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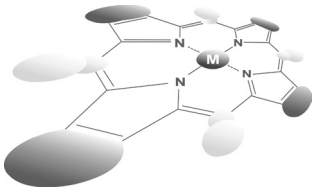

Bioinformatic and chemoneurocytological analysis of the pharmacological properties of vitamin B_{12} and some of its derivatives

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ABSTRACT: More than three thousand five hundred biological properties of vitamin B_{12} and four of its derivatives (aquacobalamin, cyanoaquacobyrinic acid heptamethyl ester, dicyanocobyrinic acid heptamethyl ester and stable yellow corrinoid) have been assessed by bioinformation analysis. Based on the data obtained (including the assessments of the interaction of molecules with *the proteins of rat proteome*), conclusions were drawn about the potential effects and safety of the investigated substances. In particular, it has been shown that heptamethyl esters of cyanoaquacobyrinic and dicyanocobyrinic acids, as well as a stable yellow corrinoid (antivitamin), can be recommended for further study as analgesics, anti-inflammatory drugs and, also, antitumor agents aimed at the therapy of glioblastoma, hepatoblastoma and T-cell leukemia. Estimates of the LD50 constants for rats and the TD50 and IC50 constants for rat muscle cells in culture, along with the results of assessments of the interaction of molecules with the rat proteome, showed that all the compounds studied were of low toxicity. At the same time, cyanocobalamin and aquacobalamin are distinguished by the least cumulative properties in comparison with other studied compounds. Chemoneurocytological analysis of compounds showed that cyanocobalamin and aquacobalamin may have the greatest neuroprotective effects: increase in the concentration of the substances by 1 mmol/l causes the estimate of neuronal survival to increase by 25%.

KEYWORDS: vitamin B_{12}, vitamin B_{12} derivatives, chemoreactomic analysis, chemoneurocytological analysis, pharmacological properties.

INTRODUCTION

Vitamins are the most important class of micronutrients essential for human life. Each vitamin serves a different number of genes, proteins, enzymes and is characterized by specific functions in certain tissues [1]. Vitamin B_{12} mainly compartmentalizes in bone marrow, liver, intestinal epithelium, and neurocites. In medicine, vitamin B_{12} is used to treat painful syndrome, to restore myelin and for anemia prevention. It is essential for folate metabolism and homocysteine neutralization, DNA methylation, nucleotide biosynthesis, and anemia prevention. Failures in these processes associated with vitamin B_{12} deficiency contribute to carcinogenesis [2].

It should be noted that such a wide range of biological roles of vitamin B_{12} is determined by specific interactions of its derivatives *with the proteins of the*

[◊] SPP full member in good standing.

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proteome. Cyanocobalamin does not interact with either genomic DNA or transcriptome RNA, and products of biotransformations of vitamin B_{12} are elements of human metabolome. A search of the databases of the human proteome (NCBI PROTEIN, EMBL, UNIPROT, Human Proteome Map, BIOCYC-HUMAN) shown the existence of 24 B_{12}-dependent proteins in the human proteome [3].

Targeted delivery of medicines to the place of action is one of the most current branches in modern pharmacology. A delivery of vitamin B_{12} to the bone marrow and nerve cells is of paramount importance, and at the same time being the most challenging of tasks. Accordingly, before the synthesis and experimental studies of synthetic derivatives of vitamin B_{12} it is advisable to conduct a comprehensive assessment of their pharmacological efficiency and safety.

Existing sources describe the pharmacological properties of the cyanocobalamin molecule, but contain very little information on the pharmacology of vitamin B_{12} derivatives. Therefore, to evaluate the properties of promising synthetic derivatives of vitamin B_{12} and other corrinoids, the method of chemoreactomic analysis was employed. This is the newest direction in post-genome pharmacology, assessing biological activities of a substance under study in the context of the reactome (*i.e.* all known chemical reactions) of given organism (a human, a rat, a mouse or other) and including simulations of interactions with a proteome (all proteins of the organism).

Within the post-genomic paradigm, a molecule of any drug "mimics" certain metabolites (due to the presence of some kind of similarity in the chemical structure), and, by binding to certain proteins of the proteome, creates the effects corresponding to the drug (both positive and negative). For a molecule under study, the data on its interaction with proteome obtained by chemoreactomic analysis provides an indication of its potential effectiveness and safety.

