Diarylurea: A Privileged Scaffold in Drug Discovery and Therapeutic Development

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Diarylurea (or bis-arylurea, Fig. 1) and its derivatives receive considerable attention from organic and medicinal chemists. Diarylureas in which the aryl moieties consist of unsubstituted or substituted phenyl groups (Ar_1, Ar_2 = phenyl) are also known as diphenylureas or bis-phenylureas.

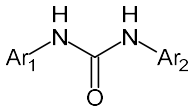


Figure 1. Structure of diarylurea

Diverse pharmacological activities have been described for this class of compounds. The most important activity is the one that brought them into therapy, *i.e.* the antitumor activity [1]. Sorafenib (BAY-43-9006, Nexavar®, Tab. 1) was the first diarylurea introduced in therapy acting as tyrosin kinase inhibitor (TKI). It was followed by Regorafenib (BAY 73-4506, Stivarga®), Linifanib (ABT-869, Abbott Laboratories, Abbott Park, IL, USA), Tivozanib (AV-951, KRN-951, FOTIVDA®), and Ripretinib (DCC-2618, QINLOCK™). They all belong to the diarylureas class. With the only exception of Tivozanib, they are also diphenylureas. They have been recently extensively reviewed [2]. Donafenib (Zepsun®) is a deuterium derivative of sorafenib. It is an oral small molecule multikinase inhibitor, developed for the treatment of various cancers [3,4]. In June 2021, it received its first approval in China for the treatment of patients with unresectable hepatocellular carcinoma who have not previously received systemic treatment [5].

Several other diarylureas have been studied for their anticancancer properties. Recently, Thidiazuron (TDZ), a cytokinin bearing the diarylurea structure that is a plant growth regulator, has been demonstrated to have anticancer activity towards both cervice cancer and breast cancer cells [6]. Forchlorfenuron (FCF or CPPU) is a small synthetic diarylurea currently used in agriculture as a plant fertilizer that increases fruit size because of its potent cytokinin activity. It has been found to decrease viability and proliferation of malignant mesothelioma cells *in vitro* and *in vivo* [7] and to suppress HIF-1α and HER2, both of them playing a crucial role in cancer cell survival in gastric cancer [8]. Diarylurea PQ401 is a diarylurea that behaves as an inhibitor of IGF-1R signaling. It induces apoptosis and inhibits growth, proliferation and migration of glioma and osteosarcoma cells [9].

Besides the very well known antitumor activity, diarylureas have shown several other actions, such as antimicrobial, antiviral, antithrombotic, antimalarial, and anti-inflammatory: these activities have been recently reviewed [10]. Triclocarban (TCC) is a diarylurea, specifically a diphenylurea, endowed with high antimicrobial and antiseptic activity for the prevention of spoilage and infections. In September 2016 it was banned from the U.S. Food and Drug Administration in over-the-counter hand and body washes because of its toxicity [11]. Aggiungere tcc con faecalis

Recently, several interesting analogues of TCC have been reported. Some of them showed the same or higher activity than TCC against Gram positive bacteria and were, at the same time, devoid of cytotoxicity [12,13]. Diarylurea MMV665852, a structural analog of TCC taken from Malaria Venture (MMV) Malaria Box, showed antimalarial and antischistosomicidal activity against *Plasmodium falciparum* and *Schistosoma japonicum* and *S. mansoni* [10]. Flucofuron is a halogenated diphenylurea that is an insecticide known to be highly toxic to fish and invertebrates. It has been recently considered for its antibacterial activity [14].

Other activities have been described for diarylureas. For instance, Frentizole acts as an immunosuppressant and is used for the treatment of Alzheimer's disease being a weak inhibitor of the Aβ–ABAD interaction (IC_{50} = 200 μM) [15]. Some other diarylureas were studied for the treatment of Parkinson's disease as they showed high activity in alleviating haloperidol-induced catalepsy and oxidative stress in mice [16]. Diarylurea BPTU showed good binding affinity for $P2Y_1$ receptor (K_i = 6 nM), a G-protein coupled P2 purinergic ADP receptor involved in antiplatet activity and moderate antiplatelet activity in the ADP-induced platelet aggregation assay *in vitro* [10]. Sorafenib has been recently studied as Strong Inhibitors of the Fungal Pathogen Histoplasma capsulatum, a dimorphic fungal pathogen endemic to the midwestern and southern United States, that most frequently causes pneumonia, but can also disseminate and proliferate in diverse tissues.

