様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

令和　６ 年　 ６ 月 １０ 日現在

機関番号：１４４０１
研究種目：若手研究
研究期間：2022～2023
課題番号：２２Ｋ１５２５２

研究課題名（和文）天然資源と金属ナノ粒子触媒を用いる非天然創薬リート化合物の創製

研究課題名（英文）Creation of New Lead Compounds using Natural Resources and Metal Nanoparticle Catalysts

研究代表者
ＳＩＲＩＭＡＮＧＫＡＬＡＫＩＴＴＩ　ＮＡＴＣＨＡＮＵＮ（Sirimangkalakitti, Natchanun）

大阪大学・大学院薬学研究科・特任助教

研究者番号：１０９０９１２０

交付決定額（研究期間全体）：（直接経費）　　3,600,000円

研究成果の概要（和文）：我々は、天然資源と反応性の高い金属ナノ粒子触媒を用いて、新しい生物学的活性化合物を創製・発見する方法論を開発した。私たちのアプローチでは、Pdなどのナノ粒子触媒を独自に用いて、C-H結合の活性化、C-C開裂、クロスカップリング反応を効率的に触媒し、天然物類似の新規化合物を一段階で生成することを容易にしている。私たちの研究は、海綿から抽出した天然物エキスを直接化学的に多様化することに成功し、新規化合物であるrac-6-OEt-シリンドラジンAの発見につながった。この発見は、より迅速で効率的な創薬・医薬品開発に対する私たちの手法の可能性を強調するものである。研究業績：査読付き論文2件、学会発表2件

研究成果の学術的意義や社会的意義
Our research advances drug discovery by using metal nanoparticle catalysts to create new biologically active compounds from natural product extracts. This innovative approach accelerates pharmaceutical development, offering potential treatments for various diseases.

研究成果の概要（英文）：We have developed a methodology for creating and discovering new biologically active compounds using natural resources and highly reactive metal nanoparticle catalysts. Our approach uniquely employs nanoparticle catalysts, such as Pd, to efficiently catalyze C-H bond activation, C-C cleavage, and cross-coupling reactions, facilitating the formation of new natural product-like compounds in one step. Our research successfully demonstrated the direct chemical diversification of natural product extracts from marine sponges, leading to the discovery of a new compound, rac-6-OEt-cylindradine A. These findings underscore the potential of our method for faster and more efficient drug discovery and development. We are further enhancing this methodology by developing highly reactive Rh nanoparticle catalysts. Research Achievements: two peer-reviewed publications and two conference presentations, one at an international conference

研究分野：Natural Product Drug Discovery and Development

キーワード：natural product extract　chemical diversification　metal catalyst　lead compound

１．研究開始当初の背景

Natural products (NPs) have played invaluable roles in drug discovery and development. However, over the past two decades, the de-emphasis on NP research has correlated with an overall reduction in the discovery of new lead compounds and drug approvals. To address this gap and create brand new biologically active compounds from NPs, we estrablished our methodology using diversity-oriented synthesis of NP extracts via metal nanoparticle catalysts. This approach allows for the direct access to a number of NP-like compounds in a one-step, promising faster and more efficient drug discovery and development.

２．研究の目的

The aim of this research is to develop a new methodology for creating and discovering new biologically active compounds using natural resources and highly reactive metal nanoparticle catalysts. Our synthesis approach is distinct from previous methods as it employs metal nanoparticle catalysts, such as Pd and Rh, which can efficiently catalyze C-H bond activation, C-C cleavage, and/or cross-coupling to form other scaffolds via C-C and/or C-heteroatom bond formation. This promising method which combines natural product chemistry and diversity-oriented synthesis will lead to the formation of novel natural product-like compounds that are not found in nature. Additionally, our new approach is crucial for retaining the usefulness of natural products and their derivatives as leads for drug development.

