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Review

Diarylureas as Antitumor Agents

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Abstract: The diarylurea is a scaffold of great importance in medicinal chemistry as it is present in numerous heterocyclic compounds with antithrombotic, antimalarial, antibacterial, and anti-inflammatory properties. Some diarylureas, serine-threonine kinase or tyrosine kinase inhibitors, were recently reported in literature. The first to come into the market as an anticancer agent was sorafenib, followed by some others. In this review, we survey progress over the past 10 years in the development of new diarylureas as anticancer agents.

Keywords: diarylureas; antitumor agents; bis-aryl ureas; hepatocellular carcinoma (HCC); renal cell carcinoma (RCC); gastrointestinal stromal tumors (GISTs); metastatic colorectal cancer (mCRC); B-cell lymphomas

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1. Introduction

Ureas (R-NHCONH-R') are known organic compounds that possess biological activities and serve as templates for numerous medicinal chemistry researches [1]. Barbital is a diethylmalonyl urea discovered at the beginning of 1900, used as sleep aid and hypnotic [2]. In the following century, the urea scaffold has represented the pharmacophore the backbone motif for entire classes of therapeutic agents [3]. This review focuses on diarylureas, i.e., ureas substituted with two aromatic moieties also known as bis-aryl ureas. Diarylureas are found in numerous heterocyclic compounds with various biological activities [4], such as antithrombotic, antimalarial, antibacterial, antinflammatory, and anticancer [5,6]. In particular, diarylurea is a prominent pharmacophore in anticancer drugs. This activity is due to its near-perfect binding with certain acceptors. The NH moiety behaves as hydrogen bond donor and the urea oxygen atom acts as acceptor (Figure 1) [7].

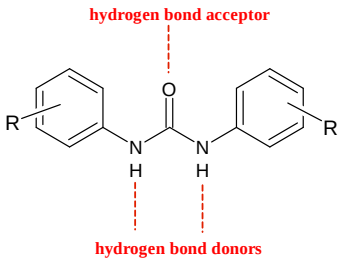


Figure 1. H-bonds in diarylureas.

This structure provides urea derivatives endowed with capability of binding several enzymes and receptors [8–10]. Moreover, it may link different pharmacophore fragments of new biological active compounds. A urea linker has been used to overcome the poor solubility of some phenyl N-mustards [11]. In this way, the authors obtained water soluble N-mustards, some of which showing high anticancer activity against various human tumor

xenograft models and were able to introduce cross-linking within the DNA double strand. Diarylurea-based compounds present strong inhibitory activity against kinases, including RAF kinases [12], platelet derived growth factor receptor (PDGF) [13], vascular endothelial growth factor receptor 2 (VEGFR-2) [14], receptor tyrosine kinase (RTKs) [15], and Aurora kinases [16]. The diarylurea moiety is, in fact, widespread in type II kinase inhibitors. These compounds circumvent kinases in an inactive state, the so-called DFG-out, and occupy a hydrophobic pocket next to the ATP-binding site. The diarylurea fragment is able to link the hinge-binding moiety with the portion that occupies the hydrophobic pocket that is in the inactive conformation of kinases [17] (Figure 2).

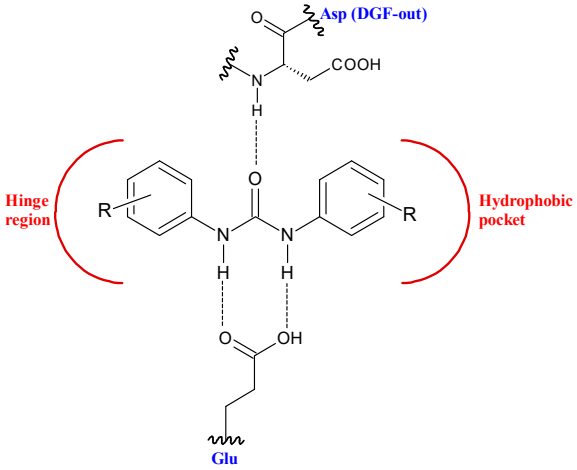


Figure 2. Diarylureas in the type II kinase inhibitor.

Diarylureas represent the skeleton of the main systemic therapies for several cancers, as advanced, metastatic hepatocellular carcinoma (HCC) [18], advanced renal cell carcinoma (RCC) [19], gastrointestinal stromal tumors (GISTs) [20], metastatic colorectal cancer (mCRC) [21]. Sorafenib is a multi-targeted small molecule tyrosine protein kinase that improves median survival over placebo for unresectable HCC patients [22]. In 2008 it obtained Food and Drug Administration (FDA) and European Medicinal Agency (EMEA) approval for the treatment of RCC and HCC [23]. Basing on sorafenib as the lead compound, several other diarylurea derivatives, such as regorafenib, linifanib, tivozanib, and ripretinib have been synthesized and evaluated as kinase inhibitors. Regorafenib was approved by the FDA in the United States in February 2013 in patients with advanced GISTs for those who had failed on imatinib and sunitinib [24,25]. Linifanib is currently being studied in HCC clinical trials [26]. Unlike the other inhibitors of VEGFR and PDGFR, linifanib seems to be also involved in adipocyte browning, thus being considered for the treatment of obesity [27]. Tivozanib is a diarylurea which is to be considered as third and fourth line therapy in patients with metastatic RCC in phase 3 study [28]. By end of 2019, the Chinese and European regulatory authorities have marketed five small-molecule protein kinase inhibitors (PKIs), including tivozanib [29]. Ripretinib has been suggested as a promising treatment for advanced GISTs [30]. In this paper, these already known drugs bearing a diarylurea skeleton are reviewed, along with new synthetic diarylureas described in the literature as promising agents for the treatment of diverse type of tumors.

