Materials Chemistry Horizons REVIEW

An Overview on New Anticancer Drugs Approved by Food and Drug Administration: Impending Economic and Environmental Challenges

Mohammad Reza Sarfjoo[1*], Arya Shad[2], Mahnaz Hassanpour[3], Rajender S. Varma[4*]

[1] Department of Chemistry, Isfahan University of Technology, Isfahan 415683111, Iran
[2] Department of Mechanical Engineering, Islamic Azad University, Rasht Branch, Rasht, Iran
[3] Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), Zanjan, 45137–66731 Iran
[4] Regional Centre of Advanced Technologies and Materials, Czech Advanced Technology and Research Institute, Palacký University in Olomouc, ˇSlechtitelů, Olomouc, Czech Republic

Corresponding authors: mrsarfjoo@gmail.com (M. R. Sarfjoo); Varma.Rajender@epa.gov (R.S. Varma)

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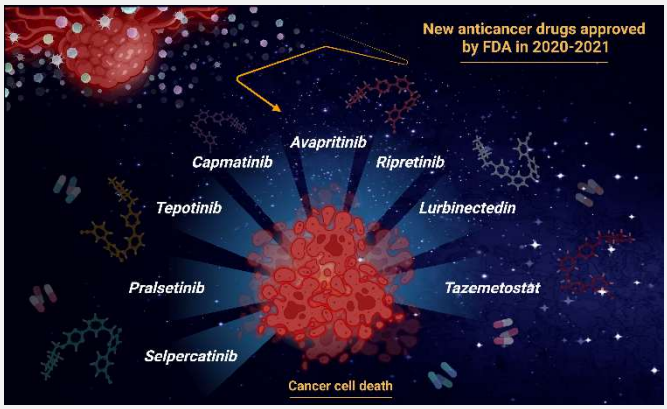
ABSTRACT

One of the leading causes of death worldwide these days is cancer, and new anticancer drugs have been developed to treat it with all the vigor of the advancement of science and technology. Unfortunately, these drugs are very expensive, and besides, they cause great economic hardship for cancer patients and society as a whole. On the other hand, the deployment of hazardous chemicals, and especially the common commercial solvents in the production of anti-cancer drugs, causes environmental pollution thus contributing to the drug purification costs. Herein, recent FDA-approved anticancer drugs in 2020-2021, their mechanism of action, financial challenges, and associated environmental hazards are deliberated, with possible solutions that may reduce not only the costs of the drugs but also the environmental pollution involved in the synthesis of anticancer drugs via greener pathways by appropriate substitution.



Keywords: Anticancer drug, environmental, green chemistry

1. Introduction

Cancer is one of the leading causes of human beings worldwide death with its most common types such as lung, colon, prostate, and breast cancer [1,2]. The occurrence, mortality, and disability-adjusted life year burden of cancer vary greatly by country and region, especially between developing countries and developed countries. GLOBOCAN 2020 estimated that there were 19,292,789 cancer cases and 9,958,133 cancer deaths globally in 2020 [3].

In today's world, concerns have been raised about the cost-effectiveness and safety of high-cost cancer medications at the end of life, which have caused these practices to come under fire [4]. It is debatable whether these new cancer drugs add any value, despite their continued approval and use. There are many academic groups as well as research and developments (R&D) in pharmaceutical companies that work on anticancer drugs, analysis, and delivery approaches [5–7].

New drug approvals are generating a multi-billion dollar market due to the ever-rising prices of drugs [8]. It is estimated that 19 million people worldwide suffer from cancer in today's society. To treat cancer, anti-cancer drugs are needed, which imposes huge costs on cancer patients, their families, and society as a whole; bankruptcy appears to be associated with cancer diagnosis and treatment for underinsured patients [3,9–11]. ACS and the Green Chemistry Institute established the ACS-GCI Pharmaceutical Roundtable in 2005 (ACS-GCIPR, hereinafter referred to as the Roundtable). It was expanded in 2018, with the inclusion of several major pharmaceutical companies, including AstraZeneca, Pfizer, and Merck, among others devoted to fostering innovation and integration of green chemistry and engineering tenets into the entire pharmaceutical process [12]. Since 2020, nine anti-cancer drugs have been approved

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by the FDA, which are the subject of discussion here in terms of the challenges pertaining to the cost-effectiveness and environmental impact of these compounds from the green chemistry perspective.

