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Review article

A medicinal chemistry perspective of drug repositioning: Recent advances and challenges in drug discovery

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ABSTRACT

Drug repurposing is a strategy consisting of finding new indications for already known marketed drugs used in various clinical settings or highly characterized compounds despite they can be failed drugs. Recently, it emerges as an alternative approach for the rapid identification and development of new pharmaceuticals for various rare and complex diseases for which lack the effective drug treatments. The success rate of drugs repurposing approach accounts for approximately 30% of new FDA approved drugs and vaccines in recent years. This review focuses on the status of drugs repurposing approach for various diseases including skin diseases, infective, inflammatory, cancer, and neurodegenerative diseases. Efforts have been made to provide structural features and mode of actions of drugs.

Contents

1. Introduction

"The most fruitful basis for the discovery of a new drug is to start with an old drug."

Sir James Whyte Black, winner of the 1988 Nobel Prize in Medicine [1].

It is reported that the Food and Drug Administration (FDA) has approved agents against about 400 human proteins [2], 90% of which comes under the classification of enzymes, transporters, G

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protein-coupled receptors (GPCRs), cluster of differentiation (CD) markers, voltage-gated ion channels, and nuclear receptors. It is a fact that the typical *de novo* drug discovery program takes 10–15 years [3,4] from the identification of lead molecule to market the drug and the probability of success rate is less than 10% [5]. Over five years, the number of new drugs approved by FDA has been around 40 per year, although billions of US dollars spent by various pharma industries on the research and development [6–8]. The success rate is less than 6% of new drug discovery and development, which is far away from addressing an unmet clinical need for disease treatments. Because, the effective therapeutics for complex diseases like Alzheimer's disease (AD), Parkinson's disease (PD), cardiovascular diseases, and neglected diseases are still lacking. This outcome strongly suggests that new strategies, approaches, and technologies are needed to accelerate drug discovery to advance the success rate of drug development.

Drug repurposing is a strategy consisting of finding new indications for already known marketed drugs used in various clinical settings or highly characterized compounds despite they can be failed drugs [9]. It is a drug discovery program, which is faster and safer to develop medications against diseases/disorders for which no potential treatment is available. In recent years, the success rate of drug repurposing approach accounts for approximately 30% of the newly FDA approved drugs, and vaccines. This is one of the main reasons for pharmaceutical companies to show their interest in drug repurposing approach. This approach does not require the initial six to 10 years typically needed for the development of new drugs. Additionally, many phases of *de novo* drug discovery and development can be by-passed, since clinical and pre-clinical studies of the re-purposed candidates are already being documented in the original indication(s). Thus, it reduces the time and cost needed to reach the market and risk intrinsic to any research and development program. Moreover, the risk of clinical failure is also low. As an added advantage, this approach gives a possibility to widen the market and to prolong the application of the patent life of a drug. There are mainly two ways to proceed drug-repositioning approach such as experimental strategies and computational strategies.

Experimental repurposing strategies include binding assays and phenotypic screening methods, which can be to find binding interactions of drug molecules to assay components and to identify lead compounds from a vide range of compound libraries, respectively [10]. Computational approaches are categorized into target-/mechanism based, knowledge-based, pathway- and network-based approaches. These approaches are proven economic in discovering novel therapeutic ligands. Most notably, computational methods augment the drug discovery process by effectively utilizing cheminformatics, bioinformatics, network biology and systems biology. More specifically, these methods exploit known targets, drugs, disease biomarkers or pathways to establish novel methods and accelerate the planning of crucial clinical trials [11].

In this perspective, we focused on the status of drugs repurposing approaches for various diseases including skin diseases, infective, inflammatory, cancer, and neurodegenerative diseases. Efforts have been made to provide structural features, and mode of action of drugs, which are exclusively small molecules, peptidomimetics, and macrocyclic compounds. Antibodies, vaccines, and any other biological drugs are not discussed.

Drugs repositioning for skin whitening activity. Melanin is a collection of natural pigments that primarily determine the skin, hair and hair color of the human. Melanocytes, which are found in the basal layer of the epidermis, produce melanin by the process called melanogenesis upon the skin exposure to the ultra-violet (UV)-radiation [12,13]. Although, melanin protects human skin from the radiation, continuing irradiation can result in the risk of skin damage and malignant melanoma, a cancer of melanocytes. Besides, the abnormal production of melanin leads to a serious of dermatological disorders including melasma [13–16], freckles, age spots, and post-inflammatory melanoderma [15,17].

Melanogenesis, a process of synthesis of melanin, is a complex enzymatic and biochemical catalyzed reactions, in which tyrosinase plays a rate-limiting step: hydroxylation of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) followed by the oxidation of L-DOPA to L-dopaquinone, which serves as a substrate for the production of melanin [18]. Therefore, targeting tyrosinase has been recognized as a potential approach for controlling the abnormal production of melanin. Tyrosinase is also an important target in the food industry as inhibition of tyrosinase can prevent the enzymatic browning of fruits and vegetables. Besides, it is essential for wound healing process and immune responses in many plants, sponges and some invertebrates. Abnormal activities of tyrosinase have been linked to neurodegenerative disorders including Parkinson's [19] and Huntington's diseases [20–24].

Thiourea and analogs. Tyrosinase inhibitors can be broadly classified into two categories: (a) polyphenols, which are mostly natural products such as arbutin, hydroquinone and kojic acids, and b) thiourea and its derivatives. Since the 1940's, phenylthiourea (PTU, **1**) has been well known as a tyrosinase inhibitor [25,26]. Many research groups including ours have extensively studied the structure-activity relationships for PTU as tyrosinase inhibitors [27,28].

Choi et al. screened the FDA approved drug library that has close structural similarity to PTU (see Fig. 1) [29]. For example, ethionamide (**2**), a second-line antituberculosis drug used for the treatment of multi-drug resistant tuberculosis, shares a chemical similarity that led to the discovery of a new mushroom tyrosinase inhibitor with an IC_{50} value of 4.0 μM. Other commercially available analogs of **2** including, prothionamide (**3**), thioisonicotinamide (**4**), pyridine-3-carbothiomide (**5**), pyridine-2-carbothiomide (**6**), and thiobenzamide (**7**) were identified as potent tyrosinase inhibitors. In particular, compound **7** had a strong inhibitory activity than other molecules, which suggests that the pyridine ring in compound **2** can be replaced by other aromatic moieties, including a benzene ring. However, the poor inhibitory activity of isoniazid (**8**), a first-line antituberculosis drug, suggests that carbothiomide group was crucial for tyrosinase inhibitory activity. Moreover, comparing the inhibitory activities of drugs **2** and **3** implies that the additional aliphatic tail was not required for inhibiting the tyrosinase. Inhibitory kinetic studies suggest that drug **2**, and its analogs **3**–**7** were reversible and non-competitive. In cellular assay, drugs **6** and **7** markedly decreased the melanin content in B16 cells to the values of 44% and 37%, respectively, without inducing any cytotoxicity up to 50 μM concentration. Further studies suggest that the drug **7** had strong inhibition of mammalian tyrosinase. However, the inhibition exhibited by drug **2**, and its analogs were weaker than those obtained by PTU observed in enzyme, and melanin content assays.

The same research group continued to search for molecules that are in clinical usage, and contain thiourea moiety [30]. As a result, they could retrieve some thiourea containing drugs such as thioacetazone (**9**), ambazone (**10**), methimazole (**11**), carbimazole (**12**), thiouracil (**13**), methylthiouracil (**14**), and propylthiouracil (**15**). Thioacetazone (**9**) (also called as thiacetazone) is an antituberculosis drug [31]. Ambazone (**10**) is an oral antiseptic drug used in Europe [32]. The other five molecules (**11**–**15**) are antithyroid drugs [33]. These drugs, except **12**, exhibited remarkable inhibitory activities against mushroom tyrosinase (see IC_{50} values of each in Fig. 1), although they were comparatively weaker than **1** (1 μM). Kinetics studies of tyrosinase inhibition assigned these thiourea-containing drugs as non-competitive inhibitors. In

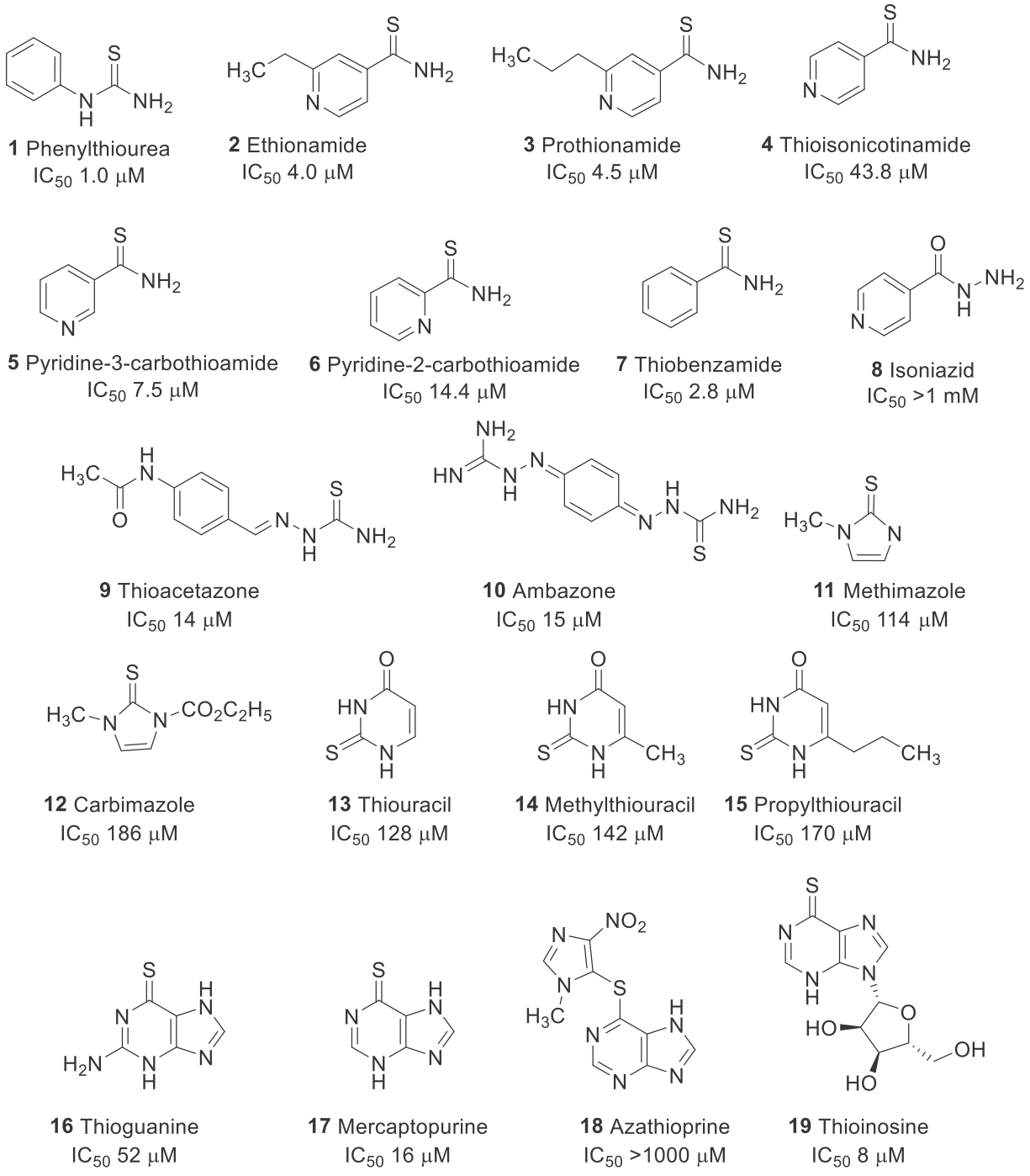

Fig. 1. Repurposing of thiourea related drugs for skin whitening activity.

cellular assay, using B16 cells, drug **10** among other thioureas, significantly decreased the melanin content by 20% without inducing any cytotoxicity up to 20 μM. Further, enzymatic studies with cell extracts of B16F10 cells confirmed that thiourea-containing drugs affected the function of mammalian tyrosinase.

In an extended study, the same group repositioned thiopurine drugs **16**–**19** as tyrosinase inhibitors [34]. Thioguanine (**16**), a drug used for the treatment of leukemia, is one of the essential medicines required for a basic health system, recommended by the world health organization (WHO). It inhibited tyrosinase activity with a K_i value of 52 μM. In addition to that, two other thiopurine drugs such as mercaptopurine (**17**) and azathioprine (**18**) were discovered as tyrosinase inhibitors, and among them, drug **17** showed stronger K_i value (K_i 52 μM) than the drug **16**. Azathioprine (**18**) exhibited a poor tyrosinase inhibition. These results suggest that the sulfur atom possibly plays an important role in the interaction of tyrosinase. Interestingly, thioinosine (**19**), a metabolic product of mercaptopurine through the attachment of sugar moiety exhibited an excellent tyrosinase inhibitory activity with a K_i value of 8.0 μM. Further, kinetics studies classified the drugs **16**, **17**, and **19** as competitive inhibitors. In the cellular assay, these drugs inhibited the melanin content without cytotoxicity up to 50 μM. In

particular, drug **16** at 50-μM concentration, remarkably reduced the melanin content by 57%, without any apparent cytotoxicity.

The thiopurine drugs were docked into four different crystal structures complexed with inhibitors tropolone, kojic acid, hydroquinone and PTU (Fig. 2) [35–37]. In the molecular docking study, thiopurine moieties of drugs **16**, **17**, and **19** exhibited an almost similar pattern of binding mode to that of PTU. Thioinsoine (**19**) (Fig. 2 D) made additional contacts with the side-chains of N-260, F-264, and V-283 that were thought to have the stronger inhibition. It also predicted that the intramolecular hydrophilic contacts with the residue of E-256 disappeared in mercaptopurine (Fig. 2C), whereas thioguanine (Fig. 2B) and thioinosine possess the contacts within 3.8 Å.

