Antivitamins $\text{B}_{12}$—Some Inaugural Milestones

Bernhard Kräutler*\[a\]

Dedicated to the memory of Professor Duilio Arigoni
Abstract: The recently delineated structure- and reactivity-based concept of antivitamins B_{12} has begun to bear fruit by the generation, and study, of a range of such B_{12}-dummies, either vitamin B_{12}-derived, or transition metal analogues that also represent potential antivitamins B_{12} or specific B_{12}-antimetabolites. As reviewed here, this has opened up new research avenues in organometallic B_{12}-chemistry and bioinorganic coordination chemistry. Exploratory studies with antivitamins B_{12} have, furthermore, revealed some of their potential, as pharmacologically interesting compounds, for inducing B_{12}-deficiency in a range of organisms, from hospital resistant bacteria to laboratory mice. The derived capacity of antivitamins B_{12} to induce functional B_{12}-deficiency in mammalian cells and organs also suggest their valuable potential as growth inhibitors of cancerous human and animal cells.

Introduction

Vitamin B_{12}, the Co^{111-}corrin cyanocobalamin (CNCbl), is a most fascinating and intriguing natural product,\textsuperscript{[1]} that was discovered as the original isolation form of the life-saving ‘extrinsic’ anti-pernicious anemia factor.\textsuperscript{[2]} An exceptional 5,6-dimethylbenzimidazole pseudonucleotide appendage to the corrin core coordinates to the cobalt-centre of CNCbl, establishing the unique and characteristic three-dimensional architecture of the cobalamins (Cbls). Cbls belong to the larger family of the cobamides (Cbas), also including the related natural ‘complete’ coronoids\textsuperscript{[3]} with other pseudonucleotide heterocycles\textsuperscript{[4,5]} or linker units.\textsuperscript{[5]} These complex cobalt-corrrns are all generated in Nature by intricate B_{12}-biosynthetic paths,\textsuperscript{[6]} an exclusive capacity of some bacterial procaryotes and archaea.\textsuperscript{[6b]} Indeed, according to Eschenmoser’s proposal, the natural B_{12}-derivatives may originate from structurally simpler cobalt-corrinoid precursors, presumed to have developed in early forms of life.\textsuperscript{[7]}

In spite of many years of intense medicinal,\textsuperscript{[8]} molecular biological and biochemical\textsuperscript{[9]} research, new physiological roles of B_{12} in humans keep emerging\textsuperscript{[9b,10]} while some further Cbl-related medical findings remain puzzling,\textsuperscript{[11]} so that B_{12} has been classified as a ‘moonlighting’ vitamin.\textsuperscript{[12]} The association of the B_{12}’s own cobalt with a ‘Kobold’, the German word for goblin, appears to fit the occasionally puzzling situation. In fact, vitamin B_{12} (CNCbl) itself is not a directly physiologically active vitamin in humans and other mammals.\textsuperscript{[6b,13]} In order to set free its functional capacity, CNCbl needs to be converted by the mammalian metabolism,\textsuperscript{[10c,13]} into the organometallic B_{12}-cofactors methylcobalamin (MeCbl) and coenzyme B_{12} (adenosylcobalamin, AdoCbl).\textsuperscript{[14]} CNCbl is, thus, the role of a ‘provitamin’.\textsuperscript{[14]} In fact, various Cbas, more directly functional physiologically than CNCbl, among them AdoCbl, are preferred B_{12}-vitamers for the treatment of some patients (Figure 1).\textsuperscript{[15]}

The possible physiological effects of artificial intact Cbls designed to closely mimic the molecular shape of vitamin B_{12} and to resist metabolic conversion into the B_{12}-cofactors, have begun to attract our interest.\textsuperscript{[10]} The highly efficient and complex B_{12}-uptake and transport system in humans\textsuperscript{[17]} and higher animals\textsuperscript{[18]} should bind such inactive vitamin B_{12} analogues rather indiscriminately (as would, typically, also be the case for B_{12}-using bacteria\textsuperscript{[19]}), with the consequence of the cellular import of (inactive) B_{12}-dummies competing with the natural cobalamins and effectively impairing B_{12}-metabolism. In consequence, B_{12}-analogues designed according to these criteria, would act as antivitamins B_{12} that induce functional Cbl-deficiency in humans and other mammals in vivo; a concept presented in this Journal about 5 years ago.\textsuperscript{[16]} Antivitamins B_{12} relate to the broader class of the B_{12}-antimetabolites and were discussed in this context.\textsuperscript{[14,20]} Typical B_{12}-based antimetabolites, which are not covered in this Minireview, are Cbls (or other Cbas), modified at their periphery, that counteract, or fail to fulfil adequately, the physiological roles of natural B_{12}-derivatives in various B_{12}-dependent organisms, including many microorganisms. B_{12}-deficiency deprives some bacteria, animal