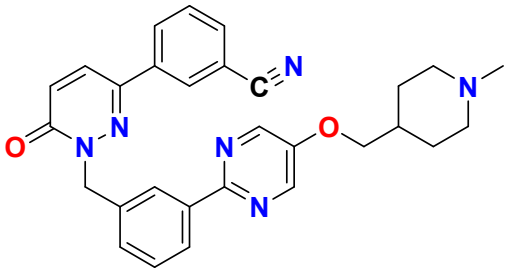
Herein, recent FDA-approved anticancer drugs in 2020-2021, their mechanism of action, financial challenges, and associated environmental hazards are deliberated, with possible solutions that may reduce not only the costs of the drugs but also the environmental pollution involved in the synthesis of anticancer drugs via greener pathways by appropriate substitution.

2. FDA-approved anticancer drugs in 2020-2021 and mechanism of action

Our first step is to have an overview of the new FDA-approved anticancer drugs for 2020-2021, which is followed by a synopsis of their prices and performances.

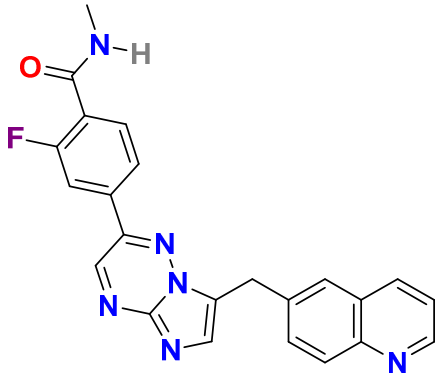
2.1. Tepotinib

In March 2020, the Japanese Food and Drug Administration approved Tepotinib for use in metastatic NSCLC with MET alterations, and the US Food and Drug Administration granted accelerated approval in 2021 under the brand name Tepmetko in the treatment of adult patients with metastatic NSCLC and MET exon 14 skipping alterations [13,14].



2.2. Capmatinib

It is marketed under the brand name Tabrecta which is a Kinase Inhibitor. In addition to inhibiting Mesenchymal Epithelial Transition, this drug also inhibits Cytochrome P450 1A2, P-Glycoprotein, and Breast Cancer Resistance Protein, as well as Multidrug and Toxin Extrusion Transporter 1. According to an FDA-approved 2020 treatment, capmatinib is indicated for adults with metastatic non-small cell lung cancer in which the tumors have an exon 14 skipping mutation [15–17].



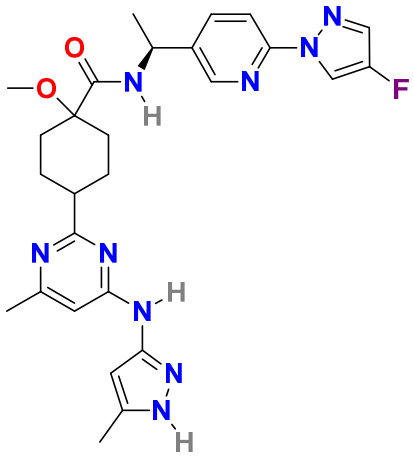
2.3. Pralsetinib

In 2020, the FDA approved Pralsetinib, also known as Gavreto, as an orally bioavailable selective inhibitor that treats non-small cell lung cancer (NSCLC) for:

(i) adult and pediatric patients aged 12 and older with advanced or metastatic RET fusion-positive thyroid cancer requiring systemic therapy

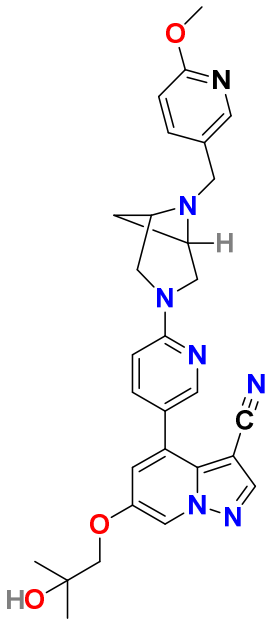
(ii) adult and pediatric patients aged 12 and older with advanced or metastatic RET-mutant medullary thyroid cancer requiring systemic therapy.

(iii) adult patients with metastatic RET fusion-positive NSCLC [18–20].



