of imipenem **124**, a carbapenem antibacterial, cilastatin **126**, a renal dehydropeptidase inhibitor, and relebactam **125**, a beta-lactamase inhibitor. The combination prevents the degradation of **124** by serine beta-lactamases. Recarbio was approved for the treatment of cIAI and cUTI in 2019. In 2020, the drug is also approved for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Lefamulin (**104**), which exerts its action by binding to the peptidyl transferase center of the ribosomal bacterial 50S subunit and omadacycline (**99**), a minomethylcycline subclass of tetracycline antibiotics were approved for the treatment of community-acquired bacterial pneumonia (CABP). Tuberculosis, which is estimated to infect one in every three people is caused by *Mycobacterium tuberculosis*.[74] Pretomanid (**106**) is indicated for the treatment of pulmonary forms of non-responsive multidrug-resistant (MDR) tuberculosis, in combination with bedaquiline and linezolid.[75]

Delafloxacin (**89**), an anionic fluoroquinolone, which inhibits the activity of bacterial topoisomerase II was approved in 2017 for the treatment of acute bacterial skin and skin structure infections caused by *Staphylococcus*, *Enterococcus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.[76] Ozenoxacin (**90**), which targets bacterial DNA replication enzymes DNA gyrase A and topoisomerase IV was approved in 2017 for the topical treatment of impetigo. Secnidazole (**92**), a second-generation 5-nitroimidazole was approved in 2017 for the treatment of bacterial vaginosis in adult women.[77] In 2016, two mAbs, bezlotoxumab for *Clostridium difficile* infection[78] and obiltoxaximab for the prevention and treatment of infection caused by anthrax toxin were approved.[78] Further analysis revealed that three small molecules and one mAb were approved in the anti-HIV category. The approved small molecules, in general, were combination drugs which target HIV-1 integrase strand transfer (involves in concerted integration of viral DNA into the host chromosomes), nucleoside and nucleotide reverse transcriptase (reverse transcribes viral RNA into DNA for insertion into the host DNA sequence). An anti-HIV mAb, Ibalizumab which, targets CD4 receptors on the surface of CD4-positive cells and prevent HIV particle entry into the lymphocytes was approved in 2018. Influenza is an acute respiratory disease caused by the influenza A or B virus with an annual incidence of 3−5 million cases of severe illness and about 250,000 to 500,000 deaths worldwide.[79] Baloxavir marboxil (**101**), a prodrug, the hydrolysis of which results in baloxavir, is responsible for activity against influenza A and B virus infection. **101** exerts its activity by selectively inhibiting influenza cap-dependent endonuclease which prevents polymerase function leading to influenza virus mRNA replication. **101** is the only new flu drug to be approved since the 1999 approval of Roche's neuraminidase inhibitor oseltamivir.

Hepatitis C virus (HCV), belonging to family *Hepadnaviridae*, affects around 170 million people worldwide.[80] Five single and/or combination of small-molecule drugs were approved for the treatment of HCV between 2015 - June 2020. Most of the approved drugs target HCV nonstructural protein 5B (NS5B), the RNA-dependent RNA polymerase responsible for the complete copy of the RNA viral genome, HCV nonstructural 5A (NS5A) protein involved in modulation of the host cell

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Table 7. Illustrative Compilation of U.S. FDA Approved Drugs from the Year 2015 until June 2020 for Drugs for Treating Auto-Immune Disorders Featuring Their Indication, Year of Approval, Sponsor, Target, Chemical Class, Major Drug Metabolizing Enzyme(s), Route of Administration/Elimination, and Drug Interactions (Perpetrator or/and Victim)

Brand name (Active ingredient/Route of Administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Cosentyx (Secukinumab/SC)	Monoclonal Antibody	Plaque psoriasis	2015/Novartis/S	Interleukin-17A antagonist	Humanized IgG1	Hydrolytic Enzymes	Avoid live vaccines	Similar to endogenous IgG
Eucrisa (Crisaborole/Topical)	Small Molecule	Atopic dermatitis	2016/Pfizer/Anacor Pharmaceuticals/S	Phosphodiesterase 4 inhibitor	Organic oxygen compounds	Hydrolytic Enzymes	---[a]	Renal excretion of metabolites
Zinbryta (Daclizumab/SC)	Monoclonal Antibody	Multiple sclerosis	2016/Biogen/S	Interleukin-2 receptor	Two humanized gamma-1 heavy chains and two humanized kappa light chains	Hydrolytic Enzymes	Avoid hepatotoxic drugs	Similar to endogenous IgG
Taltz (Ixekizumab/SC)	Monoclonal Antibody	Plaque psoriasis	2016/Eli Lilly/S	Interleukin-17A antagonist	Humanized IgG4	Hydrolytic Enzymes	Avoid live vaccines	Similar to endogenous IgG
Ocaliva (Obeticholic acid/PO)	Small molecule	Primary biliary cholangitis	2016/Intercept/P, O, A	FXR agonist	Bile acids, alcohols and derivatives	Conjugation (glycine and taurine conjugates)	Victim, avoid with bile acid binding resins such as cholestyramine, colestipol, or colesevela; Perpetrator, avoid with CYP1A2 substrates with narrow therapeutic index (e.g. theophylline and tizanidine)	Feces (87%)
Siliq (Brodalumab/SC)	Monoclonal Antibody	Plaque psoriasis	2017/Valeant Pharmaceuticals/S	Interleukin-17A antagonist	Humanized IgG2	Hydrolytic Enzymes	Avoid for patientswith Crohns' disease; Avoid live vaccines	Similar to endogenous IgG
Dupixent (Dupilumab/SC)	Monoclonal Antibody	Atopic dermatitis	2017/Regeneron/Sanofi /P, B	IL-4 receptor alpha antagonist	Humanized IgG4	Hydrolytic Enzymes	Avoid live vaccines	Similar to endogenous IgG
Kevzara (Sarilumab/SC)	Monoclonal Antibody	Rheumatoid arthritis	2017/Sanofi/Regeneron /S	IL-6 receptor antagonist	Humanized IgG1	Hydrolytic Enzyme	---[a]	Similar to endogenous IgG
Ocrevus (Ocrelizumab/IV)	Monoclonal Antibody	Multiple sclerosis	2017/Roche/Genentech /P, B	CD20-directed cytolytic antibody	Humanized IgG1	Hydrolytic Enzymes	Avoid with Active hepatitis B virus infection	Similar to endogenous IgG
Tremfya (Guselkumab/SC)	Monoclonal Antibody	Plaque psoriasis	2017/Johnson & Johnson/P	IL-23 blocker	Humanized IgG1/λ	Hydrolytic Enzymes	Avoid live vaccines	Similar to endogenous IgG
Ilumya (Tildrakizumab/SC)	Monoclonal Antibody	Plaque psoriasis	2018/Sun Pharma/S	IL-23 antagonist	humanized IgG1/k	Hydrolytic Enzymes	Avoid live vaccines	Similar to endogenous IgG
Tavalisse (Fostamatinib/PO)	Small Molecule	Chronic immune thrombocytopenia	2018/Rigel Pharmaceuticals/S, O	Kinase inhibitor	Aniline and substituted anilines	Alkaline phosphatase (major); CYP3A4 and glucuronidation (UGT1A9)	Victim, avoid with strong CYP3A4 inhibitors and inducersPerpetrator, avoid with CYP3A4, BCRP and P-Glycoprotein (P-Gp) substrates	Feces (80%); urine (minor)
Doptelet (Avatrombopag/PO)	Small Molecule	Thrombocytopenia	2018/Dova Pharmaceuticals/P	Thrombopoietin receptor agonist	Piperazines	CYP2C9 and CYP3A4	Victim, avoid with moderate or strong dual inhibitors and inducers of CYP2C9 and CYP3A4	Feces (88%); urine (minor)
Olumiant (Baricitinib/PO)	Small Molecule	Rheumatoid arthritis	2018/Incyte/Eli Lilly/S	JAK1 and JAK2 inhibitor	Pyrrolo [2,3-d]pyrimidines	CYP3A4	Victim, avoid with strong OAT3 inhibitors (such as probenecid)	Urine (~75%)
Ultomiris (Ravulizumab/IV)	Monoclonal Antibody	Paroxysmal nocturnal hemoglobinuria	2018/Alexion /S, O	Complement protein C5 inhibitor	Protein engineered "IgG2/4"	Hydrolytic Enzymes	Contraindicated in patients with unresolved *Neisseria Meningitidis* infection	Similar to endogenous IgG
Firdapse (Amifampridine/PO)	Small Molecule	Lambert-Eaton myasthenic syndrome	2018/Catalyst Pharmaceuticals/P, O	Symptomatic treatment that increases acetylcholine	3,4-Diaminopyridine	N-acetyltransferase 2 (NAT2)	Victim, avoid with drugs that lower seizure threshold, and provokes cholinergic effect	Urine (95-100%)
Gamifant (Emapalumab-lzsgemapalumab-lzsg/IV)	Monoclonal Antibody	Hemophagocytic lymphohistiocytosis	2018/Novimmune/P, O, B	IFNγ blocking antibody	Humanized IgG1	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Revcovi (Elapegademase-lvlr/IM)	Enzyme	Adenosine Deaminase-Severe Combined Immunodeficiency	2018/Leadiant Biosciences /P, O	Recombinant adenosine deaminase	Enzyme	Hydrolytic Enzymes	---[a]	-

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Table 7. continued

Brand name (Active ingredient/Route of Administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Mulpleta (Lusutrombopag/PO)	Small Molecule	Thrombocytopenia	2018/Shionogi/P	Thrombopoietin receptor agonist	Cinnamic acids and derivatives	CYP4A11	---[a]	Fecal excretion (83%)
Rinvoq (Upadacitinib/PO)	Small Molecule	Rheumatoid arthritis	2019/AbbVie/S	JAK inhibitor	Pyrrolidine-1-carboxamide	CYP3A4, CYP2D6	Victim, avoid with CYP3A4 inhibitors (such as ketoconazole) or CYP3A4 inducers (such as rifampin)	Urine (24%) and feces (38%). Rest is excreted as metabolites
Skyrizi (Risankizumab-rzaa/SC)	Monoclonal Antibody	Plaque psoriasis	2019/AbbVie/S	IL-23 antagonist	Humanized IgG1	Hydrolytic Enzymes	Avoid live vaccines	Similar to endogenous IgG
Mayzent (Siponimod/PO)	Small Molecule	Multiple sclerosis	2019/Novartis/S	S1P receptor modulator	Trifluoromethylbenzenes	CYP2C9 is major, followed by CYP3A4	Victim, warnings and precaution on use with anti-neoplastic, immune-modulating or immunosuppressive therapies, class Ia (e.g., quinidine, procainamide) and class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs and beta blockers	Biliary/fecal excretion (90%)
Zeposia (Ozanimod/PO)	Small Molecule	Relapsing forms of multiple sclerosis	2020/Celgene/BMS/S	S1P receptor modulator	Benzonitrile	ALDH/ADH, CYP3A4, NAT-2 or MAO-B	Victim, warnings and precaution same as that of Mayzent	Urine: 26% & feces: 37%
Tepezza (Teprotumumab-trbw/IV)	Monoclonal Antibody	Thyroid eye disease	2020/Horizon Therapeutics Ireland/O	Insulin-like growth factor-1 receptor inhibitor	Humanized IgG1	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Uplizna (Inebilizumab-cdon/IV)	Monoclonal Antibody	Neuromyelitis optica spectrum disorder	2020/Viela Bio/O	CD19-directed cytolytic antibody	Humanized IgG1	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG

[a]No interaction reported. [¶]FXR: farnesoid X receptor; IL-6: interleukin-6; IL-4: interleukin-4; IL-23: interleukin-23; JAK1: janus kinase 1; JAK2: janus kinase 2; IFNγ: interferon gamma; S1P: sphingosine 1-phosphate; A, accelerated; B, breakthrough; O, orphan; P, priority; S, standard; PO: peroral: IV: intravenous: SC: subcutaneous; IM: intramuscular; NAT2: N-acetyltransferase 2; CYP: cytochrome P450; UGT: UDP-glucuronosyltransferase; P-gp: p-glycoprotein; CES: carboxylesterases; NA: not applicable; IgG: immunoglobulin G.

interferon (IFN) response and HCV NS3/4A protein, a membrane-targeted serine protease responsible for maturation of the viral polyprotein.[81]

Cytomegalovirus and smallpox infections are caused by β-herpesvirus (HHV-5) and variola virus, respectively. Letermovir (**93**) inhibits the activity of the DNA terminase complex of cytomegalovirus (CMV) and was approved for prophylactic treatment of CMV infection in allogeneic hematopoietic stem cell transplant patients. Tecovirimat (**100**), an inhibitor of the orthopoxvirus VP37 envelope wrapping protein was approved for the treatment of smallpox.[82] As per the World Malaria Report 2018, there were 219 million cases of malaria globally in 2017 with around 4,35,000 malaria deaths.[83] Artesunate **107**, (2020) was approved for the treatment of severe malaria and it generates free radicals that inhibit the normal function of *Plasmodium* parasites. Tafenoquine (**96**), an 8-aminoquinoline analogue of primaquine which acts through its active moiety 5,6-orthoquinone tafenoquine generates hydrogen peroxide and hydroxyl radicals which further causes the parasitic death.[84] Benznidazole (**91**) was approved in 2017 for the treatment of Chagas disease caused by *Trypanosoma cruzi* in children. For triclabendazole (**105**), the mechanism of action is not fully known and is currently the only FDA-approved drug for patients affected with fascioliasis. It is postulated to inhibit tubulin function and synthesis of proteins and enzymes in the parasite. Onchocerciasis (river blindness) is caused by a nematode worm, *Onchorcerca volvulus*. Moxidectin (2018) which binds to the parasite's GABA-A and glutamate-gated chloride ion channels was approved for the treatment of river blindness. Isavuconazonium (**87**), a second-generation triazole antifungal inhibits the sterol 14-α-demethylase (Erg11p), and thereby disrupts the fungal membrane integrity. **87** was approved in the year 2015 by the FDA for the treatment of invasive aspergillosis and invasive mucormycosis.

Majority of the drugs in this category were proved for the treatment of bacterial and viral infections. Agreement to Lipinski's criteria for majority of the approved small molecules (27) continued to be the case with anti-infective drugs. A total of 16 small molecules are metabolized through CYPs, wherein major enzyme involved is CYP3A4 (14 out of 16) and behave as victims when codosed with CYP3A inducer/inhibitor. For ~70% of the small molecule drugs, peroral route has been approved for administration and 8 drugs are approved for use through intravenous route.