Finally, basing on the numerous properties exerted by diarylureas, often as small molecules, they can be viewed as promising treatment options against various diseases. A multitarget therapeutic strategy could be favorable against new pandemics, such as COVID-19 [17], and deserve further studies for these diseases.

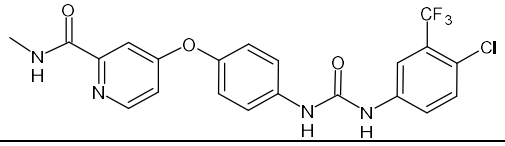
Conflict of Interest

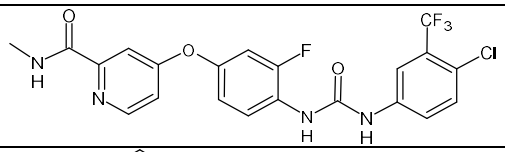
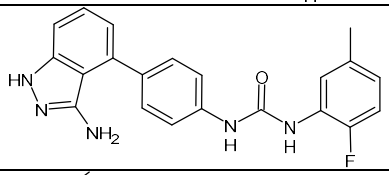
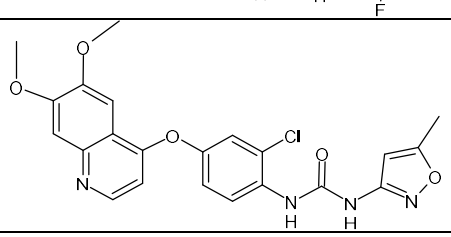
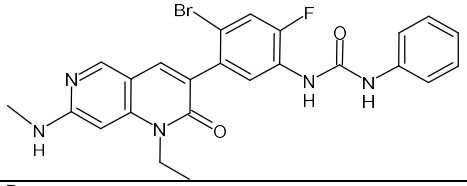
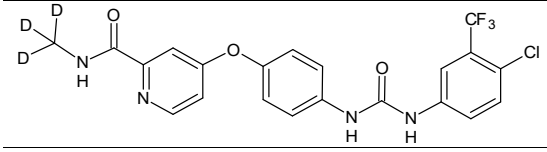
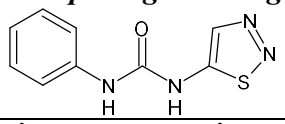
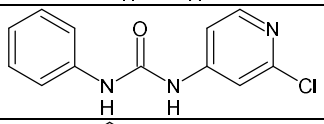
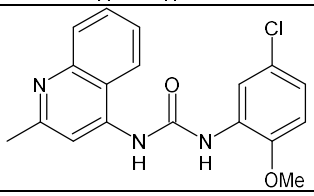
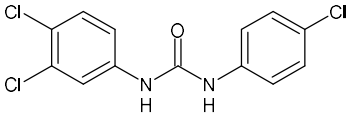
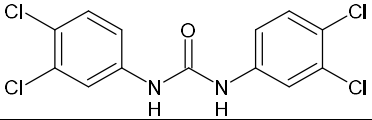
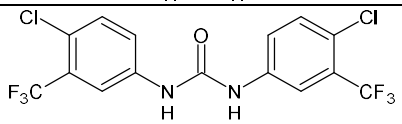
No conflict of interest.

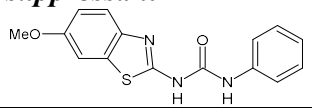
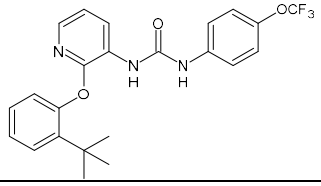
Acknowledgment

None.

Table 1. Structures of the compounds described in the text

Structure	Name	Ref
Anticancer agents		
	Sorafenib (BAY-43-9006)	[2,10]

	Regorafenib (BAY-73-4506)	[2,10]
	Linifanib (ABT-869)	[2,10]
	Tivozanib (AV-951, KRN-951)	[2,10]
	Ripretinib (DCC-2618)	[2,10]
	Donafenib (CM-4307)	[4-6]
Cytokinin-like plant growth regulators		
	Thidiazuron (TDZ)	[2,3]
	Forchlorfenuron (FCF or CPPU)	[2,7,8]
	PQ401	[2,9,10]
Antimicrobials		
	Triclocarban (TCC)	[7,11–13]
	MMV665852	[10]
	Flucofuron	[7,14]

Immunosuppressant 	Frentizole	[15]
Antiplatelet activity 	BPTU	[7]

References

1. Garuti, L.; Roberti, M.; Bottegoni, G.; Ferraro, M. Diaryl urea: A privileged structure in anticancer agents. *Curr. Med. Chem.,* **2016**, *23*, 1528–1548.

