ejpmr, 2022,9(1), 558-572

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

REPOSITIONING OF DRUGS: AN APPROACH FOR NEW DRUG DISCOVERY

Gayatri Chhatre and Dr. Vithal M. Kulkarni*

Department of Pharmaceutical Chemistry, Poona College of Pharmacy, Bharati Vidyapeeth (Deemed to be) University Pune-411038, Maharashtra, India.

***Corresponding Author: Dr. Vithal M. Kulkarni**
Department of Pharmaceutical Chemistry, Poona College of Pharmacy, Bharati Vidyapeeth (Deemed to be) University Pune-411038, Maharashtra, India.

Article Received on 21/11/2021 **Article Revised on 11/12/2021** **Article Accepted on 31/12/2021**

ABSTRACT

Drug repositioning (DR) (also known as repurposing or reprofiling) is the new strategy of research of nonexistent therapeutic indications and implementations for the existing drugs. It is basically recycling of approved, failed or banned drugs for various complex and deadly diseases. Currently, on an average, the cost for conventional de novo discovery and development of a drug is enormous and requires a minimum of 10 years for the drug to reach the market. On the contrary, Drug Repositioning is known to be the fastest and cost effective method of drug discovery. Few sources estimate the average cost of repositioning is cut down to $300mn and takes about 6.5 years to launch in the market. Cancer has been a challenge and a battle to overcome. The International Agency for Research on Cancer (IARC) estimated the global cancer burden to be risen to 19.3 million. World is working for the development of new drugs along the timeline of cancer to put patient suffering at ease with less toxic and effective drugs. Repositioning is a proficient way to discover new drugs and is a suitable approach to find remedy for cancer. This paper reviews repositioning of known drugs that display significant anti-cancer activity.

KEYWORDS: Drug repositioning, Anti-HIV, Proton pump inhibitors, Anti-fungal, Anti-diabetics, NSAIDs, Anti-cancer.

INTRODUCTION

Drug repositioning (DR) is the new strategy of research of nonexistent therapeutic indications and implementations for the existing drugs. It can be linked to a drug multitasking and showing equivalent or better effects other than its original use. It claims to be one of the faster ways of drug discovery since it reduces the time and investment as the safety and toxicology data is already available for the existing drugs. The discovery process for de novo drugs is costly and time-consuming. Currently, on an average, the cost for conventional de novo discovery and development of a drug is almost unaffordable and requires around 10-15 years for the drug to reach the market. As a result, the current status of drug discovery also encompasses a wide range of repurposed drugs for malignancy and are ongoing clinical trials and development process. The success rate accounts for nearly 30% of newly approved drugs.[1] The better approach to repurposing might be understanding the traits of cancer rather than encompassing visionless similar target studies to pit out the hidden potentials of existing drugs so as to not slip out on metformin like success.[2] And that's how metformin came into clinical practice and is currently employed as a successful anti-tumor agent.

For the pharmaceutical industry, the real itch is economical consideration. Bringing a new drug into the market easily totals $3bn and the costs are going up with passing time even though the drugs approved per year rests flat or decreased for the past decade. This apparent contrast between the efforts spent in the input with fewer or no outcomes suggests that there are few underlying apprehensions that need to be taken under consideration for the research and development trade. The Scannell *et al's* systemic analysis discusses four major factors of the productivity crisis which they summed up as 'better than the Beatles' problem; the 'cautious regulator' problem; the 'throw money at it' tendency; and the 'basic research–brute force' bias.[3] The destiny of old discoveries is paving way for systematic searches for the same because of technological advancements which should be the new attitude for the drug discovery. Few sources estimate the average cost of repositioning is cut down to $300mn and takes about 6.5 years to launch in the market.[4] Technological approaches to drug repurposing for cancer therapy include mainly computational approaches as the bioinformatics has developed over time. The empirical drug repurposing take account of phenotypic screening and binding assays. This recycling strategy based on empirical screening goes back to 1940s which had poor rationalization and selectivity of cancer therapy and it heavily depended on chemo and radiation usage. Along the timeline, by 1970, the empirical strategy used unbiased targeting. The 1990 saw the rise in awareness and implication of computational practice. 10 years

down the line, the computational use evolved and included molecular docking, genetic association, pathway mapping, signature matching and clinical analysis based on real world data (RWD). This is known as scientific drug repurposing. It habituates special mono targeted and repurposing multi targeted drugs and has high selectivity. The recent scheme is more towards flexibility and collaborative use together with comprehensive treatment. It again has highest selectivity and rationalization of therapy.

Cancer has been one of the deadliest diseases from time unknown. It is a challenge and a battle to overcome. Cancer is characterized by the cells overcoming the apoptosis stage and multiplying uncontrollably. This results in formation of a tumor of malignant cells which could be metastatic. There has been a constant search of the best therapy possible to put the patient suffering at ease. Since the discovery of first anti-cancer class of drug, the nitrogen mustard, there are around 200 drugs including cytotoxics, anti-metabolites, supportive care and molecular targeted therapy. Regardless of the innumerous surviving therapies, there has been two additional social drawbacks apart from the safety and toxicology data which includes drug accessibility and financial toxicity which are explained by Gonzalez-Fierro in their paper. The cancer burden is highest in low and middle income classes since they cannot fully afford the therapy which either keeps them away from starting the drug course or to discontinue midway.[5] The IARC estimated the global cancer burden to be risen to 19.3 million with 10 million deaths last year. India alone reported 8.5 lakh deaths in 2020. In both sexes combined, lung cancer accounts for 11.6% of the total cases and is the most commonly diagnosed cancer and the leading cause of cancer death, closely followed by female breast cancer (11.6%), prostate cancer (7.1%), and colorectal cancer (6.1%). The colorectal cancer (9.2%), stomach cancer (8.2%), and liver cancer (8.2%) are leading causes in case of mortality.[6] Hence, discovery and development of a drug in shorter period of time is indispensable especially throughout the pipeline for cancer. This review covers of those drugs which have been repositioned or repurposed successfully as anti-cancer agent/drug.

Anti- Human immunodeficiency virus (Anti-HIV) Drugs

Human immunodeficiency virus type 1 (HIV-1) protease inhibitors (PI) are the peptidomimetics that have an analogue of peptide bond between phenylalanine-167 and proline-168 (PDB ID: 2BPX).[7] The first PI that was discovered was saquinavir (SQV) and since then there are 10 FDA approved PIs which include nelfinavir (NFV), ritonavir (RTV), lopinavir (LPV) and indinavir (IDV) and are favored in the treatment of HIV infection. Studies have shown that PIs possess antitumor activity which can be independent of their ability to inhibit HIV protease. One of the studies bared that SQV, RTV, and IDV induced the growth arrest and differentiation of NB4 and HL-60 human myeloid leukemia cells, and enhanced the ability of all-trans retinoic acid (ATRA) to decrease proliferation and increase differentiation in these cells.[8] Other study implied that PIs may be effective against virus-associated cancers as they hamper KS-associated herpesvirus and cytomegalovirus replication *in vitro*.[9]

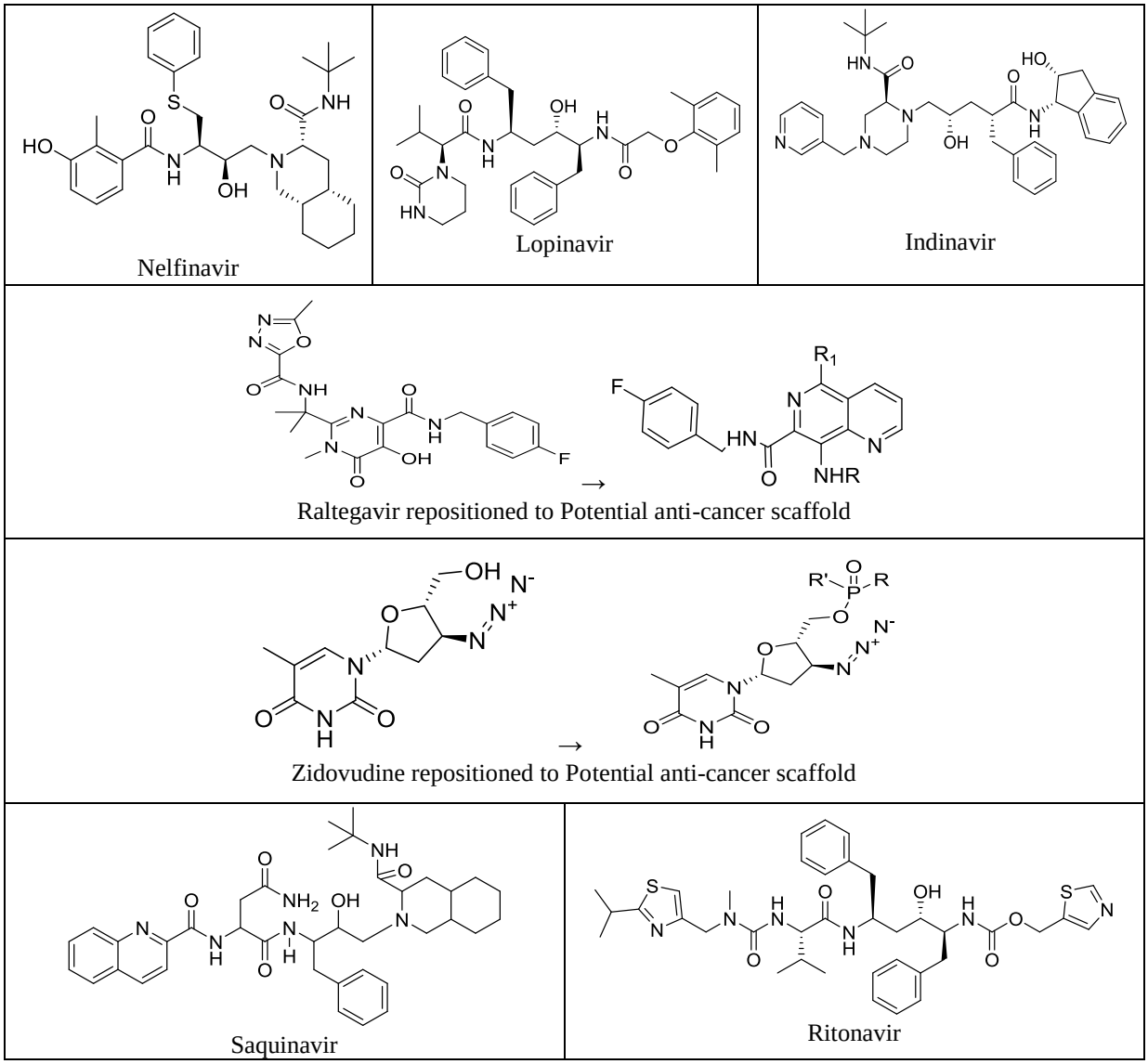
Because the toxicities associated with HIV PIs are similar to those observed with inhibition of the phosphoinositide 3-kinase (PI3K)/Akt pathway, Gills *et al* hypothesized that HIV protease inhibitors might function as Akt inhibitors.[10] NFV was found to be the most potent inhibitor of the PI3K-Akt pathway in pre-clinical studies. In Highly active antiretroviral therapy (HAART) NFV is prescribed in a dose of 1250 mg BID. The most commonly observed side-effects of NFV are diarrhea (>10%), transaminase elevations (around 2%) and nausea.[11]