Chemoreactomic analysis is based on topological theory of data analysis [4–7] and has been previously verified in a number of biomedical projects [5–7]. For example, chemoreactomic analysis [8] of ethylmethylhydroxypyridine succinate (EMGPS) showed that this molecule can be an agonist of acetylcholine and GABA-A receptors and a neuroprotective agent with neurotrophic properties. Neuroprotective and neurotrophic properties of EMGPS are confirmed in independent neurocytological studies [9] and in experiments on animals [10]. By means of chemoreactom information technology, a series of works was carried out to analyze the synergy between non-steroidal anti-inflammatory drugs (NSAIDs) and myorelaxant crowperizone [11], NSAIDs and glucosamine sulfate [12], the presence of which is confirmed in clinical trials [13].

It is worth supplementing the chemoreactomic analysis with the analysis of the interaction of molecules under study with proteins of the proteome. This also provides valuable information on the biological properties of molecules. For example, earlier a comparative proteomic analysis of the effects of vitamins B_1, B_6 and B_{12} was conducted [14, 15], which indicated the feasibility of applying the chemoreactomic methodology to the analysis of the pharmacological effects of vitamin B_{12}. Based on the systematic biological analysis of vitamin B_{12}-dependent proteins annotated in accordance with the international Gene Ontology nomenclature, biological roles of proteins associated with the effects of vitamin B_{12} were established. Vitamin B_{12} has been shown to have an effect on fat metabolism, hematopoiesis, neuroprotective and neurotrophic effects, metabolism of micronutrients, and probably has an antibacterial effect (synthesis of alpha-defensin, an antimicrobial peptide) [6].

From the chemical point of view, vitamin B_{12} is a unique natural cobalt complex which contains a substituted corrin ring and 5.6-dimethylbenzimidazole, a nucleotide base. Cobalt in vitamin B_{12} can take different oxidation states: Co(III), Co(II), Co(I). Thanks to this, vitamin B_{12} is able to act as a catalyst in redox processes. The biological functions of vitamin B_{12} as well as the possibility of its chemical modification [16] make it a promising tool in the design and development of new drugs. In particular, it has been shown that aquacobalamin and its derivative, diaquacobinamide, can be antidotes for cyanide and hydrogen sulfide poisoning [17, 18].

Previously, vitamin B_{12} was encapsulated in micron-sized polymeric capsules and found that nanostructures of vitamin formed inside the capsules [19]. Once vitamin B_{12} is encapsulated in the different carriers, comprehensive studies of the state of the drug is necessary. In fact, the process of incorporation of complex organic compounds, including ones of porphyrin nature, can be accompanied by the formation of 2D and 3D micro- and nanoaggregates [20–23], due to the self-assembling ability of such compounds [24–28]. Such ensembles formed in confined space at the nanolevel can have drastically different properties as compared to the initial compounds in solutions, and in some cases the changes are irreversible [29–35] which is especially important for targeted delivery.

Vitamin B_{12} has various functional groups that can be changed to produce derivatives of the vitamin. Sometimes one has to use substances reducing or inhibiting the effect of vitamins instead of cyanocobalamin. Currently known possible antivitamins — hydrophilic (stable yellow corrinoids [36]) and hydrophobic (heptamethyl ether of cyanoaquacobyrinic and dicyanocobyrinic acids [37, 38]) derivatives of vitamin B_{12} and others — have not yet found wide application in medicine, as there have been no studies of their pharmacological properties. The chemoreactomic analysis is the first step in this direction.

This work is the first part of a set of studies aimed at creating nanosystems for targeted delivery of vitamin B_{12} and its derivatives. A comparative chemoreactomic analysis was performed of vitamin B_{12} and its derivatives:

aquacobalamin, heptamethyl ether of cyanoaquacobyrinic acid, heptamethyl ether of dicyanocobyrinic acid and stable yellow corrinoid.

EXPERIMENTAL

In this work more than 3500 biological properties of vitamin B_{12} and four of its derivatives (aquacobalamin, cyanoaquacobyrinic acid heptamethyl ester, dicyanocobyrinic acid heptamethyl ester and stable yellow corrinoid) have been assessed by bioinformation analysis [39].

