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A comprehensive review of discovery and development of drugs discovered from 2020–2022

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ABSTRACT

To fully evaluate and define the new drug molecule for its pharmacological characteristics and toxicity profile, pre-clinical and clinical studies are conducted as part of the drug research and development process. The average time required for all drug development processes to finish various regulatory evaluations ranges from 11.4 to 13.5 years, and the expense of drug development is rising quickly. The development in the discovery of newer novel treatments is, however, largely due to the growing need for new medications. Methods to identify Hits and discovery of lead compounds along with pre-clinical studies have advanced, and one example is the introduction of computer-aided drug design (CADD), which has greatly shortened the time needed for the drug to go through the drug discovery phases. The pharmaceutical industry will hopefully be able to address the present and future issues and will continue to produce novel molecular entities (NMEs) to satisfy the expanding unmet medical requirements of the patients as the success rate of the drug development processes is increasing. Several heterocyclic moieties have been developed and tested against many targets and proved to be very effective. In-depth discussion of the drug design approaches of newly found drugs from 2020 to 2022, including their pharmacokinetic and pharmacodynamic profiles and in-vitro and in-vivo assessments, is the main goal of this review. Considering the many stages these drugs are going through in their clinical trials, this investigation is especially pertinent. It should be noted that synthetic strategies are not discussed in this review; instead, they will be in a future publication.

1. Introduction

Drug discovery and development is a process that involves the identification, optimization, pre-clinical and clinical studies to extensively test and characterize the new drug molecule for its pharmacological properties and toxicity profile (Sleire et al., 2017). After the successful completion of the Human Genome project in 2003, a rough draft of the human genome has been produced, and this has led to an estimated 50 % increase in spending of OECD countries on drug discovery and development (Data, 2017).

During the process of new drug discovery (R&D) ventures in different pharmaceutical industries, researchers are more focused towards the development of new molecular entities (NMEs) and novel dosage forms. Since the 1990 s, there has been a decline in the new drug approval by FDA (Mullard, 2015) probably cause of reduced R&D expenditure on the production of NMEs (Munos, 2009). Moreover, the average time

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duration for all the experiments to complete various regulatory review ranges from 11.4 to 13.5 years (Paul et al., 2010). However, the costs of NMEs are growing at a fast pace with an average financial increment rate of 13.4 % per year and the overall successful accomplishment rate of clinical trials is only about 10 % (Hay et al., 2014; Smietana et al., 2016). The unmet medical needs of patients is one of the major driving forces behind the advancement in the discovery of new innovative drugs (Brown and Wobst, 2021).

There have been fewer new FDA approvals as evidenced by only 22 new drug approvals in 2016 and 46 in 2017 (Mullard, 2018). Afterwards, there has been some promising development in the drug discovery and development process as in 2020 FDA approved 53 new drug molecules including 40 NMEs and 13 biologics license applications (BLAs) which are by far the second-highest count in the past two decades (Mullard, 2021). New advancements in drug discovery and development processes involve the inclusion of in-silico analysis as such CADD-based drug design which includes structure-based design and ligand-based design (Hung and Chen, 2014; Brogi, 2019), high throughput screening, omics technology etc. which has decreased the overall duration of the drug discovery process.

Current advances in scientific exploration leading to identification of various novel mechanisms of drug metabolism as well as expanded diseased populations, the design of new clinical agent have become even more complex; a probable reason of longer and more costly drug development. The use of different types of diagnostic tests which are sometimes named as companion diagnostic tests might help to predict the right patient population and will mitigate the problems of expensive and longer clinical trials (Brown and Wobst, 2021).

In-depth discussion of the drug design approaches of newly found drugs from 2020 to 2022, including their pharmacokinetic and pharmacodynamic profiles and in-vitro and in-vivo assessments, is the main goal of this review. Considering the many stages these drugs are going through in their clinical trials, this investigation is especially pertinent.

2. Brief description

In order to meet the unmet medical need of patients all around the globe, every year new drug molecules are introduced in the market with the potential to treat the particular diseases. Over the years, many revolutionary drugs have been discovered and approved by FDA as in 2017 a total of 46 and in 2020, 53 new drug molecules were approved by FDA (Mullard, 2018; Mullard, 2021).

For the purpose of this review a total of 52 clinical candidates that are currently in different phases of clinical trials were selected. All of the clinical candidates were discovered in 2020–2022 and all passed the aggressive pre-clinical testing. The disease wise total number of drugs is mentioned in Fig. 1. The detailed parameters such as pharmacokinetic (PK), pharmacodynamic (PD) for each drug belonging to each class, along with the IUPAC names of selected drugs are shown in Table 1 and Table 2.

2.1. Anticancer drugs

One of the major classes of the drugs that are in continuous phase of research and development is anti-cancer medications, due to the drastic increase in the cancer cases, scarce curative resources and development of resistance against the existing drugs. The global incidence and mortality of cancer is increasing at a brisk rate. The reasons for this rapidly increased incidence include both age and growth of population along with several changes in prevalence and dispensation of the major risk factors for cancer. Many of the major factors are associated with the socioeconomic development (Gersten and Barbieri, 2020; Fidler et al., 2018). In 2020, according to GLOBOCAN the estimated number of new cases of all types of cancers on global scale is 19.7 million with the worldwide total number of estimated deaths of approximately 10.0 million (Deo et al., 2022).

In this review, the selected 18 drugs are currently in clinical trials in different parts of the world and have passed the phases of drug discovery and pre-clinical processing. The chemical structures of the 18 anticancer drugs are shown in Fig. 2.

2.1.1. BMS-986260

Recently in 2020, a group of researchers at Bristol-Myers Squibb, Princeton, New Jersey, United States designed and synthesized novel imidazole based Transforming growth factor beta 1(TGFβR1) inhibitors which were further optimized for potency, selectivity,

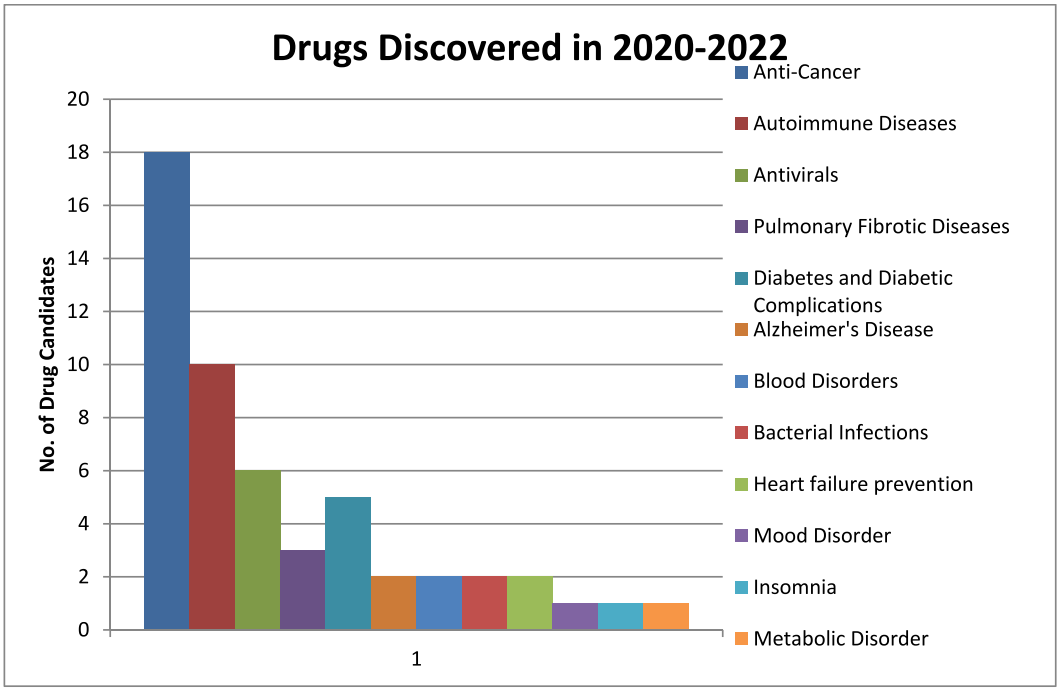

Fig. 1. Drugs discovered in 2020–2022 that are currently in clinical development phase.

Table 1
Shows the Names, IUPAC names, Nature of drug action, study models, Pharmacokinetic (PK) Profile, Pharmacodynamic (PD) profile and the targeted disease(s).

Name of compound	Nature of drug action and target receptor	Study model (s)	Pharmacokinetic (PK) parameters	Targeted Disease (s)	References
BMS-986260	Potent and selective inhibitor of TGFβR1	Mouse MC38 tumor model	**Rat PK profile:** Dose (mg/kg) iv/po = 5/10 Cmax (μM) po = 12.7 $T_{½}$ (h) iv = 5.7 CL (mL/min/kg) iv = 5.6 Vss (L/kg) iv = 2.4	Clinical candidate as Immuno-oncology agent for the treatment of different types of cancers	(Velaparthi et al., 2020)
BAY-069	BCAT1/2 Inhibitor	Female NMRI nude mice	**Mice PK profile:** Dose (mg/kg) iv/po = 0.3/0.6 F % = 89 $T_{½}$ (h) iv = 1.6 CL (L/hr/kg) iv = 0.64 Vss (L/kg) iv = 0.25	Different types of Cancers	(Günther et al., 2022)
MRTX1719	Lethal Inhibitor of the PRMT5•MTA Complex	CD-1 mouse model Beagle dog model	**Mouse PK profile:** Dose (mg/kg) iv/po = 3/30 F % =80 $T_{½}$ (h) iv = 1.5 CL (mL/min/kg) iv = 83 Vss (L/kg) iv = 6.3 **Dog PK profile:** Dose (mg/kg) iv/po = 2/10 F % =59 $T_{½}$ (h) iv = 4.8 CL (mL/min/kg) iv = 14 Vss (L/kg) iv = 3.4	MTAP deleted Cancers	(Smith et al., 2022)
Merck hArg1 inhibitor	Bicyclic inhibitor of human arginase	CL57BL/6 Mice tumor model	**Mice PK Profile** Dose (mg/kg) i.v/p.o = 1.0/10 CL (mL/min/kg) i.v = 10 F % = 7 V_d (L/kg) i.v = 0.84	Cancer	(Mitcheltree et al., 2020)
Constellation EZH2 inhibitor	EZH2 Inhibitor	Mouse Tumor model	**Mouse PK Profile:** Dose (mg/kg) p.o = 25 CL (mL/min/kg) i.v = 3.35 F % = 15 Residence time (h) = 57 **Recommended phase 2 doses > 800 mg BID**	Hematologic malignancies and solid tumors	(Khanna et al., 2020)
Merck IDO1 inhibitor	Heme-Displacing Inhibitors of IDO1	Rat Tumor model	**Rat PK Profile:** Dose (mg/kg) = CL_{int} (mL/min/kg) = 590 V_{du} (L/kg) = 99 MRT (h) = 3.2 Human dose (Projection) = 26 mg QD	Cancer	(White et al., 2020)
AZD4205	Potent and Selective Janus Kinase 1 Inhibitor	NSCLC xenograft NCI-H1975 rat model. (Han Wistar rat male)	**Rat PK Profile:** Dose (mg/kg) p.o/i.v = 10/5 CL (mL/min/kg) i.v = 20 F % = 100 Vss (L/kg) i.v = 8.7 $T_{1/2}$ (h) i.v = 6	Non-small cell carcinoma (NSCLC)	(Su et al., 2020)
GNE-149	Full Antagonist and Efficient Degrader of Estrogen Receptor alpha	Mice In-vivo Xenograft Breast cancer model	**Rat PK Profile:** CL (mL/min/kg) = 19 F % = 31 **In-Vitro rat Profile:** Liver microsome CL (mL/min/kg) = 29 Hepatic CL (mL/min/kg) = 31	ER + Breast Cancer	(Liang et al., 2020)
ONO-8430506	Autotaxin Inhibitor that Enhances the Antitumor Effect of Paclitaxel	Rat breast cancer model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 0.3/1 CL (mL/min/kg) i.v = 8.2 ± 2.3 F % = 51.6 Vss (L/kg) i.v = 1474 ± 153	Breast cancer	(Iwaki et al., 2020)

(*continued on next page*)

Table 1 (*continued*)

