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Click approach to the discovery of 1,2,3-triazolylsalicylamides as potent Aurora kinase inhibitors

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ABSTRACT

A series of 1,2,3-triazolylsalicylamide derivatives has been developed from the antiproliferative agent **7** and was evaluated for their Aurora kinase inhibitory activity. The novel 1,2,3-triazolylsalicylamide scaffold could be readily assembled by Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition, allowing rapid access to the structurally diverse analogues. The synthesized 1,2,3-triazolylsalicylamide derivatives revealed a significant Aurora kinase inhibitory activity. In particular, **8g** inhibited Aurora A with IC_{50} values of 0.37 μM. The critical role of phenolic –OH in the binding was confirmed by a molecular modeling study.

1. Introduction

Aurora kinases are members of serine/threonine kinases regulating cell division.[1] Three human isoforms of Aurora kinase (Aurora A, B and C)[2] have distinct functions and different subcellular localizations during cell mitosis. Aurora A localizes to the centrosome and is involved in centrosome maturation and dipolar spindle formation,[3] while Aurora B localizes to the centromeres, the central spindle and the spindle midbody[4] and is involved in centrosome separation, chromosome segregation and cytokinesis. It is a chromosome passenger protein kinase and regulates the phosphorylation of histone H3 at serine 10.[5] Aurora C localizes to the spindle poles late in mitosis and is also considered as a chromosome passenger complementing the Aurora B function in mitotic cells.[6]

An overexpression of Aurora A and Aurora B causes an overphosphorylation of normal cell cycle targets and an aberrant phosphorylation of cytoplasmic targets, leading to chromosomal instability, oncogenic transformation, tumor progression and the development of chemoresistance.[7] Indeed, an overexpression of Aurora kinases is frequently observed in various cancer cells such as in colon, pancreas, breast, lung, thyroid cancers and in leukemia.[8] A number of notable recent researches have validated Aurora kinases as an attractive anti-cancer drug target. The inhibition of Aurora A triggers an abnormal formation of spindles and immature centrosomes leading to a monopolar spindle formation and accumulation in mitosis, and the inhibition of Aurora B induces mitotic exit resulting in polyploid cell formation.[9]

Since **1** (VX-680) entered human clinical trials as the first Aurora kinase inhibitor,[10] many Aurora-selective small-molecule inhibitors have been developed and are currently undergoing preclinical and clinical assessments. The selected examples include **2** (SNS-314),[11] **3** (MLN8237),[12] **4** (MK-5108),[13] **5** (AZD1152)[14] and **6** (GSK1070916)[15] (Fig. 1). Based on the Aurora subfamily selectivity, **1** (VX-680) and **2** (SNS-314) are classified as pan-Aurora inhibitors; **3** (MLN-8237) and **4** (MK-5108) are Aurora A specific inhibitors; **5** (AZD-1152) and **6** (GSK-1070916) are Aurora B specific inhibitors. Despite intensive effort to date, no Aurora-selective drug has been approved by the Food and Drug Administration (FDA) yet. As part of our ongoing program towards the development of anti-cancer kinase inhibitors, we have developed 1,2,3-triazolylsalicylamide inhibitors showing Aurora A kinase selectivity. Herein, we report the design, synthesis and biological evaluation of 1,2,3-triazolylsalicylamide inhibitors.

2. Results and discussion

2.1. Design

In our previous report, we have identified antiproliferative agent **7** through a rapid synthesis of natural product lavendustin-mimetic small molecules using the click fragment assembly.[16]

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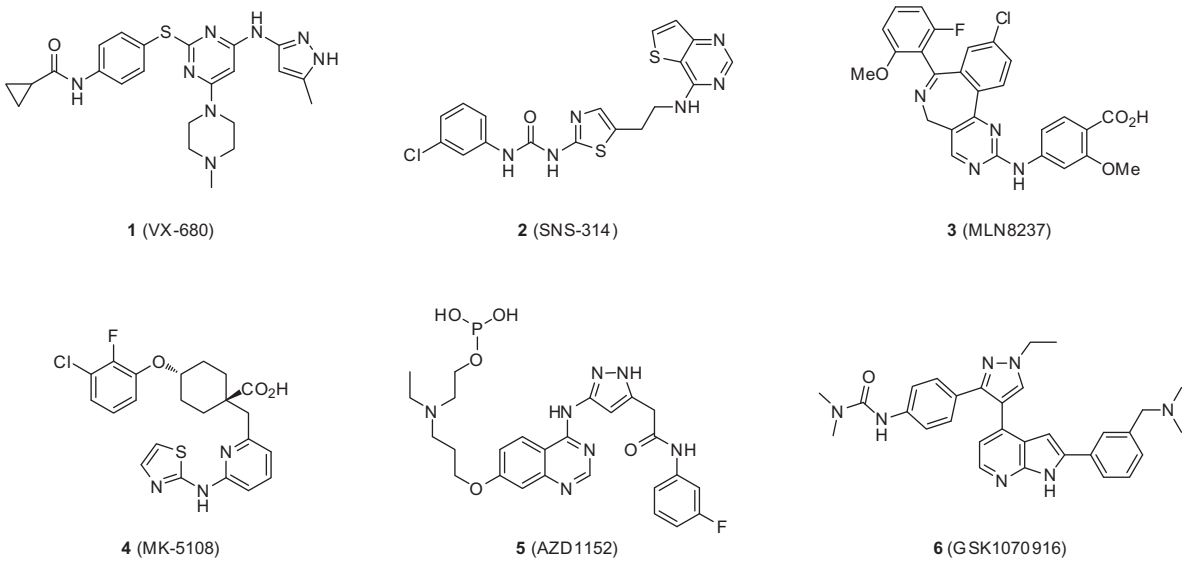

Figure 1. Aurora kinase inhibitors.