Chemoreactomic analysis involves a problem-oriented theory within the boundaries of the combinatorial theory of the solvability of pattern recognition problems [4–7]. The latter is an extension of the algebraic approach to machine learning and presents the researcher with modern mathematical tools for complex analyses of the feature descriptions of objects.

During the mathematical formulation of the problems of analysis of molecular structure, the objects of study are chemographs (χ-graphs): *i.e*. mathematical objects each of which is given by a set of vertices and a set of edges — connections between vertices. A chemograph is a finite, connected, undirected and labeled graph without loops, with a clique number not exceeding 3 [4]. In accordance with the postulates of the theory of combinatorial solvability, χ-graphs are objects and so-called "invariants" of χ-graphs are features (recall that invariant is a numerical function over a graph). With respect to χ-graphs, the theorem on the completeness of invariants and the theorem on the criterion for the correspondence between solvability/regularity and completeness of invariants, formulated in [4–7], are extremely important.

Combinatorial analysis allows calculating tuple-invariants that guarantee the solvability and regularity of the feature descriptions of molecules [40]. During chemoinformatic analysis, a kind of "chemical distance" is calculated between any pair of molecules. The first step in the analysis is to establish a list of molecules that are closest in structure to the molecule being evaluated (*i.e.* calculate distances for a particular database of molecules). The second step of the analysis is the extraction of experimental information on molecules similar to the given one from the databases. The third step of the analysis is the assessment of the biological activities of the studied molecule (including modeling the interaction with the proteome), *i.e*. the actual chemoreactomic analysis.

Algorithms for predicting the properties of molecules, derived on the basis of the above formalism and methods for predicting numerical target variables, developed in the scientific school of Yu, I. Zhuravlev and K.V. Rudakov [41], are characterized by high generalizing ability and accuracy. For all biological activities mentioned in this work, cross-validation was carried out according to the "7:3, 10" scheme (70% of the data set for training, 30% for the control, 10 such partitions of the initial "molecule-property" set). The rank correlation coefficients for experiment and theory in the control samples in cross-validation were 0.7–0.9, indicating the practical importance of the algorithms. The method of chemoreactomic analysis is described in detail in the above works and provided as supporting information.

RESULTS AND DISCUSSION

Compounds (Table 1) were compared using the method of chemoreactomic analysis. The method is based on the theory of isomorphism of labeled graphs and modern techniques of forecasting of numerical target variables [41]. Values of more than 3500 pharmacological and biological properties were estimated for substances presented in Table 1.

Simulation of ADME parameters (Adsorption, Distribution, Metabolism, Excretion) in humans for the studied substances taken per os has shown that B12-1 and B12-2 have higher total clearance (54.5 $ml \cdot min^{-1}$, B12-3, B12-4–16-17 $ml \cdot min^{-1}$, B12-5–40.8 $ml \cdot min^{-1}$) and higher maximum concentration in blood plasma (35–36 $\mu g \cdot ml^{-1}$, B12-3, B12-4 – 26-27 $mg \cdot ml^{-1}$, B12-5–32.9 $mg \cdot ml^{-1}$). A clearance is the rate of removal of the substance from biological fluids or tissues of the body through biotransformation, redistribution within the body, and excretion from the body. Thus, B12-1 and B12-2 forms of vitamin B_{12} feature lower cumulative effect and, therefore, may be safer.

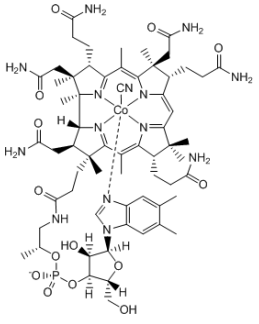
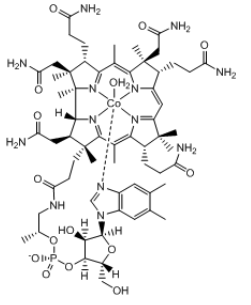
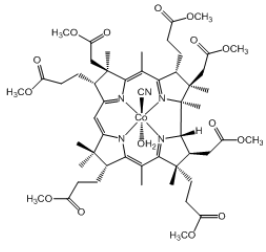
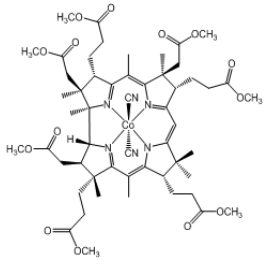
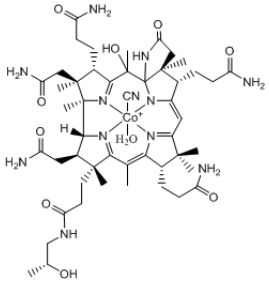
Chemoreactomic assessments of the accumulation of studied substances in various tissues (Fig. 1) showed that accumulation of B12-1 and B12-2 is 1.7–1.8 times higher on the average for all tissues. B12-5 has higher affinity to myelin, keratinocytes and neutrophils (20%, 31%, and 12% respectively as compared to B12-1).

