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Syntheses and biological evaluation of 1,2,3-triazole and 1,3,4-oxadiazole derivatives of imatinib

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ABSTRACT

Three novel series of 1,2,3-triazole and 1,3,4-oxadiazole derivatives of imatinib were prepared and evaluated in vitro for their cytostatic effects against a human chronic myeloid leukemia (K562), acute myeloid leukemia (HL60), and human leukemia stem-like cell line (KG1a). The structure–activity relationship was analyzed by determining the inhibitory rate of each imatinib analog. Benzene and piperazine rings were necessary groups in these compounds for maintaining inhibitory activities against the K562 and HL60 cell lines. Introducing a trifluoromethyl group significantly enhanced the potency of the compounds against these two cell lines. Surprisingly, some compounds showed significant inhibitory activities against KG1a cells without inhibiting common leukemia cell lines (K562 and HL60). These findings suggest that these compounds are able to inhibit leukemia stem-like cells.

Chronic myelogenous leukemia (CML) is a hematological disorder that is associated with a characteristic translocation between chromosomes **9** and **22**. This translocation forms a gene encoding the Bcr-Abl fusion protein with constitutively activate kinase activity, which is necessary for cell transformation.[1–3] Bcr-Abl kinase plays an important role in cell signal transformation and activates several downstream survival pathways, including NF-κB and STAT5/Bcl-xL, eventually leading to uncontrolled cell proliferation and reduced apoptosis. Because Bcr-Abl kinase is not expressed in normal cells, it is an ideal target to treat CML.[4–6]

Imatinib (Gleevec, STI571), an effective Bcr-Abl tyrosine-kinase (TK) inhibitor, is now the first-line treatment for most cases of CML. The inhibitor competitively binds the ATP-binding site of Bcr-Abl. This binding prevents a conformational switch to the active form and reduces the activity of Bcr-Abl.[7,8] Imatinib is a successful model for targeting a dominant oncogene with a small molecule.[9] Despite achieving great success in the treatment of CML, imatinib has been associated with acquired resistance that ultimately leads to relapse. Postulated reasons for this resistance include overexpression of the Bcr-Abl protein, point mutations in the Abl kinase domain, amplification of the BCR-ABL gene, overexpression of P-glycoprotein, and yet-unknown resistance mechanisms.[10–12]

Cancer stem cells remain in a quiescent state and, as a result, are resistant to conventional cancer therapies. These cells can provide a sanctuary for the development of mutations in BCR-ABL, resulting in drug resistance.[13] One important cause of resistance in CML is thought to be the existence of quiescent leukemia stem cells (LSCs) that are highly tumorigenic and resistant to conventional chemo and radiation therapies. Thus, new therapeutics targeting LSCs are urgently needed.[14] Human promyeloblastic leukemia KG1a cells are characterized by the $CD34^+$ biomarker. As they exhibit many characteristics similar to LSCs,[15] KG1a cells maybe a suitable cellular model for LSC research. Some synthesized imatinib analogs[16–18] have demonstrated improved bioactivity against certain cell lines, such as K562 and KU812, but it is unknown whether they have activity against KG1a cells.

Bioisosterism is a widely accepted concept in medicinal chemistry and has been used to elicit changes in a lead structure to obtain various goals, such as enhancement of the chemical stability or pharmacokinetic properties while maintaining or even improving biological activity.[19–21] The 4-(pyridin-3-yl)-*N*-(*o*-tolyl)pyrimidin-2-amine scaffolds in imatinib play a crucial role in blocking the ATP-binding site.[22] Bioisosteres of the amide bond include a 1,2,3-triazole ring and 1,3,4-oxadiazole. Similarities between the two moieties can be seen in the dipolar character, size, and H-bond

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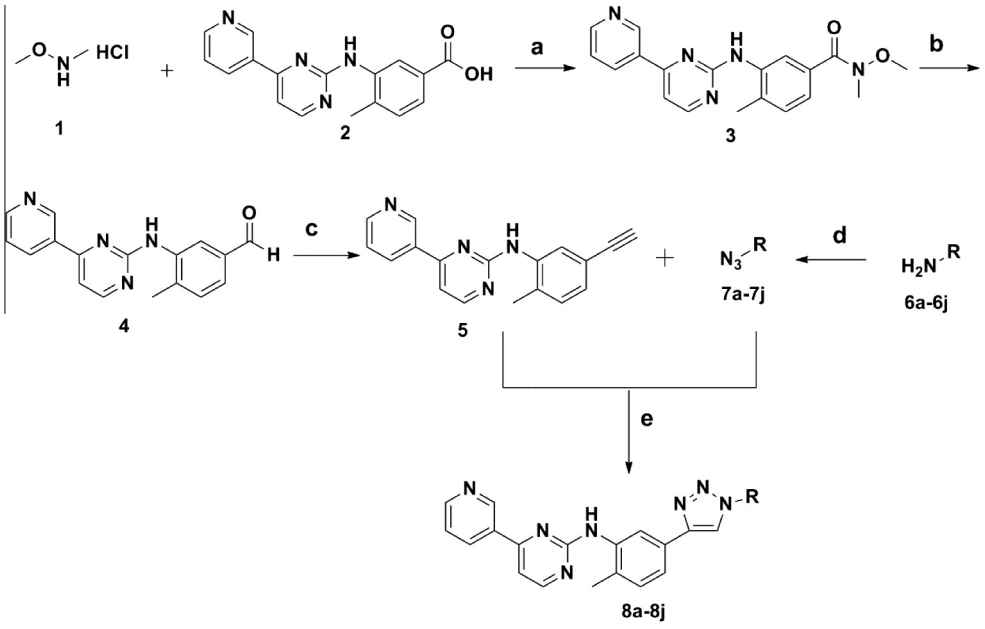
acceptor capacity.[23] 1,2,3-Triazole also acts as a linker and can be easily constructed under mild conditions at any stage of target molecule preparation.[24] 1,3,4-Oxadiazole is a five-member ring that is seen in the structure of drugs, such as zibotentan[25] and raltegravir.[26] Regioisomeric forms of this ring are frequently occurring motifs in drug-like molecules and often are used as bioisosteres for ester and amide functionalities, offering increased aqueous solubility,[27] decreased hERG inhibition, and improved metabolic stability.