Drugs repositioning for cancer therapy. As cancer is one of the leading cause of death worldwide [38], pharmaceutical companies invest billions of dollars in developing new anti-cancer drugs. The drug discovery and development process for the cancer treatment takes an average of 13 years at a cost of approximately $ 1.8 billion [39]. However, only 5% of the drugs that enter clinical trials are approved. This prolonged duration for the drug development and enormous cost of the (pre)clinical trials for their approval emphasizes the need for a drug repurposing approach (see Fig. 3 for drugs repurposing in cancer therapy).

Aspirin (**20**), also known as acetylsalicylic acid, is one of the non-steroidal anti-inflammatory drugs (NSAIDs), which has been widely used as an analgesic and an antipyretic to prevent the heart attack and stroke. For the first time, Gasic and co-workers reported the possible role of aspirin in cancer therapy. They discovered that the antiplatelet activity of **20** in tumor-bearing mice was associated with a 50% reduction in lung metastasis [40]. A recent study also indicated that the daily intake of the drug **20** (75 mg) produced a significant beneficial effect against gastrointestinal, esophageal, pancreatic, brain, prostate, and lung cancer [41]. The mode of action aspirin is reported to modulate numerous molecules, which are associated with the tumorigenesis process [42]. Preclinical studies revealed that the anticancer activity of drug **20** has been attributed by its inhibition of cyclooxygenase (COX) enzymes that promotes carcinogenesis through the synthesis of prostaglandins (PG), including PGE2 [43]. Besides, drug **20** was reported to inhibit the activation of transcription factor NF-κB, which is critical in regulating the expression of genes involved in apoptosis [44]. In a study reported by Li Ling et al. compound **20** not only inhibited proliferations and promoted apoptosis of cancer cells, but also delayed and overcame acquired resistance to targeted therapy. The

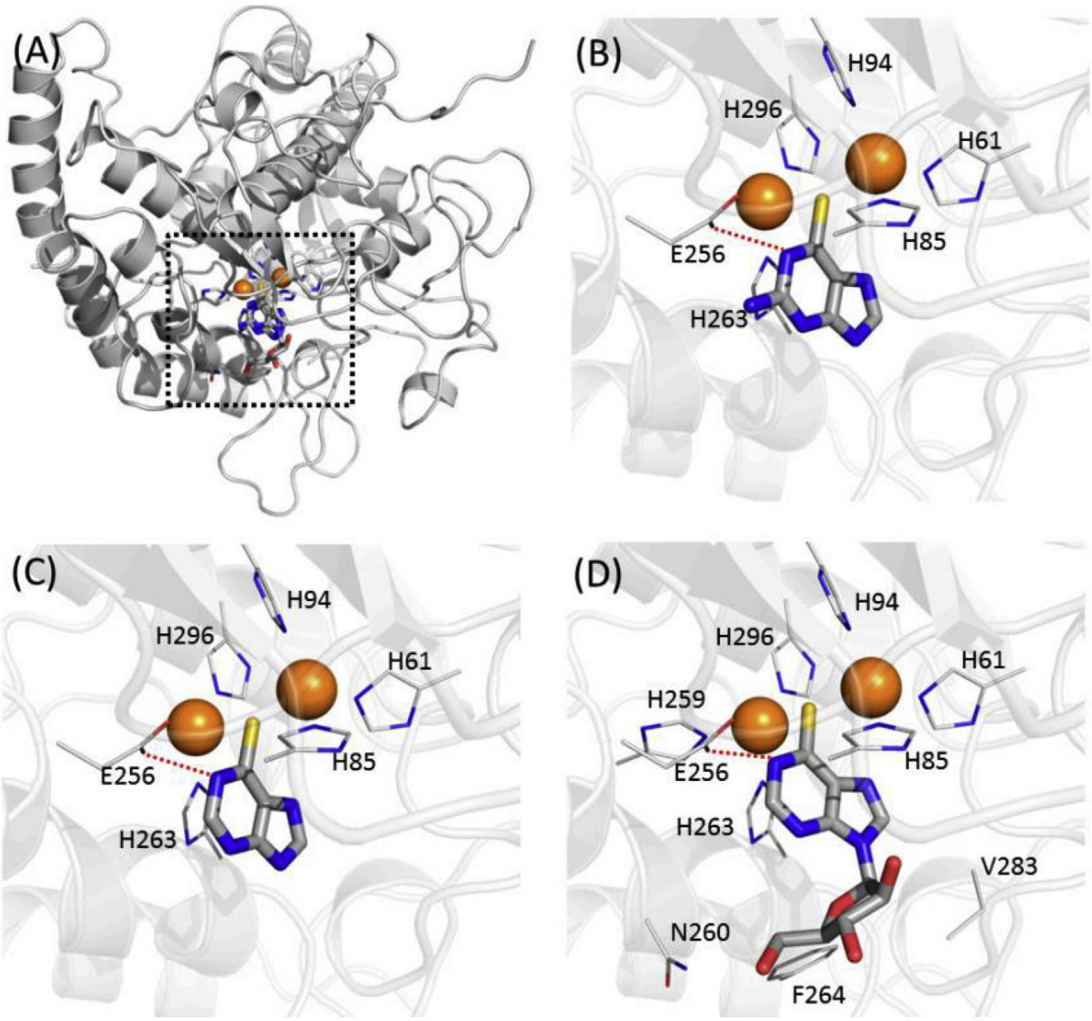

Fig. 2. Binding modes of thiopurine inhibitors. (A) Overlaid poses against mushroom tyrosinase. Two copper atoms in tyrosinase are indicated as orange spheres. Predicted binding modes in (B) thioguanine (**16**), (C) mercaptopurine (**17**) and (D) thioinosine (**19**) are represented. This Figure was adopted from the publication of Choi, J. et al. [28]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

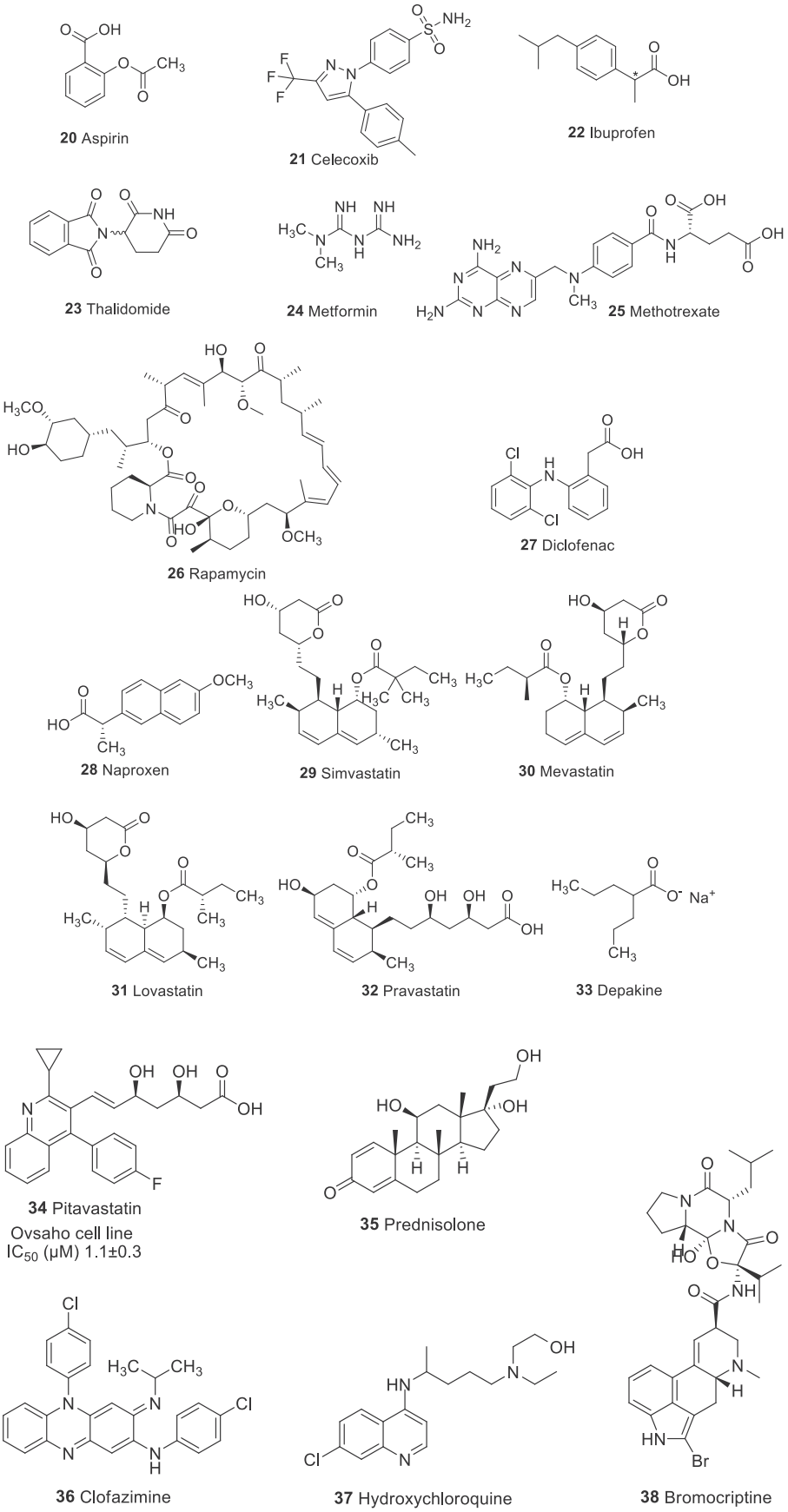

Fig. 3. Chemical structures of drugs repurposed for cancer therapy.

underlying mechanism could be attributed to enhanced cancer stemness and activated NF-kB signaling in acquired resistant tumors were suppressed by aspirin and rendered resistant tumors more sensitive to aspirin than parental, sensitive cells in terms of proliferation, apoptosis and cancer stemness. On the contrary, aspirin has no effects on normal lung and mammary epithelial cell proliferation at concentrations used on lung and breast cancer cells. Hence, aspirin could be a potential candidate for combination therapy for lung and breast cancers [45]. Other studies suggest that the anticancer property of aspirin (**20**) has been linked to the phosphatidylinositol-3-kinase (PI3K) pathway, and Ras-Raf-MEK-ERK signaling cascade. While numerous studies suggest the potent anticancer activities of drug **20**, the overall benefit is limited as it is associated with serious side effects including the gastrointestinal and renal toxicities. Therefore, there is no clear recommendation to take **20** for population-wide use. On the other hand, as a primary cancer prevention tool, many reports revealed using **20** would have a greater benefit in the population at age 40–85. Thus, U.S. preventive services task force recommendation statement (USPSTF), recommended for daily intake of **20** for patients above 40 years with increased risk of cardiovascular disease and colorectal cancer.

Celecoxib (**21**) belongs to the family of NSAID, which has been used to treat pain and inflammation associated with rheumatoid arthritis (RA) and osteoarthritis (OA) [46]. In 1999, the FDA approved celecoxib, which is a highly selective reversible inhibitor of COX-2, a well-known inflammatory cancer target. Because of its COX-2 inhibitory activity, the antitumor activities of drug **21** have been extensively studied and shown to have chemopreventive activities against various cancer types. Other than COX-2, celecoxib targets glycogen synthase kinase (GSK) 3β, β-catenin, NF-κB, AKT8 virus oncogene cellular homolog (AKT), and B cell lymphoma (Bcl)-2 families [47]. In people with familial adenomatous polyposis (FAP), a daily dosage of drug **21** (400 mg) significantly reduced the risk of colorectal adenomas. FDA approved this compound to reduce colon and rectal polyps in people with familial adenomatous polyposis [48]. However, it was associated with some drawbacks including gastrointestinal, renal, and cardiotoxic effects.

Ibuprofen (**22**) is an NSAID, which has been primarily used to treat fever, pain, and inflammation. At the molecular level, ibuprofen inhibits COX, which converts arachidonic acid to prostaglandin. However, it is not selective towards any isoform of COX. The drug was marketed for the treatment of rheumatoid arthritis in the United Kingdom (1969), and in the United States (1971) as well. The anticancer activity of drug **22** has been investigated in various cancer cell types. Ibuprofen has been shown to inhibit the growth of prostate cancer cells [49]. In adenocarcinoma gastric cells, drug **22** showed antitumor effects, which have been mediated by the anti-angiogenesis, induction of apoptosis, and reduction of cell proliferation [50]. The administration of drug **22** induces apoptosis in metastatic melanoma cell lines [51]. Ibuprofen also reported to increase the chemosensitivity of cisplatin by decreasing the levels of heat shock protein 70s (Hsp70s) in lung cancer cells. Hsp70s are an important part of the cell's machinery for protein folding, and their function was associated with resistance to apoptosis [52]. Therefore, by blocking Hsp70s, ibuprofen increased the apoptosis by increasing the sensitivity of cisplatin.

Thalidomide (**23**) is an immunomodulatory drug, which was originally developed as a sedative-hypnotic for the treatment of nausea during pregnancy. However, it was withdrawn due to its teratogenic effects. The drug was demonstrated whether it could be used for treating patients with refractory myeloma, because of its anti-angiogenic activity. After successful clinical evaluations, FDA approved the drug **23** for treating multiple myeloma. Additionally, molecule **23** also showed efficacy against several malignancies, including acute myeloid leukemia [53], myelodysplasia [54], and myelodysplastic syndrome [55]. Mechanistically, thalidomide binds to cereblon, which forms an E3 ubiquitin ligase complex, resulting in the rapid ubiquitination and proteasomal degradation of transcription factors, Ikaros and Aiolos [56]. These two transcription factors are transcriptional regulators of B and T cell development [57].