Estimates of constants of cell growth inhibition (IC50) and percent of tumor cells growth inhibition were obtained by means of chemoreactomic simulations of influence of investigated substances at the fixed concentration of 10 μmol/L on various tumor cells in culture (Fig. 2). Inhibition constants of B12-3, B12-4, B12-5 were lower in case of colon adenocarcinoma cells (SW480, BE lines), adenocarcinoma (BXPC-3 line) and carcinoma (PT-45 line) of pancreas, small cell lung cancer (NCI-H69, NCI-H446 lines) and T-cell leukemia (CEM-SS line). In all other cases the IC50 constants were lower in B12-1 and B12-2.

Higher inhibition percentage with respect to cells of glioblastoma (SF-268 line), hepatoblastoma (HepG2 line) and T-cell leukemia (CEM-SS line) were found for B12-3, B12-4, B12-5 (Fig. 2). For all other cell lines the antitumor effects were higher for B12-1 and B12-2.

Chemoreactomic assessments of the parameters of pharmacokinetics, pharmacodynamics and toxicity of B1-B5 substances were also performed on a model of a

Table 1. Studied substances.

Name	Symbol	Formula
Vitamin B12	B12-1	
Aquacobalamin	B12-2	
Heptamethyl ester of cyanoaquacobyrinic acid	B12-3	
Heptamethyl ester of dicyanocobyrinic acid	B12-4	
Stable yellow corrinoid	B12-5	

reactom of the rat (Rattus Norvegicus). Estimates of pharmacokinetic parameters in rats are similar to the results of chemoreactomic simulations in humans. For example, B12-1 and B12-2 in rats similarly feature higher clearance and higher maximum concentration after *per os* intake than all other substances (Table 2). This corresponds to the higher area under the concentration curve (AUC) at the intake of sufficiently high doses of the substances (40 $mg \cdot kg^{-1}$). The accumulation of B12-1 and B12-2 in the liver and brain of rats is comparable.

Acute toxicity parameters were assessed, including LD50 (semi-lethal dose, *i.e.* the average dose of a substance that causes the death of half of the animals under test) and TD50 (average toxic dose, *i.e.* the dose that causes toxic effects in 50% of cells under test) (Table 3). Although the values of LD50 for rats and TD50, IC50 for rat muscle cells in the culture were slightly lower for B12-3, B12-4, B12-5, no significant difference in toxicity is found.

Indirect toxicity indicators based on estimates of the interaction of the studied molecules with proteome proteins of the rat were also obtained. For this purpose, estimates of 6533 biological activities describing interactions with 520 proteome proteins of the rat were calculated. Reliable differences in the obtained estimations of constants of interaction with proteins (activation constants (EC50), inhibition constants (IC50 and Ki), dissociation constants of substance-protein complexes (Kd)) were obtained for 224 proteins of the rat proteome. Then constants of different types were averaged. As a result, average values of constants characterizing the degree of interaction of each substance with proteome proteins were obtained (Fig. 3). On average over the rat proteome, studied substances showed similar values of interactions with proteins, confirming the absence of significant differences in toxicity of these substances.

The differences found in profiles of affinity of B1-B5 to proteins of rat proteome possibly explain the differences in pharmacodynamic effects of the substances in rats. Apparently, B12-3, B12-4 and B12-5 in rather high doses (about milligrams) showed somewhat higher anti-inflammatory, antiaggregant and analgesic effects (Table 4). It is known that vitamin B_{12} itself has dose-dependent analgesic effects [42, 43].

