# Corrin Ring Modification in Peptide Drug Development – a Brief History of "Corrination"

Nancy Cham and Robert P. Doyle*

Recently, the term "corrination" was coined to describe the conjugate modification of a peptide, protein, small molecule, or radionuclide with a corrin ring-containing molecule. By exploiting the innate chemicophysical properties of corrin ring-containing compounds, corrination has been explored for drug development and targeted/localized delivery of probes and therapeutics. Most recently, it is in the field of peptide-based therapeutics that corrination is generating significant interest. Peptide-based drugs possess several limitations that restrict their clinical application, including poor solubility and stability, low oral bioavailability, and negative side effects often due to drug distribution. In this mini review, the design and synthetic approaches to peptide corrination are described, along with examples of in vitro, ex vivo, and in vivo biological evaluations of corrinated conjugates, which demonstrate the broad applicability of the technique, namely 1) mitigated peptide aggregation, 2) improved protection against proteolysis, 3) reduced negative side effects via targeted localization, 4) regioselective production of peptide disulfide bonds, and 5) improved oral drug absorption. Herein, it is described how corrination offers a facile route to improving peptide pharmacokinetic and pharmacodynamic properties, making this a useful platform technology in the field of peptide drug development.

## 1. Introduction

Vitamin $B_{12}$ ($B_{12}$) or cobalamin, a water-soluble molecule with a centrally coordinated cobalt (III) atom in a tetrapyrrole ring system, is an essential cofactor in human health, playing a significant role in red blood cell formation and maintenance of the nervous system (**Figure 1**A). Only by synthesizing it with select bacteria do mammals obtain the vitamin through external sources such as dietary intake of animal protein. A complex transport system of soluble binding/transport proteins (haptocorrin, intrinsic factor, and transcobalamin) and receptors (cubilin, megalin, CD320, etc.) evolved to facilitate binding (see Figure 1B for TC-$B_{12}$ complex), transport, and delivery of $B_{12}$ into target cells (**Figure 2**) where it is used by metabolic enzymes methylmalonyl CoA-mutase and methionine synthase.[1,2] Conjugation to $B_{12}$ offers compounds improved physico-chemical properties (steric, charge, hydrophilicity, and/or innate transport), serving as a tool for drug development and targeted/localized delivery of probes and therapeutics. The Doyle group coined the term "corrination" to describe this well-documented conjugate modification of a peptide, protein, small molecule, or radio tag with a corrin ring.[3]

*N. Cham, R. P. Doyle*
*Department of Chemistry*
*Syracuse University*
*111 College Place, Syracuse, NY 13244, USA*
*E-mail: rpdoyle@syr.edu*

*R. P. Doyle*
*Department of Pharmacology and Medicine*
*State University of New York Upstate Medical University*
*750 East Adams Street, Syracuse, NY 13210, USA*



Recent highlights (**Table 1**) in this space include the use of $B_{12}$ as a carrier for targeted delivery of drugs (e.g., antibiotics, peptide nucleic acids, chemotherapeutics) and as an imaging agent into mammalian tumor cells and bacterial cells (*f*-side chain and β-axial modified $B_{12}$ derivatives were developed via light-facilitated reactions and "Trojan horse" conjugation for treatment and imaging).[4–17] Corrination allows selective and controlled drug release to the cancerous or pathogenic site where cells show a preferential accumulation of $B_{12}$ compared with healthy cells, resulting in improved efficacy and reduction in off-target toxicity and consequent side effects. Others have explored the creation of so-called "antivitamins $B_{12}$" as potential antibiotics and anticancer agents akin to antifolate.[18–24] Structurally designed to mimic $B_{12}$ via the replacement of cobalt by other transition metals (e.g., rhodium, nickel, zinc), the functionally inert antivitamins $B_{12}$ or non-natural corrins are recognized by key enzymes, repressing the metabolic effects of $B_{12}$ and inducing $B_{12}$ deficiency.

However, one area of corrination that has seen a renaissance over the past decade is that involving peptides, concomitant with the field of peptide-based therapeutics experiencing an explosion of growth due to their use now in various pathologies, writ large by glucagon-like peptide-1 receptor (GLP-1R) agonists such as semaglutide (Ozempic) and tirzepatide (Zepbound) for the treatment of obesity and T2DM. We, and others, have been actively exploring corrination for novel applications in peptide-based therapeutics with a view to overcoming peptide-based drug limitations that restrict their clinical application, including poor solubility and stability, low oral bioavailability, aggregation, and negative side effects often due to biodistribution.[25–39] Numerous reviews of corrination outside the peptide space have been published including Kräutler's review of antivitamins $B_{12}$,[18,40] Gryko's synthetic protocol of $B_{12}$ conjugates with peptide nucleic acid oligomers,[41] Lawrence's account of $B_{12}$ associated

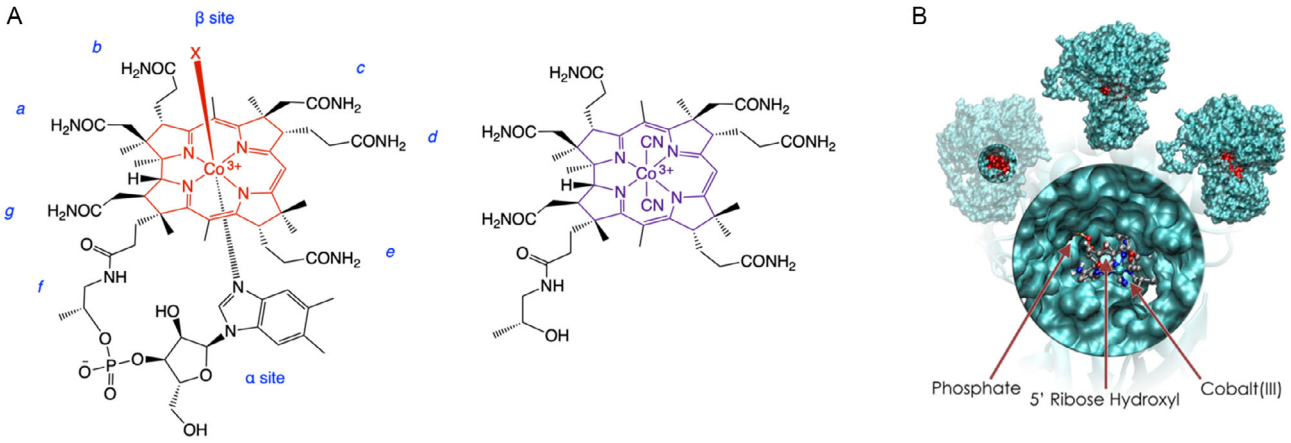


**Figure 1.** Vitamin $B_{12}$ structure and metabolism. A) Structures of $B_{12}$ (left) and dicyanocobinamide (right). B) Binding pocket of $B_{12}$ within transcobalamin II showing solvent-accessible fragments of $B_{12}$, including the 5′ hydroxyl group.