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**Figure 1.** General structural formula of the cobalamins (centre), symbolic formulations of some important B_{12}-vitamins (left: vitamin B_{12} (CNCbl), methylcobalamin (MeCbl) and coenzyme B_{12} (AdoCbl)), and of (potential) Cbl-based antivitamins B_{12} (right: the aryl-Cbl EtPhCbl and the alkynyl-Cbls PhEtCbl and F2PhEtCbl).
and human cells of vital metabolic processes, which is a desirable consequence of the administration of metabolism based antibiotics and anti-cancer agents.\textsuperscript{[14c, 16, 20a]} Hence, broad biological\textsuperscript{[5]} and biomedical research interests\textsuperscript{[6, 12, 14, 16, 20, 21]} are exploring means of inducing (functional) $\text{B}_{12}$-deficiency and are devoted to studies of its pathological effects.\textsuperscript{[8]}

**From vitamin $\text{B}_{12}$ to antivitamins $\text{B}_{12}$—the cobalamin strategy**

In line with the original concept\textsuperscript{[16]} the complete Cbl-scaffold of vitamin $\text{B}_{12}$ was used as starting point for a (most efficient) preparation of antivitamins $\text{B}_{12}$. The aryl-Cbl 4-ethylphenyl-cobalamin (EtPhCbl), a novel type of organometallic $\text{B}_{12}$-derivative, was generated as a first such Cbl-based antivitamin $\text{B}_{12}$ (Figure 1).\textsuperscript{[25]} The critical design criteria for EtPhCbl were (i) its predicted (and verified) structural similarity with for example, CNCbl and (ii) its expected resistance against the metabolic removal of its aromatic capping group by the cellular $\text{B}_{12}$-tailoring enzyme CblC.\textsuperscript{[16c]} Thus inhibiting a later conversion into the organometallic $\text{B}_{12}$-cofactors.\textsuperscript{[16, 22]} The aryl-Cbl EtPhCbl bound well to the human $\text{B}_{12}$-transporter proteins, intrinsic factor, transcobalamin and holocobalamin, and was resistant against its tailoring by the enzyme CblC, as postulated.\textsuperscript{[22]} Most critically, EtPhCbl also led to functional Cbl-deficiency in experiments with laboratory mice.\textsuperscript{[23]} However, while fulfilling the criteria of an antivitamin $\text{B}_{12}$, EtPhCbl is photosensitive and visible light degrades it into the $\text{B}_{12}$-vitamer hydroxocobalamin (HOCbl),\textsuperscript{[22]} although with a low quantum yield.\textsuperscript{[24]} Hence, since EtPhCbl has the (often undesirable) property of a ‘photo-conditional antivitamin $\text{B}_{12}$’,\textsuperscript{[24]} our interest has turned to light stable Cbl-based $\text{B}_{12}$-dummies. Suitable variants of the barely explored alkynylcobalamins\textsuperscript{[25]} with a strong organometallic Co–C bond appeared attractive as presumed light stable potential antivitamins $\text{B}_{12}$.\textsuperscript{[26]} The previously unknown phenylethynyl-cobalamin (PhEtCbl) was prepared, which turned out to be slightly hydrolysis-sensitive, but was light stable and thermally robust and exhibited similar binding-affinity as CNCbl for the human proteins of $\text{B}_{12}$-transport.\textsuperscript{[26a]} Furthermore, the fluorinated 2,4-difluorophenyl-derivative F2PhEtCbl was not only light-stable,\textsuperscript{[27]} but also rather inert against acid-induced hydrolytic cleavage of its Co–C bond, as expected.\textsuperscript{[26b]} F2PhEtCbl bound and inhibited the holoenzyme CblC loaded with the co-substrate glutathione, allowing for a first crystal-structure analysis of fully assembled human CblC.\textsuperscript{[26]} Investigations, not only from our laboratory, but also from the Gryko group\textsuperscript{[28]} have meanwhile expanded the methodology for the preparation of organometallic alkynyl-cobalt-corrinoids. Indeed, the robust alkynyl-Cbls have become attractive potential cellular import vehicles (‘Trojan Horses’) with a range of biological and biomedical applications.\textsuperscript{[26b, 26c]}