Name of compound	Nature of drug action and target receptor	Study model (s)	Pharmacokinetic (PK) parameters	Targeted Disease (s)	References
			$T_{1/2}$ (h) i.v/p.o = 3.4 ± 0.9/2.5 ± 0.3		
BAY 1,895,344	Potent, Highly Selective, Orally Available ATR Inhibitor	Rat cancer xenograft model	**Rat PK Profile:** Dose (mg/kg) = $CL_{biliary}$ (mL/min/kg) = 1.2 F % = 87 Vss (L/kg) = 1.7 $T_{1/2}$ (h) = 1.3	Solid tumors and Lymphomas	(Lücking et al., 2020)
A-1331852	Potent BCL-XL Inhibitor	Rat Cancer model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 5/5 CL (mL/min/kg) = 0.08 F % = 13 Vss (L/kg) = 0.18 $T_{1/2}$ (h) i.v = 3.9	Cancer	(Wang et al., 2020)
AB680	Potent and Selective Inhibitor of CD73	Rat Inflammation model	**Rat PK Profile:** Dose (mg/kg) = 0.5 CL (mL/min/kg) = 0.020 F % = 0.17 Vss (L/kg) = 0.12 $T_{1/2}$ (h) = 5.3	Cancer Currently being evaluated in Phase 1 clinical trials	(Lawson et al., 2020)
BMS-986242	Potent and Selective Inhibitor of Indoleamine-2,3-dioxygenase 1	Mice xenograft model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 0.5/2 CL (mL/min/kg) i.v = 3.70 F % = 127 Vss (L/kg) i.v = 0.97 $T_{1/2}$ (h) = 4	Clinical candidate for Metastatic melanoma and renal cell carcinoma	(Cherney et al., 2021)
Dosimertinib	Potent and Selective Deuterated EGFR inhibitor	Mouse xenograft model	**Rat PK Profile:** Dose (mg/kg) i.v/i.g = 2/6 CL (mL/min/kg) i.v/i.g = 22.3 ± 11.1/ 19.5 ± 5.1 F % = 29.6 $T_{1/2}$ (h) i.v/i.g = 5.40 ± 1.84/ 3.27 ± 0.43	Clinical candidate for Non-small cell lung cancer	(Meng et al., 2021)
JNJ-63576253	Androgen Receptor Antagonist	LNCaP F877L Tumor Xenograft Model	**Mice PK Profile:** Dose (mg/kg) i.v/p.o = 2/10 CL (mL/min/kg) = 15 F % = 45 Vss (L/kg) = 6.11 $T_{1/2}$ (h) = 5.99	F877L Mutant and Wild-Type Castration-Resistant Prostate Cancer (mCRPC)	(Zhang et al., 2021)
TAK-981	SUMO-Activating Enzyme inhibitor	Rat xenograft model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/10 CL (mL/min/kg) = 3.7 F % = 10 Vss (L/kg) = 8.5 $T_{1/2}$ (h) = 2.6	Cancer	(Langston et al., 2021)
Encequidar	Intestine Specific P-glycoprotein Inhibitor	Male Sprague-Dawley rat model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 3/10 F % = 6.25 $T_{1/2}$ (h) = 14.8	Combination therapy with anticancer drugs which have poor oral bioavailability	(Smolinski et al., 2021)
CPI-1612 (compound 17)	Potent and Selective EP300/CBP Histone Acetyltransferase Inhibitor	JEKO-1 tumor mouse Xenograft model	**Mouse PK Profile:** Dose (mg/kg) i.v/p.o = 0.5/2.5 CL (mL/min/kg) = 1.88 F % = 79 Vss (L/kg) = 0.99 $T_{1/2}$ (h) = 1.40	Cancer and inflammatory disorders	(Wilson et al., 2020)
S-217622 (Ensitrelvir)	Non-Covalent Inhibitor of SARS-CoV-2 3C-like Protease	In-vivo mouse model infected with SARS-CoV-2.	**Rat PK profile:** CL (mL/min/kg) = 1.7 Oral F(%) = 96.7 $T_{1/2}$ (h) = 2.4 Metabolic stability = 88 % in liver microsomes	Clinical candidate for Covid-19	(Unoh et al., 2022)
GSK2818713	Hepatitis C NS5A Replication Complex Inhibitor	Huh-luc/neo-ET replicon cells	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/5 CL (mL/min/kg) i.v =	Hepatitis C	(Kazmierski et al., 2020)

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Table 1 (*continued*)

Name of compound	Nature of drug action and target receptor	Study model (s)	Pharmacokinetic (PK) parameters	Targeted Disease (s)	References
			33.8 F % = 9 Vss (L/kg) i.v = 1.3 $T_{1/2}$ (h) p.o = 4.8		
JNJ-53718678	Potent fusion inhibitor of respiratory syncytial virus	Rat model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 2.5/10 CL (mL/min/kg) = 3.9 F % = 42	Lower respiratory tract infections caused by respiratory syncytial virus Currently Under clinical investigation in Phase II studies in both infants and adults	(Vendeville et al., 2020)
GS-9688 (Selgantolimod)	Potent and Selective Oral Toll-like Receptor 8 Agonist	Sprague Dawley Rat model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/5 CL (mL/min/kg) = 1.8 ± 0.2 F % = 8.8 % ± 5.7 % Vss (L/kg) = 1.1 ± 0.0 $T_{1/2}$ (h) = 1.45 ± 0.12	Chronic Hepatitis B Under clinical development for the treatment of CHB.	(Mackman et al., 2020)
Sisunatovir (RV521)	Inhibitor of Respiratory Syncytial Virus Fusion	Balb/C mouse model of RSV infection	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/10 CL (mL/min/kg) = 164 F % = 102 Vss (L/kg) = 22 $T_{1/2}$ (h) i.v/p.o = 1.8/9.9	Lower respiratory tract infections caused by Respiratory Syncytial Virus	(Cockerill et al., 2021)
Cyclic Boronic Acid QPX7728	Ultrabroad-Spectrum Inhibitor of Serine and Metallo-β-lactamases	Neutropenic mouse thigh infection model	**Mouse PK Profile:** Dose (mg/kg) i.v = 10, 100, 300 Dose (mg/kg) p.o = 30, 100, 300 CL (mL/min/kg) i.v = 0.29 ± 0.06, 0.47 ± 0.16, 0.49 ± 0.01 CL (mL/min/kg) p.o = 0.91 ± 0.18, 1.11 ± 0.13, 1.71 ± 0.28 F % = 53.2 ± 3.7, 42.6 ± 4.8, 28.0 ± 4.4 $T_{1/2}$ (h) p.o = 4.40 ± 1.23, 3.23 ± 0.61, 3.65 ± 0.25	A wide range of multidrug resistant Gram-negative bacterial infections	(Hecker et al., 2020)
ETX0282	Diazabicyclooctane Inhibitor of Class A, C, and D Serine β-Lactamases	Murine infection Models	**Rat PK Profile:** Dose (mg/kg) p.o = 11.6 CL (mL/min/kg) = N/A F % = 98 Vss (L/kg) = N/A $T_{1/2}$ (h) = 1.1 ± 0.3	Multidrug resistant and carbapenem-resistant Enterobacterales infections.	(Durand-Reville et al., 2020)
Lanraplenib (GS-9876)	Spleen tyrosine kinase Inhibitor	Spontaneous lupus efficacy model	**Rat PK profile:** Dose (mg/kg) iv = 1.0 Dose (mg/kg) po = 5.0 CL (L/h/kg) = 1.77 Vss (L/kg) = 2.5 $T_{1/2}$ (h) = 3.7 F % = 60	Currently under clinical evaluation for the treatment of different autoimmune diseases such as systemic lupus erythematosus (SLE) and Lupus Nephritis (LN) etc.	(Blomgren et al., 2020)
"Compound 25"	Allosteric inhibitor of RORγt	Acute PD model	**Rat PK Profile:** CL (mL/min/kg) = 13 $T_{1/2}$ (h) = 3.7 Vd (L/kg) = 0.6 F % = 35 %	Under clinical investigation for the treatment of autoimmune diseases	(Zhang et al., 2020)
LOU064 (Remibrutinib)	Potent and Highly Selective Covalent Inhibitor of Bruton's Tyrosine Kinase	Female Lewis Rat collagen induced arthritis model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/3 CL (mL/min/kg) = 44 ± 12 F % = 29 ± 3 Vss (L/kg) = 1.4 ± 0.3 $T_{1/2}$ (h) = 0.5 ± 0.03	Currently being tested in phase 2 clinical studies for chronic spontaneous urticaria and Sjoegren's syndrome.	(Angst et al., 2020)
BMS-986251	Potent, and Selective RORγt Inverse Agonist	Mouse acanthosis and imiquimod-induced models of skin inflammation	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 2/4 CL (mL/min/kg) i.v = 1.3 ± 0.3 F % p.o = 94 Vss (L/kg) i.v = 1.2 ± 0.3 $T_{1/2}$ (h)i.v = 11 ± 0.8	Psoriasis and other inflammatory diseases of skin	(Cherney et al., 2020)

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Table 1 (*continued*)

Name of compound	Nature of drug action and target receptor	Study model (s)	Pharmacokinetic (PK) parameters	Targeted Disease (s)	References
JTE-052 (Delgocitinib)	Janus Kinase Inhibitor	Rat 2,4-dinitrochlorobenzene (DNCB)-induced dermatitis model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/10 CL (mL/min/kg) i.v = 2.1 F % = 78 Vss (L/kg) = 2.1 $T_{1/2}$ β (h) = 1.7	Inflammatory Skin Disorders Recently approved in Japan for the treatment of atopic dermatitis	(Noji et al., 2020)
BAY 1,003,803	Potent non-steroidal glucocorticoid receptor modulator	Female Wistar rat model	**Rat PK Profile:** Dose (mg/kg) = 5 CL_{plasma} (mL/min/kg) = 3 F % = 83 Vss (L/kg) = 7 $T_{1/2}$ terminal (h) = 1.9	Psoriasis and Severe atopic dermatitis	(Berger et al., 2020)
Compound 7f	Antagonists of Toll-like Receptors 7/8/9	Mouse model (Lacking functional TLR8)	**Mouse PK Profile:** Dose (mg/kg) iv/p.o = 3/15 CL (mL/min/kg) i.v = 7.7 F % = 62 Vss (L/kg) i.v = 7.7 $T_{1/2}$ (h) i.v = 32	Autoimmune diseases	(Mussari et al., 2020)
PF-06826647 Ropsacitinib	TYK2 Inhibitor	Imiquimod-induced skin inflammation model Sprague-Dawley rats	**Mice PK Profile:** Dose (mg/kg) = 30 CL (mL/min/kg) = 12 F % = 63 Vss (L/kg) = 1.1	Autoimmune diseases Phase I completed	(Gerstenberger et al., 2020; Tehlirian et al., 2021)
LYS006	Potent and Highly Selective Inhibitor of Leukotriene A4 Hydrolase	Male Wistar Rat inflammation model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/3 CL (mL/min/kg) = 0.662 F % = 56.8 ± 9.0 Vss (L/kg) = 3.29 $T_{1/2}$ (h) = 169	Currently at phase II clinical trial for the treatment of inflammatory acne, hidradenitis suppurativa, ulcerative colitis, and NASH	(Markert et al., 2021)
GLPG1972/ S201086	Potent and Selective ADAMTS-5 Inhibitor	Mouse cartilage explant model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/5 CL (mL/min/kg) = 1.65 F % = 58 Vss (L/kg) = 1.38 $T_{1/2}$ (h) = 0.630	Clinical candidate for the treatment of osteoarthritis	(Brebion et al., 2021)
RO7185876	Highly Potent γ-Secretase Modulator (GSM)	Wistar rat model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/3 CL (mL/min/kg) = 5 F % = 53 Vss (L/kg) = 1.1 $T_{1/2}$ (h) i.v = 3.4	Alzheimer's disease	(Ratni et al., 2020)
Atabecestat (JNJ-54861911)	Thiazine-Based β-Amyloid Precursor Protein Cleaving Enzyme 1 Inhibitor	Sprague-Dawley Rat models	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 0.3/1 CL (mL/min/kg) i.v = 22.8 F % = 55 Vss (L/kg) i.v = 4.46 $T_{1/2}$ (h) i.v = 5.52	Advanced to the Phase 2b/3 EARLY Clinical Trial for the treatment of Alzheimer's disease	(Koriyama et al., 2021)
ORN0829	Potent dual orexin 1/2 receptor antagonist	Rat Insomnia Model	**Rat PK Profile:** Dose (mg/kg) = 1/3 CL (mL/min/kg) i.v = 2370 F % p.o = 5.5 Vd (L/kg) p.o = 853 $T_{1/2}$ (h) = 0.238	Insomnia	(Futamura et al., 2020)
Compound 12	Selective GluN2B Negative Allosteric Modulator	Male Sprague Dawley Rat model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 0.5/2 Dose (mg/kg) p.o = 5 CL (mL/min/kg) p.o = 30 ± 0.9 F % (5 mg/kg) = 132 ±39 Vss (L/kg) (2 mg/kg) = 1.9 ± 0.1	Mood disorder	(Chrovian et al., 2020)