Recently, Veschi *et al.* evaluated the effects of nelfinavir against pancreatic cancer cell lines AsPC-1, Capan-2 and BxPC-3. Cell viability was tested by MTT assay: IC_{50} values (μM) were 21.3, 24.5, and 20.9 in AsPC-1, Capan-2 and BxPC-3 respectively.[12] NFV has also been shown to exert anticancer activity through multiple pathways including inhibition of the chymotrypsin-and trypsin-like activities of 20S human proteasome, inhibition of AKT, of hypoxia-inducible factor 1α (HIF-1α) and of HSP90, although the precise mechanism for its anticancer activity remains elusive.[13]

Promising preclinical data regarding NFV, as a single agent or in combination with other cancer therapies, on multiple cancers (like Kaposi's sarcoma, multiple myeloma, NSCLC (Non-small cell lung cancer), prostate cancer, breast cancer, advanced rectal cancer), prompted a series of clinical trials.[14] In a few studies, NFV was tried as a monotherapy rather than in combination with chemotherapy and with or without radiation therapy. Hoover *et al*. reported a phase II clinical trial in patients with recurrent adenoid cystic carcinoma that no longer responded to the available standard therapeutic options.[15] Conversely, in a phase I study conducted by Pan *et al.* 30% of the patients having recurrent, metastatic or unresectable liposarcoma, showed clinical benefits at different dose levels of NFV.[16] A recent phase-2 study conducted from Mar 2017 to Oct 2020 for Kaposi's sarcoma (NCT03077451); Kawabata *et al.* demonstrated that NFV presented cytostatic effect at 10 μM and cytotoxicity at 20 μM (cell lines- H526, H82, H146, and H69) *in vitro* and *in vivo*. It is well-tolerated in patients with cancer and showed its efficacy against NETs in a phase I trial.[17] Lopiccolo *et al*. expanded the *in vitro* findings to an *in vivo* study and the data indicated that combining nelfinavir with chloroquine enhances the growth inhibition of H157 and A549 cells and hence greatly affects the inhibition of NSCLC growth and proteotoxicity.[18]

HIV Integrase has been an attractive target for the therapeutics to act on as it is responsible for replication of the virus. The well-developed class of IN inhibitors is aryl diketoacid and its bioisoster, 8-hydroxy-7-carboxy-1,6-naphthyridine. Li-Fan Zeng *et al.* synthesized 1,6-naphthyridine-7-carboxyamide-based focused library with variation on 5- and 8- substitutions. These were repositioned to check anti-tumor activity tested against C8166 cells through MTT assay. Interestingly, the 8-aliphatic diamino derivatives that were inactive in the IN assay showed cytotoxicity while the 5-alkylamino substituted 8-hydroxy derivatives were inactive. The 5-sulfoxide counterparts showed low cytotoxicity. The data indicated that diamino substitution at position-8 was important for showing anti-proliferative activity. During the lead optimization, the open chain alkyl diamino, the aryl diamino, and the aliphatic cyclic diamino groups present at position 8 were examined as the second generation of the cytotoxic series.[19]

In a recently published study, scientists discovered a novel series of hybrid pyrimidine–hydrazone moieties, dihydronaphthalene and alkylamine chain as they expected pyrimidine, 3,4-dihydronaphthalene and alkylamine to have a synergistic anticancer effect. They evaluated the effect on LoVo colon adenocarcinoma, LoVo/DX-resistant colon adenocarcinoma, MCF-7 breast cancer, A549 lung cancer, cervical cancer (HeLa), human leukemic lymphoblasts (CCRF-CEM) and human monocytic (THP-1) cell lines including their QSAR studies. The design of synthesis starts with the reaction between 4,6-dichloro-pyrimidine and hydrazine hydrate. The resulting compound was dissolved in ethanol and reacted with 6-methoxy-1-tetralone. It was then refluxed in a nitrogen atmosphere at normal pressure. The lipophilicity studies suggest that the compounds being lipophilic increase the probability of penetration of the novel compounds into the cancer cells. In conclusion, the proposed compounds inhibit the activity of TopoisomeraseII and intercalate DNA. In addition, all derivatives can decrease the number of cells in the proliferation (S) and G2/M phase and exhibit proapoptic activity.[20]

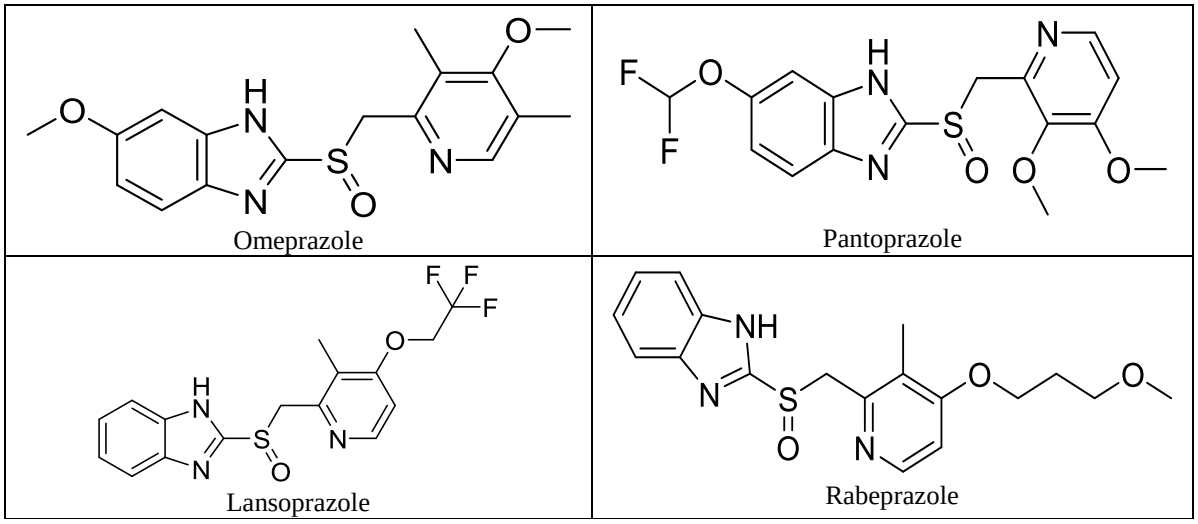


Proton Pump Inhibitors

Proton Pump Inhibitors (PPIs) are FDA-approved benzimidazoles that act as antacids. Fako *et al.* searched for PPIs that could potentially inhibit Fatty Acid Synthase (FASN) using a crystal structure of fatty acid synthase thiosesterase (FASN TE). The study exhibited findings of virtual screening of these drugs followed by a fluorogenic assay using recombinant TE protein. They concluded that PPIs effectively inhibited TE activity. Further examination showed that these inhibited lipid synthesis, binding of a serine hydrolase probe to FASN, pancreatic cancer cell proliferation, and induced apoptosis of pancreatic cancer cells.

To identify potential FASN TE inhibitors, an *in silico* screening was carried out using DOCK programs along with the crystal structure of FASN TE (PDB code: 3TJM). The 200 top-scoring compounds were huddled based on their chemical structure, and 25 archetypal drugs from various clusters were selected for testing their ability to inhibit TE. Using this assay and purified TE, they tested the 25 top-scoring FDA-approved drugs with orlistat, a known inhibitor of FASN TE, as a positive control. Three drugs, pantoprazole, 13-cis-retinoic acid and sulcotidil, reduced ≥40% of TE activity and, thus, were selected for further investigation. However, only pantoprazole inhibited FASN TE activity in a dose-dependent manner with a Ki of 4.1 μM. Other PPIs omeprazole, lansoprazole, and rabeprazole similarly inhibited TE in a dose-dependent manner with Ki values of 3.4−5.9 μM with an activity ranking of omeprazole > pantoprazole > lansoprazole > rabeprazole. These findings suggest that increasing the size of either the 2-pyridylmethyl or the benzimidazole group of the compounds may slightly decrease the activity of PPI in inhibiting TE activity.