Metformin (**24**) is an orally available first-line drug and has been widely used for the treatment of type 2 diabetes. The molecular mechanism of metformin involves the activation of adenosine monophosphate (AMP)-induced protein kinase (AMPK), a key enzyme regulating cellular metabolism. Rapamycin (mTOR), a gene that is involved in the survival of cancer cells is negatively regulated by AMPK. Metformin is also able to reduce the signals of mTOR by inhibiting Rag-mediated activation of mTOR [58]. In general, diabetic patients have an increased risk of several cancer types; especially diabetic women have a 20% risk of developing breast cancer. Several studies suggested the anticancer property of drug **24**. The drug **24** at the dose of 250–500 mg/day has been shown to reduce the risk of cancer as well as its daily dose reduces the incidence of gastrological cancer in patients with diabetes [59,60]. Several reviews and meta-analysis suggests that taking drug **24** was associated with reduced risk of all cancer mortality in patients with diabetes [61]. In a recent meta-analysis of several anti-diabetic drugs, it was found that the patients using drug **24** had an overall reduced risk of cancer and decreased mortality rate by 14 and 30%, respectively. Whereas, the use of insulin was associated with an increased risk of cancer and mortality. The recent phase 3 clinical trial studies using the occurrence of colorectal adenomas as a biomarker for cancer as a primary endpoint at 1 year after intervention revealed that metformin reduced both occurrence and number of adenomas/polyps in the patients at low dosage level.

Methotrexate (**25**) is a competitive inhibitor of dihydrofolate reductase (DHFR); a critical enzyme that involved in the synthesis of DNA, RNA, thymidylates, and proteins. The hydrofolate inhibitory activity of drug **25** was responsible for its anti-leukemia activity. Besides, drug **25** was effective against a wide range of malignancies including breast, head and neck, leukemia, lymphoma, lung, osteosarcoma, bladder, and trophoblastic neoplasms [62]. FDA approved this compound in 1988 for the treatment of osteosarcoma, breast cancer, acute lymphoblastic leukemia, and Hodgkin lymphoma. Several reports suggest that the antitumor activity of methotrexate is also due to its ability to target inflammatory pathways. For instance, methotrexate was reported to suppress the NF-κB through the release of adenosine in cancer cells [63].

Rapamycin (**26**), also known as sirolimus, which was originally developed as an anti-fungal agent. However, drug **26** was withdrawn due to its potent immunosuppressant and antitumor activities. Mechanistically, the drug inhibits T cells and B cells by decreasing their sensitivity to IL-2 through inhibition of mTOR, which is highly upregulated in many tumor cells [64]. In the year 1999, FDA, approved rapamycin for the prevention of allograft rejection. After that, this drug has been investigated for its anticancer properties. In recent studies, drug **26** was reported to reduce the colony formation of leukemia progenitor cells in patients with acute myeloid leukemia [64]. In addition to that, drug **26** also showed efficacious in patients with imatinib-resistant chronic myelogenous leukemia through the suppression of vascular endothelial growth factor (VEGF) mRNA levels in leukemia cells with mild side effects [65].

Diclofenac (**27**) is an acetic acid derivative of NSAID class, which has been used to treat pain and inflammatory diseases such as gout. Its mode of action was believed to suppress the production of prostaglandin through inhibition of both COX-1 and COX-2. The drug came into use in the year 1988 in the US. The anticancer

activity of drug **27** has been reported in several cancer types including hepatoma, colon, and fibrosarcoma, pancreatic, and ovarian cancer.

In rat models of fibrosarcoma and hepatoma, the drug **27** significantly reduced the growth rate and the level of vascularization [66]. The drug **27** was found to have an anti-proliferative effect on human colon cancer cell lines [67]. The tumor inhibitory activity of drug **27** was also proved in ovarian cancer [68]. At the molecular level, diclofenac induces apoptosis through inhibition of antioxidant superoxide dismutase 2 (SOD 2), leading to increased levels of reactive oxygen species [69]. Recent Phase II clinical trial study of diclofenac for the treatment of basal cell carcinoma concluded that topical application of diclofenac was highly effective in tumor regression with 64% [70,71].

Naproxen (**28**) is a member of the propionic acid family of NSAID class, which has been used to treat pain and inflammatory diseases such as rheumatoid arthritis, and fever. This drug works by non-selectively inhibiting both COX-1 and COX-2 enzymes, which results in inhibition of prostaglandin synthesis. In 1976, the drug was marketed in the USA for its medical use. Recently the drug **28** has been repurposed for its anticancer activity as it was shown to inhibit cell proliferation, induce apoptosis, and suppress metastasis in various cancer cell types. *In vitro* studies of drug **28** in human urinary bladder cancer cell lines showed that it induces cell-cycle arrest and apoptosis through targeting PI3K [72]. The combination of atorvastatin and naproxen significantly inhibited the colonic adenocarcinomas *in vivo* in animals [73]. In the Phase II clinical trial, it has been investigated in combination with calcitriol for recurrent prostate cancer. The results showed that the combination was well tolerated.

Statin family of drugs are lipid-lowering agents that inhibit the rate-limiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. Statins are commonly prescribed to reduce cholesterol synthesis in patients with a high risk of cardiovascular disease. In addition to that, statins inhibit the mevalonate pathway that provides mevalonate, farnesyl, and geranyl pyrophosphate. These molecules are important for the cell cycle progression and cell proliferation, and therefore statins represent promising candidates in cancer therapeutics. In chronic myeloid leukemia cells, simvastatin (**29**) [74]. and other natural statins including mevastatin (**30**), lovastatin (**31**), and pravastatin (**32**) displayed TNF-induced apoptosis through the down-regulation of NF-κB mediated anti-apoptotic gene products [75]. The anti-cancer activity of statins was also investigated in animal studies, in which statins were effective in reducing the incidence and growth of tumors [76].

Several observational studies and meta-analysis supports the positive correlation of using statins with their chemopreventive effect in humans. Meta-analyses revealed that the use of statins reduced the risk of patients with gastric cancer [77]. as well as esophageal [78], and hepatocarcinoma cancer types [79]. In a case-control study, drug **29** with a dosage of 40 mg/day for 2−5 years significantly reduced the incidence of colorectal cancer [80].

Depakine (**33**) or valproic acid (VPA) is a short-chain free fatty acid mainly used to treat epilepsy, bipolar disorders, and migraine. Its anticonvulsant activity has been attributed to the blockade of voltage-gated sodium channels and increased levels of gamma-aminobutyric acid (GABA) in the brain. Anti-cancer activity of drug **33** was first established in leukemia cells, in which the drug **33** was shown to inhibit histone deacetylase (HDAC) [81]. Depakine has also been found to suppress the production of cytokine and to modulate inflammatory signaling cascade. In human leukemia and human glioma cells, drug **33** was able to suppress the production of IL-6 and TNF-α [82]. In prostate cancer cells, drug **33** suppressed the IL-6 through inhibition of NF-κB activity [83]. Some of the clinical trials of drug **33** have advanced to Phase II for sarcomas, thyroid cancers, acute myelogenous leukemia, B cell lymphoma, breast cancer, melanoma, non-small, and small-cell lung cancers, prostate cancer, recurrent glioblastoma, and relapsed/refractory leukemia (www.clinicaltrials.gov.)

Recently, Abdullah et al. [84] has shown that pitavastatin (**34**) has potential to treat ovarian cancer if dietary geranylgeraniol is controlled. However, relatively high doses of statins are required to induce apoptosis in cancer cells, increasing the risk of myopathy, the most common adverse efect associated with statins. This makes it desirable to identify drugs which reduce the dose of pitavastatin necessary to treat cancer. A drug-repositioning strategy was employed to identify suitable candidates. Screening a custom library of 100 of-patent drugs for synergistic activity with pitavastatin identifed prednisolone (**35**) as the most prominent hit. Prednisolone potentiated the activity of pitavastatin in several assays measuring the growth, survival or apoptosis in several ovarian cancer cells lines. Prednisolone, alone or in some cases in combination with pitavastatin, reduced the expression of genes encoding enzymes in the mevalonate pathway, providing a mechanistic explanation for the synergy pitavastatin inhibited the growth of tested cell lines with an IC_{50} ranging from 1.1 to 4.8 μM. Therefore, clinical trials of prednisolone with pitavastatin in patients with ovarian cancer may be highly warranted.

In case of triple-negative breast cancer (TNBC) and several other cancers, Wnt signaling is overactivated and hence, its suppression emerges as an effective anticancer treatment. However, no drugs targeting the Wnt pathway exist on the market nor in advanced clinical trials. Very recently, Ahmed et al. have provided a comprehensive body of preclinical evidence that an anti-leprotic drug clofazimine (**36**) is effective against TNBC [85]. Clofazimine specifically inhibits canonical Wnt signaling in a panel of TNBC cells *in vitro*. For example, an IC_{50} of 6 μM and 7 μM was exhibited in HEK293T and BT-20 cells respectively. In several mouse xenograft models of TNBC, clofazimine efficiently suppresses tumor growth, correlating with *in vivo* inhibition of the Wnt pathway in the tumors. Clofazimine is well compatible with doxorubicin, exerting additive effects on tumor growth suppression, producing no adverse effects. Its excellent and well-characterized pharmacokinetics profile, lack of serious adverse effects at moderate (yet therapeutically effective) doses, its combinability with cytotoxic therapeutics, and the novel mechanistic mode of action make clofazimine a prime candidate for the repositioning clinical trials. Our work may bring forward the anti-Wnt targeted therapy, desperately needed for thousands of patients currently lacking targeted treatments.

Multiple myeloma (MM, also known as plasma cell myeloma, is a cancer of plasma cells) is an incurable hematological malignancy driven by several genetic and epigenetic alterations. This MM is associated with a variety of genetic and epigenetic events (namely aberrant DNA methylation, histone modifications including methylation, acetylation, ubiquitylation and phosphorylation, actin, and non-coding RNA expression) as well as deregulation of various signaling pathways that regulate DNA repair, RNA editing, protein homeostasis. These epigenetic events have been associated with abnormal signaling by dysregulation of critical pathways controlling cell cycle, apoptosis and drug resistance. Catalano, Raffaella, et al. recently reported anti-tumor activity of hydroxychloroquine (**37**), derivative of chloroquine and an anti-malarial agent also known as autophagy inhibitor). They demonstrated that **37** inhibits the allosteric binding of Polycomb repressive complex 2 (PRC2) to catalytic subunit (EED) within the lysine 27 of histone H3 (H3K27me3) binding pocket and thereby antagonizing the PRC2 catalytic activity [86].

Treatment for acute myeloid leukemia (AML) has not

significantly changed in the last decades and new therapeutic approaches are needed to achieve prolonged survival rates [87].

Bromocriptine (**38**) is an ergoline derivative and dopamine agonist that is used in the treatment of Parkinson's disease, acromegaly, hyperprolactinemia and galactorrhoea, and recently repositioned for diabetes mellitus [88,89].

Repurposing strategy handled by Lara-Castillo, María Carmen et al. has shown bromocriptine as a potent anti-leukemia drug that mainly targets leukemia stem cells [90]. Treatment with **38** reduced cell viability of AML cells by activation of the apoptosis program and induction of myeloid differentiation. Moreover, the LSC-enriched primitive AML cell fraction was more sensitive to the presence of bromocriptine. In fact, bromocriptine decreased the clonogenic capacity of AML cells. Interestingly, a negligible effect is observed in healthy blood cells and hematopoietic stem/progenitor cells. The results support the use of bromocriptine as an anti-AML drug in a repositioning setting and the further clinical validation.

Drugs repositioning for infectious diseases. Severe-acute respiratory syndrome (SARS) is an atypical form of pneumonia, which is caused by a human coronavirus (CoV) called SARS-CoV. The major outbreak was happened in 2003, and it affected more than 800 cases across three continents with a mortality rate of about 10% [91–94]. In 2012, a novel human coronavirus called Middle-East respiratory syndrome coronavirus (MERS-CoV) was discovered, which was associated with severe respiratory tract infection, acute kidney injury, and coagulopathy. The major outbreak was happened in the Republic of Korea in the year 2015. As of July 2015, this virus infected around 1401 people, of which 543 (~39%) was died [95–97]. Typically, the drug-discovery program to develop new potent anti-viral agents and to obtain approval for clinical use takes more than 10 years. Until now, no effective vaccines or drugs are approved treat these infections, although many are in (pre)clinical development. Hence, the drugs that have been used for the treatment of other diseases or disorders that may inhibit the replication of coronaviruses (CoVs) might be useful in an attempt to save the life of several affected patients.