The global market size of anti-infectious agents was valued at ~ USD 47 billion in the year 2016. The market can be broadly segmented into HIV, malaria, hepatitis, influenza, human Papillomavirus and tuberculosis. In 2016, the HIV segment held the largest share followed by hepatitis therapeutics segment.[85] The major pharmaceutical companies dominating anti-infective drug development include Merck & Co., F. Hoffmann-La Roche Ltd., Pfizer, Johnson & Johnson Services and GlaxoSmithKline.[86]

DRUGS FOR AUTOIMMUNE DISORDERS

Autoimmune diseases comprise more than 70 different disorders affecting approximately 5% of the general population.[87] The autoimmune disorders are reported to be among the 10 most frequent underlying or contributory causes of mortality in females (women have increased prevalence of autoimmune

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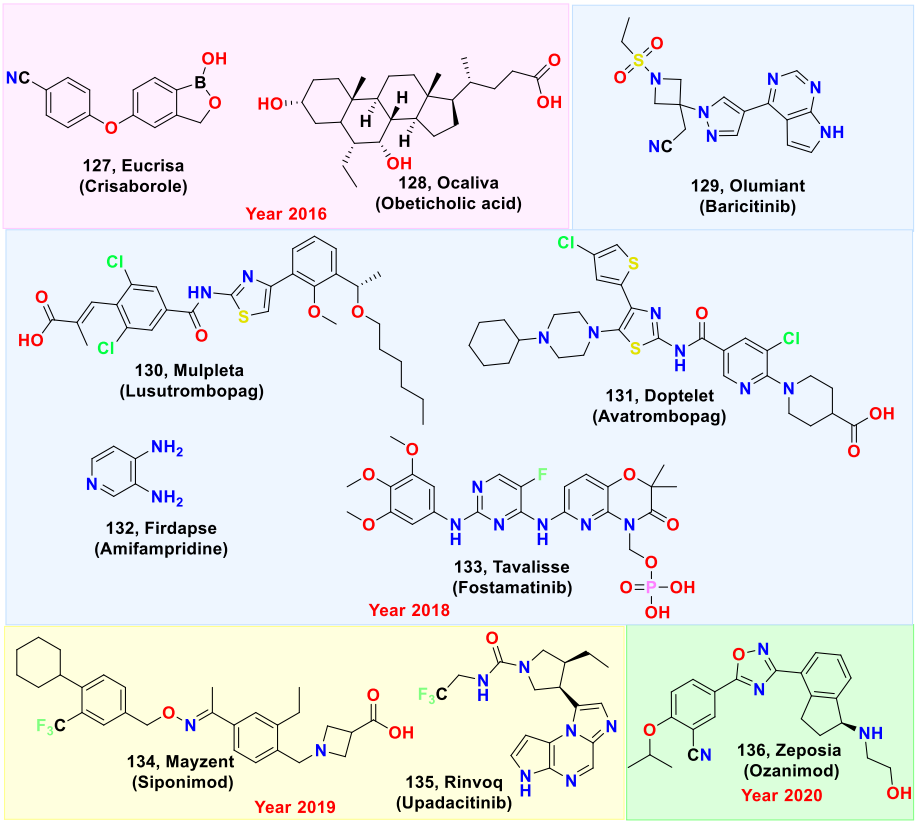

Figure 8. Chemical structures of small molecules used for the treatment of various autoimmune disorders approved by FDA from the year 2015 until June 2020.

diseases as compared with men) of all age groups with the peak mortality rate of ∼5% between 55 and 74 years.[88]

Unitl 2014, there were a total of 168 new molecular entities approved for the treatment of autoimmune diseases.[89] In the last five years, the FDA approved a total of 25 therapeutic agents with a majority of them being mAbs (14 drugs) and one enzyme, while small molecules contributed toward approval of 10 drugs (Table 7 and Figure 8).

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS).[90] Drugs modulating sphingosine-1-phosphate (S1P) receptors, interleukin-2 (IL-2) receptor, and CD-20 on B lymphocytes were approved for MS in the period of study. The S1P1 receptor family comprises five members with effects on cell proliferation, migration and survival, intercellular communication, vascular tone, and endothelial barrier function.[91] Two small-molecule modulators, siponimod **134** (S1P1) and ozanimod **136** (S1P1 and S1P5), were approved for MS in 2019 and 2020, respectively. Further, in addition to T lymphocytes, B lymphocytes could also produce pro-inflammatory cytokines in MS. Ocrelizumab (2017), a second-generation recombinant humanized monoclonal IgG1 antibody that selectively targets the B lymphocytes which express the CD20 antigen was approved for MS.[92] Interleukin-2 (IL-2) and its receptor play a key role in the proliferation of autoreactive T cells and loss of immune tolerance in MS. Considering this rationale, daclizumab (2016), a humanized mAb that binds to CD25, the alpha subunit of IL-2 receptors was approved for the relapsing forms of MS. However, the drug was withdrawn from the market in March 2018 due to safety concerns involving inflammatory brain disorders in patients.[93] Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by strong itching resulting from *amplified immune response* to environmental pollutants and toxins.[94] The prevalence of AD is reported to be 10.7% in children in the United States.[95] The amplified immune response is mediated by interleukin (IL)-4 signaling through IL-4 receptor alpha (IL4Rα), which also mediates IL-13 signaling.[96] Dupilumab (2017) acts against the interleukin-4 receptor subunit α (IL-4Rα) of IL-4 and IL-13 receptors. The phosphodiesterase 4 (PDE4) enzyme is responsible for inflammatory cytokine production. Crisaborole (**127**), a novel PDE4 inhibitor, was approved by the FDA in 2016 through the topical route for the treatment of moderate AD. Interleukin-23 is a key cytokine connecting the innate and adaptive components of the immune response.[97] Elevated levels of IL-23 are related to several autoimmune diseases including rheumatoid arthritis and psoriasis.[98] The worldwide prevalence of psoriasis is reported to be up to 11.43% in adults. Guselkumab (2017) and risankizumab (2018) are IL-23 antagonists and were approved for the treatment of patients with moderate-to-severe psoriasis for administration through the subcutaneous route. Th17 cells are the subset of helper T cells and are reported to play a major role in the pathology of multiple autoimmune diseases through the production of interleukin-17. Blocking of the Th17 axis, either by inhibition of IL-17 directly or by intercepting Th17 cell differentiation, was considered as one of the therapeutic strategies.[99] Three IL-17A antagonists, namely, ixekizumab, secukinumab, and brodalumab, were approved for treatment of psoriasis in the period of study. Interleukin-6 (IL-6) is reported to be present in higher levels in both the synovium and serum of rheumatic arthritis (RA) patients.[100] The worldwide prevalence of RA was reported to be 0.25%.[101] Sarilumab (2017), an IL-6

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Table 8. Illustrative Compilation of U.S. FDA Approved Drugs from the Year 2015 until June 2020 for Drugs for Treating Cardiovascular Diseases Featuring Their Indication, Year of Approval, Sponsor, Target, Chemical Class, Major Drug Metabolizing Enzyme(s), Route of Administration/Elimination, and Drug Interactions (Perpetrator or/and Victim)[¶]

Brand name (Active ingredient/Route of Administration)	Type of Molecule	Indication	Year of approval/Sponsor/ Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Uptravi (Selexipag/PO)	Small Molecule	PAH	2015/Actelion/S, O	Prostacyclin receptor agonist	Organonitrogen compounds	Carboxylesterases, CYP2C8, CYP3A4	Victim, avoid with CYP2C8 inhibitor (gemfibro*), and CYP2C8 inducer (rifampin)	93% in feces and only 12% in urine
Entresto (Sacubitril/PO)	Small Molecule	Heart failure	2015/Novartis/P	Neprilysin inhibitor	Benzene and substituted derivatives	Esterase	Avoid with ACE inhibitor, potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium, NSAIDs, including COX-2 inhibitors	Urine (50-70%)
Entresto (Valsartan/PO)				Angiotensin II receptor blocker	Carboxylic acids and derivatives	Minimal metabolism		Feces (86%)
Kengreal (Cangrelor/IV)	Small Molecule	Avoid blood clots	2015/Medicines Company/S	P2Y12 platelet inhibitor	Purine nucleotides	Dephosphorylation	Perpetrator, avoid with Thienopyridines (clopidogrel or prasugrel)	58% via urine. and 35% via feces
Corlanor (Ivabradine/PO)	Small Molecule	Heart failure	2015/Amgen/P	HCN-channels inhibitor	Benzazepines	CYP3A4	Victim, avoid with CYP3A4 inhibitors, azole anti-fungals, macrolide antibiotics, HIV protease inhibitors and nefazodone. diltiazem, verapamil, and grapefruit juice; Negative chronotropes	Feces (50%) and urine (50%)
Savaysa (Edoxaban/PO)	Small Molecule	Systemic embolism	2015/Daiichi Sankyo/S	Factor Xa inhibitor	Carboxylic acids and derivatives	Edoxaban remain predominantly unchanged, minimal metabolism via hydrolysis mediated by carboxylesterase 1	Victim, avoid with Anti-coagulants, Antiplatelets, Thrombolytics, SSRIs/SNRIs and P-gp Inducers	Feces (50%) and urine (50%)
Praxbind (Idarucizumab/IV)	Antibody Fragment	Reverse Pradaxa's blood-thinning effects	2015/Boehringer Ingelheim/P, O, A, B	Binds to dabigatran	Fab derived from an IgG1	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Repatha (Evolocumab/SC)	Monoclonal Antibody	High cholesterol	2015/Amgen/S, O	PCSK9 inhibitor	Humanized IgG2	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Praluent (Alirocumab/SC)	Monoclonal Antibody	High cholesterol	2015/Sanofi/P	PCSK9 inhibitor	Humanized IgG1	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Defitelio (Defibrotide sodium/IV)	Oligonucleotide	Hepatic veno-occlusive disease	2016/Gentium /P, O	Increase levels of prostaglandin I2, E2, and prostacyclin	Single-stranded oligodeoxyribonucleotides	Nucleases	---[a]	-
Bevyxxa (Betrixaban/PO)	Small Molecule	Venous thromboembolism	2017/Portola Pharmaceuticals/P	Factor Xa inhibitor	Anilides	Predominantly remain unchanged	Victim, avoid using with P-gp inhibitors, potential DDI with anti-coagulants, anti-platelets and thrombolytics	85% via feces and 11% via urine
Hemlibra (Emicizumab/SC)	Monoclonal Antibody	Hemophilia A	2017/Roche/Genentech/P, O, B	Bispecific factor IXa- and factor X-directed antibody	Humanized IgG4	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Giapreza (Angiotensin II/IV)	Small Molecule	Septic or other distributive shock	2017/La Jolla Pharmaceutical Company /P	Angiotensin II receptor agonist	Amino acids, peptides, and analogues	Aminopeptidase A and angiotensin converting enzyme 2 (ACE2) to angiotensin	Victim, avoid with ACE inhibitors and ARBs	-
Vyndaqel (Tafamidis meglumine/PO)	Small Molecule	Cardiomyopathy	2019/Pfizer/Foldrx/ P, O, B	Transthyretin stabilizers	Benzoxazole derivatives	Glucuronidation	Perpetrator, avoid with BCRP substrates	59% via feces (unchanged) and 22% of via urine
Cablivi (Caplacizumab-yhdp/IV or SC)	Antibody Fragment	Acquired thrombotic thrombocytopenic purpura	2019/Sanofi/Ablynx /P, O	A1-domain of vWF	vWF-directed Fab	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Nexletol (Bempedoic acid/PO)	Small Molecule	Familial hypercholesterolemia	2020/Esperion Therapeutics/S	Adenosine triphosphate-citrate lyase (ACL) inhibitor	Fatty acids and conjugates	Glucuronidation, UGT2B7 (*in vitro*)	Perpetrator, avoid with simvastatin and pravastatin	70% via urine

[a]No interaction reported. [¶]PAH: pulmonary arterial hypertension; HCN: hyperpolarization-activated cyclic nucleotide-gated; PCSK9: proprotein convertase subtilisin kexin type 9; FXa: factor Xa; Fab: monoclonal antibody fragment; vWF: von Willebrand factor; A, accelerated; B, breakthrough; O, orphan; P, priority; S, standard; PO: peroral: IV: intravenous: SC: subcutaneous; CYP: cytochrome P450; UGT: UDP-glucuronosyltransferase; P-gp: p-glycoprotein; NA: not applicable; IgG: immunoglobulin G.

receptor antagonist binds to soluble as well as membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and was approved for the treatment of adult patients with moderately to severely active RA. JAKs (intracellular tyrosine kinases) play a significant role in

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cytokine signaling pathways involving immunity and hematopoiesis.[102] The different types of JAKs identified are JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAK signaling inhibition offers a novel mechanism through which a range of cytokines can be inhibited using a small-molecule drug. Tofacitinib (a first-generation JAK inhibitor) is a pan-JAK inhibitor having the ability of inhibiting JAK3/1/2 and to a minor extent TYK2, and it was approved for the treatment of RA. Baricitinib (**129**), a selective JAK1 and JAK2 inhibitor, was approved for the treatment of RA in 2018.[103] Recently, second-generation JAK inhibitors that exert a selective inhibition of JAK1 or JAK3 have been explored.[104] Upadacitinib (**135**) is an oral JAK1-selective inhibitor, with a negligible effect on JAK3, leading to an improved drug safety profile. **135** was approved for the treatment of RA in August 2019.[105] Thrombocytopenia is the most common hematologic complication in patients with chronic liver disease defined by a platelet count below 150 000/μL. The prevalence of thrombocytopenia in patients with chronic hepatitis was reported to be 6%; however, a prevalence of up to 78% was reported in cirrhotic patients.[106] *Immune thrombocytopenia* (*ITP*) is identified by *immune*-mediated destruction of platelets which results in thrombocytopenia and mucocutaneous bleeding. Thrombopoietin receptor agonists belong to a class of platelet growth factors that mimic the action of endogenous thrombopoietin (TPO) on megakaryocytes and their precursors leading to promotion of their growth and differentiation and thereby increasing platelet production.[107] Avatrombopag (**131**) and lusutrombopag (**130**) were approved in May and July 2018, respectively, for the treatment of thrombocytopenia as a result of chronic liver disease. Fostamatinib (**133**) is a small-molecule inhibitor of spleen tyrosine kinase (Syk) and was approved in the year 2018 for the treatment of ITP.[108] Upregulation of FNγ leads to hemophagocytic lymphohistiocytosis (HLH).[109] Emapalumab, a monoclonal antibody that binds to and neutralizes interferon gamma (IFNγ), was approved in the year 2017 for the treatment of primary HLH in patients. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired condition resulting from defective synthesis of GPI-anchored proteins due to a somatic mutation in the Pig-A gene in bone marrow stem cells.[110,118] The true incidence of PNH is unknown, but it was estimated at 1.5−2.0 cases per million of the population per year.[111] Ravulizumab was approved in 2018 for the treatment of PNH. Ravulizumab binds to complement protein 5 (C5) and blocks its activation by complement pathway convertases, thus inhibiting the formation of the terminal complement complex.[112] Lambert-Eaton myasthenic syndrome (LEMS) is a neuromuscular junction disorder that is characterized by the presence of autoantibodies against P/Q type voltage-gated calcium channels, which results in improper release of acetylcholine at presynaptic membrane.[113] The estimated global prevalence of LEMS is about 2.8 per million. Amifampridine, approved in 2018, is a symptomatic treatment that increases acetylcholine concentrations at the neuromuscular junction. Adenosine deaminase (ADA) is an important enzyme involved in the purine salvage pathway.[114] Mutation of the ADA gene results in accumulation of toxic metabolites such as adenosine, 2'deoxyadenosine, and deoxyadenosine triphosphate, which further results in a form of severe combined immunodeficiency (SCID) characterized by severe lymphocytopenia and NK cells.[115] Adenosine deaminase deficiency is very rare with the global incidence of approximately 1 in 200 000 to 1 000 000 newborns.[116] Elapegademase has the ability to increase adenosine deaminase activity while reducing the concentrations of toxic metabolites and was approved in 2018.[117] Primary biliary cholangitis (PBC) is an autoimmune liver disease, characterized by biliary destruction, progressive cholestasis, and liver damage.[118] Farnesoid X Receptor (FXR) is a bile acid receptor, and its activation controls enterohepatic bile acid homeostasis, inflammation, and fibrosis in response to liver injury.[119] Obeticholic acid (**128**), a FXR agonist, was approved in 2016 for the treatment of PBC.[120] Thyroid eye disease (TED) is an autoimmune disease resulting in permanent facial deformity. Teprotumumab (2020), directed against IGF-1R (insulin-like growth factor-1 receptor), causes internalization and degradation of IGF-1R, which results in ameliorating the symptoms of thyroid eye disease.

