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Research paper

# Design, synthesis, broad-spectrum antiproliferative activity, and kinase inhibitory effect of triarylpyrazole derivatives possessing arylamides or arylureas moieties

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ABSTRACT

A novel series of 1,3,4-triarylpyrazole derivatives possessing terminal arylamide or arylurea terminal moieties has been designed and synthesized. Their *in vitro* antiproliferative activities were investigated against a panel of 58 cell lines of nine different cancer types at the NCI, USA. The urea analogues **2b**, **2c**, and **2f** as well as the amide derivatives **3e** and **3f** exerted the highest mean % inhibition values over the 58 cell line panel at 10 μM, and thus were further tested in 5-dose testing mode to determine their $GI_{50}$, TGI, and $LC_{50}$ values. The above mentioned compounds have shown stronger antiproliferative activities in terms of potency and efficacy upon comparing their results with Sorafenib as a reference compound. Among them, compounds **2c** and **2f** possessing 3,4-dichlorophenylurea terminal moiety showed the highest mean %inhibition value of about 99.85 and 104.15% respectively over the 58-cell line panel at 10 μM concentration. Also compounds **2b**, **3e**, and **3f** exhibited mean % inhibition over 80% at 10 μM concentration. The $GI_{50}$ value of compound **3e** over K-562 cancer cell line was 0.75 μM. Accordingly, compound **2f** was screened over seven kinases at a single-dose concentration of 10 μM to profile its kinase inhibitory activity. Interestingly, the compound showed highly inhibitory activities (90.44% and 87.71%) against BRAF (V600E) and RAF1 kinases, respectively. Its $IC_{50}$ value against BRAF (V600E) was 0.77 μM. Compounds **2b**, **2c**, **2f**, **3e**, and **3f** exerted high selectivity towards cancer cell lines than L132 normal lung cells.



## 1. Introduction

Cancer is one of the serious public health problems in the world. The statistics show that its incidence and mortality is growing in the developing as well as developed countries. Despite significant advances in the diagnostic and therapeutic techniques nowadays, cancer is considered the second most frequent cause of death after cardiovascular diseases [1,2]. According to the World Health Organization (WHO) report [3], more than 13 million deaths from cancer worldwide are expected to occur in 2030. Considering numerous reports and publications on the synthesis of anticancer agents, there is no drug with 100% efficacy. Therefore, there is still instant demand for more drug discovery leading to efficient anticancer compounds with specific mechanism of action to overcome the side effects associated with current chemotherapeutics in cancer treatment, such as toxicity and drug resistance.

Many research articles have recently reported the potential antiproliferative activity of arylureas and arylamides against a variety of cancer cell lines [4–24]. Sorafenib (Fig. 1) possessing arylurea terminal moiety is an example of anticancer that has been approved by the U.S. Food and Drug Administration (FDA) for

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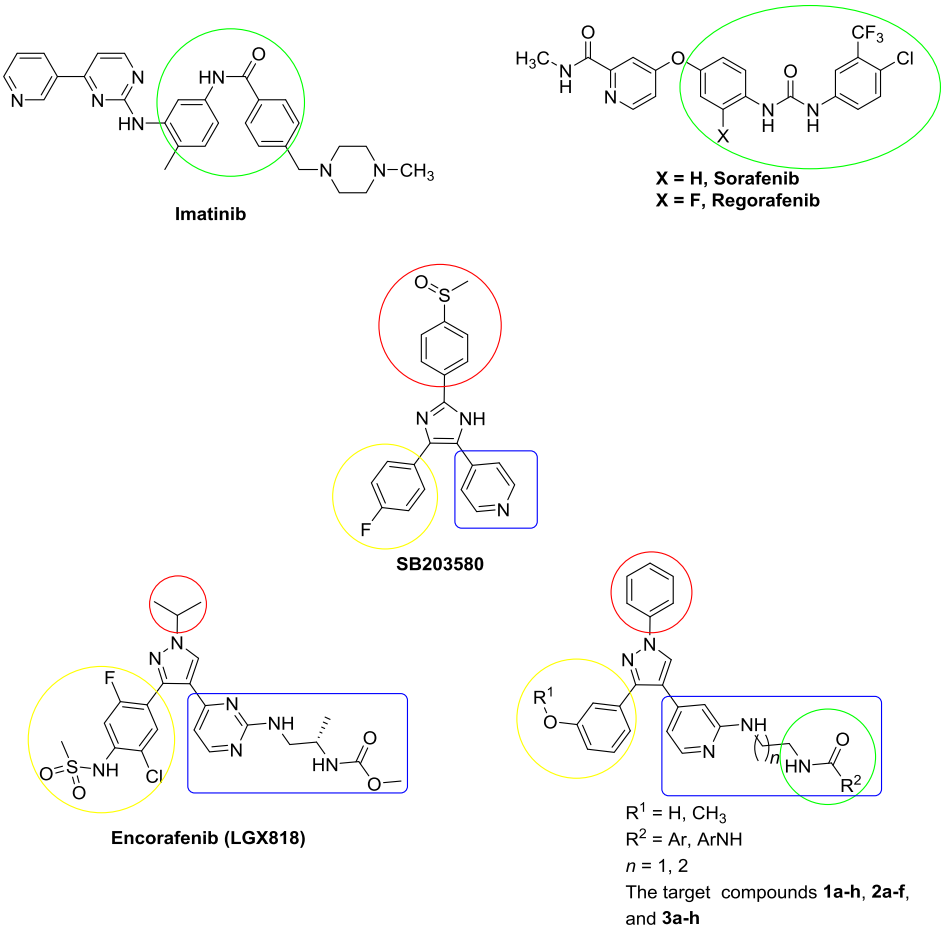


