CARNA BIOSCIENCES

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Carna Biosciences, Inc.

Publication in Journal of Medicinal Chemistry Describing the Discovery of CDC7 Inhibitor AS-0141

Carna Biosciences, a clinical-stage biopharmaceutical company focusing on the discovery and development of innovative therapies to treat serious unmet medical needs, announces that the research paper on the discovery of AS-0141, a potent, selective, and orally bioavailable small molecule inhibitor of CDC7 kinase, has been published in Journal of Medicinal Chemistry. Carna is conducting a clinical study of AS-0141 in patients with unresectable, advanced, recurrent, or metastatic solid tumors in Japan. The publication in the Drug Annotations Series section of Journal of Medicinal Chemistry describes Carna's strategy and scientific findings to identify AS-0141.

Abstract of the paper

Cell division cycle 7 (CDC7), an evolutionally conserved serine/threonine kinase, plays crucial roles in regulation of DNA replication. It has been reported that the expression level of CDC7 is frequently elevated in various cancer cell lines and human tumor tissues. In addition, CDC7 overexpression has been reported to be associated with poor prognosis in various types of cancers. Thus, CDC7 has been recognized as a potential target for therapeutic intervention in cancer. CDC7 has proven to be difficult as a pharmacological target, probably due to its unique structural feature as well as to its low Km for ATP that permits efficient competition with ATP in cellular environment. In a previous report, we implemented the compound screening in the presence of 100 μM ATP which corresponds to 36-times higher than the Km value, expecting to find compounds that are insensitive or resistant to high ATP concentration. In the subsequent optimization study, we have succeeded in identifying a series of furanone-based CDC7 kinase inhibitors represented by compound **1** (Figure 1), which potently inhibited CDC7 with good selectivity. Compound **1** showed extremely potent inhibitory activity for CDC7 even in the presence of 1 mM ATP, which is close to physiological environment. Interestingly, this series of compounds showed a unique time dependent inhibition. Namely, compound **1** binds to CDC7 in a reversible fashion but has a slow off-rate after preincubation with the enzyme.

In this paper, we describe the optimization study of compound **1** to improve its ADME/PK property. Starting from **1**, we discovered compound **24** as a potent and selective CDC7 kinase inhibitor with good ADME and PK properties suitable for clinical development (Figure 1). As seen in the previous study using compound **1**, compound **24** exhibited a unique time-dependent inhibition and slow-off rate after preincubation with CDC7 (Figure 2). This preincubation effect was observed specific to CDC7 kinase, and IC50 values for other kinases were not affected by preincubation. These results strongly suggest that compound **24** would induce the conformational change of CDC7 to bind more tightly. We examined the antiproliferative activity of compound **24** against a panel of 44 cancer cell lines of various cancer types and found that compound **24** potently inhibited growth in a wide range of tumor cell lines. SW620, colorectal cancer cell line, was found to be the most sensitive cell line for compound **24** treatment. Compound **24** exhibited robust antitumor activity in the SW620 xenograft mouse model and was selected as a clinical candidate compound. Compound **24** (AS-0141) is currently in phase 1 clinical trials for the treatment of solid cancers.

Figure 1. Optimization of Lead compound **1** led to the discovery of AS-0141

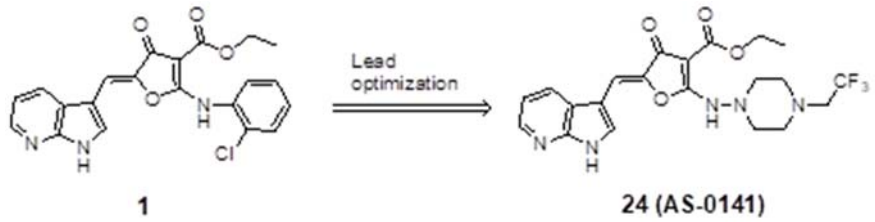
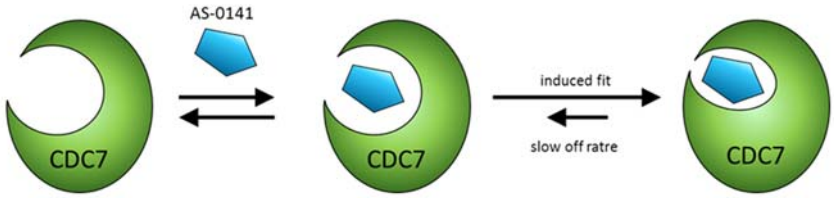