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Table 1 (*continued*)

Name of compound	Nature of drug action and target receptor	Study model (s)	Pharmacokinetic (PK) parameters	Targeted Disease (s)	References
			$T_{1/2}$ (h) (2 mg/kg) = 0.8 ± 0.0		
Nidufexor (LMB763)	Non-bile acid FXR modulator (Agonist)	Murine NASH model	**Rat PK Profile:** **Dose IV** = 3 mg/kg **Dose PO** = 10 mg/kg CL (mL/min/kg) = 5.6 F % = 52 Vss (L/kg) = 0.6 $T_{1/2}$ (h) = 4.4	Under phase 2 clinical trial investigation for the treatment of non-alcoholic steatohepatitis and diabetic nephropathy	(Chianelli et al., 2020)
GNF2133	Selective inhibitor of DYRK1A	Rodent Diabetes model	**Mice PK Profile:** **Dose IV** = 2 mg/kg **Dose PO** = 30 mg/kg **Plasma IV Parameters** CL (mL/min/kg) = 23.5 Vss (L/kg) = 11 $T_{1/2}$ (h) = 6.6 **Plasma P.O** F % = 22.3 $T_{1/2}$ (h) = 3.4	Clinical candidate for Type 1 Diabetes	(Liu et al., 2020)
LSN3318839	Positive Allosteric Modulator of the Glucagon-like Peptide-1 Receptor	Rat hyperglycemia model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/3 CL (mL/min/kg) = 41.9 ± 9.4 F % = 45 ± 14 Vss (L/kg) = 1.6 ± 0.2 $T_{1/2}$ (h) = 2.9 ± 0	Diabetes myelitis (Hyperglycemia)	(Willard et al., 2021)
GCC5694A	Potent and selective sodium glucose co-transporter 2 inhibitor	SD and STZ-rat models	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/5 CL (mL/min/kg) = N/A F % = 77.4 AUC_{inf} (hr.ng/mL) p.o/i.v = 16160.3/4175.0 $T_{1/2}$ (h) p.o = 4.9 $T_{1/2}$ (h) i.v = 4.6	Type 2 Diabetes myelitis	(Kong et al., 2022)
Runcaciguat (BAY 1101042)	Soluble Guanylate Cyclase Activator	Hypertensive rat model NO model of experimental hypertension associated with heart and kidney damage.	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 0.3/0.3 $CL_{biliary}$ (mL/min/kg) = 0.21 F % = 95 Vss (L/kg) = 1.4 $T_{1/2}$ (h) = 7.5	Chronic kidney disease and nonproliferative diabetic Retinopathy	(Hahn et al., 2021)
BMS-986235/ LAR-1219	A Potent FPR2 Selective Agonist	Mouse heart failure mode	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/1 CL_{total} (mL/min/kg) i.v = 49 F % = 67 Vss (L/kg) = 3.0 $T_{1/2}$ (h) p/o = 3.8	Prevention of Heart Failure	(Asahina et al., 2020)
Compound 6f	High Affinity Macrocyclic FXIa Inhibitor	Rabbit electrically-induced carotid artery thrombosis (ECAT) model Rabbit Bleeding model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 0.6/1.2 CL (mL/min/kg) = 10 ± 1.3 F % = 62 Vss (L/kg) = 1.1 ± 0.2 $T_{1/2}$ (h) = 1.7 ± 0.2	Blood clotting (thrombotic diseases)	(Yang et al., 2020)
Compound 19	Hypoxia-Inducible Factor Prolyl Hydroxylase Domain Inhibitor	Anemic Rat Model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/1 CL (mL/min/kg) = 34 F % = 77 Vss (L/kg) = 249	Renal Anemia	(Goi et al., 2020)
Compound 14	APJ Receptor Agonist	Male Sprague-Dawley Rat model	**Rat PK Profile:** Dose (mg/kg) = 3 CL (mL/min/kg) = F % = 77 $T_{1/2}$ (h) = 2.5 ± 0.2	Clinical candidate for heart failure	(Johnson et al., 2021)
X-165 (compound 1)	Autotaxin Inhibitor	Mice and rat models	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/5 CL (mL/min/kg) = 36	Idiopathic Pulmonary Fibrosis Approved by the FDA for a Phase I clinical trial	(Cuozzo et al., 2020)

(*continued on next page*)

Table 1 (*continued*)

Name of compound	Nature of drug action and target receptor	Study model (s)	Pharmacokinetic (PK) parameters	Targeted Disease (s)	References
GLPG2451	CFTR modulator	Beagle dog model	F % = 24 Vss (L/kg) = 1.98 $T_{1/2}$ (h) i.v/p.o = 1.5/1.8 **Dog PK Profile:** Dose (mg/kg) i.v/p.o = 1/1 CL (mL/min/kg) = 0.14 F % = 93 Vss (L/kg) = 2.7 $T_{1/2}$ (h) = 15	Cystic fibrosis	(Van der Plas et al., 2021)
GLPG1205	Unique GPR84 Negative Allosteric Modulator	Mouse dextran sodium sulfate-induced chronic inflammatory bowel disease model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 0.5/5 CL (mL/min/kg) i.v/p.o = 0.7/14 F % = >100 Vss (L/kg) i.v = 1.2 $T_{1/2}$ (h) i.v/p.o = 1/1.9	Inflammatory and fibrotic diseases	(Labéguère et al., 2020)
GDC-0310	Acyl-sulfonamide Na_v 1.7 Inhibitors	Mouse IEM model	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/5 CL (mL/min/kg) = 1.4 F % = 68 Vss (L/kg) = 0.60 $T_{1/2}$ (h) = 5.0	Chronic pain	(Safina et al., 2021)
PF-06835919	Inhibitor of Ketohexokinase (KHK)	Rat Models	**Rat PK Profile:** Dose (mg/kg) i.v/p.o = 1/5 CL_p (mL/min/kg) = 0.358 F % = 95 Vss (L/kg) = 0.20 $T_{1/2}$ (h) i.v/p.o = 7.71/5.7	Clinical candidate for treatment of Metabolic Disorders Driven by the Overconsumption of Fructose	(Futatsugi et al., 2020)

Abbreviations: ADAMTS-5 (A disintegrin and metalloproteinase with thrombospondin motifs 5), APJ (Appelin), ATR (Ataxia telangiectasia and Rad3-related protein), BCAT1/2 (Branched chain amino acid ½), BCL-XL (B-cell lymphoma-extra-large), CFTR (cystic fibrosis transmembrane conductance regulator), CL (Clearance), DYRK1A (Dual-specificity tyrosine–phosphorylation regulated kinase-1A), EGFR (Epidermal Growth factor), EP300/CBP (E1A binding protein p300), EZH2 (Enhancer of zeste homolog 2), F (Bioavailability), FPR2 (Formyl Peptide Receptor 2), FXR (Farnesoid X Receptor), GluN2B (Glutamate N2B receptor), GPR84 (G-Protein coupled receptor-84), GSM (Gamma Secretase Modulator), IDO1 (Indoleamine-2,3-dioxygenase-1), KHK (Ketohexokinase), MTAP (methylthioadenosine phosphorylase), NS5A (Nonstructural protein 5A), PD (Pharmacodynamics), PK (Pharmacokinetics), RORγt (Retinoic acid-related orphan receptor gamma-t), SUMO (Small ubiquitin-related modifier), $T_{1/2}$ (Half Life), TGFβR1 (Transforming growth factor beta receptor 1), TLR (Toll like receptors), TYK2 (Tyrosine Kinase 2), Vss (Steady state volume).

pharmacokinetic (PK) and physiochemical features. Out of many compounds that were screened via structure activity relationship (SAR) study, a robust and selective TGFβR1 inhibitor called as BMS-986260 was recognized from a singular imidazole containing imidazo-pyridine lead and the chemical structure for the drug candidate is shown in Fig. 2. The primary objective of the mentioned SAR studies was to improve the efficacy, PK profile and solubility profile of the drug candidate as seen in Table 1 and 2**.**

BMS-986260 was found to be orally efficacious in mouse MC38 tumor model, when given in combination with anti-programmed cell death protein 1 (anti-PD-1) antibody remedy. However, the drug was found to impart cardiovascular toxicities in preclinical studies which were due to the continuous dosing intervals. In order to reduce those, a dose break schedule was explored which was proved to be effective. An intermittent dosing interval of alternate days in a week in a single month provided comparable efficacy. Moreover, currently BMS-986260 is being evaluated as the clinical candidate as an immune-oncology agent for the treatment of different types of cancer (Velaparthi et al., 2020).

2.2. Antiviral drugs

The year 2019 marked the beginning of a global pandemic in the form of Covid-19 and since then millions of people have been infected by the virus and many have lost their lives to the deadly pathogen. The drugs to treat Covid-19 have been of paramount importance in order to combat the deadly disease (Miller et al., 2020)**.** Since then many pharmaceutical companies are spending millions of dollars in exploration of lead compounds for the treatment of Covid-19.

Other viral diseases like hepatitis B, C and respiratory syncytial virus are also among high burden viral diseases worldwide. According to WHO in 2019, the global total estimated number of hepatitis B cases are approximately 296 million with estimated 1.5 million new infections every year (Schmit et al., 2021; Organization, 2017). The chemical structures and detailed parameters are shown in Fig. 3 and Table 1 and 2**.**

2.2.1. S-217622 (Ensitrelvir)

In the early phases of the drug discovery program, almost all of the already known inhibitors were peptide substrate mimetic compounds which attain covalent warheads such as some electrophilic groups that bound covalently with the Cys145 in the active site of $3CL^{pro}$. Virtual screening with the help of CADD models followed by the biological screening produced numerous hit compounds with varying IC_{50} values. Out of those potential hit molecules, X-ray co-structure, Structure based drug design (SBDD) based optimization led to the production of above mentioned drug with > 600 fold increase in activity and excellent PK profile. S-217622 showed a good pre-clinical profile as a once-daily oral medicinal drug for the treatment of Covid-19. With a prolonged in vivo half-life in monkeys and dogs, spectacular oral bioavailability, and good activity in an in vivo mouse model infected with SARS-CoV-2, the