Interestingly, 80% of the approved small molecules (8 out of 10) for the treatment of autoimmune disorders followed Lipinski's rule. Half of the drugs (5 out of 10) were implicated as victims when coadministered with drugs causing modulations in enzymes (CYP3A4, CYP2C9, and CYP2C8) and transporters (BCRP and OAT3). Nine out of 10 small molecule drugs are approved for use through the peroral route and only one drug is approved through the topical route. Five mAbs are approved for administration through the intravenous route, and nine are approved for use through the subcutaneous route. The key players currently involved in discovery and development of drugs for autoimmune diseases are AbbVie, Trinity Biotech, Biorad Laboratories, F. Hoffmann-la Roche, Inova Diagnostics along with Johnson & Johnson, Eli Lilly & Co., Bristol Myers Squibb, Abbott Laboratories, Pfizer, and AstraZeneca.[121]

CARDIOVASCULAR DRUGS

A report from the WHO (2019) indicated that cardiovascular diseases (CVDs) result in a mortality of 17.9 million (31% of all deaths worldwide) globally.[122] The CVDs include cerebrovascular disease, deep vein thrombosis, coronary heart disease, rheumatic heart disease, peripheral arterial disease, congenital heart disease, and pulmonary embolism. Among the CVDs, heart attacks and strokes are primarily responsible for the mortality.[123] From the period of 1937− 2013, there were 201 new molecular entities approved for treatment of CVDs.[124] During the last five years, a total of 15 therapeutic agents for CVDs were approved by US FDA, with a majority of them being small molecules (9 drugs), while macromolecules constituted the remaining (Table 8 and Figure 9). The drugs approved under this category are described subsequently.

A drug combination comprising of sacubitril (**142**) and valsartan (**141**) was approved in 2015 for the treatment of chronic heart failure.[125] The combination is based on the inhibition of neprilysin by active metabolite of **142**, LBQ657, which in turn increases the bioavailability of brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), and c-type natriuretic peptide (CNP), which promote vasodilation, while the antihypertensive effect of **141** was mediated by its selective binding to angiotensin receptor 1 (AT1) and prevents angiotensin II from binding. Ivabradine was approved in 2015 for the management of symptomatic chronic heart failure for its heart rate lowering effect mediated by inhibition of the cardiac pacemaker current, a mixed sodium−potassium inward current. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is reported to play a major role in cholesterol metabolism, by reducing the expression of the LDL receptor.[126] Nonvitamin K antagonist oral anticoagulants (NOACs) are preferred because of their selective action, shorter half-life, and safety.[127] Edoxaban (**139**) exerts its action by inhibiting factor Xa (FXa), an

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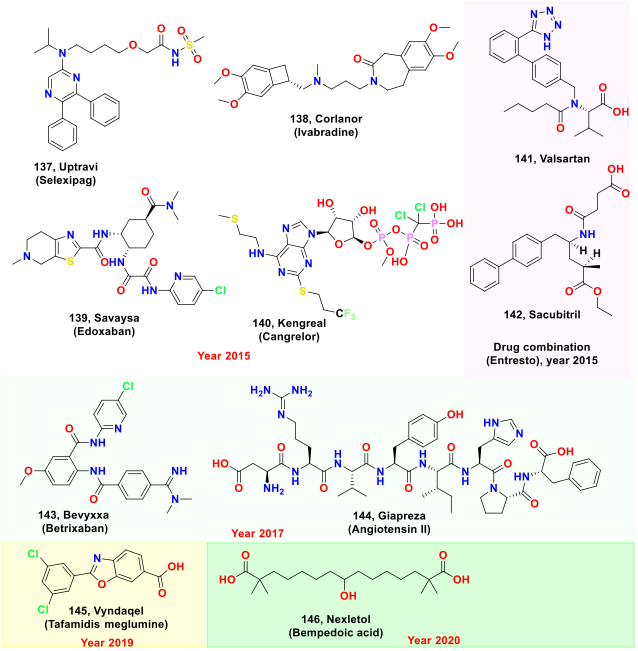

Figure 9. Chemical structures of small molecules used for the treatment of various cardiovascular diseases approved by FDA from the year 2015 until June 2020.

important component of the coagulation cascade, and it was approved in 2015 for reducing the risk of embolism. Selexipag (**137**), a selective prostacyclin receptor agonist, was approved for the treatment of pulmonary arterial hypertension. Inhibition of PCSK9 results in increased LDL cholesterol receptors with the decrease in serum LDL cholesterol.[128] Two monoclonal antibodies alirocumab and evolocumab targeting PCSK9 were approved in 2015 for the treatment of hypercholesterolemia. Considering the role of Angiotensin II by causing vasoconstriction with a resultant increase in blood pressure, first synthetic human Angiotensin II was approved in 2017 for increasing blood pressure in patients with septic shock.[129] Emicizumab, which mimics the function of the coagulation Factor VIII, was approved in 2017 as a prophylaxis to prevent the frequency of episodes of bleeding patients with hemophilia A. Tafamidis (**145**), a transthyretin stabilizer, was approved in 2019 to treat cardiomyopathy caused by transthyretin-mediated amyloidosis.[130] Caplacizumab, approved in 2019 for the treatment of thrombotic thrombocytopenic purpura in conjunction with plasma exchange, acts by targeting the A1 domain of the ultralarge von Willebrand factor and prevents the interaction between the von Willebrand factor and platelet aggregation.

Almost all approved small molecules (8 out of 9) in this category followed Lipinski's rule. Data in Table 8 show that some of the approved drugs (small molecule) were implicated as victims during coadministration with other drugs causing modulations in enzymes (CYP2C8 and CYP3A4) and transporters (P-glycoprotein). The major route of administration for small molecules cardiovascular drugs continues to be the peroral one, and only two drugs are approved for use through the intravenous route. Five monoclonal antibodies are approved through the subcutaneous route, and one is approved for administration through the intravenous route. Catabolism is primarily responsible for the elimination of all the macromolecules. The cardiovascular drugs market is expected to be dominated by North America, the United States, Canada, the U.K., and Europe (Germany, Spain, Italy, and France). The pharmaceutical companies such as Bristol Myers Squibb, Abbott, AstraZeneca, Takeda, Novartis, Bayer, Roche, GlaxoSmithKline, Daiichi Sankyo, Pfizer, Johnson & Johnson, and Solvay SA are currently researching the discovery and development of novel drugs for cardiovascular diseases. The rise in diabetic patients also holds a potential role in elevating the global cardiovascular drugs market, which is already hampered by stringent regulations and patent expiry of numerous blockbuster drugs in near future.[131]

DIAGNOSTIC AGENTS

Diagnostic agents are primarily used to aid in detecting abnormalities at cellular and molecular levels.[132,133] These agents should possess high quantum yield (sensitive) and photostability and should be expeditious to cross the cell membrane with low or no cytotoxicity at a concentration of investigation.[134] In the late 19th century, fluorescein and rhodamine derivatives were first reported as diagnostic agents for bioimaging.[135] The meagre photostability of these dyes restricts their application in bioimaging applications, where prolonged illumination is essential.[136] Therefore, *de novo* design and development of a safe, quick, and effective diagnostic agent continues to be a prominent area of research.[137]

In the last five years, the FDA has approved eight diagnostic agents (seven small molecules and one polymer). Fluciclovine F18 (**148**), fluorodopa F18 (**150**), flortaucipir F18 (**152**), and fluoroestradiol F18 (**153**) are approved for the diagnosis of prostate cancer, Parkinsonian syndrome, Alzheimer's disease, and breast cancer, respectively. Two gallium-containing radioactive diagnostic agents (**147** and **151**) have been approved for the diagnosis of a neuroendocrine tumor. A general mechanism behind these diagnostic agents lies in their uptake through the targeted receptors present on the diseased organ; for example, uptake of **148** will increase through L-type amino acid transporter (LAT) receptors present on the prostate cancer cell. The details of the approved drugs are compiled in Table 9, and chemical structures are illustrated in Figure 10. A majority (6 out of 7) of small-molecule diagnostic agents are approved for use through the intravenous route, and only one is approved through the peroral route. One polymer (Giskit) was approved in 2019 through the intrauterine route for diagnosing fallopian tube patency.

According to the recent market trends, the global market for the imaging/diagnostic agents is expected to rise to $2.5 billion USD by 2024 at a CAGR of roughly 3.1%. The diagnostic radiopharmaceuticals are expected to grow at a rate of 3.5% with the market to rise to $6.4 billion USD.[138] The major global market includes the United States, Europe, and Germany. Aytu BioScience, Bayers Health Care, Bracco Diagnostic Inc., Curium, and Eli Lilly will be emerging key players.[139]

MISCELLANEOUS DRUGS

Drugs which could not be classified under any of the disease areas discussed in this review are reported under this category (<10% of the total number of approvals). A total of 25 drugs were approved by the FDA in the last five years (20 small molecules, 2 peptides, and 3 macromolecules). These can be further categorized into drugs for ophthalmic disorders (6 drugs), gastrointestinal diseases (10 drugs), reproductive disorder (3 drugs), dermatology (2 drugs), opioid withdrawal

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Table 9. Illustrative Compilations of U.S. FDA Approved Diagnostic Agents from the Year 2015 until June 2020 Featuring Their Indication, Year of Approval, Sponsor, Target, Chemical Class, Major Drug Metabolizing Enzyme(s), Route of Administration/Elimination, and Drug Interactions (Perpetrator or/and Victim)[¶]

Brand name (Active ingredient/Route of Administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Netspot (Gallium Ga 68 dotatate/IV)	Small Molecule	Detection of somatostatin receptor positive neuroendocrine tumors in adult and pediatric patients	2016/Advanced Accelerator Applications/P, O	Somatostatin receptors	Gallium Ga 68 dotatate	---[b]	Victim, avoid with non-radioactive somatostatin analogs	12% of injected dose is excreted via urine during first four hours post-injection
Axumin (Fluciclovine F 18/IV)	Small Molecule	Used in PET for detecting prostate cancer recurrence based on elevated PSA levels	2016/Blue Earth /P	Prostate specific antigen levels	Fluciclovine F 18	---[b]	---[a]	-
Macrilen (Macimorelin acetate/PO)	Small Molecule	Diagnosis of adult growth hormone (GH) deficiency	2017/Aeterna Zentaris /S, O	Stimulates GH release by activation of growth hormone secretagogue receptors	Macimorelin acetate	CYP3A4 (*in vitro*)	Victim, avoid with drugs that prolong QT interval and CYP3A4 inducers	-
ExEm Foam (Air polymer-type A/ intrauterine infusion)	Polymer	A diagnostic agent for fallopian tube patency in women with known or suspected infertility.	2019/Giskit/S	Ultrasound contrast agent	Air polymer-type A	---[b]	---[a]	-
Fluorodopa F 18 (Fdg/IV)	Small Molecule	PET imaging for assessment of abnormal glucose metabolism in patients with an existing diagnosis of cancer, coronary artery disease and epileptic seizures	2019/Feinstein Institutes/S	Ultrasound contrast agent	Fluorodopa F 18	Phosphorylation and dephosphorylation	---[a]	Urine
Ga-68-Dotatoc(Edotreotide gallium Ga-68/IV)	Small Molecule	Detect somatostatin receptor positive neuroendocrine tumors	2019/UIHC PET Imaging Center/S, O	Somatostatin receptor agonist	Ga-68-DOTATOC	---[b]	Victim, avoid with non-radioactive somatostatin analogs	16% of the injected dose is excreted via urine in the first 2-4 h post-injection
Tauvid (Flortaucipir F18/IV)	Small Molecule	PET agent used for brain imaging to estimate the density and distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment under evaluation for Alzheimer's disease.	2020/Avid Radiopharms Inc /P	Binds to aggregated tau protein	Pyridine derivative	---[b]	---[a]	Hepatobiliary and renal excretion
Cerianna (Fluoroestradiol F18/IV)	Small Molecule	PET agent used for detection of estrogen receptor (ER)-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer	2020/Zionexa/S	Binds to estrogen receptor	Analog of estrogen	---[b]	Victim, avoid with endocrine therapies, including ER modulators and ER down-regulators	Biliary and urinary excretion

[a]No interaction reported. [b]No information available. [¶]GH: growth hormone; PS: parkinsonian syndrome; ER: estrogen receptor; A, accelerated; B, breakthrough; O, orphan; P, priority; S, standard; IV: intravenous: SC: subcutaneous; CYP: cytochrome P450; P-gp: p-glycoprotein; NA: not applicable; IgG: immunoglobulin G.

(1 drug), and nutrition supplements (3 drugs). The drugs approved under these categories are briefly discussed in this section (see Table 10 and Figure 11).