light-facilitated reactions,[6] and Zelder's feature article on $B_{12}$ derivatives for medicinal applications.[42]

In this review, we focus on the design, synthetic approaches, and in vitro and in vivo outcomes associated with peptide corrination, along with examples that demonstrate the broad applicability of the technique specific to peptides, namely 1) mitigated peptide aggregation, 2) improved protection against proteolysis, 3) reduced side effects via targeted localization, 4) production of peptide disulfide bonds with regioselectivity, and 5) improved oral drug absorption (**Table 2**). Overall, corrination demonstrates considerable promise as a platform technology and offers a great scope for exploration in the field of drug development.

## 2. Peptide Corrination Applications

Early research in $B_{12}$ corrination to peptides focused on oral drug delivery by exploiting the $B_{12}$ uptake pathway to protect drugs from proteolytic degradation in the gastrointestinal tract and ultimately cross the intestines into blood circulation. Continued research has revealed that conjugation to $B_{12}$ can alter the physiochemical properties of the drug itself, such as stability/solubility in the solution. Below, we summarize recent specific highlights of peptide corrination from Doyle et al. that demonstrate its versatility as a platform technology in drug development.

### 2.1. Corrination Mitigates Peptide Aggregation

Pharmaceutical development of peptide-based drugs for clinical use has proved challenging due in large part to poor solubility, poor stability, and aggregate formation. One such peptide that has a short half-life of less than 5 min and is highly prone to aggregation is glucagon, an emergency treatment for severe hypoglycemia.[43] The two existing FDA-approved formulations of glucagon, GlucaGen HypoKit from Novo Nordisk and Glucagon Emergency Kit from Eli Lilly are supplied as lyophilized powders that must be fully dissolved with solvent by the user prior to injection.[44] Due to the propensity of dissolved glucagon to form aggregates, the product must be used immediately after reconstitution, making it inadequate for prolonged use and prohibiting the user from preparing the medication in advance for urgent cases. Therefore, there is a need to develop a method to improve both the physical and chemical stability of peptides such as glucagon, which are often unstable in aqueous solutions.

Using the commercially available $B_{12}$ precursor Cbi, Liles et al. generated highly soluble, low aggregating glucagon conjugates that retain full stimulatory action at the human glucagon receptor for potential use in acute hypoglycemia.[26] By incorporating an azido group into the glucagon sequence and preparing Cbi with an available alkyne group, the corrinated analogs were easily synthesized via copper-catalyzed alkyne-azide cycloaddition (CuAAC)[45] (**Figure 3**). When tested in a chemical stability assay in 50 mM phosphate buffer, all corrinated compounds retained

**Nancy Cham** is a Ph.D. candidate in the Department of Chemistry at Syracuse University, NY, USA where she also obtained her BS in biochemistry and forensic science (2022). Her research under the supervision of Prof. Robert P. Doyle addresses the bioconjugation of peptide-based therapeutics to alter PK/PD via the vitamin $B_{12}$ uptake pathway for the treatment of diabetes and comorbidities.

**Robert P. Doyle** is the inaugural Jack and Laura H. Milton professor in the Department of Chemistry at Syracuse University and professor of medicine and pharmacology at the State University of New York, Upstate Medical University, NY, USA. He obtained his BA in Natural Sciences (1998) and Ph.D. in Chemistry (2002; Advisor-Prof. Paul E. Kruger) at the University of Dublin, Ireland and was a postdoctoral fellow at the Australian National University and then Yale University. His lab is interested in developing new peptide-based therapeutics for the treatment of metabolic diseases.