To determine the utility of PPIs in inhibiting cancer cell proliferation, they performed colony formation assay of BxPC-3 pancreatic cancer cells in the presence of PPIs along with orlistat as a control. The survival of BxPC-3 cells was dose dependently inhibited by all four PPIs. The relative potency of PPIs is lansoprazole > rabeprazole > omeprazole > pantoprazole with IC_{50} values ranging from 6.7 to 18.5 μM. Then they tested lansoprazole against another pancreatic cancer cell line, PANC-1 and showed a dose-dependent inhibition with an IC_{50} of 58.6 μM. To determine if PPIs possibly induce apoptosis, they performed ELISA to quantitate the amount of cytoplasmic histone associated DNA-fragments using a cell death detection ELISA kit and Western blot. This demonstrated that lansoprazole dose-dependently caused formation of DNA fragments and cleaved Poly adenosine diphosphate-ribose polymerase (PARP-1), indicating that lansoprazole treatment causes apoptosis in a dose-dependent manner.[21]



Antifungal Drugs

Itraconazole (ITZ) belongs to the family of azole antifungal drugs with several generations of structurally and mechanistically related analogues. Chong *et al.* reported potent antiangiogenic activity of ITZ both *in vitro* and *in vivo*. It displayed potent and selective inhibitory activity towards the endothelial cells and has little effect on the proliferation of human foreskin fibroblasts (HFF), with an IC_{50}>20μM in comparison to HUVEC (human umbilical vein endothelial cells) (IC_{50}=0.16μM). While it potently inhibited the proliferation of bovine aortic endothelial cells (BAEC), it is much less effective against Jurkat T cells or HeLa cells. The other reported values for terconazole, ketoconazole, miconazole, econazole, sulconazole, fluconazole, voriconazole against HUVEC assay were 7.1, 10.4, 2.47, 4.80, >100, >100, >100 respectively. The significant influence of stereochemistry on ITZ's activity suggested that the 4S-cis diastereomer (IC_{50}= 0.056± 0.01μM) is ~20-fold more potent than the 4R-cis stereoisomer (IC_{50}= 1.1± 0.13μM). In comparison, the racemic ITZ has an IC_{50} of 0.16μM.[22] In follow-up studies, ITZ, either alone or in combination with other anticancer drugs, showed strong anticancer activities in preclinical models including NSCLC, medulloblastoma, and basal cell carcinoma. High dose (600 mg/day) of ITZ

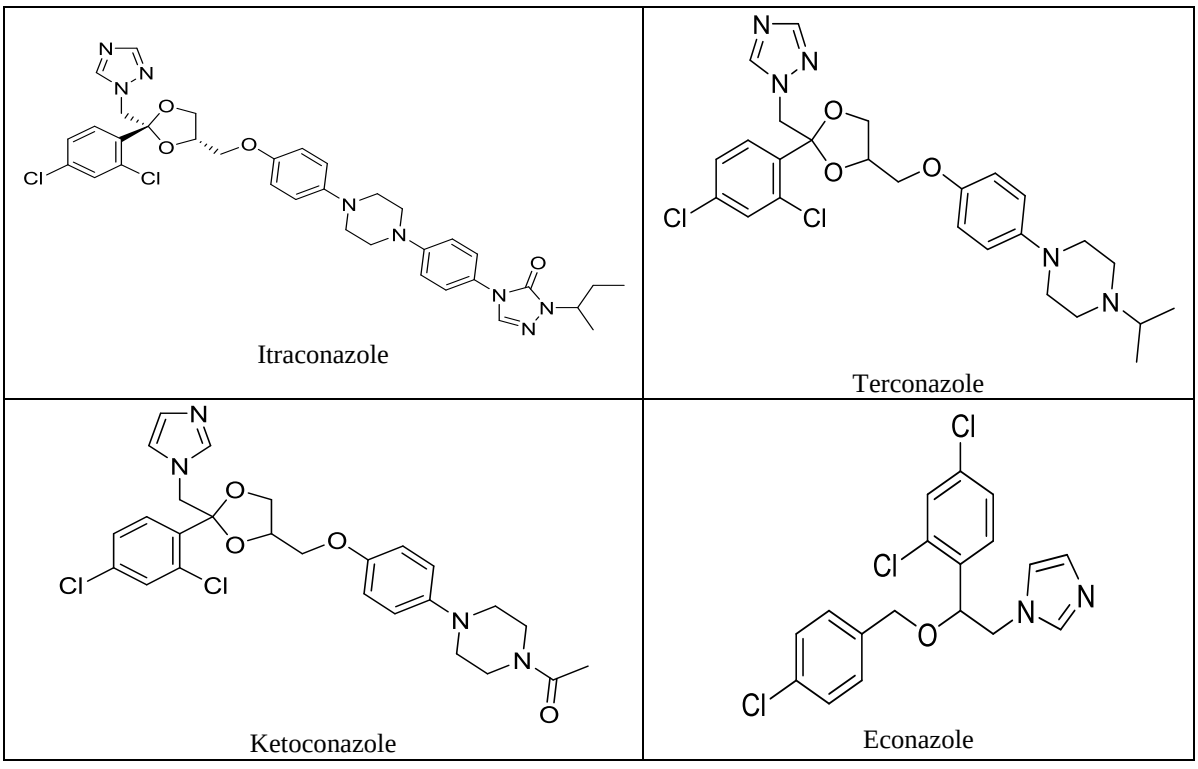
also showed modest anticancer activity in patients with metastatic castration-resistant prostate cancer. Prompted by such encouraging preclinical results, ITZ entered phase II clinical studies for a possible treatment of various types of cancer.[5]

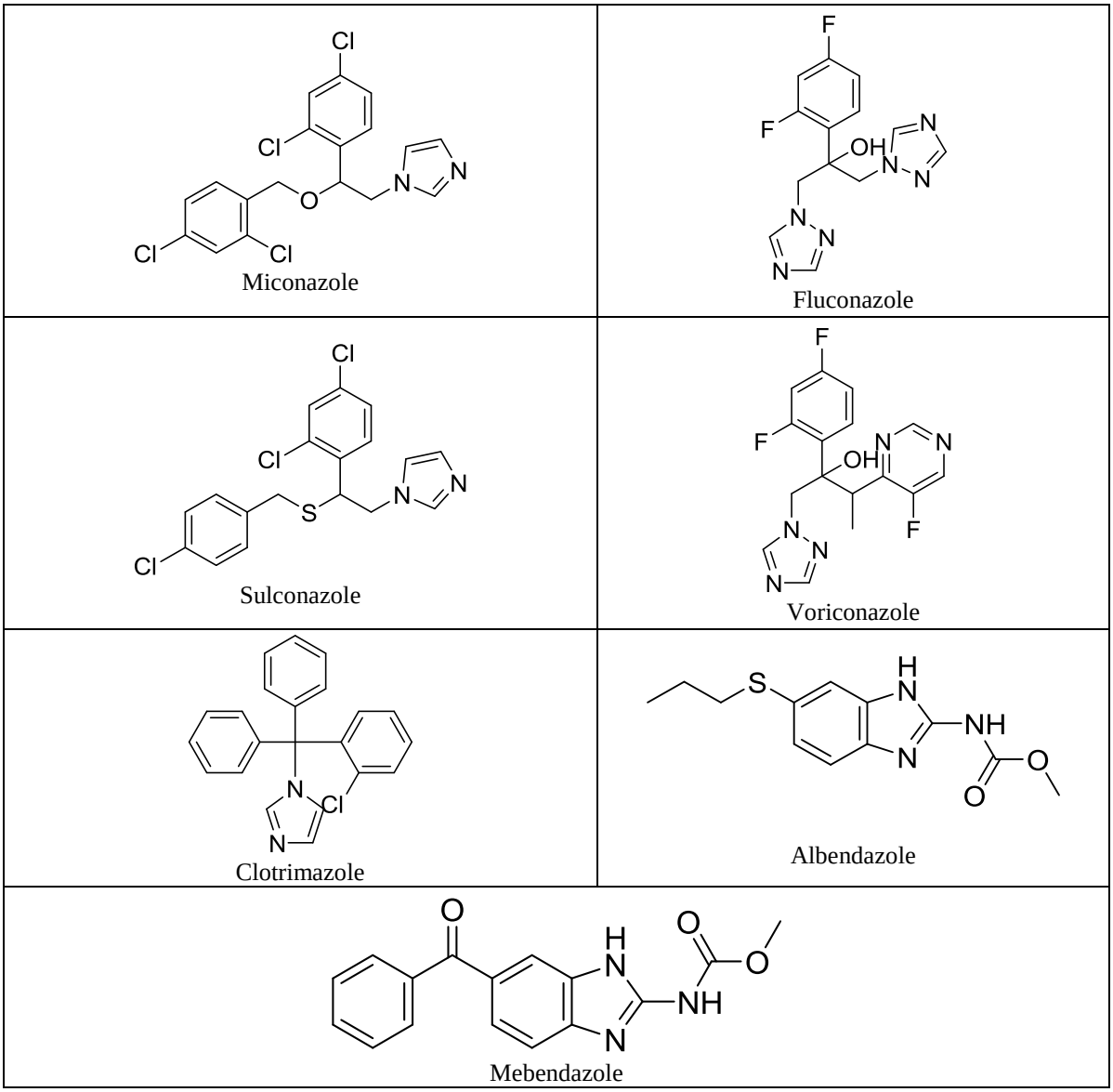
Although significant progress has been made in characterizing the molecular heterogeneity present between tumors, functional heterogeneity is evidently also present and will confound both targeted treatments and traditional cytotoxic therapies currently used as adjuvant treatments. For the first time, Buczacki *et al.* functionally and molecularly characterize dormant tumor cells across CRC molecular subtypes, finding they are a subset of differentiated cells, capable of contextual clonogenicity. They concluded that ITZ releases dormancy by inducing tumor-wide proliferation followed by arrest, inhibits Wingless- related integration site (Wnt) signaling and induces global senescence in responsive Clear Cell Sarcoma 1 (CCS1) cell lines, suppresses tumor growth using in vivo and in vitro preclinical assays.[23]

Bae *et al.*, tested the effect of antifungals for breast cancer, as they showed promising results on major carcinomas. They demonstrated that imidazole antifungal drugs inhibited the proliferation of breast cancer cell lines. They found that imidazole compounds CTZ and KCZ (clotrimazole and ketoconazole) exhibited a greater anti-proliferative activity against MC-7 and MDA-MB-231 cells than the triazole compounds, fluconazole and ITZ; this effect was concentration-dependent. The concentrations of CTZ and KCZ that inhibited cell growth by 50% (IC_{50}) were 21.0 and 35.1 μM, respectively, for MCF-7 cells and 23.1 and 41.8 μM, respectively, for MDA-MB-231 cells. The imidazole drugs (CTZ and KCZ) significantly increased apoptosis in both MCF-7 and MDA-MB-231 cells, while the triazole drugs only increased apoptosis in MCF-7 cells.[24]

