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Synthesis of Chlorosunitinib Analogs as Novel Antiangiogenic Anticancer Agents

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Current cancer therapeutics is surgery, radiotherapy, chemotherapy and target therapy. Today cancer is a more treatable disease than at any time in the past. But cancer treatment is still far from ideal due to many cancers not be cured. Anti-angiogenesis, one of targeted cancer therapies, possessing highly specificity and selectivity for cancer cells and lower toxicity for normal cells, is a novel development of milestone in cancer therapy. Drugs with anti-angiogenic properties such as sunitinib (Sutent) and sorafenib (Nexavar) have been shown to be useful against cancers. Sunitinib is one of the small-molecule drugs for the treatment of cancer with GIST and RCC. It's a multiple tyrosine kinase inhibitor, which competes with the ATP-binding sites within the tyrosine kinase receptors to prevent angiogenesis and tumor formation. For the reason that lots of anti-cancer drugs have resistance to anti-angiogenic therapy, the finding of new anti-angiogenic agents with higher therapeutic efficacy, lower toxicity and minor drug resistance is a hot task to be resolved. In search of better drugs, the potent anti-angiogenic anticancer agents are in active progress in our laboratories.

Modification of pyrrole ring of sunitinib which inhibit PDGF-, Kit-, and VEGF-mediated signaling is conducted. Current preliminary screening of experiments on inhibition of tube formation were conducted in triplicate in 24-multiwell dishes, cultured with HUVECs co-cultured with human fibroblasts, using angiogenesis kit (Kurabo, Okayama, Japan), according to the manufacturer's instruction. The area and tube length were measured quantitatively with the Kurabo angiogenesis image analyzer (Kurabo, Okayama, Japan) in five different fields per well, and analyzed statistically. Further structural modification and optimization of target compounds and study of structure-activity relationships are in progress.