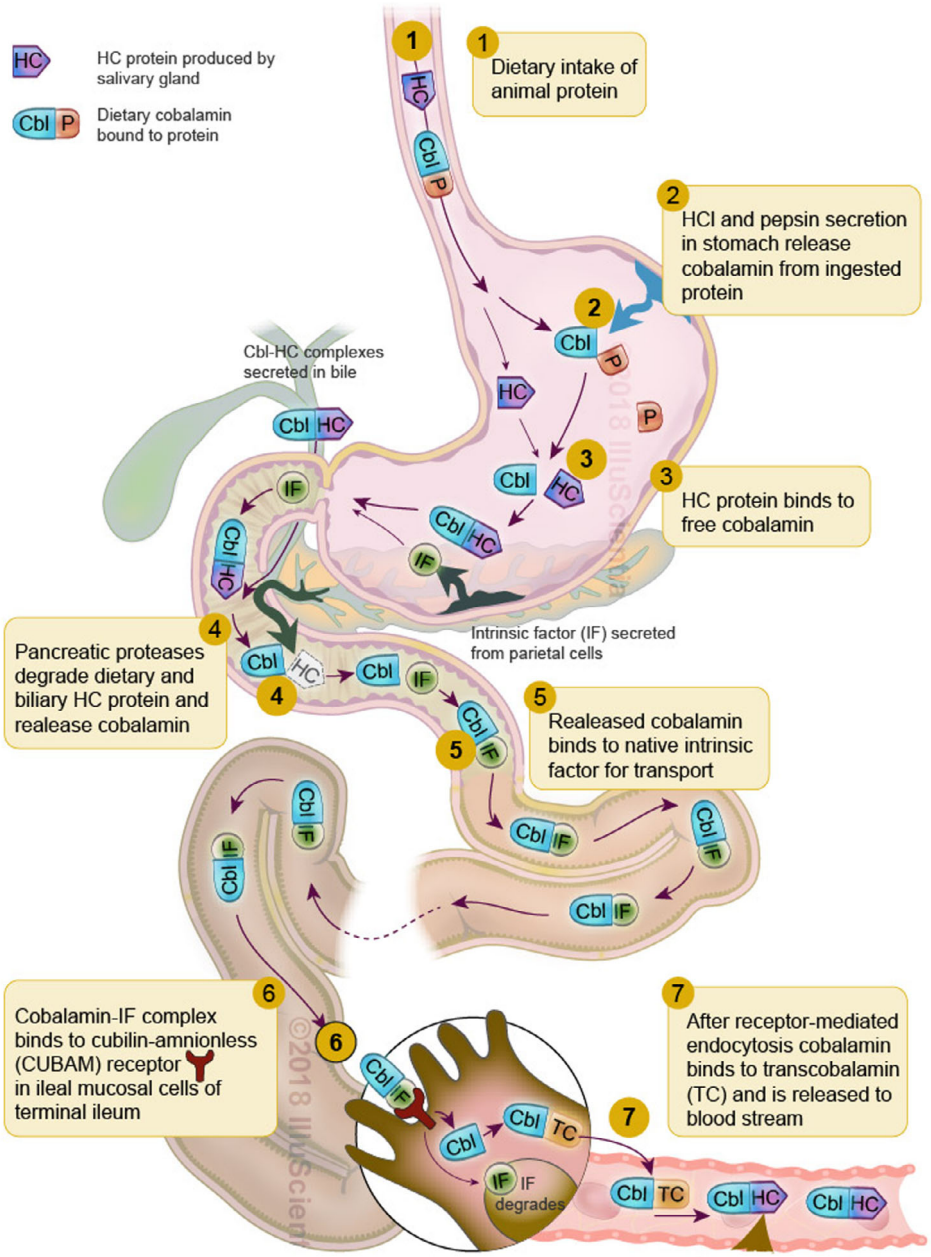


**Figure 2.** Dietary uptake pathway of $B_{12}$ in humans. Since $B_{12}$ is only synthesized by certain bacteria, the absorption and uptake of $B_{12}$ begins with dietary intake of animal protein. In the stomach, HCl and pepsin secretion releases $B_{12}$ from the protein, allowing HC to bind to free $B_{12}$. This complex travels to the duodenum where HC is degraded and free $B_{12}$ binds to IF. The $B_{12}$-IF complex is taken up through the intestine into the terminal ileum where it undergoes endocytosis into the ileal enterocyte via mucosal receptors. After internalization, $B_{12}$ is released from IF and becomes bound to TC, which facilitates its secretion into the blood plasma and transports it to target cells.

their original concentration to a higher degree than glucagon controls. By improved stability, the corrinated compounds showed markedly decreased aggregation compared to their respective non-corrinated analogs when the formation of fibrils was measured on a thioflavin (ThT) fluorescence-based assay (see Figure 3). With the improvement of the physical and chemical properties of glucagon via corrination, glucagon, **2** and its corrinated conjugate **5** were monitored for their functional activity using an in vitro assay. When freshly solubilized, **2** maintained equipotent activity in comparison to unmodified glucagon, while corrinated **5** led to reduced potency while retaining full efficacy. However, following a 24 h incubation, corrinated **5** exhibited a 6.6-fold increased potency relative to glucagon. The relative potency of **5** was also improved compared to that of **2** with $EC_{50}$ values of 5.5 and 9.6 nM for **5** and **2**, respectively. The data indicates that corrination of glucagon improves stability and mitigates aggregation while preserving glucagon receptor agonism after 24 h incubation. The use of corrination with unstable peptides in aqueous solution, such as glucagon and amylin, offers a compound with prolonged stability and agonism, potentially extending the shelf life and increasing bioavailability.

**Table 1.** Examples of corrinated conjugates outside the peptide space.

| Compound | Classification | $B_{12}$ conjugation site | Significance | References |
|---|---|---|---|---|
| Dexamethasone | Anti-inflammatory | β-axial of Co (III) | Use of RBCs as carriers for site-specific light activation triggers release of drug | [4] |
| Taxane | Antitumor | | | [5] |
| Bodipy650 | Far-red fluorescence dye | Ribose 5′-OH | Red light and X-ray-activated cobalamin scaffold that selectively targets pancreatic adenocarcinoma | [7,8] |
| Peptide nucleic acids | Antibacterial | Ribose 5′-OH | Use of $B_{12}$ as a carrier of PNA oligonucleotides into bacterial cells | [9,10] |
| Ampicillin | Antibiotic | Ribose 5′-OH | Conjugates exhibited more than 500 times improved activity against *E. coli* compared with ampicillin itself | [11] |
| Pt(II) complexes | Antitumor | β-axial of Co (III) | Fluorescent $B_{12}$ metal complexes showed enhanced capability to inhibit cell viability compared with inactive precursors | [12,13] |
| Sericin Micelles | Antibacterial | Ribose 5′-OH | Exhibited cancer targeting abilities and enhanced cellular drug uptake on CD320-overexpressed GC cells | [16] |
| $^{89}$Zirconium-labeled $B_{12}$ | PET Tracer | Ribose 5′-OH | Suitable for both in vivo and ex vivo studies of $B_{12}$ trafficking and with the potential to visualize tumors expressing TC receptors | [17] |
| Antivitamins $B_{12}$ (alkynyl-$B_{12}$) | Potential Antibiotic | β-axial of Co(III) | F2PhEtyCbl binds to $B_{12}$-processing enzyme CblC with high affinity in the presence of co-substrate glutathione; light-stable | [21] |
| Acetylrhodibalamin | Non-natural Corrins | Rh(III) or Ni(II) on metal free site of $B_{12}$ or Cbi | Both analogs were *iso*-structural to the natural cobalt corrins, potentially functioning as selective inhibitors of $B_{12}$-biosynthesis | [23] |
| Nibiamide | | | | [24] |

**Table 2.** List of corrinated peptides reported to date (March 2025).

| Corrin ring molecule | Peptide | Applications | References |
|---|---|---|---|
| Cbi | Glucagon | Mitigated peptide aggregation, improved stability/solubility, and preserved receptor agonism after 24 h | [26] |
| IF-$B_{12}$ | Ex4 | Increased peptide stability against proteolysis | [27] |
| Cbi | Ex4 | Maintained glucoregulation and near absence of emetic events in shrews | [28] |
| $B_{12}$ | Oxytocin | Preserved food intake suppression effects of OT, conditioned taste avoidance, and locomotor depression in rats; reduction in emetic events in shrews | [30] |
| $B_{12}$ | Insulin | Improved glycemic response when administered in rats | [32] |
| $B_{12}$ | PYY (3-36) | Decreased food intake compared to native peptide upon subcutaneous administration in male rats | [33] |
| $B_{12}$ | Polymyxin (Colistin) | $B_{12}$ conjugates showed improved Caco-2 cell permeability | [34,35] |
| $B_{12}$ | Hexapeptide Cys-Phe-Phe-Phe-Lys-Lys-$NH_2$ | Developed a novel $B_{12}$ derivative suitably tailored for disulfide-based conjugation that can undergo cleavage in the presence of glutathione (GSH) | [36] |
| $B_{12}$ | DP3 | Oral administration of $B_{12}$-Hex-DP3 and $B_{12}$-DP3 resulted in absorption of 42% and 23% respectively | [37] |
| $B_{12}$ | LHRH | Oral administration of $B_{12}$-LHRH resulted in absorption of 45% | [37] |
| $B_{12}$ | erythropoietin | Conjugates were actively transported across CaCo-2 cells and from intestine to circulation in a biologically active form | [38] |
| $B_{12}$ | ANTIDE | Conjugates had similar activity to ANTIDE both in vitro and in vivo and were found to be more water soluble than ANTIDE | [39] |

