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

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研究課題名（和文）A Combinatorial Approach Towards Multimetallic Artificial Receptors for Cancer-Related Biomarkers

研究課題名（英文）A Combinatorial Approach Towards Multimetallic Artificial Receptors for Cancer-Related Biomarkers

研究代表者
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交付決定額（研究期間全体）：（直接経費）　　2,200,000円

研究成果の概要（和文）：この研究により、標準的な鈴木カップリング条件によってボロン酸／エステルと結合できる新しいブロモビサリチルアルデヒド構成単位が調製されました。金属錯体への結合はまだ行われていないが、原理的には、生体分子-金属相互作用を利用した水中での生体分子の新しい金属レセプターにつながる可能性がある。サリチルアルデヒドユニットを用いて、将来的には動的共有結合化学によって受容体の第2配位圏を変化させ、その選択性をチューニングしようと考えています。サリチルアルデヒドユニットは、従来のアルデヒドユニットに比べて、水系媒体中での酸化に対する安定性が高いという利点があります。

研究成果の学術的意義や社会的意義
Artificial bioreceptors are important for the detection of diseases via recognition of disease-related biomarkers. Previous receptors required long and difficult synthetic protocols. The herein attempted strategy aims to give simple access to a receptor framework whose target can be tuned on demand.

研究成果の概要（英文）：The research led to the preparation of a new bromo-bissalicylaldehyde building block, which can be coupled to boronic acids/esters via standard Suzuki coupling conditions. Its attachment to metal complexes has not been performed yet, but could in principle lead to new metal receptors for biomolecules in water using biomolecule-metal interactions. Using the salicylaldehyde units, I plan to vary the second coordination sphere of the receptor in the future via dynamic covalent chemistry to tune its selectivity. The advantage of the salicylaldehyde units over conventional aldehyde units is their increased stability in aqueous media against oxidation.

研究分野：Supramolecular Chemistry

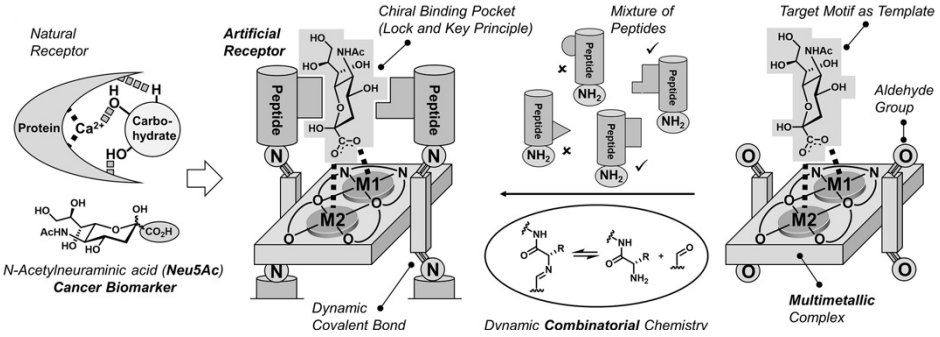
キーワード：Artificial Bioreceptor　Molecular building block　Metal Complex

１．研究開始当初の背景

Carbohydrate alterations on cell surfaces and on glycoproteins are associated with various cancer processes and the selective recognition of such biomarkers provides an excellent opportunity for the detection and treatment of cancer. The structural diversity of carbohydrates, including closely related stereoisomers, however, renders the development of artificial carbohydrate receptors extremely challenging. Previously developed artificial receptors mainly rely on noncovalent interactions or reversibly formed B-O bonds. On the other hand, there are only a few reports on artificial receptors that exploit the interaction between metal ions and carbohydrate functional groups, despite the promising potential for high molecular binding constants and pronounced selectivity due to the inherent directionality of coordination bonds. The currently known systems only show limited differentiation between the structurally versatile carbohydrate motifs, creating an unmet demand for highly selective artificial carbohydrate receptors.