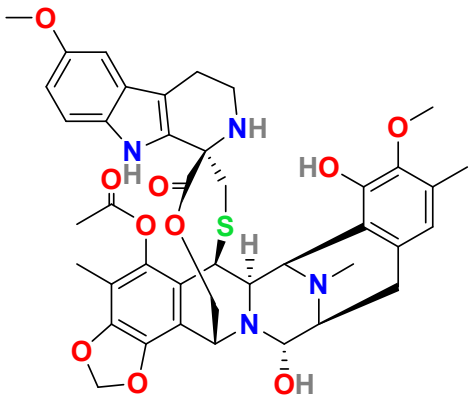
2.4. Selpercatinib

In 2020, Selpercatinib (RETEVMO™) was approved for use in the US as an orally bioavailable selective RET (rearranged during transfection) inhibitor for adults and children with advanced or metastatic RET-mutant MTC. Selpercatinib has also been approved for treating patients with advanced or metastatic RET fusion-positive thyroid cancer who are reactive to radioactive iodine (if radioactive iodine is appropriate) [21].



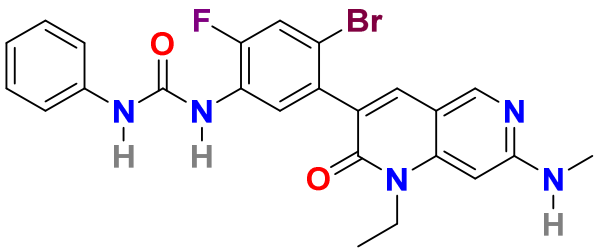
2.5. Lurbinectedin

Oncogenic transcription inhibitor, lurbinectedin (ZEPZELCATM™) has been approved in the USA for the treatment of adult patients with metastatic SCLC that progressed after platinum-based chemotherapy in June 2020 and has been used in treatment for mesothelioma, chronic lymphocytic leukemia (CLL), breast cancer, and small-cell lung cancer (SCLC) [22,23].



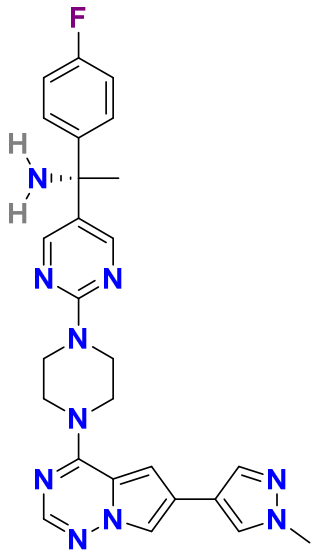
2.6. Ripretinib

Rimatinib (QINLOCK™), an oral kinase inhibitor, received its initial FDA approval in May 2020 for the treatment of adults with advanced GIST who have previously received 3 or more kinase inhibitors. A novel type II tyrosine switch inhibitor, Ripretinib inhibits KIT and PDGFRA kinases including wild-type mutations, primary and secondary mutations, as well as other kinases, including PDGFRB, TIE2, VEGFR2, and BRAF [24,25].



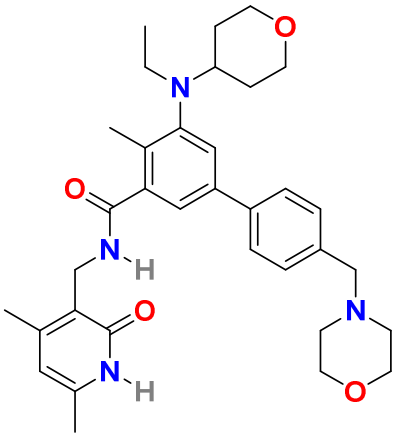
2.7. Avapritinib

Avapritinib (ayvakit™), one of a class of medical drugs known as kinase inhibitors, functions by blocking the activity of a protein that signals cancer cells to multiply; it was approved by the FDA in 2021 for PDGFRA exon 18 (including D842V) mutant GIST and is in the USA for clinical development of this treatment for systemic mastocytosis and late-stage solid tumors [26,27].



2.8. Tazemetostat

As of January 2020, Tazemetostat (Tazverik™), a first-in-class small molecule inhibitor of zeste homolog 2 (EZH2), is approved for the treatment of adults and adolescents aged 16 and older with locally advanced or metastatic epithelioid sarcoma. Several other tumor types, including diffuse large B-cell lymphoma and mesothelioma, are also being evaluated in various countries around the world, with the US FDA accepting a new drug application for its use in follicular lymphoma for priority review [28,29].