### 2.2. Corrination Enhances Peptide Stability against Proteolysis

Free peptides are not systemically stable due to protease digestion, making this a significant limitation in peptide therapeutic development. Conveniently, the dietary pathway of $B_{12}$ consists of the transport protein, intrinsic factor (IF), which is resistant to pancreatic protease digestion and facilitates $B_{12}$ uptake by intestinal cells via cubilin-amnionless-based receptor-mediated enterocyte passage (see Figure 2). Bonaccorso et al. demonstrated that conjugation of the incretin peptide exendin-4 (Ex4) to $B_{12}$ provided improved stability, and the subsequent step of binding the $B_{12}$-peptide conjugate to IF exhibited greater protection against protease digestion.[27]

Ex4 was discovered in the saliva of the Gila monster in 1992 and was found to exhibit 53% sequence homology with human GLP-1.[46] Due to its slight difference in amino acid sequence involving substitution of alanine with glycine at the second position, Ex4 is resistant to degradation by dipeptidyl peptidase IV (DPP-IV) and has a longer half-life of 2.5 h compared to GLP-1's half-life of 2 min.[46] Exenatide, the synthetic form of Ex4, was the first FDA-approved GLP-1 analog for treating T2DM. It stimulated

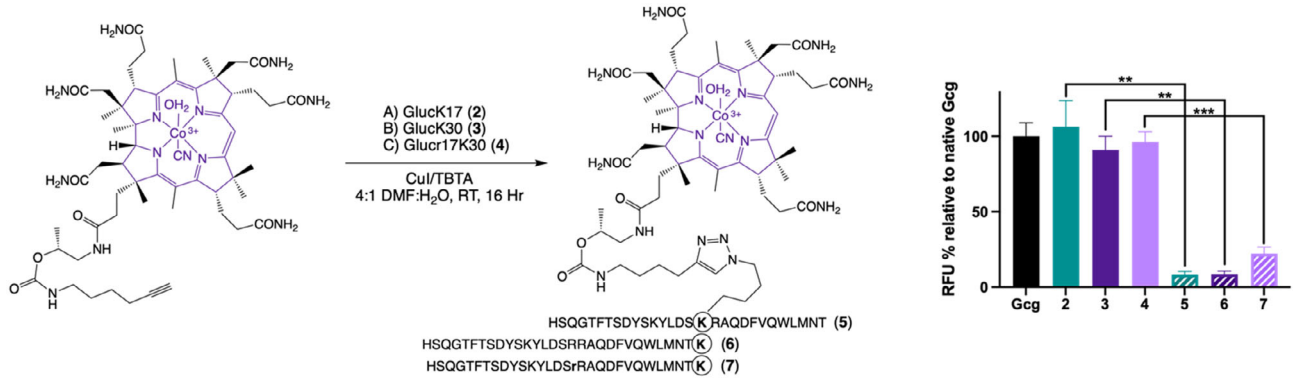


**Figure 3.** Synthesis of corrinated glucagon conjugates using CuAAC and graph of aggregate formation assays in 0.1 M HCl using the ThT fluorescence assay. $^{**}p < 0.01$, $^{***}p < 0.001$.[26]

the release of insulin through agonism of the GLP-1R, effectively lowering blood glucose levels. However, stability studies show that Ex4 is digested by pancreatic proteases trypsin and chymotrypsin.

Bonaccorso et al. synthesized a novel $B_{12}$ corrinated analog of Ex4 (Byetta) with and without binding to IF, termed IF-$B_{12}$-Ex4 and $B_{12}$-Ex4, respectively. Ex4 was conjugated to $B_{12}$ at the lysine 12 position using click chemistry as previously described. $B_{12}$-Ex4 and IF-$B_{12}$-Ex4 demonstrated picomolar agonism at the GLP-1R.[27] The compounds were tested for stability against proteolysis by measuring the remaining function at the receptor compared to undigested controls. Prebinding the $B_{12}$ conjugate to IF resulted in up to a 4-fold greater activity relative to Ex4 when exposed to 22 $\mu g\,mL^{-1}$ of trypsin, 2.3-fold greater activity when exposed to 1.25 $\mu g\,mL^{-1}$ of chymotrypsin, and there was no decrease in function at up to 5 $\mu g\,mL^{-1}$ of meprin β, a common kidney brush-border membrane protein. The ability of IF-bound Ex4 to maintain increased function compared to Ex4 at the GLP-1R when exposed to proteases supports its use in improving peptide stability against proteases and protection against intestinal degradation, making this a possible approach for oral administration of potent peptides with known gut receptors such as GLP-1R agonists.

### 2.3. Corrination Reduces CNS Penetrance and Mitigates CNS Effects While Maintaining Peripheral Effects in Rodents and Shrews

#### *2.3.1. Corrinated Conjugates of GLP-1R Agonist Exendin-4*

Despite being a common medication for T2DM, activation of GLP-1 R in the brain, particularly the area postrema (AP) and nucleus tractus solitarius (NTS), results in gastrointestinal (GI) side effects such as nausea and emesis.[47] These side effects were a significant reason for the discontinuation of this medication among patients with T2DM, and due to the resulting weight loss, certain subpopulations with comorbidities where nutritional status is critical, such as those with cystic fibrosis, cannot use GLP-1R analogs. Therefore, there is a clinical need for effective GLP-1-based analogs that circumvent such GI side effects. Corrination is a feasible method to alter peptide pharmacology by reducing CNS penetration and mitigating associated side effects. In the adult brain, the uptake of $B_{12}$ by the CNS is very low, and $B_{12}$ level in cerebrospinal fluid (6–28 pmol $L^{-1}$) is considerably lower than in serum (200–517 pmol $L^{-1}$).[48] Corrination offers an efficient drug delivery system via the $B_{12}$ uptake pathway and would theoretically avoid penetration into the CNS while retaining peripheral activity.