Few studies have elaborated on selection of anthelmintic mebendazole as anticancer drug.[25] In a study, 2000 small molecules were screened, mebendazole was selected for further mechanistic studies of cancer cell growth inhibition based on its promising pharmacokinetic profile. While it was largely nontoxic to normal melanocytes, it inhibited the growth of M-14 and SK-Mel-19, two chemo resistant melanoma cell lines.[26] In combination treatment with a gemcitabine derivative, mebendazole exerted cytotoxic activity against chemoresistant mammary adenocarcinoma SKBr-3 cells.[27]

Albendazole has been increasingly recognized as an effective anticancer agent due to its low toxicity to normal cells and high efficacy against certain cancer types. It strongly inhibited the proliferation of human paclitaxel-resistant 1A9PTX22 ovarian cancer cells.[28] It also evaded the MDR phenotype in epothilone- and paclitaxel-resistant leukemic CEM/dEpoB300 cells.[29]





Anti-diabetic Drugs

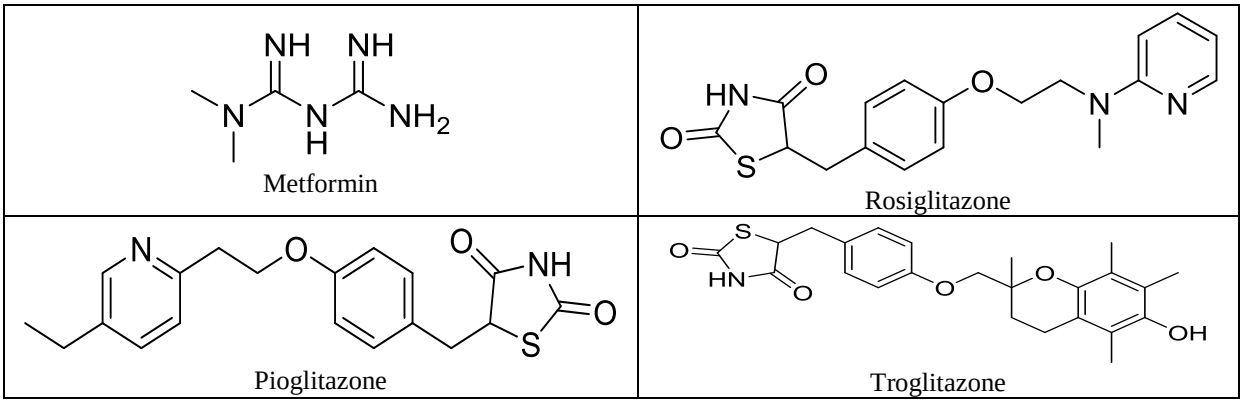
Metformin, the famous oral biguanide class of drug is the first line treatment option for diabetes mellitus. It principally inhibits gluconeogenesis, reduces insulin resistance and lowers insulin levels.[30] Studies and meta-analyses have provided evidence for metformin having anti-cancer activity.[31] Several mechanisms of action for the anticancer effect of metformin have been displayed and most of which involve the activation of AMP-activated protein Kinase(AMPK): Phosphoinositide-3-Kinase (PI3K)/Protein kinase B (AKT)/Mammalian target of rapamycin (Mtor) and Mitogen-activated protein kinase (MAPK) pathways which slowed the growth of precancerous and cancerous cells, induces cell cycle arrest and cell death; and another that targets the respiratory complex I of the electron transport chain in the mitochondria, thus hindering energy consumption in the cell. Metformin works for endometrial cancer in a way that it controls the hyperinsulinemia and hyperandrogenism linked anovulatory cycle of the PCOS. The epidemiological data compares increased risk of endometrial cancer in obese vs non-obese patients (risk ratio, 6.25).[32] Due to its ability to activate the AMPK pathway it can be administered with various drugs to reverse the natural and chemical toxicities and shows protective effect on cardiovascular [33] and nervous system.[33] Meshkani and group compiled the drugs which can be combined with metformin as a therapy to reduce their toxic effects. These drugs include haloperidol, scopolamine, tacrolimus, indomethacin, methotrexate, amiodarone, methimazole, dauxorubicin, cisplatin, tamoxifen, monosodium glutamate etc.[35] A recent study disclosed the metformin-propranolol combination on colorectal (HCT116, HT29 and CT26) and triple negative breast cancer (4T1) cell lines by evaluating the impact on cellular processes such as migratory capacity, apoptosis (TUNEL assay with 5-FU as the positive control) and proliferation (MTT assay).[36] However, clinical application of MET has been limited due to its low bioavailability caused by high hydrophilicity, short half-life, and non-selective biodistribution. This problem was tackled by Ji-Yeon

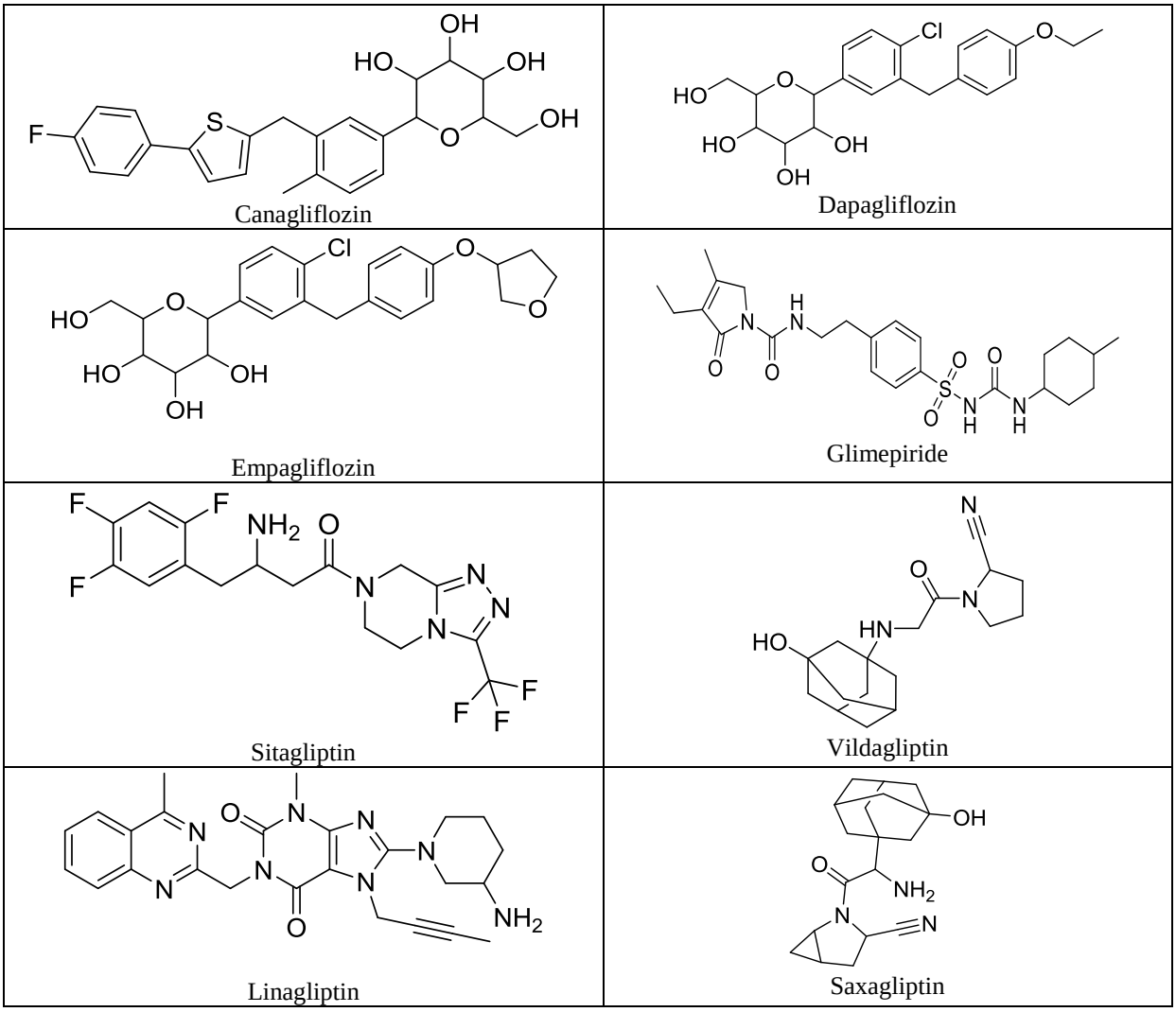
Lee and group as they developed a herceptin-conjugated PEGylated liposome incorporating MET (Her-LP-MET) for efficient drug delivery and specific targeting to the BCSCs.[31]