2. Diarylureas in Therapy or in Clinical Studies as Anticancer Agents

2.1. Sorafenib

Sorafenib (BAY-43-9006, Nexavar®, Figure 3) is an oral receptor TKI that determines the inhibition of Raf serine/threonine kinases and receptor tyrosine kinases (VEGF 1, 2, 3 and PDGF-β, FMS-like tyrosine kinase-3 (FLT-3), and c-KIT) that are components of signaling pathways controlling tumor growth and angiogenesis [31].

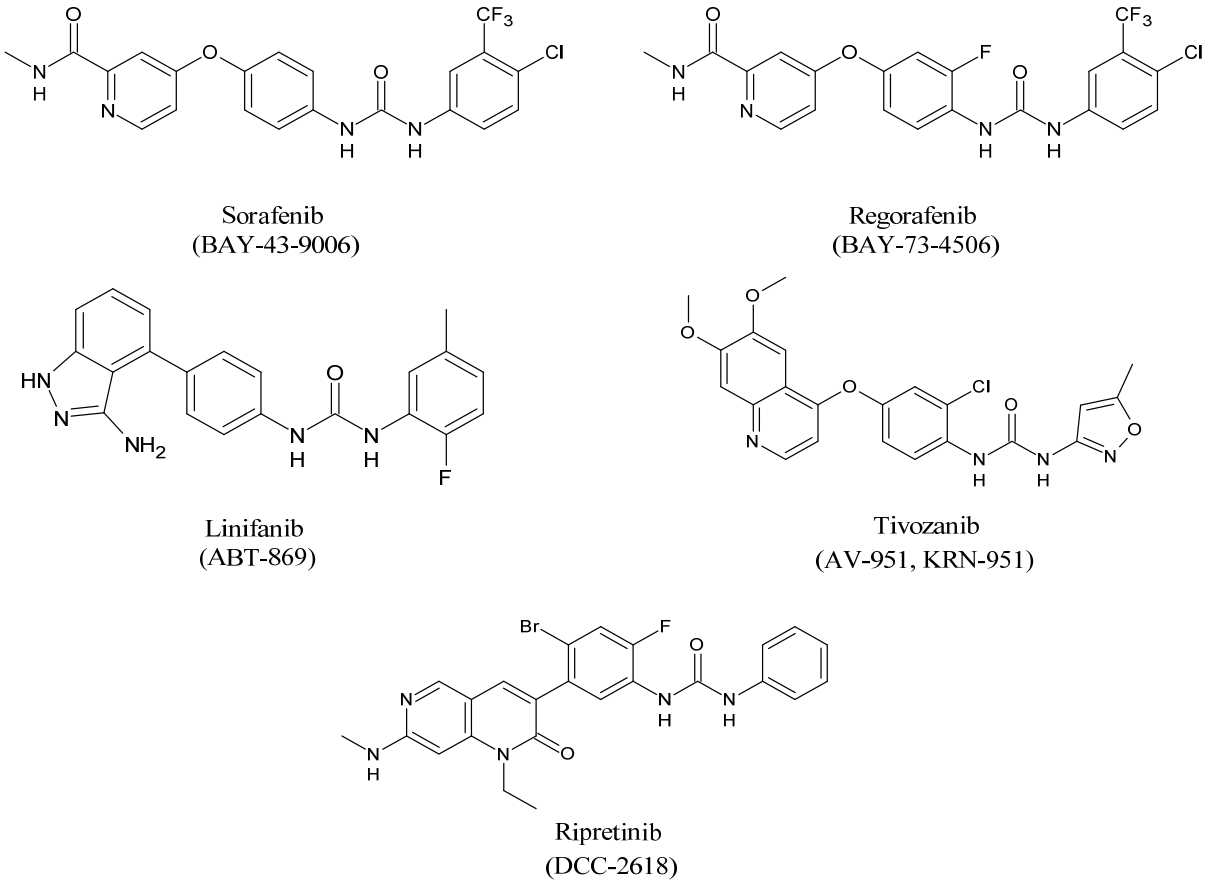


Figure 3. Structures of diarylureas.