Ophthalmology. The leading causes of blindness and low vision are primarily diseases such as age-related macular degeneration (AMD), cataract, diabetic retinopathy, and glaucoma.[140] The global prevalence of vision impairment or blindness is around 2.2 billion. Latanoprostene bunod (**158**, a prostaglandin analogue) and Netardusil (**159**) are a Rho kinase and a norepinephrine transporter inhibitor, respectively, approved by the FDA in 2017 for patients with glaucoma or ocular hypertension through reduction of intraocular pressure (IOP). Lifitegrast **156** (the first lymphocyte function-associated antigen-1 antagonist) is indicated for the treatment of dry eye

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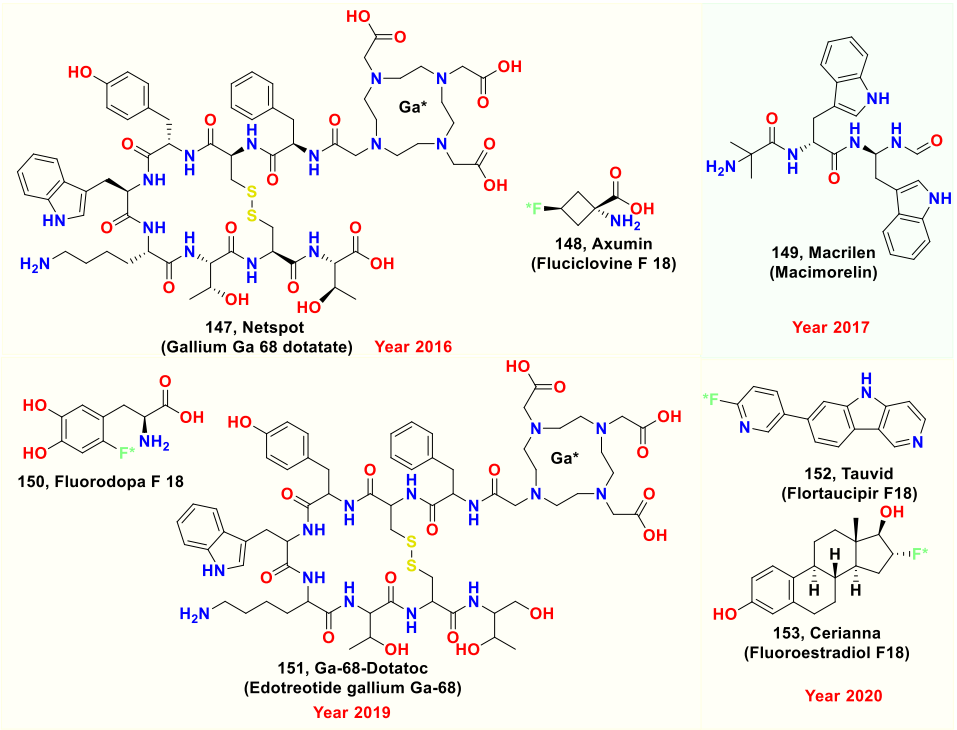

Figure 10. Chemical structures of diagnostic agents approved by FDA from the year 2015 until June 2020.

disease.[141] Two macromolecules, cenegermin (human nerve growth factor; 2018) and brolucizumab (human VEGF inhibitor; 2019) were approved for the treatment of neurotropic keratitis and wet AMD, respectively.

Gastrointestinal Disorders. Nausea/vomiting, constipation, and irritable bowel syndrome (IBS) broadly constitute functional gastrointestinal disorders (FGID) and are the three conditions for which nine new molecular entities were approved from the year 2015 until June 2020. FGID are reported to cause a serious reduction in the quality of life of people, which in turn put a huge impact on health care worldwide.[142] Discovering drugs for treating FGID are challenging as these are complex conditions, and the pathophysiology is affected by multiple factors including genetic predispositions, infection, chronic stress, and psychological symptoms.[143] Drugs approved for nausea and vomiting in this period are rolapitant (**154**) and amisulpride (**169**), which act as substance P/NK1 receptor antagonist and D2 antagonist, respectively. Chemotherapy-induced nausea and vomiting (CINV) is the most devastating side effect of chemotherapy in cancer patients.[144] Akynzeo, a combination of fosnetupitant (**171**) and palonosetron (**172**), was approved in 2018 through the intravenous route by the FDA because of its ability to prevent both nausea and vomiting associated with cancer chemotherapy. Irritable bowel syndrome (IBS) affects the large intestine, which results in diarrhea or constipation or both.[145] Eluxadoline (**155**) is a mixed opioid receptor agonist (Mu) and antagonist (delta) used for treating patients with diarrhea-predominant IBS.[146] Another drug, tenapanor (**167**), was the first sodium/hydrogen exchanger isoform 3 (NHE3) transporter inhibitor. It was approved for the treatment of constipation-predominant irritable bowel syndrome (IBS-C). Chronic idiopathic constipation (CIC) accounts for the global prevalence of 14% and is more common in women.[147] Three drugs, namely, plecanatide, prucalopride, and lactitol, were introduced into the market for CIC in this period. Plecanatide and lactitol (**170**) accelerate GI transit through the increased intestinal fluid.[148] Prucalopride (**165a**) is a selective 5-HT4 stimulator in the GI tract and increases intestinal motility by releasing acetylcholine.[149] The main advantage of prucalopride is that it has no interaction with the hERG channel or 5-HT1 receptors, which further reduces the cardiovascular risk. Opioids are known to cause constipation through inhibition of gastric emptying and peristalsis.[150] By antagonizing opioid receptors, naldemedine (**157**) inhibits opioid-induced constipation.[151] The tryptophan hydroxylase inhibitor xermelo (**160**) was approved for the treatment of carcinoid syndrome diarrhea in the year 2017.

The key players of global gastrointestinal drugs market are Takeda Pharmaceuticals, Allergan Plc, Novo Nordisk, AstraZeneca Plc, and AbbVie.[152]

Nutrition Supplements. Iron deficiency is one of the most common nutritional disorders prevalent in women and children that could result in restless legs syndrome (RLS), impaired cognitive function, fatigue, diminished quality of life, and infertility.[153] Accrufer (**161**; ferric maltol), approved in July 2019, is a novel, stable, nonsalt-based oral treatment for adults with iron deficiency. A calorie supplement (fish oil triglycerides and triheptanoin) was also approved in this study period.

Dermatology. Acne vulgaris is the inflammatory disease characterized by the formation of pustules, comedones, nodules, cysts, and/or papules, due to obstruction and inflammation of pilosebaceous units.[154] The market size of global acne drugs was around USD $4.1 billion in 2017. Two small-molecule drugs, sarecycline (**165**) and tifarotene (**163**), were approved by the FDA for acne vulgaris treatment during the study period.

Reproductive Disorders. Annovera (a combination of segesterone acetate **173** and ethinyl estradiol **174**) was approved for the prevention of pregnancy in 2018.[155] Elagolix sodium (2018), a GnRH receptor antagonist, which reduces the levels of

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Table 10. Illustrative Compilation of U.S. FDA Approved Drugs from the Year 2015 until June 2020 for Drugs for Treating Miscellaneous Drugs Featuring Their Indication, Year of Approval, Sponsor, Target, Chemical Class, Major Drug Metabolizing Enzyme(s), Route of Administration/Elimination, and Drug Interactions (Perpetrator or/and Victim)

Brand name (Active ingredient/Route of Administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
Varubi (Rolapitant/PO)	Small Molecule	Nausea and vomiting (emesis)	2015/Tesaro/S	Substance P/NK1 receptor antagonist	Organic acids and derivatives	CYP3A4	Perpetrator, avoid with CYP2D6 substrates with a narrow therapeutic index (thioridazine and pimozide), CYP2D6 inhibitor (dextromethorphan); Victim, avoid with strong CYP3A4 inducers (rifampin) andBCRP substrates	hepatic/biliary route
Viberzi (Eluxadoline/PO)	Small Molecule	Irritable bowel syndrome	2015/Allergan/P	Opioid receptor agonist (Mu) and antagonist (delta)	Amino acids, peptides, and analogues	Glucoronidation	Victim, avoid with OATP1B1 inhibitors, drugs causing constipation; BCRP substrate	82% via feces, <1% via urine
Xiidra (Lifitegrast ophthalmic solution/Ocular)	Small Molecule	Dry eye disease	2016/Shire Pharmaceuticals/P	LFA-1 antagonist	Phenylalanine and derivatives	---[b]	---[a]	-
Trulance (Plecanatide/PO)	Peptide	Chronic Idiopathic Constipation	2017/Synergy Pharmaceuticals/S	Guanylate cyclase-C agonist	Polypeptides	Proteolytic degradation	---[a]	-
Symproic (Naldemedine/PO)	Small Molecule	Opioid-induced constipation	2017/Shionogi/S	Opioid antagonist	Alkaloids and derivatives	CYP3A (major), UGT1A3 (minor)	Victim, avoid use with strong CYP3A inducers and opioid antagonists, monitor use with moderate CYP3A inhibitors and strong P-gp inhibitors	Excreted via urine (57%) and feces (35%)
Vyzulta (Latanoprostene bunod ophthalmic solution/Ocular)	Small Molecule	Open-angle glaucoma and/or ocular hypertension	2017/Bausch and Lomb/Valeant Pharmaceuticals/S	Lower intraocular pressure by increasing outflow of aqueous humor	Prostaglandin analog	Fatty acid β-oxidation	---[a]	-
Rhopressa (Netarsudil/Topical and Ocular)	Small Molecule	Glaucoma or ocular hypertension	2017/Aerie Pharmaceuticals/P	Rho kinase inhibitor	Amino acids, peptides, and analogues	Esterases in the eye	---[a]	-
Xermelo (Telotristat ethyl/PO)	Small Molecule	Carcinoid syndrome diarrhoea	2017/Lexicon Pharmaceuticals/P, O	Tryptophan hydroxylase inhibitor	Amino acids, peptides, and analogues	Carboxylesterases (CES)	Perpetrator, avoid with CYP3A4 substrates; Victim, avoid with short-acting octreotide	Feces (major, 97%)
Orilissa (Elagolix sodium/PO)	Small Molecule	Pain associated with endometriosis	2018/AbbVie/P	GnRH receptor antagonist	Amino acids, peptides, and analogues	CYP3A (major) Minor pathways include: CYP2D6, CYP2C8, and uridine glucuronosyl transferases (UGTs)	Perpetrator, avoid with CYP3A inducers, CYP2C19 and P-gp substrates	Feces (major, 97%)
Akynzeo (Fosnetupitant and palonosetron/IV)	Small Molecule	Chemotherapy-induced nausea and vomiting (emesis)	2018/Helsinn Group/S	Fosnetupitant: selective NK-1 receptor antagonist; Palonosetron: antagonist of 5-HT3 receptors	Fosnetupitant: 1-methylpiperazin-1-ium derivative; Palonosetron: Isoquinolones and derivatives	Fosnetupitant: CYP3A4; Palonosetron: CYP2D6	Victim, avoid use with Strong CYP3A inducers and inhibitors	Fosnetupitant: Urine (3.95%), Feces (70.7%); Palonosetron: Urine (93%), Feces (5%)
Motegrity (Prucalopride/PO)	Small Molecule	Chronic idiopathic constipation	2018/Shire/Takeda/S	Serotonin-4 (5-HT4) receptor agonist	Dihydrobenzofurancarboxamide derivative	94% drug remains unchanged, O-demethylation and oxidation are minor routes	---[a]	Urine (83%), Feces (13%)
Lofexidine (Lucemyra/PO)	Small Molecule	Opioid withdrawal	2018/US WorldMeds/P	α2-adrenoceptor agonist	Dichlorobenzenes	CYP2D6, with CYP1A2 and CYP2C19 (in vitro)	Avoid use with paroxetine	Primary route is via the kidney
Seysara (Sarecycline/PO)	Small Molecule	Acne vulgaris	2018/Allergan/S	Not known	Tetracycline-class drug	Remain unchanged, minor metabolism via O-/N-demethylation, hydroxylation	Victim, avoid use with oral retinoids (tetracyclines), antacids and iron preparations, penicillins, anti-coagulants and P-gp substrates	Both urine and Feces
Oxervate (Cenegermin-bkbj/Ocular)	Protein	Neurotrophic keratitis	2018/Dompé/P, O, B	Recombinant human nerve growth factor	Recombinant human nerve growth factor	Hydrolytic Enzyme	---[a]	-

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Table 10. continued

Brand name (Active ingredient/Route of Administration)	Type of Molecule	Indication	Year of approval/Sponsor/Review classification	Target	Chemical Class	Major Drug Metabolising Enzyme(s)	Drug Interactions	Route of Elimination
TissueBlue (Brilliant Blue G Ophthalmic Solution/Ocular)	Small Molecule	Dye used in eye surgery	2019/Dutch Ophthalmic Research /P, O	Disclosing agent indicated to selectively stain the internal limiting membrane	Benzene-1-sulfonate	---[b]	---[a]	-
Vyleesi (Bremelanotide)/SC	Peptide	Hypoactive sexual desire disorder	2019/Amag/S	Melanocortin receptor agonist	Heptapeptide	Hydrolytic Enzymes	Perpetrator, avoid with oral drugs that depend on threshold concentrations (e.g., antibiotics); Naltrexone	Via urine (64.8%) and feces (22.8%)
Beovu (Brolucizumab–dbll/ intravitreal)	Antibody Fragment	Wet age-related macular degeneration	2019/Novartis /S	Human VEGF inhibitor	Humanized monoclonal single-chain Fv (scFv) antibody fragment	Hydrolytic Enzymes	---[a]	Similar to endogenous IgG
Aklief (Tifarotene/Topical)	Small Molecule	Acne vulgaris	2019/Galderma/S	RAR agonist	Terphenyls	CYP2C9, CYP3A4, CYP2C8	---[a]	Feces
Ibsrela (Tenapanor/PO)	Small Molecule	Irritable bowel syndrome	2019/Ardelyx /S	NHE3 inhibitor	4-Phenyltetrahydroisoquinolines	CYP3A4/5	---[a]	Feces (Major); Urine (minor)
Accrufer (Ferric maltol/PO)	Small Molecule	Iron deficiency anemia in adults	2019/Shield Therapeutics/ S	Iron deficiency	3-Hydroxy-2-methyl-4H-pyrane-4-one iron (III) complex (3:1)	UGT1A6	Victim, avoid with iron products	Urine
Barhemsys (Amisulpride/IV)	Small Molecule	Nausea and vomiting	2020/Acacia/ S	D2 antagonist	Aminobenzamides	---[b]	Victim, avoid with drugs prolonging QT interval and dopamine agonists (e.g., levodopa)	Via urine (74%) and feces (23%)
Pizensy (Lactitol/PO)	Small Molecule	Chronic idiopathic constipation	2020/Braintree Labs/S	Osmotic laxative	Fatty acyl glycosides of mono- and disaccharides	---[b]	Perpetrator, reduce the absorption of concomitantly administered oral medications	-
Dojolvi (Triheptanoin/PO)	Small molecule	Long-chain fatty acid oxidation disorders	2020/Ultragenyx Pharm Inc/S, O	Source of calories and fatty acids	Glycerolipids	Hydrolytic enzymes	Contradicted to co-administer with pancreatic lipase inhibitors	Minimal excretion in Urine

[a]No interaction reported. [b]No information available. [g]NK1: neurokinin 1; LFA-1: lymphocyte function-associated antigen-1; CGPR: calcitonin gene-related peptide receptor; GnRH: gonadotropin-releasing hormone; VEGF: vascular endothelial growth factor; RAR: retinoic acid receptors; NHE3: sodium/hydrogen exchanger 3; D2: dopamine-2; A, accelerated; B, breakthrough; O, orphan; P, priority; S, standard; IV: intravenous: SC: subcutaneous; CYP: cytochrome P450; P-gp: p-glycoprotein; IgG: immunoglobulin G.

estrogen, was approved for the management of pain associated with endometriosis.[156]

Around 70% of the approved small molecules under the miscellaneous category (14 out of 20) followed Lipinski's rule of 5. Evaluation of DDI data of these drugs revealed a majority of them are classified as victims (5 out of 20) when dosed along with CYP3A inhibitors and inducers. Three drugs are classified as perpetrators based on their role of the substrate to P-gp, OATP1B1, and BCRP.