The neurocytological analysis data model was built on the basis of the results of neurocytological studies of cerebellar granular neuron cell cultures, presented in more than 300 publications. Also, the results of the original neurocytological studies obtained by the team of O.A. Gromova and at the Federal State Budgetary Scientific Center "Neurology". The latest methods of topological theory of machine learning [35] were used to process the collected data. Estimates of the survival of neurons in culture under moderate-severe glutamate stress (100 $\mu M \cdot l^{-1}$ glutamate, survival rate of 50% of cells) were obtained for concentrations of studied substances in the range of 0.1–1 $mM \cdot l^{-1}$. Chemoneurocytological analysis of compounds showed that cyanocobalamin (B12-1) and aquacobalamin (B12-2) may have the greatest neuroprotective effects: Increase in the concentration of the substances by 1 mmol/l causes the estimate of neuronal survival to increase by 25% (Fig. 4).

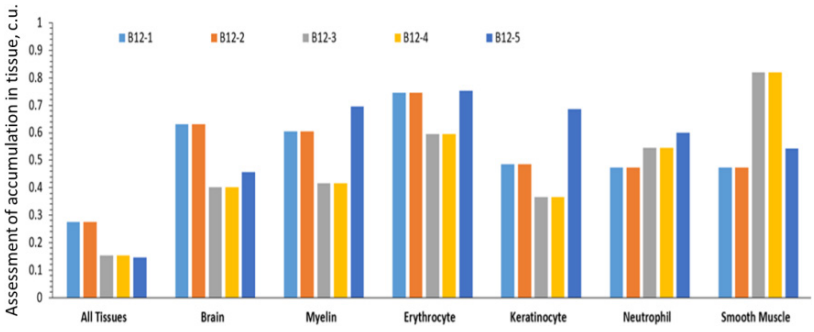


Fig. 1. Chemoreactomic assessments of the accumulation of the studied molecules in various tissues.

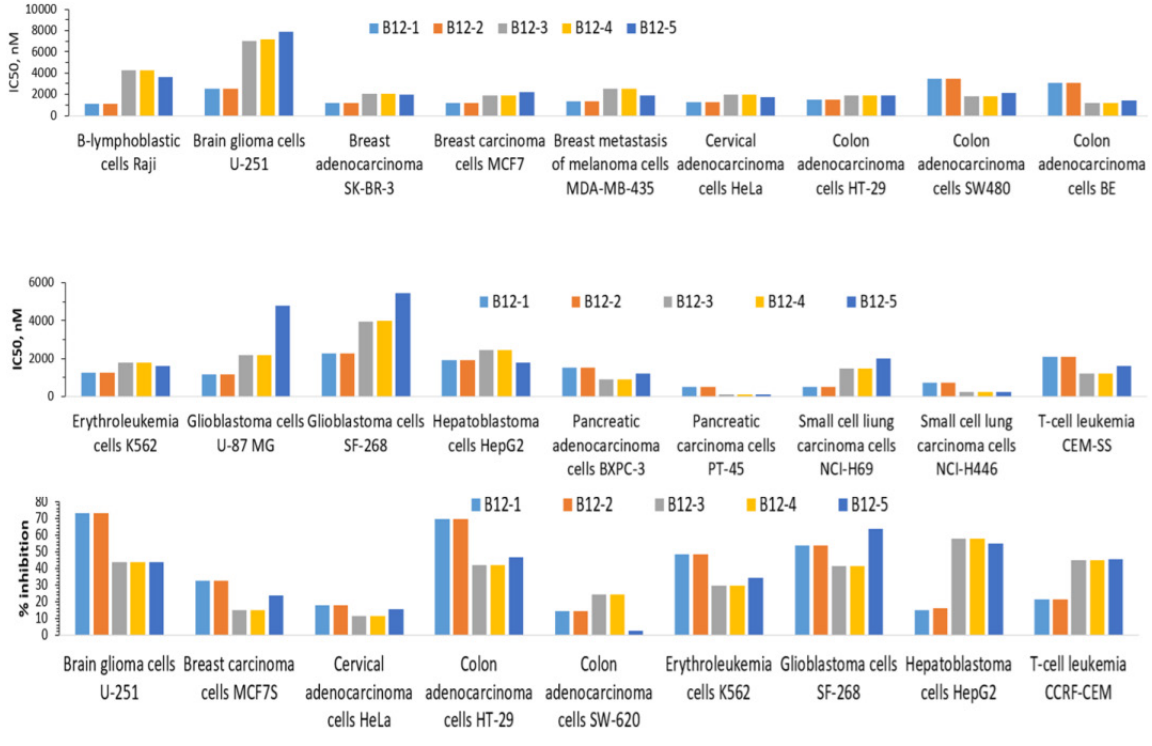


Fig. 2. Chemoreactomic simulations of influence of investigated substances on tumor cells of various types.