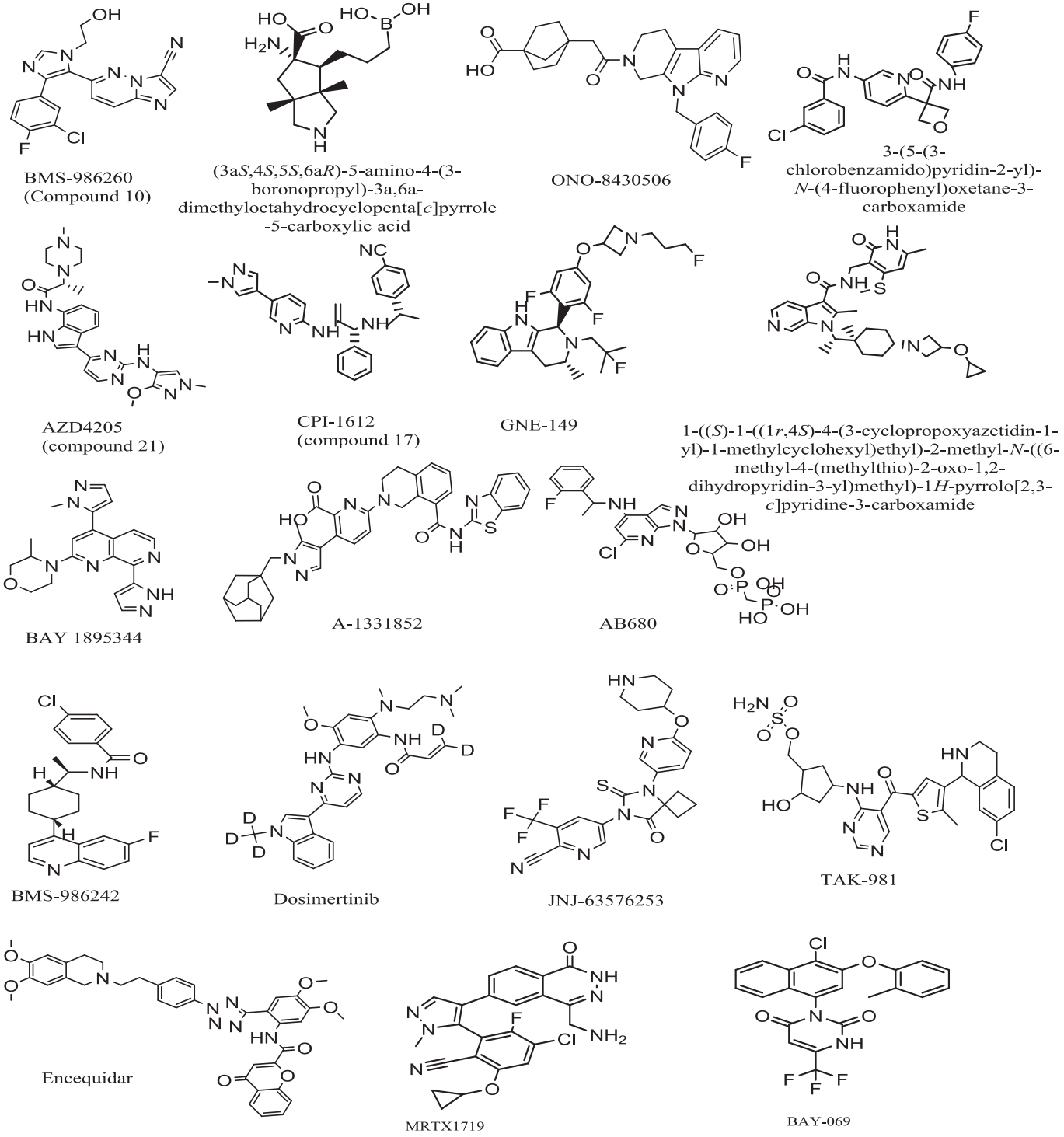


Fig. 2. The chemical structures of the anti-cancer drugs discovered in 2020–2022.

therapeutic molecule exhibits promising antiviral properties against all known variants of concern (Unoh et al., 2022).

2.3. Antibacterial drugs

Antibacterial resistance is one of the most important problems in several developing nations but now it is becoming a severe concern in many developed countries which may be due to the poor distribution and over the counter accessibility of antibacterial drugs (Croft et al., 2007). In this modern era, there is an evident necessity for novel antibacterial drugs without cross-resistance properties. However, antibacterial research and development is slow and scarce which ultimately fails to provide the novel antibacterial drugs to counteract the rapidly emerging MDR bacteria (Theuretzbacher, 2013). However, some novel drugs have also been discovered recently and are currently in clinical development processes. The structures of recently discovered antibacterial drugs are shown in Fig. 4.

2.3.1. ETX0282

ETX1317 is a novel drug which retains the antibacterial potency of

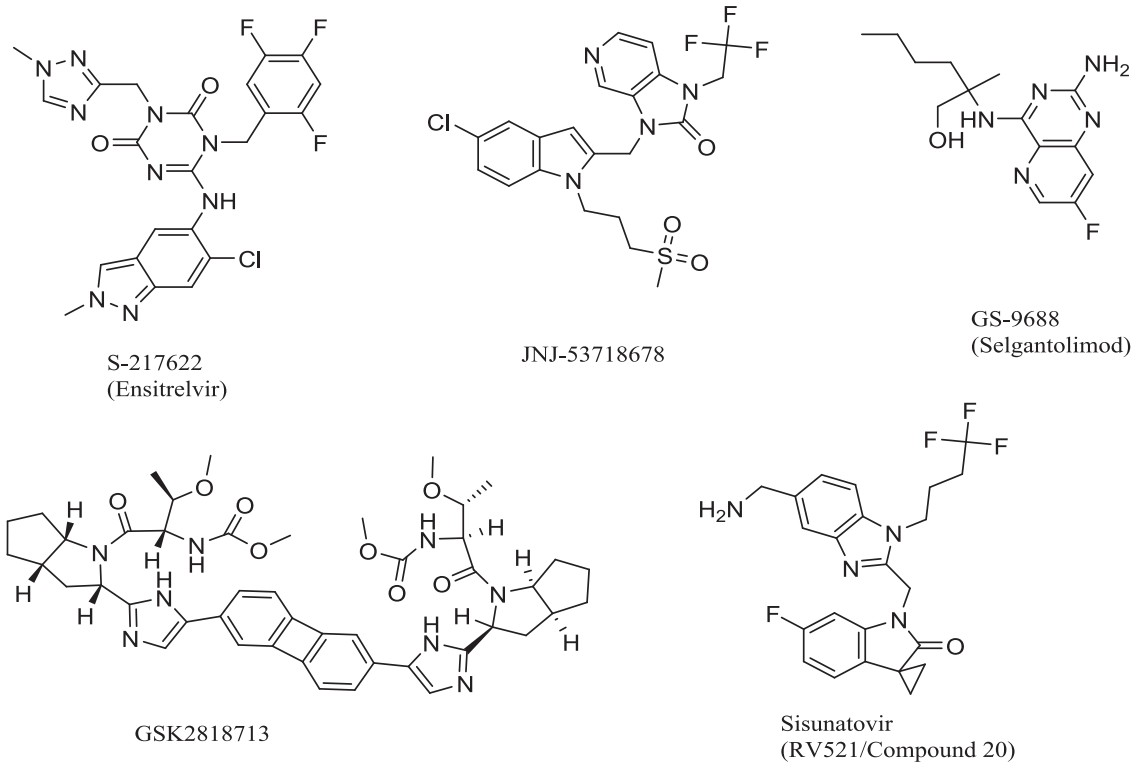


Fig. 3. The chemical structures of the anti-viral drugs discovered in 2020–2022.

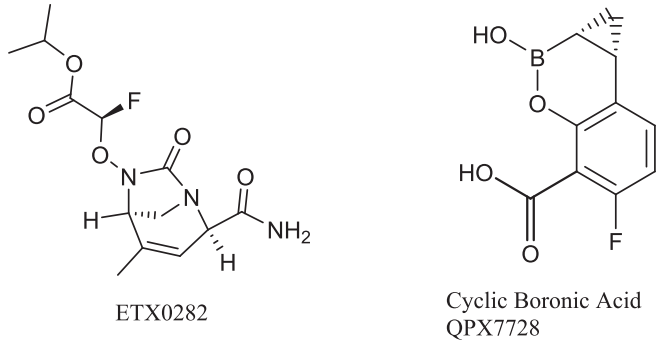


Fig. 4. The chemical structures of the antibacterial drugs discovered in 2020–2022.

durlobactam and is a broad spectrum inhibitor of Class A, C and D serine beta lactamases. In order to improve the oral bioavailability of the drug, an ester modification was done and the drug was converted to a prodrug called ETX0282. The clinical use of the drug is currently limited to β-lactamase resistance. The prodrug was tested in combination with cefpodoxime and proxetil and showed good efficacy in murine models with comparable tolerability in pre-clinical studies. ETX0282 in combination with cefpodoxime and proxetil is currently in clinical development for the treatment of several infections caused by Enterobacterales, including multidrug-resistant (MDR) and carbapenem-resistant Enterobacterales (CRE). Moreover, the synergistic effects of ETX0282 could be seen if administered with orally available β-lactam antibiotics. This combination would be beneficial against non-fermenter highly resistant and potentially problematic pathogens such as Gram-negative species including (Pseudomonas aeruginosa and Acinetobacter baumannii (Durand-Reville et al., 2020).

2.4. Autoimmune diseases

Autoimmune disorders are also considered as multi-factorial diseases because both host genes and the environment play a significant part in the initiation and progression of the disease. They usually affect the overall reactivity and quality of cells of the immune system thereby, enhancing the susceptibility towards autoimmunity (Marrack et al., 2001). Approximately 7.6–9.4 % of the global population is affected by one of the several autoimmune diseases. Although considered as rare diseases, the overall global prevalence of autoimmune diseases is increasing due to unknown reasons (Cooper et al., 2009).

Several drugs are in the R&D pipeline with some of the drugs emerging as the clinical candidate for a variety of autoimmune diseases. The chemical structures and PKPD parameters of the newly discovered drugs are shown in Fig. 5 and Table. 1 and 2.

2.4.1. Lanraplenib (GS-9876)

Lanraplenib is a second generation Spleen Tyrosine kinase (SYK) inhibitor, which was designed to possess human pharmacokinetic parameters appropriate for once daily administration. Lanraplenib was also designed in such a way that it should not have any drug interaction with proton pump inhibitors (PPIs). Lanraplenib is suggested to be a strong inhibitor of downstream signaling of B-cell receptors and causes reduction in the expression of markers such as CD86 and CD69 that are usually involved in the cell-surface activation. Lanraplenib also causes the reduction in release of pro-inflammatory cytokines from human macrophages initiated by the formation of immune-complexes. Furthermore, the T-cell proliferation assay showed very good activity in an Edu incorporation assay. Moreover, after testing in subjects individually and in combination with omeprazole, it was concluded that there is no impact of pH on the retention of the drug. Lanraplenib is currently under clinical evaluation for the treatment of different autoimmune diseases such as systemic lupus erythematosus (SLE) and Lupus Nephritis (Blomgren et al., 2020).

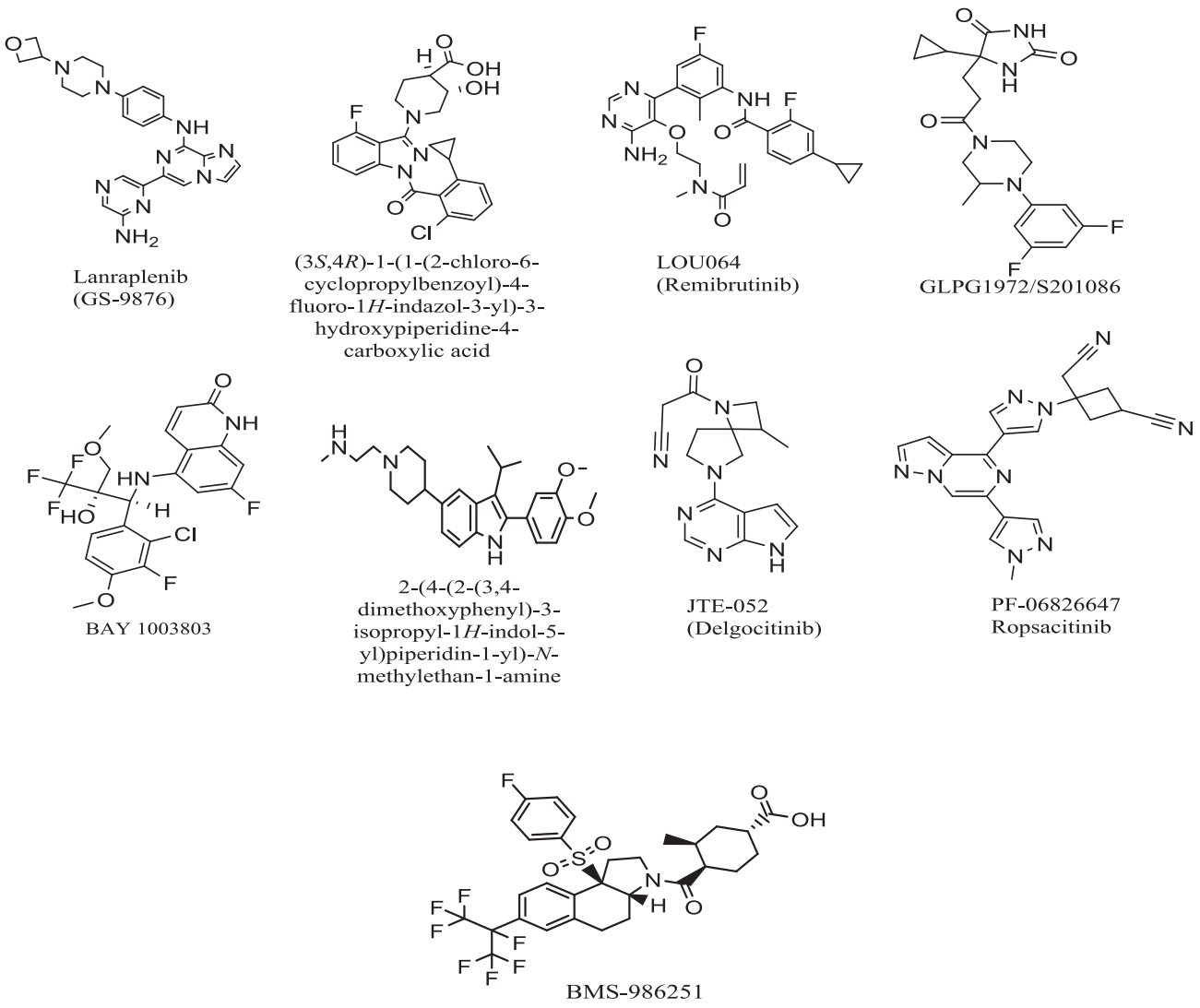


Fig. 5. The chemical structures of the drugs for autoimmune diseases discovered in 2020–2022.