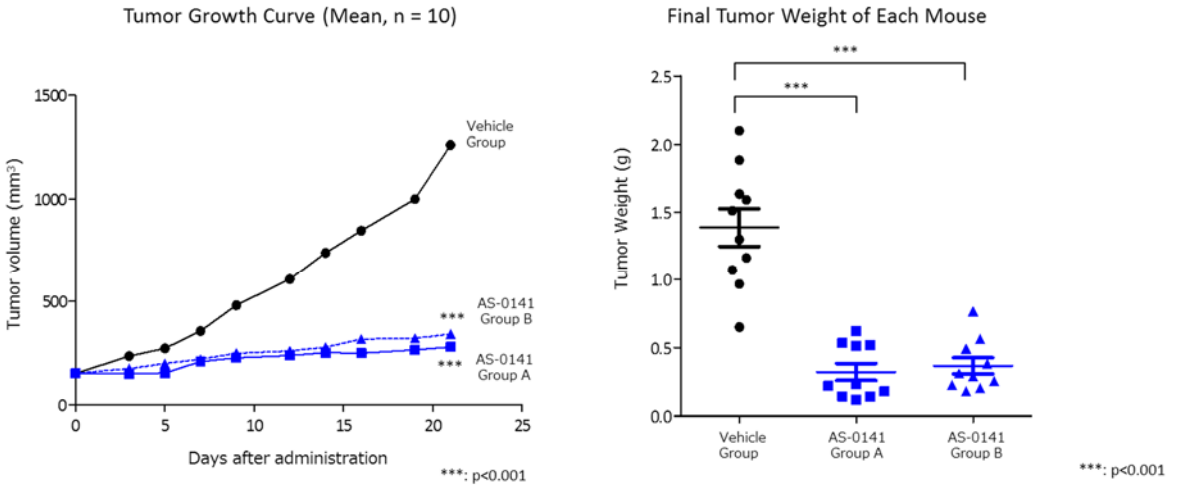
Figure 2. Unique time-dependent behavior of AS-0141



Inhibitory potency (IC_{50}) for CDC7 in the presence of 1 mM ATP

Without Preincubation	With Preincubation
503 nM	2.4 nM

Figure 3. In vivo antitumor efficacy of AS-0141 in the SW620 xenograft mouse model



AS-0141 group A: 60 mg/kg TID, 4d ON/2d OFF
AS-0141 group B: 120 mg/kg QD

References

(1) Irie, T.; Asami, T.; Sawa, A.; Uno, Y.; Hanada, M.; Taniyama, C.; Funakoshi, Y.; Masai, H.; Sawa, M. Discovery of Novel Furanone Derivatives as Potent Cdc7 Kinase Inhibitors. *Eur. J. Med. Chem.* **2017**, *130*, 406–418

Publication

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About AS-0141

CDC7 (cell division cycle 7) is a serine-threonine kinase that plays a critical role in DNA synthesis and is required for the activation of DNA replication origins throughout the S phase of the cell cycle. Inhibition of CDC7 in cancer causes lethal S phase or M phase progression, whereas normal cells survive, most likely through induction of cell cycle arrest at the DNA replication checkpoint. It has been reported in the literature that CDC7 is overexpressed in many types of cancers, therefore CDC7 is an attractive target for cancer drug development. Carna has successfully identified a selective and potent CDC7 inhibitor, AS-0141, with a unique mechanistic slow off-rate.

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