Thiazolidinediones (TZDs) such as troglitazone (TGZ), pioglitazone (PGZ) and rosiglitazone (RGZ) are synthetic agonists of PPAR-γ (Peroxisome Proliferator-actiavted receptors) although TGZ has been discontinued due to hepatotoxicity and lipolysis.[37] They work as anti-cancers by resulting in decreased cellular growth, inflammation, increased differentiation and cell death of cancer cells. Wang *et al.* reported for better understanding of action of rosiglitazone which acts on pancreatic cancer. Pancreatic cell lines PANC1 and PaTu8988 were incubated for the MTT assay that revealed the viability of the cells was inhibited in a dose-dependent manner. 40 µmol/L rosiglitazone resulted in around 80% cells viable in the two pancreatic cell lines.[38] Vincent Pomel *et al.* disclosed a novel series of furan-2-ylmethylene TZDs as selective and ATP-competitive PI3Kγ inhibitors. The SAR information obtained from the compounds indicated that the 2-hydroxy group plays a decisive role in conferring PI3K binding and inhibition in the range 30-50 nM. Addition of other substituents around the 2-hydroxyphenyl moiety has no major impact on the potency. However, introduction of a fluorine atom specifically at the 4-position leads to a notable increase in selectivity against PI3Kα. Molecular modeling studies suggested that the fluorine atom at C-4 is located in the proximity of a nonconserved area of the binding site, where the nonpolar Ala885 (present in PI3Kγ) is replaced by the polar Ser606 (present in PI3Kα). This could account for the increased isoform selectivity.[39]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors limit the resorption of glucose from the kidneys into plasma. Common examples of SGLT2 inhibitors are dapagliflozin (DAPA), canagliflozin (CANA), and empagliflozin. Lately, SGLT2's dynamic expression has been observed in prostate and pancreatic tumors tissues where SGLT2 inhibitors may decrease pancreatic cancer growth, potentially via blockage of glucose uptake. A Japanese study on anti-proliferative action of DAPA on HCT116 (colon cancer) cell line showed promising results. The activity was further confirmed by XTT assay and immunoblotting against cleaved and uncleaved PARP and caspase-3 which shows non-apoptotic kind of cell death.[40] In a comparative study between glimepiride and empagliflozin indicated that the latter drug is better at controlling proliferation and inducing apoptosis which was confirmed by *in silico* evaluation. The cell lines employed were MCF7 (breast cancer) and A549 (lung cancer) and IC_{50} values (µg/ml) were reported to be 70 and 80 for the former and 110 and 245 for the latter cell line in case of empagliflozin and glimepiride respectively. For the *in silico* validation, three tumor proteins were selected IGJH, ITUP and 2XYG. The E-values for these proteins with glimepiride as a ligand were -336.25, -300.66 and -190.20 and with empagliflozin were seen to be -348.12, -300.12 and -203.36. The values confirm the *in vitro* study.[41]

Dipeptidyl peptidase-4 (DPP4) inhibitors, such as vildagliptin, sitagliptin, and saxagliptin, prevent degradation of GLP-1 (Glucagon-like peptide), a hormone critical for glucose homeostasis.[42] The overexpression of DPP4 altered cell morphology and stimulated cell proliferation, invasion *in vitro* and *in vivo*. It also promoted hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor A (VEGFA) expression to promote HIF-1α-VEGFA signaling. The hypothesis includes controlling the tumorigenesis mechanism using DPP4 inhibitors.[43] The study on sitagliptin as an individual anti-tumor agent didn't have much effect but when used in combination, enhanced Tyrosine Kinase Inhibitor (like sunitinib) repression on anti-proliferative activity of RCC tumor lines ACHN and 769-P. It is also used in case of sunitinib resistant RCC tumour.[44] Yong li *et al.* studied the anticancer efficacy of linagliptin on colorectal cancer cell line, HCT 116, the liver cancer cell line, HepG2, and the breast cancer cell line, MCF7. Linagliptin inhibited HCT 116, MCF7, and HepG2 cell viability in dose- and time-dependent manner. It inhibited cell proliferation in vitro, induced cycle arrest at G2/M, S phase, induced apoptosis and reduced tumor growth.[45]





Nonsteroidal anti-inflammatory drugs (NSAIDS)

Inflammation is strongly related to cancer and plays a key role in tumor development and progression. It is now clear that chronic inflammation promotes carcinogenesis by inducing proliferation, angiogenesis and metastasis and reducing the response to the immune system and chemotherapeutic agents.[46]

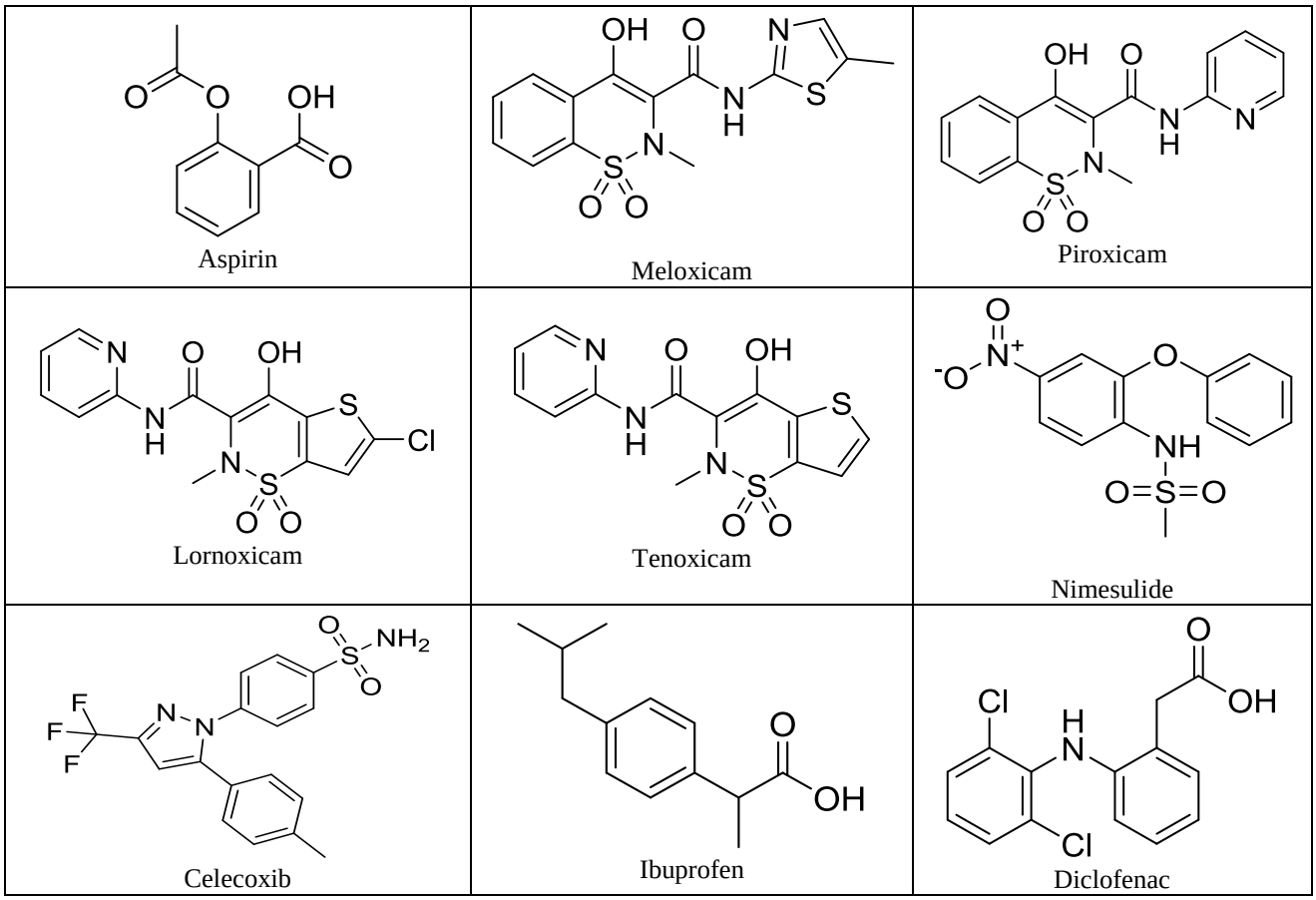
The 1,2-benzothiazine derivatives, or oxicams are an important family of heterocyclic NSAIDs used to treat rheumatoid and osteoarthritis. Important members of this compound class include meloxicam, piroxicam, tenoxicam, lornoxicam and ampiroxicam of which piroxicam and meloxicam have shown promising anticancer activity against lung, colon and breast cancer. Piroxicam has a long half-life of 50 hrs, hence it shows side effects like darkening of the skin. Since it has a longer $t_{1/2}$, repurposing it as anti-cancer will be beneficial. Aman *et al.* deliberated that oxicams can act as scaffolds to obtain linkage isomers of metal complexes like Ruthenium and Osmium that produce interesting biologically-active compounds. The IC_{50} values/µM for most stable compounds i.e, Ru(cymene)Cl_2 and Os(cymene)Cl_2 compounds of meloxicam and Ru(cym) and Os(cym) compounds of piroxicam were 79, 70, >150, >150 respectively assessed on human colorectal cell line (HCT116) whereas 97, 88, >150, >150 respectively for Cervical cell line (SiHa) and >150, 109, >150, >150 respectively for NSCLC (NCI-H460). The meloxicam derivatives were more active than piroxicam analogues, despite showing only moderate activity which is however similar to that of other Ru complexes that have been shown to be non-cytotoxic but demonstrated promise in anticancer drug development.[47] Khodaie *et al.* determined the cytotoxic effects of piroxicam and nimesulide on A431 squamous carcinoma cells using MTT colorimetric assay. Piroxicam caused a decrease in cell proliferation in a time (24, 48 and 72 hours), and concentration (100 - 1000µM/L) dependent manner. A significant reduction in cell viability was observed from 500 µM/L of piroxicam in 24 hours treatment ($P < 0.05$); however, in 48 and 72 hours treatment, the concentration of 100 µM/L of drug caused significant cytotoxic effects ($P < 0.05$ and $P < 0.001$, respectively). The IC_{50} (µmol/L) values were reported as 691.4, 454.4 and 338.8 for 24, 48 and 72 hrs.[48]

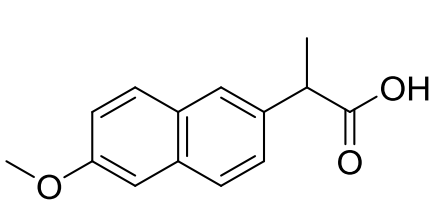
Aspirin, the well-known cox (cyclooxygenase) inhibitor is not only used as an analgesic and an antipyretic but

also to prevent the heart attack and stroke. Only just, it's stated that the daily intake of the drug (75 mg) produced a significant effect against gastrointestinal, esophageal, pancreatic, brain, prostate, and lung cancer. Preclinical studies revealed that the anticancer activity of drug is attributed to reduction of prostaglandin (PGE2) synthesis. In a study reported by Li Ling *et al.* it not only inhibited proliferations and promoted apoptosis of cancer cells, but also delayed and overcame acquired resistance to targeted therapy.[49] U.S. preventive services task force (USPSTF), recommended for daily intake of 75mg for patients above 40 years with increased risk of cardiovascular disease and colorectal cancer.[1] Aspirin promoted apoptosis of lung cancer HCC827 and breast cancer MCF-7 cells by increasing the expression of cleaved PARP or caspase-3. Flow cytometry also showed significantly increased percentage of apoptotic cells when treated with aspirin. Cell viability assays and IncuCyte growth curves both showed that combination of aspirin with targeted drugs dramatically inhibited proliferation of cancer cells. However, aspirin had no effects on the proliferation of normal lung (16HBE) or breast epithelial cells (MCF-10A).[30]