3. Financial challenges and solutions

Table 1 illustrates the high average cost of these drugs. Hence, it makes sense to find ways to reduce the price of anticancer drugs for patients. Medicaid Drug Rebate Program provides one example of the impact that such negotiations may have on drug prices. In 1990, section 1927 of the Social Security Act authorized this program, which required drug manufacturers to enter into a national rebate agreement with the Secretary of Health and Human Services (HHS) in exchange for Medicaid coverage. In addition to the minimum rebate, manufacturers had to provide a rebate for price increases above the inflation rate after the drug was introduced. According to the Congressional Budget Office (CBO), Medicaid's average drug price was 27-38 % less than Medicare's part D average in 2010 [30–32].

Table 1. A price list of anticancer drugs

Number	Name	Amount	Price	Reference
1	*Tazemetostat*	240 tablets (200 mg)	18,696$	[33,34]
2	*Avapritinib*	30 tablets (25mg)	37,089$	[33,35]
3	*Ripretinib*	90 tablets (50mg)	37,074$	[33,36]
4	*Lurbinectedin*	4 mg powder	7,417$	[33,37]
5	*Selpercatinib*	120 capsules (80mg)	22,471$	[33,38]
6	*Pralsetinib*	60 capsules (100mg)	10,650$	[33,39]
7	*Capmatinib*	56 tablets (150mg)	10,528$	[33,40]
8	*Tepotinib*	30 tablets (225mg)	11,976$	[33,41]

On the other hand, medicinal chemistry and drug discovery and development have been affected by cross-coupling reactions for more than two decades, a common pathway in the assembly of quite a few of these drugs. Drug discovery has been largely successful because chemists are attracted to reproducible and reliable reactions [42]. The palladium-catalyzed cross-coupling reaction is involved in half of all C-C and C-heteroatom bond-forming reactions in the

development, discovery, and production of drugs [43,44]. A number of new anticancer approved by the FDA in 2020-2021 have been synthesized deploying expensive and rare palladium, including Tepotinib [13,14], Capmatinib [15–17], Pralsetinib [18–20], and Selpercatinib [21].

Palladium is a precious and expensive metal and its use as a disposable catalyst can be wasteful, and their complete removal from a reaction mixture is a challenging proposition, thereby contaminating both the products and the waste fluids [45]. Researchers have demonstrated that alternatives to palladium, such as cobalt, or other earth-abundant materials can be deployed for the synthesis of FDA-approved anti-cancer drugs by using inexpensive 3d transition metals [46,47].

4. Environmental challenges and greener solutions

Different drugs have been synthesized and produced in various pharmaceutical industrial factories in the past years, and the global community is aware of this need. Those industries that do not properly dispose of their waste can cause serious damage to aquatic ecosystems [48,49]. According to the principles of green chemistry, processes must be designed and used to reduce or eliminate hazardous substances so that the desired substances can be synthesized without producing toxic or hazardous substances [50–52]. As stated in the ACS report, half of the mass of a synthetic reaction is contained in the standard state, resulting in between 50-80 % of the waste from the reaction, which contributes to the degradation of the environment and pollution of water resources [53].

According to the green chemistry tenets, dipolar aprotic solvents are to be avoided for reasons. Waste streams of large volumes of aqueous fluid are produced when separating products and removing or recovering bipolar dipolar aprotic solvents like DMF, THF, DMAc, and DMSO. These solvents can have CMR (Cancer-Mutagen-Reprotoxic) issues, such as reproductive toxicity, which puts human health at risk once they are introduced into the environment. Considering the issues raised above, it seems prudent to seek alternatives to common and harmful solvents. Although water or alcohol derivatives are green solvents, they are not as polarized as classic solvents [54–57].

Using the methods described in the references, new anticancer synthesis methods approved by the FDA in 2020-2021 were examined, and 2-4 hazardous solvents were deployed in the manufacture of these drugs, as shown in **Table 2**.

Table 2. Hazardous solvents used in synthesis new anticancer drugs

Name	DCE[1]	DMF[2]	DMSO[3]	DCM[4]	THF[5]	DMA[6]	TEA[7]	DMAP[8]	Ref
Tazemetostat	-	DMF	DMSO	-	-	-	-	-	[33,34]
Avapritinib	-	-	-	-	THF	-	TEA	-	[33,35]
Ripretinib	-	-	-	DMC	THF	-	TEA	-	[33,36]
Lurbinectedin	-	-	DMSO	-	-	-	-	DMAP	[33,37]
Selpercatinib	DCE	DMF	DMSO	-	-	-	-	-	[33,38]
Pralsetinib	-	DMF	-	-	THF	DMA	-	-	[33,39]
Capmatinib	-	DMF	DMSO	DMC	-	-	TEA	-	[33,40]
Tepotinib	-	DMF	-	-	THF	-	-	-	[33,41]

[1]DCE: 1,2-dichloroethane; [2]DMF: ***N,N***-Dimethylformamide; [3]DMSO: Dimethyl sulfoxide; [4]DMC: Dimethyl carbonate; [5]THF:Tetrahydrofuran; [6]DMA: Dimethylacetamide; [7]TEA: Triethylamine; [8]DMAP: 4-Dimethylaminopyridine

Table 3, describes which drugs require each solvent usage, along with the associated risk of each solvent separately.