Sorafenib inhibits the kinase activity of C-RAF and B-RAF (wild type and V600E mutant) showing IC_{50} = 6.22 and 38 nM, respectively. This compound is considered the most important drug in the late stage of injury for advanced stages of HCC [32] which is the second cause of cancer-related mortality all over the world [33]. For more than ten years, sorafenib has been the sole systemic treatment for advanced HCC [34]. However, some advanced HCC patients do not respond to therapy with sorafenib. Thus, combination studies of sorafenib with other drugs have been studied. Combined treatment with interferon-lambda 3 (IFN-λ3) and sorafenib show an effect of synergism in suppressing HCC cancer growth and in the promotion of cell apoptosis in vitro and in vivo [35]. A more recent study demonstrated that combination immunotherapy of sorafenib with atezolizumab, an immune checkpoint inhibitor (ICI) that target the programmed-cell death-1 receptor/ligand (PD-1/PD-L1) pathway, and bevacizumab, an anti-VEGF mAb, is superior to sorafenib alone as the first-line therapy of advanced HCC [36]. Moreover, given that liver function is essential for a correct prognosis, a precise rating for the safe prescription and clinical development of ICI in HCC is required. Recently, the albumin-bilirubin (ALBI) grade was used as an alternative biomarker for the prognosis [37]. The efficacy of sorafenib is limited by several factors as systematic tolerance and the poor solubility in water. Furthermore, the hydrophobicity of sorafenib is responsible of its low bioavailability as it decreases the absorption by the gastrointestinal tract. Nexavar® (Bayer Healthcare Pharmaceuticals–Onyx Pharmaceuticals) is used as tablets containing sorafenib tosylate to slightly improve the solubility. In order to increase the solubility and bioavailability of the drug, sorafenib-loaded lipid-based nanosuspensions were used [38]. The administration of sorafenib to the target cells could ameliorate patient survival and reduce the further proliferation of the tumor [39]. Thus, a drug delivery system for sorafenib has been recently studied in order to help the administration of therapies in malignant cells and raise its clinical efficacy [40]. Recently, the treatment of cancers of the gastrointestinal tract during

the COVID-19 pandemic [41] has been studied: coronavirus-adapted institutional recommendations have been formulated. Sorafenib was recommended in the first-line setting only in patients with disease subtype Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 and Child-Pughscore A hepatocellular carcinoma [42]. In spite of its selectivity, sorafenib can determine adverse effects, such as severe respiratory and liver failure, fatigue, stomatitis, hand-foot syndrome, diarrhea, and myelosuppression, thus posing a challenge for oncologists [43]. The therapy with sorafenib might be done ad hoc to increase the therapeutic effects and reducing adverse effects [44]. Sorafenib is also studied for iodine-resistant advanced thyroid carcinoma [45]. Finally, it is important to note that sorafenib is also involved in cytoskeleton alteration that leads to cancer cells death by apoptosis. Wang et al. [46] reported that the treatment of Hep3B and PLC/PRF/5 human hepatoma cells with sorafenib induces a drastic loss of actin fibers and the redistribution of F-actin around the cell nuclei. This effect is due to the regulation of protein kinases and phosphatases that ends with cofilin dephosphorylation, which is an actin-binding factor necessary for the reorganization of actin. Chen et al. [47] demonstrated that the ability of sorafenib in inducing human prostate cancer cell line PC-3 apoptosis, through cytoskeleton destabilization, increased if combined with zinc exposure, suggesting that zinc may sensitize prostate cancer cells to sorafenib treatment. D'Alessandro et al. [48] demonstrated a synergistic effect on HCC cells migration using combined doses of sorafenib and/or vitamin K1 with insulin like growth factor I receptor (IGF1-R) antagonists enhancing the reduction and reorganization of F-actin, probably through the modulation of MAPK cascade.

2.2. Regorafenib

Regorafenib (BAY 73-4506, Stivarga®, Figure 3) is the fluorinated analogue of sorafenib. It is an orally active diphenylurea multikinase inhibitor that targets stromal (PDGFR-β, FGFR-1), angiogenic (VEGFR1-3, TIE-2), and oncogenic receptor tyrosine kinases (c-KIT, RET, and RAF-1) [49]. It is the first multi-targeting kinase inhibitor which was approved by FDA in 2012 for the treatment of mCRC patients in refractory to standard chemotherapy [50]. In addition, regorafenib treatment determined an important amelioration in progression-free survival (PFS) in comparison with placebo in patients with metastatic GISTs after standard treatments; thus, it has also received FDA-approval for this indication since 2013. Then, in 2017, FDA approved regorafenib as a therapy for patients with advanced HCC [51]. Regorafenib showed a significant amelioration of PFS and overall survival (OS) in comparison with placebo. Regorafenib has been described in phase II clinical trials in different tumors, including RCC, soft-tissue sarcoma (STS), second- and third-line treatments for medullary thyroid cancer. However, several post-marketing observational studies, after the treatment of mCRC patients showed extensive data of toxicities (CORRELATE, REBECCA, RECORA, Japanese post-marketing study) [52–54]. It was found that adverse reactions due to regorafenib frequently occurred in the initial stages of treatment, mostly in the first cycle [55]. Thus, in patients with mCRC during the first cycle of regorafenib, the use of a dose-escalation strategy treatment was suggested [56]. This strategy was then supported by a multicenter, open-label, phase II study [57]. Recently, during the COVID-19 outbreak, regorafenib has been considered as a therapy for gastrointestinal cancer [42]. A drug-delivery system has been studied for regorafenib, too [40]. The pivotal RESORCE (NCT01774344) phase III trial studied regorafenib therapy in patients with HCC who were tolerant to sorafenib, but who had progressed during sorafenib treatment [58]. Regorafenib has been demonstrated to inhibit glioblastoma multiforme (GBM) growth through PSAT1-mediated autophagy arrest [59], and to have beneficial effect in Alzheimer's disease (AD) and formation of dendritic spine in vitro and in vivo [60].