Table 2. Chemoreactomic assessments of pharmacokinetic parameters in rats (the model of reactom of rats Rattus Norvegicus).

Unit	Symbol	Parameter	B12-1	B12-2	B12-3	B12-4	B12-5
mg · h	AUC	The area under the concentration curve after taking 40 μg/kg per os	13	13	1.3	1.3	1.3
μM · h	AUC	The area under the curve, 3 mg/kg dose	0.8	0.8	5.0	5.0	4.2
μM · h	AUC	The area under the curve, 5 mg/kg dose, after 4 h	3.3	3.3	2.3	2.3	4.3
h^{-1}	CI	The clearance at the 3 mg/kg dose	12	12	4.4	4.4	7.0
kg^{-1}	Vdss	Volume of distribution in blood plasma	1.19	1.19	0.65	0.7	1.1
mM	Cmax	Maximum concentration in plasma after *per os* administration	0.33	0.33	0.29	0.29	0.24
$mg \cdot g^{-1}$	—	Accumulation in rat liver, 10 μg/kg dose, per os, after 6 h	2.68	2.70	3.86	3.90	3.94
μM	—	Accumulation in rat liver, 10 μg/kg dose, per os, after 1 h	2.27	2.27	0.87	0.87	0.88
%	–	Concentration in bile of rat	0.8	0.8	3.2	3.2	0.6

Table 3. Chemoreactomic assessments of toxicity.

Unit	Symbol	Parameter	B12-1	B12-2	B12-3	B12-4	B12-5
mM	IC50	Skeletal muscle myoblasts	15.8	15.8	11.3	11.3	13.1
μM	TD50	Skeletal muscle myoblasts	31	31	21	21	20
mg·k	LD50	2 h after intraperitoneal injection	390	390	337	337	260

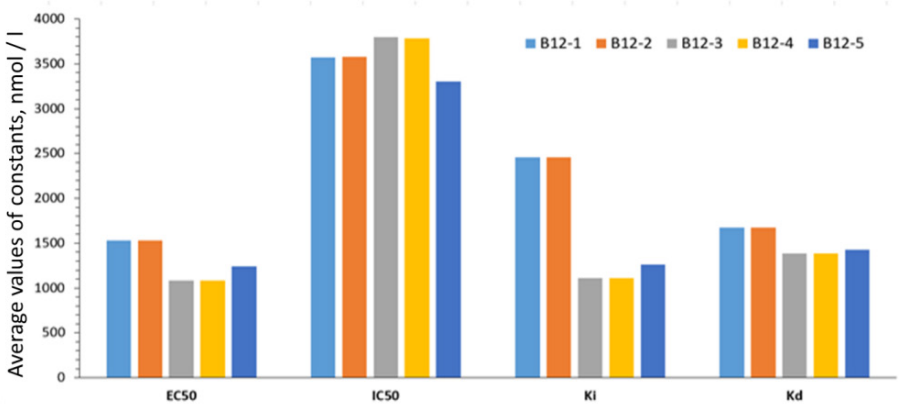


Fig. 3. Values of constants of interaction with proteins averaged over 224 proteins of the rat proteome.

Table 4. Results of chemoreactomic simulation of pharmacodynamic effects of studied substances in oral administration.

Unit	Symbol	Parameter	B12-1	B12-2	B12-3	B12-4	B12-5
$\mu g \cdot kg^{-1}$	ED10	Dose that causes a 10% drop in heart rate	16	16	0.8	0.8	16
$\mu g \cdot kg^{-1}$	ED2	Dose required for removal of 2 mEq/kg of sodium with urine	49	49	14	14	34
mM	Ki	Inhibition of ADP-induced platelet activation	2.6	2.6	1.0	1.0	0.8
$mg \cdot kg^{-1}$	ED30	Anti-inflammatory activity as a dose to inhibit carrageenan-induced paw edema by 30%	3.7	3.7	2.2	2.2	1.8
%	—	Analgesia in the test on a hot plate after oral administration of 300 μg/kg	36	36	25	25	16