In a search of potential anti-viral agents against MERS-CoV, de Wilde et al. identified four drugs such as chloroquine (**39**), chlorpromazine (**40**), loperamide (**41**), and lopinavir (**42**) from the screening of FDA approved drugs library (Fig. 4) [98]. They all were able to inhibit the replication of MERS-CoV in the low micromolar range. In addition to that, all four drugs inhibited SARS-CoV as well as human coronavirus (HCoV)-229E, which suggests that they could be used for broad-spectral anti-viral activity. As a mode of action, drug **39** inhibited the replication of MERS-CoV in a dose-dependent manner with an EC_{50} value of 3.0 μM through the blockade of the virus at a very early stage. Chloroquine was previously reported as an effective anti-viral agent against flavivirus, influenza virus, HIV [99], Ebola virus [100], and Nipha-Hendra virus [101]. Chlorpromazine (**40**) was another hit compound resulted from the screening and inhibited the replication of MERS-CoV with an EC_{50} of 4.9 μM. It is the first antipsychotic drug developed for the treatment of schizophrenia [102], and mechanistically it inhibited the clathrin-mediated endocytosis. It has also been reported to inhibit the replication of hepatic C virus (HCV) [103], alphavirus [104], mouse hepatitis virus (MHV-2) [105], and another coronavirus SARS-CoV [106]. The mechanistic study of drug **40** on MERS-CoV indicated that it inhibited the virus at both an early and postentry stage, suggesting that an effect on clathrin-mediated endocytosis was not only the sole antiviral mechanism. Loperamide (**41**), an antidiarrheal opioid receptor agonist, which reduces the intestinal motility [107], inhibited the replication of MERS-CoV. Additionally, it inhibited the other two coronaviruses in low micromolar range (4–6 μM). Lopinavir (**42**) is an anti-HIV protease inhibitor, which also inhibited the replication of MERS-CoV with an EC_{50} of 8.0 μM. It was previously reported to inhibit the SARS-CoV main protease (M^{pro}) [108], and therefore, it was presumed that it might also target the M^{pro} of MERS-CoV.

Current anti-MERS-CoV agents have been primarily resulted from previous drugs used for the SARS-CoV infection. To identify potential antiviral agents against MERS-CoV, Shin et al. screened a library consisting of 2334 approved drugs and pharmaceutically active compounds [109]. This yielded a series of hit compounds, primarily categorized as, anticancer (**41**,**42**), antipsychotics (**43**), antidepressent (**44**) and antipsychotic (**45**) with inhibitory activity ranging from 2.1 to 14.4 μM (Fig. 4). Among them, saracatinib (**46**) was particularly important as it showed an excellent anti-MERS-CoV activity with an EC_{50} of 2.9 μM and a CC_{50} > 50 μM. Saracatinib (**46**) is an orally available small molecule drug used for the treatment of tumor malignancies through the inhibition of Src-family tyrosine kinases (SFKs). It also inhibited other coronaviruses SARS-CoV (EC_{50} 2.4 μM) and HCoV-229E (EC_{50} 5.1 μM) and feline infectious peritonitis (FIPV, EC_{50} 7.0 μM) within a not-toxic range of concentration.

An *in vitro* study of the anti-viral effect of the drug **46** had found to inhibit the early stages of MERS-CoV life cycle in Huh-7 cells through a possible suppression of SFK signaling pathways. Interestingly, co-treatment of the drug **46** with gemcitabine, a deoxycytidine analog that is commonly used for the treatment of cancers [110,111], showed a synergistic anti-viral effect with a minimal cytotoxic effect. This supports the hypothesis of using them in a combination therapy to treat CoV diseases.

Drugs repurposed against dengue virus infection. Dengue fever is a life-threatening disease caused by four antigenically distinct dengue virus serotypes. It became a global burden, which causes approximately 390 million infections each year, of which around 10,000 to 20,000 people die. Even though a vaccine against dengue is available, its long-term protective action against each of the serotypes of dengue virus remains yet to be determined. Besides, currently, no clinically approved antiviral therapy is available to combat this virus. Among the many approaches applied to identify novel drugs for dengue fever, drug repurposing gained much attention to the scientific community.

Several antiviral, antimalarial, antidiabetic, antihistamine, anticancer, antipsychotic, antiparasite, and anticholesteremic drugs have been repurposed to combat dengue virus infection. A recent publication by Botta et al. discussed each class of drugs and its repositioning in detail [112]. To identify novel and potent drug candidates, approved drugs such as lovastatin (**31**), chloroquine (**39**), prednisolone (**51**), balapiravir (**52**), and celgosivir (**53**) were investigated for the proof-off concept clinical trials for dengue viral infection (Fig. 5). Although the results showed that they were safe in patients with acute dengue, drugs failed to meet prior–defined trial endpoints [112–116]. Besides, two clinical trials conducted in Thailand and Singapore involving ivermectin (**54**) and ketotifen (**55**), the preliminary result was quite promising as phase 2 study of the drug **54** suggested a reduction in serum NS1 levels and body temperature [117].

Recently, Malakar et al. screened various classes of FDA approved drugs including aminolevulinic acid (**56**), azelaic acid (**57**), mitoxantrone hydrochloride (**58**), quinine sulfate (**59**) and tested their ability to inhibit dengue virus (DENV) replication [118,119].

Aminolevulinic acid (**56**), an endogenous non-proteinogenic amino acid, and azelaic acid (**57**) are used to treat skin diseases [120,121], while mitoxantrone hydrochloride (**58**), an anthracenedione antineoplastic agent is used for the treatment of leukemia [122]. Quinine sulfate (**59**) is a natural compound extracted from Cinchona bark, which is commercially available in 324-mg tablets under the brand name qualaquin. It has been widely used to treat

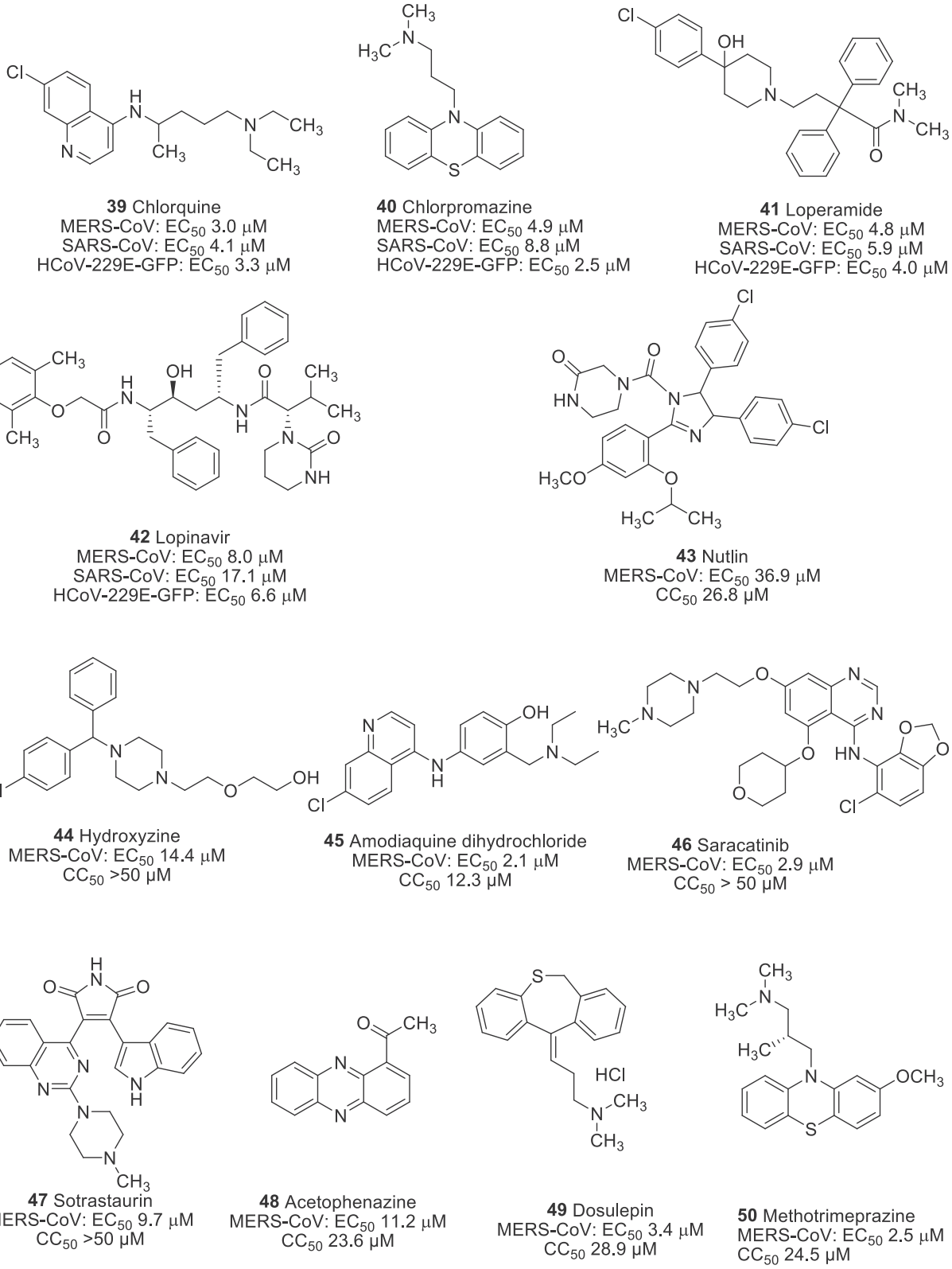

Fig. 4. Drugs repurposed on MERS-CoV and SARS-CoV infections.

chloroquine-resistant *plasmodium falciparum* [123]. Its ability to reduce the viral replication was also demonstrated against herpes simplex virus (HSV) [124], and influenza virus [125]. Among these four drugs investigated, the drug **59** was found to be very effective in inhibiting the replication of DENV by about 80% compared to untreated controls, while the others showed only moderate

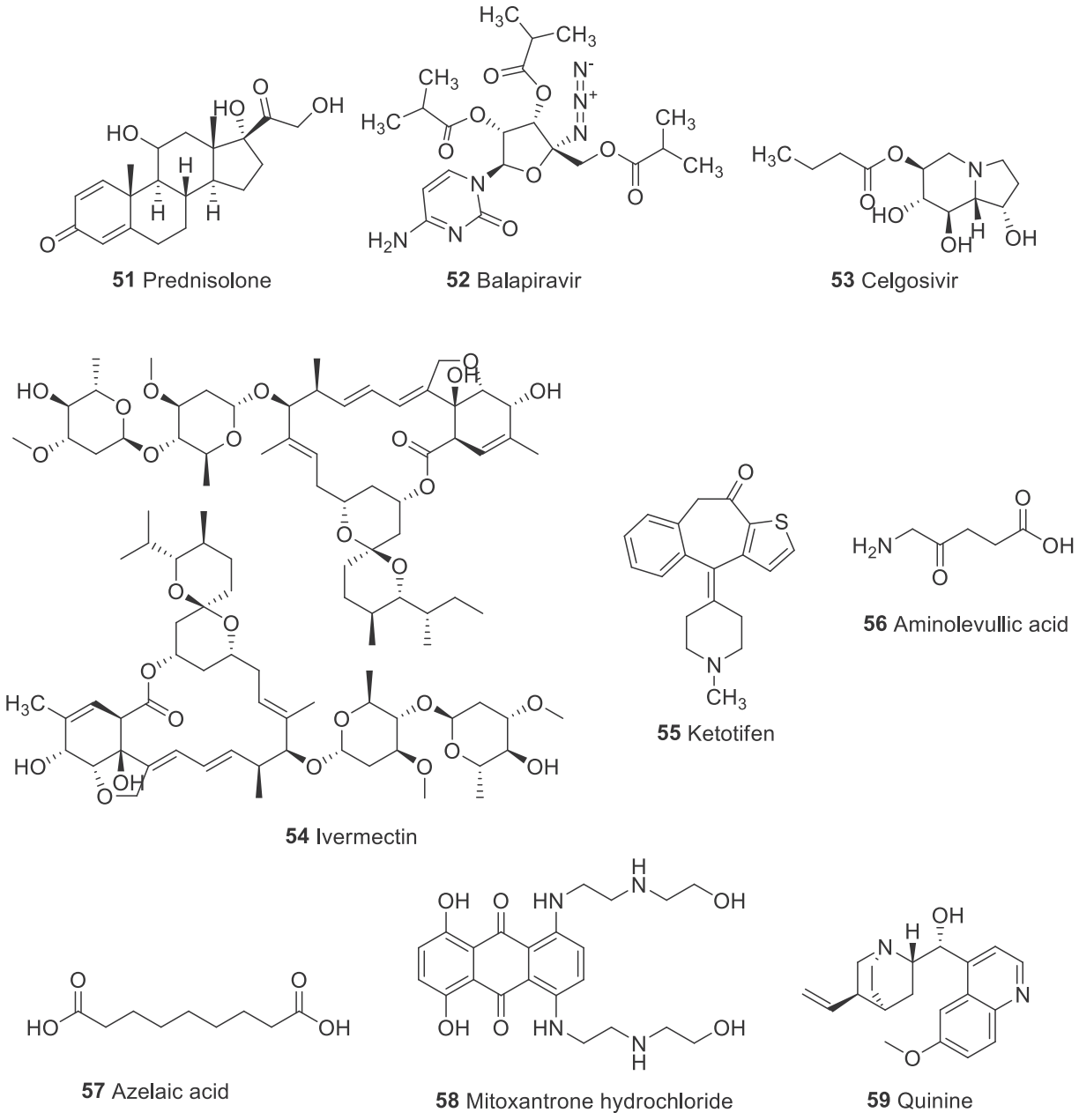

Fig. 5. Representative example of drugs repurposed for dengue infections.

reduction of about 50%.

It was very impressive that drug **59** was able to reduce virus replication of all four serotypes of DENV in three different cell lines of human origin. At the molecular level, it inhibited DENV replication by reducing viral protein and RNA synthesis in a dose-dependent manner. Moreover, drug **59** enhanced the expression of genes related to innate immune response. These findings suggest that the efficacy of drug **59** for stimulating antiviral genes, which led to reduce DENV replication.

Repurposing on malarial infection. Malaria is a life-threatening disease caused by protozoan *Plasmodium* parasites. In 2017, it was estimated that approximately 219 million people were affected by malarial infections, of which 435000 died [126]. Huge efforts have been taken to prevent or cure malaria over the decades, and as a result, the mortality rates are reduced to 60%. Nevertheless, it continues to be a big problem around the world.