**Engineered $\text{B}_{12}$-biosynthesis opens direct non-cobalt synthetics-paths to antivitamins $\text{B}_{12}$**

The possible conversion of aryl- and alkynyl-Cbls into the $\text{B}_{12}$ vitamers hydroxocobalamin (HOCbl) or aquocobalamin (H$_4$O$_2$Cbl), by light or acid, respectively, was seen as a drawback as to their use as antivitamins $\text{B}_{12}$\textsuperscript{[22, 26d]} prompting us to look out for strategic alternatives. Indeed, our simple structure-based design criteria for the antivitamins $\text{B}_{12}$, that is, structural similarity with CNCbl and resistance against metabolic tailoring by the enzyme CblC\textsuperscript{[16d]} would not only be an inbuilt feature of some inert Cbls, but a select and suitably designed group of metabalamins (Metbls)\textsuperscript{[14b, 30]} transition metal analogues of the Cbls, might also serve this purpose. In this respect, rhodium, the group IX homologue of cobalt, appeared to offer a most promising access to effective potential antivitamins $\text{B}_{12}$ by furnishing rhodibalamins (Rhbls), the Rh-based Cbl-analogues, presumed to be largely iso-structural to corresponding Cbls.\textsuperscript{[16]} (Figure 2).

In the 1970s Koppenhagen and co-workers reported the preparation of partially characterized Rhbls.\textsuperscript{[28]} In their exploratory tests with microorganisms and human cell cultures, adenosylrhodobalamin (AdoRhbl),\textsuperscript{[14b]} the Rh-homologue of AdoCbl, was indicated to behave as a $\text{B}_{12}$, antimetabolite.\textsuperscript{[22]} We have recently developed an intricate chemical-biological total synthesis of AdoRhbl in a team with the Warren group in Canterbury (UK). AdoRhbl was first synthesized using the biotechnologically prepared natural metal-free $\text{B}_{12}$-ligand hydrogenobyrinic acid (H$_4$O$_2$Cbl).
a,c-diamide (Hbad) as starting material, followed by an adequate cocktail of further chemical and enzymatic transformations of Hbad. AdoRhbl was fully characterized in detail as a close structural, non-functional AdoCbl mimic that efficiently inhibited an AdoCbl-dependent enzyme diol dehydratase, as well as the growth of the bacterial pathogen Salmonella enterica. In an additional welcome contrast to the antivitamin B\textsubscript{12} EtPhCbl and to the coenzyme AdoCbl, the related AdoRhbl proved stable when irradiated with sunlight.

As Rhbls, the Rh-analogues of the Cbls, appeared to constitute a group of promising antivitamins B\textsubscript{12}, a systematic and more direct synthesis methodology of Rhbls was developed. Its basis was a newly bioengineered preparative route to the now thoroughly characterized metal-free B\textsubscript{12}-ligand hydrogenoboronic acid (Hby). The metal-free Hby also constituted an excellent basis for the partial synthesis of hydrogenobalamin (Hbl), the complete metal-free ligand of the Cbls (Figure 3). The metal-free Hbl in turn, is a rational general starting material for the synthesis of specific Metbls, a long-standing dream and topical subject in the B\textsubscript{12}-field, and in bioinorganic chemistry. The biosynthetically available Hbl has meanwhile served in our hands for the one-step synthesis of chlororhodobalamin (CRhbl), and from there, of methylrhodobalamin (MethylRhbl), that is, of the Rh-analogues of chlororhodobalamin (CICbl) and of MeCbl, respectively (see Figure 2). As revealed by the crystal structures of the organometallic AdoRhbl and of the 'inorganic' CRhbl, Rh\textsuperscript{II}-corrins and Co\textsuperscript{III}-corrins are closely isostructural and the slightly larger Rh\textsuperscript{III}-ion appears to fit strikingly better into the corrin ligand of the Cbls than the 'natural' Co\textsuperscript{III}-ions.

