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Design, synthesis, and evaluation of hinge-binder tethered 1,2,3-triazolylsalicylamide derivatives as Aurora kinase inhibitors

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ABSTRACT

A series of hinge-binder tethered 1,2,3-triazolylsalicylamide derivatives were designed, synthesized, and evaluated for the Aurora kinase inhibitory activities. The novel hinge-binder tethered 1,2,3-triazolylsalicylamide scaffold was effectively assembled by Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC). A variety of alkynes with hinge binders were used to search proper structures–binding relationship to the hinge region. The synthesized 1,2,3-triazolylsalicylamide derivatives showed significant Aurora kinase inhibitory activity. In particular, **8a** inhibited Aurora A kinase with an IC_{50} value of 0.284 μM, whereas **8m** inhibited Aurora B kinase with an IC_{50} value of 0.364 μM.

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1. Introduction

Aurora kinases are the members of serine/threonine kinases and have attracted significant attention as promising anticancer targets up to date.[1] Both Aurora A and B are commonly overexpressed in human tumor cells and play important roles in various organ tumors including the colon, breast, pancreatic, gastric, and prostate cancer. The overexpression of Aurora A causes aberrant phosphorylation of normal cell cycle targets and cytoplasmic targets, leading to chromosomal instability, oncogenic transformation, tumor progression, and development of chemoresistance.[2] Similarly, the overexpression of Aurora B increases the phosphorylation of histone H3, forming more aggressive tumors in transgenic mouse models.[3]

Mechanistically, Aurora kinases (A, B, and C) are regulatory proteins and play key roles in the mitotic events of cell division.[4] Aurora A associates with the spindle poles and regulates centrosome duplication, maturation, and mitotic spindle assembly;[5] Aurora B is involved in chromatin remodeling, phosphorylation of histone H3 at Ser-10, centrosome separation, chromosome segregation, and cytokinesis;[6] the third isozyme, Aurora C is believed to have overlapping function with Aurora B and similar localization patterns; however, its function is not yet clearly understood.[7]

Over the past decade, extensive research has been directed toward the discovery of Aurora-selective small-molecule inhibitors. As a result, a handful of Aurora inhibitors has been identified. Among them, **1** (VX-680)[8] and **2** (SNS-314)[9] have entered human clinical trials as pan-Aurora kinase inhibitors (Fig. 1), and **3** (MLN8237)[10] and **4** (MK-5108)[11] are undergoing clinical assessment as Aurora A specific inhibitors. As another clinical candidate drug, **5** (AZD1152)[12] has been also reported to selectively inhibit Aurora B. Although several Aurora inhibitors have currently reached the clinical evaluation stage, the ideal inhibitor profile for therapeutic use has not yet been defined. As a part of our ongoing effort to develop Aurora kinase inhibitors, herein, we describe the design, synthesis, and biochemical evaluation of hinge-binder tethered 1,2,3-triazolylsalicylamide inhibitors.

2. Results and discussion

2.1. Design

Previously, we constructed a small molecule library mimicking a natural kinase inhibitor, lavendustin, using a rapid 'click fragment assembly' and screening method, leading to the identification of antiproliferative agent **6** (Fig. 2).[13] Later, following study to improve the potency and selectivity of compound **6** led to the discovery of an effective Aurora A kinase inhibitor **7** through a systematic synthesis of 1,2,3-triazolylsalicylamide small molecules.[14] The identified 1,2,3-triazolylsalicylamide **7** inhibited Aurora A kinase with an IC_{50} value of 0.375 μM. The molecular modeling study also exhibited that the salicylamide moiety of compound **7** interacts with Lys175 and Glu194 of Aurora A through

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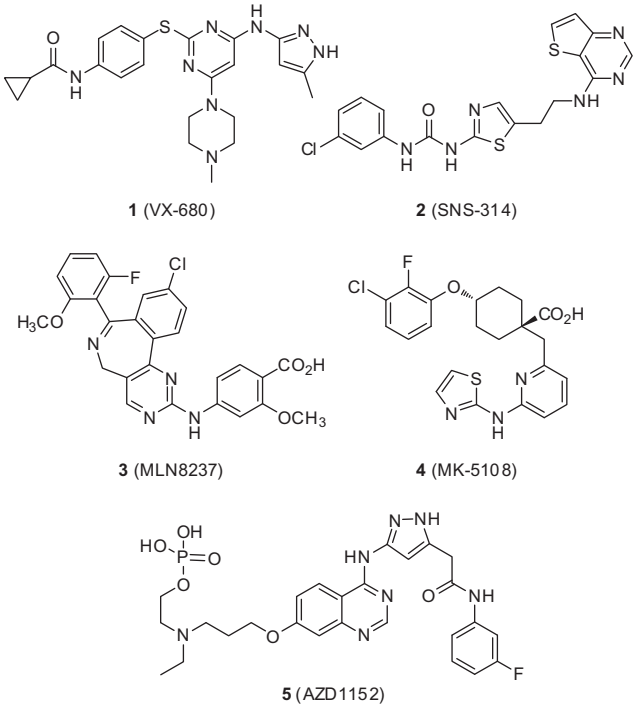

Figure 1. Aurora kinase inhibitors in clinical trials.

