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Design, synthesis and biological activities of Nilotinib derivates as antitumor agents

Xiaoyan Pan, Fang Wang, Yanmin Zhang, Hongping Gao, Zhigang Hu, Sicen Wang, Jie Zhang *

School of Medicine, Xi'an Jiaotong University, No. 76, Yanta West Road, Xi'an, Shaanxi Province 710061, PR China

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ABSTRACT

A novel class of Nilotinib derivatives, **B1–B20**, were synthesized in high yields using various substituted anilines. All the title compounds were evaluated for their inhibitory activities against Bcr-Abl and antiproliferative effects on human leukemia cell (K562). The pharmacological results indicated that some compounds exhibited promising anticancer activity. In particular, compound **B14** containing tertiary amine side chain exhibited Bcr-Abl inhibitory activity similar to that of Nilotinib. It was suggested that the introduction of the tertiary amine moiety could improve Bcr-Abl inhibitory activity and antitumor effects.

1. Introduction

CML is a haematological malignancy caused by a chromosomal rearrangement which generates a fusion protein (Bcr-Abl kinase).[1,2] It arises from the juxtaposition of Abelson gene (Abl) on chromosome 9 to the break point cluster region (Bcr) gene on chromosome 22.[3] This fusion gene encodes a chimeric Bcr-Abl protein, in which the tyrosine kinase activity of Abl is constitutively activated.[4] Therefore, Bcr-Abl kinase plays an important role in the pathogenesis of CML. It is becoming an attractive target for CML targeted therapy.[5]

Nilotinib is a phenylamino-pyrimidine derivative which was rationally designed as second generation Bcr-Abl inhibitor.[6] It was approved to treat adult patients in all phases of CML with resistance to Imatinib. However, nilotibib could not suppress the proliferation of leukemia cells harboring some Bcr/Abl mutants (T315I).[7–9] Crystallographic studies have revealed that Nilotinib bound to Bcr-Abl through four key interactions (Fig. 1).[10–12]

Nilotinib was designed to fit into the ATP binding site of Bcr-Abl which was quite conserved. The allosteric binding region was considered as selectivity site. Therefore, the pharmacophore bound with allosteric region was optimized so as to improve the selectivity and activity. Similar to Nilotinib, we attempted to design novel derivatives which bind to Bcr-Abl more tightly, thereby enhancing the inhibitory activity. Aniline containing halogen substituents is useful for anticancer agents design. Halogen introduction can enhance the persistence and lipid solubility.[13] Therefore, various halogen-substituted anilines were introduced to develop novel Bcr-Abl inhibitors. Moreover, some heterocyclic amines or anilines containing tertiary amine side chain were used to afford new compounds with structural diversity.

2. Chemistry

In the present study, the facile total synthesis of Nilotinib from commercial available reagents was firstly performed.[14] In this study, the synthesis of one key intermediate 4-methoxyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino] benzoic acid was similar to that of Nilotinib. The key intermediate (**5**) was prepared in five steps. At first, carboxylate group of 3-amino-4-methoxyl benzoic acid (**1**) was protected by esterizing.[15] Then refluxing of (**2**) and acetonitrile in the presence of concentrated HCl yielded 3-guanidino-4-methoxyl benzoic acid ethyl ester nitrate (**3**).[16,17] Reaction of (**3**) with 3-dimethylamino-1-(3-pyridyl)-2-propen-1-one afforded (**4**).[18,19] This reaction was carried out in the presence of NaOH. The hydrolysis of 4-methoxyl-3-[[4-(3-pyridyl)-2-pyrimidinyl] amino] benzoic acid ethyl ester (**4**) in NaOH aqueous afforded intermediate (**5**).[20] Finally, compound (**5**) condensed with various anilines to yield title compounds using active ester method.[21]

Twenty pyrimidin-2-ylamino-benzamides (**B1–B20**) were prepared as Bcr-Abl inhibitors. The synthetic route was shown in Scheme 1. Synthesis of **B1–B9** was similar to that of Nilotinib. Various heterocyclic amines were used in the synthesis of

* Corresponding author. Address: College of Medicine, Xi'an Jiaotong University, No. 76, Yanta West Road, Xi'an, Shaanxi Province 710061, PR China. Tel.: +86 29 82657740; fax: +86 29 82655451.
E-mail address: zhj8623@mail.xjtu.edu.cn (J. Zhang).