The metal-free B\textsubscript{12}-ligands Hby and Hbl are starting materials, not only for the syntheses of Rhbls, but also, obviously, of other Metbls. So far, we have reported on the synthesis and on the detailed structural characterization of zincoboralin (Znbl), the Zn\textsuperscript{II}-analogue of vitamin B\textsubscript{12} and of the novel Ni\textsuperscript{II}-analogue, nibalamin (Nibl) (see Figure 3). According to detailed structural and computational studies, the redox-inactive pentacoordinate ('base-on') Znbl constitutes a luminescent structural mimic of the penta-coordinate 'base-on' Co\textsuperscript{III}-cobalamin (Cbl\textsuperscript{III}). The tetra-coordinate diamagnetic 'base-off' Ni\textsuperscript{II}-corrin Nibl represents a largely redox-inactive structural mimic of the highly activated tetra-coordinate 'base-off' Co\textsuperscript{III} and Co\textsuperscript{I}-Cbls. The reduced Cbls represent the often cryptic high-energy intermediates in many Cbl-dependent enzymatic reactions, as well as in some essential B\textsubscript{12}-biosynthetic organometallic transformation, for example, as catalysed by adenosyl transferases.

Together with the newly available hexa-coordinate Rhbls, penta-coordinate ('base-on') Znbl and tetra-coordinate ('base-off') Nibl constitute a complete suite of structural transition metal mimics of the Cbls in their biologically accessible redox states, that is, hexa-coordinate 'base-on' Co\textsuperscript{III}-Cbls, penta-coordinate 'base-on' Co\textsuperscript{III} and tetra-coordinate 'base-off' Co\textsuperscript{III} or Co\textsuperscript{I}-Cbls, providing us with a structurally 'complete' small set of biochemically inactive B\textsubscript{12}-antimetabolites, inhibitors of B\textsubscript{12}-enzymes and (some of them) potential antivitamins B\textsubscript{12} (Figure 4). The 'base-on' Metbls Rhbls and Znbl are likely to function as genuine antivitamins B\textsubscript{12}, the 'base-off' Nibl as a B\textsubscript{12}-antimetabolite that inhibits some B\textsubscript{12}-dependent enzymes but may not be bound well by the mammalian B\textsubscript{12}-transporter proteins. Hence, in order to clarify the capacity of Metbls to serve as antivitamins B\textsubscript{12} according to our concept, their ability to mimic the Cbls with respect to high-affinity binding to the very structure-selective B\textsubscript{12}-uptake and transport system of humans (and other mammals) needs to be analysed.

Application of antivitamins B\textsubscript{12} induces functional B\textsubscript{12}-deficiency

As delineated above, antivitamins B\textsubscript{12} are structural Cbl-mimics designed to counteract the effect of CNCbl (and of its B\textsubscript{12} vtamers forms) in humans and animals by causing (functional) B\textsubscript{12}-deficiency upon their cellular uptake, a deadly metabolic defect. Such an uptake of antivitamins B\textsubscript{12} leads, first of all, to the inactivity of the mammalian B\textsubscript{12}-dependent enzymes methionine synthase (Meth)

![Figure 3](Image) Biosynthetic hydrogenoboronic acid (Hby) is starting material for the partial synthesis of hydrogenobalamin (Hbl), a direct synthesis platform for transition metal analogues of vitamin B\textsubscript{12} (Metbls), such as zincoboralin (Znbl) and nibalamin (Nibl).

![Figure 4](Image) The Metbls Rhbls, Znbl and Nibl (blue field) are (largely) inert structural mimics of Co\textsuperscript{III}, Co\textsuperscript{I} and Co\textsuperscript{III}-cobalamins (red background), and are efficient inhibitors of B\textsubscript{12}-dependent enzymes useful for basic biochemical studies.
biomarkers of B<sub>12</sub>-deficiency. Functional B<sub>12</sub>-deficiency induced by antivitamins B<sub>12</sub> in humans and in other mammals, results, on the one hand, from the inability of these B<sub>12</sub>-dummies to assign the specific ‘canonical’ roles of the B<sub>12</sub>-cofactors of MethH and MCM, which are based on the organometallic reactivity of MeCbl and of AdoCbl, respectively. However, antivitamins B<sub>12</sub> will, on the other hand, extensively mimic the (merely) structure-based (‘non-canonical’) regulatory functions of the Cbls, giving fake signals for the availability of genuine B<sub>12</sub>-cofactors by imitating effectively their binding capacity to natural bio-macromolecular targets, such as B<sub>12</sub>-responsive regulatory proteins and RNA. As described below, a multitude of gene-regulatory roles of the natural B<sub>12</sub>-cofactors have been discovered in microorganisms. However, so far, in humans only two such bio-macromolecular binding interactions have been detected. Further ‘non-canonical’ roles of Cbls in humans and in other mammals are suggested, for example, by the observation of a cytokine and growth-factor imbalance in the central nervous system in laboratory rats due to Cbl-deficiency as well as of insulin resistance and hyperglycemia induced by B<sub>12</sub>-deficiency in human cell cultures. Antivitamins B<sub>12</sub> may be particularly helpful in imitating and identifying such puzzling roles, as well as in discovering new ‘non-canonical’ ones.