**Fig. 1.** Structures of Imatinib, Sorafenib, Regorafenib, SB203580, Encorafenib (LGX818), and the target compounds **1a**–**h**, **2a**–**f**, and **3a**–**h**.

treatment of advanced renal cancer, and also currently being in clinical trials for treatment of many other cancer types as metastatic colorectal, ovarian, brain, esophageal/gastroesophageal, leukemia, glioblastoma, Hodgkin's lymphoma, metastatic breast, advanced gastric, hepatocellular carcinoma (HCC), thyroid, non-small cell lung cancer (NSCLC), pancreatic, prostate, bladder, skin/ocular melanoma and neuroendocrine cancers [25,26]. Imatinib (Fig. 1) is an example of anticancer agents having arylamides terminal moiety that is used for treatment of chronic myeloid leukemia (CML) with diminished side effects [27]. It has been studied in clinical trials for treatment of gastrointestinal stromal tumor (GIST), thyroid cancer, breast cancer, meningioma, ovarian cancer, and non-small cell lung cancer (NSCLC) in combination with other drugs [28].

In addition, much attention has been paid to the chemistry and biological activities of 1,3,4-triarylpyrazole scaffold. Several compounds possessing 1,3,4-triarylpyrazole scaffold have been recently reported as potential antiproliferative agents [7,10,14,17,29,30].

In the present study, a new series of 1,3,4-triarylpyrazole derivatives possessing terminal arylamide or arylurea moieties were designed with similarity to SB203580 and Encorafenib (LGX818) (Fig. 1). SB203580 was reported to bind to P38/MAP kinase through hydrophobic/hydrogen bonding interactions of the fluorophenyl ring with a hydrophobic region, hydrogen bonding of the pyridyl and imidazole rings with the kinase hinge region, and the methylsulfinylphenyl ring with the phosphate binding region [32,33]. There is another hydrophobic region below the pyridyl ring which was not occupied by SB203580 [32]. That's why the terminal chain on the pyridyl ring was important. Our target compounds were also designed similar to Encorafenib through ligand-based design approach. The *N*-phenyl ring on the pyrazole ring mimics the *N*-isopropyl group of Encorafenib, and estimated to undergo similar interaction. The two aryl rings at positions 3 and 4 of the pyrazole ring mimic the two aryl rings at the same positions on the Encorafenib structure. And the side chain on the pyridyl ring mimics that of Encorafenib with replacement of the terminal methoxy group of the carbamate moiety of Encorafenib with arylamino or aryl moiety. The designed target compounds were synthesized and tested for *in vitro* antiproliferative activities against NCI-58 cancer cell line panel of nine different cancer types. Kinase inhibitory activities of the most active compounds against wild-type BRAF, V600E mutated BRAF, RAF1, EGFR, P38α/MAPK14, ABL1 and ABL1 (T315I) were also examined in order to test their possible mechanism of action.

## 2. Results and discussion

### 2.1. Chemistry

Synthesis of the target compounds **1a**–**h** & **2a**–**f and 3a**–**h** was achieved through the pathway illustrated in Scheme 1. Refluxing the 3-methoxybenzoic acid with methanol in the presence of few drops of sulfuric acid afforded the corresponding methyl ester **5** [34]. Reacting the ester with 4-picoline in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) led to formation of the ketide intermediate **6**. Cyclization to the pyrazole compound **7** was carried