2.5. Alzheimer's disease

Alzheimer's disease is a progressive neuro-degenerative disease which is accompanied by dementia and in severe cases inability to carry on conversation and response to environment. Furthermore, according to NCBI the global prevalence of Alzheimer's disease has been estimated to be 24 million. Moreover, the direct cost in patients with no comorbidity is around US$526 and in patients with comorbidities is around US $10435 (Zhu and Sano, 2006). The most prominent pathological features that are observed in Alzheimer's disease are Amyloid β-plaques that are catalyzed by an enzyme called the β-secretase and intracellular aggregation of hyper-phosphorylated Tau (tau-proteins) in the form of neurofibrillary tangles (Winblad et al., 2016).

Currently only a few drugs have been proved to be successful in modulating the pathologies and some of them are still in clinical development phase. The chemical structures and PKPD parameters of the newly discovered clinical candidates for the treatment of Alzheimer's disease are shown in Fig. 6 and Table. 1 and 2.

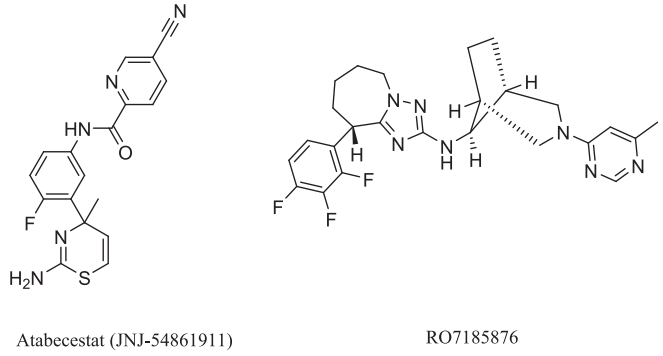


Fig. 6. The chemical structures of the drugs for Alzheimer's diseases discovered in 2020–2022.

2.5.1. RO7185876

RO7185876 is a novel, potent and selective modulator of γ-secretase that belongs to a novel chemical class known as the triazolo-azepines which was discovered as a result of extensive lead optimization program. The compound demonstrated excellent in-vitro and in-vivo efficacy in the modulating γ-secretase by reducing the amount of potentially pathogenic larger fraction of Amyloid β-peptides (Aβ40) and by elevating the amount of smaller fractions of amyloid β-peptides (Aβ37 and Aβ38) without the modulation of Notch pathway. Moreover, the compound exhibited excellent efficacy in in-vivo pharmacodynamic mouse model and the outcome of toxicological profile studies in two different species necessitates the further clinical development of this

compound. Currently, RO7185876 is in the phases of clinical development for the effective treatment of Alzheimer's disease without the conventional side effects associated with currently available γ-secretase inhibitors (Ratni et al., 2020).

2.6. Insomnia and mood disorder

One of the most prevalent sleep disorders, insomnia, places a heavy strain on the US healthcare system and vulnerable patient populations (Winkelman, 2015). Over $100 billion is spent each year in the United States on the direct and indirect costs of insomnia (Wickwire et al., 2016). Due to its prevalence, insomnia appears to inflict a bigger annual loss of quality-adjusted life years than other physical and mental illnesses like depression, hypertension, and arthritis (Olfson et al., 2018). Between 1993 and 2015, there was an 11-fold increase in the number of patients who were diagnosed with insomnia during office visits, going from 800,000 to 9.4 million (Moloney et al., 2019). The structure of the drug discovered for the treatment of insomnia is shown in Fig. 7.

The emotions, energy, and drive of an individual can all be affected at once by a group of mental conditions known as mood disorders. The subject of this essay is major depressive illness and bipolar disorder, the two most notable cases. The lifetime prevalence of major depressive disorder is 16 % (Kessler et al., 2003) while the lifetime prevalence of bipolar disorder, which includes all individuals on the bipolar disorder spectrum, is close to 5 % (Merikangas et al., 2007). Major depressive disorder is the second most common cause of disability worldwide (Ferrari et al., 2013), whereas depression and bipolar disorders are linked to worse life quality (Papakostas et al., 2004; Michalak et al., 2005) and higher mortality (Brandao et al., 2019; Miller and Bauer, 2014). The structure of the drug discovered for the treatment of mood disorders is shown in Fig. 7.

2.6.1. ORN0829

The extremely effective Dual orexin receptor antagonist 3-benzoyl-1,3-oxazinane ORN0829 was designed by keeping the basic structural features of pyrazolylethylbenzamide and having incorporated the iterative design and compound optimization approaches. The compound showed strong antagonist activity, low lipophilicity, and short half-life pharmacokinetic profile (DORA). The 1,3-oxazinane moiety of ORN0829 possesses a unique structure that might be essential for generating the bioactive U-shaped conformation of the molecule and subsequently lowering the lipophilicity. ORN0829 demonstrated potent sleep-inducing effects in a rat polysomnogram investigation at oral dosages as low as 1 mg/kg, and it displayed optimal PK characteristics in rats and dogs, including a rapid Tmax and brief half-lives, predicting an anticipated human half-life of 0.9–2.0 h. ORN0829 is now being developed as a clinical candidate for the efficient treatment of insomnia in light of its preclinical findings as a potent hypnotic with a low risk of next-day sleepiness (Futamura et al., 2020).

2.7. Diabetes and diabetes related complications

Insufficient insulin production and the resulting hyperglycemia are hallmarks of type 1 diabetes, a chronic autoimmune illness (DiMeglio et al., 2018). The rising prevalence of diabetes mellitus, which throws overwhelming burdens on patients, those who care for them, treatment centers, and society at large, is a significant public health concern. The most recent estimates indicate that there were 425 million cases of diabetes worldwide in 2017 and that figure is expected to rise to 629 million by 2045 (Forouhi and Wareham, 2019).

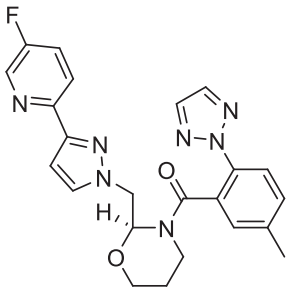
There have been efforts made to find novel drugs that can safely and effectively treat diabetes and the complications that are associated to it. The structures of recently discovered anti-diabetic drugs or drugs used to treat complications related to diabetes are shown in Fig. 8 and their detail is shown in Table. 1 and 2.

2.7.1. GNF2133

The discovery of GNF2133, a powerful and highly specific dual specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A) inhibitor, was made possible by the optimization of 6-azaindole compound screening hit 8a. Enzymatic DYRK1A and GSK3 inhibition measurements, liver microsomal stability, and hERG inhibition served as the basis for SAR studies. GNF2133 was found to increase the number of both rat and human crucial beta-cells in vitro. In comparison to the group that received vehicle treatment, GNF2133 treatment resulted in increased -cell proliferation as well as better pharmacodynamic biomarkers Ki67 and cyclin D1. However, in a 2-week rodent tolerance test GNF2133 also showed proliferation in other tissues, including the exocrine pancreas, liver, heart, and kidney. The results suggested that in order to establish GNF2133 as an oral medicinal drug for beta - cell growth and therapy of type-1 diabetes, new techniques would be required to lessen the hypertrophic effects in tissues other than the pancreas. Clinical trials for GNF2133, a potential drug for the treatment of type 1 diabetes, are currently being conducted (Liu et al., 2020).

2.8. Cardiovascular diseases

The leading cause of hospital admission for cardiovascular conditions in people over 60 is heart failure (Braunwald, 2013). Worldwide, the incidence of heart failure is rising due to population ageing, poorly treated risk factors such obesity, diabetes, and hypertension, and an increase in the prevalence of these conditions (Zannad, 2018).. Heart failure is a clinical illness characterized by exhaustion and dyspnea that is brought on by left (or worldwide) ventricular dysfunction, frequently accompanied by congestion symptoms. The newly discovered drugs for the treatment of cardiovascular diseases such as heart failure and



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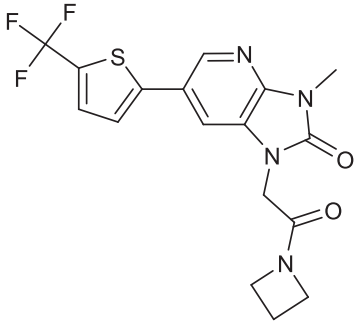

1-(2-(azetidin-1-yl)-2-oxoethyl)-3-methyl-6-(5-(trifluoromethyl)thiophen-2-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one

Fig. 7. The chemical structures of the drugs for Insomnia and Mood disorder discovered in 2020–2022.

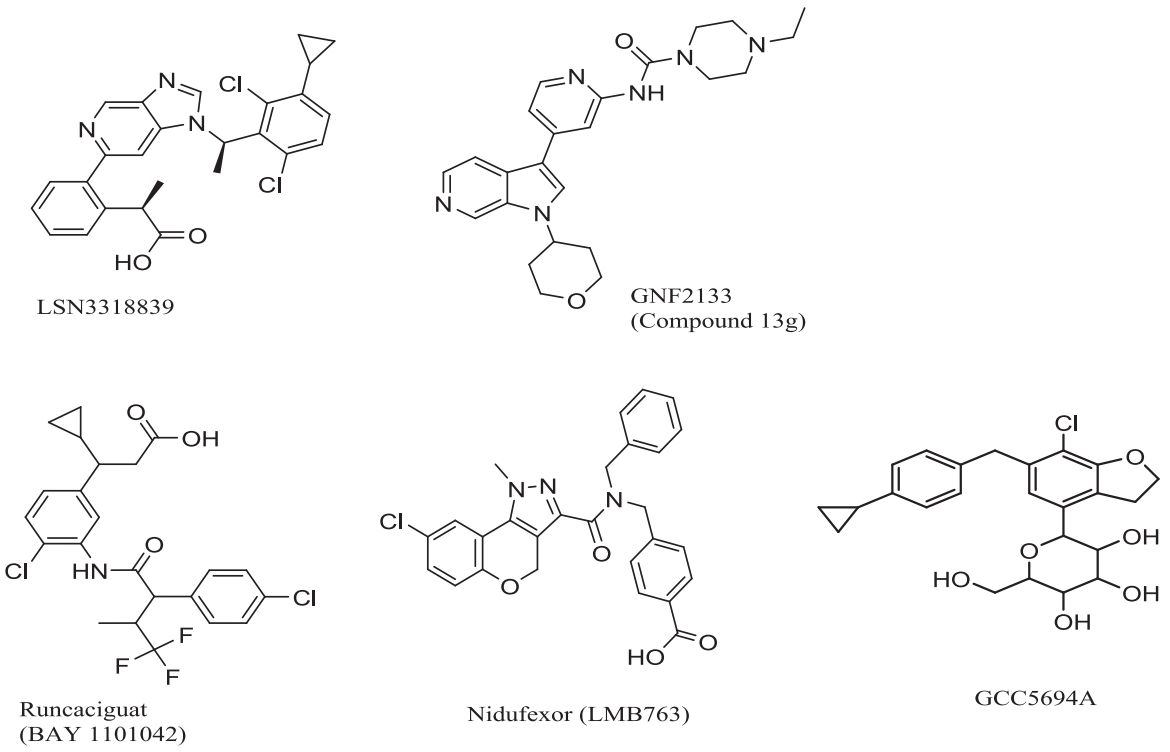

Fig. 8. The chemical structures of the drugs for type 1 diabetes and diabetes related complications discovered in 2020–2022.

thrombotic diseases are shown in Fig. 9.