Table 3. Solvents used to make cancer-fighting compounds and the risks involved

Solvent		Hazards	Reference
DCE	*Selpercatinib*	Chemical Burns, Pulmonary Edema, Liver, and Renal Dysfunctions	[58]
DMF	*Tazemetostat* *Selpercatinib* *Pralsetinib* *Capmatinib* *Tepotinib*	kidneys Toxic for Reproduction, Explosion	[59]
DMSO	*Tazemetostat* *Lurbinectedin* *Selpercatinib* *Capmatinib*	Explosion	[60–62]
DCM	*Ripretinib* *Pralsetinib* *Capmatinib*	Biliary-tract Cancer and nonHodgkin Lymphoma	[63]
THF	*Avapritinib* *Ripretinib* *Pralsetinib* *Tepotinib*	Flammable, Exposure, Damage the liver and	[64]
DMA	*Pralsetinib*	Toxic Hepatitis	[65]
TEA	*Avapritinib* *Ripretinib*	Damage to liver and kidneys, Flammable and dangerous fire hazard	[66]
DMAP	*Lurbinectedin*	Highly toxic by skin absorption	[67]

In looking for a high-polarity and non-dangerous green solvent, one comes across biobased solvent gamma (γ)-valerolactone (GVL) with distinct physicochemical properties. The estimated K-T parameters (α=0, β=0.6, π*=0.83) suggested that GVL is an excellent choice of a sustainable alternative to common polar aprotic solvents [68–70]. GVL can be synthesized from renewable feedstock (e.g., biomass waste and food waste) and the chemical is a naturally existing, safe, biodegradable, and nontoxic, chemical that even can be utilized as a food additive [71–73]. GVL shows promise as an alternative solvent to hazardous commercial solvents in the synthesis of FDA-approved anticancer drugs Fedratinib (treatment of myelofibrosis in adults with bone marrow cancer) and Abemaciclib (treatment of hormone-receptor-positive breast cancer) and Ponatinib (multi-tyrosine kinase inhibitor, anti-sarcomas cancer agent, and a drug for common neurodegenerative diseases) [46,47,74–77].

5. Conclusions

The impetus required to address the issue of excessive costs of anticancer and associated environmental challenges for the synthesis is strong, and proposals as to how to best address this issue have been both diverse and creative. We believe the untenable option is the existing condition. As a result: i) programs have already been implemented by organizations such as Health and Human Services (HHS); ii) alternatives to precious metals such as palladium, and deployment of cobalt or other coinage metals, can be used to synthesize FDA-approved anti-cancer drugs, especially pathway exploiting the use of inexpensive 3d transition metals; and iii) biobased solvents, such as gamma-valerolactone (GVL), instead of hazardous solvents can be used to overcome economic and environmental challenges.

Authors' contributions

All authors contributed to drafting and revising of the paper and agreed to be responsible for all the aspects of this work.

Declaration of competing interest

The authors declare no competing interest.

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Data availability

Not applicable.

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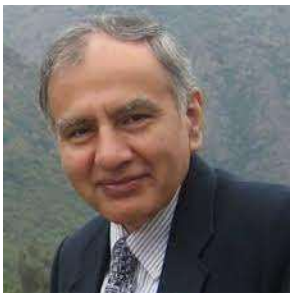
Author Biography



Prof. Rajender Varma born in India (Ph.D., Delhi University 1976) is a senior scientist at U.S. EPA with a visiting position at RCPTM, Palacky University, Olomouc, Czech Republic. He has over 48 years of multidisciplinary research experience ranging from eco-friendly synthetic methods using microwaves, ultrasound, etc. to greener assembly of nanomaterials and sustainable appliances of magnetically retrievable nanocatalysts in benign media. He is a member of the editorial advisory board of several international journals, published over 700 papers, and awarded 17 U.S. Patents, 6 books, 26 book chapters, and 3 encyclopedia contributions with 47,200 citations.