**Antivitamins B<sub>12</sub> as molecular probes**

A range of remarkable recent discoveries in the B<sub>12</sub>-field has put Vitamin B<sub>12</sub> in the spotlight again. Indeed, B<sub>12</sub>-derivatives play essential roles as organometallic biocatalysts not only in humans, animals, bacteria and archaea but, surprisingly, in a range of algae, as well. Some forms of bacterial photo-regulation involve natural cobamides as do critical steps of the biosynthesis of photosynthetic tetrapyrroles and of other complex metabolites including the anaerobic metabolism of hydrocarbons. Mechanistic insights into the exceptional biochemistry of the involved B<sub>12</sub>-dependent enzyme reactions or means of the B<sub>12</sub>-based control of essential cellular processes are areas of continuous interest. Studies with antivitamins B<sub>12</sub> and other structurally characterized Metblds may potentially contribute to this study relying on two key structure-based factors: (i) By imitating the structures of the B<sub>12</sub>-cofactors or of reactive intermediate B<sub>12</sub>-species in the course of enzyme reactions, suitably structured (inactive) B<sub>12</sub>-mimics have an excellent capacity to inhibit the corresponding enzymatic steps. Hence, for example, the Ni<sup>II</sup>-analogue of the cryptic intermedi- ated Co<sup>II</sup>-form cob(II)aemin inhibits an AdoCbl-generating Ado- transferase in an in vitro study (see above for corresponding pertinent findings with the alkynyl-Cbl F2PhEtyCbl and with AdoRhbl). (ii) By mimicking the structures of the B<sub>12</sub>-type ligands in B<sub>12</sub>-dependent regulatory functions in various organisms, antivitamins B<sub>12</sub> are, on the other hand, presumed to simulate the availability of the corresponding physiologically active B<sub>12</sub>-derivatives, for example, via B<sub>12</sub>-riboswitches and in B<sub>12</sub>-responsive regulatory proteins. The observed strong growth-inhibition of Salmonella enterica by AdoRhbl was, hence, ascribed to its specific binding to the BtuB B<sub>12</sub>-ribo-switch as a structural AdoCbl-mimic, inhibiting the expression of a B<sub>12</sub>-uptake protein in this microorganism. Similar further in vitro and in vivo experiments with AdoRhbl and some Cbl-based antivitamins B<sub>12</sub> have recently been carried out, signifying the ability of structurally competent antivitamins B<sub>12</sub> to simulate the presence of physiologically functional Cbls. Indeed, as long as the cellular and organismal import of antivitamins B<sub>12</sub> and of other Metblds by the natural pathways would be feasible, as expected, their capacity for generating functional B<sub>12</sub>-deficiency should also be maintained in vivo, even in living animals.

**Antivitamins B<sub>12</sub> as antibiotics and as cellular growth-inhibitors for human and animals**

Antivitamins B<sub>12</sub> and other B<sub>12</sub>-antimetabolites may function as B<sub>12</sub>-dummies and act as inhibitors of B<sub>12</sub>-dependent enzymes, impairing the growth and reproduction of bacteria and of other microorganisms. This early explored effect of modified vitamin B<sub>12</sub>-derivatives as B<sub>12</sub>-antimetabolites (see for example) could recently be extended to the critical case of hospital-resistant Gram-negative bacteria. The broad antibiotic activity of sulfonamides was boosted decisively by the addition of the antivitamin B<sub>12</sub>, EtPhCbl to the bactericidal sul- fonamide cocktail. Addition of the antivitamin B<sub>12</sub> was proposed to result in an effective methotrexate trap by blocking the formation of free tetrahydrofolate by methionine synthase. In addition to their proposed role in impairing the biosynthetic formation and in reducing the cellular availability of the (active) B<sub>12</sub>-cofactors, antivitamins B<sub>12</sub> may also intercept the uptake of the essential B<sub>12</sub>-derivatives by B<sub>12</sub>-depend- ent microorganisms due to their B<sub>12</sub>-mimetic regulatory activity as ligands of (for example) B<sub>12</sub>-riboswitches. The response of B<sub>12</sub>-regulatory elements to binding of a B<sub>12</sub>-type ligand is expected not to differentiate between the functional classification of the latter as ‘vitamin’ or as ‘antivitamin’. In consequence, both the ‘canonical’ bio-catalytic and the ‘non-canonical’ B<sub>12</sub>-regulatory roles played by the natural cobamides bestow antivitamins B<sub>12</sub> with a potentially very effective two-pronged bactericidal activity, as verified recently with AdoRhbl, the rhodium analogue of AdoCbl.