2.8.1. BMS-986235/LAR-1219

BMS-986235/LAR-1219 is a potent and selective agonist of Formyl peptide receptor 2 (FPR2) that is designed to prevent heart failure. Agonists of the FPR2 may be useful in the treatment of disorders like heart failure that are brought on by chronic inflammation since they can promote the resolution of inflammation.

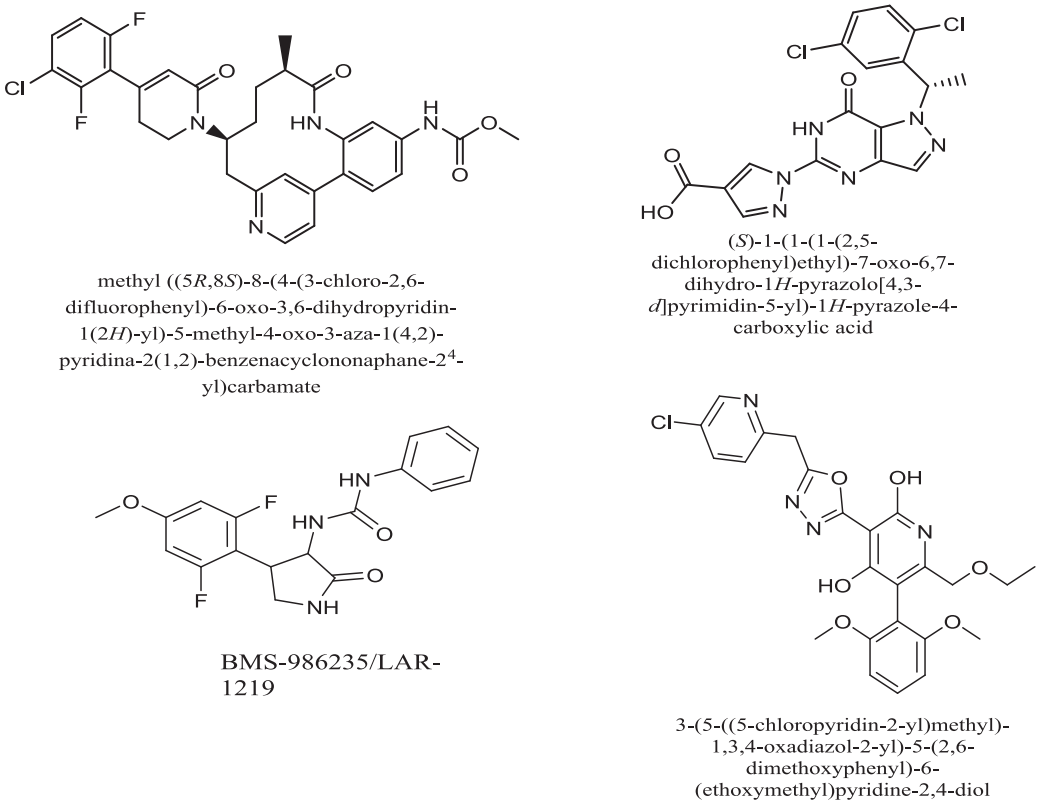

Fig. 9. The chemical structures of the drugs for CVS diseases discovered in 2020–2022.

By restricting the structure of a simple phenylethyl urea FPR2 agonist, an efficient FPR2 agonist with selectivity over FPR1 was discovered. To generate more potent FPR2 agonists, the pyrrolidinone core was then optimized. Studies on metabolic profiling and the assessment of lead molecules in a lung LPS model enabled for the establishment of BMS986235/LAR-1219 as a therapeutic candidate. Following oral administration for 28 days, BMS986235/LAR-1219 showed excellent efficacy on both structural and function endpoints in a mouse myocardial infarction heart failure model. These findings suggest that this orally available, selective small molecule FPR2 agonist may very well be able to prevent the pathological remodelling that leads to undesirable consequences, such heart failure (Asahina et al., 2020). The PK and PD parameters are mentioned in Table.1 and 2.

2.9. Fibrotic Diseases

The hallmark of several fibrotic illnesses, including systemic sclerosis and lung, liver, and kidney fibrosis, is abnormal and disproportionate extracellular matrix deposition. Treatment of fibrotic disorders is extremely difficult because of the variety of afflicted organs, the fact that the fibrotic process is typically progressive, the sheer number of people affected, and the lack of a viable cure. A solid foundation for the development of efficient treatments has been established by the delineation of the central function of transforming growth factor- (TGF-), as well as by the identification of the particular cellular receptors, kinases, and other mediators involved in the fibrotic process (Rosenbloom et al., 2010). Fig. 10 shows the chemical structures of drugs discovered for the treatment of fibrotic diseases such as cystic fibrosis.

2.9.1. GLPG2451

GLPG2451 is a novel and potent once daily potentiator for the treatment of cystic fibrosis. Potentiators are the chemical compounds that have the ability to improve the gating function of CFTR channel. The discovery process involved extensive lead optimization studies. By substituting a picolinic amide-derived series for the thiophene amide scaffold, the novel potentiator GLPG2451 was identified. To eliminate the in vitro genotoxic risks associated with certain of the thiophene derivatives, this scaffold hop was required. Although the PK profile of the thiophene amide series was previously generally favorable, the scaffold hop led to a lower clearance and prolonged half-life. Final adjustments were required to reduce the CYP induction potential because the created potentiator will be used with additional CFTR modulators to increase its effectiveness. GLPG2451 is chemically different from GLP1837 as GLP1837 possess the distinct thiophene ring which was subsequently replaced in GLPG2451. While having the same initial source and it may only need to be taken once daily as opposed to twice daily as GLP1837 and Ivacaftor do (VX-770).

2.10. Metabolic disorders and chronic pain

Increased fructose consumption and the subsequent metabolism of the sugar have been linked to metabolic diseases like insulin resistance and non-alcoholic steatohepatitis and fatty liver disease. The first stage in the metabolic cascade is the conversion of fructose to fructose-1-phosphate (F1P) by ketohexokinase (KHK). Metabolic disorders can also lead to several other conditions such as obesity, diabetes myelitis and renal disease. Consuming foods with a high fructose content can cause oxidative stress, Monocyte Chemoattractant protein-1 (MCP-1) activation, and proinflammatory alterations in the proximal tubule through a direct KHK-dependent pathway (Cirillo et al., 2009). Fig. 11 represents the chemical structures of drugs which have been discovered for the purpose of treating metabolic disorder and chronic pain.

The aberrant sensitivity that distinguishes chronic pain is caused by the pain being produced in response to the activation of low-threshold mechano-receptive A-beta fibers which ordinarily provide harmless sensations. This radical shift in the somatosensory system of sensory processing can be attributed to three distinct processes occurring in the spinal cord: increased excitability, decreased inhibition, and structural remodeling (Greene, 2010).

2.10.1. PF-06835919

A new and powerful inhibitor of ketohexokinase is PF-06835919 (KHK). The pyrrolidine-based lead chemical 1 served as the initial step in the discovery process, which resulted in the discovery of extremely potent and targeted acidic KHK inhibitors. The first stage of lead optimization focused on increasing potency. Targeting Arg-108 and simulating high-energy water nearby required early identification of rotations in the binding process caused by the azetidine-based inhibitors. It was possible to discover incredibly powerful KHK inhibitors

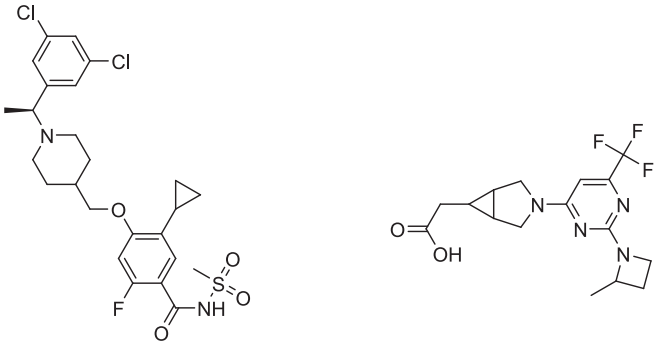

Fig. 11. The chemical structures of the drugs for metabolic disorder and chronic pain discovered in 2020–2022.

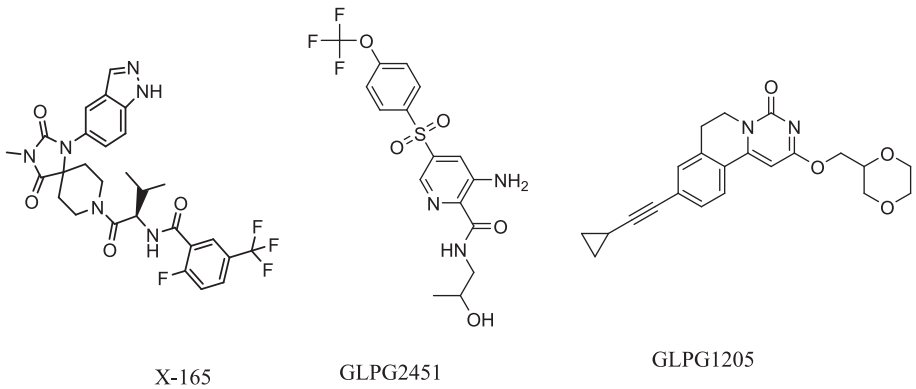

Fig. 10. The chemical structures of the drugs for Fibrotic diseases discovered in 2020–2022.

with a 3-azabicyclo [3.1.0] hexane acetic acid group by using PMC and the ionisation switch with SBDD, as well as additional optimization. By strategically removing the hydroxyl group (the key location of the glucoronidation metabolism) and using the pyrimidyl central core, the final modification work to blend potency, glucoronidation metabolism, and cell permeability profile was effective. This led to the discovery of PF-0.6835919. It is assumed that PF-06835919 is the first KHK inhibitor of its kind to have begun clinical testing (Futatsugi et al., 2020).

3. Conclusion

The persistent rise of new medical illnesses, antimicrobial resistance, premature demise of drug molecules and unmet medical needs warrant the discovery and development of new molecular entities (NMEs). However, the process of discovering and developing NMEs is time taking and very expensive. Despite these limitations, research organizations and big pharma companies are consistently putting their efforts into discovering and developing new drugs in order to address the rising medical needs. With the advancement in drug discovery and development processes such as incorporation of computer aided drug design (CADD) has significantly reduced the time taken by the drug in the drug discovery phases. FDA has approved 40 NMEs and 13 BLAs in 2020 which is by far the highest count in the last two decades which gives us hope for the future. Our pharmaceutical industries are advancing into novel mechanisms and comparatively newer patient population which poses some new challenges such as complicated clinical trial designs which could lead to longer and more expensive drug development. The use of companion diagnostic and screening test may help in order to identify the specific population and could help in reducing the time and cost of the process. Finally, newly discovered medicines must be cost effective and efficient, accessible to the general public and provide distinction of any existing standards of care. The success rate of the drug discovery processes is improving which provides hope that the pharmaceutical industry would be able to address the current and future challenges and will continue to develop new medicines and bring these new drugs to those who need them.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2023.101913.

References

Angst, D., Gessier, F., Janser, P., Vulpetti, A., Wälchli, R., Beerli, C., et al., 2020. Discovery of LOU064 (Remibrutinib), a potent and highly selective covalent inhibitor of Bruton's Tyrosine Kinase. J. Med. Chem. 63 (10), 5102–5118.

Asahina, Y., Wurtz, N.R., Arakawa, K., Carson, N., Fujii, K., Fukuchi, K., et al., 2020. Discovery of BMS-986235/LAR-1219: a potent formyl peptide receptor 2 (FPR2) selective agonist for the prevention of heart failure. J. Med. Chem. 63 (17), 9003–9019.