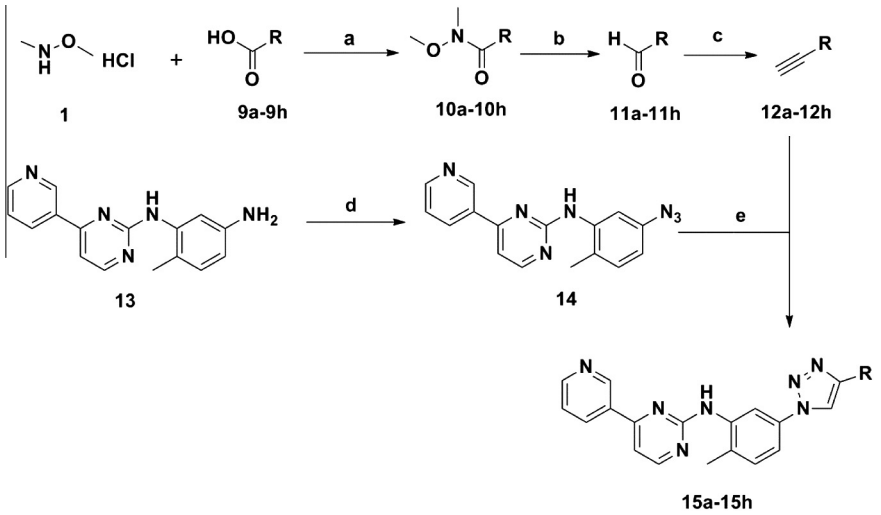
Many natural products have the ability to inhibit cancer stem cells.[28] For example, recent investigations revealed that the combination of imatinib with sulforaphane[29] or curcumin[30,31] could enhance the inhibitory activity of imatinib against leukemia cells. Analysis of the structure–activity relationship of these combined molecules suggested that isothiocyanate and the conjugate structure of curcumin are the groups of sulforaphane and curcumin, respectively, needed to maintain the inhibitory activity. Irreversible TK inhibitors can enhance potent and selective inhibition, and may overcome tumor resistance.[32] These inhibitors target specific cysteine residues but only a few kinases specific location with cysteine.[33,34]

In this study, we replaced the amide bond of the 4-(pyridin-3-yl)-*N*-(*o*-tolyl)pyrimidin-2-amine scaffold in imatinib with a 1,2,3-triazole ring or 1,3,4-oxadiazole ring to form imatinib analogs. We added isothiocyanate, curcumin or acrylamide to the 'tail' of the analogs, with the goal of enhancing the inhibitory activity of the drugs against leukemia cells. We report the synthesis and biological evaluation of the resulting compounds.

Scheme 1 outlines the routes used to synthesize compounds **8a**–**8j**. Briefly, compound **3** was synthesized from benzoic acid derivative **2** by acylation with starting material **1**. Benzaldehyde derivative **4** was synthesized by a reduction reaction from intermediate **3** with $LiAlH_4$ in anhydrous THF. Alkyne intermediate **5** was obtained by Seyferth–Gilbert homologation.[35] Reaction of



Scheme 1. Reagents and conditions: (a) NMM, EDCI, HOBT, rt, 6 h, 60%; (b) $LiAlH_4$, THF, 0 °C, 3 h, 80%; (c) dimethyl(1-diazo-2-oxopropyl)phosphonate, K_2CO_3, MeOH, rt, 6 h, 80%; (d) $NaNO_2$, HCl, NaN_3, H_2O, 3 h, 0 °C; (e) Cu_2O nanoparticles, CH_3CN, rt.



Scheme 2. Reagents and conditions: (a) 4-methylmorpholine, HOBt, EDCI, CH_2Cl_2, rt, 6 h, 72%; (b) $LiAlH_4$, THF, 0 °C, 3 h, 78%; (c) dimethyl(1-diazo-2-oxopropyl)-phosphonate, K_2CO_3, MeOH, rt, 5.5 h, 82%; (d) $NaNO_2$, HCl, NaN_3, H_2O, 3 h, 0 °C; (e) Cu_2O–NPs, EtOH–H_2O, rt.