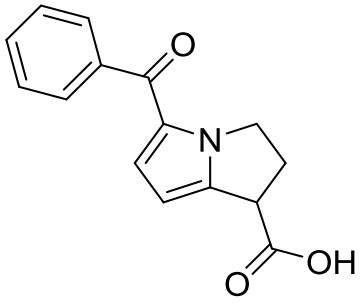
Ibuprofen is an NSAID, which is primarily used to treat fever, pain, and inflammation. At the molecular level, ibuprofen inhibits COX, which converts arachidonic acid to prostaglandin. However, it is not selective towards any isoform of cox. The drug was marketed for the treatment of rheumatoid arthritis. Ibuprofen has been shown to inhibit the growth of prostate cancer cells.[50] In adenocarcinoma gastric cells, drug showed antitumor effects, which have been mediated by the anti-angiogenesis, induction of apoptosis, and reduction of cell proliferation.[51] The administration of the drug induced apoptosis in metastatic melanoma cell lines.[1]

Moon *et al*'s findings on comparative analysis of certain NSAIDS indicate that tolfenamic acid was most cytotoxic to cells at a dose(mMol) of 25 and 100 at all time-points until 96 hours. Naproxen was found to be most cytotoxic at 25, 50, 60, and 75 mM. Ibuprofen and diclofenac were most cytotoxic at 75, 60, 100, and 50mM, respectively, at all-time points. Celecoxib was cytotoxic to cells at 25, 75, and 100 mM at all time-points.[52]

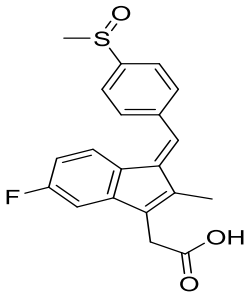




Naproxen



Ketorolac



Sulindac

Miscellaneous Drugs

Nitroxoline

Findings support the repurposing of an FDA-approved antibiotic, nitroxoline, for tumor therapy. It has been widely used in Asian, African and European countries since 1960 for UTI. With the unique pharmacokinetic property and current dosage regimen, human clinical studies of nitroxoline (NXQ) for the treatment of bladder cancer are justified. The proto-oncogene MDM2 is a nuclear-localized E3 ubiquitin ligase, which promotes tumor formation by targeting tumor suppressor proteins, such as p53, for proteasomal degradation. In the mechanistic study performed by Jin guo yu *et al*. NXQ downregulated the MDM2 expression by inducing its proteasomal degradation, and thus upregulated p53 expression, which was a substrate protein of MDM2. Moreover, overexpression of MDM2 decreased the cytotoxicity of NXQ on SCLC (Small cell lung cancer) cells.[53]

Epithelial-mesenchymal transition (EMT), a process by which tumor epithelial cells acquire the capability to migrate, participates in cell invasion and metastasis. In a model of bladder cancer *in vivo*, Naijin Xu *et al*. found that NXQ (60 mg/kg) reversed bladder cancer cells' EMT and regulated the expression of apoptosis-related proteins. It suppressed cell viability. Bladder cancer cell lines MBT-2 and J82 were used.[54]

Mirkovic *et al.* showed that NXQ inhibited cathepsin B activity and suppressed breast cancer cell invasion. Cathepsin B plays a role in degradation of extracellular matrix (ECM) and is implicated in tumor cell migration, invasion and metastasis. It's activity is regulated by endogenous protein inhibitors, the cystatins. However, these are general cysteine protease inhibitors, and as such are not appropriate for therapeutic applications. The K_i for Capthesin B endopeptidase was reported to be 154.426.7 and 39.52.8 which shows that it acts as a mixed inhibitor whereas for exopeptidase, K_i reported was 271.811.2 mm and acted as a non-competetive inhibitor. Effect of NXQ on MCF-10A neoT cell viability was evaluated using an MTS assay.[55]

In a separate study, Jiang *et al.* recently reported that NXQ showed strong anticancer activity against lymphoma (Raji & DHL-4), leukemia (HL-60), pancreatic cancer (Panc-1) and ovarian (A2780) cancer cells and assayed using MTS reagent. IC_{50} value was lowest for NXQ (0.438±0.20μM) compared to rest of the analogues indicating it is more potent. The IC_{50} values reported for leukemia cell line was 6.26±0.10, lymphoma cell line was 0.89±0.28, pancreatic cancer cell line was 1.46±0.14 and ovarian cancer cell line was 0.18±0.02.[56]

A comparative article on Nitroxoline and Nelfinavir alone and in combination with erlotinib by Serena Veschi *et al.* concluded that when used as single agents, NFV and NXQ decreased viability, affected cell cycle and reduced the expression of relevant cell cycle proteins. Moreover, these agents drastically impaired clonogenic activity of the three PC cell lines. The effects of the drugs on the viability of AsPC-1, Capan-2 and BxPC-3 PC cell lines were assessed by MTT.[4]

Thalidomide

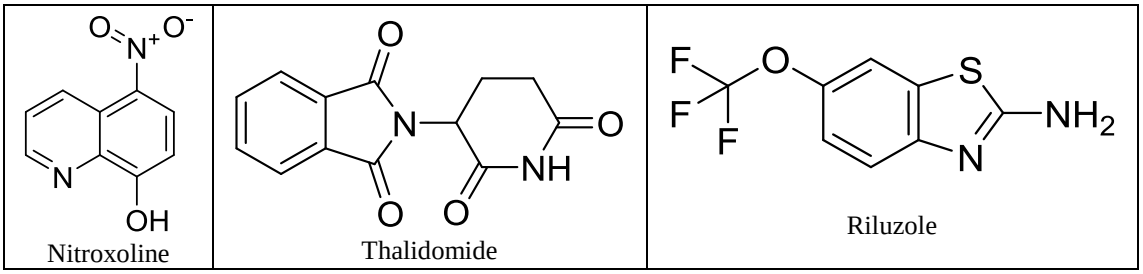
Thalidomide rose from the ashes in mid 1960s for treatment related to granulomas associated with leprosy after the famous Thalidomide tragedy. It's aptitude of binding to the limb growth protein, Cereblon, makes it thinkable to repurpose it to inhibit the tumour growth. Potent derivatives, such as lenalidomide and pomalidomide have been approved by the FDA to treat multiple myeloma, mantle cell lymphoma, and myelodysplastic syndromes associated with the deletion 5q abnormality. [57] In a 1994 study by Robert D'amato *et al*, they tested thalidomide's effect on angiogenesis. Chicken chorioallantoic membrane (CAM) assays were performed and the effects on the developing vasculature were recorded. Treatment with a terato-genic dose (200 mg/kg) of thalidomide resulted in an inhibition of the area of vascularized cornea that ranged from 30 to 51% in three experiments with a median inhibition of 36%. It suppressed tumor necrosis factor α (TNF α) production from macrophages. [58] Singhal and Mehta have summarizied the investigations of clinical trials for thalidomide in their report. Thalidomide fairly treated patients suffering from multiple myelomas, Kaposi's sarcoma, prostate cancer, Hodgkin's disease relapsing after autotransplantation, follicular non-Hodgkin lymphoma, langerhans cell histiocytosis, hepatocellular carcinoma and chronic myeloproliferative disorders. There was no to less effect seen for breast cancer, glioma, renal cell carcinoma, ovarian cancer when thalidomide was used as a single agent. It nullified the GIT side effects and showed synergism when

administered with irinotecan for colon cancer.[59] Furthermore, the molecule also showed efficacy against several malignancies, including acute myeloid leukemia, myelodysplasia, and myelodysplastic syndrome.[60] Another study showed that fibroblast growth factor receptors (FGFRs), involved in embryo development and cancer pathophysiology, could be potential targets of thalidomide and its analogs, also endorsing the link between the teratogenicity and antitumor activities of these drugs.[61] Hence, thalidomide may not be an excellent candidate to fight off all kinds of tumor but studies suggest it could be added in the regimen with potent anti-tumor drugs.

Riluzole

Riluzole is a benzothiazole that has been used to treat patients with amyotrophic lateral sclerosis (ALS). Glutamate is one of the major excitatory neurotransmitter. Recently, several R&D instituitions have started to investigate the involvement of glutamate signaling in cancer. This compound has been reported to inhibit the glutamate release from nerve terminals in the central nervous system, the binding of excitatory amino acids to glutamate receptors and the activity of the voltage-gated Na+ channels. There is a lot of evidence that ion channels play important roles in regulating the tumor cell cycle, cell proliferation and apoptosis. The study focused the effectiveness of the drug on pancreatic cell lines LNCaP and C4-2. In this study it was found that riluzole inhibited DNA and induced inhibition of cell proliferation and apoptotic cell death via ER stress in both androgendependent and androgen-independent prostate cancer cells. It may also be a useful adjuvant to current chemotherapy as many drugs induce ER stress.[62]

Another research by Namkoong *et al* studied the MTT cell proliferation assays to assess the biological consequences of C8161and HEM treated with riluzole. A dose-dependent suppression of C8161 cell growth was detected. Apoptosis was induced in C8161 cells as evident by PARP cleavage. Furthermore, it is shown to be effective in suppression of tumor growth in a xenograft model. They concluded that riluzole is a good candidate for melanoma therapy.[63] In a 2018 report, a mouse model was developed for chronic oxaliplatin-induced neuropathy, which mimics deficits observed in patients. They reported that it prevents both sensory and motor deficits induced by oxaliplatin as well as the depression-like phenotype induced by cumulative chemotherapeutic drug doses. All the beneficial effects are due to riluzole's action on the TREK-1 potassium channel, which plays a central role in its therapeutic action. Likewise, it decreases human colorectal cancer cell line viability *in vitro* and inhibits polyp development *in vivo*.[64] This makes it clear that riluzole would be an excellent candidate employed as synergistic with another potent anti-cancer drugs.