Berger, M., May, E., Rehwinkel, H., Schäcke, H., Neuhaus, R., Rottmann, A., et al., 2020. Discovery of the potent non-steroidal glucocorticoid receptor modulator BAY 1003803 as clinical candidate. Bioorg. Med. Chem. Lett. 30 (16), 127298.

Blomgren, P., Chandrasekhar, J., Di Paolo, J.A., Fung, W., Geng, G., Ip, C., et al., 2020. Discovery of Lanraplenib (GS-9876): a once-daily spleen tyrosine kinase inhibitor for autoimmune diseases. ACS Med. Chem. Lett. 11 (4), 506–513.

Brandao, D.J., Fontenelle, L.F., da Silva, S.A., Menezes, P.R., Pastor-Valero, M., 2019. Depression and excess mortality in the elderly living in low-and middle-income countries: systematic review and meta-analysis. Int. J. Geriatr. Psychiatry 34 (1), 22–30.

Braunwald, E., 2013. Heart failure. JACC Heart Fail 1 (1), 1–20.

Brebion, F., Gosmini, R., Deprez, P., Varin, M., Peixoto, C., Alvey, L., et al., 2021. Discovery of GLPG1972/S201086, a potent, selective, and orally bioavailable ADAMTS-5 inhibitor for the treatment of osteoarthritis. J. Med. Chem. 64 (6), 2937–2952.

Brogi, S., 2019. Computational approaches for drug discovery. Multidisciplinary Digital Publishing Institute, p. 3061.

Brown, D.G., Wobst, H.J., 2021. A decade of FDA-approved drugs (2010–2019): Trends and future directions. J. Med. Chem. 64 (5), 2312–2338.

Cherney, R.J., Cornelius, L.A., Srivastava, A., Weigelt, C.A., Marcoux, D., Duan, J.-J.-W., et al., 2020. Discovery of BMS-986251: A clinically viable, potent, and selective RORγt inverse agonist. ACS Med. Chem. Lett. 11 (6), 1221–1227.

Cherney, E.C., Zhang, L., Nara, S., Zhu, X., Gullo-Brown, J., Maley, D., et al., 2021. Discovery and preclinical evaluation of BMS-986242, a potent, selective inhibitor of indoleamine-2, 3-dioxygenase 1. ACS Med. Chem. Lett. 12 (2), 288–294.

Chianelli, D., Rucker, P.V., Roland, J., Tully, D.C., Nelson, J., Liu, X., et al., 2020. Nidufexor (LMB763), a novel FXR modulator for the treatment of nonalcoholic steatohepatitis. J. Med. Chem. 63 (8), 3868–3880.

Chrovian, C.C., Soyode-Johnson, A., Stenne, B., Pippel, D.J., Schoellerman, J., Lord, B., et al., 2020. Design, Synthesis, and Preclinical Evaluation of 3-Methyl-6-(5-thiophenyl)-1, 3-dihydro-imidazo [4, 5-b] pyridin-2-ones as Selective GluN2B Negative Allosteric Modulators for the Treatment of Mood Disorders. J. Med. Chem. 63 (17), 9181–9196.

Cirillo, P., Gersch, M.S., Mu, W., Scherer, P.M., Kim, K.M., Gesualdo, L., et al., 2009. Ketohexokinase-dependent metabolism of fructose induces proinflammatory mediators in proximal tubular cells. J. Am. Soc. Nephrol. 20 (3), 545–553.

Cockerill, G.S., Angell, R.M., Bedernjak, A., Chuckowree, I., Fraser, I., Gascon-Simorte, J., et al., 2021. Discovery of sisunatovir (RV521), an inhibitor of respiratory syncytial virus fusion. J. Med. Chem. 64 (7), 3658–3676.

Cooper, G.S., Bynum, M.L., Somers, E.C., 2009. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. J. Autoimmun. 33 (3–4), 197–207.

Croft, A.C., D Antoni, A.V., Terzulli, S.L. 2007. Update on the antibacterial resistance crisis. Medical science monitor. 13(6):RA103.

Cuozzo, J.W., Clark, M.A., Keefe, A.D., Kohlmann, A., Mulvihill, M., Ni, H., et al., 2020. Novel autotaxin inhibitor for the treatment of idiopathic pulmonary fibrosis: A clinical candidate discovered using DNA-encoded chemistry. J. Med. Chem. 63 (14), 7840–7856.

Data, O. 2017. Gross domestic spending on R&D. https://www.un.org/esa/sustdev/natlinfo/indicators/methodology_sheets/econ_development/resesarch_development_expenditure.pdf. Retrieved May 14, 2023.

Deo, S., Sharma, J., Kumar, S., 2022. GLOBOCAN 2020 report on global cancer burden: challenges and opportunities for surgical oncologists. Ann. Surg. Oncol. 29 (11), 6497–6500.

DiMeglio, L.A., Evans-Molina, C., Oram, R.A., 2018. Type 1 diabetes. Lancet 391 (10138), 2449–2462.

Durand-Reville, T.F., Comita-Prevoir, J., Zhang, J., Wu, X., May-Dracka, T.L., Romero, J.A.C., et al., 2020. Discovery of an orally available diazabicyclooctane inhibitor (ETX0282) of class A, C, and D serine β-lactamases. J. Med. Chem. 63 (21), 12511–12525.

Ferrari, A.J., Charlson, F.J., Norman, R.E., Patten, S.B., Freedman, G., Murray, C.J., et al., 2013. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 10 (11), e1001547.

Fidler, M.M., Bray, F., Soerjomataram, I., 2018. The global cancer burden and human development: A review. Scand. J. Public Health 46 (1), 27–36.

Forouhi, N.G., Wareham, N.J., 2019. Epidemiology of diabetes. Medicine 47 (1), 22–27.

Futamura, A., Suzuki, R., Tamura, Y., Kawamoto, H., Ohmichi, M., Hino, N., et al., 2020. Discovery of ORN0829, a potent dual orexin 1/2 receptor antagonist for the treatment of insomnia. Bioorg. Med. Chem. 28 (13), 115489.

Futatsugi, K., Smith, A.C., Tu, M., Raymer, B., Ahn, K., Coffey, S.B., et al., 2020. Discovery of PF-06835919: a potent inhibitor of ketohexokinase (KHK) for the treatment of metabolic disorders driven by the overconsumption of fructose. J. Med. Chem. 63 (22), 13546–13560.

Gersten, O., Barbieri, M., 2020. The Epidemiologic Transition Theory and Evidence for Cancer Transitions in the US, Select European Nations, and Japan. Medrxiv, 11.

Gerstenberger, B.S., Ambler, C., Arnold, E.P., Banker, M.-E., Brown, M.F., Clark, J.D., et al., 2020. Discovery of tyrosine kinase 2 (TYK2) inhibitor (PF-06826647) for the treatment of autoimmune diseases. J. Med. Chem. 63 (22), 13561–13577.

Goi, T., Nakajima, T., Komatsu, Y., Kawata, A., Yamakoshi, S., Okada, O., et al., 2020. Pyrazolo [4, 3-d] pyrimidine Derivatives as a Novel Hypoxia-Inducible Factor Prolyl Hydroxylase Domain Inhibitor for the Treatment of Anemia. ACS Med. Chem. Lett. 11 (7), 1416–1420.

Greene, S.A., 2010. Chronic pain: pathophysiology and treatment implications. Top. Companion Anim. Med. 25 (1), 5–9.