■ ANALYSIS OF APPROVED DRUGS

As per a report by the Global Burden of Disease (WHO), noncommunicable diseases are expected to be responsible for 7 out of 10 deaths in developing nations. Further, stroke, cardiovascular, respiratory, and neurological disorders along with cancer are the major causes of mortality worldwide. In line with the trend of anticancer drugs leading the total number of approvals, the highest number of approved drugs in any single year was also for this dreaded disease (i.e., 16 in the year 2018). Neurological disorders with high unmet medical need accorded the next spot with 11 approvals in the year 2019. Further, considering the ongoing viral pandemic due to Covid-19, drug approvals for infectious and respiratory diseases are expected to rise along with more immunotherapies coming into the market in the foreseeable future.

While the focus of research on large molecules is steadily increasing across the pharmaceutical industry and the number of approvals in this area have increased, the data suggest that during the study period, more than 2/3rd of the approved drugs were small molecules. Approvals for TIDES that include peptides and nucleotides have also increased in the past five years or so, and overall, their contribution is ∼10% of the total approvals. Among the macromolecules, the major share has been taken by mAbs followed by enzymes and oligonucleotides. Most of the biologics have been approved for the treatment of cancer followed by autoimmune and cardiovascular diseases.

An interesting observed trend during the study period was the increased number of approvals with the pricier "orphan drug"

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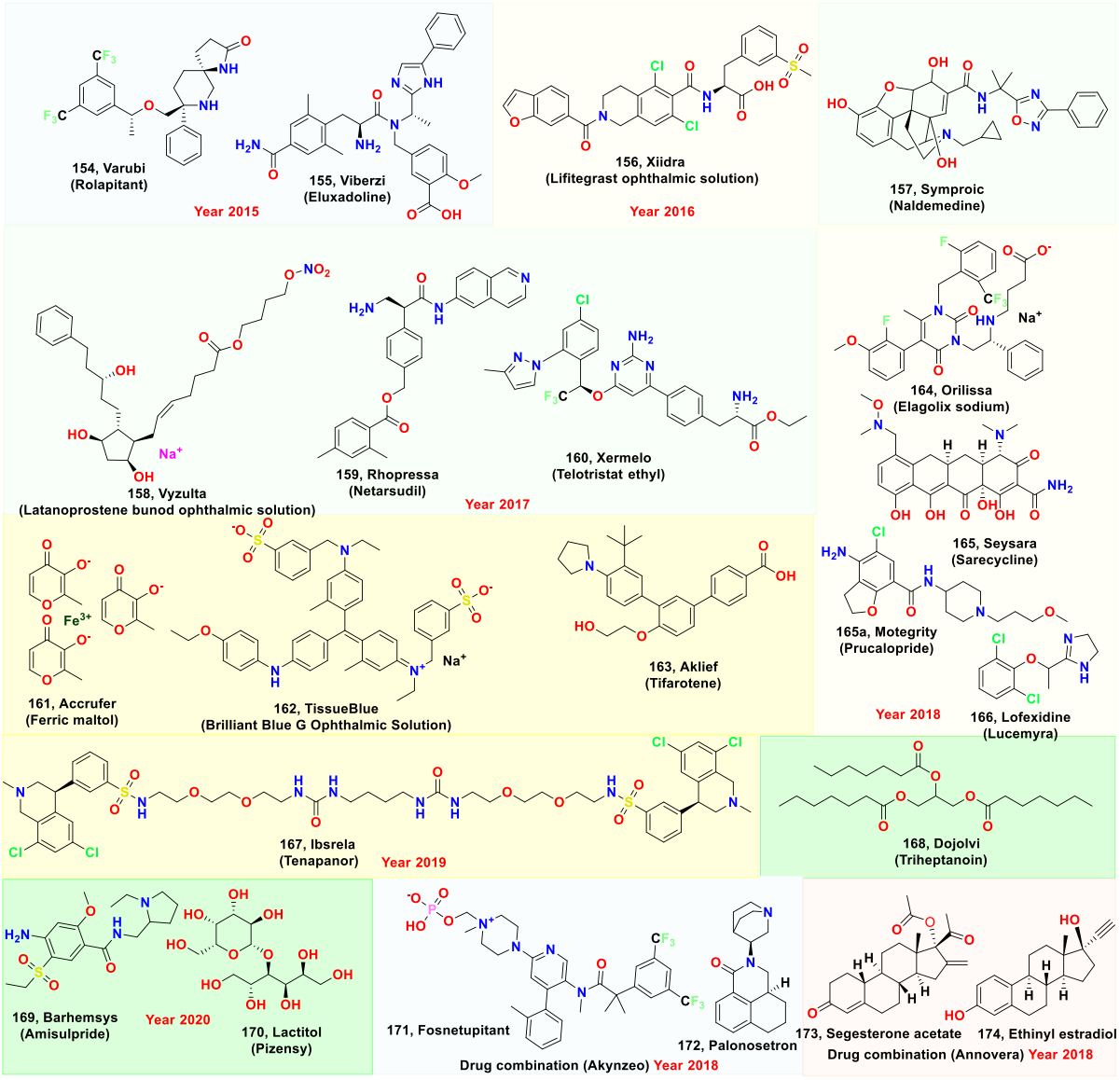

Figure 11. Chemical structures of miscellaneous drugs approved by the FDA from the year 2015 until June 2020.

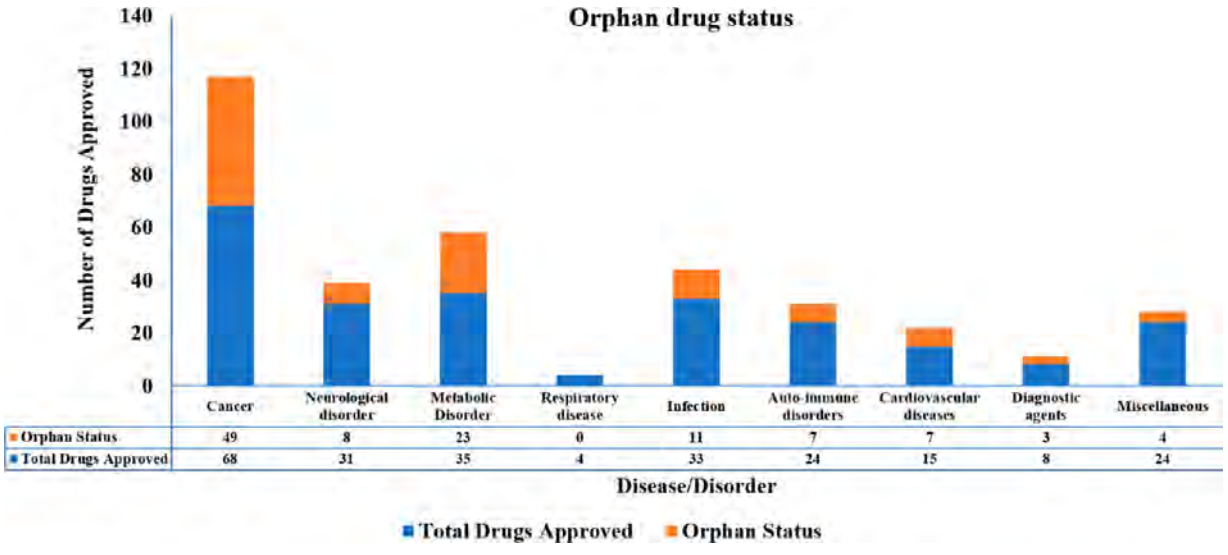

Figure 12. Bar graph represents approved FDA drugs with orphan status from the year 2015 until June 2020.

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tag, which are used for the treatment, prevention, or diagnosis of a rare disease. Until 2015, a total of 281 orphan drugs were approved, consisting primarily of biologics (60%). The number of "orphan drug" approvals during the last five years (total approvals: 106) have almost doubled compared with the preceding five years, that is, 2010−2014 (total approvals: 56). Figure 12 illustrates orphan status versus the total number of approved drugs for different therapeutic areas during the study period. Cancer and metabolic disorders had the maximum number and percent share as orphan drugs.

Further, the major route of administration for the approved drugs during the study period was oral (53%) followed by intravenous (26%) and subcutaneous (14%) routes. Because of ease of administration and increased patient compliance, the oral route continues to be the preferred one. This is in line with a published report which tracked the routes of drug administration for 37 years starting from 1980 to 2017 and concluded that the oral delivery route (62%) makes the largest contribution to pharmaceutical products.[157] With increasing contribution from macromolecules including TIDES in the development pipeline and obvious challenges with the oral delivery of these compounds, the percentage of drugs that can be administered through the oral route has started to show a decline, and the overall trend is expected to remain similar in the near future though. The major route of administration of macromolecules might continue to be subcutaneous or intravenous.

Structural Diversity of Pharmacophores of FDA Approved Drugs. The assessment of 164 FDA approved small-molecule data sets of the last five years (Figure 13)

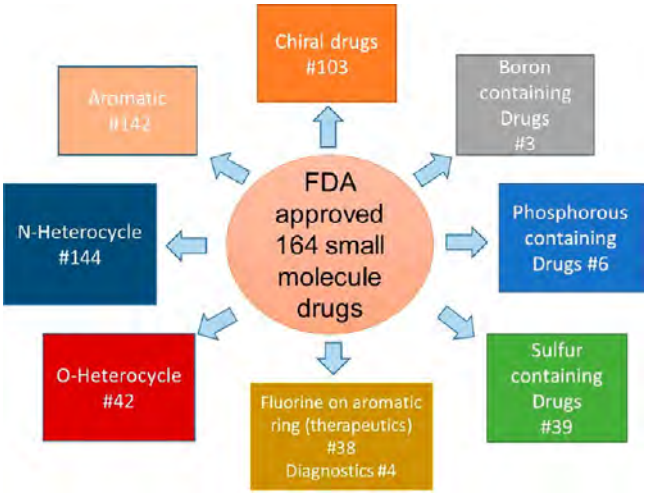

Figure 13. Breakdown of U.S. FDA approved small molecules (2015−June 2020).

indicates a high percentage of N-heterocycles (88%) and aromatic scaffolds (87%), followed by the chiral molecules (63%). The representation of oxygen heterocycles (26%) was less than nitrogen counterparts, and this situation was consistent as observed until 2014[158] and later in 2017.[159] As expected, the share of sulfur-containing drugs (39) was approximately 6.5 times higher than phosphorus counterparts (6), which in turn was 2 times higher than boron counterparts (3). Sulfur was constituted either as sulfate, sulfonate, or a heterocyclic ring system.[160−162] In the recent past, a significant positive effect of fluorine has been observed through its strategic introduction into an aliphatic or aromatic system on drug potency and target selectivity by modulating physicochemical parameters and drug metabolism.[163−166] The authors have noticed that FDA approved 38 drugs containing one or more fluorine atoms on the aromatic ring system (excluding $-CF_3$ or other combination) in the last five years. Further, the ^{18}F isotope owing to its optimum and favorable half-life (109.8 min) as compared to other isotopes such as ^{11}C (20.4 min) and ^{124}I (4.2 days) is better utilized in positron emission tomography (PET).[167] On the basis of this fact, 4 drugs were approved by the FDA but limited to the diagnosis of cancer only. Further, the literature supports that strategic replacement of hydrogen with deuterium in a drug, in general, reduces the metabolism and toxicity, stabilizes unstable stereoisomers, and increases bioactivation and thus could be explored further in addition to elucidation of mechanism. However, the FDA approved only one drug (e.g., **59**) for the treatment of choreas associated with Huntington's disease in the last five years. Pirali et al. recently discussed the possible issues with the development and approvals of deuterium-based drugs in a Perspective.[168] Recently, deucravacitinib (BMS-986165), a selective tyrosine kinase 2 allosteric inhibitor has exhibited the convincing clinical trial results.[169] It is expected that the number of FDA approvals for deuterium containing drugs may rise in the coming years.

Recently, medicinal chemists are engaged in exploring boron-based small molecules owing to Lewis acid properties of boron which makes it reactive toward nucleophiles of enzymes, nucleic acid, and carbohydrates.[170−172] FDA approved three boron-containing compounds: two pertaining to a class of boronic acids (**2** and **117**) and one in the benzoxaborole class (i.e., **127**). Boronic acids act as transition state analogues for enzymes such as proteases and lactamases and therefore are successful in inhibiting them (Figure 14A).[173,174] Ixazomib citrate (**177**), a

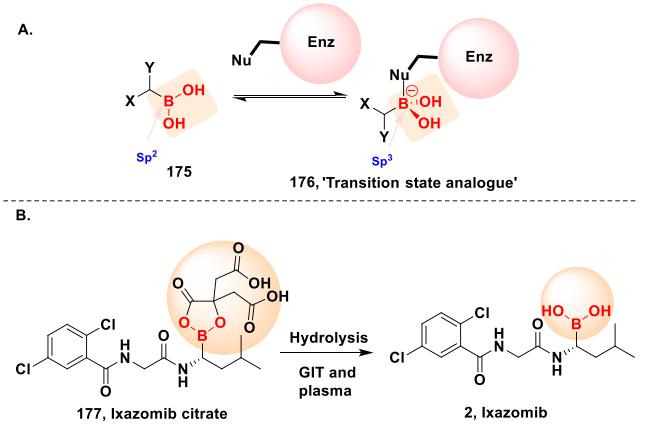

Figure 14. (A) Boronic acids act as transition state analogues for enzymes; (B) Prodrug activation of ixazomib.

citrate ester of boronic acid (prodrug), gets hydrolyzed into free boronic acid metabolite (Figure 14B; **2**), which inhibits proteasome subunit beta type-5 (PSMB5) and produced the anticancer effect.[175]

117 is the first boron-containing non-β-lactam but β-lactamase inhibitor of serine β-lactamases approved by the FDA.[174] The presence of boron provides the ability to "morph" between sp^2 and sp^3 hybridization states, leading to enzyme inhibition.[173] **127** was approved for atopic dermatitis, and chemically it is a benzoxaborole having a boronic acid hemiester with a phenolic ether. The presence of the boron atom facilitates

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its skin penetration. Mechanistically, **127** inhibits PDE4B selectively by binding of boron to the bimetal center of the PDE4B.[176]

Nitro-Containing Drugs. Development of nitro-based drugs especially with nitroaromatic and heteroaromatic compounds is challenging because of the association of mutagenicity and genotoxicity.[177,178] However, discovery scientists were successful in inducing selective toxicity via bioreduction of nitro functionality by enzymes leading to the killing of bacteria, parasites, or tumor cells.[179] The U.S. FDA approved a total of six nitro containing drugs in the last five years. **71**, a nitro-catechol, was approved for the treatment of PD to increase the blood concentration of levodopa. It inhibits COMT and its nitro-catechol motif coordinates with Mg^{2+} ion, and its nitro group is aligned toward protonated Lys144 favoring electrostatic interactions between them.[180] **91**, a 2-nitro-imidazole derivative, was approved for the treatment of Chagas disease using the Accelerated Approval pathway. It is believed to inhibit protozoal growth because of parasite DNA damage induced as a result of electrophilic metabolites produced by reduction of a nitro group by nitroreductases inside the parasite.[181,182] FDA approved **92**, a 5-nitroimidazole compound and structurally similar to metronidazole and tinidazole, as an anti-infective. The mechanism of action is similar to other nitroimidazoles. However, the drug possesses a better pharmacokinetic profile in the class.[183] **106**, a nitroimidazopyran derivative, was approved as an antitubercular against drug-resistant hypoxic, nonreplicating *Mycobacterium tuberculosis* by FDA.[184,185] It disrupts mycolic acid synthesis, which is a major constituent of the cell envelope of the mycobacterium. However, Singh et al. illustrated an alternate mechanism of action via deazaflavin-dependent nitroreductase (Ddn) that reduces the drug (hydride ion transfer as the first step) into the corresponding des-nitroimidazole (**179**, des-nitro; a major metabolite) along with the production of HNO_2. The reduction is unlike single-electron reduction of other nitroimidazoles and is driven by flavin-dependent F420 - nitroreductases (Ddn). The released HNO_2 would quickly decompose into NO and other reactive nitrogen intermediates leading to the killing of mycobacterium (Figure 15).[186] Another NO-releasing drug,

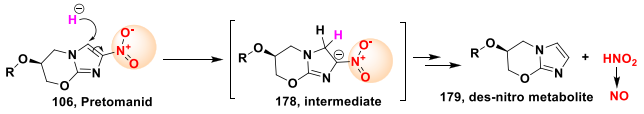

Figure 15. Bioactivation of pretomanid.