Nitroxoline Thalidomide Riluzole

Structure based Drug Repostioning

Virtual screening methodology is the current effective method to prioritize the best effective structures for lead optimization. Structure based repositioning allows interactions between large number of ligands' libraries with the interested target binding site in a time consuming and cost effective manner. The combining of structure based screening along with the repositioning outlook is an encouraging attitude for drug discovery.[65] The start of structure based repositioning is to find appropriate structural information regarding the target sites on proteins as well as the drugs. As of now the Protein Drug Bank contains over 13500 macromolecular structures with 60% of these complexed with biologically relevant ligands. The structure is determined using X-ray Crystallography or NMR techniques. There are three approaches to structure based repositioning including disease centric approach, target centric approach and drug centric approach. Widely used tactic is the disease centric followed by target centric and only 6% of drugs were repositioned using drug centric approach because it is an indirect way and has limited information relying on drug-target relations. Current tools for carrying out repositioning are Docking (AutoDock, Glide, FlexX, GOLD, MolDock), Binding site prediction (SiteMap, FindSite, PDBeMotif, LigASite), Pharmacophore based screening (LigandScout), and Interaction similarity (PLIP, TIFP, SIFt).[66]

CONCLUSION

This review is not aimed to cover the tremendous literature available on various classes of repositioned drugs, but to highlight those drugs which have been repositioned as potential anti-cancer drugs, though further work remains to establish that these drugs could successfully be used for the treatment of cancer. Repositioning, like many other, is just an approach for the discovery of new drugs, where modification of the chemical structure of the existing old drug or the drug itself for new indication is attempted. Hopefully, in the

years to come an anticancer drug may be available for the treatment discovered by this approach.

Author contributions

Both the authors have equally contributed to the research work and approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest concerning to this manuscript.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Shivajirao Kadam, Chancellor, Bharati Vidyapeeth (Deemed to be) University, Pune for encouragement. The help of Mrs. Dharti Modh, (Ph.D. scholar) for suggestions and in preparing this article is much appreciated.

Abbreviations	Full form
ATRA	All-trans retinoic acid
HAART	Highly active antiretroviral therapy
HIF-1α	Hypoxia-inducible factor 1α
NSCLC	Non-small cell lung cancer
FASN TE	Fatty acid synthase thiosesterase
HFF	Human foreskin fibroblasts
HUVEC	Human umbilical vein endothelial cells
BAEC	Bovine aortic endothelial cells
Wnt	Wingless- related integration site
CCS1	Clear cell sarcoma 1
AMPK	AMP- activated protein Kinase
PI3K	Phosphoinositide-3-Kinase
AKT	Protein kinase B
Mtor	Mammalian target of rapamycin
MAPK	Mitogen-activated protein kinase
PPAR-γ	Peroxisome proliferator-activated receptors-γ
USPSTF	U.S. preventive services task force

REFERENCES

1. Pillaiyar T, Meenakshisundaram S, Manickam M, Sankaranarayanan M. A medicinal chemistry perspective of drug repositioning: Recent advances and challenges in drug discovery. European Journal of Medicinal Chemistry, 2020; 195: 1-25.
2. Zhang Z, Zhou L, Xie N, Nice E, Zhang T, Cui Y, Huang C. Overcoming cancer therapeutic bottleneck by drug repurposing. Sig Transduct Target Ther, 2020; (5): 113.
3. Scannell J, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov, 2012; (11): 191–200.
4. Nosengo N. Can you teach old drugs new tricks? Nature, 2016; 534: 314–316.
5. Gonzalez-Fierro A, Duenas-Gonzalez A. Drug repurposing for cancer therapy, easier said than done. Seminars in Cancer Biology, 2021; 68: 123–131.
6. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A cancer journal for clinicians, 2018; 68(6): 394-424.
7. Protein Drug Bank, Research Collaboratory for Structural Bioinformatics, https://www.rcsb.org/structure/2bpx.
8. Ikezoe T, Saito T, Bandobashi K, Yang Y, Koeffler P, Taguchi H. HIV-1 protease inhibitor induces growth arrest and apoptosis of human multiple myeloma cells via inactivation of signal transducer and activator of transcription 3 and extracellular signal-regulated kinase. Mol Cancer Ther. 2004; 3:473-479.
9. Gantt S, Carlsson J, Ikoma M, Gachelet E, Gray M, Geballe A, Corey L, Casper C, Lagunoff M, Vieira J. The HIV protease inhibitor nelfinavir inhibits Kaposi's sarcoma-associated herpesvirus replication in vitro. Antimicrob Agents Chemother, 2011; 55: 2696–703.
10. Gills J, LoPiccolo J, Tsurutani J, Shoemaker R, Best C, Abu-Asab M, Borojerdi, Warfel N, Gardner E, Danish M, Hollander C, Kawabata S, Tsokos M, Figg W, Steeg P, Dennis P. Nelfinavir, A lead HIV protease inhibitor, is a broad-spectrum, anticancer agent that induces endoplasmic reticulum stress, autophagy, and apoptosis in vitro and in vivo. Clin Cancer Res, 2007; 13: 5183-94.
11. Buijsen J, Lammering G, Jansen R, Beets G, Wals J, Sosef M, Boer M, Leijtens J, Riedl R, Theys J, Lambin P. Phase I trial of the combination of the Akt inhibitor nelfinavir and chemoradiation for locally advanced rectal cancer. Radiotherapy and Oncology, 2013.
12. Veschi S, Lellis L, Florio R, Lanuti P, Massucci A, Tinari N, Tursi M, Sebastiano P, Marchisio M,

Natoli C, Cama A. Effects of repurposed drug candidates nitroxoline and nelfinavir as single agents or in combination with erlotinib in pancreatic cancer cells. J Exp Clin Cancer Res, 2018; 37: 236.
13. Shim S, Liu O. Recent Advances in Drug Repositioning for the Discovery of New Anticancer Drugs. International Journal of Biological Sciences, 2014; 10(7): 654-663.
14. Subeha M, Telleria C. The Anti-Cancer Properties of the HIV Protease Inhibitor Nelfinavir. Cancers, 2020; 12: 3437.
15. Hoover A, Milhem M, Anderson C, Sun W, Smith B, Hoffman H, Buatti J. Efficacy of nelfinavir as monotherapy in refractory adenoid cystic carcinoma: Results of a phase II clinical trial. Head Neck, 2015; 37: 722–726.
16. Pan J, Mott M, Xi B, Hepner E, Guan M, Fousek K, Magnusson R, Tinsley R, Valdes F, Frankel P, Synold T, Chow W. Phase I study of nelfinavir in liposarcoma. Cancer Chemother, Pharmacol, 2012; 70: 791–799.
17. Kawabata S, Connis N. Nelfinavir inhibits the growth of Small-cell Lung Cancer Cells and patient-derived Xenograft Tumors. Anticancer Research, 2021; 41: 91-99.
18. Lopiccolo J, Kawabata S, Gills J Dennis P. Combining Nelfinavir with Chloroquine Inhibits In Vivo Growth of Human Lung Cancer Xenograft Tumors. In vivo, 2021; 35: 141-145.
19. Zeng LF, Yong Wang Y, Kazemi R, Xu S, Xu ZL, Sanchez TW, Yang LM, Debnath B, Odde S, Xie H, Zheng YT, Ding J, Neamati N, Long YQ. Repositioning HIV-1 Integrase Inhibitors for Cancer Therapeutics: 1,6-Naphthyridine-7-carboxamide as a Promising Scaffold with Drug-like Properties. J Med Chem, 2012; 55: 9492−9509.
20. Tylinska B, Wiatrak B, Czyżnikowska Z, Cieśla-Niechwiadowicz A, Gębarowska E, Janicka-Kłos A. Novel Pyrimidine Derivatives as Potential Anticancer Agents: Synthesis, Biological Evaluation and Molecular Docking Study. Int J Mol Sci, 2021; 22: 3825.
21. Fako V, Wu X, Pflug B, Liu JY, Zhang JT. Repositioning Proton Pump Inhibitors as Anticancer Drugs by Targeting the Thioesterase Domain of Human Fatty Acid Synthase. J Med Chem, 2015; 58: 778−784.
22. Chong C, Xu J, Bhat S, Sullivan DJ, Liu JO. Inhibition of Angiogenesis by the Antifungal Drug Itraconazole. ACS Chemical Biology, 2007; 2(4): 263–270.
23. Buczacki S. Itraconazole targets cell cycle heterogeneity in colorectal cancer. J. Exp. Med, 2018; 215(7): 1891–1912.
24. Bae SH, Park JH, Choi HG, Kim H, Kim SH. Imidazole Antifungal Drugs Inhibit the Cell Proliferation and Invasion of Human Breast Cancer Cells. Biomol Ther, 2018; 26(5): 494-502.
25. Nygren P, Fryknäs M, Ågerup B, Larss R. Repositioning of the anthelmintic drug mebendazole for the treatment for colon cancer. J Cancer Res, Clin Oncol, 2013; 139: 2133–2140.
26. Doudican N, Rodriguez A, Osman I, Orlow SJ. Mebendazole induces apoptosis via Bcl-2 inactivation in chemoresistant melanoma cells. Mol Cancer Res, 2008; 6: 1308–1315.
27. Coyne C, Jones T, Bear R. Gemcitabine-(C4-amide)-[anti-HER2/neu] antineoplastic cytotoxicity in dual combination with mebendazole against chemotherapeutic- resistant mammary adenocarcinoma. J Clin Exp Oncol, 2013; 2.
28. Chu S, Badar S, Morris DL, Pourgholami MH. Potent inhibition of tubulin polymerisation and proliferation of paclitaxel-resistant 1A9PTX22 human ovarian cancer cells by albendazole. Anticancer Res, 2009; 29: 3791–3796.
29. Dinić J. Repurposing old drugs to fight multidrug resistant cancers. Drug Resistance Updates, 2020; 52.
30. Gadducci A, Biglia N, Tana R, Cosio S, Gallo M. Metformin use and gynecological cancers: A novel treatment optionemerging from drug repositioning. Crit Rev Oncol/Hematology, 2016; 105: 73–83.
31. Lee J, Shin D, Kim JS. Anticancer effect of Metformin in Herceptin-Conjugated Liposome for Breast Cancer. Pharmaceutics, 2020; 12: 11.
32. Irie H, Banno K, Yanokura M, Iida M, Adachi M, Nakamura K, Umene K, Nogami Y, Masuda K, Kobayashi Y, Tominaga E, Aoki D. Metformin: A candidate for the treatment of gynecological tumors based on drug repositioning (Review). Oncol Lett, 2016; 11: 1287-1293.
33. Varjabedian L, Bourji M, Pourafkari L, Nader ND. Cardioprotection by metformin: beneficial effects beyond glucose reduction, Am J Cardiovasc Drugs, 2018; 18(3): 181–193.
34. Markowicz-Piasecka M, Sikora J, Szydłowska A, Skupień A, Mikiciuk-Olasik E, Huttunen KM. Metformin— a future therapy for neurodegenerative diseases. Pharm Res, 2017; 34(12): 2614–2627.
35. Meshkani S, Mahdian D, Abbaszadeh-Goudarzi K, Abroudi M, Dadashizadeh G, Lalau JD, De Broe ME, Hosseinzadeh H. Metformin as a protective agent against natural or chemical toxicities: a comprehensive review on drug repositioning. J Endocrinol Invest, 2020; 43: 1-19.
36. Anselmino L, Baglioni M, Malizia F, Laluce NC, Etichetti CB, Marignac VM, Rozados V, Scharovsky OG, Girardini J, Rico MJ, Márquez MM. Repositioning metformin and propranolol for colorectal and triple negative breast cancers treatment. Sci Rep, 2021; 11: 8091.
37. Joshi H, Pal T, Ramaa CS. A new dawn for the use of thiazolidinediones in cancer therapy. Expert Opin Investig Drugs, 2014; 23(4): 501-510.
38. Wang Z. The PPARγ Agonist Rosiglitazone Enhances the Radiosensitivity of Human Pancreatic Cancer Cells. Drug Des Devel Ther, 2020; 14: 3099–3110.