Günther, J., Hillig, R.C., Zimmermann, K., Kaulfuss, S., Lemos, C., Nguyen, D., et al., 2022. BAY-069, a Novel (Trifluoromethyl) pyrimidinedione-Based BCAT1/2 Inhibitor and Chemical Probe. J. Med. Chem. 65 (21), 14366–14390.
Hahn, M.G., Lampe, T., El Sheikh, S., Griebenow, N., Woltering, E., Schlemmer, K.-H., et al., 2021. Discovery of the soluble guanylate cyclase activator runcaciguat (BAY 1101042). J. Med. Chem. 64 (9), 5323–5344.
Hay, M., Thomas, D.W., Craighead, J.L., Economides, C., Rosenthal, J., 2014. Clinical development success rates for investigational drugs. Nat. Biotechnol. 32 (1), 40–51.
Hecker, S.J., Reddy, K.R., Lomovskaya, O., Griffith, D.C., Rubio-Aparicio, D., Nelson, K., et al., 2020. Discovery of cyclic boronic acid QPX7728, an ultrabroad-spectrum inhibitor of serine and metallo-β-lactamases. J. Med. Chem. 63 (14), 7491–7507.
Hung, C.L., Chen, C.C., 2014. Computational approaches for drug discovery. Drug Dev. Res. 75 (6), 412–418.
Iwaki, Y., Ohhata, A., Nakatani, S., Hisaichi, K., Okabe, Y., Hiramatsu, A., et al., 2020. ONO-8430506: a novel autotaxin inhibitor that enhances the antitumor effect of paclitaxel in a breast cancer model. ACS Med. Chem. Lett. 11 (6), 1335–1341.
Johnson, J.A., Kim, S.-H., Jiang, J., Phillips, M., Schumacher, W.A., Bostwick, J.S., et al., 2021. Discovery of a hydroxypyridinone APJ receptor agonist as a clinical candidate. J. Med. Chem. 64 (6), 3086–3099.
Kazmierski, W.M., Baskaran, S., Walker, J.T., Miriyala, N., Meesala, R., Beesu, M., et al., 2020. GSK2818713, a novel biphenylene scaffold-based Hepatitis C NS5A replication complex inhibitor with broad genotype coverage. J. Med. Chem. 63 (8), 4155–4170.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., et al., 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 289 (23), 3095–3105.
Khanna, A., Côté, A., Arora, S., Moine, L., Gehling, V.S., Brenneman, J., et al., 2020. Design, synthesis, and pharmacological evaluation of second generation EZH2 inhibitors with long residence time. ACS Med. Chem. Lett. 11 (6), 1205–1212.
Kong, Y.K., Song, K.-S., Jung, M.E., Kang, M., Kim, H.J., Kim, M.J., 2022. Discovery of GCC5694A: A potent and selective sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes. Bioorg. Med. Chem. Lett. 56, 128466.
Koriyama, Y., Hori, A., Ito, H., Yonezawa, S., Baba, Y., Tanimoto, N., et al., 2021. Discovery of atabecestat (JNJ-54861911): a thiazine-based β-amyloid precursor protein cleaving enzyme 1 inhibitor advanced to the phase 2b/3 EARLY clinical trial. J. Med. Chem. 64 (4), 1873–1888.
Labéguère, F., Dupont, S., Alvey, L., Soulas, F., Newsome, G., Tirera, A., et al., 2020. Discovery of 9-cyclopropylethynyl-2-((S)-1-[1, 4] dioxan-2-ylmethoxy)-6, 7-dihydropyrimido [6, 1-a] isoquinolin-4-one (GLPG1205), a unique GPR84 negative allosteric modulator undergoing evaluation in a phase II clinical trial. J. Med. Chem. 63 (22), 13526–13545.
Langston, S.P., Grossman, S., England, D., Afroze, R., Bence, N., Bowman, D., et al., 2021. Discovery of TAK-981, a first-in-class inhibitor of SUMO-activating enzyme for the treatment of cancer. J. Med. Chem. 64 (5), 2501–2520.
Lawson, K.V., Kalisiak, J., Lindsey, E.A., Newcomb, E.T., Leleti, M.R., Debien, L., et al., 2020. Discovery of AB680: a potent and selective inhibitor of CD73. J. Med. Chem. 63 (20), 11448–11468.
Liang, J., Blake, R., Chang, J., Friedman, L.S., Goodacre, S., Hartman, S., et al., 2020. Discovery of GNE-149 as a full antagonist and efficient degrader of estrogen receptor alpha for ER+ breast cancer. ACS Med. Chem. Lett. 11 (6), 1342–1347.
Liu, Y.A., Jin, Q., Zou, Y., Ding, Q., Yan, S., Wang, Z., et al., 2020. Selective DYRK1A inhibitor for the treatment of Type 1 Diabetes: Discovery of 6-azaindole derivative GNF2133. J. Med. Chem. 63 (6), 2958–2973.
Lücking, U., Wortmann, L., Wengner, A.M., Lefranc, J., Lienau, P., Briem, H., et al., 2020. Damage incorporated: Discovery of the potent, highly selective, orally available ATR inhibitor BAY 1895344 with favorable pharmacokinetic properties and promising efficacy in monotherapy and in combination treatments in preclinical tumor models. J. Med. Chem. 63 (13), 7293–7325.
Mackman, R.L., Mish, M., Chin, G., Perry, J.K., Appleby, T., Aktoudianakis, V., et al., 2020. Discovery of GS-9688 (Selgantolimod) as a potent and selective oral toll-like receptor 8 agonist for the treatment of chronic hepatitis B. J. Med. Chem. 63 (18), 10188–10203.
Markert, C., Thoma, G., Srinivas, H., Bollbuck, B., Lüönd, R.M., Miltz, W., et al., 2021. Discovery of LYS006, a Potent and Highly Selective Inhibitor of Leukotriene A4 Hydrolase. J. Med. Chem. 64 (4), 1889–1903.
Marrack, P., Kappler, J., Kotzin, B.L., 2001. Autoimmune disease: why and where it occurs. Nat. Med. 7 (8), 899–905.
Meng, Y., Yu, B., Huang, H., Peng, Y., Li, E., Yao, Y., et al., 2021. Discovery of dosimertinib, a highly potent, selective, and orally efficacious deuterated EGFR targeting clinical candidate for the treatment of non-small-cell lung cancer. J. Med. Chem. 64 (2), 925–937.
Merikangas, K.R., Akiskal, H.S., Angst, J., Greenberg, P.E., Hirschfeld, R.M., Petukhova, M., et al., 2007. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch. Gen. Psychiatry 64 (5), 543–552.
Michalak, E.E., Yatham, L.N., Lam, R.W., 2005. Quality of life in bipolar disorder: a review of the literature. Health Qual. Life Outcomes 3 (1), 1–17.
Miller, C., Bauer, M.S., 2014. Excess mortality in bipolar disorders. Curr. Psychiatry Rep. 16 (11), 1–7.
Miller, M.J., Loaiza, J.R., Takyar, A., Gilman, R.H., 2020. COVID-19 in Latin America: Novel transmission dynamics for a global pandemic? PLoS Negl. Trop. Dis. 14 (5), e0008265.
Mitcheltree, M.J., Li, D., Achab, A., Beard, A., Chakravarthy, K., Cheng, M., et al., 2020. Discovery and optimization of rationally designed bicyclic inhibitors of human arginase to enhance cancer immunotherapy. ACS Med. Chem. Lett. 11 (4), 582–588.
Moloney, M.E., Ciciurkaite, G., Brown, R.L., 2019. The medicalization of sleeplessness: Results of US office visit outcomes, 2008–2015. SSM-Population Health. 8, 100388.
Mullard, A., 2015. 2014 FDA drug approvals: the FDA approved 41 new therapeutics in 2014, but the bumper year fell short of the commercial power of the drugs approved in 2013. Nat. Rev. Drug Discov. 14 (2), 77–82.
Mullard, A., 2018. 2017 FDA drug approvals. Nat. Rev. Drug Discov. 17 (2), 81–86.
Mullard, A., 2021. 2020 FDA drug approvals. Nat. Rev. Drug Discov. 20 (2), 85–91.
Munos, B., 2009. Lessons from 60 years of pharmaceutical innovation. Nat. Rev. Drug Discov. 8 (12), 959–968.
Mussari, C.P., Dodd, D.S., Sreekantha, R.K., Pasunoori, L., Wan, H., Posy, S.L., et al., 2020. Discovery of potent and orally bioavailable small molecule antagonists of Toll-like receptors 7/8/9 (TLR7/8/9). ACS Med. Chem. Lett. 11 (9), 1751–1758.
Noji, S., Hara, Y., Miura, T., Yamanaka, H., Maeda, K., Hori, A., et al., 2020. Discovery of a Janus kinase inhibitor bearing a highly three-dimensional Spiro scaffold: JTE-052 (delgocitinib) as a new dermatological agent to treat inflammatory skin disorders. J. Med. Chem. 63 (13), 7163–7185.
Olfson, M., Wall, M., Liu, S.-M., Morin, C.M., Blanco, C., 2018. Insomnia and impaired quality of life in the United States. J. Clin. Psychiatry 79 (5), 9151.
Organization WH. Global hepatitis report 2017: web annex A: estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2017. 2018.
Papakostas, G.I., Petersen, T., Mahal, Y., Mischoulon, D., Nierenberg, A.A., Fava, M., 2004. Quality of life assessments in major depressive disorder: a review of the literature. Gen. Hosp. Psychiatry 26 (1), 13–17.
Paul, S.M., Mytelka, D.S., Dunwiddie, C.T., Persinger, C.C., Munos, B.H., Lindborg, S.R., et al., 2010. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat. Rev. Drug Discov. 9 (3), 203–214.
Ratni, H., Alker, A., Bartels, B., Bissantz, C., Chen, W., Gerlach, I., et al., 2020. Discovery of RO7185876, a highly potent γ-secretase modulator (GSM) as a potential treatment for Alzheimer's disease. ACS Med. Chem. Lett. 11 (6), 1257–1268.
Rosenbloom, J., Castro, S.V., Jimenez, S.A., 2010. Narrative review: fibrotic diseases: cellular and molecular mechanisms and novel therapies. Ann. Intern. Med. 152 (3), 159–166.
Safina, B.S., McKerrall, S.J., Sun, S., Chen, C.-A., Chowdhury, S., Jia, Q., et al., 2021. Discovery of Acyl-sulfonamide Nav1. 7 Inhibitors GDC-0276 and GDC-0310. J. Med. Chem. 64 (6), 2953–2966.
Schmit, N., Nayagam, S., Thursz, M.R., Hallett, T.B., 2021. The global burden of chronic hepatitis B virus infection: comparison of country-level prevalence estimates from four research groups. Int. J. Epidemiol. 50 (2), 560–569.
Sleire, L., Førde, H.E., Netland, I.A., Leiss, L., Skeie, B.S., Enger, P.Ø., 2017. Drug repurposing in cancer. Pharmacol. Res. 124, 74–91.
Smietana, K., Siatkowski, M., Møller, M., 2016. Trends in clinical success rates. Nat Rev Drug Discov. 15 (6), 379–380.
Smith, C.R., Aranda, R., Bobinski, T.P., Briere, D.M., Burns, A.C., Christensen, J.G., et al., 2022. Fragment-based discovery of MRTX1719, a synthetic lethal inhibitor of the PRMT5• MTA complex for the treatment of MTAP-deleted cancers. J. Med. Chem. 65 (3), 1749–1766.
Smolinski, M.P., Urgaonkar, S., Pitzonka, L., Cutler, M., Lee, G., Suh, K.H., et al., 2021. Discovery of encequidar, first-in-class intestine specific P-glycoprotein inhibitor. J. Med. Chem. 64 (7), 3677–3693.
Su, Q., Banks, E., Bebernitz, G., Bell, K., Borenstein, C.F., Chen, H., et al., 2020. Discovery of (2 R)-N-[3-[2-[(3-Methoxy-1-methyl-pyrazol-4-yl) amino] pyrimidin-4-yl]-1 H-indol-7-yl]-2-(4-methylpiperazin-1-yl) propenamide (AZD4205) as a Potent and Selective Janus Kinase 1 Inhibitor. J. Med. Chem. 63 (9), 4517–4527.
Tehlirian, C., Peeva, E., Kieras, E., Scaramozza, M., Roberts, E.S., Singh, R.S.P., et al., 2021. Safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of the oral TYK2 inhibitor PF-06826647 in participants with plaque psoriasis: a phase 1, randomised, double-blind, placebo-controlled, parallel-group study. The Lancet Rheumatology. 3 (3), e204–e213.
Theuretzbacher, U., 2013. Global antibacterial resistance: The never-ending story. JGAR. 1 (2), 63–69.
Unoh, Y., Uehara, S., Nakahara, K., Nobori, H., Yamatsu, Y., Yamamoto, S., et al., 2022. Discovery of S-217622, a non-covalent oral SARS-CoV-2 3cl protease inhibitor clinical candidate for treating COVID-19. J. Med. Chem. 65, 6499–6512.
Van der Plas, S.E., Kelgtermans, H., Mammoliti, O., Menet, C., Tricarico, G., De Blieck, A., et al., 2021. Discovery of GLPG2451, a novel once daily potentiator for the treatment of cystic fibrosis. J. Med. Chem. 64 (1), 343–353.
Velaparthi, U., Darne, C.P., Warrier, J., Liu, P., Rahaman, H., Augustine-Rauch, K., et al., 2020. Discovery of BMS-986260, a potent, selective, and orally bioavailable TGFβR1 inhibitor as an immuno-oncology agent. ACS Med. Chem. Lett. 11 (2), 172–178.
Vendeville, S., Tahri, A., Hu, L., Demin, S., Cooymans, L., Vos, A., et al., 2020. Discovery of 3-({5-Chloro-1-[3-(methylsulfonyl) propyl]-1 H-indol-2-yl} methyl)-1-(2, 2, 2-trifluoroethyl)-1, 3-dihydro-2 H-imidazo [4, 5-c] pyridin-2-one (JNJ-53718678), a Potent and Orally Bioavailable Fusion Inhibitor of Respiratory Syncytial Virus. J. Med. Chem. 63 (15), 8046–8058.
Wang, L., Doherty, G.A., Judd, A.S., Tao, Z.-F., Hansen, T.M., Frey, R.R., et al., 2020. Discovery of A-1331852, a first-in-class, potent, and orally-bioavailable BCL-XL inhibitor. ACS Med. Chem. Lett. 11 (10), 1829–1836.
White, C., McGowan, M.A., Zhou, H., Sciammetta, N., Fradera, X., Lim, J., et al., 2020. Strategic incorporation of polarity in heme-displacing inhibitors of Indoleamine-2, 3-dioxygenase-1 (IDO1). ACS Med. Chem. Lett. 11 (4), 550–557.
Wickwire, E.M., Shaya, F.T., Scharf, S.M., 2016. Health economics of insomnia treatments: the return on investment for a good night's sleep. Sleep Med. Rev. 30, 72–82.

Willard, F.S., Wainscott, D.B., Showalter, A.D., Stutsman, C., Ma, W., Cardona, G.R., et al., 2021. Discovery of an orally efficacious positive allosteric modulator of the glucagon-like peptide-1 receptor. J. Med. Chem. 64 (6), 3439–3448.
Wilson, J.E., Patel, G., Patel, C., Brucelle, F., Huhn, A., Gardberg, A.S., et al., 2020. Discovery of CPI-1612: a potent, selective, and orally bioavailable EP300/CBP histone acetyltransferase Inhibitor. ACS Med. Chem. Lett. 11 (6), 1324–1329.
Winblad, B., Amouyel, P., Andrieu, S., Ballard, C., Brayne, C., Brodaty, H., et al., 2016. Defeating Alzheimer's disease and other dementias: a priority for European science and society. The Lancet Neurology. 15 (5), 455–532.
Winkelman, J.W., 2015. Insomnia disorder. N. Engl. J. Med. 373 (15), 1437–1444.
Yang, W., Wang, Y., Lai, A., Clark, C.G., Corte, J.R., Fang, T., et al., 2020. Discovery of a high affinity, orally bioavailable macrocyclic FXIa inhibitor with antithrombotic activity in preclinical species. J. Med. Chem. 63 (13), 7226–7242.
Zannad, F., 2018. Rising incidence of heart failure demands action. Lancet 391 (10120), 518–519.
Zhang, Z., Connolly, P.J., Lim, H.K., Pande, V., Meerpoel, L., Teleha, C., et al., 2021. Discovery of JNJ-63576253: a clinical stage androgen receptor antagonist for F877L mutant and wild-type castration-resistant prostate cancer (mCRPC). J. Med. Chem. 64 (2), 909–924.
Zhang, H., Lapointe, B.T., Anthony, N., Azevedo, R., Cals, J., Correll, C.C., et al., 2020. Discovery of N-(Indazol-3-yl) piperidine-4-carboxylic acids as RORγt allosteric inhibitors for autoimmune diseases. ACS Med. Chem. Lett. 11 (2), 114–119.
Zhu, C.W., Sano, M., 2006. Economic considerations in the management of Alzheimer's disease. Clin. Interv. Aging. 1 (2), 143.