Tinsley et al. synthesized a library of Cbi conjugated constructs of Ex4 involving azido modification at two sites (K12 and K40) in the sequence and various linkers (see **Figure 4**) to optimize the lead conjugate in terms of GLP-1R agonism and binding for subsequent testing in vivo in shrews for glucoregulatory and emetic behavior, relative to Ex4.[28,29] Several constructs demonstrated comparable binding and agonism at GLP-1R as Ex4, with the leading conjugate having an $IC_{50}$ 11.9 ± 2.5 nM and $EC_{50}$ 20.7 ± 8.3 pM. Corrination of Ex4 exhibited glucoregulation comparable with Ex4 and observed near absence of CNS-associated side effects of emesis and mild bodyweight lowering actions compared to profound emesis and body weight loss observed for Ex4 in the musk shrew. 80% of the shrews exhibited emesis upon administration of Ex4 within minutes after injection (29 ± 16 min), whereas only 20% of shrews that received Cbi-Ex40 experienced emesis with an average latency of 70 ± 29 min.

Removal of the CNS-associated side effects accompanied by GLP-1R agonists will improve patient compliance during use and expand its use to patients with comorbidities where weight loss must be avoided (e.g., cancer, sarcopenia, HIV, and cachexia).

#### *2.3.2. Peripherally Restricted Oxytocin*

Oxytocin (OT), a small cyclic peptide hormone synthesized in the hypothalamus and secreted via the pituitary gland, also possesses undesired side effects due to activation of receptors in the CNS. Although OT is clinically known for its role in reproductive behaviors, it has recently emerged as a contributor to energy homeostasis regulation due to the presence of OT receptors in peripheral tissues relevant to energy balance regulation.[49] Asker et al. generated a novel BBB-impermeable OT (OT-$B_{12}$) (**Figure 5**) to determine whether peripheral OT receptor activation is sufficient to alter energy intake and expenditure in rats.[30]

Intraperitoneally injected OT and OT-$B_{12}$ were equipotent at food intake suppression in rats, indicating that reduced BBB penetration of OT does not affect the anorexic effect of the compound. However, OT, not OT-$B_{12}$, induced a potent conditioned

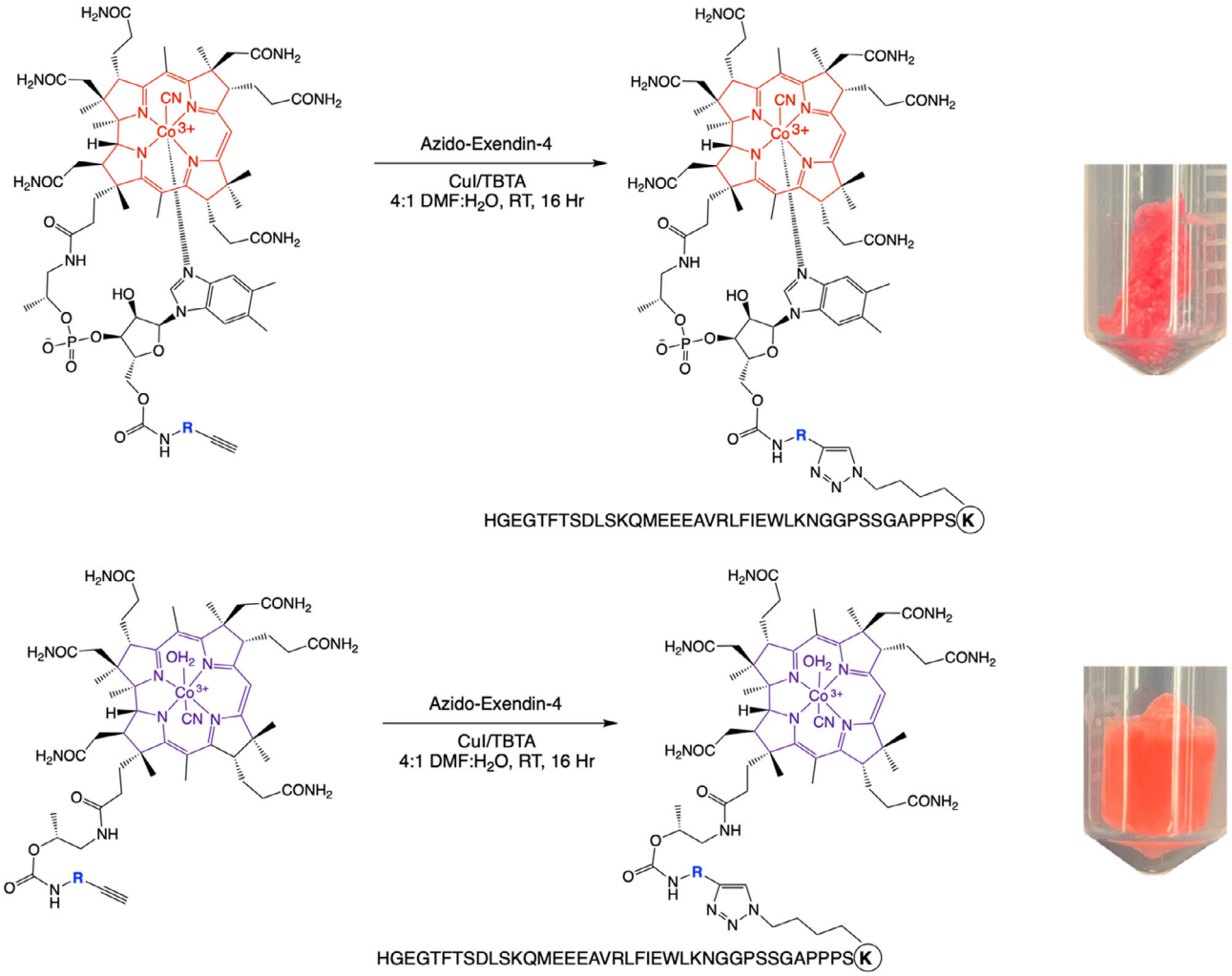


**Figure 4.** Synthesis of $B_{12}$-Ex4 (top) and Cbi-Ex4 (bottom) conjugate using CuAAC. Corrination of Ex4 maintains GLP-1R agonism in the pancreas and mitigates agonism in the CNS. (R = linkers including short hydrophobic alkane chains, amphiphilic PEG, and rigid substituted ethynyl phenyl methanamines).[28]

taste avoidance. Importantly, preventing CNS penetration of OT resulted in a dose-dependent reduction of emesis in male shrews and mitigated locomotor depression. These observations indicate that corrination preserves the food intake suppression effect of OT and diminishes the undesired side effects of the peptide, such as emesis, taste avoidance, and locomotor depression. Overall, targeting peripheral receptors via corrination offers a possible strategy to beneficially alter the pharmacodynamic properties of CNS penetrating peptides such as OT and GLP-1 receptor agonists.