2.3. Linifanib

Linifanib (ABT-869, Abbott Laboratories, Abbott Park, IL, USA, Figure 3) is an orally available TKI which targets VEGFR and PDGFR with relevant specificity and low off-

target inhibition. Linifanib can also inhibit FLT-3 [61]. It does not show significant activity against representative cytosolic tyrosine and serine/threonine kinases [62]. Linifanib is a colony-stimulating factor-1 receptor (CSF-1R) inhibitor through the inhibition of the phosphorylation of CSF-1R tyrosine kinase in transfected cells [63]. It is used as a therapy for non-small cell lung carcinoma (NSCLC), liver cancer, breast cancer, colorectal cancer [45]. Preclinical and early clinical trials showed interesting activity in various human neoplasms with a satisfactory profile of toxicity. Linifanib competes with ATP in the binding site domain of tyrosine kinase, thus it prevents downstream signaling [64]. Phase II trial studies show that linifanib is useful for the treatment of patients with advanced, refractory colorectal cancer that expresses k-Ras mutations [65]. In an open-label phase II trial linifanib showed interesting clinical activity, as monotherapy, in patients with advanced HCC [66]. Linifanib versus sorafenib was studied in terms of efficacy and tolerability. Linifanib and sorafenib showed similar OS in advanced HCC. Linifanib did not meet predefined superiority and non-inferiority OS boundaries; thus, the study did not reach the primary end point. Secondary end points, time to progression (TTP), and objective response rate (ORR), favored Linifanib; safety results favored sorafenib [67]. Although linifanib is currently examined in HCC clinical trials, it has not yet been studied in preclinical and clinical studies for gastric cancer. 5-Fluorouracil (5-FU) and cisplatin represent the first-line chemotherapy for patients with gastric cancer and the combined use with linifanib inhibits synergistically the viability of some gastric cancer cell lines and led to remarkable suppression of VEGF-induced angiogenesis in vitro and in vivo [68]. Linifanib has demonstrated to be also useful in the treatment of anaplastic thyroid cancer (ATC), that is considered the most aggressive form of thyroid cancer. The synergistic use of linifanib and irinotecan significantly increased the survival of ATC-affected mice. These observations have been made by using an orthotopic in vivo model that better recapitulates features of human tumors than the more simplistic subcutaneous xenograft models, suggesting a potential role of this co-treatment in ATC patient's treatment [69]. Finally, linifanib was demonstrated to interfere with adipocyte browning. It suppresses STAT3 signaling pathway, thus leading to the enhancement of adipocyte browning and inhibition of adipogenesis. Linifanib's blocking browning effect was demonstrated as the phosphorylation of STAT3 was reduced by linifanib and the STAT3 activator SD19, as well [27].

2.4. Tivozanib

Tivozanib (AV-951, KRN-951, FOTIVDA®, Figure 3), used as the hydrochloride monohydrate salt, is a bioavailable inhibitor of angiogenesis which targets VEGFR tyrosine kinases with high antitumor activity. It is a VEGF-TKI specific for VEGFR1–3, showing an inhibitor effect at nanomolar concentrations, with IC50 values of 30 nM, 6.5 nM, and 15 nM for VEGFR1, 2 and 3, respectively. The compound is unique in that it is highly specific for VEGFR1–3, and presents minimal residual effects on c-KIT and PDGFR-β [70]. It presents a long half-life, too [71]. It has shown considerable efficacy for the treatment of advanced RCC over the past decade. In August 2017, tivozanib was approved by the EMEA as a first-line therapy for patients with advanced RCC and those who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after previous therapy with cytokines for advanced RCC. Tivozanib was compared with sorafenib in a phase III trial for patients with metastatic RCC. Tivozanib improved PFS, but not OS, and showed a differentiated safety profile, in comparison with sorafenib, as initial targeted therapy for metastatic RCC [72]. Preclinical data and phase III trials of tivozanib in RCC, TIVO-1, and TIVO-3 have been recently summarized. Given the agent's excellent tolerability profile it is appropriate for those patients with heavily pretreated disease that could exhibit clinical deterioration. Currently, the standard therapy is represented by nivolumab and ipilimumab, followed by cabozantinib. Tivozanib may represent a third-line treatment after failure of these agents [73]. The results of phase III TIVO-3 trial (American Society of Clinical Oncology Virtual Scientific Program, 2020) showed that tivozanib significantly improved PFS, compared with sorafenib, in patients with highly relapsed or refractory metastatic

RCC [74–77]. Tivozanib activity has been also investigated in hepatocellular carcinoma in association with durvalumab [78] and in recurrent, platinum-resistant ovarian cancer, fallopian tube cancer, and primary peritoneal cancer [79,80]. Tivozanib has been studied in phase I and II clinical trials as monotherapy and in combination with other drugs for the treatment of STS [81], glioblastoma [82], breast [83], and colorectal cancers, and other advanced gastrointestinal cancers [84,85].