158, was approved by the FDA for the treatment of glaucoma. Mechanistically, upon activation by corneal esterases, the drug is transformed into latanoprost acid and butanediol mononitrate, which liberates NO. Latanoprost acid increases humor outflow through metalloproteinase, while NO induces vasodilation.[187] In the anticancer category, **12**, a nitro-containing pyrrolopyridine, was approved for the treatment of CLL or SLL via Bcl-2 inhibition.[188]

Nitrogen Heterocycles. We further evaluated nitrogen heterocycles to learn about their frequency in the FDA approved drugs during the last five years as they share a high percentage in FDA approved data set of small molecules (Figure 16). It was interesting to note that until the year 2014, piperidine and pyridine were the first and second most frequent nitrogen heterocycles, respectively, in the FDA approved drugs.[189]

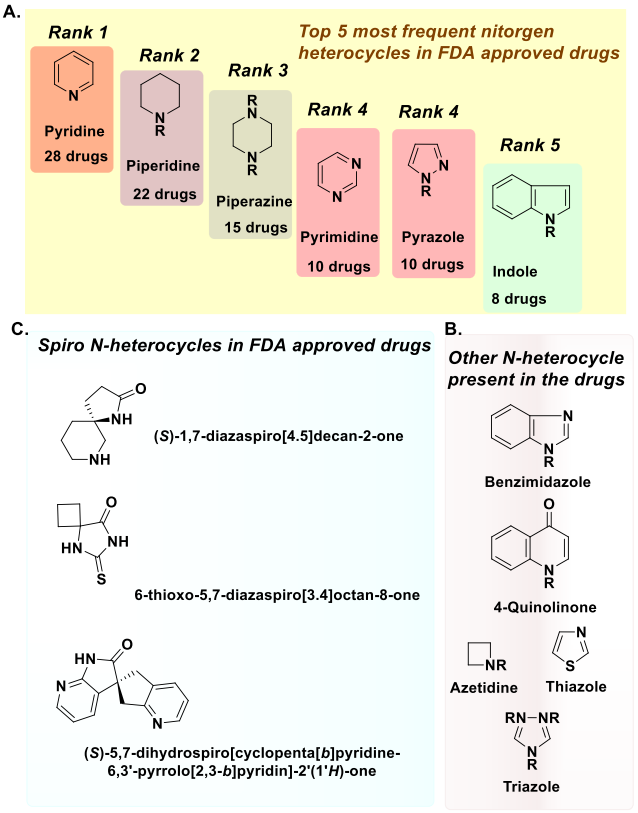

Figure 16. (A) Top five most frequent nitrogen heterocycles in the FDA approved drugs (2015−June 2020); (B) Other common N-heterocycle in the drugs; (C) Spiro nitrogen heterocycles in the drugs.

However, our results reveal that pyridine is the most common nitrogen heterocycle among the small molecules. Piperidine and piperazine are the second and third most common nitrogen heterocycles, respectively. Whereas, pyrimidine and pyrazole hold the fourth position followed by indole (Figure 16A). We further observed that benzimidazole, 4-quinolinone, azetidine, thiazole, and triazole were the next most frequent nitrogen heterocycles (Figure 16B). Hiesinger et al. discussed various synthetic routes, and medicinal chemistry aspects of spirocyclic scaffolds of drug molecules in their recent Perspective.[190] Figure 16C depicts the three important spiro N-heterocycles in the data set of approved drugs.

Analysis of Chemical Space. Next, we analyzed chemical space of FDA approved drugs considering their six molecular properties: molecular weight (MW), topological polar surface area (TPSA), number of rotatable bonds (nROTB), hydrogen bond donors (nHBDon), hydrogen bond acceptors (nHBAcc) and the octanol−water partition coefficient (AlogP), and molecular similarity (Tanimoto coefficient). The analysis was performed using the Platform for Unified Molecular Analysis (PUMA, version 1),[191] and data are compiled in Tables S1−S3 and Figure S1−S3 (see SI).

The MW analysis revealed that anticancer drugs approved in the year 2015−16 have statistically broader distribution (SD: 108.80, 384.78), which further got narrower with the preceding years with a median molecular weight (440−492 g/mol) in 2018−20 as compared with former years. The average mean computed for the MW of anticancer agents was 503.72 g/mol during the analysis period. However, the mean MW was 347.31 g/mol in the case of neurological drugs and was within the range

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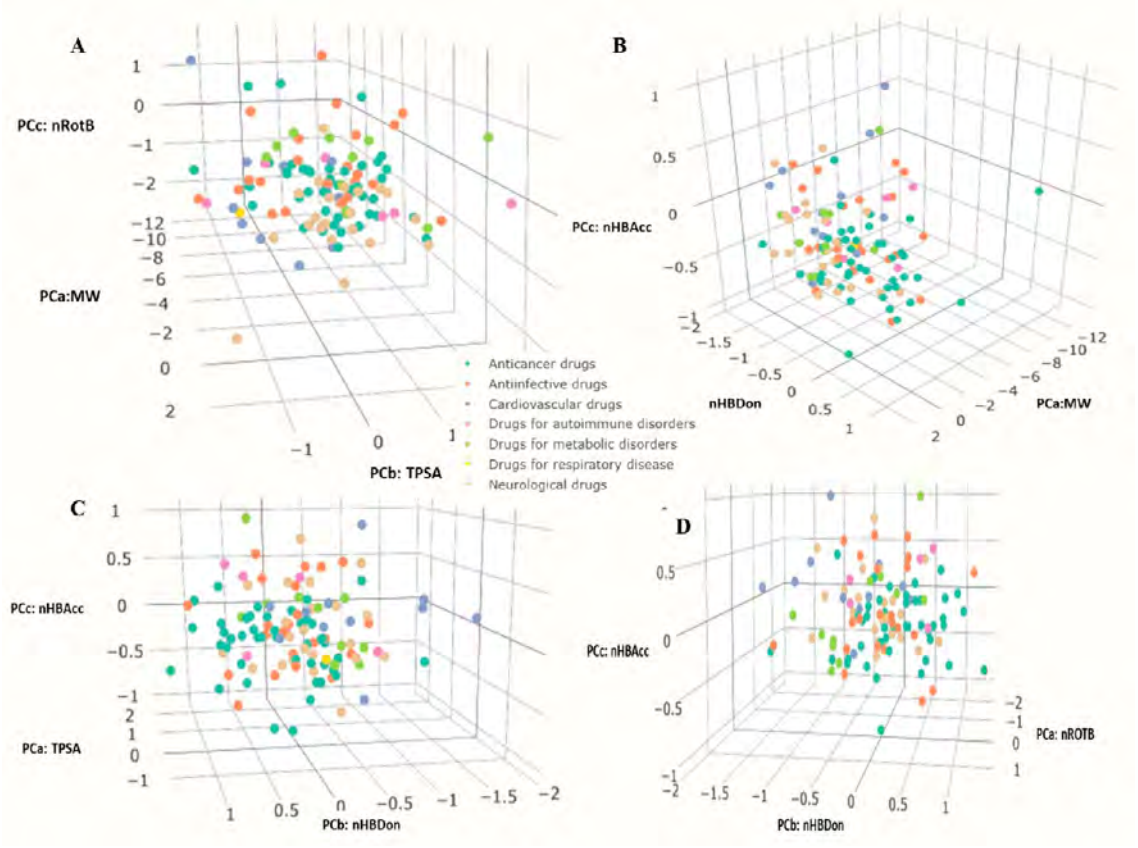

Figure 17. Three-dimensional representation illustrating the outcome of chemical space visualized on PUMA using the "Chemical Space" tab for FDA approved drugs during 2015−June 2020. The 3D graphs signify correlation between (A) MW with TPSA and nROTB, (B) MW with nHBDon and nHBAcc, (C) TPSA with nHBDon and nHBAcc, and (D) nROTB with nHBDon and nHBAcc.

of cut-offs defined by Levin (400 g/mol) and Waterbeemd (450 g/mol) to facilitate BBB penetration.[192,193] Next, the drugs for metabolic disorders also hovered over a range of MW (227−438 g/mol) with an average mean of 365.84 g/mol. Further, only one drug as a small molecule was approved in the respiratory drug (inhalation route) category during the analysis period with an MW of 597.33, which was above the Lipinski cutoff. This could be the reason that high MW drugs are preferred for respiratory diseases to avoid side effects with the CNS.[194] The anti-infective drugs were also found to possess a broad deviation in MW, with an average MW of 478.04 g/mol during the period. Altman's report suggested that most antibiotics with MW of 500 g/mol are susceptible to drug resistance.[195] Newer antibiotics approved by the FDA, particularly in 2015 and 2018, had an average mean MW ranging from 564 to 631 g/mol. Further, the drugs for autoimmune and cardiovascular disorders exhibited a broader MW deviation with a mean MW of 433.11 and 484.78 g/mol, respectively.

Many variants of Lipinski's rule question molecular weight cutoff for ≤500 g/mol and have led to the acceptable variation of the current rule (e.g., Veber rule), which considers the TPSA and nROTB to distinguish between orally active and inactive drugs. According to this rule, compounds meeting the requirement of ≤140 Å^2 TPSA and 10 or fewer rotatable bonds are predicted to possess good oral bioavailability, which could negatively impact intestinal absorption if exceeded.[196] TPSA analysis assists in improving cellular potency, oral absorption, and BBB permeation.[197] The TPSA analysis of anticancer drugs approved during 2015−20 revealed that drugs abide by TPSA norms with an average mean of 103.97 Å^2. Further, TPSA analysis of neurological drugs revealed a value less than 90 Å^2 (recommended for CNS drugs)[198] with an average mean of 66.17 Å^2. Interestingly, TPSA analysis of anti-infective drugs yielded a higher value of 131.88 Å^2 (mean value) than observed until 2014 for marketed antibacterial agents (117 Å^2).[199] This could be correlated with the increased MW of anti-infective agents during this period. Further, cardiovascular drugs possessed a higher TPSA of 140.13 Å^2, increasing their peripheral circulation and avoiding BBB permeability.

The next parameter we considered was nROTB, which estimates drug candidate flexibility and helps determine oral bioavailability.[200] The average mean nROTB was found within the recommended value for all the drug categories analyzed. Next, we analyzed the trend for nHBDon and nHBAcc. Almost all drugs in numerous categories lie within a region of Lipinski-type acceptor and donor values with mean values of 2.33 and 7.88 for nHBDon and nHBAcc, respectively.

Another parameter (i.e., AlogP) was considered over ClogP as it takes into account local hydrophobicity, molecular hydrophobicity maps, and hydrophobic interactions common in drug−receptor complexes. The acceptable range for AlogP lies in between −0.4 to +5.6 as per the Ghose filter.[201] Our analysis revealed an average AlogP of 0.390 for drugs approved during the investigation period. However, neurological drugs exhibited least AlogP (−0.009) because of high permeability requirements and the tendency to cross the BBB.

To deduce the molecular similarity, understand chemical diversity, and fingerprint drugs approved during the analysis

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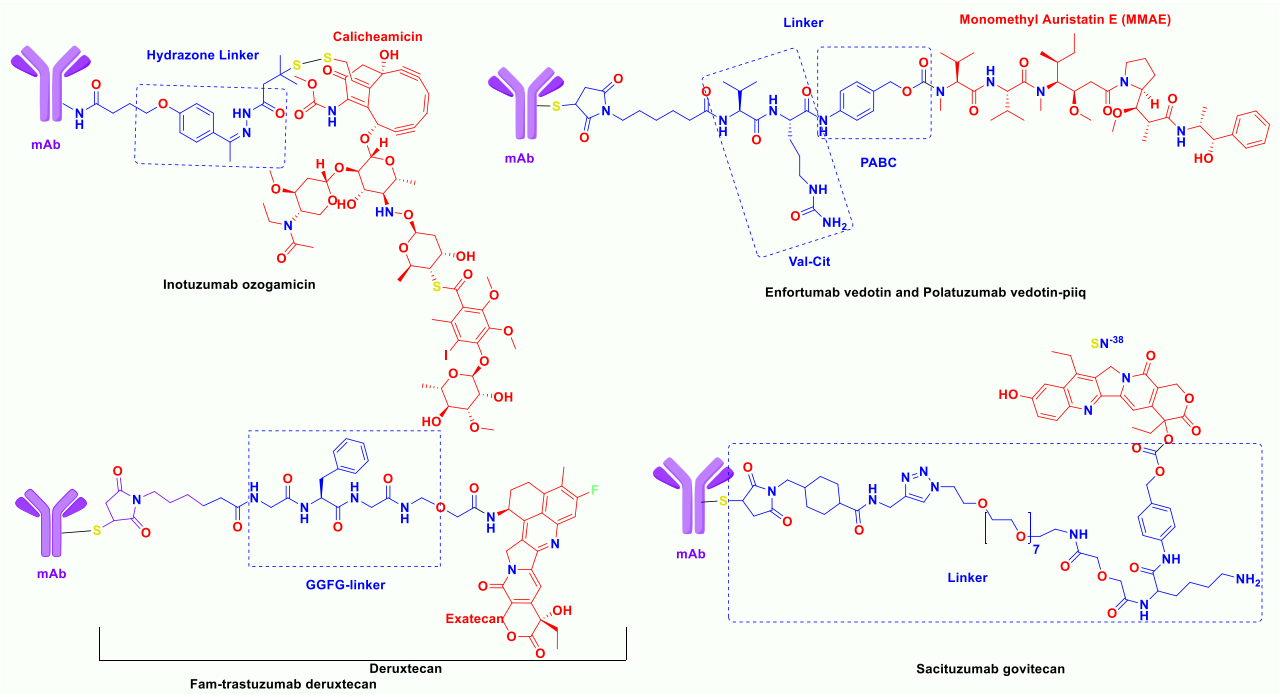

Figure 18. Chemical structures of FDA approved antibody−drug conjugates (2015−June 2020).

period (2015−20), we employed the Tanimoto algorithm (SI; Figure S2). The algorithm is used to compare the chemical structures possessing a similar subset of fingerprints. Two chemical structures are considered similar if they possess the Tanimoto coefficient (T) > 0.85.[202] The analysis of drugs approved in 2015 revealed: anticancer drugs portrayed chemotype similarity with all other drug categories; anti-infectives were found to show similarity with cardiovascular drugs, and metabolic drugs possessed similarity to neurological drugs. The year 2017 witnessed chemotype similarity between anticancer and metabolic disorders drug categories. Analysis of the year 2018 indicated: chemotype similarity of anticancer drugs with drugs for respiratory disorders and anti-infective agents; cardiovascular drugs exhibited similarity with neurological drugs. The year 2019 again witnessed the molecular similarity of anticancer drugs with all other drug categories. Further, drugs approved for metabolic disorders also exhibited high T values with cardiovascular and autoimmune disorders drugs. Considering 2020, high T values were found for anticancer drugs with all other drug categories except metabolic and anti-infective drugs.

