氏　　名	王　力
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４６３９号
学位授与の日付	平成２４年　９月２７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 the Mechanism-Inspired Design, Synthesis, and Biological Evaluation of Quinoline-Indole-Assembled Molecules for Drug Candidates （医薬候補の探索を目的とするキノリン-インドール系分子の作用機構に基づく分子設計，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　尾坂　明義　　教授　妹尾　昌治

学位論文内容の要旨

The quinoline and indole ring systems, which occupies key elements in many bioactive alkaloids, have been utilized to avoid mankind from diseases like malaria and cancer. The importances of heterocycle with quinoline and indole motifs have been witnessed in the development of many new biological active pharmaceuticals. Accordingly, the author has focused her attention in designing new protocols in synthesis of the new bioactive molecules with quinoline and indole units and evaluating them as anticancer and anti-Alzheimer's disease agents. The results of these work can be summarized as below:

1) An efficient protocol for obtaining the 5-methyl-11-chloroneocryptolepines and their 6-methyl congeners from indole-3-carboxylate, which were useful as scaffolds for the preparation of anti-malaria and anticancer agents, was developed. Both the overall yields and purities were improved by the method starting with *N*-methyl aniline, and it allowed the neocryptolepine cores bearing halogens, alkyl, trifluoromethyl, methoxy, N-acetamido, and alkoxycarbonyl groups on the C2, C3 or C4 positon.
2) The author had described the synthesis of a series of 11-amino-substituted 5*H*- and 6*H*-indolo[2,3-*b*]quinolines, whose antiproliferative activities were evaluated using the MV4-11 (human leukemia), A549 (human lung cancer), HCT116 (human colon cancer), and normal mice fibroblast (BALB/3T3) cell lines. The agents' cytotoxic selectivity between normal cell lines and cancer cell lines were described, and the cytotoxicity of agent had increased 67 times after introduction of appropriate amine, comparing with the C11-unmodified neocryptolepine.
3) The author had described the design and synthesis of the donepezil+8-hydroxiquinoleine+propargylamine (DHP) hybrids compounds, which were subjected to pharmacological evaluation as multipotent ChE and MAO inhibitors for the treatment of Alzheimer's disease. These compounds were readily prepared in good yields, in short synthetic sequences. The biological results showed that these DHPs were moderate, non-selective ChE, and MAO inhibitors. It was the first example to analyse α-aminoalkanenitriles as MAO inhibitors.
4) New tacrine-linked neocryptolepine analogues were synthesized for biological evaluation as AChE and BChE inhibitors. The alkyl chain between tacrine and neocrytplepine were varied.

論文審査結果の要旨

Nowadays cancer is a leading cause of death worldwide and the second only to heart disease as a cause of death. On the other hand, it is estimated that there are currently about 18 million people worldwide suffering from the Alzheimer's disease, which is a neurodegeneration disease. Stimulated by potency of indole-quinolines available from many natural products for the treatment of various diseases, the author has focused her attention on designing new strategies in synthesizing and evaluating the new bioactive molecules with quinoline-indole substructure as anticancer and anti-Alzheimer's disease agents.

1) An efficient protocol for obtaining the 5-methyl-11-chloroneocryptolepines and their 6-methyl congeners from indole-3-carboxylate, which were useful as scaffolds for the preparation of anti-malaria and anticancer agents, was developed. Both the overall yields and purities were improved by the method starting with N-methyl anilines, and it furnished the neocryptolepine cores with substitution of halogens, alkyl, trifluoromethyl, methoxy, N-acetamido, and alkoxycarbonyl groups on the C2, C3 or C4 positon.
2) The author described the synthesis of a series of 11-amino-substituted 5H- and 6H-indolo[2,3-b]quinolines, whose antiproliferative activities were evaluated. The agents' cytotoxic selectivity between normal cell lines and cancer cell lines were described, and the cytotoxicity of agent had increased 67 times by virture of introduction of appropriate amine, comparing with the C11-unmodified neocryptolepine.
3) The author described the design and synthesis of hybrids composed of 4-(*N*-benzylpiperidine)alkyl+(8-hydroxyquinolinyl)-5-methyl+propargylamino groups, which were subjected to pharmacological evaluation as multipotent ChE and MAO inhibitors for the treatment of Alzheimer's disease. These compounds were readily prepared in good yields, in short synthetic sequences. The biological results showed that these agents were moderate, non-selective ChE, and MAO inhibitors.
4) New tacrine-linked neocryptolepine analogues were synthesized for biological evaluation as AChE and BChE inhibitors. The alkyl chain between tacrine and neocrytplepine were varied.

Based on the aforementioned results we concluded that the thesis contains new, scientifically valuable results and represents an original contribution to the field. Therefore, we strongly recommend for the award of PhD degree in the present form.