2. Catalano, A.; Iacopetta, D.; Sinicropi, M.S.; Franchini, C. Diarylureas as antitumor agents. *Appl. Sci.,* **2021**, *11*, 374.

3. Lin, Y.S.; Yang, H.; Ding, Y.; Cheng, Y.Z.; Shi, F.; Tan, J.; et al. Donafenib in progressive locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer: results of a randomized, multicenter phase II trial. *Thyroid*, **2021**, *31*(4), 607–615.

4. Yang, Y.; Zhu, H.; Li, Q. Partial response of donafenib as the third-line therapy in metastatic colon cancer: A case report. *Medicine*, **2021**, *100*(37).

5. Keam, S.J.; Duggan, S. Donafenib: First Approval. *Drugs*, **2021**, 1–6

6. Rajendran, P.; Ammar, R.B.; Al-Saeedi, F.J.; *et al.* Thidiazuron decreases epithelial-mesenchymal transition activity through the NF-kB and PI3K/AKT signalling pathways in breast cancer. *J. Cell. Mol. Med.,* **2020**, *24*, 14525–14538.

7. Blum, W.; Henzi, T.; Pecze, L.; *et al.* The phytohormone forchlorfenuron decreases viability and proliferation of malignant mesothelioma cells *in vitro* and *in vivo*. *Oncotarget*, **2019**, *10*, 69446956.

8. Dai, B.; Fan, M.; Yu, R.; *et al.* Novel diphenyl urea derivative serves as an inhibitor on human lung cancer cell migration by disrupting EMT via Wnt/β-catenin and PI3K/Akt signaling. *Toxicol. In Vitro,* **2020**, *69*, 105000.

9. Qi, B.; Zhang, R.; Sun, R.; et al. IGF-1R inhibitor PQ401 inhibits osteosarcoma cell proliferation, migration and colony formation. *Int. J. Clin. Exp. Pathol.,* **2019**, *12*, 1589–1598.

10. Catalano, A.; Iacopetta, D.; Pellegrino, M.; *et al.* Diarylureas: Repositioning from antitumor to antimicrobials or multi-target agents against new pandemics. *Antibiotics,* **2021**, *10*, 92.

11. Iacopetta, D.; Catalano, A.; Ceramella, J.; *et al.* The Different Facets of Triclocarban: A Review. *Molecules,* **2021**, *26*, 2811.

12. Catalano, A.; Iacopetta, D.; Rosato, A.; *et al.* Searching for small molecules as antibacterials: Non-cytotoxic diarylureas analogues of triclocarban. *Antibiotics,* **2021**, *10*, 204.

13. Catalano, A.; Rosato, A.; Salvagno, L.; *et al.* Benzothiazole-containing analogues of triclocarban with potent antibacterial activity. *Antibiotics,* **2021**, *10*, 803.

14. Chang, H.C.; Huang, Y.T.; Chen, C.S.; *et al. In vitro* and *in vivo* activity of a novel sorafenib derivative SC5005 against MRSA. *J. Antimicrob. Chemother.,* **2016**, *71*, 449–459.

15. Hroch, L.; Guest, P.; Benek, O.; *et al.* Synthesis and evaluation of frentizole-based indolyl thiourea analogues as MAO/ABAD inhibitors for Alzheimer's disease treatment. *Bioorg. Med. Chem.* **2016**, *25*, 1143–1152.

16. Azam, F.; Prasad, M.V.V.; Thangavel, N. Structure-based design, synthesis, and molecular modeling studies of 1-(benzo[*d*]thiazol-2-yl)-3-(substituted aryl) urea derivatives as novel anti-Parkinsonian agents. *Med. Chem. Res.* **2012**, *21*, 2630–2643.

17. Catalano, A. COVID-19: Could irisin become the handyman myokine of the 21st century? *Coronaviruses,* **2020**, *1*, 32–41.