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学位論文内容要旨

学位論文題目　Synthesis and Molecular Docking of Bioactive Natural Products Containing (6*H*-Dibenzo[*b,d*]pyran-6-one) Framework

6*H*-Dibenzo[*b,d*]Pyran-6-one 骨格を有する生物活性天然物の合成と分子ドッキングに関する研究

先端ナノ・バイオ科学専攻

（ふりがな）　イシティアク ジラーニ
氏名　　Ishtiaq Jeelani

Abstract

A variety of natural products, which possess the 6*H*-dibenzo[*b,d*]pyran-6-one core have attracted our interest because of their unique biological activities. Among them, Hyalodendriol C was isolated from endophytic fungus associated with the hybrid '*Neva of Populus deltoides*', *P. nigra L* along with hyalodendriol A and B. A variety of biological activities have been stated for hyalodendriol A-C, but only hyalodendriol C has shown significant antibacterial, larvicidal, and anti-fungal properties as mentioned previously in the literature. The interesting structural feature of this compound is the aromatic ring bearing chlorine atom on it. Natural products comprising a halogen on an olefinic, aromatic, heteroaromatic moieties as a substituent have gained considerable interest because of their multiple biological activities. Conversely, hyalodendriol A and B which do not possess chloro substituent, exhibited weaker activities than hyalodendriol C. Therefore, it was suspected that the presence of a chlorine atom was essential for the cytotoxicity of hyalodendriol C. In addition, urolithin is a metabolite of a class of compounds known as polyphenols which are found in various fruits, including pomegranates, nuts, and strawberries. In recent years, research on urolithins has mainly focused on the first metabolite consisting of Uro-A and Uro-B, but we are interested in the second metabolite of urolithins that can reach systemic tissues. Uro-A glucuronide (Uro-A glur) and Uro-B glucuronide (Uro-B glur) have already been chemically synthesized by Villapharma Research S. L. (Parque Tecnológico de Fuente Alamo, Murcia, Spain). On the other hand, the chemical synthesis of Urolithin C 3-glucuronide

(Uro-C 3-glur) has not been achieved, and the bioavailability of Uro-A glur and Uro-B glur is shown to be higher than that of Uro-C 3-glur. Therefore, we decided to synthesize Urolithin C 3-glucuronide, which needs to pursue beneficial health benefits.

Urolithin is a biologically active compound that has anti-inflammatory, antioxidant, and anticancer properties. Urolithins, which are hydroxylated dibenzo[b,d]pyran-6-one derivatives, contain urolithin A (uro-A), urolithin B (uro-B), urolithin C (uro-C) and urolithin D (uro-D) derivatives which are produced in vivo by the gastrointestinal microbiota of humans and different animals upon intaking ellagitannins (ETs), which are high molecular weight polyphenols and ellagic acids (EAs). There are many different phenolic antioxidants such as ETs and EAs in walnuts and pomegranates, which have been linked to potential preventive effects against chronic diseases like diabetes, cancer, cardiovascular diseases, and neurodegenerative diseases.

A palladium-mediated intramolecular aryl-aryl coupling reaction was applied to the total synthesis of the bioactive natural products, Hyalodendriol C, and Urolithin C 3-Glucuronide. Keeping in view, the indispensable biological values of these compounds, we took the advantage of our established strategy to chemically synthesize hyalodendriol C and Urolithin C 3-Glucuronide. The total synthesis of hyalodendriol C got accomplished in 10 steps beginning with the preparation of phenol derivative from the commercially available 5-methylbenzene-1,3-diol and synthesis of the corresponding benzoic acid derivative. On the other hand, the total synthesis of Urolithin C 3-Glucuronide has been accomplished in 11 steps starting from commercially available 3,4-dimethoxybenzaldehyde. Our group has reported several natural product syntheses using the Pd-mediated intramolecular biaryl coupling reaction with phenyl benzoate derivatives for forming the *6H*-dibenzo[*b,d*]pyran-6-one ring system. Utilizing this transformation, we achieved the efficient total syntheses of hyalodendriol C and urolithin C 3-glucuronide. Molecular docking of the synthesized compounds was also performed against CYP1B1 and BCL2 protein.

（様式第10号）　　（課程博士用）

博士学位論文審査結果の要旨

令和 3 年 7 月 29 日

富山大学大学院生命融合科学教育部長　殿

審査委員会

委員長　　豊岡　尚樹

本学大学院生命融合科学教育部における博士（理学又は工学）の学位論文審査取扱要領２８項第２号の規定により，博士学位論文審査結果要旨を下記のとおり報告します。

記

１．学位申請者：Ishtiaq Jeelani

２．論文題目：Synthesis and Molecular Docking of Bioactive Natural Products Containing (6*H*-Dibenzo[*b,d*]pyran-6-one) Framework

３．審査結果要旨：

申請者，Ishtiaq Jeelani 氏は(6*H*-Dibenzo[*b,d*]pyran-6-one)骨格を有する興味ある天然物の全合成ならびにその分子ドッキング研究を行った。その結果，Hyalodendriol C の初の全合成，Urolithin C 3-glucuronide の初の全合成，および Graphislactone G, Palmariol A, B の全合成を達成した。これら合成研究では，パラジウム触媒分子内ビアリールカップリングを駆使した斬新な合成戦略を用いており，この鍵反応が当該骨格構築法として極めて有力であることを示した。

また，合成した化合物を用いた分子ドッキング研究も展開し，乳がん治療・予防薬として期待される CYP1B1 に対する阻害剤としての構造最適化に一定の方向性を示した。これらの成果は，学術論文３篇としてすでに公表されている。よって，評価委員会は Ishtiaq Jeelani 氏の成果が博士学位論文として十分な内容を含むものと判断した。