### 2.4. Disulfide Bond Formation Using Cbi

Disulfide bond formation is a critical step in post-solid-phase synthesis for the folding and structural stabilization of many important peptides in which its configuration may play a major part in its biological function. However, current methods possess drawbacks such as long reaction times of up to two days, formation of undesired side products, and use of environmentally harmful organic solvents. For example, disulfide bond formation of oxytocin via air oxidation using dimethyl sulfoxide takes 2 days, resulting in the undesired production of dimers. To shorten reaction time and avoid use of reportedly cytotoxic DMSO, Spear et al. achieved a rapid, green, and facile oxidation of a series of peptides with up to three disulfide bonds utilizing Cbi as a catalyst in aqueous solution (**Figure 6**).[31] This technique generated disulfide bond formation in under 1 h with a simple removal step of Cbi and allowed the control of regioselectivity in the TrCART series, which contained two or three disulfide bonds. Use of Cbi provides chemists with a rapid, affordable, and aqueous route to produce peptide disulfide bonds.

### 2.5. Oral Peptide Delivery via the $B_{12}$ Pathway

Oral drug delivery is often the preferred route of administration in drug development due to improved convenience and patient compliance. However, poor bioavailability and slow onset of action due to gastrointestinal instability and limited absorption are major challenges in oral peptide development. $B_{12}$ has an efficient uptake pathway in the mammalian body that begins with oral intake of food and undergoes protection and movement through the GI tract by three main transport proteins, such as IF, which binds $B_{12}$ and facilitates its transport through the

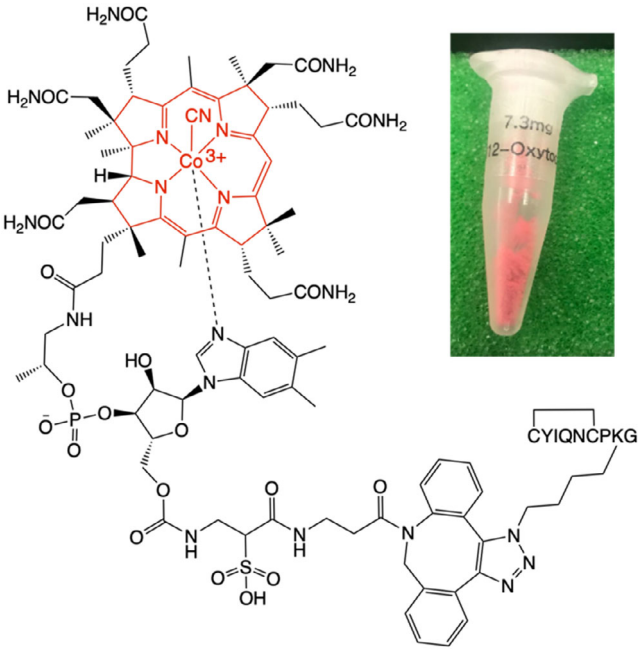


**Figure 5.** Structure of OT-$B_{12}$ with lyophilized powdered form shown in inset.

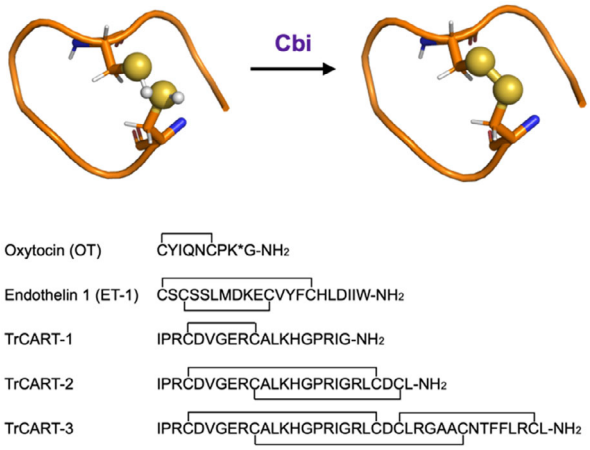


**Figure 6.** Cbi catalysis of disulfide oxidation. Peptide sequences and disulfide bond connections. (* = ε-azido-lysine).[31]

intestines (see **Figure 7** for human IF-$B_{12}$ complex).[50] This pathway can be exploited to make drug delivery easier and more effective. Petrus et al. have shown that a noninvasive oral delivery route for insulin is possible by utilizing $B_{12}$ as a carrier for novel insulin-$B_{12}$ conjugates.[32]

In streptozotocin-induced diabetic rat model, orally administered insulin-$B_{12}$ achieved a 4.7-fold greater decrease in the area under the blood glucose curve relative to the blood glucose response to the administration of free insulin, indicating that the conjugate is more effective in decreasing blood glucose levels. When dissolved in excess $B_{12}$, there was a significant decrease in blood glucose response, suggesting the glucose-lowering effects of the insulin-$B_{12}$ conjugate are mediated by the $B_{12}$ uptake mechanism. Therefore, the noninvasive delivery of peptide-based

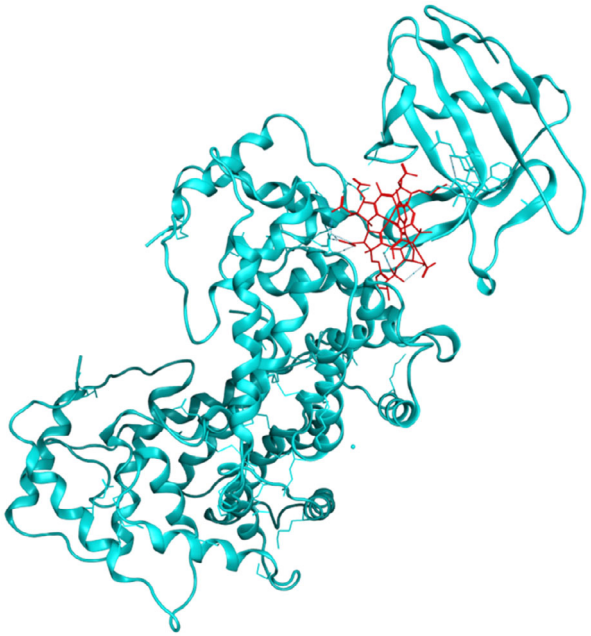

**Figure 7.** Structure of human IF-$B_{12}$ complex. PDB ID = 2PMV.

medications is possible through oral-enteric administration by exploiting the highly efficient $B_{12}$ uptake pathway.[51]

## 3. Outlook

Corrination provides additional benefits to a peptide than previously anticipated, going beyond the "Trojan Horse" approach and addressing various inherent drawbacks in peptide-based drug development. However, limitations of corrination include low absorption of $B_{12}$ to target cells as ileal receptors have a finite threshold for $B_{12}$ and excess is excreted in bile or urine.[52] Prebinding $B_{12}$ conjugates to transport proteins is an area of ongoing research and could significantly impact the absorption and distribution of the drug in vivo by oral delivery.