2.5. Ripretinib

Ripretinib (DCC-2618, QINLOCK^{TM}, Figure 3) is an oral inhibitor of tyrosine kinase that primarily inhibits KIT proto-oncogene receptor tyrosine kinase and platelet-derived growth factor receptor A (PDGFRA) kinase signaling. Ripretinib also inhibits other kinases, such as PDGFRB, TIE2, VEGFR2, and BRAF. It was designed for cancers and myeloproliferative neoplasms, especially GISTs. Ripretinib is a "switch-control" kinase inhibitor that forces the activation loop (or activation "switch") into the inactive conformation. In preclinical cancer models it has shown efficacy, and preliminary clinical data show that Ripretinib inhibits a broad range of KIT mutants in patients with drug-resistant GISTs [86]. The INVICTUS study demonstrated the efficacy and safety of ripretinib as the fourth-line treatment *versus* placebo in patients with advanced GISTs [87]. In May 2020, ripretinib received approval from the US FDA for the treatment of patients with advanced GISTs who had received previous treatment with more than two kinase inhibitors [88]. Ripretinib is being evaluated in an ongoing phase III study (INTRIGUE) as a second-line therapy in comparison with sunitinib after progressing on imatinib [89]. Recently, ripretinib is being investigated in clinical trials for systemic mastocytosis (SM) [90], and has been also proposed for the treatment of STS [91].

2.6. Mechanisms of Inhibition of Diarylureas

The proposed inhibitory mechanisms of diarylureas depend on their structure. Garuti et al. [5] reported the crystal structure of ^{V600E}B-RAF kinase domains in complex with sorafenib. The pyridyl ring is shown to occupy the ATP adenine-binding pocket and to interact with three amino acids residues. The trifluoromethyl phenyl, that is a lipophilic moiety, fits into a hydrophobic pocket. The urea moiety forms two hydrogen bonds with ^{V600E}B-RAF, one with the aspartate, and one with the glutamate residue. Recently, the 2D interaction of the co-crystallized sorafenib inside the active site of B-Raf has been reported [92]. Regorafenib differs from sorafenib only for a fluorine atom, thus its interactions are similar to those of sorafenib. Chen et al. (2017) proposed an alternative mechanism for colorectal cancer for regorafenib. It seems that it interacts with microRNA-21 (miR-21), an oncogenic miRNA which plays a crucial role in resisting programmed cell death in CRC cells. RNA–ligand docking, molecular dynamics simulation showed that regorafenib can directly bind to miR-21 pre-element [93]. Docking studies of linifanib with FLT3 were recently reported, evidencing that 3-amino-indazole interacts with the ATP-bind site [61]. Kajal et al. (2018) has reported the 2D co-crystal-binding conformation of VEGFR2-Tivozanib, in which tivozanib mimics the binding pattern of ATP [94]. Finally, studies on the mechanism of action of ripretinib have been recently reported [86].

3. Other Diarylureas

In this paragraph several studies on other diarylureas are described (Table 1). Babić et al. synthesized several diarylurea derivatives in order to study their cytostatic activity [95]. The compounds were tested on tumor cell lines: HCT 116 (colon carcinoma), SW 620 (colon carcinoma), MCF-7 (breast carcinoma), H460 (lung carcinoma), L1210 (murine leukemia), CEM (human lymphoma), and HeLa (cervix carcinoma). Compounds **1a**–**e** exerted the highest effect (IC_{50} from 1 to 4.3 μM, with an average of 2.6 ± 1.6 μM) even though with low selectivity for the different tumor cell lines. The compounds were also cytostatic against primary human embryonic lung (HEL) fibroblast cells. Kapuriya et al. [11] studied a series of water-soluble *N*-mustard-benzene conjugates containing a urea linker. The urea

linker was introduced in order to overcome the low solubility of compounds previously studied. The authors studied a series of water-soluble *N*-mustards, in which the phenyl *N*-mustard is linked to a benzene ring through a urea linker. In particular, the diarylurea **2** (BO-1055), as the hydrochloride salt, exhibited high in vitro cytotoxicity and therapeutic efficacy against various human tumor cell lines. It was demonstrated to possess potent therapeutic effect against several human solid tumor cell lines, including human breast cancer (MX-1), colon cancer (HCT-116), and prostate cancer (PC3), in xenograft model. The DNA repair capacity of compound BO-1055, named ureidomustin, was then studied. It was proposed for the treatment of tumors with deficient nucleotide excision repair (NER), homologous recombination (HR), and O^6-methylguanine-DNA methyltransferase (MGMT) DNA repair genes, or in synergy with other drugs in tumors in which DNA damage response has been repressed [96].BO-1055 was also proposed as a therapeutic agent for Ewing sarcoma and rhabdomyosarcoma given its potency and relative lack of toxicity against normal tissue [97]. It also showed a potent activity against B-cell lymphomas, as mantle cell lymphoma (MCL) and diffuse large B-cell lymphoma (DLBCL) [98].