39. Pomel V, Klicic J, Covini D, Church DD, Shaw JP, Roulin K, Burgat-Charvillon F, Valognes D, Camps M, Chabert C, Gillieron C, Françon B, Perrin D, Leroy D, Gretener D, Nichols A, Vitte PA, Carboni S, Rommel C, Schwarz MK, Rückle T. Furan-2-ylmethylene Thiazolidinediones as novel, potent and selective inhibitors of PP3γ. J. Med. Chem, 2006; 49: 3857-3871.
40. Saito T, Okada S, Yamada E, Shimoda Y, Osaki A, Tagaya Y, Shibusawa R, Okada J, Yamada M. Effect of dapagliflozin on colon cancer cell. Endocr J, 2015; 62(12): 1133-1137.
41. Faridi U, Al-Mutairi F, Parveen H, Khateeb S. An in-vitro and in Silico Anticancer Study of FDA Approved Antidiabetic Drugs Glimepiride and Empagliflozin. Int J Life Sci Pharma Res, 2020; 10(2): 52-57.
42. Kirtonia A, Gala K, Fernandes SJ, Pandya G, Pandey AK, Sethi G, Khattar E, Garg M. Repurposing of drugs: An attractive pharmacological strategy for cancer therapeutics. Elsevier, Semin Cancer Biol, 2021; 68: 258–278.
43. Yang X, Zhang X, Wu R, Huang Q, Jiang Y, Qin J, Yao F, Jin G, Zhang Y. DPPIV promotes endometrial carcinoma cell proliferation, invasion and tumorigenesis. Oncotarget, 2017; 8(5): 8679-8692.
44. Kamada S, Namekawa T, Ikeda K, Suzuki T, Kagawa M, Takeshita H, Yano A, Okamoto K, Ichikawa T, Horie-Inoue K, Kawakami S, Inoue S. Functional inhibition of cancer stemness-related protein DPP4 rescues tyrosine kinase inhibitor resistance in renal cell carcinoma. Oncogene, 2021; 40: 3899–3913.
45. Li Y, Li D, Li D, Li K, Quan Z, Wang Z, Sun Z. Repositioning of Hypoglycemic Drug Linagliptin for Cancer Treatment. Front Pharmacol, 2020; 11(187).
46. Thor KB, Ashburn TT. Drug repositioning: Identifying and developing new uses for existing drugs. Nat Rev Drug Discov, 2004; 3: 673-683.
47. Aman F, Hanif M, Kubanik M, Ashraf A, Söhnel T, Jamieson SM, Siddiqui WA, Hartinger CG. Antiinflammatory Oxicams as Multi-donor Ligand Systems: pH and Solvent Dependent Coordination Modes of Meloxicam and Piroxicam to Ru and Os. Chemistry, 2017; 23(20): 4893-4902.
48. Khodaie F, Khazaei-poul Y. Anti-Proliferative Effects of Piroxicam and Nimesulide on A431 Human Squamous Carcinoma Cell Line. Int J Cancer Manag, 2017; 10(4).
49. Li L, Hu M, Wang T, Chen H, Xu L. Repositioning aspirin to treat lung and breast cancers and overcome acquired resistance to targeted therapy. Front Oncol, 2020; 9: 1503.
50. Costea T, Nagy P, Ganea C, Szöllősi J, Mocanu MM. Molecular mechanisms and bioavailability of polyphenols in prostate cancer. Int. J. Mol. Sci, 2019; 20(5): 1062.
51. Akrami H, Aminzadeh S, Fallahi H. Inhibitory effect of ibuprofen on tumor survival and angiogenesis in gastric cancer cell. Tumour Biol, 2015; 36(5): 3237-43.
52. Moon A, Saonerkar T, Ninad N, Lakkakul R. Repositioning of NSAIDS for Lung Cancer treatment and augmentation by Quercitin. World J Pharmaceutical Research, 2020; 9(7): 1795-1806.
53. Yu J, Ji C, Shi MH. Nitroxoline induces cell apoptosis by inducing MDM2 degradation in small-cell lung cancer. Kaohsiung J Med Sci., 2019; 35: 202–208.
54. Xu N, Li W, Sun J, Sadahira T, Xu A, Watanabe M, Guo K, Araki M, Li G, Liu C, Nasu Y, Huang P. Nitroxoline inhibits bladder cancer progression by reversing EMT process and enhancing anti-tumor immunity. J Cancer, 2020; 11(22): 6633-6641.
55. Mirković B, Renko M, Turk S, Sosič I, Jevnikar Z, Obermajer N, Turk D, Gobec S, Kos J. Novel mechanism of cathepsin B inhibition by antibiotic nitroxoline and related compounds. ChemMedChem, 2011; 6: 1351-1356.
56. Jiang H, Taggart JE, Zhang X, Benbrook DM, Lind SE, Ding WQ. Nitroxoline (8-hydroxy-5-nitroquinoline) is more a potent anti-cancer agent than clioquinol (5-chloro-7-iodo-8-quinoline). Cancer Lett, 2011; 312: 11-7.
57. Schein C. Repurposing approved drugs on the pathway to novel therapies. Med Res Rev, 2020; 40(2): 586–605.
58. D'Amato R, Loughnan M, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc. Natl Acad Sci, 1994; 91: 4082-4085.
59. Singhal S, Mehta J. Thalidomide in cancer. Biomed Pharmacother, 2002; 56: 4-12.
60. Hiramatsu T, Yoshizawa J, Miyaguni K, Sugihara T, Harada A, Kaji S, Uchida G, Kanamori D, Baba Y, Ashizuka S, Ohki T. Thalidomide potentiates etoposide-induced apoptosis in murine neuroblastoma through suppression of NF-kB activation. Pediatr Surg Int, 2018; 34.
61. Sundaresan L, Kumar P, Manivannan J, Balaguru UM, Kasiviswanathan D, Veeriah V, Anishetty S, Chatterjee S. Thalidomide and its analogs differentially target fibroblast growth factor receptors: thalidomide suppresses FGFR gene expression while pomalidomide dampens FGFR2 activity. Chem Res Toxicol, 2019; 32: 589–602.
62. Akamatsu K, Shibata MA, Ito Y, Sohma Y, Azuma H, Otsuki Y. Riluzole Induces Apoptotic Cell Death in Human Prostate Cancer Cells via Endoplasmic Reticulum Stress. Anticancer Res, 2009; 29(6): 2195-2204.
63. Namkoong J, Shin S, Lee HJ, Marín YE, Wall BA, Goydos JS, Chen S. Metabotropic Glutamate Receptor 1 and Glutamate Signaling in Human Melanoma. Cancer Res, 2007; 67(5): 2298-2305.
64. Poupon L, Lamoine S, Pereira V, Barriere DA, Lolignier S, Giraudet F, Aissouni Y, Meleine M, Prival L, Richard D, Kerckhove N, Authier N,

Balayssac D, Eschalier A, Lazdunski M, Busserolles J. Targeting the TREK-1 potassium channel via riluzole to eliminate the neuropathic and depressive-like effects of oxaliplatin. Neuropharmacology, 2018; 140: 43-61.
65. Ma D-L, Chan D, Leung CH. Drug repositioning by structure-based virtual screening. Chem Soc Rev, 2013; 42: 2130-2141.
66. Adasme M, Parisi D, Sveshnikova A, Schroeder M. Structure-based Drug repositioning: Potential and Limits. Semin Cancer Biol., 2021 Jan; 68: 192-198.