Of particular interest is the application of corrination in targeted localization via reduced blood brain barrier penetration. There are numerous biological barriers (e.g., blood retinal barrier, and blood placental barrier) present in the human body that, with reduced penetration of certain therapeutics, would enhance the safety profile and expand therapeutic index.[53]

## 4. Summary

The innate biological characteristics of $B_{12}$ and the $B_{12}$ uptake pathway have prompted significant research on using $B_{12}$ in targeted drug delivery, from small molecule imaging agents, antivitamins, and antibiotics to larger peptide nucleic acids, proteins, and polymers. As summarized in this review, recent successes in the corrination of peptides have produced compounds that mitigate common issues associated with peptide synthesis, ranging from instability in solution to undesired side effects while

maintaining peptide functionality. Along with reduced aggregation and increased stability against proteolysis, corrination potentially allows for effective oral peptide delivery through the $B_{12}$ uptake pathway. Corrination has promise as a platform technology in clinical peptide drug development as the full potential of such in delivery, targeting, and improved PK/PD has yet to be explored.

## Acknowledgements

This work was supported by the National Institute of Health (NIDDK) R01DK128443 to R.P.D. and N.C. acknowledges a Souder Graduate Fellowship from the Department of Chemistry at Syracuse University.

## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** cobinamide · corrin ring · corrination · peptides · vitamin $B_{12}$