In a following paper, the same research group indicated that compound **2** has a quite narrow therapeutic window; thus, following a bioisosteric approach, an inversion of the carboxamide functionality was addressed. Compound **3** was superior to compound **2** against colon cancer (HCT-116) and lung cancer (H460) cell lines, and displayed minor toxicity. Cotreatment of compound **3** and 5-fluorouracil suppressed the growth of HCT-116 xenografts. Moreover, compound **3** could induce DNA cross-linking and cell-cycle arrest at the G2/M phase. This compound was selected for early preclinical studies [99]. A series of diarylureas was studied for in vitro antiproliferative activities against HepG2, MGC-803, and A549 cancer cell lines [100]. Compound **4** displayed optimal antiproliferative activity against the three cell lines in comparison with sorafenib and gefitinib. Indeed, it induced A549 cells apoptosis through the cell cycle block at the G0/G1 phase, the increase of intracellular reactive oxygen species, and the reduction of mitochondrial membrane potential. This compound also influenced the Raf/MEK/ERK pathway. A series of diarylurea derivatives was studied for its cytotoxicity in vitro against H-460, HT-29, A549, and MDA-MB-231 cancer cell lines [101]. Some of them showed higher activity than sorafenib (IC_{50} between 0.089 and 5.46 μM). In particular, compound **5** was the most potent both in cellular (IC_{50} = 0.15, 0.089, 0.36, and 0.75 μM, respectively) and enzymatic assay (IC_{50} = 56 nM against EGFR). The antiproliferative activity of diarylureas bearing a 4-anilinoquinazoline group was evaluated via MTT assay against A431 and A549 cells [102]. Three compounds showed high antiproliferative activities and their inhibitory activity against EGFR-TK was evaluated. Compound **6** was a potent EGFR-TK inhibitor. This completely inhibited cancer growth in established nude mouse A549 xenograft model in vivo, at 50 mg/kg. Diarylureas were studied as LIM-kinase (Limk) inhibitors for their therapeutic potential against prostate cancers [103]. Limk is a serine-threonine protein kinase existing in two isoforms, LIM kinase 1 (Limk1) and LIM kinase 2 (Limk2). The inhibition of Limk1 activity in cancer prostate cells and tissues determines reduction of phosphorylated cofilin and cancer cells motility, thus reducing invasiveness of the tumor and evolution to metastasis. The substituted diarylurea **7**, at 1 μM, inhibited only Limk1 and STK16 with ≥80% inhibition. The use of Limk inhibitors has been also suggested to target the invasive machinery in GBM [104]. Recently, a diarylurea, N69B, was evaluated for its anticancer activity and its molecular mechanism was investigated [105]. The compound was shown to inhibit proliferation of murine and human cancer cells in vitro, and reduce tumor growth in mouse 4T1 breast tumor model in vivo. Compound N69B significantly increased protein levels of cathepsins, in particular cathepsin D, a lysosomal aspartyl protease with various biological functions. Several diarylureas bearing a coumarine moiety [106,107] have been recently tested for their in vitro antiproliferative activities against the H4IIE and HepG2 cancer cell lines, and has been proposed as a promising lead for further optimization [108]. Compound **8b** exhibited a higher inhibition of H4IIE cells compared to sorafenib. **8a** also showed a better inhibition against HepG2 cells than sorafenib. In particular, **8b** arrested cell cycle at the S

phase and induced H4IIE cells apoptosis. A library of diarylureas has been designed and the in vitro antiproliferative activities was studied against HT-29 and A549 cancer cell lines. Compound **9** was the most active against HT-29 cells showing an IC_{50} value of 3.38 μM, compared to that of sorafenib (IC_{50} = 17.28 μM). It induced cell cycle arrest at G_0/G_1 phase, interfered with Raf/MEK/ERK signaling pathway, increased intracellular reactive oxygen species level, and led to HT-29 cells apoptosis [109]. The same research group studied a series of benzo[*b*]thiophene-diarylureas with potential anticancer effects, too. Compound **10** was the most active (IC_{50} = 5.91 and 14.64 μM on HT-29 and A549 cells, respectively). It induced apoptosis and cell cycle arrest at the G0/G1 phase on HT-29 cells, too [110]. Several diphenyl indazoles, containing diarylurea moieties, in the low micromolar range, inhibited cell viability of various cancer cell lines including murine metastatic breast cancer 4T1, murine glioma GL261-luc2, human triple negative breast cancer MDA-MB-231, human pancreatic cancer MIAPaCa-2, and human colorectal adenocarcinoma WiDr. The lead candidate **11** significantly reduced the tumor growth in aggressive stage IV breast cancer 4T1 syngraft model in vivo [111]. A series of diarylureas bearing a substituted thiadiazole as one of the two aryl moieties was studied against human chronic myeloid leukemia (CML) cell line K562. The diarylurea **12** exhibited the least cytotoxicity and higher biological activity (IC_{50} = 0.038 μM). It also displayed good induced-apoptosis effect for human CML cell line K562; its effect seems to happen via a significant reduction of protein phosphorylation of PI3K/AKT signal pathway by human phospho-kinase array analysis [112]. Forchlorfenuron (FCF; N-(2-Chloro-4-pyridyl)-N′-phenylurea) is a small synthetic diarylurea currently used in agriculture as a plant fertilizer that increases fruit size because of its potent cytokinin activity. FCF inhibits proliferation, anchorage-independent growth, migration, and invasion of cancer cell lines in various cancer types, such as prostate, mesothelioma, lung, colon, breast, ovary, and cervix [113]. FCF was also found to be effective in a mouse model, in which tumor growth was inhibited. FCF treatment caused the suppression of HIF-1α and HER2, both of them playing a crucial role in cancer cell survival [114]. Recently, several FCF analogues (UR214-1, UR214-7, and UR214-9) were demonstrated to be more effective in decreasing viability and proliferation in both ovarian and endometrial cancer cell lines, and suppress HER2 expression at a concentration lower than that of FCF. Moreover, FCF and its analogues were found to decrease the expression of human epididymis protein 4 (HE4), which is commonly upregulated in ovarian and endometrial cancers [115]. Diarylurea PQ401 is a small molecule that behaves as an inhibitor of IGF-1R signaling. It is also able to prevent breast cancer cells growth in in vivo mouse models [116]. It has also shown anti-cancer properties in glioma by inducing cellular apoptosis in U87MG cells, thus reducing cell viability and proliferation and attenuating cell mobility in vitro. Moreover, through a mouse xenograft model, PQ401 administration led to the suppression of glioma tumor growth in vivo in mice [117]. Recently, PQ401 potential as a putative chemotherapy drug in osteosarcoma cells has been investigated. PQ401 effectively suppressed osteosarcoma cell growth, migration, and colony formation in vitro, as well as induced apoptosis in vitro. PQ401 inhibited U2OS cell viability almost as effective as *cis*platin. PQ401 can significantly cause U2OS cell apoptosis and clonogenesis at the IC_{50} concentration with the blockade of IGF1-R phosphorylation and related downstream signaling [118]. The diphenyl urea-derivative DUD was designed on the basis of a docking study for the optimization of a natural product, taspine. The anti-metastatic potential of DUD for NSCLC was studied in vitro. DUD inhibited A549 cells migration by reversing EMT via Wnt/β-catenin and PI3K/Akt signaling, thus it has been suggested as a potential therapy for NSCLC treatment [119]. Several fluorinated diarylureas were studied as activators of adenosine monophosphate-activated kinase (AMPK). Compound FND-4b determined the induction of phosphorylated AMPK and the decrease in markers of cell proliferation, as cyclin D1, in all CRC cell lines. Apoptosis was also increased in CRC cells treated with FND-4b [120]. Thidiazuron (TDZ, 1-phenyl-3-(1,2,3-thiadiazol-5-yl) urea) is a synthetic plant hormone which has been widely used as herbicide, pesticide, and as growth regulator in plant tissue culture [121]. Given its cytotoxic effect on HeLa (human