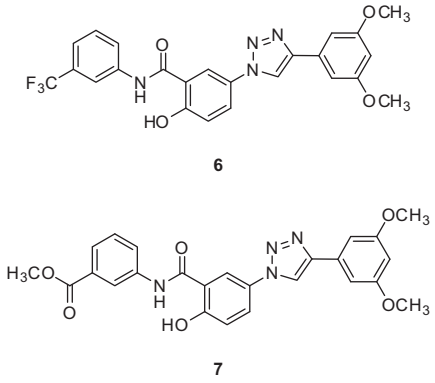

Figure 2. 1,2,3-Triazolylsalicylamide Aurora kinase inhibitors.

hydrogen-bonding network: the carbonyl group of the salicylamide plays an important role as a hydrogen bond acceptor, and both the phenolic OH and amide NH as hydrogen bond donors interact with the carboxylate of Glu194 (Fig. 3). According to the co-crystal structure of humanized mouse Aurora A and compound **2** (SNS-314),[15] the urea moiety of compound **2** interacts with Lys175 and Glu194 as well. In addition, the thienopyrimidine N1 of compound **2** forms a hydrogen bond with the main chain NH of Ala226 in the hinge region. Therefore, we scrutinized the structural difference of compounds **2** and **7**. The extensive examination of their binding mode guided us to incorporate a functional group capable of forming hydrogen bond in the hinge region.

Structurally, the ATP-binding pocket of kinase is located deep inside of the cleft between the N- and C-terminal lobes.[16] The 'hinge' is a single string amino acid segment connecting these two lobes. The ATP adenine ring binds to the hinge string through two hydrogen bonds: one with the NH and the other with the carbonyl group in the amide backbone of the hinge. Most of the marketed kinase inhibitors mimic this interaction and form one to three hydrogen bonds to the hinge. In this study, we introduced

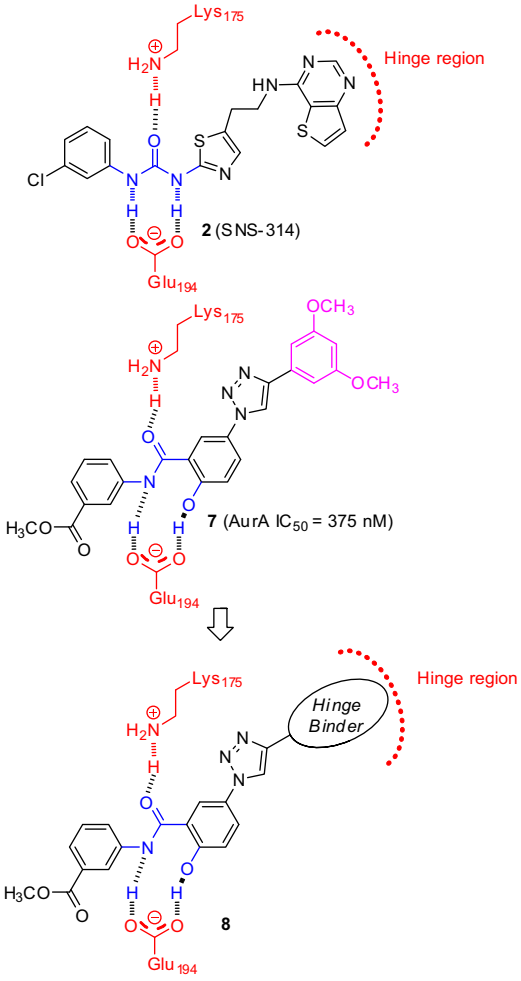

Figure 3. Design of 1,2,3-triazolylsalicylamide derivatives.

functional groups being able to form hydrogen bonds with the hinge region to the 1,2,3-triazole moiety. The functional groups include nitrophenyl, quinoxalin-6-yl, 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl, benzo[*d*][1,3]dioxol-5-yl, aminophenyl, and morphorinyl group to form one hydrogen bonding as well as ((5-methylisoxazol-3-yl)amino)methyl, ((6-methylpyridin-2-yl)amino)methyl, (pyrimidin-2-ylamino)methyl, and (thieno[3,2-*d*]pyrimidin-4-ylamino)methyl groups to make two or more hydrogen bonds. In addition, the length between the 1,2,3-triazole and the hydrogen-bonding site was also varied to get an insight of the distance between the 1,2,3-triazole and the hinge.

2.2. Synthesis

For the installation of hinge binders on the inhibitors, click chemistry was used because it offers a number of attractive benefits for the development of kinase inhibitors:[17] (i) the resulting 1,2,3-triazole scaffold is a mimic of the purine of ATP and a bioisostere of flat heteroaromatic rings such as imidazole, pyrazole, and oxazole observed in many kinase inhibitor drugs; (ii) the structure of the substituent can be easily varied by using readily available alkynes. Hence, we envisioned that 1,2,3-triazolylsalicylamide derivatives bearing hinge-binding functionalities could be synthesized via the Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) of azidosalicylamide and various alkynes with hydrogen-bonding donor/acceptor. Twenty-four alkyne building blocks **9a**–**x** bearing hydrogen-bonding donor/acceptor were

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