# 論文 / 著書情報
# Article / Book Information

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| 著者(和文) | UTOMORohmad Yudi |
| Author(English) | Rohmad.Yudi Utomo |
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# 論 文 要 旨

THESIS SUMMARY

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| 系・コース：<br>Department of, Graduate major in | Department of Life Science and Technology, Human Centered Science and Biomedical Engineering　系 コース | 申請学位（専攻分野）：<br>Academic Degree Requested | 博士<br>Doctor of (Science) |

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| 学生氏名：<br>Student's Name | Rohmad Yudi Utomo | 指導教員（主）：<br>Academic Supervisor(main) | 中村 浩之 |
| | | 指導教員（副）：<br>Academic Supervisor(sub) | 岡田 智 |

要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）


The title of this thesis is "SAR Matrix-Assisted Design of Curcumin Derivatives as Amyloid β Inhibitors and Their Application to MRI Contrast Agents for Alzheimer's Disease". This thesis contains five chapters written in English. The contents of this thesis cover the utilization of the Structure-Activity Relationship Matrix (SARM) for developing amyloid β (Aβ) inhibitors and their further application in designing MRI contrast agents targeting Aβ.

Chapter 1 (Introduction) discusses the importance of Aβ as the target of drug and biomarker of Alzheimer's disease (AD). This chapter also describes the progress of drug candidates targeting Aβ by inhibiting the aggregation process or inducing its disaggregation. In addition, this chapter introduces the recent developments of MRI contrast agents targeting Aβ, which are still in preclinical study. Among the reported compounds, curcumin shows promising results in preclinical studies as the drug candidate targeting Aβ but has limitations in the clinical study mainly due to the requirement of high dose and side effects. The preclinical study about the application of curcumin structures conjugated with gadolinium (Gd) complex as MRI contrast agents targeting Aβ is also reported, informing possible further improvement. Furthermore, this chapter also discusses the possibility of SARM for generating new compounds, especially curcumin derivatives with improved biological activity.

Chapter 2 (Development of Curcumin-based Amyloid β Aggregation Inhibitors for Alzheimer's Disease using the SAR Matrix Approach) introduces the successful application of SARM on designing curcumin derivatives and avoiding the possible compounds with Pan-assay interference compounds (PAINS) profiles. Based on curcumin derivatives-activity cliff and molecular grid map (MGM) analysis, ten curcumin derivatives were generated. After synthesizing all compounds by microwave irradiation followed by biological screening using thioflavin t (ThT) assay, compound **B** was identified as the most potent inhibitor with 100-times stronger than curcumin ($IC_{50}$ = 0.007 ± 0.001 μM). Based on transmission electron

microscopy (TEM) image, inhibition of Aβ aggregation by compound **B** caused the increase of Aβ oligomers in a concentration-dependent manner so that it attenuated the Aβ-induced cytotoxicity on neuroblastoma (N2a) cells. In chapter 2 also introduces compound **K**, in which the tert-butyl ester replaced the methyl ester of compound **B**. Compound **K** also showed considerable inhibitory activity and attenuated the cytotoxicity of Aβ, suggesting the possibility of further optimization by modifying the ester group of compound **B**.

Chapter 3 (Development of an MRI Contrast Agent for Both Detection and Inhibition of the Amyloid β Fibrillation Process) demonstrates the further application of a curcumin derivative generated from SARM, compound **B** as the ligand for Gd-based MRI contrast agent (**Gd-DO3A-Comp.B**). As the comparison, **Gd-DO3A-Cur** and **Gd-DO3A-Chal** were used as the reported Gd compounds detecting Aβ. Based on ThT assay, Congo Red (CR) assay, and TEM image **Gd-DO3A-Comp.B** performed stronger inhibitory activity compared to **Gd-DO3A-Cur** and **Gd-DO3A-Chal**. Cytotoxicity study on N2a cells demonstrated **Gd-DO3A-Comp.B** showed no significant cytotoxicity at a concentration of 200 μM. **Gd-DO3A-Comp.B** also sensitively detected Aβ fibril based on NMR longitudinal relaxation time ($T_1$) measurement, and the inhibitory activity could be estimated by $T_1$ change depending on the growth stage of Aβ fibril formation. This study also revealed that **Gd-DO3A-Comp.B** detected Aβ fibril in $T_1$-weighted image MRI. Such unique modalities would be useful for diagnostics and the direct evaluation of the therapeutic efficacy *in vivo*.

Based on the finding of **Gd-DO3A-Comp.B**, which could bind to Aβ fibril, in chapter 4 (Detoxification by Curcumin Derivative via Dissociation of Amyloid β Fibrils and its Verification in Drosophila Alzheimer's Model), compound **B** and its derivative, compound **N**, which the methyl ester was replaced by benzylamide, were proposed as the inducer of Aβ fibril disaggregation. The results of the ThT assay, CR assay, and TEM image demonstrated that both compounds strongly inhibited fibril formation and induced Aβ fibril disaggregation at a low concentration. The Aβ fibril disaggregation was also demonstrated by both compounds in N2a cells allowing the alleviation of Aβ fibril-induced cytotoxicity. Intravenous injection in healthy mice showed the possibility of compound **N** accumulating in the brain. The oral intake of compounds **B** and **N** contained in the food rescued the locomotor dysfunction of Aβ-expressed Drosophila as the AD-model flies. These results suggested that compounds **B** and **N** might be promising for clinical applications, considering the problem of Blood-Brain Barrier (BBB) permeability common to AD therapeutic candidates.

Chapter 5 (conclusion) summarizes the overall thesis about the development of curcumin derivatives that inhibit Aβ aggregation using SARM and enable Gd-based MRI contrast agent targeting Aβ. This thesis also proposes a new approach to drug discovery for Alzheimer's disease, making a significant contribution to science.