Since the deactivation of the B<sub>12</sub>-dependent enzymatic processes in humans and other mammals leads to an impaired metabolism, disrupting physiological function and also causing fundamental neuropsychopathological deficiencies, regular cellular growth is inhibited as consequence of a (functional) B<sub>12</sub>-deficiency. Antivitamins B<sub>12</sub> may, hence, be useful as anti-cancer agents. As already explored in early in vitro investigations, B<sub>12</sub> rhodium analogues were observed to inhibit as di- versely active B<sub>12</sub>-antimetabolites, the growth of human normo- and megaloblastic bone marrow cells. It will be of interest to learn more about the diagnostic and therapeutic applications of well-characterized, pure antivitamins B<sub>12</sub> as agents for anti-cancer diagnosis and treatment in humans and other mammals. Indeed, suitably fluorescence labelled, radiola- belled and other bio-conjugated B<sub>12</sub>-derivatives have proved useful over the recent years, as ‘Trojan Horses’ for the cellular
import of diagnostic loads and for targeted drug delivery,\cite{20a,64} helpful in inhibiting the growth and the detection of malignant cells,\cite{65a,65b,65c} and useful for a range of other biomedical applications.\cite{66}

**Summary and Outlook**

Our original interest in the subject of antitumour B12s was kindled by the expectation that these B12-dummies would offer insights into functional B12-deficiency in animals by an effective alternative methodology\cite{23} replacing total gastrectomy.\cite{67} This work has led to fruitful research collaborations, discovering new organometallic Cbl-chemistry, photochemistry and biochemistry.\cite{22,24,68} It has, likewise, opened up new avenues in the field of the fascinating transition metal analogues of the Cbls and of other natural corrinoids.\cite{34,36,39,42} The helical, ring-contracted natural corrin ligand has been characterized as an exceptional ‘Procrustean Bed’ for bound transition metal ions, important for tightly binding and specifically activating the bound cobalt-ions in their low-spin states.\cite{35} As discovered with synthetic NiII-corrons,\cite{29} the natural corrin ligand also imposes the diamagnetic low-spin state on bound NiII-ions,\cite{36} contrasting with the situation in related porphyrin-type NiII-corphinsoids.\cite{7,7a} Interestingly, the 5,6-dihydroxy-corrin variant of a ‘B12-type’ NiII-complex, recently prepared and studied in the Zelder group, also features a low-spin 4-coordinate NiII-centre.\cite{37b}

Cbl-based antitumour B12s promise to represent exceptional antibiotics,\cite{50} an important area to be developed further in view of the acute problem of hospital-resistant bacteria. As some bacteria use preferentially cobamides (Cbas) other than Cbls,\cite{71} the eventual adaptation of the methodology for the synthesis of Cbl-based antitumour B12s to the generation of corresponding Cba-forms is expected to enhance their selective antibiotic import as antibiotics, while simultaneously reducing the likelihood of the undesired uptake in human cells by their B12-transporters.\cite{7a,72} In ongoing collaborative studies, antitumour B12s and some other metalbamins are used as specifically targeted B12-antimetabolites, under investigation with respect to their capacity to serve as, for example, enzyme inhibitors, as ligands of regulatory proteins and of B12-riboswitches, as antibiotics, and as potentially useful anti-cancer agents. Having now set up some inaugural milestones, a broad further impact of studies on antitumour B12 and (further) B12-transition metal analogues in the bio-structural, biological and biomedical fields can be foreseen.

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**Conflict of interest**

The author declares no conflict of interest.

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