cervical carcinoma) cell lines, it has been recently proposed as a potential agent to act against cervical cancer cells. It has also suggested to have a role on apoptosis in cancer cells through DNA damage. Furthermore, the activity of TDZ as anticancer was tested against Hela cells by mitochondrial dysfunction, DNA damage, in silico caspase-3 inhibition, and some gene expression [122]. This observation has been recently confirmed by radiolabeling TDZ with 99mTc. The in silico study supported the ability of 99mTc-TDZ complex to bind caspase-3 protein that is overexpressed in cancers, suggesting that 99mTc-TDZ might be a potential agent for diagnosis of solid tumors, such as the cervix cancer [123].

Table 1. Structures of compounds described in the literature.

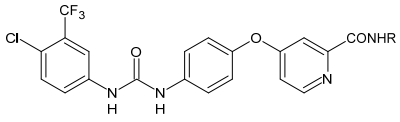
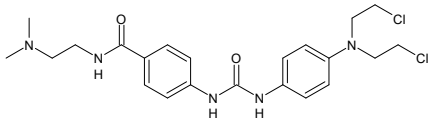
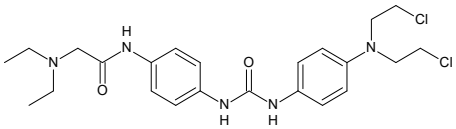
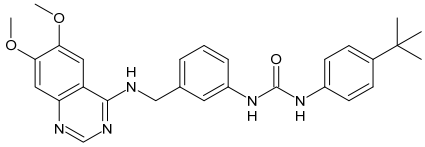
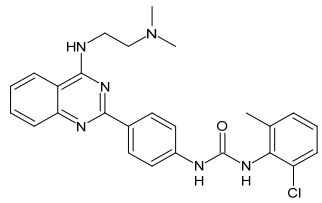
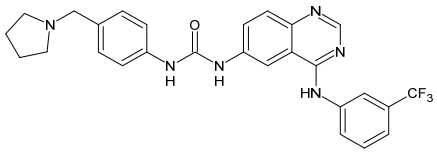
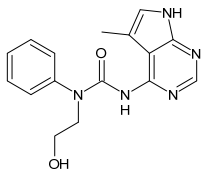
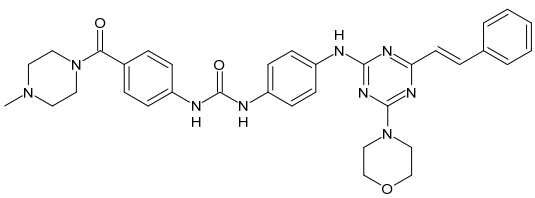
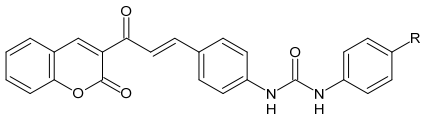
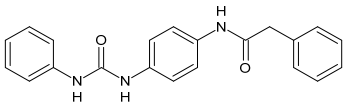
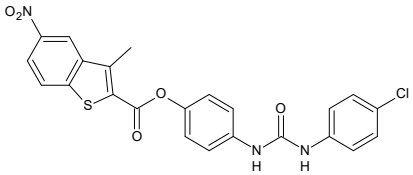
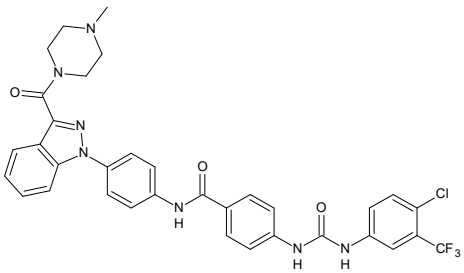
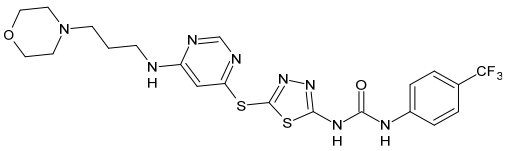
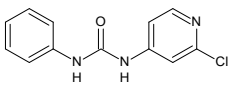
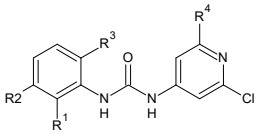
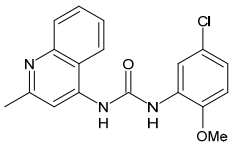
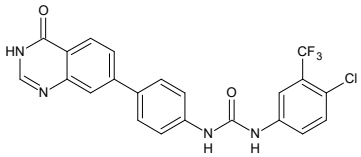
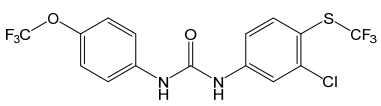
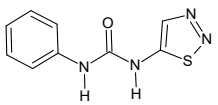
Structure	Compd	Ref
 **a:** R = cyclophenyl **b:** R = cyclohexyl **c:** R = cyclohexylmethyl **d:** R = benzyl **e:** R = phenylethyl	**1a–e**	[95]
	**2** (BO-1055)	[11]
	**3**	[99]
	**4**	[100]
	**5**	[101]
	**6**	[102]
	**7**	[103]
	N69B	[105]