Although several drugs including quinine and quinoline derivatives [127,128] could moderately treat the infection, the emergence of drug-resistant strains of *Plasmodium falciparum* makes it more challenging in malaria treatment. Therefore, the discovery and development of new antimalarial agents with a different mechanism of action that may not only reduce mortality and morbidity of the disease, but also reduce the risk of resistance to existing antimalarial drugs are highly required.

To identify potential drug candidates, two groups [129–131] conducted drug-repositioning approach of FDA approved drugs. Chong et al. screened around 189 drug molecules at 10 μM concentration against blood-stage *P. falciparum*. Derbyshire et al. analyzed 37 drugs in a liver-stage *P. berghei* model. Out of tested 226 drug molecules, 18 were selected as highly potent candidates with an IC_{50} value of ~2.5 μM (see Fig. 6) [129]. It is interesting to note that out of 18 drugs, four including clemastine fumarate (**60**),

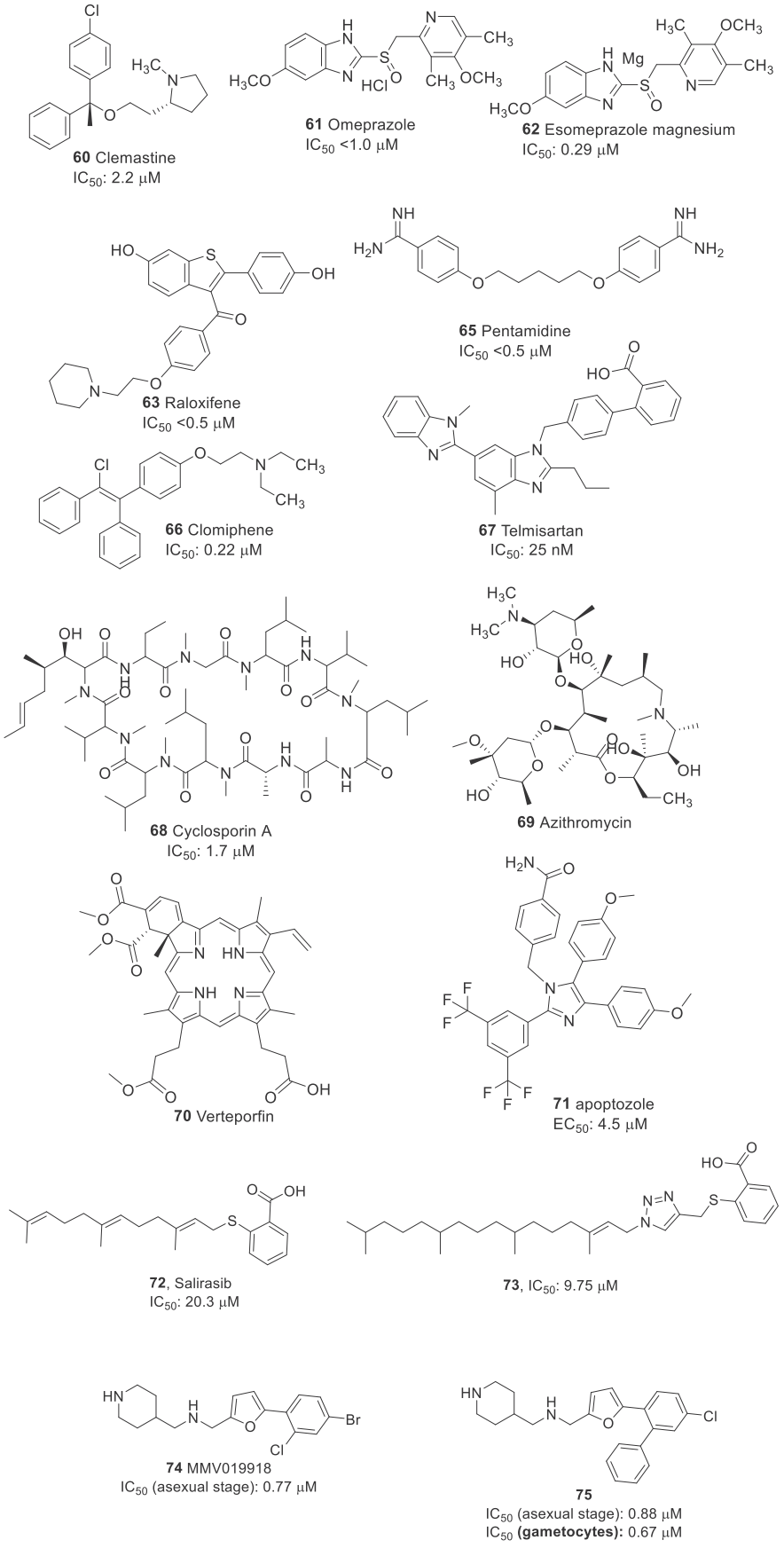

Fig. 6. Repurposing of potent drug molecules for malarial infection.

loperamide hydrochloride (**36**), omeprazole (**61**), and esomeprazole magnesium (**62**) are the over-the-counter (OTC) drugs, which can be easily accessed by patients in high-risk areas, while other 14 drugs can be obtained *via* prescription only. Clemastine (**60**), an ethanolamine derivative is a first-generation H1 antagonist (antihistamine) associated with anticholinergic properties.

This drug came into use in the year 1967 to prevent hay fever and allergy symptoms. Loperamide (**41**) is a medication used to decrease the frequency of diarrhea. Both drugs **41**, and **59** were effective against blood-stage *P.falciparum* with IC_{50} values of 2.2 μM and 0.29 μM, respectively. Omeprazole and esomeprazole are used in the treatment of gastroesophageal reflux disease, peptic ulcer, and Zollinger-Ellison syndrome. They were tested against liver-stage *P.berghei* and showed IC_{50} values < 2 μM, make them potential lead for the development of novel anti-malarial agents. These all four OTC drugs are orally administered, which has the advantageous to develop as anti-malarial therapy.

From another set of prescribed drug candidates (**63**–**70**) were tested against blood-stage *P. falciparum* cultures (Fig. 6**)** and liver-stage *P. berghei* [129,130]. They all showed promising antimalarial activity with IC_{50} values ranged from 2.8 μM to 1.7 nM. Drugs raloxifene hydrochloride (**63**), gramicidin A (**64**, structure was not shown), pentamidine isethionate (**65**), clomiphene citrate (**66**), telmisartan (**67**) and cyclosporin A (**68**) showed IC_{50} values < 1 μM [129,130]. The rank order potency of them are as follows: **67** (25 nM) ≫**66** (0.22 μM) >**63** (<0.5 μM) ~ **64** (<0.5 μM) ~**65** (<0.5 μM) >**68** (1.7 μM).

Most of these prescribed drugs (11 of 14) can be injectable, oral or topically administered. Other drugs like azithromycin (**69**), **65**, and **68** can be administered through multiple routes. Azithromycin (**69**), an azalide antibiotic, can be administered orally, topically or intravenously. Drug **65**, an antiprotozoal agent, can be administered either as an intravenous, intramuscular injection or as an inhalable powder. Cyclosporin A, an immunosuppressant drug, can be administered orally, topically or intravenously.

Recently Chen et al. repurposed chaperone inhibitors that are anticancer agents, at the PfGRP78 as a potential drug target against *P. falciparum*, and identifed apoptozole (**71**, Fig. 6), a novel chemical scafold that inhibits chaperone function and prevents parasite growth *in vitro* [132]. Further, the identifcation of apoptozole as a PfGRP78 inhibitor open the possibility to use this compound as a chemical probe to study the role if this chaperone in artemisinin resistance mechanisms.

Salirasib (**72**, Fig. 6) is a promising cancer drug candidate inhibits isoprenylcysteine carboxyl methyltransferase (ICMT), a validated target for cancer drug development. Recently, Salirasib and its analogs with 1,2,3-triazole were repuposed for their pontential antimalarial activity [133]. In general, triazole derivatives are known to have potent antimalarial activity [134]. Compound were investigated the *in vitro* toxicity to *P. falciparum* in the asexual stages and in Vero cells. An antiplasmodial activity assay was performed using a simple, high-sensitivity methodology based on nanoluciferase (NLuc)-transfected *P. falciparum* parasites. The results showed that some of the analogs were active at low micromolar concentration, including Salirasib. The most potent member of the series has *S*-farnesyl and the 1,2,3-triazole moiety substituted with phytyl, for example compound **73** (Fig. 6. Moreover, compounds show less cytotoxicity in eukaryotic cells indicates good therapeutic indices, being starting point for the development of antimalarial drug. Vallone et al. recently discovered MMV019918 (**74**, 1-[5-(4-bromo-2-chlorophenyl)furan-2-yl]-N-[(piperidin-4-yl) methyl]methanamine, Fig. 6) and its analog **75 (**Fig. 6), for their dual activity against *P. falciparum* asexual stages and gametocytes through the standard membrane-feeding assay [135]. They both significantly prolonged atrioventricular conduction time in Langendorff-isolated rat hearts, and showed inhibitory activity of Ba^{2+} current through Cav1.2 channels. Compound **75** showed interesting activity against PfPMT, which could be an important starting point for the identification of more potent inhibitors active against both sexual and asexual stages of the parasite.

Drug repurposed on Neurodegenerative diseases. In general, neurodegenerative diseases including amyotrophic lateral sclerosis, Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD) occurs because of several neurodegenerative processes.

Drug repositioned on Alzheimer's disease (AD). Dementia is a general term for a decline in mental ability severe enough to interfere with daily life. Memory loss is an example. Alzheimer's is the most common type of dementia. It affects around 5% of people over the age of 65, 20% over the age of 80, and more than a third of those over the age of 90 [136]. In the year 2015, there were approximately 29.8 million people worldwide with AD of which dementia resulted in about 1.9 million deaths. It is estimated that there will be more than 115 million people with dementia worldwide by 2050. Therefore, AD represents a major and rising public health concern, and there is an urgent need to develop more therapies that are effective.

AD refers to a devastating condition leading to progressive cognitive decline, functional impairment, and loss of independence. Accumulation of amyloid-β peptide (Aβ)-enriched neuritic plaques, and neurofibrillary tangles, synaptic, and neuronal dysfunction, as well as loss in combination with the associated neurochemical changes in the brain, are the crucial pathological event for AD [137]. Recent work suggests that higher levels of total tau may potentiate the toxic effects of Aβ [138]. Other factors such as inflammatory processes and mitochondrial function are also likely to have an important role [139].

Three acetylcholinesterase inhibitors including donepezil (**76**), rivastigmine (**77**) and galanthamine (**78**, Fig. 7) are approved for the treatment of patients with mild to moderate AD. Memantine, an NMDA (*N*-methyl-*D*-aspartate) receptor antagonist, is approved for the treatment of patients with moderate to severe AD. Meta-analyses and cost-effectiveness evaluations have demonstrated that this repurposing confer moderate symptomatic benefits and are cost-effective [140]. For example, acetylcholinesterase inhibitors improve cognition to above pre-treatment performance for ~6–12 months. The availability of these drugs has substantially advanced the treatment of patients with AD, but there is a persistent need to build on our increasing understanding of disease pathogenesis to develop more effective symptomatic treatments and disease-modifying therapies.

Current study carried out by Hassan et al. [141] utilized both computational and enzyme inhibitory experimental kinetic approaches to evaluate the repositioning of known FDA approved drugs for AD. The computational shaped-based virtual screening results showed that from 1516 FDA approved drugs, 36 displayed good structural similarity with standard template donepezil. Moreover, docking profile and pharmacogenomics evaluations depicted that out of 36 only five drugs were most active and showed good results compared to other drugs. The MD simulation results exposed that these five drugs (Risperidone, Domperidone, Verapamil, Tamsulosin and Cinitapride) showed better profiles with respect to their RMSD, RMSF, SASA and Rg evaluations graphs and steady stable behavior in all docking complexes. *In-vitro* AChE inhibition assay of the above best-screened drugs were performed by spectrophotometric method using acetylthiocholine iodide as substrate. The enzyme inhibition and kinetic mechanism of these drugs showed that Cinitapride (**79**) has good therapeutic potential with respect to standard and other drugs. It is well known that, Cintapride (**79**) is a gastroprokinetic agent and antiulcer agent of

