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Plk2 選択的阻害剤の合成および構造活性相関

清水 謙志郎

細胞周期、特に細胞分裂期において重要な役割を示すキネシンはがんを選択的に死滅させる分子標的として注目されている。Polo like kinase1 (PLK1) はその中の一つであり、多くのグループから PLK1 阻害剤の報告がされている。しかし、同じファミリーメンバーである PLK2 阻害剤の報告はなされていない。今回、筆者らは以前に合成した cyclin-dependent kinase (CDK4)阻害剤の骨格を元に PLK2 を特異的に阻害する化合物を見出し、さらにその構造活性相関および様々ながん細胞に対する試験を行った論文が発表されたため紹介する。

紹介論文

Discovery of 2-(1H-indol-5-ylamino)-6-(2,4-difluorophenylsulfonyl)-8-methylpyrido[2,3-d]-pyrimidin-7(8H)-one (7ao) as a potent selective inhibitor of Polo like kinase 2 (PLK2)
M.V. Ramana Reddy *et al*. *Bioorganic & Medicinal Chemistry* **24** (2016) 521-544.

Abstract

Several families of protein kinases have been shown to play a critical role in the regulation of cell cycle progression, particularly progression through mitosis. These kinase families include the Aurora kinases, the Mps1 gene product and the Polo Like family of protein kinases (PLKs). The PLK family consists of five members and of these, the role of PLK1 in human cancer is well documented. PLK2 (SNK), which is highly homologous to PLK1, has been shown to play a critical role in centriole duplication and is also believed to play a regulatory role in the survival pathway by physically stabilizing the TSC1/2 complex in tumor cells under hypoxic conditions. As a part of our research program, we have developed a library of novel ATP mimetic chemotypes that are cytotoxic against a panel of cancer cell lines. We show that one of these chemotypes, the 6-arylsulfonyl pyridopyrimidinones, induces apoptosis of human tumor cell lines in nanomolar concentrations. The most potent of these compounds, **7ao**, was found to be a highly specific inhibitor of PLK2 when profiled against a panel of 288 wild type, 55 mutant and 12 lipid kinases. Here, we describe the synthesis, structure activity relationship, in vitro kinase specificity and biological activity of the lead compound, **7ao**.

参考文献

M.V. Ramana Reddy *et al*. *Journal* of *Medicinal Chemistry* **2014**, *57* (3), 578-699