Bioorganic & Medicinal Chemistry 24 (2016) 750–758

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

# Expanding the structural diversity of diarylureas as multi-target tyrosine kinase inhibitors

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ARTICLE INFO

*Article history:*
Received 7 December 2015
Revised 19 December 2015
Accepted 23 December 2015
Available online 23 December 2015

*Keywords:*
Diarylurea
Multi-target
Receptor tyrosine kinase
Inhibitor
Structural diversity

ABSTRACT

Recently approved multi-target inhibitors of receptor tyrosine kinases (RTKs) have significantly improved the clinical treatment of cancers. A series of *N,N′*-diarylureas incorporated with aromatic heterocycle have been designed, synthesized and evaluated as novel multi-target RTK inhibitors. The preliminary biological evaluation indicated that several compounds exhibited comparable potency with Sorafenib. Among them, compound **6f** was identified as the most potent multikinase inhibitor of EGFR, KDR and FGFR1 with $IC_{50}$ values of 14.83 nM, 21.57 nM, and 28.23 nM, respectively. These compounds expanded the structural diversity of diarylureas as RTK inhibitors. The results demonstrated that compound **6f** could be served as novel lead compound for further development of multi-target RTK inhibitors.



## 1. Introduction

Receptor tyrosine kinases (RTKs) have been shown not only to be key regulators of normal cellular processes but also to have a critical role in the development and progress of cancers.[1] RTKs play fundamental roles in transformation, proliferation, migration, differentiation, and metastasis of cancer cells.[2] Dysregulation of various RTKs such as EGFR, KDR, and FGFR1 have been correlated with progression of cancers with different histological origins. Inhibition of these RTKs has been validated by recently launched all RTKs share a similar molecular architecture, including a ligand binding extracellular region, a single transmembrane helix, an intracellular regulatory domain, and a cytoplasmic tyrosine kinase domain. Therefore, these RTKs have been validated as attractive targets for anticancer drugs.[3]

It has been demonstrated that multiple inhibition of RTK have become an important strategy for the treatment of cancers and have achieved significant clinical benefits.[4] Recently, several multi-target RTK inhibitors such as Sorafenib (Bayer), Altiratinib (Deciphera Pharmaceuticals), Linifanib (Abbott) and Regorafenib, (Bayer) have been approved or investigated in clinical trials (Fig. 1).[5] The diarylurea BAY 43-9006 is a potent inhibitor is a small molecular inhibitor of several RTKs (VEGFR/PDGFR/ERK) and Raf kinases.[6] Altiratinib is a MET/TIE2/VEGFR2/TRK kinase inhibitor in Phase 1 clinical development for the treatment of invasive solid tumors.[7] Another diarylurea, regorafenib, is a multi-target inhibitor for VEGFR1, VEGFR2, VEGFR3, PDGFRβ, Kit, RET and Raf-1.[8] ABT-869 is an oral active multi-target RTK inhibitor of KDR and PDGFR. It was discovered in Abbott Laboratories through a structure-based rational design, by incorporating an *N,N′*-diarylurea moiety at the C4-position of 3-aminodazole.[9]

Therefore, diarylurea scaffold has been identified as an effective scaffold for multikinase inhibitors. Remarkably, this framework was widely used as scaffold in the design of RTK inhibitors.[10] Moreover, diarylureas exhibited a multitude of biological activities, such as anticancer, antioxidant, antimicrobial, and antiviral activities. Numbers of reports have recently disclosed diarylureas as promising and effective anti-cancer agents.[11]

The ATP-binding site of RTK shares remarkable sequence homology and structural resemblance with each other such as EGFR, KDR, and FGFR1. Many research have recently highlighted diarylureas as potential antiproliferative agents.[12] Encouraged by the interesting RTK inhibition of diarylureas, we selected *N,N′*-diarylurea as core structure to obtain novel multi-target RTK inhibitors.[13] In order to expand the structural diversity of *N,N′*-diarylureas, our initial design strategy utilized incorporation of various aromatic heterocycles to form interaction with ATP-bind site (Fig. 2). In addition, we investigated the influence of the terminal aniline which was replaced with pyridine or thiazole on considering its broadly biological activity in anticancer drugs.

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http://dx.doi.org/10.1016/j.bmc.2015.12.038
0968-0896/