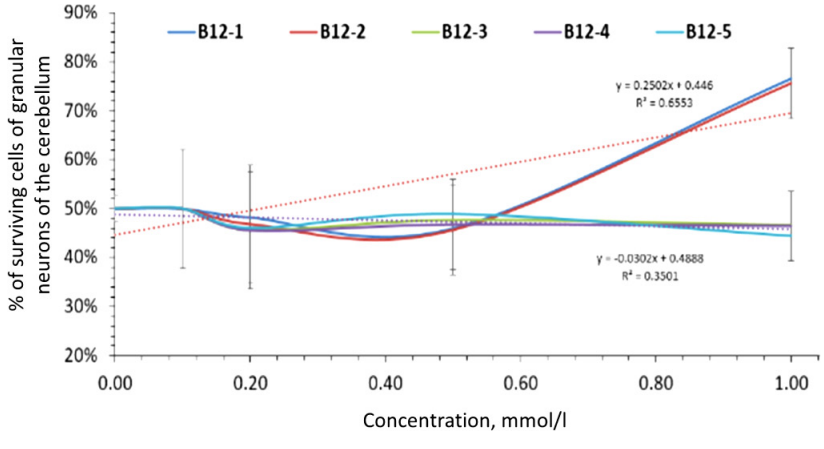


Fig. 4. Results of chemoneurocytological analysis.

All the vitamin B_{12} derivatives studied in this paper have been synthesized and characterized. Research has begun on their associative behavior in layers at the water-air interface and redox activity in films on solid substrates. It is shown that derivatives tend to aggregate on the water surface and reveal redox activity in thin films.

A preliminary study of the anticonvulsant and remyelinating potential of cyanocobalamin and its derivatives in a model of primary generalized seizures in rats showed that the use of cyanocobalamin and aquacobalamin does indeed have a pronounced protective effect. The compounds reduce the severity, duration and number of primary generalized seizures, stimulate anticonvulsant effects.

CONCLUSION

Estimates of more than 3500 pharmacological properties of synthetic derivatives of vitamin B_{12} were obtained in this *in silico* study. On the basis of the obtained data (on interaction with proteome proteins considered in the course of chemoreactomic analysis) the following conclusions about potential effects of the studied molecules were made.

Cyanocobalamin and aquacobalamin are safer than the others, as they have lower cumulative properties (as indicated by the higher total clearance value). These compounds accumulate in various tissues, whereas stable yellow corrinoid is more affine to myelin, keratinocytes and neutrophils. These results are important for further research. For example, stable yellow corrinoid features anti-inflammatory properties, so its accumulation in neutrophils is important for more effective inflammation reduction.

Cyanoaqua- and dicyanocobyrinic acid heptamethyl ester, and stable yellow corrinoid may have slightly larger anti-inflammatory, antiaggregant and analgesic effects, so these substances can be recommended for further study as pain relievers. These compounds are also promising for studies aimed at the treatment of glioblastoma, hepatoblastoma and T-cell leukemia (SF-268; HepG2 and CEM-SS). They are characterized by somewhat higher accumulation in the liver of rats than cyano- and aquacobalamin. Conversely, these latter ones produced greater accumulation in the rat brain compared to the rest of the studied substances. These compounds may be useful in the treatment of tumors corresponding to the rest of the studied tumor cell lines (SW480, BE; BXPC-3; PT-45; NCI-H69, NCI-H446; CEM-SS).

No significant difference in toxicity was found for the studied substances. Also, no differences were found in the indices of acute toxicity in rats (LD50) in cytological experiments (values of IC50 and TD50 constants for muscle cells in culture). One can conclude from the analysis of constants characterizing the degree of interaction of each substance with proteins of the proteome that chronic toxicity (which is realized through interaction with the proteome) is similar for all five studied compounds. According to the classification of medicinal substances, all studied compounds belong to class IV: Low toxicity (LD50 = 76-500 mg/kg).

The results of chemoneurocytological modeling suggest that further study of cyanocobalamin and aquacobalamin in neurocytological experiments is a particularly promising area. Data obtained in preliminary experiments on animals correlate with the conclusions drawn from simulations of activity of the compounds.

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Supporting information

The method of chemoreactomic analysis is described in detail in the supplementary material. This material is available free of charge *via* the Internet at https://www.worldscientific.com/doi/suppl/10.1142/S1088424621500644.

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