２．研究の目的

Development of a highly modular, multimetallic metalloreceptor, whose peptide-based binding pocket can be readily optimized via dynamic combinatorial chemistry (DCC) using the targeted carbohydrate as the template. This new class of artificial metalloreceptor will be specifically employed for the binding of cancer-related carbohydrate motifs. The coordinative bonding between the metal ions and the target in combination with the non-covalent interactions with the peptide residues should result in an unprecedented degree of selectivity and binding affinity by mimicking natural protein binding pockets.

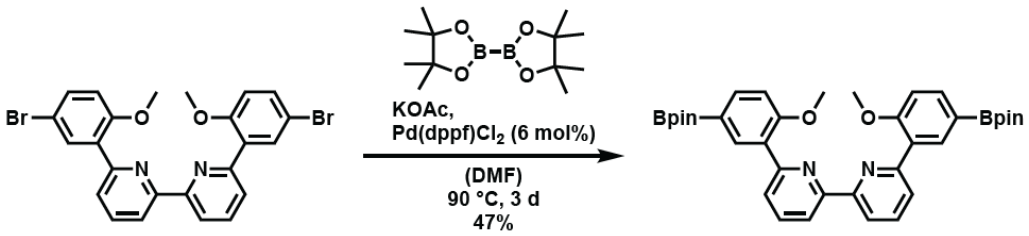


３．研究の方法

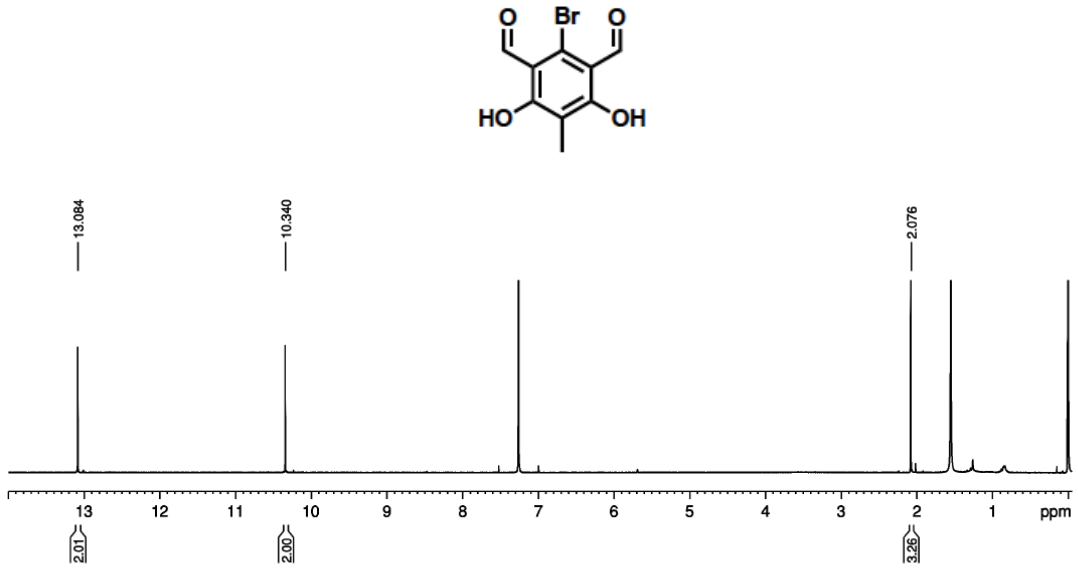
The planned research method comprised the synthesis of a monometallic proof-of-principle metalloreceptor framework, attachment of the orthogonal aldehyde units, and subsequent interactions studies with carbohydrates under variation of the peptide-based second coordination sphere through dynamic covalent imine (or acylhydrazone) chemistry. The targeted metalloreceptor uses a novel bis-salicylaldehyde unit (please see part 4), whose synthesis requires the search for an appropriate synthetic route.

４．研究成果

The novel core ligand for the monometallic proof-of-principle metalloreceptor framework was successfully synthesized. Since bioapplications require stability of the receptor in water, the design was changed during the course of this study from a salen ligand framework to a water-stable bipyridine framework.



Attachment of an orthogonal bis-salicylaldehyde required the synthesis of a new bromo-bis-salicylaldehyde. This kind of building block was not reported before, but after several tries the targeted building block was successfully synthesized.



