IL-14

Discovery and Development of Novel VEGFR3 Inhibitors as the Targeted Cancer Therapies

Li-Hsun Chen (陳立勳)[1], Chih-Hau Chen (陳志豪)[1], Wei-Jiunn Lee (李維駿)[2], Min-Liang Kuo (郭明良)[2*], Chung-Ming Sun (孫仲銘)[1*]

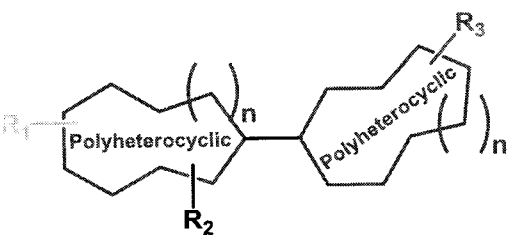
[1] *Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300, Taiwan*

[2] *Graduate Institute of Toxicology, National Taiwan University, Taipei100, Taiwan*

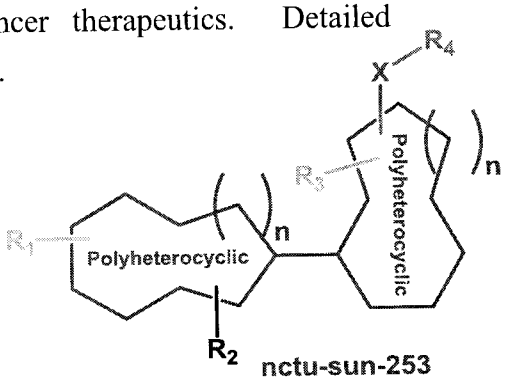
Recently, some report describing small molecule protein kinase inhibitors are widely employed as biological reagents and as leads in the design of drugs for the treatment of various tumors. We herein disclose a novel chemical series of Bis-heterobicyclic compound nctu-194 as inhibitor of VEGFR-2 and VEGFR-3 kinase receptors, both of which are implicated in angiogenesis of tumor growth.

We have modified the target molecule to improve the aqueous solubility, an important characteristic for an oral drug. Consequently, continuous research was focused on the optimization of #194. Besides, target set of >1000 heterobicyclic compound derivatives are synthesized to provide new lead compounds for biological screening. The result from the case study reveals that compound #253 superior to compound #194 in overall performance by the inhibition of VEGFR-3. In animal studies, #253 exhibited unprecedented inhibition for the tumor cell growth and metastasis.

The integration of microwave irradiation and soluble polymer support strategy provides an efficient and convenient approach for high throughput and diversity-oriented synthesis of drug-like molecules. Preliminary screening results have shown that some of these compounds exhibited moderate to good inhibition against vascular endothelial growth factor receptor 3 which is related to invasion and migration of cancer cells. This may provide a hint to design more potent VEGFR-3 inhibitors as the potential cancer therapeutics. Detailed biological data will be reported in due course.



nctu-sun-194



nctu-sun-253