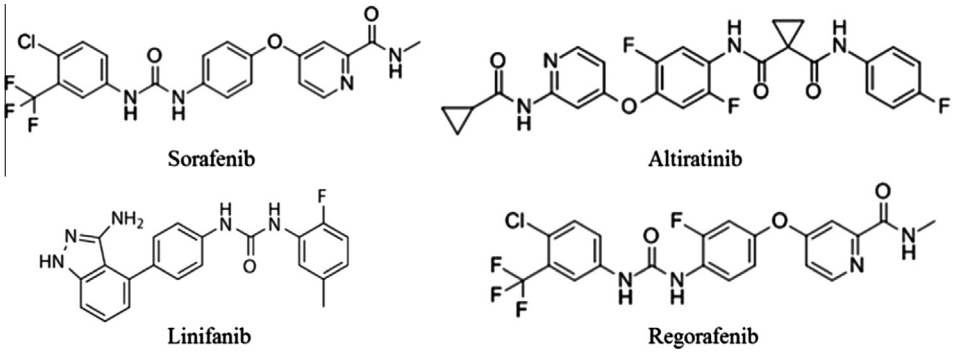


**Figure 1.** Structures of multi-target receptor tyrosine kinase inhibitors.

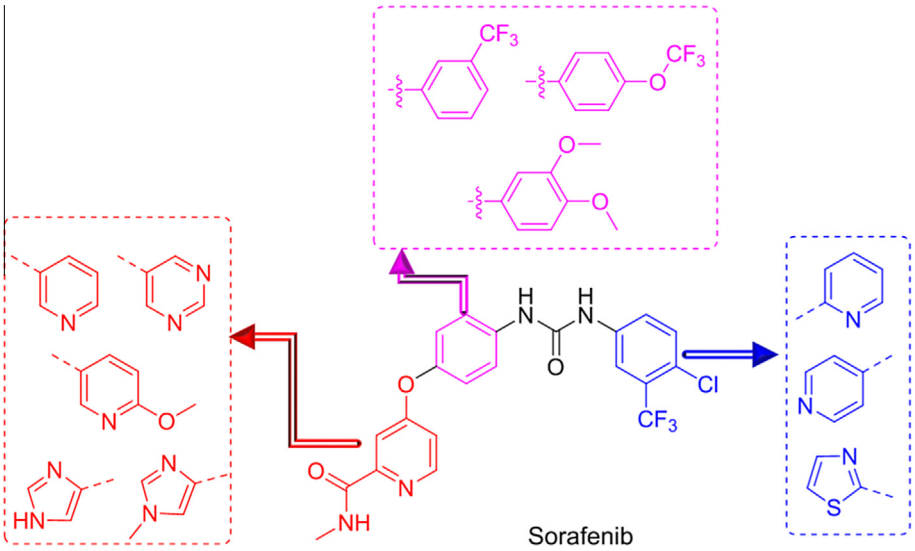


**Figure 2.** Expanding the structural diversity of diarylureas as multikinase inhibitors.

In the present investigation, we intended to expand structural diversity of *N,N′*-diarylureas through introducing various aromatic heterocycles. The results indicated that the novel *N,N′*-diarylurea was a potentially interesting scaffold for design of multi-target RTK inhibitors.

## 2. Chemistry

In order to expand the structural diversity of *N,N′*-diarylurea, twenty six derivatives were prepared according to the sequence of reactions illustrated in Schemes 1 and 2. All the title compounds were synthesized with various anilines and aromatic heterocycles bearing boric acid. Various *N,N′*-diarylureas (**3a–3h**) were obtained through reaction of commercially available aromatic heterocyclic amines (**1a–1c**) and bromo anilines (**2a–2c**) using a previous described synthetic method.[14] All the target compounds could be classified into two types: six-member heterocyclic derivatives and five-member heterocyclic derivatives. Scheme 1 depicts the general synthetic route for the six-member heterocyclic derivatives (**5a–5e, 6a–6i, 7a–7g**).[15] They were prepared by palladium-catalyzed Suzuki cross coupling of the bromo intermediates (**3a–3h**) with the appropriate arylboronic acid (**4a–4h**) in the presence of $Pd(PPh_3)_4$ and potassium carbonate.[16]

For preparation of the five-member heterocyclic derivatives (**8a–8e**), the similar synthetic procedure outlined in Scheme 2 was accomplished. The key previously yielded intermediates (**3d–3g**) was reacted with commercially available (1-methyl-1*H*-imidazol-4-yl)boronic acid (**4d**) or (1*H*-imidazol-4-yl)boronic acid (**4e**) using the classic Suzuki reaction.[17] All of the title compounds were characterized by $^1H$ NMR, $^{13}C$ NMR, mass spectroscopy and melting point. Detailed synthetic procedures were described in Section 5.

## 3. Results and discussion

All the title compounds were evaluated for their enzymatic inhibition against EGFR, KDR and FGFR1. The tyrosine kinase inhibitory potency was assayed by using the well-established ADP-Glo assays.[18] The enzymatic inhibitory activity of two series of diarylureas was summarized in Tables 1 and 2. For the six-member heterocyclic derivatives, compounds incorporated with pyrimidine were generally more potent than that bearing pyridine. Moreover, compounds with trifluoromethyl at $R_2$ or trifluoromethoxyl at $R_3$ were more potent than methoxyl substitituent. This suggested that introduction of trifluoromethyl or trifluoromethoxyl on this phenyl ring in favorable for the activity. Among these diarylureas, compound **6f** was the most potent inhibitor against EGFR, KDR and FGFR1 with $IC_{50}$ values of 14.83, 21.57 and 28.23 nM, respectively. Meanwhile, compound **6i** was also a potent multi-target RTK inhibitor with similar $IC_{50}$ values.

The RTK inhibitory activities of the five-member heterocyclic derivatives were summarized in Table 2. As shown in Table 2, most