The identified 1,2,3-triazolylsalicylamide **7** inhibited both, CCRF-CEM and HCT116 cancer cell lines with GI_{50} values of 6.41 μM and 4.37 μM, respectively. However, compound **7** showed no EGFR inhibitory activity when it was subjected to the in vitro kinase assay against EGFR kinase. This was an unexpected result because natural product lavendustin has been known to inhibit EGFR kinase.[17] In order to get an insight of the kinase inhibitory profile of compound **7**, we tested it at a single dose concentration of 10 μM over a panel of 40 kinases at Reaction Biology Corporation.[18] As shown in Fig. 2, compound **7** moderately inhibited kinase activities of mutant EGFR (L858R), GSK-3β and PIM1 at the test concentration. Particularly, it exhibited a very good selectivity for Aurora A kinase among 40 kinases with an inhibition percentage of 74.5%. Accordingly, we decided to develop novel 1,2,3-triazolylsalicylamide scaffold inhibitors targeting Aurora kinases.

1,2,3-Triazole is a metabolically stable and versatile connecting unit. Although 1,2,3-triazole does not occur in nature, a number of synthetic 1,2,3-triazole compounds show various biological activities such as anticancer, antifungal, antibacterial, anti-HIV and antituberculosis activities.[19] 1,2,3-Triazole acts as a hydrogen bonding acceptor, thereby improves water solubility and facilitates binding to biological targets.[20] Especially, 1,2,3-triazole scaffold offers several advantages in the development of kinase inhibitors: (i) 1,2,3-triazole can be a mimic of the purine of ATP binding to the active site in protein kinases; (ii) 1,2,3-triazole can be a bioisostere of flat heteroaromatic rings such as imidazole, pyrazole and purine,

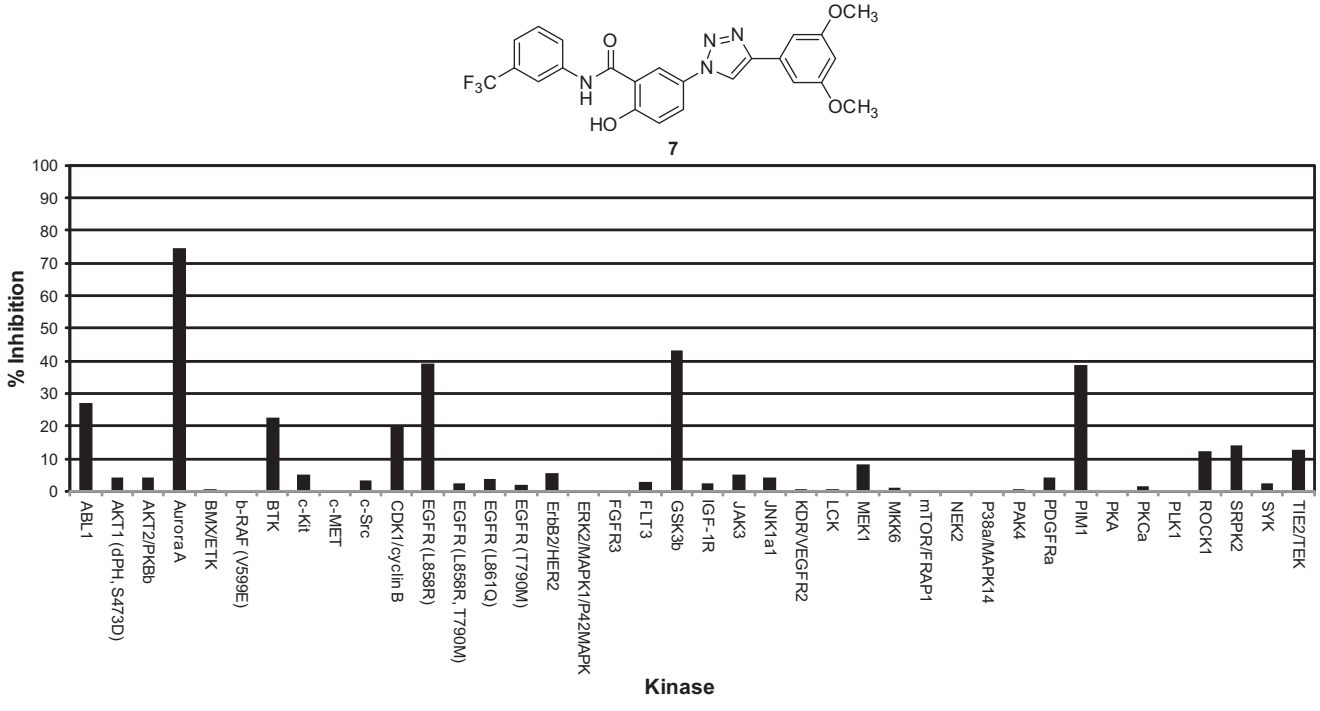

Figure 2. % Inhibition of compound **7** at 10 μM concentration over 40 kinases.