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Original article

Design, synthesis and antitumour activity of bisquinoline derivatives connected by 4-oxy-3-fluoroaniline moiety

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ABSTRACT

A series of novel bisquinoline derivatives connected by a 4-oxy-3-fluoroaniline moiety were synthesized and evaluated for their *in vitro* antitumour activities against a panel of five cancer cell lines (H460, HT-29, MKN-45, U87MG, and SMMC-7721). Most of compounds tested showed a potent activity and high selectivity towards the H460 and MKN-45 cell lines. Among the compounds tested, six (**15d**, **15e**, **15m**, **15n**, **16a**, and **16i**) were further examined for their c-Met kinase activity; the compounds showed high efficacy with IC_{50} values in the single-digit nM range. An analysis of structure–activity relationships indicated that an unsubstituted or a halogen-substituted phenyl ring on the 2-arylquinoline-4-carboxamide moiety was favourable for antitumour activity.

1. Introduction

The leading causes of death worldwide remain cardiovascular disease and cancer, although a recent report disclosed a tendency for an increase in cancer mortality [1,2]. Although cancer chemotherapy has entered a new era of molecularly targeted therapeutics, drug resistance and side effects remain serious problems [3,4]. Therefore, the search for safer and more efficient chemotherapeutic agents is very important [5].

Foretinib (**1**, Fig. 1), a novel oral multi-kinase inhibitor targeting c-Met, vascular endothelial growth factor receptor 2 (VEGFR-2), RON, KDR, and Flt-1, is currently undergoing phase II clinical trials for different types of cancer [6]. Due to its dual mechanism of action and broad-spectrum anticancer potency, researchers drew attention to the optimization of foretinib. In the past few years, a variety of 4-(2-fluorophenoxy) quinoline derivatives have been reported as potent c-Met kinase inhibitors [7–12]. During the course of studying these analogues (Fig. 1) [13–15], we found that modification of moiety A usually occurs at position 7 of quinoline, where the methoxy group is replaced by a water-soluble fragment, such as 3-morpholinopropoxy group. Furthermore, the modification of the linker is variable, but the reported linkers have two common characteristics, namely, a distance of six chemical bonds between moiety A and moiety B, which is known as '5 atoms regulation', and the linker contains both a hydrogen-bond donor or acceptor and at least one amide group. In contrast, there is little change to B moiety except for a phenyl ring or a substituted phenyl ring. These structural characteristics suggest that exploring a satisfactory linker is a practicable way of designing this series of quinoline derivatives.

To date, many studies have reported that compounds with a 2-arylquinoline-4-carboxamide framework display a multitude of biological activities, including antitumour, antiviral, and anti-inflammatory activities [16–18]. A novel candidate for the signal transducer and activator of transcription 3 (STAT3) inhibitor, STX-0119 (**I**, Fig. 2), displays a potent anti-proliferative effect with an IC_{50} of 5–10 μM on haematological cancer cells *in vitro*, as well as potent antitumour activity *in vivo* in SCC3-bearing nude mice through down-regulation of STAT3 target genes and induction of apoptosis in the tumours [16,19,20]. Interestingly, the 2-arylquinoline-4-carboxamide skeleton conformed to the two structural characteristics of the linkers mentioned above. Based on these observation, we designed a series of bisquinoline derivatives connected by a 4-oxy-3-fluoroaniline moiety (**II**, Fig. 2), in which the A moiety of foretinib was preserved, and the 2-phenylquinoline-4-carboxamide framework was attached to the C-4′ position of the A moiety as the linker and B moiety. In addition, the morpholinyl group was replaced by other water-soluble substituents, including piperidinyl, pyrrolidinyl, and 4-methyl piperidinyl groups. Furthermore, various substituents (R_3), especially mono-electron-withdrawing groups (mono-EWGs), such as halogen atoms (F and