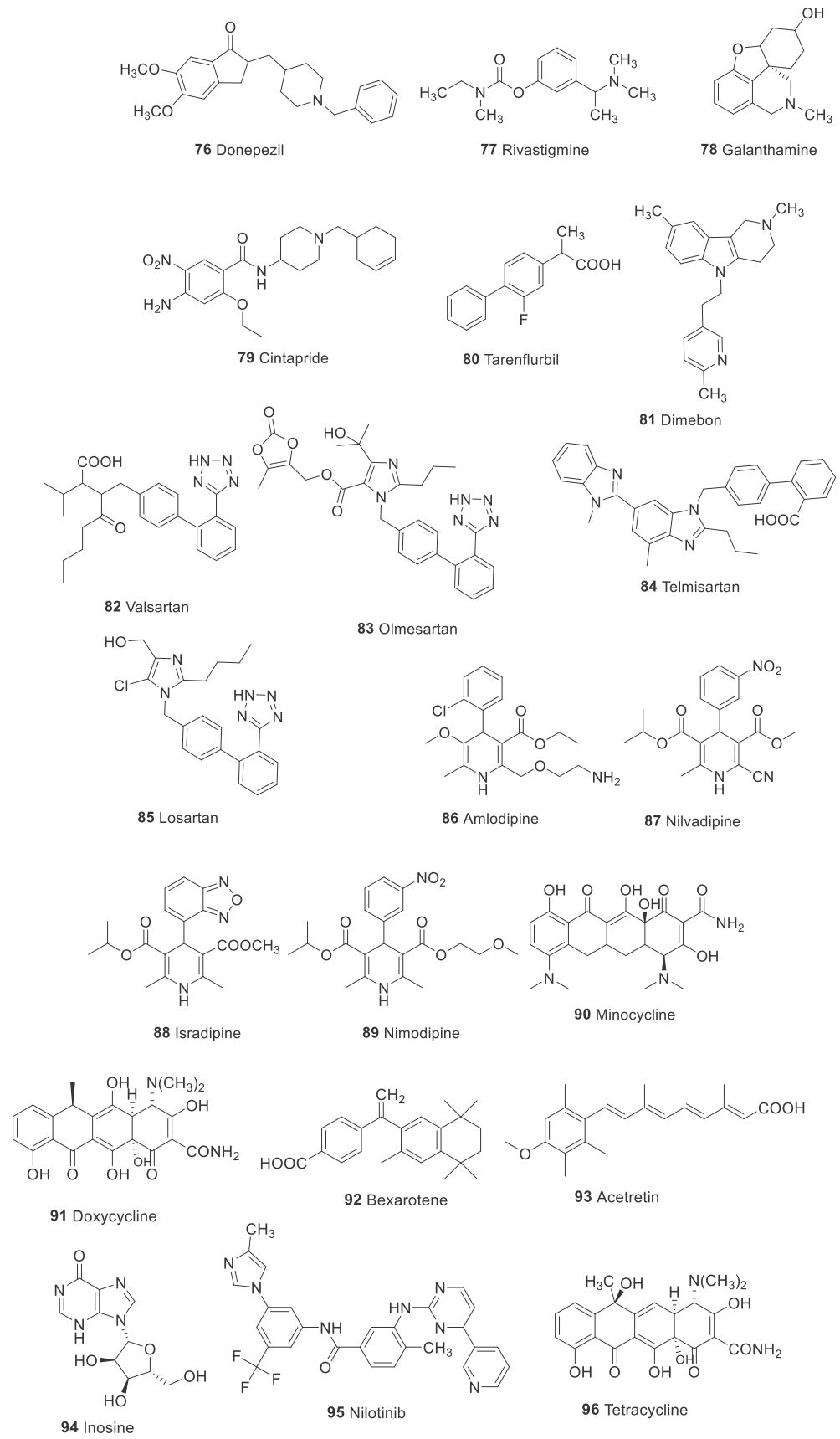

Fig. 7. Drugs repurposed for Alzheimer's disease.

the benzamide class [142]. It is an agonist of 5-HT_1 and 5-HT_4 receptors and as an antagonist of the 5-HT_2 receptors [143]. Based on aforementioned results, it is justified that Cinitapride has better repositioning profile which may be used in the treatment of AD after clinical assessment.

Efforts to develop more effective therapies have so far been unsuccessful with several high-profile clinical trial fails to demonstrate the benefit. The reasons for this are probably multifactorial. The majority of putative disease-modifying therapies that have been evaluated have targeted amyloid pathology. This lack of breadth in treatment approaches has been criticized, and some commentators have argued that a more sophisticated knowledge of disease pathways is needed before we can develop more effective candidate therapies.

For example, Phase II trial of tarenflurbil (**80**, Fig. 7) only provided a suggestion of benefit in a posthoc subgroup analysis [144,145]; the putative mechanism of action via γ-secretase modulation and its related impact on amyloid pathology was never confirmed in patients with AD. Subsequent Phase III trial had negative outcomes. Although, the results of a Phase II trial of dimebon (**81**) were much more favorable than of analog **80** (Fig. 7). It seems that the significant benefit seen in the treatment group was driven by a larger-than-expected deterioration in the group receiving placebo treatment, and the mechanism of action was not well characterized.

In the central nervous system (CNS), angiotensin II mediates key processes including, the release of inflammatory mediators, vasoconstriction, mitochondrial dysfunction, and inhibition of acetylcholine release at central synapses. All of which are proposed to be relevant to AD and are potential targets for therapeutic intervention [146,147]. Based on this background, it has been proposed that angiotensin receptor blockers (ARBs) may confer symptomatic benefits on cognition.

A large-scale screen of 55 antihypertensive drugs by Want et al. [148], identified the ARB valsartan (**82**, Fig. 7) as the only compound that was able to reduce Aβ accumulation in cultured neurons and inhibit Aβ aggregation *in vitro*. The same group was demonstrated that the reduced plaque burden as well as the improved learning and memory in cognitive tests (including the Morris water maze task) following 5 months of treatment with valsartan in 6-month-old Tg2576 transgenic mice. As a result, the greatest benefits were seen at a dose of 40 mg/kg/day, which is equivalent to 1.5 times the maximum recommended dose for treating patients with hypertension.

Using another ARB, olmesartan (**83**, Fig. 7) by Takeda et al. [149], demonstrated that daily treatment of young APP23 mice for one month improved cerebral blood flow without affecting Aβ1-40 and Aβ1-42 levels. In the Aβ1-40-injected mouse model, in which Aβ fragments are injected intracranially to generate deficits, pretreatment with telmisartan (**84**, Fig. 7) increased cerebral blood flow and inhibited the plaque deposition [150]. However, the physiological relevance of this model is unclear. Perhaps, the most striking preclinical evidence comes from a study in which losartan (**85**, Fig. 7) was administered intranasally to APP/PSEN1 mice, at a dose much lower than that mediating hypotensive effects; drug **80** led to a 3.7-fold reduction in Aβ plaques compared to vehicle-treated mice but also reduced the levels of pro-inflammatory mediators and increased the levels of anti-inflammatory mediator IL-10 in the serum of these animals [151,152]. Overall, there was significant reduction in the incidence of dementia in patients taking ARBs compared to those taking the comparator cardiovascular drugs (hazard ratio: 0.76; 95% confidence interval: 0.69–0.84) and those taking angiotensin-converting enzyme (ACE) inhibitor lisinopril (hazard ratio: 0.81; 95% confidence interval: 0.73–0.90).

Although the evidence for the potential of ARBs in AD is conflicting, and difficult to interpret, in our view, there is a sufficient indication of potential benefit to merit further *in vivo* work to clarify the relative importance of different mechanisms, the optimal dose, and the optimal agent, which could lead to proof-of-concept study in patients with AD. The best evidence from *in vitro* and *in vivo* studies points to either drug **85** or **84** as a preferred ARB, with some animal studies also highlighting drug **83** as a potential candidate. However, there is an unfortunate disconnect between *in vivo* and clinical studies, as no formal studies to provide direct clinical evidence have so far been conducted on any of the most promising candidates.

Calcium channel blockers (CCBs) of the dihydropyridine class are widely used to treat hypertension and angina through their vasodilatory activity on smooth muscle vasculature. Most of the drugs in this class have good blood-brain barrier penetration and induces cerebral vasodilatation, increased cerebral blood flow in animals and humans [153]. *In vitro* studies have revealed that certain CCBs reduce Aβ production, oligomerization, and accumulation, rescue Aβ-induced neurotoxicity, and improve cell survival in the presence of Aβ [154–156]. CCBs have also been shown to reduce glutamate-induced cell death and levels of intracellular calcium [157]. The ability of CCBs to prevent Aβ1-40 and Aβ1-42 production was investigated in Chinese hamster ovary cells (CHO) by Paris et al. and Iwasaki et al. In that study, amlodipine (**86**) and nilvadipine (**87**) (Fig. 7) were identified as the only agents that inhibited Aβ production [158]. However, the concentrations studied were several-fold higher than can be achieved therapeutically.

Isradipine (**88**, Fig. 7) was shown to have a neuroprotective effect against Aβ-induced apoptosis in neuroblastoma MG65 cell lines. A protective effect in a *Drosophila melanogaster* model of Aβ-induced neurotoxicity and it's brain-penetrant in the 3xTg-AD mouse model of AD was also reported [156,159]. The differential effects of CCBs indicate that their potential benefits in AD are probably independent of their anti-hypertensive activity and may be specific to individual drugs within this class. Dihydropyridines seem to be more effective than compounds with different chemical structures (such as verapamil or diltiazem), with evidence from preclinical studies that highlighted nilvadipine (**87**) as the best therapeutic candidate.

There was some clinical evidence regarding the potential benefit of the CCB nimodipine (**89**, Fig. 7) in patients with clinically significant dementia. The evidence has been summarized in a Cochrane review 51 of 15 nimodipine trials in more than 3000 patients with dementia. The review reported that the treatment showed efficacy in improving cognition, but not activities of daily living, at doses of 90 mg/day [160]. However, the evidence was limited by small size and duration (mostly 12 weeks) of trials as well as the lack of operational diagnostic criteria for AD or vascular dementia.

Tetracycline antibiotics are widely used to treat bacterial infections and are well tolerated in older people, but most of the treatment data pertain to short-term periods of exposure. Studies related to AD have predominantly focused on minocycline (**90**, Fig. 7) because it is the most lipophilic tetracycline, with greater blood-brain barrier penetration than other agents in this class. Concerning preclinical studies, the drug **90** has been shown to reduce Aβ1-42 aggregation, and promote disassembly of preformed fibrils *in vitro* studies.186 Various groups have independently shown that drug **90** reduces the levels of proinflammatory mediators and microglial activation in a range of mouse models of AD [161–165]. Besides, two of the three studies using transgenic mouse models of AD for 28 days or more of treatment have shown a significant decrease in cerebral Aβ accumulation and improvements in behavioral outcomes as well [165]. One of these studies used 8-month-old 3xTg-AD mice and reported reductions in

cortical amyloid levels following 4 months of minocycline treatment, but no changes in tau pathology was observed.190 The third study reported that no benefit concerning amyloid accumulation or behavior over a treatment period of 12 months.194 An additional study in a rat model of diabetes demonstrated a reduction in Aβ1-40 and Aβ1-42 levels and associated improvements in behavioral outcomes over 8 weeks of treatment [165].

Doxycycline (**91**) is a second generation antibiotic of the tetracycline class that are promising drugs tested in many clinical trials for a number of different pathologies. Compound **91** is endowed with antiamyloidogenic properties and better crosses the blood-brain barrier, but its efficacy has never been tested in AD mice. Balducci, Claudia, et al. showed that 15- to 16-month-old APP/PS1dE9 (APP/PS1) AD mice receiving 96 under different treatment regimens recovered their memory without plaque reduction. An acute 96 treatment was, also, sufficient to improve APP/PS1 mouse memory, suggesting an action against soluble AbOs. This was confirmed in an AbO-induced mouse model, where the AbO-mediated memory impairment was abolished by a its pretreatment. Although AbOs induce memory impairment through glial activation, assessing the anti-inflammatory action of 96, we found that in both the AbO-treated and APP/PS1 mice, the memory recovery was associated with a lower neuroinflammation. Our data promote 96 as a hopeful repositioned drug counteracting crucial neuropathological AD targets [166].

Drugs that activate retinoic acid receptors (RARs) are used to treat several skin-related conditions such as acne and psoriasis. Retinoic acid is also vital for normal nerve function and repair. There is genomic and epidemiological evidence suggest that impaired retinoic acid signaling may contribute to the etiology of AD [167]. Chronic deprivation of retinoic acid in rats leads to deposition of Aβ in the vasculature [168] and dysregulation of amyloid processing in the cortex [169]. It has been shown that treatment with retinoid X receptor (RXR) agonist bexarotene (**92**, Fig. 7), which is approved for the treatment of cutaneous T cell lymphoma, leads to pathological and behavioral improvements in transgenic mouse models of AD. Acute treatment with drug **92** (lasting less than 14 days) caused a rapid reduction (25%) in Aβ1-40 and Aβ1-42 levels and Aβ plaque burden in both young and old mice [170]. Chronic 90-day treatment resulted in a sustained reduction (30%) insoluble Aβ levels.

Mechanistically, drug **93** resulted in the upregulation of components of the high-density lipoprotein (HDL) pathway such as apolipoprotein E (APOE), which promotes the proteolytic degradation of Aβ [171]. Further, potential mechanism of action of retinoids may include the upregulation of enzymes involved in amyloid clearance such as insulin-degrading enzyme [172] and components of the APOE pathway [170]. Retinoids may also induce potentially beneficial changes related to insulin signaling and increased neurogenesis and promote neuronal differentiation of progenitor cells [173,174]. Retinoids also act as antioxidants (by regulating SOD and inhibiting glutathione depletion to reduce mitochondrial damage) as well as anti-inflammatory agents (by reducing the production of IL-6) *in vitro*. Both of these activities have potential importance in AD pathology [175,176]. Therefore, there was a strong mechanistic rationale for the potential benefit of retinoid therapies beyond amyloid modulation, but there is a need to further clarify the impact of treatment on these pathways through *in vivo* studies. Overall, studies in the literature indicate that retinoids have strong potential mechanistic plausibility as therapies for AD owing to their effects on APP processing, Aβ clearance, insulin signaling, and neurogenesis. Out of the approved drugs, data for bexarotene have provided proof of concept as potential candidate for the treatment of Alzheimer's disease as noted above, whereas acitretin (**93**, Fig. 7), which is known to penetrate tissues including brain may also be a promising candidate for AD [177].