Table 1. *Cont.*

Structure	Compd	Ref
 **a:** R = NO_2 **b:** R = CF_3	**8a**,**b**	[106–108]
	**9**	[109]
	**10**	[110]
	**11**	[111]
	**12**	[112]
	Forchlorfenuron (FCF)	[113,114]
 **UR214-1:** $R^1 = R^4 = H$; $R^2 = S\text{-}CF_3$; $R^3 = Cl$ **UR214-7:** $R^1 = F$; $R^2 = CF_3$; $R^3 = R^4 = H$ **UR214-9:** $R^1 = F$; $R^2 = CF_3$; $R^3 = H$; $R^4 = Cl$	UR214-1 UR214-7 UR214-9	[115]
	PQ401	[116–118]
	DUD	[119]
	FND-4b	[120]
	Thidiazuron (TDZ)	[121–123]

4. Summary

Diarylureas are considered a privileged structure in medicinal chemistry, particularly for anticancer drugs. Sorafenib is a neovascular blocker that prevents the formation of new blood vessels, followed by the growth of cancer tissue, through multiple kinase inhibitors that target angiogenesis. It is approved for the treatment of advanced inoperable HCC and advanced RCC. An alternative for the treatment of these tumors under study may be represented by tivozanib. Regorafenib is an effective therapy for patients with advanced GSTIs or mCRC. Linifanib may represent a promising therapeutic agent for human gastric cancer, NSCLC, liver cancer, breast cancer, colorectal cancer. Ripretinib is addressed to GISTs. In this paper, we report an overview of the development and application of these drugs. The current treatment trends in oncology have shifted to immunotherapy combinations with ICI, as anti-PD-L1-directed monoclonal antibodies. Pending improved understanding of HCC, RCC, GSTIs, and mCRC tumorigenesis, it would be very interesting to evaluate the combination of various treatment modalities. Diarylurea combined with a checkpoint inhibitor could be a promising treatment strategy to be deeply investigated in the future. Moreover, this review encompasses the recent advances in scientific literature in the broad area of diarylureas as anticancer agents. The newly synthesized compounds of this class, that are now in phase of study, may represent promising small molecules able to unseat or help the already known existing drugs.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AD	Alzheimer's disease
AMPK	adenosine monophosphate-activated kinase
ATC	Anaplastic thyroid cancer
CML	chronic myeloid leukemia
CSF-1R	colony stimulating factor-1 receptor
DLBCL	diffuse large B-cell lymphoma
ECOG PS	Eastern Cooperative Oncology Group performance status
EMEA	European Medicinal Agency
FCF	Forchlorfenuron
FDA	Food and Drug Administration
FLT-3	FMS-like tyrosine kinase-3
5-FU	5-Fluorouracil
GBM	glioblastoma multiform
GIST	gastrointestinal stromal tumors
HCC	hepatocellular carcinoma
HE4	human epididymis protein 4
HEL	human embryonic lung
HR	homologues recombination
ICI	Immune checkpoint inhibitors
IFN-λ3	Interferon-lambda 3
IGF1-R	insulin like growth factor I receptor
Limk	LIM-kinase
MCL	mantle cell lymphoma
mCRC	metastatic colorectal cancer
MGMT	O^6-methylguanine-DNA methyltransferase
NER	nucleotide excision repair
NSCLC	non-small cell lung carcinoma
ORR	objective response rate
OS	overall survival
PD-1/PD-L1	programmed-cell death-1 receptor/ligand
PDGFR	platelet derived growth factor receptor

PFS	progression-free survival
PKIs	protein kinase inhibitors
RCC	renal cell carcinoma
RTKs	receptor tyrosine kinases
SM	systemic mastocytosis
STS	soft-tissue sarcoma
TDZ	Thidiazuron
TKIs	tyrosine protein kinases
TTP	time to progression
VEGFR-2	vascular endothelial growth factor receptor 2

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