[1] M. J. Nielsen, M. R. Rasmussen, C. B. F. Andersen, E. Nexø, S. K. Moestrup, *Nat. Rev. Gastroenterol. Hepatol.* **2012**, *9*, 345.
[2] T. Borner, I. C. Tinsley, R. P. Doyle, M. R. Hayes, B. C. De Jonghe, *Br. J. Pharmacol.* **2022**, *179*, 542.
[3] R. P. Doyle, US 11207415B2, **2021**.
[4] E. M. Zywot, N. Orlova, S. Ding, R. R. Rampersad, E. M. Rabjohns, V. A. Wickenheisser, Q. Wang, J. G. Welfare, L. Haar, A. M. Eudy, T. K. Tarrant, D. S. Lawrence, *Adv. Ther. (Weinheim, Ger.)* **2022**, *5*, 2100159.
[5] C. M. Marvin, S. Ding, R. E. White, N. Orlova, Q. Wang, E. M. Zywot, B. M. Vickerman, L. Harr, T. K. Tarrant, P. A. Dayton, D. S. Lawrence, *Small* **2019**, *15*, 1901442.
[6] T. A. Shell, D. S. Lawrence, *Acc. Chem. Res.* **2015**, *48*, 2866.
[7] L. N. Gendron, D. C. Zites, E. P. M. LaRochelle, J. R. Gunn, B. W. Pogue, T. A. Shell, J. R. Shell, *Photodiagn. Photodyn. Ther.* **2020**, *30*, 101637.
[8] M. M. Haghdoost, E. Sauvageau, P. Oguadinma, H.-V. Tran, S. Lefrancois, A. Castonguay, *J. Inorg. Biochem.* **2020**, *210*, 111105.
[9] M. Równicki, M. Wojciechowska, A. J. Wierzba, J. Czarnecki, D. Bartosik, D. Gryko, J. Trylska, *Sci. Rep.* **2017**, *7*, 7644.
[10] T. Pieńko, J. Czarnecki, M. Równicki, M. Wojciechowska, A. J. Wierzba, D. Gryko, D. Bartosik, J. Trylska, *Biophys. J.* **2021**, *120*, 725.
[11] S. Zhao, Z.-P. Wang, X. Wen, S. Li, G. Wei, J. Guo, Y. He, *Org. Lett.* **2020**, *22*, 6632.
[12] D. Porębska, Ł. Orzeł, D. Rutkowska-Żbik, G. Stochel, R. van Eldik, *Polyhedron* **2023**, *230*, 116230.
[13] R. Mehder, E. de la Torre-Rubio, I. de la Cueva-Alique, C. O'Malley, A. Pérez-Redondo, L. Gude, E. Royo, L. Ronconi, *Inorganics* **2024**, *12*, 91.
[14] B. J. Stackpole, J. M. Fredericksen, N. E. Brasch, *J. Inorg. Biochem.* **2024**, *254*, 112504.
[15] A. Jackowska, D. Gryko, *Org. Lett.* **2021**, *23*, 4940.
[16] W. Guo, L. Deng, Z. Chen, Z. Chen, J. Yu, H. Liu, T. Li, T. Lin, H. Chen, M. Zhao, L. Zhang, G. Li, Y. Hu, *Nanomedicine* **2019**, *14*, 353.
[17] A. N. W. Kuda-Wedagedara, J. L. Workinger, E. Nexo, R. P. Doyle, N. Viola-Villegas, *ACS Omega* **2017**, *2*, 6314.
[18] B. Kräutler, in *Vitamins and Hormones*, Vol. *119* (Ed: G. Litwack), Academic Press, Cambridge, MA **2022**, pp. 221–240.
[19] F. Zelder, M. Sonnay, L. Prieto, *ChemBioChem* **2015**, *16*, 1264.
[20] M. Ruetz, M. Koutmos, B. Kräutler, in *Methods in Enzymology*, Vol. *668* (Ed: E. N. G. Marsh), Academic Press, Cambridge, MA **2022**, pp. 157–178.
[21] M. Ruetz, A. Shanmuganathan, C. Gherasim, A. Karasik, R. Salchner, C. Kieninger, K. Wurst, R. Banerjee, M. Koutmos, B. Kräutler, *Angew. Chem., Int. Ed.* **2017**, *56*, 7387.
[22] P. D. Mestizo, C. Brenig, R. Stephan, F. Zelder, F. Muchaamba, *LWT* **2024**, *191*, 115641.
[23] M. Wiedemair, C. Kieninger, K. Wurst, M. Podewitz, E. Deery, M. D. Paxhia, M. J. Warren, B. Kräutler, *Helv. Chim. Acta* **2023**, *106*, e202200158.
[24] C. Kieninger, E. Deery, A. D. Lawrence, M. J. Warren, B. Kräutler, *J. Porphyrins Phthalocyanines* **2023**, *27*, 627.
[25] A. K. Petrus, D. G. Allis, R. P. Smith, T. J. Fairchild, R. P. Doyle, *ChemMedChem* **2009**, *4*, 421.
[26] A. Liles, N. Cham, M. L. Opp, I. C. Tinsley, O. G. Chepurny, G. G. Holz, R. P. Doyle, *Peptides* **2024**, *171*, 171134.
[27] R. L. Bonaccorso, O. G. Chepurny, C. Becker-Pauly, G. G. Holz, R. P. Doyle, *Mol. Pharm.* **2015**, *12*, 3502.
[28] I. C. Tinsley, T. Borner, M. L. Swanson, O. G. Chepurny, S. A. Doebley, V. Kamat, I. R. Sweet, G. G. Holz, M. R. Hayes, B. C. De Jonghe, R. P. Doyle, *J. Med. Chem.* **2021**, *64*, 3479.
[29] T. Borner, J. L. Workinger, I. C. Tinsley, S. M. Fortin, L. M. Stein, O. G. Chepurny, G. G. Holz, A. J. Wierzba, D. Gryko, E. Nexø, E. D. Shaulson, A. Bamezai, V. A. R. Da Silva, B. C. De Jonghe, M. R. Hayes, R. P. Doyle, *Cell Rep.* **2020**, *31*, 107768.
[30] M. Asker, J.-P. Krieger, A. Liles, I. C. Tinsley, T. Borner, I. Maric, S. Doebley, C. D. Furst, S. Börchers, F. Longo, Y. R. Bhat, B. C. De Jonghe, M. R. Hayes, R. P. Doyle, K. P. Skibicka, *Diabetes, Obes. Metab.* **2023**, *25*, 856.
[31] A. Spear, O. Orativskyi, S. Tran, J. A. Zubieta, R. P. Doyle, *Chem. Commun.* **2023**, *59*, 9836.
[32] A. K. Petrus, A. R. Vortherms, T. J. Fairchild, R. P. Doyle, *ChemMedChem* **2007**, *2*, 1717.
[33] K. E. Henry, C. T. Elfers, R. M. Burke, O. G. Chepurny, G. G. Holz, J. E. Blevins, C. L. Roth, R. P. Doyle, *Endocrinology* **2015**, *156*, 1739.
[34] M. Stepanova, M. Levit, T. Egorova, Y. Nashchekina, T. Sall, E. Demyanova, I. Guryanov, E. Korzhikova-Vlakh, *Pharmaceutics* **2024**, *16*, 1080.
[35] N. V. Dubashynskaya, A. N. Bokatyi, T. S. Sall, T. S. Egorova, Y. A. Nashchekina, Y. A. Dubrovskii, E. A. Murashko, E. N. Vlasova, E. V. Demyanova, Y. A. Skorik, *Int. J. Mol. Sci.* **2023**, *24*, 11550.
[36] A. Wierzba, M. Wojciechowska, J. Trylska, D. Gryko, *Bioconjugate Chem.* **2016**, *27*, 189.
[37] J. Alsenz, G. J. Russell-Jones, S. Westwood, B. Levet-Trafit, P. C. de Smidt, *Pharm. Res.* **2000**, *17*, 825.
[38] G. J. Russell-Jones, S. W. Westwood, A. D. Habberfield, *Bioconjugate Chem.* **1995**, *6*, 459.
[39] G. J. Russell-Jones, S. W. Westwood, P. G. Farnworth, J. K. Findlay, H. G. Burger, *Bioconjugate Chem.* **1995**, *6*, 34.
[40] B. Kräutler, *Chem. - Eur. J.* **2020**, *26*, 15438.
[41] A. J. Wierzba, M. Wojciechowska, J. Trylska, D. Gryko, in *Peptide Conjugation: Methods and Protocols* (Eds: W. M. Hussein, R. J. Stephenson, I. Toth), Springer US, New York, NY **2021**, pp. 65–82.
[42] F. Zelder, *Chem. Commun.* **2015**, *51*, 14004.
[43] P. A. Mroz, D. Perez-Tilve, J. P. Mayer, R. D. DiMarchi, *Commun. Chem.* **2019**, *2*, 2.
[44] A. G. Ranjan, S. Schmidt, K. Nørgaard, *Diabetes/Metab. Res. Rev.* **2020**, *37*, e3409.
[45] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2004.
[46] D. Sharma, S. Verma, S. Vaidya, K. Kalia, V. Tiwari, *Biomed. Pharmacother.* **2018**, *108*, 952.
[47] B. L. Furman, *Toxicon* **2012**, *59*, 464.
[48] K. A. Tiani, P. J. Stover, M. S. Field, *Annu. Rev. Nutr.* **2019**, *39*, 147.
[49] E. A. Lawson, P. K. Olszewski, A. Weller, J. E. Blevins, *J. Neuroendocrinol.* **2020**, *32*, e12805.
[50] F. S. Mathews, M. M. Gordon, Z. Chen, K. R. Rajashankar, S. E. Ealick, D. H. Alpers, N. Sukumar, *Proc. Natl. Acad. Sci.* **2007**, *104*, 17311.
[51] S. Clardy-James, D. G. Allis, T. J. Fairchild, R. P. Doyle, *MedChemComm* **2012**, *3*, 1054.
[52] A. Sobczyńska-Malefora, E. Delvin, A. McCaddon, K. R. Ahmadi, D. J. Harrington, *Crit. Rev. Clin. Lab. Sci.* **2021**, *58*, 399.
[53] F. A. Elzinga, B. Khalili, D. J. Touw, J. R. Prins, P. Olinga, H. G. D. Leuvenink, H. van Goor, S. J. Gordijn, A. Nagelkerke, P. Mian, *J. Clin. Med.* **2023**, *12*, 4315.

Manuscript received: February 14, 2025
Revised manuscript received: March 12, 2025
Version of record online: April 7, 2025