Repurposing on Parkinson's disease (PD). It is a long-term degenerative disorder of the CNS, which mainly affects the motor system. As of 2015, PD affected 6.2 million individuals, of which 117400 people died. It usually occurs people over the age of 60, of whom about one percent are affected. In addition to the classic motor symptoms caused by the death of dopaminergic neurons, Parkinson's disease encompasses a wide range of nonmotor symptoms. Although novel disease-modifying medications that slow or stop Parkinson's disease progression are being developed, drug repurposing, which is the use of existing drugs that have passed numerous toxicity and clinical safety tests for new indications, can be used to identify treatment compounds. This strategy has revealed that tetracyclines (**96**) are promising candidates for the treatment of Parkinson's disease [178]. Tetracyclines, which are neuroprotective, inhibit proinflammatory molecule production, matrix metalloproteinase activity, mitochondrial dysfunction, protein misfolding/aggregation, and microglial activation. Two commonly used semisynthetic second-generation tetracycline derivatives, minocycline (**90**) and doxycycline (**91**), exhibit effective neuroprotective activity in experimental models of neurodegenerative/neuropsychiatric diseases and no substantial toxicity. Moreover, novel synthetic tetracyclines with different biological properties due to chemical tuning are now available. In this review, we discuss the multiple effects and clinical properties of tetracyclines and their potential use in Parkinson's disease treatment. In addition, we examine the hypothesis that the anti-inflammatory activities of tetracyclines regulate inflammasome signaling. Based on their excellent safety profiles in humans from their use for over 50 years as antibiotics, we propose the repurposing of tetracyclines, a multitarget antibiotic, to treat Parkinson's disease.

Isradipine (**88**) is an L-type calcium channel blocker of the dihydropyridine class, which has been widely used for the treatment of high blood pressure to reduce the risk of heart attack and stroke. This drug **88** came into medical use in the year 1989. Epidemiological data support that calcium channel blockers may have the potential to reduce the risk of developing PD. Among dihydropyridines, drug **88** has attracted very much as it inhibits the subtype Cav1 Ca2+ channels Cav1.2 and Cav1.3, which are most likely mediate the risk in PD. Moreover, the good brain bioavailability of drug **88** has made it the most promising candidate for repurposing [178,179]. Studies have shown that drug **88** dose repentantly protect the dopaminergic neurons from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine MPTP) and 6-hydroxydopamine (6-OHDA)-induced toxicity by reverting dopaminergic neurons to a latent juvenile pacemaking mechanism independent of calcium [180,181]. An open-label, dose-escalation study assessing safety (STEADY-PD) of drug **88** controlled release 5−20 mg/day in patients with early PD suggested that the acceptable tolerability at doses of $\leq$10 mg per day; however at higher doses caused leg edema and dizziness [182]. Isradipine (**88**) with 10 mg being the highest dosage was again confirmed in another STEADY-PD-II, a randomized, double-blinded trial, which was undertaken in 99 subjects with early PD not requiring dopaminergic therapy [183]. Results suggest that the most common adverse effect was peripheral edema, which occurred in 34% of patients receiving drug **88** (10 mg). Placebo-controlled phase III clinical study to assess the efficacy of drug **88** (10 mg daily) as a disease-modifying agent in early PD was completed in November 2018 [184]. The study recruited 336 patients with early PD not requiring dopaminergic therapy and followed them prospectively for 36 months, with the primary outcome designated as a change in the unified Parkinson Disease Rating Scale (UPDRS) Part I-III score as measured

in the ON state. The results are expected in the middle of 2019. In animal models, drug **88** reported with neuroprotection effect in a dose-dependent manner, higher doses confirmed better protection.

Inosine (**94**, Fig. 7) is a purine nucleoside, which has been used as a dietary supplement by athletes for improving aerobic performance. It has been shown to have neuroprotective roles by elevating the level of serum urate, a natural antioxidant and peroxynitrite scavenging property with potential benefits to patients with multiple sclerosis. Many studies suggest that individuals with increased levels of urate in serum have a reduced risk of developing PD, as well as in patients with PD are associated with a reduced rate of disease progression. Moreover, in toxin-based models of PD, increased urate levels have conferred protection against dopaminergic cell death stimulated by MPTP, 6-OHDA, and rotenone. Akt-GSK-3B signaling and nuclear factor (erythroid-derived-2)-like 2 (Nrf2) were thought to involve in these effects. Therefore, given the data supporting a neuroprotective role of urate, inosine has been repurposed in the pathogenesis of PD. The ability to raise urate level of drug **88** in serum was demonstrated in SURE-PD, a randomized, double blind, placebo-controlled in 75 patients with early PD not yet requiring any medication. The results showed that inosine raised the mild urate level (6.1–7.0 mg/dl) or moderate urate elevation (7.1–8.0 mg/dl) after 25 months and well-tolerated with favorable progression rate in UPDRS score, which amounted to ~1 point per year on the total UPDRS scale. On the other hand, the elevated level of urate in serum have the risk of hypertension, coronary heart disease, and stroke over the long term. These side effects are potentially limiting its utility in older patients with PD. However, in patients of Asian origin with PD, inosine elevated urate levels (6.1–7.0 mg/dl) without side effects after 1 year of treatment was reported. The multicenter SURE-PD3 trial, which involves a large number of patients (240 patients), is currently underway intending to elevate the urate level to 7.1–8.0 mg/dl. The result of the study will be expected in the year 2020.

Simvastatin (29), Since statins are also known to modulate various biological processes relevant to the pathogenesis of PD [185,186]. Simvastatin has been repurposed for treating this disease. Pretreatment with simvastatin preserved dopaminergic cells and motor behavior in rodents treated with 6-hydroxydopamine (6-OHDA), promoting antioxidant protein expression or *via* modulation of NMDA receptor and pro-inflammatory cytokine expression [187-189]. Similarly, in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) models, pretreatment with simvastatin suppressed activation of NF-κB, protected dopaminergic neurons, and improved the motor function [190,191]. Although, stains, in general, have given encouraging preclinical studies, epidemiological data regarding the association between usage of statins and the risk of PD are unclear. Moreover, the modest protective effect of statins that disappeared when adjusted for cholesterol level [192]. However, due to the promising biochemical and pharmacological properties of simvastatin, it is currently being examined with 235 patients having moderate-stage PD in phase II double-blind, randomized, controlled, multicenter trial.

Nilotinib (**95**, Fig. 7) is a selective c-Abl tyrosine kinase inhibitor approved for the treatment of imatinib-resistant chronic myelogenous leukemia (CML). Accumulating evidence suggests that c-Abl activation has been linked in the pathogenesis of PD and other synucleinopathies. Activated (phosphorylated) c-Abl has been found in a high level in post-mortem studies of patients with PD [193,194]. It was also reported that activation of c-Abl in mice induces neurodegeneration in the hippocampal and striatal brain areas [195]. Continuous work has demonstrated that c-Abl phosphorylation occurs as a result of mitochondrial dysfunction, and oxidative stress [196], which can promote the accumulation of α-synuclein in through effects on autophagy mechanisms [195] and can further promote phosphorylation of parkin, causing inhibition of its ubiquitin E3 ligase activity, inducing mitochondrial dysfunction and dopaminergic neuronal death [194]. All the above evidences propose that c-Abl may be a promising therapeutic target in the management of PD. The CNS penetration of nilotinib over other Abl inhibitors has favored it to fetch more data in PD related studies. Indeed, in preclinical models of PD, drug **92** has been shown to cross the blood-brain barrier and reduces c-Abl activity, ameliorating autophagic clearance of α-synuclein in transgenic and lentiviral gene-transfer models [195]. More importantly, these effects were seen at doses far lower (1–10 mg/kg/day) than those used to treat CML, which is considered as the key characteristics for potential drug repurposing. Furthermore, nilotinib prevented dopaminergic cell loss and motor impairments induced by MPTP in mice, which were associated with inhibition of parkin phosphorylation and reduced accumulation of parkin substrate PARIS, thus hinting at another potential mechanism of action [197,198]. Based on these preclinical data, a small, open-label proof-of-concept study was recently conducted to evaluate the safety and tolerability of nilotinib in 12 patients with PD dementia or dementia with Lewy bodies followed-up for 24 weeks, followed by a final assessment 12 weeks later [199]. The necessary lowest choice of dose for the clinical study was taken as 150–300 mg. The authors reported that nilotinib was well tolerated, though one patient receiving 300 mg was diagnosed with myocardial infarction, and two had transient QTc prolongations. There was also evidence of CNS penetration with nilotinib CSF plasma ratio of 12 and 15% with 300 and 150 mg, respectively. Due to numerous methodological limitations, these findings should be interpreted with caution [200]. Due to unwanted off-target nonselective tyrosine kinase inhibition; side effects of nilotinib at doses used to treat CML include cardiac conduction abnormalities. Therefore, claims of tolerability should be interpreted with caution. Indeed, the effects on efficacy was also highly impossible to be concluded. Besides, it was also reported in the CSF, none of the markers used were validated as biomarkers in PD; they can also vary greatly between patients and track poorly with disease stage and progression. This situation again raises questions about the optimum dose of nilotinib, its brain penetrance, assessments of cardiovascular effects in patients.

Parkinson's disease (PD) is a neurodegenerative disorder for which a greater prevalence and incidence is described in men. This suggests a protective effect of sex hormones in the brain. Sex steroids and related drugs are already used in clinic for treatment of menopause symptoms, cancer and use for contraception; thus they could be repositioned for PD in both men and women. Steroids are modulators of neurotransmitters system, for this reason their effects may help to control PD symptoms and side effect of DA medication. Animal studies provide good support for a protective effect of 17β-estradiol (**97**, Fig. 8), progesterone (**98**, Fig. 8), raloxifene (**99**, Fig. 8), DHEA and dutasteride (**100**, Fig. 8) on dopaminergic system. Sex specific treatment options may thus be proposed, with non-feminizing agents (raloxifene, DHEA, progesterone, dutasteride) for men. Indeed, the SERMs, 5α-reductase inhibitors and DHEA are alternatives to estrogens and could be used for both men and women. In the current trend to develop personalized medicine, estrogens could be used in priority for women. Because a variety of estrogens and progestins are available and clinically used, additional studies are needed to optimize the formulation of these agents, timing of initiation and duration of treatment to provide a beneficial therapeutic approach on PD risk and symptoms management [201].

Advantageous and limitations of drug re-purposing/re-positioning. Drug re-purposing has gained significance attention among scientists and pharmaceutical companies involved in the identification of new therapeutic uses/indications for discontinued

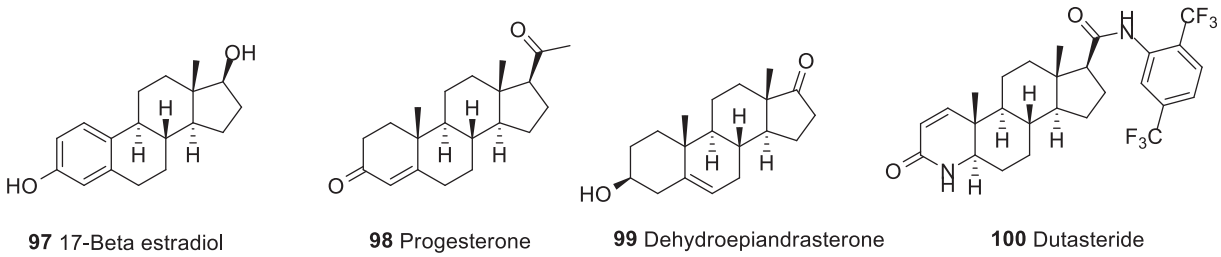

Fig. 8. Drugs repurposed for Parkinson's disease.

during the clinical development phase because of efficacy or commercial reasons. Recently, this approach has accounted for ~30% of all newly approved drugs by the FDA. This means the success rate of drug approval is so high when compared to the traditional methods [202]. During the year 2012–2017 [203], almost 170 re-purposed drugs entered the drug development pipeline. Currently, these 170 drugs are at different stages of development. Around 72% are in Phase II clinical development, 7% are in proof of concept clinical studies, 8% are in pre-clinical stages, and regulatory bodies have approved 3% in research and development and 10%. Almost 70% of the Phase I and II trials for repurposed drugs were sponsored by academia and 30% by industry.

Besides, drug-repositioning approach increases the fruitful collaborations and funding opportunities. During the year 2012–2017, there were almost 40 collaborations relating to drug repurposing. Among these, around 50% of collaborations were between two industries mainly focused on rare diseases. Almost, 20% between an industry and a Non-profit Organization (NPO) and 9% between industry and academia. Regarding funding opportunities, there was a substantial increase in funds (US$1 million to US$100 million) for drug repurposing projects by various funding agencies like National Center for Advancing Translational Sciences (NCATS), Cures within Reach (CWR, an NPO), the Canadian Institutes of Health Research (CIHR), Findacure.

Investigational New Chemical Entities (NCEs) that failed to show efficacy/potency and lack of safety for a pre-intended indication typically provides a good start for their revival against new indications by repurposing. This can be very much useful in cases of rare diseases such as autoimmune disorders, bacterial infections, neglected diseases and rare cancers such as pediatric cancers where unmet medical need owing to non-availability of standard therapies, worsening clinical outcomes and more difficult to treat. Unlike NCEs, all re-purposed molecules possess all required safety, preclinical and efficacy data enables the investigator to make an informed decision at much earlier stage of drug development substantially reduces the costs, time and efforts required for successfully bringing a repositioned drug to the market. Drug repositioning also offers significant potential for out-licensing as well, because of availability of potential buyers. Drug re-purposing also provides an opportunity to broaden our knowledge without limiting the existing information.

On the other hand, this approach has some limitations due to lack of a clear exclusivity path/well-defined regulatory guidelines. It is still a big hurdle/uphill task in utilizing repurposed drug candidates for human use. In general, a repurposing candidate carries a potential time risk because it has failed previously for a pre-intended indication. Hence, it is advisable to design a branched development program, in which the lead compound is evaluated for several indications simultaneously. Drug repurposing requires thorough comprehension of biological and molecular pathways that a drug can modulate as well as its interactions with endogenous bio-molecules in order for a successful repurposing of that drug molecule. When repurposing a drug for rare and neglected diseases, there is no assurance that the economic returns will be substantial as expected for a pharmaceutical company. Lack of financial incentives and research funding is another challenge for pharmaceutical companies. Problems in clinical trials: chance of failure of proof of studies for new indications as well as limited availability of volunteers for large clinical studies in case of rare diseases due to scarcity of patients. Intellectual property related issues hinder the commercialization of repositioned molecule.