Next, we drew a comparison of molecular descriptors based on routes of drug administration of small-molecule drugs. The thorough statistical analysis (SI; Table S2 and Figure S3) revealed that drugs intended for intravenous, inhalation, and intramuscular routes exhibited higher MW with a mean of 599.36, 597.33, and 659.32, respectively. As per data available, the mean MW of orally bioavailable drugs approved until 2014 was 449 g/mol.[203] The data during the current analysis (the year 2015−20) suggested that mean MW increased slightly and was 458.59 g/mol (SI; Figure S3). TPSA analysis revealed that intravenous drugs possessed the highest mean value of 204.83 Å^2. An interesting trend was seen in the AlogP parameter. Drugs administered via topical (0.68), ocular (0.26), inhalation (0.49), and subcutaneous (0.29) routes portrayed higher mean AlogP to avoid their systemic absorption. However, mean AlogP values were less for drugs administered through intramuscular (−1.75) and intravenous (−2.71) routes for their quick and better systemic tolerability.

Furthermore, we observed a good correlation between MW and TPSA (0.802991) and a medium to low correlation in the case of MW and nROTB (0.745) and TPSA and nROTB (0.673) (Figure 17A). The key outliers were lutathera, Ibsrela, giapreza, and venclexta with significantly high values of the descriptors employed (SI, Table S3). The analysis also predicted aristada and vyzulta to possess high nROTB values (>20). A low correlation was observed between MW and nHBDon (Figure 17B; 0.641). However, a good correlation was observed between MW and nHBAcc (0.8581) and nHBDon and nHBAcc (0.750). Next, we explored the correlation of TPSA with nHBDon and nHBAcc. The analysis revealed a strong correlation (Figure 17C) of TPSA with nHBDon (0.842) and nHBAcc (0.912). However, correlations of nROTB with nHBDon and nHBAcc emerged to be 0.580 and 0.697, respectively (Figure 17D). Lutathera and giapreza were found to be major outliers. A low negative correlation was observed in the case of MW with AlogP (−0.4167) and TPSA with AlogP (−0.609). The analysis indicated that high MW drugs were having high values of TPSA and are likely to be absorbed to a lesser extent by the oral route. Further, if the polarity of the drug candidate is reduced, transcellular routes will dominate and improve fractional absorption.

Antibody−Drug Conjugates (ADCs). Further, chemical investigation of five FDA approved ADCs in cancer therapeutic indicated the mAb was conjugated with a cytotoxic compound via a linker (Figure 18). The antibody−drug conjugation was accomplished either through C−S (sacituzumab govitecan, enfortumab vedotin, and polatuzumab vedotin), C−N (inotuzumab ozogamicin), or C−C (fam-trastuzumab deruxtecan) bond formation depending upon the type of linker (6-maleimidohexanoyl linked to the N-amino of Val-Cit, carbon-

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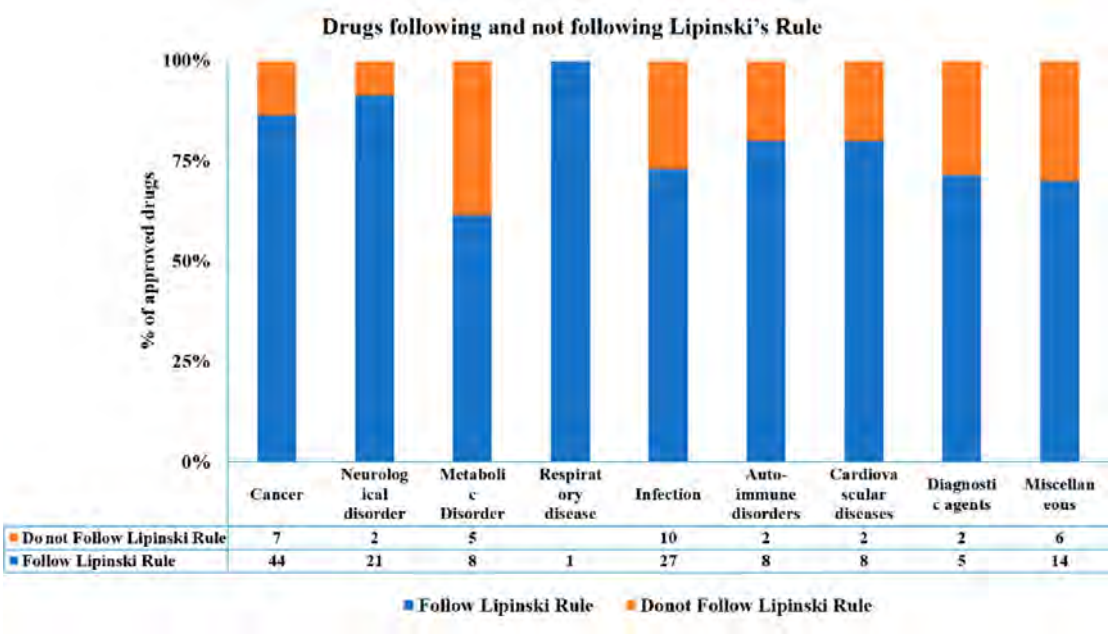

Figure 19. Bar graph represents percent of approved FDA drugs from the year 2015 until June 2020, following and not following Lipinski's Rule.

yl-containing carboxylic acid, or maleimide group in deruxtecan).

Drug-likeness. The approved drugs were analyzed for a parameter usually applied for small molecules to predict the probability for a compound's success during development (i.e., Lipinski's rule of 5 (RO5)). Considering the current study (Figure 19), out of 164 approved small-molecule drugs, more than 3/4th of the approved drugs follow the RO5. This indicates that even after 23 years of its inception, Lipinski's rule continues to be an indicator of the probability of success for a new chemical entity.

Drug Metabolism. Understanding drug metabolism via structure-metabolism relationship studies based on chemical or enzymatic pathways provides ample opportunities to medicinal chemists for performing design strategies to overcome high clearance (e.g., in sonidegib and trifluridine, when a benzylic methyl group is identified as a metabolic soft spot and is replaced with the $-CF_3$ group), using deuterium replacement to further optimize a lead (**59**), and implementing prodrug approaches to circumvent formulation and delivery difficulties (**101** and **50**) for lead optimization with an aim to deliver clinical candidates. These could be either having new chemical templates with bioisosteric replacements or in the form of prodrugs overcoming the issues related to pharmacokinetic, pharmacodynamics, and safety profiles. We summarized few strategies for optimizing metabolism utilized in the discovery of some FDA approved drugs (Figure 20) of the mentioned period. For example, replacement of hydrogen of tetrabenzine (**180**) with deuterium (**59**) offered increased metabolic stability toward CYP2D6, increased half-life, and reduced clearance.[168] Likewise, insertion of the *m*-trifluoromethyl phenyl group (e.g., **96**) in primaquine (**181**) imparted resistance to enzymatic cleavage by CYPs and thus considerably reduced toxicity.[204] Furthermore, several more examples and the strategies utilized for optimizing their metabolism[205−211] are illustrated in Figure 20.

We also attempted to analyze the percentage share of various metabolic enzymes, such as CYPs, UGTs, AO, and so on, involved in the metabolism of the drugs approved from 2015 to June 2020 by the U.S. FDA (Figure 21). CYP-mediated metabolism continues to be the leading pathway for elimination of majority of small molecules.

Only two drugs, **46** and **7**, have been approved in this study period that were metabolized by AO. Because of high interspecies variability and challenges associated with selection of appropriate animal species for toxicology studies, many innovator pharmaceutical companies have tried to avoid progressing any compound for which AO contributes significantly to the clearance.[212] Mostly, nucleases are involved in the metabolism of oligonucleotides, and catabolism continues to be the primary pathway for the elimination of macromolecules.

Prodrugs commonly have functional groups of esters, amides, phosphates, carbonates, or carbamates which are mostly cleaved enzymatically in the body. **133** (a phosphate prodrug; designed to increase solubility of parent) has been approved for the treatment of chronic immune thrombocytopenia and is cleaved through alkaline phosphatase to release the parent, R406.[213,214]

Drug−Drug Interaction Potential. Around the world, a large number of the patient population consumes two or more drugs concomitantly, and hence, there is a possibility of occurrence of DDI. DDIs could be driven by altered pharmacodynamics through the additive, synergistic, or antagonistic therapeutic effect or pharmacokinetics through alteration in inhibition/induction of drug-metabolizing enzymes or transporters.[215]

The term "perpetrator" is used to imply the drug that is responsible for the DDI, while "victim" or "substrate" implies the drug that is being interacted with. In metabolic inhibition, the perpetrator impairs the clearance of the victim drug, systemic exposure increases, and the clinical concern is toxicity. With metabolic induction, clearance of the victim increases, systemic exposure decreases, and the clinical concern is lack of efficacy. Figure 22 depicts data on the number of victims and perpetrators from drugs approved for various therapeutic categories during the study period.

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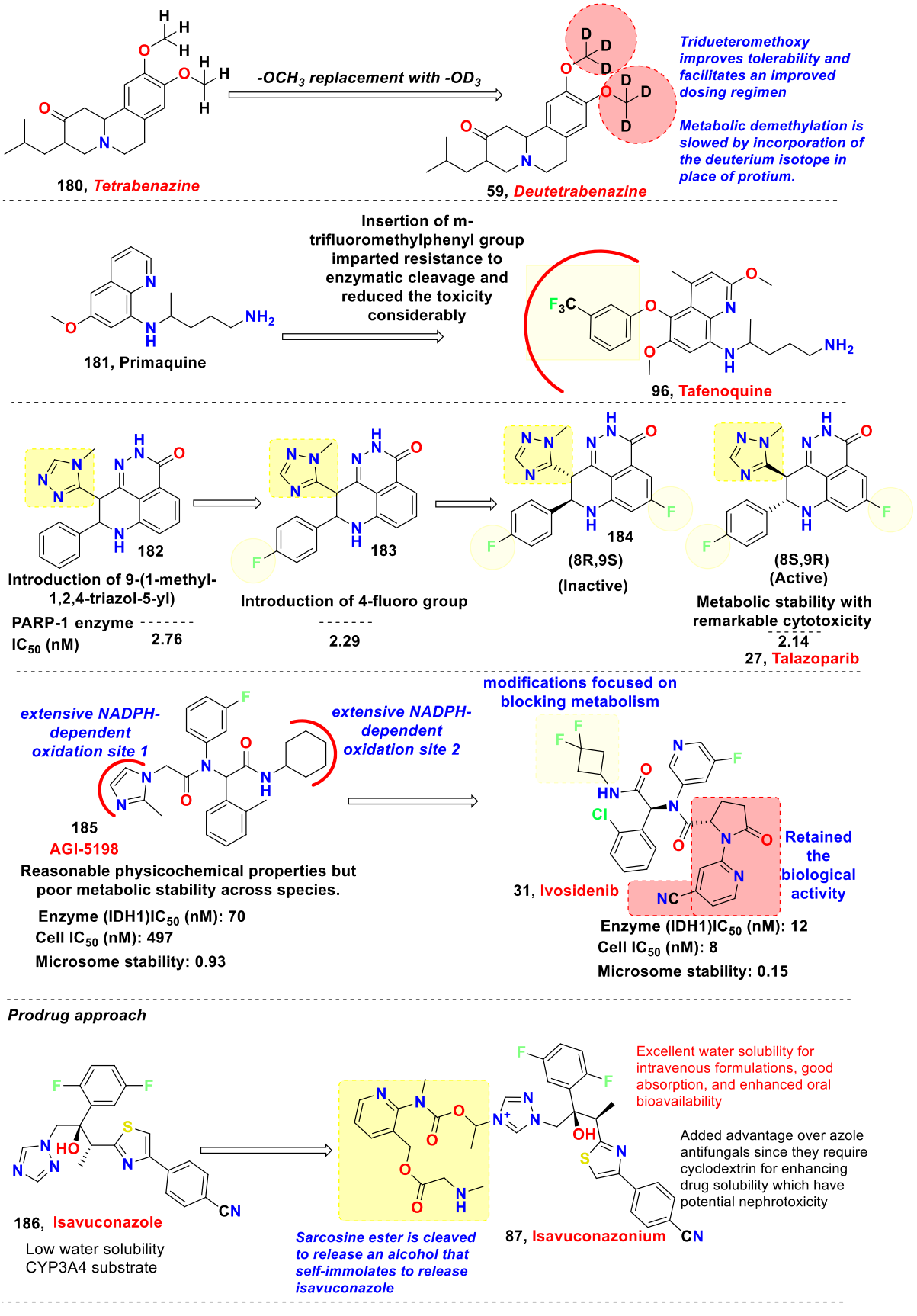