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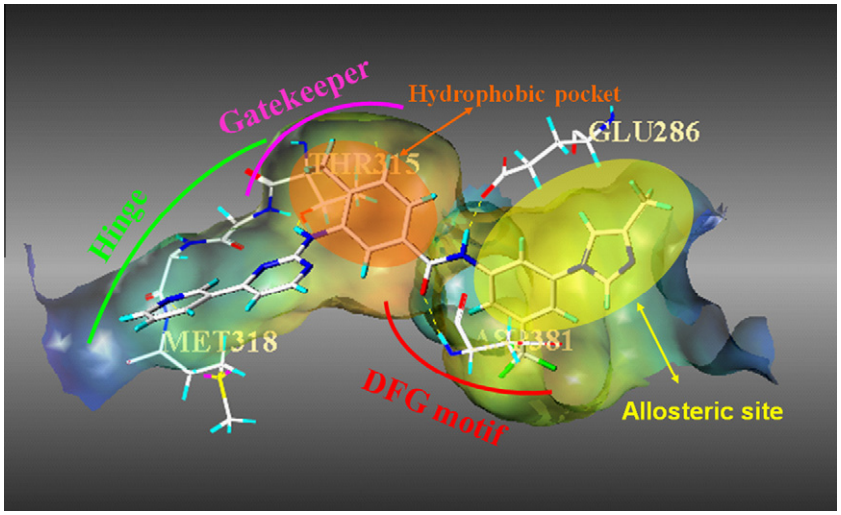
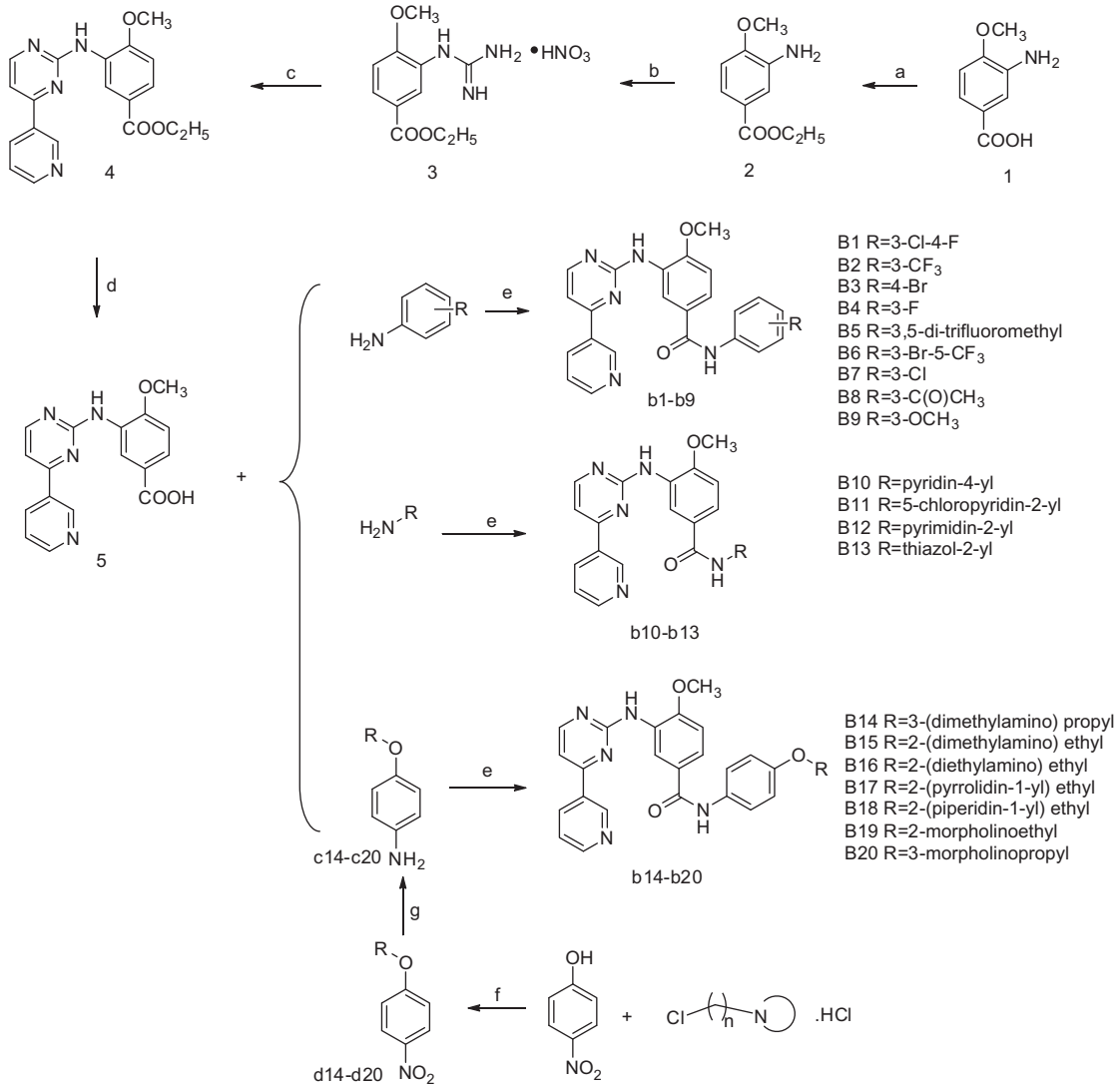


Figure 1. The interactions between Nilotinib and Bcr-Abl kinase.



Scheme 1. Reagents and conditions: (a) abs EtOH, concd H_2SO_4, reflux, 8 h; (b) H_2NCN, concd HCl, EtOH, reflux, 15 h, NH_4NO_3(aq); (c) 3-(dimethyl amino)-1-(3-pyridinyl)prop-2-en-1-one, NaOH, *n*-BuOH, reflux, 72 h; (d) 2 M NaOH, EtOH/H_2O(v:v = 1:1), 50 °C, 2 h; (e) isobutyl chloroformate, 4-methylmorpholine, 0 °C, 30 min; substituted benzamides or substituted heterocyclic amines or compound **c14**–**c20**, 4-methylmorpholine, rt, overnight; (f) Cs_2CO_3, DMF, 100 °C, 2–4 h; (g) Pd/C, MeOH, 4 h.