氏　　名	王　寧
授与した学位	博　士
専攻分野の名称	工　学
学位授与番号	博甲第４９７０号
学位授与の日付	平成２６年　３月２５日
学位授与の要件	自然科学研究科　機能分子化学専攻 （学位規則第５条第１項該当）
学位論文の題目	Studies on Design, Synthesis, and Biological Evaluation of Indoloquinolines of Antimalarial and Anticancer Activities （抗マラリアおよび抗ガン活性を有するインドロキノリン分子の設計, 合成および活性評価に関する研究）
論文審査委員	准教授　井口　　勉　　教授　菅　　誠治　　教授　大槻　高史

学位論文内容の要旨

Malaria is still one of the most frightening parasitic diseases in the world. Exploring new drugs to meet the needs against drug-resistant diseases is an everlasting topic in the theraptic practice. Plants are still an important resource for the discovery of new drugs. The author thus paid her attention to modify the indoloquinoline scaffolds and evaluate biological activities of their derivatives as antimalarial and anticancer agents.

1) The author described the synthesis of 6-methyl-5*H*-indolo[2,3-*b*]quinoline and evaluated their antimalarial activity against *P.falciparum* (NF54), cytotoxicity toward L6 cells and *β*-haematin inhibition activity. Introduction of Me group at N6 and modification to the urea and thiourea derivatives were not favorable for antimalarial activity, but the cytotoxicity was improved against normal cells.
2) Author developed a feasible method to introduce the methyl group to at N11 of indolo[3,2-*c*]quinoline, affording the C6-alkylamino analogues. At the same time, the author compared the amination reactivity at the C6 of 6-chloro-11-methyl-indolo[3,2-c]quinoline and 6-chloro-11H-indolo[3,2-c]quinolines.
3) A series of 11*H*- and 11Me-indolo[3,2-*c*]quinoline derivatives were synthesized, modified them with various alkylamino groups at C6 along with various substituents at C2. The anticancer activities of them *in vitro* were tested against MV4-11 (human leukemia), A549 (non-small cell lung cancer) and HCT116 (colon cancer) and BALB/3T3 (normal murine fibroblasts). All the *N*11 methylated compounds significantly increased the anticancer activity, and also exhibited a selective activity.
4) All the indolo[3,2-*c*]quinoline derivatives showed potent antimalarial activity against the CQS strain (NF54) and the CQR strain (K1) *in vitro*. The chlorine atom at C2 and urea derivatives increased activity against the CQS strain (NF54). The methyl branched pendant decreased cytotoxicity and increased antimalarial activity. The linear correlation analysis revealed that there were three contributing factors, namely water solubility, hydrophilic surface area, and *β*-haematin inhibition that influence biological activity of this series against CQS (NF54) parasites.
5) The artemisinin-indoloquinoline hybrids were synthesized and screened for antimalarial activity against two different strains (CQS: NF54 and CQR: K1) and the cytotoxicity activity against normal L6 cells were evaluated. All hybrids showed significant antimalarial activity and *β*-haematin inhibition activity.

論文審査結果の要旨

Malaria is still one of the most frightening parasitic diseases in the world. Exploring new drugs to meet the needs against drug-resistant diseases is an everlasting topic in the theraptic practice. Plants are still an important resource for the discovery of new drugs. The author thus paid her attention to modify the indoloquinoline scaffolds and evaluate biological activities of their derivatives as antimalarial and anticancer agents.

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From these results, it can be seen that the research indicated by this paper is worth as a doctoral dissertation (Dr., engineering).