2. Conclusions and perspectives

In conclusion, repurposing of drugs has the potential to find and improve treatments for various diseases. The drugs listed above are only a few of plenty drugs that can be repurposed in various therapies. The drugs discussed in the perspective are summarized in Table 1 and compared to the previous uses of each drug with the repurposed use. The opportunities for drug repurposing are diverse, but a lot still has to be done for its exploration. Drug repurposing or drug repositioning offers a new strategy to academic centers, research council programs, and not-for-profit organizations, as well as pharmaceutical and biotechnology companies for drug development. The main advantage of drug repurposing is the established safety of the known candidate compounds when compared to that of the development of novel therapeutic compounds. The time and cost required to advance a candidate into clinical trials can be substantially reduced because *in vitro* and *in vivo* screening, chemical optimization, toxicity studies, bulk manufacturing, and formulation development have already been completed in many cases, and can, therefore, be bypassed. Moreover, these drugs have been on the market for many years, and consequently, the side effects are already known, and safety is therefore very high. For medicinal chemists, the repurposing of drugs on cancer is a rewarding job for the global healthcare system and possibly a step forward for people to get cheaper and safer medicines rather than afford for cancer therapy. However, time and minimum investment have to be spent to conduct further studies to improve the safety and success of the repurposed drugs.

Drug repurposing also offers the possibility to develop multitarget drugs that can interact with more than one pathway/protein at the same time. For complex diseases such as (neuro) inflammatory and degenerative disorders, the development of multitarget drugs will be an emerging area for the treatment having multiple advantages such as i) synergistic effect ii) reduced drug-resistance iii) better compliance iv) simplified pharmacokinetic and pharmacodynamic profile and a reduced risk of drug-drug interactions.

On the other hand, the limitations of drug repurposing should also be considered. They involve a) technical challenges and legal requirements such as intellectual property rights which could hamper the whole process and are often hard to overcome b)

Table 1
List of approved drugs repurposed on various diseases.

Drug	Previous use(s)	Repurposed use(s)
Ethionamide (**2**)	Treatment of multi-drug resistant tuberculosis	Anti-melanogenesis (Tyrosinase inhibitor)
Prothionamide (**3**)	Antituberculosis	Anti-melanogenesis (Tyrosinase inhibitor)
Isoniazid (**8**)	Antibiotic used for the treatment of tuberculosis	Anti-melanogenesis (Tyrosinase inhibitor)
Thioacetazone (**9**)	Antibiotic used for the treatment of tuberculosis	Anti-melanogenesis (Tyrosinase inhibitor)
Ambazone (**10**)	Antiseptic	Anti-melanogenesis (Tyrosinase inhibitor)
Methimazole (**11**)	Antithyroid	Anti-melanogenesis (Tyrosinase inhibitor)
Antithyroid	Antithyroid	Anti-melanogenesis (Tyrosinase inhibitor)
Thiouracil (**13**)	Antithyroid	Anti-melanogenesis (Tyrosinase inhibitor)
Methylthiouracil (**14**)	Antithyroid	Anti-melanogenesis (Tyrosinase inhibitor)
Propylthiouracil (**15**)	Antithyroid	Anti-melanogenesis (Tyrosinase inhibitor)
Thioguanine (**16**)	Anti-cancer (treatment of leukemia)	Anti-melanogenesis (Tyrosinase inhibitor)
Mercaptopurine (**17**)	Cancer and autoimmune diseases	Anti-melanogenesis (Tyrosinase inhibitor)
Azathioprine (**18**)	Immunosuppressive agent for rheumatoid arthritis, Crohn's disease, ulcerative colitis and in kidney transplants to prevent rejection	Anti-melanogenesis (Tyrosinase inhibitor)
Aspirin (**20**)	Analgesic drug for treatment of pain, fever or inflammation	Anticancer (COX-inhibitor)
Thalidomide (**21**)	Immunomodulatory drug- used as sedative and hypnotic for the treatment of nausea during pregnancy	Anticancer (NF-κB inhibitor)
Metformin (**22**)	Treatment of type 2 diabetes	Anticancer (Activator of AMP-induced protein kinase)
Methotrexate (**23**)	Osteosarcoma, breast cancer, acute lymphoblastic leukemia and Hodgkin lymphoma	Anticancer (inhibitor of dihydrofolate reductase)
Rapamycin (**24**)	Anti-fungal agent	Anticancer (Inhibitor of T cells and B cells)
Celecoxib (**25**)	Pain and inflammation associated with rheumatoid arthritis (RA) and osteoarthritis	Anticancer (inhibitor of COX-2)
Ibuprofen (**26**)	Treatment of pain and inflammation	Anticancer (inhibitor of COX)
Diclofenac (**27**)	Pain and inflammatory diseases such as gout	Anticancer (inhibitor of COX-1 and 2)
Naproxen (**28**)	Pain and inflammatory diseases such as rheumatoid arthritis and fever	Anticancer (inhibitor of COX-1 and 2)
Statins (**29**–**32, 80**–**82**)	Lipid lowering agents that reduce illness and mortality in those who are at high risk of cardiovascular disease	Anticancer, Schistosomiasis (Inhibition of adult and immature S. *mansoni*worms), Treatment of dengue virus infection and Parkinson's disease
Depakine (**33**)	Epilepsy and bipolar disorder as well as migraines	Anticancer (suppress the production of IL-6 and TNF-α)
Chloroquine (**39**)	Anti-malarial	Anti-infective (SARS-and MERS-CoV inhibition)
Chlorpromazine (**40**)	Anti-psychotic drug (for the treatment of schizophrenia)	Anti-infective (SARS-and MERS-CoV inhibition)
Loperamide (**41**)	Diarrhea, gastroenteritis, inflammatory bowel disease and short bowel syndrome	Anti-infective (SARS-and MERS-CoV inhibition), Anti-malarial (*P. falciparum* inhibition)
Lopinavir (**42**)	Anti-HIV agent (protease inhibitor)	Anti-infective (SARS-and MERS-CoV inhibition)
Saracatinib (**46**)	Tumor malignancies (Src-family of tyrosine kinases (SFKs) inhibition)	Anti-infective (MERS-CoV inhibition)
Chloroquine (**39**)	Anti-malarial	Dengue virus infection
Prednisolone (**51**)	Allergies, inflammatory conditions, autoimmune disorders and cancers	Dengue virus infection
Balapiravir (**52**)	HCV (polymerase inhibitor)	Dengue virus infection
Celgosivir (**53**)	HCV (alpha-glucosidase-I inhibitor)	Dengue virus infection
Ivermectin (**54**)	Parasite infestation (head lice, scabies, river blindness, strongyloidiasis, trichuriasis and lymphatic filariasis)	Dengue virus infection
Ketotifen (**55**)	Anti-allergic (noncompetitive H_1-antihistamine and mast cell stabilizer)	Dengue virus infection
Aminolevulinic acid (**56**)	Skin diseaes also used in photodynamic detection and surgery of cancer	Dengue virus infection
Azelaic acid (**57**)	Skin diseaes and being used as a component in hair and skin conditioners	Dengue virus infection
Mitoxantrone hydrochloride (**58**)	Anthracenedione antineoplastic agent (metastatic breast cancer, acute myeloid leukemia and non-Hodgkin's lymphoma)	Dengue virus infection
Quinine sulfate (**59**)	Anti-malarial (used to treat chloroquine-resistant falciparum)	Dengue virus infection
Clemastine fumarate (**60**)	Hay fever and allergy symptoms (Antihistamine with anticholinergic properties and sedative side effects)	Anti-malarial (*P. falciparum* inhibitor)
Raloxifene hydrochloride (**63**)	Prevention and treatment of osteoporosis in postmenopausal women and those on glucocorticoids	Anti-malaria (*P. falciparum* inhibitor)
Gramicidin A (**64**)	Anti-bacterial (against gram-positive bacteria)	Anti-malarial (*P. falciparum* inhibitor)
Pentamidine isethionate (**65**)	Antimicrobial (to treat African trypanosomiasis, leishmaniasis, babesiosis)	Anti-malarial (*P. falciparum* inhibitor)
Clomiphene citrate (**66**)	Infertility in women who do not ovulate	Anti-malarial (*P. falciparum* inhibitor)
Telmisartan (**67**)	High blood pressure, heart failure and diabetic kidney disease	Anti-malaria (*P. falciparum* inhibitor)
cyclosporin A (**68**)	Immunosuppressant agent for rheumatoid arthritis, psoriasis, Crohn's disease, nephrotic syndrome and in organ transplants to prevent rejection	Anti-malaria (*P. falciparum* inhibitor

Table 1 (*continued*)

Drug	Previous use(s)	Repurposed use(s)
Donepezil (**76**)	Acetylcholinesterase inhibitor	Alzheimer's disease
Rivastigmine (**77**)	Acetylcholinesterase inhibitor	Alzheimer's disease and Parkinson's disease
Galanthamine (**78**)	Acetylcholinesterase inhibitor	Alzheimer's disease
Dimebon (**81**)	Antihistamine drug	Alzheimer's disease
Valsartan (**82**)	High blood pressure, heart failure and diabetic kidney disease	Alzheimer's disease
Olmesartan (**83**)	High blood pressure, heart failure and diabetic kidney disease	Alzheimer's disease
Telmisartan (**84**)	High blood pressure, heart failure and diabetic kidney disease	Alzheimer's disease
Losartan (**85**)	High blood pressure, heart failure and diabetic kidney disease	Alzheimer's disease
Amlodipine (**86**)	High blood pressure and coronary artery disease	Alzheimer's disease
Nilvadipine (**87**)	Calcium channel blocker for the treatment of hypertension and chronic major cerebral artery occlusion	Alzheimer's disease
Isradipine (**88**)	Calcium channel blocker to reduce the risk of stroke and heart attack	Alzheimer's disease and Parkinson's disease
Nimodipine (**89**)	Calcium channel blocker for the treatment of high blood pressure	Alzheimer's disease
Minocycline (**90**)	Antibiotic used to treat a number of bacterial infections such as pneumonia	Alzheimer's disease
Bexarotene (**92**)	Anticancer (treatment for cutaneous T cell lymphoma)	Alzheimer's disease
Acitretin (**93**)	Treatment of severe resistant psoriasis	Alzheimer's disease

serious problem on the development of resistant germs on account of consuming a drug for a variety of diseases c) owing to target selectivity, it is difficult to identify a drug that can cure or treat two different diseases on its own. Nevertheless, drug repurposing is only a part of the solution for the sinking numbers of new diseases and its treatment. However, it is quite hard to replace the common way of identifying new drug candidates.

Further, this approach could be improved in many differents ways: Integrating data about repositioning drugs which are available in many public platforms, such as PubChem), CheEMBL, DrugBank, and DrugCentral. Various informations including bioactivities, combined with their chemical structure, physical properties, and clinical indications, have been recorded in these databases. Integrating these approaches can extend the domain of applicability of each method and provide novel information. Combining *in silico* prediction and *in vitro* validation may lead to new therapeutic ligands

High throughput screening of chemicals using *in vitro* and/or *in vivo* systems can also strongly drive drug repositioning. However, most *in vitro* systems currently used for high throughput screening are two-dimensional monolayer cultures that differ from physiological conditions.

Notes

The authors declare no competing financial interest.

CRediT authorship contribution statement

Thanigaimalai Pillaiyar: Writing - original draft. **Sangeetha Meenakshisundaram:** Data curation. **Manoj Manickam:** Data curation. **Murugesan Sankaranarayanan:** Data curation.

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Abbreviations used

NSAID	nonsteroidal anti-inflammatory drugs
COX	cyclooxygenase
PG	prostaglandins
PI3K	phoshatidylinositol-3-kinase
USPSTF	preventive services task force recommendation statement
AMP	adenosine monophosphate
DNA	deoxyribonucleic acid
RNA	ribonucleic acid
IL	interleukin
VEGF	vascular endothelial growth factor
Bcl	B cell lymphoma
FDA	food and drug administration
SOD	superoxide dismutase
PSADT	prostate specific antigen doubling time;
TNF	tumor necrosis factor
GABA	gamma-aminobutyric acid
VPA	valproic acid
HDAC	histone deacetylase
WHO	world health organization
MERS	middle-east respiratory syndrome
SARS	severe acute respirator syndrome
CoV	coronavirus
HCoV	human coronavirus
CQ	chloroquine,
HIV	human immunodeficiency virus
DENV	dengue virus
HCV	hepatic C virus
AD	Alzheimer's disease
PD	Parkinson's disease
MHV	mouse hepatitis virus
FIPV	feline infectious peritonitis
HSV	herpes simplex virus
DNDi	drugs for neglected disease initiative;
ROS	reactive oxygen species
PZQ	praziquantel
HMG-CoA	3-Hydroxy-3-methyl-glutaryl-coenzyme A
Abl-TKs	Abelson tyrosine kinases
AMPA	amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AML	acute myeloid leukemia
ALL	acute lymphocytic leukemia
CML	chronic myeloid leukemia
GVBD assay	competitive germinal vesicle breakdown assay
HAT	human African trypanosomiasis
VL	visceral leishmaniosis
PUVA	psoralen and ultraviolet A
IBD	inflammatory bowel disease

UC	ulcerative colitis
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine;
6-OHDA	6-hydroxydopamine.

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