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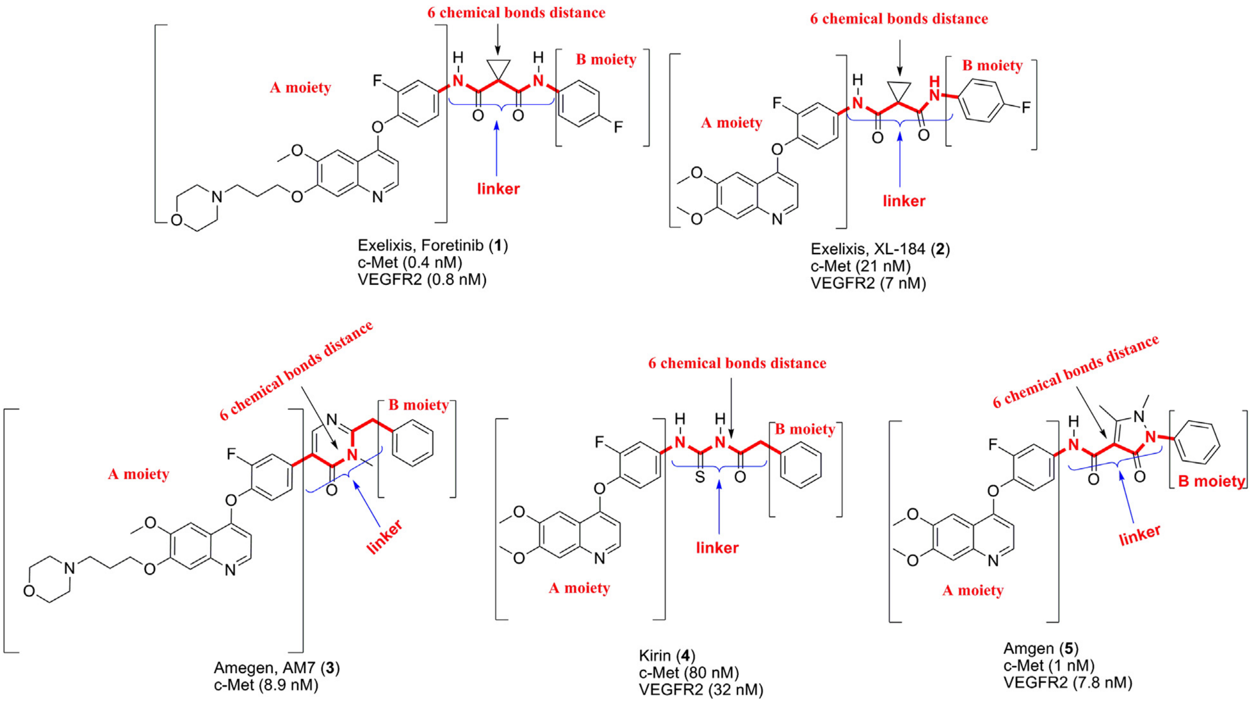


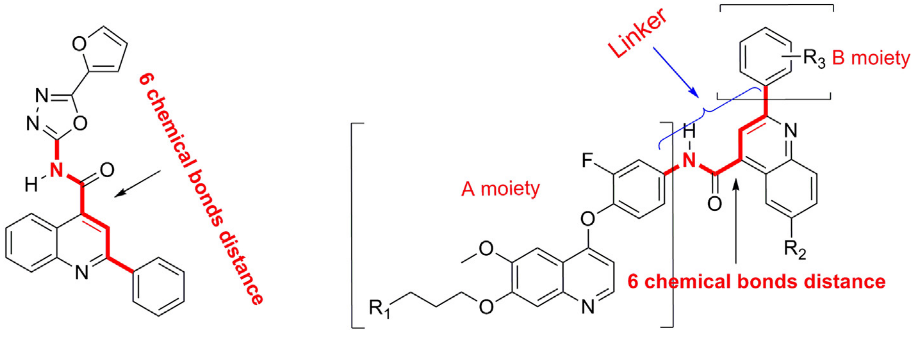
Fig. 1. Structures of foretinib and other 4-(2-fluorophenoxy)quinoline derivatives.

Cl), were introduced into the phenyl ring (B moiety) to investigate their effect on activity. In this study, we report newly synthesized target compounds and their *in vitro* antitumour activities against five human cancer cell lines and c-Met kinase.

2. Chemistry

The key intermediates **8a**–**d** were synthesized using the convenient eight-step procedure starting from 1-(4-hydroxy-3-methoxyphenyl)ethanone depicted in Scheme 1. Commercially available acetophenone was alkylated with 1-bromo-3-chloropropane in acetone under basic conditions to give intermediate **1** [21], which was converted to nitro-ketone **2** by using fuming nitric acid as a nitration reagent in dichloromethane at −20 °C for 6 h, with a 70% yield [22]. Then, condensation of **2** with dimethyl formamide dimethyl acetal (DMF–DMA) in refluxing toluene provided yellow solid **3** [23], which was reduced and cyclized using glacial acetic acid and iron powder to afford hydroxy-quinoline **4**, with a high yield and purity in a single step [24]. The reaction of **4** with excessive secondary amines (piperidine, 4-methyl piperidine, morpholine, and pyrrolidine) in acetonitrile at reflux provided intermediates **5a**–**d** [25], which were converted to chloro-quinolines **6a**–**d** by refluxing in the mixed solvent of phosphorus oxychloride and acetonitrile in sequence [26]. Next, the etherification reaction of **6a**–**d** with 2-fluoro-4-nitrophenol afforded purified **7a**–**d**, which were reduced using iron powder and catalytic amounts of ammonium chloride in ethanol to obtain amides **8a**–**d**.

Target compounds **15a**–**s** and **16a**–**n** were prepared as outlined in Scheme 2. The side chains **13a**–**h** and **14a**–**g** were synthesized from aniline and 4-fluoroaniline, which refluxed with chloralic hydras and hydroxylamine hydrochloride in the diluted aqueous solution of hydrogen chloride to afford indoline-2,3-dione **9** and 5-fluoro-indoline-2,3-dione **10**, respectively [27]. Subsequently, via Pfitzinger–Borsche reaction with variously



I STX-0119

II
The general structure of target compounds

Fig. 2. Structure of STX-0119 and the target compounds.