Figure 20. continued

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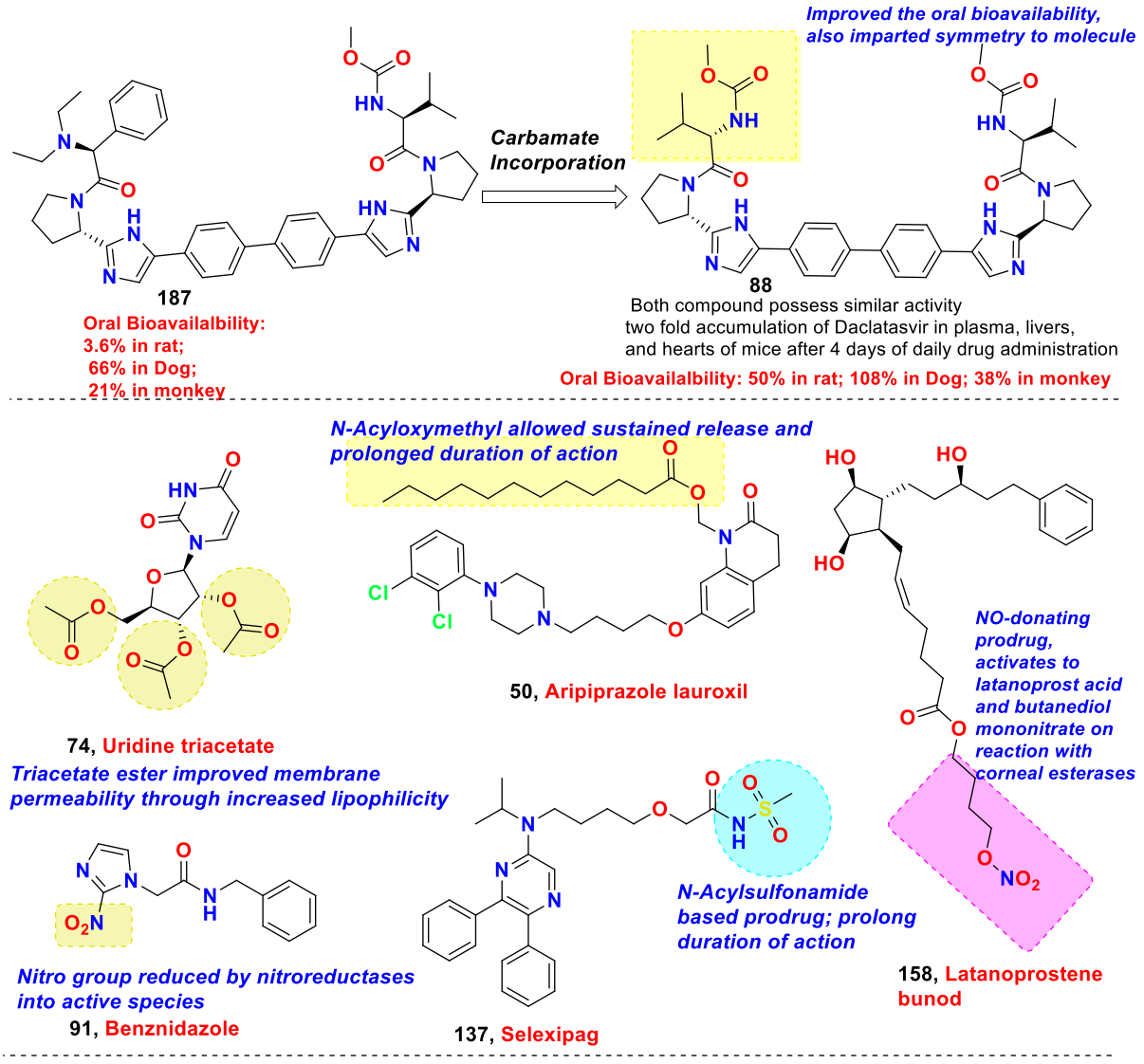

Figure 20. An illustration showing several strategies utilized for optimizing metabolism leading to discovery of clinical candidates.

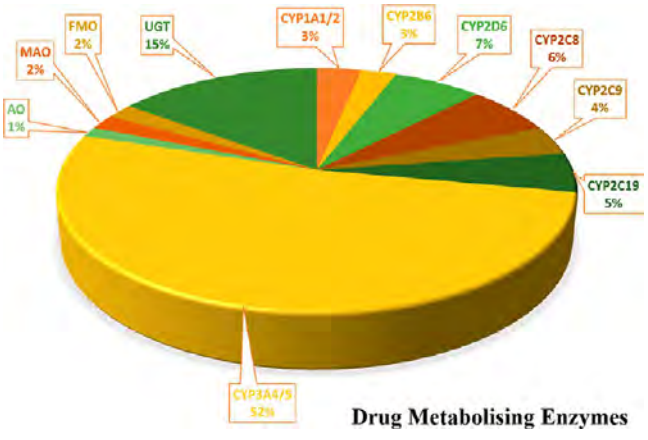

Figure 21. Percentage of the drugs approved in the study period (2015−June 2020) metabolized by various drug-metabolizing enzymes.

Diseases such as cancer, neurological disorders, and infections have a significant number of approved drugs with DDI potential. Moreover, it is pertinent to note here that the majority of the drugs for neurological disorders have a narrow therapeutic window, and hence, the potential impact of DDI could be even higher. One of the challenges with clinical DDI studies that are performed regularly during the new drug development is their inability to decipher all the potential DDIs because of polymorphism of drug-metabolizing enzymes, genetic variations among populations, patient-to-patient variability due to altered physiology, and so on. Terfenadine and cisapride are examples of victims that were withdrawn from the market postapproval due to significant DDIs.[216,217] The classical anticoagulant warfarin is another example of a victim, which is reported to have severe interactions with multiple marketed drugs.[218]

SUMMARY

In conclusion, we have comprehensively discussed the U.S. FDA approved drugs and compiled them according to the year of approval, target, chemical class, Lipinski criteria (for small molecules), and potential DDI liability (perpetrator or/and victim) for the last five years or so. The analysis of drugs indicated that the major share of approved drugs belongs to cancer therapeutics. This could be due to the continuous focus

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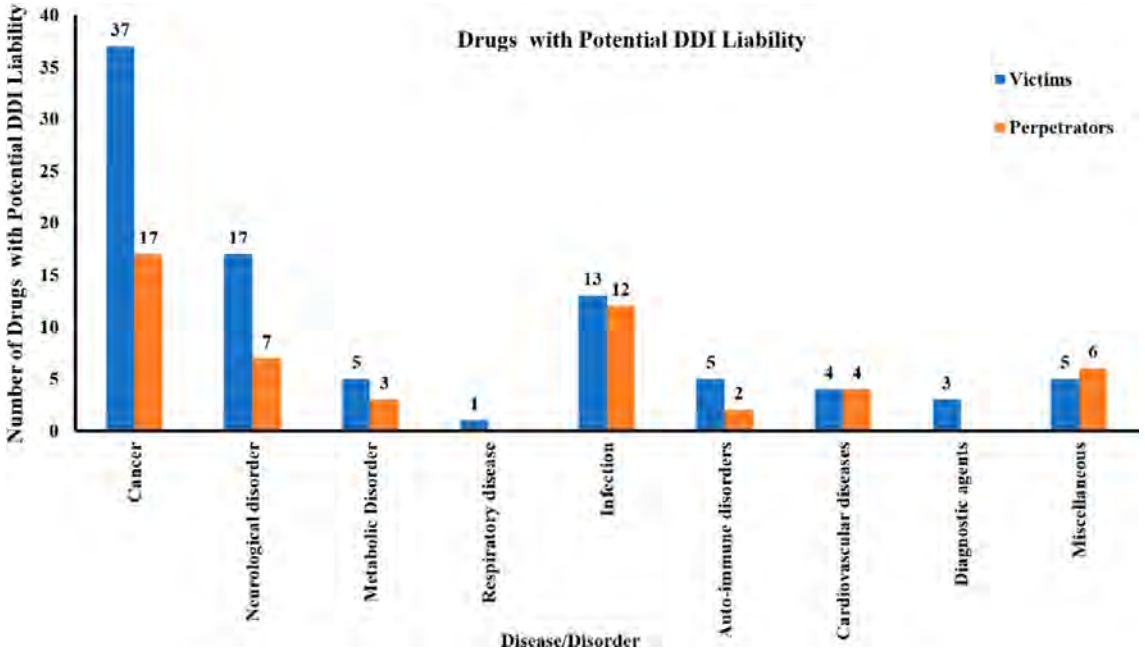

Figure 22. Bar graph represents the share of victims and perpetrators during the study period (2015−June 2020).

on finding the treatment and improving the life expectancy or quality of life for cancer patients. Improved understanding of cancer biology is certainly helpful in finding novel therapies; however, a lot in this area still remains to be understood, especially the spectrum of genetic mutations. Infectious diseases continue to be an area of interest due to the rise of microbial and bacterial resistance and deadly viral diseases such as Covid-19. In the near future, significant efforts are anticipated to be directed in the areas of cancer and infectious diseases. Drugs for the treatment of noncommunicable diseases including but not limited to neurological, genetic, metabolic, autoimmune, and cardiovascular disorders contributed significantly to the approved drugs in the past five years, and because of high unmet medical need in these areas, the trend is likely to continue. Our analysis of structural diversity of pharmacophores revealed that in a data set of small molecules, the percentage and frequency of nitrogen heterocycles continue to rise, of which pyridine is the most common nitrogen heterocycle among the small molecules, followed by piperidine and piperazine. The assessment indicated that drugs with a strategic introduction of groups, such as nitro for inducing bioreductive cytotoxicity, boron for enhancing reactivity toward nucleophiles of enzymes, nucleic acid and carbohydrates or fluorine on aromatic moiety/deuterium for hindering metabolism, induce potency or as diagnostics were approved. The descriptor-based chemical space analysis of FDA approved small molecules could be used for a wide range of endeavors including drug design, drug repurposing, SAR studies, and improving pharmacokinetic parameters. We deliberated approaches that demonstrated a few innovative strategies for optimizing drug metabolism, leading to the drug candidates that could be considered to design new drugs.

Further, the examination of biologics indicated that there had been a rise in approvals of ADCs and TIDES in addition to mAbs, particularly in cancer therapeutics. It is anticipated that the cost of new drug discovery and development will continue to rise, and the median cost is estimated to be upward of USD $2 billion. With a greater number of drugs of biological origin being developed, the cost could go further northwards. Technologies like artificial intelligence and machine learning would help increase the efficiency of the drug discovery engine and make it quicker and cost-effective.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.0c01786.

Tables S1−S3 and Figures S1−S3 (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Atish T. Paul − *Department of Pharmacy, Birla Institute of Technology and Science (BITS) Pilani, Rajasthan 333031, India*; Email: atish.paul@pilani.bits-pilani.ac.in

Raj Kumar − *Laboratory for Drug Design and Synthesis, Department of Pharmaceutical Sciences and Natural Products, Central University of Punjab, Bathinda 151001, India*; orcid.org/0000-0001-5113-6627; Email: raj.khunger@gmail.com, raj.khunger@cup.edu.in

Authors

Priyadeep Bhutani − *Pharmaceutical Candidate Optimization, Biocon Bristol-Myers Squibb R&D Centre, Syngene International Limited, Bangalore 560099, India; Department of Pharmacy, Birla Institute of Technology and Science (BITS) Pilani, Rajasthan 333031, India*

Gaurav Joshi − *Laboratory for Drug Design and Synthesis, Department of Pharmaceutical Sciences and Natural Products, Central University of Punjab, Bathinda 151001, India*; orcid.org/0000-0002-7812-2871

Nivethitha Raja − *Pharmaceutical Candidate Optimization, Biocon Bristol-Myers Squibb R&D Centre, Syngene International Limited, Bangalore 560099, India*

Namrata Bachhav − *1015 E Cozza Drive # 12, Spokane, Washington 99208, United States*

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Prabhakar K. Rajanna − *Pharmaceutical Candidate Optimization, Biocon Bristol-Myers Squibb R&D Centre, Syngene International Limited, Bangalore 560099, India;* orcid.org/0000-0003-0765-8609

Hemant Bhutani − *Pharmaceutical Development, Biocon Bristol-Myers Squibb R&D Centre, Bristol-Myers Squibb India Private Limited, Bangalore 560099, India;* orcid.org/0000-0001-5443-7257

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jmedchem.0c01786

Author Contributions

#P.B. and G.J. contributed equally.

Author Contributions

The manuscript was written with the contribution of all the authors.

Notes

The authors declare no competing financial interest.

Biographies

Priyadeep Bhutani is senior scientist in Pharmaceutical Candidate Optimization (PCO) at Biocon-Bristol Myers Squibb R&D Centre (BBRC), Syngene International Limited, Bangalore, India. She earned Masters of Pharmacy from Panjab University, Chandigarh. She has 15 years of industrial research experience in the area of DMPK and preclinical bioanalysis and is currently pursuing Ph.D. from Department of Pharmacy, Birla Institute of Technology and Science (BITS), Pilani, India.

Gaurav Joshi received his Ph.D. in Medicinal Chemistry at Central University of Punjab, Bathinda, India with Professor Raj Kumar. The area of his interest is the development of small molecules as inhibitors of numerous oncological targets.

Nivethitha Raja received the veterinary medicine degree from Tamil Nadu Veterinary and Animal Sciences University in 2016. She currently works at Department of Discovery Toxicology, PCO, BBRC at Syngene International Limited, Bangalore where she along with her colleagues provide safety assessment of new chemical entities during early discovery. She is specialized in applying novel algorithms to quantitatively measure the end points in preclinical studies and their translatability to humans.

Namrata Bachhav is a freelancer researcher in the field of pharmaceutical sciences in the USA. She graduated with Master in Pharmaceutics degree in 2014 from Marathwada University, Aurangabad, India and thereafter worked for 3 years in analytical research and development (stability) department at BBRC, Syngene International Limited, Bangalore India.

Prabhakar K. Rajanna received PhD in the field of Experimental Pharmacology from Manipal Academy of Higher Education, Manipal in 2007. He has more than 15 years of experience in academic and industrial research in the areas of preclinical & clinical bioanalysis and DMPK. He is currently associated with PCO, BBRC at Syngene International Limited, Bengaluru as Senior Principal Investigator

Hemant Bhutani is Director and Head of Analytical R&D at Pharmaceutical Development, BBRC, Bristol Myers Squibb, Bangalore, India. His team works on analytical and mechanistic aspects of different phases of drug development and life cycle management. His Ph.D. work on antituberculosis fixed-dose combinations with Dr. Saranjit Singh at NIPER, SAS Nagar provided significant input for WHO guidelines on fixed-dose combinations (FDCs).

Atish T. Paul obtained his M.S. (Pharm.) and Ph.D. in Natural Products with Prof. KK Bhutani from the National Institute of Pharmaceutical Education and Research (NIPER), S.A.S Nagar. Thereafter, he joined the research group of Prof. Ikhlas Khan as a postdoctoral fellow at the National Center for Natural Product Research (University of Mississippi, USA). Currently, he is working as Assistant Professor, Department of Pharmacy.

Raj Kumar received his Ph.D. in Medicinal Chemistry at National Institute of Pharmaceutical Education and Research (NIPER), Mohali, India with Professor Asit K. Chakraborti following postdoctoral fellowship with Professor Ramachandra S. Hosmane at University of Maryland Baltimore County (UMBC), MD, where he codiscovered RK-33 molecule as DDX-3 inhibitor for lung cancer therapeutic. He started his independent research career at ISF College of Pharmacy, Moga in 2007. Dr. Raj Kumar is at present working as Professor at Central University of Punjab, Bathinda since 2011.

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■ ABBREVIATIONS USED

ADME, absorption, distribution, metabolism, and excretion; ADC, antibody−drug conjugates; BSEP, bile salt efflux pump; BCS, Biopharmaceutics Classification Scheme; CDER, Centre for Drug Evaluation and Research; CD, cluster of differentiation; DDI, drug−drug interaction; DMEs, drug-metabolizing enzymes; DALYs, global disability adjusted life years; FDA, Food and Drug Administration; Fab, monoclonal antibody fragment; MW, molecular weight; OAT3, organic anion transporter 3; PK, pharmacokinetics; VMAT2, vesicular monoamine

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