^{1}H NMR of the bromo-bis-salicylaldehyde in $CDCl_3$.

The coupling of the bromo-bis-salicylaldehyde to the bipyridine framework was not yet attempted due to a lack of time. In the future, I plan to attach the bromo-bis-salicylaldehyde to the ligand framework and introduce the metal ion after deprotection of phenol groups. Then the binding of carbohydrates will be investigated and the possible attachment of peptide groups via dynamic covalent chemistry.

The knowledge obtained about artificial receptors was utilized for the preparation of a review on aqueous artificial bioreceptors (Catti *et. al.*, Coordination Chemistry Reviews, Volume 460, 2022, 214460).

In addition, my gained knowledge of carbohydrates was utilized for the synthesis of a carbohydrate-coated aqueous polyaromatic micelle (Angew. Chem. Int. Ed. 2021, 60, 12791-12795).

I believe that the synthesized bromo-bis-salicylaldehyde building block will be useful for not only the proposed target, but in general for synthetic chemists, especially those working with salen complexes.

５．主な発表論文等

〔雑誌論文〕　計4件（うち査読付論文　4件／うち国際共著　4件／うちオープンアクセス　0件）

１．著者名 Catti Lorenzo、Sumida Ryuki、Yoshizawa Michito	４．巻 460
２．論文標題 Aqueous polyaromatic receptors for biomolecules with high selectivity	５．発行年 2022年
３．雑誌名 Coordination Chemistry Reviews	６．最初と最後の頁 214460～214470
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.ccr.2022.214460	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 該当する

１．著者名 Catti Lorenzo、Narita Haruna、Tanaka Yuya、Sakai Hayato、Hasobe Taku、Tkachenko Nikolai V.、Yoshizawa Michito	４．巻 143
２．論文標題 Supramolecular Singlet Fission of Pentacene Dimers within Polyaromatic Capsules	５．発行年 2021年
３．雑誌名 Journal of the American Chemical Society	６．最初と最後の頁 9361～9367
掲載論文のDOI（デジタルオブジェクト識別子） 10.1021/jacs.0c13172	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 該当する

１．著者名 Narita Haruna、Catti Lorenzo、Yoshizawa Michito	４．巻 60
２．論文標題 An Aromatic Micelle‐Based Saccharide Cluster with Changeable Fluorescent Color and its Protein Interactions	５．発行年 2021年
３．雑誌名 Angewandte Chemie International Edition	６．最初と最後の頁 12791～12795
掲載論文のDOI（デジタルオブジェクト識別子） 10.1002/anie.202102547	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 該当する

１．著者名 Huck Fabian、Catti Lorenzo、Reber Gian Lino、Tiefenbacher Konrad	４．巻 87
２．論文標題 Expanding the Protecting Group Scope for the Carbonyl Olefin Metathesis Approach to 2,5-Dihydropyrroles	５．発行年 2021年
３．雑誌名 The Journal of Organic Chemistry	６．最初と最後の頁 419～428
掲載論文のDOI（デジタルオブジェクト識別子） 10.1021/acs.joc.1c02447	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 該当する

〔学会発表〕　計3件（うち招待講演　0件／うち国際学会　3件）

1．発表者名 Lorenzo Catti, Michito Yoshizawa
2．発表標題 Pyridinium Core Units for V-shaped Anthracene Dimers: Rapid Access to New Polyaromatic Amphiphiles
3．学会等名 The 102nd CSJ Annual Meeting (2022)（国際学会）
4．発表年 2022年

1．発表者名 Lorenzo Catti, Haruna Narita, Michito Yoshizawa
2．発表標題 Saccharide modification of an aromatic micelle and its guest-dependent fluorescence in water
3．学会等名 Pacifichem 2021（国際学会）
4．発表年 2021年

1．発表者名 Lorenzo Catti, Holger Flechsig, Noriyuki KOdera, Mark J. MacLachlan, Shigehisa Akine
2．発表標題 Reversible photoswitch-controlled structure transitions of biomolecules and their real-time visualization by high-speed atomic force microscopy
3．学会等名 The 101st CSJ Annual Meeting (2021)（国際学会）
4．発表年 2021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