３．研究の方法

To create and discover new biologically active compounds from NPs, we collected largely unexplored natural sources, including marine sponges and fungi, and extracted them using appropriate organic solvents to yield crude extracts. The crude extracts were roughly fractionated using MPLC (Medium Pressure Liquid Chromatography) to obtain sub-fractions with varying polarity. These sub-fractions were then subjected to chemical conversion using highly reactive metal nanoparticle catalysts, with reactions varied by parameters such as heating method, solvent, temperature, and time. The resulting changes in chemical composition of the extracts after treatment were analyzed using various techniques, including LC-MS (Liquid Chromatography-Mass Spectrometry), HPLC (High Performance Liquid Chromatography), NMR (Nuclear Magnetic Resonance), and bioactivity assays such as antimicrobial and anticancer activities. The extracts showing significant changes were isolated and purified using column chromatography to yield pure NP-like compounds. The chemical structures of new/bioactive compounds were elucidated using spectroscopic techniques including NMR, MS, UV, and IR. Finally, the bioactivities of the newly obtained NP-like compound were studied and evaluated.

４．研究成果

Our research successfully demonstrated the direct chemical diversification of natural product extracts, leading to the discovery of novel compound, rac-6-OEt-cylindradine A, from the

marine sponge *Petrosia* (*Strongylophora*) sp. Additionally, we reported the presence of (-)-dibromophakellin and 4,5-dibromopyrrole-2-carboxylic acid for the first time in this genus. Studies on the possible reaction mechanisms and bioactivities were also conducted. The results indicate that direct chemical diversification of substances present in natural product extracts can be a speedy and useful strategy for the discovery of new compounds. Based on our successful study, we have applied this method to natural sources using Pd nanoparticle catalysts. We are further enhancing this methodology by developing highly reactive Rh nanoparticle catalysts, which hold promise for further expanding the scope and efficacy of chemical diversification. Our research achievements include two peer-reviewed publications and two conference presentations, one of which was at an international conference.

５．主な発表論文等

〔雑誌論文〕　計2件（うち査読付論文　2件／うち国際共著　0件／うちオープンアクセス　1件）

１．著者名 Sirimangkalakitti Natchanun、Harada Kazuo、Yamada Makito、Arai Masayoshi、Arisawa Mitsuhiro	４．巻 28
２．論文標題 A New Tetracyclic Bromopyrrole-Imidazole Derivative through Direct Chemical Diversification of Substances Present in Natural Product Extract from Marine Sponge Petrosia (Strongylophora) sp.	５．発行年 2022年
３．雑誌名 Molecules	６．最初と最後の頁 143～143
掲載論文のDOI（デジタルオブジェクト識別子） 10.3390/molecules28010143	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 －

１．著者名 Yamada Makito、Hirose Yu、Lin Bangzhong、Fumimoto Megumi、Nunomura Kazuto、Natchanun Sirimangkalakitti、Takahashi Naoyuki、Ohki Yuuta、Sako Makoto、Murai Kenichi、Harada Kazuo、Arai Masayoshi、Suzuki Sayo、Nakamura Tomonori、Haruta Junichi、Arisawa Mitsuhiro	４．巻 13
２．論文標題 Design, Synthesis, and Monoamine Oxidase B Selective Inhibitory Activity of N-Arylated Heliamine Analogues	５．発行年 2022年
３．雑誌名 ACS Medicinal Chemistry Letters	６．最初と最後の頁 1582～1590
掲載論文のDOI（デジタルオブジェクト識別子） 10.1021/acsmedchemlett.2c00228	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 －

〔学会発表〕　計2件（うち招待講演　0件／うち国際学会　1件）

１．発表者名 Natchanun Sirimangkalakitti
２．発表標題 A New Tetracyclic Bromopyrrole-Imidazole Derivative through Direct Chemical Diversification of Substances Present in Natural Product Extract from Marine Sponge Petrosia (Strongylophora) sp.
３．学会等名 The American Society of Pharmacognosy 2023 Annual Meeting Innovation Through Interaction（国際学会）
４．発表年 2023年

１．発表者名 Natchanun Sirimangkalakitti
２．発表標題 A New Tetracyclic Bromopyrrole-Imidazole Derivative through Direct Chemical Diversification of Substances Present in Natural Product Extract from Marine Sponge Petrosia (Strongylophora) sp.
３．学会等名 24th Symposium on the Development and Application of Naturally Occurring Drug Materials
４．発表年 2023年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関